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Abstract Supplement

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Abstract Supplement

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- Translational Sessions
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- Educational Symposia
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TH-OR001

Osmolarity-Dependent Gene Expression Enables Spatial Resolution of Cells from Whole Kidney Single Cell RNA Data

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Background: In whole organ single cell data, spatial information of cells is usually lost but can sometimes be restored if regional marker genes are identifiable. In the kidney, certain cell types exist in regions of different microenvironments along the corticomedullary axis. For instance, cells of the proximal tubule, thick ascending limb or collecting duct extend from the serum-isosmotic renal cortex into the hyperosmotic renal medulla. We hypothesized that differences in regional gene expression between cortex, outer and inner medulla driven by different microenvironments and osmolarity-dependent genes might provide information on the spatial origin of cells in single cell data.

Methods: We obtained mouse kidneys and prepared single cell suspensions of whole kidneys as well as of microdissected cortical, outer and inner medullary tissue and applied single cell RNA sequencing. We assigned cell type information based on known marker genes and systematically analyzed regional gene expression differences and differences in expression of osmolarity-dependent genes (osmogenes) within different tubular cell types. In addition, we developed an unsupervised algorithm based on osmogene expression and used this information to spatially assign cells in whole kidney single cell suspensions.

Results: Our data show that the expression of osmogenes is tubule segment-specific and increases towards the inner medulla. We show that osmogenes are substantial drivers of gene expression differences within a given cell type along the corticomedullary axis. They harbor spatial information especially for tubule cells present in the outer and inner medulla but also to a lesser extent for other cell types. Applying our algorithm to spatially assign whole kidney single cell data reveals an imbalanced composition of regional origin of kidney cells in whole kidney single cell suspensions with a marked underrepresentation of medullary kidney cells.

Conclusions: Osmolarity-dependent genes show cell type-specific regional expression patterns and harbor spatial information of kidney cells. They can be used to spatially assign cells within whole kidney single cell RNA sequencing data and uncover a previously unrecognized regional bias in whole kidney single cell preparations.

TH-OR002

The Hypertension Induced by Renal Snx5 Silencing Is Associated with Increased Renal Protein Abundance of NHE3, NaPi2, NKCC2, and NCC in Mice

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Background: Sorting nexin 5 (SNX5) plays an important role in the function of renal dopamine receptor subtype 1 (D_1R). The gene silencing of renal Snx5 by its siRNA decreases renal D_1R but increases blood pressure (BP) in rats; it also decreases renal expression of insulin receptor and insulin degrading enzyme and causes insulin resistance in mice.

Methods: In order to test the hypothesis that SNX5 deletion affects renal sodium absorption and develops hypertension, we measured BP, water and sodium balance, and renal protein expression of sodium transporters in C57BL6/J mice treated with siRNAs of SNX5 or mock. 8 male C57Bl6 mice (5-6 months old) were uninephrectomized 3 weeks prior to the infusion of SNX5-siRNA or mock-siRNA (3 mg/kg.day, n=4/group) via osmotic mini-pump into sub-capsular space for 1 week.

Results: In SNX5-siRNA-treated mice, systolic (119±5.2, mm Hg, under anesthesia) and diastolic BPs (91.8±7.3) were elevated, relative to mock-siRNA-treated mice (SBP=101.5±0.5, DBP=72±2.3). Food and water intake, body weight, urine volume and heart rate were similar in the two groups. The gene silencing decreased the protein expression of SNX5 and D_1R by 70% and 30% respectively (immunoblotting). In control mice, SNX5 and D_1R colocalized mainly in the apical membrane of the proximal tubules, thick ascending limbs of loop of Henle, but not in collecting ducts. The two proteins also co-immunoparticipated in mouse kidney homogenates and cell lysates from cultured mouse proximal tubule cells. The gene silencing of Snx5 increased renal protein expressions of NHE3 (172±30, % of control), NaPi2 (223±12), NKCC2 (286±54), NCC (177±23), but did not alter the protein expressions of ENaCs and Na^+K^+ATPase.

Conclusions: These findings suggest that inhibition of SNX5 by siRNA increases the apical sodium transporters in proximal and distal nephron segments, in which SNX5 and D1R were co-localized. This may cause the impaired sodium excretion that may be responsible for the increased blood pressure in SNX5-siRNA-treated mice.

Funding: Other NIH Support - Nanjing Science and Technology Development Plan Project

TH-OR003

Dietary Fructose Enhances Protein Kinase C Activity and Angiotensin II-Dependent Transport in Proximal Tubules

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Background: In both humans and model organisms fructose causes salt-sensitive hypertension. This is in part due to increasing the sensitivity of proximal nephron Na reabsorption to angiotensin II (Ang II) such that lower concentrations stimulate transport to a greater extent. Ang II stimulates Na transport in proximal tubules by activating protein kinase C (PKC) α, a calcium- and lipid-dependent kinase. We hypothesized that dietary fructose increases the ability of Ang II to elevate intracellular calcium (Cai) and, thereby, activate PKC α in proximal tubules. This, in turn, stimulates Na/H exchange activity, the primary transporter involved in Na reabsorption.

Methods: Rats were fed a diet of normal chow plus tap water or normal chow plus 20% fructose in drinking water for 7-8 days. The effect of Ang II on Cai was measured using Fura2 in isolated, perfused S2 segments of proximal tubules. Na/H exchange (NHE) activity was measured in perfused tubules using the pH-sensitive dye BCECF. PKC α activity was measured by separating particulate and soluble fractions, performing Western blots and recording the particulate to soluble ratio. Increases in this ratio was taken as activation.

Results: Basal Cai was 143±29 nM in proximal tubules from control rats while it was 160±30 nM in those given fructose, not significantly different. Ang II (1 nM) increased Cai by 43±10 nM in control tubules and by 148±53 nM in tubules from rats fed fructose ($p < 0.03$). A higher concentration of Ang II (100 nM) increased Cai by 237±100 nM in proximal tubules from rats fed fructose and by 190±34 nM in tubules from rats fed the control diet. Ang II increased the particulate to soluble ratio of PKC α by 0.134±0.026 in tubules from rats fed fructose ($p < 0.001$) but not significantly in control tubules (0.060±0.061). Finally we measured NHE activity. Ang II (1 pM) increased NHE activity by 0.7±0.1 fluorescent units/s in tubules from rats given fructose but had no effect on NHE activity in control tubules ($p<0.01$). With Go6976, a PKC $\alpha/\beta1$ inhibitor, Ang II was unable to stimulate NHE activity in tubules from rats fed fructose.

Conclusions: We concluded that dietary fructose increases the ability of Ang II to elevate Cai, and consequently PKCα. This, in turn, stimulates NHE activity which likely contributes to fructose-induced salt-sensitivity of blood pressure.

Funding: Other NIH Support - NHLBI

TH-OR004

Potassium Directly Regulates WNK (With No Lysine Kinases)

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Background: Plasma potassium concentration is maintained within a narrow range, implying the ability to sense deviations from normal. WNK mutations in mice and humans result in abnormal potassium concentrations, and WNKs have been proposed to indirectly sense plasma potassium via effects on intracellular chloride. Here, we investigate whether WNKs are directly regulated by potassium. Our lab has previously shown that the WNK signaling cascade is conserved in *Drosophila* Malpighian (renal) tubules.

Methods: We used differential scanning fluorimetry and mass spectrometry to measure WNK kinase domain thermal stability and autophosphorylation *in vitro* in the presence of varying concentrations of potassium. We also examined the activity of DmWNK (*Drosophila* WNK) and HsWNK3 (human WNK3) activity in the *Drosophila* Malpighian tubule, using phosphorylation of transgenically expressed kinase-dead rat SPAK as a readout. We developed baths with varying extracellular potassium and fixed intracellular chloride concentrations (16 mM or 30 mM, measured using the transgenic sensor ClopHensor). We measured intracellular potassium in the tubule using inductively coupled plasma mass spectrometry.

Results: Potassium directly binds to the kinase domain of DmWNK (*Drosophila* WNK) and human WNK1 *in vitro*, as assayed by differential scanning fluorimetry. Potassium also inhibits autophosphorylation, required for kinase activation, of DmWNK and HsWNK3 (human WNK3) kinase domains *in vitro*. We also examined the activity of DmWNK or HsWNK3 in Malpighian tubules. Compared to the normal potassium bath, there was no change in DmWNK or HsWNK3 activity in low potassium bath, but there was no change in intracellular potassium under these conditions. Intracellular potassium was increased in the high potassium bath, and high potassium inhibited both DmWNK and HsWNK3 in both the 16 mM and 30 mM intracellular chloride conditions. High potassium bath also inhibited chloride-insensitive $HsWNK3^{L295F}$ activity in the tubule.

Conclusions: Our data suggest that potassium directly inhibits WNK kinases, in a manner that is additive to chloride inhibition, with implications for potassium sensing in the kidney and other organs.

Funding: NIDDK Support, Private Foundation Support

TH-OR005

Mg^{2+} Restriction Downregulates NCC Through NEDD4-2 and Prevents Its Activation by Hypokalemia

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Background: Hypomagnesemia is associated with lower kidney function and life-threatening complications, and sustains hypokalemia. The distal convoluted tubule (DCT) determines final urinary Mg^{2+} excretion, and via activity of the Na^+-Cl^- cotransporter (NCC) plays a key role in K^+ homeostasis by metering Na^+ delivery to distal segments. We previously showed that short-term (3 days) or long-term (14 days) Mg^{2+} restriction lowered abundances of total NCC (tNCC) and the active phosphorylated NCC (pNCC), but this did not involve the NCC-activating WNK-SPAK pathway.

Methods: We set out to further explore the mechanisms involved and determine interactions with K^+ restriction, a strong activator of NCC, by performing dietary manipulations in mice then Western blotting.

Results: We confirmed a previous report that long-term Mg^{2+} restriction does not alter NCC mRNA abundance, and found the same with short-term Mg^{2+} restriction. The E3 ubiquitin-protein ligase neural precursor cell expressed developmentally downregulated gene 4-2 (NEDD4-2) is known to target NCC for proteasomal degradation. We found that short-term Mg^{2+} restriction did not lower tNCC abundance in inducible nephron-specific NEDD4-2 knockout mice. We next examined interactions with K^+ restriction. tNCC and pNCC abundances were similar after short- or long-term Mg^{2+} or combined Mg^{2+}-K^+ restriction, but were dramatically lower compared with low K^+ diet, suggesting that Mg^{2+} restriction overrides the effects of K^+ restriction on NCC. After combined Mg^{2+}-K^+ restriction, adding back K^+ alone to the diet had no effect on tNCC abundance, but adding back Mg^{2+} either at the same time or after K^+ replenishment increased tNCC abundance. NEDD4-2 mediates degradation of the epithelial sodium channel (ENaC) during dietary K^+ restriction so we next examined the effect of Mg^{2+} restriction on ENaC by performing amiloride response tests. Compared with normal diet the natriuretic effect of amiloride was strongly blunted after K^+ restriction but not after Mg^{2+} restriction.

Conclusions: Together, these data suggest that NEDD4-2 mediates proteasomal degradation of NCC during Mg^{2+} restriction, Mg^{2+} restriction exerts differential effects on NCC and ENaC, and sustained NCC downregulation may enhance distal Na^+ delivery during states of hypomagnesemia, maintaining hypokalemia.

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

TH-OR006

Angiotensin II Stimulates ENaC by an Aldosterone-Independent Mechanism

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Background: Epithelial Na^+ channel (ENaC) is expressed in the aldosterone-sensitive distal nephron and both aldosterone and angiotensin II (AngII) have been shown to stimulate ENaC activity. The aim of the present study is to test whether AngII is able to stimulate ENaC by an aldosterone-independent mechanism.

Methods: We employed the patch-clamp technique and renal-Na^+ clearance method to study the effect of AngII on ENaC in the DCT and CCD of WT and kidney-specific mineralocorticoid receptor knockout (MR-KO) mice, where MR is knocked out in adult mice.

Results: High dietary K^+ (HK) intake stimulates ENaC in both DCT and CCD in WT mice but this effect is absent in MR-KO mice. In contrast, low sodium (LS) stimulates ENaC only in the CCD but not in the DCT and the effect of LS on ENaC in the CCD was completely absent in MR-KO mice. Under control conditions the amiloride-sensitive Na^+ currents (ENaC) in DCT2 were significantly higher than in the CCD. The deletion of MR partially inhibited ENaC in the DCT but completely abolished ENaC in the CCD. Furthermore, application of losartan (AT1R antagonist) inhibited ENaC in the DCT of both WT and MR-KO mice, suggesting the role of AT1R in regulating ENaC activity in the DCT. In contrast, losartan did not have a significant effect on ENaC in the CCD of WT mice. Infusion of AngII for 3 days increased ENaC activity in the DCT and in the CCD of WT mice. Moreover, AngII infusion still robustly increased ENaC currents in the DCT of MR-KO mice whereas the stimulatory effect of AngII on ENaC was modest in the CCD. Renal clearance study further demonstrated that angiotensin II infusion for three days augmented benzamil-induced natriuresis in MR-KO mice and increased the renal K^+ excretion. Consequently, the infusion of AngII completely corrected hyperkalemia of MR-KO mice.

Conclusions: Angiotensin II-induced stimulation of ENaC occurs mainly in the DCT and to a lesser degree in the CCD. In contrast, aldosterone plays a dominant role in determining ENaC activity in the CCD but to a lesser degree in the DCT. Thus, AT1R plays an important role in the regulation of ENaC activity in the DCT.

Funding: NIDDK Support

TH-OR007

Collecting System Specific Deletion of Kcnj10 Predisposes for Thiazide- and Low K^+ Diet-Induced Hypokalemia

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Background: The basolateral K^+ channel KCNJ10, is expressed in the renal distal convoluted tubule (DCT) and controls the activity of the thiazide-sensitive NaCl cotransporter (NCC). Loss-of-function mutations of KCNJ10 cause EAST/SeSAME syndrome with salt wasting and hypokalemia. KCNJ10 is also expressed in the principal cells of the collecting system (CS); however, its role in this segment has not been studied in detail.

Methods: To address this question, we generated the mouse model $AQP2^{cre}$:$Kcnj10^{flox/flox}$ with a deletion of Kcnj10 specifically in the CS (CS-Kcnj10-KO).

Results: CS-Kcnj10-KO mice responded normally to standard and high K^+ diet. However, CS-Kcnj10-KO exhibited a higher kaliuresis and lower plasma K^+ than control mice when treated with thiazide diuretics. Likewise, CS-Kcnj10-KO displayed an inadequately high kaliuresis and renal Na^+ retention upon dietary K^+ restriction. In this condition, CS-Kcnj10-KO mice became hypokalemic due to an insufficient downregulation of the epithelial Na^+ channel (ENaC) and the renal outer medullary K^+ channel (ROMK) in the CS. Consistently, the phenotype of CS-Kcnj10-KO was ameliorated by either pharmacological inhibition of ENaC or by genetic inactivation of ROMK in the CS.

Conclusions: In conclusion, KCNJ10 in the CS contributes to the renal control of K^+ homeostasis by regulating ENaC and ROMK. Impaired KCNJ10 function in the CS predisposes for thiazide- and low K^+ diet-induced hypokalemia and likely contributes to the pathophysiology of renal K^+ loss in EAST/SeSAME syndrome.

Funding: Government Support - Non-U.S.

TH-OR008

Renal Inflammation, Vascular Pathology, and Splenomegaly Are Induced in a Mouse Model of Spontaneous Chronic Metabolic Acidosis

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Background: Recent studies have shown that alkali treatment retards the progression of chronic kidney disease. However, whether long-term metabolic acidosis alone can cause development and progression of renal and vascular pathology is not known. We used a model of spontaneous chronic metabolic acidosis to examine this issue.

Methods: We used 4 and 8 month old female mice with proximal tubule $NaHCO_3^-$ cotransporter, NBCe1-A, deletion (KO) and their WT littermates. We used immunohistochemistry to determine inflammatory cell type (macrophage/monocyte, F4/80; B lymphocyte, B220; T lymphocyte, CD3).

Results: At both 4 and 8 mo KO mice had marked metabolic acidosis (4 mo, serum HCO_3^- WT, 25.4±0.8 vs KO, 12.5±1.5, n=4 per group; 8 mo, WT 21.8±1.5 vs KO 11.2±0.5 n=5 and 4). Urine albumin, measured at 8 mo, was increased significantly (WT 19.1±11.3 mg/d; KO 56.8±9.7, P<0.02); urea clearance was unaltered. Toluidine blue-stained semi-thin sections and transmission electron microscopy showed mesangial expansion with increased mesangial matrix deposition in KO at 4 and 8 mo compared to WT. Trichrome and picrosirius red stains showed mild-to-moderate increase in interstitial collagen in KO at 4 mo and 8 mo. Routine light microscopy showed mild cellular infiltrates, particularly in perivascular regions, in 4 mo KO kidney that was markedly increased at 8 mo. There was an increase in interstitial macrophages in KO cortex at 4 mo that was accentuated at 8 mo. The perivascular infiltrate in 8 mo KO kidney was predominantly T lymphocytes, but also included B lymphocytes and macrophages. The thoracic aorta had increased wall thickness with thickening and fragmentation of the elastin layers in 4 and 8 mo KO mice. KO mice had marked splenomegaly, which appeared due predominantly to increased macrophages in the splenic parenchyma.

Conclusions: Long-term metabolic acidosis induced by NBCe1-A deletion causes significant inflammatory activation, with renal inflammatory infiltrates and expansion of the splenic macrophage/monocyte population, along with development of mild mesangial expansion, renal interstitial fibrosis, and vascular defects. These data suggest chronic metabolic acidosis may independently contribute to the development and progression of renal and vascular disease.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR009

Derivatives of FMP-API-1/27 Robustly Activate AQP2 Water Channels Independently of Vasopressin

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Background: Congenital nephrogenic diabetes insipidus (NDI) is characterized by the inability of the kidney to concentrate urine. Congenital NDI is mainly caused by loss-of-function mutations in the vasopressin type 2 receptor (V2R), leading to impaired aquaporin-2 (AQP2) water channels activity in renal collecting ducts. Direct activators of protein kinase A (PKA) are novel therapeutic targets of congenital NDI. The intracellular distribution and activity of PKA are largely controlled by A-kinase anchoring proteins (AKAPs). We found that a low molecular weight compound, FMP-API-1/27, dissociated AKAPs binding to PKA and activated PKA/AQP2. We promoted further development of FMP-API-1/27 derivatives in terms of pharmaceutical potency and feasibility.

Methods: The effects of compounds on PKA/AQP2 were examined by a mouse cortical collecting duct (mpkCCD) cell line and a V2R-inhibited NDI mouse model.

Results: We examined the effects of screening compounds with similar structures to FMP-API-1/27 from TMDU Chemical Biology Database and derivatives of FMP-API-1/27 using mpkCCD cells. Hit compounds that increased PKA/AQP2 activity had similar chemical structures. We then developed compound X, which phosphorylated AQP2 at S269 to the same extent as vasopressin in mpkCCD cells. *In vivo*, compound Y significantly increased urine osmolality and decreased urine output in a V2R-inhibited NDI mouse model.

Conclusions: Derivatives of FMP-API-1/27 are promising therapeutic targets for congenital NDI caused by V2R mutations.

TH-OR010

Investigation of the Renal Phenotype of a Novel Mouse Model with Dent Disease

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Background: Dent disease is a rare hereditary renal proximal disorder that predominantly affects young males. The disease is characterized by low molecular weight (LMW) proteinuria, hypercalciuria, kidney stones and progressive renal failure. Inactivating mutations of the *CLCN5* gene encoding the $2Cl^-/H^+$ exchanger ClC-5 have been identified in more than 60 % of patients with Dent disease. ClC-5 is essentially expressed in early endosomes of proximal tubules (PT) where it optimizes the function of the V-type H^+ ATPase to ensure an efficient endocytosis of LMW proteins, and therefore to avoid their loss into the urine. The functional consequences of *CLCN5* mutations have previously been investigated in heterologous expression systems. It has been shown that 60 % of the mutations lead to a defect in protein folding and processing, such as the previously published N340K pathogenic ClC-5 mutation. As a consequence, the misfolded ClC-5 are retained within the endoplasmic reticulum (ER). Here, we have investigated the consequences of the N340K mutation using a transgenic mouse model.

Methods: Daily food, water intake, body weight and urine excretion data were collected in metabolic cages for N340K and WT mice. Urine as well as blood samples were analysed for ions, proteins, glucose and creatinine to detect kidney dysfunction as observed in patients with Dent disease. Expression and localization of proteins involved in receptor-mediated endocytosis of LMW proteins were studied by Western blot and on kidney sections by immunofluorescence in WT and N340K male mice.

Results: The N340K mice showed an increased urinary calcium and glucose excretion, a decreased urinary pH, and a severe LMW proteinuria, recapitulating common features of Dent disease. Megalin, a multi-ligands receptor involved in the endocytosis of LMW proteins was less expressed at the apical border of N340K mouse PTs.

Conclusions: The present study validates a new Dent disease mouse model carrying a pathogenic mutation of ClC-5. It will help to better understand the molecular basis of Dent disease, such as the link between an altered ClC-5 and defective proximal tubule endocytosis. In the long term, our mouse model could be used to assess therapeutic approaches for the rescue of a proper proximal tubule cell function.

Funding: Government Support - Non-U.S.

TH-OR011

Polyploidization Is Essential to Survive AKI but It Contributes to CKD Development

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Background: Acute kidney injury (AKI) is a global health concern. If not lethal in the acute phase, AKI is considered reversible. However, even mild AKI episodes carry a risk of developing chronic kidney disease (CKD). Recently, we demonstrated that tubular epithelial cells (TECs) can undergo endoreplication-mediated hypertrophy after AKI. Endoreplications are incomplete cell cycles that lead to the formation of polyploid cells. As polyploid cells can provide increased cell function without restoring tissue integrity, we hypothesized that this mechanism is essential to survive AKI but it can be potentially maladaptive.

Methods: To address this hypothesis, we employed a series of *in vitro* and *in vivo* models based on the FUCCI technology to monitor cell cycle phasing in combination with YAP1 overexpression or downregulation. In the *in vivo* models, mice were subjected to unilateral ischemia reperfusion injury (IRI) to induce AKI. Polyploid cells have been then characterized by single cell RNAseq, cell sorting, super-resolution STED microscopy and transmission electron microscopy.

Results: *In vitro*, human renal tubular cells undergo polyploidization. The fraction of polyploid cells significantly decreases when YAP1 nuclear translocation is blocked. After AKI in mice, the inhibition of YAP1 significantly reduces the number of polyploid cells and worsens kidney function, while YAP1 overexpression leads to an increase in the number of polyploid cells up to 20% of all TECs. Electron microscopy and STED analysis revealed the presence of both mononucleated and binucleated polyploid cells with a chromatin distribution typical of actively transcribing cells. Strikingly, these mice appear to be more prone to develop tubulointerstitial fibrosis acquiring a marked senescent phenotype along with significant decline in renal function thus suggesting an association between polyploidization and CKD development. Indeed, isolation of polyploid cells proved that these cells actively transcribe and secrete pro-fibrotic and senescent factors thus confirming their role in CKD progression.

Conclusions: These data suggest that: 1) polyploidization is crucial to survive AKI by maintaining renal function in the acute phase and 2) polyploid cells are senescent and in the long run they are involved in the progression of AKI to CKD.

TH-OR012

A Comprehensive Single Nucleus RNA-Sequencing Atlas of Mouse and Human AKI

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Background: After acute kidney injury (AKI), many patients make an apparently full recovery ("complete repair") whereas others transition to chronic kidney disease (CKD, "failed repair"). To better define the cellular and molecular mechanisms of AKI and the AKI to CKD transition, we performed comprehensive single nucleus RNA-seq (snRNA-seq) on both mouse and human AKI.

Methods: We generated 122,828 single-nucleus transcriptomes from mouse kidney after IRI: 4 hours, 12 hours, 2 days, 14 days, 6 weeks and sham (n = 3 for each), and 37,636 nuclei from a healthy and AKI adult human kidney using the 10X platform and performed a comprehensive informatic analysis and gene expression validation.

Results: Mouse had on average 1317 and human 2007 unique genes/nucleus. We identified over 30 cell types including rare ones (juxtaglomerulus, macula densa) in both mouse and human datasets. We define transcriptional states that distinguish proximal tubule destined for successful vs. failed repair. Using receptor-ligand analysis, we identify and define profibrotic and pro-inflammatory signals secreted by failed repair epithelia to fibroblasts, endothelial cells and leukocytes, driving the AKI to CKD transition. We show that a scattered cell population in healthy kidney exists that recapitulates the epithelial repair signature and that likely represents the cell type that prior reports characterized as a fixed stem cell population. We define 9 stromal subtypes including four novel fibroblast and 3 novel pericyte cell types and find that a subset transiently upregulate aSMA after injury. These results were validated in the human AKI snRNA-seq dataset.

Conclusions: The first comprehensive snRNA-seq atlas of mouse and human AKI kidney revealed four novel insights: (1) injury-repair cycles occur in situ in single epithelial cells in healthy kidney, (2) a population of pro-fibrotic proximal tubule cells drives failed repair in a non cell-autonomous manner, (3) novel stromal subtypes are identified including a population with reversible expression of aSMA, suggesting plasticity amongst myofibroblast progenitors and (5) a receptor-ligand analysis between all major kidney cell types during injury and repair reveals dynamic intercellular communication patterns.

Funding: Private Foundation Support

TH-OR013

Sirtuin 5 Regulates a Metabolic Switch in Fatty Acid Oxidation That Protects Against AKI

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Background: There are currently no targeted drug therapies for the treatment of acute kidney injury (AKI). The proximal tubule compartment is particularly vulnerable to injury, owing to high energy demands. Fatty acids are a preferred energy source for proximal tubule cells and are oxidized at high rates through both the mitochondrial and peroxisomal fatty acid oxidation (FAO) pathways. Sirtuins are a class of enzymes which reverse post-translational lysine acylation and regulate many biological processes including FAO. Multiple sirtuins, including 1, 3, and 6 have been shown to play roles in AKI, but the role of mitochondrial-based Sirtuin 5 (Sirt5) during AKI has yet to be determined.

Methods: Male germline Sirt5 deficient mice (either +/- or -/-) and wild-type controls at 8-12 weeks old were subjected to two different AKI models: 1. unilateral ischemia-reperfusion injury (22 minutes) or 2. single high dose cisplatin-induced AKI (20 mg/kg). Mice were evaluated for injury by histopathological analysis and by serum chemistry. FAO was measured by the catabolism of ^{14}C-labeled palmitate to $^{14}CO_2$. Peroxisome-specific FAO was measured by inhibition of mitochondrial FAO via etomoxir (100uM). Primary mouse proximal tubule cells were isolated from Sirt5-/- or WT mice and exposed to 24 hours hypoxia (FiO_2 1%) or treated with 20μM cisplatin for 24 hours. hPTEC cells were exposed to combined glucose-oxygen deprivation with or without Sirt5 siRNA knockdown and evaluated for cell death by LDH efflux.

Results: No overt kidney phenotype was observed in Sirt5-/- mice at baseline. However, following IRI and cisplatin-induced AKI, Sirt5-/- and Sirt5+/- mice had significantly improved kidney function and less evidence of tissue injury compared with controls. The cell-based assays confirmed that knockdown of Sirt5 in proximal tubule cells was protective against both types of injury. This protection coincided with increased peroxisomal FAO and decreased mitochondrial FAO in the Sirt5-/- proximal tubules.

Conclusions: Subsequently, SIRT5 deficiency confers protection against multiple models of acute kidney injury. This identifies a therapeutically attractive mechanism whereby increased peroxisomal FAO and decreased mitochondrial FAO drives protection of kidneys from injury.

TH-OR014

High Mobility Group Box 1(HMGB1)-Induced Ferroptosis Accelerates Ischemia-Reperfusion-Incited AKI

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Background: Regulated necrosis (RN), which is identified as cells death in a regulated manner but with the morphologic features of necrosis, has been implicated to be involved in the process of AKI and improve chronic kidney injury. The common hallmark of RN in kidneys is the rupture of tubular epithelial cell membrane and the release of the unprocessed intracellular components known as damage-associated molecular patterns (DAMPs) resulting in activation of immune system. As a representative DAMP molecular, high mobility group box-1 (HMGB1) involving in many inflammatory diseases has less determined on the effect of RN.

Methods: Mice with conditional alleles of HMGB1 were crossed with mice harboring Ksp-CreERT transgenes to knock out HMGB1 in renal tubular epithelial cells. 8-10 weeks old $HMGB1^{fl/fl}$; Ksp-$CreERT^{+/+}$ mice were randomly divided into two groups: KH+TMX group and KH+Vehi group. The two groups were injected with tamoxifen(TMX) at a dose of 100 mg/kg body weight and Vehicle for 5 consecutive days respectively. After two weeks of elution, the mice were subjected to 30 min of bilateral ischemia reperfusion (I/R). One day later, the mice were sacrificed and the serum, kidney, liver, and other organs were sampled for evaluating the role of HMGB1 in I/R.

Results: Renal tubular specific HMGB1 knockout mice underwent a pronounced pathological shift including decreased expression of KIM-1 and NGAL and upregulated expression of Klotho after I/R. Serum creatinine and urea nitrogen were reduced in KH+TMX group with less renal inflammatory cell infiltration. Ferroptosis and necroptosis are the most described in RN. We found that HMGB1 knockout ameliorated ferroptosis in I/R. KH+TMX group got a higher expression of GPX4 and lower level of ACSL4 in kidney with less accumulation of lipid peroxidation. However, the key enzymes of necroptosis, RIP1/RIP3/MLKL, have less changed in KH-TMX group compared to the control group. RNA-seq further indicated 710 genes differentially expressed between KH-TMX and KH-Vehi group. The results of GO analysis and the KEGG pathway analysis illustrated that a large amount of differentially expressed genes (DEGs) were involved in lipid metabolic and amino acid process which is tightly linked to the regulation of ferroptosis.

Conclusions: HMGB1-dependent ferroptosis impairs the ischemia-induced AKI, which might serve as a novel target for I/R treatment.

Funding: Government Support - Non-U.S.

TH-OR015

Optogenetic Stimulation of the Vagus Nerve Identifies Distinct Pathways That Mediate Kidney Protection from Ischemia-Reperfusion Injury

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Background: We recently showed that electrical vagus nerve stimulation (VNS) in the neck protected mouse kidneys from ischemia-reperfusion injury (IRI) by activating the cholinergic anti-inflammatory pathway (CAP) (PMID: 27088805). Stimulation of vagal efferent neurons is believed to be essential in the activation of CAP. However, electrical stimulation of the cervical vagus nerve excites both the efferent (motor) and afferent (sensory) neurons. It is still unclear which pathway is important in ameliorating kidney injury.

Methods: Channelrhodopsin-2 (ChR2) is a light-sensitive, non-selective cation channel; the gate is opened only during blue light application. We generated choline acetyltransferase (*Chat*)-*ChR2* mice and vesicular glutamate transporter 2 (*Vglut2*)-*ChR2* mice, which express ChR2 in vagal efferent and afferent neurons, respectively. Thus, when the cervical vagus nerve is illuminated with blue laser, vagal efferent and afferent neurons are selectively stimulated in *Chat-ChR2* and *Vglut2-ChR2* mice, respectively. For selective ablation of C1 neurons, which are a group of lower brainstem catecholaminergic/glutamatergic neurons, *AAV2-flex-taCasp3-TEVp* was injected bilaterally into the rostral ventrolateral medulla (the area where C1 neurons are localized) of dopamine beta-hydroxylase (*Dbh*)-*Cre* mice 6 weeks before electrical afferent/efferent VNS. Optogenetic VNS with blue laser or electrical VNS was performed 24 h before bilateral renal IRI, and mice were euthanized 24 h after IRI.

Results: Optogenetic VNS protected kidneys from IRI in both *Chat-ChR2* mice (pCr: 1.53±0.20 vs. 0.48±0.05 mg/dL) and *Vglut2-ChR2* mice (pCr: 1.09±0.22 vs. 0.44±0.06 mg/dL), which was supported by improved kidney histology and decreased renal Kim-1 expression in the VNS groups. Next, based on our recent study (PMID: 28288124), we hypothesized that the C1 neurons mediate the afferent VNS pathway. Electrical VNS significantly increased the number of cFos-positive C1 neurons, and selective ablation of C1 neurons eliminated the protective effect of afferent VNS, but not efferent VNS.

Conclusions: Both stimulation of vagal efferent and afferent neurons protected the kidneys from IRI. C1 neurons in the lower brainstem were involved in the protective pathway elicited by afferent VNS.

Funding: NIDDK Support

TH-OR016

A Functional Genomic Screen Identifies a CDKL5-SOX9 Regulatory Axis in Epithelial Cell Death and Kidney Injury

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Background: Numerous clinical conditions are associated with inflammatory, toxic, and hypoxic insults to tubular epithelial cells. The resulting epithelial cell dysfunction and cell-death are the hallmarks and underlying cause of acute kidney injury (AKI), a common disorder that predominantly develops in hospitalized patients. Importantly, the patients that recover from an episode of AKI are at increased risk of developing chronic kidney disease, end-stage renal disease and cardiovascular dysfunction- disorders that are associated with significant morbidity and mortality. To identify novel regulators of renal epithelial cell death and AKI, here, we have used a kinome-wide functional genomic screening to identify protein kinases that contribute to the pathogenesis of AKI.

Methods: An unbiased kinome-wide siRNA screen for regulators of renal epithelial cells was carried out in a murine epithelial cell line. Through subsequent in vivo validation experiments, we identified cyclin-dependent kinase-like 5 (CDKL5) also known as serine/threonine kinase 9 (STK9) as a key regulator of renal cell-death and injury. To directly define the role of CDKL5 in vivo, kidney tubule specific CDKL5 knockout mice were generated. In addition, a pharmacological inhibitor of CDKL5 kinase was evaluated in cisplatin nephrotoxicity and ischemia-associated AKI. Later proteomic studies were carried out to identify the transcription factor Sox9 as a bona fide Cdkl5 substrate and a key downstream target in renal epithelial cells.

Results: High-throughput siRNA screening and validation studies identified CDKL5 kinase as a crucial, previously unknown regulator of renal epithelial cell-death. In vivo studies showed that genetic or pharmacological ablation of CDKL5 function provides mitigates AKI in both cisplatin and ischemia-associated kidney injury. We also found that Sox9 is phosphorylated on the Ser-199 residue by Cdkl5 during kidney injury in vivo. Cdkl5-mediated phosphorylation reduced the stability of Sox9 protein.

Conclusions: Here we have found that Cdkl5 also known as Stk9 is a stress responsive kinase that controls epithelial cell fate during AKI. We propose that Cdkl5 activation promotes renal dysfunction through phosphorylation-mediated destabilization of pro-survival transcription factor Sox9.

Funding: Private Foundation Support

TH-OR017

Ubiquitin-Proteasome System Actively Maintains Homeostasis of Proximal Tubules

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Background: Autophagy and ubiquitin-proteasome system (UPS) are two major protein degradation pathways essential for cellular protein homeostasis. While the role of autophagy in the kidney has been extensively analyzed in the proximal tubules of the kidney, the impact of UPS function in the maintenance the proximal tubules has been unclear.

Methods: In order to analyze the role of UPS function in the proximal tubule, we crossed conditional knockout mice of the proteasome subunit Rpt3 with proximal tubule specific inducible Cre (*Ndrg1-*Cre^{ERT2}), to generate *Rpt3fl/fl:Ndrg1-*Cre^{ERT2}(PT-Rpt3-CKO) mice, in which the expression of Rpt3 can be deleted in proximal tubules at desired time points by tamoxifen administration. Utilizing PT-Rpt3-CKO mice, we investigated how UPS regulates the maintenance of proximal tubules.

Results: As early as one day after tamoxifen administration for 5 consecutive days, proximal tubules of PT-Rpt3-CKO mice showed mild injury in light microscopy, whose mitochondria were fragmented in electron microscopy. Proximal tubule injury at this time point was also confirmed by the upregulation of Kim1, cleaved caspase 3, and gH2AX in immunostaining. Immunoblotting also revealed the upregulation of ubiquitin and p62, and downregulation of LC3 1/2ratio, indicating autophagy insufficiency. Four days after tamoxifen administration, serum creatinine and blood urea nitrogen (BUN) were elevated and proximal tubules were detached from the basement membrane. In addition to further upregulation of Kim1, cleaved caspase 3, and gH2AX, and p62 compared to those in day 1, the expression of p21was upregulated and cyclinD1 was downregulated indicating possible G1 cell cycle arrest. 8 days after tamoxifen administration, all PT-Rpt3-CKO mice died possibly due to renal insufficiency. The administration of the proteasome inhibitor MG-132 to a proximal tubule cell line NRK52E resulted in decreased mitochondrial membrane potential and oxygen consumption rate.

Conclusions: Our results provide strong evidence showing that the dysfunction of UPS rapidly triggers mitochondrial dysfunction, autophagy insufficiency, cell cycle arrest

and apoptosis of proximal tubules, leading to renal insufficiency and death. Compared to mild phenotypes of conditional knockout mice of autophagy related molecules in the proximal tubules, UPS plays a crucial role in the active maintenance of proximal tubules.

TH-OR018

Organelle-Specific Oxidant Stress and CORE Disruption Mediate Proximal Tubule Cell Injury During Gentamicin Exposure

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Background: The Cross-Organelle Stress Response (CORE) is an adaptive mechanism that maintains mitochondrial and endoplasmic reticulum (ER) proteostasis. We hypothesized that gentamicin causes nephrotoxic acute kidney injury (AKI) by causing both mitochondrial specific oxidative stress and fragmentation resulting in CORE disruption before activating the lethal unfolded protein response (UPR).

Methods: Mito HyPer, a mitochondrial-specific H_2O_2 probe, was used to detect early mitochondrial ROS accumulation in human proximal tubule epithelial cells (HK2) during gentamicin exposure. Mitochondria and ER were stained with MitoTracker and ER Tracker, respectively, and time course experiments were performed using a Nikon Super Resolution microscope. Mitochondrial-ER disassociation, mitochondrial morphology and immunoblots of CORE-associated mitochondrial pro-fission proteins (Total DRP1 and pDRP1) were used as surrogates of CORE function. Misfolded protein stains (Thioflavin T), protein ubiquitination, and immunoblots for whole cell oxidative stress (4HNE) were measured to assess proteotoxicity. The efficacy of preserving CORE on protein misfolding, lethal UPR activation (CHOP), and cell survival was assessed using geranylgeranylacetone (GGA), a protein chaperone inducer, prior to the introduction of gentamicin.

Results: Gentamicin exposure caused characteristic features of disrupted CORE, including mitochondrial-specific H_2O_2 accumulation, DRP-1 activation and organelle fragmentation, followed by mitochondrial-ER dissociation. Importantly, CORE disruption occurred before detectable changes in whole cell oxidative stress, protein ubiquitination, protein misfolding or lethal UPR activation (CHOP) were observed. GGA significantly decreased mitochondrial-specific oxidative stress, prevented fragmentation, preserved mitochondrial-ER association and ameliorated lethal UPR activation.

Conclusions: Gentamicin exposure causes early mitochondrial H_2O_2 accumulation and disrupts the CORE. These untoward events contribute to gentamicin-induced proteotoxicity and lethal UPR activation. GGA preserves the CORE and decreases subsequent lethal UPR activation that contributes to the proximal tubule cell injury caused by gentamicin.

Funding: NIDDK Support

TH-OR019

Matricellular Protein Tenascin C Has a Protective Effect in Renal Ischemia-Reperfusion Injury

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Background: Interstitial microenvironment is critical in regulating cell proliferation and injury/repairing process. Tenascin-C is a matricellular protein which is transiently expressed during development and can be re-induced after injury, suggesting a potential role in tissue injury/repairing. The present study examined the role of TNC in acute kidney injury using a ischemia-reperfusion (IR) model.

Methods: A tenascin-C promoter driven inducible CreER2 knock-in mouse line with an eGFP reporter was generated. TNC-CreER$^{+/+}$ (TNC$^{-/-}$) mice were used to examine the role of TNC in of AKI.

Results: Following IR, TNC was markedly induced in the interstitium of the kidney as early as 3 hours and peaked at 24-48 hours. To examine the role of TNC in AKI, we used the TNC-CreER$^{+/+}$ (TNC$^{-/-}$) mice. Deletion of TNC in mice significantly aggravated IR induced AKI, showing significantly lower survival rate, higher BUN and more severe tubular injury after IR comparing to their wild type littermates. We Then examined the mechanism by which TNC is induced following injury. Four hypoxic response elements (HRE) were identified in the promoter region of TNC, suggesting a role of hypoxia-inducible factor(HIF). DMOG, a HIF stabilizer, significantly induced TNC expression both in mice and in primary cultured renal interstitial cells. Luciferase reporter assay showed that hif-2α promoted the transcription of TNC, while mutation of the HRE of the TNC luciferase reporter abolished this effect. The bindiong of hif-2α to endogenous TNC promoter was also supported by ChiP assay. To explore the mechanism by which TNC protects kidney from AKI, we isolated the primary tubular epithelial cells and treated the cells with commercially available TNC protein. TNC protected primary tubular epithelial cells from hypoxic injury. Our further experiments suggest that the EGF-like domain in TNC was involved in the protective effect via EGFR-STAT3 pathway.

Conclusions: TNC, which is immediately induced following IR, has a protective effect on ischemia-reperfusion injury.

TH-OR020

Enhancer and Super-Enhancer Dynamics in Repair After Ischemic AKI

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Background: The endogenous repair process of the mammalian kidney allows rapid recovery after acute kidney injury (AKI) through robust proliferation of tubular epithelial cells. There is currently limited understanding of which transcriptional regulators activate these repair programs. Here we investigate the existence of enhancer dynamics in the regenerating mouse kidney.

Methods: RNA-seq and ChIP-seq (H3K27ac, H3K4me3, BRD4, Pol II) were performed on samples from repairing kidney cortex 2 days after ischemia/reperfusion injury (IRI) to identify activated genes, transcription factors, enhancer and super-enhancers associated with kidney repair. Further we investigated the role of super-enhancer activation in kidney repair through pharmacological BET inhibition using the small molecule JQ1 in acute kidney injury models in vivo.

Results: Response to kidney injury leads to genome-wide alteration in enhancer repertoire *in*-vivo. We identified 16,781 enhancer sites (H3K27ac/BRD4 positive, H3K4me3 negative) active in SHAM and IRI samples; 6,512 lost and 9,774 gained after IRI. The lost and gained enhancer sites can be annotated to 62% and 63% of down- and up-regulated transcripts, respectively. The top 3 transcription factor binding motifs enriched in lost enhancer sites are Hnf4a, Esrrb and PPARE and in gained enhancer sites Fra1, Fosl2 and Atf3. ChIP-seq profiles of selected transcription factors show specific binding at corresponding enhancer sites. Super-enhancer analysis revealed 164 lost and 216 gained super-enhancer sites at IRI day 2. 385 super-enhancers maintain activity during repair. Pharmacological inhibition of enhancer activity by BRD4 inhibition before IRI leads to suppression of 40% of injury-induced transcripts associated with cell cycle regulation and significantly increased mortality between days 2 and 3 after AKI.

Conclusions: This is the first demonstration of BRD4 enhancer and super-enhancer function in the repairing kidney. In addition, our data call attention to potential caveats for use of small molecule inhibitors of BET proteins that are currently being tested in clinical trials in cancer patients who are at risk for AKI. Our analyses of enhancer dynamics after kidney injury in vivo have the potential to identify new targets for therapeutic intervention.

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

TH-OR021

HIMALAYAS: A Phase 3, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Incident-Dialysis Patients

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Background: Roxadustat (FG-4592) is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and regulates iron metabolism.

Methods: ESA-naïve or limited prior use, incident dialysis pts were randomized (1:1) to roxadustat (ROXA) or epoetin alfa (EPO). Oral iron was allowed;parenteral iron was restricted. Oral ROXA was dosed thrice weekly. The initial roxadustat dose was weight-based. EPO was prescribed according to the country-specific product labeling. An algorithm determined ROXA doses. The primary endpoint for the US FDA was mean Hb change from baseline (BL) to Weeks (Wk) 28-52. The primary endpoint for EU EMA was the % of pts achieving a Hb response through Wk 1-24. An Hb response was defined at 2 consecutive visits during the first 24 Wk as achieving a Hb level of 11 and an increase of 1 g/dL if BL Hb was >8 gor 2 g/dL if baseline Hb was <8 g/dL. Safety and tolerability were assessed by adverse events, vital signs, electrocardiogram findings, and clinical laboratory values.

Results: 1,043 pts (522=ROXA, 521=EPO) ≥18 years old were randomized in 17 countries. Pts were majority Caucasian with 8.4% Black pts in the ROXA arm and 9.6% Black pts in the EPO arm. The % of pts with type 2 DM in the ROXA arm was 35.1% (n=183) and 34.4% (n=179) in the EPO arm. Mean BL Hb was 8.43 g/dL in the ROXA arm and 8.46 g/dL in the EPO arm. Mean Hb change from BL to the average over Wk 28-52 was 2.57 (ROXA) vs. 2.36 g/dL (EPO). The non-inferiority criteria were met as the lower bound of 95% CI was above the non-inferiority margin of -0.75 g/dL, and superiority over EPO was also achieved, p=.0005. ROXA pts had an Hb response rate of 88.2% compared with 84.4% in the EPO arm meeting EU's primary endpoint non-inferiority criterion. The overall safety profile was consistent with results observed in prior ROXA trials and pooled safety findings will be submitted as a late breaker abstract.

Conclusions: ROXA was non-inferior and subsequently demonstrated superiority over EPO in the mean change in Hb from BL in pts incident to dialysis.

Funding: Commercial Support - Fibrogen Inc.

TH-OR022

ROCKIES: An International, Phase 3, Randomized, Open-Label, Active-Controlled Study of Roxadustat for Anemia in Dialysis-Dependent CKD Patients

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Background: Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron absorption and utilization.

Methods: This Phase 3 trial evaluated roxadustat vs epoetin alfa (epo) in patients (pts) with ESRD and anemia receiving dialysis. Pts with baseline (BL) hemoglobin (Hb) of <12 g/dL if treated with an erythropoietin analog or <10 g/dL if not were recruited. Pts were randomized 1:1 to receive oral roxadustat or epo. For pts receiving epo at BL, initial roxadustat dose was based on epo dose; for epo-naïve pts initial roxadustat dose was weight-based. Roxadustat dose was constant for first 4 wks; a dose adjustment algorithm for roxadustat (20 mg qw–400 mg tiw to max 3 mg/kg) was used to maintain Hb between 10–12 g/dL. Oral iron was allowed; IV iron was used as standard-of-care in epo arm and with evidence of iron deficiency in roxadustat arm. Primary efficacy endpoint was mean Hb change from BL to Hb averaged over wks 28–52. Roxadustat safety data integrated across multiple appropriate dialysis trials will be reported separately.

Results: 2133 dialysis pts were randomized (1068 roxadustat, 1065 epo). Mean age was 54.0 years, 59% male, 57% white. Mean duration of dialysis was 37.5 months, 19.5% were incident pts (2 wks to 4 months). Mean (SD) BL Hb was 10.01 (1.22) g/dL. Mean Hb change from BL to average over wks 28–52 was higher with roxadustat (+0.77 g/dL) vs epo (+0.68 g/dL; p=0.036) in the overall cohort. Mean Hb change from BL to average over wks 28–52 in pts with elevated BL high-sensitivity C-reactive protein (hsCRP) was greater with roxadustat (+0.80 g/dL) vs epo (+0.59 g/dL; p=0.012). Roxadustat-treated pts had Hb ≥10 g/dL for a similar proportion of time over wks 28–52 vs epo-treated pts (79% vs 76%, respectively; p=0.045). Proportion of pts who received red blood cell transfusion was comparable between roxadustat and epo arms (HR=0.83; 95% CI: 0.64–1.07). Roxadustat-treated pts used less monthly IV iron from wk 36 to end of study (58.7 vs 91.4 mg, respectively; p<0.0001).

Conclusions: Roxadustat effectively increased Hb, overall and in pts with elevated hsCRP, and reduced IV iron use in pts with dialysis-dependent CKD.

Funding: Commercial Support - AstraZeneca

TH-OR023

OLYMPUS: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, International Study of Roxadustat Efficacy in Patients with Non-Dialysis-Dependent (NDD) CKD and Anemia

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Background: Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron absorption and utilization. Here, we report efficacy results for 1 of 3 trials for US and EU applications for treatment of anemia in patients (pts) with NDD CKD. Integrated safety will be reported separately.

Methods: Pts with NDD CKD stages 3–5 and anemia (hemoglobin [Hb] <10.0 g/dL) were randomized 1:1 to receive 70 mg oral roxadustat or placebo (PBO) three times weekly. A dose-adjustment algorithm was used to achieve and maintain Hb values of 10–12 g/dL. Primary efficacy endpoint was mean change from baseline (BL) Hb to average Hb over Wks 28–52 (US [FDA] submission) or proportion of pts with Hb response at two consecutive visits during the first 24 wks of treatment without anemia rescue therapy (EU [EMA] submission).

Results: 2781 pts were randomized (1393 roxadustat, 1388 PBO). Mean age was 61.7 years, 42% were male, 45% white, and 55% had type 2 diabetes. Mean (SD) BL Hb was 9.1 (0.7) g/dL and estimated glomerular filtration rate was 19.8 (11.7) mL/min/1.73 m^2. Mean (SD) study drug exposure was 19.6 (10.3; roxadustat) and 15.2 (10.5; PBO) months. Mean change in Hb from BL to the average over Wks 28–52 was +1.75 g/dL with roxadustat vs +0.40 g/dL with PBO (p<0.001). In 411 pts with BL elevated high-sensitivity C-reactive protein (hsCRP), changes from BL Hb were +1.75 g/dL (roxadustat) and +0.62 g/dL (PBO; p<0.001). Proportion of pts achieving Hb response at two consecutive visits without rescue during the first 24 wks was 77.0% with roxadustat vs 8.5% with PBO (p<0.001). Percentage of total time with interpolated Hb values ≥10 g/dL for Wks 28–52 was 82% with roxadustat vs 33% with PBO (p<0.001). Roxadustat reduced risk of rescue therapy by 74% (HR=0.26), including red blood cell transfusion by 63% (HR=0.37), IV iron by 59% (HR=0.41), and erythropoietin analog by 87% (HR=0.13; all p<0.001).

Conclusions: Roxadustat achieved prespecified primary endpoints for US and EU submissions, effectively increased Hb in the subgroup of pts with elevated hsCRP, and reduced rescue therapy use in pts with NDD CKD and anemia.

Funding: Commercial Support - AstraZeneca

TH-OR024

Randomized, Double-Blinded, Active-Controlled (Darbepoetin Alfa), Phase 3 Study of Vadadustat in CKD Patients with Anemia on Hemodialysis in Japan

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Background: Vadadustat (VDT) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) being assessed in Japan and Global Phase 3 studies. This is the first result of phase 3 study (NCT03439137), evaluates the efficacy and safety of VDT for 52 weeks in 323 Japanese hemodialysis-dependent (HD) chronic kidney disease (CKD) subjects with anemia receiving erythropoiesis stimulating agents (ESA). Prespecified primary analysis results up to week 24 are presented here.

Methods: Subjects on maintenance hemodialysis receiving ESA were randomized to VDT (n=162) or darbepoetin alfa (DA) group (n=161). After the initial VDT dose of 300 mg daily, doses were adjusted to achieve a Hb target of 10–12 g/dL, within 150–600 mg. Primary endpoint was average Hb at weeks 20 and 24. Iron parameters were measured. Safety was assessed up to 24 weeks.

Results: The baseline Hb of both groups was 10.74 g/dL. The LSMean of average Hb at weeks 20 and 24 was 10.61 (95%CI: 10.45, 10.76) and 10.65 g/dL (10.50, 10.80) in the VDT and DA groups, respectively; 95% CI of both groups were within the target range of 10–12 g/dL. Difference in LSMean between the groups was –0.05 g/dL (–0.26, 0.17); the 95% CI lower limit was above the predefined noninferiority margin of –0.75 g/dL, confirming the noninferiority of VDT to DA. At week 24, 104 (75.4%) and 115 (75.7%) subjects in the VDT and DA groups, respectively, had Hb within the target range. VDT regimen was associated with significant increases in total iron-binding capacity and decreases in hepcidin from baseline to week 24, not found in the DA group. At least one adverse event (AE) was seen in 89.5% (VDT group) and 88.2% (DA group) subjects. The most common AEs in the VDT group were nasopharyngitis (VDT: 19.8%, DA: 28.6%), diarrhea (VDT: 10.5%, DA: 9.9%), and shunt stenosis (VDT: 8.0%, DA: 12.4%). The incidence rates of serious AEs (SAEs) were 13.0% (VDT group) and 10.6% (DA group). No SAE related to the study drug was considered.

Conclusions: VDT was generally well tolerated and effective as DA in maintaining Hb levels within the target range, indicating the usefulness of VDT for treating anemia in Japanese HD CKD patients converting from ESA.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation

TH-OR025

Effects of Ziltivekimab, an Antibody to IL-6, on Inflammation, Nutritional Markers, and Anemia in Hemodialysis Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Patients with chronic kidney disease on hemodialysis (HD) and hyporesponsiveness to erythropoiesis stimulating agents (ESA) exhibit functional blockade in iron release from body stores due to inflammation-induced expression of hepcidin. We assessed the effects of ziltivekimab, a novel antibody against the proinflammatory cytokine interleukin (IL)-6, in HD patients with a genotypic variation in the *TMPRSS6* gene, hypothesized to induce a heightened susceptibility to IL-6-induced inflammation.

Methods: After a screening period documenting stable ESA and IV iron dosing, patients with high IL-6 (≥4 pg/mL) received double-blinded placebo or ziltivekimab at 2, 6 or 20 mg every 2 weeks during HD for 12 weeks. ESA dose adjustments were permitted after 4 weeks. Pharmacodynamic endpoints included markers of anemia, malnutrition and inflammation. Differences from placebo in changes from baseline were obtained from analysis of covariance with treatment as factor and baseline as covariate. Trend p-values for ordered dose treatment groups were calculated using Jonckheere-Terpstra test.

Results: 61 patients were randomized; 53 were included in the pharmacodynamic analysis population (12 received placebo; 16, 13 and 12 received 2, 6 and 20 mg, respectively). Across the treatment groups, baseline epoetin-equivalent doses ranged from 11,250-15,000 U/L, hemoglobin (Hgb) from 9-8-10.5 g/dL and high-sensitivity C-reactive protein (hsCRP) from 4-13 mg/L. Ziltivekimab significantly reduced hsCRP and increased serum albumin and Hgb while reducing ESA requirements in a dose-dependent manner (Table).

Conclusions: We demonstrated that IL-6 inhibition with ziltivekimab significantly improved markers of malnutrition-inflammation and reduced ESA requirements in hyporesponsive, inflamed dialysis patients.

Funding: Commercial Support - Corvidia Therapeutics

	Placebo	Ziltivekimab			P-trend
		2 mg	6 mg	20 mg	
	Median Change from Baseline at Week 4[1]				
hsCRP, mg/L	-0.2	-3.5*	-12.1*	-13.0*	**<0.001**
Hgb, g/dL	-0.0	0.5	0.8	0.9*	**0.019**
Transferrin saturation, %	-0.5	7.3	0.0	15.8*	**0.015**
ESA dose (x10^3), U	12.6	-8.0	-7.5*	-25.7*	**0.005**
ESA resistance index, U/kg per g/dL Hgb	-0.5	-0.7	-1.1*	-2.4*	**0.038**
Albumin, g/dL	0.0	0.1	0.3	0.4*	**<0.001**

[1]ESA resistance index and albumin timepoints are weeks 8-12 and week 12, repectively; *p<0.05

Change from Baseline in Pharmacodynamic Endpoints by Treatment Group

TH-OR026

Prognostic Evaluation by Different Target Hemoglobin Levels During Treatment with Epoetin Beta Pegol in Hemodialysis Patients with ESA Hyporesponsiveness: PARAMOUNT-HD Study

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Background: The incidence of cardiovascular (CV) events is especially high in HD patients in association with hyporesponsive to erythropoiesis stimulating agents (ESAs). However, there is no recommended target ranges of hemoglobin for patients with ESA hyporesponsiveness.

Methods: We randomly assigned 304 HD, ESA-treated, patients with ESA hyporesponsiveness to a proactive treatment group (target hemoglobin [Hb] level; 11g/dL) and a maintenance treatment group (target Hb level; 9-10g/dL) by the use of epoetin beta pegol (CERA). The time from the date of study treatment initiation to the earliest CV event was evaluated as the primary endpoint. The CV events included cardiac death, heart failure requiring hospitalization, and acute coronary syndrome requiring hospitalization. The patients were followed for 24 months.

Results: The proactive and maintenance groups had a mean baseline Hb level of 9.34 and 9.32g/dL, respectively. Mean Hb levels during the observation period were 10.58 and 10.26g/dL (p=0.001) and mean length of Hb level of over 10.5g/dL were 11.5 and 8.6 months (p=0.0002), respectively. Median doses of CERA for 6 months after study treatment were 166.7 and 150.0μg/4 weeks (p=0.298). However, there was a significant difference in frequency CERA administration (once every 4 weeks: 10.9% and 26.4%; once every 2 weeks: 86.5% and 72.3% [p=0.0006], respectively). Kaplan-Meier analysis showed a significant difference in the primary endpoint between the two groups (9 and 18 events; log-rank test, p=0.033). Cox proportional hazards analysis showed a significant lower risk of CV events in the proactive group (Hazard ratio [HR], 0.429; 95% CI; 0.193-0.955). Also, the longer length of Hb level of over 10.5g/dL was associated with lower risk of CV events (HR, 0.919 per month; 95% CI; 0.865-0.977).

Conclusions: Our results suggest that targeting Hb level of 11g/dL with CERA reduces the incidence of CV events in HD patients with ESA hyporesponsiveness. Twice-monthly administration of CERA can maintain adequate Hb levels in these patients.

Funding: Commercial Support - Chugai Pharmaceutical Co., Ltd

TH-OR027

Maintenance Intravenous Iron Treatment on Erythropoietin Dose in Chronic Hemodialysis Patients: A Multicenter Randomized Controlled Trial

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Background: Although the benefits of intravenous iron (IV) treatment in chronic hemodialysis (HD) patients were demonstrated in recent studies, IV iron regimens for optimal target levels of iron status are still not established in several guidelines. To explore these questions, we conducted a multicenter, randomized, open label study to demonstrate the effectiveness of IV iron supplement on erythropoietin dose in chronic HD patients.

Methods: Two hundred adult chronic HD patients with transferrin saturation less than 30%, and serum ferritin 200-400 ng/mL, receiving recombinant erythropoietin were randomized 1:1 for maintaining serum ferritin of 200-400 ng/mL (low serum ferritin group, N=100) or serum ferritin of 600-700 ng/mL (high serum ferritin, N=100). During 8-week titration period, subjects randomized to high serum ferritin group received total IV iron of 600 mg (100 mg every week), whereas the subjects in low serum ferritin group did not obtain initial IV iron. During 6-month follow up period, the dose of IV iron was adjusted following the protocol. The primary endpoint was to evaluate the efficacy of IV iron supplement on erythropoietin dose index [erythropoietin dose (unit/week) divided by hemoglobin level (g/dL)]. The study was registered with the Thai Clinical Trials Registry TCTR20180903003.

Results: The mean dose of IV supplement was 108.3±28.2 mg/month in low ferritin group and 192.3±36.2 mg/month in high ferritin group. The mean serum ferritin was 367.0±224.9 ng/mL in low ferritin group and 619.6±265.2 ng/mL in high ferritin group. At 3-month follow up, the erythropoietin index was significantly decreased in high serum ferritin group when compared with low serum ferritin group (921.4±369.1 vs. 756.1±372.2 unit/week/g/dL, P=0.002, and 873.8±329.4 vs. 767.9±392.1 unit/week/g/dL, P=0.05, respectively). At 6-month follow up, only high serum ferritin group showed a significant decrease of erythropoietin index from randomization (854.0±371.7 to 765.3±368.0 unit/week/g/dL, P<0.001).

Conclusions: Maintaining serum ferritin of 600-700 ng/mL by IV iron treatment approximately 200 mg per month can decrease erythropoietin dose in chronic HD patients.

Funding: Government Support - Non-U.S.

TH-OR028

Effect of Ferric Citrate on Erythropoiesis-Stimulating Agent (ESA) Use in ESRD Patients with Elevated Ferritin

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Background: Iron deficiency anemia is common in ESRD patients on hemodialysis. Dialysis facilities infuse intravenous Iron to ESRD patients based on protocols. Patients with elevated serum Ferritin (>1000 mcg/dL) are poorly responsive to IV Iron and concerns about infection risks lead to withholding IV Iron for ESRD patients with Ferritin >1000 mcg/dL. We investigated the efficacy of orally available Iron (Ferric Citrate) used as a phosphate binder on Iron parameters and ESA use in ESRD patients that have low Transferrin Saturations (Iron deficient) but high Ferritins in a pragmatic pilot clinical trial.

Methods: Protocol was approved by the BCM IRB. All patients on hemodialysis for at least 3 months at the US Renal Care Scott Street Dialysis unit were eligible. Patients were included if: Mean Serum Ferritin >1000 on 2 consecutive samples in 3 months, TSAT <30% on 2 consecutive samples in 3 months. Information collected at enrollment: Ferritin, TSAT, hemoglobin, ESA dose, Calcium, Phosphorus, and PTH. Subjects given Ferric Citrate 210 mg 2 tabs to be taken with meals (minimum 6/day) for 3 months. Clinicians and dieticians were allowed to change the dose of Ferric Citrate as clinically indicated. Monthly monitoring for labs was performed. This is an interim report after 25 patients

Results: Mean serum Ferritin and mean TSAT at enrollment were1169 ng/ml and 23.3 %. After 90 days of Ferric Citrate, the mean TSAT increased to 36% (31% increase) and the mean serum Ferritin was 1075 ng/ml (15% decrease). ESA use decreased from 59 units/week to 28 units/week by the end of the trial representing a 52% reduction in mean ESA dose/week/patient. Adverse events were minimal with diarrhea being the most common. 1 patients withdrew before starting drug and another withdrew after 1 month on drug due to constipation.

Conclusions: Ferric Citrate is a phosphate binder that can increase iron stores in ESRD patients that have high Ferritin and low TSAT and appears to reduce ESA use by 50% in these patients. ClinicalTrials.gov Identifier:NCT03055598

Funding: Commercial Support - Keryx Bio-Pharmaceuticals

Effect of Ferric Citrate on ESA and Iron Parameters

Parameter	Baseline	Visit 3	Difference
Hemoglobin g/dL	10	10.6	5%
TSAT %	23.3	36.1	55%
Iron mcg/dL	54.4	78.2	44%
ESA dose units/week	59	28	-52%

TH-OR029

Effect of Ferric Citrate vs. Ferrous Sulfate on Iron, Hemoglobin, and Mineral Metabolism in CKD

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Background: Iron deficiency is common in CKD. Ferric citrate is a novel oral agent for treating iron deficiency anemia in CKD, but little is known about the efficacy of ferric citrate vs. ferrous sulfate (standard of care) in improving iron levels in CKD patients with iron deficiency.

Methods: 60 patients with stage 3b-4 CKD and iron deficiency (transferrin saturation [TSAT] <30% and ferritin <300 ng/ml) were randomized to ferric citrate (FC; n=30,2 grams tid with meals) or ferrous sulfate (FS; n=30,325 mg po tid) for 12 weeks. Primary outcomes were change in TSAT and ferritin. Secondary outcomes were change in hemoglobin, phosphate, and FGF23.

Results: There were no significant differences in baseline characteristics by treatment arm except FGF23, which was higher in the FS vs. FC arm (Table 1). A total of 25 patients in the FC arm and 26 patients in the FS completed all visits. There were no significant changes in TSAT or phosphate in either arm. Serum ferritin and hemoglobin significantly increased in the FC but not the FS arm (Fig.1). Intact FGF23 decreased 19% in the FC arm (P<0.001) and 3% in the FS arm (P=0.33), and c-terminal FGF23 decreased 15% in the FC

arm (P=0.08) and 14% in the FS (P=0.01) arm after 12 weeks. Adverse events were similar in both arms, and mostly involved gastrointestinal complaints.

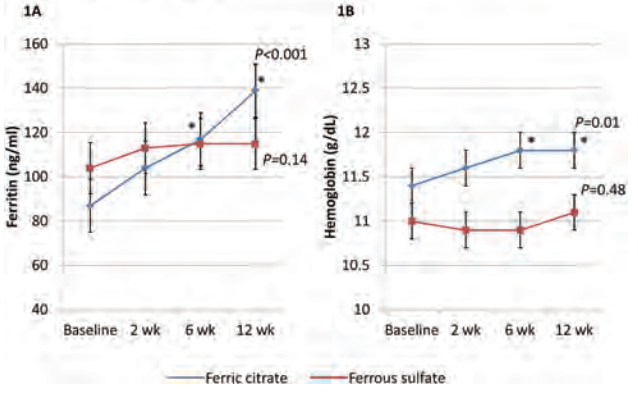
Conclusions: As compared to FS, treatment with FC resulted in greater increases in ferritin and hemoglobin and a greater decrease in intact FGF23 in CKD patients.

Funding: Commercial Support - Keryx Biopharmaceuticals

Table 1: Baseline characteristics of the study sample by randomization arm

	Ferric citrate	Ferrous sulfate	P-value
N	30	30	
Age, years	60 ± 12	63 ± 11	0.20
Male sex, N(%)	10 (33)	11 (37)	0.79
Black race, N(%)	16 (53)	17 (57)	0.79
Body mass index, kg/m²	37 ± 8	36 ± 9	0.73
Co-morbidities, N(%)			
Diabetes	16 (53)	18 (60)	0.70
Hypertension	30 (100)	28 (93)	0.14
Coronary artery disease	4 (13)	3 (10)	0.61
Heart failure	3 (10)	6 (20)	0.33
Stroke	3 (10)	3 (10)	1.0
Dyslipidemia	15 (50)	19 (63)	0.36
COPD	2 (6)	2 (6)	1.0
Laboratory Values			
Phosphorus, mg/dL	3.7 ± 0.5	3.9 ± 0.8	0.28
Calcium, mg/dL	9.3 ± 0.4	9.3 ± 0.7	0.62
eGFR, ml/min/1.73m²	33 ± 12	26 ± 14	0.05
TSAT, %	18 ± 6	19 ± 6	0.76
Ferritin, ng/ml	90 ± 70	100 ± 59	0.54
Hemoglobin, g/dL	11.4 ± 1.0	11.0 ± 1.0	0.15
iFGF23, pg/ml	91.6 [65.1,119.8)	160.1 [97.2,240.6]	0.01
cFGF23, RU/ml	178.7 [130.1,241.9]	277.5 [181.2,526.0]	0.01

Figure 1. Change in ferritin and hemoglobin in response to ferric citrate vs. ferrous sulfate for 12 weeks



TH-OR030

Association of Erythropoietin Resistance and Fibroblast Growth Factor 23 in Dialysis Patients: Results from the J-DOPPS Study

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Background: High fibroblast growth factor 23 (FGF23) levels are associated with low hemoglobin levels and increased risk of anemia development in non-HD CKD patients. FGF23 negatively regulates erythropoiesis. We hypothesized that higher FGF23 levels would be associated with increased erythropoietin hyporesponsiveness among HD patients.

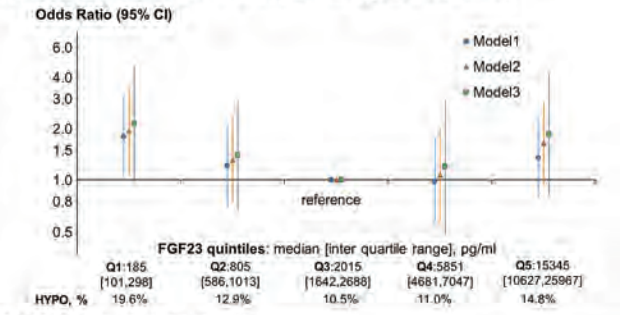
Methods: This study included 1048 patients from the Japanese Dialysis Outcomes and Practice Patterns Study (J-DOPPS) phase 5 (2012-2015). The outcome was erythropoiesis-stimulating agent (ESA) hyporesponsiveness, which was defined dichotomously as mean Hgb <10 g/dL and a standardized mean ESA dose >6,000 u/week over the 4 months following FGF23 measurement. The association between ESA hyporesponsiveness and FGF23 was estimated using multivariable adjusted logistic generalized estimating equation (GEE) regression models. We estimated the effect of FGF23 with increasing levels of covariate adjustment in three models for each outcome (See footnote in Figure).

Results: Patients with higher levels of FGF23 were younger and had higher levels of serum albumin, creatinine, albumin-corrected calcium, phosphorus, PTH, 25(OH)-Vitamin D and a higher percentage of IV iron, IV Vitamin D and cinacalcet use. ESA hyporesponsiveness was found in 144 patients (13.7%). Compared with the 3rd quintile of FGF23 levels, patients had increased risk of ESA hyporesponsiveness in the first (odds ratio [OR]=2.10, 95% confidence interval [CI]: 0.97-4.58) and fifth quintiles (OR=1.79, 95% CI: 0.79-4.04).

Conclusions: The lowest and highest levels of FGF23 were associated with increased ESA hyporesponsiveness in patients on maintenance HD.

Funding: Commercial Support - Kyowa Hakko Kirin Co. Ltd.

Figure. Association between FGF23 and ESA hyporesponsiveness



Model 1: accounting for facility clustering.
Model 2: model 1 + age, gender, vintage, summary comorbidities, post dialysis weight, body mass index, Kt/V, treatment time, hospitalization in past 3 months.
Model 3: model 2 + albumin, TSAT, ferritin, hemoglobin, creatinine, residual kidney function, phosphorus, CRP, PTH, and cinacalcet use.

To standardize the ESA dose between these different preparations, we converted Mircera doses to darbepoetin doses using a 1.2:1 ratio and converted darbepoetin doses to epoetin doses using a 250:1 ratio .

TH-OR031

Application of 3D Kidney-on-a-Chip for the Evaluation of Contrast-Induced Nephropathy

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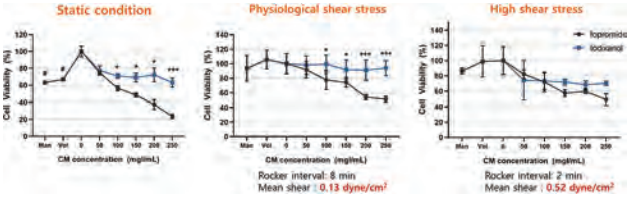
Background: Among the pathogenic mechanisms of contrast-induced nephropathy (CIN), increased viscosity of concentrated contrast media (CM) in renal tubule can perturb renal hemodynamics and have a detrimental effect on tubular epithelial cells. However, the impacts of viscosity in CIN are still poorly understood. Conventional in vitro culture studies cannot reflect the rheological properties of CM. Therefore, we investigated the effects of CM viscosity on the renal tubule using kidney-on-a-chip and two different types of contrast media.

Methods: Renal proximal tubule epithelial cells (Ronza) were cultured in OrganoPlate (Mimetas), applying time-averaged shear stress of 0.13 dyne/cm². We treated the cells with two types of CM, low-osmolar agent (iopromide, LOCM) and iso-osmolar agent (iodixanol, IOCM), varying iodine concentrations (50-250mgI/mL). We evaluated cell viability of each group with WST-8 assay. The results of cell viability in Organoplates were compared with those in static conditions. Further, to examine the effects of viscosity-induced renal damage, we increased time-averaged shear stress to 0.52 dyne/cm². Numerical simulations were also performed with different fluid viscosities.

Results: Overall, increased cell viability was observed under physiological shear stress compared to the static condition. While both LOCM and IOCM decreased cell viability compared with the negative control, LOCM was significantly less viable than IOCM at high concentrations. However, highly increased shear stress resulted in reduced viability in IOCM; no difference between IOCM and LOCM was found under the shear stress of 0.52 dyne/cm². Numerical simulations revealed that high viscosity slowed the flow rate and augmented fluid shear stress. Viscosity-mediated damage was prominent in high shear stress condition, which may represent CKD conditions with increased single nephron GFR.

Conclusions: CM-induced cytotoxicity was reduced under physiological shear stress compared to static conditions. Nevertheless, under highly increased shear stress, CM viscosity-mediated cytotoxicity was prominent, showing similar viability between IOCM and LOCM.



TH-OR032

Modeling the Renal Epithelial-Microvascular Niche with Perfusable, Pericyte-Lined Capillary Networks In Vitro

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Background: Failed renal epithelial recovery after acute kidney injury is linked to decreased capillary density and expansion of pericyte-derived fibroblasts. How this altered microvascular niche contributes to epithelial regeneration is incompletely understood. Here we report an in vitro model to study how the microvascular niche alters the regeneration of renal epithelial cells.

Methods: Microvascular networks were generated from the self-assembly of human endothelial cells and fibroblasts under established vasculogenic culture conditions. Preformed, non-perfused networks were then co-cultured with renal proximal tubular epithelial cells using Transwell inserts. Next, a culture device was developed to study effects from microvascular perfusion. The device housed multiple polydimethylsiloxane culture chambers to increase experimental throughput. Each chamber contained a perfusable microvascular network formed between gravity-fed 300 μm channels just below a porous membrane. Epithelial cells were seeded on the membrane after network formation. Microvascular network function was assessed by perfusion of 70 kDa fluorescent dextran and immunostaining. Markers of renal epithelial phenotype were measured using real time RT-PCR and immunostaining.

Results: Networks of interconnected, lumenized endothelium developed in all models. Fibroblasts occupied the interstitial space and adopted a pericyte-like morphology around vessels. Co-culture of renal epithelial cells with non-perfused microvascular networks did not affect epithelial morphology or polarity but suppressed expression of SLC22A6, AQP1 and GGT1. In our custom culture device, microvascular networks had a vessel diameter of 18.6±1.7 μm and a density of 6.4±2.0 cm/cm^2, spanned 0.33 cm^2, were perfusable in 76% of chambers seeded, and could form within ~10 μm of the epithelia. Epithelial cells seeded adjacent to the perfused capillary networks formed polarized monolayers.

Conclusions: Co-culture with non-perfused microvascular networks reduced expression of proximal tubular epithelial differentiation markers. A model with perfusable microvasculature containing capillary-scale, pericyte-lined vessels in co-culture with epithelial cells in a high-throughput culture platform was developed to better mimic the epithelial-microvascular niche in vivo.

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TH-OR033

An Immunoprotected Bioreactor for Implanted Renal Cell Therapy

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Background: An implantable bioartificial kidney will use a bioreactor containing human cells to provide renal cell therapy. The bioreactor must provide an immunoprotected environment for renal tubule cells (RTC) that obviates the need for immunosuppression. Furthermore, RTC differentiation and functionality must be maintained in vivo.

Methods: We developed an immunoprotection chamber using silicon nanopore membranes (SNM) with sub-10nm wide slit pores and evaluated primary human renal epithelial cell viability and functionality in a benchtop model and in vivo. For the benchtop, we created a stacked dual-chamber vessel, with human RTC in the inferior chamber isolated by SNM. After exposure to 500ng/mL TNF-α, RTC were evaluated for viability and monolayer integrity using cell viability assay, transepithelial electrical resistance, and immunohistochemistry. Thereafter, we implanted an analogous bioreactor in a pig without systemic anticoagulation, with the device perifused by connections to the carotid artery and jugular vein. A static in vitro control was used for comparison. The device was explanted after three days for RTC evaluation. ELISA and quantitative PCR (qPCR) were used to examine RTC-specific markers that are surrogates for RTC functionality.

Results: Benchtop testing showed that isolated RTC were confluent and >90% viable, whereas cells directly exposed to TNF-α were nonviable. In vivo, there were no thrombi in the device. Cells were confluent with >90% viability and maintained intercellular interaction/signal transduction via tight junctions/diffuse expression of Zona Occludens-1 protein similar to static control. Implanted RTC had low *NAG*expression at <10% the rate of positive control indicating minimal damage to RTC while implanted. Expression of AQP1, 1a Hydroxylase, and NHE3 was up-regulated in implanted cells and twofold higher than static controls, suggesting greater functionality of implanted cells.

Conclusions: We present a kidney bioreactor tested in vivo that sustains implanted human renal cells in a xenogeneic environment without systemic anticoagulation. These data demonstrate the promise of a SNM-based bioreactor for use in implantable bioartificial kidney without immunosuppression.

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TH-OR034

Single Bioreactor Culture System for Mass Production of Kidney Organoids

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Background: Pluripotent stem cell (PSC)-derived kidney organoids have great potential to recapitulate multicellular relationships and microenvironments of native kidneys, which can be used for drug screening, toxicology assays, disease modeling, and regenerative therapy. Mass production of kidney organoids by a robust, reproducible, and low labor-load approach is a prerequisite for the transition from laboratory to industrial applications. However, the process hasn't been established yet. Here, we employ stirred bioreactor culture system to manufacture kidney organoids and demonstrate a method of mass production of organoids with a well-established quality control.

Methods: We used Biott stirred bioreactor system. Bioreactors were inoculated with single cell suspension of human PSCs at optimal cell density in StemFit® Basic02 in a final 5-ml culture volume. Then, kidney organoids were differentiated by 6-step growth factor treatment which were modified from our previously reported protocols. Induction of nephron progenitor cells (NPCs) and kidney organoids were validated using a combination of immunostaining and qPCR.

Results: 500-1000 organoids were generated in a 5-ml bioreactor. Kidney organoids cultured in this system contained proximal tubular cells (LTL+), podocytes (NEPHRIN+), distal tubular cells (LTL-ECADHERIN+), interstitial cells (MEIS1/2+/ PDGFRβ+), and endothelial cells (CD31+). The sphere size at the beginning of differentiation was identified as a dominant factor which affected induction efficiency of NPCs and organoids. Optimization of CHIR concentration was also important for efficient NPC differentiation. Of note, higher expression of SIX2 at the NPC differentiation stage was positively correlated with more nephron structures in organoids which were viable for a longer time (>35 days) without apoptosis.

Conclusions: We established stirred bioreactor culture system for manufacturing kidney organoids whose yield was 10 times more efficient than the conventional culture system (96 organoids in 96 well culture plates). Our results also indicated SIX2 expression in NPCs is a predictive marker for production of high-quality kidney organoids. This process could be readily scaled up to support development of cell-products for clinical use at industry levels in the future.

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TH-OR035

A High-Throughput Microfluidic Renal Proximal Tubule Model to Study CKD and CVD Risk Factors

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Background: Chronic kidney disease (CKD) and cardiovascular disease (CVD) are highly interdependent conditions that share several risk factors, including hypertension. In the United States, hypertension affects nearly a third of CKD patients and is the second leading cause of kidney failure. However, the mechanisms contributing to the interdependency of CKD progression and hypertension are not fully understood, and platforms for studying the conditions *in vitro* are limited. An *in vitro* system capable of supporting kidney-specific function and mimicking vascular pathology in a replicable format has the potential to increase understanding of the physiological interplay and to provide a tool for drug development.

Methods: Draper has developed a high-throughput microfluidic platform, PREDICT96, that controls fluid flow to 96 independent bilayer tissue replicates. Here, we demonstrate the potential of the PREDICT96 platform for modeling renal proximal tubule responses to elevated flow rates with high fluid shear stress (5 dynes/cm^2). Human renal proximal tubule epithelial cells (hRPTEC) and human microvascular endothelial cells (hMVEC) were cultured in adjacent channels under different medium perfusion rates mimicking normal and elevated blood pressure (BP) in the renal microvasculature.

Results: After 7 days, tissue was characterized based on barrier function indicated by trans-epithelial electrical resistance (TEER) and expression of proteins involved in BP regulation including luminal sodium-hydrogen exchanger 3 (NHE3) and basolateral Na^+/K^+–ATPase, both previously found to be upregulated in hypertension. Preliminary data shows increased RPTEC barrier function, transporter expression and cell alignment with flow-induced shear stress in the renal and microvascular channels.

Conclusions: A high-throughput *in vitro* model of hypertension in the renal microvasculature will have powerful implications for studying interactions between CKD and CVD and for predicting toxicity responses of human tissue.

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TH-OR036

Kidney Proximal Tubule Engineering via Melt-Electrowriting

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Background: Tubular tissue engineering generally relies on large scaffolds (>1 mm) or smaller tubes within bulk hydrogels. However, for the engineering of kidney tubuli, these structures must preferably be both small-sized to increase surface area and freely

accessible for rapid waste removal. Here, we report on the fabrication of a small scale and self-standing living proximal tubule by combining well-organized tubular fiber scaffolds obtained by melt-electrowriting (MEW) with human kidney cells.

Methods: A custom-built MEW device was used to fabricate poly(ε-caprolactone) scaffolds with defined microarchitectures (square, rhombus or random) and inner Øs of 0.5-1 mm (Fig. 1A). Well-characterized human conditionally immortalized proximal tubular epithelial cells (ciPTEC) were seeded inside the scaffolds and tested for monolayer integrity, organization, matrix production and cell functionality.

Results: Scaffolds were manufactured by controlling acceleration voltage, dispensing pressure and mandrel rotation and translation speed. The pore resolution was 200-500 µm (Ø 5-10 µm microfibers, 400 µm scaffold thickness and inner Ø 0.5-1 mm) (Fig. 1B). ciPTEC formed tight monolayers in all scaffolds; rhombus shaped pores facilitated unidirectional cell orientation (Fig. 1C). The cells deposited extracellular matrix (ECM) directly after seeding, and collagen IV quantity increased over time. Viability was proven by enzymatic conversion of calcein-AM into calcein, and active uptake of RH-123; transport inhibitor sensitivity proved cell functionality.

Conclusions: Here, we present self-standing, small diameter kidney tubes that show cell functionality. Due to the well-organized tubular scaffold microstructure with large, interconnected pores, the self-produced ECM is the only barrier between the inner and outer compartment, facilitating rapid and active solute uptake. We are currently evaluating the potential for application in micro-physiological test systems and for fine-tuning towards implantable tissues with sufficient mechanical stability.

Funding: Government Support - Non-U.S.

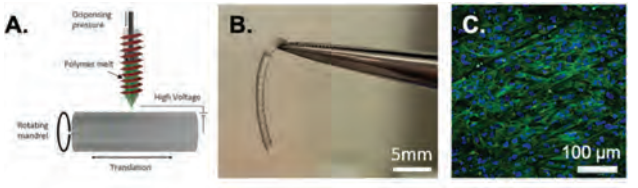

Figure 1. A. Graphical overview of the MEW tubular fabrication process. **B.** MEW tube (Ø1 mm) **C.** ciPTEC formed aligned monolayers on rhombus MEW scaffolds (green: F-actin, blue: nuclei).

TH-OR037

Matrix Elasticity Regulates Multiple Podocyte Functions

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Background: The extracellular matrix provides biomechanical signals to adherent cells. Chronic kidney disease is associated with changes in the structural and mechanical properties of the glomerular basement membrane (GBM) that may be relevant to disease progression. The aim of this work was to use polyacrylamide hydrogels as GBM analogs to determine how variations from physiological substrate stiffness regulate podocyte proliferation, migration, and traction force generation. In addition, YAP activation, an established regulator of cellular mechanotransduction was evaluated in podocytes grown on hydrogels with varying levels of stiffness.

Methods: Conditionally immortalized mouse podocytes were cultured on soft (0.5 kPa) and stiff (10-50 kPa) polyacrylamide hydrogels. Podocyte force generation was measured using traction force microscopy (TFM). Podocyte proliferation was evaluated based on nuclear EdU incorporation. Cell migration rates were measured by live-cell imaging. YAP nuclear localization was determined by quantitative immunofluorescence staining. Gene expression for downstream targets of YAP activation were evaluated by qRT-PCR.

Results: TFM analysis showed that cell generated forces were orders of magnitude higher on stiff (10 kPa) compared to soft (0.5 kPa) hydrogels. Podocyte spreading was also significantly lower on soft gels. Tractions stresses were also higher on stiff hydrogel showing that increased force generation was not simply related to differences in cell spreading. Proliferation rate was nearly doubled on stiff gels compared to soft and the rate of podocyte migration was approximately 25 µm/hr on stiff substrates compared to <5 µm/hr on soft gels. Stiff substrates induced nuclear localization of YAP and resulted in up-regulation of gene expression for *CTGF, CYR61, ANKRD1,* and *BIRC5*, all which are known downstream targets of YAP activation.

Conclusions: These data show that the elasticity of podocyte substrata is important in regulating multiple podocyte functions that may be relevant to maintenance of normal physiological function and/or progression of chronic kidney injury. Additional work is needed to understand the pathological significance of changes in GBM stiffness in different chronic kidney injuries and to elucidate the molecular mechanisms that regulate stiffness-induced changes in cell behavior.

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TH-OR038

Application of a Newly Engineered Podocyte Culture System to Study Intracellular Complement Production and Activation

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Background: Current technologies do not support long-term cell viability, differentiation and maintenance of podocytes. We developed a biophysical approach, termed macromolecular crowding(MMC), to create extracellular matrix(ECM)-rich tissue equivalents and decellularization. This approach generates decellularized grafts that scaffold podocytes to grow in an environment similar to native conditions. To show a potential application of this newly designed culture system we studied complement(C) activation in podocytes exposed to IgG from individuals with lupus nephritis(LN).

Methods: Human skin fibroblasts were cultured under MMC and then decellularized. Human immortalized podocytes were cultured on the decellularized matrix(DCM) at 33°C for 7 days and subsequently at 37°C for 14days. ECM deposition in the DCM-coated dishes was analyzed by SDS-PAGE, immunofluorescence(IF) and scanning EM and expression of podocyte markers by western blotting(WB) and IF. Podocytes were then exposed to IgG from patients with LN and C production and activation was studied.

Results: We found that DCM-coated dishes contained all major ECM molecules(laminin, fibronectin, collagen I & IV) and podocytes survived and differentiated on DCM-coated plates significantly better than on noncoated plates, as shown by development of interdigitating foot process (fig.a) and increased expression of nephrin and synaptopodin. Podocytes exposed to LN IgG displayed increased levels of C factors(C3, C4, C5, C5b9) and C3 activation products(fig.b).

Conclusions: Engineering *in vitro* microenvironment with DCM enhances podocyte viability, native physiology and morphology. This novel system enabled us to demonstrate increased C factor production by podocytes exposed to LN IgG and intracellular complement activation.

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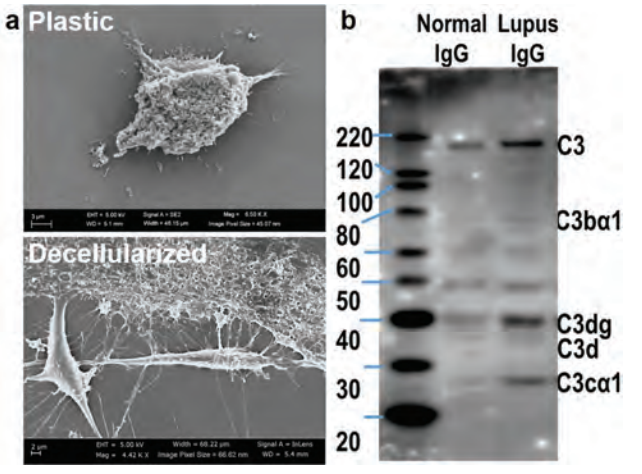

(a) Better podocyte morphology with interdigitating foot process on decellularized culture dishes (b) Lupus IgG enhances production of activated C3 molecules

TH-OR039

Hepatocyte Growth Factor-Producing Mesothelial Cell Sheets Reduce Apoptosis of Renal Tubular Epithelial Cells in Ischemia-Reperfusion Injury

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Background: Ischemia-reperfusion injury (IRI) is a model of acute kidney injury and chronic kidney disease which are clinically important problems to be solved. We have recently reported that renal subcapsular transplantation of hepatocyte growth factor (HGF)-producing cell sheets improved renal IRI in rats from acute to chronic phase. However, the mechanism is not well understood. Therefore, we assessed the apoptosis of the renal tubular epithelial cells after IRI with or without transplantation of the HGF-producing cell sheets.

Methods: HGF-transgenic human mesothelial cells (HGF-tg MC sheet) were cultured in temperature-responsive dishes for 4 days to prepare cell sheets. At day 7 after right nephrectomyon a nude rat, two cell sheets were transplanted under the left renal capsule, and the left renal pedicle was clamped for 60 min. Reperfusion was performed after the ischemia, and the left kidney was harvestedat day 2, 14, and 28 after IRI. Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) staining and caspase-3 staining were performed to evaluate apoptosis with paraffin-embedded sections of the kidney. HGF-tg MC sheet group was compared to other groups; a sham operation without IRI or treatment (Sham); IRI with no treatment (NT); IRI with intravenous administration of recombinant human HGF protein (IV HGF); or IRI with transplantation of non-transgenic MC sheets under the renal capsule (MC sheet).

Results: The number of caspase-3-positive cells was highest in the Sham group, lowest in the NT group, and somewhat higher in the other groups. WithTUNEL staining, positive cells were significantly suppressed in the HGF-tg MC sheet group and MC sheet group, compared to NT group and IV HGF group.

Conclusions: Transplantation of HGF-producing cell sheets under the renal capsule may reduce apoptosis in renal tubular epithelial cells. These results suggested that the suppression of apoptosis is one of the mechanisms to improve IRI by HGF-producing cell sheets.

Funding: Government Support - Non-U.S.

TH-OR040

Transdermal Delivery of Kidney-Targeting Nanoparticles

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by cyst formation and kidney enlargement, resulting in end-stage renal failure. Most available therapies offer only controlling secondary consequences of ADPKD and are systemically administered via oral/intravenous routes in which drugs are eliminated by first pass metabolism, degraded by gastrointestinal tract, and cause off-target side effects. Herein, we aim to engineer a transdermal patch containing ADPKD treatment by combining 1) a dissolvable microneedle (DM) patch allowing controlled transdermal delivery of 2) kidney-targeted nanoparticles (KNP) with ADPKD-specific drugs. We hypothesize these KNP can deliver drugs specifically to diseased renal cells, thereby limiting systemic side effects while enhancing kidney bioavailability.

Methods: KNP were synthesized by self-assembly of DSPE-PEG(2000)-methoxy:DSPE-PEG(2000)-Folate:DSPE-PEG(2000)-FITC in 70:20:10 mol ratio and non-targeting NP consists of DSPE-PEG(2000)-methoxy:DSPE-PEG(2000)-FITC in 10:90 mol ratio. NP were studied by transmission electron microscopy (TEM), dynamic light scattering (DLS), and zeta potential. In vitro biocompatibility and binding were evaluated using MTS assay and confocal microscopy on human renal proximal tubule epithelial cells (RPTECs). The KNP incorporated DM (polyvinyl alcohol) patches were fabricated via micro-molding technique, evaluated for dissolution and NP release.

Results: Non-targeting and KNP exhibit a diameter of 15.0 ± 0.0 and 12.6 ± 1.2 nm as confirmed by TEM and DLS, and zeta potentials were found to be neutral (0.07 ± 0.2 and –0.32 ± 0.5 mV, respectively). When NP (1-100 μM) biocompatibility were assessed after 24 h on RPTECs, over 90% of cells were found to be viable and were comparable to the PBS-treated group. Additionally, KNP (100 μM) shown an enhanced binding as compared to non-targeting NP after 30 min. KNP incorporated DM patches consists of uniform microneedles of 600 μM height and 300 μM width. These patches showed complete dissolution within 120 ± 30 seconds in PBS at physiological pH 7.4, indicating potential for rapid transdermal release of NP.

Conclusions: Our transdermal delivery strategy of KNP offer a promising drug delivery system for ADPKD. Future studies will incorporate a library of drugs to test therapeutic efficacy in vivo.

TH-OR041

High Fibroblast Growth Factor 23 Levels Induce Ventricular Arrhythmogenesis via Intracellular Ca^{2+} Mishandling

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Background: Fibroblast growth factor (FGF)23 is a phosphaturic hormone synthesized as response to increased serum phosphate levels. FGF23 action requires the presence of its cofactor *Klotho* (KL). Chronic kidney disease patients show decreased soluble KL and high FGF23 levels. High FGF23 levels have been associated to renal dysfunction and recently considered as a non-conventional cardiovascular risk factor. However, it is unknown whether FGF23 might alter cardiac contractile function and rhythm. Our study analyze FGF23 effect on calcium (Ca^{2+}) handling, key regulator of contractile function and ventricular rhythm, and the Ca^{2+} handling in an animal model with high circulating levels of FGF23 (KL *hypomorphic* mice, *kl/kl*).

Methods: Isolated adult rat ventricular myocytes (ARVM) were perfused with FGF23 (100 ng/mL). To determinate FGF23-dependent pathways, ARVM were pre-incubated with the FGF-receptor inhibitor PD173074 (10 mM) or recombinant KL (rKL; 100 ng/mL). Adult mouse ventricular myocytes (AMVM) were isolated from Wildtype (WT, +/+) and *kl/kl* littermates mice. L-type Ca^{2+} current (I_{CaL}) was recorded by the whole-cell patch-clamp technique. Ca^{2+} handling and contractile function were analyzed using confocal microscopy.

Results: FGF23 reduced I_{CaL} ($p<0.001$), intracellular systolic Ca^{2+} transients amplitude ($p<0.01$) and sarcoplasmic reticulum (SR) Ca^{2+} load ($p<0.01$). These alterations were functionally translated to a deterioration of cellular contraction ($p<0.01$). FGF23 exposure increased diastolic Ca^{2+} leak ($p<0.01$) and ryanodine receptors activity. FGF23 perfusion induced a pro-arrhythmogenic phenotype in paced ARVM ($p<0.05$). FGF23 effects were blocked in PD173074- or rKL-pretreated ARVM. Moreover, *kl/kl* mice showed a significant increment of FGF23 serum levels versus WT ($p<0.001$). *kl/kl* AMVM presented a reduction of intracellular systolic Ca^{2+} transient amplitude ($p<0.001$), contraction ($p<0.001$) and SR-Ca^{2+} load ($p<0.05$). Diastolic Ca^{2+} release was increased in *kl/k* ($p<0.01$) which lead finally to a pro-arrhythmogenic phenotype in *kl/kl* AMVM ($p<0.001$).

Conclusions: Our study uncovers FGF23 as new target in the intracellular Ca^{2+} handling, able to induce contractile dysfunction and pro-arrhythmogenic phenotype in adult cardiomyocytes.

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TH-OR042

A NPT2A-Selective Inhibitor Increases Phosphate Excretion in FGF23-Null and CKD Mice

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Background: The sodium-phosphate co-transporters NPT2a and NPT2c play key roles in reabsorbing filtered phosphate in proximal renal tubules thus contributing critically to phosphate (Pi) homeostasis. Expression of both transporters is regulated by parathyroid hormone (PTH) and Fibroblast Growth Factor 23 (FGF23). Consequently, inactivating mutations in FGF23, GALNT3, or KLOTHO lead to tumoral calcinosis because of increased tubular Pi reabsorption resulting in hyperphosphatemia. Increased plasma Pi levels are also observed in disorders with abnormal PTH synthesis or function, i.e. hypoparathyroidism and pseudohypoparathyroidism, respectively. Furthermore, acute and chronic kidney disease (CKD) typically leads to a significant elevation of plasma Pi and FGF23, which are associated with kidney disease progression and increased mortality.

Methods: A novel NPT2a-selective small molecule inhibitor, PF-06869206, which reduces phosphate uptake in human proximal tubular cells was given by oral gavage (10-500 mg/kg) to wild-type mice, to mice lacking either Npt2a, Npt2c, or Fgf23, and to mice with folic acid-induced AKI or adenine-induced CKD. Plasma Pi levels were measured at different time points after PF-06869206 administration, along with urinary Pi and creatinine.

Results: Administration of PF-06869206was well-tolerated and elicited a dose-dependent increase in fractional Pi excretion in wild-type mice that resulted in a reduction of plasma Pi levels by approximately3.0 mg/dl. The increase in urinary Pi excretion and the resulting reduction in plasma Pi after a single oral dose of PF-06869206 (300 mg/kg) was indistinguishable in wild-type mice and in animals lacking Npt2c, while no changes were observed in Npt2a-null mice. Furthermore, in Fgf23-null mice a single dose of the NPT2a inhibitor increased urinary Pi excretion by approximately 4-fold, which reduced plasma Pi levels from 15.8±0.84 to 11.6±0.49 mg/dl. In AKI and CKD mice, treatment with PF-06869206 increased urinary Pi excretion thereby reducing plasma Pi levels.

Conclusions: The selective pharmacological inhibition of NPT2a holds promise as a novel therapeutic option for genetic and acquired hyperphosphatemic disorders.

Funding: NIDDK Support

TH-OR043

Calciprotein Particles Cause FGF23 Induction via TLR4 Stimulation in Osteoblasts

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Background: Calciprotein particles (CPP) are polydispersed colloidal nanoparticles composed of solid-phase calcium-phosphate (CaPi) and serum protein fetuin-A. Two types of CPP with different CaPi properties exist: Primary CPP contain amorphous CaPi, whereas secondary CPP contain crystalline CaPi. We previously reported that CPP induced FGF23 expression/secretion in cultured osteoblastic cells (UMR106). We also reported that a single dose of phosphate gavage in mice increased plasma CPP levels followed by increase in FGF23 expression in the bone and FGF23 levels in the blood. However, the mechanism by which osteoblasts sense CPP remains unknown. In this study, we tested the hypothesis that Toll-like receptor-4 (TLR4) might function as a receptor for CPP. We also determined which CPP, primary or secondary, contribute to FGF23 induction.

Methods: In vitro experiments: CPP were generated in the culture medium of UMR106 by increasing concentrations of calcium (Ca) and phosphate (P). To inhibit formation of secondary CPP, we added bisphosphonate (BP) to the medium (BP inhibits transition of CaPi from the amorphous phase to the crystalline phase) and measured physical properties of CPP in the medium by small angle X-ray scattering (SAXS). FGF23 mRNA levels were determined by quantitative RT-PCR. In vivo experiments: To inhibit formation of secondary CPP in vivo, we injected BP in wild-type (WT) mice fed high P diet for 10 days. To test if FGF23 induction might depend on TLR4, we administered a single dose of P by oral gavage in WT mice and mice lacking TLR4 (TLR4 KO). These mice were evaluated by measuring P, Ca, and FGF23 levels in the blood and FGF23 mRNA levels in the cranial bone.

Results: Secondary CPP with a hydrostatic diameter of approximately 35 nm were generated in the medium. In the presence of BP, these CPP disappeared and primary CPP with a diameter of around 9.2 nm were generated. FGF23 mRNA levels were much higher when BP was present in the medium. Administration of BP increased FGF23 levels in the blood, but suppressed FGF23 mRNA levels in the skull. A single dose of P ingestion increased FGF23 mRNA and circulating FGF23 levels in WT mice but not in TLR4 KO.

Conclusions: Primary CPP were a more potent inducer of FGF23 expression than secondary CPP. We also suggest that TLR4 is necessary for appropriate regulation of FGF23 expression/secretion.

TH-OR044

Calciprotein Particle (CPP)-Inhibition Explains Magnesium-Mediated Protection Against Vascular Calcification

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Background: Phosphate (Pi) toxicity is a strong determinant of vascular calcification in chronic kidney disease (CKD). Pi induces the formation of calciprotein particles (CPP), which drive the calcification process. Magnesium (Mg^{2+}) may prevent vascular calcification, but the mechanisms are poorly understood. Here, we investigated the role of Mg^{2+} in calcification and crystal maturation induced by Pi and secondary crystalline calciprotein particles (CPP2).

Methods: Vascular smooth muscle cells were treated with high Pi or CPP2 and supplemented with Mg^{2+} and calcification was analyzed by medium absorbance, electron microscopy and energy dispersive spectroscopy. Effects of increased dietary Mg^{2+} intake on aortic calcification were assessed in Klotho knock-out mice. The effects of Mg^{2+} on calcification propensity (T_{50}) were measured in sera from CKD patients and healthy controls.

Results: Mg^{2+} supplementation prevented Pi-induced calcification in vascular smooth muscle cells. In contrast, Mg^{2+} failed to inhibit CPP2-induced calcification, indicating that it acts before the formation of CPP2. Increased expression of the osteogenic genes osteopontin and alkaline phosphatase remained stable after Mg^{2+} supplementation. In CPP2 cultures, Mg^{2+} dose-dependently delayed the maturation of CPP2 by several days *in vitro*. Elemental analysis showed that CPP2 contain 37 % oxygen, 19% Pi and 39% Ca^{2+}, all remaining stable upon Mg^{2+} supplementation in already matured CPP2. Furthermore, in Klotho knock-out mice, high dietary Mg^{2+} intake effectively prevented aortic calcification. In human serum, addition of 0.2 mmol/L Mg^{2+} increased T_{50} in healthy controls from 371 ± 16 minutes to 422 ± 20 minutes and in CKD patients from 323 ± 19 minutes to 367 ± 23 minutes (both $P < 0.05$). Each further 0.2 mmol/L addition of Mg^{2+} led to increases of ~40 minutes in both groups, resulting in a T_{50} of 566 ± 3 and 505 ± 21 minutes in healthy controls and CKD patients after addition of 1.0 mmol/L Mg^{2+}, respectively.

Conclusions: Our results demonstrate CPP2 mediate Pi-induced calcification. Mg^{2+} prevents CPP2 formation and thereby prevents Pi toxicity leading to calcification. Mg^{2+} supplementation, even at low dosages, is a potential therapeutic strategy to reduce vascular calcification in CKD.

Funding: Government Support - Non-U.S.

TH-OR045

Lipocalin 2 Regulates FGF23 Production in CKD

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Background: Production of fibroblast growth factor 23 (FGF23) is increased during chronic kidney disease (CKD) progression and associated with left ventricular hypertrophy (LVH), cardiac failure, and mortality. *Lcn2*, encoding a pro-inflammatory and iron-shuttling molecule, is the topmost expressed gene in the kidneys of the *Col4a3*^{KO} mouse model of CKD. Serum Lcn2 and FGF23 levels are strongly correlated, suggesting that Lcn2 might control FGF23 production. Here, we investigated the role of Lcn2 in FGF23 regulation in health and CKD.

Methods: First, we injected WT mice with recombinant Lcn2 and measured serum FGF23 levels. Then, we crossed *Lcn2*^{KO} mice with *Col4a3*^{KO} (CKD) mice and analyzed the renal and cardiac functions of WT, *Lcn2*^{KO}, CKD, and CKD/*Lcn2*^{KO} littermates at 23 weeks of age. We next exposed WT and *Lcn2*^{KO} mice to 3 established models of FGF23 induction: acute inflammation, a low iron diet or a high phosphate diet- to identify if Lcn2 mediates the increase in FGF23 in response to these stimuli. In addition, we tested whether Lcn2 directly controls *Fgf23* transcription in osteoblast cultures.

Results: Administration of Lcn2 to healthy mice increased mRNA and serum FGF23 levels by 3-fold. As previously shown, mice with advanced CKD displayed impaired kidney function, increased levels of serum Lcn2, hyperphosphatemia, increased bone and serum FGF23, anemia, hypertension, LVH and reduced lifespan. Deletion of *Lcn2* in CKD mice partially improved kidney function and prevented hypertension. Compared to CKD mice, CKD/*Lcn2*^{KO} mice had normal levels of serum iron, ferritin and transferrin saturation. Importantly, CKD/*Lcn2*^{KO} mice displayed 90% reductions in *Fgf23* mRNA and serum FGF23 levels ($p<0.05$) and did not develop LVH. CKD/*Lcn2*^{KO} mice lived significantly longer than CKD littermates (+6.7 weeks, i.e. +30%, $p<0.05$). As expected, serum FGF23 levels increased in WT mice in response to acute inflammation, low iron diet and high phosphate diet. Interestingly, *Lcn2* deletion only prevented FGF23 elevations in response to acute inflammation. Finally, we showed that Lcn2 increased *Fgf23* transcription in cultured osteoblasts and we identified cAMP / PKA signaling as a pathway mediating the stimulation of FGF23 by Lcn2.

Conclusions: Our results show that Lcn2 is an important regulator of FGF23 production in CKD that might mediate FGF23 response to inflammation.

Funding: NIDDK Support

TH-OR046

Physiologic Regulation of Systemic Klotho Levels by Renal CaSR Signaling in Response to CaSR Ligands and Extracellular pH

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Background: Chronic kidney disease (CKD) progresses to end-stage renal disease accompanied by complications resembling the premature multi-organ failure akin to the Klotho-hypomorphic - mice (*Kl/Kl*). The kidney is the source of soluble Klotho (sKlotho), and as renal disease progresses serum and urine sKlotho levels fall, and patients acquire characteristics resembling the of *Kl/Kl* mice. Pharmacologic or dietary alkaline supplementation slows progression of CKD even in stages 3 and 4. The mechanism(s) by which HCO3 supplementation or alkaline diets work and physiologic mechanisms by which sKlotho levels might be regulated are unknown.

Methods: We measured: 1) urine and serum Kotho in mice treated with calcimimetics or alkali: 2) Klotho release in medium from minced mouse kidneys, and 3) medium Klotho from HEK-293 cells treated with calcimimetics, HCO_3, and ADAM protease inhibitors and expressing the calcium-sensing receptor (CaSR) and Klotho. The CaSR, Klotho, and ADAM10 were co-localized in mouse kidneys and in cells expressing the CaSR and Klotho using differential centrifugation, co-IP, and immunofluorescent staining visualized by confocal microscopy.

Results: In intact mice, minced kidneys, and cultured cells, (CaSR) activation with high Ca or calcimimetics increases sKlotho levels via ADAM10-mediated shedding. Alkaline pH values increase, and acid pH values decrease CaSR signaling. Alkali treatment increases serum and urine sKlotho in mice, Klotho shedding in mouse kidney homogenates and cultured cells in a CaSR-dependent manner. Oral K citrate for 72 hrs increases serum and urine Klotho in human volunteers. ADAM10-dependence was demonstrated using the ADAM10 inhibitor GI 254023X and siRNA. In HEK-293 cells the CaSR, Klotho, and ADAM10 form cell surface aggregates that disperse following CaSR activation, but not with ADAM10 inhibition.

Conclusions: We define a novel physiologic mechanism for regulation of sKlotho levels by the renal CaSR-ADAM10-Klotho pathway that can be modified by pH. We predict that acidosis accelerates, and alkalinization slows the rate of loss of renal function in CKD partly because acid decreases, and alkaline increases renal CaSR-stimulated Klotho shedding from the kidney.

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

TH-OR047

Novel Mechanism of Cardiac Hypertrophy Within the CKD-MBD

Matthew Williams, Keith A. Hruska. *Washington University in St. Louis, St Louis, MO*.

Background: Cardiac Hypertrophy is a predecessor of cardiac morbidity associated with CKD and caused by factors that are components of the CKD - MBD syndrome: vascular calcification (VC) and elevated levels of FGF23. In a murine model of Alport syndrome, we show that CKD causes cardiac hypertophy due to mechanisms independent of VC and FGF23 due to signaling through activin receptor type 2A (ActRIIA).

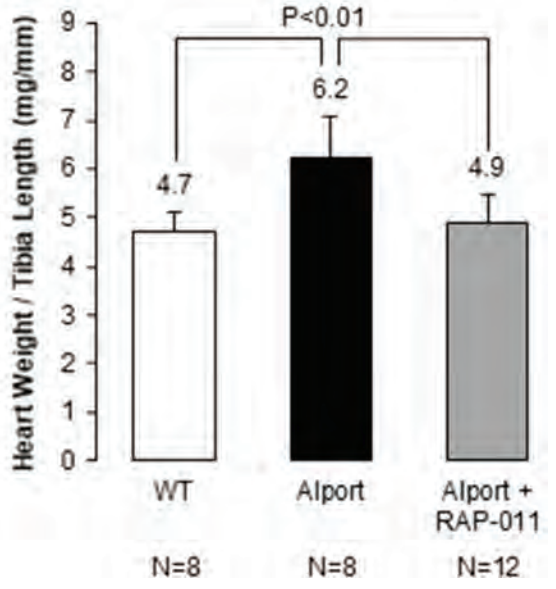
Methods: Cardiac size and function were determined by heart weight/tibial length (HW/TL) and echocardiography in 200 day old (do) Col4a5 deficient male mice on the C57Bl6J background. BUN, inulin clearance were used to measure kidney function. Aortic compliance was determined by pressure - diameter relationship. FGF23 levels were by Elisa. Mitochondrial morphometry was by electron microscopy, and OXPHOS was by respirometry. ActRIIA signaling was inhibited by an ActRIIA-Fc ligand trap.

Results: 200 do Alport mice had BUNs of 50 -90 and 70-85 % reduction in inulin clearance. Cardiac levels of psmad 2 and inhibin βa were increased in Alport mice and cardiac PGC1α levels were decreased. These effects of CKD were reversed by ActRIIA signaling inhibition. Aortic compliance was unchanged compared to WT mice, and elevated FGF23 levels were not altered by the ActRII-Fc treatment. HW/TL was 6.2 mg/mm in 200 do Alport mice compared to 4.7 in WT control mice, and 4.9 in ActRIIA-Fc treated Alport mice, $p<0.01$ (Fig.1). Cardiac hypertrophy was confirmed by echocardiography, but function was not significantly altered. Mitochondrial OXPHOS and morphology were significantly altered in 200 do Alport mice indicating a metabolic cause for the compensated hypertrophy.

Conclusions: Compensated cardiac hypertrophy in 200 do Alport mice was due in part to cardiac activation of ActRIIA signaling and prevented by its inhibition in the absence of vascular stiffness and without change in FGF23 levels.

Funding: NIDDK Support

Figure 3



TH-OR048

Identification of an Extracellular pH-Sensitive Residue in the Calcium-Sensing Receptor

Patricia Pacios centeno, Donald T. Ward. *The University of Manchester, Manchester, United Kingdom*.

Background: The calcium-sensing receptor (CaR) is the principal controller of parathyroid hormone (PTH) secretion. Mild acidosis (pH_o 7.2) inhibits CaR signalling in HEK-293 and bovine parathyroid cells, so permitting increased PTH secretion from human parathyroid cells [1]. Thus, acidosis could contribute to the CaR underactivation and secondary hyperparathyroidism of CKD but where the molecular site of the pH_o sensitivity remains unknown [1]. The crystal structure of the CaR reveals that CaR^{R62} and CaR^{R66} stabilize its active conformation. Therefore, here we investivated whether these residues mediate CaR pH_o sensitivity.

Methods: CaR activity was measured as $Ca^{2+}{}_i$ mobilization (Fura-2) and extracellular signal-regulated kinase (ERK) phosphorylation in HEK-293 cells transfected with (wild-type) CaR^{WT} or CaR^{R66A}. CaR stimulated with HEPES buffer containing the EC_{50} concentration for Ca^{2+} (3.5mM CaR^{WT}, 5 CaR^{R66A}) at either pH 7, 7.4 or 7.6.

Results: The CaR crystal structure predicts that following activation, CaR^{R66} creates a hydrogen bond with CaR^{S301} that is supported by a bound, negatively-charged bicarbonate ion (pKa 6.1). We hypothesize therefore that in pathophysiological acidosis, the more neutral bicarbonates will no longer bind CaR^{R66}, impairing the hydrogen bond and inhibiting CaR activity. Indeed we found that lowering pH_o from 7.4 to 7.0 inhibited CaR-induced $Ca^{2+}{}_i$ mobilisation in CaR^{WT} (-40 ±5%; P<0.001 ANOVA) whereas in CaR^{R66A} there was no significant effect (-14 ±9%; ns). Similarly, pH_o 7.0 inhibited CaR-induced ERK phosphorylation in CaR^{WT} (-86 ±5%; P<0.01) but not significantly in CaR^{R66A} (-30 ±12%; ns). Then in alkalosis, higher pH_o renders bicarbonate more negative which we hypothsize will better support the R66-S301 hydrogen bond, and thus enhance receptor activity. As predicted, raising pH_o from 7.4 to 7.6 stimulated CaR-induced $Ca^{2+}{}_i$ mobilisation in CaR^{WT} (+25 ±11%; P<0.001) but not in CaR^{R66A} (+3 ±12%; ns). Similarly, pH_o 7.6 enhanced CaR-induced ERK phosphorylation in CaR^{WT} (24±17%; P<0.05) but not in CaR^{R66A} (+9±12%; ns). Unlike for CaR^{R66A}, the CaR^{R62A} mutant retained its CaR^{WT}-like pH_o senstivity.

Conclusions: Together, these data identify CaR^{R66} as a site of pH_o sensitivity in CaR representing another potential contributor to the secondary hyperparathyroidism of CKD where acidosis is present. [1] Campion *et al* (2015) J Am Soc Nephrol 26, 2163-2171.

Funding: Government Support - Non-U.S.

TH-OR049

In Vivo Deletion of Complex Genomic Enhancers Reveal a Kidney-Specific, Endocrine-Deficient Cyp27b1 Pseudo-Null Mouse and Loss of Reciprocally Regulated Cyp24a1 by FGF23 and PTH

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Background: *Cyp27b1* and *Cyp24a1* are reciprocally regulated in the kidney by the key hormones PTH, FGF23, and $1,25(OH)_2D_3$. Our recent genomic studies in mice identified a complex kidney-specific enhancer module located within the introns of adjacent *Mettl1* (M1) and *Mettl21b* (M21) genes that mediate basal and PTH induction of *Cyp27b1* as well as suppression by FGF23 and $1,25(OH)_2D_3$. Gross deletion of these segments in mice has severe consequences on skeletal health, but does not affect *Cyp27b1* regulation in non-renal target cells (NRTCs).

Methods: Using CRISPR/Cas9-mediated deletions of genomic enhancers (non-coding segments) in mice, we can separate tissue specific responses in both *Cyp27b1* and *Cyp24a1*. We used ChIP-seq from adult human kidney cortex to explore conservation to mouse.

Results: Our current studies reveal a bimodal activity in the M1 intronic enhancer with components responsible for induction of *Cyp27b1* by PTH and repression by $1,25(OH)_2D_3$. The deletion of both M1 and M21 submodules fully eliminates basal *Cyp27b1* expression and regulation in the kidney, leading to a systemic and skeletal phenotype similar to that of the *Cyp27b1*-KO mouse due to depletion of $1,25(OH)_2D_3$ and high PTH. *Cyp24a1* levels in the double KO mouse were low due to compensatory regulation by elevated PTH and reduced FGF23. However, expression of *Cyp27b1* and retention of its regulation by inflammation (LPS) in the NRTCs remained unperturbed. Importantly, dietary normalization of calcium, phosphate, PTH, and FGF23 rescues this aberrant phenotype and creates an ideal *in vivo* model with which to study NRTC production of $1,25(OH)_2D_3$ and its potential impact on disease. Using a separate set of mouse enhancer deletions, we found that basal as well as PTH and FGF23 regulation of *Cyp24a1* in the kidney was controlled by a set of downstream enhancers distinct from those that mediate $1,25(OH)_2D_3$. Finally, we confirm the presence of a conserved chromatin landscape for both *CYP27B1 and CYP24A1* in human similar to the mouse.

Conclusions: Collectively, these studies define a finely balanced homeostatic control mechanism employed by PTH and FGF23 with catastrophic toxicity protection from $1,25(OH)_2D_3$ in the genomic regulation of vitamin D metabolism and its accompanied control of mineral maintenance.

Funding: NIDDK Support

TH-OR050

Nanomolar Potency Inhibitors of SLC26A3 (DRA) Anion Exchanger as First-in-Class Treatment of Enteric Hyperoxaluria and Nephrolithiasis

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Background: Nephrolithiasis affects 9% of the US population in their lifetime. Two thirds of kidney stones are composed of calcium oxalate, for which hyperoxaluria is a major risk factor. Dietary oxalate is absorbed by intestine, and oxalate is also generated by liver as a metabolic end product. The majority of oxalate is excreted in urine with some excretion in stool. Gastrointestinal conditions such as bariatric surgery, inflammatory bowel disease and pancreatic insufficiency are associated with hyperabsorption of oxalate in colon (enteric hyperoxaluria). DRA (down-regulated in adenoma, SLC26A3) is an anion (Cl^-, HCO_3^-, oxalate) exchanger predominantly expressed in colon and is the main pathway for colonic oxalate absorption, with knock-out mice having 70% lower urine oxalate excretion. DRA is thus an attractive target for treating enteric and idiopathic hyperoxaluria, and calcium oxalate nephrolithiasis, by redirecting the majority of oxalate excretion through stool rather than urine.

Methods: We previously identified, by high-throughput screening, first-in-class DRA inhibitors (*JCI Insight* 2018; 3(14): 121370). The work herein includes the synthesis and characterization of a nanomolar potency (IC_{50} 40 nM) inhibitor (DRA_{inh}-A270), and demonstration of its efficacy in mouse models of hyperoxaluria and oxalate nephropathy.

Results: Single dose oral or intraperitoneal (ip) DRA_{inh}-A270 (10 mg/kg) gave predicted therapeutic levels in serum for at least 72 h in mice. In a model of acute hyperoxaluria, bolus oral administration of sodium oxalate (2.5 micromol/kg) produced approximately 3-fold increased urine oxalate/creatinine ratio that was largely prevented by DRA_{inh}-A270 treatment. In a diet-induced model of oxalate nephropathy involving a high-oxalate, low-calcium diet, vehicle-treated mice developed marked hyperoxaluria and renal failure by day 14; DRA_{inh}-A270 treatment (10 mg/kg, ip, BID starting day 0) largely prevented hyperoxaluria, renal failure (per serum creatinine), renal injury and calcium oxalate crystal deposition (per histology). In toxicity studies, one week high-dose DRA_{inh}-A270 administration did not affect CBC or serum chemistries.

Conclusions: DRA inhibition by DRA_{inh}-A270 represents a novel approach for treatment of enteric and idiopathic hyperoxaluria, and prevention of calcium oxalate nephrolithiasis.

Funding: NIDDK Support, Private Foundation Support

TH-OR051

Pragmatic Cluster-Randomized Trial of an Electronic Clinical Decision Support System (eCDSS) to Improve CKD Management in Primary Care

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Background: Whether eCDSS improves CKD management in primary care is not well known.

Methods: We conducted a 12-month, 3-arm, pragmatic, cluster-randomized trial to evaluate feasibility and preliminary effectiveness of two eCDSS strategies to improve CKD management in primary care. We used electronic health record to identify participants, deliver intervention, and ascertain outcomes. We randomized 524 adults with two $eGFR_{Cr}$ <60 mL/min/1.73m^2 ≥90 days apart in clusters by primary care provider (PCP) to: (1) eCDSS; (2) eCDSS plus pharmacist; or (3) usual care. Intervention included risk

stratification with creatinine, cystatin C, albumin-to-creatinine ratio, followed by eCDSS embedded in EHR for individually tailored clinical guidance and patient education. eCDSS PLUS added a pharmacist follow up call. Primary clinical outcome was blood pressure (BP) change. Secondary outcomes were PCP CKD awareness, and appropriate use of ACEi/ARB and statin.

Results: All 81 eligible PCPs agreed to participate. Mean patient age was 70, 47% non-white, median $eGFR_{creat}$ 57 ± 0.6 mL/min/1.73m^2. At baseline, there was high use of ACEi/ARB (61%), statin (67%) and BP control (71%). Among intervention patients (n=336), 178 (53%) completed triple-marker labs and 138 (41%) had labs and PCP visit with eCDSS deployed. eCDSS was opened by the PCP for 102/138 (74%) eligible encounters, with at least one suggested order or education material signed for 83/102 (81%). Among eCDSS PLUS 29/40 (73%) completed pharmacist call. After 12 months, BP change (SBP: -2.0 ± 0.9 mmHg; DBP: -0.2 ± 0.4 mmHg), PCP CKD awareness (50%) and use of ACEi/ARB (49%) and statin (56%) were similar across groups. In as-treated analyses, PCP CKD awareness was higher in eCDSS and eCDSS PLUS (73% and 69%) vs. usual care (47%) at study end, adjusted p=0.01.

Conclusions: This tailored, automated CKD eCDSS embedded in the EHR was highly utilized by participating PCPs. Due to insufficient uptake of testing and high baseline guideline-concordant CKD care in the practice, we were unable to determine eCDSS effectiveness to improve CKD management. We did demonstrate increased PCP CKD awareness. This easily usable tool can be used in large pragmatic trials engaging PCPs to improve CKD management.

Funding: NIDDK Support

TH-OR052

Patiromer vs. Placebo to Enable Spironolactone in Patients with Resistant Hypertension and CKD According to Baseline Kidney Function (AMBER Trial)

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[1]Indiana University School of Medicine, Indianapolis, IN; [2]University of Lorraine and FCRIN INI-CRCT, NANCY, France; [3]Relypsa, Inc., a Vifor Pharma Group Company, Redwood City, CA; [4]University of Connecticut School of Medicine, Farmington, CT; [5]University College London, London, United Kingdom.

Background: Spironolactone (SPIRO) is effective at reducing BP in patients (pts) with resistant hypertension (RHTN); however, its use in pts with CKD is often limited by hyperkalemia. In AMBER, patiromer (PAT) enabled more persistent use of SPIRO in pts with RHTN and eGFR 25 to ≤45 mL/min/1.73 m^2. We report results in prespecified subgroups with eGFR <30 and ≥30 mL/min/1.73 m^2.

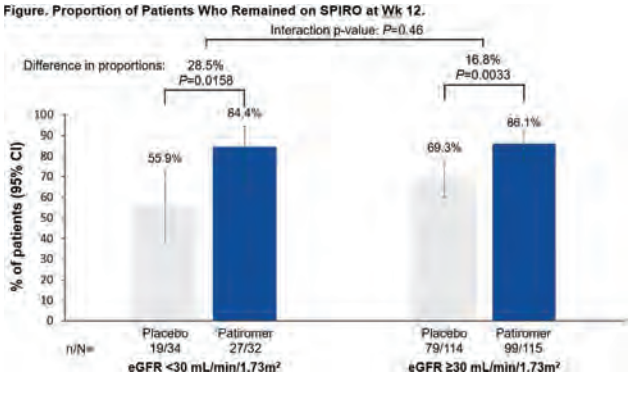
Methods: This was a randomized, double-blind, placebo (PBO)-controlled RCT in adults with eGFR 25-≤45 mL/min/1.73 m^2 and uncontrolled RHTN. Pts were assigned (1:1) to receive PBO or PAT, and SPIRO 25 mg QD, with dose titrations permitted after 1 wk (PAT) and 3 wk (SPIRO). The primary endpoint (between-group difference at wk 12 in the % of pts on SPIRO) was assessed in prespecified subgroups with eGFR <30 and ≥30 mL/min/1.73m^2.

Results: 295 pts were randomized, 66 (22.4%) and 229 (77.6%) with baseline (BL) eGFR <30 (median [Q1, Q3], 27 [25, 29]) and ≥30 (median [Q1, Q3], 38 [34, 42]) mL/min/1.73 m^2, respectively. BL mean (SD) automated office systolic BP (mmHg) was 143.7 (6.7) and 144.2 (6.8) and serum K^+ (mEq/L) was 4.78 (0.38) and 4.70 (0.36), respectively. Significantly more pts treated with PAT than with PBO remained on SPIRO at wk 12 in both subgroups (between treatment difference of 28.5% [*P*=0.0158] for pts with eGFR <30 mL/min/1.73 m^2 and 16.8% [*P*=0.0033] for pts with eGFR ≥30 mL/min/1.73 m^2) with *P*=0.46 for interaction between subgroups (**Figure**). Mean (SE) cumulative SPIRO dose was higher with PAT than PBO, by 732 (274) mg and 274 (140) mg in pts with eGFR <30 and eGFR ≥30 mL/min/1.73 m^2, respectively. Adverse events occurred in 56% (PBO) and 63% (PAT) with eGFR <30 and in 53% (PBO) and 54% (PAT) with eGFR ≥30. No pts had serum Mg <1.2 mg/dL; 1 PBO and 3 PAT pts (all with eGFR ≥30) had serum Mg 1.2 to <1.4 mg/dL.

Conclusions: PAT enabled more pts with advanced CKD and RHTN to continue treatment with SPIRO, regardless of whether eGFR is <30 or ≥30 mL/min/1.73 m^2.

Funding: Commercial Support - Funded by Relypsa, Inc., a Vifor Pharma Group Company

Figure. Proportion of Patients Who Remained on SPIRO at Wk 12.



TH-OR053

Glomerular Hyperfiltration Predicts Cardiovascular Outcomes in Apparently Healthy Individuals

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Background: Glomerular hyperfiltration (GHF) is associated with increased risk of cardiovascular (CV) diseases in high risk conditions, but its significance in low risk individuals is uncertain. The aim of this study was to determine the CV risk associated with GHF in apparently healthy individuals.

Methods: 9,515 apparently healthy individuals without hypertension, diabetes, CV disease, stages 3-5 CKD and statin/aspirin with available follow-up data (governmental database) were identified from a large population study. From these, patients with GHF (eGFR > 95th percentile after stratification for sex/age) were compared to controls (eGFR 25th to 75th percentiles). Cardiovascular events (CVE) included CV mortality, myocardial infarction, unstable angina, heart failure, stroke and transient ischemic attack. CVE risk was assessed using Cox proportional hazard model and fractional polynomial regression.

Results: Baseline characteristics of individuals with GHF [eGFR 102 (95% CI 107, 115) ml/min/1.73m^2] and normal filtration [eGFR 92 (87, 97)] are presented in Table 1. During a median follow-up of 70 months, 245 CVEs occurred. GHF was associated with an increased risk of CVE [HR 1.78 (1.19, 2.64), p=0.005; Figure 1]. When evaluated continuously, only the highest eGFR percentiles were associated with increased CV risk (Figure 2).

Conclusions: GHF is independently associated with increased CVE risk in apparently healthy individuals. Whether this association is causal or not remains to be determined.

Table 1: Baseline characteristics

Baseline characteristics	Normal filtration (n=4,761)	Hyperfiltration (n=473)	p-value
Age	51 (46-56)	50 (43-53)	<0.001
Male sex	43%	43%	0.97
Afro-American race	1%	10%	<0.001
Body mass index (kg/m^2)	26 ± 5	26 ± 5	0.65
Lean body mass (kg)	52 ± 11	51 ± 11	0.027
Smoking (active)	19%	26%	<0.001
Glucose (mmol/L)	5.4 ± 1.0	5.2 ± 1.0	0.003
LDL-cholesterol (mmol/L)	3.2 ± 0.8	3.1 ± 0.8	0.003
Systolic BP (mmHg)	118 ± 11	118 ± 11	0.64
Heart rate (bpm)	67 ± 10	69 ± 10	0.001

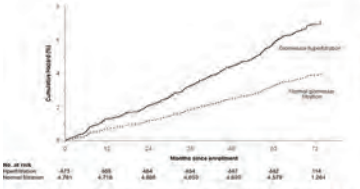


Figure 1: Cumulative incidence of CVE with a Cox proportional hazard model adjusted for age, sex, Afro-American race, active smoking, BMI, lean-body mass (bio-impedance), fasting glucose, LDL-c, total cholesterol, mean arterial pressure and heart rate.

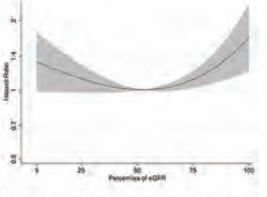


Figure 2: Fractional polynomial regression with HR of CVE occurrence for each 5 percentile increments of eGFR. Adjustments as described in Figure 1 legend.

TH-OR054

Acute Treatment Effects in Randomized Clinical Trials of CKD Progression

Lesley Inker, Hocine Tighiouart. Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration *Tufts Medical Center, Boston, MA.*

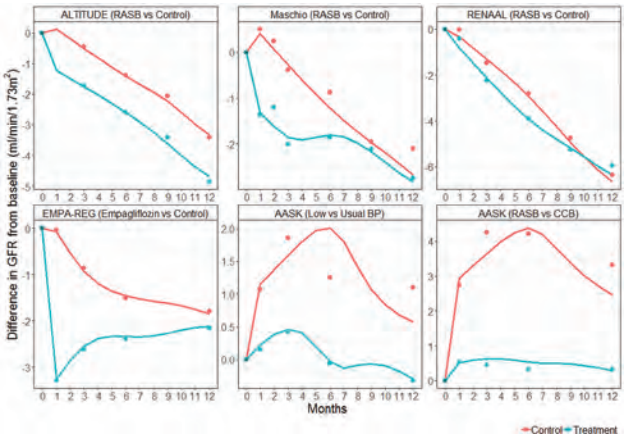
Background: Interventions in CKD trials often produce early short-term treatment effects on GFR slope (i.e. acute effect) that differ from its late long-term effects. The presence of acute effects complicates the design, interpretation and reduces statistical power of randomized clinical trials (RCT) with GFR slope as endpoint.

Methods: We computed the acute effect in past RCTs included in Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) using repeated measures models (N RCTs 57; N participants 60620). For the 30 studies with sufficient measurements prior to 18 months we truncated the follow-up time to 18 months to ensure that the long term trajectory did not overly influence the acute effect. We estimated GFR using the CKD-EPI 2009 creatinine equation. We included time since baseline, treatment, time by treatment interaction and baseline GFR as covariates and used an unstructured variance-covariance matrix to account for the correlated longitudinal measurements within each patient. We modeled time as a fixed effect using restricted cubic splines and then as a categorical variable with follow-up times fixed at each study specific scheduled visits.

Results: In the total set of CKD-EPI RCTs, the overall mean (SD) acute effect of 0.19 (1.27) mL/min/1.73 m^2 over 3 months but both negative and positive acute effects were observed with 95% confidence intervals ranging from -2.3 to 2.7 mL/min/1.73 m^2/3 months indicating large heterogeneity. The figure shows trajectories from baseline to 12 months for 6 example RCTs.

Conclusions: Acute effects are common but there is wide heterogeneity among RCTs. Understanding the timing, magnitude and nature of the acute effect of a specific intervention and population will inform optimal study design.

Funding: Private Foundation Support



Smoothed trajectories of mean GFR differences from baseline by treatment group for 6 example RCTs. Dots show the observed means at the study-specific follow-up visit times. RASB, renin-angiotensin system blocker; BP, blood pressure; CCB, calcium channel blocker

TH-OR055

Reduced Kidney Function Is Associated with a Greater Burden of Atrial Fibrillation: The KP-RHYTHM Study

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Background: Atrial fibrillation (AF) is the most potent risk factor for ischemic stroke. Previous studies have reported that reduced kidney function is associated with a higher risk of developing AF. Having a greater burden of AF (i.e., amount of time spent in AF is also an independent risk factor for stroke However, whether kidney function influences the burden of AF is unclear.

Methods: The Kaiser Permanente (KP) RHYTHM Study included all adult members of KP Northern and Southern California integrated healthcare delivery systems who underwent 14-day continuous, beat-to-beat ambulatory ECG monitoring using the ZIO® XT Patch between October 2011-October 2016. We identified patients who had known estimated glomerular filtration rate (eGFR) by CKD-EPI within the year before monitoring, who were not receiving renal replacement therapy, and who had AF detected during the monitoring period. Patient demographic characteristics and stroke risk factors were obtained from electronic health records. We examined the multivariable association of log-transformed AF burden (% analyzable wear time spent in AF) per 10 mL/min/1.73 m² decrease in eGFR.

Results: Among 1069 eligible adults with detected AF on continuous ambulatory monitoring, mean age was 69.1 years, 45% were women, and 25% were persons of color. Overall, median AF burden was 4% (IQR:1% to 13%). After adjustment for proteinuria, age, gender, race/ethnicity, heart failure, hypertension, diabetes mellitus, and prior stroke/transient ischemic attack, every 10 mL/min/1.73m² lower level of eGFR was independently associated with a 10% higher burden of AF (adjusted relative estimate 9.7%, 95% CI:1.1%-19.0%).

Conclusions: Among adults found to have AF on 14-day continuous ambulatory ECG monitoring, lower eGFR level was independently associated with a higher burden of AF. Reduced kidney function may contribute to excess risk of stroke through promoting both a higher incidence of developing AF as well as a greater burden of AF.

Funding: Commercial Support - iRhythm Technologies

TH-OR056

Diminished Efficacy of the Angiotensin Receptor Blocker Losartan During High Potassium Intake in CKD Patients

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Background: High potassium intake increases natriuresis and lowers blood pressure (BP). Whether these beneficial effects are also present in chronic kidney disease (CKD) patients and whether potassium intake affects BP and proteinuria-lowering efficacy of angiotensin receptor blockade (ARB) is unknown. We set out to address the effect of potassium intake on BP and proteinuria response to losartan in non-diabetic proteinuric CKD patients.

Methods: We performed a post-hoc analysis of a placebo-controlled interventional cross-over study in which 33 non-diabetic proteinuric patients (mean baseline proteinuria 3.8 g/d) were treated for 6 weeks with placebo, losartan 100mg, and losartan/hydrochlorothiazide (HCT) 100mg/25mg, respectively. Patients underwent the 3 interventions during both a habitual (~200 mmol/d) and low-sodium diet (<100 mmol/d), in randomized order. To analyze the effects potassium intake, we categorized patients based on median split of 24-hour urinary potassium excretion, reflecting potassium intake.

Results: Mean potassium intake was stable during all 6 treatment periods. Patients with high potassium intake (≥92 mmol/d) had similar BP reductions across all treatments as compared to low potassium intake (<92 mmol/d), whereas a lower proteinuria reduction (p=0.014) was observed for all treatments. Proteinuria reduction to losartan monotherapy and to losartan/HCT, respectively, was significantly lower during high potassium intake (20% vs 41%, p=0.011; and 48% vs 64%, p=0.036). These differences in antiproteinuric response abolished when adding a low sodium diet. In multiple regression analysis, potassium intake was a significant independent predictor of the antiproteinuric response to losartan monotherapy (-23%, 95%CI -37, -8%), but not to losartan combined with HCT.

Conclusions: In proteinuric CKD patients, the proteinuria, but not BP-lowering response to losartan was hampered during high potassium intake. Differences disappeared after low sodium diet, suggesting that intervention in sodium status outweighs the modulating effects of potassium intake on ARB efficacy.

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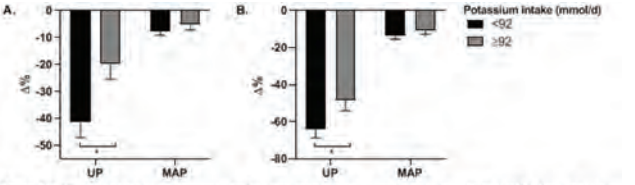

Figure 1 A. The antiproteinuric response to losartan monotherapy was higher in patients with a low potassium intake compared to patients with a high potassium intake (p=0.011). **B.** This difference became smaller after adding HCT (p=0.036). UP: proteinuria, MAP: mean arterial pressure. Values are mean±SEM. *p<0.05

TH-OR057

ACEi/ARB Discontinuation and Adverse Outcomes in CKD

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Background: Treatment with ACEi/ARB is standard of care for CKD with albuminuria as it can slow disease progression. However, ACEi/ARB treatment can increase risk of hyperkalemia, hypotension, and acute kidney injury, especially in the setting of intercurrent illnesses. We investigated the association of ACEi/ARB discontinuation with patient characteristics and outcomes among VA patients with non-dialysis dependent CKD.

Methods: Patients followed at the VA who had eGFR<60ml/min/1.73 for >90 days, 2005-13, were identified; those with CKD G5 or ESKD were excluded. Patients entered the cohort at time of incident ACEi/ARB use, 2005-13; discontinuation (based on pharmacy fill data) was treated as a time-varying risk factor. Different durations of discontinuation (<90,90-180, >180 days) were investigated, and death and incident dialysis were the outcomes. We used Cox regression, adjusting for demographic and clinical factors.

Results: We identified 238,615 people who met the inclusion criteria; 96.7% were male, and mean age was 71±10 years. 69,544 deaths and 6,100 dialysis initiations were observed. ACEi/ARB discontinuation was associated with more than doubling the risk of subsequent mortality, with a <90 day discontinuation having a hazard ratio for mortality (compared to no discontinuation) of 2.74 (95%CI 2.67-2.81) on adjusted analysis. Longer discontinuation intervals were also associated more than doubling of mortality risk (Table). ACEi/ARB discontinuation was also associated with more than two-fold increased risk for incident dialysis, with a <90 day discontinuation having a hazard ratio of 2.36 (95%CI 2.17-2.56) on adjusted analysis, and longer durations having similar risk.

Conclusions: ACEi/ARB discontinuation was associated with increased subsequent risk of death and incident dialysis in an elderly male VA cohort. Additional investigation, including causes of discontinuation and outcome circumstances, will elucidate relative contributions of ACEi/ARB discontinuation as a cause of the poor outcomes or a marker of worsening health.

Table. Associations of ACEi/ARB discontinuation with mortality and dialysis initiation, adjusted models (HR [95% CI])

ACEi/ARB discontinuation	Mortality	Dialysis initiation
No discontinuation	1 (ref)	1 (ref)
<90 days	2.74 (2.67-2.81)	2.36 (2.17-2.56)
90-180 days	2.62 (2.54-2.71)	2.90 (2.53-3.09)
>180 days	2.12 (2.08-2.16)	2.52 (2.37-2.68)

TH-OR058

Autophagy Protects Podocytes from Diabetes-Related Glomerular Endothelial Dysfunction

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Background: In diabetic nephropathy, glomerular endothelial dysfunction is a primary event leading to albuminuria, and impaired podocyte autophagy is recently focused as a factor associated with progression to massive albuminuria. However, an interaction between these two events is still unclear. This study was designed to examine a renoprotective role of autophagy in podocyte injury during the development of diabetes-related glomerular endothelial dysfunction.

Methods: We generated tamoxifen (TM)-inducible podocyte-specific *Atg5*-deficient (TM-PodoAtg5KO) mice by crossbreeding *Atg5*-floxed (Atg5$^{f/f}$) mice and TM-inducible *Nphs2*-Cre transgenic mice. Age-matched TM-injected Atg5$^{f/f}$ mice (TM-Atg5$^{f/f}$) were used as the control group. Glomerular endothelial dysfunction was induced by a high-fat diet (HFD) feeding, crossbreeding with eNOS knockout mice, or an intravenous injection of neuraminidase that can remove endothelial glycocalyx.

Results: In both TM-Atg5$^{f/f}$ and TM-PodoAtg5KO mice, HFD-feeding induced glomerular endothelial dysfunction, which was characterized by increased urinary nitric oxide excretion, collapsed endothelial fenestrae, and decreased endothelial glycocalyx. HFD-fed TM-Atg5$^{f/f}$ mice showed slight albuminuria and nearly normal podocyte morphology. In contrast, HFD-fed TM-PodoAtg5KO mice developed massive albuminuria accompanied by severe podocyte injury. The severe podocyte damage in HFD-fed TM-PodoAtg5KO mice was observed in the podocytes adjacent to damaged endothelial cells. Interestingly, podocyte-specific autophagy deficiency did not exacerbated eNOS-deficiency-induced albuminuria, whereas it markedly exacerbated neuraminidase-induced albuminuria along with sever podocyte injury. Finally, we found that ER stress was accelerated in the podocytes of TM-PodoAtg5KO mice stimulated with neuraminidase, and that a treatment with molecular chaperone, TUDCA, was able to improve neuraminidase-induced severe podocyte injury in the mice.

Conclusions: Podocyte autophagy protects podocytes from diabetes-related endothelial structural dysfunction. Insufficient autophagy leads to severe podocyte injury and subsequent massive albuminuria via activation of ER stress during the development of endothelial dysfunction in diabetic nephropathy.

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TH-OR059

Unanticipated Effect of C3a Receptor Antagonist in the Podocyte Injury of Diabetes

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Background: Podocyte damage is a crucial determinant for the development of diabetic nephropathy (DN) and is associated with mitochondrial dysregulation. Activation of the complement (C) system and C3a generation at glomerular level have been described in patients with DN. We previously demonstrated that C3a promoted podocyte dysfunction, although the intracellular mechanism is still ill-defined. Given the causal link between C activation and the derangement of mitochondrial homeostasis in different cellular systems, here we studied whether abnormal glomerular C activation could cause podocyte injury through its harmful effect on mitochondrial functions in DN.

Methods: Changes in podocyte phenotype and mitochondrial structural and functional integrity were investigated in BTBR *ob/ob* mice treated with vehicle or C3a receptor (C3aR) antagonist SB290157 between 9 and 14 weeks of age, and in cultured podocytes treated with C3a (1μM, 6h).

Results: BTBR *ob/ob* mice exhibited increased albuminuria over time, podocyte loss and glomerular damage accompanied by increased C3 and C3a staining and C3aR overexpression. Decreased glomerular nephrin and a-actinin4 levels, coupled with induction of integrin-linked kinase, were observed. Treating DN mice with C3aR antagonist enhanced podocyte density and preserved their phenotype, thus limiting albuminuria (SB290157: 120±21 vs vehicle: 303±49 μg/day, $p<0.01$) and glomerular injury. Ultrastructural and functional mitochondrial changes in podocytes were associated with increased protein oxidation, and were normalized by SB290157. In cultured podocytes exposed to C3a, mitochondrial fragmentation and altered membrane permeability, associated with downregulation of the antioxidant SOD2, proved that C3a induced mitochondrial dysfunction directly. C3a also altered podocyte energy production without affecting the glycolytic pathway. Notably, C3a-induced podocyte motility was inhibited by SS-31, a peptide with mitochondrial protective effects, suggesting that disturbances in mitochondrial function in response to C3a affect podocyte adhesive properties.

Conclusions: These data indicate that C3a blockade is a novel therapeutic strategy in DN for preserving podocyte integrity through the maintenance of mitochondrial functions.

Funding: Private Foundation Support

TH-OR060

Gut Microbiome-Derived Phenyl Sulfate Contributes to Albuminuria in Diabetic Kidney Disease (Part 1)

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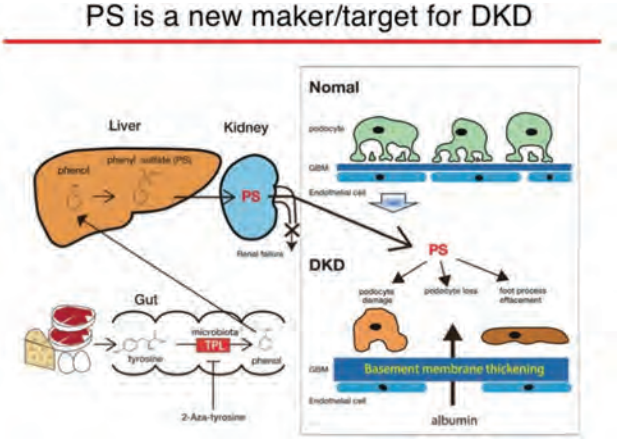
Background: Diabetic kidney disease (DKD) is a major cause of renal failure in urgent of breakthrough in disease management. Type 2 diabetes causes significant changes in an array of plasma metabolites, and in humans, SLCO4C1 is the only transporter contributes to transport into urine. We generated transgenic (Tg) rats overexpressing SLCO4C1 in the proximal tubule, a typical human renal excretion model. Using this model, we characterize metabolites increased in diabetic wild type, but reduced in diabetic Tg rats.

Methods: Diabetes was induced by STZ. Untargeted metabolomics was performed by UHPLC-QTOF/MS. Phenyl sulfate (PS) and other uremic toxins were measured by LC/MS/MS. Mitochondrial function was analysis by Flux analyzer. The fecal 16S rRNA were analyzed by MiSeq.

Results: PS was increase with the progression of diabetes and was decreased in Tg rats with limited proteinuria. In diabetic mouse models, PS administration induced albuminuria and podocyte damage due to mitochondrial damage. By DKD cohort analysis, the PS level is correlated with basal and 2-year progression of albuminuria. Phenol is synthesized from dietary tyrosine by gut bacterial-specific tyrosine phenol-lyase (TPL) and absorbed phenol is metabolized into PS in the liver. Administration of TPL inhibitor reduced not only circulating PS level but also albuminuria in diabetic mice. Furthermore, TPL inhibitor ameliorated renal dysfunction in adenine-induced renal failure model. Because TPL inhibitor did not alter the major composition, the non-lethal inhibition of microbial-specific enzymes has a therapeutic advantage for the development of drug resistance.

Conclusions: PS is a modifiable cause and a target for the treatment of DKD. Chemical reduction of TPL should represent another aspect for developing drugs preventing DKD (Nat. Commun. 10: 1835, 2019).



TH-OR061

PLK1 Inhibitor Can Reverse the Diabetic Nephropathy in OVE26 Type 1 Diabetic Mice

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Background: Diabetic kidney disease (DKD) remains the leading cause of ESRD. However, treatment options are very limited. Since DKD is caused by multiple factors and its pathogenesis is complicated, it would be important to apply the systems biology to analyze the major gene signatures which are responsible for DKD and therefore, we could identify drugs which could reverse these gene signatures as potential treatment of DKD.

Methods: We analyzed all public transcriptomic dataset L1000CDS2 as a LINCS L1000 characteristic signature search engine has been applied widely in repurposing drugs for treatment of various diseases. Using this, we analyzed all public transcriptomic datasets related to DKD and GEO2Enrichr analysis to identify potential drugs, which reverse the gene signatures in DKD. We validated the findings by in vitro and in vivo studies.

Results: Gene expression datasets from 24 studies that compared DKD to normal kidney tissue were identified from GEO and Nephroseq. Differential expression was analyzed with GEO2Enrichr. We further performed meta-analysis of 27 DKD signatures from 24 studies using GEN3VA. Then L1000CDS2 was employed with each signature to prioritize matching above signatures created from over 20,000 drugs treatments of multiple human cell lines. We selected BI2536 from the top 5 most consistent drugs across the L1000CDS2 results, also considering their novelty and applications in other fields. BI2536 is a PLK1 inhibitor which

can lead to cell cycle arrest and has been studied broadly in tumor treatments. We found PLK1 expression was increased in mouse glomeruli and localized mostly in mesangial cells. In vivo, we found that treatment of BI2536 attenuated albuminuria and renal histological changes, and expression of renal fibrosis and inflammation markers. We further compared the gene and pathways regulated in DKD but reversed by BI2536, which revealed Smad3 and NF-kB as the major pathways affected by BI2536. In vitro, we confirmed that BI2536 inhibited Smad3 and NF-kB phosphorylation in primary mesangial cells probably through direct interaction between PLK1 and these transcription factors.

Conclusions: Our data indicate that systems analysis could help to identify potential new drugs for treatment of DKD. BI2536 could be a potential drug which could reverse the gene signatures in DKD and the renal protective effect of BI2635 is validated in vivo animal model of DKD.

Funding: NIDDK Support

TH-OR062

High Glucose and High Osmolarity Modulate Function of FRMD3/Protein 4.1O: A Candidate Gene of Diabetic Nephropathy

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Background: FRMD3 has been proposed as a candidate gene for susceptibility of diabetic nephropathy (DN) in type 1 diabetes. FRMD3 encodes for protein 4.1O, which is a member of the 4.1 protein family. The molecular function of FRMD3/protein 4.1O is unknown so far. Albuminuria is the earliest sign of DN and results from a defect in the glomerular filtration barrier. Linkage of the slit diaphragm protein nephrin to the actin cytoskeleton via adapter proteins are essential for the integrity of the glomerular slit diaphragm.

Methods: RNA was isolated from human podocytes and qPCR for FRMD3 was performed. Nephrin and protein 4.1O were stained in mouse glomeruli. In Cos7 cells, protein 4.1O and actin were visualized via immunofluorescence. Zebrafish larvae were treated with morpholinos against the orthologue of FRMD3 in zebrafish. Injection of fluorescently labeled FITC-dextran was monitored via eye fluorescence. A reduction of fluorescence was an indirect sign of glomerular tracer loss. Cells expressing protein 4.1O, its truncations and nephrin were subjected to cell lysis. Co-immunoprecipitation and Western blot analysis were performed. Kidney samples from patients with T1DN or T2DN were stained for protein 4.1O. Cells were treated with different glucose concentrations and mannitol for osmolarity control.

Results: Protein 4.1O is expressed in human podocytes. Protein 4.1O interacts with nephrin and actin*in vitro* and*in vivo*. Injection of *frmd3* paralogue morpholinos in zebrafish larvae leads to zebrafish yolk sac edema, slit diaphragm disruption and increase in glomerular permeability. The increase in glomerular permeability can be rescued by reconstitution of protein 4.1O AA 506-553, the nephrin binding domain. Protein 4.1O expression is increased in human T1 and T2DN. High glucose levels increase protein 4.1O expression while high osmolarity increases nephrin protein 4.1O interaction and protein 4.1O threonine phosphorylation.

Conclusions: Protein 4.1O is a novel linker of nephrin to the actin cytoskeleton and essential for the glomerular filtration barrier. High glucose increases expression of protein 4.1O while high osmolarity leads to posttranslational modifications on protein 4.1O mediating an increased interaction with nephrin.

TH-OR063

Short-Term Pulse Treatment with Nicotinamide Mononucleotide in Diabetic Nephropathy: Therapeutic Application of Metabolic Legacy Effect

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Background: We previously demonstrated that the derangement of nicotinamide adenine dinucleotide (**NAD$^+$**) metabolism and the inactivation of **Sirt1**, an NAD$^+$-dependent deacetylation enzyme, initiated diabetic nephropathy (**DN**) (Nat Med, 2013). Sirt1 is activated by NAD$^+$ precursor, nicotinamide mononucleotide (**NMN**). We tested short-term pulse treatment with NMN against DN.

Methods: We divided 8-week-old db/db and db/m mice into five groups: db/m + saline (**db/m**); db/db + saline (**db/db**); db/db + NMN 100 mg/kg (**NMN100**); db/db + NMN 300 mg/kg (**NMN300**); and db/db + NMN 500 mg/kg (**NMN500**). Short-term pulse treatment with NMN was performed via i.p. injection for two weeks. We terminated the treatment at 10 weeks of age and evaluated remote effects of NMN therapy at 10, 24, and 30 weeks of age. We also evaluated tissue NAD$^+$ metabolite levels and the expressions of some enzymes of NAD$^+$ metabolism, including **Nampt** that convert nicotinamide (NAM) into NMN and **Nmnat1** that converts NMN into NAD$^+$.

Results: At 24 weeks of age, db/db exhibited higher levels of HbA1c and albuminuria, as well as more foot process effacement and reduced expression of Sirt1 and Synaptopodin in renal histology as compared to those in the db/m. Although the HbA1c levels in the NMN500 and db/db were not different, NMN treatment resulted in lower albuminuria at even 14 and 20 weeks after the termination of therapy in a dose-dependent manner. NMN treatment ameliorated foot process effacement and preserved Sirt1 and Synaptopodin expressions. Renal NAD$^+$ levels reduced with age in both db/m and db/db. In contrast, the NMN500 maintained NAD$^+$ levels at 24 weeks of age. Nampt expression in the NMN500 was higher than those in the db/m and db/db. Nmnat1 expression was lower in the db/db than those in the db/m and NMN500, although Nmnat1 expression between the db/m and NMN500 was not different. These results indicated that the NMN treatment maintained renal NAD$^+$ concentration by increasing Nampt expression and maintaining Nmnat1 expression.

Conclusions: Short-term pulse treatment with NMN at the early phase of DN had long-lasting renoprotective effects via restoration of NAD$^+$ and preservation of Sirt1, Nampt, and Nmnat1 expressions independently of glycemic control. This intervention suggested the introduction of metabolic legacy effects during the course of DN.

TH-OR064

DcR2 Mediates Senescent Phenotype of Tubular Cell by Interacting with PRDX1: A Novel Mechanism of Renal Fibrosis in Diabetic Nephropathy

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Background: Premature senescence of renal tubular epithelial cell (RTEC), which is involved in renal fibrosis, is a key event in the progression of DN. However, the underlying mechanism remains unclear. Our study investigated the role of Decoy receptor DcR2 in renal fibrosis and explored the mechanism of DcR2 mediated the senescent phenotype of RTEC.

Methods: 215 DN patients which diagnosed by renal biopsy were enrolled. Renal DcR2 and senescent markers, P16 and SA-β-gal were detected with confocal immunostaining. The degree of renal fibrosis and cell senescence were evaluated after regulation of DcR2 expression in vivo and vitro. Co-IP combining with LC-MS/MS were screened the DcR2-interaction proteins in renal tissue and high glucose (HG) induced-proximal tubular epithelial cells (PTECs). The interaction of DcR2 and PRDX1 was detected by Co-IP and pull down assay. Peroxidase activity of PRDX1 was assessed by the kits of ROS and specific 2-cys peroxidase activity. The level of PRDX1 phosphorylation was detected through WB.

Results: DcR2 was high specifically expressed in RTEC and associated with renal fibrosis. Confocal analysis indicated DcR2 co-expressed with senescent markers in the development of DN. Knockdown of DcR2 effectively decreased renal fibrosis and alleviated renal function in streptozotocin (STZ)-induced DN mice. Furthermore, DcR2 knockdown significantly inhibited RTEC senescence and promoted the secretion of senescence-associated secretory phenotype (SASP), such as IL-1β, MMP-2 and TGF-β1. However, DcR2 overexpression showed the opposite effects. In vivo and vitro studies revealed that DcR2 interacts with peroxiredoxin 1 (PRDX1) using quantitative proteomics, which have peroxidase and antioxidant activity in cytoplasm. Following study indicated PRDX1 was co-expressed with senescent phenotype, and PRDX1 knockdown accelerated whereas overexpression inhibited RTEC senescent phenotype. The interaction of DcR2-PRDX1 mediated RTEC senescent phenotype. Moreover, DcR2 inhibited the peroxidase activity of PRDX1 resulting in oxidative stress through promoting PRDX1 phosphorylation.

Conclusions: DcR2 interacts with PRDX1 and aggravates renal fibrosis by mediating RTEC senescent phenotype, suggesting DcR2 as a potential therapeutic target for the amelioration of DN progression.

Funding: Government Support - Non-U.S.

TH-OR065

Genetic Deletion of MIOX Ameliorates Obesity-Associated Tubulointerstitial Injury via Modulating O-GlcNAcylation of Sterol Regulatory Element Binding Protein (SREBP)

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Background: Myo-inositol oxygenase (MIOX), a tubular enzyme, is involved in the pathogenesis of various forms of tubulo-interstitial injury

Methods: We assessed if genetic ablation of MIOX alone or in the background of ob*/ob* ameliorates obesity-associated tubulo-interstitial injury. Four weeks old Wild type (WT), MIOX overexpressing (MIOX-TG), and MIOX knockout (MIOX-KO) mice were fed HFD for four months. Also, double knockout (*MIOX$^{-/-}$/ob/ob*) mice were evaluated at five months of age.

Results: Increased proteinuria, serum creatinine and urea was observed in HFD-fed WT and MIOX-TG, and *ob/ob* mice, suggestive of renal injury. These pathophysiologic parameters were normalized in HFD-treated MIOX-KO and *MIOX$^{-/-}$/ob/ob* mice. The expression and activity of MIOX increased in the renal tubules of HFD-fed WT, MIOX-TG mice and *ob/ob* mice, which were associated with decreased levels of myo-inositol (MI); whereas MI levels remained relatively high in HFD-fed MIOX-KO and *MIOX$^{-/-}$/ob/ob* mice. MIOX overexpression was accompanied with accentuated ROS generation, DNA damage, lipid and protein peroxidation. These changes were minimally observed in HFD-fed MIOX-KO and *MIOX$^{-/-}$/ob/ob* mice. In addition, MIOX overexpression was accompanied with increased post-translational modification (O-GlcNAcylation) of cellular proteins via upregulating the expression of *O-GlcNAC* transferase in renal compartments in vivo. Likewise, such increase of modification of cellular proteins was observed in proximal tubular (HK-2 cells) treated with palmitate-BSA in vitro. Perturbation in cellular redox decreased the expression of various metabolic sensors, including p-AMPK, SIRT1, SIRT3, YY-1 and PGC1α, in HFD-treated MIOX-TG mice. These parameters were partially restored in HFD-fed MIOX-KO mice and *MIOX$^{-/-}$/ob/ob* mice. Interestingly, SREBP was heavily glycosylated in HK-2 cells treated with palmitate-BSA. The SREBP exhibited a strong binding to PAI-1 promoter in HFD-fed MIOX-TG mice, leading to an

increased synthesis of ECM. These aberrant metabolic and fibrogenic perturbations were normalized with MIOX gene disruption

Conclusions: In conclusion, these findings suggest that ablation of MIOX shields the kidney against obesity-induced tubulo-interstitial damage

Funding: NIDDK Support

TH-OR066

Murine Diabetic Nephropathy at Single Cell Resolution

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Background: Diabetic nephropathy (DN) is the most common cause of ESRD, but the transcriptional changes driving disease progression at the single cell level remain undefined. We hypothesized that single nucleus RNA-seq could provide insight into the cellular mechanisms of diabetic nephropathy.

Methods: We collected urine and kidney samples from control(n=2) and *db/db*(n=4) female mice at 17 weeks. We generated a total of 70,437 single nucleus transcriptomes and performed a comprehensive bioinformatics analysis.

Results: *db/db* mice had 255±35 μg/mg urine Alb:creatinine ratio compared to 24±6 in control. On average we detected 2,940 unique genes/nucleus. By unbiased clustering, we could identify 18 major cell types representing all major cell types, including macula densa, with differential expression of hundreds of genes across all clusters. Diabetic kidney had higher leukocyte infiltration including T cells, dendritic cells and macrophages. Diabetic macrophages upregulated the receptor Plxdc2, whose ligand PEDF ameliorates DN when administered exogenously. We generated a detailed diabetic glomerular intercellular communication map between podocytes, glomerular endothelium, mesangium and Cdh6+ parietal epithelia. This revealed podocyte – parietal epithelial cell signaling via b-catenin suppressive Igfbp4-Lrp6 signaling among others. We identified evidence for compensatory gene expression to combat podocyte damage, including downregulation of protein kinase C epsilon and upregulation of type 1 adenylate cyclase, proteins known to mediate susceptibility to proteinuria. Other upregulated podocyte genes included angiogenic EphA6 and Shroom3, a GWAS hit for CKD. Unexpectedly, diabetic stroma cells showed the largest gene expression changes including genes related to integrin linked kinase, cell adhesion and calcium signaling.

Conclusions: This is the first comprehensive single nucleus transcriptional atlas of a mouse model of DN. We demonstrate the utility of this approach by revealing (1) activated macrophage recruitment, (2) detailed diabetic glomerulus intercellular communication, (3) podocyte-specific expression of proteinuria susceptibility genes and (4) stromal cell activation.

Funding: Commercial Support - Janssen Pharmaceuticals

TH-OR067

Tankyrase Inhibition Upregulates Mitochondrial Master Regulator PGC-1α in the Kidney of db/db Mice

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Background: Mitochondrial oxidative stress contributes to the cellular damage occurring in diabetic conditions. Peroxisome proliferator-activated receptor γ (PPARγ) coactivator 1α (PGC-1α) co-activates transcription factors that boost mitochondrial biogenesis and oxidative metabolism and interestingly, PGC-1α is downregulated in the kidney in diabetes. Tankyrase 1 and 2 (TNKS1 and TNKS2) are closely related homologs belonging to the poly-ADP-ribose-polymerase (PARP) family of proteins. TNKSs regulate their binding partners by post-translational modification (PARylation), typically increasing protein degradation. The aim of this study was to investigate whether pharmacological inhibition of TNKSs in *db/db* mice protects against kidney injury by regulating PGC-1α.

Methods: We treated 6 weeks old obese and diabetic *db/db* and non-diabetic *db/+* controls with the TNKS1/TNKS2-specific inhibitor G007-LK with 14 mg/kg/day dosing for 15 weeks and investigated the effect on systemic and kidney parameters.

Results: We found that TNKS inhibition reduces body weight gain and fat mass, and upregulates genes associated with β-oxidation in muscle in *db/db* mice. In cultured C2C12 myocytes TNKS inhibition stimulated fatty acid oxidation and impoved mitochondrial function. TNKS inhibitor treatment reduced glomerular area in the *db/db* mice albeit the albuminuria was not alleviated. Proximity ligation assay indicated that PGC-1α and TNKSs form a complex in the kidney cortex and that PGC-1α PARylation is decreased upon TNKS inhibition in renal tubules. This apparently increased the stability of PGC-1α leading to its upregulation. Additionally, immunoblotting of mitochondrial respiratory chain markers indicated that TNKS inhibition upregulates complex V ATP synthase subunit alpha (ATP5A) in *db/db* kidney cortices. Electron microscopy analysis of proximal tubule cells revealed that TNKS inhibitor treatment upregulates crista density of mitochondria. These data indicate that TNKS inhibition increases mitochondrial respiration rate.

Conclusions: We found that TNKS inhibition increases PGC-1α expression and improves oxidative metabolism. Along with existing clinical approaches, enhancing mitochondrial function by TNKS inhibition could offer an additional strategy to improve renal structural and functional parameters in diabetes.

TH-OR068

Electrocardiographic Manifestations of Acute vs. Chronic Hyperkalemia

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Background: Hyperkalemia from kidney failure may cause life-threatening arrhythmias. Patients with end-stage renal disease (ESRD) have been thought to better tolerate high potassium levels than those with acute hyperkalemia. Thus, we postulated that patients with chronic hyperkalemia from ESRD have fewer electrocardiography (ECG) changes and less arrhythmias than patients with acute hyperkalemia from acute kidney injury. This study aims to determine the incidence of ECG changes in all patients presenting with hyperkalemia, and tests for differences in the incidence of hyperkalemic ECG changes between chronic and acute hyperkalemic groups.

Methods: We reviewed 256 adult admissions to William Beaumont Hospital Royal Oak Emergency Center with primary or secondary diagnoses of hyperkalemia in patients with chronic hyperkalemia from ESRD, and patients with acute hyperkalemia without ESRD. Initial ECGs were assessed for hyperkalemic changes by a single blinded cardiologist. The overall incidence of ECG changes was measured, and differences between the two groups were assessed using unpaired t-tests, chi-square tests, and multivariate analysis with logistic regression.

Results: ECG changes attributed to hyperkalemia were seen in 32% of encounters. There was no difference in the incidence of ECG changes between chronic (ESRD) and acutely (non-ESRD) hyperkalemic patients. However, with univariate analysis, increased patient age (69.9 vs 61.7 years, p= 0.0003), increased serum potassium (7.05 vs 6.8, p= 0.0424), and history of ischemic heart disease (p= 0.03) increased the risk of ECG changes. Multivariate analysis additionally demonstrated that higher endogenous serum calcium levels were independently associated with less T-wave peaking (Odds ratio 0.68, p= 0.0235).

Conclusions: This study demonstrated no difference in ECG changes between acute and chronic hyperkalemic groups, thus did not support the hypothesis that clinical arrhythmias are less prevalent with chronic hyperkalemia. As expected, increasing age, increasing potassium levels, and prior ischemic heart disease predisposed patients to ECG changes. Although pharmacologic calcium is known to protect against hyperkalemic arrhythmias, this study is unique in finding less T-wave peaking with higher endogenous serum calcium levels, implying that higher nonpharmacologic calcium serum levels may be protective against arrhythmias.

TH-OR069

ECG12Net: A Deep Learning Algorithm Capable of Suprahuman Detection of Hypokalemia and Hyperkalemia by Electrocardiography

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Background: Detection of dyskalemias (hypo- and hyperkalemia), important causes of sudden cardiac death, currently depends on laboratory tests. Since cardiac tissue is very sensitive to dyskalemias, electrocardiography (ECG) may be able to uncover clinically important dyskalemias before laboratory results. Our study aimed to develop a deep learning model, ECG12Net, to detect dyskalemias based on ECG presentation and to evaluate the logic and performance of this model.

Methods: Between May 2011 and December 2016, 66,321 ECG records with corresponding serum potassium (K^+) concentrations were obtained from 40,180 patients admitted to the emergency department. ECG12Net is an 82-layer convolutional neural network, which estimates serum K^+ concentration. Six clinicians (three emergency physicians and three cardiologists) participated a human-machine competition. We used sensitivity and specificity as evaluation measures to compare the performance of ECG12Net with these physicians.

Results: In a human-machine competition including 300 ECGs of different serum K^+ concentrations, the area under curve in detecting hypo- and hyperkalemia by ECG12Net was 0.926 and 0.958, respectively, which was significantly better than that of our best clinicians. Moreover, the sensitivities and specificities of detecting hypokalemia and hyperkalemia were 96.7% and 83.3%, and 93.3% and 97.8%, respectively. In the test set including 13,222 ECGs, ECG12Net had the same performance with sensitivities for severe hypokalemia/hyperkalemia achieving 95.6% and 84.5%, respectively with the mean absolute error of 0.531. The specificities of detecting hypokalemia and hyperkalemia were 81.6% and 96.0%, respectively.

Conclusions: A deep learning model based on 12-lead ECG may help physicians to promptly recognize severe dyskalemias and thereby reduce cardiac events.

TH-OR070

Is Tissue Sodium Storage Driving Systemic Inflammation in CKD? A Sodium Magnetic Resonance Imaging Study

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Background: Tissue sodium accumulation is intimately related to immune system function, and has been shown to occur in CKD patients due to impaired sodium elimination. However, the systemic effects of sodium accumulation, such as malnutrition

and inflammation, have not been explored in man. The aim of this study was to investigate the associations of tissue sodium accumulation in a sample of healthy controls and CKD patients using noninvasive 23-sodium (^{23}Na) magnetic resonance imaging (MRI).

Methods: Axial MR images of the lower leg were acquired in 10 controls and 35 CKD patients (eGFR 10-58 ml/min/1.73m^2) on a 3T MRI. Proton images for anatomical reference and ^{23}Na images for calculating mean tissue sodium concentration were acquired. Regions of interest included skin, pretibial tissue, bone, soleus, and gastrocnemius muscles (fig 1). Pearson correlation analysis between sodium concentration in different tissues and standard serum biomarkers was performed.

Results: Sodium concentration in all storage compartments was elevated in CKD patients relative to controls (data not shown), and significantly associated with serum albumin as a marker of malnutrition/inflammation complex (fig 2).

Conclusions: The negative association between serum albumin and tissue sodium concentration suggests that sodium accumulation may be a relevant factor driving systemic malnutrition/inflammation complex in the CKD population.

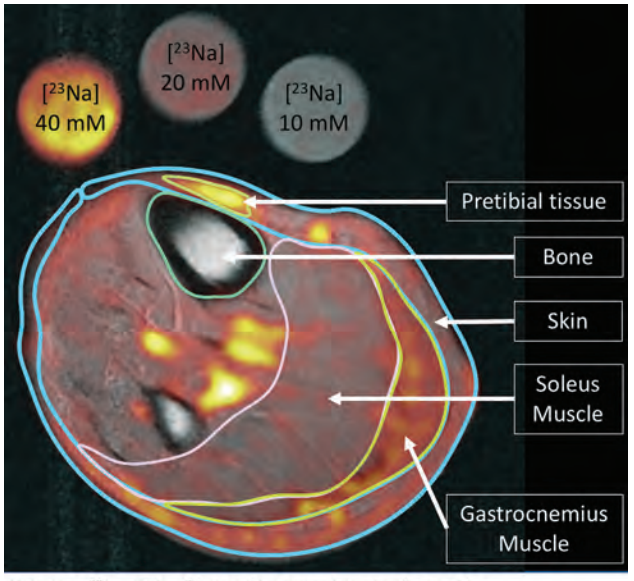

Figure 1. ^{23}Na MRI of lower leg superimposed over the corresponding anatomical proton MR image. The different tissues are represented by colored sections.

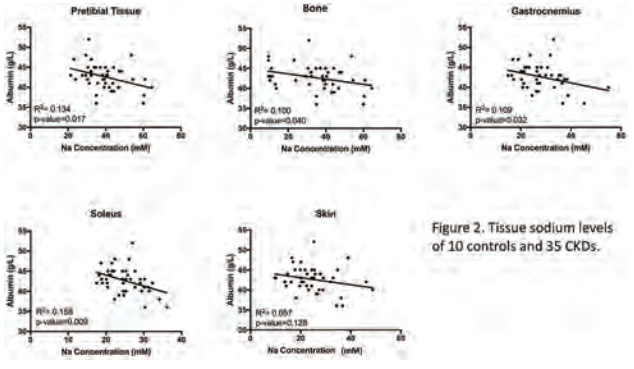

Figure 2. Tissue sodium levels of 10 controls and 35 CKDs.

TH-OR071

Renoprotection by Long-Term Low-Dose Tolvaptan for Congestive Heart Failure Is Pronounced in Hyponatremia

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Background: Reportedly, tolvaptan (TLV), a selective vasopressin V2-receptor antagonist, did not lead to 1-year renoprotection in congestive heart failure (CHF), when its dose was set to be 30 mg/day. We aimed to examine the effects of its lower-dose therapy on long-term renal outcome in CHF.

Methods: In this retrospective cohort study, we enrolled hospitalized patients with acute decompensated heart failure (ADHF) in an educational hospital. TLV users were defined as patients receiving flexible doses of TLV for at least consecutive 180 days or those who continued TLV therapy until death, renal replacement therapy, implantation of a ventricular assist device, or heart transplantation, even if duration of the therapy was less than 180 days. We compared estimated glomerular filtration rate (eGFR) trajectories between TLV users and never-users, using multivariable mixed effects models with time-dependent eGFR as a dependent variable. We explored effect modification by baseline serum sodium levels for the relationship between TLV therapy and annualized eGFR slope, using a multivariable fractional polynomial interaction algorithm.

Results: Of total 584 patients, 78 TLV users were found. The median TLV dose, baseline B-type natriuretic peptide (BNP), and eGFR were 7.5 mg/day, 243 pg/mL, and 54 mL/min/1.73m^2, respectively. TLV users had higher eGFR trajectories than never-users (P <0.01) during a median follow-up period of 66 weeks (Figure 1). Additional adjustment for time-dependent BNP levels, ADHF hospitalization, and the number of loop diuretics' dose reductions extinguished the difference in eGFR. In hyponatremic patients, renoprotection by TLV was pronounced in terms of eGFR slope ($p_{interaction}$ =0.02) (Figure 2). This effect modification was extinguished when the analysis was restricted to patients without subsequent cardiac events or those receiving a stable dose of loop diuretics.

Conclusions: Long-term therapy of low-dose TLV is renoprotective in patients with CHF, in particular, hyponatremic patients, possibly by dose sparing in loop diuretics and improvement of CHF.

Figure 1

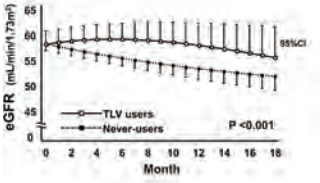
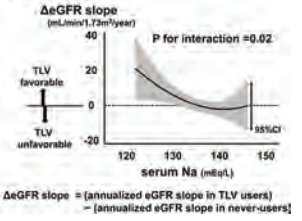


Figure 2



TH-OR072

Impact of Fluid Status, Serum Sodium, and Their Interaction on Survival: A Study in an Interactional Hemodialysis Patient Cohort

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Background: While hyponatremia and fluid overload (FO) are associated with mortality in hemodialysis (HD) patients (pts), little is known about their interaction. We aimed to investigate whether the relation between serum sodium (SNa) and mortality differs in HD pts with different fluid status (FS) assessed by whole-body bioimpedance spectroscopy.

Methods: We included all incident in-center adult HD pts treated 01/2010 to 12/2018 in Fresenius Medical Care clinics in 18 European countries and with ≥1 pre-HD SNa and body composition measurements within the first 3 months on HD. We excluded pts with ≥1 SNa value outside 125 to 150 mmol/L. Baseline was defined as the first year on HD, follow-up comprised years 2 and 3. We averaged laboratory and clinical parameters during baseline. A smoothing spline analysis of variance Cox proportional hazard model was applied to explore the joint effects of SNa and FS on mortality (adjusted for age, gender, ultrafiltration rate(UFR), diabetes(DM), and CHF).

Results: Out of the 5938 pts, 4407(74%) were normovolemic, and 1531(26%) had FO. Compared with pts with normovolemic status, FO pts had lower SNa levels, higher Na gradient, higher UFR and DM prevalence (Table1). For normovolemic pts, higher SNa levels (≥138 mmol/L) were associated with better survival. Mortality risk was highest for pts with FO, independent of SNa (Figure1).

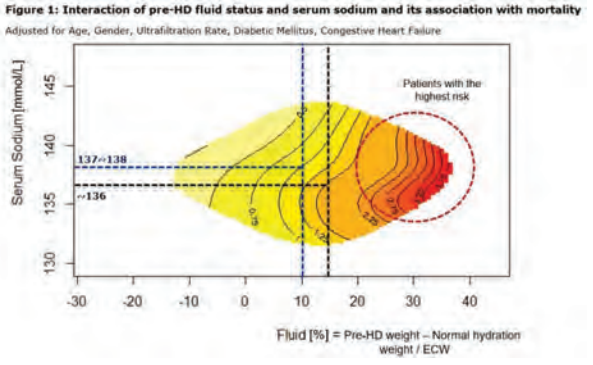
Conclusions: The relation between SNa and mortality is dependent on pre-HD FS. Whereas low SNa appears to be disadvantageous in normovolemia and FO pts, the relative effect of FO on outcome appears to be stronger than the effect of low SNa per se. In normovolemic pts the relation between SNa and outcome should be interpreted in the context of FS and not as an isolated risk marker.

Table 1. Patients with normal hydrated and over hydrated status

	Normovolemic	Fluid Overloaded	P-value
Number of patients	N = 4,407	N = 1,531	
Pre-HD serum sodium [mmol/L]	138.3 (136.8, 139.8) [a]	137.6 (136.1, 139.2) [a]	< 0.001
Pre-HD fluid [%]	7.5 (3.7, 10.7) [a]	17.9 (15.9, 21.3) [a]	< 0.001
Sodium gradient [mEq/L]	0.57 (3.1) [b]	1.1 (3.2)	< 0.001
Age [years]	61.0 (49.0, 71.0) [a]	61.0 (48.0, 70.0) [a]	0.004
Male [%]	63.0	57.0	< 0.001
Diabetic mellitus [%]	27.0	43.0	< 0.001
Congestive heart failure [%]	23.0	26.0	0.02
Ultrafiltration [ml/hour/kg]	2.5 (2.0, 3.0) [a]	2.8 (2.2, 3.4) [a]	< 0.001

*Fluid Overloaded defined as: >15% for Male, > 13% for Female.
[a] Presented as median (interquartile range); [b] presented as mean (standard deviation).

Figure 1: Interaction of pre-HD fluid status and serum sodium and its association with mortality



TH-OR073

Increased Short-Term and Long-Term Mortality in Community- and Hospital-Acquired Hypernatremia and in Patients with Delayed Sodium Correction

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Background: This study examined short- and long-term mortality (i) in a large cohort of general hospitalized adults with community- and hospital-acquired hypernatremia and (ii) in hypernatremic patients with and without serum [Na+] correction within three days of hospital stay.

Methods: Adult patients admitted to Mayo Clinic Rochester in a three-year (2011-2013) period were examined. Patients were categorized into 3 groups based on serum [Na^+] at admission and during hospitalization; 1) normal serum [Na^+], 2) community-acquired hypernatremia, and 3) hospital-acquired hypernatremia. Normal serum [Na^+] was defined as serum [Na^+] at admission and all during hospitalization within 138-142 mEq/L. Community-acquired hypernatremia was defined as serum [Na^+] at admission ≥ 143 mEq/L, whereas hospital-acquired hypernatremia was defined as serum [Na^+] at admission 138-142 mEq/L but any serum [Na^+] during hospitalization ≥ 143 mEq/L. Outcomes included hospital and 1-year mortality

Results: Of the total 25,781 patients, 44.7% (n=11,531) were normonatremic, 20.3% (n=5,229) were community-acquired hypernatremia and 35.0% were hospital acquired hypernatremia. In fully adjusted models, ORs (95% CIs) for hospital mortality and HRs (95% CIs) for one-year mortality were 4.91 (3.47-6.94) and 2.25 (2.01-2.53) for community-acquired and 4.11 (2.94-5.73) and 2.35 (2.12-2.60) for hospital-acquired hypernatremia. Hospital-acquired hypernatremia showed a higher hospital, but not one-year, mortality than community-acquired hypernatremia. Among patients with community-acquired hypernatremia, 36.1% (n=1,893) remained hypernatremic by hospital day three ([Na+] 145±3 mEq/L). Fully adjusted hospital- and one-year mortality were significantly increased in patients without [Na+] correction, 3.01 (2.01-4.49), 1.51 (1.26-1.81), respectively, compared to those with [Na+] correction.

Conclusions: Hypernatremia, regardless of acquisition origin, is associated with elevated short-term and long-term mortality. Hospital-acquired hypernatremia was more common and had a higher short-term mortality than community-acquired hypernatremia. Failure to correct hypernatremia by hospital day three is associated with increased morbidity and mortality.

TH-OR074

The Potential Utility of Urine Estimated Ammonium-to-Creatinine Ratio in Patients with CKD

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Background: Renal ammonium (NH_4^+) excretion plays a critical role in the elimination of acid. Recent studies have reported that the impairment in urinary NH_4^+ excretion is an important determinant of the development of metabolic acidosis and is an independent factor for predicting loss of renal function. However, urine ammonium measurements are not widely available in routine diagnostic laboratories, and its clinical significance is still unknown. We hypothesized that urine estimated ammonium-to-creatinine ratio (u-eNH_4^+/u-Cr), as an indicator of urinary NH_4^+ excretion, would be surrogates for early metabolic acidosis in patients with CKD.

Methods: We measured u-eNH_4^+/u-Cr in outpatients without receiving oral alkali, hypokalemia, urinary acid-base imbalance, and negative value of urine anion gap (UAG) and urinary osmolar gap (UOG). The urine estimated ammonium concentration (u-eNH_4^+) from UOG was calculated as u-eNH_4^+ = 0.5 x (urine osmolality - 2[Na^+ + K^+] - [urea] - [glucose]). In a multiple regression model, the factors that had affected u-eNH_4^+/u-Cr ware examined. Receiver operating characteristic (ROC)-plot area under the curve (AUC) was used to show the effectiveness of u-eNH_4^+/u-Cr.

Results: A total of 464 outpatients were identified (Mean age, 66.4 ± 15.8 years old; Male, 57.7%; CKD, 58.8%; Hypertensives, 70.9%; Diabetes, 40.0%). u-eNH_4^+/u-Cr was associated positively with sex, eGFR, potassium, uric acid, blood glucose, UAG, and urine protein creatinine ratio. Interestingly, u-eNH_4^+/u-Cr was significantly lower in CKD stage 4-5 than in non-CKD groups, even though there were no overt metabolic disorders. Sex, eGFR, serum potassium level, and blood glucose were independently associated with u-eNH_4^+/u-Cr in a multiple regression model. In addition, AUC values for u-eNH_4^+/u-Cr had greater identity with the metabolic acidosis than ROC-plot AUC values for serum or urinary anion gap (mean ROC-plot AUC for u-eNH_4^+/u-Cr, 0.638; 95% CI, 0.550 to 0.726; p=0.007).

Conclusions: u-eNH_4^+/u-Cr is easily measured in clinical practice and would be more tightly linked with ammonium excretion than serum or urinary anion gap.

TH-OR075

The Cystic Fibrosis Urine Test

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Background: Cystic fibrosis (CF) patients commonly present with systemic electrolyte abnormalities and metabolic alkalosis, likely caused by renal dysfunction of base excretion. In mouse studies, we have identified the physiological mechanism of CFTR-dependent urine bicarbonate excretion in the collecting duct, which depends on functional pendrin and CFTR in β-intercalated cells. Remarkably, CFTR and pendrin knock-out mice cannot respond to increase their urine bicarbonate excretion during the first 3 hours following a defined acute gastric load.

Methods: We have developed a human, non-invasive *CF urine test* that is simple and quantifies the ability to excrete bicarbonate with the urine after oral intake of 79 mg/ kg BW NaHCO3.

Results: In human CF patients (homozygote for ΔF508, n=6), we can show a reduced ability (~ 40% as compared to normal) to excrete urinary bicarbonate after application of this *CF urine test*. We hypothesized that the *CF urine test* can verify and quantify therapy success in CF patients treated with the novel CF modulator drug Orkambi®. Currently, 6 CF patients have been studied before and after 4 weeks of treatment with Orkambi®. The results showed an appr. 2-fold increase of the urinary [HCO_3^-] in the treated CF group.

Conclusions: These results indicate that CFTR knock-out mice and human CF patients present with the inability/reduced ability to excrete a defined oral HCO_3^- load. Furthermore, the CF modulator drug Orkambi® can partially normalize the challenged urinary HCO_3^- excretion in CF patients.

Funding: Government Support - Non-U.S.

TH-OR076

Intravenous Sodium Bicarbonate Replacement in Patients with Toluene Intoxication

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Background: Toluene is widely available in over-the-counter products and is used as an inhaled abuse substance in developing countries. The treatment is not established and is expert opinion based on hydration and potassium replacement; however, acidosis treatment is not established.

Methods: Randomized single blind controlled clinical trial, in patients with toluene intoxication, in the emergency department. Inclusion criteria were patients >18 years, toluene poisoning clinical diagnosis, recently inhaled toluene history (<7 days), pH ≤7.25, and serum potassium between 1.1-5.5mmol/L. Patients were randomized to the administration on Group A, sodium bicarbonate (HCO3) and group B, No HCO3. Group A were given 100 mmol HCO3 as 4 hours infusion for up to 3 doses if the pH was still <7.30. In group B, HCO3 was not administered. All patients underwent serum electrolytes and venous or arterial blood gases every 4 hours since admission for up to 3 samples. The main outcome is to evaluate the time of metabolic acidosis resolution.

Results: In the study 19 patients were included, the mean age was 27 years, 53% were male. The resolution time of group A was 34.6 hours, while the group B was 19.5 hours, without significant difference (Table1). The hospital stay days (4.5 vs 3.2 days, p 0.14), the amount of potassium administered (568 vs 476 mEq, p 0.53) and the amount of fluid administered (8194 vs 7777 mL, p 0.859) were not significant between groups.

Conclusions: In the first clinical trial on toluene intoxication, there is no clear benefit of sodium bicarbonate intravenous replacement in patients with metabolic acidosis due to toluene intoxication. It is relevant to note no difference was found in the potassium administered between groups.

Table 1. Time to resolution, blood gases and serum potassium between groups.

Parameter	Group A	Group B	p
Time to resolution, h	34.7	19.6	0.344
pH	.	.	.
0 h	7.10	7.14	0.528
4 h	7.22	7.19	0.601
8 h	7.27	7.20	0.301
12 h	7.32	7.27	0.275
24 h	7.34	7.32	0.413
K+	.	.	.
0 h	1.94	1.78	0.684
4 h	2.21	2.18	0.964
8 h	2.51	2.57	0.784
12 h	2.66	2.32	0.296
24 h	3.12	3.10	0.937
Hospital stay, days	4.6	3.2	0.149
Saline solution, mL	8,194	7,777	0.859
Administered K, mEq	568	476	0.539
Number, (%)	7 (70)	6 (66)	0.835

Group A, Saline solution + Sodium Bicarbonate 100 mmol; Group B, Saline solution, K+, potassium.

TH-OR077

Development of a Novel Predictive Equation for Ionized Calcium in Hospitalized Subjects: Albumin-Corrected Calcium Equation Is Extremely Inaccurate

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Background: In clinical practice total serum Ca is often corrected according to albumin (0.8mg/dL per each 1g/L Alb<4 g/L). Recently, hidden Ca disorders have been associated to higher mortality in dialysis. Our objective was to develop a novel-specific correction equation for ionized Ca.

Methods: We reviewed electronic data from all hospitalized patients of a single tertiary-care center (2017-2018). Hidden hypocalcemia and hidden hypercalcemia were defined as: normal Alb corrected-Ca & ionized Ca <4.3 or >5.2 mg/dL respectively.

Results: We analyzed 7,158 Ca samples from 5,618 subjects (age 54±18 y, female 55%, 44% with AKI or CKD). Hypercalcemia and hypocalcemia according to ionized Ca occurred in 3.8% (275/7158) and 28.8% (2059/7158) respectively. Alb corrected-Ca had a poor correlation with ionized Ca (r:0.56, p<0.001). Hidden hypercalcemia and hidden hypocalcemia occurred in 2.2% (160/7158) and 3.7% (271/7158) measurements respectively; 5.1% (362/7158) and 10.7%(766/7158) were erroneously diagnosed as hypercalcemia or hypocalcemia respectively when Alb corrected-Ca was employed. Agreement between Alb corrected-Ca for hypo, normo or hypercalcemia was poor (kappa 0.23). A novel laboratory-specific prediction equation was developed: *Ionized Ca* (mg/dL, reference value 4.3-5.2 mg/dL)=0.44*total Ca – 0.27*Alb (g/L) – 0.06*P(mg/dL) – 0.02*CO_2 (mEq/L) + 2.16. This new equation substantially improved adjusted R^2 to 0.81 (95% CI 0.78-0.82, p<0.001) when compared with Alb corrected-Ca equation (R^2=0.56). Area under ROC curve for hypercalcemia and hypocalcemia diagnosis with new equation were 0.98 (95% CI 0.97-0.99, p<0.001) and 0.86 (95% CI 0.84-87, p<0.001) respectively. In univariate models, SCr and eGFR were associated with Ca-status misdiagnosis (OR:18.1, p<0.001) yet this association disappeared when multivariate analysis was adjusted to P and CO_2 levels.

Conclusions: The novel equation proposed for prediction of ionized Ca is superior to the Alb corrected-Ca equation and could be useful when ionized Ca is not available. The conventional formulas currently used in practice are inaccurate and misclassify many patients, in particular when renal dysfunction with phosphorus or bicarbonate disturbances are present.

TH-OR078

Cell-Based Therapy and Podocyte Cell Fusion Rescue Type IV Collagen Composition in Alport Syndrome

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Background: Loss of function mutations in the genes encoding either of the three chains of type IV collagen forming the a3/a4/a5 protomer (*COL4A3*,*COL4A4*, and/or *COL4A5*genes) in Alport syndrome (AS) compromise the glomerular basement membrane (GBM) integrity and filtration function. Potential cure relies on restoring the missing chain(s) of type IV collagen; and cell-based therapies successfully delayed renal failure in mouse models of AS ($Col4a3^{KO}$).

Methods: To guide the development of cell-based therapies for AS, novel genetically engineered mouse models (GEMMs) were generated and used to define which glomerular cell(s) presents with rate-limiting function in GBM type IV collagen synthesis.

Results: In the new GEMMs, conditional deletion of *Col4a3* gene ($Col4a3^{cKO}$), following its breeding with a constitutively expressed Cre-recombinase transgene (CMV-Cre), proved functional and phenocopied the renal disease observed in $Col4a3^{KO}$ mice. Using endothelial cells (Cdh5-Cre) and podocytes (Podocin-Cre) transgenics, we find that podocytes, in contrast with endothelial cells, are requisite for functional type IV collagen GBM composition in AS. Exogenously administered cells (bone marrow derived-, embryonic, and induced-pluripotent stem cells (iPSC)) rescue the renal phenotype in AS mice by restoring a functional GBM a3/a4/a5 type IV collagen composition. Using lineage-tracing genetic strategies, we uncovered that cell-based therapies ensues from the formation of a heterokaryon with recipient podocytes and rescues GBM type IV collagen composition in AS mice.

Conclusions: Such fusion-dependent tissue regeneration was associated with TGFb1-dependent genetic reprogramming of the injured kidney glomerular cells and required de novo synthesis of the missing type IV collagen by the fused stem cells. These experiments highlight cell fusion as a mechanistic driver of stem cell-induced tissue regeneration.

TH-OR079

Lysosomal β-Mannosidase (Manba) Is a CKD Risk Gene

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Background: Chronic kidney disease (CKD) is a complex gene-environmental disease affecting close to 10% of the population worldwide. Through the computational integration of CKD genome-wide association study (GWAS) variants and kidney compartment-based expression of quantitative trait loci (eQTLs) analysis, we identified lysosomal β-Mannosidase(Manba) as a candidate CKD risk gene. Manba is a lysosomal glycosyl hydrolase. Here we studied mice with genetic manipulation of Manba to understand the role of Manba in CKD.

Methods: We generated gene expression and genotype information and conducted eQTLs analysis on 121 microdissected human kidney glomerular and tubule samples. Bayesian colocalization method was performed to integrate the GWAS and eQTL data. We performed single cell RNA-sequencing on healthy mouse kidneys. We generated Manba knock-out mice and induced kidney disease by aging or by folic acid injection. We examined renal histology and gene expression. We analyzed lysosomes and autophagy in vivo and in cultured tubular epithelial cells in vitro.

Results: EQTLs analysis indicated that in human kidney tissue samples with CKD risk variant, the expression of Manba was significantly lower when compared to the reference allele kidneys. Manba was mostly expressed in kidney tubule cells including proximal tubules and principal cells in the mouse kidney single cell dataset. Double immunofluorescence staining confirmed its expression pattern. Aging (at 70 weeks age) Manba knock-out mice exhibited an increase in numbers of lysosomes and autophagic vacuoles in tubular cells. In FA-induced kidney fibrosis model, Manba knock-out mice showed more severe fibrotic changes by histological analysis and an increase in profibrotic genes by QRT-PCR. Manba knock-out mice and cultured Manba knock-out tubular cells demonstrated altered lysosomal dynamics. As lysosomes play a key role in autophagy, Manba knock-out mice also showed lower autophagic flux.

Conclusions: Taken together, these findings indicate that Manba is a CKD risk gene. Manba deficiency exacerbates kidney fibrosis, likely via lysosomal alterations and an impaired autophagic clearance.

Funding: NIDDK Support

TH-OR080

Novel Neuroendocrine Features of Macula Densa Cells Suggest Their Chief Role in Glomerular Tissue Remodeling

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Background: Macula densa (MD) cells are strategically positioned at the glomerular entrance and traditionally known to regulate renal hemodynamics and renin release. The present study aimed to explore the emerging new neuron-like and secretory function of MD cells and their role in glomerular angiogenesis and tissue maintenance.

Methods: A newly developed MD cell research toolbox was applied including MD-GFP, MD-GCaMP5, Cdh5-Confetti mouse models for tracking MD and endothelial genetic cell fate and $[Ca^{2+}]_i$ dynamics with intravital multiphoton imaging (MPM), freshly isolated single live MD cells, the newly established immortalized mouse MD cell line MD^{Geo}, and MD gene profiling.

Results: Mouse MD cell gene profile suggested axon guidance and growth as key MD cell functions, and high expression of secreted tissue remodeling and angiogenic factors Ccn1, Nov, Cxcl14, Pappa2, Sema3c. MD-GFP mice enabled the visualization of single MD cells in high detail and confirmed the presence of a dense network of long (up to 100 um) basal cell processes arborizing into the glomerular mesangium and vasculature, with highly dynamic features including rapid and extensive vesicular transport and outgrowth. MD^{Geo} cells showed high expression of nerve growth factor receptor (NGFR) and the regulation of nNOS and COX2 expression by NGF. In vivo MPM of MD cell $[Ca^{2+}]_i$ revealed that unlike in other renal epithelia, MD cells show robust (5-fold compared to baseline), rapid, and propagating calcium transients (2-4 s spikes) that were due to several

neuron-specific calcium entry, mobilization, and extrusion pathways. MD^{Geo} cells but not control M1 cells implanted under the renal capsule of Cdh5-Confetti mice induced within 4 days robust endothelial sprouting, neovascularization (angiogenesis). The radial pattern of new vessel growth towards the implanted MD cells' epicenter was formed by clonally expanding local endothelial precursor cells and contained circulating red blood cells.

Conclusions: The newly identified MD cell morphological and functional features suggest that the MD plaque is a single nephron-level ganglion of individual neuron-like MD cells that play chief sensory, effector, and neuroendocrine functions in the kidney. Novel MD-derived secreted angiogenic factors may contribute to glomerular tissue maintenance and repair after injury.

Funding: NIDDK Support

TH-OR081

Extracellular Matrix Component Mediated DDR1 Activation Causes Podocyte Lipotoxicity and Progression of Renal Disease in Alport Syndrome

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Background: The GBM is primarily composed of laminin and Collagen type IV. *De novo* production of the collagen type I (Col I) has been observed in mouse models of Alport Syndrome (AS mice, Col4a3KO). Discoidin domain receptor 1 (DDR1) is activated by collagens. Deletion of DDR1 in AS mice was shown to improve survival and renal function. We reported that lipid (LD) accumulation in mice with AS contributes to disease progression. However, how DDR1 activation by aberrant collagen production may contribute to podocyte lipotoxic injury and proteinuria in AS is poorly understood

Methods: AS mice were obtained from the Jackson Laboratory for the determination of DDR1 phosphorylation and for the treatment with ezetimibe (EZ) or in combination with Ramipril (RM). Following Col I treatment (50ug/mL, 18hrs), podocyte lipid content was determined by BODIPY 493/503 and Cell Mask Blue staining. Free fatty acid (FFA) uptake was assessed using a fluorometric kit.

Results: We demonstrate that pDDR1 is increased in kidney cortexes of AS mice and pDDR1 levels correlate with blood urine nitrogen (BUN, R2 =0.7, p<0.01). *In vitro*, DDR1 is activated by Col I in human podocytes. Increased LD accumulation (p<0.05), FFA uptake (p<0.01) and triglyceride (TG) levels (p<0.01) were observed in Col I treated podocytes. DDR1 interacts with CD36, a protein involved in FFA uptake. Podocytes transfected with DDR1(DA) showed increased FFA uptake and TG level compared to cells transfected with WT and DDR1(DN) (p<0.05). A similar phenotype was observed in immortalized podocytes isolated from AS mice. We show that EZ interferes with the interaction between CD36 and DDR1 in HEK 293 cells. *In vivo*, administration of EZ or RM to AS mice preserves renal function. While EZ restores normal renal triglyceride content, we discovered an unexpected effect of RM, which lowered renal cholesterol content. Interestingly, we also observed an additive effect on renal fibrosis when a combination of EZ and RM was used compared to when either of the drugs was given to AS mice.

Conclusions: Our study suggests that Col I/DDR1-mediated lipotoxicity may represent a novel mechanism leading to podocyte injury in AS that is amenable to therapeutic intervention through a repurposing strategy of EZ.

Funding: NIDDK Support

TH-OR082

Differential Expression of Parietal Epithelial Cell and Podocyte Extracellular Matrix Proteins in Focal Segmental Glomerulosclerosis and Diabetic Kidney Disease

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Background: The differential expression of extracellular matrix (ECM) protein isoforms in focal segmental glomerulosclerosis (FSGS) and diabetic nephropathy is not well defined. In activated parietal epithelial cells (PECs), upregulation of CD44 is associated with ECM expansion. PEC-derived ECM proteins include Laminin β1 (LAMB1), Perlecan and collagen type IV α2 (COL4A2). Podocyte-specific ECM proteins include Laminin β2 (LAMB2), Agrin and collagen type IV α4 (COL4A4). This study aimed to demonstrate differential ECM protein expression by PECs in experimental and human FSGS and diabetic nephropathy, and to determine if CD44 plays a role in regulating ECM protein expression.

Methods: FSGS was induced in CD44 null ($CD44^{-/-}$) and wild-type mice, using a cytotoxic podocyte antibody. Kidney tissues were obtained at baseline and day 28 of FSGS. Diabetic BTBR *ob/ob* mice with leptin deficiency obesity mutation, *ob*, in which severe hyperglycemia manifested resulting in advanced diabetic nephropathy at 24 weeks of age, were used. BTBR non-diabetic wild-type mice of similar age acted as controls. Human biopsies of normal kidney, FSGS and diabetic nephropathy were analyzed.

Results: In normal mouse and human glomeruli, PEC-derived ECM proteins were found along the Bowman's capsule while, podocyte-specific ECM proteins were found at the glomerular basement membrane. However, in experimental FSGS, LAMB1, Perlecan and COL4A2 staining were significantly increased in PECs, and there was *de novo* expressions of LAMB2 and Agrin along Bowman's capsule. In diabetic *ob/ob* mice, as well as in human biopsies with FSGS and diabetic nephropathy, similar findings were observed. Because our previous results showed lower ECM expansion in $CD44^{-/-}$ mice, we compared the difference of each ECM protein between $CD44^{-/-}$ and wild-type mice, to determine if ECM expansion was CD44-dependent. Perlecan, COL4A2, LAMB2 and Agrin were significantly lower in $CD44^{-/-}$ mice, but not LAMB1 or COL4A4.

Conclusions: Therefore, CD44 plays a role in regulating ECM protein expression. Activated PECs result in increased PEC-derived matrix production, and *de novo* production of podocyte-specific matrix.

Funding: NIDDK Support

TH-OR083

CD44 Impacts Glomerular Parietal Epithelial Cell Changes in the Aged Mouse Kidney

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Background: CD44, an activated parietal epithelial cell (PEC) marker, increases with aging, and colocalizes with pERK to increase extracellular matrix and epithelial-mesenchymal transition (EMT). The purpose of the current study was to determine the effect of CD44 on PECs with aging.

Methods: CD44 knockout and wildtype control mice at 4 or 24 months were used in this study. Immunohistochemistry and immunofluorescence staining were performed and glomeruli were assessed as follows; outer cortex (OC) vs. juxta-medulla (JM), young vs. aged, and wildtype (WT) vs. CD44 knockout (KO).

Results: Aged WT mice had an increase in segmental and global glomerulosclerosis in JM glomeruli, whereas aged CD44KO mice did not develop either segmental or global glomerulosclerosis. Bowman's capsule length increased with age and was longer in JM than in OC glomeruli. It was significantly less in aged CD44KO mice compared with WT mice in both OC (212.4±11.7μm vs. WT, 252.4±16.5μm, P<0.0001) and JM glomeruli (325.1±24.0μm vs. 373.1±32.2μm, P<0.0001). In WT mice, PEC number was higher in JM versus OC glomeruli, and was increased with age in JM glomeruli, while knockout of CD44 prevented this aged-related increase. PEC density was higher in JM than in OC glomeruli, and was lower in aged mice than in young mice, however there was no significant difference between WT and CD44KO mice. Glomerular tuft area was larger in JM than in OC and was significantly less in aged CD44KO mice versus WT mice, in both OC (2801±241μm2 vs. 4415±379μm2, P<0.0001) and JM glomeruli (6011±823μm2 vs. 8391±892μm2, P<0.0001). Podocyte number was higher in aged CD44KO mice versus WT mice in JM glomeruli. Podocyte density was higher in aged CD44KO versus WT mice in both OC and JM glomeruli. The expression of EMT markers, α-SMA and vimentin, and activated form of ERK (pERK) and a downstream target of mTOR, pS6RP was increased in aged WT mice especially in JM glomeruli, and was decreased in CD44KO mice.

Conclusions: We showed that knockout of CD44 attenuated age-related increase of glomerulosclerosis, Bowman's capsule length, glomerular hypertrophy, pERK, pS6RP, and EMT marker expression. Our data suggest that CD44 is involved in aged-related changes of glomeruli and CD44 is associated with activation of ERK and mTOR signaling.

Funding: NIDDK Support

TH-OR084

MAD2B Contributes to Parietal Epithelial Cell Activation and Crescentic Glomerulonephritis via Skp2

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Background: Mitotic spindle assembly checkpoint protein 2 (MAD2B), a well-defined anaphase-promoting complex/cyclosome (APC/C) inhibitor and a small subunit of DNA polymerase zeta, is critical for mitotic control and DNA repair. Previously, we reported that upregulation of MAD2B is involved in several renal diseases. However, the pathological role of MAD2B in crescentic glomerulonephritis (CGN) has not been fully elucidated.

Methods: The objects of this study included patients with CGN, anti-glomerular basement membrane (anti-GBM) rats and in vitro cultured mouse PECs. In vivo, the anti-GBM model was established by intravenous injection of sheep anti-GBM serum and intraperitoneal administration of recombinant human TNF receptor-Ig fusion protein (TNFR:Fc) and prednisolone (PNS) were adopted to slow down crescent formation. In vitro gene silence of MAD2B and Skp2 were carried out by small interfering (si) RNA.

Results: In the present study, we found an obvious MAD2B enhancement in glomeruli of CGN patients and anti-GBM rats, which mainly originated from PECs. Consistently, MAD2B was increased in tumor necrosis factor-α (TNF-α)-treated PECs in vitro, accompanied by cell activation, proliferation and extracellular matrix accumulation. Importantly, knocking down MAD2B with siRNA dramatically attenuated PECs activation. Furthermore, we found that the expression of Skp2, an APC/C-CDH1 substrate, was increased in glomeruli of anti-GBM rats and TNF-α-induced PECs, which could be suppressed by MAD2B depletion. Also, genetic deletion of Skp2 inhibited TNF-α-induced PECs activation. Lastly, the administration of TNFR:Fc and PNS in anti-GBM rats reversed MAD2B and Skp2 accumulation, PEC activation, and subsequent crescent formation.

Conclusions: Our data suggests a pivotal role of MAD2B in the pathogenesis of glomerular PEC activation, proliferation and crescent formation by inducing Skp2 expression. MAD2B-Skp2 axis may be a promising potential target for glomerular crescent formation interventions.

Funding: Government Support - Non-U.S.

TH-OR085

Fatty Acid Receptors GPR40/GPR84: Two Promising Targets in Kidney Fibrosis

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Background: Numerous clinical conditions can lead to organ fibrosis and functional failure. There is a great need for therapies that could effectively target pathophysiological pathways involved in fibrosis. GPR40 and GPR84 are G protein–coupled receptors stimulated by free fatty acid ligands. Although both receptors have been associated with metabolic regulation and inflammation, they have not been previously linked to organ fibrosis. The dual GPR40 agonist/GPR84 antagonist PBI-4050 is a novel antifibrotic drug candidate entering phase III in idiopathic pulmonary fibrosis (IPF) and Alström syndrome. The aim of this study was to determine the role of GPR40 and GPR84 receptors and the effect of PBI-4050 treatment in models of acute kidney injury (AKI) and chronic kidney disease (CKD).

Methods: PBI-4050 was tested in cells involved in fibrosis (macrophages, fibroblasts and epithelial cells) and in various animal models of CKD/DKD (5/6-nephrectomized rat, *db/db* and *db/db* eNOS$^{-/-}$ mice, adenine-induced CKD), AKI (IRI, LPS, UUO, doxorubicin) and in GPR40- and GPR84-knockout mice.

Results: PBI-4050 acts on cells involved in the fibrotic pathway: macrophages, fibroblasts and epithelial cells by regulating cytokines, fibrotic and remodeling markers. GPR40 is also expressed in proximal tubules and collecting duct while GPR84 is mainly expressed in podocytes. In experiments using either GPR40- or GPR84-knockout mice in models of kidney fibrosis (UUO, IRI, and adenine-induced CKD), GPR40 was found protective and GPR84 deleterious. Through binding to GPR40 and GPR84, PBI-4050 significantly attenuated fibrosis in other models of AKI (doxorubicin, LPS) and CKD/DKD (5/6-nephrectomy, *db/db* mice). Moreover, in two phase II clinical trials (type 2 diabetes with metabolic syndrome, Alström syndrome) involving a total of 36 patients, PBI-4050 reduced kidney injury urinary biomarkers.

Conclusions: GPR40 and GPR84 may represent promising molecular targets in fibrosis pathways. We conclude that PBI-4050 is a first-in-class compound that may be effective for managing inflammatory and fibrosis-related kidney diseases.

Funding: Commercial Support - Prometic Life Sciences Inc.

TH-OR086

Endothelial Glycocalyx Hyaluronan Is Required for Glomerular Integrity and Is Determined by Shear Stress-Regulated Glucobiosynthesis

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Background: Endothelial cells are covered by a glycocalyx envelop, both luminal and abluminal, which predominantly consists of proteoglycans and adhering proteins. Conditional EC loss of glomerular hyaluronan (HA) resulted in mesangiolysis and capillary ballooning and albuminuria. Over time this process develops into glomerular capillary rarefaction and glomerulosclerosis. Laminar shear stress is required to preserve glycocalyx expression, but how downstream cellular regulation of production and maintenance of glycocalyx hyaluronan occurs is unknown.

Methods: EC-HA production and expression were tested *in vitro* and *in vivo* using primary glomerular derived EC or conditional EC HAS2-KO mice by fluorescent staining for HA, CRISPR-CAS9 editing of the *HAS2* gene and NMR of ^{13}C labelled glucose to determine cellular glucose metabolite concentrations.

Results: Here, we show how biosynthesis of the major structural component of EC glycocalyx, hyaluronan (HA), is regulated by shear. Both *in vitro* as well as in *in vivo*, HA expression on the endothelial surface is increased upon laminar shear and reduced when exposed to oscillatory flow, which is regulated by KLF2. We demonstrate increased expression and translocation of HAS2 to the endothelial cell membrane during laminar shear. HA production by HAS2 was shown to be further driven by availability of the HA substrates UDP-glucosamine and UDP-glucuronic acid. KLF2 inhibits endothelial glycolysis and allows for glucose intermediates to shuttle into the hexosamine- and glucuronic acid biosynthesis pathways. In addition, we found that HA harbours a specific binding site for the key regulator of endothelial quiescence and maintenance in glomerular endothelial barrier function, angiopoietin 1 (Ang1), and show that endothelial loss of HA resulted in disturbed Tie-2 kinase dependent glomerular endothelial stabilization.

Conclusions: These data demonstrate how endothelial glycocalyx function and functional adaptation to shear is coupled to KLF2 mediated regulation of endothelial glycolysis and HAS2 expression and HA is a critical growth factor signaling platform enabling effective Ang1/Tie2 signaling. As such, glomerular endothelial hyaluronan is a hitherto unrecognised key ECM component required for glomerular structure and function, which is lost in diabetic nephropathy.

TH-OR087

Functional Intrarenal Alterations and Morphological Glomerular Basement Changes in Mice Deficient of the Angiotensinase Aminopeptidase A

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Background: Aminopeptidase A (APA) is an enzyme abundantly expressed in the kidney glomeruli and tubules which degrades both Angiotensin (Ang) I and Ang II and thereby potentially important for downregulating renal RAS overactivity. Our objective was to examine whether there is a kidney phenotype associated with APA deficiency.

Methods: Urinary albumin excretion rate (AER) and glomerular filtration rate (GFR) were evaluated in BALB/c mice with global APA deficiency (APA$^{-/-}$) and compared to wild-type (WT) mice. Kidneys harvested from 8-month-old mice were examined by light microscopy (LM) and electron microscopy (EM). Abundance of endogenous kidney Ang II and the ability of the kidneys to degrade exogenous Ang II *ex vivo* were evaluated. In addition, kidney Ang-converting enzyme (ACE) expression and activity were measured.

Results: APA$^{-/-}$ mice had normal urinary AER and a GFR similar to that of wild-type (WT) littermates. By LM, kidneys from APA$^{-/-}$ mice showed mild mesangial expansion and mild to moderate thickening of the glomerular basement membrane (GBM). By EM, the APA$^{-/-}$ also exhibited mild increase of the mesangial matrix and moderate thickening of the GBM with a striking appearance of knob-like structures and sub-endothelial expansion. Kidney lysates of APA$^{-/-}$ showed a markedly slower degradation of exogenous Ang II (10 μM) compared to those of WT as shown by residual Ang II levels after 30 minutes (48.6 ± 4 vs 16.0 ± 5 %, respectively, $p<0.001$). Endogenous Ang II levels in APA$^{-/-}$, however, were not different compared to WT kidneys (1.04 ± 0.2 vs 0.89 ± 0.3, fmol/mg, p=ns). In addition, kidney lysates of APA$^{-/-}$ mice showed a profound decrease in ACE activity (2981 ± 374 vs 10021 ± 897 rfu/μg, respectively, $p<0.001$), mRNA (RT-real time PCR) and protein (Western blot) levels. The downregulation of ACE by decreasing Ang II formation likely counterbalances the impaired Ang II degradation due to APA deficiency.

Conclusions: Deficiency of APA results in glomerular morphological alterations in the mesangial stalk and the GBM and functional adaptations in intrarenal ACE expression and activity. These findings support a role of APA in maintenance of glomerular structure and intrarenal Ang homeostasis.

Funding: NIDDK Support

TH-OR088

Adoption of Home Remote Monitoring to Improve Outcomes in Peritoneal Dialysis (PD) Patients

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Background: The use of virtual health technologies has the potential to transform care of end-stage renal disease patients, allowing ongoing biometric data capture and virtual in-home interactions between patients and the healthcare team. Tracking biometric data through home remote monitoring (HRM) platforms, especially for high-risk patients, can promote a more proactive approach to care management and may improve outcomes.

Methods: We examined the acceptance and utilization of HRM by high-risk PD patients of a large dialysis organization (LDO); patient risk status was determined using a predictive clinical algorithm in conjunction with care team clinical judgement. Each home dialysis facility's governing body approved the HRM protocol prior to use; patient consent and a physician's order was required to place a patient on the HRM protocol. Alerts were designed for all biometric values tracked (blood pressure, weight, temperature). Patients could also engage via an iPad in Daily Health Sessions, which included questions about symptoms as well as educational content designed to reinforce training concepts.

Results: Since April 2017, over 12,000 patients have used HRM and over 4700 patients were actively using the platform in May 2019; more than 1 million data points have been collected to date. Metrics tracked during implementation included: patient enrollment rate, consistency of patient data transmission, and speed of alert resolution by the care team. Adoption metrics were assessed by program, along with hospitalization rates and mean time on therapy.

Conclusions: HRM was shown to be feasible among high-risk PD patients of an LDO. Uncontrolled blood pressure, treatment weight > target weight, and an increase in positive answers to health questions could all be indicative of changes in patient health status that warrant action: use of HRM to track these metrics may help to drive action steps and improve outcomes. Areas of ongoing focus include improving adherence and adoption into clinic workflow, ensuring timely closure of HRM alerts, and consistency in targeting HRM to appropriate high-risk patients.

Funding: Commercial Support - DaVita Inc

TH-OR089

A Transitional Start Unit (TSU) Improves Home Dialysis Adoption by Incident ESKD Patients

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Background: Pre-dialysis education remains inadequate for incident ESKD patients. This is important as the first 90 days of dialysis is a vulnerable time with a high risk of hospitalization and death. To address this problem, we designed a pilot quality improvement program, the TSU, to orient, educate and empower incident patients on key aspects of ESKD. Here, we report results through 26 months.

Methods: The TSU program provides 4-6 weeks of 1:1 dialysis education on nutrition, access, finances, modalities and transplant delivered by an interdisciplinary team following a set curriculum. Setting was two University of Virginia academic dialysis units. Only in-center incident patients were eligible for enrollment. Exclusion criteria included: prior selection of home therapy, permanent long-term care residency, hospice, unstable living arrangements or severe cognitive disability. Patients received four times weekly dialysis on M/T/Th/F using NxStage S1 machines for 3-4 hours followed by the typical "long break". Modest prescription changes by the primary nephrologist were allowed. Primary outcome was uptake of home therapies. Secondary outcomes included: comparison of weekend interdialytic weight gain (WE-IDWG) during TSU and after TSU program for patients who remained on in-center hemodialysis (ICHD) and other relevant quality metrics.

Results: 81 patients enrolled in the TSU. Participants were 52% male, 60.9% black with median age of 62. ESKD cause included 35% type 2 diabetes, 34% hypertension. **After education in the TSU, 30.4% of participants chose home therapy** (23% PD and 7.4% home HD). Overall prevalence of home therapy in our program is 14.3% with adoption among in-center new starts lower at 5-10%. The above result represents a significant increase in home therapy adoption. **Average WE-IDWG was 32% less in the TSU (1.58 kg) versus subsequent thrice weekly ICHD (2.33 kg) (p-value < 0.01)**. **There were no hospitalizations for volume overload during the TSU program**. Antihypertensive medications were reduced 12% at the end of the TSU period.

Conclusions: A TSU education program significantly increases home therapy adoption among incident ESKD patients and reduces IDWG over the long weekend break. Larger studies are required to determine the effect on hospitalizations.

TH-OR090

Early Transitions from In-Center Hemodialysis to Home Dialysis

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Background: Most patients starting dialysis urgently and unplanned receive in-center hemodialysis (ICHD) but might prefer and have better outcomes on home dialysis. We identified those who transitioned from ICHD to home dialysis early following an unplanned dialysis start and determined whether those who transitioned early had a lower risk of death compared to those remaining on ICHD.

Methods: We identified adults in the USRDS who initiated ICHD from 2005-2013 with a central venous catheter and no maturing arteriovenous access who had no nephrology referral prior to dialysis. We used logistic regression to identify factors associated with an early transition to home dialysis (within 90 days of dialysis initiation). Among those who survived to day 90 of dialysis, we applied a Cox proportional hazards model to find the risk of death for those who transitioned compared to those who did not.

Results: Of 190,642 patients, 3923 (2%) transitioned to peritoneal dialysis (PD) and 853 (0.4%) to home HD (HHD) with an average time on PD and HHD of 413 and 224 days, respectively. Younger age, white race, private insurance, rural neighborhoods, and initiating dialysis in a unit that has a PD program were associated with higher odds of an early PD transition. In contrast, older age, frailty, urban neighborhoods, and initiating dialysis in a unit that has a HHD program was associated with making an early HHD transition. Those who had transitioned to PD at any time during the first 90 days were less likely to die compared to those who had never transitioned to home dialysis [adjusted HR 0.86; 95%CI: 0.82-0.91]. In contrast, transition to HHD in the first 90 days was associated with a higher risk of death compared to those who had never transitioned (adjusted HR 1.31, 95%CI: 1.19-1.44).

Conclusions: Few patients who start ICHD urgently and unplanned make an early transition to home dialysis. Initiating dialysis in a center with home dialysis may help facilitate these transitions by increased exposure, awareness and education about home dialysis. The different risk factors and demographics of patients transitioning to PD and HHD early suggest that these therapies may attract different types of patients and may explain the differences in outcomes between HHD and PD that we observed. However, further research is needed to understand the higher mortality among early transitions to HHD.

Funding: NIDDK Support

TH-OR091

The Effect of a Combined Resistance and Cardiovascular Exercise Program on Peritoneal Dialysis Patients: A Pilot Randomized Control Trial

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Background: Patients receiving peritoneal dialysis (PD) are physically inactive, resulting in poor physical function. The aims of this study were to test the feasibility, and measure the effect of a combined resistance and cardiovascular exercise program on physical function and patient reported outcome measures (PROMs).

Methods: Pilot randomized controlled trial (RCT). Intervention (I) group received monthly exercise physiologist consultations, exercise prescription (resistance and aerobic exercise program using exercise bands) and four phone calls over 12 weeks. Control (C) group received normal care. Feasibility outcomes were exercise adherence rates and adverse events. Physical function effect was measured by change in I compared to the C group in 30 second sit to stand test (STS), pinch strength test (PST) and the 8 foot timed up and go test (8TUG). PROMs were measured using the London Evaluation of Illness (LEVIL) instrument.

Results: From a single center with 75 PD patients, 18 (24%) did not meet inclusion criteria (7 unable to understand English, 4 PD<6 weeks, 3 significant amputations, 2 medically unstable, 2 unable to independently ambulate). 21 (28%) patients declined to participate resulting in a recruitment rate of 48% consisting of 36 patients randomized into 2 groups of 18 (1:1). 10 patients did not complete the study resulting in a retention rate of 72% and analyzable data for 26 patients (13 in each arm). 10 out of 13 (77%) intervention patients completed greater than 50% of sessions. No serious adverse events caused by the exercise program were reported. In all physical function measures the intervention exercise group improved more than the control group without reaching statistical significance. PROMs improved in the exercise group and worsened in the control group in the domains of wellbeing, fatigue, shortness of breath and appetite; sleep improved more in the exercise group; and pain worsened more in the control group.

Conclusions: This study is the largest reported US RCT demonstrating a resistance and cardiovascular exercise program is feasible and safe and can increase physical activity and physical function in PD patients. A future PDEx study using a larger sample size, is feasible in the US peritoneal dialysis context.

TH-OR092

Training Duration Is Associated with Adverse Events in Home Hemodialysis Patients

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Background: Home hemodialysis (HHD) training varies significantly at the center- and patient-levels. This study aimed to explore the clinical outcomes associated with HHD training length.

Methods: All HHD patients successfully trained in a single-center dialysis center between January 2006 and July 2017 were included. Poisson models were built to assess hospitalization rate after start of HHD in the home environment. Potential confounding were defined a priori and included age, sex, diabetes, cause of primary kidney disease and year of HHD start. Time to first adverse event (hospitalization, definitive transfer to in-center hemodialysis [CHD] or death) was evaluated using a Kaplan-Meier curve and log-rank P.

Results: Forty-nine patients graduated from HHD training in our program (1 patient was excluded due to delays related to dialysis machine unavailability). HHD training was offered using a thrice weekly schedule with a median duration of 86 (67-108) days. Mean hospitalization rate was 0.33 (95% CI 0.24-0.44) episode per patient-year. Longer training duration was associated with a trend toward higher hospitalization rates (unadjusted incidence rate ratio [IRR] 1.12 per month, 95% CI 0.99-1.27, p=0.07) and a statistically significant increase in hospitalization rates when adjusted for confounding (adjusted IRR 1.20, 95% CI 1.01-1.41, p=0.03). During the total follow-up time of 131 patient-year, 4 patients died on HHD, 9 were definitively transferred to HD, 18 received a kidney transplantation and 17 patients had a least 1 hospitalization. There was a trend toward lower event-free survival (hospitalization/ definitive transfer to CHD/ death) in the extended training group (≥4 months of training, log-rank p=0.09)

Conclusions: In this small cohort, patients with longer HHD training had more frequent hospitalizations. Enhanced home support could be offered to these more vulnerable patients once they graduate from HHD training.

Table1. Study cohort

Baseline Characteristics	n=48
Age	44 (37-55)
Male	35 (73)
Race - Caucasian	42 (88)
Black	3 (6)
Other	3 (6)
RRT vintage at HHD training start (years)	1.7 (0.6-6.1)
Diabetes	14 (29)
Year of trainig start 2005-2009	15 (31)
2010-2013	13 (31)
2014-2017	18 (38)
Primary kidney disease - Diabetes	11 (23)
Hypertensive disease	5 (10)
Glomerulonephritis	21 (44)
Others	11 (23)

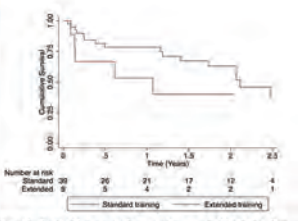

Figure 1. Kaplan-Meier curve for event-free survival (including first hospitalization, technique failure or death), Log-rank p=0.09

Table 2. Adjusted risk factors of hospitalization rates after start of HHD

Variables	IRR	95% CI	p-value
Age (per 10 years increase)	1.15	0.88-1.52	0.31
Male	1.29	0.57-2.94	0.54
Glomerulonephritis (versus other causes)	0.75	0.35-1.60	0.45
Diabetes	1.13	0.45-2.83	0.79
Most recent cohort (2014-2017 vs. 2005-2009/2010-2013)	0.53	0.22-1.29	0.16
Training duration (per month)	1.2	1.02-1.41	0.03

TH-OR093

Dialysis Modality Choice Among Healthcare Workers: A UK Perspective

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Background: Whilst health care workers are closely involved in the decision making process of patients in regard to dialysis modality, very little is known about their personal preferences.

Methods: We conducted an anonymised online survey of UK renal healthcare workers on their preferred dialysis modality if they needed dialysis. In addition to collecting their baseline demographics, we asked "Assume you are an otherwise well 40 year old (and, separately, 75 year old) person approaching ESRD. You have no living kidney donor options at present. There are no contraindications to any of the following dialysis options. Which renal replacement therapy would you choose?"

Results: A total of 858 individuals participated in the survey. The median age 44.3 years, 70.2% were female, 37.4% were doctors, 31.1% senior nurses and 15.2% junior nurses or health care assistants. The remainder were allied healthcare staff including dietitians and pharmacists. Over 60% of respondents had been involved in renal healthcare for over 10 years. There was a preference for peritoneal dialysis (PD) over in-centre haemodialysis (50.47% v. 6.18%; p <0.001 for 40 year and 49.18% v. 17.83%%; p<0.001 for 75 year old assumption) and home haemodialysis (HHD) (50.47% v. 39.28%; p<0.001 for 40 year old and 49.18% v. 18.41% for 75 year old assumption). There was a preference for HHD over in-centre haemodialysis if the respondents assumed they were 40 years old (39.28% v. 6.18%; p <0.001) but not if they assumed they were 75 years old (18.41% v. 17.83% p=0.778). There was a preference for automated peritoneal dialysis over continuous ambulatory peritoneal dialysis for both assumptions, 40 years old (34.85% v. 15.62%; p <0.001) and 75 years old (36.48% v. 12.7%; p<0.001). There was no difference in choice of treatment between doctors and senior nurses. Junior nurses and health care assistants, however, preferred haemodialysis over PD (p<0.001). The area of work had an impact on choice of treatment with the more staff involved in the care of HHD choosing HHD when compared to staff looking after patients receiving PD (<0.01).

Conclusions: In conclusion this survey showed that most healthcare workers in renal medicine, irrespective of age, gender, role and experience would choose home-based dialysis, in contrast to current practice in the UK where less than 20% of dialysis patients are on home therapies.

TH-OR094

Patient and Caregiver Perspectives on Burnout in Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) can offer patients more autonomy and flexibility compared with in-center hemodialysis. However, burnout – defined as mental, emotional, or physical exhaustion that leads to negative attitudes towards PD or an inability to perform PD safely – is associated with an increased risk of peritonitis or transfer to hemodialysis. We aimed to describe the perspectives of burnout among patients on PD and their caregivers.

Methods: 81 patients and 45 caregivers from 9 dialysis units in Australia, Hong Kong, and the US participated in 14 focus groups. Transcripts were analyzed thematically.

Results: We identified two themes. *Suffering an unrelenting responsibility* contributed to burnout as patients and caregivers felt overwhelmed by the daily regimen, perceived their life to be coming to a halt, tolerated the PD regimen for survival, and had to bear alone the burden and uncertainty of what to expect from PD. *Adapting and building resilience* encompassed establishing a new normal, drawing hope and support from family, relying on faith and hope for motivation, and finding meaning in other activities.

Conclusions: Patients on PD and their caregivers describe burnout as an unrelenting responsibility that they cope with by adapting and building resilience. Better informing patients and caregivers about the challenges of living with PD could prevent or delay burnout. Recognizing and providing resources to cope with burnout are essential to ensuring the well-being of patients on PD and their caregivers. Further research is needed to develop tools to screen for burnout and interventions for improved care and outcomes in patients on PD.

Funding: NIDDK Support

Illustrative Quotes

Theme	Subtheme	Quote
Suffering an unrelenting responsibility	Overwhelmed by the daily regimen	"Sometimes I feel like, when it comes to five or four times a day, five hours and then, sometimes I feel like I don't want to do it. Leave it. Let me die, I can't take this anymore."
	Life coming to a halt	"At the moment it's like a full stop. I can't move forward in my life."
	Tolerating PD regimen for survival	"And it's like, girl, you're dying. You don't have a choice."
	Bearing alone the burden and uncertainty of what to expect from PD	"You need social workers and psychologists for people that are feeling that way, they need to have counselling and support groups, because I can understand being in that frame of mind, where you would go okay, yeah, okay I've just had enough. I've had too much pain, I'm too tired, I'm too tired of fighting, right. They need support to know that there are still people here, and if it is their choice, then that's okay, and then the support to handle the side effects, the pain and the fear that they go through, dealing with it."
Adapting and building resilience	Establishing a new normal	"So it does depress you, it does do some things with you, but I'm still here, and my new normal is, I have to do dialysis. My new normal is, I have to have shots."
	Drawing hope and support from family	"I think if I hadn't have had supportive people around me at that stage and also being strong in myself, I could've gone no, bugger it, why go through this, why do dialysis every day, why put up with it."
	Relying on faith and hope for motivation	"I'm a strong believer in the Bible, so that gives me a foundation of hope."
	Finding meaning in other activities	"I notice for a caregiver that you have to make her happy. Sometimes I go to things, and it's a party...luau. I take them with me. That's the most happiest thing even if it's two hours just to be there and come back home."

TH-OR095

The Effect of Non-Visual Learning Preferences on Early Home Dialysis Adverse Events

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Background: Current approaches to home dialysis training are not individualized according to patients' learning preference. We hypothesize that visual learning preferences were associated with fewer adverse events in both peritoneal dialysis (PD) and home hemodialysis (HHD) patients within 6 months of training completion.

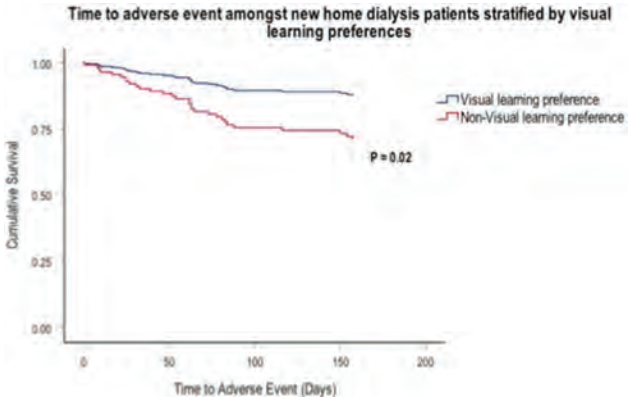
Methods: We performed a retrospective single centre cohort study at a large academic medical centre of prevalent HHD and PD patients. Patients received a VARK questionnaire at enrollment. VARK is a validated questionnaire that assesses a combination of individual learning preferences: visual (V), auditory (A), reading-writing (R) and Kinesthetic (K). Adverse events were defined as peritonitis, exit-site and tunnel infection, contamination episodes, access disruption along with needle dislodgement. We performed logistic regression analysis to determine the odds ratio of a single adverse event. We also performed multivariate cox regression analysis, adjusted for age, gender, modality, visual impairment, dialysis vintage, training duration and level of education.

Results: We enrolled 118 (78 HHD and 40 PD) patients with an average age of 52.0 ± 13.5 years. 38% (44) of study participants were non-visual learners. Thirty patients had at least one adverse event within 6 months of training completion; 63% (19) of these patients were non-visual learners. Non-visual learners were 4 times more likely to an adverse event, occurring sooner after training completion compared to visual learners (Table 1 & Figure 1).

Conclusions: Visual learning preference is associated with fewer adverse events in home dialysis patients within the first 6 months of completing training. Individualization of home dialysis training by learning preference is warranted.

Adverse Events

	Number of Patients N (%)	*Age (yrs,) mean ± SD*	*Weeks of Training mean ± SD*	*Patients with Any Adverse Event*	*Unadjusted OR*	*Adjusted OR*
Visual Learners (VARK, VAR, VAK, VRK, VK, VR, V)	*74 (63)*	*55.5 ± 14.4*	*6.6 ± 5.1*	*11 (36.7%)*		
Non-Visual Learners (ARK, AR, AK, K, R, RK)	*44 (37)*	*52 ± 14*	*6.2 ± 5.5*	*19 (63.3%)*	*4.35 (1.82-10.44) P = 0.001*	*4.04 (1.44 – 11.34) P= 0.008*



TH-OR096

Short-Term Gaps in Insurance Lead to Long-Term Disparities in Peritoneal Dialysis Use

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Background: Peritoneal dialysis (PD) offers improved quality of life over hemodialysis without compromising health outcomes. Uninsured patients do not become Medicare eligible until the first day of the fourth month of treatment. Using a quasi-experimental method, we studied whether short-term gaps in insurance were associated with long-term disparities in PD use.

Methods: Because Medicare eligibility starts on the first day of the fourth month of dialysis, patients starting dialysis at the end of the month have a shorter Medicare waiting period than patients starting dialysis at the beginning of the month. After identifying uninsured adults starting dialysis between 1/1/2006 and 12/31/2014 in the United States from a national registry, we studied whether starting dialysis at the end of the month was associated with higher PD use at day 360 than starting at the beginning of the month. Using two-stage least squares regression, we investigated whether gaps in insurance were associated with long-term disparities in PD use.

Results: The distribution of dialysis start day was distributed randomly (one-sample Kolmogorov-Smirnov, $p>0.05$). Patients starting dialysis in the first half of the month had a 10.7% (95% CI: 10.2-11.1%) probability of using PD at 360 days, while those starting in the last half of the month had an 11.8% (95% CI: 11.3-12.1%) probability (difference: 1.1% [0.5-1.7%]). Patients starting dialysis on the 31st had a 2.3% (95% CI: 1.1-3.5%) higher probability of PD use at day 360 than those starting on the 1st. Our second-stage regression showed that every 10 day gap without insurance was associated with a 1.0% (95% CI: 0.5-1.5%) absolute decrease in PD use at day 360. We projected that eliminating the Medicare waiting period entirely could increase the probability of long-term PD use in patients without insurance, from 11.2% to 19.8% (95% CI: 16.3, 23.3%).

Conclusions: Patients starting dialysis later in the month have shorter Medicare waiting periods and are more likely to use PD long-term. We exploited this difference to show that that longer periods of time without insurance lead to persistent decreases in PD use. Extending Medicare coverage to the first three months of dialysis or earlier could substantially improve PD penetration.

Funding: NIDDK Support

TH-OR097

Use of Machine Learning to Inform Decision Making and Optimal Renal Replacement Therapy

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Background: We deployed a machine learning (ML) model to identify patients at risk of requiring RRT to support clinical care decision making in a multidisciplinary care (MDC) team. We compare the difference in optimal renal replacement therapy (RRT) starts pre and post implementation. To the knowledge of the authors, this is the first live application of ML to inform transition workflows.

Methods: An EHR database of 110,998 patients was used to create an ML model to predict progression to an eGFR <10 or RRT start in the next six months (see Kidney Week 2018 SA-PO953). The system calculates weekly risk scores for non-dialysis patients with an eGFR <35. For high risk patients an alert is sent to the patient's nephrologist suggesting prompt referral to the PEAK MDC team. The team reviews high risk patients and provides education to inform their decision making. Optimal dialysis starts were defined as outpatient starts with access via AV fistula, AV graft, or peritoneal dialysis catheter.

Results: Since deployment of the ML model in October 2018, 54% of patients enrolled in PEAK had an optimal dialysis start. This is almost three times the national average of 20% (USRDS 2018 data) and 14% better than the 47.3% rate prior to use of the ML model. PEAK home dialysis rates have increased 20% vs. before deployment (24% vs 20%), and is now eight times the NYC average 24% vs 2.5%. PEAK members also received pre-emptive transplants at a rate five times the NYC average 12.5% vs 2.5%. PEAK patients with optimal starts had significantly greater provider interactions, as measured by unique appointment days prior to dialysis, than non-optimal starts (3.9 vs. 2.5 appointments, $p<0.0001$, unequal variances t-test). Optimal start patients are also associated with earlier enrollment, defined as the time from the first PEAK appointment to dialysis (329 vs. 179 days, $p<0.02$, unequal variances t-test).

Conclusions: The PEAK MDC-pulseData partnership has improved optimal dialysis starts and home dialysis modality rates by 14% and 22% respectively. Enrollment to the PEAK program has increased by 22% since Oct. 2018. Our results demonstrate that purpose-built AI tools used by an MDC team can increase optimal RRT outcomes.

Funding: Commercial Support - pulseData

TH-OR098

Efficacy and Safety of the Standard and Reduced Apixaban Dose Compared with No Anticoagulation in Dialysis Patients with Newly Diagnosed Atrial Fibrillation

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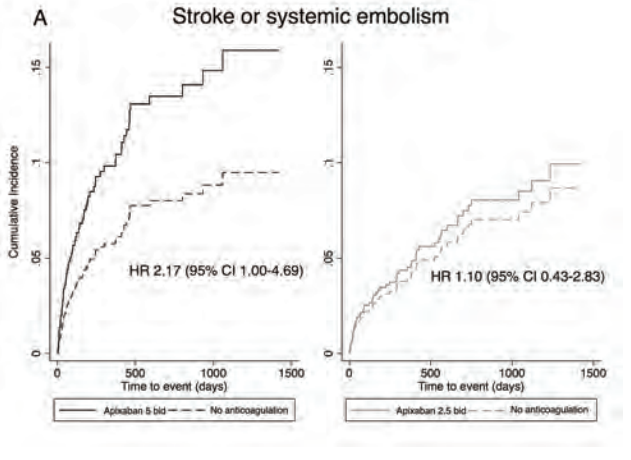
Background: The relative efficacy and safety of apixaban compared with no anticoagulation for atrial fibrillation (AF) has not been studied in dialysis patients.

Methods: This retrospective cohort study utilized 2012-2015 United States Renal Data System data. Dialysis patients with incident, non-valvular AF treated with apixaban (521 patients) were matched for relevant baseline characteristics with patients not treated with any anticoagulant agent (1561 patients). Competing risk survival models were used.

Results: Compared with no anticoagulation, apixaban was not associated with reduced risk of stroke or thromboembolism: HR 1.23, 95% CI 0.68-2.20, p=0.49. A significantly higher incidence of fatal or intracranial bleeding was observed with apixaban compared with no treatment: HR 2.48, 95% CI 1.25-4.90, p=0.009. A higher rate of stroke or systemic thromboembolism (**Figure**) and fatal or intracranial bleeding was seen in the subgroup of patients treated with the standard apixaban dose (5 mg twice daily) but not with the reduced apixaban dose (2.5 mg twice daily). A similar incidence of clinically significant bleeding events and major cardiovascular events was seen with apixaban compared with no treatment.

Conclusions: Randomized studies are needed to assess the efficacy of apixaban compared with no anticoagulation in chronic dialysis. Awaiting randomized data, prudence in prescribing apixaban to dialysis patients, especially at the standard dose, is warranted. Disclaimer The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

Funding: Private Foundation Support



Stroke or systemic embolism in patients treated with the standard and the reduced apixaban dose compared with no anticoagulation.

TH-OR099

Rivaroxaban vs. Warfarin for Prevention of Ischemic Stroke/Systemic Embolism (ISSE) in Patients with Non-Valvular Atrial Fibrillation (NVAF) and Stage 4-5 CKD

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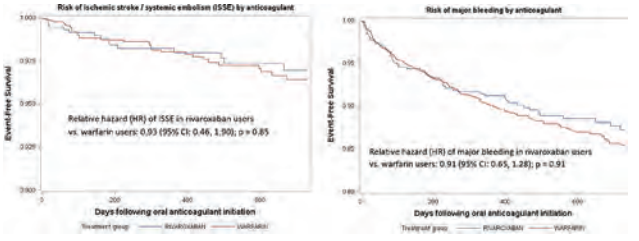
Background: There is limited evidence on the effectiveness and safety of direct-acting oral anticoagulants (DOACs) among patients with NVAF and advanced CKD. This study compared the risks of ISSE and major bleeding in patients with NVAF and stage IV-V CKD treated with rivaroxaban or warfarin.

Methods: Using data from the Optum Deidentified Electronic Health Record (EHR) Database, we selected patients with NVAF and stage IV-V CKD who initiated therapy with rivaroxaban or warfarin from November 1, 2011 through June 30, 2018. Selected patients were required to both be diagnosed with CKD and have an estimated creatinine clearance <30 mL/min and/or evidence of dialysis. Propensity score (PS) matching was used to balance rivaroxaban and warfarin patients on 97 measured baseline covariates. Hospitalizations for ISSE and major bleeding over 2 years following treatment initiation were ascertained with validated endpoint definitions. Outcomes were analyzed as time-to-event data using Kaplan-Meier survival estimators and Cox regression.

Results: 781 rivaroxaban patients were PS-matched to 1,536 warfarin patients; after matching, all baseline covariates were well balanced (absolute standardized difference<0.1). The mean patient age was 80 years; 62% were female; 82% and 18% had CKD stage IV and V, respectively. The relative hazard (HR) of ISSE associated with rivaroxaban use compared to warfarin use was 0.93 (95% CI: 0.46, 1.90; p=0.85), and the corresponding HR for major bleeding was 0.91 (95% CI: 0.65, 1.28; p=0.91).

Conclusions: No statistically significant difference in the risk of ISSE or major bleeding was found between patients treated with rivaroxaban or warfarin. While further study is needed, rivaroxaban appears to be a reasonable alternative to warfarin for ISSE prevention in the setting of NVAF and stage IV-V CKD.

Funding: Commercial Support - Janssen Scientific Affairs



TH-OR100

Effect of Evolocumab, an Anti-PCSK9 Antibody, on Vulnerable Coronary Plaque in CKD Patients Taking Statins

Keiji Hirai,[1] Shigeki Imamura,[2] Aizan Hirai,[2] Susumu Ookawara,[1] Yoshiyuki Morishita.[1] *[1]Saitama Medical Center, Jichi Medical University, Saitama, Japan; [2]Chiba cerebral and cardiovascular center, Chiba, Japan.*

Background: Coronary artery disease is a crucial complication in patients with chronic kidney disease (CKD). This study investigated the effects of evolocumab, a fully human monoclonal antibody against proprotein convertase subtilisin kexin type 9 (PCSK9), on vulnerable coronary plaques in CKD patients taking statins.

Methods: Vulnerable coronary plaques were defined by coronary computed tomography (CT) as having a density of <60 HU within the region of interest and remodeling index >1.1. Fifty-two CKD patients who had a vulnerable coronary plaque and who were taking stains (35 males, 17 females; mean age, 75.8 ± 7.0 years; mean estimated glomerular filtration rate, 51.4 ± 6.1 mL/min/1.73 m^2) were administrated evolocumab (140mg every two weeks) for 6 months. The change in 155 vulnerable coronary plaques from 52 CKD patients was evaluated before and after evolocumab administration. The changes in lipid metabolism were also evaluated.

Results: Evolocumab significantly increased the CT density (from 50.5 ± 9.9 HU to 102.4 ± 32.5 HU, p < 0.001) and reduced the remodeling index (from 1.28 ± 0.10 to 1.19 ± 0.09, p < 0.001) in vulnerable coronary plaques in CKD patients. Evolocumab also decreased low-density lipoprotein cholesterol (from 65.6 ± 22.2 mg/dL to 18.1± 11.8 mg/dL, p < 0.001), triglyceride (from 156.5 ± 172.3 mg/dL to 98.1 ± 61.4 mg/dL, p < 0.01), and lipoprotein (a) (from 23.9 ± 25.9 mg/dL to 14.5 ± 19.5 mg/dL, p < 0.001), and increased high-density lipoprotein cholesterol (from 52.5 ± 12.7 mg/dL to 57.8 ± 12.4 mg/dL, p < 0.001).

Conclusions: Evolocumab stabilized and reduced coronary vulnerable plaques and improved lipid metabolism in CKD patients taking stains. These results suggest that evolocumab has protective effects against coronary artery disease progression in CKD patients taking statins.

TH-OR101

Changes in eGFR After Left Ventricular Assist Device Implantation

Bethany Roehm, Lesley Inker, Amanda Vest, Hocine Tighiouart, Daniel E. Weiner. *Tufts Medical Center, Boston, MA.*

Background: Patients with advanced heart failure have a one-year survival of 25% which increases to more than 80% with left ventricular assist device (LVAD) support. Lower glomerular filtration rate (GFR), generally <30 ml/min/1.73m^2, is a relative contraindication to LVAD implantation. However reduced GFR may be secondary to decreased kidney perfusion that may improve after LVAD implantation. Our goal was to investigate kidney function following LVAD implantation.

Methods: We evaluated the change in eGFR among all patients at Tufts Medical Center who received an LVAD between 2010 and 2018 from baseline to 6 months, 1 year, and 2 years after implantation. Primary outcome was increase or decrease in eGFR by 30% or more, death on LVAD support, or heart transplantation, which were examined overall and by baseline eGFR category (>60, 30-59 and <30 ml/min/1.73m^2).

Results: Among 288 patients, mean baseline eGFR was 62 ±23 ml/min/1.73m^2. There were 144 patients with baseline eGFR ≥60, 122 with eGFR 30-59, and 22 with eGFR <30 ml/min/1.73m^2. Most LVAD recipients had an increase in eGFR or remained stable (Figure), and none with an eGFR <30 had a decline in eGFR. Death was also common, particularly in those with an eGFR<60. Among those with eGFR ≥60, 23% died within two years compared to 40% for those with eGFR <60 (p=0.004).

Conclusions: Substantial decreases in eGFR are rare in patients following LVAD implantation, even among patients with lowest baseline eGFR. One-year survival for patients with lower baseline eGFR is low, but remains better than reported one-year survival among LVAD eligible patients who do not receive LVAD support. Carefully selected patients with lower eGFR should not necessarily be excluded from receiving LVADs for treatment of heart failure.

Funding: Other NIH Support - NIH T32 grant

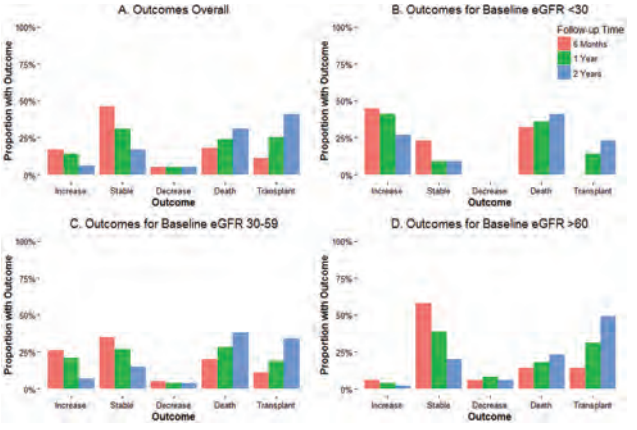


Figure: Outcomes over time post LVAD. Increase and decrease are defined as 30% increase or decrease in eGFR at follow-up.

TH-OR102

Predictors to Identify Diuretic Resistance Early in Acute Decompensated Heart Failure (ADHF)

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Background: Resistance to loop-diuretics occurs frequently in patients hospitalized for ADHF, resulting in inadequate decongestion, readmission and poor outcomes. Early identification of diuretic resistance during the hospital course may avoid delay in institution of appropriate therapies. We aimed to identify clinical biomarkers that predicted diuretic resistance in a study conducted to evaluate usefulness of high-dose spironolactone in loop-diuretic resistant ADHF patients.

Methods: The parent trial was a prospective, non-randomized trial in ADHF patients. Diuretic resistance was identified if subjects had weight loss<1lb/day despite intravenous furosemide>160mg/day (at least one dose of 80mg/day) or no change in dyspnea 48H after admission with usual care. Baseline clinical characteristics, blood chemistry including neurohormones and urine electrolytes were compared between diuretic-responsive and resistant subjects.

Results: Twenty of 47 enrolled subjects met loop-diuretic resistance criteria. The mean age was 61±15 yrs, 60% were male, and 50% were Hispanic. There was no difference in age, gender and race, co-morbidities, sign and symptoms of hypervolemia, renal function, EF%, presence of pulmonary HTN between diuretic-responsive and resistant subjects. However, serum sodium was lower (137[134,139] vs. 139[137,141]meq/L, p<0.03) and blood urea nitrogen was higher (11.42[7.60,3.18] vs. 7.68[5.71,8.92]mmol/l, p=0.009) in diuretic resistant compared to responsive subjects. Diuretic-resistant subjects had higher plasma renin activity (7.2[1.5,29.5] vs. 2[0.2,10.9]ng/ml/hr, p=0.03) and aldosterone (26.5[9.9, 56] vs. 5.2[3.7, 8.2] ng/dL, p<0.001), and lower urine sodium-potassium

ratio (2.63±1.2 vs. 8.2±4.8, p<0.001). Plasma aldosterone had an inverse relationship with urine sodium-potassium ratio and (r=-0.46, p=0.003), but not with serum sodium or urea nitrogen. Urine sodium-potassium ratio at admission predicted loop-diuretic resistance with an AUC (95%CI) 0.69 (0.68, 0.71). A cutoff value of 2.96 had a sensitivity of 76% and specificity of 65% to identify loop-diuretic resistance (lower the value, more the resistance).

Conclusions: The admission urine sodium-potassium ratio may serve as a surrogate for high aldosterone activity, and is an inexpensive and rapidly available biomarker to recognize diuretic resistance in ADHF patients.

Funding: Commercial Support - Relypsa, Inc, a Vifor Pharma Group Company

TH-OR103

Incorporating Kidney Disease Measures into Cardiovascular Risk Prediction: Evaluation Using Electronic Health Record Data from 37 Health Care Organizations

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Background: Clinical guidelines for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) increasingly use absolute risk to guide decision-making, often relying on the AHA/ACC Pooled Cohort Equation (PCE) for risk estimation. Two kidney measures, estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (uACR), are CVD risk enhancers but they are not included in the PCE. We hypothesize that when eGFR and uACR data are available, their inclusion will meaningfully enhance ASCVD risk assessment.

Methods: 836,047 patients in the OptumLabs® Data Warehouse's EHR-derived data with no evidence of baseline ASCVD and data on PCE variables plus eGFR and uACR, from 37 health care organizations (HCOs) were followed (mean (SD), 3.6 (2.4) years) for EHR evidence of ASCVD events (myocardial infarction and stroke). We developed a " CKD patch" to add eGFR and ACR data to the existing PCE.

Results: Patients were age 59 (10) (mean (SD)) years, had total cholesterol 175 (35) mg/dL, HDL 45 (15) mg/dL, SBP 128 (16) mmHg, eGFR 81 (21) ml/min/1.73 m^2, and uACR 10 (2-29) mg/g (median (IQR)), 51% were female, 74% had diabetes, and 4.5% were smokers. The original PCE predicted a 5-year risk of 8.4%, and observed rate of ASCVD was 4.2%. Adding eGFR and ACR to PCE improved the C-statistic by 0.022 (95% CI 0.020-0.024) overall, 97% of HCOs (36 of 37) improved by ≥ 0.01. Overall, reclassification of 5-year ASCVD risk from low (< 3.75%) to intermediate (3.75%–9.9%) risk and intermediate to high risk (≥ 10%) was 5.1% (range by HCO: 3.0–8.9%) and 6.2% (4.1 – 10.9%), respectively. ASCVD reclassification rates were higher with higher CKD risk (intermediate to high ASCVD risk: 2.6% at no CKD, 11.9% at intermediate-risk CKD, 15.8% at high-risk CKD and 20.4% at very high-risk CKD). Recalibrating PCE in each HCO prior to adding kidney measures yielded similar results.

Conclusions: CKD measures (eGFR and uACR) are often available, and their integration into the PCE is feasible and results in meaningful risk reclassification across HCOs, particularly among higher risk CKD. Implementation in EHRs should include rigorous validation, attending to limitations, e.g., EHRs are blind to events occurring outside the HCO.

TH-OR104

Trends in Hypertension Control in Those with and Without CKD in the United States: 1999-2016

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Background: We examined temporal trends in hypertension (HTN) control overall and in those with and without CKD.

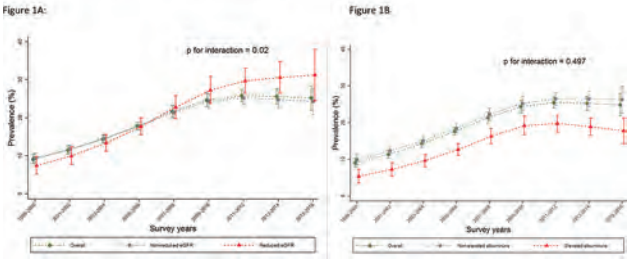
Methods: A total of 19,856 adults (≥20 years) with HTN from NHANES 1999-2000 to 2015-2016 were examined. HTN was defined as mean systolic blood pressure (BP) ≥130 or mean diastolic BP ≥80 or anti-hypertension medication use. HTN control was defined as BP <130/80 mmHg among hypertensives (as defined above). Age, sex and race adjusted estimates were obtained using logistic regression analysis. Restricted cubic splines were used to flexibly model trends over time, with predefined knots at 2004, 2008, and 2012. We tested the combined interaction of spline terms with reduced eGFR (<60 ml/min/1.73m^2) and elevated albuminuria (ACR ≥30mg/g), separately.

Results: HTN control improved overall between 1999-2000 and 2015-2016, from 9.1% to 25.2% (p<0.001). Greater improvement in HTN control was observed in the period from 1999-2000 to 2007-2008 (12.5%, p<0.001), than thereafter (3.5%, p=0.08). The temporal trend in HTN control differed by reduced eGFR status (p for interaction=0.02). HTN control was comparable in individuals with reduced and non-reduced eGFR until 2007-2008 and thereafter control improved more in those with reduced eGFR (Fig.1A). Difference in HTN control between those with and without reduced eGFR was -2.0% in 1999-2000 (p=0.07), 1.4% in 2007-2008 (p=0.4) and 7.0% in 2015-2016 (p=0.06). The temporal trend in HTN control by albuminuria status was similar to the overall trend (p for interaction=0.5) (Fig.1B). Persons with albuminuria had lower HTN control throughout. Difference in HTN control between those with and without albuminuria was -4.5% in 1999-2000 (p<0.001), -5.9% in 2007-2008 (p<0.001) and -8.5% in 2015-2016 (p=0.001).

Conclusions: Overall, improvement in HTN control has slowed in the last ten years, particularly among persons without reduced eGFR. Those with and without albuminuria experienced a similar trend in HTN control, though HTN control remained consistently lower in persons with albuminuria

Funding: Other U.S. Government Support

Figure 1: Prevalence of hypertension control by measures of CKD



TH-OR105

White-Coat Hypertension Has a Predictive Role for Renal Outcome in Patients with Non-Dialysis CKD: Results from the C-STRIDE Study

Qin Wang, Jinwei Wang, Yu Wang, Luxia Zhang, Ming Hui Zhao. *Renal Division, Department of Medicine, Peking University First Hospital; Peking University Institute of Nephrology, Beijing, China.*

Background: Data on the predictive value of white-coat hypertension (WCH) for renal and cardiovascular (CV) outcomes in patients with chronic kidney disease (CKD) is controversial.

Methods: Totally, 1734 CKD stage 1-4 patients with both ambulatory BP (ABP) and clinic BP (CBP) data from the Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE) were enrolled in the present study. The BP pattern was categorized as normotension(NT), WCH, masked hypertension (MH) and sustained hypertension (SH) according to ABP and CBP values, respectively. The association of BP pattern with CKD outcomes, including initiation of renal replacement therapy and CV events, was evaluated by Cox regression model.

Results: The mean age of the cohort was 48.8±13.7 years with 43.2% females. The average value of ABP and CBP were 128±17/79±11mm Hg and 130±18/81±10mm Hg, respectively. And NT, WCH, MH and SH each had 678(39.1%), 83(4.8%), 538(31%) and 435(25.1%) patients. During a median follow-up of 4.7 years, 287 renal events and 128 CV events occurred, respectively. Compared with NT, the fully adjusted risk for renal events was significantly increased in WCH(hazard ratio [HR] 2.43; 95% confidence interval [CI] 1.38-4.31), MH (HR 2.42; 95%CI 1.66-3.50), and SH (HR 2.56; 95%CI 1.75-3.74), respectively. With regard to CV events, WCH, MH and SH also showed higher risk after adjusting for traditional CV risk factors (HR 2.53, 95%CI 1.21-5.29; HR 1.85, 95%CI 1.13-3.01; HR 2.63, 95%CI 1.63-4.25, respectively). After further adjusting baseline logarithm transformed 24h-urinary protein and estimated glomerular filtrationrate, only SH showed a significantly increased risk for CV events (HR 1.81; 95%CI 1.10-2.99).

Conclusions: WCH is independently associated with an increased risk for renal events in non-dialysis CKD patients.

TH-OR106

PRN Use of Antihypertensive Medications and Adverse Renal Outcomes: A Propensity Score-Matched Analysis

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Background: Despite absence of data demonstrating a clear benefit, hospitalized patients are often treated with PRN antihypertensive medications (PRNBPMeds) for asymptomatic increases in blood pressure. We hypothesized that use of PRNBPMeds can be associated with abrupt lowering of blood pressures (BP) and worsening renal function.

Methods: Single center retrospective study of all adult patients admitted between Jan 2012 and April 2016 who received antihypertensive medications. We excluded those with possible hypertensive emergency, end stage renal disease and acute kidney injury (AKI) on admission. Patients who received PRN and scheduled antihypertensive medications were matched (1:1) by propensity scores which included systolic blood pressure on admission, demographic factors and comorbidities. Outcomes of interest were abrupt decrease in blood pressure, defined as >25% decrease in systolic blood pressures (SBP) within one hour of administration of PRN or scheduled medications and AKI.

Results: Mean age was 62±16 years. 52% were females, and 68% Caucasian. 82% of patients had hypertension. PRNBPMeds were used in 4,850 (13%) out of a total of 37,145 admissions. 93% of these patients had scheduled and PRN medications while 7% received PRNBPMeds alone. The propensity score-matched cohort included 3,707 patients each in the PRNBPMeds and scheduled antihypertensive groups. The abrupt decrease in SBP rates

were 11.6% and 3.5% for PRN and scheduled medications groups, respectively, (p<0.001). The AKI occurrence rates were 14.7% and 11.6% for PRN and scheduled medications groups, respectively, (p<0.001). Using the propensity score-matched analysis, the use of PRN medications was associated with 138% increased risk of abrupt decrease in SBP (OR, 2.38 [95%CI, 1.74-3.26]; p<0.001), and 29% increased risk of AKI (OR, 1.29 [95%CI, 1.13-1.47]; p<0.001).

Conclusions: To our knowledge, this is the first propensity-scored matched analysis of PRN vs scheduled antihypertensive medications. Our results suggest that use of PRNBPMeds is associated with increased risk of abrupt BP lowering and AKI. Pragmatic randomized controlled trials are required to assess the risk benefit of treating asymptomatic increases in BP in hospitalized patients.

TH-OR107

Resistant Hypertension Potentiates the Risk of ESRD in African Americans in the Million Veteran Program (MVP)

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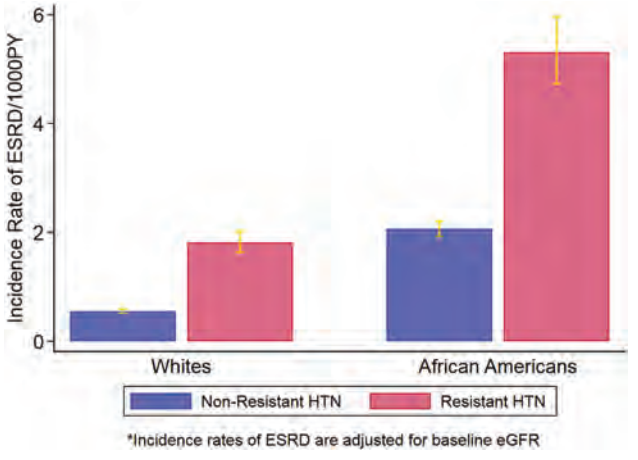
Background: African Americans (AAs) are 4 times as likely as Whites to develop ESRD. Resistant hypertension (RH), a severe form of hypertension (HTN) is associated with increased risk of cardiovascular (CV) and renal outcomes. We investigated how ESRD risk is modified by race.

Methods: We designed a retrospective cohort of 240,038 veterans with HTN, enrolled in the MVP with a GFR >30 ml/min. The primary exposure was incident RH (time-varying). The primary outcome was incident ESRD during a 13.5 yr follow up: 2004-2017. Secondary outcomes were myocardial infarction (MI), stroke, and death. Incident RH was defined as failure to achieve outpatient BP <140/90 mmHg with 3 anti-HTN drugs, including a thiazide, or use of ≥4 drugs, excluding BPs when pain score was >5, when interfering medications or secondary HTN were present. Poisson models were used to estimate incidence rates (IR) and test biologic interaction with race. Cox (and competing-risks) models were used to identify independent effects.

Results: Median age was 60 yrs; 20% were African American and 6% were women with 23,385 incident RH cases (9.7%). RH patients had higher IR (per 1000 PY) of ESRD (4.5 vs. 1.3), MI (6.5 vs 3), stroke (16.4 vs 7.6) and death (12 vs 6.9) than non-resistant HTN (NRH). In Cox models adjusted for traditional CV risk factors; RH patients had a 2.0, 1.67, 1.9 and 1.14-fold higher risk of ESRD, MI, stroke, and death, respectively. In Poisson models, AAs with RH had a 2.5-fold higher risk of ESRD compared to AAs with NRH; 3-fold the risk of Whites with RH, and 9-fold the risk of Whites with NRH [p-interaction < 0.01].

Conclusions: RH was associated with a higher risk of ESRD (and CV outcomes), especially in AAs. Interventions (behavioral, drug choices) that improve reaching BP targets in RH patients, could have a major impact on ESRD incidence in this high-risk population, particularly in AAs.

Funding: Veterans Affairs Support



TH-OR108

Relationship Between Treatment Effects for Proteinuria and eGFR Slope over 2 Years in Patients with IgA Nephropathy

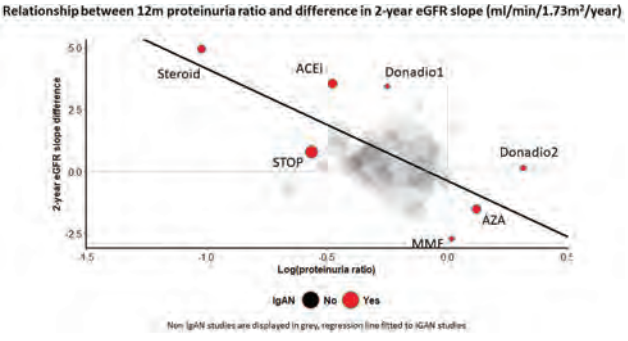
Andrew M. Stone,[1] Daniel C. Cattran,[2] Jürgen Floege,[3] Richard A. Lafayette,[4] Vladimir Tesar,[5] Hernan Trimarchi,[7] Brad H. Rovin,[6] Jens Kristensen,[8] Jonathan Barratt.[9] *[1]Stone Biostatistics Ltd, Crewe, United Kingdom; [2]Toronto General Hospital, Toronto, ON, Canada; [3]RWTH University of Aachen, Aachen, Germany; [4]Stanford University, Stanford, CA; [5]General University Hospital in Prague, Prague, Czechia; [6]Ohio State University Wexner Medical Center, Columbus, OH; [7]Hospital Britanico de Buenos Aires, Buenos Aires, Argentina; [8]Calliditas Therapeutics AB, Stockholm, Sweden; [9]University of Leicester, Leicester, United Kingdom.*

Background: A challenge for evaluating treatments for IgA nephropathy (IgAN) is the usually long time course for progression to ESKD. Recent meta-analyses have separately explored the role of proteinuria reduction and the rate/slope of eGFR decline as surrogate endpoints. In this meta-analysis we describe the relationship between treatment effects on proteinuria, recorded at 1 year, and 2-year eGFR (CKD-EPI) slope.

Methods: Study level data from 1037 patients in 12 IgAN studies, aggregated into 7 study groupings, were obtained from the databook provided at the March 2018 NKF/FDA/EMA workshop. A weighted linear regression was performed to quantify the relationship between baseline adjusted treatment effects for proteinuria, expressed as the log of the ratio of geometric means, and treatment effects for total 2-year eGFR slope, expressed as the difference in arithmetic means. Studies were weighted in inverse proportion to the variance of the 2-year eGFR slope treatment effect.

Results: There was a statistically significant association seen between treatment effects for proteinuria at 12 months and treatment effects for 2-year eGFR slope for the IgAN studies, p=0.043. On average, the between arm, annualized difference in the rate of decline in eGFR was estimated to increase by 4.53 ml/min/1.73m²/year (95%CI: 0.21, 8.84) for every 1 log (63%) reduction in the proteinuria treatment arm ratio.

Conclusions: In IgAN treatment effects on 12m proteinuria are reasonably likely to predict subsequent treatment differences in the rate of decline in eGFR over 2 years.



TH-OR109

Change in Proteinuria as a Surrogate End Point for GFR Slope: Individual Patient Meta-Analysis of 12 Randomized Clinical Trials in IgA Nephropathy

Lesley Inker. Chronic Kidney Disease-Epidemiology (CKD-EPI) Collaboration *Tufts Medical Center, Boston, MA.*

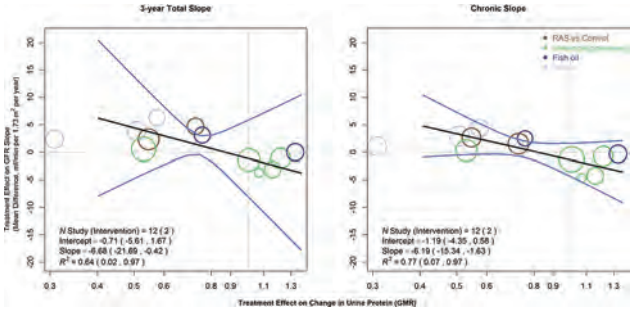
Background: A recent study demonstrated associations between treatment effects on urine protein (UP) and clinical endpoint (i.e. ESKD). Reasonably likely surrogate endpoints can be used as a basis for accelerated or conditional approval of therapies intended to treat serious or life-threatening conditions, such as IgAN. The clinical benefit of products approved under this program would need to be verified in a post-marketing confirmatory trial. For patients with IgAN, endpoints to such confirmatory trials may be GFR slope given the low likelihood of sufficient clinical endpoints.

Methods: Using a pooled dataset of 990 participants from 12 studies, we computed change in UP from baseline to 6 months (25th,75th 5.9, 6.9 month), and the GFR slope from randomization to 1, 2, and 3 years (total slope[TS]) as well as after excluding the initial 3 months after randomization (chronic slope[CS]). We performed Bayesian mixed models to relate the treatment effects on change in UP to GFR slope and to those on the clinical endpoint (CE), defined as ESKD, eGFR<15 or doubling of creatinine.

Results: Figure shows associations of treatment effects on change in UP compared to that of TS at 3 years and CS. Slopes are significant and intercepts are nonsignificant, supporting strong trial level associations. For TS, associations are consistent at 2 years [R^2 0.62 (0.01, 0.96)]. In sensitivity analyses, similar associations were noted for CS computed using truncated data with follow-up time of 18-24 months and when computing change in UP at 9 and 12 months. Associations between treatment effects on TS and CS to the clinical endpoint are very strong (e.g. TS 3 years R^2 0.99 (95% CI 0.28, 1.00)).

Conclusions: Our results suggest that treatment effects on early changes in UP confirmed by treatment effects on GFR slope might be a useful strategy for evaluation of treatment benefit in IgA.

Funding: Commercial Support - Retrophin



To convert to percentage UP reduction (1-GMR)*-100. Black line is meta-regression line and blue lines are 95% confidence intervals around the regression line.

TH-OR110

The Clinical Utility of Immunosuppression Treatment Decisions Based on Personalized Risk Assessment from the International IgA Nephropathy Prediction Tool

Sean Barbour,[1] Mark Canney,[1] Rosanna Coppo,[6] Hong Zhang,[5] Yusuke Suzuki,[3] Dilshani Induruwage,[4] Heather N. Reich,[2] Daniel C. Cattran.[2] International IgA Nephropathy Network *[1]University of British Columbia, Vancouver, BC, Canada; [2]Toronto General Hospital, Toronto, ON, Canada; [3]Juntendo University School of Medicine, Tokyo, Japan; [4]BC Provincial Renal Agency, Vancouver, BC, Canada; [5]Peking University First Hospital, Beijing, China; [6]Fondazione Ricerca Molinette, Torino, Italy*.

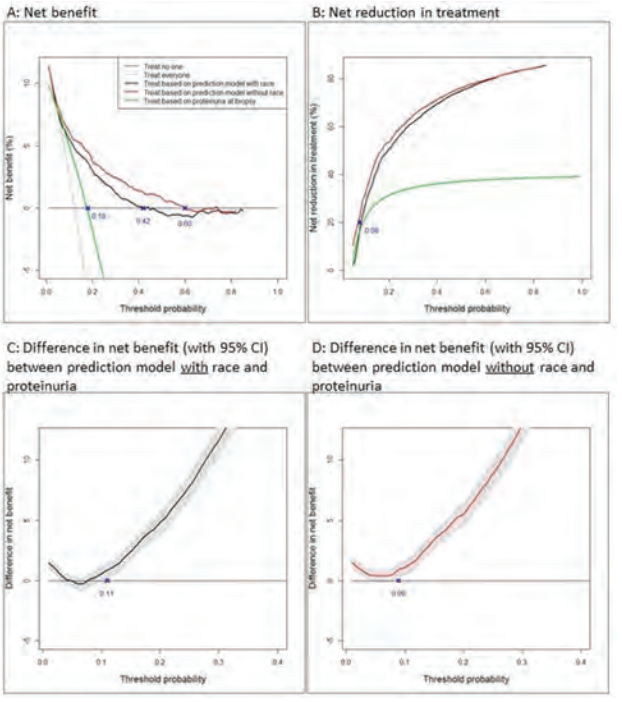
Background: The KDIGO guidelines recommend risk-stratifying patients with IgA nephropathy (IgAN) based on proteinuria ≧1g/day to guide immunosuppression treatment decisions. Because this approach does not accurately discriminate the risk of disease progression, we evaluated whether treatment decisions could be improved by using individual risk assessment from the International IgAN Prediction Tool, which estimates the 5-year risk of a 50% decline in eGFR or ESRD.

Methods: We used a net benefit and net reduction in treatment analysis, which for any given threshold probability of disease progression (P_t) balances correct decisions to give or withhold immunosuppression accounting for the relative harm to patients from incorrect decisions. In a multi-ethnic cohort of 3299 adults with biopsy-proven IgAN (median follow-up 5.1 years), decision rules for immunosuppression treatment were created based on proteinuria ≧1g/day or based on the Prediction Tool (predicted risk ≥P_t). The net benefit and reduction in treatment were calculated for all P_t from 0 to 1.

Results: Using proteinuria ≧1g/day to make treatment decisions was net harmful to patients for P_t ≥0.18 (Fig A). Compared to using proteinuria, decisions using the Prediction Tool had a larger net benefit and net reduction in treatment for P_t ≥0.09 and ≧0.08 (Fig B, C, D), and more accurately allocated or withheld immunosuppression in up to 23.4% and 35.1% more patients respectively.

Conclusions: These results demonstrate the benefit to patients from a precision-medicine approach to immunosuppression treatment using individual risk of disease progression from the International IgAN Prediction Tool instead of a single generic categorization of proteinuria.

Funding: Government Support - Non-U.S.



TH-OR111

Serum and Urine Biomarkers Related to Renal Fibrosis Predict Renal Outcome in Patients with IgA Nephropathy

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Background: IgA nephropathy (IgAN), the most common primary glomerulonephritis worldwide, has serious outcomes with end-stage renal disease developing in 30-50% of patients. Clinical predictors such as proteinuria, hematuria, hypertension as well as renal fibrosis may play a role in IgAN onset and/or progression. Here, we assessed serum and urine biomarkers related to renal fibrosis and histological findings in renal-biopsy specimens from patients with IgAN, ANCA associated vasculitis and compared with healthy controls.

Methods: We evaluated 46 patients with biopsy-proven IgAN, 45 patients with ANCA associated vasculitis, who were assessed at time of diagnosis for estimated glomerular filtration rate (eGFR), proteinuria, microscopic hematuria, hypertension, then followed prospectively and compared to 9 healthy controls (mean follow-up 51.8 months). Serum and urine samples collected at diagnosis were analyzed for biomarkers related to renal fibrosis using a novel enzyme-linked immunosorbent assay as well as histological evaluation of renal tissues at time of kidney biopsies were assessed. Linear discriminant analysis, logistic regression model and Kaplan-Meier (survival) analysis were used for statistic processing.

Results: We found serum and urine biomarkers such as EGF, PRO-C6, PRO-C3, which correlated with the level of histological fibrosis in kidney biopsies ($P<0.05$) and exactly predicted renal outcome of patients with IgAN ($P<0.05$). Moreover, addition of two other biomarkers such as serum LG1M and urine C3M completely differentiated patients with IgAN compared to patients with ANCA associated vasculitis and healthy controls (accuracy of classification 100 %).

Conclusions: In conclusion, serum and urine biomarkers related to renal fibrosis such as EGF, PRO-C6, PRO-C3 predicted renal outcome of patients with IgAN. Future studies are needed to validate these preliminary findings and to determine the power of these urinary and serum markers for assessment of responses to treatment.

TH-OR112

Association of IgM Deposition with Renal Outcomes in IgA Nephropathy: A Multicenter, Prospective, Observational Study

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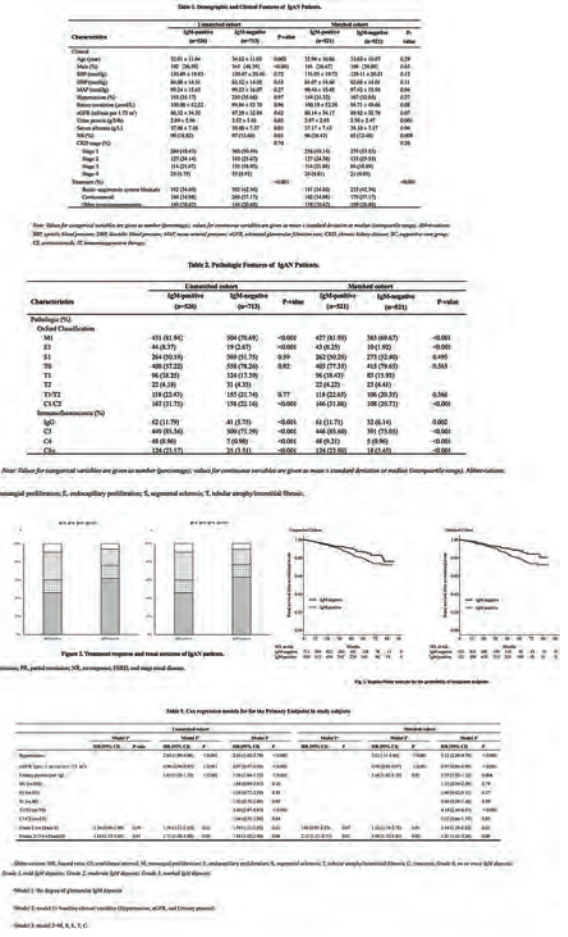
Background: The aim of this study was to investigate the relationships between co-deposition of IgM, clinicopathological features, and renal outcomes and whether IgM deposition is a novel marker for the response to patients with IgA nephropathy (IgAN).

Methods: A total of 1239 patients with primary IgAN diagnosed by renal biopsy were enrolled l from January 2013 to May 2018. The primary endpoint was the combined endpoint of a 50% decline in eGFR and/or ESRD. Responses to therapy included complete remission (CR), partial remission (PR), no response (NR) and ESRD. A 1: 1 propensity score matching (PSM) method was used to balance the covariates in all patients.

Results: Compared with IgM negative deposition(n=521), patients with IgM positive depositon (n=521) had higher level of Urine protein and higher proportion of M1, E1, C1/C2, deposition of IgG, C3, C4 and C1q (all P<0.05) at the time of biopsy. During the follow-up period (39.07±23.82 months), 76.39%, 60.08% patients in groups of IgM positive and negative deposition achieved CR or PR (P<0.001) respectively. According to Kaplan–Meier, renal survival rates in IgM negative and IgM positive groups were better both in unmacthed and matched cohort (both P<0.05). Furthermore, with 50% decline in eGFR and/or ESRD as the combined endpoint, multivariate Cox regression analysis of unmatched and matched cohort showed IgM deposition was an independent risk factors influencing renal survival.

Conclusions: IgM deposition in the glomerulus is associated with a poor renal outcome and severe pathologic features and did play a decisive role in renal progressio in IgAN patients.

Funding: Government Support - Non-U.S.



TH-OR113

Analysis of 40-Year Prognosis of 1149 cases of IgA Nephropathy and Validation Study of Oxford Classification

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Background: Half a century has passed since IgA nephropathy (IgAN) was firstly reported, however, very long term prognosis over 40 years has been unknown. In 2016, Oxford classification of IgAN was revised, and crescent formation was newly added. In this study, we showed 40 years prognosis of IgAN and validation study of Oxford classification in our cohort.

Methods: 1,149 IgAN patients diagnosed in our institution since 1974 were analyzed. At first, 40 years prognosis of whole cohort was analyzed. Then, 872 patients observed over 1 years and diagnosed by renal biopsy with more than 8 glomeruli were divided into two groups with or without immunosuppressant and evaluated about the Oxford classification.

Results: Renal survival rate of whole cohort was 86.8% in 10 years, 72.2% in 20 years, 58.2% in 30 years, and 49.9% in 40 years. In whole Oxford analysis cohort (n=872), only T lesion was related with 20 years renal prognosis (81.9 in T0, 58.7 in T1, and 34.7% in T2, P<0.0001). In group without immunosuppressant (n=416), 20 years renal survival rate was significantly higher in S0 than S1 (75.7 vs. 65.0%, P=0.04), in T0 than T1 and 2 (77.4 vs. 59.1 vs. 18.0%, P<0.0001), in C0 than C1+2 (71.9 vs. 60.1%, P=0.023), but not significant in M and E. In group with immunosuppressant (n=456), it was significantly higher in only T0 than T1 and 2 (87.3 vs. 55.7 vs. 54.7%, P<0.0001). Interestingly, survival rate in C1 (80.8%) was increased similar to C0 (76.6%) by immunosuppressant, but C2 was still low (58.8%). Multivariate Cox regression analysis showed lower eGFR and higher amount of proteinuria in every cohorts and T lesion in whole Oxford analysis cohort were independent risk factors. After propensity score matching (n=266/group), renal survival rate in group with immunosuppressant was significantly higher than without immunosuppressant (78.4 vs. 68.1%, p=0.0099), and it was also significantly higher than in M0 (83.0 vs. 70.1%, p=0.0277), E1 (85.2 vs. 65.1%, p=0.0051), S1 (80.0 vs. 63.5%, p=0.0031), T0 (91.6 vs. 81.6, p=0.003), T2 (62.5 vs. 0.0%, p=0.035), and C1 (82.5 vs. 62.5%, p=0.014).

Conclusions: Half of IgAN patients progressed to end stage within 40 years, and Oxford classification was evaluated to suspect prognosis especially T lesion, and immunosuppressant improved its prognosis especially in M0, E1, S1, T0, T2 and C1.

TH-OR114

Characterization of Recombinant IgG Autoantibody That Binds Galactose-Deficient IgA1 and Forms Immune Complexes Mimicking Those in IgA Nephropathy

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Background: Immune complexes (IC) containing galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1-specific IgG autoantibodies (autoAbs) play a key role in the pathogenesis of IgA nephropathy (IgAN). However, the molecular interactions between autoAb and Gd-IgA1 in IgAN are not well understood. To gain a better insight, we used a recombinant IgG (rIgG) autoAb derived from an IgAN patient and assessed its structural and functional features.

Methods: rIgG autoAb was produced in Expi293F cells. Gd-IgA1 was isolated from plasma of a patient with IgA myeloma. Surface plasmon resonance was used for kinetic analysis of autoAb binding to Gd-IgA1. Fab of rIgG was used for crystallographic studies and the structure was solved by molecular replacement method. We formed *in vitro* engineered IC (EIC) that mimic those in IgAN patients by incubating Gd-IgA1 and rIgG in the presence of human serum. The formed EIC were isolated by size-exclusion chromatography and their biological activity was evaluated using human primary mesangial cells (MC). Furthermore, IC formed from purified Gd-IgA1 and rIgG were injected to immunodeficient mice and then the kidney histopathology was assessed.

Results: The rIgG formed complexes with Gd-IgA1. Kinetic analysis showed intermediate affinity of rIgG to Gd-IgA1 (KD=3.16 E-07 M). The structure of the Fab was solved at the resolution of 1.69 Å. The structure revealed a loop in the heavy chain that adopts a unique conformation, unveiling a surface-accessible pocket located in close proximity to the CDR3. Binding modes from an *in silico* docking study of a glycopeptide mimicking the hinge region of Gd-IgA1 showed potential binding to this region. The EIC, but not Gd-IgA1 alone, stimulated proliferation of cultured MC (2.88±0.69-fold increase over control). IC injected into immunodeficient mice increased glomerular cellularity (48.4±13.3 nuclei per glomerulus *vs.* 40.4±10.5 in control; p<0.0001; n=4 each).

Conclusions: This study provides the first structure of an autoAb that binds Gd-IgA1 and forms biologically active EIC. We envision that better understanding of the interactions of Gd-IgA1 and autoantibodies will enable design of inhibitors to block the formation of pathogenic IC in IgAN.

Funding: NIDDK Support, Private Foundation Support

TH-OR115

Mizoribine Prevents M2-Type Macrophage-Mediated Development of Chronic Lesions in Childhood IgA Nephropathy

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Background: We have previously reported that CD163$^+$ M2-type macrophages (MQ) are associated with the development of chronic lesions such as glomerular matrix expansion and interstitial fibrosis in the progression of IgA nephropathy (IgAN). On the other hand, the immunosuppressant mizoribine (Miz) has been shown to reduce the progression of childhood IgAN. To investigate the mechanism of Miz protection, we examined the effect of Miz on MQ function.

Methods: A total of 73 children with IgAN were divided into groups treated with prednisolone (PSL) only (P group; n=33) or PSL plus Miz (PM group; n=40), and their

clinicopathological findings compared retrospectively. For in vitro studies, normal human monocyte-derived MQ were incubated with dexamethasone (Dex), or Dex plus Miz, for 48 hours and then analysed by DNA microarray.

Results: There were no differences in clinical and histological findings at the first (diagnostic) biopsy between the P and PM groups. Although there was no significant difference in the urinary findings, the protocol biopsy after 2-years of treatment showed that the number of sclerotic glomeruli, the degree of interstitial fibrosis, and the number of interstitial $CD163^+$ MQ were significantly reduced in the PM group, but not in the P group. Dex stimulation of cultured human MQ induced up-regulation of scavenger receptor characteristic of M2-type MQ (CD163). Dex also induced up-regulation of cytokines and growth factors associated with inflammation and fibrosis (CCL13, CXCL12, NOS1, NOS2, FGF-8, FGF-21 and CTGF) which was prevented by Miz. In addition, Miz inhibited expression of CD300e, an activating receptor capable of providing survival signals to prevent monocyte apoptosis and to regulate the innate immune response. Immunohistochemistry revealed expression of CD300e which co-localized with $CD163^+$ MQ in biopsies from IgAN patients treated with steroid which was reduced by Miz treatment.

Conclusions: Our data suggest that Miz suppresses M2-type MQ mediated interstitial fibrosis by inhibiting expression of profibrotic cytokines, and reducing MQ life-span by inhibiting steroid-induced CD300e expression.

TH-OR116

Immunological and Genomic Analysis of Phenotype Discordant Monozygotic Twins Reveals a Novel Role of T-Follicular Helper Cells in IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common glomerulonephritis caused by deposition of IgA dominant immune complexes in the glomerulus. The cause of the excess IgA1 production is unclear, and has been attributed to self-proliferation of IgA antibody secreting cells (ASC) or an imbalance in the B-cell-T-cell interactions. T-follicular helper cells (T_{FH}) have been shown to play an essential role in antibody responses.

Methods: We studied 15 IgAN, 10 Lupus Nephritis (LN), 10 Polycystic Kidney Disease (PKD) patients, 20 healthy controls (HC), and 3 pairs of discordant monozygotic twins for IgAN, using flow cytometry and antibody repertoire sequencing.

Results: IgAN patients had a 3.6-fold increase in the IgA ASC, and 1.6-fold increase in the T_{FH}-like cells compared to HC and PKD patients, that correlated with the elevated plasma concentrations of IgA and IgA1. Immunoglobulin sequencing revealed no differences in the usage of heavy chain V, J and kappa genes. However, there was an enhanced usage of the lambda light chain IGLV2-8 gene in IgAN patients (12.9%) compared to HC (7.9%, $p<0.01$). Autologous co-culture experiments of the T_{FH}-like cells with naïve B-cells demonstrated an elevated IgA production for cells derived from IgAN patients (17.2±6.1 ng/ml) compared to HC, LN and PKD patients (5.8±1.3, 7.7± 2.9, and 7.0±1.7 ng/ml, respectively). We performed co-culture experiments in cells from IgAN discordant monozygotic twins. Co-culture of cells derived from the IgAN twins yielded significantly higher IgA production compared to the cells from the healthy twins. In addition, T_{FH}-like cells from the IgAN twins significantly increased IgA production in the naïve B-cells from their corresponding healthy twins (14.2±4.3 ng/ml). Whereas, T_{FH}-like cells from the healthy twins only elicited a baseline IgA production from naïve B-cells from their corresponding IgAN twins (6.7±1.1 ng/ml).

Conclusions: Our data demonstrates an essential interaction of naïve B-cells and T_{FH}-like cells in the augmented generation of IgA in IgAN patients, identifying a new pathway for intervention to reduce IgA production.

Funding: NIDDK Support

TH-OR117

Enzymatic Inactive Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) Promotes Antibody-Mediated Podocyte Injury

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Background: Membranous nephropathy (MN) is an autoimmune disease of the glomerulus characterized by upregulation of the ubiquitin proteasome system (UPS) in podocytes. Thereby, ubiquitin C-terminal hydrolase L1 (UCH-L1) is among the highest upregulated UPS enzymes and *de novo* expressed in injured podocytes. Preliminary work demonstrates that proteasomal impairment and altered proteostasis depends on the enzymatic activity of UCH-L1 in naïve podocytes. We hypothesize that in MN oxidative-modification of UCH-L1 (secondary to oxidative stress) leads to the formation of a dysfunctional UCH-L1 enzyme, which perpetuates podocyte injury. Aim of this study is to understand the underlying mechanism for toxic loss of function of UCH-L1 in antibody-mediated podocyte injury.

Methods: *In vivo* experiments were performed by using unique mouse models with podocyte-specific overexpression of active UCH-L1 wildtype protein or inactive UCH-L1 I93M mutant protein (comparable to oxidative-modified UCH-L1). Mice were treated with anti-podocyte nephritis (APN) antibodies, sacrificed after 14 days, and analyzed by WB, enzyme activity assays, IHC and ELISA for proteinuria. For mechanistic studies, flag-tagged wildtype or mutant I93M UCH-L1 were cloned and transiently overexpressed in HEK-293T cells and used for proteasome interaction studies.

Results: Mice overexpressing dysfunctional UCH-L1 I93M protein exhibited an accelerated disease course with an increased accumulation of polyubiquitinated proteins accompanied by elevated expression of proteasomal and lysosomal proteins in isolated glomeruli. We also observed reduced levels of slit membrane proteins such as nephrin and α-actinin-4 correlating with podocyte loss. Contrastingly, mice overexpressing active wildtype UCH-L1 in podocytes exhibited milder proteinuria and stable expression of podocyte-specific proteins in response to anti-podocyte antibodies after 14 days. *In vitro* immunoprecipitation experiments demonstrated an interaction of wildtype UCH-L1 and UCH-L1 I93M with the proteasome, however only binding of UCH-L1 I93M decreased proteasomal activity.

Conclusions: These results strengthen the hypothesis that during MN a shift of UCH-L1 enzymatic activity to a dysfunctional protein negatively influences podocyte protein homeostasis by aberrant interactions with the proteasome.

TH-OR118

Common Risk Variants in NPHS1 and TNFSF15 Are Associated with Childhood Steroid-Sensitive Nephrotic Syndrome

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Background: Although steroid-sensitive nephrotic syndrome (SSNS) is the most common cause of glomerular disease in children, the pathogenesis remains unclear. Recent genome-wide association studies (GWASs) have shown that variants in the *HLA-DR/DQ* region are significantly associated with the disease in different populations. However risk loci outside of the *HLA* region are largely unknown.

Methods: We conducted a GWAS in 1,017 Japanese children with SSNS and 3,332 ancestry matched controls. We performed replication studies and trans-ethnic meta-analysis in Korean, South Asian, sub-Saharan African, European, and Hispanic populations.

Results: The most significant association was detected in *HLA-DR/DQ* region ($p=2.8 \times 10^{-33}$, odds ratio [OR]=2.49, 95%CI: 2.15-2.89). In addition, common variants in *NPHS1-KIRREL2* ($p=4.94 \times 10^{-20}$, OR=1.70, 95%CI: 1.66-2.18), *TNFSF15* ($p=2.54 \times 10^{-8}$OR=0.72, 95%CI: 0.64-0.81) and *TNFRSF11A* ($p=7.68 \times 10^{-8}$, OR=1.38, 95%CI: 1.23-1.56) regions achieved genome-wide or marginal genome-wide significance. Trans-ethnic meta-analysis confirmed the significant associations in *NPHS1* ($p_{meta}=7.06 \times 10^{-2}$, OR=1.91) and *TNFSF15* ($p_{meta}=4.05 \times 10^{-13}$, OR=0.72) loci. **Discussion:** *NPHS1* encodes nephrin and mutations in *NPHS1* cause congenital nephrotic syndrome of the Finnish type (CNSF). The two synonymous variants in *NPHS1* may induce aberrant splicing which could decrease the wild-type nephrin production and may affect the glomerular filtration barrier function. In addition, one of the two variants in *NPHS1* has been previously reported to induce *TRPC6* activation. *TNFSF15* encodes the TNF super-family member 15 (TNFSF15), ligand of death receptor 3. Activation of TNFS15 enhances the proliferation of human regulatory T cells (Tregs). The risk allele in *TNFS15* is associated with reduced expression of TNFSF15, which attenuate the proliferation of Tregs, consistent with findings reported in SSNS patients.

Conclusions: The present study markedly improves the understanding of genetic background of childhood SSNS, and provides another evidence that the gene responsible for a monogenic rare disease (CNSF) could be the susceptibility gene for a relatively common multifactorial disease (SSNS). [Collaborators: Xiaoyuan Jia, Yuki Hitomi, Katsushi Tokunaga]

Funding: Government Support - Non-U.S.

TH-OR119

Response to Intensified Immunosuppression in Genetically-Stratified SRNS Patients Predicts Outcomes and Indicates Distinct Underlying Mechanisms

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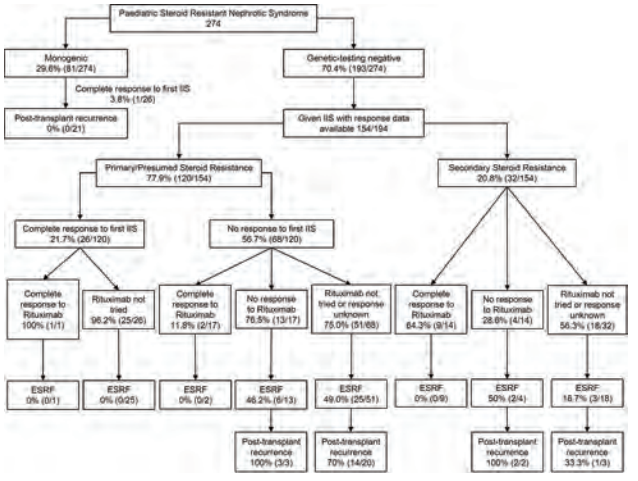
Background: We previously showed that secondary steroid resistance (SSR) in nephrotic syndrome is a reliable predictor of circulating factor disease that recurs post-transplantation. This follow-up study aimed to improve disease stratification by determining if response to intensified immunosuppression (IIS) in genetically-screened SRNS predicts disease progression and/or recurrence.

Methods: Paediatric patients with steroid resistant nephrotic syndrome (SRNS) were recruited via the United Kingdom RaDaR registry. 274 patients were whole genome, whole exome or SRNS-gene-panel sequenced. Complete response (CR) or partial response within six months of starting IIS was ascertained.

Results: Of 274 patients, 180 (93 male, median onset age 4.7 years, 99 focal segmental glomerulosclerosis) received IIS medications with responses available. 3.8% of monogenic disease patients showed CR, compared to 25.2% of genetic-testing negative (GTN) patients ($p=0.018$). None of the former recurred post-transplantation. In GTN patients, 97.4% with CR to first IIS showed no progression, whereas 43.2% of non-responders developed renal failure with 73.1% recurrence post-transplant. SSR had a higher CR rate than primary/presumed resistance (42.5% vs 23.0%, $p=0.0014$). Highest

CR rate was to Rituximab (64.3%). Biopsy findings showed no correlation with response to IIS or outcome.

Conclusions: This stratifies SRNS into three subgroups of prognostic utility based on genotype-phenotype correlation: monogenic disease responds poorly to IIS but doesn't recur, GTN SRNS that responding early to IIS with good long-term outcome, and multi-drug resistant GTN SRNS with poor renal survival and high post-transplant recurrence risk. This supports at least two different underlying immune mechanisms in non-genetic SRNS, able to determine disease outcome.



TH-OR120

Long-Term Efficacy of Rituximab and Mycophenolate Mofetil (MMF) Maintenance Therapy in Children with Steroid-Dependent Nephrotic Syndrome: RITURNS Trial Follow-Up

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Background: In the RITURNS study we demonstrated superior efficacy of Rituximab over Tacrolimus in children with steroid dependent nephrotic syndrome (SDNS), with 88 vs. 69 % relapse-free survival during a 12-month observation period (Basu et al. JAMA Pediatr 2018). Here we present the long-term outcomes of the patients in the Rituximab arm.

Methods: 59 of the 60 patients who had received a course of Rituximab (two infusions @375mg/m^2) in the RITURNS Study were available during a 2-year follow-up period after the end of the RITURNS study. Relapsing patients received a second course of Rituximab, either with (n=44) or without MMF co-treatment (n=15).

Results: During the extended follow-up, all patients developed relapses, with a median time to first relapse of 63 weeks for the entire cohort (Fig.1). Those patients who received co-treatment with MMF after the second course of Rituximab showed longer remission than those who received Rituximab alone (80% relapse-free survival 84 vs. 30 weeks) (Fig.2), whereas the total relapse rate (1.34 ± 0.75 vs. 1.47 ± 0.64) and cumulative prednisolone exposure (41.9 ± 35.0 vs. 45.5 ± 28.0 mg/kg) did not differ significantly. Both treatment protocols were equally well tolerated.

Conclusions: Recurrence of nephrotic syndrome occurred in all SDNS patients within 6 to 24 months following the first course of Rituximab. Co-treatment with MMF after Rituximab re-treatment substantially extended the duration of remission, with 75% of patients remaining relapse-free two years after the second Rituximab course.

Funding: Government Support - Non-U.S.

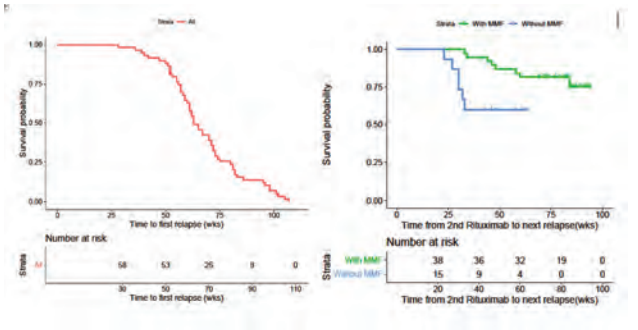

Figure 1: Time to first relapse (whole cohort).

Figure 2: Time from Rituximab re-treatment to relapse in patients with and without MMF co-treatment.

TH-OR121

A Global Anti B-Cell Strategy with Obinutuzumab and Daratunumab in Severe Pediatric Idiopathic Nephrotic Syndrome

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Background: The efficacy of B-cell depletion and Immunoglobulin adsorption in the treatment of patients with Steroid Dependant Nephrotic Syndrome (SDNS) and Steroid Resistant NS supports the involvement of B cells in the physiopathology of INS. However, rituximab (RTX) targets only CD20 positive B-cells and especially not plasma cells. Furthermore, RTX mediated B-cell depletion may paradoxically induce the settlement of autoreactive long-lived plasma cells which may account for some RTX failure. In this pilot study, we investigate in patients with severe SDNS the association of Obinutuzumab (OBZ), a 2nd generation anti CD20 monoclonal antibody, with higher in vitro B-cell cytotoxicity than RTX, with Daratumumab (DAR), an anti CD38 monoclonal antibody with high plasma cell cytotoxicity in addition to an immunomodulatory activity.

Methods: Patients received an infusion of 1000mg/1,73m^2 of obinutuzumab at day 0 and 1000mg/1,73m^2 of daratumumab at day 15. All other immunosuppressive treatments were discontinued within two months, and biological monitoring was performed monthly until B cell recovery.

Results: 9 patients with SDNS and resistance (n=3) or early relapse after prolonged B-cell depletion with rituximab (n=6) were included. Median ages at INS onset, first RTX and OBZ were respectively of 2.9, 7.7 and 10.9 years old. B-cell depletion was achieved in all patients. Median follow-up was 10 months (IQ 8.3-10.3), and all patients remained relapse-free. Six patients had still undetectable peripheral B-cells, while B-cell reconstitution occured at 7.9, 8.1 and 9.3 months in the 3 others. Mild infusion reactions were reported in 2/9 patient during OBZ and 3/9 during DAR infusions. Mild neutropenia (500-1000/mm^3) occured in 2/9 patients. 7/9 patients received IV immunoglobulins because of hypo-IgG. Hypo-IgA was noted in 8 patients and hypo-IgM in all patients. No severe infection was reported.

Conclusions: Global anti-B cell strategy with obinutuzumab and daratumumab induces prolonged peripheral B-cell depletion and nephrotic syndrome remission in children with severe SDNS. However, it induces frequent and profound hypogammaglobulinemia and further investigation of the safety and the long-term efficacy of this strategy is needed.

TH-OR122

Effect of Updated Hypertension Guidelines on Blood Pressure Staging in Pediatric Kidney Transplant Recipients

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Background: In 2017, pediatric hypertension (HTN) guidelines were updated with 2 major changes compared to the 2004 NHBPEP 4th Report: normative blood pressure (BP) values excluded overweight children and simplified staging was provided for children ≥13 yo using the adult nominal cutoffs. This study evaluated the effect of the new guidelines on BP staging in children with kidney transplant (KT) using registry data from the Improving Renal Outcomes Collaborative (IROC).

Methods: We examined the last accurate BP measurement for patients <18 yo and >90 days post-KT in the IROC registry and compared BP staging using percentile (%tile) cutoffs in the 4th Report versus 2017 AAP HTN Guidelines. BP staging using AAP %tile versus adult nominal cutoffs for children ≥13 yo were also compared. Associations between overweight or short stature and change in BP staging were assessed with Chi-square tests, odds ratios (OR), and 95% confidence intervals (CI).

Results: A total of 563 patients met inclusion criteria. When applying AAP %tile cutoffs, 71/563 (13%) had increased BP stage compared to 4th Report classification, with most changing from normal to elevated or pre-HTN to stage 1 (see table). Overweight/obese children were more likely to have increased staging using AAP %tiles (OR 1.7, CI 1.05-2.90) compared to 4th Report cutoffs. When applying adult cutoffs for children ≥13 yo, BP stage decreased in 13% (31/241) compared to the %tile cutoffs in the AAP Guidelines. This age group had below-average height (median height %tile 11.2, IQR 1.9-38.5). Height percentile was a significant risk factor for decreased BP stage using adult cutoffs (p=0.01).

Conclusions: Short stature and obesity, which are common in pediatric KT recipients, affect BP staging when applying updated HTN guidelines. The application of adult BP cutoffs in children with kidney transplant ≥13yo may under-report uncontrolled BP, especially in those with short stature. Transplant physicians may consider applying percentile-based cutoffs until adulthood in this population with high cardiovascular risk.

Funding: NIDDK Support

BP Staging <18yo		AAP %tile cutoff				
		Normal	Elevated	Stage 1	Stage 2	Row total (% overall)
4th Report	Normal	339	*32*			371 (66%)
	Pre-HTN	1	65	*35*		101 (18%)
	Stage 1		1	71	*4*	76 (14%)
	Stage 2				9	9 (2%)
	Column total (% overall)	340 (61%)	98 (17%)	106 (19%)	19 (3%)	563

TH-OR123

Low Albumin Is Associated with Neonatal AKI During the First Post-Natal Week of Life: Report from the AWAKEN Study Group

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Background: Hypoalbuminemia is an established risk factor for morbidity and mortality in adults and children. Adult studies showed an association between low albumin (alb) and acute kidney injury (AKI) in different settings. Low alb was found to be associated with AKI in children undergoing cardiac surgery. In this analysis of newborns (NB) enrolled in the Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) we hypothesize that low alb is associated with increased risk of AKI in the first postnatal week of life. To our knowledge, this is the first study to examine this relationship in NB

Methods: AWAKEN included 2162 NB admitted to the neonatal intensive care units at 24 institutions (4 countries) from 01/14-03/14. Inclusion criteria: intravenous fluids for ≥48 hrs. Exclusion criteria: congenital heart disease repair at <7 days of life, lethal anomaly or death at ≤48 hrs. For this analysis, we excluded 1461 NB who had no alb levels documented, 19 NB who didn't have at least 2 serum creatinines or at least one day of urine output recorded during first postnatal week. Analysis was done for the entire cohort and for 3 stratified groups; <29 weeks (wks), ≥29 to <36 wks and ≥36 wks gestational age (GA)

Results: A total of 682 babies were included, 47.8% had at least 1 episode of AKI. Table 1 shows that mean minimum alb was significantly lower in AKI group versus the no-AKI group ($p < 0.0001$) for the entire cohort and for each of the 3 stratified groups. Mean maximum Alb was higher in the no-AKI group versus the AKI group ($p= 0.0001$) for the entire cohort and for the <29 wks and ≥39 wks groups. Low alb levels were independently associated with AKI. For every 1 g/dL decrease in alb the odds of developing AKI increased by 4%. Even after adjusting for confounders including fluid status; for every alb of 1 there was 4.6% higher odds of having AKI

Conclusions: AWAKEN describes for the first time the association between low alb and AKI in the first postnatal week. This association remained regardless of fluid balance and other potential confounders

Table 1: Mean and SD of Minimum and Maximum Albumin Levels Among Studied Groups

	Whole Group n=682			GA< 29 weeks n= 99			GA ≥29<36 n=237			GA≥36 weeks n= 346		
	No AKI n= 356	AKI n= 326	p-value	No AKI n= 41	AKI n= 58	p-value	No AKI n= 145	AKI n= 92	p-value	No AKI n= 170	AKI n= 176	p-value
Minimum albumin	2.7±0.6	2.4±0.6	< 0.0001	2.6±0.5	2.2±0.6	0.001	2.7±0.5	2.4±0.6	0.001	2.8±0.6	2.5±0.7	<0.0001
Maximum albumin	3.0±0.5	2.8±0.7	0.0001	2.8±0.5	2.5±0.6	0.003	2.9±0.5	2.9±0.7	0.79	3±0.6	2.9±0.7	0.004

TH-OR124

Effect of Erythropoietin (Epo) on Outcomes at 24-26 Months in Extremely Low Gestational Age Neonates (ELGAN)

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Background: Changes in EPO in premature infants may have a critical role in glomerulogenesis. The REPAIReD study examines kidney outcomes of ELGANS enrolled in PENUT, a randomized placebo-controlled trial of Epo. We compare prevalence and risk factors of chronic kidney disease (CKD), albuminuria, and hypertension at 24 months corrected gestational age (cGA) by treatment group.

Methods: Patients who survived to 24-26 months cGA with blood, urine or blood pressure at follow-up were included. We defined CKD as estimated glomerular filtration rate (eGFR) via the Schwartz cystatin C equation <90 ml/min/1.73m^2; hypertension as either systolic blood pressures (SBP) or diastolic (DBP) > 95%ile for height, age and gender; and albuminuria as a urine albumin/creatinine ratio ≥ 30 mg/g. Associations between baseline characteristics, maternal race and pre-eclampsia, and outcomes were assessed.

Results: 778 (84%) of enrolled babies had a 24-26 month follow up visit. 54 (16%) had an eGFR < 90mL/min/1.73m^2, 155 (36%) had albuminuria, 119 (24%) had systolic hypertension and 163 (33%) had diastolic hypertension. We found no difference by treatment group. An eGFR <90 was associated with lower birthweight ($p<0.001$), small for gestational age ($p<0.05$) and pre-eclampsia ($p<0.05$).

Conclusions: A low GFR, albuminuria, and hypertension are common in ELGANS and present at 24-26 months of age. Long-term kidney follow up of all premature infants less than 28 weeks GA is needed starting at 2 years old.

Funding: NIDDK Support

Table 1. Baseline characteristics and 24-month follow-up by treatment arm

	Placebo	Epo Treatment
Gestational age, n (%) 24 weeks 25 weeks 26 weeks 27 weeks	 117 (25.8%) 122 (26.9%) 117 (25.8%) 98 (21.6%)	 110 (23.5%) 120 (25.6%) 103 (22.0%) 136 (29.0%)
Alive at hospital discharge, n (%)	410 (90.3%)	418 (89.1%)
24-month follow-up conducted, n (%)	395 (87.0%)	383 (81.7%)
24 mo height/weight available, n (%) Weight kg, mean (sd) Height cm, mean (sd)	358 (78.9%) 11.4 (1.7) 84.5 (4.5)	344 (73.3%) 11.3 (1.9) 85.1 (4.8)
24 mo blood collected, n (%)	190 (41.9%)	170 (36.2%)
24 mo urine collected, n (%)	218 (48.0%)	227 (48.4%)
eGFR value available, n (%) Median mL/min/1.73m2 (IQR) <90 mL/min/1.73m2, n (%)	179 (39.4%) 101.3 (93.8, 113.8) 29 (16.2%)	157 (33.5%) 102.7 (96.6, 112.7) 25 (15.9%)
Alb/Creat ratio available, n (%) Median mg/g (IQR) ≥30 mg/g, n (%)	212 (46.7%) 21.8 (13.4, 37.7) 78 (36.8%)	223 (47.5%) 22.0 (14.3, 38.2) 77 (34.5%)
eGFR and Alb/Creat ratio available, n (%) eGFR≥90 and/or Alb/Creat<30, n (%) eGFR<90 and Alb/Creat≥30, n (%)	131 (28.9%) 125 (95.4%) 6 (4.6%)	114 (24.3%) 104 (91.2%) 10 (8.8%)
Hypertension value available, n (%)	258 (56.8%)	234 (49.9%)
SBP >=95th %ile, n (%)	70 (27.1%)	49 (20.9%)
Median SBP (IQR)	98.5 (90, 106.75)	97 (90, 104)
DBP >=95th %ile, n (%)	87 (33.7%)	76 (32.5%)
Median DBP (IQR)	58.0 (52.0, 65.8)	58.0 (50.0, 66.0)

TH-OR125

Stable Calcium Isotopes: A Novel Biomarker of Bone Mineral Density in Children with CKD

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Background: In CKD dysregulated calcium (Ca) homeostasis is common and causally associated with reduced bone mineral content and vascular calcification. Currently available radiological measures and biomarkers do not allow an accurate evaluation of bone mineralisation.

Methods: We measured stable Ca isotope fractions ($\delta^{44/42}Ca$) by plasma ionization mass spectrometry in blood and urine as biomarkers for bone mineralization. The relationship between bone Ca gain and loss is described mathematically using a compartment model based on Ca kinetics. 104 children in CKD4-5 and on dialysis (CKD4-5D) and 40 matched controls underwent Ca isotope measurement, bone biomarkers, dual energy x-ray absorptiometry (DXA) and tibial peripheral quantitative CT scan (pQCT). pQCT accurately defines cortical and trabecular bone mineral density (BMD), and tibial cortical BMD Z-score is shown to predict fracture risk.

Results: Both the $\delta^{44/42}Ca_{Blood}$ and $\delta^{44/42}Ca_{Urine}$ were significantly different in children with CKD4-5D compared to healthy controls ($p<0.001$ for both). In healthy children the $\delta^{44/42}Ca_{Blood}$ and $\delta^{44/42}Ca_{Urine}$ were higher than values reported in adults (-0.27 vs -0.84 ‰ for $\delta^{44/42}Ca_{Blood}$ and 0.94 vs 0.35‰ for $\delta^{44/42}Ca_{Urine}$), reflecting avid Ca uptake during bone formation. There was a linear association between estimated GFR and $\delta^{44/42}Ca_{Urine}$ ($p<0.0001$) in CKD. $\delta^{44/42}Ca_{Blood}$ positively correlated with cholecalciferol ($p=0.01$) and alfacalcidol ($p=0.002$) doses, implying increased bone Ca uptake when Ca bioavailability is increased. $\delta^{44/42}Ca_{Blood}$ showed a linear association with established biomarkers of bone formation (alkaline phosphatase, $p=0.05$) and bone resorption (TRAP5b, $p<0.001$ and CTX, $p=0.006$). $\delta^{44/42}Ca_{Blood}$ strongly correlated with tibial cortical BMD Z-score ($p<0.0001$, $R^2=0.39$), and DXA hip Z-score ($p=0.02$). On multivariable linear regression analysis significant and independent predictors of tibial cortical BMD Z-score were $\delta^{44/42}Ca_{Blood}$ ($\beta=0.68$, $p=0.006$) and PTH ($\beta-0.39$, $p=0.04$), together predicting 67% of the variability in BMD.

Conclusions: Ca isotope ratios provide a novel, non-invasive method of assessing bone mineral density in children with CKD and may be used to guide safe and effective treatment that prevents Ca deficiency or overload.

Funding: Government Support - Non-U.S.

TH-OR126

Pediatric CKD Is Associated with Abnormal White Matter Integrity

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Background: Children with chronic kidney disease (CKD) are at risk for neurocognitive deficits. Neuroimaging studies provide an opportunity to accurately assess the brain and yield clues to the underlying mechanisms of observed neurocognitive abnormalities. To date, few published studies exist evaluating brain structure in pediatric CKD and often involve heterogenous samples with late CKD/end-stage populations of varying etiologies.

Methods: We describe the effect of mild to moderate CKD on brain white matter integrity (WMI) using quantitative MRI diffusion tensor imaging. Patients age 6-16 with congenital, non-glomerular causes of CKD (eGFR 30-90 ml/min/1.73m2) were invited to participate [N_{cases} = 20, $N_{control}$ = 26]. Participants completed a neurocognitive evaluation and MRI scan. WMI was calculated utilizing measurement of fractional anisotropy (FA). Voxel-wise linear regression models were calculated using R where FA values were predicted by CKD-status. Sex, age, blood pressure, and parental socioeconomic status were included as covariates.

Results: Relative to controls, CKD participants showed significant decreases in WMI within multiple brain regions including the right orbitofrontal cortex (Fig 1: t(54)=-3.74, p=0.000452, q=0.00722). Linear regression was performed to predict the relationship between regions with FA deficit and executive function. For males, lower FA within the right orbital frontal cortex was related to poorer executive function as measured by the Behavior Rating Inventory of Executive Function global executive composite (p = 0.006). In models adjusted for age, sex, participant type, and systolic blood pressure, lower FA within this region remained associated with poorer executive function (p = 0.011).

Conclusions: Our data demonstrate distinct white matter abnormalities in early pediatric CKD due to congenital anomalies of the kidney/urinary tract. Furthermore, these alterations in WMI are associated with executive function.

Funding: NIDDK Support

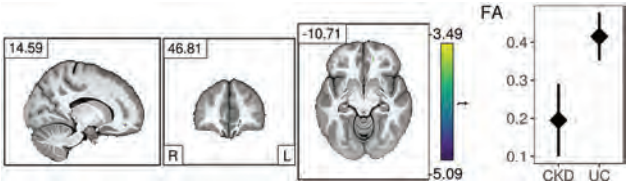

Figure 1: Localization of the right orbitofrontal WMI difference between cases (CKD) and controls (UC) [voxel coordinates xyz: 14.6, 46.8, -10.7].

TH-OR127

Sleep Problems and Fatigue and Their Relationships with Emotional-Behavioral Symptoms and Neurocognitive Outcomes in Pediatric CKD

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Background: Children with CKD are at risk for deficits in neurocognitive function. It is not known how sleep problems/fatigue within the context of CKD may contribute to these deficits.

Methods: Data from the Chronic Kidney Disease in Children (CKiD) study was used to evaluate the prevalence of sleep problems/fatigue among children with mild to moderate CKD, and to examine whether sleep problems or fatigue predict neurocognitive or emotional-behavioral outcomes. Four variables were created: fatigue, sleep disturbance, low energy, and trouble sleeping. Linear mixed models were used to determine if fatigue or sleep problems were associated with neurocognitive and emotional-behavioral outcomes. Each model was adjusted for sociodemographic and disease-related covariates.

Results: Baseline data was available for 1030 participants (median disease duration 6 years; 63% male; mean eGFR was 53 ml/min|1.73m^2). Prevalence was 26% (fatigue), 30% (sleep disturbance), 52% (low energy), 39% (trouble sleeping). Sleep disturbance (β=1.28, CI=0.25, 2.32; p=.02), low energy (β=1.85, CI=0.79, 2.9; p=.0006), and trouble sleeping (β=1.87, CI=0.87, 2.87; p=.0003) were significantly associated with worse parent ratings of overall executive functions. Low energy was significantly associated with lower working memory (Digit Span Forward β=-0.37, CI=-0.72, -0.01, p=.05; Digit Span Backward β=-0.48, CI=-0.87, -0.09, p=.02). Low energy was significantly associated with lower inhibition (B=-0.92, CI=1.57, -0.28, p=.0006) and lower problem-solving B=-0.67, CI=-1.25, -0.09, p=.02). Each of the four sleep measures was significantly related to more internalizing symptoms on a measure of emotional-behavioral functioning, and sleep disturbance, low energy, and trouble sleeping were associated with more externalizing symptoms.

Conclusions: A significant proportion of children with CKD report fatigue and problems with sleep. Sleep problems and fatigue were associated with lower executive functioning and increased emotional-behavioral symptoms over time after adjusting for key sociodemographic and CKD-related covariates. Assessing sleep problems/fatigue and treating co-morbidities may promote more positive emotional-behavioral and neurocognitive outcomes for children with CKD.

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

TH-OR128

Economic Evaluation of Lifelong Medicare Immunosuppressive Drug Coverage for Kidney Transplant Recipients

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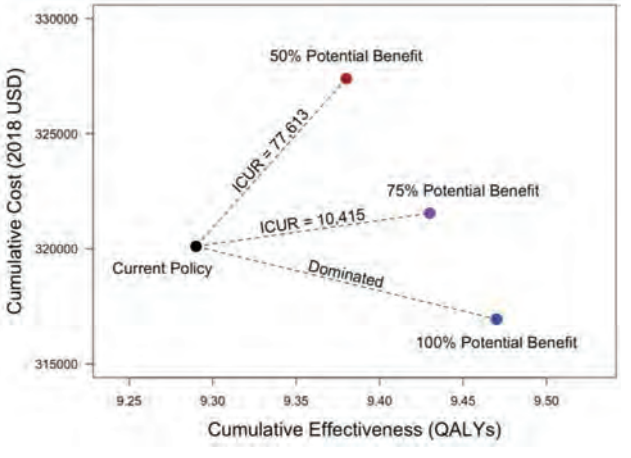
Background: Medicare coverage for kidney transplant recipients ceases 36 months after transplantation. This policy removes coverage for life-saving immunosuppressive medications essential to prevent rejection and maintain transplant function. A contemporary economic analysis of extending Medicare coverage for the duration of transplant survival using mean cost of immunosuppressant medications in the era of generic equivalents which accounts for that fact that many transplant recipients currently continue to receive Medicare coverage beyond 36 months due to medical disability is not available.

Methods: A Markov model was used to determine the incremental cost and effectiveness of extending Medicare coverage for immunosuppressive drugs for the duration of transplant survival compared with the current policy from the perspective of the Medicare payer. The model used contemporary mean costs of immunosuppressive medications, and incorporated assessment of continuation of Medicare coverage beyond 36 months in patients who are designated medically disabled. The expected graft survival of extending immunosuppressive drug coverage was estimated from a cohort of privately insured transplant recipients using multivariable survival analysis.

Results: Extension of immunosuppression coverage under Medicare for kidney transplant recipients led to lower costs of -$3,163 and 0.18 additional quality adjusted life years (QALYs). When the improvement in transplant survival associated with extending immunosuppressive coverage was reduced to 50% of that observed in privately insured patients, the strategy of extending drug coverage had an ICUR of $77,613/ QALY gained.

Conclusions: Extending immunosuppressive drug coverage under Medicare from the current 36 months to the duration of transplant survival will result in better patient outcomes and cost savings, and remains cost-effective if only a fraction of anticipated benefit is realized.



TH-OR129

Absence of Additional Predictive Ability Value of Preimplantation Biopsies for Long-Term Allograft Outcome

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Background: A significant number of kidneys are discarded worldwide due to the suboptimal use of large kidney resources. The main cause of discard is the result of the preimplantation biopsy.

Methods: We included patients who underwent kidney transplantations from a deceased donor in 2 French referral centers between 2004 and 2014 with preimplantation biopsy. Two external validation cohorts were included: 1,107 deceased donors from Belgium and 1,103 discarded kidneys based on biopsy results from the US.

Results: A total of 1,629 patients were included in the development cohort. After adjusting for donor, recipient, and transplant characteristics as well as for preimplantation biopsy findings (IFTA, cv and ah Banff score, and glomerulosclerosis percentage) and baseline immunological parameters, we identified the KDRI score (HR=2.50; 95% CI, (1.38 to 3.40); p<0.001), the presence of circulating DSA on the day of transplantation (HR=1.76; 95% CI, (1.36 to 2.28); p<0.001), prior kidney transplantation (HR=1.34; 95% CI, (1.01 to 1.78); p=0.045), and the IFTA score (HR=1.51; 95% CI, (1.00 to 2.26); p=0.048) as the main independent determinants of long-term allograft loss. However, the biopsy results had no additional value to predict long term allograft outcome when compared to the model without the biopsy results. In the Belgium validation cohort, none of the biopsy results were associated with allograft loss. Kidneys discarded based on histology results in the US were matched to transplanted kidneys in France. French kidneys with similar histological results as discarded kidneys in the US did not have worse allograft survival compared to the unmatched transplanted kidneys (p=0.156).

Conclusions: Given this result and the fact that preimplantation biopsies increase the cold ischemia time, the current practice of discarding kidneys based on preimplantation biopsy results may not be optimal for allocation decision-making.

TH-OR130

Recipient Outcome After Declining a Deceased-Donor Kidney Offer

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Background: The decision to accept a deceased-donor kidney depends on organ quality, and also recipient factors, such as an estimate of mortality on dialysis, and the likelihood of receiving a more favourable offer. Whilst outcome after transplantation has been well studied, with several donor-related risk factors widely accepted, little is known about the outcome after declining a kidney, such as the influence of recipient factors on the chance of subsequent transplantation.

Methods: Over a 12 month period at a single UK centre, all potential recipients were identified for whom a deceased-donor kidney offer was declined, with subsequent transplant outcomes recorded.

Results: Kidneys were declined for 145 patients, aged 24 - 78 (mean 54.1), due to donor / organ quality (57.2%), recipient illness / unavailability (26.2%), and positive crossmatch (4.8%) with the remaining offers withdrawn (11.8%), largely due to delayed cardiac death. Over a mean follow-up of 12 months, 83 patients (57.2%) received at least one further offer. Second offers tended to be from slightly younger donors (53.5 vs 58.8 years, p=0.103) with the same HLA match (3.2/6 antigens matched). By the end of observation 59 (40.7%) had been transplanted, 46 (31.7%) remained on the wait-list, 38 (26.2%) were temporarily or permanently suspended from the wait-list, and 2 (1.4%) had died. Compared to those less sensitised, highly sensitised patients (calculated HLA reaction frequency over 75%) were less likely to be transplanted (23.1 vs 47.3%, p=0.025). Older patients (over 60) were more likely to be suspended (39.3 vs 22.0%, p=0.028) with a similar tendency also seen in those waiting over 4 years for their first offer (40.5 vs 25.3%, p=0.082).

Conclusions: After declining a deceased-donor kidney, around 40% of patients may expect to be transplanted during the following year, whilst around 25% may be suspended from the wait-list. Risk factors for suspension or non-transplantation include older age, longer wait-time and greater HLA sensitisation. These data will be helpful to patients and clinicians making kidney offer decisions.

TH-OR131

Decreasing Risks of Kidney Transplantation Using High KDPI Kidneys by Preferred Recipient Matching

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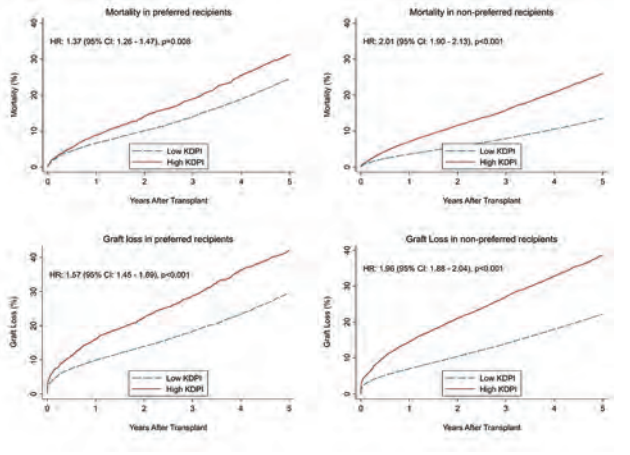
Background: Kidneys with a high Kidney Donor Profile Index (KDPI, ≥ 85%) are often discarded due to an increased risk of mortality and graft loss. However, we hypothesized that some recipients might tolerate high KPDI kidneys well, and are therefore best suited to receive these grafts.

Methods: Using national registry data from SRTR from 2006-2017, we compared 10,361 kidney transplant recipients of high KDPI (≥ 85%) kidneys to 120,983 recipients of low KDPI (< 85%) kidneys. We identified recipient factors that amplified (or attenuated) the impact of high KDPI on mortality and graft loss using interaction analysis, classifying recipients without amplifying factors and with attenuating factors as preferred recipients. We compared mortality and graft loss with high KDPI versus low KDPI kidneys in preferred and non-preferred recipients using Cox regression.

Results: Preferred recipients were determined to be recipients who were ≥ 60 years old, non-white, with diabetes, and without glomerular or cystic disease as the cause of their ESRD. The increased mortality risk associated with high KDPI kidneys was 32% lower (interaction ratio: $_{0.62}0.68_{0.74}$, p<0.001) in preferred vs. non-preferred recipients, whereas the increased risk of graft loss was 21% lower (interaction ratio: $_{0.73}0.79_{0.85}$, p<0.001). This translated to a 1.37-fold higher mortality risk (HR: $_{1.26}1.37_{1.47}$, p<0.001) with a high KDPI kidney versus a low KDPI kidney in preferred recipients, compared to a 2.01-fold higher mortality risk (HR: $_{1.90}2.01_{2.13}$, p<0.001) for non-preferred recipients (Figure). Similarly, there was a 1.57-fold higher risk of graft loss (HR: $_{1.45}1.57_{1.69}$, p<0.001) with a high KDPI kidney versus a low KDPI kidney in preferred recipients, in comparison to a 1.96-fold higher risk of graft loss (HR: $_{1.88}1.96_{2.04}$, p<0.001) for non-preferred recipients (Figure).

Conclusions: The risks of kidney transplantation with high KDPI kidneys can be decreased by appropriate recipient selection.

Funding: NIDDK Support



TH-OR132

Cognitive Function and Waitlist Outcomes in Kidney Transplant Candidates With and Without Diabetes

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Background: Kidney transplantation (KT), while contraindicated for those with diagnosed dementia, improves cognitive function in ESKD patients. However, KT candidates may have unrecognized cognitive impairment, which can lead to difficulties navigating the health system and poor health behaviors that may prolong KT evaluation, elevate mortality risk, and hinder access to KT. Therefore, we estimated the burden of cognitive impairment at KT evaluation and its association with access to KT and waitlist mortality.

Methods: In a 2-center cohort study of 3,630 ESKD participants, we estimated adjusted chance of listing (Cox), risk of waitlist mortality (competing risks), and KT rate (Poisson) by cognitive impairment (3MS<80). Given potential differences in etiology in cognitive impairment in those with and without diabetes, we tested if associations differed by diabetes (Wald test).

Results: At evaluation, 6.4% had cognitive impairment, which was independently associated with 25% lower chance of listing (aHR=0.75, 95%CI:0.61-0.91); this association did not differ by diabetes ($p_{interaction}$=0.07). However, associations between cognitive impairment and waitlist mortality ($p_{interaction}$=0.02), as well as KT rates ($p_{interaction}$=0.048) differed by diabetes. In candidates without diabetes, those with cognitive impairment had 2.47-times (95%CI:1.31-4.66) greater risk of waitlist mortality and reduced KT rate (aIRR=0.58, 95%CI:0.36-0.93); cognitive impairment was not associated with these outcomes in candidates with diabetes.

Conclusions: Clinicians should screen for cognitive impairment in KT candidates, especially among those without predisposing conditions like diabetes, and identify interventions to improve access to KT so that these vulnerable patients can experience post-KT cognitive improvements.

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Table. Cumulative incidence (%) and associations of listing, waitlist mortality, and kidney transplantation (KT) by global cognitive impairment. Participants were classified as cognitively impaired if they had a 3MS score <80. Adjusted associations were controlled for age, sex, race, diabetes, educational attainment, and the Charlson Comorbidity Index adapted for ESKD. To explore the association between waitlist mortality and cognitive impairment by diabetes status, an interaction term was added between cognitive impairment and diabetes status. Abbreviations: HR, hazard ratio; SHR, subdistribution hazard ratio; IRR, incidence rate ratio.

Outcome by Global Cognitive Impairment	n	Unadjusted Cumulative incidence (%) 6 months	1 year	3 year		
Chance of Listing					**Adjusted HR (95% CI)**	**p-value**
Overall						
Not impaired	233	50.5	59.1	63.8	Reference	
Impaired	3,397	32.0	43.7	51.5	0.75 (0.61-0.91)	0.004
Diabetes						
Not impaired	1,201	52.4	63.8	69.5	Reference	
Impaired	91	42.2	57.3	65.0	0.92 (0.70-1.22)	0.56
No Diabetes						
Not impaired	1,682	63.8	73.3	79.8	Reference	
Impaired	93	37.9	52.9	67.7	0.63 (0.48-0.83)	0.001
Risk of Waitlist Mortality					**Adjusted SHR (95% CI)**	**p-value**
Overall						
Not impaired	2,101	0.04	1.4	9.0	Reference	
Impaired	115	0.07	2.2	14.2	1.35 (0.83-2.18)	0.23
Diabetes						
Not impaired	793	0.7	1.9	13.5	Reference	
Impaired	56	0.6	1.8	12.7	0.90 (0.48-1.70)	0.75
No Diabetes						
Not impaired	1,281	0.3	0.9	6.3	Reference	
Impaired	57	0.8	2.3	16.0	2.47 (1.31-4.66)	0.01
Rate of KT					**Adjusted IRR (95% CI)**	**p-value**
Overall						
Not impaired	2,101	6.3	17.8	42.7	Reference	
Impaired	115	4.7	13.5	33.8	0.78 (0.56-1.09)	0.14
Diabetes						
Not impaired	793	4.3	13.0	31.5	Reference	
Impaired	56	4.5	13.7	33.0	1.12 (0.71-1.77)	0.64
No Diabetes						
Not impaired	1,281	7.8	20.9	49.8	Reference	
Impaired	57	4.9	13.6	35.1	0.58 (0.36-0.93)	0.03

TH-OR133

Self-Reported vs. Measured Physical Function in Kidney Transplant Candidates at the Top of the Waitlist

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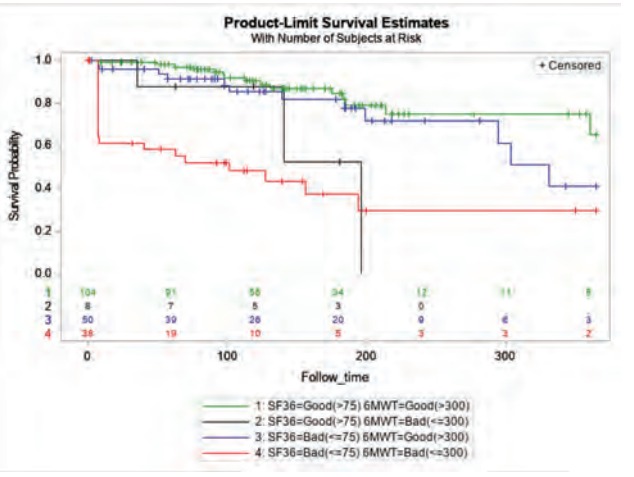
Background: Poor physical function of waitlisted kidney transplant candidates is associated with adverse waitlist outcomes, but the optimal metric is not known. We compared self-reported versus measured functional assessments in patients at the top of the waitlist.

Methods: Patients were evaluated from May 2017 to December 2018. Self-reported SF36 physical function subscale score (SF36 PF) was compared to results of the 6-minute walk test (6MWT) and sit-to-stand (STS) test by linear regression. We estimated the association between each metric and time to adverse waitlist outcomes (waitlist removal or death), with transplant as the competing event, by the Fine-Grey model, and adjusted for clinical covariates. We estimated model fit by AIC and likelihood ratios and compared hierarchically nested models, starting with demographics and comorbidities and sequentially adding physical assessment metrics.

Results: Out of 200 patients, the median SF36 PF, 6MWT, and STS results were 80, 396 meters, and 18, respectively. Physical function metrics were highly correlated (R^2=0.49 for STS-6MWT, 0.32 for STS-SF36 PF, and 0.54 for 6MWT-SF36 PF). Over median follow-up of 118 days, 29 patients were removed from the waitlist, 6 died, and 23 were transplanted. All three metrics were strongly associated with waitlist outcomes and improved model fit for adverse waitlist outcomes over standard exposures of demographics and comorbidities alone. 6MWT and SF36 PF results improved model fit more than STS. See figure.

Conclusions: Self-reported and measured assessments of physical function are strongly associated in kidney transplant candidates. Addition of SF36 and/or 6MWT results to standard exposures significantly improves association with waitlist outcomes. Combining self-reported and measured physical function metrics may provide the best assessment of global functional status in kidney transplant candidates.



TH-OR134

Living Kidney Donor Visceral Adipose Tissue Predicts Donor Histopathology and Post-Donation Kidney Functional Decline

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Background: Living kidney donors have become increasingly complex with increased obesity and older age. Given the association of visceral adipose tissue (VAT) and kidney functional decline in the general population, we hypothesized that VAT in living donors may predict baseline histopathology and post-donation kidney function.

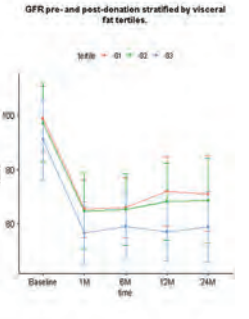
Methods: We measured VAT in 170 living kidney donors using pre-donation computerized tomography (CT) imaging and computerized software at a single lumbar level: L3-L4 for females and L2-L3 for males. All donor kidneys had preimplantation biopsies. Chronic histologic findings were defined as 2 of 3 biopsy findings: >5% global glomerulosclerosis, any interstitial fibrosis with tubular atrophy, or the presence of any arteriosclerosis. Kidney function was recorded by estimated glomerular filtration rate (eGFR) pre-donation and at 1, 12, and 24 months post-donation. GFR decline was defined as the percent drop in eGFR at 12 months vs. pre-donation.

Results: Greater VAT by tertiles correlated with older donor age, male gender, smoking, higher blood pressure, lipid abnormalities, and body mass index (BMI), (TABLE). Donor glomerulosclerosis and interstitial fibrosis on biopsy also correlated with VAT (TABLE). The highest tertile of VAT also correlated with lower pre-donation eGFR and less GFR recovery (FIGURE). After controlling for all associated donor variables including age, gender, and BMI, donor VAT remained an independent predictor of chronic histologic findings (OR: 1.02, 95% CI 1.01-1.04, p<0.001), and GFR decline after donation (b = 0.04, 95% CI: 0.02 to 0.07, p=0.001).

Conclusions: Living kidney donor VAT using standardized CT measurements correlated independently with both histopathologic findings and kidney functional decline after donation. VAT measurement may allow for donor risk stratification and may identify donors at higher risk for long term kidney functional impairment.

Funding: Private Foundation Support

Variable	First tertile (7-56 cm²) n=67	Second tertile (51-121 cm²) n=67	Third tertile (122-284 cm²) n=66	p Value
Age, yrs	38 ± 10	43 ± 10	46 ± 9	<0.001
Male gender (%)	25	37	83	<0.001
Black race (%)	4	12	5	0.213
Smoker (%)	4	25	13	0.004
SBP, mmHg	112 ± 13	118 ± 15	119 ± 12	0.016
DBP, mmHg	73 ± 9	75 ± 9	78 ± 10	0.011
Total Chol (mg/dl)	177 ± 28	184 ± 34	180 ± 40	0.182
HDL (mg/dl)	68 ± 15	58 ± 14	48 ± 12	<0.001
LDL (mg/dl)	95 ± 25	106 ± 34	114 ± 35	0.007
BMI (kg/m²)	24 ± 3	28 ± 4	30 ± 3	<0.001
Arteriosclerosis (% of donors)	40	42	57	0.235
Glomerulosclerosis (% of donors)	0	7	32	<0.001
Interstitial Fibrosis (% of donors)	5	9	23	0.040
Predonation GFR, ml/min	99 ± 12	97 ± 15	91 ± 15	0.006
Post donation GFR, one month	85 ± 10	85 ± 14	57 ± 12	<0.001
Post donation GFR, one year	72 ± 13	68 ± 14	57 ± 11	<0.001



TH-OR135

Improvement in Waiting Times for Recipients of A_2 to B Kidney Transplants: Refining Our Understanding

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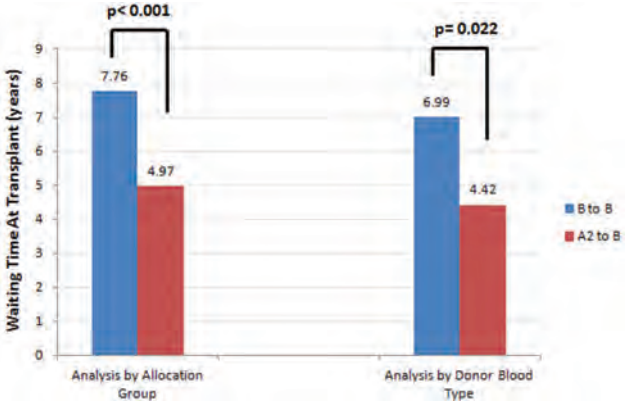
Background: The creation of a new allocation priority in the new Kidney Allocation System (KAS) for transplants from blood group A_2 donors to blood group B recipients has allowed more rapid transplantation of the group B list. However, no analysis has looked at the decrease in waiting times controlling for differences in sensitization or other priority factors (such as HIV or HCV positive kidneys). We undertook to do this type of robust analysis.

Methods: We conducted a retrospective analysis of 396 consecutive recipients who received a deceased donor kidney transplant in the time period from December 4, 2014 (the beginning of KAS) to November 1, 2018. We determined the waiting time based on the distribution pool in which the kidney was allocated and compared patients receiving kidneys in the local or regional blood type B for blood type A_2/A_2B donor only pools with those receiving kidneys within the local, regional, or national blood type identical or permissible pools.

Results: There were a total of 17 transplants of A_2/A_2B organs from deceased donors into blood group B recipients. 15 of the 17 were allocated within the A_2/A_2B pools (the other 2 were allocated in high cPRA pools). In the same period there were 57 B to B transplants of which 37 were allocated in the blood type identical or permissable pools. The 15 patients receiving A_2/A_2B organs had a mean waiting time of 4.97 ± 1.55 years, significantly lower than the 37 patients receiving standard B to B transplants (7.76 ± 3.91 years, p <0.001). This amounted to a 35.9% reduction in waiting time.

Conclusions: The benefits of A_2 to B transplantation in decreasing waiting times to transplant have been thus far underestimated due to the confounding factors of high sensitization and other high priority allocation. An A_2 to B transplant protocol can reduce waiting times by more than a third for hard to transplant patients.



Improvement in Waiting Times for Recipients of blood group A2 kidneys

TH-OR136

Normothermic Ex Vivo Kidney Perfusion Preservation Reliably Improves Extreme Marginal Graft Function Compared with Hypothermic Machine Perfusion

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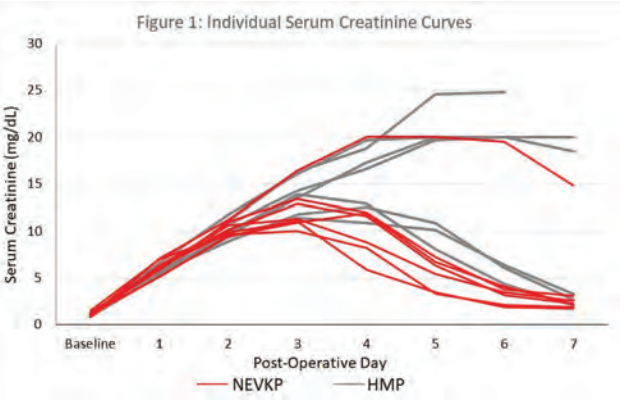
Background: Normothermic ex-vivo kidney perfusion (NEVKP) is an emerging technique for renal graft preservation. We investigated whether NEVKP promoted improved marginal graft function compared to anoxic hypothermic machine perfusion (HMP) in a model of donation-after-cardiac-death (DCD).

Methods: Kidneys from 30kg-Yorkshire pigs were removed following 120min of warm ischemia (WI). These grafts were preserved with HMP (LifePort1.0, n=7) or NEVKP (n=7) for 8h prior to heterotopic autotransplantation.

Results: During NEVKP, 120min WI grafts cleared perfusion lactate (0h:10.48±0.93mmol/L vs 7h:1.48±0.85mmol/L,p<0.01), had decreasing intra-renal resistance (IRR) (0h:2.26±0.9mmHg/mL/min vs 7h:0.37±0.6mmHg/mL/min, p<0.01), and produced urine. IRR also decreased in HMP (0h:1.71±0.30mmHg/mL/min vs 7h:1.19±0.37mmHg/mL/min, p=0.01). Post-transplant, 120min WI grafts with NEVKP trended towards earlier and decreased serum creatinine (SCr) peak values compared to HMP (POD3:12.29±2.16mg/dL vs POD5:16.62±6.74mg/dL,p=0.13). From POD5-7, the HMP group demonstrated a bimodal distribution in SCr leading to increased variance compared to NEVKP (standard deviation = 6.74, 9.28, 9.38mg/mL vs 5.72, 6.25, 4.75mg/mL, respectively). In the HMP group, 4 of 7 grafts were poor performing with 2 developing renal vein thrombosis. Conversely, only 1 in 7 grafts was poor performing with NEVKP with no evidence of renal vein thrombosis (Figure 1). The consistent improvement in NEVKP vs heterogeneity in HMP was also observed through the variation in creatinine clearance (POD7: 26.31±11.54mL/min vs 16.8±18.9mL/min) and on histological analysis of tubular injury.

Conclusions: Marginal kidney grafts showed reliable improvement in function following 8h of continuous NEVKP compared to HMP where improvement was inconsistent. This suggests NEVKP would be a preferable storage strategy for DCD procured grafts with extended WI times.



TH-OR137

Genome-Wide Non-HLA Donor-Recipient Mismatches in Intronic Regions Independently Associate with Graft Survival

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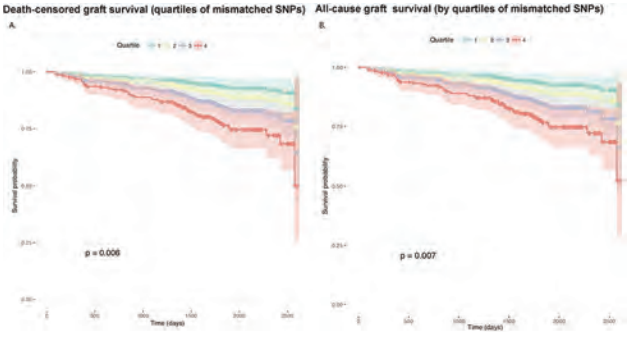
Background: Donor-recipient (D-R) mismatches at human leukocyte antigen (HLA) loci are used for management decisions. Recent work has showed the role of global non-HLA D-R mismatches, specifically exonic loci within genes coding transmembrane and secreted proteins in graft survival in Caucasian deceased donor cohorts. Since non-coding regions constitute ~98% of human genome, and these elements have demonstrable regulatory activity, we hypothesized that non-coding D-R genetic differences could also contribute to unchecked alloimmunity impacting graft survival.

Methods: We utilized genome-wide SNP array data on all D-Rs in the GOCAR study excluding HLA region (n=385 D-Rs). We quantified the genome-wide numbers of mismatches of all SNPs, and annotated those in non-coding regions, or exomes [divided further into nonsynonymous within genes coding transmembrane and secreted proteins] - all as separate continuous variables. Long-term death censored graft loss [DCGL] data were from UNOS/ANZDATA.

Results: Our multi-ethnic D-R cohort represented greater genetic diversity and included living donors vs published data. There were 73 DCGL events during median follow-up of 1824 days (IQR: 1392-2188 days). Genome-wide- & Tm-mismatches were all increased in inter-race vs intra-race transplants (p<0.001). The total numbers of SNP mismatches quantified as quartiles respectively impacted DCGL & all-cause GL in adjusted Cox models [Fig. 1A-B]. However, in multivariate Cox models after adjusting for protein-coding mismatches, non-coding D-R mismatches remained independently associated with graft survival. Surprisingly, non-HLA mismatch variables had no association with acute T-cell mediated rejection phenotypes (subclinical or clinical; with/without borderline lesions) in regression models.

Conclusions: Our data from a multi-ethnic cohort compliments recent work supporting the role of non-HLA D-R mismatches in long term allograft survival. In addition, we showed that non-coding loci based mismatches had independent impact on graft survival.

Funding: Other NIH Support - NIAID, Private Foundation Support



TH-OR138

Preliminary Results of the PHYSICALFAV Trial

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Background: Hemodialysis with autologous arteriovenous fistula (AVF) is associated with higher survival, lower costs, and fewer complications. Distal forearm AVF is the best option, but not all patients are good candidates for this approach and the primary failure rate ranges from 20% to 50%. The optimal AVF depends mainly on the anatomical and hemodynamic characteristics of the artery and the vein chosen for the anastomosis. These characteristics can be modified by performing physical exercise.

Methods: The PHYSICALFAV trial (NCT03213756) is an open-label, multicenter, prospective, controlled, randomized trial designed to evaluate the usefulness of preoperative isometric exercise (PIE) in pre-dialysis or prevalent hemodialysis patients who are candidates for a new AVF. Patients are randomized 1:1 to the PIE group (Exercises combining hand grip and elastic band for 8 weeks) or the control group (no exercise).

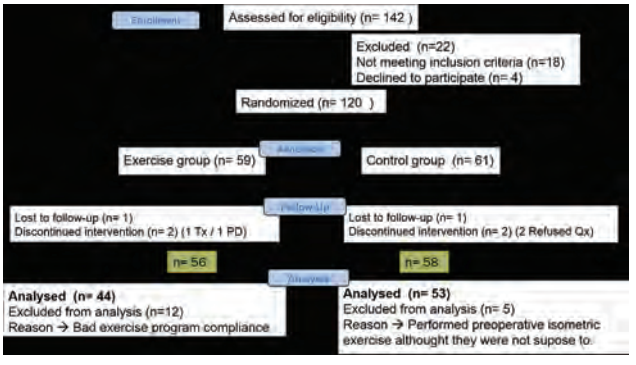
Results: After 20 months recruitment, 120 patients have been randomized. After 8 weeks of preoperative isometric exercise we have found significant differences on vein diameter (p<0.001), arterial peak systolic velocity and diameter (p 0.041- p 0.001) and maximum strength (p<0.001) on PIE group patients (table 1). We have been able to perform 76% of distal AVF in PIE group compared to 53% in the control group (p 0,043). Global primary failure rate was very low in both groups (6,9% PIE group vs 5,7% control group, pNS) and intervention free rate at 3 months was 82,8% PIE group vs 80% in control group (pNS).

Conclusions: Isometric preoperative exercise can improve vascular calipers and increase the possibility of performing distal AVF. The final results of this trial will be available in September 2019.

Funding: Other NIH Support - Grant founding from the Spanish Society of Nephrology.

Before and after exercise

	Baseline visit	After 8 weeks of exercise	p
Vein diameter (mm)	2,88 (1,05)	3,55 (0,97)	<0.001
Artery diameter (mm)	2,57 (0,90)	2,76 (0,89)	0.001
PSV (cm/sg)	66,67 (20,4)	72,84 (22,3)	0.041
Maximun strength(kg)	27,4 (10,3)	31,32 (11,9)	<0.001



TH-OR139

Ferumoxytol MR Angiography vs. Doppler Ultrasound for Vascular Mapping Before Hemodialysis Arteriovenous Fistula Creation

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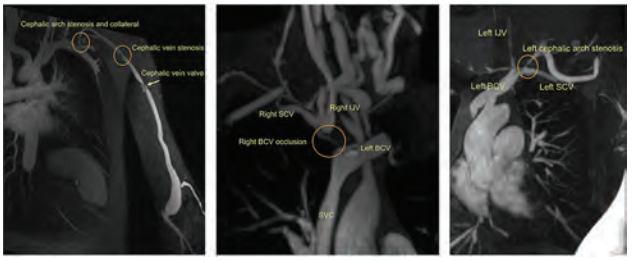
Background: Doppler ultrasound (DUS) is routinely performed for vascular mapping prior to placement of a hemodialysis arteriovenous fistula (AVF) but can not adequately visualize the central vasculature. Ferumoxytol, an iron oxide nanoparticle, is an alternative to gadolinium for magnetic resonance angiography (MRA). We compared ferumoxytol-enhanced MRA (FeMRA) with DUS for assessment of the central and upper extremity vasculature in patients with renal disease due for autologous AVF creation.

Methods: In a prospective comparative study, paired FeMRA and DUS were obtained on the same day. Three readers independently assessed arterial and vein diameter and the presence of stenosis or occlusion (central or peripheral) with FeMRA and US. Interclass correlation coefficients (ICC) and Bland-Altman plots examined inter-reader variability. Based on accepted standards for the creation of an AVF, an algorithm was created to predict AVF outcome relying on mapping findings. Two binomial logistic regression models were created with AVF outcome as the dependent variable and age, sex, and US prediction algorithm (model 1) or FeMRA prediction algorithm (model 2) as the predictor variables.

Results: From the 59 patients that had FeMRA and DUS, 51 had an autologous AVF created. FeMRA showed excellent inter-reader repeatability (ICC 0.84-0.99). Vessel course, accessory veins, anatomical variants and the presence of stenosis or occlusion in arm vessels were better assessed with FeMRA. FeMRA identified 15 central vasculature stenoses (CVS). On multivariable regression analyses FeMRA mapping was an independent predictor of AVF outcome [odds ratio (OR): 6.49 (95% CI 1.7 - 24.8); p=0.02].

Conclusions: FeMRA prior to AVF creation better predicted outcome compared to DUS. Its value is not limited in identification of central vessels pathology but it also showed peripheral vascular disease under-recognized with US.

Funding: Commercial Support - AMAG Pharmaceuticals, Inc.



Representative images of CVS with FeMRA.

TH-OR140

Inactivation of Lysyl Oxidase in Smooth Muscle Cells Improves Arteriovenous Fistula Function in Mice

Roberto I. Vazquez-Padron,[1] Diana R. Hernandez,[1] Laisel Martinez,[1] Marwan Tabbara,[2] Juan C. Duque,[1] Loay H. Salman.[3] Vazquez-Padron's team *[1]University of Miami, Miami, FL; [2]University of Miami, Miller School of Medicine, Miami, FL; [3]Albany Medical College, Albany, NY.*

Background: Over 400,000 patients in the U.S. depend on vascular access to receive hemodialysis (HD) and prolong their lives. Unfortunately, arteriovenous fistulas (AVFs), the preferred vascular access for HD, frequently fail (~40%) because venous stenosis compromises blood flow. We recently discovered that stenosis occurs due to excessive medial fibrosis and is aggravated by intimal hyperplasia. Herein, we hypothesize that it is possible to prevent AVF failure by targeting lysyl oxidase (LOX), a copper-dependent amine oxidase involved in collagen and elastin crosslinking and in the epigenetic control of gene expression in smooth muscle cells (SMCs).

Methods: We created a LOX conditional knockout mouse[$Lox^{f/f}$Myh11-$CreER^{T2}$] that is fertile, normal in size, and without any gross abnormalities. AVF were created by anastomosing the jugular vein to the nearby carotid artery. Mechanistic studies were performed with primary cultures of mouse venous SMC.

Results: Tamoxifen (TAM) injections significantly downregulated LOX gene expression[3 folds vs. control, p<0.01] and protein accumulation in the vasculature of conditional KO mice but not in those of control littermates[$Lox^{+/+}$Myh11-$CreER^{T2}$]. Inactivation of LOX in SMCs decreased immature collagen crosslinking in the aorta[1.3 ± 0.1 vs. 1.7 ± 0.1 HLNL+DHLNL/collagen], and reduced carotid pulse wave velocity[2.2 ± 0.2 vs. 2.9 ± 0.4 m/s] as determined by ultrasound microscopy. AVFs in mice with LOX-deficient SMCs showed higher distensibility and blood flow by day 21 post-surgery. Importantly, gene deletion caused aneurysms neither in the fistula nor in other parts of the vasculature. Mechanistically, we demonstrated that inhibition of LOX with BAPN increased H3K4me2 and H3K4me1 marks in the SMC genome, and specifically in the promoters of SMC contractile genes, to keep them in an open chromatin state and promote the binding of the SRF-myocardin transcription complex. We further confirmed the increased abundance of SRF in the CArG boxes of contractile gene promoters in SMCs treated with BAPN compared to the vehicle using a quantitative ChIP assay.

Conclusions: These data indicate, for the first time, the importance of LOX not only in post-operative vascular remodeling after AVF creation but also in the control of the SMC phenotype.

TH-OR141

Assessment of Fistula Flow Using Smartphone Video Analysis

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Background: Frequent, non-invasive assessment of arterio-venous fistula (AVF) blood flow (ABF) is desirable to timely detect access malfunction. Given the almost universal availability of smartphones with video capabilities, we assessed ABF by video image processing.

Methods: Fify-eight hemodialysis patients were studied after endovascular interventions where ABF was measured invasively using thermodilution (HVT100, Transonic, Ithaca, NY). A 1-minute video of the skin above the AVF was recorded (iPhone 6; Fig.1). Frame-to-frame pixel changes were quantified and followed over time. These time series were then transformed into the frequency domain. The frequency domain signal was characterized by the squared ratio of the maximal-to-median magnitude (M2; an example is shown in Fig.2). Forty randomly selected patients (derivation cohort) were

used to construct multiple regression models with ABF as dependent variable, 18 patients served as validation cohort.

Results: Visual inspection of the derivation cohort ABF vs. M2 scatterplot indicated 2 distinct populations, one with M2≤100 (n=30) and M2>100 (n=10; Table 1). In the validation cohort 17 patients had M2≤100, and 1 patient >100. In the derivation cohort a multiple regression model including M2, sex, body weight, and race explained 64% of the ABF variance in patients with M2≤100 (Fig 3A) and 44% in patients with M2>100 (Fig. 3B), respectively. In the validation cohort we predicted 51% of the ABF variance in patients with M2≤100 (Fig 4); the one patient with M2>100 was not analyzed.

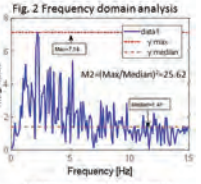
Conclusions: Our results show that advanced mathematical analysis of smartphone videos may have the potential to assess AVF blood flow. If corroborated in more extensive clinical studies, smartphone video analysis provides an attractive and low-cost means to non-invasively evaluate AVF blood flow.

Funding: NIDDK Support

Fig. 1

TABLE 1. Derivation cohort characteristics (n=40)

	M2 ≤ 100 (n=30)	M2>100 (n=10)	P value
Gender	57 % males	40 % males	
Race	20 % Black	80 % Black	
Age (years)	58.1±15	75±12	<0.01
BMI (kg/m²)	29.4±7.6	31.5±7.8	ns
SBP (mmHg)	156.8±24	150.2±21	ns
Measured ABF (ml/min)	1907±800	1409±403	0.07



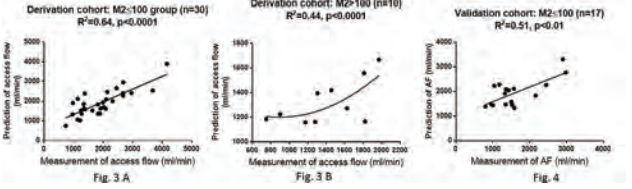


Table and Figures

TH-OR142

Automatic Classification of Arteriovenous Fistula Aneurysms Using Artificial Intelligence

Hanjie Zhang,[1] Murat Sor,[5] Elsie Koh,[5] Priscila Preciado,[1] Dugan Maddux,[2] Len A. Usvyat,[2] John W. Larkin,[3] Peter Kotanko.[1,4] *[1]Renal Research Institute, New York, NY; [2]Fresenius Medical Care North America, Waltham, MA; [3]Fresenius Medical Care, Waltham, MA; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]Azura Vascular Care, Woodland Park, NJ.*

Background: Trained professionals examine arteriovenous fistulas and diagnose aneurysm (AVFA) stages, but there is no fully automated classification method. Our goal is to build a convolutional neural network (CNN) to automatically classify AVFA stages.

Methods: We collected 15-20 sec "panning" videos from 30 patients with two AVFA categories, 23 patients with AVFA stage 2 (enlarged AVF with hypopigmented skin) and 7 patients with AVFA stage 3 (enlarged fistula with open ulcer). The videos were collected against a white background. Patients had diverse skin tones. We extracted the video frames that then comprised our image set. Each image has three color channels, the image shape was 960 x 540 (Figure 1). We used 80% of the patients' videos for CNN training and the remainder for validation using the Amazon SageMaker machine learning platform (Amazon, Seattle, Washington).

Results: We trained the CNN in two modes. First, the transfer learning mode, utilized the pre-trained Amazon SageMaker image classification algorithm, fine-tuned to our image data set. Second, the full training mode, where the CNN was trained from scratch with our image data set. With both of these training modes, we were achieved a > 90% classification accuracy in the validation images.

Conclusions: CNN is able to automatically classify AVFA. Automation of that process is expected to reduce workload, provide timely AVFA diagnosis, and improve patient care.

Funding: Commercial Support - Fresenius Medical Care North America

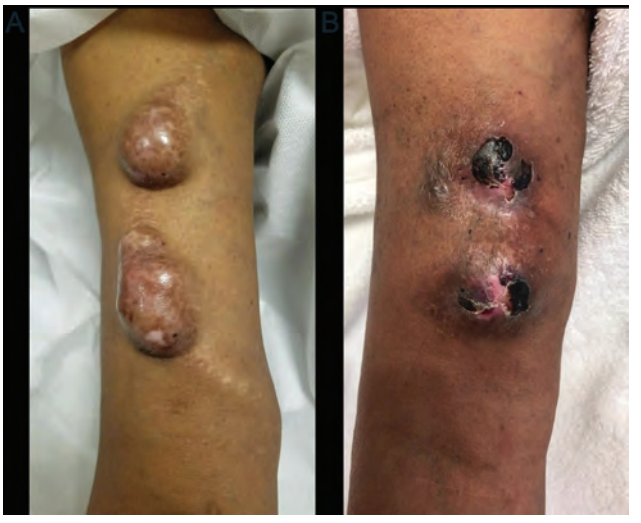


Figure 1: A: AVFA with enlarged fistula and hypopigmented skin, B: AVFA with enlarged fistula and ulceration.

TH-OR143

Comparison of Drug-Coated Balloon Angioplasty vs. Conventional Balloon Angioplasty for Arteriovenous Fistula Stenosis: A Meta-Analysis

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Background: Arteriovenous fistula (AVF) is the most preferred form of vascular access for maintenance hemodialysis (HD) but access stenosis treated by balloon angioplasty are prone to restenosis due to neointimal proliferation. Multiple trials have been published with regards to use of paclitaxel coated balloon (DCB) to prolong lesion patency when compared to conventional balloon. Though DCB has theoretical appeal, its use has not been widespread with access centers nationwide due to factors related to cost and lack of large scale multicenter studies. We performed this meta-analysis to evaluate whether use of DCB outperforms conventional balloon to prolong target lesion patency.

Methods: Medical electronic databases, including PubMed/Medline, Clinical Trials. gov, EMBASE, Scopus, Web of Science and Cochrane Central were searched from inception through April 2019 for studies that investigated use of DCB in HD AVF. 15 studies (6 Randomized control trials (RCT) and 9 observational studies) were considered for qualitative and quantitative analysis.

Results: Ten studies were included in the final meta-analysis. 6 of the studies were RCTs and 4 were retrospective (cohort) studies. There were 915 participants with a mean age of 65.40 (+/-5.96) years and 61.89% were male. The outcome of interest was target lesion primary patency (TLPP), recorded at a longitudinal follow-up time, i.e. 1, 3, 6, 7, 12 and 24 months. Meta-analysis of all RCTs shows that drug-coated balloons (DCBs) did not statistically improve TLPP compared to traditional balloons at months 1 (OR 4.27, p-value 0.06), 3 (OR 0.9, p-value0.99), 6 (OR 0.80, p-value 0.54), 7 (OR 0.93, p-value 0.75), 12 (OR 0.61, p-value 0.17) and 24 (OR 0.69, p-value 0.15). The effect of DCBs was statistically significant for cohort studies at 6 months (OR 0.26, p-value 0.0007), 12 months (OR 0.21, p-value 0.0001) and 24 months (OR 0.23, p-value 0.01). Studies using AV-Graft were excluded. There was no publication bias as assessed by funnel plots.

Conclusions: Drug-coated balloons showed no statistically significant improvement over conventional balloons in decreasing fistula stenosis in meta-analysis of RCT at 1,3,6,7,12 and 24 months but were significant for cohort studies at all follow up months of 6, 12 and 24. Our analysis does not justify the use of DCB at this time.

TH-OR144

Patient, Care Partner, and Provider Perspectives on Arteriovenous (AV) Access Creation Prior to Hemodialysis (HD) Initiation

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Background: More than 80% of individuals in the U.S. start maintenance HD with a catheter, despite substantial evidence that starting HD with an AV access improves quality of life, lowers mortality, and decreases healthcare costs. Barriers to AV access creation prior to HD initiation have been under-investigated. We sought to identify patient, care partner, medical provider, and clinic personnel perspectives on the AV access creation process in the pre-HD period.

Methods: We conducted 4 focus groups (N=24 participants) and 16 semi-structured interviews across 2 diverse health systems (UNC and GH). Focus groups included advanced chronic kidney disease patients (GFR <20 mL/min/1.73m^2), and separately, HD patients within 1 year of HD initiation as well as care partners of such patients. Interviewees included nephrologists, surgeons, clinic nurses, imaging specialists, and other staff. Transcripts were coded independently by 3 researchers and thematically analyzed.

Results: Participants identified a range of patient- and healthcare system-related barriers to starting HD with an AV access. Key modifiable barriers included: siloed provider views of the AV access creation process; negative patient emotions (e.g. fear, denial, uncertainty); inadequate and inconsistent patient education; and lack of systematic approaches to tracking patients through AV access care processes. Key facilitators included: early and sustained dedicated vascular access education (i.e. separate from modality and transplant education); care partner inclusion in education; and positive peer interactions. Participants identified 4 essential aspects of pre-HD vascular access care: strong patient—provider relationships (trust, shared decision-making); focused, iterative multi-format education; peer support; and assistance in process navigation (e.g. care navigation, vascular access-specific electronic health record reports, consistent provider communication).

Conclusions: Programs aimed at improving rates of HD initiation with an AV access must address both patient- and healthcare system-related barriers. Key components include strong patient-provider relationships, targeted education, peer support, and care navigation.

Funding: NIDDK Support

TH-OR145

Ultrafiltration and Cerebral Microbleeds in Haemodialysis Patients

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Background: Ultrafiltration of dialysis patients were variable. The detailed studies on the impact of different ultrafiltration are still rare. Variable ultrafiltration may contribute to brain lesions by inducing hemodynamic instability. Cerebral microbleeds (CMBs) in dialysis patients have recently attracted much attention. The risk factors of CMB in dialysis patients are not very clear. The association of dialysis ultrafiltration with CMB is unknown.

Methods: A total of 119 chronic haemodialysis patients were enrolled in our study. Demographic and Clinical Characteristics of Patients were recorded. Multiple ultrafiltrate information of every patient before MRI examination was recruited with Ultrafiltrate volume(UV) mean, UV standard deviation(SD), UV coefficient of variation(CV), the difference between UV mean and 6% of weight, the ratio of UV to weight mean, and the ratio of UV to weight SD. CV was calculated as the ratio of SD to the mean. CMBs were defined as small (2–10 mm) areas of homogeneous signal loss on susceptibility weighted imaging images. The correlation between ultrafiltration and CMB was investigated by logistic regression analysis.

Results: Recorded dialysis period ranged from 2.0 to 14.0 months, and recorded dialysis times ranged from 11.0 to 54.0. Urea removal ratio was 0.7±0.1, and Kt/V was 1.4±0.2. UV mean ranged from 0.2 to 4.6 kg, and UV CV ranged from 0.0 to 78.1 percent. The prevalence of CMBs was 35.3% in the total study population. Ten subjects (8.4%) suffered lobar CMBs, Nine subjects (7.6%) suffered mixed CMBs, and 23 subjects (19.3%) suffered deep group. UV mean, the difference between UV mean and 6% of weight, and the ratio of UV to weight mean were risk factors of CMB (OR=1.59, 1.48, and 1.31 respectively, p=0.031, 0.042, and 0.039 respectively) and mixed CMB (OR=2.23, 2.07, and 1.66 respectively, p=0.036, 0.057, and 0.030 respectively). UV CV was negatively associated with CMB(OR=0.96, p=0.022 respectively). The association of UV mean and UV CV with CMB was still significant after adjusting for gender, age, serum albumin, urea removal ratio, lacunes, and white matter hyperintensity(OR=1.72 and 0.96 respectively, p=0.044 and 0.046 respectively).

Conclusions: UV was closely associated with CMB in dialysis patients. Reducing UV may protect dialysis patients from CMB.

TH-OR146

Trends in Use and In-Hospital Outcomes of Subcutaneous Implantable Cardioverter Defibrillators in Dialysis Patients: A Report from the National Cardiovascular Data Registry

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Background: Dialysis patients are at high risk of infectious and vascular complications related to implantable cardioverter defibrillator (ICD) implantation; many have advocated for the preferential use of subcutaneous (S-ICD) over transvenous devices (TV-ICD) due to the potential benefits of reduced risk of blood stream infection and interference with vascular access sites. We evaluated trends in use and in-hospital outcomes of S-ICD compared to TV-ICDs among dialysis patients in the United States

Methods: This was a retrospective analysis of 23,136 ICD implants among dialysis patients reported between 2012 and 2018 to the National Cardiovascular Data Registry ICD Registry, a nationally representative US ICD registry. We first examined the utilization and patient and procedure characteristics of dialysis patients receiving S-ICD. Next, among dialysis patients eligible to receive an S-ICD, we examined trends in S-ICD adoption as a proportion of all ICD implants and compared in-hospital outcomes (death, complications) among S-ICD and TV-ICD recipients using inverse probability weighted estimators.

Results: Of all ICDs implanted among dialysis patients during the study period, 3,195 (13.81%) were S-ICD. Among eligible first-time ICD dialysis recipients, the proportion of S-ICDs utilized increased yearly from 10.3% in 2012 to 68.5% in 2018. Compared to TV-ICD recipients, S-ICD recipients were more likely to be black (42.6% vs. 34.3%) and undergo implantation in teaching hospitals (62.8% vs 53.2%). In the inverse probability weighted estimators analysis of 3,327 patients, compared to TV-ICD, dialysis patients receiving S-ICDs had a higher rate of in-hospital cardiac arrest (1.53% vs 0.36%, p=0.002); in-hospital complications ((2.4% vs 1.48% p=0.08) and length of hospitalization ((1.57 vs. 1.24 days, p=0.08) were not significantly different between the 2 groups.

Conclusions: There has been a steady increase in the utilization of S-ICD among dialysis patients in the United States. The increased risk of in-hospital cardiac arrest in S-ICD recipients could have been due to residual confounding and selection bias, but randomized clinical trials are needed to definitively compare the outcomes of TV-ICD with S-ICDs in dialysis patients.

Funding: Private Foundation Support

TH-OR147

Intradialytic Hypotension and Incident Peripheral Artery Disease in Patients with ESKD on Hemodialysis

Eun Young Seong,[1] Sai Liu,[2] Sang Heon Song,[1] Nicholas J. Leeper,[2] Wolfgang C. Winkelmayer,[3] Maria E. Montez-Rath,[2] Tara I. Chang.[2] *[1]Pusan National University Hospital, Busan, Republic of Korea; [2]Stanford University School of Medicine, Palo Alto, CA; [3]Baylor College of Medicine, Houston, TX.*

Background: Intradialytic hypotension (IDH) may decrease systemic circulation to the lower extremities, exacerbating symptoms of peripheral artery disease (PAD). We sought to evaluate the relationship between IDH and incident PAD among patients on hemodialysis (HD).

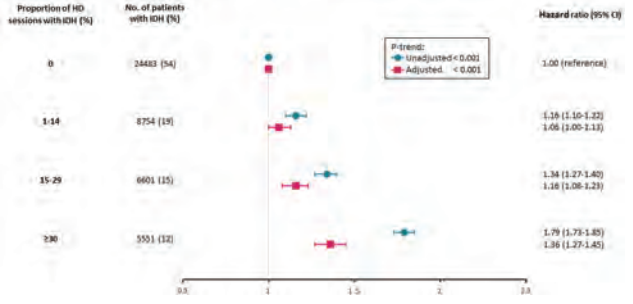
Methods: Using the data from USRDS linked to a large dialysis provider, we identified adults without pre-existing PAD who initiated HD between 2006-2011. Exposure: time-varying proportion of HD sessions with IDH, defined as nadir systolic blood pressure <90 mmHg, categorized as 0%, 1-14%, 15-29%, and ≥30% in 30-day intervals. Outcome: incident PAD, ascertained using PAD diagnosis codes or procedure codes for amputation or revascularization, in the subsequent 30-day interval. We estimated unadjusted and adjusted sub-distribution hazard ratios using Fine and Gray models with time specified in the counting-process style, assuming death and kidney transplant as competing events. Models were stratified by incident HD year and adjusted for baseline characteristics, comorbidities, healthcare use and laboratory values. Missing data were handled using multiple imputation by chained equations as implemented in R.

Results: In our cohort (N=45,489), patients with a more frequent IDH were more often women and of white race, and had a higher prevalence of diabetes, coronary artery diseases and heart failure. During 61,842 person-years of follow-up, 8,111 patients had incident PAD. We found a graded, direct association of IDH with incident PAD. For example, the presence of IDH in ≥30% of dialysis sessions was associated with an adjusted 36% increase in the hazard of incident PAD (95% CI, 27%-45%) compared to 0% IDH, in patients without PAD or who have experienced the competing events (Figure 1).

Conclusions: Patients with ESKD on HD with more frequent IDH have a higher hazard of incident PAD in the subsequent 30 days. Patients with more frequent IDH may warrant a careful examination for PAD such as foot examinations or other diagnostic testing.

Funding: Government Support - Non-U.S.

Figure 1. Association of proportion of dialysis sessions with intradialytic hypotension (IDH) and incident peripheral artery diseases.



FR-OR001

Targeting the Cell Cycle in ADPKD: The Role of Cyclin-Dependent Kinase 1

Bruno Eduardo Pedroso Balbo,[2,4] Chao Zhang,[2] Xin Tian,[3] Yiqiang Cai,[2] Max Spitzer,[1] Rachel Gallagher,[2] Ke Dong,[2] Stefan Somlo.[1] *[1]Yale University, New Haven, CT; [2]Yale University School of Medicine, New Haven, CT; [3]Yale School of Medicine, New Haven, CT; [4]USP, Sao Paulo, Brazil.*

Background: Cilia ablation reduces cyst formation after polycystin inactivation, suggesting that a cilia-dependent cyst-activating (CDCA) mechanism is a driver in ADPKD. To investigate this pathway, we conducted transcriptomic profiling in adult-onset ADPKD models at an early stage following cyst initiation. We identified cyclin-dependent kinase 1 (*Cdk1*) as one of the most upregulated genes in incipient cyst cells following *Pkd1* inactivation and we investigated its role in ADPKD pathogenesis.

Methods: To enrich for transcriptomes from cells destined to form cysts in the kidney, we isolated RNA by translating ribosome affinity purification (TRAP). RNAseq profiling was performed in 10wk-old mice (4/group): *Pkd1$^{fl/+}$;R26^{Rpl10a};Pax8^{rtTA};TetO^{Cre}* (non-cystic; NC), *Pkd1$^{fl/fl}$;R26^{Rpl10a}; Pax8^{rtTA};TetO^{Cre}* (cystic, single KO; SKO) and *Pkd1$^{fl/fl}$;Kif3a$^{fl/fl}$;R26^{Rpl10a};Pax8^{rtTA};TetO^{Cre}* (non-cystic *Pkd1*-cilia double KO; DKO). Differential gene and KEGG pathway analyses were performed. Mouse models with early- (*Pkd1$^{fl/fl}$;Pkhd1^{Cre}*) and late-onset *Pkd1* deficiency (*Pkd1$^{fl/fl}$;Pax8^{rtTA};TetO^{Cre}*) were combined with the *Cdk1*-floxed allele, generating single KO (*Pkd1-KO*) and double KO (*Cdk1-Pkd1-KO*) models. The early and late onset groups were evaluated respectively on P24 and on the 18th wk of life (after doxycycline induction from P28-42).

Results: 155 genes were identified from the overlap between groups that shared differential expression in both NC vs SKO and SKO vs DKO groups. KEGG pathway analysis identified the cell cycle pathway as the most enriched and upregulated. *Cdk1* emerged as one of the most upregulated genes in this group. Polycystic kidney disease in *Cdk1-Pkd1-KO* group was significantly milder in both early onset and adult models when compared with *Pkd1-KO* models, as indicated by lower kidneys to body weight ratio, cystic index, and BUN. Cell proliferation rate (EdU incorporation) was significantly decreased in *Cre*-active tubule segments while no difference in apoptosis (TUNEL) was detected.

Conclusions: TRAP RNAseq on adult-onset ADPKD model at the early cystic stage has identified the cell cycle pathway as the most enriched one, suggesting that cell cycle changes occur early during the cyst formation. *Cdk1* emerged as one of the most upregulated cell cycle genes during cyst formation, and inactivation of *Cdk1* decreased cyst progression in ADPKD.

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

FR-OR002

Single-Cell Transcriptomics Reveals Direct Target Genes Regulated by Pkd1 in Mouse Kidneys

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Background: While PKD gene mutations are known to be responsible for ADPKD, no study has yet been performed to tour the kidneys cell-by-cell to identify genes that are directly and significantly regulated by PKD mutations in individual kidney cells, and to address whether PKD mutation in a specific renal cell type affects gene expression profiles in neighboring cells with wildtype PKD genes. The recently developed technique of single-cell transcriptome analysis (scRNA-seq) can be used to monitor global gene regulation in thousands of individual cells at the same stage of the disease in the same kidney, to provide insights into the mechanisms that determine how PKD gene deletion results in cystogenesis.

Methods: We performed scRNA-seq with kidneys from *Pkd1$^{flox/flox}$;Pkhd1*-Cre (*Pkd1*-cKO) mice, in which the *Pkd1* gene is selectively deleted in collecting ducts, and *Pkd1$^{flox/flox}$* (*Pkd1*-WT) mice collected at postnatal day 7 (PN7) (before cyst initiation), day 14 (PN14) (after cyst onset) and day 21 (PN21) (later stage of cyst formation) (n ≥ 3 per group) to investigate the dynamic gene transcription profiles of each individual renal cell.

Results: Our scRNA-seq analysis indicated that the gene transcription profiles are affected in several PKD associated signaling pathways and in pathways not previously studied in PKD in collecting duct (CD) cells with *Pkd1* deletion. In addition, we found that the specific markers for principal cells (PCs) of the collecting duct, *Aqp2* and *Hsd11b2*, were upregulated in *Pkd1* knockout CD cell clusters, and the cell numbers of these clusters were also increased compared to the *Pkd1*-WT CD cluster, whereas the cell numbers of the clusters of intercalated cells (ICs) (marked by *Atp6v1g3* and *Atp6v0d2*) were decreased, suggesting that loss of *Pkd1* increases the transition of CD cells from ICs to PCs, possibly leading to renal metabolic acidosis and high blood pressure. Interestingly, we found that deletion of *Pkd1* did not affect the expression levels of *Pkd2* in most cell clusters, including the CD cell cluster. However, deletion of *Pkd1* in CD cells did affect the gene expression profiles in cell clusters of neighboring cells.

Conclusions: Deletion of *Pkd1* in collecting duct cells promotes cyst formation by affecting signaling pathways in CD cells and neighboring cells but not *Pkd2* gene transcription in most cell clusters.

Funding: NIDDK Support

FR-OR003

The Polycystin Complex Is Essential for Cilia Disassembly

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease, attributed almost exclusively to mutations in two genes, *PKD1* and *PKD2*, encoding a receptor-channel complex (Polycystins or PKD1/PKD2) at the cell surface and the primary cilium. However, how mutations in *PKD1* and/or *PKD2* contribute to cyst formation/progression is unknown. The primary cilium is an antenna-like organelle present in every cell, and excessive ciliary signaling has been linked to cyst progression in ADPKD. A unique feature of the primary cilium is that it is formed when cells exit the cell cycle and disassembled upon cell cycle re-entry. Moreover, acceleration or deceleration of cilia disassembly suppresses or exaggerates cystic growth, respectively. Here, we examined whether the Polycystin complex has an essential role in cilia assembly and disassembly.

Methods: **Mice** *Ubc-Cre^{ERT2};Pkd1$^{f/f}$* and *Pkd1$^{f/f}$* mice were induced by 4-Hydroxytamoxifen from P2-P6 and sacrificed at P21. **Immunofluorescence** Cilia or cells in S phase were labeled with an Arl13b antibody (1:500, Proteintech) or EdU (ThermoFisher), respectively. **Signaling pathways** Activity of signaling pathways was determined by the Cignal 45-pathway Reporter Array (Qiagen).

Results: Mouse embryonic fibroblasts, NIH3T3, or mouse inner medullary collecting duct (mIMCD3) cells lacking PKD1 or PKD2 showed severely delayed ciliary disassembly, whereas ciliary assembly was unaffected. These effects were specific to the deletion of *Pkd1* or *Pkd2* genes, as adding back wild type PKD1 or PKD2, but not pathogenic mutants, normalized ciliary disassembly. Consistently, the number of ciliated cells positive for EdU, an indicator of G1-S transition, was increased in mutant cells in cell culture and in the cystic epithelium of mice lacking *Pkd1*. An important intermediary was p53, which was induced in *Pkd1* mutant cells and kidneys and downregulation or inhibition of p53 restored delayed disassembly in *Pkd1/2*-null NIH3T3 cells. Consistent with delayed disassembly in *Pkd1/2*-null cells, several cilia-based pathways including the TGFβ/Smad pathway, which is causally linked to cyst progression, were overactivated in mutant cells.

Conclusions: Our studies identify an essential role of Polycystins in cilia disassembly. Delayed disassembly in cells lacking Polycystins leads to prolonged/excessive activation of ciliary pathways that could contribute to ADPKD progression.

Funding: NIDDK Support, Private Foundation Support

FR-OR004

Deletion of Ift-A Gene, Thm1, in a Pkd2 Early-Onset ADPKD Mouse Model Has Renal Tubular-Specific Attenuating and Synergistic Effects

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Background: Primary cilia are signaling organelles that have emerged as powerful modifiers of ADPKD. Primary cilia are synthesized by intraflagellar transport (IFT) complexes B and A. Ift-B gene deletion in renal tubules in *Pkd1* or *Pkd2* conditional knock-out (cko) mice ablated primary cilia and attenuated renal cystic disease, suggesting that cilia-mediated signaling within an ADPKD background may be pro-cystogenic. In contrast to Ift-B gene deletion, which often results in cilia loss, Ift-A gene deletion causes shortened cilia with protein accumulation in bulbous distal tips and can have opposing effects on signaling. Thus we examined the effect of Ift-A deficiency on a *Pkd2* mutant background.

Methods: Using the ROSA-Cre^{ERT} recombinase, *Pkd2* and *Thm1* were globally deleted alone or together in mice at postnatal day (P) 0 generating early-onset disease models, which were analyzed at P21.

Results: At P21, *Thm1* cko kidneys were similar to those of control littermates. *Pkd2;Thm1* double knock-out (dko) mice had reduced KW/BW ratios and smaller collecting duct-derived cysts than *Pkd2* cko mice. Yet BUN levels were similar between *Pkd2;Thm1* dko and *Pkd2* cko mice. Unlike *Pkd2* and *Thm1* single mutants, *Pkd2;Thm1* dko mice developed proximal tubular-derived cysts. Additionally, *Pkd2;Thm1* dko kidneys showed enhanced fibrosis and STAT3 activation relative to *Pkd2* cko kidneys. In *Pkd2;Thm1* dko collecting ducts, many primary cilia were shortened with accumulation of IFT81 protein at the distal tip, characteristic of an IFT-A cilia mutant phenotype and in contrast to *Pkd2* cko collecting duct primary cilia, which were lengthened.

Conclusions: In *Pkd2;Thm1* dko mice, reduced KW/BW ratios and collecting duct-derived cysts indicate that IFT-A is required for a component of *Pkd2* renal cystogenesis. Yet the presence of proximal tubular-derived cysts reveals there is also synergy between *Pkd2* and *Thm1* deletion. Further, enhanced renal fibrosis and STAT3 activation indicate that *Thm1* deletion exacerbates *Pkd2*-mutant renal disease. Thus the role of *Thm1* or IFT-A deficiency on an ADPKD background may be renal tubular/cell-specific.

FR-OR005

Molecular Regulation of Polycystin TRP Channels

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Background: Autosomal dominant polycystic kidney disease (ADPKD) causes progressive renal failure and can be caused by variants in the PKD2 genes which encode the polycystin-2 transient receptor ion channel (TRP). Despite our strong understanding of the genetic basis of ADPKD, we still do not know how polycystin-2 ion channel function is molecularly regulated. This basic question remains outstanding because polycystin-2 localizes to the primary cilium—an antenna-like organelle that requires innovative tools to study. Recently, our lab achieved the first heterologous and native electrophysiological characterization of TRPP2 in the primary cilia membrane. With our collaborators, we also published the first high-resolution structure of polycystin-2, which has provided a molecular context for understanding ADPKD variants and clues to its structural regulation.

Methods: We have developed novel methodologies which include: cilia electrophysiology, cilia-specific calcium sensors, super-resolution imaging, cryo-EM structural determination and ADPKD animal models to assay polycystin activity directly from the primary cilia membrane. We have deployed these state-of-the-art methods to provide the most accurate description of the biophysical regulation of polycystin-2 and the related polycystin-like (encoded by PKD2L1) channels, providing results in real-time and atomic resolution.

Results: We have interrogated multiple mutations within three structural domains within polycystin-2 and assessed their impact on the opening and closing of the ion

conductive pore, the oligomictic stability of the tetrameric channel and their trafficking to the primary cilia membrane.

Conclusions: Our results provide a biophysical framework for understanding of polycystin-2's molecular regulation. We have determined that polycystin-2 integrates polymodal stimuli to control the channels voltage dependent gating. Domains within the channel independently respond to stimuli (e.g. intra-ciliary calcium), but the final open step is ultimately controlled by four-helix bundle which senses membrane potential. Based on these structural observations, we propose mechanistic hypotheses regarding the impact variants found within these domains.

Funding: NIDDK Support, Private Foundation Support

FR-OR006

Regulation of PKD2 Channel Function by PKD1

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Background: Mutations of PKD1 and 2 cause autosomal-dominant polycystic kidney disease (ADPKD). PKD1 peptide has a very large extracellular N-terminus (Nt), 11 transmembrane (TM) domains, and intracellular C-terminus (Ct). PKD2 is 6-TM domains channel with intracellular N and C-terminus. The function and relationship of PKD1 and PKD2 and in the pathogenesis of ADPKD remain elusive. Previous studies show PKD1 and PKD2 interact with its C-terminus. Recent cryo-EM structural studies reveal the last 6 TM of PKD1 can interact with PKD2 to form presumably non-functional channel complexes.

Methods: Wild-type (WT) PKD2 and phenylalanine-604 to proline (F604P) mutant PKD2 were expressed in Xenopus oocytes with or without WT and mutant PKD1. PKD2 channel function was studied by using two-electrode voltage-clamp. Extracellular Ca^{2+}-inhibitable inward K^+ currents were measured.

Results: We found that currents in oocytes expressing WT- PKD2 were not different from in control oocytes. WT-PKD1 itself did not produce currents, and had no effects on WT-PKD2 currents when coexpression with it. It is known that F604P mutation on the 5th TM domain of PKD2 leads to widening of the lower gate and constitutive activation of the channel. We then used F604P-PKD2 to study the regulation by PKD1. Oocytes expressing F604P-PKD2 showed ~3 fold higher currents than background currents in control oocytes, confirming gain-of-function of F604P. Coexpression with WT-PKD1 completely inhibited F604P-PKD2, to the level of control oocytes. To map regions of PKD1 that regulate PKD2, we made five PKD1 mutant constructs with deletion of Nt, deletion of Ct, deletion of the last 6 TM domains, deletion of both Nt and Ct or deletion of Nt as well as the first 5 TM domain. Comparing with WT-PKD1, deletion of Nt and/or the first 5 TM did not alter PKD1's ability to inhibit F604P-PKD2. Deletion of Ct or the last 6 TM resulted in partial reduction in the ability of PKD1 to inhibit F604P-PKD2.

Conclusions: PKD1 inhibits PKD2 channel activity. The C-terminus and last 6 TM domains of PKD1 are involved. The results support the implication of structural studies that PKD1 and PKD2 complexes are non-conducting. Further, they support the hypothesis that ligands or factors target PKD1 to activate channel activities of PKD1/PKD2 complexes.

Funding: Private Foundation Support

FR-OR007

The Role of Polycystin 1 in the Polycystin-1/Polycystin-2 Channel

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in either polycystin-1 (PC1), a polycystic kidney disease protein, or Polycystin-2 (PC2), a transient receptor potential channel. PC1 and PC2 form a receptor-ion channel complex with a 1 (PC1) : 3 (PC2) stoichiometry. The molecular mechanism of the function of this complex, especially the role of PC1, is largely unknown.

Methods: Full-length or fragments of PC1 was co-expressed with a gain-of-function (GOF) mutant of PC2 (PC2-GOF) in *Xenopus laevis* oocytes. Ion channel activity and ion permeability of the PC1/PC2 channel was measured with a two-electrode voltage clamp (TEVC) method and compared with the homomeric PC2 channel. Co-immunoprecipitation (co-IP) and surface biotinylation were used to evaluate the interaction and surface expression level.

Results: Our results show that PC1 can form a channel with PC2-GOF with distinct properties from that of the homomeric PC2-GOF channel. Compared to the homomeric PC2-GOF channel, PC1/PC2-GOF channel is not blocked by extracellular divalent ions and has significantly higher Ca^{2+} permeability than PC2-GOF channel. We also found that the GPS cleavage-produced PC1 C-terminal fragment (PC1-CTF) has almost identical channel function as full-length PC1 when assembled with PC2-GOF. Further analysis shows that not only Ca^{2+}, a lot of other monovalent ions, including some big organic ions, also permeate better through the PC1/PC2-GOF channel, compared to that of the PC2-GOF channel, indicating a relatively larger pore of the complex channel. More importantly, mutations in the pore region of either PC1 or PC2 alter the ion permeability of the PC1/PC2-GOF channel, confirming that both proteins contribute to the formation of the ion-conducting pore.

Conclusions: Full-length PC1 can associates with PC2-GOF to form a GOF PC1/PC2 complex channel in *Xenopus* oocytes. We were able to successfully record the channel current from this channel and dissect the role of PC1. In this channel, the PC1 subunit directly contributes to the channel pore formation, and the PC1-CTF is sufficient for its channel activity. The PC1/PC2-GOF channel has a distinct ion-conducting pore from that of the homomeric PC2-GOF channel and is more Ca^{2+} permeable.

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FR-OR008

Ketosis Inhibits and Reverses Renal Cyst Growth in Polycystic Kidney Disease

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Background: PKD cells have been shown to exhibit an altered metabolism, favoring aerobic glycoysis. Our lab recently found that a mild reduction in food intake slowed progression of PKD in a mouse model of the disease. We hypothesized that the effects we observed in the PKD mouse model were not due to calorie restriction per se, but were instead due to the effects brought on by the state of ketosis.

Methods: To test if ketosis was capable of ameliorating PKD, we use the Han rat model of PKD or the Nestin-Cre Pkd1 mouse model. Animals were treated beginning at age week 3 to week 8 or from week 8 to week 12 with induction of ketosis utilizing several methods including, 1-time-restricted feeding, 2-ketogenic diet, 3-acute starvation and 4-beta-hydroxybutyrate supplementation. Both male and female animals were tested using these approaches of inducing ketosis.

Results: Treatment using approaches that induce a state of ketosis produced profound effects in the animals tested, reducing or reversing the progression of PKD in treated animals. Interestingly, we found that supplementation with the ketone body, beta-hydroxybutyrate, was capable of eliciting the beneficial effects in a dominant way in the context of a normal rodent diet.

Conclusions: Our research shows that dietary interventions that induce a state of ketosis are capable of preventing PKD progression in a rodent model of PKD and that the small molecule beta-hydroxybutyrate underlies the effects observed by the diet. These findings have significant implications for the treatment of human ADPKD and may be readily transferrable to clinical practice.

Funding: Private Foundation Support

FR-OR009

Urinary Alanine/Citrate Ratio Associates with the Rate of Kidney Function Decline in ADPKD Patients

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Background: The disease course of autosomal dominant polycystic kidney disease (ADPKD) is highly variable, and the option to prescribe renoprotective treatment make early risk stratification important. Therefore, novel biomarkers to select patients at high-risk of rapid progression are required. We applied metabolomics to evaluate whether changes in the urinary metabolome are associated with progressive loss of eGFR in ADPKD.

Methods: Targeted, quantitative metabolic profiling (^{1}H NMR-spectroscopy) was performed on single, spot urine samples using the KIMBLE workflow (Verhoeven et al, Anal Chim Acta, 2018). Multivariate linear regression analysis was used to dissect the association between urinary metabolites and the rate of disease progression, expressed as annual change in estimated glomerular filtration rate (eGFR; using CKD-EPI equation).

Results: A total of 309 patients with ADPKD were included (age 46±10 years, 57% female, median eGFR 62.1 ml/min/1.73m^2 [IQR 45 to 85]). From the NMR spectra, 29 known urinary metabolites were identified and quantified. In a model with annual change in eGFR (median -3.3 ml/min/1.73m^2 per year [IQR -5.3 to -1.3]) as a response variable and all quantified metabolites and their binary ratios (449 features in total) as predictors, the alanine/citrate ratio was found to be most strongly associated with eGFR decline (F=51.07, P=7.26e-12, r^2=0.15), and remained significant after adjustment for potential confounders. Moreover, it outperformed the model built on the clinical risk markers including baseline eGFR and height-adjusted total kidney volume (htTKV). When only young patients (age <35 years) with an eGFR ≥75ml/min/1.73m^2 were selected (n=33), this ratio was significantly higher in those with fast disease progression (rate of eGFR decline >3.3ml/min/1.73m^2 per year, n=16) as compared with slow progressors (n=17; P=0.015).

Conclusions: Urinary alanine/citrate ratio is associated with the rate of eGFR decline in ADPKD, and showed additional value beyond that of the conventional clinical risk markers. Based on this ratio in a single urine sample, early-stage ADPKD patients with fast disease progression could be identified when eGFR is still relatively preserved. Therefore, urinary alanine/citrate ratio is potentially useful as predictive marker for ADPKD progression.

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FR-OR010

Dissection of the Therapeutic Effect of Glucosylceramide Synthase Inhibition on Polycystic Kidney Disease Progression in Adult Pkd1 RC/RC Mice

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Background: Glucosylceramide synthase inhibitors (GCSi) have been shown to inhibit cystogenesis in multiple preclinical models of PKD. To determine how GCSi treatment impacts kidney disease progression in an adult, orthologous mouse model of ADPKD over a sustained period, we have treated homozygous *Pkd1*$^{tm1.1Pcha}$ mice carrying the R3277C mutation (Pkd1 RC/RC) with a GCSi for one year. To assess the impact on liver cyst formation, we treated Pkd1 conditional knockout (cKO) mice with a GCSi from 7-36 days of age.

Methods: Pkd1 RC/RC mice were randomized into vehicle or GCSi treatment groups at 4 months of age. Genz-667161 was delivered ad libitum in feed (0.03% w/w) until sacrifice at 16 months of age. Periodic high-field (7T) Magnetic Resonance Imaging (MRI) analysis was used to determine total kidney volume (TKV) changes over time. Pkd1 cKO mice were treated with the GCSi Genz-123346 from 7-36 days of age. Kidneys and livers were isolated for histological analysis at the end of study for both Pkd1 RC/RC and cKO mice.

Results: Kidney volume in Pkd1 RC/RC mice was increased compared to wild-type mice prior to treatment at 4 months of age. GCSi treatment reduced the TKV of Pkd1 RC/RC mice within 1 month of treatment; in contrast, vehicle treated Pkd1 RC/RC mice showed a gradual increase in TKV over the same time period. This anti-cystic effect was observed for the duration of the study. At sacrifice, kidney/body weight ratio was significantly decreased in GCSi-treated animals compared to controls. Liver cyst growth was reduced in GCSi treated animals compared to vehicle controls.

Conclusions: GCSi treatment inhibits kidney and liver cyst growth in Pkd1-linked mouse models. Moreover, GCSis have a sustained effect on kidney cyst growth.

Funding: Commercial Support - Sanofi

FR-OR011

Membrane Filtration of Contaminated Water with Used Dialyzers Reduces the Incidence of Diarrhea in Rural Communities in Developing Countries

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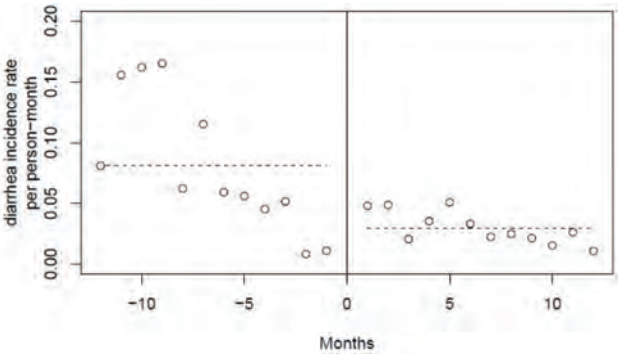
Background: Access to clean water remains unavailable for a large fraction of the world population. Consequent infectious diarrhea, dehydration and acute kidney injury too often leads to death. Membrane filtration using recycled hemodialyzers is a recent innovation. We quantified its effect on health outcomes in rural communities in Ghana.

Methods: From 2015 to 2018 we provided membrane filtration devices (NUFiltration Israel) to 9 communities in Ghana (Greater-Accra region). We calculated incidence rates of self-reported diarrhea and compared monthly counts for 12 months before and 12 after implementation by negative binomial and Poisson regression (Pois) with the log(exposure time) as the offset. Models were compared by likelihood ratio test (LRT) and Akaike Information Criterion (AIC). Logistic regression for recurrent events on a subject-level (LogReg) was used to determine the effect of device implementation and seasonality (rainy versus dry season).

Results: We studied 2605 villagers (10.4% younger than 5 and 5.1 % older than 65 yrs). Incidence rates were significantly lower after device implementation (0.08 versus 0.03; P<0.01). LRT and AIC determined Pois to fit best and Pois showed a significant treatment effect [0.4 (95% CI 0.3 to 0.5)]. LogReg confirmed a lower OR of diarrhea after implementation [0.3 (95% CI 0.2 to 0.3)] with a higher OR of 1.1 (95% CI 1.0 to 1.3) during the rainy season. Lower rates during Month -1 and -2 can possibly be explained by concomitant handwashing and hygiene education initiatives.

Conclusions: Our data shows decrease in the incidence rates and odds of contracting infectious diarrhea with the use of membrane filtration device in rural villages in West Africa. A possible effect of seasonality should be recognized as a potential risk factor. These data emphasize the remarkable public health effect achievable by provision of these low-cost devices.



FR-OR012

Relationship of Acute Kidney Disease (AKD) to Long-Term Outcomes After AKI

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Background: Acute Kidney Disease (AKD) is a term that has been advocated by the Acute Disease Quality Initiative (ADQI) and others to describe ongoing renal dysfunction after AKI that persists beyond 7 days. Currently there is very little available epidemiological data regarding AKD. We sought to study its relevance to long term renal and patient outcomes.

Methods: All patients from the AKI arm of a large parallel group cohort study of AKI were included in this study. Participants were recruited following hospitalisation and followed up prospectively. Renal function, proteinuria and patient outcomes were assessed at 3 months, 1 year and 3 years after AKI. CKD progression was defined as a ≥25% decline in eGFR from baseline with a decline in eGFR stage. Patients were categorized into three groups depending on duration of AKI: AKI that resolved in <48hours (rapid recovery, r-AKI), AKI duration of 2-6 days (persistent AKI, p-AKI) and AKD (AKI duration ≥7 days). Outcomes were compared across these three groups.

Results: In total, 506 patients with AKI were studied. There were 109 (22%) in r-AKI group, 302 (60%) in p-AKI group and 95 (19%) with AKD. Patients in the AKD group had lower baseline eGFR and a higher proportion of AKI stage 3. CKD progression was more common in AKD group as compared to other two groups. At one year, CKD progression was 46% in AKD group versus 11% (r-AKI) and 22% (p-AKI), p<0.001. eGFR was lower in AKD group at all time-points; at year 3, eGFR was 66.9±23ml/min, 60.1±20ml/min and 53±20ml/min in r-AKI, p-AKI and AKD groups respectively, p<0.001. Proteinuria was more common and more severe in AKD. Hospital readmission occurred more frequently in the AKD group. Using binary logistic regression analysis adjusting for age, gender, diabetic status, baseline eGFR, AKI stage and biochemical variables, AKD remained independently associated with CKD progression at 1 (OR 5.4, 95% CI 2.2-13.2, p<0.001) and 3 years (OR 2.2, 95%CI 1.0-4.6, p=0.04).

Conclusions: AKD is common and is associated with a number of clinical variables including chronic comorbidities and markers of AKI severity. However, AKI duration remains an important independent determinant of subsequent progression of kidney disease, and AKD appears to be a useful way to categorize this to identify patients at higher risk of long-term adverse outcomes.

FR-OR013

Renal Recovery Patterns After AKI Influence Mortality

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Background: Renal recovery from acute kidney injury (AKI) in hospitalized patients is variable and non-recovery has been associated with an increased mortality and resource utilization. There is limited information on different patterns of renal recovery following AKI in the ICU setting. We hypothesized that the AKI course and duration in the ICU influences the length of stay and mortality.

Methods: A retrospective multinational cohort study of critically ill adult patients admitted to 4 centers in Germany, UK, and USA was conducted between Jan2014 and Dec2017. We excluded patients who stayed <72hrs in the ICU, patients with ESRD and kidney transplant. AKI was defined by sCr KDIGO criteria and the course characterized as a single episode (SE) or stuttering course (SC) if the patient had multiple AKI during the ICU stay. Recovery of AKI was defined as no longer meeting criteria for even stage 1 AKI. No recovery was defined as an episode of AKI during ICU stay and the last recorded sCr higher than the patient's reference sCr. The primary outcome was ICU and hospital mortality.

Results: Of 20,560 eligible patients, 9,712 (47.2%) developed AKI, 5,303 (25.8%) at Stage 1, 3,358 (16.3%) Stage 2, 2,290 (11.1%) Stage 3 and 9,613 (46.7 %) no AKI. 2,156 patients (10.5%) received dialysis. 7,086 (74 %) patients had a SE while 2,494 (26 %) patients had a SC. Overall, more than half of the patients recovered from AKI (6,128; 65.9%); 65% in SE versus 58.5% in the SC. Amongst dialyzed patients, 51.8% recovered from AKI; 61.7% of the patients with a SE, 42.1% in the SC. The development of AKI significantly increased length of hospital stay (no AKI: 14.2 (±17.4), SE: 20.3 (±21.1); SC: 40.1 (±38.8) days; p<0.001). Patients with AKI had significantly higher mortality which was influenced by the course (no AKI: 8.2%, SE 14.5%, SC: 19.9%; p<0.001). Patients who recovered from AKI had significantly lower hospital mortality (10.9% versus 25.6%; p<0.05). However, mortality in patients with non-recovery was similar in SC 27.9% and SE (24.6%). Overall, we observed four recover patterns.

Conclusions: We have identified four distinct recovery patterns on the basis of the clinical course. These phenotypes may identify patients amenable to therapeutic intervention. The pattern of renal recovery from AKI in the ICU influences resource utilization and mortality.

Funding: NIDDK Support, Commercial Support - FRESENIUS

FR-OR014

Hospitalizations, AKI, and Longitudinal Kidney Function in HIV+ Patients

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Background: Whether AKI contributes to the excess CKD burden in HIV+ persons or simply marks poor overall health is unclear. We conducted a substudy in the Johns Hopkins HIV Clinical Cohort to examine if hospitalizations with and without AKI were each associated with longitudinal eGFR.

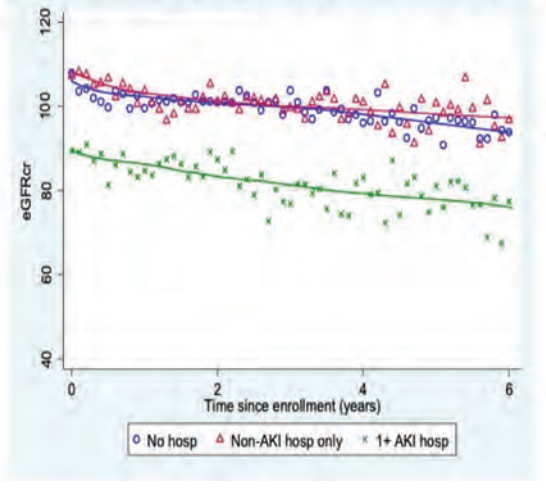
Methods: We included HIV+ persons followed from 1/2005-5/2016 and had baseline eGFR ≥15 ml/min, ≥3 eGFRs and sufficient creatinine (Cr) data to assess AKI status. We classified patients into 3 mutually exclusive groups: never hospitalized, hospitalized without AKI or hospitalized with AKI (≥0.3 mg/dL Cr rise within 48h or max inpatient Cr ≥50% above outpatient baseline). We used mixed effects models, adjusted for demographics, comorbidities, serum albumin, BMI, proteinuria, HIV factors and number of primary care visits.

Results: Among 1731 HIV+ persons, mean age was 43y, 77% were black, and 70% were on antiretrovirals at baseline. During a median follow-up of 3.7y, 730 had ≥1 hospitalization, of whom 43% had ≥1 complicated by AKI. Versus other groups, the hospitalized AKI group was more likely to have IV drug use history, greater comorbidity burden, lower CD4 count, less HIV suppression and lower mean eGFR at baseline (96 vs. 107-109 ml/min) at baseline. In adjusted models, there was little difference in annual eGFR change in those with non-AKI hospitalizations vs. no hospitalizations (Δ 0.12 ml/min; 95%CI: -0.46, 0.71). Conversely, patients with hospitalized AKI vs. no hospitalizations had faster eGFR decline (Δ -1.68 ml/min; 95%CI: -2.69, -0.67) (Figure). This association weakened in sensitivity analyses with inverse weighting for death (Δ -0.85; 95%CI: -1.83, 0.14).

Conclusions: Hospitalized AKI is associated with faster kidney function decline, but hospitalization without AKI had no association. These findings underscore AKI as a potential pathway leading to CKD in HIV+ persons.[Figure]

Funding: NIDDK Support

Figure. eGFR trajectories among HIV+ persons, by hospitalization and AKI status



FR-OR015

Nephrologist Follow-Up vs. Usual Care After an AKI Hospitalization (FUSION): A Randomized Pilot Trial

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Background: Survivors of AKI are at increased risk of CKD and death but few patients see a nephrologist post-discharge. Our objectives were to determine the feasibility of randomizing survivors of AKI to structured follow-up with a nephrologist or usual care, as well as to collect data on clinical outcomes for event rate calculations.

Methods: We performed a 52-week randomized pilot trial in patients hospitalized with KDIGO stage 2-3 AKI in 4 hospitals in Toronto, Canada. We randomized patients to usual care or nephrologist-led follow-up within 90-days of discharge, which consisted of a standard assessment that emphasized blood pressure control, cardiovascular risk reduction, and medication safety. The feasibility outcome was the proportion of patients recruited. The primary clinical outcome was a major adverse kidney event, which is a composite of death, chronic dialysis, or a sustained decrease in eGFR≥25%, at 52-weeks post-discharge.

Results: We screened 269 patients and randomized 71 (26%) from July 2015 to June 2017 (37 to usual care and 34 to nephrology follow-up). The most common reasons for declining to participate were patient fatigue (33%) from recent hospitalization and reluctance to see additional specialists (30%). Baseline characteristics included age 65±10 years (mean, SD), 30% female, baseline eGFR 76±22mL/min/1.73m^2, 47% admitted to the ICU, and median length of stay 14 (IQR 13) days. The median time from hospital discharge to nephrology follow-up was 48 (IQR 40) days, and 22/34 (65%) patients in the intervention group attended their nephrology appointment. The primary outcome occurred in 18/37 (49%) patients in the usual care group and 17/34 (50%) patients in the intervention group (P=0.91). There were no differences between usual care and the nephrology follow-up group in death (8% vs 18%, P=0.23), ≥25% decrease in eGFR (46% vs 38%, P=0.51), or rehospitalization for AKI (24% vs 24%, P=0.94). No patients in either group received maintenance dialysis.

Conclusions: Patient recruitment was lower than anticipated primarily because of patient fatigue and resistance to in-person visits post-discharge, which suggests a more pragmatic intervention may be needed that actively engages patients in its development. The high number of major adverse kidney events observed suggests more work is warranted to improve patient follow-up after AKI.

FR-OR016

Clinical Outcomes and Disparities Associated with ESKD due to AKI in the United States

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Background: Acute kidney injury (AKI) is associated with increased mortality. Mortality in end-stage kidney disease (ESKD) patients is highest during the first year of dialysis. ESKD due to AKI is common, but little is known about the rate of recovery and its impact on long-term outcomes in incident dialysis patients.

Methods: We evaluated a retrospective cohort of 1,045,540 incident ESKD patients from the United States Renal Data System. Using Cox proportional hazard models, we examined the impact of AKI as the ESKD cause on the primary outcome of all-cause mortality. Additionally, we determined the impact of sex and race on renal recovery and associated mortality in patients with AKI as the ESKD cause.

Results: Mean age was 63±15 years. Of the study cohort, 3.3% had ESKD due to AKI. The majority were men (58.1%) and white (75.8%). One-year all-cause mortality was 21.8%. Compared to ESKD due to diabetes (46% of the sample, the most common cause), ESKD due to AKI was associated with changes in the adjusted mortality across the follow-up period – higher adjusted hazards of mortality in first 0-3 months following dialysis initiation (HR, 1.27; 95% CI, 1.23-1.31) and 3-6 months (HR, 1.15; 95% CI, 1.11-1.20), followed by lower adjusted hazards of mortality at 6-12 months (HR, 0.93; 95% CI, 0.90-0.97) that continued to decrease through 84-96 months of follow up (HR, 0.46; 95% CI, 0.41-0.52). Of the patients with ESKD due to AKI, 35.3% eventually recovered their kidney function. The median time of recovery was 2 months (IQR, 1.2-3.5 months). Women had lower adjusted hazards of renal recovery than did men (HR, 0.86; 95% CI, 0.82-0.89). As compared to whites, blacks (HR, 0.67; 95% CI, 0.65-0.71), Asians (HR, 0.77; 95% CI, 0.66-0.90), and Hispanics (HR, 0.80; 95% CI, 0.74-0.86) had a lower likelihood of renal recovery. Heart failure and diabetes were other risk factors associated with non-recovery.

Conclusions: About one-third of patients with ESKD due to AKI recover kidney function. Mortality risk changes across the follow-up period in patients with ESKD due to AKI. Women have a 14% lower likelihood of recovery than men. Black, Asian, and Hispanic patients have a lower likelihood of recovery than do white patients. The study suggests that the need for customized dialysis care in patients with ESKD due to AKI.

FR-OR017

Outcomes of AKI Patients Receiving Dialysis in ESRD Facilities

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Background: Medicare beneficiaries with Acute Kidney Injury (AKI) have received dialysis in outpatient end stage renal disease (ESRD) facilities since 2017 as a result of a CMS policy change allowing payment for dialysis services provided to AKI patients. Outcomes of AKI patients relative to ESRD patients have not been reported.

Methods: AKI patients were identified from 2017 Medicare claims with at least one bill type 072x with condition code 84 (Dialysis for AKI), CPT G0491 (Dialysis for AKI without ESRD) or a select group of ICD-10 codes. We determined patient transition to ESRD from CROWNWeb and other sources; vital status was obtained from the Medicare Enrollment Database. Patients were followed through 3/31/18. We used Cox proportional hazards modeling to compare survival between AKI and non-AKI Medicare incident ESRD patients.

Results: 10,717 of 399,936 (2.7%) patients on dialysis had at least one AKI claim. AKI patients were more likely to be white (72% v. 47%) and age 60+ (82% v. 61%) than ESRD patients. Overall 64% of AKI patients developed ESRD, 13% died without developing ESRD, 17% were alive without ESRD, and 6.1% were lost to follow up. Hospital based facilities had a larger proportion of AKI claims relative to free standing facilities (mean 1.9% v. 0.7% of all dialysis claims). After adjustment for age, race, sex, and ethnicity, AKI patients had a 27% higher mortality risk compared to incident ESRD patients (HR 1.27, p<0.0001).

Conclusions: Patients with AKI represented a small proportion of patients in ESRD facilities in 2017. Almost two-thirds developed ESRD during our limited follow-up. Mortality in the AKI population was higher compared to incident ESRD patients suggesting additional investigation is needed to understand the differences and monitor their outcomes.

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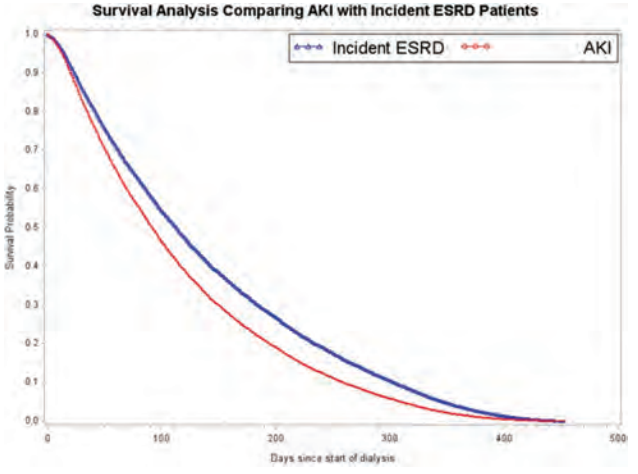

FR-OR018

Incidence and Clinical Outcomes of Outpatient Dialysis for AKI Among Medicare Beneficiaries

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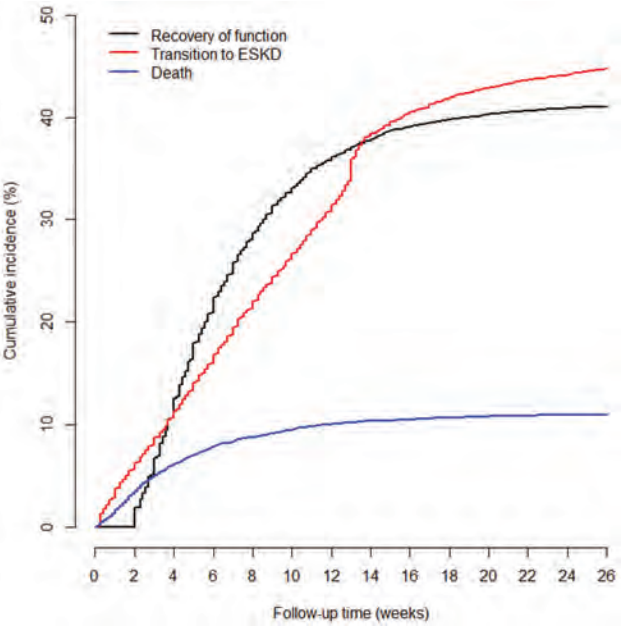
Background: As of January 1, 2017, Medicare Part B covers outpatient (OP) dialysis for acute kidney injury requiring dialysis (AKI-D). We analyzed Medicare claims to describe the incidence and clinical outcomes of beneficiaries initiating OP dialysis for AKI-D in 2017.

Methods: We analyzed the 100% sample of institutional claims in 2014–2017 Medicare Limited Data Sets. To identify initiation of OP dialysis for AKI-D, we located the first OP dialysis facility claim in 2017 with condition code 84 and HCPCS code G0491. We excluded patients with Medicare claims history of OP dialysis for end-stage kidney disease (ESKD), dating to January 1, 2014. We followed patients from initiation of OP dialysis for AKI-D to the earliest of recovery of kidney function (≥2 weeks without OP dialysis for AKI-D), transition to ESKD (OP dialysis facility claim with condition code 71–74), death, or December 31, 2017.

Results: We identified 9634 Medicare beneficiaries undergoing OP dialysis for AKI-D and 9070 (94%) satisfying inclusion criteria. Mean age was 69.9 ± 11.2 years, 24% were age 20–64 years, 76% were white, 16% were black, 44% were female, and 27% were enrolled in Medicaid. During follow-up, 3208 (35%) recovered kidney function, 3381 (37%) transitioned to ESKD, and 896 (10%) died. The cumulative incidence of these events is displayed. At 13 weeks after initiation of OP dialysis for AKI-D, 37% had recovered function, 36% had transitioned to ESKD, and 10% had died. In 7485 patients who reached any endpoint, mean (median) days between first and last OP dialysis sessions were 45 (34) and mean (median) number of sessions was 17 (13).

Conclusions: Most Medicare beneficiaries who initiate OP dialysis for AKI-D recover kidney function or transition to ESKD within 3 months. Long-term follow-up of those who recover function is needed.



FR-OR019

Electronic Alert and a Bundle of Care Reduces Progression and Mortality of AKI Patients

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Background: Acute kidney injury (AKI) is potentially preventable but its early diagnosis is essential to ensure appropriate management. The aim of this study was to evaluate the impact of an electronic AKI alert and a bundle of care (BoC) in the progression and mortality of patients with AKI.

Methods: An algorithm examined all serum creatinine reported by the laboratory. An alert was issued in the electronic medical record (accessed by physicians and nurses) and a BoC was suggested in case of AKI (KDIGO criteria). Prescription audit was performed by a clinical pharmacist. Individuals > 18 years were included and patients in palliative care, nephrology and renal transplantation wards were excluded. The study was divided in two periods: pre-alert initiation group (PRE, January-June/2018) and post-alert group (POS, July-December/2018).

Results: 3174 patients developed AKI (8.3% of hospitalizations). The PRE (n= 1613) and POS (n=1561) groups were similar in age, gender, serum creatinine, baseline glomerular filtration rate (GFR) and ICU admission rate. Dialysis was performed in 514 patients (15%) and was not different between groups (PRE 14.9% vs POS 15.1%; NS). At the time of AKI alert, the prevalence of KDIGO I was similar between groups (PRE 73.5% vs. POS 75.1%; NS), but a higher number of patients remained at this stage in POS (PRE 51% vs. POS 56.1%, P=0.004). Lower percentage evolved to KDIGO III in POS (PRE 33.3% vs POS 30%, P=0.04). Nephrologist was called to 832 patients (26.2%) and the median time to the consultation was lower in the POS (PRE 1.0 day vs POS 0.0 day; P=0.04). The 30-day mortality was 33.6% and was lower in POS (PRE 36.7% vs 30.5%, P <0.001). The independent 30-day mortality risk factors were: age 40 to <65 years (HR 1.37; CI 1.04-1.81, P = 0.02); age 65 to <75 years (HR 1.72; CI 1.29-2.3, P <0.001), age ≥ 75 years (HR 2.36; CI 1.77-3.14, P = 0.003), ICU admission (HR 1.24; CI 1.08-1.43, P = 0.003), baseline GFR (each increase of 10 mL/min) (HR 0.96; CI 0.94-0.98, P <0.001) and AKI eletronic alert (HR 0.87; CI 0.77-0.98, P = 0.02).

Conclusions: An electronic AKI alert and a multidisciplinary BoC reduced progression and 30-day mortality of patients with AKI.

FR-OR020

Development of Machine Learning Models for Predicting AKI Onset Using Electronic Medical Records

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Background: Acute kidney injury (AKI) is a common disease associated with high morbidity and mortality, and the prediction of its onset will help the prevention and appropriate intervention. Recent studies have reported some machine learning models for predicting onset of AKI up to 72 hours in general patient population using electronic medical records (EMR), but studies for predicting in a relatively longer period such as one week have been limited.

Methods: We used the EMR data of adult patients who presented to Kyoto University Hospital, a tertiary teaching hospital in Japan, and received a measurement of renal function between January 2006 and November 2018. Based on the KDIGO guideline, the onset of stage 1 or severer AKI was determined by serum creatinine (sCr) values. Baseline sCr values were calculated by averaging within the windows according to KDIGO's 48-hour and 7-day AKI definitions. The comprehensive results of blood tests, medications, and vital signs were used as explanatory variables. By using random forest algorithm, seven models were constructed to classify whether or not to develop AKI during day 1 to day 7. The models were constructed and validated by 5-fold cross-validation in the cohort. The performance of the models was evaluated by area under the curve (AUC) of receiver operating characteristic curve.

Results: Of the 154,745 patients included in the analysis, it was determined that 10,460 patients (6.8%) had developed AKI. The amount of data with positive and negative labels was considered sufficient for training and validation of the seven models (positive labels, 2,528 ± 274; negative labels 8,571 ± 470 [mean ± standard deviation]). The AUC values were 0.910 ± 0.013, 0.885 ± 0.006, and 0.853 ± 0.012 in predicting onset of AKI after 1 day, 3 days, and 7 days, respectively.

Conclusions: Our models showed high performance equivalent to previous studies with AUC of more than 0.9 in prediction of onset after 1 day. In addition, the models achieved near performance even after periods of up to 7 days, which are longer in compared to previous studies. In future studies, implementing these predictive models in a clinical decision support system that presents risk scores may lead to appropriate interventions to prevent AKI.

Funding: Commercial Support - FUJITSU Ltd.

FR-OR021

Macrophage COX-2 Protects Against AKI via Promotion of M2 Polarization and Efferocytosis

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Background: Efferocytosis, the clearance of apoptotic cells by macrophages, plays a key role in recovery from acute kidney injury (AKI) by promoting the production of anti-inflammatory cytokines. Our previous studies show that macrophage cyclooxygenase-2 (COX-2) plays an essential role in polarization and maintenance of a macrophage alternatively activated, tissue-reparative M2 phenotype. Macrophages with an M2 phenotype exhibit higher efferocytotic capacity and play a pivotal role in recovery from AKI. We examined the role of macrophage COX-2 in efferocytosis, recovery from AKI and subsequent development of fibrosis.

Methods: Wild type (COX-$2^{f/f}$) or CD11b-Cre; COX-$2^{f/f}$ mice (male, 8 weeks, FVB background) were uninephrectomized, immediately followed by unilateral ischemia-reperfusion with 29-min renal pedicle clamping. Mice were sacrificed at different time points after AKI. Renal macrophages were isolated with a mixture of CD11b and CD11c microbeads and used for efferocytosis assay with phagocytosing fluorescent beads or apoptotic neutrophils.

Results: Compared to WT mice, CD11b-Cre; COX-$2^{f/f}$ mice had delayed recovery after AKI, as indicated by BUN and creatinine and had subsequent increases in renal fibrosis as indicated by Masson's Trichrome and Sirius red staining, increased profibrotic and fibrotic components, and increased renal macrophage and lymphocyte infiltration. In WT mice, renal proinflammatory cytokines such as iNOS, TNF-α, CCL3, and IL-23α increased 6 hours after AKI, peaked at 16 hours, and returned to baseline at day 3. In CD11b-Cre; COX-$2^{f/f}$ mice, these cytokines increased to a greater extent and were still elevated 7 days after AKI. Two days after AKI, CD11b-Cre; COX-$2^{f/f}$ mice had increased proinflammatory Th1/M1 but decreased anti-inflammatory Th2/M2 cytokines, in association with decreased expression levels of components of efferocytosis, including TIM4, Axl, and Tyro3 and Gas6. Renal macrophages isolated from CD11b-Cre; COX-$2^{f/f}$ mice 2 days after AKI showed significantly decreased efferocytotic ability in both the fluorescent bead phagocytosis assay and the neutrophil efferocytosis assay.

Conclusions: Macrophage COX-2 protects against AKI and development of renal fibrosis after severe AKI, at least in part due to COX-2-derived PGE2-mediated macrophage M2 polarization and efferocytosis.

Funding: NIDDK Support

FR-OR022

Genetically Augmenting Renal Lymphangiogenesis Protects Against Inflammation Following AKI

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Background: Acute kidney injury (AKI) is a major cause of patient mortality and experimental data suggest AKI as an increased risk factor for progression to chronic kidney disease (CKD). The pathological transition from AKI to CKD is not well understood. Not only the degree of the initial AKI inflammatory response, but also how well it resolves - both in time and in function - are likely factors dictating the potential for future CKD progression. Lymphatic vessels and lymphangiogenesis (LAG) are necessary to maintain tissue homeostasis through fluid, macromolecule, and immune cell clearance. Inflammation-associated LAG is necessary for a timely resolution of peripheral inflammation. What roles renal lymphatics play in AKI recovery or CKD progression is largely unknown.

Methods: We have recently characterized transgenic mice that overexpress the potently lymphangiogenic signal VEGF-D only in the kidney upon doxycycline administration. These conditional "KidVD" mice exhibit marked lymphangiogenesis throughout the kidney. To test if a kidney-specific increase in lymphatic density was protective in AKI, we utilized KidVD mice in the well-characterized surgical bilateral ischemia reperfusion (I/R) model. We also crossed KidVD mice to the POD-ATTAC mouse line, a model of inducible podocyte apoptosis and proteinuria.

Results: First, we identified an endogenous upregulation of lymphatic growth factors VEGF-C and VEGF-D with a small degree of inflammation-associated LAG in both models absent genetic LAG induction. Second, when renal LAG was first induced on the KidVD background prior to injury, we found reduced expression of inflammatory cytokines and matrix fibrosis at 7 days post insult in both models. POD-ATTAC x KidVD mice demonstrated reduced interstitial fibrosis and reduced immune cell numbers 28 days following podocyte loss. Interestingly, despite improvements in inflammation, serum creatinine and eGFR were not improved in KidVD mice in either AKI model and KidVD mice demonstrated increased sodium excretion.

Conclusions: These data suggest that specifically increasing renal LAG signaling may reduce inflammation and fibrosis, but may concurrently disturb transport homeostasis. Renal lymphatic density in response to AKI may thus be predictive in identifying and targeting inflammatory CKD progression.

FR-OR023

Neutrophil Extracellular Traps Are Triggered by C3 and Contribute to AKI

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Background: Infiltration neutrophils can be stimulated to formed neutrophil extracellular trap (NETs), which may lead to renal injury. Complement C3 play a prominent role in inflammatory processes, its activation exacerbates AKI. But the relationship between the formation NETs and activation C3 in IR injury-induced AKI was not clear.

Methods: C57BL/6 mice (WT) were subjected to renal IR injury-induced AKI model by clamping both renal pedicle for 45 min. To deplete neutrophil, mice were treated with intraperitoneal injection of anti-Ly6G IgG (1A8) or control IgG 24h and 2h before bilateral IR injury. C3KO mice were subjected to renal IR injury. The level of renal neutrophils were evaluated by MPO, LY6G and ICAM-1 immunohistochemistry. NETs formation was defined by the colocalization of diffused DAPI, Ly6G and CitH3 signal by immunofluorescence and protein level of CitH3 by western blot. The expression of C3 in renal were estimated by immunofluorescence, qPCR and ELISA. In vitro, neutrophil were isolated from normal individuals and were assessed by Wright-Giemsa stain. Neutrophils in RPMI were simulated with PMA and C3a.

Results: The expression of neutrophil, NETs and C3 of each temporal point after IR increased obviously. At 24h, post-ischemic kidneys represent positivity for DAPI, CitH3 and Ly6G colocalizing of NETs in the outer medulla. Injection of 1A8 suppressed the increase in BUN and Scr 24h after renal IR injury, with a concomitant reduction of neutrophils infiltration and NETs formation, while there were no significant differences in the expression of C3 in mice with and without neutrophil depletion. Compared with WT-sham group, C3KO can ameliorate the accumulation of neutrophil and protect renal against IR injury. Kidney sections from C3KO mice contained less NETs formation with WT mice, corroborating the CitH3 western blot. In vitro, neutrophils were assessed to be >90% pure. After 4h of incubation, 0.1 μM C3a simulated the formation of NETs which reflected by amorphous extracellular DNA structures that colocalized with CitH3 and MPO. PMA altered neutrophil phenotype with decondensed chromatin, while C3a remained intact neutrophil phenotype with lobulated nuclei.

Conclusions: C3 activation can stimulate neutrophil motivation and lead to the formation of NETs in renal IR injury.

FR-OR024

IL-6-Mediated Hepatocyte Production Is the Primary Source of Plasma and Urine Neutrophil Gelatinase-Associated Lipocalin (NGAL) During AKI

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Background: NGAL (*Lcn2*) is the most widely studied biomarker of acute kidney injury (AKI); however the ability of NGAL to predict AKI has been mixed, possibly because it is produced by cell types outside of the kidney or in response to other stimuli

such as systemic inflammation. In the present study, we investigated renal and extra-renal NGAL production in response to the proinflammatory cytokine IL-6.

Methods: Mice: C57Bl/6J (WT)/ B6.IL6<tm1Kopf>/J (*IL-6*$^{-/-}$), hepatocyte specific *Lcn2* deficient (*Lcn2*$^{hep-/-}$)/cre- littermates. Procedures: sham, kidney ischemia reperfusion (IR) (27 minutes bilateral renal pedicle clamping); bilateral nephrectomy (Bnx). Injections: anti-mouse Ly6G clone 1A8/rat IgG2a isotype control clone 2A3 500μg, IP; recombinant murine (rm)IL-6 (200 ng, IV). Measurements: BUN, plasma creatinine, Kim1 mRNA, NGAL mRNA (liver kidney, spleen and lung); NGAL protein concentrations (liver, kidney, spleen, lung, plasma and urine).

Results: Plasma NGAL was increased in WT 4 and 24 hours after sham, IR, and BNx and was decreased in *IL-6*$^{-/-}$ mice in all three conditions; similarly, urine NGAL was increased after sham and IR in WT and decreased in *IL-6*$^{-/-}$ mice. Kidney function was similar between WT and *IL-6*$^{-/-}$ mice as judged by serum creatinine, BUN, and kidney histology. NGAL mRNA was most upregulated in the liver (versus the kidney, lung, and spleen) 4 and 24 hours after sham, IR, and BNx, and reduced in *IL-6*$^{-/-}$ mice. IV injection of recombinant IL-6 to normal mice resulted in a significant increase in hepatic, but not renal, NGAL mRNA and an increase in plasma and urine NGAL. In vitro, addition of recombinant IL-6 to hepatocytes resulted in a significant increase in NGAL levels in the supernatant. To further examine the specific contribution of hepatocytes to plasma and urine NGAL levels, mice with hepatocyte specific NGAL deletion (*Lcn2*$^{hep-/-}$) were studied; plasma and urine NGAL were 90% and 80% reduced, respectively, after IR. Neutrophil depletion after IR did not affect plasma and urine NGAL levels after sham and IR.

Conclusions: IL-6 mediates hepatic production of NGAL during AKI. The results of these experiments shed new insights into the mechanism behind the increases in plasma and urine NGAL after AKI.

Funding: Veterans Affairs Support

FR-OR025

Lung Double Negative (αβ+CD4-CD8-) T Cells Respond to AKI and Can Directly Protect from Lung Injury: A Protective Mediator During Kidney-Lung Cross-Talk?

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Background: Kidney-lung cross talk during AKI contributes to the high mortality and reveals key interactions between lung and kidney. CD4-CD8- (double-negative; DN) αβ T cells have been recently described in kidney and rapidly respond to local ischemia reperfusion injury (IRI) with a protective anti-inflammatory cytokine profile, but the response to remote injury is unknown. We hypothesized that DN T cells serve a potential protective role as an immunologic mediator of kidney-lung crosstalk following remote as well as local injury.

Methods: B6 Wild type (WT) mice were subjected to IRI on either kidney or in lung by a established methods. Lymphocytes from lung was isolated and analysed by flow cytometry. H&E staining was performed with lung tissue to assess lung edema. Immunoblotting with cleaved caspase-3 was evaluated for apoptosis. To test the role for DN T cells in lung IRI, adoptive transfer of DN T cells prior to lung IRI was performed.

Results: Our data show that the frequency of lung DN T cell was significantly increased following both lung (39.1%) and kidney IRI (23.5%), $p<0.05$, compared to sham (10.7%). Immunoblotting of cleaved caspase-3 revealed higher levels of apoptosis at 3 and 6 hours of both renal and lung IRI. Evans blue extravasation demonstrated that adoptive transfer of DN T cells significantly decreased interstitial thickening and lung permeability (39.5 μg vs. 28 μg, $p<0.05$). Quantitative analysis of cleaved caspase-3 immunoblotting showed that DN T cell transfer attenuated cellular apoptosis (3.2 vs. 0.8, $p<0.01$). To assess the human relevance of lung DN T cells, lung samples were studied during implantation of lung transplants which were exposed to ischemia reperfusion, and DN T cells were also found in the human lungs (18.4% at ischemia, 39.2% at reperfusion).

Conclusions: These data demonstrate that DN T cells are a potential immunologic mediator of kidney-lung cross talk, and studies in lung IRI extend the role of DN T cells from kidney IRI to importance in lung injury as well. Further studies are needed to elucidate the mechanism of this potentially immunoregulatory response and human correlates

Funding: NIDDK Support

FR-OR026

CD4 T Cell-Derived Neutrophil Gelatinase-Associated Lipocalin (NGAL) Mediates Ischemia Reperfusion-Induced AKI

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Background: T cells mediate tissue injury and repair processes following ischemia reperfusion (IR) and nephrotoxin induced acute kidney injury (AKI). While exploring underlying mechanisms involved in T cell mediated AKI/repair, we unexpectedly identified lipocalin 2 (*Lcn2*) as the most upregulated gene in post IR kidney CD4 T cells. Functional studies of *Lcn2* encoded neutrophil gelatinase-associated lipocalin (NGAL), a biomarker for early detection of AKI, showed important role in T cell mediate AKI pathophysiology.

Methods: WT mice were subjected to IR and kidney CD4 T cells flow sorted after 24 hours. An unbiased RNA sequencing was carried out to determine transcriptional effects of IRI on kidney CD4 T cell response. Flow cytometry and ELISA was performed to validate RNA-seq data. Adoptive transfer studies were performed using NGAL KO, CD 4 KO and WT mice. Pre and post clamp human kidney samples from RCC nephrectomies were also evaluated.

Results: RNA-seq analysis showed *Lcn2* mRNA as the top upregulated (60-fold) gene in CD4 T cells from post IR mouse kidney. RT-PCR validated RNA-seq data and showed increased *Lcn2* expression ($P< 0.05$) in post IR renal CD4 T cells. ELISA showed increased NGAL protein in renal CD4 T cells (244±24 vs 8±5 ng/mg; $p < 0.001$) and spleen CD4 T cells (261±44 vs. 42±19 ng/mg; $p < 0.01$) post IR compared to controls. Adoptive transfer of splenic CD4 T cells from NGAL KO mice significantly increased serum creatinine (SCr) than CD4 T cell from WT mice or the PBS in CD4 KO recipients (1.80±0.26; 1.06±0.21 and 0.97±0.25 mg/dL respectively; p=0.04) and in the WT recipients (1.47±0.17; 0.93±0.17 and 0.73±0.17 mg/dL respectively; p=0.02). *In vitro* simulated hypoxia increased *Lcn2* (1.7-fold) and *Ifn*-γ (8.8- fold) mRNA expression in CD4 T cells from NGAL KO mice compared to CD4 T cells from WT mice. NGAL increased significantly (38.8±3.9 % vs.15.4±5.9 %, $P < 0.05$) in post clamp human kidney T cells compared to pre clamp.

Conclusions: These data show that kidney CD4+ cell *Lcn2*/NGAL responds rapidly to IRI, directly mediates kidney structural and functional responses to ischemic AKI, and modifies CD4 cell *Ifn*-γ. NGAL, traditionally thought to be a candidate biomarker for AKI, is an important molecular regulator of the CD4+ T cell response during ischemic AKI

Funding: NIDDK Support

FR-OR027

Autophagy Stimulation of FGF2 in Tubular Cells Activates Renal Fibroblasts and Promotes Interstitial Fibrosis During AKI-CKD Transition

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Background: The mechanisms that trigger AKI-CKD transition are poorly understood. We recently reveal an autophagy-mediated tubular maladaptive repair and its contribution to renal fibrosis after ischemic AKI. However, it is unclear how autophagy in renal tubules promotes interstitial fibrosis.

Methods: We generated a doxycycline-inducible, conditional *Atg7* knockout mouse model (i*Atg7* KO) with *Atg7* specifically deleted from renal tubules at a desired time after ischemic AKI without affecting initial injury. We also exposed proximal tubular cells to TGFB1 and collected conditioned medium (CM) to treat renal interstitial fibroblasts. Using these models we examined how tubular cell autophagy regulates fibrosis with a focus on tubular paracrine activation of fibroblasts.

Results: Autophagy was activated in proximal tubules during post-ischemic fibrosis in wild-type (WT) mice. i*Atg7* KO blocked tubular autophagy and suppressed fibrosis. Along with autophagy, the expression of several profibrotic cytokines (TGFB1, FGF2, CTGF and PDGFB) was increased in WT fibrotic kidneys. Among them, only the expression of FGF2 (both mRNA and protein) was reduced in i*Atg7* KO mice. In WT kidneys FGF2 accumulated predominantly in the basolateral cytoplasm of atrophic tubules, which was suppressed in i*Atg7* KO mice. Costaining of FGF2 in autophagy reporter mice further revealed a partial colocalization of FGF2 with LC3 puncta in autophagic tubules. In cultured mouse proximal tubular cells, TGFB1 induced the production of FGF2, CTGF and PDGFB, and also enhanced tubular secretion of FGF2 and CTGF. Defective autophagy by *Atg7* KO reduced both the production and tubular secretion of FGF2, but not CTGF or PDGFB. CM from TGFB1-treated WT tubular cells induced proliferation and activation of renal fibroblasts and accumulation of ECM proteins, whereas these effects were attenuated in fibroblasts treated with *Atg7* KO tubular cell-CM. FGF2 neutralizing antibody recapitulated the inhibitory effects of *Atg7* KO tubular cell-CM on renal fibroblasts, further supporting a role for FGF2 in autophagy-dependent tubular paracrine activation of fibroblasts.

Conclusions: Dysregulated autophagy in renal tubules may specifically stimulate tubular production and secretion of FGF2. This autophagy-mediated paracrine then activates interstitial fibroblasts and promotes kidney fibrosis after AKI.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR028

Inactivation of Endothelial HIF Polyhydroxylases Following Ischemic AKI Promotes Kidney Fibrosis

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Background: Key regulators of hypoxic vascular responses are Hypoxia-Inducible-Factors (HIF)-1 and -2, transcription factors whose activity is negatively regulated by prolyl-hydroxylase domain proteins 1 to 3 (PHD1 to PHD3). Little is known about endothelial cell (EC) specific functions of PHDs in response to acute kidney injury (AKI), a common problem associated with significant morbidity and mortality. Here, we used a genetic approach to investigate the function of endothelial PHDs in renal ischemia-reperfusion injury (IRI).

Methods: Cdh5(PAC)CreER^{T2} inducible system was used to induce conditional deletion of PHD1,2,3 in ECs (Cdh5(PAC)CreER^{T2}; Phd1$^{f/f}$Phd2$^{f/f}$Phd3$^{f/f}$ referred as EC-PHD1/2/3 mutants) while the recombination efficiency was assessed by crossing Cdh5(PAC)-CreER ^{T2} transgenic mice to ROSA26-ACTB-tdTomato,-EGFP reporter mice. Mice were subjected to unilateral IRI and at Day 1 post IRI they were started on tamoxifen (total of 4 doses) to inactivate PHDs. Samples were collected at day 14 after IRI.

Results: The Cdh5(PAC)CreER^{T2} showed efficient recombination in the kidney endothelium based on FACs analysis and imaging of kidney tissue from the reporter mice. Immunofluorescence analysis of PHDs showed persistent expression of PHDs following IRI. Post-ischemic inactivation of endothelial PHDs (1-3) exacerbated infiltration of inflammatory cells and tubular damage at day 14 after IRI assessed by histopathological analysis of injured kidneys. EC-PHD1/2/3 mutants showed increased expression levels of profibrotic genes *Loxl2* (n=6-8, P= 0.03). and *Tgf*-β (n=6-8, P= 0.005). Significant deposition of matrix in interstitial spaces was observed in kidneys of EC-PHD1/2/3 mutants compared to Cre-controls as indicated by Sirius red staining. Transmission electron microscopic examination showed prominent endothelial cell damage in the kidney of EC-PHD1/2/3 mutants, which was associated with peritubular capillary rarefaction as indicated by endomucin staining. Furthermore, treatment of human ECs with a PHD inhibitor following the induction of hypoxia-reoxygenation led to significant suppression of EC-proliferation.

Conclusions: Our data show a critical role for endothelial PHDs following ischemic AKI. Inactivation of endothelial PHDs following ischemic AKI promotes kidney inflammation, peritubular capillary rarefaction and fibrosis.

Funding: NIDDK Support

FR-OR029

ATR Deletion Drives TOR-Autophagy Spatial Coupling Compartment (TASCC) Formation and Kidney Fibrosis

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Background: Acute kidney injury (AKI) occurs in ~20% of hospitalized patients. While the kidney can functionally recover from AKI, AKI predisposes patients to subsequent chronic kidney disease (CKD), which effects 13% of the global population. Our lab, and others, have shown the AKI-CKD transition involves maladaptive repair leading to G2/M arrest regulated by DNA damage response (DDR) genes. Recently, we have identified target of rapamycin–autophagy spatial coupling compartments (TASCCs) as components of the secretory response in G2/M arrested cells. To determine how the DDR modulates AKI-CKD transition, we tested if the loss of ataxia telangiectasia and Rad3-related (ATR) regulates TASCC formation and fibrosis.

Methods: 1: ATR flox/flox mice were breed to SLC34a1-Cre-ERT2 mice to generate proximal tubular cell (PTC) specific ATR deletion (ATR$^{RPTC-/-}$) upon tamoxifen injection. ATR floxed mice lacking the Cre acted as control (ATR^{Ctrl}). ATR^{Ctrl} and ATR$^{RPTC-/-}$ received unilateral ureteral obstruction (UUO). Kidneys were taken at day 7 and analyzed for fibrosis, G2/M arrest markers, injury markers and TASCC formation by immunostaining. TASCCs were identified by super-resolution microscopy. 2: Fucci2a mice were breed to γGT-Cre mice to generate PTC specific Fucci2a expression. The PTCs were then isolated and treated with aristolochic acid (AA), with/without the ATR inhibitor VE-821. Cells were analyzed for increased connective tissue growth factor (CTGF) by western blot.

Results: Inhibition of ATR in PTCs resulted in increased numbers of G2/M arrested cells following AA treatment, as measured by the Fucci cell cycle reporter, and greater production of CTGF, *in vitro*. *In vivo*, ATR$^{RPTC-/-}$ mice had more sever and rapidly progressing fibrosis compared to ATR^{Ctrl} mice. Deletion of ATR from PTCs resulted in increased tubular cell injury, caspase 3 staining, and G2/M arrest in response to UUO. G2/M arrest was associated with formation of TASCCs in PTCs. ATR$^{RPTC-/-}$ mice had greater numbers of TASCC/cell compared to controls.

Conclusions: ATR deletion sensitized PTCs to injury and G2/M arrest, which drove TASCC formation and production of CTGF. These data indicate the DDR modulates the AKI-CKD transition through a pathway involving G2/M arrest, TASCC formation and profibrotic factor secretion, as well as identifying novel targets for therapeutic intervention.

Funding: NIDDK Support

FR-OR030

Long-Acting Thioredoxin Prevents AKI to CKD Transition via Its Anti-Oxidative and Anti-Inflammatory Action

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Background: Renal fibrosis is common finding in CKD and is induced by the sustained oxidative stress and inflammation after AKI. Therefore, an effective strategy is highly desirable for preventing AKI to CKD transition. Thioredoxin-1 (Trx) is a redox-active protein that has anti-oxidative and anti-inflammatory properties. Although, Trx has great potential for use as a therapeutic agent against several types of oxidative stress-related diseases, its short half-life limits its clinical application. To overcome this problem, we produced a recombinant fusion protein that is comprised of human serum albumin and Trx (HSA-Trx), and examined its preventive effect against AKI to CKD transition.

Methods: Recombinant HSA-Trx was expressed using Pichia expression system. AKI to CKD transition model mice were generated by renal ischemia-reperfusion (IR).

Results: From day 1 to day 14 after renal IR, recovery of renal function and body weight were accelerated by HSA-Trx administration. HSA-Trx ameliorated excessive extracellular matrix deposition and the increase in hydroxyproline content and Col1a2 mRNA expression in the kidney on day 14 after renal IR. HSA-Trx also suppressed epithelial-endothelial transition, is known as the process of fibrosis progression. To elucidate the suppressive mechanism of HSA-Trx on AKI to CKD transition, we examined at the early phase of fibrogenesis (day 7) after renal IR. HSA-Trx treatment ameliorated renal histological alterations and decreased the increase in renal mRNA expression of Kim-1 and Sox9, which is injury marker and regeneration marker in renal tubule, respectively. In addition, the increase in oxidative stress, pro-inflammatory cytokine expression, and the number of macrophages in the kidney of PBS-treated mice were suppressed by HSA-Trx. Similarly, HSA-Trx treatment inhibited G2/M cell cycle arrest and apoptosis in renal tubule cells, which are involved in CKD progression. While renal Trx protein level were significantly decreased by renal IR, HSA-Trx suppressed the decrease in renal Trx protein level, suggesting that HSA-Trx exerts renoprotective effect partially due to preserve renal Trx protein level.

Conclusions: HSA-Trx has potential for use in the treatment of AKI to CKD transitionvia its extended effects of modulating oxidative stress and inflammation.

FR-OR031

A Randomized Trial of Optimal Phosphate Range for Coronary Artery Calcification in Dialysis Patients

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Background: In dialysis patients, mortality risk due to cardiovascular diseases is remarkably high and prognosis is poor; coronary artery calcification (CAC) is considered one of the major contributing factors. It is known that hyperphosphatemia is associated with CAC. Therefore, controlling serum phosphate level could improve the poor prognosis of dialysis patients. However, the optimal phosphate level in dialysis patients remains unknown; hence, this study was planned to compare the effects of two types of non-calcium-based phosphate binders, and examine the effect of strict control of phosphate on CAC.

Methods: Evaluate the new Phosphate Iron-based binder Sucroferric Oxyhydroxide in Dialysis patients with the goal of advancing the practice of E.B.M. (EPISODE) study is a randomized, open-label, multi-center, interventional trial with a two-by-two factorial design (UMIN000023648). We enrolled 160 hemodialysis patients, who were randomized to the sucroferric oxyhydroxide (SO) or lanthanum carbonate (LC) group in order to reduce serum phosphate to two target levels (3.5 - 4.5 mg/dL in strict group and 5.0 - 6.0 mg/dL in standard group) for 12 months. The primary endpoint was percent change in CAC score (% CACS change).

Results: Median CAC score was 840 (IQR 270-2705) at baseline. In 160 dialysis patients, 115 patients were analyzed as full analysis set. There was no significant difference in % CACS change between two phosphate binders (SO; median 12.46% [IQR -2.78-24.12], vs. LC; 13.23% [4.87-30.19], P=0.369) at 12 months. On the contrary, strict phosphate control (achieved phosphate level; 4.98±0.11 mg/dL) significantly suppressed % CACS change (median 7.57% [IQR -1.84-23.93], vs. 20.16% [9.85-30.19], P=0.020) compared with standard control (phosphate level; 5.61±0.11 mg/dL). Strict phosphate control significantly decreased c-terminal FGF23 (-130.31±327.65 pmol/L) compared with standard control (168.69±730.73, P=0.012). Of interest is that therapeutic effect of strict phosphate control was observed even in dialysis patients with baseline-CAC score>1000 (strict; 4.87% [IQR -3.90-4.87], vs, standard; 11.88% [IQR 5.78-21.41], P=0.030).

Conclusions: Strict phosphate control may retard the progression of CAC among dialysis patients.

Funding: Commercial Support - Kissei

FR-OR032

Effects of Long-Term Burosumab, a Fully Human Monoclonal Antibody Against FGF23, on Phosphorus, Calcium, and Nephrocalcinosis in Adults with X-Linked Hypophosphatemia

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Background: In XLH, nephrocalcinosis and hyperparathyroidism are complications of treatment with oral phosphate and active vitamin D. Burosumab significantly improved serum phosphorus, fracture/pseudofracture healing, stiffness, and physical functioning compared to placebo in a Phase 3, double-blind, multicenter study in adults with XLH (CL303, NCT02526160). Here, we evaluate the effects of long-term burosumab on nephrocalcinosis and related measures using data from the completed trial.

Methods: 134 subjects were randomized 1:1 to receive burosumab 1 mg/kg or placebo subcutaneously every 4 weeks. At Week 24, subjects receiving placebo crossed-over to receive burosumab, and all subjects remained on burosumab up to Week 96, remaining blinded to prior treatment. Groups were combined for the Week 96 analysis.

Nephrocalcinosis score determined by ultrasound, ranging from 0 (normal) to 4 (stone formation), was assessed by central readers blinded to treatment.

Results: 90% (121/134) of subjects had previously received oral phosphate and active vitamin D. At baseline, nephrocalcinosis was present in 54% (73/134) of subjects, with scores of 1, 2, and 3 observed in 41%, 12%, and 1%, respectively. At Week 96, nephrocalcinosis score remained unchanged from baseline in most subjects (101/120, 84%), decreased by 1 in 9 subjects (8%), and increased by 1 in 10 subjects (8%). Serum phosphorus levels and TmP/GFR increased significantly with burosumab. Serum calcium and GFR remained stable, and mean PTH decreased modestly. Urine calcium trended upward, with 4 (3%) subjects having values above the ULN at Week 96.

Conclusions: In adults with XLH receiving burosumab for 96 weeks, renal phosphate reabsorption and serum phosphorus increased significantly and PTH decreased toward normal levels. Mean urine calcium excretion increased slightly, but nephrocalcinosis scores were not significantly changed.

Visit	Serum Calcium, mg/dL	Serum PTH, pg/mL	Serum 1,25(OH)2D, pg/mL	Urine Calcium Excretion, mg/24-hour	Serum Phosphorus, mg/dL	TmP/GFR, mg/dL
Baseline	9.15 (0.45)	97 (51)	33 (14)	102 (57)	1.98 (0.31)	1.64 (0.39)
Week 48	9.09 (0.44)	87 (40)	40 (14)	117 (66)	2.47 (0.47)	2.21 (0.56)
Week 72	9.12 (0.40)	78 (39)	38 (14)	124 (63)	2.49 (0.45)	2.19 (0.52)
Week 96	9.10 (0.40)	79 (36)	34 (11)	145 (99)	2.42 (0.46)	2.07 (0.52)

Data are mean (SD); Measurements were assessed at the end of the dose interval

FR-OR033

EOS789, a Novel Pan-Inhibitor of NaPi-IIb/PiT-1/PiT-2, Decreased Intestinal Phosphate Absorption in Hemodialysis Patients Measured by Sensitive and Direct Method Using 33P: A Phase 1b Clinical Trial

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Background: Elevated serum phosphorus (P) remains problematic in dialysis patients. EOS789, a novel pan-phosphate transporter inhibitor (NaPi-IIb, PiT-1, PiT-2), showed increased fecal phosphate excretion in healthy subjects in phase 1 study. Here we report safety and efficacy of EOS789 in hemodialysis (HD) patients (pts).

Methods: We conducted two cross-over, randomized sequence studies of identical design. The first compared EOS789 50 mg to placebo tid with meals. The second compared EOS789 100 mg vs EOS789 100 mg + 1600 mg sevelamer carbonate tid with meals. Pts undergoing thrice weekly HD, with a rise in serum P of 0.5 mg/dL after 15-19 days without a phosphate binder were eligible. Pts consumed a standardized diet containing 900 mg of P for 2 weeks. Study drug was given on days 4 to 14 with the diet. On day 10 subjects were admitted to the CRC for 3 days. Pts had pre-dialysis blood drawn, dialysis treatment, a meal with an oral dose of 10 uCi of 33P, and the next day they received 10 uCi 33P by IV. Serial blood draws were taken over 48h post-oral 33P dose, serum was analyzed for 33P activity, and percent P absorption was determined by kinetic modeling.

Results: A total of 12 to 14 patients were randomized to each study; 10 completed all assessments. There were no study drug related SAEs. Eight patients had gastrointestinal disorders (2 patients in each group). For efficacy, percent P absorption was 56% for placebo vs. 51% for EOS 50 mg (p=0.52) and 40% for EOS 100 mg vs. 36% for EOS 100 mg + sevelamer (p=0.45). Within each individual cross over study, these differences did not reach significance. When the 6 pts that completed both studies awere analyzed, percent P absorption was significantly lower with EOS 100 mg (44%) compared with placebo (63%) (p=0.013) and trended lower compared with EOS 50 mg (55%, p=0.12).

Conclusions: In this phase 1b study in HD pts, EOS789 was well tolerated. There was a significant decrease in intestinal P absorption at EOS789 100 mg tid. Importantly, 33P is a sensitive and direct measure of intestinal absorption, and is a superior method to serum P that is confounded by dialysis P clearance and bone remodeling.

FR-OR034

Fractional Phosphorus Absorption Is Inappropriately Normal and Does Not Correlate with 24-Hour Urine Phosphorus in Patients with Moderate CKD Compared with Healthy Adults

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Background: Intestinal phosphorus (P) absorption in patients with CKD is understudied, yet current therapies focus on reducing intestinal P absorption to lower the risk of cardiovascular dysfunction and mortality. Rodent studies suggest that intestinal P absorption remains inappropriately normal in early CKD, despite elevations in FGF23 and declining calcitriol. We have previously shown that 24h urine P is not related to net P absorption from metabolic balance studies in CKD patients (Stremke et al. CJASN 2018), and thus more direct measures of absorption are needed.

Methods: In this controlled feeding study, we aimed to determine P absorption in patients with moderate CKD vs healthy subjects using a 33P radioisotope tracer method. CKD and controls were matched for age (+/-10y), sex, and race. Subjects ate a controlled study diet of ~1500 mg/d P, ~1400 mg/d Ca, ~3200 mg/d K, ~2400 mg/d Na, and 0.8 g/kg/d protein for 1 week. The final two study days consisted of a clinical research center (CRC) inpatient P absorption test utilizing oral and IV doses of 33P. Fractional P absorption was determined by multi-compartment kinetic modeling. 24h urine P (uP) was determined by ICP-OES as a 2-day average. Paired analyses were performed to determine differences between CKD and controls. The relationship between fractional P absorption and 24h uP was determined by Pearson's correlation.

Results: N=6 CKD patients (eGFR=29-55 mL/min/1.73m^2) and N=6 controls completed the study. Fractional P absorption was similar between CKD patients and controls (0.68 vs 0.66, p=0.91). 24h uP also did not differ (856 vs 878 mg/d, p=0.91). 24h uP did not relate to fractional P absorption overall (r=0.07, p=0.37), nor within either group (CKD, r=0.09, controls, r=0.11, p>0.50).

Conclusions: Fractional P absorption is similar between moderate CKD patients and healthy control subjects consuming a controlled diet. This supports the animal data that P absorption is maintained at inappropriately normal levels in early/moderate CKD despite hormonal changes that should suppress P absorption. We also show no association between CRC collected 24h uP and fractional P absorption supporting that 24h uP is not reflective of P intake or net P absorption in CKD.

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FR-OR035

Prevalence, Progression, and Implications of Breast Artery Calcification in Patients with CKD

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Background: Breast artery calcification (BAC) is increasingly recognized as a specific marker of medial calcification. In this retrospective observational cohort study, we aimed to define the prevalence and progression rate of BAC in CKD patients across disease stage, to identify clinical and biochemical correlates of BAC and to explore the association of BAC with incident cardiovascular morbidity and overall mortality.

Methods: Presence and extent (BAC score) were determined on mammograms in 311 females (58.7 ± 10.8 yrs, Caucasian) with CKD across disease stage (CKD 2-5D n=133; transplant recipients [Tx]: n=178). In a subset of 88 patients (CKD5D n=14, Tx n=74), a repeat mammography was performed after a mean interval of 3.5 ± 2.2 years, allowing to calculate the annualized BAC rate. Relevant clinical and laboratory parameters, including parameters of mineral metabolism and inflammation, and outcomes were extracted from electronic files. Survival analysis was performed in the TX group by Kaplan-Meijer analysis.

Results: BAC was observed in 34.7% of the patients. Prevalence and extent of BAC increased parallel to the decline of kidney function. In the overall cohort, patients with BAC were older, suffered more from CVD and inflammation, had higher pulse pressure, and borderline higher prevalence of diabetes. The BAC progression rate was significantly higher in patients with CKD5D as compared to Tx patients (2.2 ± 1.2 vs 1.0 ± 0.4 mm/yr, mean ± SE; p=0.02). Progressors were characterized by more inflammation, worse kidney function and higher BAC score at baseline. In the Tx subcohort, progressors moreover showed higher serum phosphate levels at baseline. Presence of BAC associated with poor overall (Log-Rank p=0.0007) and cardiovascular event free (Log-Rank p=0.007) survival in Tx.

Conclusions: BAC is common among CKD patients, progresses at a slower pace in Tx as compared to CKD5D, and associates with dismal (cardiovascular) outcomes. BAC score, kidney function and serum phosphate at baseline are important determinants of progression. Measurement of BAC may offer a personalized, non-invasive approach to risk-stratify CKD patients for cardiovascular disease at no additional cost or radiation since a majority of women over the age of 40 undergo regular breast cancer screening.

FR-OR036

Sevelamer Therapy Associates with a Disturbed Microbial Metabolism in Patients with ESRD

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Background: Sevelamer is a commonly used phosphate binder (PB) in patients(pts) with ESRD. Gastrointestinal discomfort and constipation are frequently reported by sevelamer users, which raises the hypothesis that sevelamer may disturb microbial metabolism. Here we investigate if sevelamer therapy is associated with microbial metabolism in ESRD pts.

Methods: We analyzed serum levels of indoxyl sulphate (IndS) and trimethylamine-N-oxide (TMAO) (as important representatives of colonic microbial metabolism) in a large cohort of ESRD pts (n=423, 65% males, median age 54 years) listed for renal transplantation in Leuven (Belgium, n=347) or Stockholm (Sweden, n=76). Since gut microbial metabolism besides nutritional intake is an important source of VitK, we measured desphospho-uncarboxylated Matrix Gla-Protein (dp-ucMGP) levels, as a proxy of VitK status. Pts treated either with non-calcium containing PB other than sevelamer or VitK antagonist were excluded. Relevant demographics and biochemistry data were extracted from electronic files. Descriptive and multivariate linear regression analyses were performed to define the role of sevelamer therapy.

Results: Compared with sevelamer non-users, pts treated with sevelamer were characterized with younger age, higher BMI, worse phosphate control, lower albumin,

higher serum creatinine, higher serum IndS, TMAO and higher dp-ucMGP levels. In multivariate regression models adjusted for age, gender, phosphate control, serum calcium, calcium containing PB users, dialysis vintage and cohort, sevelamer therapy was identified as an independent determinant of IndS (Odds ratio, [OR 1.41; 95% confidence interval [95%CI], 1.15 to 1.71] and dp-ucMGP (OR[95%CI], 1.46 [1.17 to 1.83]), but not TMAO (1.19 [0.97 to 1.47]). A further adjustment of dp-ucMGP showed that dp-ucMGP is associated with IndS (1.32 [1.19 to 1.46]) and TMAO (1.20 [1.08 to 1.33]).

Conclusions: Sevelamer therapy associates with poor VitK status and an unfavorable microbial metabolism pattern, characterized by high IndS levels. Though the design of our study precludes causal inference, present findings point to a disturbed gut microbial metabolism and VitK deficiency as potential trade-offs of sevelamer therapy and should be considered a call for caution.

Funding: Government Support - Non-U.S.

FR-OR037

Serum Sclerostin: A Useful Biomarker of CKD-MBD

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Background: Sclerostin is a glycoprotein secreted by osteocytes and antagonizing the bone catabolic effects of the wnt/beta-catenin pathway. Mounting evidence indicates that circulating sclerostin may qualify as a biomarker of CKD-MBD. In this study we report data from a clinical study in which correlations between circulating sclerostin, skeletal sclerostin expression, bone histomorphometric parameters and serum markers of bone metabolism were investigated.

Methods: A transiliac bone biopsy was taken and serum samples were collected in a cohort of 68 ESRD patients (19 males) at the time of transplantation. Serum sclerostin levels were measured using 4 different commercially available assays (BioMedica, Diasorin, Tecomedical and R&D). Skeletal sclerostin expression was evaluated on immunohistochemically stained tissue sections by counting the % of sclerostin positive osteocytic lacunae. Quantitative bone histomorphometry was performed on Goldner stained undecalcified tissue sections. Different serum markers of bone metabolism were analysed using commercially available kits.

Results: 43 ± 13% of the osteocytic lacunae were positive for sclerostin expression. Median; interquartile range (IQR) serum sclerostin concentrations (pg/ml) with the 4 assays were: 213; 159 (R&D), 1155; 848 (Diasorin), 1687; 1501 (Tecomedical), 3109; 2524 (BioMedica). Despite these large inter-assay variation, significant correlations with the skeletal sclerostin expression were found for the 4 assays under study with the Biomedica assay showing the best correlation: Rs=0.3989, p<0.001. Furthermore, both skeletal and serum (except for the Diasorin assay) sclerostin levels negatively correlated with static bone histomorphometric and serum parameters reflecting bone metabolism (formation/-turnover/-mineralization) i.e. osteoid width (p<0.05), osteoblast perimeter (p<0.05), bone-specific alkaline phosphatase (p<0.05), N-terminal propeptide of type I collagen (p<0.01), PTH (p<0.01).

Conclusions: In ESRD patients, circulating sclerostin levels significantly correlate with skeletal expression of the protein and can be regarded as a metabolic bone marker. Further research investigating extra-osseous production (e.g. calcifying vascular smooth muscle cells) of sclerostin is warranted since variation in circulating sclerostin cannot be explained by its variation in skeletal expression only.

Funding: Government Support - Non-U.S.

FR-OR038

Impact of Kidney Transplantation on Bone Microarchitecture: A Longitudinal Study

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Background: Patients with chronic kidney disease (CKD) who undergo kidney transplantation experience increased risk of fracture. Bone microarchitecture is a major contributor to overall bone strength. High bone remodeling has been reported to be associated with cortical bone loss in CKD. The present prospective observational study aimed to investigate the impact of kidney transplantation on cortical and trabecular microarchitecture.

Methods: Bone biopsies were performed in 49 patients (56 yrs, males 69%) at the time of transplantation, with paired samples available in 30 patients 1 year after transplantation. Structural parameters were analysed by histomorphometry (trabecular bone only) and micro-CT including trabecular bone volume, thickness (TbTh), separation (TbSp) and cortical thickness (CtTh) and porosity (CtPo). Cortical region of interest was independently defined in baseline and follow-up scans. Parameters of mineral metabolism (including PTH, sclerostin, FGF23) and bone turnover markers (BTMs, including trimeric N-terminal propeptide [P1NP] and tartrate-resistant acid phosphatase 5b [TRAP5B]) were monitored as well.

Results: Changes of parameters of mineral metabolism were as expected (e.g. 1-84 PTH 320 vs 85 ng/ml, median, pre vs post) and bone turnover markers showed a significant decrease after transplantation (e.g. P1NP 109 vs 60 µg/L; TRAP5B 6.2 vs 3.9 U/L, median). Parameters of microarchitecture, overall remained stable, with only TbTh (as assessed by µCT) showing a modest but significant decline. Parameters of mineral metabolism and BTMs failed to correlate with parameters of microarchitecture. µCT and histomorphometry derived parameters of microarchitecture showed moderate correlation (r between 0.4 and 0.6).

Conclusions: Contemporaneous kidney transplantation has no or minimal impact on bone microarchitecture, noteworthy on cortical indices. This beneficial outcome may be a reflection of (adequate) suppression of bone remodeling following transplantation.

	parameter	Baseline	Year 1	p-value
Histomorphometry	BAr/TAr (%)	18.0 (13.4-24.2)	18.9 (14.5-23.7)	1.0
	TbTh (µm)	134.9 (113.1-148.6)	124.1 (110.9-140.5)	0.7
	TbSp (µm)	409.0 (303.5-504.1)	383.7 (313.7-949.6)	0.2
µCT	BV/TV (%)	16.2 (13.5-21.6)	14.5 (11.5-17.8)	0.02
	TbTh (µm)	134.7 (118.2-151.9)	125.3 (115.2-129.4)	0.03
	TbSp (µm)	677.8 (557.0-754.5)	653.6 (596.3-763.2)	0.9
	CtPo (%)	10.2 (8.0-16.3)	9.5 (7.3-14.6)	0.2
	CtTh (mm)	0.676 (0.548-0.853)	0.610 (0.507-0.941)	0.5

FR-OR039

Vitamin D3 Repletion Improves Vascular Function, as Measured by Full-Length Osteopontin, in a High-Risk African American Cohort

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Background: Vitamin D deficiency is common among patients with chronic kidney disease (CKD). African Americans (AAs) suffer disproportionately fromCKD and cardiovascular (CV) disease, and 80% of AAs are vitamin D deficient. The effects of vitamin D on vascular and renal health in patients with CKD have been contradictory, in part due to different study designs. Hence, the impact of vitamin D therapy on CV health in CKD patients, especially AAs is unknown. We examined the effect of vitamin D supplement on the cardio-renal biomarkers: full-length osteopontin (flOPN), c-terminal fibroblast growth factor-23 (cFGF23), and plasminogen activator inhibitor-1 (PAI-1), which have been implicated in the pathology of both vascular and renal function in CKD.

Methods: We performed a randomized, placebo-controlled study of high-risk, overweight AAs with controlled hypertension, normal renal function and vitamin D deficiency, treated with 100,000 IU vitamin D3 (N=65) or placebo (N=65) every 4 weeks for 12 weeks. We measured renal function (CKD-EPI eGFR, urinary albumin-to-creatinine ratio (ACR)), and quantified plasma cFGF23, PAI-1 and flOPN by ELISA, vascular function (pulse wave velocity (PWV), augmentation index, waist circumference (WC), and 24h-ambulatory blood pressure (BP)). We performed multiple regression controlling for the placebo-treated group to understand the relationship between the log values of flOPN, cFGF23, and PAI-1 with cardiovascular and renal risk factors.

Results: Compared to placebo vitamin D3 repletion did not change eGFR and BP values. Vitamin D3 levels increased 2-fold (p<0.0001) and iPTH levels decreased 13% (p=0.007) with repletion, which was associated with a 10% reduction in log-flOPN levels (p=0.03). There were no significant changes in log-cFGF23 or log-PAI-1 with vitamin D3 repletion. Multiple regression analysis indicated that flOPN was associated with reduced PWV (p=0.04) and diastolic BP (p=0.02), while cFGF-23 was associated only with reduced diastolic BP (p=0.05), and a trend for increased eGFR (p=0.06).

Conclusions: Vitamin D3 repletion may improve vascular function in a subset of AAs with controlled hypertension and vitamin D3 deficiency. Compared to cFGF-23 and PAI-1, flOPN may be a more sensitive vascular function biomarker in this population.

Funding: Other NIH Support - NIH/NIMHD

FR-OR040

Phosphate Lowering to Treat Vascular Dysfunction in CKD

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Background: Individuals with CKD exhibit vascular endothelial dysfunction and arterial stiffness, independent predictors of cardiovascular disease (CVD) events. Elevated serum phosphorus, even within the normal range, is associated with CVD and mortality in CKD. An acute increase in serum phosphorus impairs endothelial function and increases vascular oxidative stress. We hypothesized that lowering serum phosphorus would improve vascular function and endothelial markers of oxidative stress in CKD.

Methods: We randomized 52 participants with CKD 3b-4 and serum phosphorus within normal limits to receive 12 weeks of lanthanum carbonate or placebo. Primary endpoints were change in brachial artery flow-mediated dilation (FMD_{BA}) and aortic pulse-wave velocity (aPWV). Secondary endpoints were change in FMD_{BA} and aPWV after ascorbic acid infusion and vascular endothelial cell protein expression of NADPH oxidase and NFκB.

Results: Mean age was 65±8 years and mean eGFR was 38±14 mL/min/1.73m^2. Baseline serum phosphorus (3.44±0.47 mg/dL) in the lanthanum carbonate group did not change after 12 weeks (p=0.94) while serum phosphorus increased (3.42±0.80 mg/dL to 3.74±1.26 mg/dL; p = 0.09) after 12 weeks in the placebo group. Randomization to lanthanum carbonate did not improve FMD_{BA} or aPWV compared to placebo: lanthanum carbonate baseline FMD_{BA} 3.13%±2.87% and 12-week FMD_{BA} 2.73%±2.48% *vs.* placebo baseline FMD_{BA} 3.74%±2.86% and 12-week FMD_{BA} 3.09%±2.49%; p=0.52; and lanthanum carbonate baseline aPWV 1214±394 cm/sec and 12-week aPWV 1216±322 cm/sec *vs.* placebo baseline aPWV 993±289 cm/sec and 12-week aPWV 977±254 cm/sec; p=0.66. Supraphysiologic infusion of ascorbic acid to inhibit superoxide production did not differentially change FMD_{BA} or aPWV between groups at the end of the study (p>0.1 for all). Vascular endothelial cell protein expression of NADPH oxidase and NFκB did not change in either group (p>0.6 for all groups).

Conclusions: Compared to placebo, lanthanum carbonate did not improve vascular endothelial function or stiffness nor did it change endothelial markers of oxidative stress among participants with CKD 3b-4. Infusion of ascorbic acid to inhibit oxidative stress did not differentially affect FMD_{BA} or aPWV.

Funding: Veterans Affairs Support

FR-OR041

Disruptions to Neurovascular Patterning Affect Kidney Development and Adult Function

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Background: Kidney neurovascular networks are critical to maintaining mammalian physiology and homeostasis. Despite their important roles, we know little about how they form and pattern in the embryonic kidney or how neurovascular interactions affect kidney development. Netrin-1 (*Ntn1*) is a secreted ligand critical for neurovascular guidance during embryogenesis and is highly expressed by stromal progenitors. Therefore, netrin-1 is an ideal candidate for regulating these processes during kidney development. In turn, the neurovascular networks can release factors important for development and maturation of tissues. We set out to identify candidate angiocrine factors released by the kidney endothelium and confirm their role in renal development.

Methods: We conditionally deleted *Ntn1* from kidney stromal progenitors. We utilized immunofluorescent staining, lightsheet and confocal microscopy, and cellular analyses to interrogate the embryonic phenotype. Adult kidneys were assessed for EPO and Renin production, subjected to histological analyses, and blood collected from animals for clinical chemistry. Additionally, we developed a novel vascular labeling and imaging methodology to generate 3D images for our adult analyses. We utilized publicly available single-cell RNA-seq and array data to identify putative angiocrine factors produced by the developing kidney vasculature.

Results: Conditional deletion of *Ntn1* results in hypoplastic kidneys and aberrant patterning of the neurovascular networks. Nephron progenitor proliferation is reduced and nephrogenesis is extended. Vasculature mis-patterning persists in the adult *Ntn1* mutant kidney. These animals have altered EPO and red blood cell production, and abnormal histology. Utilizing expression data, we identified Insulin-like growth factor 1 (*Igf1*) as a putative angiocrine factor in the developing kidney. Current efforts focus on conditional *Igf1* deletion from the kidney vasculature and assessing the effects on development.

Conclusions: Taken together, our studies provide novel insights into the establishment of neurovascular networks in the developing kidney and implications for adult function. Such findings will help inform regenerative strategies and efforts to engineer kidneys de novo, where establishing proper kidney filtration and nephron function will be essential.

Funding: Private Foundation Support

FR-OR042

Observation of Renin Lineage Cell Migration Following Local Laser Damage by Longitudinal Intravital Multiphoton Microscopy

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Background: Several studies demonstrate intraglomerular migration of renin lineage cells (RLC) after antibody-induced damage of glomeruli. The aim of our study was to trigger and trace RLC migration patterns by non-systemic, spatially defined glomerular injury. Using an inducible transgenic RLC reporter mouse strain we were able to track cell migration by intravital 2-photon microscopy.

Methods: Renin lineage reporter mice expressing tdTomato (mRen-rtTAm2-LC1-tdT) were induced for 16 days. 24 hours before initial microscopy, abdominal body windows were implanted to allow repeated kidney imaging without further surgery. Single glomeruli were longitudinally examined six times (d0, d1, d2, d3, d6, d10) by 2-photon laser scanning microscope. Blood plasma was visualized by FITC dextran injection. Spatially defined damage was induced by intraglomerular scanning with a femtosecond pulsed 2-photon laser at high zoom factor, with a second observation 10 minutes after injury. Neighbouring non-damaged glomeruli in the same animal served as controls. Data was 3D analysed with Bitplane Imaris. Glomerular volume, total volume of intraglomerular tdTomato positive cells and maximal migration distance from the juxtaglomerular apparatus to tdTomato positive area were evaluated.

Results: RLC migration into the injured glomeruli could be observed as early as day 3 after damage. The total glomerular volume was reduced by injured glomerular over time. Compared to controls, intra-glomerular tdTomato positive cell volume continuously elevated on day 3, day 6 and day 10 (0.4 ±0.7%, 2.4 ±2.2%, 7.3 ± 7.8%). Maximal migration distance also progressively increased during observed times (day 3: 7.1 ± 6.7 μm, day 6: 21.3 ±11.9 μm and day 10: 26.8 ± 14.1 μm).

Conclusions: We were able to evaluate the temporal and spatial migration pattern of RLC into single glomeruli, starting as early as 3 days after injury. Moreover, we quantitatively assessed this process by 3D analysis. This new approach gives us the opportunity to characterize the migratory path of RLC after glomerular injury and evaluate the impact of local signalling due to spatially restricted damage.

FR-OR043

Differentiation of Stromal Cells to Renin Cells During Embryonic Vascular Development

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Background: Kidney arterioles are formed by the assembly of different cell types such as smooth muscle cells, endothelial cells and renin cells. Foxd1 positive stromal cells are precursors of all mural cells of the renal vasculature including the renin producing cells. How the Foxd1 cells convert to renin cells is not known. Therefore, we aimed to understand the cell fate changes during differentiation of renin producing cells from their $Foxd1^+$ stromal cell precursors throughout kidney development using single cell genomic approaches. In the current study we analyzed the transcriptome profile of GFP^+ cells FACS sorted from the kidneys of E15.5-Foxd1Cre.mTmG mice embryos.

Methods: Single cell capture was performed using the Fluidigm C1 platform and subsequent RNA sequencing was done using Illumina HiSeq4000.

Results: Sequencing analyses with Fluidigm-Singular software revealed that within the Foxd1 lineage cells, cells specific for various mural cell lineage markers clustered separately, indicating the unique molecular repertoire acquired by them during their differentiation from a common precursor population. Approximately 7.5% of the Foxd1 lineage single cells captured from E15.5 kidneys were renin positive. Unsupervised hierarchical clustering was able to identify renin positive cells as a distinct cell cluster separated from the rest of the group. Pathway analyses using the PANTHER classification system for differentially expressed genes between renin positive and negative cells detected pathways critical for vascular morphogenesis such as Angiogenesis (*Dlk1, F2r, Rhob, Crk*), Wnt signaling (*Smarcb1),* and Notch signaling (*Dlk1*) only in renin positive cells. *Smarcb1* regulates actin cytoskeleton network and loss of *Smarcb1* enhances the migratory potential of the cells. Earlier studies in our lab showed that disruption of Notch pathway in renin cells and Foxd1 precursor cells results in deregulation of genes associated with vascular smooth muscle cells and defective vascular morphogenesis. The non-canonical Notch ligand Delta-like 1 (*Dlk1*) exhibits an inhibitory role in the regulation of angiogenesis and its precise role in renin producing cells needs to be investigated further.

Conclusions: Our results suggests that Notch and Wnt pathways govern the differentiation of stromal cells to renin cells as they assemble to form the kidney vasculature.

Funding: NIDDK Support

FR-OR044

Tubule Interconnection After Zebrafish Kidney Injury

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Background: Nephrons made during kidney development and newly made during zebrafish kidney regeneration must establish tubule lumen interconnections with the collecting system. The zebrafish adult kidney regenerates after gentamicin injury from an adult progenitor cell population, forming 20-100 new nephrons that subsequently invade and "plumb into" the pre-existing collecting system and restore renal function. Using the zebrafish adult kidney as a model of synchronous nephron-collecting duct fusion, we investigated the role of growth factor signaling pathways in this process.

Methods: *Tg(TCFLef-miniP:dGFP)* Wnt reporter expression was used to reveal high Wnt signaling domains in new nephrons. The Wnt inhibitors IWR1 and IWP2 were applied to injured adult zebrafish to test requirements for Wnt signaling. Homozygous adult Crispr/Cas9 indel mutants in *fzd9b* and *wnt9b* were generated.

Results: We find that new nephron aggregates are patterned by canonical Wnt signaling. High canonical Wnt signaling cells formed a single cell thick dome within cell aggregates and polarized to form rosettes with an apical constriction predicting the site of future tubule lumen. Cells at the distal end of the new nephron extend invasive processes or invadopodia into the underlying tubular epithelium. Short term inhibition of Wnt signaling using the chemical inhibitors IWR1 and IWP2 inhibited invadopodia formation and blocked tubule interconnection events. Adult homozygous *fzd9b* mutants exhibit ectopic distal cell proliferation and a failure of convergent extension in new nephrons after injury while *wnt9b* mutants produce fewer new nephrogenic aggregates. A quantitative RT-PCR screen of candidate genes highly upregulated in both zebrafish nephron progenitors after injury and human cancer metastasis implicates new pathways involved in the invasion process.

Conclusions: Wnt signaling is required for tubule invasion and correlates with expression of multiple genes associated with metastatic cell invasiveness. Manipulation of Wnt signaling is an opportunity to engineer kidney tubule interconnections.

Funding: NIDDK Support

FR-OR045

Distinct States of Chromatin Accessibility and MicroRNA Expression in Nephron Progenitor Cells During Development

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Background: Mammalian nephrons develop from a multipotent and self-renewing population of nephron progenitors (NPs) during kidney development. All nephrons are formed prior to birth in humans, and the number of nephrons formed is largely dependent on the number of nephron progenitors during kidney development. Low nephron endowment predisposes individuals to chronic kidney disease and hypertension. NPs that exist early in nephrogenesis are known to be transcriptionally distinct from those in later nephrogenesis. We hypothesize that changes in chromatin accessibility and microRNA (miRNA) expression contribute to developmental age-related changes in the NP transcriptome.

Methods: NP cells were isolated from mouse kidneys using magnetic-activated cell separation with positive selection of Integrin alpha 8 (Itgα8) at embryonic day 14.5 (E14.5), E16.5 and postnatal day 0. To measure transcriptional activity at regulatory features genome-wide, a proportion of the NP cells were assayed for transposase-accessible chromatin (ATAC-seq). Total RNA from remaining NP cells was sequenced using small-RNA sequencing (smRNA-seq).

Results: A total of 35,172 regions of accessible chromatin were identified based on the irreproducible discovery rate (IDR = 0.1), 1,800 of which underwent a statistically significant change in read depth between age groups (FDR = 0.05). More changes in DNA accessibility are observed between E14.5 and E16.5 than between E16.5 and P0 (1,788 and 12, respectively), and a majority of these early changes (79%) represent a reduction in accessibility over time. Findings corroborate published features including reduced activity at the *Lin28b* gene promoter during nephrogenesis. 1,243 known miRNAs were detected across all NP samples, of which 170 underwent significant changes in expression between the measured time points (padj. ≤ 0.05). These include most members of the let-7 family, which see increased expression coincident with the reduced expression of Lin28b, a published let-7 repressor.

Conclusions: Chromatin accessibility and miRNA expression appear to be distinct in early versus late nephrogenesis.

Funding: NIDDK Support

FR-OR046

Mass Spectrometric Analysis of the Extracellular Matrix During Renal Development

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Background: The extracellular matrix (ECM) is a network of macromolecules that interacts with renal cells to regulate development, physiology, and pathology. Defects in specific ECM associated genes affect metanephric kidney initiation, branching, tubulogenesis, terminal differentiation of intercalated cells, and integrity of the glomerular basement membrane. However, global changes in the composition and turnover of kidney ECM as a function of development are unknown.

Methods: We used mass spectrometry (MS) to analyze embryonic (E18.5) and adult murine kidney proteins fractionated by differential solubilities and decellularization techniques for ECM 3D visualization using confocal microscopy

Results: We resolved increased expression of COL4A3, COL4A4, COL4A5, LAMA5, and LAMB2, which are critical for the integrity of the glomerular basement membrane in the adult. Additionally, FREM1, FREM2, and FRAS1, which are necessary for metanephric induction, were selectively upregulated at E18.5 (Fig 1a). The ECM of decellularized kidneys from different developmental stages could be visualized in 3D using confocal microscopy (Fig 1b).

Conclusions: Together, this work shows that the ECM changes during development can be resolved by MS. We aim to observe how global protein abundance determined by MS correlates to 3D spatiotemporal organization in ECM proteins in the kidney. This information can be used to tailor the scaffold environment in regenerative medicine applications.

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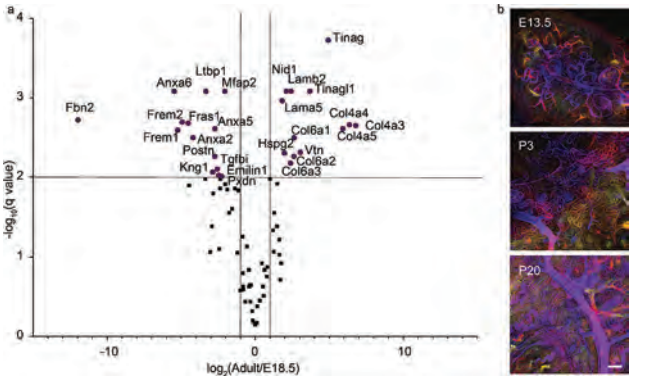

Figure 1: (a) Volcano plot comparing ECM of E18.5 and adult murine kidneys. Proteins that are different between time points (>2-fold difference with a false discovery rate of 1%) are indicated with a circle. (b) Decellularization enables the 3D visualization of E13.5-P20 kidneys stained with wheat germ agglutinin to visualize the ECM. Color portrays depth (blue to yellow), scale bar=100 μm.

FR-OR047

Generation of Functional Human Kidney Tissues from Metanephric Nephron Progenitors and Ureteric Bud Cells Separately Differentiated from Human iPS Cells

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Background: Chronic kidney disease (CKD) affects more than 10% of the global population. The lack of effective curative options has led to research on regenerative therapies using stem cells. Accordingly, recent studies using human induced pluripotent stem cells (hiPSCs) have developed protocols to induce kidney-lineage cells and reconstruct kidney organoids. However, no reports have generated human kidney tissues by recapitulating nephrogenesis using metanephric nephron progenitors (NPs) and ureteric bud (UB) cells induced separately from hiPSCs, in which NP-derived glomeruli and renal tubules and UB-derived collecting ducts are interconnected. Furthermore, no *in vivo* imaging studies have directly demonstrated that hiPSC-derived kidney organoids produce urine.

Methods: We separately and efficiently induced metanephric NPs and UB cells from hiPSCs in the original 2D differentiation culture conditions, co-cultured these two progenitors using bioreactors and performed immunofluorescent analysis using the CUBIC tissue clearing method. In addition, we transplanted mixed aggregates from the two progenitors into immunodeficient mice and examined them using *in vivo* multiphoton microscopy.

Results: After co-culture of the two progenitors, NPs constructed SIX1(+) active nephrogenic niches close to UB tips and S-shaped body-like structures. They further organized kidney structures that contained glomeruli, proximal and distal tubules, Henle's loops and collecting ducts *in vitro* and *in vivo*. By using two hiPSC lines that constitutively express fluorescent reporter proteins (GFP or mCherry), we demonstrated that the connecting points of GFP(+) NP-derived distal tubules and mCherry(+) UB-derived collecting ducts showed a marker expression pattern consistent with their counterparts in human embryonic kidneys, indicating that they were functionally interconnected. Furthermore, the intravenous injection of fluorescent-conjugated dextran confirmed that the hiPSC-derived glomeruli were functionally integrated with the host vasculature. Moreover, we observed urine-like dextran accumulation in the hiPSC-derived Bowman's space *in vivo*.

Conclusions: Our culture system should contribute to the mechanistic elucidation of human nephrogenesis and the development of regenerative therapies against kidney diseases.

Funding: Government Support - Non-U.S.

FR-OR048

Application of Cellular Extrusion Bioprinting to Improve Kidney Organoid Patterning

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Background: Organoids derived from induced pluripotent stem cells (iPSCs) are now being exploited as a model system for a variety of organs, especially for structurally complex organs such as the kidney. iPSC-derived kidney organoids show great potential for modelling kidney diseases and improving our understanding of disease pathogenesis. However, they do not yet accurately recapitulate the cellular maturity and compartmental organisation of the human kidney *in vivo*. Changes in culture format may allow for improved patterning by altering biophysical properties, cell-cell interactions and growth factor gradients. Here we report the application of 3D cellular extrusion bioprinting to i) improve quality control and ii) modify organoid morphogenesis and maturation.

Methods: A series of fluorescent reporter iPSC lines designed to report the formation of specific cellular compartments of the kidney, such as podocytes, proximal tubule and distal nephron/ureteric epithelium, were subjected to monolayer differentiation as previously described (Takasato *et al*, 2016). Generation of organoids was performed using extrusion-based NovoGen Bioprinter® MMX technology (Organovo), with variations in cell density and printing configuration, and compared to manually pelleted organoids. Organoids were analysed via live imaging for fluorescent reporters, confocal immunofluorescence and quantitative image analysis.

Results: Bioprinting facilitated rapid, uniform and highly reproducible organoid production. Organoids were well-patterned and comprised all kidney cell types and compartments previously described using the manual technique. Changes in cell density, organoid shape and thickness also modified nephron number, patterning and the formation of off-target populations.

Conclusions: Here we demonstrate that biophysical properties of organoids at the time of their generation can have a significant impact of their morphogenesis and differentiation, potentially affecting cellular maturity and differentiation trajectory. Further research into the variables of organoid generation will be fundamental to achieve and maximise future downstream applications.

Funding: NIDDK Support, Commercial Support - Organovo Inc

FR-OR049

Improved Human Pluripotent Stem Cell-Derived Kidney Organoids for Modeling Collecting Duct Biology and Tubular Injury

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Background: Maximizing the potential of human kidney organoids for drug testing, regenerative medicine and to model development and disease requires addressing cell immaturity, the lack of a branching collecting system and off target cell types.

Methods: We separately induced posterior intermediate mesoderm and anterior intermediate mesoderm from human iPS and ES cells and combined them on day 7. For the next five days, the combined organoids were incubated in a cocktail including FGF9, heparin, GDNF, retinoic acid and EGF. At day 12, we compared organoids left to mature in basal medium vs. medium supplemented with aldosterone, vasopressin and the NTRK2 inhibitor K252a. Organoid cell diversity and maturation state was assessed by scRNA-seq, immunofluorescence, AQP2 trafficking assays and nephrotoxicity responses.

Results: Our new protocol induced a definitive ureteric bud-derived branching collecting duct system interconnected to more proximal nephron segments. The hormones aldosterone and vasopressin were critical to promote maturation of collecting duct cell types including both principal and intercalated cells. The resulting principal cells express aquaporin-2 protein which undergoes translocation to the apical membrane after vasopressin or forskolin stimulation. By scRNA-seq (35,954 cells total), we define all cell types present, define their maturity and demonstrate superior proximal tubule maturation. Compared to organoids differentiated with existing protocols generated in parallel, this new protocol results in superior downregulation of progenitor cell types, substantially reduced off-target cell types and improved modeling of tubular injury.

Conclusions: We developed a new protocol for the separate induction of both metanephric mesenchyme and ureteric bud from hPSC. This results in robust collecting system development. We report that aldosterone and vasopressin drive the maturation of collecting duct cell types, including principal cells complete with vasopressin-stimulated AQP2 trafficking and the emergence of intercalated cells for the first time. Our scRNA-seq analysis demonstrates that the protocol also results in more mature nephron segments, appropriate downregulation of progentors and improved injury modeling.

FR-OR050

An Approach for Improving iPSC-Derived Ureteric Epithelial Identity In Vitro

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Background: We previously described a protocol for generating iPSC-derived human kidney organoids containing segmented nephrons, renal interstitium, endothelium and a CDH1+/GATA3+/PAX2+/CALB1+ ureteric epithelium (UE). Recent single cell analyses of mouse and human fetal kidney have identified expression of many presumed UE marker genes, including *GATA3* and *HOXB7*, within the distal nephron and connecting segment. This has raised questions about the true identity of GATA3+ epithelium within kidney organoids. Here we describe the transcriptional profile of GATA3+ epithelium isolated from organoids both prior to and after *in vitro* culture.

Methods: Kidney organoids were generated from iPSCs harboring an mCherry fluorescent reporter gene within the endogenous *GATA3* locus. We used fluorescent activated cell sorting (FACS) to isolate GATA3+/mCherry+ epithelium for subsequent culture in conditions previously shown to promote expansion of mouse UE. Immunofluorescence and RNAseq-based transcriptional profiling was performed to evaluate cell identity pre- and post-culture.

Results: We observed extensive proliferation and branching of FACs-isolated GATA3+/mCherry+ cells cultured in conditions known to promote propagation of mouse UE. GATA3/mCherry expression was maintained even after several rounds of dissociation and re-plating. Additional UE markers (KRT8, PAX2, SOX9, CALB1) were detected by immunofluorescence. Although global RNAseq of GATA3+/mCherry+ epithelium at the time of isolation suggested a cellular identity more akin to distal tubule, cultured GATA3+/mCherry cells showed loss of *KCNJ1* and induction of *WNT11* and *RET* expression. Single cell transcriptional analysis of cultured cells revealed 3 clusters representative of tip (RET+/GFRα1+/ETV4+), stalk (AQP2+) and a putative medullary compartment (UPK1A+). Notably, *WNT9B* expression was evident at a level consistent with that observed in human fetal kidney.

Conclusions: Our results redefine the identity of the GATA3+/CDH1+ epithelium within kidney organoids to early connecting segment/distal tubule. However, when cultured in appropriate conditions, this can transition to a more recognizable collecting duct fate. The capacity to expand and propagate a branching epithelial compartment with ureteric identity may represent a useful approach for the generation of collecting duct tissue.

Funding: NIDDK Support

FR-OR051

Association Between Ambient Fine Particulate Matter Air Pollution and Death due to CKD

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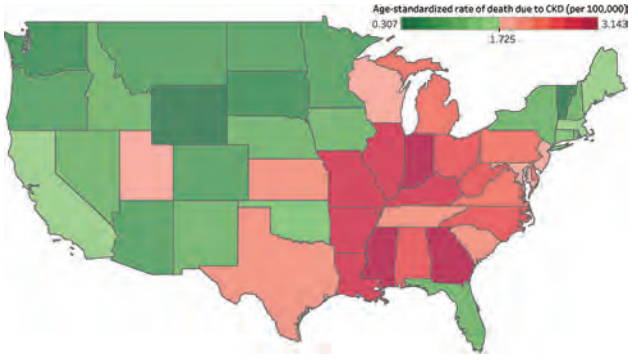
Background: Experimental and epidemiologic evidence suggest that ambient fine particulate matter ($PM_{2.5}$) is a risk factor for chronic kidney disease (CKD). However, no studies have investigated whether $PM_{2.5}$ is associated with mortality due to CKD, nor quantified the burden in the US.

Methods: Data from the Environmental Protection Agency, Department of Veterans Affairs, and National Death Index were linked. Non-linear exposure response functions were built using an ensemble survival modeling approach, and CKD death rates associated with $PM_{2.5}$ exposure were estimated.

Results: A cohort of 4,522,160 US veterans was followed for a median of 10 years. There were 29,016 deaths due to CKD during follow-up. The median $PM_{2.5}$ exposure at baseline was 11.8 ($\mu g/m^3$) (IQR: 10.0-13.8). As $PM_{2.5}$ levels increased, an increase in risk of death due to CKD was observed. In the contiguous US in 2017, it was estimated that 7,175.2 (Uncertainty Interval (UI): 5910.2-8371.9) CKD deaths were associated with $PM_{2.5}$ exposure, corresponding to an age-standardized rate of 1.9 (UI: 1.5-2.2) deaths due to CKD per 100,000 persons. Geographic heterogeneity in age-standardized rates of CKD deaths associated with $PM_{2.5}$ was observed (Figure), where states with the highest rates (per 100,000 persons) included Mississippi (3.14), Georgia (2.9), and Indiana (2.9), while states with the lowest rates included Vermont (0.31), Wyoming (0.46), and Washington (0.56). In those of black or African American race, the age-standardized CKD death rate associated with $PM_{2.5}$ was estimated to be 2.1 per 100,000 persons, 16.4% higher than the estimate in those not of black or African American race (1.8 per 100,000 persons).

Conclusions: Elevated levels of $PM_{2.5}$ is associated with increased risk of death due to CKD. The burden is disproportionately borne by those of black or African American race.

Funding: Veterans Affairs Support



Age-standardized rates of death due to CKD associated with $PM_{2.5}$ in the contiguous US

FR-OR052

Particulate Matter, Albuminuria, and CKD: The ARIC Study

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Background: Exposure to particulate matter less than 2.5 mm in diameter ($PM_{2.5}$) has been linked to detrimental health effects. This study describes the relationship between long-term exposure to $PM_{2.5}$ and estimated glomerular filtration rate (eGFR), albuminuria, and incident chronic kidney disease (CKD).

Methods: The study included 10,856 participants from the Atherosclerosis Risk in Communities cohort followed from 1996 through 2017. Monthly mean $PM_{2.5}$ concentrations (ug/m^3) were estimated at participant addresses, then averaged over 12-, 60-, and 120-month periods preceding participant examination. Covariate-adjusted cross-sectional associations of $PM_{2.5}$ with eGFR and log-transformed urinary albumin-creatinine ratio (ACR) were estimated using linear regression. $PM_{2.5}$-incident CKD associations were estimated using Cox proportional hazards regression. Modeling was stratified by ARIC site, and stratum-specific estimates were combined in random-effects meta-analyses.

Results: There was no significant $PM_{2.5}$-eGFR association at any exposure averaging period. $PM_{2.5}$ averaged over the 12- and 60-, but not 120-month periods was associated with higher log(ACR) after adjusting for demographics, socioeconomic status, and clinical covariates. Incident CKD was higher with higher 12-, but not 60- and 120-month mean $PM_{2.5}$ concentrations (Table).

Conclusions: Exposure to higher 12- and 60-month mean $PM_{2.5}$ concentrations was associated with higher albuminuria, and exposure to higher 12-month mean $PM_{2.5}$ concentration was associated with higher risk for incident CKD.

Adjustment model	eGFR, β (CI)	log(ACR), β (CI)	Incident CKD, HR (CI)
12-month: Model 1	2.05 (-2.62, 6.73)	0.80 (0.33, 1.27)†	1.96 (1.31, 2.93)†
12-month: Model 2	0.98 (-2.45, 4.40)	0.66 (0.26, 1.05)†	1.95 (1.14, 3.33)†
60-month: Model 1	-1.26 (-4.80, 2.28)	0.39 (0.05, 0.73)†	1.79 (1.08, 2.96)†
60-month: Model 2	-1.16 (-4.77, 2.44)	0.36 (0.03, 0.70)†	1.77 (0.92, 3.40)†
120-month: Model 1	-1.01 (-4.64, 2.61)	0.08 (-0.41, 0.58)	1.20 (0.73, 1.98)
120-month: Model 2	-0.72 (-4.40, 2.97)	0.08 (-0.37, 0.53)	1.14 (0.64, 2.00)

Model 1: sex, age, race, neighborhood socioeconomic score, family income, and education level.

Model 2: Model 1 + body mass index, diabetes mellitus, hypertension, coronary heart disease, cigarette smoking, eGFR,* urinary ACR,** C-reactive protein, and temperature.

Covariate omitted for eGFR outcome (*) and log(ACR) outcome (**).

† signifies $P < 0.05$. CI, confidence interval; HR, hazard ratio.

FR-OR053

Environment-Wide Association Study on CKD in the National Health and Nutrition Examination Survey (1999-2016)

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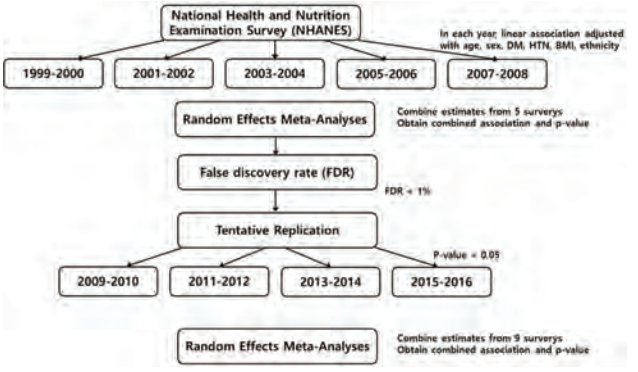
Background: Effects of environmental chemicals on the development of CKD are not well-investigated. We aimed to investigate which environmental chemicals are significantly associated with the development of CKD.

Methods: A total of 53,348 adult aged above 18 years old participants, who participated in the NHANES surveys over 18 years, were enrolled. The association between environmental chemicals and CKD was tested and validated using the environmental-wide association study (EWAS) methodology. CKD was defined as three categories (albuminuria, urinary albumin to creatinine ratio above 30 mg/g; glomerular filtration rate (GFR), GFR below 60 ml/min/1.73m^2; and composite of albuminuria and GFR).

Results: A total of 299 environmental toxins were included in the analysis. Blood lead, urinary antimony and cobalt, blood 1,2-Dichlorobenzene and nitrobenzene were positively associated with CKD defined by albuminuria. In the contrary, perfluorooctanoic acid, perfluorooctane sulfonic acid, urinary nitrate and thiocyanate were negatively associated with CKD defined by albuminuria. Blood lead and cadmium showed positive association with CKD defined by GFR. Other 31 significant environmental factors were all negatively associated with CKD defined by GFR. Blood lead, urinary tungsten, blood 1,2-dichlorobenzene and nitrobenzene, 2,4,5-trichlorophenol, mono-n-butyl phthalate, mono-benzyl phthalate were positively associated with CKD defined both albuminuria and GFR. Urinary mono-benzyl phthalate is associated with increased prevalence of CKD in various categories of albuminuria and GFR.

Conclusions: Urinary mono-benzyl phthalate as well as blood lead are consistently associated with CKD defined by various range of albuminuria, glomerular filtration rate, and composite categories. Increased exposure to lead or mono-benzyl phthalate can be associated with increased prevalence of CKD.



Schematic representation for the association analysis of environmental toxins with chronic kidney disease.

FR-OR054

Genetic Determinants of CKD Progression Among Individuals Without Diabetes: The Million Veteran Program

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Background: The rate of CKD progression among individuals with diabetes varies widely and is incompletely explained by known risk factors. While the genetic determinants of cross-sectional eGFR have been identified, only one small analysis of longitudinal change in eGFR among individuals with CKD has been conducted.

Methods: We performed a genome-wide association study of the relative rate of decline in estimated glomerular filtration rate (eGFR, % decline/year) among 41,348 individuals with CKD and free of diabetes at baseline participating in the Million Veteran Program. Analyses were stratified by race; 5,818 participants were of non-Hispanic Black race/ethnicity.

Results: Mean (SD) eGFR at baseline was 51.1 (±8.1) ml/min/1.73m^2 and median relative kidney function decline was -0.7%/year. In trans-ethnic meta-analysis, we uncovered 48 SNPs from 2 independent regions associated with decline in kidney function. The SNP with the strongest association, rs13329952, is an intronic variant in *UMOD*; every additional minor allele was associated with a 1%/year faster decline in eGFR ($p=1.7x10^{-13}$). Our GWAS also identified a novel locus associated with CKD progression (top SNP rs12805797 near *LINC02098* ($p=5.0x10^{-8}$)). Among blacks, the presence of two high-risk *APOL1* variants was associated with a 3%/year faster decline in eGFR, relative to individuals with no high-risk variants.

Conclusions: Our data suggest that CKD progression has a genetic basis beyond that of baseline eGFR alone. Better understanding of the contribution of inherited genes to CKD progression could help to build the foundation for genetic diagnosis and personalized treatment of this common condition.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR055

Kidney Function Decline Among African Americans with Sickle Cell Trait and Sickle Cell Disease

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Background: Sickle cell trait (SCT) and disease (SCD) are felt to be independent risk factors for chronic kidney disease (CKD) among African Americans (AA). However, the understanding of the trajectory of kidney function decline and its predictors in patients with SCT/SCD remains limited. We aimed to describe longitudinal kidney function decline and associated risk factors among adult AA with SCT/SCD.

Methods: We performed a multi-center observational study of adult AA patients with hemoglobin electrophoresis to ascertain the presence of SCT or SCD (exposure) and normal hemoglobin phenotype (reference). We included patients with a baseline estimated glomerular filtration rate (eGFR) ≧29 ml/min/1.73m^2, at least 3 eGFR values between 2005-2018 and at least 1 year between the first and last eGFR values. Outcomes of interest were the difference in the mean change in eGFR per year (evaluated using linear mixed models) and incident stage 3 CKD (described using Cox proportional hazards).

Results: We identified 10,210 patients (1,251 SCT, 230 SCD and 8,729 reference) with a median follow-up of 8 (IQR 5-11) years and a median of 17 (IQR 10-30) eGFR values. The mean age was 36 (±13) years, 86% were female and baseline eGFR was 113 (±27) ml/min/1.73m^2. Compared to the reference, eGFR declined 0.45 ml/min/1.73m^2/year faster in SCT (p<0.01) and 1.28 ml/min/1.73m^2/year faster in SCD (p<0.01). SCD patients' eGFR declined 0.83 ml/min/1.73m^2/year faster (p<0.01) than the SCT patients. These results were consistent after multivariable adjustment. Compared to the reference, incident stage 3 CKD was higher in SCT (hazard ratio [HR] 1.26; 95% confidence interval (CI), 1.05-1.51), and SCD (HR 2.37; 95% CI, 1.43-3.93) after multivariable adjustment. Males, diabetes mellitus, and a baseline eGFR ≥90ml/min/1.73m^2 were associated with faster eGFR decline in SCT/SCD.

Conclusions: SCT/SCD is associated with a significantly faster eGFR decline compared to normal hemoglobin phenotype among AA patients. A dose-response relationship between sickle hemoglobin and kidney dysfunction may exist. Prospective and mechanistic studies are needed to develop best practices to attenuate eGFR decline in AA patients with SCT/SCD. Physicians caring for AAs need to consider SCT/SCD status and SCT/SCD interactions with comorbidities when evaluating CKD risk.

FR-OR056

Sickle Cell Trait (SCT) and CKD Progression Among African Americans in the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: SCT has been identified as a risk factor for CKD in prior epidemiologic cohort studies. The influence of SCT upon progression of established CKD has not been previously evaluated.

Methods: SCT was imputed from genetic data in AA CRIC participants. We excluded those with hemoglobin C trait. Mixed effects models were used to analyze estimated glomerular filtration rate (eGFR) decline. Association of SCT and the CRIC composite renal outcome (end-stage renal disease or halving of eGFR) was assessed by Cox regression. Models were constructed in stepwise fashion and included demographics, African ancestry, clinical site, baseline eGFR, education, income, insurance status, nephrologist use, ACE-I/ARB use, systolic blood pressure, body mass index, diabetes, hemoglobin A1c, smoking and 24-hour urine protein. Analyses were also stratified by APOL1 risk status.

Results: We included 1,468 participants, of whom 218 (14.9%) had SCT. Median follow up was 8.6 years (IQR 6.7 - 9.6). Baseline characteristics including eGFR were similar between the SCT and non-SCT groups (TABLE) as was the unadjusted eGFR decline (-1.37 [1.43] v. -1.44 [1.55]). In the fully adjusted model, no difference was noted in eGFR slope comparing SCT to non-SCT (-0.031 [-0.567, 0.504] ml/min/1.73m^2/year, p=0.91). SCT was not associated with the composite renal outcome (HR 1.19 [95% CI 0.89 - 1.61], p=0.24). When stratified by APOL1, no association was noted between SCT and the outcomes of interest.

Conclusions: SCT is present in 8-10% of the general AA population but was enriched among AAs in the CRIC Study suggesting it may confer risk for *developing* CKD. In contrast to prior findings in population-based cohorts, SCT was not associated with *progression* of renal disease when evaluated in individuals with CKD.

Funding: NIDDK Support

Characteristics	Non-SCT AA (N=1,250)	SCT AA (N=218)
Age (years)	57.4 (10.8)	58.9 (10.3)
Female sex	631 (50.5%)	117 (53.7%)
Hypertension	1165 (93.2%)	198 (90.8%)
Diabetes	638 (51%)	116 (53.2%)
Baseline eGFR (ml/min/1.73m^2) - Mean (SD)	44.2 (16.5)	42.1 (15.0)
24hr Urine Protein (g/24hr) - Median (IQR)	0.25 (0.08 - 1.10)	0.23 (0.07 - 0.90)
eGFR slope per year - Mean (SD)	-1.44 (1.55)	-1.37 (1.43)
APOL1 high risk allele	226 (19.4%)	36 (17.2%)

FR-OR057

Progressive CKD and Mortality as Predicted by Renal Histology After Radical Nephrectomy

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Background: Nephron hypertrophy and nephrosclerosis may be important determinants of mortality and kidney failure. However, the study of adverse outcomes with renal histology has been limited to select patient populations with small tissue specimens.

Methods: We studied patients who underwent a radical nephrectomy for tumor between 2000 and 2012. Wedge sections distal to the tumor were stained and scanned into high resolution images. The areas of cortex and glomeruli (sclerotic and non-sclerotic) were annotated to calculate glomerular volume and percentage globally sclerotic glomeruli (%GSG). The percentage luminal stenosis (arteriosclerosis) and interstitial fibrosis/tubular atrophy (IFTA) of the cortex were morphometrically measured. Patients were followed with annual visits or phone calls for non-cancer death or kidney failure, censoring at cancer death. Progressive chronic kidney disease (CKD) was defined as dialysis, kidney transplant, or a 40% decline in estimated glomerular filtration rate (eGFR) from the post-nephrectomy baseline. Models adjusted for age, sex, BMI, hypertension, diabetes, smoking, and eGFR.

Results: There were 712 patients (mean age 63y, 64% male, 64% hypertension, 14% diabetic, and mean postoperative eGFR 48 ml/min/1.73 m^2) with a mean follow-up of 8.0±4.2 years, 77 progressive CKD events, 170 non-cancer deaths, and 104 cancer deaths. Larger non-sclerotic glomerular volume predicted progressive CKD, but this was no longer evident after adjustment for proteinuria. Higher %GSG and more severe arteriosclerosis predicted progressive CKD, which persisted with adjustment for proteinuria. Higher %IFTA predicted non-cancer morality, and this persisted with adjustment for proteinuria. No kidney structural finding predicted cancer mortality.

Conclusions: Larger nephron size predicts kidney failure along the same pathway as proteinuria. Subclinical glomerulosclerosis and arteriosclerosis predict kidney failure, whereas subclinical IFTA predict non-cancer mortality.

Funding: NIDDK Support

Hazard ratio of outcomes by renal histology (p-values)

	Predicted progressive CKD	Non-cancer Mortality	Cancer Mortality
Glomerular volume, log	2.17 (0.003)	1.11 (0.52)	1.18 (0.44)
IFTA %	1.07 (0.25)	1.16 (0.0002)	1.04 (0.43)
%GSG	1.32 (0.01)	1.11 (0.18)	0.98 (0.81)
Luminal stenosis %	1.90 (0.02)	1.39 (0.10)	0.95 (0.81)

FR-OR058

Effects of Different Serum Bicarbonate Levels on Muscle Mass and Renal Function Among CKD Patients with Metabolic Acidosis: A Randomized Controlled Trial

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Background: Treatment of metabolic acidosis to target high serum bicarbonate level may downregulate muscle protein degradation and retard GFR decline among CKD patients. We conducted a study to test the effects of increased bicarbonate level on muscle parameters and renal function in pre-dialysis CKD patients.

Methods: This was a randomized, controlled study. CKD stage 3-4 patients with serum HCO_3^-<22 mmol/L were randomized to either receive oral sodium bicarbonate with target bicarbonate level of 25±1 or standard level of 22±1 mmol/L as control group using the protocol-based titration of dosage adjustment. The change of muscle mass measured by bioelectrical impedance analysis (BIA), muscle strength by hand grip dynamometer, eGFR using CKD-EPI equation, nutritional markers, and muscle-related biomarkers were determined. Baseline data and after 6 months of sodium bicarbonate supplementation were compared between groups using t-test or Chi-square test as appropriate.

Results: Forty-two patients completed the study (n=21 per group). The mean age and eGFR were 61.2±9.8 years and 32.4±14.1 ml/min, respectively. Baseline data including age, sex, diabetes, serum bicarbonate level, muscle mass, and blood pressure were similar. After 6 months of treatment, the average serum bicarbonate levels in both group were 24.8 and 21.2 mmol/L. Both BIA-derived total-body muscle mass and appendicular lean balance were significantly increased at 6 months in the higher bicarbonate group (26.0±5.4 to 26.7±5.7 kg, p=0.04 and 19.8±4.1 to 20.6±4.5 kg, p=0.03, respectively) despite comparable energy and protein intake. The higher bicarbonate group also had 36% lower serum myostatin, a surrogate for muscle degradation, but unaltered insulin-like growth factor-1 level as the mediator of muscle cell growth (133.8±43.6 vs 121.3±52.7 ng/mL, p=0.3) compared to the control group. Muscle strength, eGFR as well as serum albumin were not significantly different between two groups (p>0.05). Neither worsening hypertension nor heart failure was found throughout the study.

Conclusions: Bicarbonate supplementation to achieve the serum level ~25 mmol/L demonstrates better muscle mass preservation in patients with pre-dialysis CKD. The impact of alkaline therapy on renal function may require longer period of study.

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FR-OR059

Impaired Sleep Quality Is Associated with Incident Albuminuria in Hispanics/Latinos: Findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

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Background: Emerging evidence suggests that short duration and poor quality sleep may be associated with progression of chronic kidney disease (CKD). Little is known about the relationship of sleep duration/quality with incident albuminuria.

Methods: Analyses included data from 1662 U.S. Hispanic/Latino adults aged 18-64 years enrolled in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Sueno Sleep Ancillary Study, who completed 7 days of wrist actigraphy (2011-2013) and a follow-up visit (2014-2017), and did not have CKD (estimated glomerular filtration rate [eGFR] ≥ 60 ml/min/1.73m^2 and urine albumin-to-creatinine ratio [ACR] <30 mg/g) at baseline. Incident albuminuria was defined as ACR ≥30 mg/g. Validated computer software algorithms were used to assess sleep duration and sleep fragmentation (calculated by summing the percentage of the sleep period that is spent moving and the percentage of the number of immobile phases that last 1minute or less). Poisson regression with follow-up years as an offset was used accounting for HCHS/SOL complex sampling design.

Results: At baseline, mean age was 37.5 years and 51.9% were female. In 5.7 years median follow-up, 71 individuals developed incident albuminuria. Higher sleep fragmentation was associated with higher incident rate of albuminuria after adjusting for center, age, sex, education, diabetes, systolic blood pressure, body mass index, cardiovascular disease, depression, eGFR, and ACR (Table). Sleep duration was not associated with new-onset albuminuria.

Conclusions: Among US Hispanic/Latinos, fragmented sleep was associated with new-onset albuminuria. These findings could have implications for preventive strategies in a population which experiences a high burden of CKD.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute

Predictor	Incident Density Ratio (95% CI)
Sleep duration (per 1 hr decrease)	0.91 (0.71, 1.17)
Sleep fragmentation index (per 10% increase)	1.38 (1.02, 1.85)

FR-OR060

Effect of Medicaid Expansion on the Incidence of ESRD Among Nonelderly Adults

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Background: End stage renal disease (ESRD) can be prevented or delayed with effective management of chronic disease, particularly diabetes and hypertension. However, the uninsured have limited ability to finance health services and may forego preventive and chronic disease care. We examined the impact of Medicaid expansion on the incidence of ESRD in the non-elderly adult population.

Methods: A quasi-experimental differences-in-differences study of the incidence rate of ESRD in the non-elderly adult population in the US (annual average of 194,793,035 persons aged 19-64 years). We calculated quarterly incidence rates by geolocating incident patients (347,288 persons over the study period) within Public Use Microdata Areas (PUMAs), which are contiguous geographic areas of at least 100,000 persons nested within states. We estimated linear models comparing pre- vs post-expansion changes in the incidence rate in PUMAs in expansion vs non-expansion states. Models were adjusted for age group, sex, race/ethnicity, time-varying PUMA-level economic characteristics with fixed effects for year-quarter, season, and PUMA. We confirmed parallel pre-policy trends between expansion and non-expansion PUMAs.

Results: The mean quarterly ESRD incidence rate for the 19-64 population in 2012 and 2013 was 67.8 cases per million in expansion states and 78.5 cases per million in non-expansion states. While incidence increased in both expansion and non-expansion states over the study period, Medicaid expansion was associated with 1.7 fewer incident ESRD cases per million (95% CI: -3.28 to -0.17), relative to concurrent trends in non-expansion states. This observed effect represents a 2.5% relative reduction in incidence. These findings were robust to exclusion of early- and late-expanding states, and time-varying covariates.

Conclusions: The ACA's Medicaid expansions were associated with a small but meaningful reduction in incidence of ESRD in the non-elderly adult population. The findings also demonstrate the potential for expansions of Medicaid coverage to generate offsetting reductions in spending in the Medicare program, the primary payer for the ESRD population in the US.

Funding: NIDDK Support

FR-OR061

A Novel Therapeutic Strategy for Autosomal Dominant Tubulointerstitial Kidney Disease

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Background: MUC1 kidney disease (MKD) is an autosomal dominant tubulo-interstitial kidney disease caused by a frame-shift mutation in the MUC1 gene (MUC1-fs). The disease is characterized by slowly progressive tubulo-interstitial damage that leads to end-stage renal disease. No treatment is currently available. Affected individuals require dialysis or kidney transplantation in the third to seventh decade of life. The main goal of this study was to investigate the cellular and molecular mechanisms by which MUC1-fs causes alteration in epithelial cell function, and to develop a mechanism-based therapy for this disease.

Methods: To investigate the biological mechanism responsible for MKD, three different model systems were developed: a patient-derived cell line, a knock-in mouse model and patient iPSC-derived kidney organoids. In order to identify a possible treatment for MKD, a high content screen (HCS) composed of 4,000 compounds was developed to detect the removal of mutant MUC1-fs protein from kidney epithelial cells.

Results: Immunofluorescence studies indicated that while MUC1-wt was located at the cell surface, the mutated protein MUC1-fs was accumulated intracellularly, where it induced ER stress by activation of the unfolded protein response (UPR). The HCS identified BRD, a small molecule that cleared MUC1-fs not only from patient cells, but also from kidneys of knock-in mice and from patient kidney organoids. Importantly, BRD showed no overt toxicity at any concentration tested, and in fact, it rescued cells from ER stress-induced cell death.

Conclusions: These results indicate that intracellular accumulation of MUC1-fs induces ER stress- related cell toxicity, a pathologic mechanism likely responsible for the progressive renal damage associated with the MUC1 mutation. Our findings reveal BRD as a promising lead for the treatment of MKD.

Funding: Private Foundation Support

FR-OR062

High Prevalence of C-Terminal CUBN Variants Associated with Chronic Proteinuria and Normal Renal Function in Humans

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Background: Proteinuria is considered as an unfavorable clinical condition that accelerates renal and cardiovascular disease. However, it is not clear if all forms of proteinuria are damaging. Mutations in *CUBN* cause Imerslund-Gräsbeck syndrome (IGS) featured by intestinal malabsorption of vitamin B12 and in some cases proteinuria. *CUBN* encodes for cubilin, an intestinal and proximal tubular uptake receptor containing 27 CUB domains for ligand binding.

Methods: We used next-generation sequencing for renal disease genes to genotype cohorts of patients with suspected hereditary renal disease and chronic proteinuria. *CUBN* variants were analyzed using bioinformatics, structural modeling and epidemiological methods.

Results: We identified 39 patients, in whom biallelic pathogenic variants in the *CUBN* gene are associated with chronic isolated proteinuria with childhood onset. Since the proteinuria displayed a high proportion of albuminuria, glomerular diseases such as steroid-resistant nephrotic syndrome or Alport syndrome were often the primary clinical diagnosis, motivating renal biopsies and proteinuria-lowering treatments. Yet, renal function was normal in all cases. By contrast, we did not find any biallelic pathogenic *CUBN* variants in patients with reduced renal function or focal segmental glomerulosclerosis. Unlike the more N-terminal IGS mutations, 37 out of the 41 proteinuria-associated *CUBN* variants led to modifications or truncations after the vitamin B12-binding domain. By structural modeling, we further demonstrate that all these C-terminal variants affect stability or ligand binding of CUB domains. Finally, we show that four C-terminal *CUBN* variants are associated with albuminuria and significantly higher eGFR in meta-analyses of large population-based cohorts.

Conclusions: Collectively, our data suggest an important role for the C-terminal half of cubilin in renal protein reabsorption. Defective reabsorption could be an unexpectedly common benign condition that does not require any treatment and may even have renoprotective effects. Therefore, cubilin can be defined as a safe drug target in human renal disease.

Funding: Government Support - Non-U.S.

FR-OR063

Phenome-Wide Association Study (PheWAS) of Common Genetic Variants for UMOD in the Million Veteran Program (MVP) Participants

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Background: Uromodulin (UMOD) is synthesized exclusively in the kidney and is the most abundant protein in ordinary urine. Common variants for UMOD have been considered an adaptation to protect against urinary tract infections (UTIs). Several GWAS studies of estimated glomerular filtration rate (eGFR) have shown SNPs in UMOD top hits; these variants have also been associated with chronic kidney disease (CKD) progression, ESRD and blood pressure, highlighting shared genetic pathways between these traits. In clinical settings, serum UMOD is increasingly considered a more sensitive indicator of functional kidney mass than filtration markers like eGFR, and has been associated prospectively with cardiovascular outcomes and mortality. Hypertension, vascular calcification and arterial stiffness are hypothesized mechanisms.

Methods: We tested common variants in UMOD and their association with clinically diagnosed phenotypes in a phenome-wide association study (PheWAS) in 188,008 White European Americans from the MVP. Using logistic regression adjusted for sex and 10 principal components, we regressed 1813 phenotypes against our 13 SNPs in models adjusted (and not adjusted) for eGFR.

Results: Eight of the common variants had significant associations for CKD (**Table 1**), renal failure, hypertensive heart or kidney disease and urinary calculus, and two with UTIs. Other significant associations were with premenstrual syndrome. In the eGFR-adjusted models, the strongest associations were with urinary calculus and disease groupings related to congestive heart failure, including non-hypertensive congestive heart failure.

Conclusions: This PheWAS confirms that UMOD variants are associated with CKD and ESRD. Other observed associations included kidney stones and UTIs. Mendelian Randomization studies of haplotypes for UMOD variants are underway to further elucidate the role of UMOD in vascular health.

Funding: Veterans Affairs Support

Clinical diagnosis in the electronic health record	Phecode	UMOD SNPs with phenome wide significant association
Hypertensive heart and/or renal disease	401.2	rs12917707 (p=3.09 10^{-11}), rs12922822(p=3.14 10^{-11}), rs13329952 (p=2.95 10^{-9}), rs13333226 (p=9.9 10^{-9}), rs4293393(p=4.65 10^{-11}), rs9928757 (p=1.44 10^{-9}), rs9928936 (1.68 10^{-11}).
Hypertensive chronic kidney disease	401.22	rs12917707 (p=3.5 10^{-14}), rs12922822 (p=3.59 10^{-14}), rs13329952(p=4.56 10-12), rs13333226 (p=7.25 10^{-11}), rs4293393 (p=3.93 10^{-14}), rs9928757 (2.73 10^{-11}), rs9928936 (3.26 10^{-14}).
Renal failure, Chronic renal failure	585 585.3	rs12446492 (p=3.53 10^{-11}), rs12917707 (p=4.56 10^{-28}), rs12922822 (p=4.71 10^{-28}), rs13329952 (p= 9.8 10^{-27}), rs13333226(p=6.18 10^{-25}), rs4293393 (p=1.01 10^{-28}), rs9928757 (p=4.16 10^{-22}), rs9928936 (p=4.05 10^{-29}).
Urinary tract infection	591	rs12917707 (p=7.18 10^{-6}), rs12922822 (p=6.42 10^{-6})
Calculus of kidney, lower urinary tract and ureter	594.1 594.2 594.3	rs12446492(p=2.46 10^{-17}), rs12917707 (p=1.11 10^{-31}), rs12922822(p=1.16 10^{-31}), rs13329952(p=3.42 10^{-23}), rs13333226(p=6.36 10^{-27}), rs4293393 (p=1.49 10^{-24}), rs9928757 (p=6.94 10^{-25}), rs9928936 (p=9.68 10^{-27}).
Premenstrual tension syndromes	626.4	rs188709583 (p=6.6 10^{-6}).

FR-OR064

De Novo Truncating TRIM8 Mutations Cause a Novel Pediatric Neuro-Renal Syndrome and Abrogate Protein Localization to Nuclear Bodies

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Background: Genetic forms of pediatric focal segmental glomerulosclerosis (FSGS) are usually caused by recessive mutations. The contribution of dominant *de novo* mutations (DNMs) to this trait is unknown.

Methods: We performed genetic studies using exome sequencing (ES) in 43,146 individuals. We conducted studies in tissue and human podocytes transfected with *TRIM8* cDNA constructs.

Results: A 4 year old child with epilepsy presented with FSGS. ES in the patient and unaffected parents identified a novel DNM in *TRIM8* (p.Q459*). To establish a link between *TRIM8* and FSGS, we conducted ES at Columbia University and Boston Children Hospital. We identified 6 additional *TRIM8* truncating mutations in 2,051 FSGS children as compared to 0/35,885 controls (P=2.5x10^{-8}). Parental data was available for 4/6 cases and in all instances the mutations were *de novo* (P=2.6x10^{-10}), establishing *TRIM8* as a novel FSGS gene. Review of clinical data showed that all 6 cases also had epilepsy, indicating that *TRIM8* DNMs define a novel neuro-renal syndrome. Consistent with this, we identified additional *TRIM8* mutations in 2/5,209 epilepsy patients. TRIM8 spans 551 amino acids. All mutations clustered between amino acid positions 410-460 in the last exon, predicted to escape non-sense mediated decay. TRIM8 was strongly expressed in podocytes and while overexpressed wildtype TRIM8 localized to nuclear bodies, constructs harboring patient-specific mutations (p.Q411* and p.Q459*) localized diffusely to the nucleoplasm.

Conclusions: Dominant *TRIM8* DNMs cause a novel pediatric neuro-renal syndrome due to its aberrant nuclear localization, implicating nuclear bodies in FSGS pathogenesis. Work in zebrafish and mouse is ongoing.

Funding: NIDDK Support

FR-OR065

Homozygous Variants in NOS1AP from a Patient with Steroid-Resistant Nephrotic Syndrome Cause Podocyte Polarity Dysregulation and Aberrant Glomerulogenesis in Human iPSC Kidney Organoids

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Background: Kidney organoids generated from human induced pluripotent stem cells (hiPSC) represent an emerging disease modelling platform for the study of genetic kidney diseases. Genomic sequencing is increasing the rate of novel disease gene discovery, and over 60 genes have been identified to cause steroid resistant nephrotic syndrome (SRNS). *Nitric oxide synthase 1 adaptor protein* (*NOS1AP*) is a novel gene for SRNS, whose encoded protein regulates actin cytoskeleton remodelling by promoting CDC42 activation. CDC42 regulates PAR3-PAR6-aPKC complex maintenance of apicobasal polarity. This PAR complex colocalises with the slit diaphragm in podocytes and either CDC42 or aPKC deficiency in mice causes severe proteinuria. Here, we characterise the effect of a homozygous *NOS1AP* SRNS patient variant on glomerulogenesis in hiPSC kidney organoids.

Methods: A homozygous, patient-derived *NOS1AP* variant (c.428G>A) was gene-edited into a wild type hiPSC cell line using CRISPR-Cas9. *NOS1AP* homozygous and wild-type (WT) hiPSC clones were differentiated to kidney organoids in paired experiments. Organoids were examined by blinded and semi-automated analysis of histology, immunofluorescence and electron microscopy imaging.

Results: Histology sections of WT organoids demonstrated tufts of podocyte monolayers lining an established basement membrane. In contrast, *NOS1AP* homozygous organoids showed disorganised podocyte collections with poorly established basement membranes and pyknotic nuclear figures which were CASP-3 positive. Foot process effacement was evident on electron microscopy of *NOS1AP* homozygous organoids. Whole mount immunofluorescence showed disorganisation of slit diaphragm markers and reduced aPKC expression in *NOS1AP* homozygous glomeruli suggesting dysregulation of the PAR complex.

Conclusions: A novel, SRNS patient-derived, homozygous variant in *NOS1AP* causes abnormal glomerulogenesis in kidney organoids and highlights the utility of this 3D, human, *in vitro*, functional genomic model. We propose that pathogenic variants in *NOS1AP* reduce active CDC42 which impairs polarity complex expression and foot process formation in hiPSC kidney organoid glomeruli.

Funding: Government Support - Non-U.S.

FR-OR066

Exon Skipping Therapy for COL4A5 Gene Truncating Variant Rescued Progression of Kidney Failure in X-Linked Alport Syndrome

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Background: X-linked Alport syndrome (XLAS) is a hereditary disease caused by mutations of *COL4A5* gene. Affected male patients generally develop end-stage renal disease in early or middle adulthood and patients with truncating variants show severer phenotype than those with non-truncating variants. In recent years, exon skipping (ES) therapy, which induces truncating variants into non-truncating variants, has been applied clinically in muscular dystrophy, etc. Here we applied the ES therapy for XLAS model mice and evaluated clinicopathological findings.

Methods: We generated C57B/6 mice with nonsense mutation in Col4a5 gene exon 21 (R471X) using CRISPER/Cas9 technique and clinicopathological features of this model was confirmed as typical for XLAS. In addition, we determined the antisense sequence (ASO) showed highest ES effect for exon 21 and administrated percutaneously to this model mouse once or twice a week from 4 weeks to 20 weeks of age. The effectiveness was evaluated both clinically and pathologically at 21 weeks of age.

Results: With clinical parameters, urinary albumin creatinine ratio was remarkably suppressed in ASO-treated group (n=5) compared to saline-treated group (n=6). At 21 weeks of age, serum BUN and creatinine levels were remarkably low in ASO treated group compared to vehicle treated group. With pathological evaluation by electron microscope, although even ASO-treated mice show thin basement membrane, they did not

show severe thickening with lamellation of GBM as shown in saline-treated group. With immunofluorescence, α5(IV) was completely negative in vehicle group, but it expressed clearly on tubular basement membrane and even on GBM although expression is not linear but partially on GBM. No clear side effect was recognized in the ASO-treated group.

Conclusions: It was clarified that the clinical-pathological findings of the XLAS model mouse was remarkably improved by ES therapy using ASO. ES therapy is expected to be an effective therapy for XLAS patients with truncating variants.

Funding: Commercial Support - Daiichi Sankyo company, Zenyaku Kogyo company, Government Support - Non-U.S.

FR-OR067

Copy Number Variation and Genome-Wide Association Studies Identify Risk Loci with Large Effects on Vesicoureteral Reflux

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Background: Vesicoureteral reflux (VUR) is a highly familial disease caused by malfunction of the vesicoureteral junction, resulting in retrograde flow of urine from the bladder into the ureters and kidney and accounts for 25-30% of pediatric ESRD worldwide. Very few genetic risk factors for VUR have been identified to date.

Methods: We undertook a Copy Number Variant (CNV) study on 1,737 VUR cases compared to 24,765 controls and GWAS on 1,395 unrelated VUR cases of European ancestry and 5,366 matched population controls, under additive, recessive and dominant models; we also performed sex-specific analyses.

Results: We found a significant excess of large, rare gene-intersecting CNVs in VUR cases ($P = 1.87 \times 10^{-7}$). We identified distinct known pathogenic CNV in 35 (2.01%) of cases vs. 0.65% of controls (OR = 3.12; 95% CI = 2.10 - 4.54; $P = 6.35 \times 10^{-8}$). The VUR cases were enriched for 1q21.1 deletions, 16p11.2 deletions, 22q11.21 deletions and duplications, and triple X syndrome. Our GWAS identified 3 study-wide significant ($P<7.58 \times 10^{-9}$) and 5 suggestive ($P<1.52 \times 10^{-7}$) loci with large effects (ORs = 1.41 to 3.65). The top SNPs for each of these associations were within or near genes known to be important in embryonic development and/or kidney disease (*WDPCP, OTX1, BMP5, WNT5A, VANGL1*). In addition, we estimated genetic heritability to be 15% based on the additive model results from all SNPs tested, and 4% based on a genotypic risk score from only the top 8 signals from all models. In situ hybridization confirmed that the top candidate genes are expressed in the ureter or vesicoureteral junction during mouse genitourinary development.

Conclusions: This study identifies multiple rare CNV disorders and common variants which impart large effects on the risk of VUR and implicate multiple canonical developmental pathways in the pathogenesis of disease.

Funding: NIDDK Support

FR-OR068

Genome-Wide Polygenic Score and Urinary Tract Stone Diagnosis in a Multiethnic Cohort

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Background: Urinary tract stones are highly heritable and clinical risk factors only explain a portion of stone occurrence. Additionally, urinary tract stones may occur in the absence of risk factors. We aimed to develop a polygenic score for association with urinary tract stones.

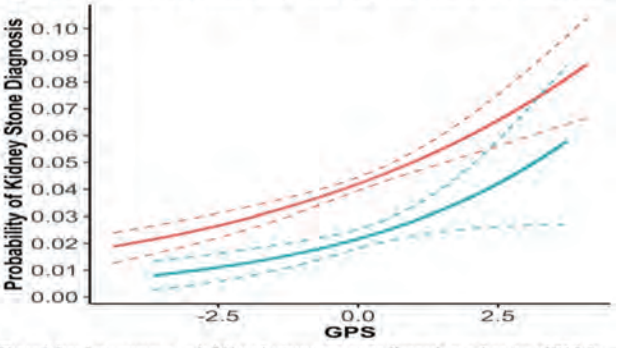
Methods: We used genome-wide association studies (GWAS) summary statistics for urinary tract stones from the UK Biobank (n=361,141), to generate polygenic scores with increasing number of single nucleotide variants (SNVs). We then determined the association of the best performing polygenic score with urinary tract stone diagnosis in individuals with and without clinical risk factors (diabetes, hypertension, gout and obesity) in a biobanked cohort using imputed genotyping data (Bio*Me* Biobank, 1208 cases, 30,233 controls) and calculated adjusted odds ratios (aOR) with 95% confidence intervals (CI) adjusting for age, sex and genetic ancestry.

Results: A genome wide polygenic score (GPS_{stone}) utilizing the most SNVs (~7 million) explained the highest variance and was chosen for further analysis. In individuals with at least one risk factor, every standard deviation (SD) increase in GPS_{stone} was associated with a 14% increase in odds of diagnosis (aOR 1.14; 1.08 – 1.22; $p = 4.3 \times 10^{-5}$). In individuals without clinical risk factors, every SD increase in GPS_{stone} was associated with a 30% increase in odds of diagnosis (aOR 1.3; 1.1 – 1.5; $p = 4.7 \times 10^{-3}$, Figure 1). In these individuals, the top 10% had four-fold increased odds of diagnosis relative to the lowest 10% (aOR 3.7; 95% CI 1.7 – 9.3; p = 0.003).

Conclusions: We developed a genomic wide risk score, GPS_{stone}, that is associated with urinary tract stones overall and even in the absence of known clinical risk factors identifies a subgroup with genetic risk comparable to a monogenic mutation.

Funding: NIDDK Support

Figure 1 Association of GPS with Kidney Stone Diagnosis Stratified by Clinical Risk.



The teal function represents probability of urinary tract stone diagnosis as a function of GPS for individuals with no clinical risk factors (BMI <25, no hypertension, no type 2 diabetes, and no gout). The red function represents probability of urinary tract stone diagnosis as a function of GPS for individuals with at least one clinical risk factor. We estimated probability of urinary tract stone diagnosis using an adjusted logistic regression function with GPS, age, sex and 10PCs.

FR-OR069

Next-Generation Sequence Analysis of Genetically Unsolved Primary Hyperoxaluria (PH) or Dent-Diagnosed Patients Resolved 10% of Cases with 11 Genes Implicated

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Background: Due to phenotypic overlap between patients with monogenic stone diseases, gene specific analysis of patient groups can result in under diagnosis. Here we employed a targeted next generation sequencing (tNGS) approach to analyze primary hyperoxaluria (PH) or Dent diagnosed patients that were genetically unresolved after analysis of the respective known genes by Sanger analysis.

Methods: A cohort of genetically unresolved patients with a presumptive diagnosis of PH (PHN, n=236) and Dent disease (DN, n=61) were screened employing a 90 gene panel that included known monogenic causes of stone disease and candidates. Variants were assessed considering American College of Medical Genetics and Genomics guidelines. Their presence was determined in disease-specific databases, Human Gene Mutation Database (HGMD) and ClinVar, and the frequency in normal populations, GnomAD, plus using variant assessment tools and by analysis of multisequence alignments. Sanger sequencing was used to confirm changes and test segregation.

Results: Biallelic pathogenic variants were found in 11 different genes and accounted for 30 patients (10.1%). Recurrent genes included ones encoding claudins, *CLDN16* [6PHN, 1DN] & *CLDN19* [1PHN, 1DN] (familial hypomagnesemia with hypercalciuria and nephrocalcinosis), the cystinuria gene, *SLC7A9* [5PHN], *CYP24A1* [4PHN], *SLC34A3* [1PHN, 2DN] (hypophosphatemic rickets with hypercalciuria), and APRT [2PHN]. The genes *ATP6V1B1* [1DN], *SLC12A1* [1DN] and *SLC34A1* [1DN] account for just one family. Mutations to *CLDN16, CLDN19, SLC34A3,* and *KCNJ1* were found to account for both PH and Dent diagnosed patients. Two additional patients were found to have copy number variants, a 72 gene deletion [1PHN] or 2 duplicated regions [1DN], that may be phenotypically significant.

Conclusions: The phenotype of monogenic stone diseases overlaps greatly. Given the emerging therapies for these disorders, including siRNA approaches for PH, making the correct diagnosis is crucial for enrollment in clinical trials and selecting the correct therapy. It is also essential to identify cohorts of patients with poorly recognized disorders, in order to better understand the natural history, and assemble cohorts for future trials.

Funding: NIDDK Support

FR-OR070

Nationwide Diagnostic Yield of Clinical Genomics in Patients with Suspected Genetic Kidney Disease

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Background: With increased understanding of genetic kidney disease (GKD), genomic testing is translating from research to clinic. Rigorous evaluation of clinical practice and patient outcomes is required to guide value-based healthcare. We aimed to describe diagnostic outcomes of clinically accredited genomic testing delivered by nationwide multidisciplinary team (MDT) clinics for patients with suspected GKD.

Methods: Sequential incident patients undergoing clinically indicated genomic testing for presumed GKD from 18 Australian MDT clinics 2016-19 were analysed (HREC/16/MH/251). A molecular diagnosis constituted clinical reporting of pathogenic and/or likely pathogenic variant/s in gene/s associated with the patient kidney phenotype with concordant inheritance. All genomic testing included restriction of variant analysis to a phenotype-derived gene list. Full author list online at KidGen.org.au

Results: Of 824 patients, 52.1% were female. Median age was 26 years. A molecular diagnosis was made in 43.7%. A further 15.4% had a variant/s of uncertain significance (VUS), of which 23.6% were clinically compelling but require further functional validation or additional segregation. The diagnostic yield for whole genome (WGS n=92, 41.3%), whole exome (WES n=231, 40.7%) and clinical exome (CES n=392, 42.3%) sequencing was similar (p=0.91). Median age at test request for WGS (42yrs) was significantly older ($p<0.00001$) than WES (27yrs) and CES (18yrs). Of all patients with a genetic finding, 53.6% involved variation in 7 genes (COL4A3, COL4A4, COL4A5, PKD1, PKD2, PKHD1, HNF1B). Stratifying by age at test request, the diagnostic rate was not significantly different between 0-15yrs (41.8%), 16-25yrs (48.5%) and 26+yrs (44.2%) (p=0.25). The gender mix in these age groups was significantly different (female 45.8% vs 51.5% vs 56.7%, p=0.015).

Conclusions: Clinical genomics delivered by MDT clinics are diagnostically effective for suspected GKD. Neither sequencing approach nor age group at test request appear to impact diagnostic yield though WGS patients in this cohort were older and gender mix changed with increasing patient group age. Clinical utility studies are required to clarify impact of these diagnostic outcomes.

Funding: Government Support - Non-U.S.

FR-OR071

Circadian BP Rhythm as a Possible Key Target of SGLT2 Inhibitors for DKD: Yokohama Add-on Inhibitory Efficacy of Dapagliflozin on Albuminuria in Japanese T2DM Patients (Y-AIDA) Study

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Background: In treating T2DM, it is important to appropriately manage glucose and lipid metabolism, body weight and BP and to suppress the development and progression of diabetic complications to restore the quality of life to a level comparable with healthy subjects. The Y-AIDA study was designed to investigate the renal and home BP modulating effects of add-on dapagliflozin treatment in Japanese T2DM individuals with albuminuria.

Methods: This study was a prospective, multicenter, single-arm study. A total of 86 T2DM (HbA1c 7.0-10.0%) individuals with albuminuria (UACR ≧ 30 mg/gCr) were enrolled, and 85 participants were administered with add-on dapagliflozin for 24 weeks. The primary and key secondary endpoints were change from baseline in the natural logarithm of UACR over 24 weeks and change in home BP profile at week 24. This study was registered at UMIN Clinical Trials Registry (UMIN000018930; http://www.umin.ac.jp/ctr/index-j.htm). All participants provided written informed consent prior to initiation of the study.

Results: Baseline median UACR was 181.5 mg/gCr (interquartile range 47.85, 638.0). Baseline morning, evening and nocturnal home systolic/diastolic BP were 137.6/82.7 mmHg, 136.1/79.3 mmHg, and 125.4/74.1 mmHg, respectively. After 24 weeks, the logarithm of UACR decreased by 0.37±0.73 ($P<0.001$). In addition, changes in morning, evening and nocturnal home BP from baseline were morning systolic/diastolic BP -8.32±11.42/-4.18±5.91 mmHg (both $P<0.001$), evening systolic/diastolic BP -9.57±12.08/-4.48±6.45 mmHg (both $P<0.001$) and nocturnal systolic/diastolic BP -2.38±7.82/-1.17±5.39 mmHg ($P=0.0079$ for systolic BP, $P=0.0415$ for diastolic BP). Furthermore, the reduction in UACR after 24 weeks significantly correlated with the improvement of home BP profile, but not with changes in other variables including office BP.

Conclusions: In Japanese T2DM individuals with albuminuric DKD, dapagliflozin not only lowered albuminuria but also improved home BP profile, suggesting that circadian BP rhythm estimated by out-of-office home BP monitoring as a possible key target of SGLT2 inhibitors for DKD.

FR-OR072

Activation of G Protein-Coupled Estrogen Receptor Ameliorates Proteinuria in Dahl Salt-Sensitive Female Rats

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Background: Recent evidence implicates a central role for the G protein-coupled estrogen receptor (GPER) in the maintenance of cardiovascular and renal health in women. The current study tested whether GPER activation ameliorates salt-induced elevation in blood pressure and renal damage in female Dahl salt-sensitive (SS) rats.

Methods: 12-14 weeks old female rats were implanted with telemetry transmitters and osmotic minipumps releasing G1 (GPER agonist, 400 μg/kg/day, IP) or its vehicle for 28 days. Two weeks after pump implantation, rats were shifted from a normal salt diet (NS, 0.4% NaCl, AIN-76A Purified Rodent Diet) to a matched high salt diet (HS, 4% NaCl) for two weeks. 24-hour urine samples were collected while on NS and HS diets.

Results: 24-hr mean arterial pressure (MAP) markedly increased in response to HS in vehicle-treated rats in comparison to NS baseline values (141±3 vs. 124±1 mmHg, respectively, n=5, $p<0.05$). This salt sensitivity was evident also in G1-treated rats (MAP: 144±4 vs. 124±2 mmHg, n=6). No differences were observed in diastolic, systolic blood pressure, heart rate or locomotor activity between G1- and vehicle-treated rats. Body weight, food intake, water intake, urine flow and urinary sodium excretion were not significantly altered by G1. HS significantly increased urinary excretion of protein, albumin, nephrin (podocyte damage marker) and KIM-1 (proximal tubule injury marker) in vehicle-treated rats, compared to NS (protein: 63.9±16.2 vs. 22.8±3.8 mg/day, albumin: 52.6±19.9 vs. 12.4±5.1 mg/day, nephrin: 65.9±8.7 vs. 16.4±5.3 ng/day, KIM-1: 30.2±7.2 vs. 16.6±1.7 ng/day, n=7, $p<0.05$). Importantly, GPER activation prevented HS-induced proteinuria, albuminuria and increase in KIM-1 excretion (n=6, $p<0.05$), but not nephrinuria suggesting that systemic GPER activation protects against HS-induced proximal tubular damage in female Dahl SS rats.

Conclusions: Collectively, we found that GPER activation ameliorates salt-induced renal damage, but not salt sensitive hypertension, in female Dahl SS rats. Our data suggest that GPER elicits a protective effect against HS-induced renal damage, specifically proximal tubular damage, in a blood pressure-independent manner.

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FR-OR073

Sex-Related Differences in the Intratubular Renin-Angiotensin System (RAS) in 2-Kidney 1-Clip Hypertensive Rats

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Background: The intratubular renin-angiotensin system (RAS) is thought to play an essential role in hypertensive renal disease, but information regarding sex-related differences in this system is limited. This study investigated the sexual differences in the intratubular RAS in 2-kidney 1-clip (2K1C) rats.

Methods: A 2.5-mm clip was placed on the left renal artery of Sprague Dawley rats, and the rats were euthanized 3 or 5 weeks following the operation.

Results: Systolic blood pressure (SBP) increased in 2K1C rats of both sexes but was significantly higher in males than in females, and an antihypertensive effect disappeared in 2K1C ovariectomized(OVX) female rats. Intratubular angiotensin-converting enzyme (ACE) and Ang II were repressed, and intratubular ACE2, Ang 1-7, and MasR were increased in both kidneys of 2K1C female rats at five weeks after surgery compared with those of male 2K1C rats. Intratubular mRNA levels of ACE and AT_1R were augmented in OVX female rats regardless of clipping surgery at three weeks after operation in comparison with those in male and female rats. The AT_2R was upregulated in female rats with or without OVX; thus, the AT_1/AT_2 ratio was higher in female rats than in male rats.

Conclusions: Female rats were protected from hypertensive injury after renal artery clipping. An increase in intratubular nonclassic RAS (ACE2/angiotensin 1-7/MasR) and a decrease in the AT_1/AT_2 ratio could limit the adverse effects of classic RAS during renovascular hypertension in female rats, and estrogen is suggested to have a primary role in regulating intratubular RAS components.

Funding: Private Foundation Support

FR-OR074

Central EP3 Receptors Mediate Salt-Sensitive Hypertension and Immune Activation

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Background: Prostaglandin E_2 (PGE_2) has been implicated in the generation of reactive oxygen species and inflammation associated with hypertension. Proteins oxidatively modified by reactive isolevoglandins (isoLGs) accumulate in dendritic cells (DCs) leading to subsequent activation of T lymphocytes. The local signals that stimulate DCs to accumulate isoLG adducted proteins remain undefined. We hypothesized that PGE_2 via its EP3 receptor contributes to DC activation in hypertension.

Methods: $EP3^{-/-}$ mice and wild type (WT) littermates were exposed to sequential hypertensive stimuli involving an initial exposure to the nitric oxide synthase inhibitor L-NAME (LN) in drinking water, a 2 week washout period, and a subsequent 4% high salt diet (HS). Lentiviral vectors encoding shRNA targeting EP3 receptor were administered intracerebroventricularly to knockdown EP3 receptor expression in the central nervous system.

Results: In WT mice, this protocol increased systolic pressure from a baseline of 123±2 to 148±8 mmHg ($p<0.05$), and renal $CD4^+$ and $CD8^+$ effector memory T cells by 2 to 3 fold. This was associated with marked increases in superoxide production in the kidney and a striking accumulation of isoLG protein adducts in splenic DCs. The increases in blood pressure, renal T cell infiltration, renal superoxide production and DC isoLG formation were completely prevented in $EP3^{-/-}$ mice. Interestingly, we found that EP3 receptor, among all EP receptors, is highly expressed in the organum vasculosum laminae terminalis (OVLT) in the brain, LNHS treatment induced an upregulation of COX-2 expression and downregulation of EP3 receptor in the OVLT. To test the hypothesis that central EP3 receptor contributes to the LNHS induced hypertension and renal inflammation, WT mice received intracerebroventricular injection of lentiviral vectors encoding shRNA targeting EP3 receptor and then subjected to the same LNHS treatment. These mice were also protected from salt induced hypertension and renal inflammation like the $EP3^{-/-}$ mice.

Conclusions: These findings provide new insight involving EP3 receptor in the central nervous system and sympathetic activation in salt induced hypertension and provide additional information as to how PGE_2 modulates inflammation in this conditions.

Funding: Other NIH Support - NHLBI, Private Foundation Support

FR-OR075

Mutation of the Furin Cleavage Site in the (Pro)Renin Receptor Attenuates Angiotensin II-Induced Hypertension and Albuminuria

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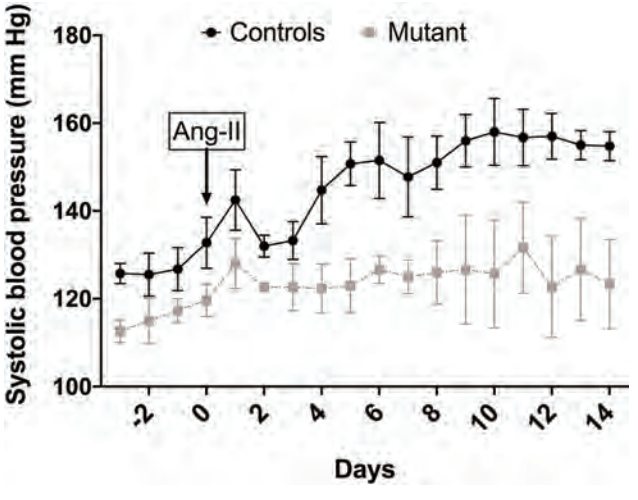
Background: Cleavage of the extra-cellular domain of the (pro)renin receptor (PRR) yields a soluble fragment (sPRR) which can promote angiotensin-II (Ang-II) formation. Although alterations in plasma sPRR levels have been reported in hypertension, the causal role of sPRR in hypertension is unknown.

Methods: To investigate this, we mutated the furin cleavage site (R276A, R279A) of the PRR using CRISPR/Cas9. Because the gene encoding PRR is on the X-chromosome and male mutant mice are infertile, only male mice were studied.

Results: Mutant mice had markedly lower plasma sPRR levels (control: 16.2 ± 0.3 vs mutant 0.2 ± 0.03 ng/ml). Mutant mice had normal survival and development and no histological renal abnormalities up to 12 months of age. During normal salt intake, no differences in blood pressure, body weight, urinary water or Na^+ excretion, or acid-base status were observed between control and mutant mice. Compared to controls, mutant mice had an attenuated hypertensive response to 2 weeks of Angiotensin-II infusion (400 ng/kg/min) (Figure 1). Mutant mice also had lower albuminuria (control: 327 ± 114 vs mutant: 58 ± 8 μg/day) at day 7 post Ang-II infusion. No differences in urinary Na^+ excretion were detected between control and mutant mice after 7 days of Ang-II infusion (control: 33.6 ± 3.1 vs mutant: 35 ± 2.7 μmol/day/gram body weight). Mesentric arteries isolated and studied ex-vivo using isometric tension procedures showed an attenuated vascular response to Ang-II (10^{-8} M) compared to controls (internal diameter control: 115 ± 7 μm vs mutant 125 ± 8 μm).

Conclusions: These results suggest that sPRR plays a role in Ang-II induced hypertension and renal injury.



FR-OR076

Connexin40 (Cx40) Knockout Rat Has Impaired Renal Autoregulation

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Background: Renal autoregulation is mediated by the generic myogenic response (MR), modulated by the kidney-specific tubuloglomerular feedback (TGF). Recent studies have indicated that TGF acts on a larger scale than individual nephrons and that the well-known synchronization of TGF dynamics operates on macroscopic scales, communicating electrically along the vasculature via gap junction intercellular communication.

Methods: A Wistar Kyoto (WKY) rat lacking Cx40 was made at the Genome Editing Rat Resource Center (https://rgd.mcw.edu/wg/gerrc/). Heterozygous parents produce wild type (WT), heterozygous (HET), and knockout (KO) offspring in Mendelian ratios. In anesthetized rats, surface perfusion of renal cortex in all genotypes was studied by laser speckle contrast imaging (LSCI) in an area 2.75×2.75 mm. ROIs captured blood flow dynamics in star vessels. Synchronization was assessed by phase coherence (PC) between all possible ROI pairs (Scully et al. IEEETBME 2014; 1989-97). Blood pressure (BP) and renal blood flow (RBF) were monitored. Data are reported as mean±SEM. Significance testing was not done because N is not yet sufficient for it to be meaningful.

Results: In WT and HET rats (N = 3 each) BP and RBF were similar (WT: 100±2 mmHg, 6.57±0.56 mL/min; HET: 98±4 mmHg, 6.12±1.84 mL/min) while in KO rats (N = 3) BP appeared higher and RBF lower (123±6 mmHg, 4.52±0.86 mL/min). There was a pronounced gene dosage effect on TGF synchronization. In N=6 WT rats 86±10% of possible connections had statistically significant PC and of those 37±14% had PC >0.6 which is considered to be significant for autoregulation. In N=6 HET rats 95±4% of possible connections were significant and of those 18±10% had PC >0.6. In N=5 KO rats 62±16% were significant and 5±2 had PC >0.6. Renal autoregulation assessed by transfer functions was visibly impaired.

Conclusions: We report a new knockout rat on the normotensive Wistar Kyoto background that lacks Cx40. Wildtype, heterozygote, and Knock-out are bred in Mendelian ratios. As expected from the Cx40 knockout mouse, KO rats appear to be hypertensive, probably due to dis-regulated renin secretion. TGF synchronization is, and autoregulatory effectiveness appears to be, grossly impaired in the absence of Cx40.

FR-OR077

Myocardial Infarction in an Inducible Hypertensive Rat Model: Does Spironolactone Reduce Renal Fibrosis?

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Background: Hypertension is a leading cause of myocardial infarction (MI), and is strongly associated with renal injury. However, superposition of MI on renal injury secondary to hypertension is not clearly defined. Likewise mineralocorticoid blockade (e.g. spironolactone; SP) has been shown to reduce cardiac fibrosis and improve cardiac outcomes post MI, but consequences for renal function are not known. We aimed to explore the effects of SP on renal fibrosis, post MI, in established hypertensive rats.

Methods: Hypertension was induced and maintained using male Cyp1a1Ren2 rats (n=20) by addition of 0.167% (w/w) indole-3-carbinol to the rat chow, and established for two weeks prior to treatment or surgical intervention. Rats (10 weeks of age) were divided into four groups: hypertensive controls (H), hypertensive controls fed SP daily (4.4mg/kg/day; H-SP), hypertensive with MI (permanent left anterior coronary ligation; H-MI) and H-MI plus daily SP (H-MI-SP). Physiological data and tissue was collected four weeks after MI for analysis.

Results: Systolic blood pressure (SBP) did not differ significantly between groups. Ejection fraction (EF) was significantly ($p<0.001$) reduced by MI induction (42±10%), but not improved by SP treatment (43±10%). MI significantly increased global cardiac fibrosis (2.2±0.5%) and renal cortical fibrosis (3.1±0.9%) when compared to hypertensive animals (1.3±0.5% and 2.6±0.9% respectively), while SP therapy post infarct significantly reduced cardiac interstitial fibrosis (1.5±0.6%) and kidney cortical fibrosis (1.4±0.6%). The reduction in fibrosis was associated with decreased expression of αSMA, TGFβ, reduced expression of MCP1 and a significant reduction in interstitial macrophages. SP significantly reduced ($p<0.01$) glomerulosclerosis in both H-SP group (from 1.2±0.07 in hypertensive controls to 0.9±0.04) and from 1.5±0.1 (H-MI) to 1.2±0.2 in the H-MI-SP group.

Conclusions: The addition of MI significantly worsened the extent of hypertension-induced renal fibrosis and glomerulosclerosis. SP treatment resulted in significant improvement in renal fibrosis and GSI scores in hypertensive animals with or without MI. Further work will aim to further define the relationship between cardiac injury and renal damage.

FR-OR078

Experimental Renovascular Disease Induces Endothelial Cell Mitochondrial Damage and Impairs Endothelium-Dependent Relaxation of Renal Artery Segments

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Background: Endothelial cell (EC) mitochondria produce energy, control redox status, and support EC function, but may be damaged during renal disease. We hypothesized that the ischemic and metabolic constituents of swine renovascular disease (RVD) induce mitochondrial damage and impair the function of renal artery EC.

Methods: Domestic pigs were studied after 16 weeks of diet-induced metabolic syndrome (MetS), renal artery stenosis (RAS), or coexisting MetS and RAS, and Lean pigs served as control (n=6 each). Mitochondrial morphology (electron microscopy), membrane potential (TMRE staining), and production of reactive oxygen species (MitoSOX) were measured in isolated primary renal artery EC. Vasoreactivity of renal artery segments was characterized in an organ bath.

Results: Lean-RAS and MetS-RAS developed significant stenosis and hypertension (Table), and showed increased mitochondrial area and decreased matrix density (Fig. A). Mitochondrial membrane potential similarly decreased in MetS, Lean+RAS, and MetS+RAS groups, whereas production of reactive oxygen species increased in MetS vs. Lean, but further increased in both RAS groups (Fig. B). Endothelial-dependent relaxation of renal artery segments was blunted in MetS vs. Lean, but further attenuated in Lean+RAS and MetS+RAS (Fig. C).

Conclusions: MetS and RAS damage mitochondria in pig renal artery EC, which may impair EC function. However, the coexistence of MetS and RAS did not aggravate EC mitochondrial injury and dysfunction in the short time of our in-vivo studies. These findings suggest that mitochondrial injury might be implicated in the pathogenesis of RVD-induced vascular damage.

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	Lean	MetS	Lean+RAS	MetS+RAS
Weight (Kg)	53.3 ± 2.2	92.8 ± 0.8*	48 ± 1.2†	92.2 ± 2.7*‡
MAP (mmHg)	103 ± 4	122 ± 4*	131 ± 8*	130 ± 7*
Stenosis (%)	-	-	72 ± 8	71 ± 5

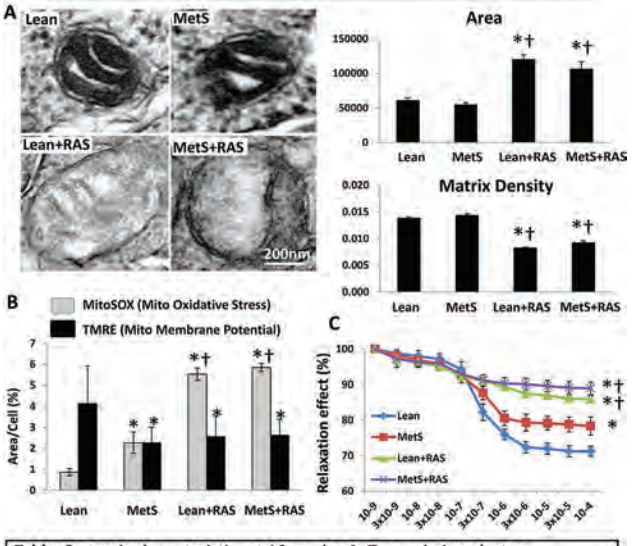

Table. Systemic characteristics at 16 weeks. **A.** Transmission electron microscopic images showing mitochondrial swelling and loss of cristae membranes in Lean+RAS and MetS+RAS renal artery endothelial cells. **B.** Mitochondrial membrane potential (TMRE) and production of reactive oxygen species (MitoSOX) in renal artery endothelial cells. **C.** MetS, Lean+RAS, and MetS+RAS impaired endothelial-dependent relaxation of renal artery segments. **p<0.05 vs. Lean; †p<0.05 vs MetS; ‡p<0.05 vs. Lean+RAS.*

FR-OR079

Opposite Regulation of Renal and Cerebral Microarteriolar Angiotensin II Contractility by Specific Endothelial Prostaglandin Pathways

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Background: The kidney requires robust angiotensin II (Ang II) responsiveness for regulation of body fluids whereas the cerebral circulation requires resilience to Ang II to prevent cerebral ischemia and dementia. RNAseq of single cerebral microarterioles (CAs) versus renal afferent arterioles (Affs) detected >30-fold greater gene expression for COX2 and >3000-fold greater expression for lipokalin type prostaglandin D synthase (LPGDS) and DP1 receptor in CAs yet Affs expressed more thromboxane synthase. We reported enhanced contractility of Affs by thromboxane (*Circulation research* 94: 1436-1442, 2004). Therefore, we hypothesized that expression of different PGs accounts for regional differences in Ang II responsiveness.

Methods: Individual mouse microarterioles (8-15μm) from the intraparenchymal frontal cerebral cortex were compared to renal cortical Affs, perfused at 40 mmHg and change in diameter (%) assessed with Ang II (10^{-12} to 10^{-6} M).

Results: Normal CAs were entirely unresponsive to 10^{-6} Ang II (0±0.03%) whereas Affs were highly responsive (-49±1 %). Ang II responses of CAs from COX1 -/- vs +/+ mice were enhanced (-15±2 vs 0±0.1% P<0.001) and enhanced further by COX2 blockade with parecoxib (-20±2 vs -15±2%; P<0.05) similar to effects of LPGDS blockade with AT56 in normal mouse arterioles (-15±4%). In contrast, COX-blockade reduced Ang II contractions of Affs. The DP1R agonist, BW450c reduced Ang II contractions of CAs from COX-blocked mice, yet was ineffective in Affs. Deendotheliaization of CAs enhances Ang II contractions in normal mouse CAs (0±0.1 vs 17.2±1.9%; P<0.001) but did not increase contractions further in COX-blocked CAs (19.8±1.5 vs 22.5±1.9%; NS).

Conclusions: The normal complete resilience of CAs to Ang II contractions depends on constitutive endothelial expression of COX1 and 2 and LPGDS generating vasodilator PGD_2 that activates DP1 whereas the robust Ang II responsiveness of Affs is independent of PGD_2 but depends on vasoconstrictor COX products. Thus, strong expression of PGD_2 protects the cerebral circulation from ischemia with Ang II but strong expression of vasoconstrictor PGs renders the renal circulation highly Ang II responsive.

Funding: NIDDK Support

FR-OR080

Sox6 Ablation in Renin Expressing Cells Has Protective Function Against Renovascular Hypertension and Kidney Damage

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Background: Renal artery stenosis (RAStenosis) is an interactable problem affecting about 6% of the people over 65 and in up to 40% of the people with coronary or peripheral vascular disease. The renin angiotensin aldosterone system (RAAS) is implicated in RAStenosis. Renin controls rate-limiting step in RAAS and is a key driver in RAStenosis induced hypertension. Sox6 is a transcription factor important for cell fate determination of muscle, bone, neurons among others.

Methods: A new transgenic mice the $Ren1d^{Cre}/Sox6^{fl/fl}$ (Sox6 KO), in which Sox6 is knockout in renin expressing cells was used to determine the impact of Sox6 ablation on renin expression and hypertension during RAStenosis. Two time-point studies, 3 weeks, and 3 days were conducted. Blood pressure was measured by tail-cuff method. The kidney injury markers KIM1, creatinine, albumin, and urea were measured using commercially available kits. Superoxide was measured using HPLC.

Results: *In 3-week study*; systolic and mean arterial blood pressure were significantly lower in Sox6 KO compared to wild-type mice. When stenosed kidneys were compared, renin expression levels were significantly lower in Sox6 KO compared to wild-type. Urine creatinine clearance was significantly higher in Sox6 KO compared to wild-type. *In 3-day study*; renin, STAT3, HIF1-α, N-Gal, and Sox6 serine-threonine phosphorylation levels were lower in the stenosed kidney of Sox6 KO compared to wild-type. This indicates that phosphorylated Sox6 triggers renin expression increase in RAStenosis and indicates that HIF1-a and STAT3 may control Sox6 expression in RAStenosis. Superoxide levels in stenosed kidney were lower in Sox6 KO compared to wild-type mice. Urine creatinine clearance was significantly higher in Sox6 KO compared to wild-type animals. KIM1, urea, and albumin levels were not different between the groups in both time-point. Altogether, our data suggest that Sox6 KO mice were protected from developing hypertension and kidney damage during RAStenosis.

Conclusions: Our data indicates that Sox6 has a new function modulating renin expression, renovascular hypertension and kidney damage induced by RAStenosis. Identification of this novel pathway and its regulators may lead to new therapies for hypertension and associated cardiovascular disease.

Funding: Other NIH Support - NHLBI

FR-OR081

Investigating the Role of CD40-CD154 Interactions in Lupus Nephritis

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Background: Disease pathology in lupus nephritis (LN) has been linked to a variety of different immune pathways, including CD40-CD154 interactions. This pathway has been shown to regulate the activation of B lymphocytes as well as macrophages and activated renal epithelia, and thus blockade of this pathway could provide therapeutic benefit in individuals with LN.

Methods: We evaluted the expression and activation of the CD40-CD154 pathway in kidney tissue from LN patients. Additionally, we evaluted the therapeutic effect of a blocking, non-depleting anti-mouse CD40 mAb (GOT40) in the NZB/W F1 model of lupus nephritis.

Results: Histological analysis of kidney biopsies from patients with proliferative LN revealed evidence of CD40 and CD154 on B cells, macrophages and T cells respectively. These results suggested that there might be ongoing T-B cell collaboration in LN kidneys and we subsequently examined whether there was evidence of CD40 pathway expression and activation in situ. Using published scRNA-seq data from LN kidney biopsies we could demonstrate evidence of CD40 transcript expression by B cells and myeloid cells and CD154 expression by subsets of CD4+ T cells. To directly address the role of CD40-CD154 in LN, we used GOT40, a novel, blocking, non-depleting anti-CD40 antibody in the NZB/W F1 model of lupus nephritis. Therapeutic treatment for 9-77 days of NZB/W F1 mice aged 24 to 37 weeks and individually enrolled into treatment groups with proteinuria ≥3 mg/ml resulted in suppression of established proteinuria and extended survival in GOT40 treated animals in comparison to isotype control treated animals. Serum autoantibody and CXCL13 levels were reduced by GOT40 treatment compared to isotype control. Similar to current treatments, we observed only minimal (not significant) reduction in various histological parameters with GOT40 treatment at this advanced stage of kidney injury, despite evidence of complete, systemic pathway blockade at the transcriptional level and suppression of a kidney gene expression with GOT40 treated animals.

Conclusions: Our data support the notion that CD40-CD154 pathway signaling may contribute to pathology in LN and that anti-CD40 treatment could provide therapeutic benefit in individuals suffering from this disease.

Funding: Commercial Support - Novartis Pharmaceuticals AG

FR-OR082

Modified Immune Cell (MIC) Therapy Ameliorates Murine Lupus Nephritis and Induces Regulatory B Cells In Vivo

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Background: MICs are mononuclear cells that gain immunosuppressive properties after incubation with mitomycin C (MMC). We recently showed that syngeneic MIC therapy controlled experimental autoimmune encephalitis (EAE). In addition, allogeneic MICs prevented rejection in rat heart and hindlimb as well as pig kidney transplantation. We wanted to translate these encouraging findings to the prevention and treatment of lupus nephritis.

Methods: Splenocytes of syngeneic BWF1 donor mice were incubated with MMC and injected into recipient's tail vein after matching for disease activity. Group 1 received no therapy, group 2 standard-dose MIC therapy with $1.5x10^8$/kg BW and group 3 high-dose MIC therapy with $1.5x10^8$/kg BW at week 1, 2 and 3. Group 4 received MIC infusions before disease onset as preemptive treatment approach. Disease activity was monitored by body weight, protein excretion, serum creatinine and dsDNA. Primary endpoint was day 40, protein excretion >3g/l and >20% loss of body weight. Kidney histopathology with PAS/HE staining was performed. Regulatory cell subsets and cytokine concentrations were measured.

Results: MIC therapy prevented the progression of lupus nephritis. Protein excretion, serum creatinine and dsDNA were lower in standard-dose and preemptive group compared to control group whereas repeated MIC therapy after disease onset had no effect. The endpoint was reached significantly more often in control group (67%) compared to groups 2 (14%), 3 (14%) and 4 (0%). Renal architecture was preserved in different MIC treatment groups with decreased glomerular and tubular damage scores. The frequency of $CD5^+CD1d^{high}$ regulatory B cells was higher in MIC-treated compared to control animals, whereas double negative T cells were markedly reduced. IL-6 serum concentration was significantly decreased in group 2 and 4.

Conclusions: MIC therapy inhibits progression of active lupus nephritis. Preemptive MIC therapy delayed the onset of disease with no significant disease activity at completion of the study. In accordance with our EAE experiments and a first in-human clinical trial in kidney transplantation (TOL-1 study), MIC therapy was able to induce regulatory cell subsets in-vivo. This clinically applicable cell therapy may control lupus nephritis by specifically silencing deleterious autoimmune responses.

Funding: Commercial Support - TolerogenixX GmbH

FR-OR083

Adeno-Associated Virus-Mediated Factor H Gene Therapy in a Murine Model of Complement-Dependent Thrombotic Microangiopathy and Systemic Thrombophilia

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Background: Atypical hemolytic uremic syndrome (aHUS) is a form of thrombotic microangiopathy (TMA) caused by complement dysregulation. It is characterized by thrombocytopenia, hemolytic anemia and renal injury, with up to 50% patients eventually progressing to end stage renal failure. Mutation in the C-terminal domain of factor H (FH), a critical plasma complement inhibitor, is the most common genetic cause of aHUS. Eculizumab, a humanized anti-C5 mAb, is effective for aHUS but whether lifetime treatment with Eculizumab is needed and what is the optimal length of therapy remains unknown. Here we tested the hypothesis that adeno-associated virus (AAV)-mediated FH gene therapy can correct complement dysregulation and replace anti-C5 therapy in FH mutation-related aHUS.

Methods: We used $FH^{R/R}$ mice which carried a homozygous mutation (W1206R) in FH. $FH^{R/R}$ mice developed characteristic TMA as well as macro-vessel thrombosis in multiple organs, and approximately 50% died prematurely. Twice weekly treatment of 4-week old $FH^{R/R}$ mice with an anti-mouse C5 mAb for 4 weeks prevented disease development as indicated by normal platelet counts and blood hemoglobin levels. The treated mice were then randomized to receive either control AAV vector or AAV-sFH encoding a mouse FH construct comprising short consensus repeats 1-4, 6-8 and 19-20 (1×10^{12} gene copies/mouse)and anti-C5 mAb treatment was discontinued one week later.

Results: When examined at 5 weeks after AAV gene therapy (4 weeks after stopping anti-C5 mAb treatment), TMA features including thrombocytopenia, low plasma hemoglobin and elevated reticulocyte count returned to control AAV-treated but not AAV-sFH-treated mice. Six months after AAV gene therapy, 9/10 AAV-sFH-treated mice were still alive whereas only 7/20 control AAV-treated mice survived. Furthermore, severe glomerular injury and fibrin deposition in the kidney, and macro-vessel thrombosis in extra-renal organs, were detected in terminally sacrificed control AAV-treated $FH^{R/R}$ mice but were almost absent in AAV-sFH-treated $FH^{R/R}$ mice.

Conclusions: These results demonstrate that AAV-mediated FH gene transfer can replace anti-C5 mAb treatment to provide curative therapy for TMA and other pathologies associated with FH point mutations.

Funding: Other NIH Support - NIH RO1 AI117410, Research grant, Commercial Support - Consultancy, equity interest and research grant from Aevitas Therapeutics, Kira Pharmaceuticals; Research grant from Alexion Pharmaceuticals

FR-OR084

Urinary Soluble CD163: A Non-Invasive Biomarker of Activity for Lupus Nephritis

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Background: Distinction between lupus nephritis (LN) patients with active inflammation and those with chronic kidney damage is challenging. Soluble CD163 derives from cleavage of the CD163 M2c-macrophage receptor, can be quantified in urine and may reflect intra-renal inflammation. We tested urine sCD163 as a biomarker of LN activity.

Methods: The cross-sectional diagnostic yield and the longitudinal course of urinary sCD163 (usCD163) was assessed in two large LN cohorts. We recruited 113 (Mexican cohort) and 129 (OSU cohort) active LN (aLN) patients with prospective follow-up. Patients with other diseases, inactive LN (iLN), and healthy donors were included as controls. ROC curves were obtained from the cross-sectional data. Then 86 LN flares from the Mexican and the OSS study cohort were followed with repeated samples and response to therapy (RTT) evaluated at 6- and 12-months. Linear mixed models were fitted to evaluate the association between usCD163 and RTT.

Results: The highest levels of usCD163 were found in aLN in the Mexican (1805ng/mmol, 760-4334) and OSU (1358ng/mmol, 811-2356) cohorts compared to iLN (10ng/mmol, 0-40, p<0.001) and other diseases. UsCD163 was higher in class IV Vs. other classes and correlated with the histologic activity index (r=+0.527, p<0.001). A usCD163>100ng/mmol differentiated aLN from iLN with 95% sensitivity and 93% specificity. UsCD163 increased from 6-months pre-flare to flare and then diminished to <500ng/mmol at 12 months in 88% of RTT, while usCD163 remained >500ng/mmol at 12-mo in 88% of non-responders. Diagnostic yield of usCD163 to discriminate 12-month RTT was better than that of currently-used biomarkers (Table 1). After adjusting for other predictors, the usCD163 slope was associated with RTT.

Conclusions: UsCD163 reflects LN renal inflammation and varies over time with LN activity and treatment. Its levels increase pre-flare and then parallel RTT, being independently associated with response to therapy.

Funding: Other NIH Support - National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Government Support - Non-U.S.

Diagnostic performance of usCD163 and serological biomarkers to discriminate 12-month responders from non-responders

	Sensitivity	Specificity	PPV	NPV	+LR	-LR
usCD163<500 ng/mmol	0.88	0.88	0.92	0.83	7.52	7.65
dsDNA-Ab disappearance	0.60	0.65	0.72	0.51	1.69	1.60
C3 normalization	0.60	0.65	0.72	0.51	1.69	1.60
C4 normalization	0.46	0.50	0.61	0.36	0.92	0.93

FR-OR085

Proliferation and Changes in Cellular Signatures in Memory B Cells from Lupus Nephritis Patients Receiving Mycophenolate or Azathioprine Maintenance

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Background: Mycophenolate mofetil (MMF) and azathioprine (AZA) are standard maintenance treatments for lupus nephritis (LN), and recent data suggested lower risk of relapse with MMF maintenance. Memory B cells have been implicated in LN relapse, and miRNA148a, BACH1, BACH2 and PAX5 can regulate memory B cell homeostasis. The effects of MMF and AZA treatment on these memory B cell signatures remain unclear.

Methods: Memory B cells were isolated from clinically stable LN patients receiving low-dose corticosteroid and MMF (n=10) or AZA (n=9) maintenance, and the cell proliferation and intracellular miRNA148a, BACH1, BACH2 and PAX5 expressions on Day 3 after *ex vivo* stimulation were compared.

Results: MMF group showed lower memory B cell proliferation on Day 3 (8.5±1.2%, compared with 20.3±2.0% in AZA group, p<0.001) (Figure 1, A). MMF group also showed lower miRNA148a expression (10-fold decrease compared to health controls (HC), vs. 2-fold decrease in AZA group, p<0.001) (Figure 1, B), but higher BACH1, BACH and PAX5 expression in memory B cells (8.2±0.8, 7.2±1.8, and 7.6±1.1 fold increase compared to HC respectively, vs. 4.0±0.7, 2.9±0.6, and 3.4±0.4 fold increase in the AZA group, p<0.001, MMF vs. AZA) (Figure 1, C).

Conclusions: LN patients receiving MMF maintenance showed reduced memory B cell proliferation and a distinct cellular signature, which may account for the lower risk of relapse observed clinically.

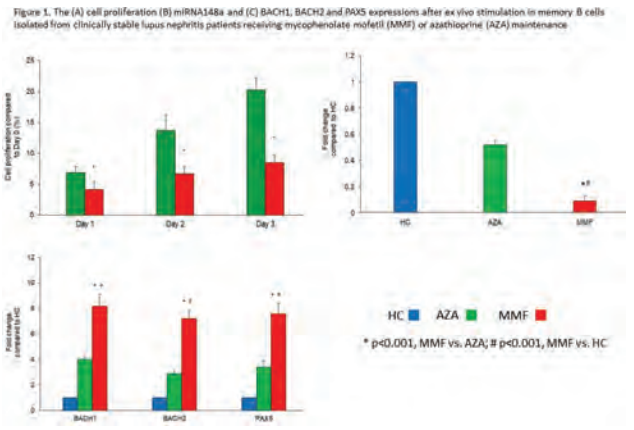

Figure 1. The (A) cell proliferation (B) miRNA148a and (C) BACH1, BACH2 and PAX5 expressions after ex vivo stimulation in memory B cells isolated from clinically stable lupus nephritis patients receiving mycophenolate mofetil (MMF) or azathioprine (AZA) maintenance

FR-OR086

Kidney Biopsy-Based Management of Maintenance Immunosuppression in Lupus Nephritis

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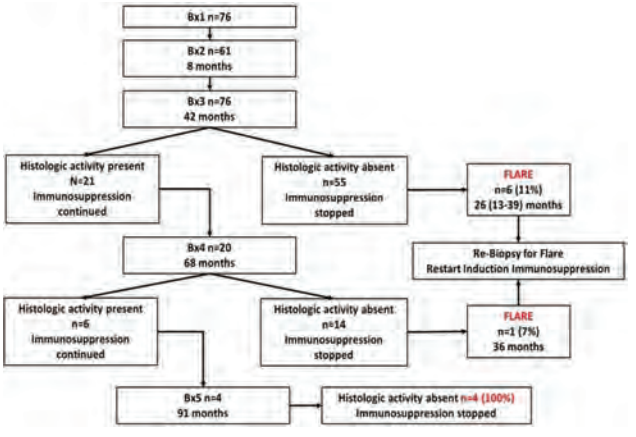
Background: The optimal duration of maintenance immunosuppression (MIS) for proliferative lupus nephritis (LN) is unknown. Management of MIS therapy must balance the risk of LN flare after IS withdrawal against the toxicities of long-term IS. We postulated that information from a protocol kidney biopsy done when withdrawal of IS is being contemplated could attenuate LN flares and improve long-term kidney outcomes, and tested this hypothesis in a large LN cohort.

Methods: A cohort of 76 Caucasian Hispanic SLE patients initiated IS for kidney-biopsy proven (Bx1) LN, was followed prospectively, re-biopsied after induction (Bx2) and again during MIS therapy (Bx3). Bx3 was done after a minimum of 36 months of IS in patients stable for at least 12 months, who had achieved a complete renal response and had no extra-renal SLE activity. Biopsies were graded using the NIH activity index (AI). If AI=0 MIS was tapered off and patients were followed for LN flare. If AI was ≥1 MIS was continued for 24 months, and patients were re-biopsied around month 68 (Bx4). If Bx4 AI=0 MIS was withdrawn; if Bx4 AI was ≥1, MIS was continued for 24 months and the decision to withdraw MIS was based on re-biopsy (Bx5).

Results: Patient outcomes are shown in the Figure. After a median follow-up of 50 months between Bx3 and last visit only 7 patients (9.2%) experienced an LN flare, no patient died, and no patient progressed to ESKD.

Conclusions: These data extend the observation that clinical remission and histologic remission even after several years of IS may be discordant. Management of MIS by histologic activity of protocol biopsies resulted in an LN flare rate of 0.012 events/patient-year, significantly better than the reported flare rates of 0.02-0.81 events/patient-year in international LN cohorts. Protocol kidney biopsies during MIS may help guide treatment duration, minimizing exposure to toxic medications and risk of LN relapse.



FR-OR087

Validation of C3 Glomerulopathy Histopathologic Index in a Large Multicenter Cohort Study

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Background: C3 Glomerulopathy Histopathologic Index (C3G-HI) has been recently proposed as a tool for assessing both activity and chronicity of kidney biopsies in patients affected with C3 glomerulopathy (C3G). The aim of this study was to evaluate the utility and reproducibility of C3G-HI for predicting renal prognosis in C3G.

Methods: Multicenter, retrospective cohort study in 37 nephrology departments belonging to GLOSEN group. All patients fulfilling diagnostic criteria of C3G were included. Kidney biopsies were evaluated by each participating center, and lesions were scored according to the C3G-HI. Demographic, clinical and biochemical parameters of prognostic interest were recorded and used to analyze the main determinants of disease progression and response to different therapeutic regimens.

Results: The study group consisted of 134 patients: 114 C3 glomerulonephritis (C3GN) and 20 dense deposit disease (DDD). Membranoproliferative glomerulonephritis was the most predominant pattern of injury. No significant differences were observed in the parameters of activity across age groups, except for interstitial inflammation that was greater in older patients. However, pediatric patients had a significant lower degree of glomerulosclerosis, tubular atrophy and interstitial fibrosis. No significant clinicopathological differences were observed between C3GN and DDD patients. During a median follow-up of 43 months, 53 patients (40%) developed end-stage renal disease (ESRD). Renal survival was significantly worse in patients in the lower tertiles of Total Chronicity Score. By Cox regression analysis, the main determinants of ESRD were: age (hazard ratio [HR]: 1.019; C.I.95%:1.003–1.034; p=0.016), serum creatinine at baseline (HR:1.131; C.I.95%:1.037–1.235; p=0.006), proteinuria at baseline (HR:1.076; C.I.95%:1.007–1.151; p=0.031), Total Chronicity Score (HR:1.326;C.I.95%:1.118–1.480;p<0.0001) and therapy with mycophenolate mofetil plus steroids (HR: 0.344; C.I.95%: 0.150–0.787; p=0.012).

Conclusions: C3G-HI provides useful predictive information in C3G, being chronicity parameters the main pathologic determinants of renal prognosis. Older age, elevated serum creatinine and proteinuria are the main clinical determinants of renal survival, whereas treatment with steroids and mycophenolate mofetil was associated with better outcome.

FR-OR088

National Observational Study Monitoring the Restrictive Regimen of Eculizumab Therapy in aHUS in the Netherlands

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Background: Nowadays eculizumab is the cornerstone of treatment in atypical hemolytic uremic syndrome (aHUS). The optimal treatment strategy in aHUS is still unknown. In October 2016, a Dutch guideline promoting a restrictive eculizumab regimen in aHUS, was implemented. Here we report the preliminary results of the CUREiHUS study, monitoring this guideline.

Methods: The data of pediatric and adult Dutch aHUS patients included in CUREiHUS study from 1-10-2016 till April 2019 were evaluated. Patients were divided in two groups; a historical cohort containing aHUS patients already on eculizumab treatment before October 2016 (n=13) and aHUS cohort who started with eculizumab after October 2016 (n=24).

Results: In the historical cohort eculizumab could be withdrawn in 5 of the 13 aHUS patients (median duration treatment 6,6 months). Four patients are treated with interval elongation ranging from 3 to 6 weeks). Three patients are on two-weekly interval dosage. In two of the 24 patients who started eculizumab after October 2016 aHUS was diagnosed <3 months and are receiving the standard two-weekly regimen according to the Dutch guideline. In 22 of these 24 aHUS patients the follow up is > 3 months. In 13 patients the eculizumab therapy could be withdrawn. The median duration of treatment was 3,2 months (range 0,3-10 months). The median follow-up after the last gift of eculizumab was 17 months (range 1-35 months). Tapering of eculizumab was seen in 6 patients (interval 3-6 weeks). Additional three patients are treated with the standard two weekly regimen treatment. Relapse of HUS occurred in 14 patients and were treated immediately with eculizumab. In total 8/34 (24%) are at the moment treated with eculizumab biweekly. Eculizumab therapy is withdrawn in 38% (5/13) and 62% (13/21) in patients with onset of aHUS before and after implementation of the guideline, respectively.

Conclusions: The majority of aHUS patients do not need eculizumab biweekly and can be safely switched to an extended interval or withdrawal of therapy. Continuous monitoring and further determination of contributing or predictive factors to relapse(s) are necessary.

FR-OR089

Evaluation of the Endothelin A Receptor Antagonist Zibotentan in Systemic Sclerosis-Associated CKD

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Background: Systemic sclerosis (SSc) causes scleroderma renal crisis (SRC) and chronic kidney disease (SSc-CKD). A previous open label trial of bosentan suggested possible benefit for CKD following SRC. We report the results of a placebo-controlled trial of zibotentan, a highly selective endothelin A receptor antagonist, in SSc-CKD.

Methods: ZEBRA-1 was a double-blind randomised placebo-controlled trial in SSc-CKD (eGFR 45-60 ml/min) comparing oral zibotentan 10 mg/day and placebo over 26 weeks with final assessment at 52 weeks (Clinical Trials NCT02047708). eGFR and candidate urinary molecular markers of SSc-CKD were measured at each time point and safety was a key secondary endpoint.

Results: 16 patients consented with 3 screen failures due to ineligible eGFR on re-testing. 7 patients received placebo and 6 zibotentan. Baseline renal function was well-matched between groups—median eGFR in placebo 51 (44-58); zibotentan 50.5 (49-59). Renal function remained equal at 26 weeks—placebo 53 (37-58); zibotentan 54 (50-58)—but significantly improved in the active treatment group at 52 weeks—placebo 50 (36-55) zibotentan 60.5 (50-74), p=0.0082 (**Figure 1**). Our previous work identified high urinary MCP-1 as a marker of SSc-CKD. In ZEBRA-1 levels declined on zibotentan but not on placebo. Median baseline MCP-1:creatinine (pg/mg/L) was 7.1 (5.2-21.9) in placebo and 5.4 (3.1-28.9) for zibotentan, increased to 8.8 (6.3-33.5) at 26 weeks on placebo and reduced to 4.4 (2.9-11.2) on zibotentan. At 52 weeks MCP-1:creatinine for placebo was 7.5 (6.4-15.8) and was significantly lower at 4.5 (4.1-6.0; p=0.0095) for zibotentan. There were 46 reported adverse events (26 placebo and 20 zibotentan) with 6 serious adverse events (3 in each arm).

Conclusions: This is the first placebo-controlled clinical trial in renal SSc. Zibotentan treatment was safe and associated with improved eGFR and reduced urinary MCP-1 at 52 weeks compared to placebo. These prelimanary results suggest potential benefit from targeting endothelin A in SSc-associated CKD.

Funding: Government Support - Non-U.S.

Figure 1. Impact of zibotentan or placebo on eGFR at baseline, 26 and 52 weeks

FR-OR090

Risk Factors for Infection in Patients with Glomerular Disease: An Analysis of the Cure Glomerulonephropathy (CureGN) Study

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Background: Infections are an important contributor to patient morbidity and mortality in glomerular disease (GD). We sought to understand risk factors for infection among patients in the Cure Glomerulonephropathy (CureGN) study.

Methods: CureGN is a prospective multi-center cohort study of patients with biopsy-proven minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), or IgA nephropathy/vasculitis (IgAN/IgAV). Risk factors for time to first infection-related hospitalization or ED visit were identified using Cox proportional hazards regression. Cox models were adjusted for patient characteristics at enrollment, including demographics [age, race, sex], immunosuppression exposure, GD subtype, number of comorbid conditions, smoking status, time from initial biopsy, and laboratory measurements [eGFR, urine protein to creatinine ratio (UPC), and serum albumin].

Results: Of 1917 participants (43% female, 42% less than 20 years, 67% white), 165 subjects (9%) experienced a first infection over a median follow-up of 15.5 (IQR 7.5 – 24.9) months. In adjusted multivariate models, age < 10 or 20-59 (versus >60) years, black race, and a higher number of comorbidities were significantly (p<0.05) associated with an increased hazard for infection (Table). An association with corticosteroid exposure was of borderline significance (p=0.06).

Conclusions: Among CureGN participants, younger age, black race, and more comorbidities were independently associated with time to first infection-related hospitalization or ED visit. These findings might inform the development of strategies aimed at preventing infection in patients with GD.

Funding: NIDDK Support

	n(%) or median	Univariate Model[a]			Multivariate Model[a]		
		HR	95% CI	p	HR	95% CI	p
Age (y)							
< 10	325 (17.0)	3.21	1.84 - 5.58	<0.0001	2.76	1.19 - 6.39	0.0183
10-19	485 (25.3)	1.32	0.73 - 2.38	0.3522	1.45	0.73 - 2.90	0.2871
20-59	856 (44.7)	1.00	0.57 - 1.75	0.9978	7.68	3.18 - 18.55	<.0001
≥60	251 (13.1)		reference			reference	
Sex							
Male	1094 (57.1)	0.85	0.62 - 1.15	0.2891	0.84	0.58 - 1.20	0.3283
Race							
White	1288(67.2)		reference			reference	
Black	305 (15.9)	1.73	1.18 - 2.54	0.0053	1.65	1.06 - 2.58	0.0267
Other	324 (16.9)	1.07	0.69 - 1.64	0.7678	1.28	0.79- 2.09	0.322
GD Subtype							
MCD	432 22.5)	1.72	1.06 - 2.79	0.0293	0.93	0.48 - 1.82	0.8331
FSGS	467 (24.4)	1.37	0.84 - 2.26	0.2097	1.04	0.57 - 1.90	0.8875
MN	359 (18.7)		reference			reference	
IgAN/IgAV	659 (34.4)	0.98	0.60 - 1.58	0.9264	1.09	0.59 - 2.02	0.7885
GD Duration Prior to Enrollme	2.6 (4.0, 32.5	1.01	1.00 - 1.02	0.0511	1.00	0.99 - 1.01	0.9593
No. of Comorbid conditions[b]	1 (0, 2)	1.11	1.00 - 1.22	0.0435	1.28	1.13 - 1.44	<.0001
Baseline Smoking	455 (23.8)	0.89	0.61 - 1.29	0.533	1.5	0.88 - 2.55	0.136
Immunosuppresion[c]							
Corticosteroids	644 (33.6)	2.21	1.62 - 3.00	<0.0001	1.45	0.99 - 2.11	0.0569
Cyclophosphamide (IV o	27 (1.4)	1.8	0.58 - 5.65	0.3116	0.98	0.23 - 4.16	0.9782
Other[2]	613 (32.0)	1.75	1.28 - 2.38	0.0004	1.34	0.90 - 2.00	0.1546
GFR ml/min/1.73m2[d]	86 (53, 110)	1.00	0.99 - 1.01	0.2263	1.00	0.99 - 1.00	0.1636
Serum Albumin g/dL[d]	3.8 (3.0, 4.2)	1.47	1.24 - 1.75	<0.0001	1.21	0.96 - 1.53	0.1117
UPC mg/mg[d]							
<0.2	376 (21.2)		reference			reference	
0.2 - 1	452 (25.5)	0.86	0.52 - 1.45	0.5802	0.94	0.52 - 1.68	0.8274
1 - 3.5	468 (26.4)	1.02	0.62 - 1.67	0.9351	0.86	0.48 - 1.52	0.5952
> 3.5	480 (27.0)	1.89	1.20 - 2.97	0.0056	1.14	0.63 - 2.07	0.6678

enrollment, b) Including diabetes, hypertension, CAD, aortic aneurysm, valvular heart disease, heart failure, PVD, stroke, asthma, COPD, sickle cell disease, IBD, cirrhosis, GI Bleed, HIV, Hepatitis B or C, sleep apnea, cancer, or psychiatric diagnosis, c) Exposure defined as occurring at or before study enrollment, d) Measurements obtained at or before study enrollment

FR-OR091

Clinical Exome Sequencing for Renal Disorders

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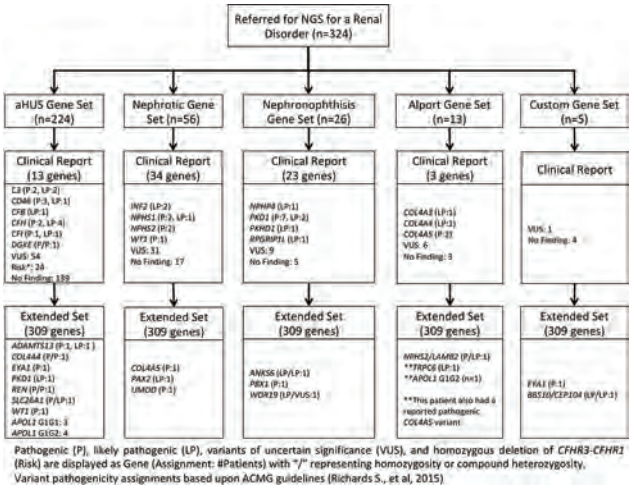
Background: Next-generation sequencing is a valuable tool for evaluating patients with suspected genetic renal disease. Clinical practice relies on targeted gene sets that are ordered based on patient phenotype and physician knowledge of the utility of genetic testing. We report the diagnostic yield of four clinically-established gene sets and employ a retrospective analysis of an expanded set of genes to characterize patients with pathogenic variants in genes that were not part of the ordered gene set.

Methods: In total, 324 patients underwent clinical exome sequencing based on physician-ordered gene sets for atypical hemolytic uremic syndrome (n=224), nephrotic syndrome/FSGS (n=56), cystic renal disease and nephronophthisis (n=26), Alport syndrome (n=13), or a custom panel (n=5). Also, patients referred for aHUS genetic testing were assessed for *CFHR3-CFHR1* deletion by multiplex ligation-dependent probe amplification. Subsequently, all patients underwent retrospective analysis using an extended panel of 309 genes to detect additional potentially pathogenic variants according to ACMG 2015 guidelines.

Results: We identified 42 pathogenic and likely pathogenic variants in 97 of 324 patients and an additional 101 patients with a variant of uncertain significance. *CFHR3-CFHR1* homozygous deletion was detected in 22 aHUS patients without a pathogenic or likely pathogenic variant. Overall, the diagnostic yield of the clinical gene sets was 20% and varied between groups (aHUS=18%, NS=16%, NPHP=46%, AS=23%). The extended gene set revealed 18 additional pathogenic or likely pathogenic variants and 8 patients with a high-risk *APOL1* genotype, increasing the overall yield to 30%.

Conclusions: These results highlight the importance of a broad and collaborative approach between the clinical laboratory and their physician clients that employs additional analysis when the ordered gene set of kidney-disease-causing genes does not return a clinically meaningful result.

Funding: Clinical Revenue Support



FR-OR092

Proliferative Glomerulonephritis with Monoclonal Light Chain Deposits

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Background: Most cases of proliferative glomerulonephritis with monoclonal immunoglobulin (MIg) deposits (PGNMID) are of the IgG isotype (particularly IgG3).

Methods: We describe the first clinicopathologic and proteomic series of PGNMID with MIg light chain (LC) deposits (PGNMID-LC).

Results: This multicenter cohort consisted of 18 patients (median age 60 years, 72% male) who presented with nephritic or nephrotic syndrome. The underlying hematologic condition was MGRS (72%) or multiple myeloma (28%). MIg was identified by serum and urine immunofixation in 61% and 69% of patients, abnormal serum FLC in 77%, and corresponding nephritogenic plasma cell clone in the bone marrow in 88%. Renal biopsy showed MPGN in most patients; glomerular deposition of MIg LC (κ in 67% and λ in 33%) and C3 (100%), without extraglomerular deposits, IgG, IgA, or C1q deposits, by immunofluorescence (IF); and subendothelial (100%), mesangial (100%) and subepithelial (72%) granular electron dense deposits by electron microscopy. Paraffin IF done in 39% of cases showed similar results to IF on frozen tissue. Laser microdissection/mass spectrometry performed on 4 cases of κ PGNMID-LC revealed spectra for Ig κ constant and variable domains and complement alternative pathway (CAP) and terminal complex proteins (particularly C3 and C9) in 3 without spectra for Ig γ, α, μ, λ, or classical complement pathway proteins. In contrast, 6 cases of κ LCDD analyzed did not show spectra for complement proteins. Complement functional assays in 1 patient revealed that a serum fraction enriched with the monoclonal Vl3 LC induced CAP activation in normal human serum. Follow up (median 66 months) was available in 16 patients. Renal response occurred in 6 of 10 patients treated with plasma cell-directed chemotherapy but not in 6 who did not. Hematologic response was evaluable in 8. All 6 with hematologic complete response achieved renal response while the 2 with hematologic partial or no response did not.

Conclusions: PGNMID-LC is a variant of PGNMID with higher detection rate of the nephritogenic plasma cell clone. Proper recognition is crucial as plasma cell clone-directly therapy appears to improve renal prognosis. Activation of CAP by MIg LC likely plays a central role in its pathogenesis.

FR-OR093

Prevalence of Exostosin 1/Exostosin 2-Associated Membranous Lupus Nephritis

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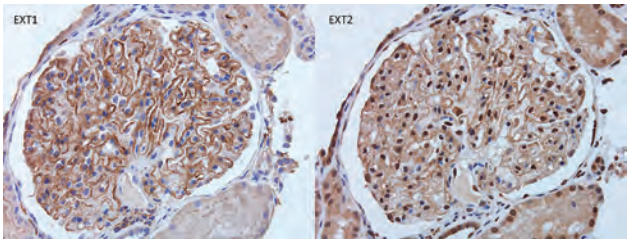
Background: Membranous nephropathy (MN) is classified as primary and secondary. Primary MN is associated with PLA2R antigen in 70-80% cases and THSD7A in 1-5% cases. The target antigens are unknown in 20-25% cases of primary MN and all of secondary MN. Two novel proteins, Exostosin1 and Exostosin 2 (EXT1/EXT2) were recently identified as likely target antigens in a small cohort of MN with an underlying autoimmune etiology (Sethi et al, JASN 2019). In this study, we validate the EXT1/EXT2 findings in a large cohort of patients with lupus membranous nephritis (LMN).

Methods: We studied 374 cases of biopsy-proven LMN from 2003 to 2018. Immunohistochemical studies (IHC) using antibodies against EXT1/EXT2 were performed on paraffin-embedded sections. Laser microdissection and mass spectrometry (MS) were performed on a subset of these cases.

Results: Of the 374 LMN cases, 122 (32.6%) were EXT1/EXT2 positive (figure 1) and 252 (67.4%) were EXT1/EXT2 negative by IHC. Among the 122 cases, 86.9% were female. At presentation, the median serum creatinine and proteinuria were 0.8 mg/dL (range: 0.4-14.7) and 4 g/day (range: 0.4-13.5). Kidney biopsies revealed an average of 16.6 glomeruli (SD: ±10.0) with an average of 1.7 globally sclerotic glomeruli (SD: ±3.3). Interstitial fibrosis and tubular atrophy was minimal (<10%) in 89 (72.9%), mild (11-25%) in 21 (17.2%), moderate (26-50%) in 8 (6.6%), and severe (>50%) in 4 (3.3%) cases, respectively. Further, 30 (24.6%) patients had proliferative features (Class III/IV). MS was performed on 8 cases which showed high spectral counts for EXT1 (average: 88.6, SD:± 37.2) and EXT2 (average: 66.1, SD:± 34.6), thus confirming the IHC findings. Among the 252 EXT1/EXT2 negative cases, 81 (32.1%) patients showed proliferative features. MS was performed in 7 of these 252 cases and was negative for EXT1/EXT2.

Conclusions: We validate our previous findings in a large cohort of LMN. Approximately one-third (32.6%) of LMN patients are positive for EXT1/EXT2, of which approximately one-fourth (24.6%) have coexisting proliferative features.



EXT1/EXT2 positive LMN

FR-OR094

Renal Polyvinylpyrrolidone Deposition from Illicit Drug Use Is Associated with Tubulointerstitial Nephropathy

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Background: Polyvinylpyrrolidone (PVP) is a water-soluble polymer used as an excipient in drugs for oral use. When injected, high molecular weight PVP can neither be metabolized nor excreted by glomerular filtration and will accumulate in the body, resulting in PVP deposition disease. From 2009 to 2016, we observed 25 kidney biopsies with PVP deposition in Norway. All biopsies were from patients with opioid addiction and chronic kidney disease (CKD). The most likely source of PVP in these patients is illicitly injected, PVP-containing opioid substitution drugs intended for oral use.

Methods: We collected clinical data from the Norwegian Kidney Biopsy Registry and from affiliated medical records. We reviewed the biopsies, assessed light microscopy, immunohistochemistry and electron microscopy, and obtained additional pathological parameters using quantitative methods.

Results: The cohort consisted of 25 adults with a mean age of 37. All were suffering from opioid addiction with a known history of injecting opioids regularly, and 22 of them were prescribed opioid substitution drugs. 22 (88%) of the patients had positive hepatitis C virus serology and none were HIV-positive. All patients had CKD with a mean serum creatinine of 205 mole/L and mean estimated glomerular filtration rate of 35 mL/min/1.73m2 (Range 14-58). The majority (64%) had stage 3b CKD. Four patients had slightly to moderately increased urinary protein:creatinine-ratio. All biopsies revealed widespread areas of tubular atrophy and interstitial fibrosis with a mean proportion 64% (Range 32-86). The interstitium of these areas contained single and grouped histiocytes with characteristic bluish vacuoles indicating PVP deposits (fig. 1). Apart from one patient with lupus nephritis, the biopsies showed no evidence of other diseases that could explain the widespread atrophy.

Conclusions: Opioid drug addiction is associated with a high burden of morbidity and various renal diseases. This large case series illustrates that PVP deposition might be a rare cause of chronic renal insufficiency in these patients.

Funding: Government Support - Non-U.S.

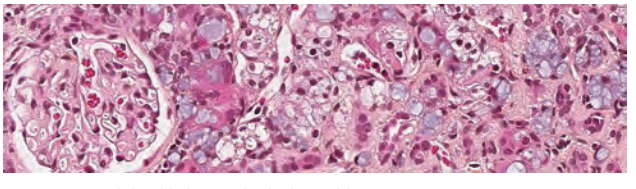

Fig. 1: PVP-containing histiocytes in the interstitium. (H&E)

FR-OR095

Chronic Interstitial Nephritis in Agricultural Communities (CINAC): A Toxin-Induced Proximal Lysosomal Tubulopathy

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Background: There is no consensus on the etiology of CINAC. Heat stress/dehydration and toxic exposure are the two most likely etiologies. There are no direct diagnostic criteria to identify CINAC patients.

Methods: Renal CINAC biopsies (18 Sri Lanka, 10 El Salvador, 1 India, 3 France) were examined by light (LM) and electron microscopy (EM) in comparison to normal kidneys at implantation and 6 and 12 months of calcineurin inhibitor (CNI) therapy, transplant patients on CNI with indication biopsies (n=24), proteinuric nephropathies (n=15), light chain disease (n=4), cases on nephrotoxic drugs (lomustine, clomiphene, lithium, tenofovir, cisplatinum) and CKD of various causes (n=20). A rat study compared histopathology of heat stress with cyclosporine nephrotoxicity.

Results: There was a unique constellation of proximal tubular cell (PTC) findings: cellular/tubular atrophy, cell fragment shedding, weak to non-proliferative capacity of the PTC and dysmorphic lysosomes increased in size and number with a light-medium electron-dense matrix containing dispersed dark electron-dense non-membrane bound "aggregates". Identical lesions were observed in 55-80% of renal transplant protocol biopsies at 6 and 12 months of CNI therapy and in indication biopsies. In implantation biopsies the prevalence was 6%. Several cases of nephrotoxic drugs (lomustine, clomiphene, lithium) and some patients with light chain disease, all conditions linkable to CNI, presented the same lesion. Controls (n=66) of normal kidney, toxic nephropathies (tenofovir, cisplatinum), and overt proteinuric patients of different etiology to some extent could demonstrate the tubular cell changes observed by LM, but not or very rarely those by EM. Rats treated with cyclosporine for 4 weeks developed similar PTC lysosomal alterations, that were absent in a dehydration group.

Conclusions: A sensitive constellation of renal PTC lesions was detected associated with CINAC and CNI nephrotoxicity in several countries, suggesting a common new paradigm where CINAC patients are experiencing a tubulotoxic mechanism similar to CNI nephrotoxicity, the latter also being known as a direct or indirect effect of pesticides.

FR-OR096

Integrative Analysis of Single Cell and Bulk Transcriptomic Data Identifies FSGS Subgroup with Endothelial Cell Activation

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Background: Single cell RNA sequencing (scRNA-seq) generates transcriptomic data at cellular resolution allowing the identification of both known and novel cell-type specific markers. These markers enable to investigate the role of distinct cell types in kidney disease. In this study, we used glomerular endothelial cell type markers identified by scRNA-seq to analyze micro-dissected glomerular mRNA data from FSGS patients in NEPTUNE Consortium.

Methods: As part of the Kidney Precision Medicine Project (KPMP), single cell analysis (10x Chromium) was performed on unaffected kidney tissue from 16 tumor-nephrectomy and 10 surveillance transplant biopsy samples. Integrated analysis was performed on the single cell data from these 26 reference datasets including normalization, batch correction, unsupervised clustering and cell-specific marker identifications. Cell specific markers were used to cluster glomerular RNA transcriptomic data from 74 NEPTUNE FSGS patients followed by functional analysis.

Results: 37 kidney cell-type clusters were identified including glomerular, tubular and immune cell types as well as 3 distinct endothelial cell types (arteriolar, peritubular and glomerular). The glomerular endothelium-specific markers were then used to sort bulk tissue gene expression from FSGS patients resulting in two main groups, 1 (n=44) and 2 (n=30). Group 2 demonstrated significant enrichment of glomerular endothelial activation markers. Higher hazards of a composite progression endpoint (>40% reduction eGFR reduction or ESRD) indicated poor prognosis for Group 2. Differentially expressed genes (DEGs) up-regulated in group 2 were involved in type-1 interferon response, ras-protein signaling, and response to endothelin receptor antagonists in model systems.

Conclusions: Glomerular endothelial marker genes identify a subgroup of patients with poor prognosis and establish a molecular correlate for the endothelin treatment response observed in clinical trials in FSGS.

Funding: NIDDK Support

FR-OR097

Evaluation of a Computer-Aided Quality Assessment of Whole Slide Images for Computational Pathology

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Background: The establishment of computational image analysis has uncovered inconsistency in quality of whole slide images (WSI) across pathology laboratories, due to pre-analytic (fixation and tissue processing) and analytic (cutting, staining and scanning) variations. While pathologists train themselves to read through artifacts, computational pathology systems are not trained to adjust to such variability. Our group developed a pipeline aided by an open-source computer-based quality control tool (HistoQC) to identify heterogeneity, qualify WSI for computational image analysis (see Figure 1-A), and output tissue masks (see Figure 1-B) that exclude the artifacts. The aim of this study is to test whether HistoQC can efficiently and reliably qualify WSI based on artifact detection.

Methods: 1814 WSIs (458 H&E, 470 PAS, 438 silver, 448 trichrome) from 512 NEPTUNE digital renal biopsies were analyzed by HistoQC and reviewed for disqualification. Disqualified (extreme outliers) WSIs and 10% of the qualified WSIs, randomly selected, were manually scored by 2 reviewers for the presence of glass slide, tissue, and scanning artifacts. Principal component analysis (PCA) of HistoQC metrics and logistic regression was used to evaluate the association between HistoQC and human assessment.

Results: 151 WSIs were considered extreme outliers by HistoQC. Only 318 (151 disqualified + 167 qualified) of the 1814 WSIs required human review. PCA components based on HistoQC metrics demonstrated good to strong prediction of human identified artifacts (C-index range 0.64-0.83, see Figure 1-C).

Conclusions: HistoQC can aid in the identification of pre-analytic and analytic artifacts and of variations in WSI presentation. Furthermore, this pipeline may enable efficient curation of digital pathology repositories and reduce computational image analysis variability.

Funding: NIDDK Support, Veterans Affairs Support

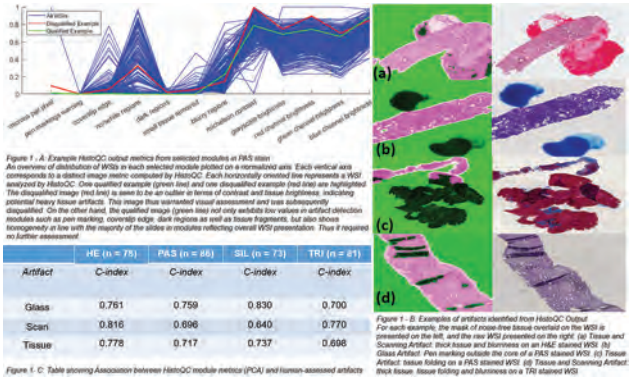

Figure 1 - A: Example HistoQC output metrics from selected modules in PAS stain

	HE (n = 75)	PAS (n = 86)	SIL (n = 73)	TRI (n = 81)
Artifact	C-index	C-index	C-index	C-index
Glass	0.761	0.759	0.830	0.700
Scan	0.816	0.696	0.640	0.770
Tissue	0.778	0.717	0.737	0.698

Figure 1 - C: Table showing Association between HistoQC module metrics (PCA) and human-assessed artifacts

Figure 1 - B: Examples of artifacts identified from HistoQC Output

FR-OR098

Assessment of Renal Function by Advanced Light Sheet Microscopy and 3D Image Analyses: Quantification of Albumin Filtration/Reabsorption at the Single-Nephron Level in Rodents

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Background: Drug development in diabetic kidney disease (DKD) and chronic kidney disease (CKD) is halted by poor translatability of preclinical animal models. Using 3D imaging techniques, we aimed to develop a new method for quantification of renal function, glomerular filtration and proximal tubular albumin absorption to assess the morphology and functionality of populations of single nephrons in preclinical rodent models of kidney disease.

Methods: Healthy mice and rats as well as 5/6 nephrectomised (Nx) rats were perfused with fluorescently labelled lectin, albumin, and 10 kDa dextran under terminal anesthesia, and intact kidneys were cleared for scanning by light sheet microscopy (LSM). Using 3D image analysis, distribution of glomerular size and nephron morphometry were determined, while proximal tubular albumin absorption was quantified based on albumin-intensity. To characterize kidney function using standard methodologies, 2D histology, plasma, and urine analyses were applied.

Results: In healthy mice and rats, LSM and 3D nephron reconstruction revealed intact nephrons with glomeruli connected to proximal then distal tubules extending from the cortex into the medulla. Juxtaglomerular proximal tubules were clearly delineated by tubular epithelial cells that were fluorescently labelled by absorbed albumin and followed by tubular epithelial cells labelled by dextran. In sharp contrast, imaging analyses suggested functional defects in the kidney remnants of 5/6 Nx rats. Nephrons in 5/6 Nx rats appeared fragmented and with limited tubular absorption of albumin and dextran, which obstructed tubular tracking from the cortex to the medulla. These findings were corroborated by albuminuria, plasma urea and creatinine, and 2D renal histopathology in 5/6 Nx vs sham-operated rats.

Conclusions: Development of advanced microscopy and 3D imaging technologies allows for assessment of renal function at a single-nephron level and by characterization of populations of single nephrons. Thereby, this 3D imaging technique can support 2D end-point histological analyses and functional endpoints in rodent models to refine the use of rodent models to study disease mechanisms and test novel therapies for DKD and CKD.

FR-OR099

Visualizing the N-Linked Glycome within Human Kidney Biopsies Using Mass Spectrometry Imaging

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Background: The current study is a part of the NIDDK Kidney Precision Medicine Project (KPMP). The observed alterations in protein glycosylation attributed to disease development has stemmed major interest in studying glycans (e.g., higher HbA1c in type 1 diabetes is associated with changes in the serum N-glycome). Currently, a limited number of methods are available for interrogating clinical tissue samples for variations in protein glycosylation. An emerging approach is on-tissue enzymatic N-glycan releasing (OtER) followed by matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI), which positionally conserves the location of N-glycan moieties and allows their composition to be registered to histological information. This method can be performed on archival, formalin-fixed paraffin-embedded (FFPE), clinical sample tissue.

Methods: We optimized the OtER MALDI-MSI workflow on FFPE preserved health human biopsy tissue provided by the KPMP. Tissue was sectioned and mounted on conductive glass slides, deparaffinized by washing with xylenes, rehydrated with EtOH:H_2O solutions, and then antigen retrieved (citraconic buffer). On-tissue application of Peptide-N-Glycosidase F was applied with a robotic sprayer, followed by incubation in a humidified environment (40 ºC). Finally, matrix (cyanohydroxycinnamic acid) was applied to samples and MALDI was performed.

Results: Several high mannose, hybrid, and paucinomannose N-glycans were spatially detected in the human kidney tissue, and many showed co-localization with different histological features, as revealed through pre- and post-MALDI autofluorescence and H&E images. MALDI performed using the high mass resolution 15T Fourier transform ion cyclotron resonance MS gave confident matches of N-glycans in the ChEBI database and with those previously reported. We were able to separate isomeric N-glycans using pre-mass analysis ion mobility separation in our MALDI-MSI method.

Conclusions: This highlights the value of using this workflow for mapping the N-glycome, where the location of species can be registered to different anatomical compartments and cell types within the human kidney. We anticipate this method can provide the ability to distinguish diseased from healthy kidney biopsies, by identifying aberrant N-glycosylation patterns.

Funding: NIDDK Support

FR-OR100

Iterative Indirect Immunofluorescence Imaging for Tissue (4iT): The First Step Towards Spatial Proteomic Maps

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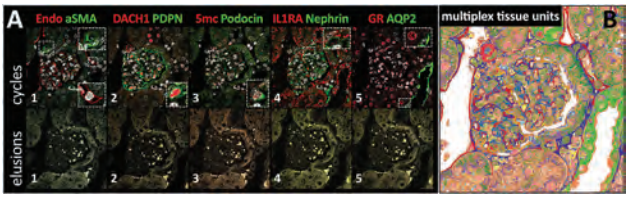
Background: With the rapid development of multi-omics techniques, there is an increasing need for methods that can localize proteins with high spatial resolution. This is particularly important in a complex system like the kidney; where a large number of interacting cell-types coexist.

Methods: We present 4iT, a new method for highly multiplexed protein measurements in paraffin-embedded tissue based on the principle of cyclic immunolabelling, including conventional indirect immunofluorescence, high-resolution fluorescence imaging, and elusion of primary and secondary antibodies. Five glomeruli and periglomerular spaces were serially imaged per mouse (n=4 controls and n=8 crescentic glomerulonephritis) for a total of 40 cycles (1 antibody per cycle). Multiplexed protein maps were generated using an in-house unsupervised integration tool based on artificial neural networks that identified shared and unique pixel profiles.

Results: We successfully identified endothelial cells, mesangial cells, basement membranes, podocytes, parietal epithelial cells, proximal tubuli, collecting ducts, immune cells, fibroblasts, innervation, subcellular units (ie. lysosomes, ER and mitochondria), and dynamic changes of extracellular matrix, integrins, tight-junctions, extra/intracellular receptors, phosphorylation sites, cell activation, and post-translational modifications. Multiplexed protein maps generated functional/pathological clusters based on proximity profiles.

Conclusions: 4iT can be used to identify functionally relevant single-cell states in paraffin-embedded tissue, providing a new roadmap for molecular tissue analysis with high spatial resolution, and thereby personalized medicine.



4iT generates complex proteomic maps with high spatial resolution. (A) Example of 5 cycles with a total of 10 proteins identified in different kidney cells - first row shows stainings and second row shows the same glomerulus after elusion. (B) Proteomic map after deep learning and cluster/proximity analyses.

FR-OR101

Effect of Automated Wearable Artificial Kidney (AWAK) Device on Toxin Clearance and Safety in Peritoneal Dialysis Patients

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Background: Patients undergoing dialysis face mobility and logistic challenges due to limited progress in dialysis technological advancement. Dialysate regeneration through use of sorbent technology led to the development of Automated Wearable Artificial Kidney Peritoneal Dialysis (AWAK PD) device.

Methods: The first-in-human (FIH) study was conducted in Singapore between March 2016 and October 2018. The study aimed to evaluate safety of AWAK PD in 15 prevalent peritoneal dialysis (PD) patients who underwent up to 9 AWAK PD therapies over 3-4 consecutive days. Incidence of adverse event was monitored and serum and dialysate samples were collected. Study also aimed to examine weekly peritoneal urea. Patients were followed up weekly up to a month.

Results: Of 15 patients with median age 65.5 [Range Min, Max: 35, 73] years, male (67%), Chinese (80%), presence of coronary artery disease (27%), anuria (33%), with a median PD duration of 21 [4-147] months, none experienced any serious adverse events during or post AWAK PD therapy. The reported adverse events included abdominal discomfort (71%), presence of fibrin in the drain (36%) and bloating (36%). There was no significant difference in pre and post therapy weight. All patients who completed at least 1 valid therapy (n=14) achieved weekly peritoneal $Kt/V_{urea} \geq 1.7$ with median weekly peritoneal Kt/V_{urea} =3.04 [IQR: 2.19-4.75]. Significant reduction in solute concentrations was observed with AWAK PD therapy **(Table 1)**. Stable serum sodium (136[134-139] mmol/L), potassium (4.0[3.6-4.4] mmol/L), and bicarbonate (24.2[23.1-25.5] mmol/L) levels were reported during the study.

Conclusions: This FIH study showed that AWAK PD device was shown to be safe on 15 PD patients with appropriate solute clearance and no observed water retention.

Funding: Commercial Support - AWAK TECHNOLOGIES PTE LTD, Government Support - Non-U.S.

Serum Solute Concentration

Solutes	Pre-AWAK PD	Post-AWAK PD	p-value^
	Median (Range Min, Max)		
Urea*	20.8 (18.2-21.8)	14.9 (13.1-15.4)	0.001
Creatinine#	976 (727-1058)	668 (540-827)	0.001
Phosphate*	1.7 (1.5-1.8)	1.5 (1.3-1.7)	0.03
B2-microglobulin*	29114 (23753-36540)	26339 (26339-34192)	0.048

^pre-post therapy serum solutes level (Wilcoxon signed-ranks test); *: mmol/L; #: µmol/L

FR-OR102

Inhibition of Hyperglycolysis in Mesothelial Cells Prevents Peritoneal Fibrosis

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Background: Progressive peritoneal fibrosis is a dreaded problem for patients receiving peritoneal dialysis (PD) because it has no reliable treatment. There also are disagreements about the identification of mechanisms that initiate and sustain peritoneal fibrosis. To overcome these problems, we developed a strategy that prevents peritoneal fibrosis by suppressing PD-stimulated mesothelial to mesenchymal transition (MMT).

Methods: We evaluated single-cell transcriptomes of mesothelial cells obtained from normal peritoneal biopsy and effluent from PD-treated patients. We then examined the metabolic reprogramming in the peritoneal fibrogenesis in mouse model and mesothelial cells using metabolomics and cellular respiration tests. We finally developed a triad of AAV1 encoded microRNA therapy, and evaluated its therapeutic potential to treat peritoneal fibrosis.

Results: We analyzed 96,446 single cell transcriptomes including cells dissociated from normal peritoneum, peritoneal cells from effluent of short-term PD and from

long-term PD patients. We found the expression of glycolytic enzymes was increased during the development of MMT. Using gene expression profiling and metabolomics analyses, we confirmed that PD fluid induces metabolic reprogramming, characterized as hyperglycolysis in peritoneum. We found that transforming growth factor β1 (TGF-β1) can substitute for PD fluid to stimulate hyperglycolysis. The mechanism involves suppressing mitochondrial respiration in mesothelial cells. Blockade of hyperglycolysis with 2-deoxy-glucose inhibited PD fluid-induced profibrotic cellular phenotype and fibrogenesis in mice. We developed a triad of adeno-associated viruses that overexpresses microRNA-26a and microRNA-200a plus inhibitor of microRNA-21a, which targets both hyperglycolysis and fibrotic signaling. Intraperitoneal injection of the viral triad in mice significantly inhibited the development of peritoneal fibrosis induced by PD fluid.

Conclusions: We conclude that hyperglycolysis is responsible for MMT and peritoneal fibrogenesis. This aberrant metabolic state can be principally corrected by modulating microRNA levels in the peritoneum. These results could provide a novel therapeutic strategy to combat peritoneal fibrosis.

Funding: Government Support - Non-U.S.

FR-OR103

Identifying MiRNA Biomarkers for Diagnosis of Encapsulating Peritoneal Sclerosis

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Background: Encapsulating peritoneal sclerosis(EPS) is a serious complication of chronic peritoneal dialysis (PD). Late diagnosis is associated with high mortality. With the advance of new diagnostic technology, such as microRNA (miRNA), we attempted to develop a non-invasive test to assist the diagnosis of EPS.

Methods: We examined miRNAs expression profiles of PD fluids from patients with or without EPS by high-throughput and quantification real-time PCR array. We used the high-throughput miRNA array cards as primary screen tool for analysis. The analysis of miRNA was conducted using the Running TaqMan® Low Density Arrays on Vii7 RealTime PCR Systems. Candidate miRNAs were selected to verify in another group of patients by single qRT-PCR assay. The model for EPS prediction was developed by multiple logistic regression.

Results: We collected overnight PD fluids from 72 non-EPS (controls) and 25 EPS patients. The **screening set** included PD fluids from 28 patients (20 of non-EPS vs. 8 of EPS-ongoing cases). We compared the ratio values of two miRNA expression levels between EPS and non-EPS samples. Eight candidate miRNAs were selected. The **training set** was conducted using 69 samples (52 of non-EPS vs 17 of EPS-ongoing) to produce the good area under curve (AUC) value of diagnostic miRNA classifier. The miRNA combination ratios with the top five ROC values were selected to calculate the combined AUC by logistic regression. The value of AUC to distinguish EPS from non-EPS with five miRNAs in PD fluid was 0.9723 (Figure 1). From results of the training set, six different miRNA expressions and two ratios of two miRNA expressions in the PD fluid showed significant difference between EPS and non-EPS patients.

Conclusions: We identify a miRNA classifier with the combination of top five miRNAs' expression in PD fluids to assist the diagnosis of EPS.

Funding: Government Support - Non-U.S.

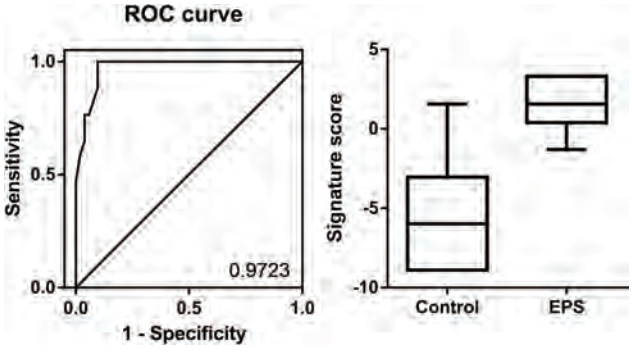

Figure 1. The ROC analysis of the EPS miRNA classifier with the combination of top five miRNAs expressions and the box plots showed that the score of non-EPS and EPS miRNA classifier distribution.

FR-OR104

Lung Ultrasound B-Lines and Oxygen Status in Automated Peritoneal Dialysis Patients

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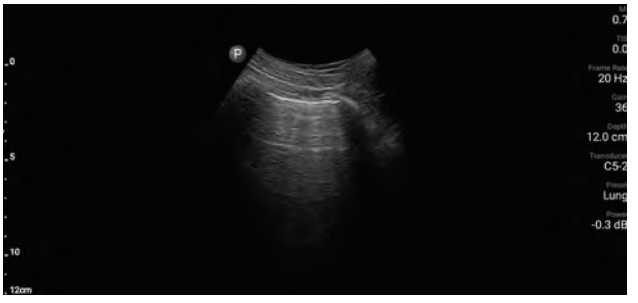
Background: Patients undergoing automated PD (APD) are frequently fluid overloaded, while anuric dialysis patients with low fluid removal depict uncontrolled hypertension, LVH and worse survival. In this report, we aim to explore the correlation of overhydration (B-lines) as detected using lung ultrasound (LUS) in APD patients with their vital signs and weight.

Methods: Fourteen chronic APD patients were recruited at the Dialysis Clinic Inc. (DCI) PD center in Albuquerque, NM and completed their first visit of the pilot study LUMIFY-PD (Lung Ultrasonography to Measure Interstitial Fluid in Your Peritoneal Dialysis patients). Demographics, personal history, and laboratory values were collected from their electronic medical records. A pre-trained physician performed LUS with a handheld scanner (Phillips©Lumify, 2-5 MHz phased-array probe). Examination of the anterolateral chest was performed with longitudinal LUS scans (28 total sectors per exam, supine position). LUS exams were scored for the presence and number of B-lines.

Results: Study participants had a mean age of 41.5 (± 3.4) years and were mostly males (52.9%), whites (57.1%) and Hispanics (50%). They were on PD for a mean of 9.9 (± 7.3) months. The two main causes of kidney disease were DM and hypertension. 57% exhibited at least 1 B-line in their LUS while 21.4% had mild lung congestion (at least 3 B-lines) (Figure). All patients with detectable B-lines had normal physical exams. A statistically significant correlation was found between age and number of antihypertensives (p=0.05) as well as between number of B-lines in LUS and % of arterial oxygen saturation (p=0.002). A negative correlation was found between number of B-lines and residual renal function volume (Pearson correlation -0.65).

Conclusions: In this report the number of LUS B-lines correlated with oxygen saturation and residual renal function volume. Larger studies are needed. Portable LUS can optimize the assessment of prescribed "dry weight" and thus improve outcomes of incident APD patients.

Funding: Other NIH Support - DCI through CTSC



A study participant with B-lines in lung ultrasound

FR-OR105

Initiation of Peritoneal Dialysis in Patients with Cardiorenal Syndrome Reduces Subsequent Hospitalization

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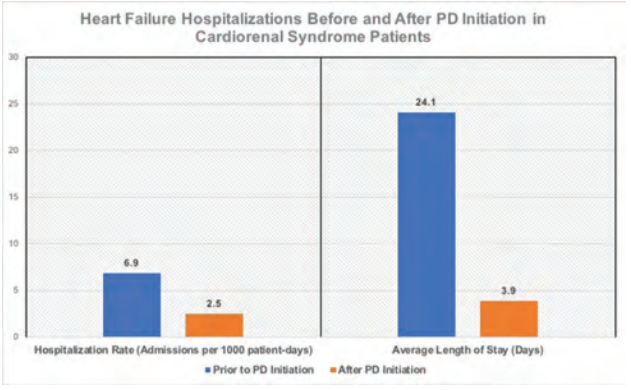
Background: Inotropic dependence and diuretic resistance in patients with cardiorenal syndrome (CRS) leads to frequent hospitalizations and is associated with high mortality. Peritoneal dialysis (PD) offers a smoother hemodynamic profile with effective volume removal for these patients. There is little data on this approach in the North American literature. The aim of our study was to determine if volume overloaded CRS patients on maximal doses of diuretic therapy had reduced heart failure hospitalization following PD initiation.

Methods: We reviewed CRS patients receiving a bedside catheter and starting PD urgently within 2 weeks of insertion at the University Health Network from January 1, 2013 to December 31, 2018. Data for heart failure-related hospitalizations and length of stay 6 months before and after PD initiation was collected. Patients who died, switched to hemodialysis or were transferred to another facility within 6 months of starting PD were excluded from analysis of the hospitalization rates.

Results: We identified 31 CRS patients who had a beside PD catheter inserted. The average age of patients was 66.0 ± 13.0 years. There were 7 (22.6%) deaths and 4 (12.9%) transfers to other programs or hemodialysis within 6 months of catheter insertion. After exclusion, we analyzed the hospitalization and length of stay data for 20 patients. The hospitalization rate 6 months prior to PD initiation was 6.9 admissions per 1000 patient-days. This decreased to 2.5 admissions per 1000 patient-days after PD initiation (Figure 1). Additionally, there was also a striking reduction in the average length of stay (24.1 to 3.9 days; p= .001).

Conclusions: Volume overloaded CRS patients receiving maximal diuretic therapy have lower hospitalization rates and shorter stays after PD initiation. Adopting quality improvement strategies such as bedside PD catheter insertions can serve as a means to facilitate acute start dialysis in this population.



FR-OR106

Associations Between Body Mass Index, Kt/V, and Outcomes Among Patients Treated with Peritoneal Dialysis

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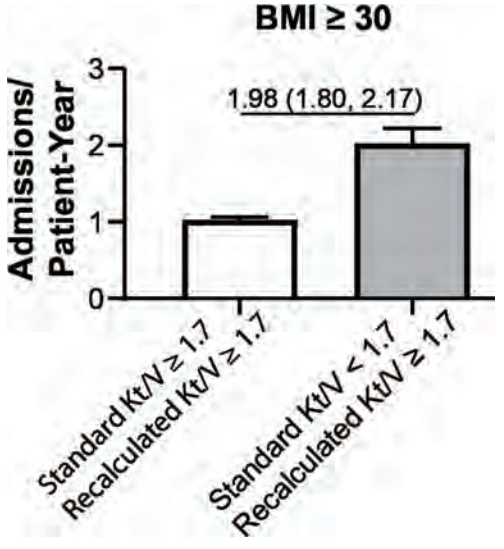
Background: Among patients treated with peritoneal dialysis (PD), achievement of Kt/V ≥ 1.7 indicates adequate dialysis. The volume of urea distribution (V) is based on bodyweight. Because the water content and metabolic activity of fat mass differ from that of lean, V may be over-estimated in obese patients, such that Kt/V under-estimates adequacy. Recalculation of V based on lean body mass might enable more accurate estimation of dialysis adequacy in such patients.

Methods: Data were derived from deidentified records of adults (body mass index [BMI] 15-45 kg/m^2) who initiated PD with a large dialysis organization Jan 2016 – June 2018. Patients were followed from PD start until death, censoring, or study end (Dec 2018). Kt/V was calculated on the basis of bodyweight or estimated lean body mass. Associations between time-updated values of BMI, Kt/V, and outcomes were estimated using Poisson models that included an interaction term for BMI and Kt/V.

Results: At baseline, among 16,443 patients, mean BMI was 28.1 ± 5.8 kg/m^2, Kt/V was 2.4 ± 0.7, and 16.1% of patients had Kt/V < 1.7. Across BMI categories, lower Kt/V was associated with higher hospitalization rate; no interaction between Kt/V and BMI was observed (p>0.05). Similar results were obtained when Kt/V was recalculated on the basis of estimated lean body mass. Among patients with BMI≥30 and recalculated Kt/V ≥ 1.7 but standard Kt/V < 1.7, hospitalization rates were 1.98-fold (95% confidence interval 1.80 – 2.17) higher than among patients with Kt/V ≥ 1.7 by both measures.

Conclusions: Associations between Kt/V and outcomes do not differ on the basis of BMI. Calculation of Kt/V on the basis of estimated lean body mass may over-estimate dialysis adequacy, with potential negative consequences for patient outcomes.



FR-OR107

Prognostic Significance of Carotid Plaque Presence in Peritoneal Dialysis Patients and Its Association with the Apolipoprotein B/Apolipoprotein A1 Ratio

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Background: Atherosclerosis has been reported as a risk factor for cardiovascular disease in the general population. As a phenotype of atherosclerosis, carotid plaque and its influence factors are rarely discussed,especially among dialysis patients. The study aimed to investigate the prognosis-predictive significance of carotid plaques in patients on peritoneal dialysis (PD), and explore risks factors for carotid plaque presence.

Methods: It was designed as an observational, prospective study. Patients that had undergone stable peritoneal dialysis for at least 3 months were recruited and divided into two subgroups: group with carotid plaques and group without carotid plaques. Cox regression model was used to identify independent predictors of all-cause mortality, cardiovascular events and cardiovascular mortality. Risk factors correlated to the plaque-occurrence were explored by logistic regression and verified by receiver operating characteristic curve (ROC) analysis.

Results: A total of 233 PD patients (141 men) with a mean age of 56.4±16.1 years were recruited. The cohort was followed for up to 86 months (median: 36.3 months; interquartile range: 21.3 months). In the multivariable Cox regression analysis, the carotid plaque presence turned out to be an independent risk factor both of cardiovascular events (HR:2.420; 95%CI:1.157-5.064; p=0.019) and cardiovascular mortality (HR:3.346; 95%CI:1.079-10.375; p=0.036). Multivariable logistic regression showed that the apolipoprotein B/apolipoprotein A1 ratio was significantly associated with the presence of carotid plaques. ROC analysis indicated that the AUC of the apoB/apoA1 ratio was 0.640, and it was higher than that of the traditional lipid metabolism index, the non-HDL-C/HDL-C ratio (p=0.012).

Conclusions: Carotid plaque presence can predict cardiovascular events and cardiovascular mortality in PD patients. The ApoB/ApoA1 ratio is significantly correlated to the plaque presence and it can be a more sensitive monitoring marker for predicting the presence of carotid plaques in this population than traditional lipid metabolism parameters.

Funding: Other NIH Support - National Natural Science Foundation of China (NSFC)

FR-OR108

Peritoneal Dialysis (PD) Modality and Interference in Daily Life: Results from the PDOPPS

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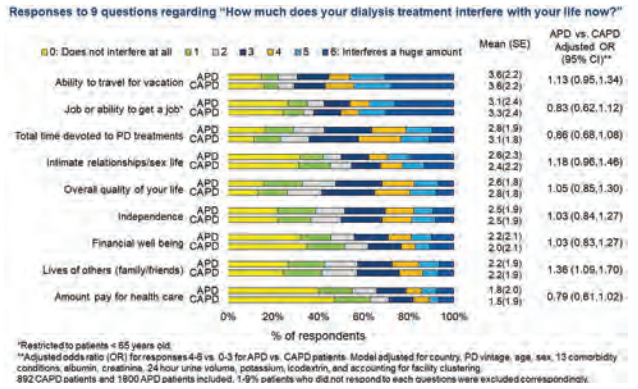
Background: Patient-reported outcomes (PROs), including quality of life and life participation activities, are important considerations for patients receiving peritoneal dialysis. The relative effects of automated (APD) vs. continuous ambulatory (CAPD) modalities on PROs remain controversial.

Methods: We analyzed cross-sectional clinical and patient-reported data from the PD Outcomes and Practice Patterns Study (PDOPPS; 2014-2017; Australia, Canada, Japan, New Zealand, UK, US). Patients rated dialysis interference with 9 aspects of daily life on a 7-point Likert scale. Linear and logistic regressions were used to estimate associations of PD modality with the interference item scores (mean and grouped as response levels 4-6 vs 0-3), KDQOL Mental Component Summary (MCS), Physical Component Summary (PCS) scores, and the 10-item CES-D depression screening scale (scale scores grouped as ≥10 vs <10), adjusted for demographic, comorbidity, and treatment variables.

Results: The analysis included 1800 APD and 892 CAPD patients. After adjustment, APD (v. CAPD) patients had 0.04 higher mean interference score (95% CI=-0.09, 0.18), 0.05 lower MCS (-1.19, 1.09), 0.73 lower PCS (-1.73, 0.26), and 1.17 (0.94, 1.45) higher odds of CES-D ≥10 vs <10. APD (v. CAPD) patients reported less interference with employment (adjusted OR=0.83, 95% CI=0.62-1.12) and total PD time (0.86, 0.68-1.08), and greater interference with intimacy (1.18, 0.96-1.46) and the lives of family/friends (1.36, 1.09-1.70).

Conclusions: Summary PROs were generally similar for APD and CAPD patients, potentially due to non-randomized modality choice. However, domain specific differences in interference scores were observed that may be informative for patients when choosing PD modality type. Across both modalities, PD appears to interfere for the majority in domains of travel and employment suggesting that these are important areas to reduce the overall interference of PD with life activities.

Funding: Commercial Support - Baxter



FR-OR109

International PD Training Practices and the Risk of Peritonitis

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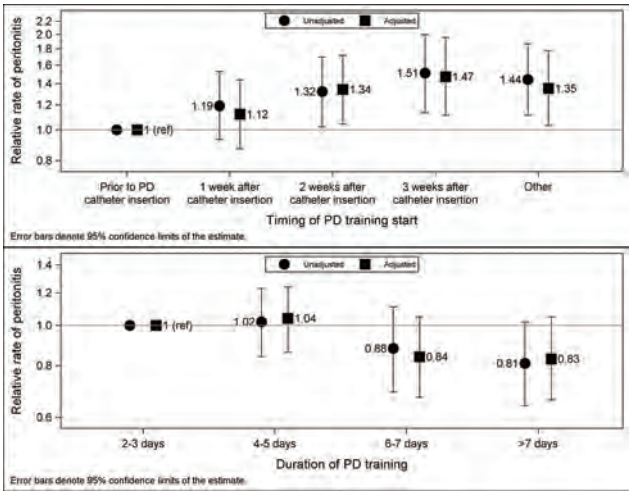
Background: Patient training for peritoneal dialysis (PD) is vital in reducing the risk of complications, including PD-related peritonitis. We describe variation in training practices across countries and assess their impact on peritonitis risk.

Methods: Using Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS; 2014-2017) data from Australia and New Zealand (A/NZ), Canada (CA), Japan (JP), Thailand (TH), the UK, and the US (non-large dialysis organization facilities), we report variation in facility-reported PD training practices and estimate associations with peritonitis using proportional rates models adjusted for patient and facility factors.

Results: 183 out of 204 facilities with peritonitis data available returned a PDOPPS Unit Practices Survey (US, n=83; other, n=14-26). Nearly all facilities reported using unit-affiliated training nurses only (UK, 72%; other, >95%), a standard training curriculum (UK, 65%; JP, 79%; other, >90%), individualized training (TH, 41%; other, >88%) and a single nurse per patient (JP, 28%; A/NZ, 71%; other, >89%). All facilities required successful technique demonstration; 50% (US, 88%; other, 4-36%) required a written test, and 55% (CA, JP, UK, 24-40%; A/NZ, TH, US: 57-70%) required an oral test. Peritonitis rate was associated with the timing of training relative to catheter insertion (HR=1.12 [95% CI=0.87, 1.44], HR=1.34 [1.04, 1.72], and HR=1.47 [1.11, 1.96] for 1, 2, or 3 weeks after catheter insertion, respectively, vs. prior to insertion; p<0.01 for trend) and longer duration of training (HR=1.04 [0.86, 1.24] and HR=0.84 [0.69, 1.02] for 4-5 and ≥6 days, respectively, vs. 2-3 days; p=0.06 for trend).

Conclusions: Variation in PD training practices was seen across PDOPPS countries. Given the patient-centered nature of PD, earlier and longer training periods may reduce peritonitis risk.

Funding: NIDDK Support, Other U.S. Government Support, Commercial Support - Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details, see https://www.dopps.org/AboutUs/Support.aspx., Private Foundation Support, Government Support - Non-U.S.



FR-OR110

Combination of Once Weekly Hemodialysis with Peritoneal Dialysis Is Associated with Lower Mortality Compared with Peritoneal Dialysis Alone: A Longitudinal Study

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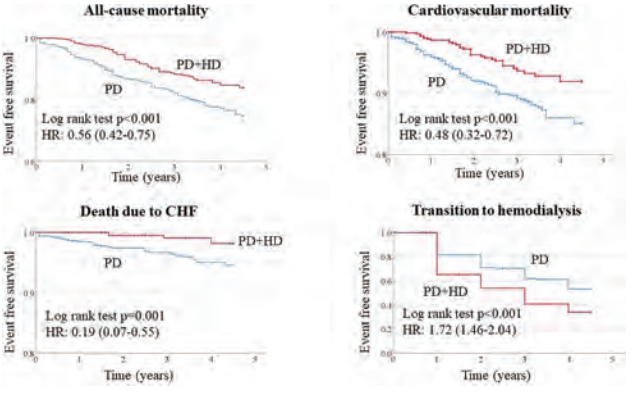
Background: Combination of once weekly hemodialysis with peritoneal dialysis is a unique type of renal replacement therapy available in Japan. Outcomes of this therapy compared with peritoneal dialysis alone has not been reported in a large cohort.

Methods: This is a longitudinal study based on Japanese Renal Data Registry (JRDR). Those on peritoneal dialysis from 2010 to 2014 in the JRDR database were included. The end of observation period was at the end of 2015. Exposure of interest was combination of once weekly hemodialysis with peritoneal dialysis compared with peritoneal dialysis alone. Outcomes were all-cause mortality, cardiovascular mortality, and death due to congestive heart failure. Those who initiated combination therapy from 2011 to 2014 were matched with those on peritoneal dialysis alone by propensity score derived from the data of previous year. The data were analyzed using Kaplan-Meier curves and Cox regression models.

Results: Six hundred and eight patients on combination therapy were matched with 869 on peritoneal dialysis alone. During median follow-up of 2.5 years, there were 224 death, 123 cardiovascular death, and 35 death due to congestive heart failure. All-cause mortality (HR [95% CI]: 0.56 [0.42-0.75]), cardiovascular mortality (HR: 0.48 [0.32-0.72]), and death due to congestive heart failure (HR: 0.19 [0.07-0.55]) were significantly lower among combination therapy group. Transition to hemodialysis was significantly earlier in combination therapy group (HR: 1.72 [1.46-2.04]). There was no effect modification by age, dialysis vintage, diabetic status, or baseline urine volume. The decrease in body weight was larger in combination group (p<0.001 by mixed effects model) in combination therapy group, suggesting better fluid removal.

Conclusions: Combination of once weekly hemodialysis with peritoneal dialysis was associated with lower mortality compared with peritoneal dialysis alone.



FR-OR111

Aptamer-Based Plasma Proteomic Profiling Reveals Candidate Proteins Associated with Slow or No Renal Decline in CKD Stage 3 Diabetic Patients

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Background: Patients with diabetes and chronic kidney disease (CKD) stage 3 are at high risk of developing end-stage renal disease (ESRD). However, the rate of renal decline leading to onset of ESRD varies tremendously among these patients. This study aimed to identify biomarkers associated with slow or no renal decline (slow decliners) in two independent cohorts of diabetic patients with CKD stage 3.

Methods: The study comprised an exploratory cohort of 214 individuals with Type 1 diabetes (T1D) with 129 slow decliners, and a replication cohort of 144 individuals with Type 2 diabetes (T2D) with 96 slow decliners. Both cohorts were followed for 7-10 years. Serial measurements of serum creatinine were used to estimate the rate of eGFR decline. Slow renal decline was defined as eGFR slope of ≥ –5 ml/min/year. Baseline plasma specimens were assayed by the SOMAscan proteomics platform. Relationships of plasma proteins with eGFR slopes were evaluated based on Spearman's rank correlation coefficients. Multivariable logistic regression models investigated the odds ratio (OR) between plasma proteins and being a slow decliner.

Results: In slow decliners, the median (25th, 75th percentiles) eGFR slope was -2.4 (-3.5, -1.3) and -1.8 (-3.1, -0.1) ml/min/year in T1D and T2D cohorts, respectively. In the exploratory cohort, 76 plasma proteins were significantly and positively associated with eGFR slope (FDR P<0.005). Eighteen of these proteins were replicated in the T2D cohort (P<0.05). Multivariable logistic analyses in the combined cohorts with T1D and T2D demonstrated that all proteins were significantly associated with slow renal decline in models adjusted for type of diabetes, eGFR and HbA1c. In models further adjusted for

TNF-R1, the ORs remained statistically significant for 11 of the 19 proteins. TNFSF12 (OR (95% CI): 1.46 (1.2, 1.9), *P*=0.0017) was the most significant independent predictor of slow or no renal decline with higher TNFSF12 plasma levels protecting against progressive renal decline.

Conclusions: Our findings suggest that several circulating plasma proteins are associated with slow or no renal decline in both types of diabetes, and these proteins may represent new targets that can be used therapeutically for slowing the progression of renal function decline.

Funding: NIDDK Support, Private Foundation Support

FR-OR112

Notch Signaling Proteins as Key Factor in the Progression to ESRD in Diabetes

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Background: It has been reported that Notch signaling proteins might regulate interstitial fibrosis development in the kidneys of mice and humans. The objective of this study was to investigate an association of circulating Notch signaling proteins on the development of ESRD in subjects with diabetes during long-term follow-up.

Methods: Using the modified aptamer-based SomaScan platform, 4 proteins including Notch1, delta like protein 1 (DLL1), delta like protein 4 (DLL4), and Jagged 1 protein (JAG1) were measured in baseline plasma specimens obtained from 363 Caucasian subjects with diabetes and CKD stage 3 (CKD3); including 219 with Type 1 diabetes (T1D) and 144 with Type 2 diabetes (T2D). Additionally, the 4 proteins were also measured in 190 T1D patients with CKD stage 1 and 2 (CKD12). All patients were followed for 10 years to ascertain onset of ESRD.

Results: In Cox regression analysis, DLL1, DLL4, and JAG1 were strongly associated with progression to ESRD in T1D patients with CKD3 ($P=1.6*10^{-10}$, $p=5.1*10^{-8}$, and $p=2.0*10^{-5}$, respectively) and in T2D patients with CKD3 ($p=3.6*10^{-4}$, $p=1.9*10^{-4}$, and $p=6.1*10^{-4}$, respectively). Importantly, this significant association with ESRD for DLL1 and JAG1 were also found in T1D patients with CKD12 ($p=2.8*10^{-6}$ and $p=4.1*10^{-2}$), and DLL1 was the strongest predictor for ESRD in the combined panel, even after adjustment for relevant covariates (Hazard Ratio 1.48, $p=8.4*10^{-6}$) (Table 1).

Conclusions: There were few previous reports about the association between circulating Notch signaling proteins and kidney diseases. Our finding is novel in that circulating ligands for Notch receptors, especially DLL1, are strongly associated with progression to future ESRD. Regulation of the specific circulating Notch ligands could become the new therapeutic targets to retard progression to ESRD in diabetes.

Funding: Other NIH Support - NIH - DK41526 and DP3DK112177.

Table 1. Cox regression model for each group

	T1D CKD3 (n=219)		T2D CKD3 (n=144)		T1D CKD12 (n=190)		Combined (n=553) Adjusted	
Proteins	HR	P value	HR	P value	HR	P value	HR	P value
DLL1	1.85	1.60E-10	1.85	3.60E-04	2.01	2.80E-06	1.48	8.40E-06
DLL4	1.67	5.10E-08	1.91	1.90E-04	1.12	3.80E-01	1.18	4.40E-02
JAG1	1.47	2.00E-05	1.78	6.10E-04	1.31	4.10E-02	1.05	5.30E-01
Notch1	1.09	3.10E-01	1.31	8.00E-02	1.14	3.20E-01	0.99	8.80E-01

Multivariate model was adjusted for baseline eGFR, HbA1c, ACR, and type of diabetes

FR-OR113

Multicentre Prospective Validation of a Urinary Peptidome-Based Classifier for the Diagnosis of Type 2 Diabetic Nephropathy

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Background: Diabetic kidney disease (DKD) is a major late complication of diabetes. The 'Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephRopathy In TYpe 2 diabetic patients with normoalbuminuria trial' (PRIORITY) is the first prospective study to evaluate the early detection of DKD in subjects with type 2 diabetes (T2D) and normal urinary albumin creatinine ratio (UACR) (<30 mg/g) using a urinary proteome-based classifier (CKD273).

Methods: Prospective multicentre observational study. The CKD273 classifier was assessed at baseline. The primary endpoint was development of confirmed microalbuminuria (moderate albuminuria) in 2 of 3 first morning urine samples (UACR >30 mg/g and with ≥30% increase (geometric mean) from baseline). For subjects with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73m^2 at baseline, development of CKD3: eGFR <60 ml/min/1.73m^2 was a secondary outcome. Mean follow-up time was 2.57 years with a minimum of 7 days and a maximum of 4.33 years.

Results: A total of 1775 participants from 15 centres were included, with 12 % (n=216) of these having a high-risk proteomic pattern. At baseline, participants in the high-risk group were more likely to be men, were older, had longer diabetes duration, lower eGFR and higher UACR than those in the low-risk group (n=1559, p<0.02). Numerical differences were small and univariate regression analyses showed weak associations (R2<0.04) of CKD273 with each baseline variable. Development of persistent microalbuminuria was seen in 28% of high risk and 8.9% of low risk subjects (p<0.0001), resulting in a hazard ratio (HR (95% CI)) of 3.924 (2.902-5.304) in a crude Cox-model; and 2.441 (1.766-3.374, p<0.0001) when adjusted for baseline age, sex, diabetes duration, HbA1c, systolic blood pressure, retinopathy, eGFR and UACR. For development of CKD3, HR (high vs. low risk) was 3.932 (2.811 – 5.499) in a crude model; and 4.089 (2.878 – 5.811, p<0.0001) adjusted.

Conclusions: In normoalbuminuric subjects with T2D, the urinary proteomic classifier CKD273 prospectively predicts progression to microalbuminuria and impaired renal function, independent of clinical characteristics.

FR-OR114

Urinary Biomarkers of Injury and Repair and Risk for Kidney Function Decline or Mortality: Results from VA NEPHRON-D

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Background: Diabetes is the leading cause of ESRD worldwide. Biomarkers of kidney injury and repair may prognosticate diabetic kidney disease beyond that of eGFR and albuminuria.

Methods: Baseline urinary biomarkers of tubular injury and repair (neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule-1 [KIM-1], interleukin-18 [IL-18], monocyte chemoattractant protein-1 [MCP-1], chitinase-3-like protein-1 [YKL-40]) were measured by multiplex immunoassays. Using Cox proportional hazards models, we studied the associations of each biomarker with kidney function decline (first occurrence of absolute decrease in eGFR≥30 ml/min/1.73 m^2 if randomization eGFR≥60, relative decrease ≥50% if randomization eGFR<60, or ESRD) and all-cause mortality. Covariates included age, sex, race, BMI, blood pressure, HgbA1c, treatment arm, eGFR, and UACR.

Results: We included 1136 VA NEPHRON-D participants with available baseline urine samples. Mean age was 65 years, 99% were male, mean eGFR was 56 ml/min/1.73 m^2, and median UACR was 840 mg/g. Over a median follow-up of 2.2 years (IQR 1.3, 3.1), 148 (13%) experienced kidney function decline and 103 (9%) died. In unadjusted models, the hazard risk of kidney function decline was ~20-30% higher per two-fold greater baseline level of urine NGAL, IL-18, MCP-1, and YKL-40. These associations attenuated and were no longer significant after adjusting for baseline eGFR and UACR. Higher levels of urine NGAL, MCP-1, and YKL-40 were independently associated with higher risk of death (Table).

Conclusions: Among diabetic individuals with CKD, baseline values of urinary biomarkers of tubular injury and repair were associated with risk of death but not kidney function decline.

Funding: NIDDK Support, Veterans Affairs Support

Table: Unadjusted and adjusted hazard ratios for kidney function decline and mortality per doubling of biomarker.

Per doubling of biomarker	Kidney Function Decline		Mortality	
	Unadjusted Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)	Unadjusted Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
NGAL (ng/mL)	**1.23 (1.12, 1.35)**	0.94 (0.83, 1.06)	**1.17 (1.05, 1.32)**	**1.14 (1.01, 1.30)**
KIM-1 (ng/mL)	1.09 (0.96, 1.23)	0.92 (0.81, 1.05)	**1.18 (1.02, 1.37)**	1.12 (0.95, 1.30)
IL-18 (pg/mL)	**1.23 (1.08, 1.39)**	0.89 (0.78, 1.02)	**1.17 (1.00, 1.35)**	1.16 (0.98, 1.38)
MCP-1 (pg/mL)	**1.32 (1.15, 1.50)**	1.01 (0.88, 1.15)	**1.22 (1.04, 1.42)**	**1.21 (1.02, 1.43)**
YKL-40 (ng/mL)	**1.22 (1.15, 1.30)**	1.04 (0.96, 1.12)	**1.12 (1.04, 1.21)**	**1.12 (1.02, 1.23)**

*Adjusted for age, sex, race, and baseline body mass index, systolic blood pressure, diastolic blood pressure, hemoglobin A1c, treatment arm, estimated glomerular filtration rate, $\log_2$(urine albumin-to-creatinine ratio).

FR-OR115

Proximal Tubular Uptake of Free Fatty Acid (FFA) by Kidney Injury Molecule-1 (KIM-1) Mediates Tubulointerstitial Damage in Diabetic Kidney Disease (DKD), Which Is Attenuated by a Novel Inhibitor

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Background: DKD is associated with tubulointerstitial damage. KIM-1, a scavenger receptor, is the most upregulated proximal tubule protein in many forms of kidney injury. Dyslipidemia is a primary feature of DKD. We hypothesized that KIM-1-mediated uptake of FFAs contributes to tubulointerstitial damage in DKD.

Methods: Human DKD renal biopsy samples were analyzed. Renal epithelial cells expressing KIM-1 (LLC-PK1 cells overexpressing KIM-1, and mouse and human primary cells) were exposed to palmitate followed by measurement of FFA uptake, cell death and pro-inflammatory and pro-fibrotic effects determined *in vitro*. To clarify the role of FFA uptake by KIM-1 *in vivo*, a DKD model induced by unilateral nephrectomy, streptozotocin and high fat diet (UNx-STZ-HFD) was studied in wild-type (WT) or KIM-1$^{\Delta mucin}$ (functional knockout of KIM-1) mice. A second new model was created whereby KIM-1 was upregulated by aristolochic acid and the effect of subsequent injection of FFA was determined (AA-FFA model). An inhibitor for KIM-1-mediated endocytosis was screened from >14,000 compounds and tested both *in vitro* and *in vivo*.

Results: KIM-1 expression in DKD patients was positively correlated with tubulointerstitial inflammation and fibrosis. FFA was taken up by the WT-KIM-1 expressing cells causing IL-1β production through activation of inflammasomes and cell death. Conditioned media from FFA-treated WT cells stimulated greater αSMA expression in mouse fibroblasts, than did media from KIM-1$^{\Delta mucin}$ cells. In the UNx-STZ-HFD model, WT mice showed greater proximal tubular atrophy, macrophage infiltration, fibrosis and albuminuria than KIM-1$^{\Delta mucin}$ mice. In the AA-FFA model, WT mice showed more macrophage infiltration, αSMA expression and loss of brush border than KIM-1$^{\Delta mucin}$ mice. Both *in vitro* and *in vivo* our newly identified compound prevented FFA uptake and injury only on WT, not on KIM-1$^{\Delta mucin}$.

Conclusions: KIM-1 mediates the proximal tubular uptake of FFA, leading to pro-inflammatory and pro-fibrotic responses and increase in cell death. Our findings support the role of KIM-1 as a target for DKD and introduce a new candidate therapeutic agent.

Funding: NIDDK Support, Commercial Support - Boehringer Ingelheim

FR-OR116

A Metabolomics-Based Pathway Analysis for How Dapagliflozin May Slow Kidney Function Decline in Patients with Type 2 Diabetes

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Background: Sodium glucose cotransporter 2 inhibitors (SGLT-2i) slow progression of diabetic kidney disease (DKD). The underlying mechanisms are not fully elucidated. We examined which metabolic pathways are targeted by the SGLT-2i dapagliflozin (DAPA) to explore the molecular processes involved in the renal protective effects with DAPA.

Methods: An unbiased serum metabolomics assay was performed on baseline and follow-up (week 12) samples from the EFFECT II trial in type 2 diabetes patients with non-alcoholic fatty liver disease (NCT02279407; Eriksson Diabetologia 2018), using the DAPA 10 mg/day treatment arm (n=19). Transcriptomic signatures from tubular compartments were identified from kidney biopsies collected from patients with DKD and healthy controls from the European Renal cDNA Biobank (ERCB). Serum metabolites that were significantly changed after 12 weeks of DAPA treatment were selected and mapped to a metabolite-protein interaction network. These proteins were then linked with intra-renal transcripts that were associated with DKD or eGFR. The impacted metabolites and their protein coding transcripts were analyzed for enriched pathways.

Results: Of all measured (n=812) metabolites, 108 changed ($p<0.05$) during DAPA treatment and 74 could be linked to 367 unique proteins with corresponding coding genes. Intra-renal mRNA expression analysis of the genes encoding the metabolite-associated proteins using kidney biopsies resulted in 105 genes that were significantly associated with eGFR in patients with DKD from the ERCB cohort, and 135 genes that were differentially expressed between patients with DKD and controls. The combination of metabolites and transcripts identified four enriched pathways that were affected by DAPA and associated with eGFR: Glycine Degradation (Creatine Biosynthesis) [mitochondrial function]; TCA Cycle II [energy metabolism]; L-carnitine Biosynthesis [energy metabolism] and Superpathway of Citrulline Metabolism [nitric oxide synthase and endothelial function].

Conclusions: The observed molecular pathways targeted by DAPA and associated with DKD suggest that modifying molecular processes related to energy metabolism, mitochondrial function, and endothelial function may contribute to the renal protective effects of DAPA.

FR-OR117

Assessing Glomerular Cellularity in Diabetic Human Kidney Biopsies with 3D Tissue Cytometry: Implications for Disease Progression

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Background: Diabetic nephropathy (DN) is a leading cause of kidney disease worldwide. At the tissue level, DN has been classified by morphology including glomerular size and cellularity. Large scale 3D multi-fluorescence imaging and 3D tissue cytometry (3DTC) provides a unique and efficient way to quantitate and characterize the cellularity of glomeruli. Here, we examined the changes in cellular density across multiple kidney biopsy specimens with DN, compared to reference nephrectomy tissue. We also sought to determine whether the changes in cellularity are indicative of a focal or diffuse response.

Methods: 5 non-DN reference nephrectomy specimens and 5 kidney biopsy specimens with DN were stained with 4 to 8 markers and imaged by confocal fluorescence microscopy. Glomeruli were isolated digitally and analyzed using 3DTC with Volumetric Tissue Exploration and Analysis (VTEA) software. Cell density and immune cell subtypes were determined for each glomerulus within each specimen.

Results: When comparing all glomeruli from diabetics to those from the reference specimens, the average cellular density was increased in the diabetic group: 592715 ± 116469 vs. 259556 ± 8107 cells/mm^3, respectively ($p < 0.05$). When comparing between individual specimen, there were no significant differences seen in glomerular cellular density across reference tissues, but three of the five diabetic specimens showed significant increases in cellularity, albeit to different levels ($p<0.05$ using one-way ANOVA compared to reference). Interestingly, within each biopsy with DN, the cellular densities in all glomeruli were comparable. When examining cell subtype, the contribution of immune cells to the increased cellularity in diabetes was minimal.

Conclusions: 3DTC using VTEA is a powerful and efficient tool to assess glomerular cellularity in biopsy specimens. Using this tool, we detected an increase in glomerular cell density in DN. Importantly, our data suggest that diabetes uniformly alters the cellularity across all glomeruli within a biopsy specimen, rather than a selective effect on a subset of glomeruli. These findings increase our understanding of the dynamics of the progression of diabetic kidney disease and may aid pathologists' interpretation of specimens.

Funding: NIDDK Support

FR-OR118

Regional Transcriptomic Profiling of the Human Kidney Uncovers Major Signature Shifts in the Interstitium During Diabetes

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Background: The expression signature of the renal interstitium is less well characterized than that of the glomerulus and tubules. Here, we examine gene expression of the human renal interstitium in reference nephrectomies and diabetic kidney biopsy specimens using laser micro-dissection (LMD).

Methods: We used LMD to collect cortical kidney interstitium from reference nephrectomies (N=9) and diabetic renal biopies (N=6). Rapid stain with DAPI, OG-Phalloidin, and Tamm-Horsfall protein antibody identified relevant renal structures. LMD excluded tubules, glomeruli and large vessels. Transcriptomic data was obtained using RNAseq on Illumina platform, and analyzed with R studio. The gene signature was compared to existing platforms such as snRNAseq and scRNAseq datasets.

Results: Our laser micro-dissected interstitial regions did not show significant expression of known tubular or glomerular markers (eg. *NPHS1, LRP2, UMOD, AQP2*). In contrast, we identified a set of markers specific to the interstitium in reference nephrectomy samples. While some of them were novel (eg. *FABP2, ADGRD1*), others were commonly expressed across all three platforms (*LTBP1, ELN, SYNM, ADCY5, COL4A1, C1R)*. The expression of these genes was localized to expected cell types such as stromal, vascular and immune cells. The renal interstitium from diabetic biopsies revealed differential expression in many pathways including extracellular matrix organization ($p=0.0037$) and chemokine signaling ($p=0.0065$).

Conclusions: We successfully isolated the interstitium of human kidney samples using LMD. Gene expression from our samples correlated well with vascular, immune and stromal cell clusters from scRNAseq and snRNAseq data. Therefore, our LMD approach allows rich deconvolution of transcriptomic signatures from single cell datasets and facilitates backmapping of unidentified clusters to the interstitium. Dramatic changes in the gene expression in diabetic kidney interstitium suggest that this compartment may be an important player in the pathophysiology of diabetic nephropathy.

Funding: NIDDK Support

FR-OR119

Single Nucleus RNA Sequencing of Early Human Diabetic Nephropathy Reveals Transcriptional Changes That Promote Potassium Secretion

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Background: Diabetic nephropathy is characterized by damage to both the glomerulus and tubulointerstitium, but relatively little is known about cell-specific transcriptional changes. We hypothesized that single nucleus RNA sequencing (snRNAseq) of cryopreserved human diabetic kidney samples would reveal genes and signaling networks in early diabetic nephropathy.

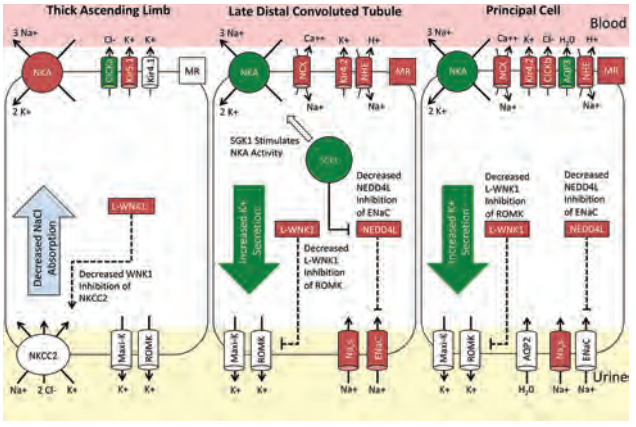
Methods: We analyzed three diabetic and three healthy human kidney samples. Diabetics had elevated A1c (mean = 7.9 +/- 1.5%) and two of three patients had proteinuria. Baseline serum creatinine (mean = 1.06 +/- 0.23 mg/dl) was not different

between groups. Nuclear preparations of cryopreserved samples were processed using 10x Genomics Chromium 5' kit and sequenced by NovaSeq. Reads were counted with zUMIS v2.0 and analyzed with Seurat v2.3.

Results: A total of 23,980 single nuclei were sequenced representing all glomerular and tubulointerstitial cell types. Infiltrating T-cells and B-cells were increased in diabetic samples. Side by side comparison showed cell-type-specific transcriptional changes important for ion transport, angiogenesis, and immune cell activation. In particular, the diabetic loop of Henle, late distal convoluted tubule, and principal cells show gene changes consistent with increased potassium secretion, including alterations in Na-K^+-ATPase, *WNK1*, *NEDD4L*, and mineralocorticoid receptor (Figure 1; green=upregulated, red=downregulated). These effects were accompanied by increased expression of *CASR* and decreased expression of *CLDN16* in the loop of Henle, which regulate calcium and magnesium reabsorption. We also identify strong angiogenic signatures in glomerular cell types, proximal convoluted tubule, distal convoluted tubule and principal cells.

Conclusions: Early diabetes induces gene expression changes in the distal nephron coordinate to promote potassium secretion and angiogenesis.

Funding: NIDDK Support, Private Foundation Support



FR-OR120

Characterizing the Bioenergetic Profile of Kidney Mitochondria in Human Diabetes

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Background: Optimal mitochondrial respiration is central to renal function. We have shown a decline in mitochondrial respiratory function in the kidney in experimental diabetes prior to development of characteristic kidney lesions. Despite a large body of work focussing on the role of mitochondrial dysfunction in diabetic kidney disease (DKD), the majority of studies have been performed in the kidneys of animal models and no study to date has determined if there is a defect in mitochondrial bioenergetics within the renal cortex of individuals with diabetes.

Methods: Renal cortical tissue was obtained after informed patient consent from the macroscopically/microscopically healthy portion of tumor nephrectomies. Renal cortices were freshly collected from non-diabetic controls (ND, n=15) and patients with diabetes (D, n=12). Oxygen consumption rates were determined with a substrate-uncoupler-inhibitor titration protocol by high resolution respirometry (Oxygraph-2k respirometer, Oroboros Instruments) in saponin-permeabilized tissue. In addition, respiration rates were also measured for a subset of specimens (n=12 ND, n=9 D) in mitochondria isolated by differential centrifugation.

Results: In permeabilized renal cortex, fatty acid-induced mitochondrial respiration was increased in patients with diabetes compared to non-diabetic patients. Coupled maximal mitochondrial respiration with electron input through electron transfer flavoprotein, complex I (CI) and CII was greater in patients with diabetes compared to non-diabetic patients. The uncoupled state of maximal respiration, experimentally induced by FCCP to collapse the proton gradient across the mitochondrial inner membrane and to measure the capacity of the electron transfer system was also increased in the setting of diabetes. Intriguingly, in isolated mitochondria, the opposite was observed in that there was a decrease in mitochondrial respiration in patients with diabetes, using all three protocols, suggesting that per unit mitochondria, there is an overall decline in mitochondrial respiratory function.

Conclusions: Our findings demonstrate for the first time that patients with diabetes display a profile of altered renal mitochondrial respiratory control. Further studies are required to determine defective sites within the mitochondria.

Funding: Government Support - Non-U.S.

FR-OR121

Non-HLA Antibodies Targeting Angiotensin II Type 1 Receptor and Endothelin 1 Type A Receptors Induce Endothelial Injury via β2-Arrestin Link to mTOR Pathway

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Background: Functional non-HLA antibodies targeting G protein-coupled receptors (GPCR) Angiotensin II Type 1 receptor (AT1R) and Endothelin-1 Type A receptor (ETAR) are implicated in the pathogenesis of transplant vasculopathy. While ERK signaling may represent general cellular response to agonist stimulation, the molecular link between receptor stimulation and development of vascular obliteration has not been fully established yet. We hypothesized the involvement of β-arrestins and PI3K/mTOR signaling and assessed functional consequences of AT1R- and ETAR-activation by non-HLA antibodies.

Methods: Human microvascular endothelial cells (HMEC) were stimulated with AT1R-Ab and ETAR-Ab IgG isolated from kidney transplant patients with chronic vasculopathy. Phospho-specific antibodies against ERK and mTOR downstream targets were used to assess activation of mTORC1 and mTORC2. β-arrestin involvement was investigated using RNA silencing and laser scanning microscopy studies in ARRB2. GFP and ETA.myc.Cherry-transfected HEK293 cells. Scratch assay was employed to study effect of non-HLA-antibodies on endothelial repair. Involvement of AT1R/ETAR activation was addressed by use of specific inhibitors.

Results: Signaling activity of both, mTORC1 and mTORC2, was increased after treatment with patient IgG compared to cells treated with IgG from healthy controls. This effect could be inhibited by specific AT1R-/ETAR- blockers. Activation of mTORC1 and mTORC2 were PI3K-dependent and independent from ERK. mTOR inhibitor rapamycin completely abolished activation of mTORC1 and in addition mTORC2 after long term treatment induced by receptor antibodies. Imaging studies revealed that β2- and not β1-arrestin was recruited to ETAR in response to ET1 and transplant patient IgG. Furthermore, AT1R and ETAR downstream signaling to ERK1/2 and mTORC2 was significantly reduced in β2-arrestin silenced HMECs. Non-HLA antibodies impaired endothelial repair by AT1R and ETAR induced mTORC2 signaling.

Conclusions: We provide evidence that functional AT1R-/ETAR-Abs induce ERK1/2 and mTOR signaling involving β2-arrestins in human microvascular endothelium. Our data may provide a translational rationale for mTOR inhibitors in combination with receptor blocker in patients with non-HLA receptor recognizing antibodies.

FR-OR122

Tissue Resident Memory T Cells in Mouse Renal Transplantation

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Background: The newly identified tissue resident subset of memory T cells (T_{RM}) provides immune surveillance in the tissue and first response against infections. They are functionally, transcriptionally, and phenotypically distinct from circulating effector and central memory T cells. The role of T_{RM} in transplantation is unknown. In this study, we investigated the formation and function of T_{RM} in a mouse kidney transplantation model.

Methods: Syngeneic B6 or allogeneic (B6xBALB/c) F1.ova kidneys were transplanted to B6 recipients and 1 million OT-I effector T cells were transferred on day 2. Graft, blood, bone marrow, SLO, and liver tissues were harvested 4 and 8 wks after transplantation. Serum creatinine was measured using i-Stat analyzer. T_{RM} were identified phenotypically as $CD44^{hi}CD62L^{low}CD69^{+}$ $CD103^{+/-}$ cells after excluding *in vivo* labeled T cells. OT-I and polyclonal T_{RM} were transcriptional characterized using scRNAseq. We tested T_{RM} residency in the graft by performing parabiosis between 4-wk transplanted CD45.1 B6 mice that contained OT-I effectors and CD45.2 B6 parabionts that had received F1.ova kidneys but no OT-I. Whether T_{RM} are sufficient for rejection was tested in a re-transplantation model using splenectomized LTBR-/- mice as secondary recipients of F1.ova grafts containing T_{RM}. Depletion experiments are underway to further establish causal relationship between T_{RM} and rejection.

Results: Mean serum creatinine (mg/dl) was significantly higher in allogeneic vs syngeneic group at wk 8 (0.8 vs 0.2, $p<0.05$). Graft histology showed mixed acute and chronic rejection in the allogeneic group. Flow analysis of allograft cells demonstrated T_{RM} cells among OT-I and endogenous T cell populations at 4 & 8 wks. The OT-I population was exclusively T_{RM} phenotype by flow and scRNAseq, rapidly produced IFNg upon re-stimulation, and was not detected anywhere else. There was no significant difference in mean number of OT-Is between wk 4 and wk 8 (125k vs 79k, $p=0.94$). OT-I T cells could not be detected in the parabiont kidney graft or tissues or in the secondary host outside the re-transplanted kidney, indicating that the T_{RM} are indeed resident in the graft and do not re-circulate. Chronic rejection progressed in re-transplanted kidneys that harbored T_{RM}.

Conclusions: Our findings show that donor-specific T_{RM} form in kidney allografts, are functional, and could contribute to rejection.

Funding: Other NIH Support - NIAID, Private Foundation Support

FR-OR123

Single Cell RNA Sequencing of Antibody-Mediated Rejection and Control Kidney Transplant Biopsies Reveals Endothelial, T-Cell, and Monocyte Intercellular Communication and Host-Donor Chimerism

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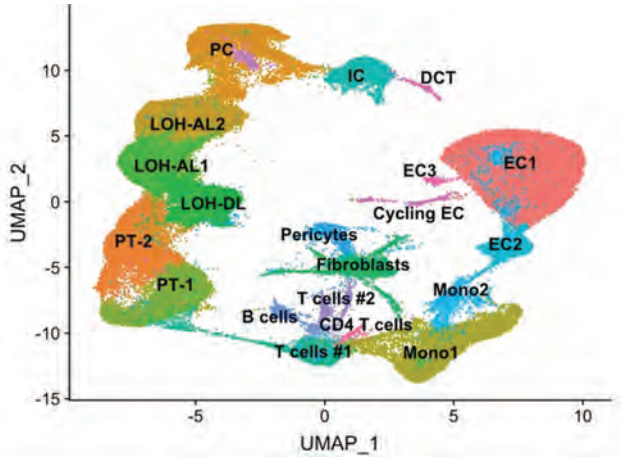
Background: Antibody mediated rejection (AMR) is one of the major causes of allograft failure yet current treatment strategies are suboptimal reflecting our poor understanding of this disease. We performed single cell(sc)RNAseq on biopsies from patients with AMR and compared them to non-AMR biopsies.

Methods: The 10X platform was used for library preparation. Sequencing depth was ~50k reads/cell. CellRanger, R and Seurat were used to make gene-cell matrices and for downstream analyses. Donor and recipeint exome sequencing was also performed. IRB approved.

Results: 96,547 cells (avg=1292 genes detected/cell) from 7 kidney transplant biopsies were included in the integrated analysis using UMAP. 21 cell clusters were identified and included all major tubular types (PT,LOH,PC,IC), stroma, endothelium, lymphocytes (T and B cells) and monocytes (figure). In AMR biopsies, monocytes expressed the B cell activator BAFF and B cells upregulated expression of its cognate receptors TACI and BMCA, suggesting monocyte driven B cell activation. Endothelial cells in AMR showed increased expression of cytokines that recruit T cells such as CXCL9, as well as the chemokine receptor ACKR1, suggesting that endothelial cells amplify the immune response. Of note, we could distinguish host from donor leukocytes based on expressed SNVs defined by exome sequencing. Whether donor-derived leukocytes exhibit differential gene expression compared to their host counterparts is under analysis.

Conclusions: Comprehensive scRNAseq of human AMR suggests that monocytes drive B cell activation and that endothelial cells recruit T cells. We also show, for the first time, that donor leukocytes persist even years after transplantation. Whether donor-derived leukocytes differentially regulate AMR represents a new and potentially important direction in transplantation research enabled by scRNAseq.

Funding: NIDDK Support



FR-OR124

Modulation of Ischemia-Reperfusion Injury (IRI) Post-Renal Transplantation in Estrogen Receptor-α Knockout (ERα-KO) Mice and by Selective Estrogen Receptor Modulators (SERM)

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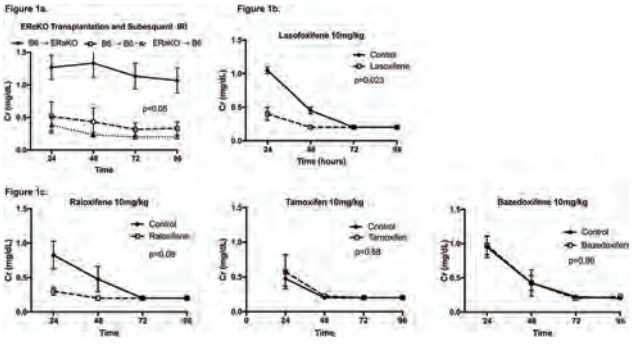
Background: IRI is a major contributor to early allograft dysfunction(EAD) post-kidney transplantation. We have demonstrated lower rates of EAD among female renal transplant recipients in UNOS, and using a murine model, showed improved IRI tolerance after administration of 17β-estradiol in both warm and cold renal IRI. We now investigate the contribution of ERα to this protection, and the utility of SERM administration in wild type mice.

Methods: Female C57BL/6(B6) and ERα-KO mice were used. We transplanted kidneys from B6→B6, ERα-KO→B6, and B6→ERα-KO, followed by native nephrectomy. All groups were treated with 17β-estradiol(1 mg/kg) and subsequently underwent temperature-controlled IRI(28min at 36°C). In a separate experiment, B6 mice received either Lasofoxifene(LAS), Raloxifene(RAL), Tamoxifen(TAM), Bazedoxifene(BAZ), or vehicle (all 10mg/kg in DMSO) prior to warm IRI. Serum creatinine(Cr) was measured at 24-hour intervals post-surgery in both experiments.

Results: Mice in the B6→ERα-KO group had significantly higher Cr compared to B6→B6 and ERαKO→B6 groups(Figure 1a). Mice treated with LAS prior to IRI had significantly lower Cr compared to controls(Figure 1b). RAL, TAM, or BAZ did not provide significant protection(Figure 1c).

Conclusions: Loss of estrogen-derived protection from warm IRI in the B6→ERα-KO group indicates that the mechanism for this protection is extrinsic to the kidney. Protection from IRI in the LAS-treated group demonstrates that selective ERα activation outside the breast and uterus, potentially sparing off-target effects, is sufficient for protection from IRI. Lack of significant protection from IRI after RAL, TAM, and BAZ is likely due to differential affinity of each drug for ERα in extra-renal tissues. Collectively, these data provide new insights into the mechanisms by which estrogen-based therapy can improve early outcomes in renal transplantation.

Funding: NIDDK Support



FR-OR125

Protective Role of Kynurenine 3-Monooxygenase in Kidney Allograft Rejection

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Background: Rejection of a transplanted kidney is a complex adaptive immune response and is the primary driver of graft loss. Kynurenine 3-monooxygenase (KMO) is an oxidoreductase involved in the kynurenine pathway of tryptophan metabolism and has been associated with inhibition of T cell proliferation. Our previous study demonstrated that indoleamine 2,3-dioxygenase (IDO) was upregulated in rejecting allografts, and was associated with reduced KMO expression. Herein, we investigated the role of KMO in preventing rejection in a pig model of kidney transplantation, and in protecting renal cortical epithelial cells (RCEC) following exposure to cytokines common to inflammation.

Methods: Outbred Yorkshire pigs underwent mismatched kidney transplants as we have described (Transplant Immunol 42:40). No immunosuppression was used and the tissue was studied 72 hours post-transplant. Immunohistochemistry (IHC) was performed to measure allograft expression of KMO. Cultured RCEC were utilized measure KMO, IDO, and the epithelial-mesenchymal transition markers E-cadherin and tight junction protein 1 (TJP1), following cytokine activation with and without treatment with the product of KMO, 3-hydroxykynurenine (3HK, 20mg/ml).

Results: RCEC-specific KMO staining was down-regulated by approximately 10-fold in rejecting allografts when compared to normal kidney. Following cytokine activation of RCEC, KMO was silenced, and the expression of E-cadherin and TJP1 was blunted. The addition of 3HK completely restored E-cadherin and TJP1 expression. In additional studies, we showed that high dose 3HK (100ug/ml) effectively inhibits human peripheral blood pan-T cell prolifereation.

Conclusions: KMO may be a key modulator of allograft immune responses as suggested by its downregulation in rejecting allografts. Moreover, KMO, through the generation of 3HK, may exert cytoprotective effects through preservation of normal renal parenchymal architecture, by retained expression of E-cadherin and TJP1 and inhibition of T cell proliferation. Inducing KMO, with the generation of 3HK in renal allografts, may provide an avenue for novel therapies in renal transplantation.

Funding: Private Foundation Support

FR-OR126

Tertiary Lymphoid Organs in Renal Chronic Allograft Rejection

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Background: Chronic allograft rejection remains a major obstacle to long-term allograft survival. Tertiary lymphoid organs (TLOs) are ectopic lymphoid structures that arise in non-lymphoid tissues in the setting of chronic inflammation. They have been documented extensively in human renal allografts and have been associated with chronic rejection. Their immunologic role in allograft rejection is unclear. Therefore, fundamental understanding of TLO function is necessary. Here, we employed a chronic renal allograft rejection model in mice and intravital time-lapse 2-photon microscopy to investigate the function of TLO in transplant rejection.

Methods: CB6F1 RIP-LTα (preformed TLO) or CB6F1 (no TLO) kidney grafts were transplanted to WT B6 recipients and survival monitored. To investigate immunologic function of TLO, we adoptively transferred B6-RIPLTα CD11c-YFP mice with 10e6 naïve dsRed OT-I T cells or 10e6 CTR-labeled NP-specific B cells + 10e6 CFP$^+$ OT-II cells and immunized with NP-OVA + alum. Intravital 2P imaging of renal TLO was performed at time points 0, 3, 6, 24 or 72 hours after immunization. Three-dimensional

image analysis was performed and mean speed, displacement, arrest coefficient (AC) and contact times (CT) with DC were calculated for OT-I, OT-II and NP-B cells.

Results: CB6F1 RIP-LTα grafts rejected significantly faster (MST= 54) than CB6F1 grafts (MST= 225), demonstrating that TLO contribute to allograft rejection. Grafts from both groups harvested at the time of rejection demonstrated interstitial fibrosis, lymphocytic infiltrates and TLO, positive for B, T and HEV-marker PNAd. CB6F1 RIP-LTα grafts contained similar numbers of, but larger TLO than CB6F1 grafts. Mean speed and displacement of OT-I and OT-II cells significantly decreased over time after immunization while AC and mean CT significantly increased. B cell mean speed, displacement and AC increased after immunization. These data are consistent with B cell activation and productive T cell-DC interactions and mirror previously reported data in secondary lymphoid organs.

Conclusions: We provide first evidence that TLO provide a local structure for T and B cell activation that might propagate anti-graft immune responses in the setting of chronic rejection. Further studies will elucidate the formation and maintenance of TLO and the consequences of local T and B cell activation.

Funding: Other NIH Support - NIAID, Private Foundation Support

FR-OR127

Deciphering Shared Gene Expression Patterns by Whole-Genome Transcriptomics of Urinary Cells and Kidney Allograft Biopsies

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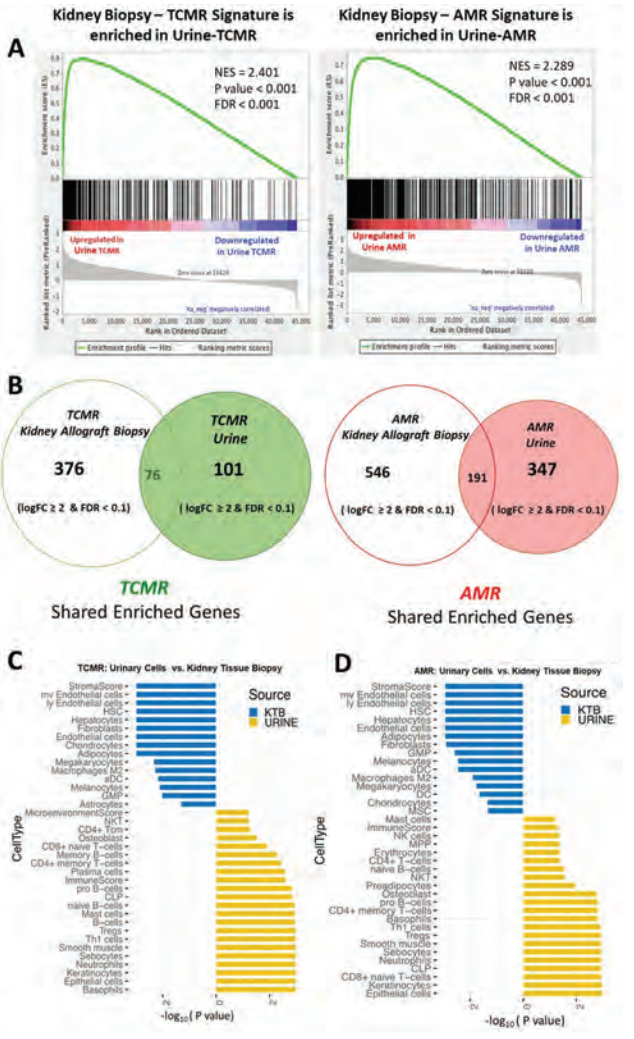
Background: Urinary cell mRNA profiling to interrogate kidney allograft (KTx) status is based on the premise that the allograft can function as an in-vivo flow cytometer and sort graft destructive/protective T cells into the urinary space. We used RNA-Seq of urinary cells to demonstrate that urinary cell mRNA profiles mirror intragraft events and urinary cells are enriched for immune cells in acute rejection

Methods: We performed global RNA-seq to characterize mRNA transcriptomes of urinary cells from 57 KTx recipients with T Cell Mediated Rejection (TCMR), n=22, Antibody Mediated Rejection (AMR), n=8, Normal, n=27, and allograft tissues from 49 KTx recipients (ACR n=12, AMR n=17, and Normal n=20). We analyzed the urine and biopsy profiles using Gene Set Enrichment Analysis (GSEA) and a gene-signature expression based cell-type deconvolution tool xCell.

Results: By GSEA analysis, genes upregulated in the KTx biopsies with TCMR and AMR were upregulated in the urinary cells with TCMR and AMR (FDR-P<0.01). There were 76 differentially expressed mRNAs that were shared between urine and biopsy profiles in TCMR, and 191 differentially expressed mRNAs that were shared between urine and biosy AMR. Deconvolution analysis revealed higher enrichment of stromal cell score in the biopsies compared to urine, whereas immune cell types were enriched in the urine.

Conclusions: GSEA of RNA-seq data from urinary cells and kidney allografts demonstrate enrichment of genes related to immune cells in urine that is undiluted by the stromal component. Our data support the use of urine as an excellent biospecimen for biomarker discovery and development as well as for deciphering the anti-allograft repertory.



(Figure 1, Panel A: GSEA, Panel B: Venn Diagram Shared Genes, Panel C&D: xCell immune cell types in TCMR and AMR, Blue=Biopsy and Yellow=urine)

FR-OR128

Altered Gut Microbial Fermentation and Colonization with Methanobrevibacter smithii in Renal Transplant Recipients

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Background: The gut microbiota of kidney transplant recipients (RTR) differs from that of healthy controls (HC). This may have consequences for gut microbial fermentation. Breath hydrogen (H_2) and methane (CH_4) concentrations are markers of fermentation in the gut, of which CH_4 is mainly produced by *Methanobrevibacter smithii* (*M. smithii*). We aimed to investigate (1) whether breath H_2 and CH_4 concentrations differs between RTR and HC, (2) whether the presence of *M. smithii* in faeces differs between RTR and HC and (3) whether presence of *M. smithii* is related to breath H_2 and CH_4.

Methods: All study subjects participated in the TransplantLines biobank cohort study. Organ donors served as HC. Breath H_2 and CH_4 concentrations were analysed using solid state-sensor gas-chromatography. Presence of *M. smithii* in faeces was determined with real-time PCR.

Results: A total of 152 RTR and 77 HC were included. Breath H_2 concentrations of RTR were not significantly different from HC (median [IQR] 11.3 [4.0-30.0] ppm vs. 10.5 [4.5-28.3] ppm, p=0.92). However, RTR had significantly lower breath CH_4 concentrations compared to HC (7.5 [3.9-10.6] ppm vs. 16.0 [8.0-45.5] ppm, p<0.001). In addition, *M. smithii* was found less frequently in RTR compared to HC (86.4% vs. 28.6%, p<0.001). In absence of *M. smithii*, there was a significant positive correlation between breath H_2 and CH_4 (r = 0.88; p<0.001). There was no correlation if *M. smithii* was present (r = 0.09; p=0.50).

Conclusions: Breath CH_4 concentrations and the prevalence of *M. smithii* in faeces were significantly lower in RTR compared to HC, which indicates RTR have altered microbiota and altered gut microbial fermentation. In absence of *M. smithii*, CH_4 is highly

dependent on H_2 production, while this is not the case in the presence of *M. smithii*. These findings provide novel insight in the alterations of gut microbiota secondary to renal transplantation and the use of immunosuppressants.

Funding: Commercial Support - This work was supported by a grant from Astellas BV.

FR-OR129

Extracellular Vesicles Mediate Complement Activation and Tubular Senescence in Renal Antibody-Mediated Rejection

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Background: Renal Antibody-Mediated Rejection (AMR) is characterized by a strong complement activation that can lead to a premature senescence in tubular epithelial cells (TEC). EVs (Extracellular vesicles), circulating microparticles able to mediate cell-to cell communication, are emerging as pivotal in different kidney diseases. The aim of this study was to investigate whether AMR derived-EVs could induce tubular inflammaging aging and complement activation.

Methods: Renal biopsies, serum and serum-isolated-EVs from 10 Acute and Chronic AMR patients were collected. TEC culture were incubated with EVs ($5E^{+4}$EVs/cells target for 24h); then to assess cellular senescence qPCR for *p21*, *p53*, *Klotho* and *CYP1B*1 and SA-β-gal staining were performed. mRNA level of *C3* and *CFH* were also measured. Inflammaging ($p16^{INK4a}$ and Klotho) markers were evaluated by IHC. Endothelial cells were grown in serum free media, incubated with AMR derived-EVs for 24h, then C4d IF was performed.

Results: Renal AMR biopsies showed significant tubular senescence as indicated by $p16^{INK4a}$ expression; $p16^{INK4a}$ was significantly upregulated in Chronic compared with Acute AMR biopsies ($p<0.05$). *In vitro*, the exposure of TEC to AMR serum induced senescence as observed by the upregulation of *p21* and *p53* gene levels ($p<0.05$). Furthermore, EVs exposed-TEC were characterized by significant increase in *p21, p53* and *CYP1B1* gene expression and down-regulation of *Klotho* ($p<0.05$) indicating that EVs can induce tubular senescence. In accordance, EVs induced a higher number of SA-β-gal+ TEC compared with control serum ($p<0.05$); the cells appeared larger and polynucleated indicating typical senescence phenotype. Finally, EVs from AMR patients induced a significant increase in *C3* gene expression with concomitant downregualtion in *CFH in TEC associated with* C4d deposition on endothelial cells in serum free medium.

Conclusions: In AMR patients, circulating EVs induced accelerated inflammaging in TEC via dys-regulation of Complement system at cellular level. This new pathogenic process might help to identify new targets for therapeutic intervention.

FR-OR130

Distinct Metabolic Signatures of Murine Kidney Allograft Rejection and Ischemia-Reperfusion Injury (IRI)

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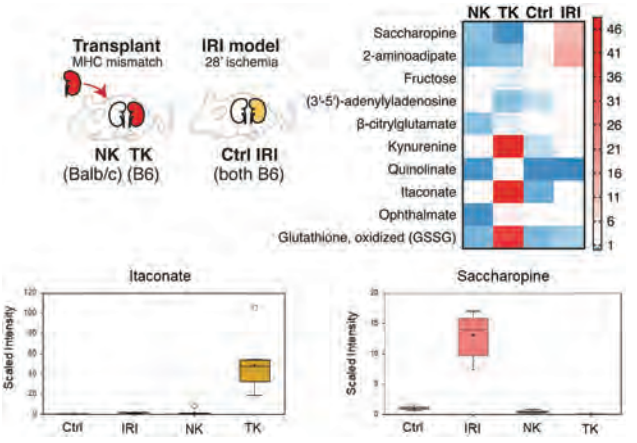
Background: Acute rejection is an important complication of kidney transplant, and must be distinguished from other causes of allograft dysfunction such as IRI. We hypothesized that tissue metabolomic profiling could identify biomarkers of rejection and IRI in murine models.

Methods: Mismatched kidney transplants were performed using C57BL/6 donors into BALB/c recipients (n=10). Allografts were harvested after 14d when rejection is prominent (TK), with BALB/c recipient kidneys as controls (NK). Separately, unilateral warm IRI was induced in C57BL/6 mice by clamping the renal pedicle for 28 mins. IRI and contralateral control (Ctrl) kidneys were harvested at 24 h, during peak IRI (n=10 each). Kidneys were snap frozen and stored at -80°C prior to mass spectrometry-based non-targeted metabolomic profiling of 879 biochemicals (Metabolon, Inc.). FDR-adjusted t-tests were used to test differences between TK vs. NK, IRI vs. Ctrl, and TK vs. IRI.

Results: Rejecting kidneys had significantly higher levels of metabolites related to the glutathione antioxidant response (GSSG; ophthalmate), tryptophan derivatives (kynurenine, quinolinate), and the TCA cycle derivative itaconate. IRI kidneys had significantly higher levels of saccharopine, 2-aminoadipate (lysine metabolism), fructose, β-citrylglutamate (mitochondrial iron carrier), and (3'-5')-adenylyladenosine (Fig.1). Key metabolites characterizing rejection and IRI, respectively, were itaconate, an immunometabolite released by activated macrophages, and saccharopine, a lysine catabolite reported to cause mitochondrial injury that is potentially relevant to IRI mitochondrial dysfunction.

Conclusions: Acute rejection and IRI have distinct tissue metabolomic signatures. These findings may help in the future development of non-invasive biomarkers to detect rejection and IRI in kidney transplant patients.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences of the National Institutes of Health, Award Number UL1TR001878.



SA-OR001

Multicenter Study of Immune Checkpoint Inhibitor-Associated AKI

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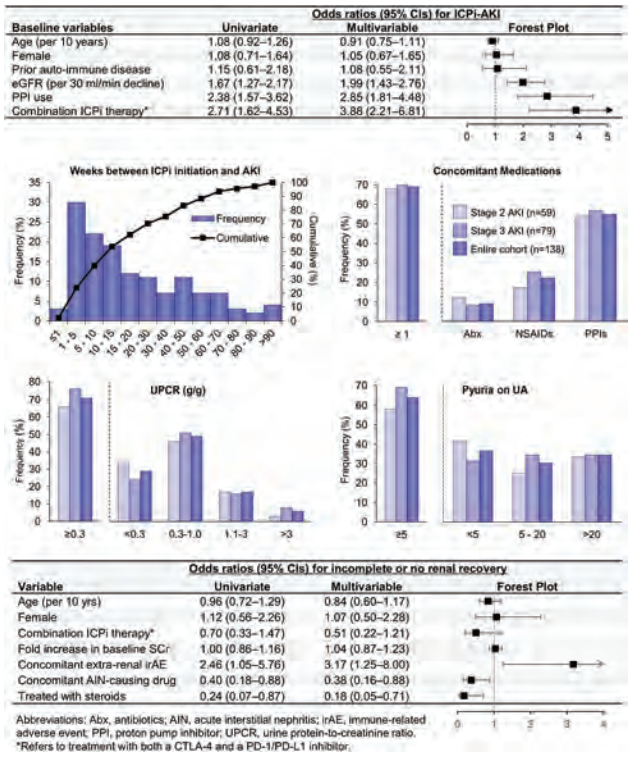
Background: Immune checkpoint inhibitor-associated AKI (ICPi-AKI) is an increasingly frequent complication of immunotherapy. However, existing data on ICPi-AKI are limited to small, mostly single-center studies.

Methods: We contacted nephrologists and oncologists at >20 major cancer centers across the U.S. and Canada, and identified 138 patients from 18 institutions with ICPi-AKI. All patients were required to have at least a doubling of serum creatinine or need for dialysis, along with a clinical diagnosis of ICPi-AKI by the provider. Detailed data were collected using a standardized case report form. We also collected data on 276 control patients who received ICPis but did not develop AKI. Multivariable logistic regression was used to determine risk factors for development of ICPi-AKI and prognostic factors for its recovery.

Results: Lower baseline eGFR, concomitant use of a PPI, and combination ICPi therapy were each associated with a greater risk of ICPi-AKI. The median time from initiation of an ICPi to AKI was 14 (IQR, 6–37) weeks. An extra-renal immune-related adverse event (irAE) occurred concomitantly with AKI in 43% of patients. Most patients had proteinuria and pyuria. A kidney biopsy was obtained in 43% of patients, with acute interstitial nephritis (AIN) found in 93%. Overall, 87% of patients were treated with steroids, of whom 43%, 43%, and 13% had complete, incomplete, and no renal recovery, respectively. Concomitant extra-renal irAEs were associated with worse renal prognosis, while concomitant AIN-causing medications and treatment with steroids were associated with improved renal prognosis. ICPi re-challenge occurred in 22% of patients, of whom 23% developed recurrence of AKI.

Conclusions: Using a multicenter approach, we present the largest clinical study to date to describe the clinical and pathologic features of ICPi-AKI.



SA-OR002

Safety of Immune Checkpoint Inhibitors for Cancer Treatment Among Kidney Transplant Patients: A Systematic Review

Sandhya Manohar,[1] Charat Thongprayoon,[1] Wisit Cheungpasitporn,[2] Sandra Herrmann.[1] *[1]Mayo Clinic, Rochester, MN; [2]University of Mississippi Medical Center, Jackson, MS.*

Background: The use of immune checkpoint inhibitors have significantly improved outcomes in multiple cancer types. Kidney Transplant (Ktx) recipients are excluded from trials due to the concern of allo-immunity and possible allograft rejection. Aim of this systematic review was to assess the safety of checkpoint inhibitors among KTx patients.

Methods: Literature search was conducted utilizing MEDLINE, EMBASE and Cochrane Database from inception through April 2019. We included studies that reported outcomes of kidney transplant recipients who received immune checkpoint inhibitors for cancer therapy. Outcomes of interest were allograft rejection and/or allograft failure, The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42019126777).

Results: 27 articles with a total of 44 KTx patients treated with immune checkpoint inhibitors were identified. Of 44 KTx patients, 18 were reported to have acute rejection of renal allograft. Among those with acute allograft rejection following the treatment, 83% were males with mean age of 62 +/- 13 years. 8 (44%) patients received nivolumab, 3 (17%) received pembrolizumab, 2 (11%) received ipilimumab, 2 (11%) received ipilimumab followed by pembrolizumab, 2 (11%) received ipilimumab followed by nivolumab, and 1 (6%) received pembrolizumab followed by nivolumab. Cancer types were melanoma (66%), lung cancer (17%), and metastatic squamous cell carcinoma of skin (12%), respectively. 3 patients had a partial remission (17%), a patient achieved cancer response (6%) and 5 patients had stable disease (28%). Median time from immune checkpoint inhibitors to acute rejection diagnosis was 24 (IQR 10-60) days. Reported types of acute allograft rejection were cellular rejection (33%), mixed cellular and antibody mediated rejection (17%), and unspecified type (50%). 15 (83%) had allograft failure and 8 (44%) died.

Conclusions: The findings of our study raise awareness of the potential risk of acute allograft rejection/failure following immune checkpoint inhibitors for cancer treatment among KTx patients. Future large-scale clinical studies are required to appraise the pathogenesis and plan optimal therapy that helps sustain graft tolerance without discouraging clinical benefits of immune checkpoint inhibitors for cancer treatment.

SA-OR003

Predictors of AKI in Patients Undergoing CAR T-Cell Therapy

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Background: Chimeric Antigen Receptor T-cell therapy (CAR-T) is an emerging immunotherapy used to treat certain malignancies. Organ dysfunction, including acute kidney injury (AKI), has been described, and hypothesized to be due to cytokine release syndrome (CRS). Predictors of AKI in patients receiving CAR-T cell therapy have not been adequately studied. We conducted a retrospective cohort study of patients receiving CAR-T cell therapy at our institution, in an attempt to identify those patients who are at risk of developing AKI after receiving this therapy.

Methods: We reviewed the charts of patients who received CAR-T between 5/2016 and 9/2018. A total of 58 patients were included in the study. Development of AKI was defined as increase in creatinine of at least 0.3 above baseline. 32% of patients (N = 19) developed AKI. Univariate analyses were conducted to delineate significant differences between patients who developed AKI compared to those who did not with regards to baseline characteristics, inflammatory markers (CRP, ferritin, albumin), markers of organ dysfunction (AST, bilirubin), and the use of any steroids or tocilizumab.

Results: Univariate analysis revealed comparable age, gender, ethnicity, as well as prevalence of hypertension and diabetes in the two groups. Patients with AKI tended to have a higher BMI (p=0.002) and baseline Cr (p=0.03). Ferritin peaked at a significantly higher level in the AKI group (p=0.008). There was no significant difference in peak CRP or albumin nadir between groups. Patients who developed AKI developed higher AST and Bilirubin levels (p=0.05, p=0.025 respectively). There was no significant difference in the rate of administration of steroids or tocilizumab in the AKI group compared to the other patients. The AKI group had a higher rate of death at 6 months after therapy (47% compared to 13%, p=0.008).

Conclusions: CAR-T cell therapy is gaining increased use for various malignancies. Models have been proposed to predict, diagnose and manage CRS, but not specifically AKI. Our findings indicate that baseline patient characteristics and inflammatory response markers, particularly ferritin, may play a role in predicting worse renal outcomes. Future work may focus on creating a broader predictive model that can help identify and guide management of patients receiving CAR-T who are at risk of AKI.

SA-OR004

AKI and Electrolyte Abnormalities in Patients Receiving Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

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Background: CAR-T therapy targets tumor antigens using genetically engineered cytotoxic T-cells, and is a breakthrough treatment for hematologic malignancies. Cytokine release syndrome (CRS), a systemic inflammatory response, is a known complication of CAR-T. CRS can lead to acute kidney injury (AKI); however, scant data exist on AKI in adults. We aimed to define the incidence, clinical features, and outcomes of AKI and electrolyte abnormalities in adults receiving CAR-T.

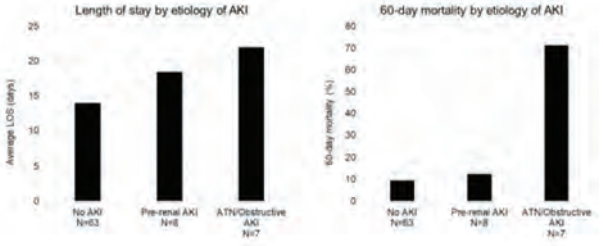
Methods: We performed a retrospective review of adults with lymphoma treated with CAR-T at 2 major cancer centers in Boston. Baseline demographics, laboratory data, and clinical outcomes were obtained from electronic health records. AKI was defined using KDIGO criteria.

Results: Among 78 patients receiving CAR-T, CRS occurred in 85%, of whom 62% required treatment with tocilizumab. AKI occurred in 15 patients (19%): 8 were pre-renal azotemia; 6 acute tubular necrosis; and 1 urinary obstruction related to disease progression. Patients with AKI were more likely to experience higher grades of CRS (grades 3,4). The association between the underlying cause of AKI and length of stay (LOS)/mortality are shown in Figure 1. All 3 patients requiring dialysis died during the hospitalization during which they received CAR-T. Electrolyte abnormalities in the first week after CAR-T were common: hypophosphatemia < 2.0 mg/dL occurred in 51% and hyponatremia < 130mEq/L in 15%.

Conclusions: In the largest report of adverse kidney events associated with CAR-T in adults, AKI and electrolyte abnormalities occur commonly in the context of CRS.

Funding: NIDDK Support, Other NIH Support - NIDCD

Figure 1. Association between AKI and LOS/Mortality



Legend:
Abbreviations: AKI: acute kidney injury; ATN: acute tubular necrosis; LOS: Length of initial hospital admission.

SA-OR005

Carfilzomib-Associated Nephrotoxicity: A Systematic Review and Meta-Analysis

Harini Bejjanki, Chintan Shah, Ankur Jain, Rohit Bishnoi, Amir Kazory. *University of Florida, Gainesville, FL.*

Background: There has been growing interest in the field of onco-nephrology with the advent of novel antineoplastic treatments, many of which portend nephrotoxic properties. Emergence of proteasome inhibitors (PI) has resulted in significant improvement in survival of patients with multiple myeloma (MM). Carfilzomib (CFZB) is a second-generation PI currently approved for relapsing or refractory MM. We sought to explore whether CFZB is associated with nephrotoxicity (NTX).

Methods: The present review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Articles cited in PubMed, Web of Science, and Clinical Trials Registry, using keywords "Carfilzomib" and "Kyprolis" were searched. A meta-analysis was performed. Cumulative incidence and odds ratios (OR) were calculated using random effect model. We used Common Terminology Criteria for Adverse Events to grade NTX.

Results: A total of 22 studies including 2489 patients were selected. The cumulative incidence of all -grade NTX (grade 1[mild] to grade 5[death]) was 15.5% (CI:11.1-22.1%); high-grade NTX, (grades 3- 5 [life-threatening or resulting in death]) was 4.7 % (CI: 3.3-6.77%). Estimated overall OR of all-grade NTX was 1.81 (CI: 1.09-3.02, p =0.02.). Similarly, the OR of high-grade NTX was 1.85 (CI: 0.93-1.75, p = 0.08). We found no difference in the incidence of all-grade (p =0.38) and high-grade (p = 0.46) NTX between newly diagnosed, relapsing, or refractory MM groups. The high dose of CFZB did not change the incidence of NTX compared to standard dose (p=0.66 and p=0.61 respectively). Similarly, the incidence of NTX was not significantly different when CFZB was used alone or in combination (p=0.63 and p=0.44 respectively). However, concomitant use of immunomodulators significantly increased the incidence of all-grade (p =<0.001), but not high-grade, CFZB-related NTX (p = 0.89).

Conclusions: Currently available data supports the notion that CFZB use is associated with increased risk of NTX. While the risk does not seem to be dose-dependent, it does increase with concomitant use of immunomodulators. Clinicians need to be aware of this complication when considering CFZB use and possibly consider alternative options in patients at risk of renal injury or for those who develop NTX. These results also call for rigorous monitoring of renal function with CFZB use.

SA-OR006

Characterization of the Acute eGFR Response to SGLT2-Inhibition with Empagliflozin

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Background: Empagliflozin (EMPA) reduces cardiovascular (CV) and renal risk in type 2 diabetes patients with established CV disease. As shown with RAAS blockade, EMPA also causes an acute eGFR decrease after treatment initiation. Although considered hemodynamic and reversible, it needs to be better understood to avoid premature drug discontinuation.

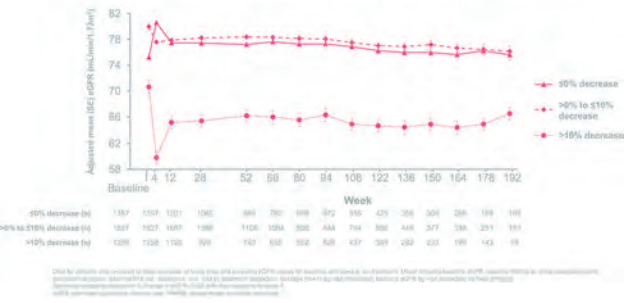
Methods: In EMPA-REG OUTCOME®, 6,668 participants who received at least one dose of study drug and had an eGFR value at both baseline and week 4 were categorized by % acute eGFR change to: >10% decrease, >0% to ≤10% decrease, ≤0% decrease. eGFR over time was analyzed using mixed model repeated measures. Acute renal failure (ARF) incidence was based on investigator-reported adverse events according to the narrow standardized MedDRA query.

Results: As expected, there were more patients with a >10% decrease in EMPA (28.3%) than in PBO (13.4%); however, an acute eGFR drop >30% with EMPA was rare (1.4%). After initial dynamics, long-term eGFR remained stable in all categories on EMPA (Figure). In multivariate regression analyses, KDIGO risk category (elevated UACR/low eGFR) and diuretic use at baseline were independent predictors of an acute eGFR decrease >10% with EMPA. From baseline to week 4, irrespective of the magnitude of the eGFR decrease, overall adverse events (AEs) and serious AEs were similar or lower with EMPA than PBO. ARF was more frequent in patients experiencing an acute eGFR decrease >10% in both groups, however most were reported as 'renal impairment'. During chronic treatment, overall and renal safety profiles were similar between PBO and all categories on EMPA.

Conclusions: Given the known renal protection with SGLT2 inhibition, our data demonstrate a relatively modest acute eGFR decrease with treatment, less likely to cause discontinuation of this reno-protective therapy.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

Figure:
Adjusted mean eGFR (CKD-EPI) over time for dipping categories of EMPA-treated patients



SA-OR007

Renin-Angiotensin-Aldosterone System Blockade Is Associated with Higher Risk of Contrast-Induced AKI in Patients with Diabetes: A Multicenter Propensity Score-Matched Study

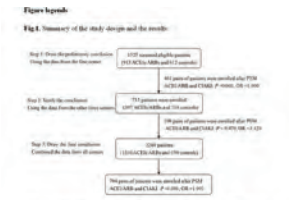
Mengqing Ma. *Sir Run Run Hospital, Nanjing, China.*

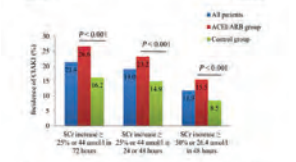
Background: CIAKI is a relatively common complication after treatment of coronary angiography (CAG) and percutaneous coronary intervention (PCI). The role of ACEIs or ARBs on CIAKI is controversial.

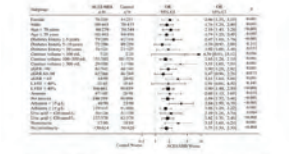
Methods: A retrospective, multi-center design with propensity score matching (PSM) was used to evaluate the effect of ACEIs/ARBs on the occurrence of CIAKI in diabetic patients undergoing CAG and PCI. The primary endpoint CIAKI was defined as an increased serum creatinine level of ≥ 25% or 44 μmol/l (0.5mg/dl) over the baseline level within 72 hours after contrast agent exposed.

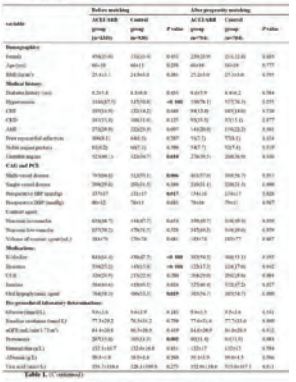
Results: A total of 2240 patients from four centers met the inclusion criteria. On the basis of PSM, 704 patients with ACEIs/ARBs were successfully matched to the control group. The incidence of CIAKI in the ACEIs/ARBs group was significantly higher than that in the control group (26.6% vs.16.2%, P< 0.001), no matter which kind of medicine was used in subgroups. In-hospital endpoints, patients with CIAKI had a higher risk of worsening heart failure (2.3% vs. 1.0%, P= 0.068). However, patients in the control group had an increased risk of overall adverse cardiovascular events (death, myocardial infarction, worsening heart failure, stroke) after PCI (3.8% vs. 1.8%, P= 0.034).

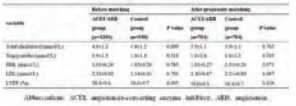
Conclusions: The ACEI/ARB was associated with an increased risk of CIAKI in patients with diabetes, but beneficial for early cardiovascular outcomes.

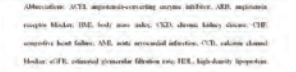


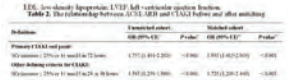


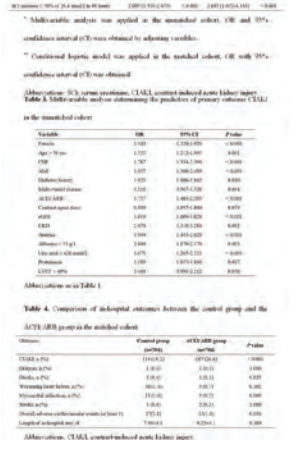












SA-OR008

Risk of AKI Among Critically Ill Patients with Concomitant Use of Vancomycin and Piperacillin-Tazobactam: A Meta-Analysis

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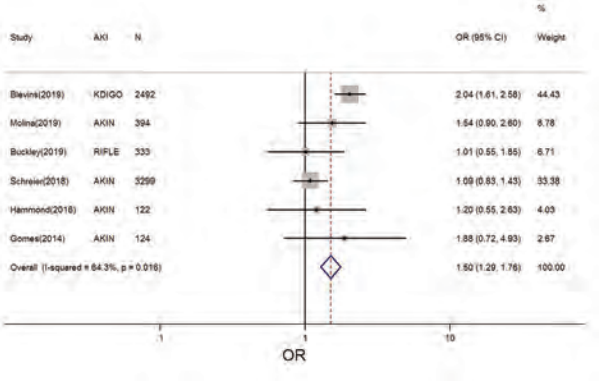
Background: Multiple studies have demonstrated that the combination of vancomycin and piperacillin-tazobactam (VPZ) is associated with increased risk of AKI compared to the combination of vancomycin and cefepime (VC) in the general population. Whether this holds true for critically ill patients is particularly important, given that AKI is very common in this population and is associated with increased mortality. Currently the data in critically ill patients is limited and the effect of VPZ in this population is controversial. Thus, the goal of this study was to determine the association between VPZ and AKI in critically ill adults.

Methods: A meta-analysis of observational studies that enrolled critically ill patients receiving VPZ or VC in the ICU setting was conducted. Electronic databases (PubMed, Cochrane and Embase) were searched through April 2019. Effect estimates and 95% CIs were pooled using the random effects model in STATA. The primary outcome was AKI as defined by the individual study. The secondary outcome was time to AKI.

Results: Literature search identified 6 published studies with 6764 patients. The definition of AKI was based on RIFLE, KDIGO or AKIN criteria. The odds of AKI in the VPZ group were higher compared to the VC group (odds ratio, 1.50; 95% CI 1.29-1.76; p<0.001) (Figure 1). There was no difference in the time to AKI between the VPZ group and the VC group (mean difference, -0.06; 95% CI, -0.09 to 0.74 days).

Conclusions: In critically ill patients, concomitant use of vancomycin and piperacillin-tazobactam is associated with an increased risk of AKI just as in the general population. This finding should be taken into consideration when choosing empiric antimicrobial coverage for critically ill patients. The included studies demonstrated some heterogeneity. Thus, future research regarding the use of VPZ in critically ill patients is warranted to confirm these findings.



Forest plot demonstrating the odds ratio of AKI in critically ill patients

SA-OR009

Does Erythropoietin (Epo) Protect Extremely Low Gestational Age Neonates (ELGANs) Against AKI?

David J. Askenazi,[1] Robert Schmicker,[3] Russell Griffin,[1] Patrick J. Heagerty,[5] Patrick D. Brophy,[4] Sandra Juul,[5] Stuart Goldstein,[2] Sangeeta R. Hingorani.[6] PENUT Investigators *[1]University of Alabama at Birmingham, Birmingham, AL; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [3]University of Washington Center for Biomedical Statistics, Seattle, WA; [4]University of Rochester, Rochester, NY; [5]University of Washington, Seattle, WA; [6]Seattle Children's Hospital, Seattle, WA.*

Background: The Recombinant Erythropoietin for Protection of Infant Renal Disease (REPAIReD) study is a randomized, placebo-controlled study designed to test the hypothesis that infants randomized to Epo will have lower rates of severe AKI than placebo-treated infants. Secondary outcomes include severity of AKI, AKI at different timepoints (postnatal days 3-7, days 8-14, and days >14), and SCr/Cystatin C values at 7, 9 and 14 postnatal days.

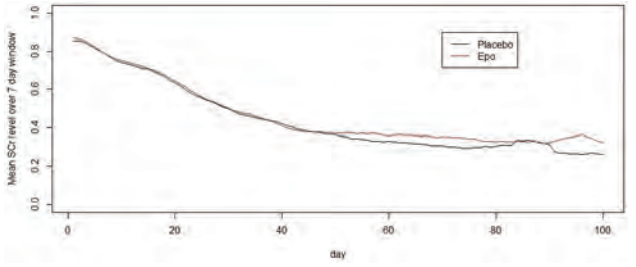
Methods: 936 infants were randomized to Epo vs. placebo. Those who died on days 0, 1, 2 are excluded (n=13) leaving 923 for analysis. Infants recevied EPO 1000 U/kg or placebo IV every other day x 6 doses and then Epo 400 U/kg SQ or sham infections every Monday, Wednesday and Friday until 33 weeks post-menstrual age. AKI is defined by the Neonatal KDIGO classification using the lowest prior SCr as the baseline value. As the first postnatal days reflect maternal SCr, day 3 was first possible AKI day. Severe AKI was defined as doubling of SCr from baseline (stage 2 or 3 AKI). GEE models including gestational age, sex, site and sibship clustering were used for analysis of our primary outcome.

Results: No maternal or neonatal differences by treatment group were observed. 374/923 (40.5%) had at least one epidose of AKI, of which 191/ 374 (51%) had severe AKI. We found no differences in the rates of severe AKI between treatment groups

(Figure 1). GEE models showed no differences in severe AKI rates between treatment groups after controlling for potential confounders (OR [95%CI] = 0.75 [0.53, 1.06]). No difference between treatment groups was seen in our secondary outcomes.

Conclusions: Up to 40% of ELGANS have at least one episode of Neonatal AKI. Epo is not protective for AKI in ELGANS. Whether Epo impacts urine kidney biomarkers or long-term CKD remains an area of investigation.

Funding: NIDDK Support, Other NIH Support - NINDS



SA-OR010

A Novel Targeting Strategy That Can Prevent Cholesterol Crystal Embolism-Induced AKI and Kidney Infarction

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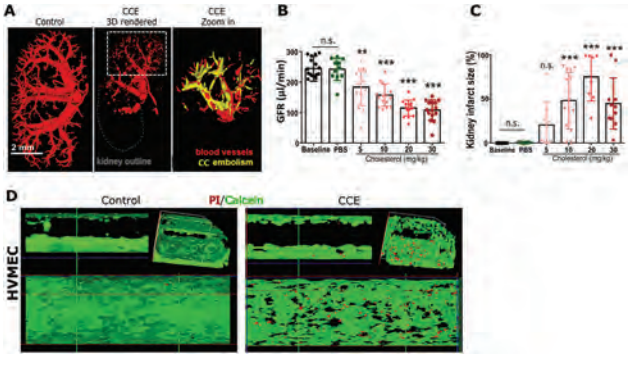
Background: Cholesterol crystal embolism(CCE) is a life-threatening complication of advanced atherosclerosis and often missed as a cause of AKI. Due to the lack of a suitable animal model, little is known about the pathophysiology of CCE.

Methods: We injected the left kidney of C57/BL6 mice with cholesterol crystals(CC). Primary endpoint: GFR. Secondary endpoints: infarct size, kidney injury, vascular injury, vascular occlusions, territorial hypoperfusion and perifocal edema(3D imaging: MRI and microCT). 2D and 3D in vitro studies CC with neutrophils, platelets, and endothelial cells.

Results: CC injection induced CCE in interlobar, arcuate, and interlobular arteries(A). Not CC alone but CC-induced clots obstructed arteries and caused a tight dose-dependent GFR decline(B), i.e. CCE-related AKI, while infarct size showed a higher variability(C). Deficiency of *Mlkl* protected mice from kidney infarction but not AKI, suggesting only targeting crystal clots but not kidney infarct may prevent AKI. Crystal clots were made of fibrin, neutrophils, platelets, and extracellular DNA. Fibrinolysis with rtPA and recombinant DNase all reduced arterial occlusions, GFR loss, and infarct size. For DNase the window-of-opportunity was 3h after CCE. To maximize the renoprotective effect in a clinically potentially feasible manner we tested a single prophylactic dose of necrostatin-1s before CCE and gave DNase 3h after CCE, which entirely prevented AKI and kidney infarction(D, E). In vitro, CC activated platelets, triggered NETs formation, and killed endothelial cells(F). All these mechanisms lead to the DNA release into extracellular space.

Conclusions: CCE induces kidney infarction but AKI develops independently from infarction due to obstruction of pre-glomerular vessels. Not CC but CC-induced clots lead to vascular obstruction. The extracellular DNA as a critical component in CC-induced clots. The window-of-opportunity for DNase therapy is 3h. A 2-step dual targeting strategy can entirely prevent AKI and infarction.



SA-OR011

Pregnancy-Related AKI and Diabetes: Hospitalizations and Clinical Outcomes

Silvi Shah,[1] Karthikeyan Meganathan,[1] Anthony C. Leonard,[1] Annette Christianson,[2] Charuhas V. Thakar.[1] *[1]University of Cincinnati, Cincinnati, OH; [2]Cincinnati VA, Cincinnati, OH.*

Background: Pregnancy-related acute kidney injury (AKI) is a public health problem and is associated with significant maternal and fetal morbidity and mortality. Clinical outcomes in pregnancy-related AKI, especially in women with diabetes are not well studied.

Methods: Using data from the 2012-2015 Nationwide Inpatient Sample, we identified hospitalizations for pregnancy, acute kidney injury (AKI), and diabetes mellitus using ICD-9-CM and DRG codes in women aged 15-49 years. We compared AKI rates, mortality, and home discharge rates in pregnancy-related AKI in women according to their diabetic status.

Results: We identified 15,550,459 pregnancy-hospitalizations in the study cohort. Rate of pregnancy-related hospitalization involving AKI was 0.1% and increased from 0.09% in 2012 to 0.12% in 2015. Women with pregnancy-related AKI were older than those who did not develop AKI (mean age, 40y vs. 30 y). Pregnancy-related AKI occurred at a higher rate in black women (0.25%) than white women (0.07%, p<0.0001) and at a higher rate in southern and midwest geographical regions (0.12%) than in northeast region (0.09%, p<0.0001). Higher rate of pregnancy-related AKI was observed in urban teaching hospitals (0.14%) than in urban non-teaching hospitals (0.07%) and rural hospitals (0.04%, p<0.0001). Women with pregnancy-related AKI had higher in-hospital mortality than those without AKI (2.6% vs. 0.01%). Overall, 1.3% of women were diabetic. Women with diabetes had higher pregnancy-related AKI hospitalizations than did women without diabetes (1.1% vs. 0.1%). Rate of pregnancy-related hospitalization involving AKI in diabetic women increased from 0.9% in 2012 to 1.2% in 2015. Diabetic women with pregnancy-related AKI did not differ with in-patient hospital mortality compared to pregnancy-related AKI in women without diabetes (3.2% vs. 2.5%) and with discharge to home (76% vs 78%).

Conclusions: Rate of pregnancy-related hospitalization involving AKI has increased overall and in diabetic women. In-hospital mortality is 260-fold higher in women with pregnancy-related AKI than those with no AKI. Women with diabetes have a 10-fold higher risk of AKI during pregnancy than those without diabetes but are not associated with a higher risk of mortality.

SA-OR012

Use of Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL) to Rule Out AKI in Children with High Nephrotoxic Medication Exposure

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Background: Nephrotoxic medication (NTMx) exposure is one of the most common causes of AKI in hospitalized children. We have demonstrated sustained reductions in NTMx exposure and associated AKI by implementation of the Nephrotoxic Injury Negated by Just in time Action (NINJA) program at our institutions. The NINJA program puts processes in place to identify high NTMx exposure and implements daily SCr assessment in exposed patients. Daily blood draws for SCr can be burdensome for the healthcare system and patients. We tested the hypothesis that daily urine NGAL assessments could be used to screen for NTMx AKI, allowing for a more limited SCr assessment.

Methods: This was a 2 center prospective study of children identified with high NTMx exposure (3 or NTMx on the same day or ≥3 days of IV vancomycin or an IV aminoglycoside). Patients had daily SCr drawn as standard of care for the NINJA program. Urine for NGAL measurement (The NGAL Test™, Bioporto, Denmark) was obtained for the first 7 days of high NTMx exposure. AKI was defined by the SCr based KDIGO criteria, and severe AKI (sAKI) was defined as KDIGO Stage 2 or 3 AKI.

Results: 117 patients had 498 urine samples available for analysis. 27 patients had AKI; 9 patients had severe AKI. The performance of NGAL at various concentrations (ng/ml) to predict AKI and severe AKI is shown in the table.

Conclusions: Urine NGAL level < 150 ng/ml has high NPV for any AKI and sAKI. We suggest NGAL can be used to complement SCr as part of the assessment for NTMx AKI, limiting the burden on providers and patients associated with a daily blood draw.

Funding: Commercial Support - Bioporto Diagnostics, Inc

NGAL level/AKI	Sensitivity	Specificity	PPV	NPV
50/Any AKI	35% (14-62%)	72% (62-80%)	18% (9-30%)	87% (82-90%)
150/Any AKI	24% (7-50%)	92% (85-96%)	33% (14-60%)	88% (84-90%)
300/ Any AKI	0% (0-20%)	96% (90-99%)	0	85% (84-85%)
50/Severe AKI	50% (7-93%)	71% (62-80%)	6% (2-15%)	98% (94-99%)
150/Severe AKI	25% (0-81%)	90% (83-95%)	8% (2-35%)	97% (95-98%)
300/Severe AKI	0% (0-60%)	96% (91-99%)	0	96% (96-97%)

Values in parentheses are 95% CI

SA-OR013

Association Between Urinary Dickkopf-3, AKI, and Subsequent Loss of Kidney Function in Patients Undergoing Cardiac Surgery: An Observational Cohort Study

Stefan J. Schunk,[1] Alexander Zarbock,[4] John A. Kellum,[3] Danilo Fliser,[2] Thimoteus Speer,[1] Stephen Zewinger.[1] *[1]Saarland University Hospital, Homburg/Saar, Germany; [2]Department of Internal Medicine IV, Saarland University, Homburg/Saar, Germany; [3]University of Pittsburgh, Pittsburgh, PA; [4]University Hospital Münster, Münster, Germany.*

Background: Cardiac surgery is associated with a high risk of postoperative acute kidney injury (AKI) and subsequent loss of kidney function. We explored the clinical utility of urinary dickkopf-3 (DKK3), a renal tubular stress marker, for preoperative identification of patients at risk for AKI and subsequent kidney function loss.

Methods: The study comprised consecutive patients who had elective cardiac surgery at the Saarland University Medical Centre (Homburg, Germany; derivation cohort) and

those undergoing elective cardiac surgery who were enrolled in the prospective RenalRIP multicentre trial (validation cohort) and who were randomly assigned to remote ischaemic preconditioning or a sham procedure. The association between the ratio of preoperative urinary concentrations of DKK3 to creatinine (DKK3:creatinine) and postoperative AKI, and subsequent kidney function loss was assessed.

Results: In the 733 patient in the derivation cohort, urinary concentrations of DKK3 to creatinine that were higher than 471 pg DKK3 per milligram of creatinine were associated with significantly increased risk for AKI (OR 1.65, 95% CI 1.10–2.47, p=0.015), independent of baseline kidney function. High urinary DKK3:creatinine concentrations were independently associated with significantly lower kidney function at hospital discharge and after a median follow-up of 820 days. In the RenalRIP trial, preoperative urinary DKK3:creatinine concentrations higher than 471 pg/mg were associated with a significantly higher risk for AKI (OR 1.94, 95% CI 1.08–3.47, p=0.026), persistent renal dysfunction (OR 6.67, 1.67–26.61, p=0.0072), and dialysis dependency (OR 13.57, 1.50–122.77, p=0.020) after 90 days compared with DKK3:creatinine concentrations of 471 pg/mg or less. Urinary DKK3:creatinine concentrations higher than 471 pg/mg were associated with significantly higher risk for AKI and persistent renal dysfunction only in patients having a sham procedure, but not remote ischaemic preconditioning.

Conclusions: Preoperative urinary DKK3 is an independent predictor for postoperative AKI and for subsequent loss of kidney function. Urinary DKK3 might aid in the identification of patients in whom preventive treatment strategies are effective.

SA-OR014

The Association Between Intraoperative Fluid Balance and Postoperative AKI in Noncardiac Surgery

Masatoshi Nishimoto,[1] Miho Tagawa,[1] Maiko Kokubu,[3] Takayuki Hamano,[2] Masaru Matsui,[3] Masahiro Eriguchi,[1] Ken-ichi Samejima,[1] Yasuhiro Akai,[1] Kazuhiko Tsuruya.[1] *[1]Nara Medical University, Kashihara, Japan; [2]Osaka University Graduate School of Medicine, Suita, Japan; [3]Nara Prefecture General Medical Center, Nara, Japan.*

Background: Insufficient fluid administration may cause prerenal acute kidney injury (AKI) though excess fluid administration was reported to be associated with postoperative AKI in cardiac surgery. Little is known about the association between intraoperative fluid balance (IFB) and postoperative AKI in non-cardiac surgery.

Methods: This is a retrospective cohort study on adults who underwent non-cardiac surgery under general anesthesia from 2007 to 2011 at Nara Medical University. Exclusion criteria were urological or obstetric surgery, those with missing data for analyses, and preoperative dialysis. The exposure of interest was IFB and outcome variable was postoperative AKI, defined as KDIGO criteria, within 1 week after surgery. IFB was defined as (amount of fluid administration – urine output – amount of bleeding) / body weight. Data were analyzed using logistic regression models.

Results: Data for 5,168 subjects were available for analyses. Median age was 63, 46.7% were male, and baseline eGFR was 78.2. AKI was observed in 309 (6.0%). Higher IFB (per 1 SD) was independently associated with postoperative AKI after adjustment for baseline characteristics, intraoperative blood pressure, and intraoperative use of medications (Table 1). A subgroup analysis indicated the association between higher IFB and AKI was similar across intraoperative urine output or amount of bleeding (p for interaction = 0.27 and 0.43, respectively). There were no effect modifications by age, sex, preoperative renal function, or prior history of cardiovascular disease.

Conclusions: Higher IFB was independently associated with postoperative AKI. Association was similar across urine output. These results suggest that the association was not due to decrease in intraoperative urine output. Excessive fluid administration might cause renal congestion and subsequent AKI.

Table 1. Odds ratio for postoperative AKI associated with per 1 SD increase of intraoperative fluid balance.

Model	Odds ratio (95% CI)
Unadjusted	1.33 (1.22–1.45)
Model 1	1.20 (1.09–1.33)
Model 2	1.19 (1.08–1.32)
Model 3	1.19 (1.08–1.32)
Model 4	1.18 (1.07–1.31)
Model 5	1.18 (1.07–1.31)

Model 1 ; Adjusted for age, sex, body mass index, hypertension, diabetes mellitus, cerebrovascular disease, cardiovascular disease, type of surgery, emergency surgery, surgery of malignancy, regular use of ACE–I or ARB, other anti–hypertensive agents, diuretics, NSAIDs, contrast agents, preoperative hematocrit, serum albumin, logCRP, estimated GFR, and preoperative proteinuria.
Model 2 ; Model 1 + lowest intraoperative systolic blood pressure (SBP) (per 1 SD).
Model 3 ; Model 2 + maximum intraoperative delta SBP* (per 1 SD).
Model 4 ; Model 3 + intraoperative use of diuretics.
Model 5 ; Model 4 + intraoperative use of vasopressor.
* delta SBP = SBP at the beginning of surgery − lowest intraoperative SBP

SA-OR015

Plasma Biomarkers to Identify Patients at Increased Risk of CKD Following an Episode of AKI

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Background: The long-term sequelae of acute kidney injury (AKI) on renal function and mortality are increasingly appreciated, but there remains the need for prospective studies to develop strategies to identify those at greatest risk. We aimed to test whether biomarkers improve prediction of long-term outcomes of AKI.

Methods: In a single centre, participants were identified using a hospital-wide electronic AKI detection system. Plasma samples were collected at 3months after hospitalisation and a panel of 14 biomarkers were measured using a multiplex biochip array method. This was done firstly in a discovery cohort (112 AKI patients) with the most promising markers assayed in the remaining 388 AKI patients (validation cohort). Measures of renal function, proteinuria and survival were assessed at 1 and 3 years. CKD progression was defined as ≧25% decline in eGFR from baseline (pre-AKI) with a decline in eGFR stage.

Results: Median age was 70yrs (IQR 14), AKI episodes were predominantly stage 1 with median duration 3 days (IQR 3) and 29% had pre-existing CKD. There was no difference in age, gender or smoking status between discovery and validation cohorts. The proportion of AKI patients with CKD progression was 21% and 22% at year 1 and 3 respectively. Mortality was 4.3% at year 1 and 15.8% at year 3. Clinical factors associated with CKD progression included eGFR at 3months, albuminuria, severity and duration of AKI. In the discovery cohort, four markers were associated with CKD progression, including NGAL and cystatin C. Multiplexed models were developed to include biomarkers and clinical variables; when the models derived in the discovery cohort were applied to the validation cohort, AUC's improved e.g. AUC of best performing model in validation cohort 0.81 (95% CI 0.75 to 0.87) to discriminate those with CKD progression at 1 year.

Conclusions: Non-recovery of renal function is common following AKI, even in a general hospital population with predominantly AKI stage 1. We present data evaluating the utility of a panel of biomarkers to identify those at highest risk.

Funding: Private Foundation Support

SA-OR016

Arterial Stiffness Independently Predicts AKI in SPRINT

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Background: Arterial stiffness is associated with increased risk for kidney function decline and cardiovascular disease in both healthy and chronic kidney disease populations, independent of blood pressure. An episode of acute kidney injury (AKI) is also associated with increased risk for kidney disease progression and cardiovascular disease. However, it is unclear if arterial stiffness predicts AKI. We hypothesized that higher arterial stiffness at baseline was independently associated with time to incident AKI among participants in the Systolic Blood Pressure Intervention Trial (SPRINT).

Methods: Arterial stiffness was measured as carotid to femoral pulse-wave velocity (CFPWV) in 613 older adults at high risk for cardiovascular events who participated in an ancillary study of SPRINT. Cox proportional hazards analysis was used to examine the association between baseline CFPWV and time to incident AKI.

Results: Mean±sd age was 72±9 years and 40% (n=244) of participants were female. Mean±sd baseline CFPWV was 10.8±2.7 m/s in the whole cohort. In the 593 individuals who did not have an AKI event, baseline CFPWV was 10.7±2.7 m/s. In the 20 participants who had incident AKI, baseline CFPWV was 12.5±2.7 m/s ($p<0.01$) and median (IQR) time to AKI was 453 (289-724) days. After adjusting for demographics, randomization group, comorbidities, smoking, number of antihypertensive medications, baseline estimated glomerular filtration rate, urinary albumin to creatine ratio, and systolic blood pressure, risk of an AKI event was 32% higher for each m/s increase in baseline CFPWV (HR: 1.32, 95% CI: 1.13-1.53).

Conclusions: Greater large-elastic artery stiffness is a strong independent predictor of incident AKI in older adults at high risk for cardiovascular events. Clinical assessment of arterial stiffness may represent a useful tool to predict AKI, as well as a potential therapeutic target.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR017

Predicting Severe AKI, Fluid Overload, and Renal Replacement Therapy with the Renal Angina Index in Critically Ill Children

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Background: The Renal Angina Index (RAI) and urinary Neutrophil Gelatinase Associated Lipocalin (uNGAL) can be used to risk stratify patients for development of severe AKI (sAKI). Our research has focused on combining the RAI and NGAL for early detection and acute kidney injury (AKI) prediction.

Methods: Patients admitted to the Pediatric Intensive Care Unit (PICU) from 7/1/18 to 11/30/18, underwent an automated RAI assessment 12 hours after admission. RAI+ patients were defined by RAI ≥ 8 and had uNGAL assessed. A cutoff value of 150ng/mL was used to stratify patients with the primary outcome measure the development of sAKI (KDIGO Stage 2 or 3) through PICU day 4. Secondary outcomes included fluid overload (FO) and renal replacement therapy (RRT) at PICU day 7, as well as PICU length of stay (LOS).

Results: Over our study period 1103 RAIs resulted from 1022 patients. After excluding patients with ESRD and with admissions less than 2 days, 627 RAIs from 569 patients were examined, of which 63 (10.0%) were RAI+. The incidence of Day 2-4 sAKI was higher in the RAI+ cohort compared to RAI- patients (38% vs. 1.8%, *p<0.001*). With the addition of uNGAL, the rate of sAKI in RAI+NGAL+ was higher than in RAI+NGAL- or RAI- patients (55.5% vs 17.6% vs 1.8%, *p<0.0001*). RAI+ patients had a higher need for RRT compared to RAI- patients (13% vs. 0.4%, *p<0.001*). PICU and hospital length of stay were also longer in RAI+ patients: PICU LOS 4.6 vs 3.1 days (*p<0.02*), Hospital LOS 17.8 vs 7.5 days (*p<0.001*). There was no significant difference between RAI+/- patients in the occurrence or duration of FO (*p=0.14, p=0.11*).

Conclusions: The RAI alone continues to be a good rule-out test for sAKI in the PICU, and addition of NGAL is promising for improved sAKI prediction. Additional research needs to be conducted on a larger sample size to better assess the clinical relevance of the RAI NGAL model in predicting sAKI and other relevant outcomes.

Funding: NIDDK Support

Performance of RAI and NGAL in Predicting sAKI

	RAI ≥ 8 on Day 2-4 sAKI	RAI ≥ 8 + NGAL ≥ 150ng/mL on Day 2-4 sAKI
Negative Predictive Value (NPV)	98.2% (97.1% to 99.0%)	97.8% (96.7% to 98.5%)
Positive Predictive Value (PPV)	38.1% (29.8% to 47.2%)	55.2% (39.6% to 69.8%)
Sensitivity	70.6% (52.5% to 84.9%)	55.2% (35.7% to 73.6%)
Specificity	93.4% (91.1% to 95.3%)	97.8% (96.2% to 98.8%)

SA-OR018

Hemoglobin A1c and Major Adverse Kidney Events After Cardiac Surgery

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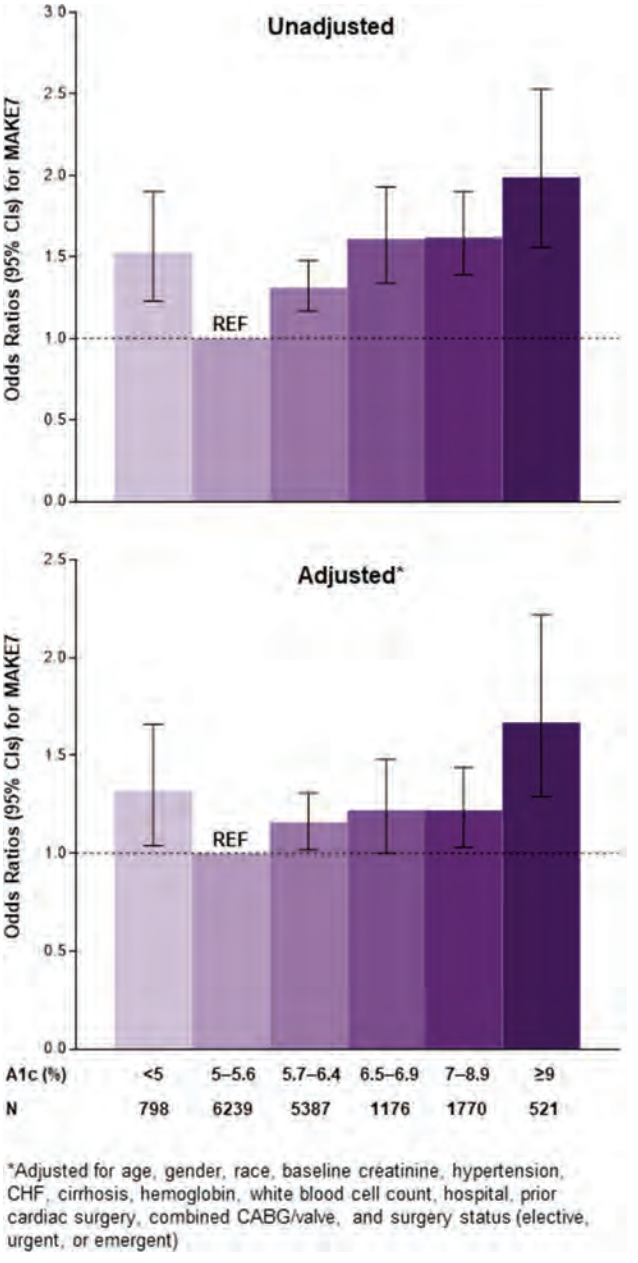
Background: Diabetes mellitus (DM) is a well-known risk factor for acute kidney injury (AKI). However, nearly all prior studies in the setting of AKI assessed DM as a dichotomous variable. We investigated whether hemoglobin A1c, assessed categorically and continuously, associates monotonically and independently with AKI following cardiac surgery.

Methods: We performed a retrospective cohort study in 15,892 patients who underwent cardiac surgery at two medical centers in Boston, MA, between 2008-2018. The primary exposure was the most recent A1c within 6 months prior to surgery. We assessed A1c in 6 categories: low (<5%), reference (5–5.6%), prediabetes (5.7–6.4%), well-controlled DM (6.5–6.9%), moderately-controlled DM (7–8.9%), and poorly-controlled DM (≥9%). The primary endpoint was any Major Adverse Kidney Event occurring within 7 days of surgery (MAKE7), defined as an increase in serum creatinine ≥50%, dialysis, or death. We used multivariable logistic regression to adjust for potential confounders.

Results: The incidence of MAKE7 was 12%. Compared to the reference group, we observed a monotonic increase in the risk of MAKE7 with higher A1c categories. Patients with an A1c ≥9 vs. 5–5.6% had a nearly two-fold higher risk of MAKE7 in unadjusted models (odds ratio, 1.99; 95% CI, 1.56 to 2.53). We found similar results in multivariable adjusted models that included 13 key variables (Figure). We also found similar results in models that assessed higher stages of AKI. When assessed as a continuous variable, the adjusted odds ratio for MAKE7 per 1-percent increase in A1c was 1.10 (95% C, 1.05 to 1.15). Finally, patients with an A1c <5% also appeared to be at increased risk of MAKE7.

Conclusions: Both higher and lower hemoglobin A1c values are independently associated with higher risk of MAKE7 following cardiac surgery.

Funding: NIDDK Support



*Adjusted for age, gender, race, baseline creatinine, hypertension, CHF, cirrhosis, hemoglobin, white blood cell count, hospital, prior cardiac surgery, combined CABG/valve, and surgery status (elective, urgent, or emergent)

SA-OR019

Contrast-Associated AKI Is Not Reflective of Intrinsic Injury

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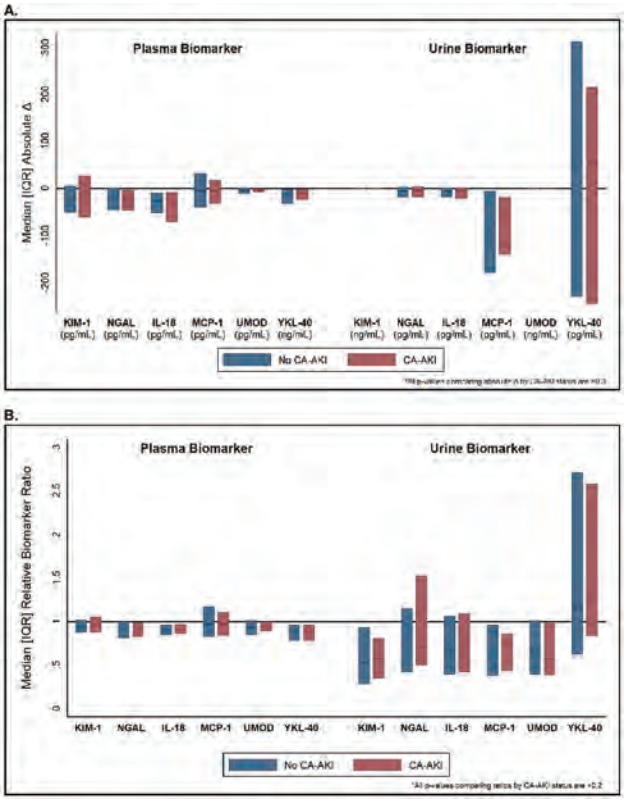
Background: There is controversy regarding the mechanism of contrast-associated acute kidney injury (CA-AKI). Biomarkers may provide insight into whether the etiology of CA-AKI is mediated by nephron injury. The PRESERVE trial followed participants for CA-AKI and 90-day major adverse kidney events and death (MAKE-D) after contrast angiography. In this sub-study, we evaluated the association of the absolute changes (Δ) and relative ratios of urine and plasma biomarkers with CA-AKI and MAKE-D.

Methods: We measured injury (KIM-1, NGAL, IL-18) and repair (MCP-1, UMOD, and YKL-40) proteins in urine and plasma at baseline and 2-4 hours post-angiography in a subset of PRESERVE trial participants. We calculated the absolute Δ and relative ratio between post-operative and baseline levels. We then assessed the association between absolute Δs and relative ratios with CA-AKI and MAKE-D.

Results: Participants (n=922) were predominately male (96%), diabetic (82%) with mean±sd age of 70±8 years. 73 and 60 participants experienced CA-AKI and MAKE-D, respectively. The absolute Δs and relative ratios were not statistically different by CA-AKI status (**Figure**). The majority of participants experienced an insignificant decrease in biomarkers regardless of CA-AKI or MAKE-D status. Findings remained after indexing urine biomarkers to urine creatinine and after adjusting for baseline eGFR and urine albumin to creatinine ratio.

Conclusions: The lack of significant differences in injury and repair biomarkers in patients by CA-AKI and MAKE-D status suggests that CA-AKI is not mediated by intrinsic nephron injury. While our findings need to be validated, our results can help advance pharmacological developments for the prevention of CA-AKI.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute (R01HL085757), Veterans Affairs Support



SA-OR020

ACE-I/ARB Use and Outcomes After Hospitalized AKI

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Background: The risk-benefit ratio of ACE-I/ARB therapy after an AKI episode is unclear.

Methods: We studied 1570 patients recently discharged from hospital and enrolled in a multi-center prospective cohort study (ASSESS-AKI). Follow-up began 3 months after index hospitalization and continued through November 2018. Half of the participants had AKI during the index hospitalization. ACE-I/ARB use and covariates were ascertained 3 months after discharge from the index hospitalization. We used multivariable Cox regression adjusting for demographics, cardiovascular disease, diabetes mellitus, heart failure (HF), blood pressure, urine protein to creatinine ratio, and eGFR to examine the association between ACE-I/ARB use and subsequent death, AKI (≥50% difference between peak and nadir inpatient serum creatinine), renal progression (ESRD or halving of eGFR), and adjudicated HF events.

Results: Among study participants who did not have AKI during index hospitalization (N=806), mean age was 65 years, mean eGFR 74 ml/min/1.73m^2, and 45% self-reported use of ACE-I/ARB 3 months after hospitalization. Among study participants who did have AKI during index hospitalization (N=764), mean age was 64 years, mean eGFR 65 ml/min/1.73m^2, and 50% self-reported use of ACE-I/ARB 3 months after hospitalization. Mean follow-up time was 3.6 years. ACE-I/ARB therapy 3 months after an AKI hospitalization was associated with a lower risk of another hospitalized AKI event and a lower risk of death (Table).

Conclusions: Use of ACE-I/ARB in survivors of hospitalized AKI was not associated with increased risk of subsequent AKI but was associated with lower risk of death.

Funding: NIDDK Support

Outcomes beyond 3 months after index hospitalization (no. of events)	Adjusted HR for ACE-I/ARB use 3-months after index hospitalization (95% CI)		P-value for interaction between ACE-I/ARB use 3 months after index hospitalization and AKI during index hospitalization
	AKI during index hospitalization (N=764)	No AKI during index hospitalization (N=806)	
AKI (442)	**0.75 (0.58, 0.97)**	1.23 (0.90, 1.67)	0.01
Death (320)	**0.73 (0.55, 0.97)**	0.69 (0.46, 1.04)	0.29
Renal progression (139)	**0.81 (0.55, 1.21)**	0.49 (0.23, 1.07)	0.74
HF (215)	**0.91 (0.64, 1.29)**	1.34 (0.82, 2.19)	0.10

SA-OR021

Clonal Hematopoiesis in ANCA-Associated Vasculitis

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Background: Antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitides (AAV) are induced by binding of ANCA IgG to myeloid cells and their subsequent activation. Autoantigen expression has been described to be dysregulated on both molecular and protein expression level in AAV patients. Recently, clonal hematopoiesis of indeterminate potential (CHIP), which is defined by the presence of a somatic mutation in the peripheral blood of individuals without evidence of hematologic neoplasms, has been linked with increased risk of hematologic cancer and cardiovascular disease. Here we aimed to characterize CHIP in patients with AAV.

Methods: 112 patients with AAV (median age 64, range 18-84) were screened for CHIP using targeted sequencing. mRNA expression of PR3 and MPO in peripheral blood leukocytes was quantified by qPCR, ANCA autoantigen expression and neutrophil reactive oxygen generation were measured by flow-cytometry.

Results: CHIP was discovered in 34 out of 112 AAV patients (in total of 46 somatic mutations), which is a higher prevalence than expected in age-matched healthy controls (30.4% vs. 13.5%, p<0.001). The overall frequency of CHIP increased with age, however, 18.2% of patients <55 years had CHIP. The most frequently mutated genes were *DNMT3A* (19/46=39.1%), *TET2* (7/46=15.2%), and *ASXL1* (4/46=8.7%). CHIP was not associated with disease activity, ANCA subtype, or therapy. No differences in blood counts, creatinine levels, comorbidities, the development of malignancies, disease activity status, and AAV relapse risk were observed. However, disease manifestation patterns differed: CHIP^{positive} GPA patients showed less renal (68.2% vs. 88.5%, p=0.049) and nervous system involvements (0% vs. 19.2%, p=0.028). Longitudinal analysis of 23 CHIP clones in 19 selected patients revealed that more than 25% of patients showed an increase in clone size over time. Finally, a downregulation of both PR3 and MPO mRNA in peripheral blood leukocytes and significant less ROS production after ANCA IgG stimulation of neutrophils from CHIP^{positive} AAV patients compared to CHIP^{negative} patients (stimulation-index aMPO 7.8±5.4 vs. 15.5±9.3 and aPR3 6.8±3.1 vs. 13.2±7.7) was found.

Conclusions: Our findings provide novel experimental evidence of CHIP in AAV patients. Additionally, we found a functional impact of CHIP on ANCA-related neutrophil functions.

SA-OR022

Staphylococcus Aureus-Induced Tissue Resident Memory T Helper 17 Cells ($T_{RM}17$ Cells) Drive Renal Autoimmune Disease

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Background: Tissue resident memory T (Trm) cells represent a new type of memory cells that reside in peripheral organs without recirculating. They provide rapid on-site immune protection against previous exposed pathogens. However, it remains to be clarified whether Trm cells also interfere with responses unrelated to the primary infection, such as organ-specific autoimmunity.

Methods: To study Trm cells, we used a combined approach of flow cytometry, histology and single cell RNA-sequencing. Human kidney tissue was obtained from tumour-nephrectomies. In mice, renal Th17 cells were induced by S. *aureus* infection. GN was induced with the nephrotoxic sheep serum or by immunisation with a fragment of the α3 chain of type IV collagen. We also used *Listeria monocytogenes* in another infection model.

Results: We found high frequencies of CD4$^+$ CD69$^+$ Trm cells of the Th17 phenotype, which we identified based on homology to published core transcriptional and protein data sets. We operationally named them Trm17 cells. CD4$^+$ Th17 cells are involved in the response to major human pathogens such as *S. aureus*, and play a critical role in autoimmunity such as crescentic glomerulonephritis (cGN). We established a mouse model of *S. aureus* infection that resulted in initially high renal bacteria titres and a profound accumulation of Th17 cells

in the kidney. Renal Th17 cells persist long-term (>100 days) after clearance of the infection, present with the phenotype of Trm cells and partially protect against re-infection. Induction of autoimmune kidney disease (cGN) in mice, which recovered from *S. aureus* infection, resulted in a more rapid and aggravated renal Th17 response and consequently developed a more severe course of cGN. By labelling renal cells in photoconvertible Kaede-transgenic mice, we were able to demonstrate that *S. aureus* induced Trm17 cells contribute significantly to the enhanced local IL-17 immune response in cGN.

Conclusions: Thus, pathogen-induced Trm17 cells in peripheral tissues are capable of rapidly responding to an antigenic unrelated challenge thereby driving renal autoimmune diseases. Our data suggest that Trm cells might have a previously unknown role in amplifying organ-specific autoimmunity.

Funding: Government Support - Non-U.S.

SA-OR023

Infiltrating Citrullinated Histone (CitH3)-Positive Neutrophils May Be Involved in Active Glomerular and Interstitial Lesions in ANCA-Related Vasculitis

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Background: Activated neutrophils release neutrophil extracellular traps (NETs), resulting in cell death called NETosis. NETs formation has been reported to be involved in the onset of systemic lupus erythematosus and ANCA-related vasculitis (AAV). However, the precise mechanism is unknown. Citrullination of histones is an essential step for NETs formation, and the presence of citrullinated histones (CitH3) in neutrophils may be involved in disease induction and activity. We examined an association between infiltrating neutrophils with/without CitH3 and disease specificity and activity in various glomerulonephritis (GN).

Methods: We selected following cases, who presented proliferative GN with neutrophil infiltration; AAV (n=8), lupus nephritis (LN) (n=5), Henoch schonlein purpura nephritis (HSPN) (n=5), and post-streptococcal acute GN (PSAGN) (n=5). We assessed clinical characteristics and histopathological findings and examined myeloperoxidase (MPO)-positive (+) infiltrating neutrophils with or without CitH3 in glomeruli and interstitium and association with the necrotizing and crescentic glomerular lesions and tubulointerstitial lesions.

Results: Number of MPO+ neutrophils in glomeruli was significantly higher in PSAGN, LN and HSPN than in AAV. In LN, MPO+ neutrophils were found mainly on the margin of glomerular tufts which formed wire-loop lesions. In part of them, CitH3+ neutrophils were seen. In PSAGN and HSPN, many MPO+ infiltrated in glomeruli, however, only a few CitH3+ neutrophils. In contrast, the frequency of CitH3+ neutrophils in AAV was significantly higher while the number of MPO+ neutrophils was significantly lower than in other diseases. CitH3+ neutrophils were observed in necrotizing lesion along glomerular capillaries. Moreover, the frequency of CitH3+ neutrophils was significantly higher not only in glomeruli but also in interstitium than in the others. In addition, peritubular capillaritis with CitH3+ neutrophils was remarkable.

Conclusions: CitH3 immunostaining was useful tool for identifying activated neutrophils. In AAV cases, the frequency of CitH3+ neutrophils in both glomeruli and interstitium was significantly higher. The frequency of CitH3+ neutrophils is not only a disease specific marker but also a possibility of becoming a marker for disease activity in AVV.

SA-OR024

CFHR5 Deposition in ANCA-Associated Glomerulonephritis

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Background: The complement system has been found to play a role in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Complement factor H (CFH) is a negative regulator of complement C3 activation. Complement factor H related protein 5 (CFHR5) competitively binds factor 3 yet enables further complement activation. We hypothesized CFHR5 facilitates more aggressive renal ANCA disease.

Methods: Here, we investigated CFHR5 deposition in biopsies of patients with ANCA-associated glomerulonephritis (GN) from a multicenter cohort (n=207) and correlated it with clinical outcome. Granular mesangial and endothelial deposition was scored semiquantitatively (0-3).

Results: Initial renal function at time of diagnosis did not correlate with CFHR5 staining. Patients, however, who reached end stage kidney disease during-follow up were found to have a more prominent CFHR5 deposition than patients who remained dialysis independent ($p<0.0001$). Patients suffering from renal relapsing disease and patients who died during follow-up showed a stronger CFHR5 positivity as well ($p=0.01$, $p=0.03$).

Conclusions: Glomerular CFHR5 positivity is associated with renal outcome in ANCA-associated GN and may serve as a prognostic marker in the disease.

SA-OR025

Induction of Eosinophilic Granulomatosis with Polyangiitis by Myeloperoxidase-ANCA in Mice with Allergic Airway Disease

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Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a phenotype of ANCA vasculitis associated with asthma, and blood and tissue eosinophilia. EGPA is characterized by eosinophil-rich infiltrates, granulomatous inflammation, necrotizing vasculitis and pauci-immune crescentic glomerulonephritis (CGN). We hypothesized that EGPA can be induced by injecting anti-MPO into mice with asthma-like disease.

Methods: Ovalbumin (OVA) or house dust mites (HDM) were used to induce acute allergic airway inflammation in C57Bl6 mice that were injected either intraperitoneally (i.p.) with 20ug OVA on days -21 and -7 and administered intranasally (i.n.) 1% OVA in saline on days 1-5; or administrated 25ug HDM protein i.n. in 20ul PBS for 5 days, followed by 2 days of rest, then repeated for another week, followed by 2 daily HDM doses. Thereafter, mice received 75ug/g body weight anti-MPO IgG i.p. Mice were sacrificed 6 days after anti-MPO injection.

Results: Control mice receiving OVA(n=3) or HDM(n=3) but no anti-MPO developed mild eosinophil-rich pulmonary airway inflammation without pulmonary hemorrhage, granulomatous lesions, or CGN. Mice receiving anti-MPO without OVA or HDM (n=3) developed CGN but no lung lesions. Six days after iv injection of anti-MPO IgG, OVA(n=3) or HDM (n=3) treated mice developed more extensive eosinophil-rich pulmonary inflammation, acute capillaritis with hemorrhage and granulomatous inflammation containing numerous eosinophils with admixed multinucleated giant cells. All mice receiving anti-MPO had similar levels of serum anti-MPO and developed similar CGN severity (avg. crescents with OVA 18.7%, HDM 18.7% and anti-MPO alone 18%); whereas control mice treated with OVA or HDM alone had no CGN.

Conclusions: Mouse models of anti-MPO induced EGPA can be generated in mice with acute allergic airway disease. We hypothesize that respiratory tract neutrophils primed by the allergic airway disease are activated by anti-MPO IgG, and amplify the eosinophil-rich inflammation resulting in pulmonary capillaritis and granulomatosis. These models provide useful tools for studying pathogenesis and therapeutic strategies for EGPA.

Funding: NIDDK Support

SA-OR026

Cathepsin C as a Treatment Target in ANCA Vasculitis

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Background: Neutrophil serine proteases (NSPs) of neutrophils and monocytes contribute to ANCA-associated vasculitis (AAV). Cathepsin C (CatC) proteolytically activates pro-NSPs in the bone marrow (BM) producing mature neutrophil elastase (HNE), cathepsin G (CatG), and PR3 - a major ANCA antigen. We showed previously that CatC gene-deficient mice were protected from AAV, implicating CatC as a treatment target.

Methods: We characterized NSPs and NSP-mediated functions in healthy individuals and Papillon-Lefèvre syndrome (PLS) patients with CatC loss-of-function mutations and developed a highly specific CatC inhibitor to reduce NSPs in a human neutrophil stem cell model and in mice.

Results: NSP proteins and proteolytical activity were abrogated in neutrophils and monocytes from PLS patients. PLS cells gave a negative PR3-ANCA, showed reduced membrane-PR3 (mPR3) on viable and apoptotic neutrophils, and supernatants (SN) from activated PLS neutrophils caused less endothelial cell (EC) damage. We developed the pharmacological CatC-inhibitor BI01169740 that strongly reduced NSP proteins (by 80% for PR3, 94% for HNE, and 99% for CatG) and the corresponding proteolytic activity (by 98% for PR3, 88% for HNE, and 79% for CatG) in differentiated neutrophils without affecting cell differentiation. mPR3 on viable and apoptotic differentiated neutrophils was diminished, viable cells showed less respiratory burst to PR3-ANCA, and SN caused less EC damage. Finally, 12-day treatment of Bl6 mice with increasing CatC inhibitor BI01169740 doses (0.05, 0.5, and 5 mg/kg/qd) lead to increasing compound plasma exposure (15±1, 164±26, and 1195±57 nM) and BM (478±52, 512±25, and 1680±190 nM), respectively. The highest dose strongly reduced NSP proteins and activity in BM cells, and reduced HNE activity in neutrophils from bronchoalveolar lavage fluid.

Conclusions: CatC gene-deficiency down-regulates NSPs and NSP-dependent neutrophil functions with relevance to ANCA. CatC inhibition with the novel BI01169740 compound recapitulates these effects in a stem cell model *in vitro* and effectively reduces NSP proteins and proteolytical activity in mice. These findings provide us with the opportunity to explore pharmacological CatC inhibition as a treatment strategy in AAV disease models and ultimately in AAV patients.

Funding: Commercial Support - Boehringer Ingelheim, Government Support - Non-U.S.

SA-OR027

Long-Term Follow-Up of a Glucocorticoid-Minimising Regimen for Remission Induction in ANCA Vasculitis (AAV)

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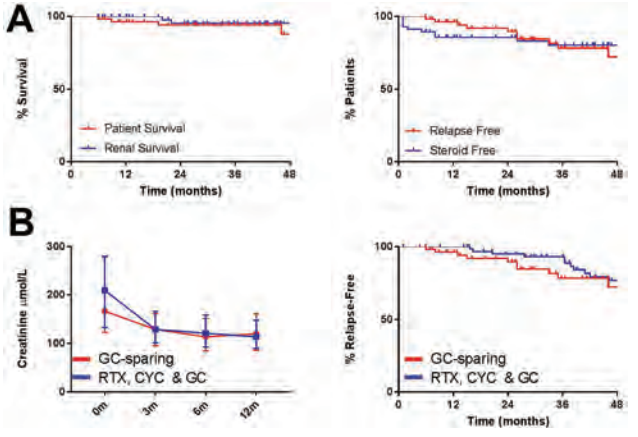
Background: Glucocorticoids (GC), though a mainstay of treatment for AAV, have significant adverse effects. We previously reported successful short-term outcomes using a GC-sparing treatment regimen. Here, we report long term outcomes in an extended cohort of patients treated with this protocol.

Methods: Patients were treated at 2 centres with rituximab (RTX) 2x1g, low-dose iv cyclophosphamide (CYC), and a short course of oral GC of <2 weeks duration, followed by maintenance azathioprine/MMF. Data reported as median ± IQR.

Results: 58 patients with new (84%) or relapsing (16%) AAV are included, with average follow up of 37 (23-46) months. 65% were MPO-ANCA+ve, 29% PR3-ANCA, 5% ANCA negative. Initial BVAS, CRP and creatinine were 14 (12-19), 46 (11-90) mg/L, and 176 (131-270) μmol/L, respectively. 90% had biopsy-proven renal involvement. The median dose of GC during induction was 960 (781-1276) mg. 5 patients (9%) required re-introduction of GC during the first 3 months for active disease; all patients subsequently achieved remission by 3 months, which was sustained in 91% at month 12. At 3 years, 96% were alive, 95% with independent renal function.19% had relapsed, however the majority (80%) remained free of GC (Figure 1A). There were no significant differences in renal or relapse-free surival compared to a previous cohort treated with a comparable RTX+CYC regimen, along with standard steroid dosing (Figure 1B).

Conclusions: Rapid GC withdrawal was safe and effective in the majority of cases following induction with RTX+CYC. Long-term patient, renal and relapse-free survival are comparable to published cohorts treated with standard GC. A small proportion required early re-introduction of GC, such that careful monitoring is required, though GC avoidance was feasible in the majority. Controlled studies are warranted to compare the efficacy of this regimen to current standards of care.



SA-OR028

A Randomized Controlled Trial of Rituximab (RTX) vs. Azathioprine (AZA) After Induction of Remission with RTX for Patients with ANCA-Associated Vasculitis (AAV) and Relapsing Disease

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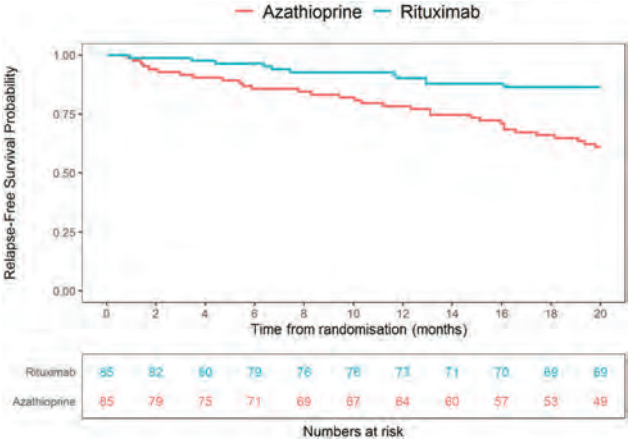
Background: RTX is an effective remission induction therapy in AAV. However, the effect of RTX is not sustained, and relapse rates are high, especially in patients with a history of relapse. The RITAZAREM trial is an international, open label, randomized, controlled trial of patients with AAV with relapsing disease comparing the efficacy, after remission induction with RTX, of repeat dose RTX or AZA as relapse prevention strategies.

Methods: Patients with relapsing AAV received induction therapy with RTX and glucocorticoids (GC). If remission was achieved by month 4, patients were randomized 1:1 to receive RTX (1000mg every 4 months for 5 doses) or AZA as maintenance therapy. Patients were followed for a minimum of 36 months, with a primary outcome of time to disease relapse.

Results: 190 patients were enrolled and 170 randomized at month 4 (85 to RTX; 85 to AZA). Data are complete on all patients up to at least month 24. Median age was 59 years (range 19-89), with a prior disease duration of 5.3 years (0.4-38.5). 123/170 (72%) of patients were historically positive for anti-PR3 ANCA; 104 (61%) were enrolled after a major relapse, and 48 (28%) received a higher dose GC induction regimen. 114 (67%) patients had prior renal involvement. RTX was superior to AZA in preventing relapse with a preliminary overall HR estimate of 0.36 (95% CI 0.23-0.57, p<0.001) and a during-treatment HR estimate of 0.30 (95% CI 0.15-0.60, p<0.001) (Figure 1). By 24 months after entry, 20 months after randomization, 11/85 (13%) patients in the RTX group had experienced a relapse compared to 32/85 (38%) in the AZA group. 9 (22%) patients in the RTX group and 31 (36%) patients in the AZA group experienced at least one severe adverse event.

Conclusions: RTX was superior to AZA in the prevention of relapse in patients with AAV with a prior history of relapse following induction of remission with RTX

Funding: Commercial Support - Genentech/Roche



SA-OR029

In Vivo Pooled CRISPR/Cas9 Screening with Single Cell Transcriptome Readout to Analyze Genetic Modifications in Primary Murine T Cells in Crescentic Glomerulonephritis

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Background: CRISPR/Cas9-based screening approaches usually lack the analysis of transcriptional perturbations caused by genetic modifications. In contrast, investigation of individual genetic modifications is time consuming and expensive. Therefore, CRISPR droplet sequencing (CROP-seq) has been developed to perform in vitro pooled CRISPR screening with single-cell transcriptome readout. However, examining changes in the cellular phenotype due to genetic modifications is strongly dependent on the local micro-environment. To address this, we have established an approach to target renal T cells in a mouse model of crescentic glomerulonephritis (cGN) to investigate transcriptional perturbations at the single cell level under the influence of a genetic modification in the context of renal autoimmunity.

Methods: CD4+ T cells from Il17a^{Cre} x Cas9^{Gfp} mice were polarized towards a Th17 phenotype and transduced with lentiviral vectors encoding BFP and individual guide-RNAs (gRNAs) targeting IL17A, CD2 or scrambled-control. In another set of experiments, cells were transduced with a pool of gRNAs targeting 28 genes. Subsequently, cells were transferred into Rag1-deficient mice and experimental cGN (nephrotoxic nephritis) was induced. At day 10 renal T cells were analyzed by flow cytometry for protein expression in case of individual gRNAs or FACS-sorted and subjected to Single Cell RNA-seq in the pooled approach.

Results: Using individual gRNAs, we identified a highly significant reduction of IL17A producing cells after treatment with anti-Il17a gRNA and of cells' surface expression of CD2 after treatment with anti-CD2 gRNA, while scrambled-gRNA had no effect on IL-17A and CD2. Furthermore, we show that a pool of gRNAs targeting 28 genes can be used to identify individual transcriptional profiles of cells with defined gene knockdowns.

Conclusions: In vivo CROP-seq is a new technique that enables CRISPR-screens with single cell transcriptome read-out in experimental mouse models for the first time. This approach might be of major interest for the investigation of genetic modifications not only in the context of T cell-driven autoimmunity but also in a broader range of applications.

Funding: Government Support - Non-U.S.

SA-OR030

RNA Sequencing of Microdissected Kidney Biopsies Differentiates HIV+ FSGS from HIV-Negative FSGS

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Background: Antiretroviral therapy (ART) has reduced the incidence of "classic" HIV-associated nephropathy (HIVAN), characterized by rapidly progressive proteinuric CKD from underlying collapsing focal glomerulosclerosis and severe tubulointerstitial (TI) disease including tubular microcysts. Whether FSGS without other histologic findings of HIVAN in HIV+ persons represents a partially treated HIVAN phenotype or FSGS unrelated to HIV infection is unclear. We therefore compared gene expression in kidney biopsies from HIV+ persons with non-HIVAN FSGS to biopsies from HIV- persons with FSGS.

Methods: 27 kidney biopsies from HIV+ persons with FSGS were microdissected, and glomerular and TI RNA were analyzed by RNAseq. We compared RNA expression from these samples to that of 22 HIV-negative FSGS biopsies which were matched for eGFR, demographic, and histologic variables. RNAseq data were processed and analyzed using the pipeline consisting of raw data processing, normalization, batch correlation and differential analysis based on LIMMA test. Differentially expressed genes were subjected to enrichment analysis for gene ontology function and KEGG pathways.

Results: Principal component analysis demonstrated that glomerular and TI RNA from HIV+ FSGS biopsies clustered separately from HIV- FSGS biopsies. 1081 genes were differentially expressed by 1.5 fold in glomeruli from HIV+ vs. HIV- biopsies, and 607 genes were differentially expressed in TI from HIV+ vs. HIV- biopsies. Pathway analysis revealed that the predominant cellular pathways represented by differentially expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. HIV sequences were detected in the majority of HIV+ biopsies and were detected in more glomerular than TI samples.

Conclusions: These results suggest that FSGS occurring in HIV+ persons may have a different molecular pathogenesis than FSGS occurring in HIV- persons and may reflect residual effects of HIV not fully treated by ART. Future studies are needed to determine whether new treatment strategies targeting deleterious effects of HIV can improve kidney outcomes in this population.

Funding: NIDDK Support

SA-OR031

HIF Stabilizer Decreases Mitochondrial Oxygen Consumption in Skeletal C2C12 Myotube

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Background: Erythropoietin (EPO) and hypoxia-inducible factor (HIF) stabilizers (PH inhibitors) are efficient therapeutic modalities against anemia in CKD. However, extra-renal action of PH inhibitors has not been fully investigated. Previous reports caution us about the actual misuse of PH inhibitors in doped athletes, but nonhematopoietic effects on skeletal muscles remain controversial.

Methods: To study direct pharmacological effects of roxadustat on skeletal muscles, cultured muscle cells were assessed from multiple perspectives including cell viability, myotube differentiation and glucose metabolism. Murine C2C12 myoblasts were cultured in media containing 2% horse serum, for differentiation. Quantitative PCR was applied for expression analysis of myogenin (Myog), differentiation marker, Myh-7, encoding a slow-twitch muscle isoform, Myh-1, 2, and 4, encoding fast-twitch isoforms and glycolytic enzymes such as lactate dehydrogenase (LDH), phosphoinositide-dependent kinase-1 (Pdk1), and glycogen synthase-1 (Gys1). Biochemical quantitative assay of lactate was also utilized. Glucose and mitochondrial metabolic profile was quantified with extracellular flux analyzer.

Results: Culture in the low serum media stimulated C2C12 myoblasts to differentiate and to fuse into multinucleated myotubes with enhanced expression of Myog and Myh-1, 2, 4, and 7. Roxadustat treatment did not affect myotube viability, morphology, or increase differentiation marker expression. However, 2-deoxyglucose uptake was enhanced. The treatment also elevated expression of Ldha, Pdk1, and Gys1, and promoted glycolytic rate with culture lactate concentration increased. By contrast, the treatment decreased the ratio of mitochondrial/nuclear DNA and down-regulated mitochondrial respiration, which lentivirus-mediated genetic silencing of HIF-1α in C2C12 cells reversed. Electron microscopic evaluation showed mitochondrial fragmentation in roxadustat-treated myotubes.

Conclusions: Roxadustat, a PH inhibitor to stabilize HIF that is beneficial for renal anemia treatment, may exert a direct effect on skeletal muscles. Although it did not affect cellular viability or morphology, roxadustat compromised the ability of cells to undergo oxidative phosphorylation, which action was mediated by HIF-1α, and directed cells to acceleration of glycolytic process and lactic acid generation.

SA-OR032

Hyperphosphatemia Contributes to Inflammation and Iron Dysregulation in Models of Normal and Impaired Renal Function

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Background: Fibroblast growth factor (FGF) 23 is a phosphaturic hormone that targets the kidney to promote urinary phosphate excretion. In patients with chronic kidney disease (CKD), serum concentrations of phosphate (Pi) and FGF23 gradually increase as renal function declines and associate with various pathologies, including systemic inflammation and anemia. Our previous studies revealed FGF23 contributes to inflammation by directly targeting hepatocytes via FGF receptor 4 (FGFR4) and inducing phospholipase Cg (PLCg) signaling and the expression of inflammatory cytokines. Experimental studies have shown Pi can accelerate CKD-associated pathologies, but direct effects of Pi on the liver are not well described. Here we compare the effects of Pi versus FGF23 on hepatocytes and determine their respective contributions to inflammation and anemia in the context of CKD.

Methods: We subject mice with global deletion of FGFR4 and wild-type littermates to increasing dietary Pi load (0.7%, 2.0%, or 3.0%) or an adenine-rich diet (used as a CKD model) in order to examine systemic inflammation and alterations in iron metabolism in the setting of normal and impaired renal function. In addition, we study primary mouse hepatocytes treated with FGF23 and increasing Pi concentrations and examine the activation of downstream signaling events and expression levels of specific target genes. Furthermore, we determine if co-treatment with inhibitors of Pi uptake and downstream signal mediators block the observed effects.

Results: A 3% Pi diet as well as an adenine-rich diet promote inflammation and iron dysregulation in mice. These effects are exacerbated in FGFR4 knockout mice. In cultured hepatocytes, expression of inflammatory cytokines, hepcidin and FGF23 are induced by Pi in a dose-dependent manner. Furthermore, Pi activates NFkB signaling and the inhibition of Pi uptake and of NFkB protects from Pi-induced effects.

Conclusions: We postulate that in CKD, gradual elevations in serum Pi promote inflammation and anemia by targeting the liver to induce gene programs which regulate the inflammatory response and iron metabolism. Our study indicates Pi effects may be independent of FGF23. Pharmacological approaches targeting hyperphosphatemia or hepatic Pi actions might alleviate various CKD-associated pathologies.

Funding: NIDDK Support

SA-OR033

PBI-4610 Improves Renal Function, Anemia, and Histopathological Abnormalities in an Adenine-Induced CKD Model

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Background: Adenine-supplementation is an effective tool to study the onset and progression of fibrosis and CKD-associated sequelae. Prometic's PBI-compounds show excellent safety and efficacy in both experimental models and in human studies. Here we tested a second-generation orally active PBI compound, PBI-4610, in adenine-induced renal injury.

Methods: Six to eight-week old male C57BL/6 mice were fed a regular (Control, n=9) or custom diet consisting of regular chow supplemented with 0.25% adenine for 30 days. After 7 days, mice were administered vehicle (H_2O, n=9) or PBI-4610 (100 mg/kg, n=10) by daily oral gavage. Blood sampling was done at day 0, 7 and 30. Reticulocytes were quantified by FACS analysis. Serum urea and creatinine levels were measured at endpoint by ELISA and HPLC respectively. Renal histology was assessed using H&E and Masson's trichrome stained kidney sections.

Results: Adenine decreased bodyweight, which was significantly improved by PBI-4610 at days 17, 21 and 24. Anemia was apparent as hematocrit (Hct) began to decline as early as 7 days post-adenine, however this was significantly improved by PBI-4610 at day 14, 21 and 30. FACS revealed reduced reticulocyte counts in vehicle-treated adenine mice compared to Control mice at day 14, however at day 30, levels were increased. PBI-4610 treatment maintained reticulocyte counts to normal levels. Similarly, hemoglobin was decreased in adenine-fed mice, but levels in PBI-4610 mice trended higher (p=0.059). At endpoint, blood urea nitrogen and serum creatinine were increased by adenine-feeding, however treatment with PBI-4610 significantly reduced these levels. Tubulointerstitial fibrosis, collagen deposition, tubular dilatation and inflammation were all significantly reduced by PBI-4610. Finally, survival rate in PBI-4610 treated mice increased from 30% in the vehicle group to 80%.

Conclusions: Taken together, PBI-4610 improves several key renal functional and structural abnormalities in adenine-induced CKD including anemia, fibrosis and renal function decline leading to improved survival rates. Although the mechanism of action remains incompletely resolved, the above findings suggest treatment with PBI-4610 may represent a novel therapeutic modality in CKD.

Funding: Commercial Support - Prometic Life Sciences Inc.

SA-OR034

C-FGF23 Peptide Protects Against Severe Hypoferremia During Acute Inflammation

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Background: Inflammatory stimuli induce functional iron deficiency, by increasing the expression of the hepatic iron regulatory peptide, hepcidin. Acute inflammation stimulates fibroblast growth factor 23 (FGF23) production in bone and leads to a dramatic increase in both *Fgf23* transcription and FGF23 cleavage and paradoxically leads to excess in C-terminal FGF23 peptides (cFGF23), but not intact hormone (iFGF23). This questions the physiological need for increased *Fgf23* transcription in this context and we hypothesized that cFGF23 peptides might actively participate in the regulation of iron metabolism by regulating hepcidin expression.

Methods: We induced acute inflammation in WT, FGF23-null and FGF23-DMP1^{cKO} mice using a single dose of 250ng/g of interleukin 1 beta (IL1b) and we analyzed the effects on iron homeostasis. We next used recombinant cFGF23 peptides as bait in cultured osteoblasts to immunoprecipitate (IP) and to identify binding partners by mass spectrometry (MS). We also verified binding between FGF23 peptides and putative partners using bio-layer interferometry (BLI). Finally, we administered cFGF23 to verify its impact on iron metabolism.

Results: As expected IL1b administration to WT mice led to low serum iron and transferrin saturation (TSAT) due to high hepcidin levels, and increased bone *Fgf23* expression and secretion of cFGF23 peptides ($p<0.05$). FGF23-DMP1^{cKO} mice had 90% lower FGF23 levels ($p<0.05$), but exhibited further reductions in serum iron and TSAT compared to IL1b-treated WT, due to higher serum hepcidin and liver *Hamp* (encoding hepcidin) mRNA, suggesting that cFGF23 reduces Hepcidin production. Using IP/MS, we next identified binding of cFGF23 peptides to members of the bone morphogenic protein (BMP) family, BMP2 and BMP9, established inducers of hepcidin, and we confirmed binding of BMP2 and BMP9 to cFGF23 by BLI. In WT mice, co-administration of cFGF23 and BMP2 or BMP9 prevented the increase in *Hamp* mRNA and circulating hepcidin levels resulting in normal serum iron levels and TSAT. In addition, injection of cFGF23 increased serum iron levels and TSAT in WT and FGF23-null mice.

Conclusions: This is the first study to provide a new direct role for bone-produced cFGF23 peptides to antagonize the inflammation-induced BMP signaling in the liver and inhibit the secretion of the iron regulatory peptide, hepcidin.

Funding: NIDDK Support

SA-OR035

Enteral Ferric Citrate Absorption Is Dependent on Ferroportin

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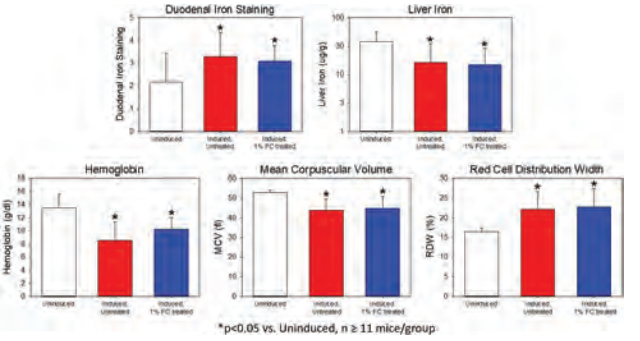
Background: Ferric citrate (FC) is approved as an iron replacement product in CKD non-dialysis patients with iron deficiency anemia. FC-delivered iron is enterally absorbed, but the specific mechanisms involved have not been specifically evaluated. The absorption of dietary iron and conventional supplements requires duodenal ferroportin (FPN). To assess whether or not enteral FC absorption is dependent on FPN, we evaluated the effects of FC in a tamoxifen-inducible, enterocyte-specific FPN knockout (KO) murine model (Villin-Cre-ERT2, FPN$^{flox/flox}$).

Methods: We assessed three groups: uninduced mice, induced mice (FPN KO), and induced mice (FPN KO) supplemented with 1% FC. Mice were injected with vehicle (uninduced group) or tamoxifen (induced groups) at ~7 weeks of age, then terminally assessed 7-8 weeks later. The treated induced mice had their diets supplemented with 1% FC for ~19 days pre-euthanasia.

Results: The FPN KO was effective, as 6 weeks after tamoxifen injection, the induced mice had ~4000 fold lower duodenal FPN mRNA expression than uninduced mice and undetectable FPN protein on the duodenal tissue Western blot. Confirming that 1% FC prevents anemia, uninduced mice placed on iron-deficient 4 ppm diets for 7 weeks (n=5) became anemic, but uninduced mice placed on iron deficient 4 ppm diets for 4 weeks, then supplemented with 1% FC for 3 weeks (n=6), were rescued from anemia (mean (SD) terminal hemoglobin of 13.8 (0.7) vs. 7.6 (0.8) g/dL, $p<0.001$). FPN KO mice on iron-sufficient 50 ppm diets developed anemia whether or not they were supplemented with 1% FC. The FPN KO groups had higher duodenal intracellular iron staining, lower liver iron concentration, lower hemoglobin, lower mean corpuscular volume, and higher red cell distribution width vs. the uninduced group (**Figure 1**). There were no differences between the untreated and 1% FC-treated FPN KO groups.

Conclusions: The 1% FC diet does not rescue iron deficiency anemia caused by enterocyte FPN KO. Enteral FC absorption is dependent on conventional enterocyte iron transport by FPN.

Funding: Commercial Support - Sponsored by Keryx Biopharmaceuticals, Inc., now a wholly-owned subsidiary of Akebia Therapeutics, Inc.



SA-OR036

Colchicine Does Not Affect Anemia or Inflammation in a Mouse Model of CKD

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Background: Previous studies point for a significant role of low grade inflammation mediated by the innate immune system in CKD and its complications. We have recently shown that anemia of CKD is associated with such increased inflammation, which impairs both HIF2-EPO-EPOR signals as well as iron homeostasis. Colchicine is a safe drug for long term use in humans, including children, mainly for the prevention of familial Mediterranean fever attacks, as well in gouty arthritis. In addition, colchicine attenuated both glomerular sclerosis and interstitial fibrosis without affecting systemic blood pressure in a model of CKD by 5/6 nephrectomy (Guan T et al, AJP 2013).

Methods: 7-8 wk old C57BL/6 mice were divided into 4 groups (C, C-Col, CKD, CKD-Col). CKD or control states were induced by adenine (0.3-0.2%) or control diet. Colchicine (30ukg/kg/day, IP) or saline were injected for 3 weeks, until sacrifice.

Results: Systemic inflammation (liver CRP, IL6, plasma platelet count) was elevated in CKD animals (140±15%, 151±37% and 239±27% respectively) but was unaffected by colchicine. Serum urea and creatinine were increased by ~ 50% in CKD animals but without differences between CKD-Col and CKD. Kidney IL6 and pSTAT3 were increased in both CKD groups but without differences between them. Anemia developed in this model of CKD (63±5% of C), in association with decreased iron (62±6% of C) and transferrin saturation (55±4% of C), decreased renal EPO (37±5% of C) and renal HIF2 mRNA (55±4% of C) but without differences between the uremic groups.

Conclusions: In this model of CKD associated anemia and inflammation (systemic and renal) colchicine was inefficient in preventing these complications, despite previous reports. Therefore, inflammation control through other pathways (sucj as IL1) may be needed.

SA-OR037

Preclinical Characterization of Vadadustat (AKB-6548), an Oral Small Molecule Hypoxia Inducible Factor Prolyl-4-Hydroxylase Inhibitor, for the Potential Treatment of Renal Anemia

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Background: We summarize preclinical pharmacological characterization of the small molecule hypoxia inducible factor-prolyl-4-hydroxylase (HIF-PHD) inhibitor, vadadustat (AKB-6548), an investigational drug in phase 3 development for the treatment of anemia in patients with chronic kidney disease (CKD). Pharmacological inhibition of PHD enzymes lead to the stabilization of hypoxia-inducible factor (HIF), a transcription factor which activates target genes that increase erythropoietin (EPO) synthesis, resulting in the production of new red blood cells.

Methods: Enzymatic IC50 values of vadadustat against the full-length human PHD isoenzymes, PHD1, PHD2, and PHD3, were measured by time-resolved fluorescence resonance energy transfer assay. Stabilization of HIF-1α and HIF-2α in the human hepatocarcinoma cell line Hep3B was measured by meso scale discovery technology. EPO and vascular endothelial growth factor (VEGF) were quantitated by ELISA. In vivo studies measured the pharmacokinetics and pharmacodynamics of vadadustat.

Results: Vadadustat inhibits PHD1, PHD2 and PHD3 at approximately equivalent nanomolar concentrations. Vadadustat metabolites are approximately 100-200 fold less potent for PHD2 compared to the parent compound. Moreover, vadadustat shows 2-oxoglutarate competitive inhibition against the human HIF-PHDs and vadadustat activity is insensitive to the presence of added iron. In Hep3B cells, PHD inhibition by vadadustat leads to the time-dependent stabilization of both HIF-1α and HIF-2α, which in turn results in the synthesis and secretion of EPO; stimulation of VEGF was not detectable. In vivo, single dose administration of vadadustat potently increases circulating levels of EPO, but not VEGF. Moreover, once daily oral dosing in mice and rats significantly increases hemoglobin, hematocrit and reticulocytes. Vadadustat exhibits a relatively short half-life in all non-clinical species evaluated and does not accumulate upon repeat dosing.

Conclusions: The pharmacology and safety of vadadustat support development for renal anemia. Vadadustat is an equipotent pan-PHD inhibitor which activates erythropoiesis through stabilization of both HIF-1α and HIF-2α without stimulation of VEGF in the preclinical setting.

Funding: Commercial Support - Akebia Therapeutics, Inc.

SA-OR038

The Association of sTNFR-1 and sTNFR-2 with Histopathologic Lesions and Progression to ESRD: The Boston Kidney Biopsy Cohort Study

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Background: The relationship of soluble tumor necrosis factor-1 (sTNFR-1) and sTNFR-2 with histopathologic lesions and progression to ESRD in individuals with biopsy-confirmed kidney disease is unknown.

Methods: We measured plasma sTNFR-1 and sTNFR-2 levels in 523 individuals enrolled into a prospective, observational cohort study of patients undergoing native kidney biopsy at three tertiary care hospitals. Two experienced renal pathologists adjudicated biopsy specimens for semiquantitative scores of histopathology. Linear regression models tested the association between biomarkers and histopathologic lesions. Proportional hazards models tested the association between biomarkers and risk of progression to ESRD.

Results: Mean age was 53±17 years and mean baseline eGFR was 56±36 ml/min/1.73m^2. sTNFR-1 and sTNFR-2 correlated with eGFR (R_s = -0.70 and -0.62, P<0.001, respectively). After adjustment for age, sex, race, and eGFR, sTNR-1 and sTNFR-2 levels were highest among individuals with glomerulopathies and diabetic nephropathy (Figure). sTNFR-1 and sTNFR-2 followed slightly different patterns of injury after multivariable adjustment (Figure). Both biomarkers were associated with more severe interstitial fibrosis/tubular atrophy and mesangial expansion. Only sTNFR-1 associated with more severe acute tubular injury and presence of inflammation in the nonfibrosed interstitium. Only sTNFR-2 associated with presence of endocapillary glomerular inflammation and segmental sclerosis. During a median follow-up time of 25 months, 78 individuals progressed to ESRD. sTNFR-1 and sTNFR-2 were each independently associated with greater than 2-fold increased risk of progression to ESRD (Figure).

Conclusions: Higher levels of sTNFR-1 and sTNFR-2 are independently associated with increased risk of progression to ESRD across a diverse set of biopsy-confirmed kidney diseases.

Funding: NIDDK Support

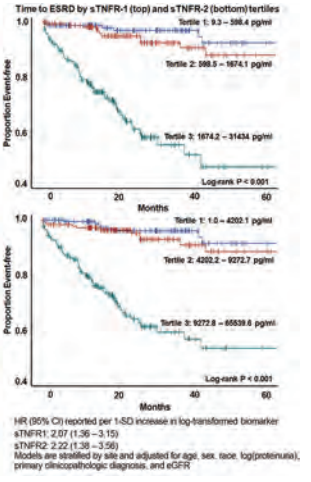
Differences in sTNFR-1 and sTNFR-2 by Clinicopathologic Diagnosis (top) and Histopathologic Lesion (bottom)

Primary Clinicopathologic Diagnosis	sTNFR-1	sTNFR-2
Proliferative glomerulonephritis	73.3**	44.8*
Non-proliferative glomerulonephritis	101**	91.6**
Paraprotein disease	20.9	-7.7
Diabetic nephropathy	87.8**	49.2
Vascular disease	24.6	24.6
Tubulointerstitial disease	16.2	-5.8
Advanced Chronic Changes	31	20.9

Percent differences are derived from multivariable linear regression models of natural log-transformed sTNFR-1 and sTNFR-2, respectively.
Models are adjusted for age, sex, race, and eGFR.
Reference category is 'Other' primary clinicopathologic diagnosis
P<0.05*
P<0.001**

Histopathologic Lesion	sTNFR-1	sTNFR-2
Endocapillary glomerular inflammation[a]	19.7	31*
Cellular crescents[a]	20.9	12.7
Fibrinoid necrosis[a]	25.9	15
Fibrocellular crescents[a]	10.5	13.9
Mesangial expansion[a]	24.6*	19.7*
Segmental sclerosis[a]	19.7	24.6*
Global glomerulosclerosis	2	-3
Acute tubular injury[b]	41.9*	18.5
Inflammation, nonfibrosed interstitium[c]	27.1*	19.7
Inflammation, fibrosed interstium[c]	4.1	8.3
Interstitial fibrosis/tubular atrophy[c]	23.4*	27.1*
Arterial sclerosis[a]	2	6.2
Arteriolar sclerosis[a]	-9.5	-9.5

Percent differences are derived from multivariable linear regression models of natural log-transformed sTNFR-1 and sTNFR-2, respectively.
Models are adjusted for age, sex, race, and eGFR
[a] Reference is absence of lesion
[b] Reference is none/mild lesion severity
[c] Reference is 0-25% of cortical volume affected
P<0.05*
P<0.001**



HR (95% CI) reported per 1-SD increase in log-transformed biomarker
sTNFR1: 2.07 (1.36 – 3.15)
sTNFR2: 2.22 (1.38 – 3.56)
Models are stratified by site and adjusted for age, sex, race, log(proteinuria), primary clinicopathologic diagnosis, and eGFR

SA-OR039

Two-Year Change in Galectin 3 and MMP-2 and Risk of ESRD: The Chronic Renal Insufficiency Cohort (CRIC) Study

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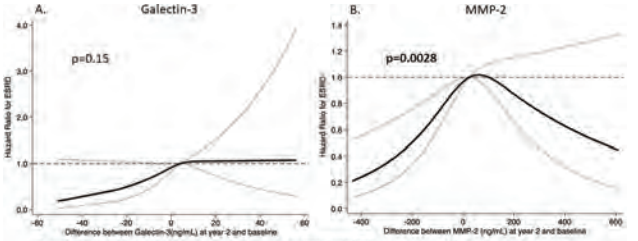
Background: Galectin-3 and matrix metalloproteinase-2 (MMP-2) have both been associated with kidney fibrosis, however, the relationship of these markers with chronic kidney disease (CKD) progression remains unclear.

Methods: A case-cohort study including a randomly selected sample of 1300 CRIC participants was conducted to characterize the association of two-year change in plasma galectin-3 and MMP-2 with subsequent development of end-stage renal disease (ESRD; N=542). Weighted Cox proportional hazards regression models used data from up to 8 years of follow-up, adjusted for sociodemographic, clinical and biochemical factors including eGFR and proteinuria in addition to galectin-3 or MMP-2 values from baseline.

Results: Two-year change in galectin-3 ranged from -51 to + 56 ng/mL with an overall mean change of 4.3 ng/mL, while change in MMP-2 ranged from -455 to +654 ng/mL (mean change: 25.4 ng/mL). Restricted cubic splines demonstrate non-linear associations for both markers (**Figure**). Increases in galectin-3 over two years did not appear to increase ESRD risk, but decreases may trend toward reduced risk of ESRD. The hazard ratio for MMP-2 reductions of 400 ng/mL was 0.2 (95% CI: 0.1-0.5).

Conclusions: Decreases in MMP-2 over two years are strongly and independently associated with marked reduction in the risk for ESRD among patients with established CKD. This pathway should be studied further to investigate possible interventions to reduce CKD progression risk.

Funding: NIDDK Support



Separate models. Adjusted for age, sex, race, education, baseline eGFR, urine protein, BMI, systolic blood pressure, hemoglobin, smoking, history of diabetes, history of CVD, urinary NGAL, Na, K, phosphate, FGF23, bicarbonate, CRP, IL1RA, IL1β, IL6, TGFβ, TNFα, Troponin T, BNP, and Galectin-3 (A) or MMP-2 (B) at baseline.

SA-OR040

The Pro-Fibrotic Serum Marker MMP7 Predicts Accelerated GFR Loss in the General Population

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Background: Age related loss of glomerular filtration rate (GFR) is a major contributor to the global chronic kidney disease (CKD) epidemic. CKD is associated with increased morbidity and mortality and there is a need for novel biomarkers that identify at risk persons at an early stage to delay or prevent CKD onset. Matrix Metalloproteinase (MMP) 2 and 7 are key players in interstitial remodeling and mediate renal fibrosis development in animal models. We investigated whether serum MMP2, MMP7 and their inhibitor TIMP1, were associated with accelerated age-related GFR decline and incident CKD in middle-aged individuals from the general population.

Methods: In the Renal Iohexol Clearance Survey (RENIS) we performed GFR measurements (using iohexol clearance) in 1627 subjects, aged 50-62 years, from the general population without self-reported diabetes, kidney or cardiovascular disease. 1324 (81%) had follow-up measurements after a median of 5.6 years. The biomarkers were analyzed in baseline serum samples with a Bioplex 200 machine. Using multiple logistic regression analysis, we evaluated the risk of accelerated GFR decline (defined as subjects with the 10% steepest GFR slope) and incident CKD (defined as GFR <60ml/min/1.73m^2).

Results: After adjustment for age, sex, baseline GFR and urinary albumin-creatinine ratio (ACR), higher levels of MMP7 were associated with an increased risk of accelerated GFR decline (Odds ratio (95% confidence interval)) per one SD increase in MMP7: 1.68 (1.39-2.04) and incident CKD: 1.71 (1.25-2.34). The results were attenuated, but remained significant in the fully adjusted model (1.48 (1.20-1.81) and 1.53 (1.08-2.18)). Prediction of accelerated GFR decline improved after addition of MMP7 to a model with age, sex, baseline GFR and ACR (aera under the ROC curve increased from 0.72 to 0.75 (p=0.054), continuous net reclassification improvement: 0.34 CI: 0.16-0.52). Similar results were obtained using alternative definitions of accelerated GFR decline such as ≤-3.0 ml/min/1.73m^2/year or a GFR decline rate twice the cohort mean (≤-1.68 ml/min/1.73m^2/year). MMP2 and TIMP1 showed no association with GFR decline.

Conclusions: The pro-fibrotic biomarker MMP7 was independently associated with increased risk of accelerated GFR decline and incident CKD in middle-aged persons from the general population.

Funding: Government Support - Non-U.S.

SA-OR041

Relation of a Parsimonious Model of Factors Derived from 10 Biomarkers of Kidney Tubule Health with Decline in eGFR in the SPRINT Trial

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Background: To move towards assimilation of the various information gained from multiple biomarkers, we have evaluated 10 urine biomarkers of kidney tubule health measured at baseline among SPRINT participants with chronic kidney disease (CKD). In prior analyses, we created summary scores of different dimensions of kidney tubule

health using unsupervised exploratory factor analyses. Four factors were derived and found to be strongly associated with CVD events; associations that were stronger than individual markers. The goal of the current study was to evaluate if these 4 factors of tubule health are related with progression of CKD in SPRINT.

Methods: The factors comprised Factor 1: "tubule injury/repair" (urine NGAL, IL-18, & YKL-40); Factor 2: "tubule injury/fibrosis" (urine KIM-1 & MCP-1); Factor 3: "tubule reabsorption" (urine alpha-1 microglobulin & beta-2 microglobulin); and Factor 4: "tubular reserve" (urine umod & serum iPTH & iFGF-23). We selected SPRINT participants with eGFR <60 ml/min/1.73m^2 at baseline and used linear mixed models to examine the association of the 4 factors of kidney tubule health with decline in kidney function.

Results: Among 2351 SPRINT participants two factors of tubule health, "tubule injury/fibrosis" and "tubular reserve" were associated with mean eGFR decline (percentage decrease per year), independent of baseline eGFR and albuminuria (Table). The magnitude of the association between these two factors and longitudinal eGFR changes was lower than the one seen with albuminuria (Table).

Conclusions: Assessment of tubule health by integrating tubule injury, fibrosis, and reserve factors provides information on CKD progression independent of baseline eGFR and albuminuria in persons with non-diabetic CKD.

Funding: NIDDK Support

Association of factors of tubule health and percentage of eGFR change per year

Factor of Tubule Health	% eGFR change/year per SD increase of vector (95% CI)*
-Injury/Repair	-0.01 (-0.19, 0.17)
-Injury/Fibrosis	-0.17 (-0.35, -0.01)
-Reabsorption	-0.03 (-0.21, 0.15)
-Reserve	-0.59 (-0.77, -0.41)
ACR	-1.65 (-1.82, -1.47)

*Adjusted for: age, sex, race, randomization arm, SBP, ACEi or ARB use, diuretic use, history of CVD or HF, current smoker, BMI, LDL, total cholesterol, baseline eGFR and albuminuria.

SA-OR042

Metabolomics of CKD Progression in CRIC and AASK

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Background: Non-targeted metabolomics is a promising tool for the identification of novel markers of CKD progression, with the goal to improve CKD diagnosis, prognosis, and therapy.

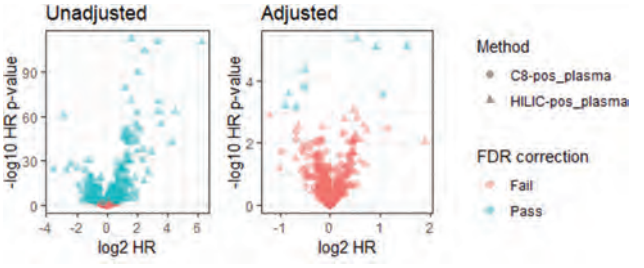
Methods: We examined the association between blood metabolites and CKD progression, defined as subsequent development of ESRD or eGFR halving. Discovery analysis was performed with the Broad Institute platform in 1800 randomly selected participants of the CRIC study. We fit Cox proportional hazards models, adjusting for age, gender, center, race/ethnicity/APOL1, CVD, smoking, alcohol, physical activity, SBP, diabetes, BMI, UPCR, and eGFR. Statistical significance was determined at a FDR <5%. For replication, we examined data generated with the Metabolon platform for 962 participants of the AASK study, adjusting for age, sex, study arm, smoking, CVD, BMI, SBP, UPCR, and mGFR.

Results: In CRIC, >160 of 547 metabolites were associated with the composite of ESRD or eGFR halving in unadjusted analysis, but only 9 metabolites remained significant following full adjustment (Fig). This attenuation in associations was driven by adjustment for eGFR. A subset of 7 of these metabolite were also measured in AASK, 3 of which were associated with CKD progression (Table): pseudouridine, 4-acetamidobutanoate, and guanidinoacetate.

Conclusions: In this large metabolomics study of CKD progression, 3 metabolites significantly associated with ESRD or eGFR halving, with discovery and replication performed in independent cohorts using different metabolomics platforms. More work is required to explore clinical utility and biologic implications.

Funding: NIDDK Support

Metabolite	Pathway	CRIC HR	P	AASK HR	P
allantoin	purine	1.43	4.4x10-6	1.00	0.99
pseudouridine	pyrimidine	2.90	7.5x10-6	1.86	3.1x10-9
4-acetamidobutanoate	polyamine	1.88	8.4x10-6	1.26	0.0088
myristoleate	fatty acid	0.70	4.5x10-5	0.94	0.37
trimethylbenzene	xenobiotic	0.56	2.6x10-4		
triacylglycerol 49:3	triglyceride	0.69	1.6x10-4		
N6-acetyllysine	amino acid	2.09	2.8x10-4	1.07	0.33
tryptophan	amino acid	0.54	6.4x10-4	0.89	0.081
guanidinoacetate	creatine	0.63	6.8x10-4	0.75	1.2x10-5



SA-OR043

Association Between Urine 6-Bromotryptophan and ESKD in the German CKD Study

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Background: Higher serum 6-bromotryptophan has been associated with lower risk of chronic kidney disease (CKD) progression, but its levels in urine have not yet been studied. We studied determinants of urine 6-bromotryptophan and its association with CKD risk factors and incident end-stage kidney disease (ESKD) in 4,843 CKD patients.

Methods: 6-bromotryptophan was measured from spot urine samples using mass spectrometry. Genetic determinants of 6-bromotryptophan levels were assessed using genome-wide association studies (GWAS) in European ancestry cohorts. The associations between urine 6-bromotryptophan and CKD risk factors were assessed by univariate tests. The risk for ESKD, defined as incident dialysis, kidney transplantation, or kidney-related death, by 6-bromotryptophan levels was assessed using Cox regression.

Results: Urine 6-bromotryptophan was detected in 57% of the patients and categorized into three groups: undetectable, low (<median), and high (≥median). GWAS of urine 6-bromotryptophan levels detected two significant loci likely related to its generation and tubular reabsorption, illuminating its biological determinants (near *SLC6A19*, p=3.2x10^{-12}; near *GPR137C*, p=2.4x10^{-14}). The locus near *GPR137C* possibly related to its generation was also associated with serum 6-bromotryptophan in an independent general population-based cohort (p=7.3x10^{-9}). Patients with higher levels of urine 6-bromotryptophan had higher baseline estimated glomerular filtration rate (eGFR, p<0.001). After four years of follow-up, we observed 216 ESKD events. Compared with the undetectable group, higher 6-bromotryptophan levels were associated with lower risk of ESKD in unadjusted models and when adjusting for all ESKD risk factors other than eGFR (low group cause-specific hazard ratio [HR]: 0.7, 95% confidence interval [CI]: 0.51 to 0.97; high group HR: 0.5, 95% CI: 0.34 to 0.74). With the addition of baseline eGFR, this association became insignificant.

Conclusions: Higher urine 6-bromotryptophan levels were associated with lower risk of ESKD, which was attenuated when adjusting for baseline eGFR. The protective direction of association is noteworthy, because higher levels of most other metabolites, such as creatinine, are associated with higher risk of ESKD.

SA-OR044

Carbamylation and the Risk of CKD Progression in the Chronic Renal Insufficiency Cohort (CRIC)

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Background: Carbamylation is a posttranslational protein modification caused, in part, by exposure to urea's dissociation product cyanate. While carbamylation associates with cardiovascular outcomes and mortality in ESRD, its effects in earlier stages of CKD are unknown.

Methods: In 2 independent nested case-control studies within CRIC, we first matched 75 subjects demonstrating CKD progression (cases, 50% reduction of eGFR or reaching ESRD) to 75 people not meeting this definition (controls, matched on baseline eGFR, 24-hour proteinuria, age, sex, and race). Regression models compared baseline levels of carbamylated albumin (C-Alb, a validated measure of total body carbamylation burden) between the groups. With the same matching approach, we next compared baseline C-Alb in 75 subjects who died during follow up (mortality cases) to 75 survivors (mortality controls).

Results: Table 1 shows baseline characteristics of the study groups. Other than urea (CKD progression) and smoking status (both CKD progression and mortality), there was no difference in any matched or other parameter. Adjusting for baseline differences, the top tertile of C-Alb was associated with an increased risk of CKD progression (OR [95% CI] 7.9 [1.9-32.8], P= 0.004) and mortality (OR 3.4 [1.0-11.4], P= 0.05) when compared to the bottom tertile.

Conclusions: In this first report of carbamylation and clinical outcomes in CKD patients not on dialysis, our data suggest carbamylation predicts CKD progression, beyond GFR and proteinuria. Impact on mortality was less robust in this small sample. Additional study is warrented as carbamylation is considered a modifiable risk factor.

Funding: NIDDK Support

Table 1 Select baseline characteristics of the study population

	CKD Progression Case	CKD Progression Control	P-value	Mortality Case	Mortality Control	P-value
Age, y	58.4 (9.5)	57.6 (9.8)	0.62	63.7 (7.4)	62.6 (8.1)	0.41
eGFR (CRIC, ml/min/1.73m^2)	33 (22-38)	34 (28-39)	0.20	36 (27-44)	34 (26-42)	0.51
Proteinuria (g/ 24 hour)	1.2 (0.4-3.9)	1.0 (0.3-2.4)	0.23	0.3 (0.1-0.8)	0.3 (0.1-1.0)	0.85
Urea (mg/dL)	32 (26-46)	30 (24-38)	0.05	36 (27-46)	33 (26-43)	0.61
Carbamylated albumin (mmol/mol)	6.9 (5.3-9.6)	5.02 (4.3-7.1)	0.0004	7.1 (5.4-10.3)	6.5 (5.2-8.5)	0.52
Current smoking, No. (%)	21 (28)	9 (12)	0.01	19 (25)	8 (11)	0.02

Data are presented as mean (SD), median (interquartile range Q1-Q3)), or count (%) as indicated. No other parameter differed by cases vs. controls across both outcomes.

SA-OR045

Blood and Urine Biomarkers and CKD After Cardiac Surgery

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Background: The use of blood and urine biomarkers of injury, inflammation and repair in the post-operative period following cardiac surgery may help identify patients at increased risk for longer-term adverse kidney outcomes. We investigated the independent associations between candidate biomarkers and CKD incidence or progression following cardiac surgery.

Methods: We prospectively enrolled adult patients undergoing cardiac surgery (CABG or valve) in 2 academic centers from 2007–2010 as part of the TRIBE-AKI Study. The cohort was separated into exploration (Canada n=613) and replication (USA n=310) cohorts due to differences in outcome ascertainment and lack of data integration. Top biomarkers were identified from candidate post-operative biomarkers (32 blood, 8 urine) in the exploration cohort and confirmed in the replication cohort, thereby reducing model selection bias. Our primary outcome was a composite of CKD incidence or progression. In those with a pre-operative eGFR≥60, CKD incidence was defined as a 25% reduction in eGFR and a fall below 60. In those with a pre-operative eGFR<60, CKD progression was defined as a 50% reduction in eGFR or a fall below 15.

Results: 172 (28.1%) patients in the exploration cohort developed the primary outcome after a median (IQR) follow-up of 5.61 (4.30-6.84) years. 8 biomarkers were associated with the primary outcome, of which 3 remained significant after full adjustment. Each log increase in post-operative levels of bFGF (HR 1.52 [1.19, 1.93]), N-terminal pro-BNP (HR 1.19 [1.01, 1.41]), and TNF-r1 (HR 1.75 [1.18, 2.59]) were independently associated with the primary outcome (Table 1). Similar estimates were found in the replication cohort, with pooled estimates showing little heterogeneity (I^2=0).

Conclusions: Elevated post-operative levels of bFGF, NT pro-BNP, and TNF-r1 were associated with the CKD outcome. These biomarkers provide additional value in evaluating CKD incidence and progression after cardiac surgery.

Funding: NIDDK Support, Other NIH Support - SM is supported by NIH T32 grant HL007024, Other NIH Support - SM is supported by NIH T32 grant HL007024

Table 1: Risk of CKD Incidence or Progression by Post-operative Biomarker Level

Blood Biomarkers (natural log-transformed)	Hazard Ratio (95% CI)			
	Unadjusted HR, exploration cohort†	Adjusted HR, exploration cohort†	Adjusted HR, replication cohort‡	Pooled HR
bFGF	1.50 (1.20, 1.87)	1.52 (1.19, 1.93) *	1.24 (1.00, 1.52)	1.36 (1.12, 1.66)
NT pro-BNP	1.21 (1.05, 1.39)	1.19 (1.01, 1.41) *	1.35 (1.07, 1.70)	1.24 (1.09, 1.42)
TNF-r1	1.77 (1.26, 1.49)	1.75 (1.18, 2.59) *	1.73 (0.94, 3.18)	1.74 (1.25, 2.43)
IL-2	1.19 (1.01, 1.40)	1.08 (0.91, 1.28)		
IL-10	1.14 (1.01, 1.29)	1.11 (0.98, 1.27)		
KIM-1	1.55 (1.14, 2.10)	1.51 (0.99, 2.32)		
VEGFr1	1.31 (1.08, 1.59)	1.21 (0.98, 1.49)		
YKL-40	1.27 (1.03, 1.56)	1.10 (0.88, 1.38)		

† Canada (n=613)
‡ United States (n=310)
* p<0.05
Adjusted for age, sex, AKI stage, pre-op albuminuria, pre-op SCr, discharge SCr

SA-OR046

Photoacoustic Ultrasound: A New Way to Assess Kidney Fibrosis

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Background: Despite advances in imaging technology(conventional ultrasound, CT, MRI), the only method for assessing fibrosis is by biopsy. Biopsy is limited by its invasiveness and the fact that it samples < 1% of the kidney. Here we show that combining ultrasound with laser technology (photoacoustic (PA) ultrasound) allows imaging of kidney fibrosis by directly measuring collagen content.

Methods: Kidneys of mice undergoing UUO (left kidney) or sham surgery were imaged ex vivo using a VevoLAZR-X PA ultrasound imaging system at 15 MHz at day 7 and 14 post surgery(n=5 per time point). Human kidney samples were obtained from the non-cancerous pole of radical nephrectomies(n=6). Spectral unmixing was performed on the collected images to produce a PA collagen score for each image. For mouse kidneys, a total of 60 PA ultrasound frames were acquired along the largest longitudinal cross-section. Human kidney cortex specimens were scanned in 60 perpendicular cross-sections(separated by 150 μm increments) to obtain a 3D representation of the collagen distribution across the entire sample. Histology was acquired at 3-4 locations within the mouse and human kidneys stained with picrosirius red (PSR) and an antibody direct against α-SMA. The relationship between PA-derived collagen scores and the above histological parameters was then analyzed by univariate linear regression.

Results: The average PSR score for UUO mouse kidneys increased with time post-surgery [day 7 (0.14±0.01) and day 14 (0.27±0.03]], and was higher than sham kidneys (0.002±0, p<0.001). α-SMA staining increased by 18.8% from 7 to 14 days post-surgery and was 26x higher than sham kidneys by 14 days. PA-derived collagen scores correlated strongly with histologic parameters of fibrosis (PSR, r^2=0.98, p<0.05; α-SMA, r^2=0.91, p<0.05), suggesting that PA imaging can accurately quantify murine renal collagen content. Human kidney specimens exhibited a 30% variation in PSR staining, which was also strongly correlated with the PA estimates of collagen (r^2=0.90, p<0.05). The technique was also capable of generating 3D collagen maps across the entire specimen with sub-mm spatial resolution across the entire kidney cortex.

Conclusions: PA ultrasound can be used to accurately quantify renal collagen content. This non-invasive, easy-to-use technique offers the potential for renal fibrosis imaging in both the pre-clinical and clinical settings.

SA-OR047

Increase of Extracellular Fluid Volume over Time Is Associated with ESKD and Mortality in Patients with CKD

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Background: Data on the association between longitudinal change in extracellular fluid volume (ECF) and end-stage kidney disease (ESKD) and mortality are lacking. The aim of the present study was to analyze whether ECF over time was associated with ESKD and mortality, in patients with chronic kidney disease (CKD).

Methods: 1588 patients of the hospital-based tricentric NephroTest cohort with CKD stage 1-4 were included. ECF and glomerular filtration rate (GFR) were measured using the distribution volume and clearance of ^{51}CrEDTA, respectively. ESKD was defined by initiation of chronic dialysis or pre-emptive transplantation. Joint models with shared random-effect were used to jointly analyze individual trajectories of ECF and the competing risks of ESKD and mortality. Time-to-event sub-model of the joint models was adjusted for age, gender, site, ethnicity, cardiovascular risk factors, underlying renal disease, measured GFR (mGFR), proteinuria, 24-h urinary sodium excretion, diuretics and renin-angiotensin system inhibitors.

Results: At baseline, patients (mean age 58.7±15.1 years, 67% men) had a mean mGFR of 44±19 mL/min/1.73m^2, and ECF was 16.1±3.6 L. After a median follow-up of 5.3[IQR: 3.0;7.4] years with a median number of ECF measurement of 2 [IQR: 1;4] per patient, the mean rate of ECF increase was 117 mL/year 95%CI [90;144]. Between the first and the last visit, the percentage of patients treated by diuretic increased from 47.6 to 50.9% and mean 24-h urinary sodium excretion decreased from 155±73 to 150±73 mmol/d. ESKD occurred in 324 (20.4%) patients and 185 (11.6%) patients died before

ESKD. In multivariable analysis, a higher current value of ECF was associated with an increased hazard of ESKD (adjusted hazard ratio [aHR] per 1L increase in ECF was 1.12 95%CI [1.06;1.18], p<0.001) and with mortality (aHR=1.08 [1.01;1.15], p=0.02).

Conclusions: In this large cohort of CKD patients, ECF over time was independently associated with ESKD and mortality. This highlights the need for a close monitoring and adjustment of treatments in these patients.

SA-OR048

Discovery of Novel Podocyte Endoplasmic Reticulum Calcium Stabilizers to treat Nephrotic Syndrome

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Background: Podocyte injury is the hallmark of primary nephrotic syndrome (NS), a leading cause of chronic kidney disease affecting approximately 500 million people worldwide. Despite the importance of podocyte endoplasmic reticulum (ER) stress in the pathogenesis of NS, currently no treatment targets the podocyte ER. For the first time, we have developed a new class of drugs-podocyte ER calcium channel stabilizers, to treat NS.

Methods: We have developed a podocyte ER stress-induced monogenic NS mouse model with an engineered human C321R mutation in laminin β2, which is synthesized and secreted by podocytes. Western blot and RNA sequencing of isolated mouse glomeruli or cultured primary podocytes were utilized to determine accelerated ER calcium efflux-mediated pro-apoptotic pathway. Moreover, a *Gaussia* luciferase-based assay utilizing secreted ER calcium-monitoring proteins (SERCaMPs) was performed to monitor ER calcium depletion in primary podocytes and to screen for novel ER calcium stabilizers. Lastly, our mouse model was exploited to test the therapeutic effect of an identified drug.

Results: We have identified a novel therapeutic target, podocyte ER type 2 ryanodine receptor/calcium release channel (RyR2). It was phosphorylated at Ser2808 under ER stress, resulting in podocyte ER calcium leak and cytosolic calcium elevation. The altered intracellular calcium homeostasis led to activation of calcium-dependent cytosolic protease calpain 2 and cleavage of its important downstream substrates, including the apoptotic molecule procaspase 12 and podocyte cytoskeletal protein talin 1. More importantly, we have identified a chemical compound K201 and a novel biotherapeutic protein mesencephalic astrocyte-derived neurotrophic factor (MANF), which can reduce RyR2 phosphorylation and inhibit pro-apoptotic calpain 2-caspase 12 signaling in podocytes undergoing ER stress. Most excitingly, K201 treatment attenuated proteinuria and improved kidney function in our podocyte ER stress-induced NS mouse model.

Conclusions: Podocyte RyR2 remodeling contributes to ER stress-induced podocyte injury. Podocyte ER calcium channel stabilizers, including K201 and MANF, could be emerging therapies for the treatment of podocyte ER stress-induced NS.

Funding: NIDDK Support, Private Foundation Support

SA-OR049

Combined Single Cell Epigenomic and Transcriptomic Analysis of Healthy vs. FSGS Adult Human Kidney

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Background: Unraveling the pathogenesis of human FSGS requires a detailed understanding of the distinct cell types, cell specific transcriptomes, chromatin status and cell state changes in healthy and FSGS kidneys. We hypothesized that combined single nucleus RNA-seq and ATAC-seq on a single human biopsy would allow definition of FSGS-specific transcriptional changes and the DNA regulatory variation driving them, at cellular resolution.

Methods: We performed combined scATAC-seq and snRNA-seq on healthy kidney from partial nephrectomy, and on each half of a human kidney biopsy from a 42 year-old transplant patient with new onset proteinuria (2.4g) and preserved renal function (Cr 0.8 mg/dL). Histologic read on the biopsy was FSGS with 30% podocyte foot process effacement by EM. Informatics was by standard workflows.

Results: After quality control, 4,626 cells (8 clusters) and 6,459 cells (13 clusters) were included in the scATAC-seq analysis from the FSGS and healthy kidney, respectively. For snRNA-seq these numbers were 4,672 cells (13 clusters) and 4524 cells (17 clusters). A matrix of cell type specific differentially accessible regions and transcription factor motifs across cell types revealed 580 significantly enriched TF motifs in healthy, and 435 in FSGS. We generated a multimodal, harmonized kidney single cell atlas using all datasets to better understand how transcription and chromatin accessibility are regulated in FSGS. This revealed strong podocyte upregulation of PRKCI, aka atypical PKC, which is required for maintenance of slit diaphragms, and decreased podocyte – mesangial NPNT-ITGA8 signaling in FSGS. The most strongly enriched TF motifs in FSGS endothelium were for ETS family members (ETS1, ETV1,3-5, ELK3-4, ERG), which are downstream of VEGF signaling, whereas snRNA-seq from podocytes showed enhanced VEGFA expression, suggesting active podocyte-endothelial signaling in FSGS.

Conclusions: A multi-omics approach in human FSGS was successfully applied, revealing that that the cell-specific landscape of chromatin accessibility changes dramatically in human FSGS. Combining this epigenome data with snRNA-seq data allows inference of intercellular communication pathways driving disease pathogenesis.

Funding: NIDDK Support

SA-OR050

A Human Model of Membranous Nephropathy on-a-Chip

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Background: Primary membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults worldwide. MN pathogenesis involves the deposition of auto-antibodies against podocyte-expressed antigens in the glomerular subepithelial space, causing podocyte injury and initiating progressive renal damage which leads to kidney failure in approximately one third of patients. While the role of complement has been confirmed, many questions are still unanswered and the study of mechanisms responsible for MN pathogenesis is challenged by the lack of in vitro systems that recapitulate human disease.

Methods: We have developed a novel glomerulus-on-a-chip system (GOAC) using primary, immortalized and amniotic fluid derived podocytes together with glomerular endothelial cells (GEC) in combination with OrganoPlates and assessed the functional response to human MN serum. Human podocytes were seeded on microfluidic chips with human GEC. Immunofluorescence and WB were performed for podocyte, endothelial and GBM markers. Barrier selective-permeability was investigated. Chips were cultured with serum from MN patients or healthy individuals. Functional response was assessed by albumin permeability assay. IgG/IgG4 deposition was assessed by immunofluorescence while mechanisms of action were explored by Western Blotting and immunostaining.

Results: This system recapitulates salient characteristics and functions of the in vivo glomerular filtration barrier. The GOAC is permeable to inulin and impermeable to albumin. When exposed to serum of subjects affected by MN, the chip displayed deposition of IgG and complement C3 on podocytes and loss of permselectivity to albumin to an extent correlated to urinary protein loss in respective patients. Moreover, we have found evidence suggesting that activation of ILK/MAPK/SNAIL signaling pathway in podocytes might contribute to injury during MN pathogenesis.

Conclusions: We have successfully developed a glomerulus-on-a-chip system that closely mimics the GFB structure and provides a powerful tool for studying pathophysiology of MN. This system will increase our ability to individualize treatments and facilitate drug discovery, thus ultimately benefiting patients affected by this and potentially other glomerular diseases.

Funding: Private Foundation Support

SA-OR051

Inflammasome-Mediated Cell Death Plays a Key Role in APOL1 Risk Variant-Induced Kidney Disease

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Background: Apolipoprotein L1 (APOL1) coding variants, termed as G1 and G2 are associated with increased kidney disease risk. We developed a mouse model by conditional and inducible expression of reference (G0) or risk (G1 or G2) variants of APOL1. Mice with podocyte-specific G1 or G2 APOL1 expression develop albuminuria, glomerulosclerosis and renal failure recapitulating the human disease condition. However, molecular pathways leading to kidney disease development in this model remains poorly understood. We hypothesized that APOL1 risk alleles induced inflammasome-mediated pyroptotic cell death contributed to the phenotype development.

Methods: We generated cells with stable or inducible G2 APOL1 expression and used inhibitors of apoptosis, necrosis, and pyroptosis to determine pathways mediating cytotoxicity. To define the role of inflammasome-mediated cell death *in vivo*, we crossed G2 APOL1 transgenic mice (Nphs1rtTA-TRE APOL1) with caspase-1 (Casp1-/-) or NLRP3 (Nlrp3-/-) knockout mice and induced podocyte G2 APOL1 expression with a 21-day doxycycline diet. Histological changes were evaluated by PAS, fibrosis was quantified using Sirius red staining. Albuminuria was determined by ELISA. Inflammasome markers were quantified by immunoblotting.

Results: We found that expression of inflammasome markers cleaved caspase-1, NLRP3, and IL-1B were higher in mice expressing risk variant APOL1. These results were recapitulated in cultured cells expressing risk variant APOL1, while pyroptosis inhibitors decreased inflammasome signaling and cytotoxicity. Nphs1rtTA-TRE APOL1/Casp1-/- mice showed a 90% reduction albuminuria, and a 73% decrease in renal fibrosis compared to Nphs1rtTA-TRE APOL1 mice. Nphs1rtTA-TRE APOL1/Nlrp3-/- mice showed an 80% reduction in albuminuria, and ~ 75% reduction in renal fibrosis, compared to G2 APOL1 littermates. Kidney histology examined by PAS and Sirius red staining showed significant improvement in kidney structure damage. Additionally, NLRP3 or caspase-1 knockout interchangeably decreased markers of inflammasome signaling and cell death.

Conclusions: Our data suggest that caspase-1 and NLRP3 inflammasome plays an important role in the development of G2 APOL1 induced kidney damage. Our results raise the possibility that inflammasome inhibition could be a potential therapeutic approach for APOL1-associated kidney disease.

Funding: NIDDK Support

SA-OR052

A Novel Small Molecule Therapy for Nephrotic Syndrome Caused by a Common Podocin Mutation

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Background: There are currently no targeted therapies for the ever-increasing number of podocyte diseases. Currently, there are over 60 different genetic disorders causing SRNS - the commonest of these by far is that of mutations in the *NPHS2* gene encoding podocin. Podocin is a key scaffolding protein of the slit diaphragm essential for intact glomerular filtration. The most frequent podocin mutation in European children is R138Q, causing retention of the protein in the ER.

Methods: A conditionally immortalized patient cell line with the R138Q mutation was used to study podocin trafficking and biology and to characterize the nature of R138Q-K8 interaction in podocin's cell type, the kidney podocyte. A conditional podocin knock-in mice carrying R140Q mutation, the mouse analogue of human R138Q, was created using doxycycline-inducible Cre-recombinase technology allowing to study the effects of the mutation in postnatal life and representing an ideal model for pharmacological studies.

Results: We provide evidence that a protein-protein interaction of misfolded podocin R138Q (but not wt podocin) with the intermediate filament K8 prevents its correct trafficking to the PM. We have also identified a small molecule that interrupts this interaction and rescues mutant protein mis-trafficking. This results in functional rescue of podocin in both human patient R138Q mutant podocyte cell line, and in a mouse inducible knock in model of the R138Q mutation. In the mouse, complete rescue of proteinuria and histological changes are seen, when the molecule is administered at disease induction, and also after proteinuria has commenced (F1).

Conclusions: Altogether, this data provided constitutes the first therapeutic option for NS patients bearing the R138Q mutation.

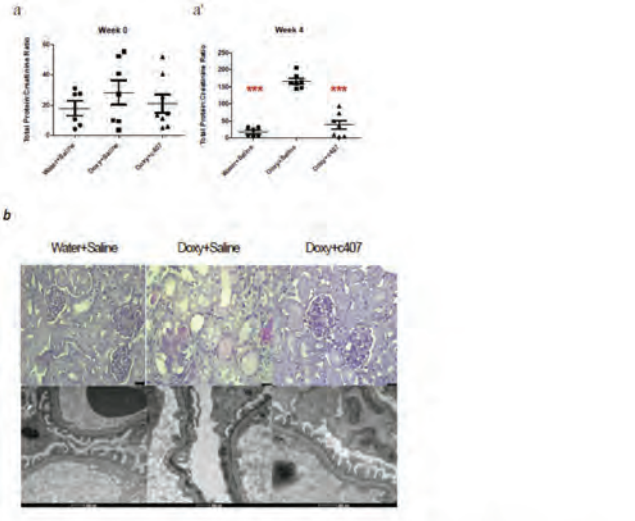

Figure 1. (a) Rescue of proteinuria. Induced control mice developed severe proteinuria at 4 weeks after doxycycline induction, which was prevented in c407 mice (treated via minipump with c407 for 4 weeks, inserted at a time of doxycycline induction). **(b)** Podocytes effacement and glomerular sclerosis were observed in doxy saline mice, while normal histology and podocyte ultrastructure were seen upon treatment with c407.

SA-OR053

An iPSC platform for Human Preclinical Evaluation of Kidney Disease Targeting Compounds

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Background: A major challenge in drug target validation and assessment of efficacy is the limited translation between preclinical animal models and human diseases, which is often invoked to explain the failure of investigational drugs to produce the expected therapeutic benefit. Human iPSC-derived cells and organoids offer an opportunity to complement preclinical animal models, but their systematic use remains challenging due to the technical complexity associated with consistent cell culture and scalability.

Methods: Here, we report a robust, reproducible and scalable platform for generating iPSC derived human podocytes and kidney organoids to enable target validation and preclinical assessment of therapeutic agents targeting the kidney. The organoid platform was characterized by immunofluorescence analysis of kidney differentiation markers and by assessing transcriptomic changes during organoid differentiation *in vitro* and following *in vivo* transplantation under the rat kidney capsule using single-cell RNA sequencing.

Results: Here, we report three examples supporting the use of these models by – a) providing a mechanistic basis for the antiproteinuric effects of cyclosporine A via protective effects on podocytes from Rac1-mediated cytoskeletal injury *in vitro*, b) exploring of the effects of disease-causing genetic mutations, and c) demonstrating the protective effect of a novel TRPC5 channel blocker, GFB-887. *In vivo* transplantation resulted in vascularization of human iPSC derived kidney organoids, with functional perfusion confirmed by pharmacokinetic measurement of GFB-887 in the organoid after dosing by oral gavage.

Conclusions: Our kidney disease-targeted human iPSC platform provides a valuable complement to pre-clinical models for target validation and assessment of drug efficacy.

SA-OR054

Proteomic Analysis of Clathrin-Coated Vesicles from Podocytes Identifies Cargo Proteins

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Background: Clathrin-mediated endocytosis (CME) plays a crucial role in podocyte health. Knockout of proteins involved in CME resulted in severe albuminuria and foot process effacement in mice. However, the cargo of clathrin-coated vesicles (CCVs) in podocytes is unknown. The goal of this study was to isolate CCVs from podocytes and identify their cargo by proteomic analysis.

Methods: Kidneys were isolated from *Podocin-Cre Rosa-DTR^{flox}* mice. The glomeruli were seeded and treated with diphtheria toxin to obtain pure primary podocyte cultures. After cell harvesting, CCVs were isolated by D_2O-sucrose density gradient centrifugation using multiple ultracentrifugation steps. Enrichment of CCVs was assessed by immunoblotting and electron microscopy (EM). LC-mass spectrometry (LC-MS) was performed for proteomic analysis. Proteins with higher abundance than transferrin receptor protein 1 were evaluated for CCV cargo potential by comparison to published impurities in CCV preparations, podocyte proteomic databases, and by searching the literature for CME-association.

Results: Immunoblotting for multiple protein markers of CME revealed enrichment in the CCV fraction. Enrichment of CCVs amongst other small vesicles was observed on electron microscopy. Clathrin-heavy chain was the fourth-most abundant protein in LC-MS analysis of the vesicle fraction. Proteomics yielded a total of over 1700 proteins. After adjustment for impurities and upregulation from whole cell expression, over 50 potential cargo proteins were identified. Among those are fibronectin, receptor of activated protein C kinase, thrombospondin-1, and vigilin.

Conclusions: This is the first time CCVs were enriched from podocytes. Enrichment was confirmed by immunoblotting, EM and LC-MS analysis. Proteomic analysis of CCV cargo and adjustment for impurities identified the most abundant cargo proteins in podocytes. These findings help to elucidate the importance of endocytic trafficking for podocyte health and disease.

Funding: NIDDK Support

SA-OR055

Mechanism of Albuminuria in Kidney Disease

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Background: Albuminuria is regarded as the most important predictor of progression in a variety of glomerular diseases including Focal-Segmental Glomerulosclerosis (FSGS). Investigating the events causing the occurrence of albuminuria is of utmost importance for future preventive and therapeutic strategies.

Methods: *NPHS2* encodes for the PHB-domain protein podocin and is the most frequently mutated gene in patients with a Steroid-Resistant Nephrotic Syndrome (SRNS) and FSGS. Using CRISPR/Cas9 mediated genome editing, we inserted two separate point mutations into the murine *Nphs2* gene which, in combination, cause late-onset SRNS and FSGS in patients. Disease occurrence and development was assessed using histological and clinical parameters. In addition, changes in the podocytes' foot process morphology and slit diaphragm integrity were investigated using Stimulation Emission Depletion (STED) microscopy.

Results: Compound-heterozygous mice exhibit a mild-onset phenotype reminiscent of patients with the equivalent mutations. FSGS lesions are detectable in young adult mice and lead to end-stage renal disease starting as early as 15-20 weeks. Investigation of the podocyte and the slit diaphragm with STED microscopy showed several distinctive morphological changes like foot process length and width and slit diaphragm length which progress over time. Strikingly, some of the changes correlate tightly with albuminuria and precede the overt onset of disease, podocyte loss and glomerular scarring. We provide evidence that shortening of the slit diaphragm reduces the podocytes' ability to counteract the hydrostatic pressure within the capillaries. This leads to a decreased compression of the glomerular basement membrane (GBM) which results in albuminuria.

Conclusions: We have generated a new mouse model that mimicks the course of disease in patients with a hereditary late-onset SRNS and FSGS. This new mouse model allows the investigation of early disease stages prior to the onset of podocyte depletion, glomerular scarring and massive proteinuria. Based on our data of foot process morphology and slit diaphragm integrity, glomerular filtration rate and albuminuria, we developed a model that attributes the occurrence of albuminuria to a decreased compression of the GBM. In addition, the proposed mechanism of albuminuria can be adapted to other albuminuric pathologies.

SA-OR056

APOL1 Risk Variants Affect Podocyte Lipid Homeostasis and Energy Production in FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) is the most common primary glomerular disorder causing chronic kidney disease. Susceptibility to FSGS in African Americans is associated with the presence of genetic variants of the Apolipoprotein L 1 gene (APOL1) named G1 and G2. We recently published that mice with a podocyte-specific, doxycycline (Dox)-inducible expression of constitutively active NFATc1nuc (NFAT;Podocin-rtTA, DT) represent a valuable new model for FSGS.

Methods: Human urinary podocyte-like epithelial cells (HUPECs) carrying different APOL1 genetic variants were established from patients with FSGS and used for *in vitro* studies and human BAC transgenic mice expressing the APOL1 genetic variants (G0, G1 or G2) under the endogenous promoter for *in vivo* studies. DT mice were expanded for consecutive breeding to G0, G1 or G2 mice to generate triple transgenic mice (TT). NFATc1nuc transgene expression was induced by feeding of Dox chow (200 ppm) for 4 months.

Results: HUPECs carrying G1/G2 alleles are characterized by lipid droplet remodeling in association with decreased oxygen consumption, ATP generation and reduced mitochondrial membrane potential, while an increased abundance of super complexes was observed. *In vivo*, we tested the relative contribution of APOL1 risk variant expression to podocyte injury in APOL1 transgenic mice at baseline as well as in TT mice. Glomerular expression of APOL1 mRNA was similar among transgenic mice carrying APOL1 G0 and G1, but significantly lower in G2 carrying mice and these mice did not develop proteinuria at least up to 7 months of age (G2 mice were then excluded due to the low APOL1 mRNA levels). Meanwhile, TT mice carrying the G1 allele showed increased proteinuria, less body weight gain, higher serum BUN levels, more severe glomerulosclerosis and kidney cortex fibrosis when compared with G0 TT and their DT littermates. A strong correlation between serum BUN and kidney cortex cholesterol esters was observed.

Conclusions: Our data reveal that APOL1 risk variant expression may play a role in modulating lipid homeostasis and energy production in podocytes. APOL1 risk variant expression in mice does not impair kidney function at baseline whereas APOL1 G1 expression may contribute to APOL1 mediated susceptibility in NFAT-mediated FSGS.

Funding: NIDDK Support, Private Foundation Support

SA-OR057

Adeno-Associated Virus Gene Therapy Prevents Progression of Kidney Disease in Genetic Human and Mouse Models of Nephrotic Syndrome

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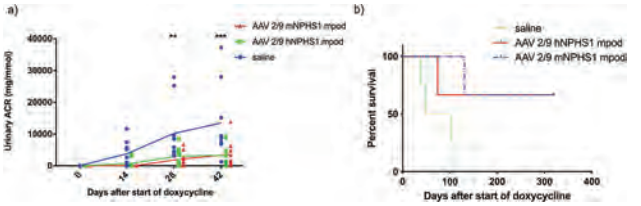
Background: Gene therapy targeting the kidney has proven challenging thus far. Adeno-Associated Virus (AAV) has been used successfully for gene therapy targeting other organs, with particular success demonstrated in targeting monogenic diseases. Here we aimed to advance gene therapy in the kidney by targeting a monogenic disease of the kidney. The commonest cause of genetic nephrotic syndrome in children is a mutation in *NPHS2* encoding podocin. Here, AAV-mediated gene therapy was tested on a conditional podocin knock-out mouse model (iPod $NPHS2^{fl/fl}$), and on human podocytes with the commonest podocin mutation, R138Q.

Methods: AAV 2/9 expressing mouse podocin with a podocyte-specific promoter (either a mouse or human nephrin promoter) was delivered via tail vein injection to iPod $NPHS2^{fl/fl}$. AAV serotypes LK03 and 2/9 were used to transduce immortalised human kidney cell lines to test for transduction efficiency. AAV LK03 expressing human podocin with a minimal nephrin promoter was used to transduce immortalised R138Q podocin mutant human podocytes.

Results: AAV 2/9 expressing podocin demonstrated successful transduction of podocytes in iPod $NPHS2^{fl/fl}$. Treated mice showed a significant improvement in urinary albumin creatinine ratio (n=9/group, p<0.001 at day 42) and prolonged survival (n=3-4/group, p=0.049). *In vitro*, AAV LK03 transduced the human podocyte with a transduction efficiency of close to 100%. Transduction of the R138Q podocin mutant human podocyte with AAV LK03 expressing podocin demonstrated functional rescue *in vitro*.

Conclusions: This is the first study demonstrating successful gene transfer using AAV 2/9 in a monogenic kidney disease in a mouse model. AAV LK03 demonstrated highly efficient transduction of the human podocyte, making it a promising potential serotype for translation of gene therapy targeting the podocyte.

Funding: Private Foundation Support



SA-OR058

Consolidation in the Dialysis Industry in the Era of Health Reform, 2006-2013

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Background: In the last 15 years, the dialysis industry has become dominated by two for-profit large dialysis organizations (LDO) that control 85% of the market. For-profit LDOs have been shown to have higher costs, greater use of expensive medications, lower transplant rates and higher mortality rates. We describe trends in dialysis industry consolidation in the current era of health reform, 2006-2013, and identify factors that put small dialysis chains and independently-owned facilities at risk of closure or acquisition by LDOs.

Methods: We conducted a retrospective cohort study of non-federal US outpatient dialysis facilities that were independently-owned or affiliated with small chains (<20 facilities) for ≥1 year in 2006-2013. These facilities were deemed to be eligible for acquisition by large dialysis organizations. We used data from Center for Medicare and Medicaid Services, US Renal Data System and Area Health Resource File to evaluate facility and market characteristics throughout the study period. The outcome of interest was change in dialysis facility ownership (i.e. acquisition) or facility closure. We used a generalized estimating equation with a logit link, clustered at the regional level, to examine the association between facility characteristics and closure or acquisition.

Results: Overall, 1686 dialysis facilities (27% of all US facilities) were eligible for acquisition for at least one year of the study period; 61% were independently-owned and 39% were affiliated with small chains. The number of independently-owned and small chain-affiliated facilities declined by 192 from 2006 to 2013 (1356 to 1164), while LDO-affiliated facilities increased by 1473 (3214 to 4687). Facilities at highest risk of acquisition or closure were not-for-profit (p<0.001), smaller in size (p=0.02), and in regions with lower hospital density (p=0.001) and more monopolistic markets (p=0.006).

Conclusions: Small dialysis chains and independent facilities retain a declining share of the dialysis market. Policy makers should work to maintain (or even increase) the current diversity of dialysis organizations and help maintain competition in markets at risk of antitrust violation. Efforts should be directed toward facilities that are particularly vulnerable to acquisition and closure.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR059

Patient Experience with Care as a Critical Component of the Medicare ESRD Quality Incentive Program (QIP)

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Background: Medicare has long required dialysis facilities to assess patient experience as a condition for Medicare participation. More recently, the ESRD QIP introduced the In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH-CAHPS) pay-for-reporting measure in payment year (PY) 2014, shifting to pay-for-performance starting in PY18. The ICH-CAHPS performance measure is based on patient-reported data from 3 global ratings and 3 composite ratings from 35 survey questions.

Methods: We used facility ICH-CAHPS survey results reported in the ESRD QIP Performance Score Summary Reports and CROWNWeb data during 2012-18 to examine facility eligibility and ICH-CAHPS performance from PY14-19. We evaluated ICH-CAHPS performance by facility case-mix and by receipt of payment reduction using linear regression.

Results: In PY18 and 19, <50% of QIP-eligible facilities were scored on ICH-CAHPS. Over 2,200 facilities were not scored due to obtaining <30 complete surveys. Among scored facilities, scores increased slightly from PY18 to PY19; the share of facilities receiving a score of 0 decreased from 8.5% to 4.2%. Performance was highest on the composite "providing information to patients" and lowest on the global rating of nephrologists. Important determinants of low ICH-CAHPS scores included facility

case-mix (e.g. patient race and Medicaid eligibility) and ownership by the two large dialysis organizations. On average, facilities with PY19 payment reductions scored 2.5 points lower on ICH-CAHPS in PY19. Similarly, facilities penalized in PY18 had lower ICH-CAHPS scores in PY19.

Conclusions: Patient experience with care is an important component of the CMS Meaningful Measures framework, and by extension, the ESRD QIP. The use of ICH-CAHPS results in the Medicare ESRD QIP was limited to about half of facilities in PY18 and 19; improving survey response rates in moderately sized facilities may include more facilities. Survey results varied by facility case-mix and ownership. QIP-penalized facilities had lower ICH-CAHPS scores in the performance year and the subsequent year.

Funding: Other U.S. Government Support

SA-OR060

Urban Segregation and Hospitalization Outcomes in Patients on Hemodialysis

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Background: Patients receiving hemodialysis treatments in communities with a high percentage of Black residents have worse morbidity and mortality outcomes. To better understand drivers of this increased risk, we analyzed data from the United States cohort of the Dialysis Outcomes and Practice Patterns Study (US-DOPPS).

Methods: This analysis included 4567 patients on hemodialysis from 154 facilities in 127 zip codes from the US-DOPPS phases 4-5 (2010-2015) linked to American Community Survey (ACS) data. Negative binomial regression was used to test the association of community, defined by tertile of percent Black residents in dialysis facility zip code, with hospitalization rates, while adjusting for multiple confounders.

Results: The hospitalization incidence rate was 1.18 per year. Patients receiving dialysis in facility zip codes located in communities with a higher (tertile 3: ≥14.4%) vs. lower (tertile 1: ≤1.8%) percentage of Black residents were more likely to be younger, Black, live in urban areas, of lower socio-economic class, more likely to have a catheter as a vascular access, and had fewer comorbidities. These tertile 3 facilities were more likely for-profit and had higher patient counts, but did not differ with respect to clinical quality benchmarks or dialysis adherence. Compared to tertile 1, the covariate-adjusted IRR (95% CI) for hospitalization was 1.32 (1.13-1.55) for tertile 2 and 1.32 (1.14-1.54) for tertile 3 of percent Black residents. This association remained significant in multiple strata examined.

Conclusions: Patients receiving dialysis in communities with a high percentage of Black residents have higher adjusted hospitalization rates, despite having equivalent dialysis care benchmarks. Prospective studies to assess the role of social support, access to pre-ESRD and specialty service care, and patient engagement strategies from healthcare systems and nephrologists caring for these vulnerable populations are warranted.

Funding: Other NIH Support - Clinical and Translational Science Award: 1UL1TR002556-01

Table 2: Incidence Rate Ratios (IRR) of Hospitalization Count with Tertile of Percent Black Residents in the Community

Tertile of %Black residents (with dialysis facility zip code as nidus for ACS data Total n=4565	Unadjusted IRR (95% CI) n-4565	P for trend	Model 1: Adjusted IRR for Age & Sex (95% CI) (n=4565)	P for trend	Model 2: Adjusted IRR in with-out subject's race data added (95% CI) (n=4565)	P for trend	Model 3: Adjusted IRR with patient race data added (95% CI) (n=4565)	P for trend
1(range: 0-1.8%) 2(range: 1.9-11.3%) 3(range: 14.4-92.6%)	1 1.11(0.96-1.30) 1.28(1.08-1.51)	0.003	1 1.11(0.96-1.30) 1.29(1.09-1.52)	0.003	1 1.18(0.99-1.40) 1.32(1.13-1.55)	0.002	1 1.17(0.99-1.38) 1.32(1.14-1.54)	0.001

CI: confidence interval

SA-OR061

Sodium Zirconium Cyclosilicate (SZC) Improves Potassium Balance in Hyperkalemic Hemodialysis Patients: Results from the Phase 3b, Randomized, Placebo-Controlled DIALIZE Study

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Background: Patients (pts) with end-stage renal disease frequently have persistent predialysis hyperkalemia (HK) despite hemodialysis (HD). The phase 3b, randomized, double-blind, placebo (PBO)-controlled DIALIZE trial (NCT03303521) investigated the effect of SZC on predialysis serum potassium (sK^+) after the long interdialytic interval in HD pts with HK. To further examine the effect of SZC, several post hoc analyses were conducted.

Methods: In DIALIZE, 196 pts of mean age 58.1 [SD 13.7] years were randomized 1:1 to receive PBO (n=99) or SZC (n=97) 5 g once daily starting dose on non-dialysis days for 8 weeks, comprising a 4-week SZC dose-titration phase (max 15 g) to achieve target predialysis sK^+ 4.0–5.0 mmol/L, and 4-week stable-dose evaluation phase (SZC 0, 5, 10 or 15 g). Post hoc analyses included assessment of the number of visits at which pts had sK^+ of 4–5 mmol/L and 3.5–5.5 mmol/L, and the maximum sK^+ during the evaluation phase. Change in K^+ gradient (difference between the predialysis sK^+ and dialysate K^+ [dK^+]) from baseline to end of evaluation phase was also assessed by cross tabulation of categorized dK^+ (dK^+ 2–3, 3–4, 4–5 and ≥5 mmol/L).

Results: A high sK^+ to dK^+ gradient at the start of HD permits rapid lowering of sK^+ but can also be associated with a greater risk of adverse events, such as cardiac arrhythmias and hospitalizations. SZC was associated with more pts achieving sK^+ 4.0–5.0 mmol/L and being maintained at sK^+ 3.5–5.5 mmol/L vs PBO for 1, 2, 3 and 4 visits. 56 pts had severe predialysis HK (sK^+ ≥6 mmol/L) in the PBO group during the evaluation period, compared with only 14 in the SZC group. A shift in K^+ gradient towards values below the reported higher risk threshold of 3 mmol/L was observed in the SZC group, with 30.6% of pts (n=11/36) moving from gradient 4–5 to 2–3 mmol/L and 55.6% (n=25/45) from 3–4 to 2–3 mmol/L.

Conclusions: These findings suggest that treatment with SZC improves management and reduces the frequency of severe HK in HD pts, which could potentially modify the risks associated with these factors.

Funding: Commercial Support - AstraZeneca

SA-OR062

Hospitalization Risk Among Younger Adult Hemodialysis Patients: Psychosocial Predictors in the ACTIVE-ADIPOSE Study

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Background: Association of younger age with hospitalization burden and 30-day readmission risk among adult hemodialysis (HD) patients is an unexpected observation in recent national studies, and predictors may be psychosocial in nature (Lin et al. 2019; Chan et al. 2017). Smoking reflects individuals' priority on health maintenance, and hospitalization risk is known to be elevated among HD patients who smoke, especially younger persons (Li et al. 2018). A dataset that captures granular patient-level data including smoking status and HD treatment adherence facilitates examination of age-stratified risk predictors.

Methods: The ACTIVE-ADIPOSE Study (AAS) is a USRDS special study of a multi-center cohort of prevalent HD patients aged 20-92 conducted 2009-2013 at 14 outpatient dialysis clinics in the Atlanta GA and San Francisco areas. Institutional review boards (Emory University, University of California San Francisco) approved the study and all participants provided written informed consent. Study coordinators conducted patient interviews and abstracted patient medical records. In a multivariable regression analysis adjusted for AAS participants' sociodemographic characteristics and comorbidity, we estimated the association of age, smoking, and HD treatment adherence with all-cause hospitalization burden.

Results: Among 759 AAS participants with data for all variables, younger age was associated with increased odds for hospitalization ($p = 0.02$). Smoking was associated with 30% increased odds ($p = 0.03$), and higher frequency of HD sessions skipped was associated with 20% increased odds ($p < 0.001$), for hospitalization. Compared with non-smokers (n=621), AAS participants who were current smokers (n=138) were younger

(52.1 [11.4] vs. 58.2 [14.5]; p <0.001) and more often reported elevated depressive symptoms (36% vs. 22%; p <0.001), and the mean number of HD treatment sessions skipped by smokers compared with non-smokers was twice as high (p = 0.02).

Conclusions: A validated risk score incorporating psychosocial factors may be useful for targeting interventions to reduce HD patients' risk of hospitalization and 30-day unplanned readmissions (Chan et al. 2017). Younger age, smoking, depression, and treatment non-adherence were prominently associated with hospitalization risk among adult HD patients who participated in the AAS.

Funding: NIDDK Support

SA-OR063

Timing of Intradialytic Exercise and Its Impact on Intradialytic Hypotension: A Randomized Crossover Study

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Background: Intradialytic cycling improves physical function and quality of life in hemodialysis and appears safe. Due to concerns regarding increased intradialytic hypotension (IDH), experts recommend that intradialytic cycling be completed during the first half of treatment. However, this recommendation limits the use of intradialytic cycling as a therapeutic tool to improve intradialytic symptoms, which are more common in the latter half of treatment. We compared the rate of IDH while cycling during the first half of hemodialysis (early) versus the second half (late).

Methods: We performed a multi-centre randomized crossover study in adults (≥ 18 years old) on chronic (>3 months), in-centre hemodialysis who were participating in a clinical intradialytic cycling program at three Canadian academic centres between July 1, 2018 and Mar 31, 2019. Group A cycled in the first half of hemodialysis for 2 weeks and then in the second half for the subsequent 2 weeks. In Group B, the exercise schedule was reversed. Blood pressure was measured every 15 minutes throughout hemodialysis. We compared *rate of IDH* (episodes IDH/100 hemodialysis hours) with early and late intradialytic exercise. IDH was defined as a >20 mmHg drop from baseline BP OR a drop in systolic BP to <90 mmHg during hemodialysis. Data was analyzed using a general linear mixed model with random intercept and negative binomial regression.

Results: Eighty-four participants were included in the analysis. Group A (n=43, 32.6% female, 64.5 ±11.9 years) had a mean time on hemodialysis of 3.93 (0.26) hours and exercised for an average of 54.7 minutes. Group B (n=41, 41.5% female, 52.6 ± 13.5 years) had a mean time on hemodialysis of 3.90 (0.23) hours and exercised for an average of 50.2 minutes. The rate of IDH per 100 hemodialysis hours was 35.7 and 37.6 when cycling during the first half and second half of hemodialysis, respectively; p=0.11.

Conclusions: There was no association between IDH and the timing of intradialytic cycling. Exercise late in hemodialysis will facilitate expansion of intradialytic cycling programs by optimizing resource use and will enable the use of cycling as a potential non-pharmacological means of improving hemodialysis-related symptoms.

SA-OR064

The Effects of a 6-Month Structured Programme of Intradialytic Cycling on Cardiovascular Remodelling, Myocardial Fibrosis, and Aortic Stiffness: Results from the CYCLE-HD Study

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Background: Cardiovascular disease (CVD) is the leading cause of death in patients on haemodialysis (HD). Traditional and non-traditional risk factors drive pathological changes in cardiovascular structure that relate directly to outcomes, including elevated LV mass (LVM), adverse LV remodelling (LVM/LVEDV), myocardial fibrosis (MF) and aortic stiffness. Exercise improves many of the risk factors that drive these processes. In this study we assessed the effects of a 6-month programme of intra-dialytic cycling (IDC) compared to usual care on prognostically significant measures of CVD in HD patients using cardiac MRI (CMR).

Methods: In an open-label, blinded end-point, cluster randomised controlled trial, adults undergoing maintenance HD were assigned to either a 6-month structured programme of IDC or usual care. Subjects underwent CMR scanning with assessment of LVM, LVM/LVEDV, native T1 mapping and aortic pulse wave velocity (aPWV) at baseline and study completion. Outcomes were analysed as intention-to-treat, using linear mixed-effects models, adjusted for baseline value.

Results: 130 subjects completed baseline assessments (65 per group) with 101 completing the study protocol (control group n=50, IDC group n=51). Patient demographics were well matched between groups. There was a significant between group reduction in LVM of -11.1g (95% CI -15.8,-6.4, p<0.001) with reverse LV remodelling (LVM/LVEDV) -0.07g/ml (95% CI -0.12,-0.07, p<0.01) favouring the IDC group. There was a significant reduction in native T1 between groups over the study period of -32.2ms [95% CI -46.1,-18.3, p<0.001), with significant reductions in septal native T1 (-23.8ms [95% CI -37.2,-10.3]) and non-septal native T1 (-37.5ms [95% CI -54.3,-20.7]) favouring the IDC group (both p<0.001). There was a significant improvement in aPWV between groups over the study period of -2.07ms^{-1} (95% CI -3.16,-0.99, p<0.01) favouring the IDC group.

Conclusions: A 6-month programme of IDC associated with significant reductions in LVM and reverse LV remodelling, as well as reductions in native T1 and aPWV. These data suggest IDC is associated with beneficial LV remodelling, improvements in extent of MF and severity of aortic stiffness compared to usual care HD.

Funding: Other NIH Support - NIHR Clinician Scientist Award to Dr James Burton CS-2013-13-014

SA-OR065

Effect of a Pedometer-Based Intervention on Body Composition in ESRD

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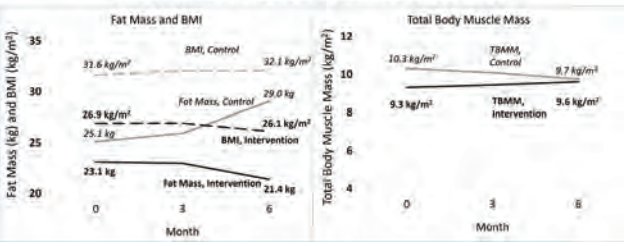
Background: A randomized trial of a pedometer-based intervention with weekly activity goals led to a modest increase in step count among dialysis patients. However, the effect of this intervention on body composition parameters has not been determined.

Methods: 60 dialysis patients were randomized to standard care or a 3-month intervention program with pedometers and weekly step count targets. We obtained bioelectrical impedance spectroscopy (BIS) data on 54 of these patients (28 control, 26 intervention) at baseline, at 3 months, and 6 months and used linear mixed modeling (adjusted for sex and dialysis modality) to estimate differences in change in total-body muscle mass (TBMM) adjusted for height^2, fat mass (kg), and body mass index (BMI) (kg/m^2) between control and intervention groups.

Results: At baseline, there was no significant difference between groups in age, BMI, race, or body composition. There was no statistically significant difference in change between groups in muscle mass, fat mass, or BMI at 3 months. However, at 6 months, participants in the intervention had a significantly greater increase in TBMM of 0.4 kg/m^2 (95% CI 0.02, 0.09) (Figure 1), decrease in fat mass (-4.5 kg [95% CI -8.5, -0.49]) and decrease in BMI (-0.8 kg/m^2 [95% CI -1.7, -0.01]) relative to controls. Each increase of 1,000 steps from 0 to 3 months was associated with a 0.4 kg decrease in fat mass (95% CI 0.03, 0.7) but there was no dose-response relationship with TBMM/ht^2 or BMI.

Conclusions: Patients assigned to a pedometer-based intervention lost weight compared with patients who did not engage in the intervention. Weight loss was driven primarily by changes in fat mass with relative preservation of muscle mass. The between-group differences appear to reflect a combination of negative changes in the control group as well as decrease of fat mass and increase of muscle mass in the intervention group. Achieved changes in step counts were correlated with changes in fat mass. These data support the use of our intervention in improving body composition measures in this population.

Funding: NIDDK Support, Private Foundation Support



SA-OR066

Development of an Automatic Risk-Prediction System for Hemodialysis Patients Using Artificial Intelligence: A Nationwide Dialysis Cohort Study in Japan

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Background: Dialysis patients are at high risks of death and cardiovascular disease. An accurate prediction of these risks at an individual level is required to improve the prognosis of dialysis patients. In this study, we developed a new system for predicting five-year death using machine learning and big data from a nationwide prospective cohort study of the Japanese Society for Dialysis Therapy Renal Data Registry.

Methods: We categorized hemodialysis patients in Japan into new clusters generated by k-means clustering method. The associations between clusters and an outcome (death) in five years were evaluated using multivariate Cox proportional hazards models. Then, the accuracy of the prediction of five-year mortality was compared among the machine learning models.

Results: Among the hemodialysis patients (n=78,854); average age, 65.7±12.2 years; male, 61.5%; and diabetes mellitus, 32.8%. The k-means clustering method using baseline characteristics in the training dataset automatically generated three new groups. Hazard ratios of the high- and middle-risk groups were 45.2 (95% confidence intervals 40.8, 50.0) and 4.8 (4.4, 5.4), respectively. In the test dataset, the accuracy of the cluster was 0.79, which was higher than those of multivariate logistic regression models including baseline characteristics (0.76). The accuracies of deep learning and support vector machine (SVM) models including baseline characteristics were 0.88 and 0.91, respectively. Moreover, that of the SVM model with the cluster was improved to 0.93.

Conclusions: It was found that artificial intelligence can categorize hemodialysis patients on the basis of their characteristics, which reflects their prognosis. This system is useful for identifying high-risk patients at an early stage.

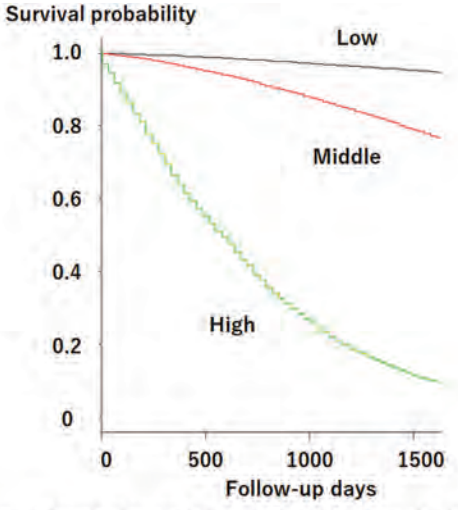

Figure 1 Survival probabilities determined on the basis of new clusters generated by k-means method

SA-OR067

Hyperkalemia Excursions and Mortality in Hemodialysis Patients: Results from the DOPPS

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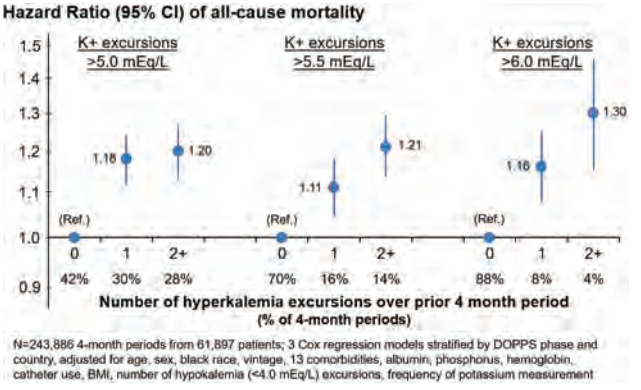
Background: Hyperkalemia (HK) has been associated with adverse clinical events in hemodialysis (HD) patients when analyzing a single potassium (K) measurement or time-averaged K values, but the mean value of serial pre-dialysis K measurements does not reflect variability or excursions out of K target range.

Methods: We used data from 21 countries in phases 4-6 (2009-2018) of the Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective cohort study. We assessed the number of HK excursions over 4-month periods using 3 definitions – serum K >5.0, >5.5, and >6.0 mEq/L – and investigated the association with all-cause mortality over the subsequent 4 months using Cox regression and adjusted for potential confounders, including hypokalemia (K <4.0) excursions and other markers of malnutrition.

Results: We studied 243,886 4-month periods across 61,897 HD patients; The prevalence of at least 1 HK excursion over a 4-month period was 58%, 30%, and 12%, respectively, for serum K >5.0, >5.5 and >6.0 mEq/L. HK excursions >5.5 were most common in Russia (68%) and least common in the US (25%). Patients with HK excursions tended to be younger, with longer HD vintage and higher serum levels of albumin and phosphorus. Compared to 4-month periods with no HK excursions, adjusted models showed that the mortality rate over the subsequent 4 months was 10-20% higher with exactly 1 HK excursion (even at only >5.0 mEq/L), and 20-30% higher with 2+ HK excursions (Figure).

Conclusions: A clear association between one or more HK excursions and all-cause mortality was observed regardless of the hyperkalemic threshold. This method to assess target K achievement may be more sensitive at identifying patients with greater mortality risk over short-term intervals at lower thresholds (5.1-5.5 mEq/L) than previously reported, prompting reassessment of existing HK severity ranges and exploration of strategies to avoid HK excursions.

Funding: NIDDK Support, Commercial Support - This analysis was supported by AstraZeneca. The DOPPS Program is supported by Amgen (since 1996, founding sponsor), Kyowa Hakko Kirin (since 1999 for Japan DOPPS), and Baxter Healthcare Corp. Additional support for specific projects and countries is provided by Akebia Therapeutics, AstraZeneca, European Renal Association-European Dialysis & Transplant Association (ERA-EDTA), Fibrogen, Fresenius Medical Care Asia-Pacific Ltd, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGfN), Italian Society of Nephrology (SIN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Otsuka America, Proteon Therapeutics, the Association of German Nephrology Centres, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Belgian Federal Public Service of Public Health in Belgium, Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN) in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN), and Kidney Research UK (KRUK) in the United Kingdom, and the Agency for Healthcare Research and Quality (AHRQ) and National Institutes of Health (NIH) in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health and not to Mr. Karaboyas directly., Private Foundation Support, Government Support - Non-U.S.



N=243,886 4-month periods from 61,897 patients; 3 Cox regression models stratified by DOPPS phase and country, adjusted for age, sex, black race, vintage, 13 comorbidities, albumin, phosphorus, hemoglobin, catheter use, BMI, number of hypokalemia (<4.0 mEq/L) excursions, frequency of potassium measurement

SA-OR068

Identification of Dicarbonyl and L-Xylulose Reductase (DCXR) as a Therapeutic Target in Human CKD

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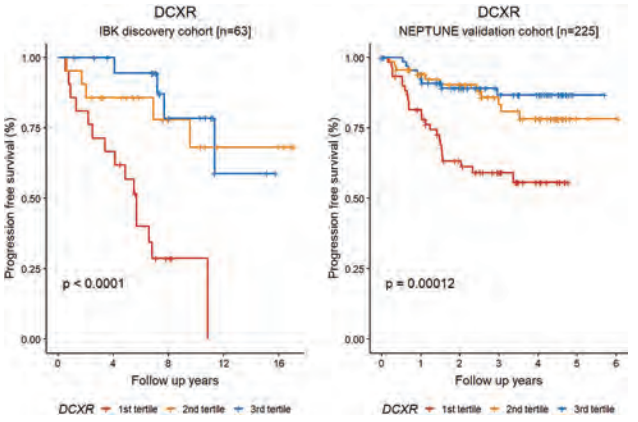
Background: Deregulation of renoprotective factors contributes to development and progression of chronic kidney disease (CKD).

Methods: Renal gene expression profiles of 197 renoprotective factors were analyzed in a cohort of 63 CKD patients. Median follow-up time was 6.9 years and association with disease outcome was assessed in Kaplan-Meier analysis and log-rank statistics. The multicenter NEPTUNE study served as validation cohort [n=225]. Associations with histological and clinical parameters were evaluated for the most significant renoprotective factor DCXR. The impact of SGLT2 inhibition on DCXR levels was furthermore assessed in human renal proximal tubular cells.

Results: DCXR was significantly associated with outcome in the discovery cohort (p-val < 0.0001) and the NEPTUNE validation cohort (p-val = 0.0001). Reduced expression of DCXR was significantly associated with the degree of histological damage as well as with lower estimated glomerular filtration rate and increased urinary protein levels. DCXR expression was positively correlated to enzymes involved in dicarbonyl stress detoxification. The SGLT2 inhibitors canagliflozin and empagliflozin showing a beneficial effect on renal proximal tubular cells under diabetic stimuli enhanced DCXR gene expression up to 2.35 and 2.22 fold.

Conclusions: Lower expression of the renoprotective factor DCXR is associated with more severe disease and worse outcome in human chronic kidney disease.

Funding: Government Support - Non-U.S.



Dicarbonyl and L-xylulose reductase (DCXR) was significantly associated with disease outcome in the discovery cohort (p-value < 0.0001) as well as in the NEPTUNE validation cohort (p-value = 0.00012) in Kaplan Meier analysis and log-rank test statistics.

SA-OR069

NLRP3 Inflammasome Inhibition Attenuates Cisplatin-Induced Renal Fibrosis by Decreasing Oxidative Stress and Inflammation

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Background: The mechanisms of cisplatin-induced chronic kidney disease are ill-defined.

Methods: Renal fibrosis was induced via a series of three injections of cisplatin to male C57BL/6 mice (7.5mg/kg body weight), and mice were euthanized at 6 weeks after the first cisplatin treatment. To validate the protective effect of NLRP3 inflammasome inhibition, MCC950 or gene deletion was used.

Results: Male C57BL/6 mice were administered three doses of cisplatin. BUN and serum creatinine increased time-dependently, accompanied tubular interstitial fibrosis. The protein level of NLRP3, ASC, and caspase-1 maturation was upregulated, and expression of IL-1β was markedly increased in renal tubular epithelium. MCC950, the specific inhibitor of NLRP3 inflammasome, was daily injected into multiple-cisplatin-treated mice intraperitoneally(20mg/kg body weight) for 14 days, starting from 4 weeks after the third dose of cisplatin. MCC950 reduced renal dysfunction, tubular damage, interstitial collagen deposit, and the expression of profibrotic parameters. MCC950 treatment also alleviated oxidative stress and inflammation. Furthermore, NLRP3 gene knockout halted the progression of cisplatin-induced renal fibrosis.

Conclusions: The activation of NLRP3 inflammasome promoted renal dysfunction and interstitial fibrosis induced by multiple injections of low-dose cisplatin. Blockade of NLRP3 inflammasome, by a selective inhibitor of NLRP3 inflammasome, MCC950, or by genetic NLRP3 deficiency, attenuated cisplatin-induced oxidative stress, inflammation, renal injury and fibrosis.

Funding: Government Support - Non-U.S.

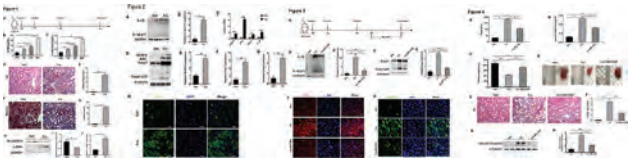

Fig.1 Multiple-cisplatin injections induces renal fibrosis.Fig.2 NLRP3 inflammasome is activated in RTPC.

Fig.3 MCC950 inhibits NLRP3 inflammasome activation.

Fig.4 MCC950 alleviates cisplatin-induced chronic renal injury.

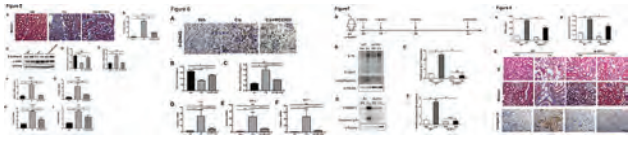

Fig.5 MCC950 attenuates CP-induced renal interstitial fibrosis.Fig.6 MCC950 attenuates CP-induced oxidative stress and inflammation.

Fig.7 NLRP3 deletion inhibits inflammasome activation and inflammation.

Fig.8 NLRP3 knockout attenuates CP-induced renal injury and fibrosis.

SA-OR070

Macrophage Mitophagy Deficiency Promotes Experimental and Human Kidney Fibrosis

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Background: Mitochondrial quality control by mitophagy is critical for normal kidney function. We examined the role of PINK1, Mitofusin 2 (MFN2) and Parkin-mediated mitophagy in macrophage-induced kidney fibrosis, using experimental models of adenine diet (AD) or unilateral ureteral obstruction (UUO) and in human kidney fibrosis.

Methods: Kidney fibrosis in *Pink1*$^{-/-}$ or *Prkn*$^{-/-}$ mice was induced by AD or UUO. Role of MFN2 was studied using *LysM-Cre*$^{+/-}$*Mfn2*$^{fl/fl}$ mice. Kidney tissues and primary macrophages were analyzed by flow cytometry, confocal and electron microscopy, qPCR, western blot, ELISA, and MitoStress test. PBMCs, plasma and kidney biopsies from patients with severe-CKD (GFR<30 ml/min/1.73m^2,*n*=15) or biopsy-proven interstitial fibrosis & tubular atrophy (IFTA,*n*=6) were compared to patients with mild/moderate-CKD (GFR>30,*n*=8) or controls (no CKD,*n*=9).

Results: Expression of PINK1, MFN2, and Parkin was decreased in kidneys and renal macrophages after AD or UUO, as well as in TGF-β1-treated bone-marrow-derived macrophages (BMDMs), human renal macrophages, and THP-1-cells. Kidneys from *Pink1*$^{-/-}$ and *Prkn*$^{-/-}$ mice showed higher fibronectin, collagen-I, TGF-β1, galectin-3, and arginase-I after AD or UUO *vs* corresponding wild-type mice. Renal macrophages from AD-fed *Pink1*$^{-/-}$ mice had a higher number of abnormal mitochondria. Ly6C^{low}CD11b+, F4.80+CD206+ cells and CCL2 levels were increased in blood and kidneys from *Pink1*$^{-/-}$ and *Prkn*$^{-/-}$ mice after AD or UUO. Mitochondria from TGF-β1-treated *Pink1*$^{-/-}$ BMDMs showed lower respiration, higher mitochondrial ROS (mROS), and reduced colocalization with LC3. Mitophagy inhibition by *Pink1*-siRNA or Mdivi-1 resulted in decreased phosphorylation of downstream MFN2 and increased fibrotic response by human macrophages. *LysM-Cre*$^{+/-}$*Mfn2*$^{fl/fl}$ macrophage mitochondria displayed lower recruitment of Parkin and mitophagy. Plasma, PBMCs, and kidney biopsies from patients with severe-CKD and IFTA showed higher CCL2 and mROS, and lower *PINK1*, *MFN2* and *PRKN* expression.

Conclusions: Our study is the first to demonstrate that deficiency of *PINK1*/*MFN2*/*PRKN*-mediated mitophagy promotes macrophage-induced oxidative stress and fibrotic response, and is associated with human kidney fibrosis. Therapeutically targeting macrophage mitophagy pathway may protect against kidney fibrosis.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-OR071

The PAR-1 Antagonist Vorapaxar Ameliorates Kidney Injury and Tubulointerstitial Fibrosis in Experimental Obstructive Nephropathy

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Background: In addition to its role in tumor invasiveness and metastasis, protease-activated receptor-1 (PAR-1) has emerged as an inducer of kidney fibrosis. Whether it can be exploited as a therapeutic target remains unknown.

Methods: We assessed the effect of direct inhibition of PAR-1 on renal fibrosis by vorapaxar (a PAR-1 antagonist), a drug currently undergoing clinical trials for cardiovascular disease, in murine unilateral ureteral obstruction (UUO) model, and in cultured rat renal proximal tubular epithelial cells (NRK-52E). PAR-1 signaling was studied by real-time quantitative PCR, Western blotting and immunohistochemical staining.

Results: In UUO kidneys, PAR-1 and its activator, thrombin, were highly expressed in tubular cells. Mice treated with vorapaxar showed diminished renal fibrotic changes with attenuated fibronectin, α-smooth muscle actin and collagen expression versus control. Macrophage infiltration and ERK1/2 activation were also reduced in vorapaxar treated UUO kidneys. In NRK-52E cells, vorapaxar inhibited PAR-1 signaling, ameliorated thrombin-induced ERK1/2 activation and suppressed the downstream TGF-β signaling via both Smad-dependent and non-Smad-dependent MAPK signaling pathways.

Conclusions: Vorapaxar protects against kidney fibrosis in UUO model, partly via inhibition of thrombin/TGF-β/Smad signaling. This PAR-1 targeted therapeutic strategy may provide a novel treatment approach for chronic renal fibrotic diseases. **Funding:** Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 05163596), Research Grants Council of Hong Kong (Collaborative Research Fund, grant no. C7018-16G), and Hong Kong Society of Nephrology/HK Kidney Foundation Research Grant 2018.

Funding: Government Support - Non-U.S.

SA-OR072

A New Therapeutic Target for CKD: Activins Facilitate TGF-β1 Profibrotic Signaling in Kidney Mesangial Cells

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Background: Chronic kidney disease (CKD) is a rising health issue for approximately 11% of the North American population and is characterized by progressive renal fibrosis and loss of kidney function leading to end-stage renal disease requiring dialysis or transplantation. The profibrotic cytokine TGFβ1 is a central mediator of kidney fibrosis in CKD; blocking it is not feasible due to adverse effects thereby requiring alternate therapeutic approaches. We have shown that TGFβ1 requires activins, a TGFβ superfamily member, for its profibrotic effects. However, since they both signal via the same canonical Smad pathway, how activins enable TGFβ1-induced fibrosis is not known and was investigated here.

Methods: Primary mouse mesangial cells were used. Activin A (AA) and B (AB) were inhibited with a neutralizing antibody, follistatin or siRNA to their receptor, ALK4. Smad3 transcriptional activity was assessed using a CAGA12 luciferase reporter.

Results: TGFβ1 induced strong early activation (60min) of Smad3, while AA/AB caused later activation (48h). TGFβ1 also induced the secretion of AA, with minimal effect on AB. Inhibition of AA, but not AB, decreased TGFβ1-induced Smad3 activation, assessed by phosphorylation and nuclear accumulation, and its transcriptional activity. This demonstrated a requirement for AA for canonical Smad3 signaling by TGFβ1. However, activin inhibition also decreased TGFβ1-induced activation of the α-smooth muscle actin (SMA) promoter more effectively than Smad3 transcriptional activity. Since SMA is a well-known Smad3-mediated TGFβ1 target which also requires non-canonical signaling, these data suggest that AA adds to TGFβ1 signaling activation via a non-canonical pathway. The transcription factors YAP/TAZ are known Smad3 comediators of SMA. Interestingly, activin inhibition prevented TGFβ1-induced YAP, but not TAZ, activation and upregulation. Finally, we confirmed that TGFβ1-induced expression of the extracellular matrix proteins fibronectin and collagen IV were prevented by activin inhibition in mesangial cells. Future experiments will investigate the relevance of Activin-induced TGFβ1 profibrotic signalling in a mouse model of CKD.

Conclusions: AA facilitates TGFβ1 profibrotic effects through regulation of both canonical and non-canonical signaling. Thus, targeting AA represents a novel antifibrotic treatment approach for CKD.

Funding: Other NIH Support - Canadian Institutes of Health Research (CIHR)

SA-OR073

A Computational Drug Screening Approach to Identify Compounds Targeting Renal Age-Associated Molecular Profiles

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Background: Aging is a key driver for chronic kidney disease (CKD) and counterbalancing of renal aging processes depicts a way of preventing development and progression of CKD.

Methods: We generated a set of renal age-associated genes (RAAGs) making use of two transcriptomics datasets complemented by information extracted from scientific literature and dedicated aging databases. We evaluated the association of RAAG expression with CKD progression in an independent trancriptomics dataset of 63 CKD patients with a median follow-up time of 6.9 years. Genes showing concordant expression in aging and CKD were used to computationally screen for compounds reversing expression patterns using the L1000 Characteristic Direction Signature Search Engine. The impact on gene expression of key RAAGs in a human renal proximal tubular cell culture model of renal aging was validated for selected compounds.

Results: 31 of the 634 identified RAAGs were significantly associated with CKD progression. 23 RAAGs (74%) showed concordant regulation with CKD progression, i.e. being upregulated in progressive CKD patients as well as with increasing age or vice versa. Among the top-ranked compounds reversing expression of these RAAGs were drugs being in use in the clinical setting in the context of diabetes and kidney disease, namely rosiglitazone, valsartan, captopril, and atorvastatin. All four compounds significantly affected gene expression in a beneficial way in the cell culture model of renal aging. Rosiglitazone had the strongest impact on RAAG expression in HK2 cells significantly downregulating levels of TNFRSF11B (p-value < 0.001), MMP7 (p-value = 0.007), CFB (p-value < 0.001), LTF (p-value = 0.029), and C3 (p-value = 0.002) as compared with untreated controls.

Conclusions: We have (i) generated a list of RAAGs, (ii) identified a subset being also associated with CKD progression, and (iii) identified compounds that have a positive impact on expression levels of the RAAG/CKD signature in renal proximal tubular cells.

Funding: Government Support - Non-U.S.

SA-OR074

Single Cell Landscapes of Human Kidney in Health and Disease

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Background: Chronic kidney disease is a global health concern and yet therapies to prevent or halt its progression remain scarce. The emergence of single-cell genomics has provided the opportunity to simultaneously characterize the transcriptomic profile of thousands of individual cells and their respective states, revealing differences previously hidden by bulk analyses. As part of an effort to expand knowledge of regional cell identity, function and diversity within the kidney as a basis to understand and treat disease, we set out to catalog the cell types in different regions of the kidney and the perturbations seen with disease. The detailed identification of cellular landscapes across a variety of kidney diseases using single-cell and single-nucleus RNA sequencing (RNA-seq), aims to illuminate therapeutic targets for the development of precision therapies.

Methods: Macroscopically normal, fresh kidney tissue from patients undergoing tumor nephrectomies and frozen tissue sampled from diagnostic renal biopsies, were used to generate single cell and nuclei suspensions respectively. Droplet-based single-cell or single-nucleus RNA-seq libraries were prepared, amplified by PCR and sequenced. Established computational analytical techniques and a panel of canonical marker genes curated in our laboratory, were used to cluster the different cell types present.

Results: We identified heterogeneous cell populations characteristic of expected kidney cell types and detected regional differences predicted from known anatomy. The changing landscape in the setting of disease was revealed by changes such as the presence of additional immune cell populations.

Conclusions: Having established single-cell dissociation and single-nuclei isolation protocols for fresh and frozen human kidney specimens, this study represents an unprecedented cell mapping effort to identify disease-specific pathophysiological mechanisms and reveal novel therapeutic opportunities. The ability to prevent the potentially inexorable decline to kidney failure would represent a major advance and revolutionize the outlook for renal patients worldwide.

Funding: Private Foundation Support

SA-OR075

Capillaries Are Primary Targets in CKD and Loss of Tie2 Signaling Increases Vascular Injury

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Background: Progressive renal diseases are associated with capillary rarefaction of peritubular capillaries, but the functional alterations and mechanisms are not well described. In both mouse models and patients a decline in endothelial tyrosine kinase receptor (Tie2) signaling can be seen in CKD. Here, we investigate the role of Tie2 signaling on capillary function and fibrosis in models of CKD.

Methods: Tie2 floxed mice were crossed with tamoxifen inducible endothelial specific Cadh5-Cre and a reporter line expressing TdTomato upon Cre-activation (Tie2 ECKO). This line enables both an endothelial specific KO of Tie2 and an endothelial lineage tracer. Mice were induced at 4 weeks of age to avoid developmental effects from the knockout. To study the role of Tie2 signaling in progressive renal disease we utilized the unilateral ureter obstruction (UUO) model. Additional lines (Pdgfra-H2b-GFP, Pdgfrb-GFP) were crossed into the line, resulting in reporters of myofibroblasts.

Results: Endothelial injury started already 1 day after UUO and was significantly worse in Tie2 ECKO mice compared to WT mice, including reduced capillary density, capillary fenestrations and vessel perfusion, increase tubular vacuolization and hypoxia. Blood pressure was not different between WT and Tie2 ECKO mice. Later than the endothelial injury was tubulointerstitial fibrosis starting 3 days after UUO. Fibrosis could be seen 3 and 10 days after UUO with significantly more fibrosis in Tie2 ECKO mice at each time point. Although capillary markers decreased and capillary morphology changed, the number of endothelial nuclei, as measured by the lineage tracer TdTomato, did not change. To investigate if the endothelial lineage had undergone endothelial-mesenchymal transition we utilized a myofibroblast reporter, Pdgfra-GFP, to investigate if GFP and TdTomato would colocalize after UUO. Investigation 3 and 10 days after UUO show no colocalization with TdTomato lineage although the up to 3-fold increase in total number of Pdgfra-GFP cells reflect the onset of fibrosis. Ongoing studies are analyzing single cell transcriptomes from the endothelial lineage in the above experiments.

Conclusions: Our results suggest that blood vessel function is central in progressive renal disease and that Tie2 signaling affects blood vessel function and that pro-Tie2 signaling could be an interesting therapy.

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

SA-OR076

Heat Shock Proteins Prevent Mitochondrial Dysfunction In Uremic Cardiomyopathy: Results from the CAIN Study

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Background: Uremic cardiomyopathy is a life-limiting condition that occurs in chronic kidney disease (CKD). Emerging evidence has shown that mitochondrial dysfunction is critical in the pathogenesis of the failing heart. We previously showed that impairment of mitochondrial bioenergetics, fusion and division activities is a cardinal event in heart failure in CKD. Heat Shock Protein (HSP) 70 is an inducible HSP that has been shown to exert self-cytoprotective effects. We previous report that HSP70 prevents vascular calcification in uremic conditions and mitochondrial dysfunction in various stress models. In this study, we hypothesized that induction of HSP70 can prevent mitochondrial dysfunction in the failure heart in CKD.

Methods: Human left ventricular tissues collected from advanced CKD on dialysis (n=15) and healthy donors (n=15) were subjected to RNA sequencing, *ex vivo*. We developed a digital cell sorting study model using deconvolution method to enhance interpretation of heterogenous transcriptomic profiles inherent of mixed-cell type tissue. Primary human cardiac myofibroblast were treated with uremic serum and calcification medium (CM, 5 mM calcium chloride and 5 mM β-glycerolphosphate disodium), *in vitro*. Cells were placed into an incubator for heat shock treatment (HST) at 43°C for 30 min to induce HSPs.

Results: Our data shows that HSP70, as well as HSP27 and HSP90 were significantly down-regulated in CKD hearts compared to control group ($p<0.01$). Additionally, cytoprotective mtHSP70 (HSPA9) and the HSP70 co-chaperone, Bcl2 associated Athanogene 1 (BAG1) were highly expressed in healthy control hearts compared to CKD. However, mitochondrial fusion regulation genes MFN1 and OPA1 were down-regulated in CKD hearts ($p<0.01$). Analysis of primary human cardiac myofibroblast treated with CM and uremic serum revealed the same pattern of changes, in vitro. Induction of HSP70 by HST in cardiac myofibroblasts significantly prevented mitochondrial dysfunction, *in vitro* ($p<0.01$).

Conclusions: Our data shows that mitochondrial dysfunction and downregulation of HSPs are involved in the development of uremic cardiomyopathy. Induction of HSP70 prevents mitochondrial dysfunction in cardiac cells under uremic stress. Further studies are critically warranted to investigate therapeutic strategies targeting HSP70 in uremic cardiomyopathy.

Funding: Private Foundation Support

SA-OR077

Inhibition of Urea Transporter A Attenuates Uremic Cardiomyopathy in CKD Mouse

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Background: Chronic kidney disease (CKD) induces retention of water, sodium, and urea within the body, and is strongly related to the cardiovascular disease named uremic cardiomyopathy. Our previous study found that urea transporter (UT)-A protein was increased in hearts from CKD mice. We hypothesize that downregulation of UT-A could attenuate volume overload, which could be a new therapeutic strategy for uremic cardiomyopathy.

Methods: The CKD model was generated by uninephrectomy (Nx) in C57BL/6 wild-type (WT) and UT-A1/A3$^{-/-}$ (KO) mice. Blood pressure (BP) was determined by the tail cuff method. Echocardiography was performed on lightly anesthetized mice using the VisualSonics system. Heart tissue was harvested for protein and mRNA analysis by Western blot, histology and real-time PCR.

Results: BUN was 29.2 mg/dL (WT-sham), 52.3 mg/dL (WT-Nx), 26.3 mg/dL (KO-sham), and 55.1 mg/dL (KO-Nx), which proved the success of the CKD model. In WT mice, systolic BP (SBP) in Nx mice was higher than sham mice at 8 weeks; 92.5 mmHg vs 121.2 mmHg (P=0.0012), but not in KO mice; 102.0 mmHg vs 106.1 mmHg (P=0.128). The heart to brain weight ratio increased in WT mice (1.03 mg/mg (WT-sham) vs 1.18 mg/mg (WT-Nx); P=0.027), but showed no significant difference for KO mice. In KO-Nx mice, 24 hr urine volume increased (P=0.014) with decreased urine osmolality (P=0.029) compared with KO-shams, but WT-shams vs WT-Nx mice showed no differences. Echocardiography showed that ejection fraction decreased (57% vs 42%; P=0.0193) and left ventricular end-diastolic volume, which indicates preload, increased in WT-Nx mice vs WT-shams (53 μL vs 62 μL; P=0.0433). Gene expression of angiotensin converting enzyme was increased 1.26-fold in WT-Nx heart compared with WT-sham (P=0.0076), but showed no significant difference between KO-Nx and KO-sham.

Conclusions: Deletion of UT-A may reduce volume retention and suppress increased SBP and renin-angiotensin system activity that accompany CKD. UT-A inhibitors may be attractive diuretics for uremic cardiomyopathy.

Funding: NIDDK Support

SA-OR078

Renal, Cardiovascular, and Safety Outcomes of Canagliflozin (CANA) According to Baseline Kidney Function: A CREDENCE Secondary Analysis

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Background: CANA is approved in people with type 2 diabetes and eGFR ≥45mL/min/1.73m^2. We assessed its efficacy and safety according to eGFR strata including the 30-<45mL/min/1.73m^2 stratum.

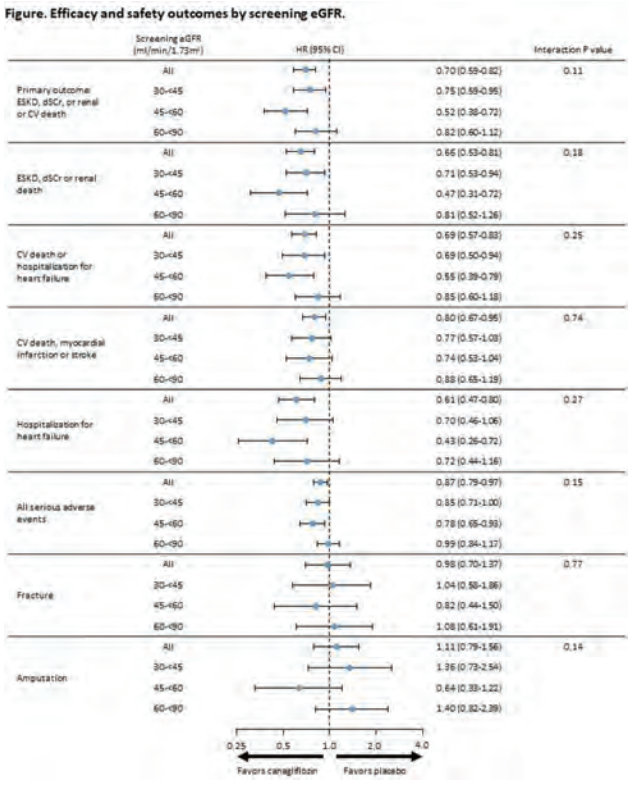
Methods: The CREDENCE study enrolled 4401 participants with eGFR 30-<90mL/min/1.73m^2 and urinary albumin:creatinine ratio >300-5000mg/g, randomizing them within eGFR-based strata to CANA 100mg daily or matching placebo. Primary and prespecified secondary composites and safety outcomes were analyzed using Cox proportional hazards regression within each screening eGFR stratum 30-<45, 45-<60 and 60-<90mL/min/1.73m^2.

Results: At screening, 1313 (29.8%), 1279 (29.1%), and 1809 (41.1%) participants had an eGFR 30-<45, 45-<60 and 60-<90ml/min/1.73m^2. Overall, CANA reduced the primary outcome, the renal composite of ESKD, sustained doubling serum creatinine (SCr) or renal death, a range of CV outcomes and serious adverse events with no impact on fractures or amputations. There was no evidence the impact of CANA differed between eGFR subgroups (all P-interaction >0.11, Figure). The benefits of CANA were individually significant in people with a screening eGFR 30-<45ml/min/1.73m^2 for the primary composite, renal composite and composite of CV death or hospitalization for heart failure (95%CI upper limit <1.00).

Conclusions: CANA safely reduces the risk of renal and CV events in people with type 2 diabetes and substantial albuminuria, and these benefits are preserved across a spectrum of eGFR 30-<90ml/min/1.73m^2, including eGFR 30-<45/min/1.73m^2.

Funding: Commercial Support - Janssen Research & Development, LLC

Figure. Efficacy and safety outcomes by screening eGFR.



SA-OR079

Canagliflozin and Renal-Related Adverse Events in Type 2 Diabetes and CKD: Results from CREDENCE

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Background: Canagliflozin (CANA), a sodium glucose co-transporter 2 inhibitor, has been shown to reduce the risk of major renal outcomes in patients with type 2 diabetes and chronic kidney disease (CKD) in the CREDENCE trial. The aim of this analysis was to examine the incidence of renal-related adverse events (AEs) during treatment with CANA.

Methods: The CREDENCE trial randomly assigned 4401 participants with type 2 diabetes, CKD, and urinary albumin:creatinine ratio >300-5000mg/g to CANA 100 mg/day or placebo (PBO). Rates of renal-related AEs were analyzed using an on-treatment approach overall and by screening eGFR strata (30-<45, 45-<60, and 60-<90 ml/min/1.73m^2).

Results: The incidence rate of renal-related AEs was lower in the CANA versus the PBO group (Table), with consistent results for the majority of specific AEs, including acute kidney injury, azotemia, blood creatinine increased, glomerular filtration rate decreased, nephropathy toxic, renal failure, and renal impairment. The incidence rate for serious renal-related AEs was also lower in the CANA compared to the PBO group (Table). The incidence rates of renal-related AEs were lower with CANA relative to PBO across three eGFR strata (HRs of 0.73, 0.60, and 0.81 for eGFR 30-<45, 45-<60, and 60-<90, respectively; P-interaction=0.31). Renal-related serious AEs were also lower with CANA relative to PBO across the three eGFR strata (Table).

Conclusions: CANA decreased the incidence of serious and non-serious renal-related AEs in patients with type 2 diabetes and CKD. These data highlight the renal safety of CANA in this population.

Funding: Commercial Support - Janssen Research & Development, LLC

Table. Renal-related AEs Using an On-treatment Approach

	PBO (N = 2197)	CANA (N = 2200)	HR (95% CI)	P value	P-interaction†
Total renal-related AEs, IR per 1,000 PY	79.12	57.12	0.71 (0.61-0.82)	<0.001	
Total renal-related AEs, n (%)	388 (17.7)	290 (13.2)			
Acute kidney injury	98 (4.5)	86 (3.9)	0.85 (0.64-1.13)	0.267	
Anuria	0	1 (<0.1)	–		
Azotemia	4 (0.2)	0	–		
Blood creatinine increased	203 (9.2)	144 (6.5)	0.67 (0.54-0.82)	<0.001	
Blood urea increased	21 (1.0)	21 (1.0)	0.97 (0.53-1.78)	0.922	
Glomerular filtration rate decreased	81 (3.7)	68 (3.1)	0.79 (0.58-1.10)	0.162	
Nephropathy toxic	2 (0.1)	0	–		
Renal failure	17 (0.8)	10 (0.5)	0.57 (0.26-1.24)	0.153	
Renal impairment	68 (3.1)	50 (2.3)	0.71 (0.50-1.03)	0.069	
Total renal-related AEs by screening eGFR, n (%)*					0.311
30-<45 ml/min/1.73m^2	177 (27.0)	135 (20.6)	0.73 (0.58-0.91)		
45-<60 ml/min/1.73m^2	117 (18.3)	77 (12.0)	0.60 (0.45-0.79)		
60-<90 ml/min/1.73m^2	94 (10.4)	78 (8.6)	0.81 (0.60-1.09)		
Serious renal-related AEs, IR per 1,000 PY	16.72	12.02	0.72 (0.51-1.00)	0.048	
Serious renal-related AEs, n (%)	82 (3.7)	61 (2.8)			
Serious renal-related AEs by screening eGFR, n (%)*					0.941
30-<45 ml/min/1.73m^2	40 (6.1)	31 (4.7)	0.75 (0.47-1.20)		
45-<60 ml/min/1.73m^2	24 (3.8)	17 (2.7)	0.66 (0.35-1.22)		
60-<90 ml/min/1.73m^2	18 (2.0)	13 (1.4)	0.72 (0.35-1.46)		

AE, adverse event; CANA, canagliflozin; IR, incidence rate; PBO, placebo; PY, patient-years.
*Percentages calculated based on n=656 PBO and n=655 CANA for eGFR 30-<45 ml/min/1.73m^2; n=638 PBO and n=640 CANA for eGFR 45-<60 ml/min/1.73m^2; and n=903 PBO and n=905 CANA for eGFR 60-<90 ml/min/1.73m^2.
†P value for interaction across eGFR categories.

SA-OR080

Cost Effectiveness Analysis of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors Treatment in Patients with Diabetic Kidney Disease for Cardiovascular and Renal Protection in Singapore

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Background: Diabetic Kidney Disease (DKD) is a major cause of end stage kidney disease (ESKD) in Singapore. Whilst major trials showed that SGLT2 inhibitors (SGLT2i) improve renal and cardiovascular outcomes in patients with DKD, drug cost is a significant deterrent. We aim to analyse the cost effectiveness of SGLT2i treatment, when added to standard therapy in patients with DKD, for the reduction of cardiovascular and renal events in Singapore.

Methods: All patients with Type 2 diabetes and CKD stages 1 to 3B on follow up with 9 primary care facilities between January 2008 to January 2011 were included in the study population. Incidence of acute myocardial infarct (AMI), ESRD and all-cause mortality were determined and the annual cost of AMI and ESRD requring dialysis and the cost of SGLT2i were calculated using data from the Regional Healthcare System (RHS) Database. Results of the risk reduction for the above outcomes were obtained from CREDENCE, CANVAS, DECLARE and EMPA-REG trials to determine the incremental cost effectiveness ratio (ICER) if SGLT2i were initiated on this historical cohort.

Results: 6281 patients with Type 2 DM and CKD stages 1 to 3B were included in the study. The rates of AMI, all-cause mortality and ESRD was 7.9/1000, 75.2/1000 and 18.1/1000 patient-year respectively. If SGLT2i were initiated, the cost to prevent 1 mortality and 1 ESRD ranged from USD $11 857-40 174 and USD $19 888-63 356 respectively but the cost to prevent 1 AMI was substantially higher. ICER of less than USD $57 827 (equivalent to GDP per capita) was determined to be cost effective in the study. Addition of SGLT2i to standard therapy to reduce cardiovascular and renal events seems cost effective for preventing deaths and progression to ESRD. (Table 1)

Conclusions: Addition of SGLT2i to standard therapy in our diabetic CKD patients can potentially improve outcomes and may be cost effective for preventing deaths and progression to ESRD.

	ICER (Cost/QALY gained) in USD	
AMI	Canagliflozin 300mg (CANVAS)	$2,396448
	Empagliflozin (EMPA-REG)	$783 038
	Dapagliflozin (DECLARE)	$636 886
All-cause mortality	Canagliflozin 300mg Canagliflozin 100mg(CREDENCE)	$155 064 $26 471
	Empagliflozin	$21 889
	Dapagliflozin	$20 473
ESRD	Canagliflozin 300mg Canagliflozin 100mg	$238 999 $46 042
	Empagliflozin	$27 812
	Dapagliflozin	$97 987

SA-OR081

Clinical Events in Type 2 Diabetes and Moderate-to-Severe CKD by Albuminuria Status: Dulaglutide vs. Insulin Glargine

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Background: In participants with type 2 diabetes and moderate-to-severe chronic kidney disease (CKD), in the AWARD-7 trial, treatment with dulaglutide (DU) compared to insulin glargine (IG) led to slower estimated glomerular filtration rate (eGFR) decline at similar levels of glycemic control and blood pressure.

Methods: To determine risk of a composite endpoint of ≥40% eGFR decline or end-stage kidney disease (ESKD) by albuminuria status, this *post hoc* analysis used Cox proportional hazards modeling for time to first event. Participants were randomized (1:1:1) to DU 0.75 mg or 1.5 mg weekly versus titrated IG daily for one year. eGFR was calculated using the CKD-epidemiology (EPI) creatinine and cystatin C equations.

Results: At baseline, treatment groups had similar eGFR within albuminuria subgroups (Table). Through the 1-year treatment period, the majority of events occurred in patients with macroalbuminuria; the incidence rate of the composite endpoint was significantly lower for DU 1.5 mg compared to IG in those with macroalbuminuria (Table). Consistent results were obtained when eGFR was calculated using either CKD-EPI creatinine or cystatin C equations.

Conclusions: The risk of the composite endpoint of ≥40% eGFR decline or ESKD was lower by approximately half for DU 1.5 mg compared to IG, which was mainly driven by effects in participants with macroalbuminuria.

Funding: Commercial Support - Eli Lilly and Company

Baseline Characteristics (mean±SD)		Dulaglutide 1.5 mg N=192		Dulaglutide 0.75 mg N=190		Insulin glargine N=194
eGFR (mL/min/1.73m^2)[a] UACR <30 UACR 30-300 UACR >300		38.1±13.2 43.8±13.0 40.2±12.6 34.0±12.8		38.3±12.3 44.2±9.0 38.9±12.5 35.0±12.6		38.5±13.0 42.9±12.5 42.0±11.8 33.9±12.6
≥40% eGFR decline or ESKD events (a. CKD-EPI creatinine; b. CKD-EPI cystatin C)		n/N (%)	HR (95%CI)	n/N (%)	HR (95%CI)	n/N (%)
Overall	a.	10/192 (5.2)	0.45 (0.20, 0.97)*	16/190 (8.4)	0.79 (0.41, 1.51)	21/194 (10.8)
	b.	11/192 (5.7)	0.49 (0.23, 1.04)	15/190 (7.9)	0.73 (0.38, 1.42)	21/194 (10.8)
Normal UACR <30 mg/g	a.	2/34 (5.9)	NA	0/44 (0.0)	NA	0/48 (0.0)
	b.	3/34 (8.8)	NA	0/44 (0.0)	NA	1/48 (2.1)
Microalbuminuria UACR 30-300 mg/g	a.	2/74 (2.7)	1.59 (0.14, 17.48)	2/61 (3.3)	1.96 (0.18, 21.66)	1/56 (1.8)
	b.	2/74 (2.7)	1.59 (0.14, 17.48)	2/61 (3.3)	1.96 (0.18, 21.66)	1/56 (1.8)
Macroalbuminuria UACR >300 mg/g	a.	6/84 (7.1)	0.25 (0.10, 0.68)*	14/84 (16.7)	0.72 (0.36, 1.43)	20/90 (22.2)
	b.	6/84 (7.1)	0.26 (0.10, 0.71)*	13/84 (15.5)	0.70 (0.34, 1.41)	19/90 (21.1)

[a]CKD-EPI creatinine; CI=confidence interval; HR=hazard ratio; N=total number, n=number with composite outcome; NA = not applicable; UACR=urinary albumin/creatinine ratio. *p<0.05 versus insulin glargine

SA-OR082

Renoprotection with Semaglutide and Liraglutide: Direct or Indirect Effects?

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Background: The SUSTAIN 6 and LEADER cardiovascular (CV) outcome trials indicated that the glucagon-like peptide-1 analogues semaglutide and liraglutide may provide renal as well as CV benefits. This post-hoc analysis investigated the degree to which the observed renoprotective effects could be mediated by glycated hemoglobin (A1C), systolic blood pressure (SBP) and body weight (BW).

Methods: SUSTAIN 6 (N=3297, NCT01720446) and LEADER (N=9340, NCT01179048) assessed CV, renal and safety outcomes for semaglutide and liraglutide versus placebo in patients with type 2 diabetes and high CV risk. A prespecified secondary outcome in these trials was a renal composite of new onset persistent macroalbuminuria, persistent doubling of serum creatinine, need for continuous renal-replacement therapy or death due to renal disease. We performed counterfactual mediation analyses of A1C, SBP and BW using absolute values at each trial visit. The direct contribution of semaglutide/liraglutide to time to first renal event was estimated assuming that the mediator values changed to those observed in the placebo group (from baseline to 2 and 3 years in SUSTAIN 6 and LEADER, respectively). In the adjusted model for A1C, both SBP alone and in combination with BW were included as confounders. Due to the limited number of events in SUSTAIN 6, 95% confidence intervals (CIs) could not be calculated.

Results: In SUSTAIN 6 and LEADER, the rate of a renal event was reduced by 36% (95% CI 12%;54%; P=0.005) and 22% (95% CI 8%;33%; P=0.003) in the semaglutide and liraglutide groups, respectively, versus placebo. A1C was estimated to mediate 26% and 25% (95% CI -7.1;67.3) of the benefits of semaglutide and liraglutide, respectively, whereas the contributions of SBP (22% and 9% [95% CI 2.8;22.7]) and BW (-8% and 9% [95% CI -7.9;35.5]) were smaller. In adjusted analyses, the contribution of A1C increased to 36% (SBP as confounder) and 30% (95% CI -4.5;81.1; SBP and BW as confounders) in the semaglutide and liraglutide groups, respectively.

Conclusions: The renal benefits of semaglutide and liraglutide appear mediated to a modest extent by changes in A1C, SBP and BW, and are therefore likely to be also driven by other, potentially direct, mechanisms.

Funding: Commercial Support - Novo Nordisk

SA-OR083

Combination Therapy of Empagliflozin and Linagliptin vs. Metformin and Insulin Glargine on Intra- and Renal Hemodynamics in Type 2 Diabetes

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Background: Combination of insulin with oral antidiabetic drugs is a valid option, but oral combination therapy emerged as an alternative treatment in type 2 diabetes (T2DM). However, the intra-, and renal hemodynamic profile of such combinations therapies has not been evaluated so far.

Methods: In this study 101 patients with T2DM were randomized to receive either empagliflozin 10mg and linagliptin 5mg (E+L group) orally or metformin and insulin glargine (M+I group, with dose adjustments according to glucose levels), for 3 months. Renal hemodynamics were assessed with the "gold-standard", namely constant-infusion input-clearance technique with para-aminohippuric acid and inulin for renal plasma flow (RPF) and glomerular filtration rate (GFR). Intrarenal hemodynamics were calculated according the model established by Gomez.

Results: Due to the multiple dose adjustment of insulin glargine, reduction in HbA1c was greater in M+I than in E+L group (p=0.001), hence all analyses between M+I and E+L were HbA1c-adjusted to evaluate the glucose independent effects between the 2 therapies. In E+L group, body weight (p<0.001), body mass index (p<0.001) and both ambulatory 24-h systolic and diastolic BP (p=0.004/0.036) were reduced compared to M+I group. Treatment with E+L reduced GFR (127±13 vs. 120±14 ml/min, p=0.003), but RPF remained unchanged (623±114 vs. 615±115 ml/min, p=0.536). In contrast, treatment with M+I not only reduced GFR (127±15 vs. 120±13 ml/min, p=0.001), but also resulted in a significant reduction of RPF (653±150 vs. 600±121 ml/min, p<0.001) that was different between the 2 groups (p<0.001). Analysis of intrarenal hemodynamics revealed that E+L did not significantly impact on resistance of afferent arteriole (R_A) (p=0.116), but diminished resistance of efferent arteriole (R_E) (p=0.001), whereas in M+I group R_A was reduced (p=0.006) and R_E remained unchanged (p=0.538). Thus, the effects on R_A (p<0.001) and on R_E (p<0.001) were significantly different between the 2 groups.

Conclusions: As expected combination therapy with E+L reduced GFR, whereas M+I resulted in both reduction of GFR and RPF. Analysis of intrarenal hemodynamics identified different underlying hemodynamic mechanism, with E+L (surprisingly) mainly decreasing R_E and M+I affecting R_A.

Funding: Commercial Support - Boehringer Ingelheim

SA-OR084

Risks of eGFR Decline Thresholds by CKD, Diabetes, and Albuminuria Status

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Background: Thresholds for estimated glomerular filtration rate (eGFR) decline are increasingly used as chronic kidney disease (CKD) outcomes and clinical trial endpoints. eGFR decline thresholds of 30%, 40%, and 50% predict end-stage kidney disease. However, data from large clinical populations to determine risks of reaching these thresholds among patients with and at-risk of CKD [diabetes mellitus (DM), pre-DM, and hypertension (HTN)] and by DM or albuminuria status among patients with CKD are lacking.

Methods: CURE-CKD is a meticulously curated registry of clinical and administrative data extracted from health records of two major healthcare systems in the western United States. eGFR (CKD-EPI) was calculated as the mean value during a 90-day baseline and for each subsequent year (2006-2017). Adults with baseline eGFR ≥15 mL/min/1.73m^2 and at least two follow-up years were included. Albuminuria was defined as urine albumin-to-creatinine ratio ≥30 mg/g. Time-to-event models examined eGFR decline thresholds, controlling for age, gender, race/ethnicity, baseline eGFR, and medication use. An alpha of p<0.001 was chosen *a-priori.*

Results: A total of 1,005,986 patients with mean follow-up of 5.4 years were included (table 1). For patients with established CKD compared to those at-risk of CKD, adjusted hazard ratios (aHRs) for eGFR decline thresholds (30%, 40%, 50%) were increased (1.93, 2.05, 2.16). For patients with CKD, those with DM compared to without DM had increased aHR (1.57, 1.71, 1.75). For patients with CKD and DM, aHR were increased for those with albuminuria compared to without albuminuria (1.38, 1.41, 1.44). Among patients with CKD and no DM, aHR were increased for those with albuminuria compared to without albuminuria (1.81, 1.93, 1.97).

Conclusions: Patients with CKD had increased risk of reaching clinically relevant eGFR decline thresholds compared to patients at-risk with DM, pre-DM, or HTN. Among patients with CKD, DM or, albuminuria independently predicted thresholds of eGFR decline. Study findings inform the design of observational studies and clinical trials in patients with and at-risk of CKD.

Funding: Private Foundation Support

Table 1. Risks of eGFR Decline Thresholds

Analysis	Comparator: Reference	Sample Size	Mean Followed (Years)	Mean (SD) Baseline eGFR (mL/min/1.73m²)	30% Decline in Mean Baseline eGFR: Risk 95%CI p	30% Decline in Mean Baseline eGFR: Adjusted HR 95%CI p	40% Decline in Mean Baseline eGFR: Risk 95%CI p	40% Decline in Mean Baseline eGFR: Adjusted HR 95%CI p	50% Decline in Mean Baseline eGFR: Risk 95%CI p	50% Decline in Mean Baseline eGFR: Adjusted HR 95%CI p
#1 N=3,005,908	CKD	105,160	4.3-4.5	53 (22)	22% to 33% 2.88	1.93 1.89-1.96 <0.0001	14% to 5% 2.63	2.05 2.00-2.09 <0.0001	9% to 3% 3.27	2.34 2.30-2.38 <0.0001
	At-Risk CKD	900,826	5.2-5.4	85 (21)	2.00-3.05 <0.0001		2.59-2.68 <0.0001		3.20-3.35 <0.0001	
#2 N=109,160	CKD, DM	36,360	4.0-4.3	57 (15)	27% to 20% 1.35	1.57 1.53-1.61 <0.0001	19% to 12% 1.49	1.71 1.66-1.77 <0.0001	12% to 7% 1.98	1.75 1.69-1.81 <0.0001
	CKD, No DM	69,800	4.4-4.7	51 (20)	1.32-1.38 <0.0001		1.45-1.54 <0.0001		1.92-2.04 <0.0001	
#3 N=76,340	CKD, DM Albuminuria	12,141	4.3-4.6	75 (16)	20% to 27% 1.06	1.38 1.33-1.44 <0.0001	13% to 18% 1.05	1.41 1.33-1.49 <0.0001	12% to 11% 1.08	1.44 1.35-1.55 <0.0001
	CKD, DM No Albuminuria	24,219	3.8-4.1	47 (17)	1.02-1.10 0.001		1.01-1.10 0.02		1.03-1.15 0.01	
#4 N=69,020	CKD, No DM Albuminuria	7,451	4.6-5.0	72 (13)	27% to 20% 1.35	1.81 1.73-1.90 <0.0001	17% to 12% 1.50	1.93 1.83-2.05 <0.0001	12% to 7% 1.70	1.97 1.83-2.13 <0.0001
	CKD, No DM No Albuminuria	61,569	4.4-4.6	48 (15)	1.26-1.41 <0.0001		1.42-1.59 <0.0001		1.59-1.82 <0.0001	

Analysis #1 Covariates: Gender, Race/Ethnicity, Age, eGFR.
Analysis #2 and #3 Covariates: Gender, Race/Ethnicity, Age, eGFR, ACE inhibitor/ARB use, SGLT2 inhibitor use, NSAID use, PPI use
Analysis #4 Covariates: Gender, Race/Ethnicity, Age, eGFR, ACE inhibitor/ARB use, NSAID use, PPI use

SA-OR085

CKD Progression for Patients with Diabetes and Reduced eGFR Treated with Metformin or Sulfonylurea

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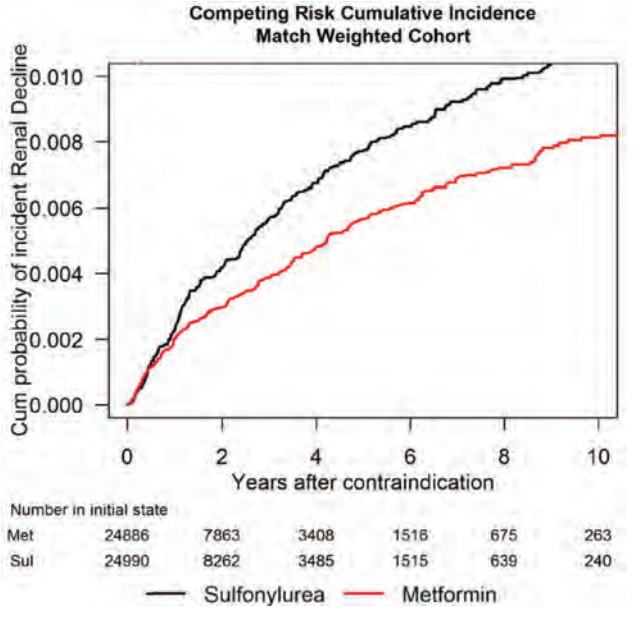
Background: Safety concerns limit metformin use in kidney disease. We compared the incidence of renal events between metformin and sulfonylureas users with reduced estimated glomerular filtration rate (eGFR).

Methods: A retrospective cohort combined Veterans Administration, Medicare, and National Death Index data. Metformin or sulfonylurea users were followed from renal function threshold (eGFR <60 ml/min/1.73m^2) until a renal event, treatment change, loss to follow up, death or study end. Renal event was defined as persistent decline in eGFR from baseline of 40% or more (eGFR event) or a diagnosis of end-stage renal disease (ESRD). The analysis compared renal event hazard for metformin vs. sulfonylurea users and estimate cumulative risk in a propensity score matched weighted cohort accounting for the competing risks of non-persistence or death.

Results: There were 74,101 and 28,976 persistent metformin and sulfonylurea users, respectively, who reached renal threshold. The weighted cohort included 24,886 metformin vs. 24,990 sulfonylurea patients; 98% male; 84% white, median (IQR) age 71 years [64, 78]. Median eGFR was 56 ml/min [51.4, 58.0], 10% of the patients had a eGFR <45 ml/min/1.73m^2 and HbA1c 6.6% [6.1, 7.2]. Metformin users had lower cause-specific hazard of renal events vs. sulfonylurea (adjusted HR 0.81, 95%CI (0.68, 0.98)).

Conclusions: Compared to sulfonylureas, metformin use in patients with reduced eGFR was associated with a lower risk of kidney function decline or ESRD.

Funding: Veterans Affairs Support



SA-OR086

Verinurad Plus Febuxostat Rapidly Reduces Albuminuria in Type 2 Diabetes Independent of Preexisting Kidney Disease

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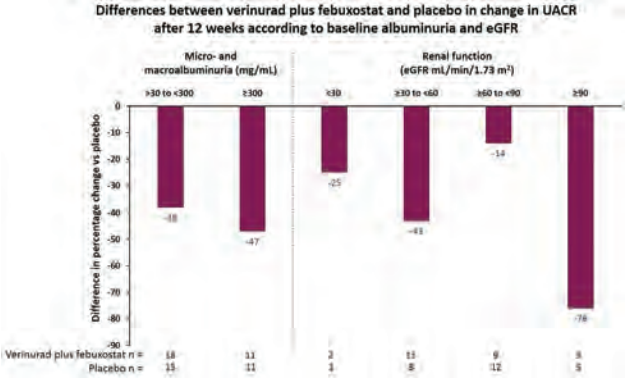
Background: Elevated serum uric acid predicts new-onset albuminuria, the earliest clinical indicator of kidney disease. We evaluated the effects of intensive uric acid lowering on albuminuria by combining verinurad with febuxostat in patients with type 2 diabetes mellitus (T2DM) and albuminuria.

Methods: In a phase 2, parallel group, multicenter, randomized, double-blind, placebo-controlled trial (NCT03118739), adults with T2DM, albuminuria, and hyperuricemia were randomized to verinurad 9 mg plus febuxostat 80 mg once daily, or placebo, and followed for 24 wks. The primary outcome was reduction in urinary albumin to creatinine ratio (UACR) at 12 wks compared with baseline. Changes in UACR were evaluated according to baseline characteristics including UACR and estimated glomerular filtration rate (eGFR).

Results: Baseline UACR was 459 (±825) mg/g in the verinurad plus febuxostat group (n=32) and 412 (±548) mg/g in the placebo group (n=28). Improvement in UACR with verinurad plus febuxostat was rapid, sustained over time, and met prespecified criteria for significance, with 39%, 39%, and 49% reductions vs placebo at wks 1, 12, and 24, respectively (wk 12 90% CI –62%, –4%; *P*=0.0747). Reduction was consistent across subgroups including those based on UACR and eGFR (**Figure**). Verinurad plus febuxostat was well tolerated.

Conclusions: Intensive urate lowering with verinurad plus febuxostat significantly reduced UACR in patients with T2DM, albuminuria, and hyperuricemia. Reduction was rapid, sustained, and similar regardless of baseline eGFR and degree of albuminuria. A larger study is underway to determine which patient groups might benefit most from verinurad combination therapy.

Funding: Commercial Support - AstraZeneca



SA-OR087

Correction of Anemia by Dapagliflozin in Patients with T2D

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Background: Type 2 diabetes (T2D) is one of the most common causes of chronic kidney disease (CKD) and the most frequent cause of renal anemia. Most patients (pts) with T2D show no overt symptoms of renal impairment, consequently, unrecognized anemia is common. Increased hemoglobin (Hb) levels have been observed with dapagliflozin (DAPA) treatment. This study investigated the efficacy and safety of DAPA 10mg in pts with and without anemia at baseline.

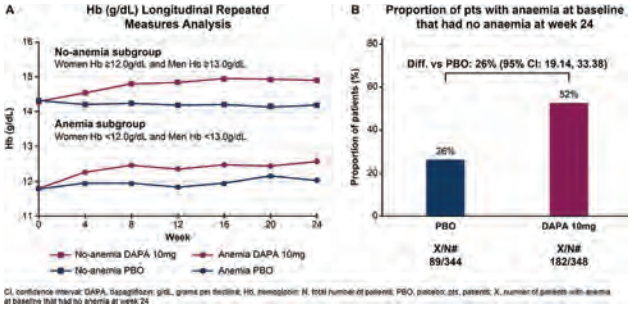
Methods: This post-hoc analysis evaluated the effect of the sodium-glucose cotransporter 2 inhibitor, DAPA 10mg, on Hb over 24 weeks (w) across 14 placebo (PBO)-controlled studies in T2D pts with or without anemia (women Hb<12.0 g/dL; men Hb<13.0 g/dL).

Results: A total of 5324 pts were included, 700 (13%) pts had anemia at baseline. There were 1168 (22%) pts with CKD (eGFR<60 mL/min/1.73m^2), 324 (28%) had anemia at baseline. As expected, pts with anemia vs those without anemia were older (mean age:63 vs 59y), had a longer duration of T2D (14 vs 9y) and more advanced CKD (mean eGFR: 66.3 vs 78.6 mL/min/1.73m^2 and mean UACR: 274 vs 89 mg/g). Longitudinal repeated measures analysis showed an Hb increase at w 24 in the DAPA 10mg anemia and no-anemia subgroups (**Fig.1A**). Anemia: (Mean g/dL(SEM)[95% CI], DAPA 0.81(0.066) [0.68,0.93], PBO 0.28(0.067)[0.15,0.41]; difference vs PBO 0.53(0.076)[0.38,0.68]). No-anemia: (DAPA 0.56(0.017)[0.53,0.60] and PBO -0.20(0.018)[-0.23,-0.16]; Difference

vs PBO 0.76(0.024)[0.72, 0.81]). DAPA 10mg corrected anemia in more pts than PBO; DAPA 10mg 52% vs PBO 26% (**Fig.1B**). Overall, DAPA 10mg was well tolerated.

Conclusions: Unrecognized anemia is common in pts with T2D. DAPA 10mg corrected anemia by increasing Hb over 24w and was well tolerated. This effect may be driven by a reduction in blood volume but the increase in Hb beyond w 4 may be explained by other mechanisms.

Funding: Commercial Support - AstraZeneca



CI, confidence interval; DAPA, dapagliflozin; g/dL, grams per decilitre; Hb, haemoglobin; N, total number of patients; PBO, placebo; pts, patients; X, number of patients with anemia at baseline that had no anemia at week 24

The effect of DAPA 10mg on Hb in pts with and without anemia over 24 weeks

SA-OR088

Polycystin 1 Regulates Actomyosin Contraction and the Cellular Response to Extracellular Stiffness

Elisa Agnese Nigro,[1] Gianfranco Distefano,[1] Marco Chiaravalli,[1] Vittoria Matafora,[2] Maddalena Castelli,[1] Angela Pesenti Gritti,[1] Angela Bachi,[2] Alessandra Boletta.[1] *[1]San Raffaele Scientific Institute, Milan, Italy; [2]IFOM-FIRC Institute of Molecular Oncology, Milano, Italy*.

Background: The Polycystins (PC-1 and PC-2) are the products of the genes mutated in Autosomal Dominant Polycystic Kidney Disease. PC-1 is a receptor with a large extracellular extendible domain postulated to act as a mechanosensor. It associates with PC-2 to form a receptor/channel complex possibly activated by the mechanical stimulus of ciliary bending and resulting in calcium influx. This model has recently been challenged, leaving the open question of what mechanical stimuli activate the polycystins.

Methods: To identify interactors of PC-1, we immunoprecipitated (IP) endogenous tagged PC-1 in mouse embryonic fibroblasts derived from *Pkd1*$^{HA/HA}$ or *Pkd1*$^{WT/WT}$ embryos, followed by liquid chromatography mass-spectrometry (LC-MS). We used SILAC (Stable Isotopes Labeling by Aminoacids in Cell culture) followed by either in-gel proteins digestion or protein digestion directly on the beads prior to LC-MS. Each assay was performed in two experiments.

Results: We identified 316 proteins, 30 of them significantly enriched in the IP versus the control in both SILAC studies. Both approaches yielded similar results. The list of binding partners all pointed to a central role for PC-1 in regulation of the actomyosin contraction machinery. Using *Pkd1* gain and loss of function cellular models, we found that PC-1 reduces myosin light chain phosphorylation (pMLC), the main regulator of actomyosin contraction. Furthermore, we confirmed that PC-1 inhibits cell contractility using a collagen disc contractility assay. Given the role of the actomyosin pathway in the response of cells to mechanical stimuli, we used hydrogels or graded epithelial density conditions to mimic different extracellular rigidity states, ranging from 0.4 to 40 kPa. We found that PC-1 negatively regulates Yes-Associated Protein (YAP) activation in response to extracellular stiffness. Finally, in an orthologous murine model of PKD we found increased pMLC, and enhanced YAP nuclear translocation and transcriptional activity, both reversed by the ROCK-inhibitor Fasudil. Notably, treatment with this compound ameliorates disease progression.

Conclusions: Our data suggest a possible direct role for PC-1 as a mechanosensor able to negatively regulate the cellular response to extracellular stiffness.

SA-OR089

Polycystin 1 Acts as an Atypical Adhesion G-Protein-Coupled Receptor (GPCR) That Responds to Non-Canonical WNT Signals and Inhibits GSK3?

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Background: A recent study demonstrates that polycystin-1 (PC1) serves as a receptor for Wnt ligands. We find that PC1 responds to Wnt9b by shedding its 350kD N-terminal fragment (NTF), which bears a striking resemblance to the activation mechanism of an adhesion GPCR (aGPCR). For aGPCRs, NTF removal liberates a short peptide sequence near the GPS cleavage site called stachel, which then interacts with an internal binding site and engages a G protein signalling cascade.

Methods: Biosensor kinase assay, western blot, morpholino in zebra fish

Results: We find that Wnt9b induces a PC1-dependent phosphorylation and inhibition of the GSK3β kinase through the RhoA GTPase-ROCK kinase pathway. Expression of a "constitutively active" aGPCR form of PC1 that lacks its NTF (NTF PHS) leads to profound suppression of GSK3β activity that is dependent upon Gα13, RhoA and ROCK. Furthermore, a form of the NTF PHS that lacks the putative "stachel" peptide (NTF PH) is unable to inhibit GSK3β kinase, indicating the importance of "stachel" peptide for the active participation of PC1 in this signalling pathway. Interestingly, GSK3β is an important negative regulator of the HIPPO/non-canonical Wnt signalling target TAZ(WWTR1), lack of which leads to the development of severe renal cysts. Furthermore, recent data show that pharmacological inhibition of GSK3β is beneficial in mouse models of ADPKD. We find that exogenous expression of an active form of TAZ in PC1 null cells or in PKD1a/b morphant zebrafish suppresses the development of relevant phenotypes. We also demonstrate that pharmacological inhibition of GSK3β leads to accumulation of the TAZ protein and to reduced cystogenesis in a 3D matrigel assay employing PC1 null cells. TAZ abundance and activity have been shown to be upregulated through the non-canonical Wnt signalling pathway. We find that HEK293 cells that express PC1 and PC2 respond to Wnt9b treatment by significantly increasing TAZ abundance as compared to the wild type HEK293 cells treated in the same manner.

Conclusions: Taken together, our data suggest that PC1 can act as an aGPCR-like receptor for non-canonical Wnt ligands and that it participates in a novel signalling pathway by linking non-canonical Wnt ligands to the GSK3β-dependent regulation of TAZ, a multifaceted signalling molecule whose absence is sufficient to induce renal cystic disease.

Funding: NIDDK Support

SA-OR090

Inhibition of Drp1, the Master Regulator of Mitochondrial Fission, Ameliorates Polycystic Kidney Disease Progression

Laura Cassina, Marco Chiaravalli, Alessandra Boletta. *San Raffaele Scientific Institute, Milan, Italy*.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a genetic disorder caused by mutations in *PKD1* gene. We reported the remodeling of glucose utilization for energy production and a wide metabolic rewiring in mouse *Pkd1* mutant cells and kidneys (Rowe 2013, Podrini 2018). Alterations in mitochondrial structure and mitochondrial respiration have also been described (Ishimoto 2017, Podrini 2018, Lin 2018). We investigated mitochondrial morphology and function in a PKD mouse model to elucidate their possible contribution to disease progression.

Methods: We analyzed mitochondria structure by transmission electron microscopy (TEM) and respiratory complexes by *in situ* activity staining on kidney sections from control and *Ksp-Cre;Pkd1*$^{fl/-}$ mice. Control and cystic mice were treated with daily intra-peritoneal injection of vehicle or Mdivi-1 (25mg/kg) from P6 to P8.

Results: We measured the number of mitochondria, their size and shape in epithelial cells of cystic kidneys from *Ksp-Cre;Pkd1*$^{fl/-}$ mouse model at P4 by TEM and, in line with previous reports, we detected a decrease in the mitochondrial mass and aberrant mitochondria in cystic kidneys in comparison to controls. Inactivation of *Pkd1* results also in the decreased activity of mitochondrial respiratory chain complexes cytochrome *c* oxidase and succinate dehydrogenase in DBA-positive cystic epithelia. Most mitochondria are in a round shape indicating fragmentation of the network in the epithelial cells of the cystic kidneys. We measured the amount of mitochondrial fusion/fission proteins by western blot and immunofluorescence and we found increased pro-fission Drp1 and decreased pro-fusion Opa1 and Mfn1 proteins in *Ksp-Cre;Pkd1*$^{fl/-}$ kidneys. In line with this, treatment with the Drp1-specific inhibitor Mdivi-1 reduces the cystic phenotype and the kidney to body weight ratio (vehicle, n=8, 7,28 ± 0,83%; Mdivi-1, n=9, 6,48 ± 0,64%, p<0,05), with amelioration of kidney function (BUN, vehicle, 233,3 ± 58,58 mg/dl; Mdivi-1, 187,9 ± 36,43 mg/dl, p<0,05).

Conclusions: Our data indicate that deletion of polycystin 1 in the kidney epithelium results in a reduction of mitochondrial respiration and increased mitochondrial fragmentation. Inhibition of the last ameliorates the PKD phenotype, indicating that mitochondrial fragmentation is a modifier of PKD progression.

Funding: Private Foundation Support

SA-OR091

ALG9 Mutation Carriers Develop Kidney and Liver Cysts

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease. Mutations in *PKD1* or *PKD2* cause typical ADPKD. Dominantly inherited polycystic kidney and liver diseases on the ADPKD spectrum are also caused by mutations in at least six other genes required for protein biogenesis in the endoplasmic reticulum (ER) whose loss results in defective production of the low abundance complex polytopic membrane protein polycystin-1 (PC1), the *PKD1* gene product.

Methods: Whole exome sequencing in a cohort of 122 patients with genetically unresolved clinical diagnosis of ADPKD or polycystic liver disease was used to identify a candidate gene, *ALG9*. This candidate was functionally validated using in vitro cell-based assays of PC1 protein maturation. For further validation, we identified carriers of *ALG9* loss of function mutations (cases) and non-carrier controls matched by gender, ethnicity, age and CKD stage at time of imaging, imaging type and year, in a large exome-sequenced population-based cohort of >92,000 individuals. We assessed kidney and liver lesions in a blinded fashion using pre-specified radiographic criteria.

Results: Two patients in the clinically-defined cohort had rare loss of function variants in *ALG9*. *ALG9* encodes an ER protein required for addition of two mannose molecules to the lipid-linked oligosaccharide precursors for asparagine-linked glycosylation. In vitro assays showed that inactivation of *Alg9* results in impaired maturation and defective glycosylation of PC1. We found 21 carriers of heterozygous *ALG9* loss of function

mutations. Eleven of these had abdominal imaging. Seven of 11 (64%) had at least 4 kidney cysts, including 7 of 8 (88%) of those over age 50, compared with none in the 22 matched controls without *ALG9* mutations ($P = 7.7 \times 10^{-5}$, $P = 2.3 \times 10^{-5}$ respectively).

Conclusions: *ALG9* is a novel disease gene in the genetically heterogeneous ADPKD spectrum. It may be considered when clinically diagnosed ADPKD or isolated polycystic liver disease remain genetically unresolved. This study supports the utility of genotype-driven validation and analysis of candidate disease gene phenotypes in the era of precision medicine.

Funding: NIDDK Support, Private Foundation Support

SA-OR092

CD4 T Cells Promote Renal Cystic Disease

Kurt Zimmerman, Michal Mrug, Bradley K. Yoder. *University of Alabama at Birmingham, Birmingham, AL.*

Background: The majority of renal cystic diseases are caused by mutations in proteins associated with primary cilia formation or function. Previous data indicate that mice with dysfunctional primary cilia have an enhanced innate immune response following injury and that these cells are required for accelerated cyst formation. Despite this knowledge, little work has studied the complementary adaptive immune system during injury induced cyst formation.

Methods: Herein, we set out to identify and determine the importance of adaptive immune cells, particularly CD4 T cells, during injury induced rapid cyst formation in conditional *Ift88* mice (here after referred to as cilia mutant mice) and in the *Ift88*^{Orpk} and adult induced conditional *Ift88* slowly progressive models of cystic disease.

Results: Our data show that the number of T cells, including CD4, CD8 and double negative (DN) T cells, are increased in injured cilia mutant mice compared to controls. In addition, we show that the number of CD4, CD8, and DN T cells are also increased in the *Ift88*^{Orpk} and adult induced, non-injured conditional *Ift88* mouse models of slow cystogenesis. Further subtyping of CD4 T cells in these models shows that the number and percentage of Foxp3+ Tregs is increased in all 3 models of cystic disease compared to their respective controls. To test our hypothesis that adaptive immune cells are promoting cystic disease, we crossed our cystic mouse models to RAG1-/- mouse that lack all adaptive immune cells. Our data indicate that loss of adaptive immune cells reduces cyst formation in the rapid injury-induced model of cystogenesis but not in the slowly progressive models. To test the hypothesis that CD4 T cells were the adaptive immune cell type driving rapid cystogenesis following injury in cilia mutant mice, we injected conditional *Ift88* and *Pkd2* mice with an IgG or CD4 depleting antibody. Our data indicate that CD4 depletion reduces renal cystogenesis in both mouse models. Finally, analysis of human patients indicate that the number of Tregs is increased in autosomal dominant polycystic kidney disease patients compared to controls.

Conclusions: Our results suggest that CD4 T regulatory cells promote cystic kidney disease.

Funding: NIDDK Support

SA-OR093

The Ciliary Phosphoinositide Pathway Controls the Dosage of Polycystins in Cilia

Chuan Chen. *Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN.*

Background: ADPKD is a progressive genetic disorder characterized by the development of fluid-filled renal cysts. It is mainly caused by mutations in *PKD1* and *PKD2* genes encoding respectively PC1 and PC2. PC1 and PC2 function as a complex and localize predominantly in primary cilia. However, the molecular mechanism underlying the trafficking and maintenance of PC1/PC2 in cilia is unclear. PIs are a group of signaling phospholipids that regulate membrane trafficking and organelle identity. Abnormal phosphoinositide metabolism correlates with variant human diseases. Recent studies showed that PI(4)P and PI(4,5)P_2 exhibit unique compartmentalization in the ciliary membrane and regulate the ciliary trafficking and signaling, suggesting this PI pathway may function in the trafficking of polycystins to cilia.

Methods: We manipulate the PI contents and determine the ciliary level of PC1 and PC2 using IF. The global protein levels are determined by immunoblotting. We use the 3D spheroid model and the embryonic kidney culture to determine the effect of the ciliary PI pathway on renal cystogenesis. Moreover, *in vitro* cellular assays are used to monitor cell survival and proliferation.

Results: We found increased PI(4,5)P2 level in ciliary membrane increases the ciliary level of PC2 in normal cells. Moreover, in renal epithelial cells carrying ADPKD mutations, the ciliary level of PC1 and PC2 can also be restored by increasing PI(4,5)P_2 in cilia. Then, we utilized 3D culture and embryonic kidney culture assays to detect the renal cystogenesis, and discovered that our specific inhibitor reduced the cyst formation both *in vitro* and *ex vivo*. In addition, the inhibitor showed no obvious effect on phosphated AKT or ERK expression, as well as cell proliferation in MTT assays, suggesting that the impaired cystogenesis were very likely resulted from recovered ciliary polycystins.

Conclusions: The effective treatment of ADPKD is extremely limited and Tolvaptan as the only FDA approved drug shows limited benefits with substantial side effects. The functional dosage of polycystins directly influences the disease severity in ADPKD patients. We found that manipulating the ciliary PI pathway as well as their products increases the ciliary polycystins, and exhibits suppression effects on cystogenesis. These results suggest that the ciliary PI pathway could be a novel therapeutic target for ADPKD.

SA-OR094

Aurora A Kinase Is Required for Development of Renal Cysts in a Ciliopathy Model

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Background: Aurora A Kinase (AURKA) is classically regarded as a mitotic cell kinase necessary for progression through the cell cycle. It is also associated with disassembly of the primary cilium. We have previously shown that in vitro inhibition of AURKA is sufficient to reverse many of the cyst associated phenotypes in cultured cells lacking the Joubert Syndrome gene, INPP5E. This raises the possibility that therapies aimed at limiting AURKA actions may represent an approach to preventing cyst development in this and other ciliopathies.

Methods: To investigate a casuative role for AURKA in renal cyst initiation and progression we have independently inhibited its kinase activity (using Alisertib) and deleted the Aurka gene in a mouse model of PKD development in Joubert Syndrome. We have then studied the impact of these alterations on cystogenesis and cell signaling.

Results: We find that treatment with Alisertib results in the generation of more, rather than less, renal cysts and provide evidence that the drug actually increases the amount of AURKA protein in kidney cells. Conversely, we find the while AURKA deletion does not affect the development or homeostasis of the collecting duct system, its co-deletion with Inpp5e is able to almost completely prevent PKD - over the long term. Analysis of these models indicates that AURKA over-expression in PKD is associated with increased AKT signalling and that genetic deletion of AURKA normalises this pathway and cyst associated DNA damage. Furthermore, we find that AKT and AURKA directly interact and co-localise to the primary cilium in a dynamic manner associated with the activation of growth factor signaling.

Conclusions: These studies demonstrate that while AURKA is dispensible for renal development and tubule homeostasis, it acts as a key driver of cyst formation. The failure of Alisertib to ameliorate cyst formation contrasts with the profound prevention of disease mediated by AURKA gene deletion. Taken together, these findings that suggest that kinase independent functions of AURKA are central to cystogenesis. The correction of AKT signaling and the close functional association identified between AURKA and AKT highlights dysregulation of this pathway as being critically important for cyst initiation, suggesting a potential avenue for therapeutic development.

Funding: Government Support - Non-U.S.

SA-OR095

Carbonic Anhydrase II (CAII) and Intercalated Cells (ICs) Drive Kidney Cystogenesis in Tuberous Sclerosis Complex (TSC)

Sharon L. Barone,[1,2] Kamyar A. Zahedi,[1,2] Marybeth Brooks,[1,2] Alicia A. McDonough,[3] Stefan Somlo,[5] Elizabeth P. Henske,[4] Jane J. Yu,[1] Manoocher Soleimani.[1,2] *[1]University of Cincinnati, Cincinnati, OH; [2]Research Services, Veterans Affairs Medical Center, Cincinnati, OH; [3]Keck School of Medicine of USC, Los Angeles, CA; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [5]Yale University, New Haven, CT.*

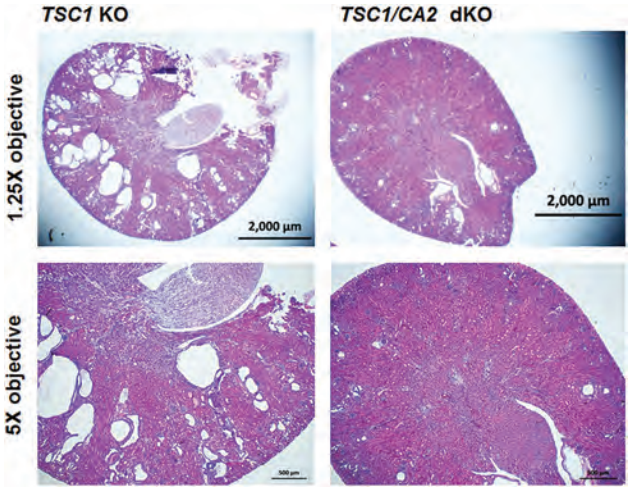
Background: TSC is caused by mutations in either TSC1 or TSC2 genes and affects multiple organs, including kidney, lung and brain. In the kidney, TSC presents with benign tumors (angiomyolipomas) and cysts, which eventually lead to kidney failure. Little is known about the factors that promote cyst generation and enlargement in tuberous sclerosis.

Methods: Principal cell (PC) specific inactivation of Tsc-1 or Tsc-2 was accomplished by crossing mice with either a Tsc-1 or Tsc-2 floxed construct with mice expressing cre recombinase under the control of Aqp-2 promoter.

Results: Tsc-1 KO as well Tsc-2 KO (Physiol. Report 2019) develop numerous cortical cysts, which are overwhelmingly (>95%) comprised of A-ICs, as identified by strong apical expression of V H^+-ATPase B subunit and basolateral AE1 (Slc4a1), with remaining cells (<5%) expressing Aqp-2, a marker of PCs. ICs lining the cysts expressed intact Tsc-1 gene and exhibited vigorous proliferation and mTORC1 activation. RNA-seq and confirmatory northern hybridization and/or immunohistochemical studies demonstrated the robust expression of the transcription factor Foxi1, a master regulator of ICs H^+-ATPase, Cl^-/HCO_3^- exchanger AE1 and CAII in cyst epithelia in Tsc-1 KO mice, but not in Pkd1 mutant mice. Given the vital role of CAII in H^+-ATPase activity and ICs viability/proliferation, we tested the hypothesis that CAII may play a critical role in the cytogenesis in TSC.

Conclusions: Our studies demonstrate that CAII deletion in Tsc-1 KO mice profoundly inhibited the cyst burden (see image). Compared with Tsc-1 single mutant mice, CAII/Tsc-1 double mutant mice displayed much smaller cysts, with significantly fewer proliferating ICs, and decreased mTORC activity. We propose that the H^+-ATPase and CAII are critical to cystogenesis, and their inhibition or inactivation is associated with significant protection against cyst generation/enlargement in TSC.

Funding: NIDDK Support, Veterans Affairs Support



SA-OR096

Innate Immunity Contributes to Tubular Cell Senescence in Nephronophthisis Type 7 Knockout Mouse Kidneys

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Background: Nephronophthisis (NPHP), an autosomal recessive disease, is the most frequent monogenic cause of chronic renal failure during the first three decades of life. Mutations in over 25 genes have been identified as causes of this disease and in several cases, like in NPHP type 7, result in chronic DNA damage. Cell senescence is a frequent outcome of chronic DNA damage. We showed that kidney tubular cells undergo cell senescence in the *Glis2* mouse model of NPHP type 7. Senescent cells secrete pro-inflammatory molecules that can induce further senescence in neighboring non-senescent cells through the activation of the Toll-like receptor/interleukin 1 receptor/NF-kB (TLR/IL-1R/NF-kB) signaling pathway. We previously reported that NF-kB is activated in kidney tubular cells of the *Glis2* knockout mice. We hypothesized that inducing apoptosis of senescent cells would protect from inflammation and fibrosis, and that genetic inhibition of the TLR/IL-1R/NF-kB signaling axis would decrease tubular cell senescence in *Glis2*-knockout kidneys. We hypothesized that inducing apoptosis of senescent cells would protect from inflammation and fibrosis, and that genetic inhibition of the TLR/IL-1R/NF-kB signaling axis would decrease tubular cell senescence in *Glis2*-knockout kidneys.

Methods: To this end we used the senolytic drug FOXO4-DRI to induce apoptosis of senescent cells, and generated two mouse lines: a double knockout line lacking both *Glis2* and *Tlr2* in all tissues (*Glis2*$^{-/-}$;*Tlr2*$^{-/-}$); and a line in which a kidney-specific promoter (Ksp) is used to conditionally inactivate the adaptor myeloid differenziation protein 88 (MyD88) downstream of TLR/IL-1R receptors in tubular cells of *Glis2*-null mice (*Glis2*$^{-/-}$;^{KspCre}*Myd88*$^{f/f}$).

Results: We found that pharmacologic elimination of senescent cells results in reduced kidney damage, fibrosis, and apoptosis in *Glis2*-knockout kidneys. Noticeably, in *Glis2*, *Tlr2* double knockouts and, to a lesser extent, in *Myd88*, *Glis2* knockout mice senescence was reduced and tubular-cell proliferation was increased, suggesting that loss of TLR2/IL-1R activity improves the regenerative potential of tubular cells.

Conclusions: Our results further suggest that a combination of TLR/IL-1R inhibition and senolytic therapy may delay the disease progression in NPHP type 7 and other forms of this disease.

Funding: NIDDK Support

SA-OR097

The Pathogenic Role of NEK8 RCC1-Domain Mutations in Inversin Compartment Assembly

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Background: The Inversin compartment (IC) is a protein module located at the proximal end of the primary cilium that consists of four known components, inversin (INVS), NEK8, ANKS6 and NPHP3. Missense mutations in inversin compartment genes, including NEK8, give rise to a wide spectrum of disease phenotypes, including Nephronophthisis (NPHP), polycystic kidney disease (PKD), as well as complex multiorgan malformation syndromes with embryonic lethality. In our previous work, we have shown that NEK8 kinase-domain mutations that specifically affect the phosphorylation mechanism give rise to cystic kidney phenotypes and randomization of embryonic L-/R-asymmetry determination. We have also shown that the NEK8 RCC1-domain is necessary for recruitment of NPHP3 to the ciliary inversin compartment. The mechanism how NEK8 RCC1-domain mutations and mutations in NPHP3 produce NPHP- and PKD-like phenotypes remains unexplained.

Methods: We cloned affinity-tagged versions of NEK8 and NPHP3 in expression vectors for transient expression in 293T cells and for stable lentiviral transduction in mIMCD3 cells. We knocked out NEK8 and NPHP3 genes in IMCD3 cells by CRISPR/Cas9. We introduced pathogenic mutations into the NEK8 ORF by fusion PCR. We analyzed protein expression levels by Western-Blot, protein localization to primary cilia by immunofluorescence and protein-protein interactions by immunoprecipitation and Western-Blot.

Results: We found that pathologic missense mutations in the NEK8 RCC1 domain fall into three categories: (1) Mutations that destabilize NEK8 protein lead to reduced or absent expression and no detectable localization to the cilium; (2) Mutations that produce soluble and detectable levels of NEK8 protein, but fail to properly localize to the primary cilium; (3) Mutations that allow NEK8 protein to localize to the cilium, but have reduced affinity to NPHP3 binding. While mutations of categories (1) and (2) correlate with NPHP phenotypes, mutations of category (3) correlate with PKD phenotypes.

Conclusions: We demonstrate that hierarchical defects in inversin compartment assembly correlate with the phenotypic spectrum of kidney disease. Reduced NEK8 and NPHP3 localization leads to NPHP-like disease, whereas proper NEK8 localization and reduced NPHP3 affinity leads to PKD.

SA-OR098

Ultra-Short-Duration Direct-Acting Antiviral Prophylaxis to Prevent Hepatitis C from Viremic Donors to Hepatitis C-Negative Kidney Transplant Patients

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Background: Direct-acting anti-viral drug (DAA) prophylaxis of of less than twelve weeks initiated at the time of transplant could have the potential to reduce the cost of deceased HCV-infected viremic donor to non-HCV-infected transplants (D+/R-). In our recently concluded single-center trial (ClinicalTrials.gov: NCT03249194; to be presented at ATC 2019; manuscript under peer review) we reported a HCV transmission rate of 13% with an ultra-short course of DAA prophylaxis given over the first 4 days of transplant. Here we present initial data on our extension open-label clinical protocol [REFORM HEPC (REgistry For the study of ORgan transplants froM HEPatitis C infected donors].

Methods: Waitlisted HCV negative adult kidney transplant candidates without significant liver fibrosis, as assessed by transient elastography, were enrolled. After administration of ultra-short course (4 days) prophylactic Sofusbuvir/Velpatasvir (SOF/VEL), patients were screened for HCV RNA at Days 7, 14, 21 and Month 3. Development of viremia (defined as two consecutive positive RNAs) triggered a full 12 week course of DAA therapy.

Results: Over a period of 4 months (Jan-April 2019), 88 patients were enrolled. Of these, 22 (25%) received D+/R- transplants. The mean wait time to transplant from enrollment was 19 days and the mean donor KDPI was 64%. Of the data available on 11 donors (50%), the median donor viral load was 2.6E+06 IU/mL (IQR:2.5E+02-7.3E+06). A majority were genotype (GT) 1a donors (88%). At a median follow-up of 97 days (IQR: 30-150 days) post-transplant, both patient and graft survivals were 100%. There were no cases of liver dysfunction. Average kidney function as measured by eGFR was 52±25mL/min/1.73m2. There were no episodes of acute rejection or de-novo donor specific antibody formation. Viral transmission rate was 4.5% (1/22; GT1a). The only patient with viremia has a declining viral load on glecapravir/pibrentasvir after 4 weeks of initiating therapy.

Conclusions: Our data suggests that ultra-short duration DAA prophylaxis is highly effective in preventing donor-derived HCV transmission and has the potential of resulting in significant cost-savings by avoiding DAA therapy in a majority of D+/R- transplants.

Funding: Clinical Revenue Support

SA-OR099

Greater Impact of Pre-Transplant Dialysis Exposure on Transplant Survival in Regions with Higher Dialysis Mortality

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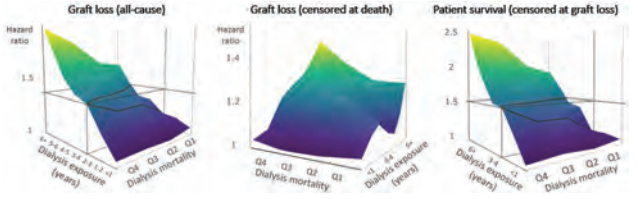
Background: Longer pre-transplant dialysis exposure is associated with a higher risk of transplant failure. Mortality rates on dialysis are known to vary between regions, and may in part reflect differences in the quality of dialysis care. We hypothesized that the association of dialysis exposure with transplant failure would be higher in patients treated in regions with higher rates of dialysis mortality.

Methods: Adult patients in the United States Renal Data System who initiated maintenance hemodialysis after May 1995, and received a kidney-only deceased donor transplant by Dec 2010 were studied (n=63,610). Dialysis mortality (per 100 patient years), adjusted for differences in patient age, sex, and race, was determined by state of residence and time period of dialysis, and grouped into quartiles. The association between the duration of dialysis exposure (years), dialysis mortality quartile and post transplant outcomes was determined in Cox regression models. Each model adjusted for differences in patient age, gender, race, cause of end stage kidney disease, body mass index, year of transplant, PRA, comorbid conditions and included an interaction term of dialysis exposure (years) with quartile of dialysis mortality.

Results: The association of different combinations of dialysis exposure (years) and dialysis mortality (quartiles), compared to the reference group of patients with <1 year

dialysis exposure treated in a region with the lowest quartile of dialysis mortality, with the outcomes of graft loss from all causes including death, death censored graft loss, and death with a functioning graft are shown in Figure 1. Longer durations of dialysis exposure were associated with a higher risk of each outcome, and this risk of dialysis exposure was magnified in regions with higher dialysis mortality.

Conclusions: The risk of pre-transplant dialysis exposure on transplant failure is higher in regions with higher rates of dialysis mortality. The findings support better integration of dialysis and transplant care, and indicate that regional differences in dialysis mortality should be accounted for in evaluation of transplant center performance metrics.



SA-OR100

Lack of Association Between Pre-Transplant Donor-Specific Antibodies and Kidney Outcomes in Simultaneous Liver-Kidney Transplant Recipients

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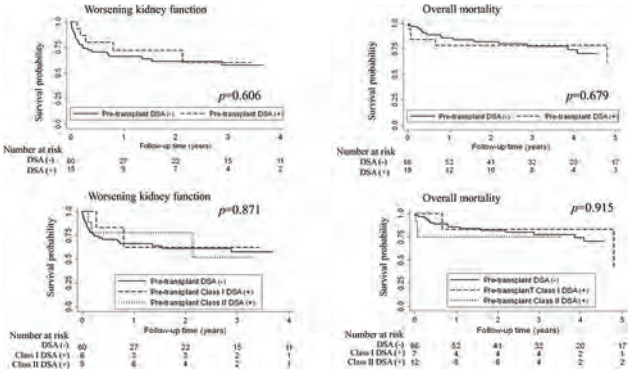
Background: The impact of pre-transplant donor-specific antibodies (DSA), especially class II DSA, on kidney allograft outcomes remains unclear in simultaneous liver-kidney transplantation (SLKT) recipients.

Methods: We examined 85 recipients who underwent SLKT between 2009-2018 in our center. Associations between the presence of pre-transplant DSA [pre-transplant DSA (+)], including class of pre-transplant DSA ([Class I DSA (+)] and [Class II DSA (+)]), and worsening kidney function (WKF), composite kidney outcome (WKF or antibody-mediated rejection or death censored allograft kidney loss), death with functioning graft, and overall mortality were examined in unadjusted and age, sex, and race-adjusted Cox proportional hazards regression and competing risks regression models. WKF was defined as eGFR decrease of 30% or greater from baseline, or two or more episodes of proteinuria, at least 90 days apart from each other.

Results: The mean age at SLKT was 56 years old and 62% of the recipients were male. Nineteen recipients (22%) had pre-transplant DSA at the time of SLKT. For the WKF, the median follow-up time was 9.6 months. The incidence rate was 148/1,000 person-years in the DSA (+) group and 169/1,000 person-years in the DSA (-) group with a non-significant difference. Pre-transplant DSA (+) groups had similar risk of not only WKF (unadjusted model: HR=0.77, 95%CI: 0.29-2.05 and adjusted model: HR=0.36, 95%CI: 0.12-1.08) but also the other outcomes compared to DSA (-) group. We found similar results when comparing different DSA sub-classes with recipients without DSA.

Conclusions: Neither pre-formed DSA nor class II DSA was associated with worse kidney allograft outcomes or patient mortality in SLKT recipients.



SA-OR101

Tertiary Lymphoid Tissues in Protocol Biopsies Predict Progressive Graft Dysfunction in Kidney Transplant Recipients

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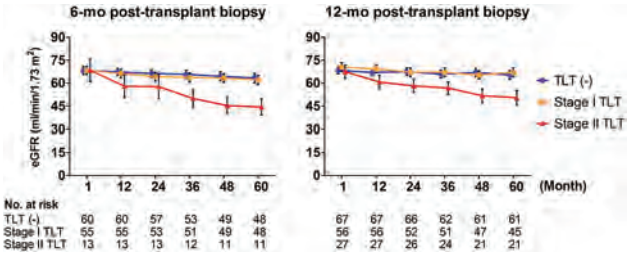
Background: Tertiary lymphoid tissues (TLTs) are inducible ectopic lymphoid tissues found in chronic inflammatory organs. Previous studies have documented TLT formation in transplanted kidneys with rejection, but their clinical relevance remains controversial. Moreover, the evidences of TLTs in transplanted kidney without rejection are limited. In this study, we examined the frequency and staging of TLTs in protocol biopsy samples without the sign of rejection, and analyzed their effects on renal function in stable kidney transplant recipients.

Methods: A total of 181 patients who lacked clinical risk factors for poor graft survival, such as biopsy-proven acute rejection, were selected among those who underwent living donor kidney transplantation. We analyzed serial protocol biopsies (0-hour, 1-month, 6-month, and 12-month) and evaluated TLTs using novel staging methods we had recently established. TLTs were defined as organized lymphocyte aggregates with signs of proliferation, and their stages were determined by the absence (stage I) or presence (stage II) of follicular dendritic cells, which support the formation of B cell area.

Results: Although only 5.1% of patients exhibited TLTs at 0-hour biopsy, the prevalence increased to almost 50% at 1-month after transplantation and was maintained at the similar levels for one year. Stage II TLTs increased gradually over time, from 2.8% at 1-month to 18.0% at 12-month biopsy. Patients with no or stage I TLTs had stable graft function over 5 years, whereas those with stage II TLTs exhibited progressive graft dysfunction. (Figure 1) These advanced TLTs were associated with severe tubular inflammation and atrophy at 1 year post-transplantation. Finally, pre-transplantation rituximab dramatically attenuated the development of stage II TLTs.

Conclusions: TLTs were commonly found in protocol biopsies of transplanted kidneys, and stage II TLTs predict progressive decline in graft function in kidney transplant recipients even in the absence of rejection

Funding: Government Support - Non-U.S.



Trends in eGFR according to TLT stages

SA-OR102

Serum Expression of Selected MiRNAs Distinguish Recurrence of Glomerulonephritis and Antibody-Mediated Rejection in Kidney Transplant Recipients

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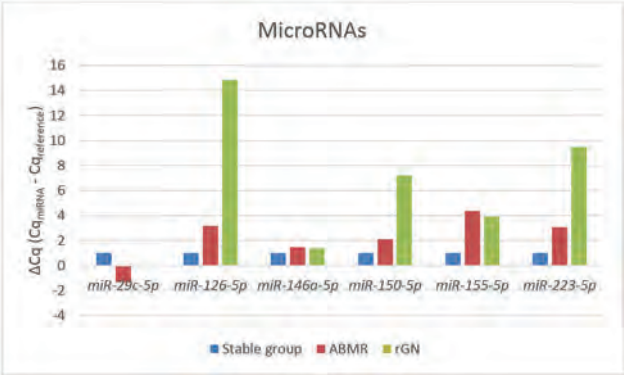
Background: Recently, many miRNAs (small non-coding regulatory RNAs) were found to be involved in pathological processes that can occur following kidney transplantation. The purpose of current study was to investigate the potential significance of different circulating miRNAs in predicting acute antibody mediated rejection (ABMR) and glomerulonephritis recurrence (rGN) regardless of the stage of renal impairment.

Methods: Total RNA was isolated from serum of 50 kidney transplanted patients with varying degrees of kidney graft failure, but stable function as estimated with CKD EPI equations (eGFR CKD-EPI), as well as precisely measured using chromium-51 labelled ethylenediamine tetraacetic acid clearance (mGFR CrEDTA). Expression of 6 selected miRNAs (*miR-29c*, *miR-126*, *miR-146a*, *miR-150*, *miR-155*, *miR-223*) was determined by qPCR, using *miR-103a-3p* as reference gene.

Results: Selected candidate miRNAs *miR-126* (p=0.002), *miR-155* (p=0.004) and *miR-223* (p=0.028) distinguished ABMR (n=6) from the stable patient group – patients without ABMR or rGN (n=41). *MiR-126* (p=0.008), *miR-150* (p=0.009) and *miR-223*

(p=0.033) distinguished rGN (n=3) from stable patient group. *MiR-126* (p=0.048), *miR-150* (p=0.024) and potentially *miR-223* (p=0.09) distinguished ABMR from rGN. Additionally, *miR-29c* expression was not detected in rGN and it was down-regulated in ABMR compared to stable group. Expression of *miR-146a* did not show association to any of the group of patients. None of the tested miRNA was associated with mGFR CrEDTA, only *miR-150* weakly correlated to eGFR CKD EPI.

Conclusions: Four of the tested miRNAs (*miR-126, miR-29, miR-155, miR-223)* are not associated with kidney graft function, but may discriminate AMBR and rGN and therefore can be used as a non-invasive biomarker to distinguish between pathologies.



Different expression of selected miRNA in stable patient group, ABMR and rGN group.

SA-OR103

Characteristics and Dysbiosis of the Gut Microbiome in Renal Transplant Recipients

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Background: Renal transplantation is life-changing in many aspects. This most likely also includes the gut microbiome, particularly because of the inevitable exposure to immunosuppressive drugs and antibiotics. As a consequence, Transplantation patients frequently suffer from intestinal dysbiosis. We aimed to investigate the gut microbiome of renal transplant recipients (RTR) and compare it with healthy controls.

Methods: We included 110 RTR and 79 healthy renal donors participating in the TransplantLines Biobank and Cohort Study (NCT03272841). We analyzed the gut microbiome using 16s rRNA sequencing and compared the composition of the gut microbiome of RTR with healthy renal donors using the Mann Whitney U-test with false discovery rate correction. Linear discriminant effect size (LEfSe) and multivariate association with linear models (MaAsLin) were used to study the relationship between the gut microbiome and the occurrence of diarrhea and the use of medication.

Results: Fecal samples of 110 RTR (38.3% female, mean age: 54.6 ± 12.0 years) and 79 healthy renal donors (34.0% female, age: 59.6 ± 11.0 years) were collected. Median time after transplantation of RTR was 1.08 [2.0-13.0] years., with a range of 1 to 26.4 years. Microbiome composition of RTR was significantly different from that of healthy donors (P=0.001). RTR had a lower diversity of the gut microbiome (P<0.001). Significantly higher levels of Proteobacteriae, Enterobacteriaceae, Streptococcus and E. coli were found in RTR (P<0.05). The levels of commensal, butyrate producing bacteria, including Clostridium spp., Eubacterium spp., Coprococcus spp. and Gemmiger formicilis were significantly lower in RTR (P<0.05). The microbiome of RTR with diarrhea contained lower levels of Ruminococcaceae and higher levels of Actinobacteria (P<0.05).

Conclusions: This study shows the gut microbiome of RTR is significantly different from the gut microbiome of healthy renal donors. RTR suffer from dysbiosis characterized by a loss of diversity and there is a preponderance towards lower levels of butyrate producing species, which may have detrimental effects on gut health in RTR.

SA-OR104

^{18}F-FDG PET/CT Imaging at 3 Months Post Transplantation Disproves Subclinical Rejection in Kidney Transplant Recipients

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Background: Subclinical kidney allograft acute rejection (SCR) corresponds to "the histological documentation of unexpected evidence of acute rejection (AR) in a stable patient". SCR detection relies on surveillance biopsy. Still, non-invasive approaches may help avoid biopsy-associated complications and limitations. Positron emission tomography (PET) coupled with computed tomography (CT) after injection of F^{18}-fluorodeoxyglucose (^{18}F-FDG) may be an option.

Methods: From 11/2015 to 01/2018, we prospectively performed ^{18}F-FDG-PET/CT in adult kidney transplant recipients (KTR) who underwent surveillance transplant biopsy at ~3 months *post* transplantation. Banff-2017 classification was used. The ratio of the mean standard uptake value (mSUVR) between kidney graft cortex and psoas muscle was measured. One-way analysis of variance (ANOVA) followed by Student t-tests was performed using the Python library SciPy to compare mSUVR among groups. Additionally, the R-squared statistic assessed the correlation between mSUVR and acute composite Banff score or total inflammation. Finally, the receiver operating characteristic (ROC) curve was built using Python programming language.

Results: In our 95-patient cohort, the median age of recipients was 57 years [min 37; max 68], with a gender ratio (M/F) of 2 and a mean BMI of 27±5kg kg/m^2. The cohort was categorized into 3 groups upon Banff-based histology: normal (n=70); borderline (n=16); AR (n=6). Three cases were excluded for PCR-proven BK nephropathy (n=2) or uninterpretable histology (n=1). No clinical or biological difference was observed between groups. The mSUVR reached 1.87±0.55, 1.94±0.35 and 2.41±0.54 in normal, borderline and AR groups, respectively. A significant difference of mSUVR was found among groups. Furthermore, mSUVR was significantly higher in AR *versus* normal (p, 0.02) or borderline (p, 0.02) groups. The area under the ROC curve (AUC) was 0.79, with 83% sensitivity and 87% specificity using mSUVR threshold at 2.4. The mSUVR positively correlated with total-i (r ^{2}=0.05; p, 0.02) and acute composite Banff score (r^2=0.04; p, 0.05).

Conclusions: ^{18}F-FDG-PET/CT imaging helps non-invasively detect SCR, with a negative predictive value of 98% using 2.4 as mSUVR threshold.

Funding: Clinical Revenue Support

SA-OR105

Galectin 3 and Graft Failure in Kidney Transplant Recipients: A 10-Year Prospective Cohort Study

Camilo G. Sotomayor,[1] Charlotte A. te Velde - Keyzer,[1] Marco van Londen,[1] Reinold O. Gans,[1] Ilja M. Nolte,[2] Martin H. De Borst,[1] Stefan P. Berger,[1] Ramon Rodrigo,[3] Stephan J. Bakker.[1] *[1]Department of Internal Medicine, University Medical Center Groningen, Groningen, Netherlands; [2]Department of Epidemiology, University Medical Center Groningen, Groningen, Netherlands; [3]Molecular and Clinical Pharmacology Program, Institute of Biomedical Science, Faculty of Medicine, University of Chile, Santiago, Chile.*

Background: Galectin-3 is associated with kidney fibrosis and kidney function decline in the general population. We aimed to study the association of galectin-3 with long-term risk of graft failure in a cohort of extensively phenotyped kidney transplant recipients (KTR).

Methods: We performed a longitudinal cohort study in 561 KTR without heart failure and with a functioning graft ≥1 year. Kaplan-Meier curve, log-rank test, and multivariable-adjusted Cox proportional-hazards regression analyses were performed to assess the prospective association of baseline serum galectin-3 with death-censored graft failure (defined as restart of dialysis or re-transplantation). Subgroup prospective analyses were performed according to significant effect-modifiers.

Results: Median galectin-3 was 21.1 (IQR, 17.0-27.2) ng/mL. During a median follow-up of 9.5 (IQR, 6.2-10.2) years, 72 KTR developed graft failure, with significantly different distribution of events across tertiles of galectin-3 (P<0.001). In multivariable Cox regression analyses, galectin-3 associated with graft failure (HR, 2.13 per 1-SD increase; 95% CI, 1.61-2.80, P<0.001), independent of well-established general and transplant-specific risk factors, including eGFR and proteinuria. Particularly strong associations were found in patients with systolic blood pressure ≥140 mmHg (HR, 2.29 per 1-SD increase; 95% CI 1.80-2.92, P<0.001) and in former or current smokers (HR, 2.56 per 1-SD increase; 95% CI 1.95-3.37, P<0.001).

Conclusions: In stable KTR, galectin-3 levels are elevated and independently associated with higher risk of graft failure at 10-years of follow-up. These results underline novel opportunities to monitor patients, target pharmacological therapy, and decrease the burden of long-term graft failure in stable KTR.

Funding: Government Support - Non-U.S.

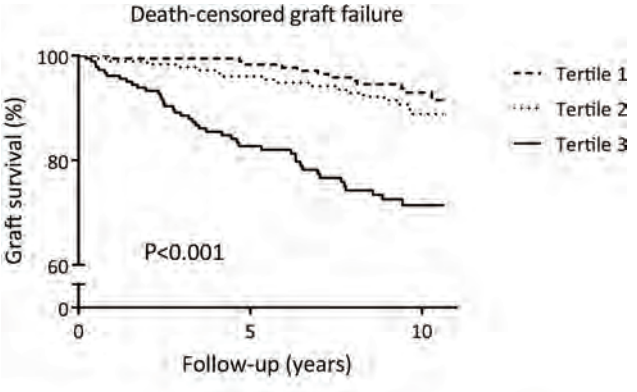

Figure 1. Kaplan–Meier curve for death-censored graft failure according to tertiles of galectin-3 in KTR. Tertile 1: 15.4 (IQR, 13.4-17.0) ng/mL; tertile 2: 21.1 (IQR, 19.8-22.9) ng/mL; tertile 3: 29.5 (IQR, 27.1-35.6) ng/mL. P value was calculated by Log-rank (Mantel cox) test.

SA-OR106

Potential for Recovery of Bone Density and Structure Following Renal Transplantation

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Background: Fracture rates increase early following renal transplant (RTxp) and then decline. The objective is to determine if trabecular and cortical bone mineral density (BMD) and cortical structure recover following RTxp treated with glucocorticoids (GC).

Methods: We enrolled 60 incident RTxp recipients, ages 20-60 yr, with DXA and peripheral quantitative CT (pQCT) scans at RTxp, 6, 12, and 24 months. Bone outcomes and DXA appendicular lean mass index (ALMI) were expressed as age and sex-specific Z-scores using concurrent controls. Regression models identified correlates of change for bone outcome Z-scores.

Results: 58 and 53 RTxp completed the 12 and 24 month visit, respectively. At transplant, DXA total hip, femoral neck, and ultradistal radius BMD, and pQCT trabecular and cortical BMD, and cortical thickness BMD Z-scores were lower in RTxp vs. controls (all $p<0.05$). Prednisone was typically tapered to a maintenance dose of 5 mg/day by 4 weeks. During the first 6 months, DXA spine and pQCT trabecular BMD decreased significantly (e.g. trabecular BMD Z from -0.53 to -0.60) then were unchanged through 24 months. Radius 1/3rd BMD was stable but ultradistal BMD Z-scores decreased from baseline onwards. Greater GC exposure was associated with decreases in DXA spine and ultradistal radius BMD and pQCT trabecular BMD Z-scores (all $p<0.01$). Cortical BMD Z-scores increased across 24 months (from -0.51 to -0.33, $p<0.01$) in association ($p = 0.02$) with decreasing PTH. Endosteal circumference increased and cortical thickness decreased progressively over 24 months (both <0.01). DXA total hip and femoral neck BMD Z-scores were unchanged during the first 6 months, then increased marginally. ALMI Z-scores increased but were not associated with changes in bone outcomes. Gains in cortical BMD were associated with gains in total hip and femoral neck BMD ($p<0.01$). Renal function, physical activity and mineral metabolites were not associated with bone outcomes.

Conclusions: RTxp is associated with early loss of trabecular bone without subsequent recovery on low dose GC. Cortical BMD recovers in association with decreases in PTH levels and may explain the marginal increase in hip BMD. Given that cortical thinning progresses following RTxp, strategies are needed to preserve cortical structure in CKD.

Funding: NIDDK Support

SA-OR107

Post-Transplant Recurrence of IgA Nephropathy: HLA as a Predictive Factor

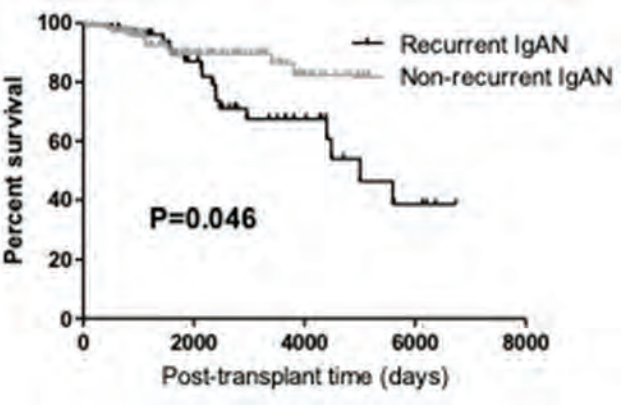
Catherine R. Kavanagh, Namrata G. Jain, Jeanne Kamal, Elena R. Vasilescu, Ibrahim Batal. *Columbia University Irving Medical Center, New York, NY.*

Background: In the native kidney, studies have suggested that specific Human Leukocyte Antigen (HLA) alleles have increased risk or protective effects for the development of IgA Nephropathy (IgAN). There remains limited knowledge of the clinical significance and specific factors that contribute to recurrence of IgAN in the kidney allograft. We aimed to study whether the degree of HLA matching and the presence of certain HLA loci in the donor and recipient can contribute to recurrence.

Methods: A retrospective cohort of 159 recipients with ESRD secondary to IgAN who were transplanted at our center between 1995 and 2017 were evaluated for recurrent disease. Clinical characteristics and HLA typing were analyzed in both donor and recipient.

Results: Of the 159 patients identified, 53 (33%) had biopsy-proven recurrent IgAN. On follow-up, 16/53 (30%) of patients with recurrent IgAN developed graft failure compared to 11/106 (10%) of patients without proven recurrence (P= 0.046, See Figure). Univariate Cox proportional hazards analysis has identified that younger recipient age at transplantation, receiving allograft from living donors, higher degree of HLA matching, recipient HLA-DR15, and donor HLA-DR3 to be significantly associated with recurrence. By multivariable Cox analysis, younger recipient age [HR 0.97 (95% CI: 0.94 – 0.99), P= 0.016], HLA mismatch [0.83 (0.70- 0.98), P=0.03], presence of HLA-DR15 in the recipient [2.58 (1.36-4.88), P= 0.004], as well as the presence of HLA-DR3 in the donor [2.57 (1.23-5.37), P= 0.012] were independently associated with recurrent IgAN.

Conclusions: Recurrence of IgAN is associated with decreased graft survival. In an effort to improve long-term outcome, it is imperative to consider factors that increase recurrence risk when evaluating potential donors, such as higher HLA matching and the presence of HLA-DR3 in the donor. Recipient variables of younger age and HLA-DR15 were also independent predictors for recurrent IgAN.



Graft Survival

SA-OR108

Novel Experimental Model of Poor Pregnancy Outcomes After Recovery from Ischemia-Reperfusion Injury

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Background: Recent clinical studies have reported that women with a history of acute kidney injury (AKI) have a greater incidence of maternal and fetal adverse outcomes during pregnancy, despite fully recovering renal function prior to conception. The mechanisms contributing to these adverse outcomes in pregnancy after AKI are not yet understood. In the current study, a rodent model of recovered AKI (r-AKI) was developed in an effort to elucidate the mechanisms contributing to adverse pregnancy outcomes after AKI. We hypothesize that female Sprague Dawley (SD) rats will have poor pregnancy outcomes after recovery from ischemia reperfusion (IR) injury, our experimental model of AKI.

Methods: IR surgery was performed on female SD rats (10 wks age) by clamping both renal arteries for 45 minutes. Rats were then allowed to recover for 1 month before they were mated. Recovery from IR was confirmed by plasma creatinine and urinary protein excretion (UPE). Vaginal smears were performed daily once mating began, with sperm on the slide indicative of day 1 of pregnancy. Rats were then sacrificed during late pregnancy on gestational day 20.

Results: UPE, a crude marker of renal injury, was significantly higher in r-AKI dams in late pregnancy (Table, *$p<0.05$, T-test). r-AKI dams also had significantly higher plasma creatinine and urea levels than control dams, suggesting that subclinical injury after IR leaves these dams unable to handle the hemodynamic changes in pregnancy, resulting in renal insufficiency (Table). In addition to adverse maternal outcomes, fetal outcomes were also significantly worse in r-AKI dams, as measured by decreases in fetal weight and an increase in fetal death (Table).

Conclusions: Pregnancy after recovery from AKI resulted in maternal renal insufficiency and significant impairments in fetal growth in the current study. This mimics what has recently been reported in the clinical population, indicating that this model is a useful tool to further explore the alterations in kidney function after AKI in females. Ongoing studies in the lab are further exploring the maternal syndrome in these rats, focusing on alterations in renal immune cells.

Funding: Other NIH Support - National Institute of Health (R01HL127091 and P01HL134604 to J.C.S.)

	UPE (mg/d)	Plasma Creatinine (mg/dL)	Plasma Urea (mg/dL)	Pup Weight (g)	Fetal Death (%)
Control	4.2±0.66	0.25±0.01	33.0±0.57	4.0±0.08	0
r-AKI	18.4±0.61*	0.37±0.01*	40.8±0.44*	2.3±0.03*	10.3±5.7*

SA-OR109

A Population Study of Pregnancy Outcomes by Pre-Conception GFR

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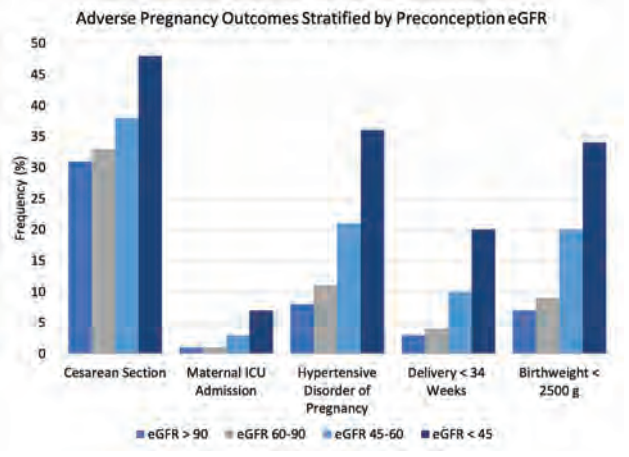
Background: Chronic kidney disease is a known risk factor for adverse pregnancy outcomes including preeclampsia and preterm delivery, however studies on CKD pregnancies are small, outdated and contain few subjects with moderate or advanced stage CKD. Our objective was to investigate the association of pre-conception GFR with the risk of adverse pregnancy outcomes in a large population-based cohort with more than 400 pregnancies in women with pre-existing moderate or advanced stage CKD.

Methods: A population-based cohort study of women in the province of Ontario, Canada, who had an obstetric delivery between 2007 and 2017. Administrative health databases linked using unique identifiers at ICES were used to capture all hospital births in Ontario and a majority of outpatient laboratory testing. Women with a serum creatinine measured within 2 years of conception were included for analysis.

Results: The mean pre-conception eGFR among the 458,206 pregnancies included in the analysis was 114 ± 14 ml/min/1.73 m^2, of which 28,232 were 60 to <90 ml/min/1.73 m^2, 330 were 45 to <60 ml/min/1.73 m^2 and 97 were <45 ml/min/1.73 m^2. There were no maternal deaths among women with eGFR < 60 ml/min/1.73 m^2. Rates of gestational hypertension, preeclampsia and preterm delivery increased monotonically across pre-conception eGFR categories (Figure 1). Maternal admission rate to the ICU during pregnancy or within 90 days after delivery was 7% among women with an eGFR < 45 ml/min/1.73 m2 compared with 1% in women with eGFR > 90 ml/min/1.73 m2.

Conclusions: In this population-based study of pre-conception CKD, low pre-conception eGFR was associated with high rates of maternal morbidity and adverse pregnancy outcomes. Absolute risk was highest in women with eGFR < 45 ml/min/1.73 m2, however even women with mildly impaired eGFR were at higher risk for adverse pregnancy outcomes.

Funding: NIDDK Support



SA-OR110

Effects of Pregnancy on Kidney Allograft Outcomes

Andrea G. Kattah, Fernando G. Cosio, Vesna D. Garovic. *Mayo Clinic, Rochester, MN.*

Background: Women with chronic kidney disease are often counseled to wait until after a successful kidney transplant (TX) to pursue pregnancy. However, pregnancy after kidney TX is still high risk and the effects on graft function and long-term graft survival are unclear.

Methods: We identified all kidney TXs in women ages 18 to 44 at all three Mayo clinic sites (MN, FL and AZ) from 1996 to 2014 who had a graft that functioned for at least 2 years. We reviewed records to identify pregnancies and evaluated the risk graft failure, death-censored graft loss, doubling of urine protein and a decrease in eGFR by 50% in women with post-TX pregnancies as compared to matched controls (matched on parity and age at TX and year of TX). Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CIs). Biopsies before and after pregnancy were reviewed.

Results: There were 818 women identified, of which 33 had at least 1 pregnancy lasting > 20 weeks gestation post-TX. The median time from TX to first delivery was 61 months (interquartile range (IQR) 35.5-76.5). Women with pregnancies were more likely to have pre-emptive TXs (51.5% vs. 24.2%, p=0.03) and lower nadir proteinuria post-TX (median 102 mg/24 hrs (IQR 67-153) vs. 135 mg/24 hrs (IQR 104-133), p=0.005) than women without pregnancies. There was no significant increase in the risk of graft failure (HR 0.49, 95% CI 0.12-1.23), death-censored graft loss (HR 0.60, 95% CI 0.23-1.57), or decrease in eGFR by 50% (HR 0.95, 95% CI 0.42-2.14) in women with pregnancies post-TX as compared to those without, even after adjusting for preemptive TX and baseline proteinuria. When adjusted for baseline proteinuria, there was a significant risk of doubling of proteinuria (adjusted HR 3.30, 95% CI 1.05-10.3). There was an increase in the number of biopsies with segmental sclerosis post-pregnancy (2 vs. 8). There was a significant mean (standard deviation) decrease in eGFR after pregnancy of 9 ml/min/1.73 m^2 (22.1) (p=0.03) and increase in women with eGFR < 45 ml/min/1.73 m^2 (3% vs. 37.5%, p=.002).

Conclusions: Women with preganancies after TX were more likely to have preemptive TXs and had lower baseline proteinuria than those without pregnancies. While pregnancy did not increase the risk of graft loss, there was a significant reduction in eGFR after pregnancy and an increased risk of doubling of proteinuria when adjusted for baseline values.

Funding: Private Foundation Support

SA-OR111

Serum Transforming Growth Factor β1 Is a Sex-Specific Risk Factor for Accelerated GFR Decline in the General Population

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Background: The health burden of chronic kidney disease (CKD) is increasing worldwide, and there is a need for novel biomarkers that can identify those at CKD risk for early preventive measures. There are sex differences in the progression of CKD and several risk factors seem to affect CKD risk differently in men and women. We investigated the association between serum transforming growth factor β1 (TGF-β1), a key mediator in kidney fibrosis development, and risk of accelerated loss of glomerular filtration rate (GFR) in women and men from the general population.

Methods: In the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6), we measured GFR by iohexol-clearance in 826 women and 801 men between 50 and 62 years of age without self-reported diabetes, cardiovascular or kidney disease. Of these, 1,324 (81%) had a follow-up GFR measurement after a median of 5.6 years in the RENIS-Follow Up. We used a multiple logistic regression model to examine the association between serum TGF-β1 and accelerated GFR decline (defined as subjects with the 10% steepest GFR slope).

Results: After adjusting for CKD risk factors, 1 SD increase in TGF-β1 levels was associated with higher odds of accelerated GFR decline in women (odds ratio (OR) 1.38 (95% confidence interval (CI) 1.01 to 1.89)), but not in men (p for interaction 0.03). Women with TGF-β1 in the upper quartile had an OR of 2.74 (95% CI 1.05 to 7.17) compared to women with TGF-b1 in the lower quartile.

Conclusions: Higher baseline TGF-β1 was independently associated with accelerated GFR decline in women, but not in men.

Funding: Government Support - Non-U.S.

SA-OR112

Sirtuin 3 Mediates Sex Differences in Ischemia-Reperfusion Kidney Injury

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Background: Biologic sex influences susceptibiity to AKI, a common condition with limited therapies. Mitochondrial dysfunction and oxidative stress play key roles in the pathogenesis of ischemic AKI. Our observations reveal higher baseline kidney expression of mitochondrial SIRT3 (mtSIRT3), a major mitochondrial deacetylase, in female vs male mice. We hypothesize that SIRT3 confers protection and mediates sex differences in response to kidney ischemia-reperfusion injury (IRI).

Methods: Male and female wild-type (WT), SIRT3 transgenic (Tg), or inducible kidney tubule-specific SIRT3 knockout (KO) mice were subjected to bilateral kidney IRI (clamping of renal pedicles for 30 min). HEK cells were treated with 17β-estradiol (E2), testosterone or veh.

Results: We observe higher mtSIRT3 expression in kidneys of WT female vs. male mice; mtSIRT3 declines with age but sex differences persist. At age 6-months, SIRT3 Tg male mice display less tubular vacuolization and ROS vs similarly aged WT males. Male Tg mice demonstrate resistance to IRI [preserved creatinine clearance (CrCl) and morphology; less ROS] and better survival vs WT males; outcomes similar to WT females. In contrast at age 6-months, SIRT3 KO males display greater tubular injury vs WT males. SIRT3 KO mice demonstrate increased susceptibility to IRI [decreased CrCl; worse morphological changes; increased ROS] and worse survival vs WT. In WT females, kidney mtSIRT3 correlates positively with plasma E2 and negatively with testosterone (T) levels. In WT males, kidney mtSIRT3 only correlates negatively with plasma T. In HEK cells, E2 treatment increases SIRT3 mRNA, and whole cell- and mtSIRT3 protein; T decreases mtSIRT3 protein with no effect on whole cell SIRT3 or SIRT3 mRNA. We previously showed that LRP2 shuttles intracrine proteins to the mitochondria and physically associates with SIRT3. Current observations show higher baseline kidney expression of LRP2 in WT female vs male. Testosterone treatment decreases LRP2 protein expression. In vitro LRP2 knockdown decreases mtSIRT3 protein.

Conclusions: 1) SIRT3 ameliorates kidney IRI, and decreased SIRT3 in males mediates the increased susceptibility to ischemic injury; 2) sex steroids regulate mtSIRT3 expression; estrogen via transcriptional regulation and testosterone via inhibition of LRP2-mediated mitochondrial targeting; 3) sex differences in AKI pathophysiology need to be studied.

Funding: Veterans Affairs Support, Private Foundation Support

SA-OR113

Association of Reproductive Lifespan Duration and CKD in Postmenopausal Women

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Background: Although animal studies have suggested estrogen to offer renoprotective effects, clinical evidence remains scarce. This study sought to investigate the relationship between endogenous estrogen exposure and renal function. Considering female reproductive lifespan duration (RLD) to be a surrogate of lifetime exposure to

endogenous estrogen, the association of RLD and chronic kidney disease (CKD) was analyzed in postmenopausal women.

Methods: Data were retrieved from the Korean Genome and Epidemiology Study_ Health Examinees cohort. A total of 57,505 postmenopausal women were included in the analysis. The RLD for each participant was determined by subtracting the age at menarche from the age at menopause. The participants were divided into groups according to RLD quartile. The association between RLD and CKD, defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2, was examined.

Results: The mean age and eGFR of the study subjects were 57.7 ± 6.1 years and 88.0 ± 16.7 mL/min/1.73m^2, respectively. The mean RLD was 34.2 ± 4.1 years. A total of 1,664 (2.89%) women were found to have CKD. The prevalence of CKD tended to decrease in groups with longer RLDs. Logistic regression analysis revealed that the odds ratio for CKD was lower in groups with longer RLDs as compared to the shortest RLD group. This finding was significant even following adjustments for confounding factors.

Conclusions: The prevalence of CKD was significantly lower in subjects with longer RLDs. The amount of endogenous estrogen exposure could be a determining factor for renal function in postmenopausal women.

Table 1. Logistic regression analysis of the association between RLD and outcomes

	Model 1 OR (95% CI)	*P* value	Model 2 OR (95% CI)	*P* value	Model 3 OR (95% CI)	*P* value	Model 4 OR (95% CI)	*P* Value
CKD based on eGFR only								
Linear[a]	0.92 (0.88–0.96)	<0.001	0.92 (0.88–0.96)	<0.001	0.91 (0.87–0.95)	<0.001	0.90 (0.85–0.95)	<0.001
Q1	Reference		Reference		Reference		Reference	
Q2	0.87 (0.76–0.98)	0.026	0.87 (0.77–0.99)	0.035	0.87 (0.77–0.99)	0.039	0.87 (0.75–1.02)	0.078
Q3	0.73 (0.62–0.85)	<0.001	0.73 (0.63–0.86)	<0.001	0.72 (0.62–0.85)	<0.001	0.71 (0.59–0.85)	0.001
Q4	0.80 (0.70–0.91)	0.001	0.80 (0.70–0.92)	0.002	0.78 (0.68–0.89)	<0.001	0.72 (0.61–0.86)	<0.001
CKD based on eGFR and proteinuria								
Linear[a]	0.91 (0.88–0.94)	<0.001	0.91 (0.88–0.95)	<0.001	0.91 (0.87–0.94)	<0.001	0.90 (0.86–0.94)	<0.001
Q1	Reference		Reference		Reference		Reference	
Q2	0.88 (0.79–0.97)	0.008	0.88 (0.80–0.98)	0.014	0.89 (0.80–0.98)	0.022	0.90 (0.80–1.01)	0.083
Q3	0.80 (0.72–0.90)	<0.001	0.81 (0.72–0.91)	<0.001	0.81 (0.72–0.90)	<0.001	0.81 (0.71–0.93)	0.003
Q4	0.78 (0.70–0.86)	<0.001	0.78 (0.70–0.87)	<0.001	0.76 (0.68–0.85)	<0.001	0.72 (0.63–0.82)	<0.001

Note: *Model 1:* Adjusted for age
Model 2: Model 1 + Number of children
Model 3: Model 2 + History of hypertension and diabetes mellitus
Model 4: Model 3 + BMI, HDL-C, triglyceride, hs-CRP, levels of education and income, history of smoking
[a]ORs for linear variable is per 1-SD change in RLD
Abbreviations: RLD, reproductive lifespan duration; eGFR, estimated glomerular filtration rate; OR, odd ratio; CI, confidence interval; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation; RLD, reproductive lifespan duration

SA-OR114

Sex Differences in Vascular Access

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Background: Although fistulas are actively promoted, studies report fewer women receive and use a fistula. Whether women undergo similar efforts at fistula creation and procedures as men is unknown. We sought to describe differences between men and women for probability of receiving a fistula attempt, achieving independent fistula use, remaining catheter-free over time, and the rate of access-related procedures as a function of sex in a cohort of Canadian incident hemodialysis patients.

Methods: Prospectively collected vascular access data on incident dialysis patients from five Canadian programs using Dialysis Measurement Analysis and Reporting (DMAR) system to determine differences in fistula related outcomes between women and men. Probability of receiving a fistula attempt and the probability of successful fistula use was determined using binary logistic regression. Catheter and fistula procedure rates were described using Poisson regression. We studied time to fistula attempt and time to fistula use accounting for competing risks of death, transplant and recovery of kidney function.

Results: We included 1,446 (61%) men and 929 (39%) women. Men had a lower body mass index (p<0.001) and were more likely to have coronary artery disease (p<0.001) and peripheral vascular disease (p<0.001) than women. 688 (48%) men and 403 (43%) women received a fistula attempt. After accounting for confounders (age, diabetes, cardiovascular disease, inpatient starts), men were more likely to receive a fistula attempt (OR 1.29 [1.08-1.54] and to achieve catheter free use of the fistula at one year (OR 2.62 [1.88-3.65]. We found an average of 2.30 procedures per person-year after start of dialysis, with no significant difference between men and women (IRR 1.04 [0.93-1.15]). Following a fistula attempt, women received more procedures (IRR men v women: 0.86 [0.77-0.96]) attributed to an increased number of catheter procedures (IRR men vs women: 0.67 [0.56-0.79]. Men received more fistula procedures IRR 1.20 [1.04-1.37]).

Conclusions: We found that, as compared to men, fewer women undergo a fistula attempt and after adjusting for comorbidities this disparity increases. Not only do women have fewer fistula creations, but they are less likely to successfully use their fistula without a catheter in place.

SA-OR115

Clinical, Angiogenic, and Immune System Markers Predict Preeclampsia in Women with CKD During Pregnancy

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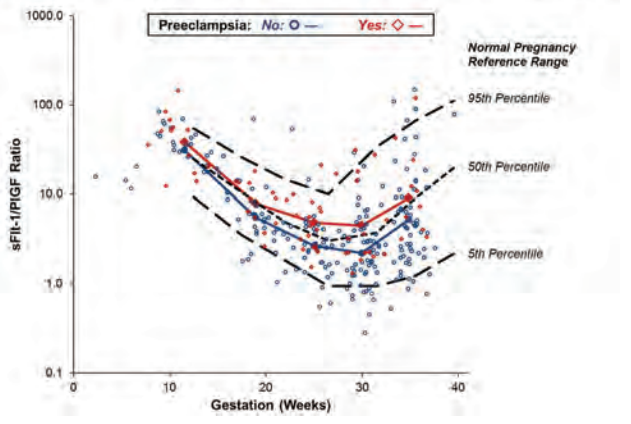
Background: Pre-eclampsia (PE) is associated with immune activation and altered circulating angiogenic factors (with elevated soluble FMS-like tyrosine kinase-1/placental growth factor or sFLT-1/PlGF ratio). There are currently limited data in pregnant women with CKD. Longitudinal changes of markers inflammation, immunity & angiogenic factors during CKD pregnancy were assessed in this study & their relationship to the development PE explored.

Methods: Women with CKD were recruited from a UK renal-obstetric clinic between 2011-2016. Baseline demographics, serial serum samples and pregnancy outcomes were recorded. Samples were analysed for IgG/A/M, high-sensitivity CRP, serum free light chains (sFLC), Beta-2 Microglobulin (B2M), complement factors 3 & 4 (C3/4), uric acid (UA), creatinine, cystatin-C & sFLT-1/PlGF using the Roche Cobas® platform. Gestational periods were split into five groups.

Results: PE was diagnosed in 23% of the 164 pregnancies (136 women) with rates increasing with CKD stage (p=0.011). White ethnicity, non-smoking, SLE, chronic hypertension and previous PE were independent predictors of PE. sFLC, B2M, creatinine, cystatin-C & UA increased significantly over the antenatal period and were higher in the PE group. The greatest predictive accuracy for PE was seen at 16-21 weeks, for sFLC & cystatin-C (AUROC 0.745, 0.810 respectively). Antenatal levels of C3 increased (p<0.001) and IgA fell (p=0.015) more rapidly in the PE vs. non-PE group. The sFlt-1/PlGF ratio was predictive for PE developing at 22-27 weeks gestation (AUROC=0.728, p=0.005) (figure 1).

Conclusions: In women with CKD, an elevated sFLT-1/PlGF ratio is predictive of PE at 22-27 weeks gestation, but not at later gestations. Its predictive accuracy is comparable to markers of kidney function, sFLC and B2M levels.

Figure 1: sFLT-1/PlGF ratio by gestation in patients that did and did not develop PE



SA-OR116

Black and Hispanic Women Are at Increased Risk of Hypertension After Preeclampsia

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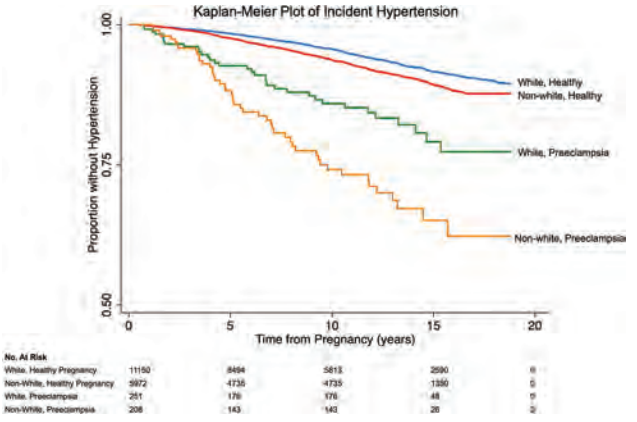
Background: Preeclampsia is a leading cause of maternal mortality and associated with increased risk of hypertension (HTN) in later life. Black and Hispanic women are at increased risk for pregnancy-related mortality compared to non-Hispanic white women in the United States. We sought to investigate whether long-term complications of preeclampsia are differentially impacted by race/ethnicity. We tested the hypothesis that black and Hispanic women have an increased risk of incident HTN after preeclampsia compared to non-Hispanic white women.

Methods: We analyzed a longitudinal observational cohort of black, Hispanic and non-Hispanic white women who had at least one pregnancy between 1998 and 2014 and were subsequently followed at an academic network of primary care practices through 2018. Patients were followed until incident HTN, using validated diagnostic criteria, or their last encounter in the hospital system. Multivariable Cox proportional hazards models were used to examine the independent association between preeclampsia and risk of incident HTN after delivery. Analyses for effect modification between preeclampsia and non-white race on the risk of HTN were performed.

Results: There were 20,864 women with a pregnancy in the cohort of which 4,959 (23%) and 1,412 (6%) were of self-reported Hispanic or black race/ethnicity, respectively. Preeclampsia developed in 524 (2.5%) of pregnancies. Preeclampsia was associated with an increased risk of incident hypertension after pregnancy in all groups, with higher rates in non-white women (adjusted HR 2.8 [1.9-4.2] p<0.01 for Hispanic women, adjusted HR 2.7 [1.3-5.7] p = 0.01 for black women and adjusted HR 1.8 [1.2-2.8] p<0.01 for non-Hispanic white women. There was evidence of effect modification between non-white race/ethnicity, preeclampsia and incident hypertension (p-interaction=0.04).

Conclusions: Preeclampsia is a major risk factor for later life HTN, particularly among black and Hispanic women.

Funding: NIDDK Support



SA-OR117

Maternal Pregnancy Outcomes in Women with Complement-Mediated TMA: Update of the Vienna TMA Cohort

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Background: Pregnancy is a high-risk scenario to trigger complement pathway dysregulation. Presentation of paternal antigens activates the maternal alternative pathway and in women with malfunctioning complement regulatory proteins or C3 life-threatening thrombotic microangiopathy (TMA) can develop.

Methods: As of 2015 we reported outcomes of 27 pregnancies in 14 women with complement-mediated TMA (cTMA) enrolled in the Vienna TMA cohort (VTC). This work presents an update on this open cohort as of May 2019: Outcomes are CKD stage at last follow-up, incidence of dialysis or kidney transplantation (KTX) and death.

Results: In 32 women of the VTC the mean age at first cTMA presentation was 30 ±16 years (figure 1). Up until 2019 in 25 women a total of 55 pregnancies were observed: 6 women 1, 9 women 2, 6 women 3, 2 women 4, 1 woman 5 pregnancies. In 14 women pregnancy occurred before diagnosis of cTMA (26 pregnancies, 6 abortions) with 8 pregnancies afterwards in 5 women. Pregnancy-associated cTMA (p-cTMA) happened in 11 women: 6 during first, 3 during second and 2 during a later pregnancy. Five women had 11 pregnancies following KTX. Thirty-nine (71%) pregnancies were untreated and not complicated by p-cTMA. Four women received preventive plasma therapy for 6 pregnancies (2 KTX; 1 p-cTMA), 2 became pregnant during ongoing eculizumab therapy (3 pregnancies,1 KTX; 0 p-cTMA), 5 received therapeutic plasma therapy for p-cTMA (1 KTX), and 2 were switched to eculizumab (0 ESRD). At last follow-up 20 had eGFR ≥60ml/min per 1.73m^2, 6 eGFR <60, 2 needed dialysis and 4 had died.

Conclusions: In summary, VTC data demonstrates good maternal outcome (1) in the majority of untreated pregnancies in women with a diagnosis of cTMA and (2) in specifically treated cTMA patients in a specialized center.

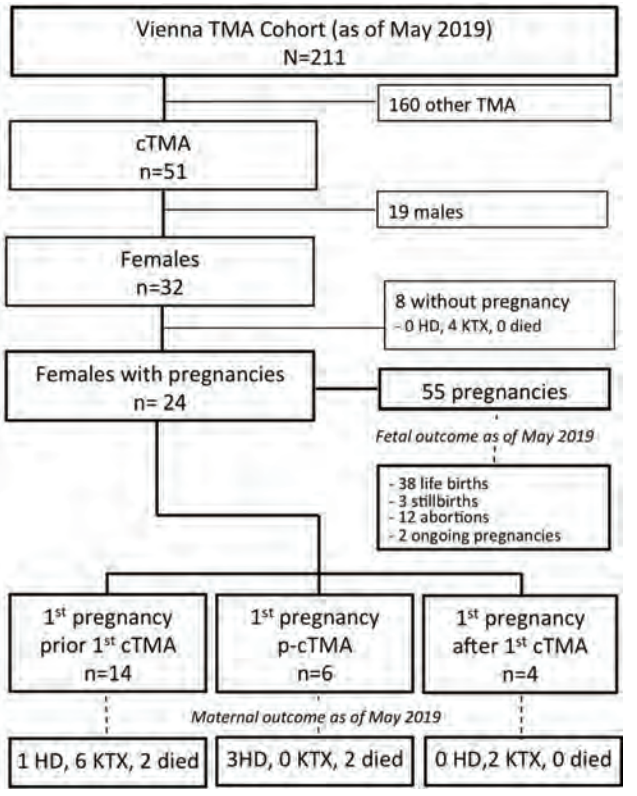

Figure 1.

TH-PO001

Transiently Dedifferentiated eR1-Active Proximal Tubule Cells Clonally Expand and Repair Proximal Tubules in Severe Injury

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Background: It is well accepted that injured proximal tubules (PT) are restored by the proliferation of surviving PT cells. However, whether this process depends on stochastic proliferation or expansion of a PT subpopulation, and how severity of injury affects repair process is uncertain. A Runx1 enhancer named Runx1+24mCNE (eR1) was shown to be active in adult long-term hematopoietic stem cells and gastric stem cells, but the role of eR1 in the kidney is unknown.

Methods: We explored the behaviors of PT cells with high eR1 activity, in 30-(moderate) and 60-min (severe) ischemia reperfusion injury (IRI), utilizing eR1-EGFP and eR1-Cre^{ERT2} mice.

Results: PT cells showed a higher rate of BrdU incorporation in 60-min IRI than in 30-min IRI, and a significant proportion of the PT cells showed RUNX1 expression after 60-min IRI, but not after 30-min IRI. In eR1-EGFP mice, after 60-min IRI, but not after 30-min IRI, EGFP$^+$ PT cells accounted for 20% of total PT cells of the superficial cortex. In eR1-EGFP:eR1-Cre^{ERT2}:R26-tdTomato mice subject to 60-min IRI, EGFP$^+$ and tdTomato$^+$ PT cells mostly overlapped in acute phase even without tamoxifen. This suggested that eR1-Cre^{ERT2} mice showed leaky Cre^{ERT2} activity when eR1 was highly activated after injury, and could be used to trace the fate of PT cells with high eR1 activity. In acute phase of 60-min IRI, tdTomato$^+$ PT cells showed a higher rate of BrdU incorporation compared to other PT cells, and clustered with several tdTomato$^+$ cells. Consistently, eR1-Cre^{ERT2}:R26-Confetti multicolor reporter mice revealed the clonal expansion of eR1-active PT cells after 60-min IRI. RNA-seq data of eR1^{CreERT2} lineage-labeled PT cells after 60-min IRI showed higher expression of genes associated with cell cycle progression and DNA replication. Notably, tdTomato$^+$ PT cells in acute phase were mostly positive for Kim-1 and vimentin, and negative for differentiation markers. In chronic phase, however, the percentages of PT cells positive for Kim-1 and vimentin were not different between tdTomato$^+$ and tdTomato$^-$ PT cells, indicating the re-differentiation capacity of this population even after severe injury.

Conclusions: eR1 marks a subpopulation of PT cells of the superficial cortex with different transcriptomic profiling, highly proliferative after severe injury.

Funding: Government Support - Non-U.S.

TH-PO002

Caspase-11-Mediated Tubular Epithelial Pyroptosis Underlies Contrast-Induced AKI

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Background: Contrast-induced acute kidney injury (CI-AKI) is a serious complication in patients after administration of iodinated contrast media. Pyroptosis is a form of programmed lytic cell death that is triggered by inflammatory caspases (caspase-11), but little is known about its role in tubular epithelial cells (TECs) death and CI-AKI.

Methods: 1. The primary mouse and human renal TECs were treated with iohexol and isosmotic mannitol in separate experiments. Experiments were performed in triplicate. The protein expression of Caspase-4/5/11, IL-1β and Gsdmd in cells by assessed by Western Blot, respectively. Caspase-4/5, and IL-1β mRNA expression in cells detected by real-time PCR. ELISA was used to detected the concentration of IL-1β in cell culture supernatants and a CytoTox 96 Non-Radioactive Cytotoxicity Assay measured cell death. 2. The model of CI-AKI mice was established. Mice were killed 24 hours after iohexol or other drugs injection, and blood and kidney tissue specimens of mice were collected. Scr and blood BUN was assessed by an automatic biochemical analyzer; the protein expression of Caspase-11, IL-1β and Gsdmd in mouse kidney was assessed by Western Blot; Acute kidney injury biomarkers (KIM-1, IL-18) and inflammatory cytokines IL-6 mRNA expression was detected by real-time PCR. H&E staining and immunolabelling were used to evaluate degree of renal tubular injury and expression of caspase-11, and IL-1β in kidneys, respectively.

Results: Here, we show that systemic exposure to contrast media causes severe tubular epithelial pyroptosis that is mediated by the inflammatory caspases, caspases 4/5 in human TECs, or the murine homolog caspase-11 in mice in vivo and in mouse TECs in vitro. Knockdown of caspase-4/5 preserved human TECs from cell death and reduced the release of mature IL-1β, and in caspase-11-deficient mice, contrast-induced acute kidney injury was abrogated, indicating a central role for caspase-11 in acute kidney injury. Additionally, deletion of caspase-11 in TECs reduced Gsdmd cleavage, which is the key process for execution of pyroptosis.

Conclusions: These results establish the requisite role of caspase-11–mediated epithelial pyroptosis in CI-AKI and suggest that epithelial inflammatory caspases are an important therapeutic target for AKI.

Funding: Other NIH Support - the National Science and Technology Major Project (No. 81570604)

TH-PO003

Role of NLRP3 in Rhabdomyolysis-Induced AKI

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Background: NOD-like receptor, pyrin domain containing-3 (NLRP3) has been suggested to contribute to various kidney through inflammasome-depedent or –independent pathways. Recent evidence showed the association of NLRP3 inflammasome in the pathogenesis of rhabdomyolysis-induced AKI (RIAKI); However, underlying mechanisms was not clarified yet. We investigated the role of NLRP3 in RAKI and evaluated the possibility of NLRP3 as the treatment target of RIAKI.

Methods: HK-2 cells and THP-1 cells were treated with ferrous myoglobin to mimic the rhabdomyolysis environment in vitro. A glycerol was injected intramuscularly to the gluteal area of the mice to generate RIAKI model in NLRP3 KO and WT ones. Selective NLRP3 inhibitor (MCC950) was used as a therapeutic agent.

Results: NLRP3 KO mice showed a marked decrease in serum creatinine, KIM-1, and tubular injury compared with WT mice although muscular injury was not different. Apoptosis markers and inflammatory cytokines, which were increased in the kidneys of WT mice, were mitigated in the kidneys of NLR3 KO mice. AKI was attenuated by the MCC950 treatment before glycerol injection. Ferrous myoglobin caused to increase apoptotic signals and to translocate NLRP3 from cytoplasm to mitochondria in HK-2 cells. NLRP3 knock down HK-2 cells identified significant decrease of apoptosis. Also, ferrous myoglobin activate NLRP3 inflammasome in THP-1 cells. Cleaved IL-1β was reduced in siNLRP3 treated THP-1 cells.

Conclusions: The deficiency of NLRP3 protected kidneys from RAKI by both inflammasome-independent and -dependent ways. NLRP3 could play the essential role in RIAKI and and be a candidate as a treatment target.

Funding: Private Foundation Support

TH-PO004

Kynureninase Is Essential for Protection from AKI by Caloric Restriction

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Background: Experimental work shows that preconditioning by caloric restriction (CR) or hypoxia (HP) prevents acute kidney injury (AKI) reliably. Recently, we have identified *Kynu* as one of the top gene candidates conveying organ protection in a transcriptome analysis of renal tissue after preconditioning. Here, we further characterize the impact of *Kynu* in a mouse model of renal ischemia-reperfusion-injury (IRI).

Methods: We generated a conventional Knockout (KO) of *Kynu* using CRISPR/Cas9 mediated genome editing and *non-homologous end joining* (NHEJ) in C57Bl6 mice. Following a functional and histological phenotyping, wildtype and KO mice were preconditioned by CR and subsequently were subject to IRI.

Results: *Kynu* encodes kynureninase, which represents a key player in tryptophan metabolism. We confirmed the knockout of our newly generated mouseline by immunoblot, immunhistochemistry and mass spectrometry. The basal phenotyping of the KO mice did not differ from that of wildtype mice (appearance, weight, kidney function, histology). Renal function as well as histological features of AKI 24h after IRI were similar in KO mice without preconditioning and wildtype mice. However, while wildtype mice were effectivly protected from AKI after CR, this effect was significantly diminished in the *Kynu* KO animals after CR.

Conclusions: The induction of *Kynu* is associated with HP and CR. Our results confirm the pivotal role of *Kynu* as a key player of preconditioning-mediated renal protection. Further investigations to determine the mechanistic features of *Kynu* are required now.

TH-PO005

Kidney-Centered Radiotherapy Attenuates Renal Ischemia-Reperfusion Injury in Mice

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Background: Whole-body irradiation has been associated with renal ischemic preconditioning in mice. Here, we investigate the functional and fundamental impact of radiotherapy centered on the kidneys before renal ischemia/reperfusion (I/R) in mice.

Methods: Experience1: Animals (n=6) were anesthetized and placed in the irradiator. Two beams of X-rays (225Kv, 13 mA) specifically targeted both kidneys to deliver a dose a 8,56Gy. One month later, a right nephrectomy was performed, and a left renal ischemia was induced for 30min. After 48 hours of reperfusion, the left kidney was collected, as well as blood. Control group (n=6) underwent a similar renal I/R procedure, with no prior irradiation. Experience 2: Unilateral irradiation of the left kidney (8.56 Gy) was performed in mice (n=10). One month later, the left (irradiated) kidney was collected. Additionally, the left kidneys were collected from non-irradiated mice (n=5). Total RNAs were extracted from irradiated and control kidneys to perform comparative high-throughput RNA-Seq. BaseSpace Sequence Hub Illumina was used. Functional enrichment analysis was performed using DAVID program. Both experimental protocols have been approved by the IACUC of ULiège, Liège, Belgium.

Results: Following kidney I/R, blood urea nitrogen (BUN) levels were significantly lower in pre-irradiated mice (148.4±93.1) compared to controls (495.7±33.3, $p<0.01$). The number of PCNA-positive proliferating cells was significantly lower in pre-irradiated mice (130.8±52.7) compared to controls (545.4±257.3, $p<0.001$). The renal infiltration by inflammatory CD11b-positive cells (90.2±32.2 *vs.* 414.5±148.6) and F4-80-positive macrophages (80.6±22.9 *vs.* 178.5±68) was significantly reduced in pre-irradiated animals *vs.* controls. Comparative transcriptomics showed a significant up-regulation of various signaling pathways, including angiogenesis (*HMOX1*) and stress response (*HSPA1A*, *HSPA1B*), and a down-regulation of oxidoreduction (*NOX4*).

Conclusions: Kidney irradiation induces ischemic preconditioning in mice, with improved renal function and decreased inflammation following renal I/R. The aforementioned signaling pathways may play a role in irradiation-associated kidney resistance to I/R.

Funding: Government Support - Non-U.S.

TH-PO006

Renal Protective Effect by Vagus Nerve Stimulation After Kidney Injury

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Background: We previously reported that the macrophages with vagus nerve stimulation (VNS) before bilateral ischemia-reperfusion injury (IRI) protect the kidney from the injury by activating the cholinergic anti-inflammatory pathway (CAP) in mice. Clinically, it would be more beneficial if VNS after injury could protect the kidney. We evaluated the effect of VNS after the injury both in vitro and in vivo model.

Methods: <LPS model> Both murine macrophage cell line RAW 264.7 and primary peritoneal macrophages were administered LPS (100 ng/ml). Human monocyte cell line U937 also received LPS (1 μg/ml). Because a7 nicotinic receptor plays an important role in the CAP, all of the cells were treated with a7nicotinic receptor agonist GTS-21 (50 mM for each) 4 and 6 hours after LPS administration, followed by assessment of the inflammatory status (TNF-α, IL-1β). In vivo, C57BL/6 mice were injected with LPS (5 mg/kg) intraperitoneally, and GTS-21 (10 mg/kg) was administered 4 and 6 hours later. Cytokine levels such as systemic TNF-α and splenic IL-1β and kidney injury markers such as Kim-1 were evaluated 8 hours after LPS administration. <IRI model> C57BL/6 mice underwent unilateral IRI (uniIRI). Followingly, VNS or sham stimulation was performed 3 times a week for 2 weeks, then the extent of kidney fibrosis (a-SMA, Masson's trichrome staining) was evaluated 2 weeks after the injury.

Results: GTS-21 decreased TNF-α expression level induced by LPS in macrophages / monocyte we used. In vivo, GTS-21 significantly suppressed LPS-induced kidney injury such as increased Kim-1 expression, as well as inflammation such as increased plasma TNF-α and splenic IL-1β. The progression of kidney fibrosis was also suppressed in VNS-treated uniIRI mice, compared to the sham stimulation-treated group.

Conclusions: CAP activation after injury could also exert organ protective effect.

Funding: Commercial Support - Kyowa-Hakko-Kirin, Government Support - Non-U.S.

TH-PO007

Human Recombinant α-1-Microglobulin Protects Against AKI in Rat Models of Ischemia-Reperfusion Injury (IRI)

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Background: Acute kidney injury (AKI) is a global health concern associated with high morbidity, mortality, and progressive chronic kidney disease (CKD). RMC-035, a recombinant human α_1-microglobulin (A1M), has demonstrated protective antioxidant effects in several injury models. The principal mechanisms of RMC-035 are heme binding, reductase activity, radical scavenging and protection of mitochondria. RMC-035 is being developed for the prevention of cardiac surgery associated-AKI, and are currently evaluated in a Phase 1 study. We present preclinical data for RMC-035, supporting its protective effect in ischemic AKI and AKI on a CKD background.

Methods: RMC-035 (0-5 mg/kg, i.v.) was administered at various time-points and doses prior and/or post renal ischemia in rats exposed to unilateral nephrectomy followed by a 30 minute pedicle clamp ischemia. AKI was evaluated at 1-5 days post injury by serum creatinine (sCr), BUN and 24 hr urinary creatinine clearances (CrCl). Furthermore, RMC-035 (2 mg/kg, i.v.) was administered prior to and post renal clamp ischemia in rats previously subjected to unilateral and renal ischemia ("AKI on CKD model"). Texas Red-x labeled RMC-035 (TR-RMC-035) trafficking and handling by proximal tubule cells (PTC) was studied via intravital imaging.

Results: RMC-035 caused a dose-dependent decrease in AKI measured as reduced proteinuria, sCr and BUN levels, and improved 24 hr CrCl, in rats subjected to a single renal IRI episode. RMC-035 given prior and post renal IRI was more effective for protection vs a single dose given either before or after IRI. In a CKD model with two successive episodes of AKI over 28 days, RMC-035 given at the second IRI episode significantly reduced renal injury by sCr and CrCl. TR-RMC-035 was rapidly filtered and bound to the apical brush border in PTC. Accumulation of RMC-035, tubular-vesicular extensions and vesicular trafficking was seen from 30 minutes through 24 hr post infusion. Cytosolic release was seen as early as 70 minutes.

Conclusions: RMC-035 demonstrates dose-dependent protective effects against AKI in multiple IRI models including AKI on CKD, had a prolonged PTC half-life including release into the cytosol, thus being a novel and promising therapeutic candidate for the treatment of cardiac surgery associated-AKI.

Funding: NIDDK Support, Other NIH Support - O'Brien Center for Renal Imaging, Commercial Support - A1M Pharma

TH-PO008

A Novel Angiotensin-Converting Enzyme 2 Truncate Markedly Improves Ischemic AKI

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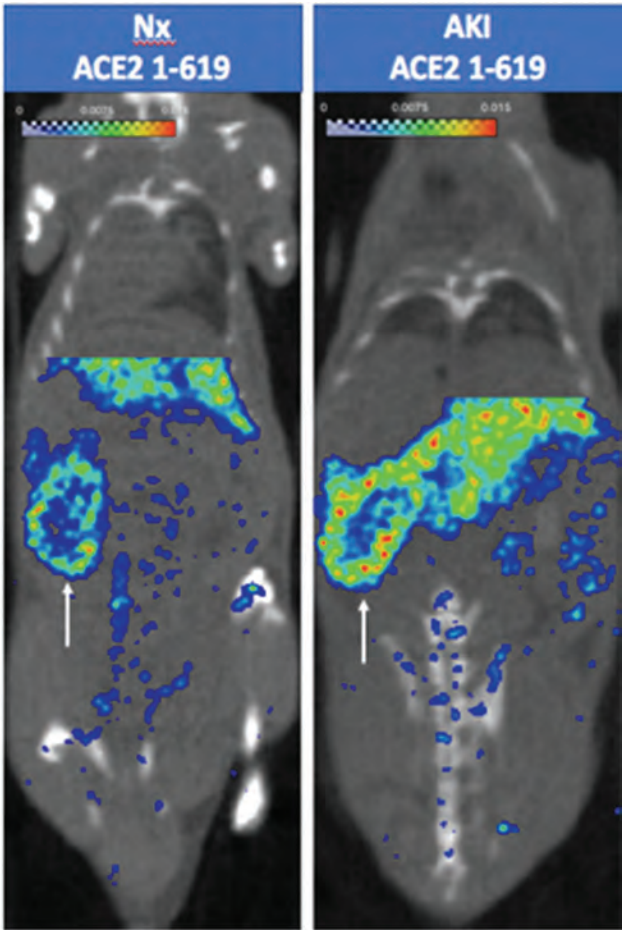
Background: RAS is overactive in AKI and therefore RAS blockers could be beneficial. Their use, however, is usually avoided because of their hypotensive and hemodynamic effects. An alternative approach to blocking the formation or action of angiotensin II (Ang II) is to foster its degradation. ACE2 is a tissue enzyme that degrades Ang II to Ang 1-7. Due to its large size, native ACE2 is not filterable. We therefore used a novel ACE2 truncate (1-619) to test the therapeutic potential in a unilateral model of ischemia-reperfusion injury (IRI).

Methods: IRI was induced in C57 mice by clamping the left renal pedicle for 30 min. ACE2 1-619 or vehicle (PBS) was administered 20 min prior to, and 5-6 h and 30 h after IRI. Renal function and tubular injury were assessed 24h and 48h post IRI. Filtration and renal uptake of 1-619 was assessed by SPECT/CT imaging.

Results: In 1-619-treated mice, GFR was higher at 24h (103±16 vs. 63±11 μl/min, $P<0.05$) and 48h (93±22 vs 38±93 μl/min, $P<0.01$) post IRI as compared to vehicle mice. Consistent with a better preserved GFR, BUN and Cr were lower in the 1-619-treated group as compared to their vehicle counterparts at 24h and 48h post IRI. ACE2 1-619 attenuated injury to the renal tubules as reflected by an improved tubular injury score and reduced kidney NGAL at 48h post IRI compared to vehicle mice. SPECT/CT showed comparable parenchymal activity of infused 1-619 in a mouse subjected to IRI 24h prior to imaging and an Nx control mouse. ACE2 activity was increased in kidneys of 1-619-injected mice as compared to vehicle mice at 48h post IRI (66±4 vs. 46±3 RFU/μg protein/h, $P<0.01$).

Conclusions: We conclude that the use of our novel ACE2 truncate downregulates the kidney RAS and provides a preventative/therapeutic approach to attenuate AKI.

Funding: NIDDK Support



TH-PO009

Knockout of Leucine Rich α-2 Glycoprotein Protects Against Renal Ischemia-Reperfusion Injury Through Reduction of Fibrosis and Apoptosis

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Background: Leucine-rich α-2 glycoprotein (LRG) is one of serum glycosylated proteins with 347 amino acids, and serum LRG is reported as a novel disease activity biomarker for inflammatory bowel disease. However, little is known about the role of LRG in acute kidney injury (AKI) pathogenesis. We examined renal LRG expression and urinary LRG level using mice AKI model and clinical samples.

Methods: We evaluated LRG function in the bilateral renal ischemia-reperfusion injury (IRI) AKI model by using LRG knockout (KO) and wild-type (WT) mice. We at first evaluate the localization of LRG in AKI of WT mice. The effects of LRG on phosphorylation of Smads were examined in primary cultured renal tubular cells. In clinical study, we measured urine LRG in AKI patients, and immunohistological examination of LRG in AKI and minimal change renal biopsy sample.

Results: In WT mice with IRI-induced AKI, renal mRNA and protein expression of LRG were induced from 6 h and 12 h and peaked at 24 h and 48 h after IRI, respectively. In control mice kidney, only a very few expression of LRG was observed. Urine and serum LRG are increased after IRI in WT mice. Immunohistological examination showed that LRG expression was observed mainly in renal distal tubular cells in AKI mice. LRG KO mice had significantly lower PCr (0.61+0.13 versus 1.67+0.38 mg/dl), BUN (102.3+21.8 versus 234.5+48.5 mg/dl) at 48h after IRI compared to WT mice. Immunohistological examination showed mild tubular injury, fibrotic change, collagen IV deposition, and fewer KIM-1 positive and apoptotic cells in LRG KO mice. In primary cultured renal tubular cells, TNF-a and LPS stimulated LRG expression. LRG KO reduced TGF-b stimulated-phosphorylation of Smad2. Notably, in contrast media-induced AKI patients, urinary LRG levels were increased from 6 h. LRG staining were enhanced in AKI renal-biopsy samples.

Conclusions: Our results demonstrate that LRG is up-regulated in renal tissues in both mice and human AKI, and that urine and serum LRG are increased in early phase of AKI. Inflammatory cytokines such as TNF- a stimulates expression of LRG in renal tubular cells. Thus, LRG could serve as a potential early biomarker in AKI, and LRG blockage could serve as a potential therapeutic target in AKI.

TH-PO010

Mineralocorticoid Receptor Antagonism Counteracts the Acute and Chronic Effects of Renal Ischemic Injury in Rodents and the Large White Pig

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Background: Mineralocorticoid receptor antagonists (MRA) prevent ischemic acute kidney injury (AKI) and its transition to chronic kidney disease (CKD) through macrophage polarization modulation. The specific contribution of interleukin-4 (IL-4) signaling to this effect is unknown. Whether the MRA protective effect reported in rodents can be translated to the human remains to be elucidated. Here, we explore the role of IL-4 signaling in the protective effect of Finerenone and we evaluate the effect of MRA against the acute and chronic effects of ischemic AKI in the Large White pig.

Methods: Male C57/B6 mice (24) were divided in: sham, renal ischemia for 22.5 min (IR), IR plus the non-steroidal MRA finerenone (10 mg/kg) at -48, -24 and -1 h before IR and IR-finerenone plus Tofacitinib (15mg/kg), a JAK3 inhibitor. The mice were followed-up for 4 weeks to evaluate the AKi to CKD transition. Large White male pigs (18) were divided in: sham, bilateral renal ischemia for 60 min + vehicle and IR + Soludactone (potassium canreonate-7mg/kg, i.v.) at 48 h, 24 h and 30 min before the induction of the ischemia and 24 h and 48 h after reperfusion.

Results: In mice, the AKI to CKD transition was evidenced by a 40% increase in plasma creatinine, interstitial fibrosis and increased mRNA levels of α-SMA, fibronectin and collagen I. Finerenone protected against these alterations while the JAK3 inhibitor partially reversed this protective effect. In the Large White pig, tubular injury protection by canrenoate was evidenced by a significant reduction in urinary protein (Vehicle: 1±0.08 g/mmol vs canrenoate: 0.49±0.02 g/mmol), L-FABP (Vehicle: 39±2 ng/mL vs canrenoate: 19±.1.5 ng/mL), NAG excretion (Vehicle: 109±3 U/L vs canrenoate: 59±2 U/L) and by the recovery of the urinary concentration capacity after 24 h of renal ischemia. After 3 months, the untreated pigs presented proteinuria (0.03±0.01 g/mmol) which was absent in the canreonate-treated pigs (0.01±0.01 g/mmol).

Conclusions: MR antagonism prevents the acute and chronic IR-kidney effects in the mice and in the Large White pig. The IL-4 receptor-JAK3 signaling pathway is involved in the benefit of the MRA finerenone. These findings support clinical trials testing the potential benefits of MRAs in the kidney transplantation setting.

Funding: Commercial Support - BAYER, Government Support - Non-U.S.

TH-PO011

The V1a Receptor Activator Terlipressin (TLP) Attenuates Hemorrhagic Shock (HS)-Induced AKI

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Background: Although HS is still the leading cause of mortality, early vasopressor use can restore hemodynamic parameters and organ perfusion, reducing the need for aggressive fluid therapy and avoiding fluid overload. In shock, TLP improves hemodynamics, decreasing pulmonary capillary leak and avoiding fluid overload. The AVP/V1a receptor system also stimulates RAS activity and inhibits apoptosis. This study aimed to compare levels of lactated Ringer's (LR) fluid therapy: aggressive (LR 3× the blood volume removed, 3LR), conservative (2LR), and minimal (1LR)—with or without TLP—in rats with HS-induced acute kidney injury (AKI).

Methods: We induced rats to HS, maintaining MAP at 30-40 mmHg for 60 min, and evaluated 4 groups of rats—control (no intervention); 3LR; 1LR+TLP (10 μg/100 g BW, iv); and 2LR+TLP. At 15 min after LR/TLP administration, we used the drawn blood to resuscitate the rats with HS. We measured MAP at various time points, studying other variables at 24 h after HS induction. Data are mean±SEM.

Results: MAP was restored in all three study groups. p21 protein expression was significantly higher in 3RL rats than in 1LR+TLP and 2RL+TLP rats (144±3.4 vs. 116±0.9 and 110±2.8%; P<0.05), and PCNA+ cell counts were lower in 3RL rats (1.1±0.1 vs. 1.8±0.7 and 2.2±0.6 cells/0.087 mm²). CD68+ cell counts were higher in 3RL rats than in 1LR+TLP and 2RL+TLP rats (10±2.2 vs. 6.3±0.7 and 5.3±0.7 cells/0.087 mm²). TUNEL+ cells counts were significantly lower in 2LR+TLP and 1LR+TLP rats than in 3LR rats (0.6±0.1 and 1.6±0.3 vs. 4.5±2.5 cells/0.087 mm²; P<0.05), as was BAX protein expression (105±5.4 and 107.5±5.2 vs. 153±14.5%, P<0.05).

Conclusions: TLP could be a viable therapy for HS-induced AKI. TLP might attenuate AKI by modulating the inflammatory response and apoptosis via the V1a receptor. (FAPESP)

Funding: Government Support - Non-U.S.

Renal function, V1a receptor expression and inflammatory pathways

	Control	3LR	1LR+TLP	2LR+TLP
Creatinine clearance (ml/min)	1.22±0.12	0.53±0.17*	0.73±0.10	1.25±0.14
FENa (%)	0.2±0.06	1.7±0.54*	0.9±0.34**	0.76±0.30**
NGAL (μg/mg urinary creatinine)	0.48±0.15	221±152*	42±9.6**	49±16.5**
eNOS (% of control)	101±1.85	27.7±1.45*	100±7.6	96.2±4.7
V1a (% of control)	94±4.7	35±5.7*	136±10.7**	137±6.6**
TLR4 (% of control)	100±2.9	132±4.4*	95±2.9	94±4.5
NFκB (% of control)	98±1.7	162±6.0*	110±2.0**	117±3.2**

*P<0.05 vs. all other groups; **P<0.05 vs. control.

TH-PO012

S100A8/S100A9 Diminishes Acute Tubular Injury After Ischemia-Reperfusion

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Background: Urinary calprotectin (S100A8/S100A9) has recently been identified as a promising biomarker in acute kidney injury (AKI). It is a mediator of the innate immune system and acts as a danger associated molecular pattern protein (DAMP). It remains elusive, however, whether calprotectin plays a pathophysiological role in AKI. Recently, there was first evidence that it might participate in the control of macrophage-mediated renal repair following ischemia/reperfusion. The present work examines whether calprotectin modulates acute I/R injury by means of a S100A9 -/- mouse model.

Methods: Since S100A8 -/- mice are not viable, S100A9 -/- knockout mice were established on a C57BL/6 background. I/R injury was induced by 25 min of unilateral ligation of the renal artery in S100A9 -/- and wildtype (WT) mice. The extent of tubular injury was assessed by a histological score and neutrophil gelatinase associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) mRNA expression.

Results: Histological tubular injury was comparable between S100A9 -/- and WT controls at 24h, while transition to fibrosis was aggravated in S100a9-/- mice. After 24h KIM-1 mRNA concentrations were higher in S100A9 -/- than in WT mice. The increase in NGAL mRNA expression was highly significantly larger in S100 A9 -/- than in WT mice at 24h. The difference of both KIM-1 and NGAL expression between the two mice strains disappeared by day 7. Sham operated animals did neither show any tubular injury nor an increase in KIM-1 or NGAL expression.

Conclusions: S100A9 deficiency is associated with increased I/R injury. Acting as an alarm signal, calprotectin may initialize tubular protective mechanisms after the induction of I/R.

TH-PO013

Aryl Hydrocarbon Receptor Agonist FICZ Alleviated Rhabdomyolysis-Induced AKI by Regulating Inflammation and Apoptosis

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Background: Aryl hydrocarbon receptors (AhR) are ubiquitous in the cytoplasm of various cells in various organs. They can bind to multiple ligands and affect different downstream pathways. Previous studies have found that activating AhR could alleviate inflammation and apoptosis through the NFκB pathway in ulcerative colitis, psoriasis and metabolic diseases induced by high-fat diet. However, whether AhR agonist FICZ can alleviate acute kidney injury (AKI) remains unclear. Thus, we explored the role of FICZ in AKI and its related mechanisms through rhabdomyolysis-induced AKI model.

Methods: C57BL/6 mice were randomly divided into three groups: control, glycerol and glycerol+FICZ. The glycerol group were injected group were injected with glycerol at bilateral back limbs. The glycerol+FICZ group was administered intraperitoneally for 3 days before the glycerol injection. The mice were sacrificed at 24h after the glycerol injection, blood and organs were collected. Renal histological injury was measured by PAS staining. Renal tissues of mice were analyzed by immunohistochemical, immunofluorescence, western blot and qPCR assay.

Results: Immunofluorescence staining and western blot showed that AhR was mainly expressed in proximal renal tubular epithelial cells, and the expression of AhR was decreased in rhabdomyolysis-induced AKI. Activation of AhR by FICZ pretreatment significantly reduced serum creatinine (Scr), urea and creatine kinase (CK) levels, as well as attenuated renal tubular damage in glycerol-injured kidneys. AhR activation also resulted in reduced TUNEL-positive tubular cells, suppressed cleaved caspase-3, BAX levels, and preserved Bcl-2, Bcl-XL expression, indicating that FICZ regulated tubular cell apoptosis. Moreover, the expressions of p-P65, p-iκBα and inflammatory factors IL-6, IL-1β and TNFα in the glycerol+FICZ group were significantly reduced, comparing with the glycerol group. The transcription levels of those inflammatory factors, MCP1 and IFNγ genes were detected by qPCR. These data suggested that FICZ showed renoprotective effects also by regulating inflammation via the NFκB pathway.

Conclusions: In summary, our findings demonstrated that AhR agonist FICZ protects against rhabdomyolysis-induced AKI via the regulation of inflammation and apoptosis in tubular epithelial cells.

TH-PO014

Effect of Bortezomib on Proximal Tubule Cells Exposed to Free Light Chains Isolated from the Urine of Multiple Myeloma Patients

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Background: Bortezomib (BTZ, also known as Velcade® and PS-341) is the first 20S proteasome inhibitor used as a drug for Multiple myeloma (MM) patients. Although, BTZ has markedly improved the treatment outcomes of MM patients; several adverse events, including acute kidney injury (AKI) can occur due to off-target effects of BTZ. Kidney proximal tubule cells (PTCs) are a primary target of a vast array of nephrotoxic compounds but direct effects of BTZ on PTC have not been explored in the presence of free light chains (FLCs) derived from the urine of MM patients.

Methods: Human kidney PTCs cultures (RPTECs and HK2 cell lines) were exposed to BTZ, κ, or λ FLCs. Cell supernatant and pellets were used for ELISA and gene expression studies. Cell proliferation, viability, cytotoxicity and apoptosis were evaluated using standard procedures. Immunofluorescence and Western blotting were used to localize NFkβ translocation in subcellular fractions. Mitochondrial membrane potential was measured using TMRE (tetramethylrhodamine, ethyl ester) assay. Data were analyzed using one-way ANOVA with post hoc Tukey test and P values <0.05 were considered significant.

Results: BTZ (50nM) alters cell morphology, significantly decreases proliferation and induces apoptosis in HK2 cells irrespective to FLCs exposure. Toxic effect of BTZ was also apparent from substantial overexpression of LCN2, a known kidney injury marker, and TLR9 upregulation. Additionally, NFkβ phosphorylation was evident in BTZ treated cells, which was further supported by the increased IKKα/β expression and decreased expression of IKβα. BTZ induced LCN2 and NFkβ showed possible immunomodulatory effects in PTCs. Our results indicate probable ROS-mediated mitochondrial injury and activation of TLR9 and LCN2, which may be unique pathway leading to injury in PTCs.

Conclusions: These results show a novel off-target, and potentially toxic action of BTZ in human PTCs.

Funding: Private Foundation Support

TH-PO015

Alpha-1 Acid Glycoprotein Ameliorates Hemolysis-Induced Renal Oxidative Stress Via Accelerating Plasma Free Hemoglobin Clearance Through CD163 Induction

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Background: In hemolysis-induced kidney disease such as paroxysmal nocturnal hemoglobinuria, increased free hemoglobin (Hb) contributes to the renal vascular endothelium injury and renal oxidative stress which play a role in the progression of AKI and CKD. In hemolytic condition, CD163, hemoglobin scavenger receptor, expressed on monocytes and macrophages takes up plasma free Hb or Hb-haptoglobin (Hp) complex. We previously found that the an acute-phase protein, alpha-1 acid glycoprotein (AGP) increased the expression of CD163 in macrophages (Komori et al. J Biol Chem 2012). The purpose of this study is to investigate the effect of exogenously administered AGP on plasma free Hb level and renal oxidative stress in hemolysis-model mice.

Methods: Hemolysis model mice were generated by intraperitoneally administered phenylhydrazine (PH). AGP was intraperitoneally administered at 24 hr and 48 hr before PH administration. The mice were sacrificed at 24 hr after PH administration.

Results: Administration of AGP to PH mice reduced plasma free Hb level and renal oxidative stress (malondialdehyde). In the same experimental condition, we found that AGP treatment increased CD163 expression in kidney and liver. In healthy mice, administration of AGP also increased the expression of CD163 in kidney and liver, but it did not affect the plasma Hp level. These data suggested that the effect of AGP on free Hb clearance could be due to the induction of CD163. In *vitro* experiments using human monocyte-derived macrophages (dTHP-1 cells), AGP treatment increased the expression of CD163 and also increased the intracellular uptake of Hb-Hp complex.

Conclusions: AGP ameliorates hemolysis-induced renal oxidative stress *via* accelerating plasma free hemoglobin clearance through CD163 induction.

TH-PO016

Treprostinil Inhibits Apoptosis During Rat Renal Ischemia-Reperfusion Injury

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Background: Kidney transplantation (KTx) is the optimal treatment for end-stage renal diseases. Ischemia-reperfusion (I/R) injury, an unavoidable process during KTx, is a major cause of delayed graft function, carrying a high mortality rate if patients are not re-transplanted immediately. No pharmacological treatment for I/R injury is available. Treprostinil (Remodulin®), an FDA-approved prostacyclin analog, has potent vasodilatory and anti-platelet aggregatory effects. We recently demonstrated the efficacy of treprostinil in reducing acute kidney injury during bilateral rat renal ischemia. The objective of this study is to determine the inhibitory role of treprostinil on renal apoptosis during rat renal I/R injury.

Methods: Male Sprague Dawley rats were randomly divided into four groups: control, sham, I/R-placebo and I/R-treprostinil groups and subjected to 45 minutes of bilateral renal ischemia followed by reperfusion for 1-168 hours. Placebo or treprostinil (100 ng/kg/min) was administered subcutaneously via an osmic mini-pump. Blood and kidney tissue were collected for analysis.

Results: Treprostinil significantly reduced elevated SCr vs. placebo (0.93 ± 0.17 mg/dl vs. 0.41 ± 0.04 mg/dl, p<0.001) and BUN (150.87 ± 20.38 md/dl vs. 74.06 ± 6.41 mg/dl, p<0.001) at 24 hr post-I/R injury. Treprostinil also reduced renal mRNA expression of kidney injury markers *Kim-1* (5.4-fold, p<0.001) and *Ngal* (8.9-fold, p<0.001) at 48 hr post-I/R injury. Histopathological analysis showed that treprostinil reduced proximal tubular necrosis by 24 hours post-reperfusion. Treprostinil reduced lipid peroxidation byproduct malondialdehyde (7.30 ± 1.43 to 3.84 ± 0.48 μM/mg protein, p<0.05) and renal pro-inflammatory cytokines *Ccl2*, *Il-6* and *Il-1*β by 2.0- (p<0.05), 2.1- (p<0.01) and 3.3-fold (p<0.001), respectively at 6 hrs post-I/R injury. Additionally, treprostinil reduced protein expression of pro-apoptotic Bax, cleaved caspase-3, and -9 by 1.4- (p<0.05), 1.8- (p<0.05), and 1.3-fold (p<0.05), respectively, at 24 hr after I/R injury.

Conclusions: Our results demonstrate that treprostinil improves renal function and inhibits renal inflammation and apoptosis after renal I/R injury. These results suggest a potential therapeutic application of treprostinil in protecting the kidney against I/R injury during KTx.

Funding: Other NIH Support - Advance-Clinical and Translational Research, Brown University

TH-PO017

Tet2 Contributes to Repression of Cisplatin-Induced AKI by Regulating Metabolic Pathway and Inflammation Response

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Background: Ten eleven translocation (Tet) methylcytosine dioxygenase family members is known to catalyze 5-methylcytosine to 5-hydroxymethylcytosineas. Previous studies have demonstrated that Tet2 was involved in various pathological process, including leukemia, atherosclerotic cardiovascular diseases and inflammation. However, the role of Tet2 in AKI remains largely unknown.

Methods: We established AKI animal model by Intraperitoneal injecting 22mg/kg cisplatin into male C57BL/6 mice. To explore the role of Tet2 in cisplatin-induced AKI, we generated Tet2 systemic knockout mice by using the cre-loxp system. Serum creatinine and BUN were measured in $Tet2^{-/-}$ mice at 48h and 72h after cisplatin injection to indicate the renal functional changes. 2mg/kg mouse Tet2 catalytic domain expression vector or Tet2 mutant catalytic domain vector or empty vector was administered intravenously for 3 days before cisplatin treatment by hydrodynamic based gene transfer technique to investigate the role of Tet2 in cisplatin-induced AKI. To broaden the role of Tet2 in repressing renal injury caused by cisplatin, we analysed dynamic expression patterns of different genes in renal RNA sequencing (RNA-seq) data of healthy and cisplatin-injected mouse.

Results: We found that Tet2 is highly expressed in healthy kidney and decreased in cisplatin-induced AKI. Exacerbation of cisplatin-induced AKI in Tet2 knock-out mice, and also administration of the Tet2 plasmid could protect Tet2 deficient mice from cisplatin-induced nephrotoxicity. Additionally, renal sequencing results showed that in cisplatin-induced AKI, Tet2 deletion was associated with down-regulation of metabolic-related genes such as the PPAR pathway and increased expression of inflammatory cytokines.

Conclusions: Tet2 may play a role in cisplatin-induced AKI by modulating metabolic and inflammatory responses.

TH-PO018

The Role of Cysteine Cathepsins in Lipopolysaccharide-Induced Preconditioning in the Mouse Kidney

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Background: Cysteine cathepsins along with legumain are associated with diverse biological processes, e.g. antigen processing and presentation. Several studies investigated the potential role of cysteine cathepsins in preconditioning in the brain and heart. The aim of our study was to examine their probable involvement in LPS-induced preconditioning in the kidney.

Methods: Kidney samples were collected from male NMRI mice injected with LPS at 40 mg/kg i.p. and sacrificed at 1.5 and 6 hours (early preconditioning, EP) or at 10 mg/kg i.p. and sacrificed at 24 and 48 hours (late preconditioning, LP). Control animals received an equal volume of saline. Renal function was assessed by plasma urea levels and NGAL mRNA expression. The inflammatory response to LPS was evaluated by TNF-α and IL-6 mRNA expression levels. Cathepsin B, H, Z (Cat B, H, Z) and legumain protein levels were measured by HPLC-MS/MS and Western blot (WB), mRNA expression was quantified using real-time PCR and legumain activity was evaluated using an enzyme assay.

Results: LPS administration induced acute kidney injury and provoked a strong inflammatory response. Only the Cat B mRNA was elevated in EP but no alteration in any Cat protein or legumain expression was detected. Cat B and Z mRNA expression peaked

at 24 hours and begun to decrease at 48 hours compared to the saline group. In align with these observations Cat B and Z protein levels were elevated at both time points. Legumain mRNA expression gradually increased after LPS administration and was markedly elevated at 6 hours in EP and 24 and 48 hours in LP. A significant increase in legumain protein levels was detected by MS at 48 hours and validated by WB. Legumain activity showed a marked increase at 48 h in comparison to the saline group.

Conclusions: The current results suggest that cysteine cathepsins and legumain may play a role only in the late phase of LPS-induced preconditioning.

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TH-PO019

Modeling of Tacrolimus Nephrotoxicity Using Kidney Organoids Derived from Human iPS Cells

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Background: Tacrolimus, a calcineurin inhibitor, was clinically used as an immunosuppressive agent in organ transplantation or glomerulonephritis. Despite the therapeutic benefits, tacrolimus's use is limited due to its nephrotoxicity. To reduce tacrolimus nephrotoxicity, the effective experimental models are essential. Recently, we and others have established protocols for the generation of kidney organoids from human pluripotent stem cells, containing nephron-like structures with podocytes, proximal tubules, and distal tubules. Here, we recapitulated tacrolimus nephrotoxicity using kidney organoids and investigated its pathogenic mechanism.

Methods: Kidney organoid differentiated from the CMC11 iPSC cell line (human male donor). Kidney organoids were re-seeded in 96-well plates and tacrolimus was treated at doses of 0 μM, 30 μM, 60 μM, or 120 μM for 24 h.

Results: The size of kidney organoids decreased at dose-dependent manner. Cell viability assessed by CCK-8 assay and live/dead cell staining decreased at dose-dependent manner. Proximal tubular cells as well as distal tubular cells were decreased according to the concentration of tacrolimus. Podocyte loss and injured podocytes with unplolarized and diffuse pattern of ZO-1 tracks were observed after treatment of tacrolimus. Ultrastructural analyses showed the vacuoles throughout the cytoplasm of tubule-like structures, which were similar to those of human tacrolimus nephrotoxicity. Autophagic activity was enhanced after treatment with tacrolimus in kidney organoids, which were similar patterns in mouse model of tacrolimus nephrotoxicity. Rapamycin, as an autophagy inducer, attenuated cell death in kidney organoids model of tacrolimus nephrotoxicity, whereas 3-methyladenine, as an autophagy inhibitor, accelerated cellular toxicity.

Conclusions: Our data suggest that human iPSC-derived kidney organoids can recapitulate tacrolimus nephrotoxicity and serve the effective in vitro model to investigate its pathogenic pathway.

TH-PO020

Spatiotemporal ATP Dynamics In Podocytes During Ischemic Reperfusion Injury Predicts Later Foot Process Effacement

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Background: Mitochondrial dysfunction, genetic or postnatal, is closely related to podocyte injury, suggesting the possibility that hypoxia or oxidative stress during ischemic AKI causes podocyte injury. Indeed, some studies report proteinuria after kidney transplantation, however, little is investigated regarding pathophysiological changes of podocytes during AKI. Here we investigated the dynamics of adenosine 5' triphosphate (ATP) in podocytes during ischemic AKI, because ATP is essential for stabilization of foot process.

Methods: To enable spatiotemporal ATP imaging, we utilized ATeam mice, which expressed the FRET-based ATP biosensor systemically, and monitored ATP changes of podocytes during IRI by multi-photon microscopy. Furthermore, we performed microstructural analysis of podocytes two weeks after IRI, and assessed the correlation between the ATP recovery in acute phase and morphological change in chronic phase.

Results: While the ATP levels of podocytes gradually decreased to the plateau level in twenty minutes after ischemia induction, they recovered rapidly in less than five minutes after reperfusion. The % ATP recoveries after 15, 30, 37, 45 and 60 minute-ischemia were 95%, 93%, 87%, 84% and 80% respectively, and were dependent on the length of ischemia. Electron microscopy two weeks after IRI revealed significant foot process effacement and mitochondrial fragmentation in mice subjected to severer IRI. Foot process widths were 367, 361, 381, 450 and 480 nm, and mitochondrial circularities, an indicator of mitochondria fragmentation, were 0.80, 0.80, 0.83, 0.86 and 0.88 after 15, 30, 37, 45 and 60 minute-ischemia, respectively. Mitochondrial circularities were strongly correlated with foot process widths, supporting the importance of energy metabolism in the maintenance of foot processes. Notably, the % ATP recoveries in acute phase were well correlated with the foot process widths and mitochondrial circularities in chronic phase.

Conclusions: We, for the first time, succeeded in visualizing ATP dynamics of podocytes during IRI. Our results show the close link between podocyte energy metabolism and ultrastructural changes during and after AKI, and provide the basis for understanding the mechanism of proteinuria after AKI or kidney transplantation.

TH-PO021

A Novel Kidney Slice Culture System Visualizing Intrarenal ATP and Segment-Dependent Energy Metabolism

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Background: The kidney constantly utilizes adenosine 5' triphosphate (ATP), and ATP depletion plays a crucial role in the progression of kidney diseases. Recently, we generated a mouse line, which expresses the FRET-based biosensor systemically, and reported spatiotemporal ATP dynamics in the kidney during AKI model using two-photon microscope. In our previous observation from the kidney surface, however, deeper nephron segments such as S3 segment of proximal tubules (PTs), glomeruli, and thick ascending limbs of Henle (TALs) cannot be observed. Additionally, we cannot analyze ATP dynamics in the presence of the reagents with systemic effects *in vivo*.

Methods: We established ATP imaging system using the kidney slice culture of ATP visualizing mice and evaluated ATP dynamics in the presence of pharmacological inhibitors of oxidative phosphorylation (OXPHOS) and glycolysis. We also evaluated ATP dynamics after cisplatin administration in this system.

Results: While the ATP levels of PTs, TALs and DTs rapidly and significantly decreased by the administration of 4mM NaN3, an OXPHOS inhibitor, those of podocytes were well maintained as long as 60 min after the administration. On the other hand, the administration of 0.2mM phloretin, a glucose transporters inhibitor, decreased ATP levels in podocytes, but not apparently in PTs, TALs, and DTs. When the kidney slice was incubated in the buffer containing 1mM cisplatin, the ATP levels of PTs and DTs decreased after 60 min, while those of podocytes and principle cells showed no apparent changes even after 120 min. Interestingly, mitochondrial cristae deformation were observed by electron microscopy in the slice incubated with cisplatin for 120min.

Conclusions: Utilizing this novel slice culture system, we, for the first time, directly demonstrated the segment-specific changes in ATP metabolism. While PTs, TALs and DTs are more or less dependent on OXPHOS for ATP production, suggesting their possible vulnerability to ischemia, podocytes rely more on glycolysis for ATP production than on OXPHOS. In addition, we succeeded in demonstrating the different sensitivity to cisplatin among nephron segments. This method could be useful for the elucidation of the metabolic changes in the pathophysiological conditions and for screening of renal toxic drugs.

TH-PO022

Pannexin 1 Channels Regulate Mitochondrial Function, Autophagy, and Cell Survival During Kidney Ischemia-Reperfusion Injury in Mice

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Background: Pannexin 1 (Panx1) channels are membrane associated non-selective channels that are activated by mechanical/physiological stimuli during injury and serve as a conduit for release of small molecules, including ATP. We have previously shown that pharmacological inhibition or genetic deletion of Panx1 in mice is protective against renal ischemia reperfusion injury (IRI), and Panx1 deficiency in murine proximal tubule-derived (TKPTS) cells results in reduced extracellular ATP and concomitant increase in intracellular ATP (PMID: 29866797). While the effects of extracellular ATP released from cells via Panx1 during injury have been extensively studied, the physiological role of Panx1 in cellular homeostasis is unknown.

Methods: Mice were subjected to IRI (26 mins of ischemia and 24 hrs of reperfusion) to assess plasma creatinine and kidney ATP levels. Control and *Panx1* deficient TKPTS cells were subjected to hypoxia reperfusion (HR). Mitochondrial biogenesis and autophagy were assessed using real-time PCR and western blotting. Mitochondrial membrane potential was assessed by flow cytometry. Mitochondrial respiration was assessed using an Agilent Seahorse® assay. Cyclic AMP levels were measured using cAMP biosensor. For ATP depletion studies, cells were pretreated with 100 nM oligomycin prior to HR.

Results: *Panx1*$^{-/-}$ mice have higher kidney ATP levels 24 hours after IRI than control mice. *Panx1*$^{-/-}$mice have higher levels of p62 in kidneys. *In vitro* findings show that *Panx1* deficient cells retain more intracellular ATP after HR and have better survivability. *Panx1* deficient cells have reduced mRNA expression of *Pgc1a* and *Tfam*, increased intensity of Mitotracker Red CMXRos® staining, and reduced cAMP-dependent signaling.

Conclusions: Our findings demonstrate that *Panx1* deficiency leads to increased intracellular ATP, reduced cAMP signaling, reduced autophagy, increased mitochondrial function, and better cell survival during hypoxia. We conclude that deficiency of Panx1 leads to improved mitochondrial health and increased tubule cell survival during hypoxia resulting in protection during IRI. The development of selective pharmacological inhibitors of Panx1 could provide a novel approach to the treatment of acute kidney injury by maintaining mitochondrial health during stress and injury.

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TH-PO023

Effects of Tubular Mitochondrial Pyruvate Carrier 1 Deletion on Redox Metabolism

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Background: Kidney injury results in mitochondrial dysfunction, oxidative stress, change to tubular glycolytic metabolism, and disruption of lactate and pyruvate metabolism. Pyruvate treatment is protective in different kidney injury models. The Mitochondrial Pyruvate Carrier 1 (MPC1) transports pyruvate from the cytosol into the mitochondrial matrix and mediates the metabolic decision committing glycolytic carbon to mitochondrial oxidative phosphorylation. Understanding the implication of impaired tubular mitochondrial pyruvate transport may provide critical knowledge on the effect of mitochondrial metabolic adaptations in redox balance and injury response.

Methods: $Pax8^{Cre}$ was bred into the $Mpc1^{f/f}$ mouse line to generate $Pax8^{Cre+/-}Mpc1^{f/f}$ (Tu-MPC1-KO) and $Pax8^{Cre-/-}Mpc1^{f/f}$ (Tu-MPC1-WT) littermates to disrupt MPC1 in tubular epithelial cells. Mice 8-13 weeks of age were assessed for renal function and biomarkers of kidney injury. C^{13}-lactate/C^{13}-pyruvate tracing was employed to determine the metabolic consequences of TMPC1-KO. Finally, upon sacrifice markers of oxidative stress were studied and kidney tissue was examined histologically. A second cohort of Tu-MPC1-KO and –WT mice underwent cisplatin-induced kidney injury to evaluate survival.

Results: Tu-MPC1-KO resulted in accumulation of C^{13} labeled lactate/pyruvate and the concomitant decrease of C^{13} labeled TCA cycle intermediate metabolites. Significant reduction of C^{13} incorporation into glutamine suggests that mitochondrial oxidative metabolism may be sustained via glutaminolysis. Tu-MPC1-KO mice show no difference in renal histology or renal function compared to TMPC1-WT. Tu-MPC1-KO kidney tissue had a significant increase in oxidative stress markers including 3-nitrotyrosine, % total glutathione as glutathione disulfide, and MnSOD activity. Finally, while Tu-MPC1-KO mice exhibited increased markers of oxidative stress prior to cisplatin treatment compared to WT, no significant difference in survival was observed.

Conclusions: *In vivo* inhibition of tubular mitochondrial pyruvate transport leads to disruption of renal redox metabolism and increased oxidative stress markers in renal tubule cells, which does not affect survival after cisplatin-induced CKD.

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TH-PO024

Treatment with Isolated Mitochondria 5 Days After Kidney Ischemia-Reperfusion Injury Reduces Progression to Interstitial Fibrosis and Tubular Atrophy

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Background: Ischemia induces altered bioenergetics with increased mitochondrial swelling, reactive oxygen species and ultimately degradation of cellular function. Therapeutic interventions that target to improve mitochondrial health to repair, reprogram or replace mitochondria to restore respiratory functions are beneficial for treatment of disease.

Methods: Renal injury was assessed by plasma creatinine (PCr; mg/dl). 8-wk old C57BL/6 mice were i.v. injected with healthy isolated mitochondria (2.5 mcg/g) 1, 3 or 5 days after unilateral IRI. Nephrectomy of contralateral control kidney was done 1 day prior to euthanizing mice. Change in fibrosis genes were measured and histological changes with Masson trichrome. For *in vitro* studies, TKPTS were treated with mitochondria (10-50 mcg/ml) 1 day prior to analysis that included measurement of ATP levels, mitochondrial functions (Seahorse), cytokines (RTPCR), and IF microscopy.

Results: *In vivo* studies demonstrated treatment of mice with 2.5 mcg/g of mitochondria at 1, 3 or 5 days after IRI significantly protected the IRI kidney compared to vehicle treated mice [PCr (0.60±0.04 (+1d) vs 0.54±0.18 (+3d) vs 0.46±0.18 (+5d) vs 1.24±0.2), $p<0.05$]. The mice treated with mitochondria 1d, 3d or 5d after IRI had significantly less MT labeling compared to vehicle treated mice. The injected mitochondria is found in kidney in proximal tubule cells (anti-CD13 labeled) and co-localizes with endogenous mitochondria. The mitochondria treated mice had significantly lower levels of fibrosis genes (Acta and Col3a1) and significantly higher PGC1α compared to vehicle treated mice. The mitochondria treated mice had significantly higher populations of Ki67 positive cells in both IRI and contralateral control kidneys compared to vehicle. Treatment of TKPTS cells with mitochondria have significantly higher levels of ATP, higher basal oxygen consumption rate and spare respiratory capacity. Similar to IRI studies, addition of mitochondria on TKPTS significant increases PGC1α gene expression, mtDNA/nDNA ratio, and induces proliferation.

Conclusions: Transfer of healthy mitochondria help maintain bioenergetics through upregulation of PGC1α and induced regeneration of PT cells to lessen progression to fibrosis after IRI. Treatment with healthy mitochondria could be used as a therapeutic modality to lessen progression to IFTA.

Funding: NIDDK Support, Private Foundation Support

TH-PO025

Mitochondrial Transplantation by Intra-Arterial Injection Prevents Renal Ischemia-Reperfusion Injury

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Background: Mitochondrial transplantation (MT) is a novel clinically validated strategy for the amelioration of organs subjected to ischemia-reperfusion injury (IRI). In this study we investigated the safety of autologous MT and the therapeutic use for renal protection in a swine model of bilateral IRI.

Methods: Yorkshire pigs (n=24; female, 40-50 kg) underwent selective catheterization of the renal arteries under fluoroscopy (Fig. 1 A). Mitochondria (1 x 10^9 in 10 ml buffer) were delivered as a single bolus (n=6) or serially (3 injections over 60 minutes, n=6) in each of the renal arteries of healthy animals. Another group of animals underwent bilateral temporary occlusion with balloon-catheters (60 minutes of ischemia) followed by 24 hours of reperfusion. Mitochondria (n=6) or Vehicle (n=6) were delivered as a single bolus in each of the renal arteries at the time of reperfusion. Uptake was confirmed by PET-CT images after intra-arterial injection of ^{18}F-Rhodamine-labeled mitochondria (Fig. 1 B).

Results: MT temporarily increased renal function in the healthy kidney. Intra-arterial injection of mitochondria had no side effects on hemodynamics, systemic inflammatory response and organ function. After 24 hours of reperfusion, MT significantly improved renal function in terms of renal output ($p=0.02$), serum creatinine ($p<0.01$), estimated glomerular filtration rate ($p=0.03$) and blood urea nitrogen ($p<0.01$) compared to vehicle treated animals (Fig. 1 C-D).

Conclusions: Mitochondrial transplantation by intra-arterial injection is safe and prevents renal IRI.

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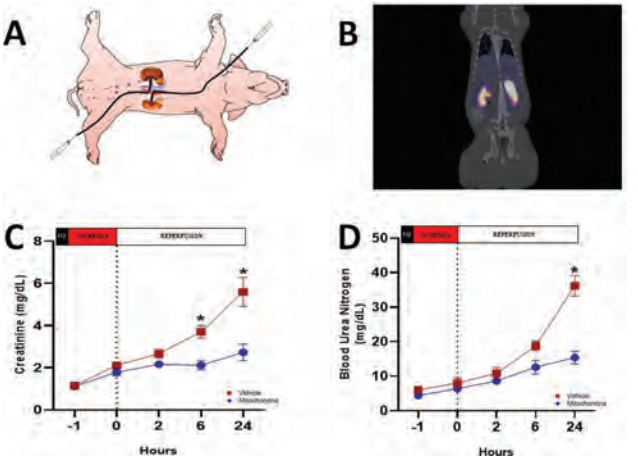

(A) Experimental Model. (B) Representative PET images 10 minutes post intra-arterial injection of ^{18}F-Rhodamine-labeled mitochondria. (C-D) Renal function during the entire experiment (C) Creatinine (mg/dL), (D) Blood Urea Nitrogen (mg/dL).

TH-PO026

Mitochondrial Damage Causes Inflammation via cGAS-STING Signaling in AKI

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Background: Acute kidney injury (AKI) is characterized by mitochondrial dysfunction and activation of the immune response. The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway detects cytosolic DNA and induces innate immunity. We investigated the role of mitochondrial damage and subsequent activation of the cGAS-STING pathway in cisplatin (cis)-induced AKI.

Methods: The human proximal tubular cell line, HK-2, treated with 20 μM of cis and the renal cortex of WT (C57BL/6) or STING KO mice injected with 25 mg/kg of cis for 48 or 72 hr were analyzed. The changes in cGAS-STING activation, mitochondrial damage, mitochondrial DNA (mtDNA) leakage or neutrophil infiltration were evaluated by flux analyzer, mitochondrial membrane potential analysis, real-time PCR, western blotting, or immunostaining. The culture supernatants of cis and/or STING siRNA-treated HK-2 were used for cytokine arrays and migration assays. Ethidium bromide (EtBr) and extracted mtDNA from HK-2 were used for mtDNA depletion and mtDNA transfection (to increase cytosolic mtDNA), respectively.

Results: In cis-treated HK-2 or kidney cortex of cis-induced AKI mice, cGAS and STING were upregulated and STING translocated from the ER to the Golgi apparatus,

indicating STING activation. Subsequently, the cGAS-STING axis was activated via cis-mediated phosphorylation of TBK-1 and P65, leading to induction of inflammatory cytokines (IL-6, IL-8, ICAM-1, CXCL10, and GM-CSF) and neutrophil chemotaxis. The inflammatory response by cis was ameliorated in STING-knockdowned HK-2 or STING KO mice. Cis impaired tubular mitochondrial function: reduction of mitochondrial respiration and mitochondrial fatty acid β-oxidation with subsequent decrease in ATP production. Moreover, cis permeabilized mitochondrial membrane. Following the mitochondrial dysfunction, cis-mediated mtDNA leakage to the cytosol was induced in tubular cells both in vivo and in vitro. mtDNA depletion inhibited the inflammation by cis in HK-2, whereas mtDNA transfection activated cGAS-STING axis, indicating that leaked cytosolic mtDNA acts as a ligand for the cGAS-STING pathway in cis-induced tubular inflammation.

Conclusions: Mitochondrial damage leads to mtDNA leakage, activating cGAS-STING signaling and subsequent inflammation in cis-induced AKI.

TH-PO027

Mitochondrial Dysfunction in an In Vitro and an In Vivo Model of Aristolochic Acid Nephropathy

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Background: Mitochondrial (mt) dynamics is a key player during AKI and CKD. Indeed, mt provide energy to cells thereby supporting many cellular processes. They are of high importance in kidneys, more specifically regarding proximal tubular epithelial cells (PTEC). Aristolochic Acid Nephropathy (AAN) is a rapidly progressive tubulointerstitial nephritis characterized by necrosis of PTEC. In these cells, mt play a major role since PTEC ensure reabsorption and secretion functions. Our study aimed to investigate the mt dysfunction during AAN using both C57Bl/6 male mice and HK-2 cells.

Methods: C57Bl/6 male mice were divided into CTL or AA groups. AA groups received four ip injections of AAI (3.5 mg/kgBW) from D1 to D4 and were sacrificed at D4, D5 and D10. The mt ultrastructure's were analyzed by TEM while kidney function and structure were assessed by BUN, plasma and urinary creatinine, GFR and histological analysis. For the *in vitro* part, confluent HK-2 cells (human PTEC) were exposed to AAI at 0, 1, 10 or 25 μM during 24h, 48h or 72h. FACS and confocal analysis were performed to analyze the mt abundance and network as well as the cellular granularity. Moreover, cellular ATP contents were quantified.

Results: During progression of AAN in mice, structural damages in mt, consisting in the loss of mt cristae and/or contents, were observed, attesting the loss of their integrity and morphology. These observations were concomitant with AAN progression and development of AKI, as shown by a significant increase in BUN and plasma creatinine as well as a significant decrease of GFR. Moreover, at day 10, mt were either absent or only observable as mt debris in necrotic cells where the population of mt exhibiting alterations was increased in remaining cells. During AA-intoxication in HK-2 cells, the fragmentation of mt network and an increase of cellular granularity were observed throughout the protocol while an increase of mt abundance was reported at three days of AA-intoxication, concomitant with a decrease of ATP contents.

Conclusions: We demonstrated the impairment of mt morphology and network during AA-intoxication in both models. Regarding the data, proteins involved in fusion and fission process must be investigated in order to identify molecular actors that may lead to mt dysfunction.

TH-PO028

TREM1/3 Deficiency Impairs Tissue Repair After AKI and Mitochondrial Metabolic Flexibility in Tubular Epithelial Cells

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Background: Long-term sequelae of acute kidney injury (AKI) are associated with incomplete recovery of renal function and the development of chronic kidney disease (CKD), which can be due to a maladaptive repair characterized by aberrant innate immune activation, mitochondrial pathology and accumulation of senescent tubular epithelial cells (TECs). TREM-1 is an innate immune receptor expressed by inflammatory and epithelial cells, both players in renal repair after ischemia/reperfusion (IR)-induced AKI. Despite this, the role of TREM-1 in renal repair has never been investigated.

Methods: WT and TREM1/3 KO mice were subjected to different models of renal IR (severe and mild). Animals were sacrificed 1, 5 and 10 day after surgery. Blood was collected to determine renal function parameters. Kidneys were harvested for hystological examination, RNA isolation and protein determination. For ex-vivo studies, primary TECs were isolated from WT and TREM1/3 KO animals and exposed to hypoxia/re-oxygenation experiments. Seahorse analysis, metabolomics, senescence and wound healing assays were used as readout for in vitro studies.

Results: TREM1/3 KO mice displayed no major differences during the acute phase of injury, but increased mortality was observed in the recovery phase. This detrimental effect was associated with maladaptive repair, characterized by persistent tubular damage, inflammation, fibrosis, TEC senescence and metabolic reprogramming. In vitro, we observed an altered mitochondrial homeostasis and cellular metabolism in TREM1/3 KO TECs. This was associated with G2/M arrest and increased ROS accumulation. Further exposure of cells to ROS-generating triggers drove the cells into a stress-induced senescent state, which was partly reverted by treatment with a mitochondria anti-oxidant.

Conclusions: In summary, we have unraveled a novel (metabolic) mechanism by which TREM1/3 deficiency drives senescence in TECs. This involves redox imbalance, mitochondrial dysfunction and a decline in cellular metabolic activities. These finding suggest a novel role for TREM-1 in maintaining tubular homeostasis through regulation of mitochondrial metabolic flexibility. Finally, this study demonstrates a novel link between immunometabolism and tubular epithelial senescence.

TH-PO029

Sulfotransferase 1C2 or Its Mitochondria Membrane Product, Cholesterol Sulfate, Increases Maximum Rates of Mitochondria Redox Reactions and Utilization of Tricarboxylic Acid Intermediates

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Background: In prior communications we have demonstrated that the SULT1C2 gene can induce a state of ischemia preconditioning in the kidney by increasing state II/III mitochondria respiration and membrane potential. In other studies, we have found sulfotransferase 1C2 increases state II/III mitochondria respiration when added to purified mitochondria. Thin layer chromatography studies demonstrated that sulfotransferase 1C2 converts mitochondria membrane cholesterol to cholesterol sulfate. Furthermore, adding cholesterol sulfate to purified mitochondria recapitulates the effect sulfotransferase 1C2 has on mitochondria function.

Methods: To assess the substrate specificity of carbon source utilization in S3 proximal tubule cells, we measure reduction rates of tetrazolian red in response to a supply of a single source of substrates. These studies were performed in permeabilized S3 cells with baseline measurements or following treatment with sulfotransferase 1C2 or cholesterol sulfate. OD_{560} was measured every 5 minutes for 12 hours at 37° C. The maximum rate of change in OD per minute was calculated from the colormetric assay.

Results: Both cholesterol sulfate or sulfotransferase 1C2 triple maximum reduction rates of tetrazolian red in response to the following substrates; cis-aconitic acid, α-keto-glutarate, succinate, fumarate, α-keto-butyrate, glutamate, glutamine, and pyruvate with 100 μM malic acid ($p \leq 0.001$ for all reactions) (See accompanying graph).

Conclusions: This data demonstrates that sulfotransferase 1C2 and its mitochondria product, cholesterol-SO4 increase substrate utilization rates of tricarboxylic acid intermediates in immortalized S3 proximal tubule cells. The results show that sulfotransferase 1C2 has a novel role in cellular control of mitochondria physiology.

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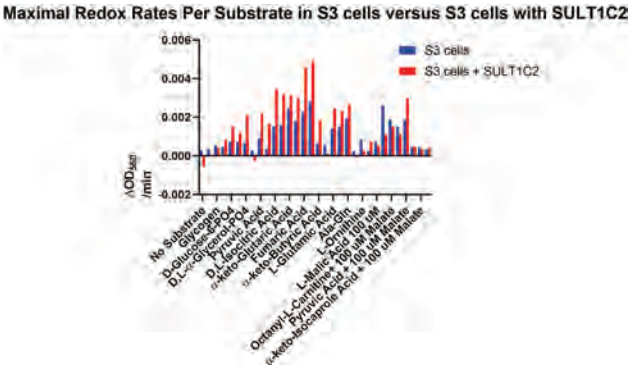

Substrate utilization rates in S3 cells ± sulfotransferase 1C2 treatment. Standard errors are on the order of 10E-6.

TH-PO030

Cyclophilin D Interacts with PPARα to Regulate Fatty Acid Oxidation in Cisplatin AKI

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Background: Regardless of the etiology, acute kidney injury (AKI) involves aspects of mitochondrial dysfunction and ATP depletion. Fatty acid oxidation (FAO) is the preferred energy source of the kidney and is inhibited during AKI. A pivotal role for the mitochondrial matrix protein, cyclophilin D (CypD) in regulating overall cell metabolism is being unraveled. We hypothesize that mitochondrial interaction of proximal tubule CypD and PPARα modulate FAO in cisplatin-induced AKI (cisplatin AKI).

Methods: Using genetic and pharmacological intervention and protein-protein interaction studies, we investigated whether proximal tubule CypD modulates FAO in cisplatin AKI through mitochondrial CypD-PPARα binding and its sequestration.

Results: Cisplatin injury resulted in histological and functional damage in the kidney with downregulation of FAO genes and increase of intrarenal lipid accumulation. However, proximal tubule (PT)-specific deletion of CypD protected cisplatin-induced renal damage by inhibiting impairment of FAO and intrarenal lipid accumulation. Immunoprecipitation and BioID methods demonstrated mitochondrial translocation of PPARα and its binding to CypD and sequestration. This led to inhibition of nuclear translocation of PPARα and transcription of PPARα-regulated FAO genes during cisplatin AKI. Genetic or pharmacological inhibition of CypD suppressed mitochondrial CypD-PPARα binding in cisplatin AKI, preventing the impairment of FAO and intracellular lipid accumulation.

Conclusions: These results uncover a novel mechanism by which mitochondrial interaction between CypD and PPARα impairs FAO in cisplatin AKI. Targeting their interaction may be a potential therapeutic strategy to prevent energy depletion and cell death in AKI.

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TH-PO031

The Role of Cyclophilin D in Acute vs. Chronic Aristolochic Acid Nephropathy

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Background: Cyclophilin D (CypD) facilitates mitochondrial-dependant cell death during pathological conditions. CypD-/- mice are protected from acute kidney injury (AKI) following ischaemia/reperfusion injury and show reduced renal fibrosis in the unilateral ureteric obstruction model. However, the contribution of CypD in aristolochic acid (AA) induced AKI or AA-induced chronic kidney disease (CKD) is unknown. We aim to determine the role of CypD in: 1) acute AA-induced nephropathy (AAN); and 2) chronic AAN.

Methods: Groups (n=10) of CypD-/- and wild type (WT) C57BL/6J mice were used. Study 1: Mice were given an intraperitoneal (IP) injection of 5mg/kg AA and killed 3 days later. Study 2: Mice were given IP injections of 2mg/kg AA every 2nd day and killed on day 28. Controls were untreated.

Results: Study 1: Acute high dose AA caused renal failure in WT mice (39.7±7.1mmol/L vs 13.5±2.3mmol/L serum creatinine (SCr) in controls; P<0.0001) with evidence of tubular damage and cell death on PAS sections and increased cleaved caspase-3+ cells. Acute AAN also caused inflammation with infiltrating neutrophils and T cells and up-regulation of IL-36a mRNA levels. CypD-/- mice were protected from AA-induced acute renal dysfunction (18.9±9.5 mmol/L SCr; P<0.0001 vs WT AAN). CypD-/- mice showed reduced tubular damage and cell death on PAS and reduced cleaved caspase-3+ cells (both P<0.001 vs WT AAN), as well as reduced neutrophil infiltration and IL-36α mRNA levels (both P<0.001 vs WT AAN). Study 2: Chronic AA administration caused renal impairment in WT mice (34.3±9.9mmol/L SCr), with evidence of chronic tubular damage (KIM-1 & a-Klotho mRNA levels), increase in tubular cell death (cleaved caspase-3+ cells), and significant renal fibrosis (increased collagen IV deposition). However, CypD-/- mice were not protected from chronic AA-induced renal dysfunction (37.0±14.3 mmol/L SCr; P=NS) and showed no reduction in tubular damage, cell death or renal fibrosis.

Conclusions: CypD contributes to tubular cell death and renal inflammation in acute AAN. However, CypD does not contribute to the transition of AKI to CKD in chronic AAN.

TH-PO032

Succinate Dehydrogenase Plays a Critical Role in Hypoxia/Reoxygenation-Induced Apoptosis in Renal Proximal Tubular Cells

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Background: Acute kidney injury (AKI) has become a worldwide public health problem because high risk of death and progression to chronic kidney disease. Renal ischemia-reperfusion (IR) injury is one of major causes of AKI. Many pathological factors and mechanisms are involved in I/R injury. Among them, overproduced reactive oxygen species (ROS) plays an important role in mitochondrial dysfunction and endoplasmic reticulum stress(ERS) which finally lead to the cell apoptosis. Succinate dehydrogenase (SDH) is an intermediate both of the mitochondrial citric acid cycle and electron cycle transport. Recent studies demonstrate that ischemia-related succinate accumulation followed by increased SDH activity after reperfusion as key drivers of ROS formation in heart and brain IR injury. But it is still unclear and controversial in kidney IR injury. We hypothesized that accumulated succinate during hypoxia and increase SDH activity during reoxygenation contribute to a large burst of ROS. Increased ROS levels induced mitochondrial damage and ERS which finally lead to cell apoptosis.

Methods: For hypoxia/reoxygenation, renal proximal tubular cells (RPTC) were cultured in hypoxic conditions for 4 hours followed by normoxic conditions for 2 hours. Succinate abundance, SDH activity were assessed by kits and mitochondrial ROS was assessed by confocal. Mitochondrial function and dynamics were assessed by measuring mitochondrial membrane potential(DY_m), ATP content, Mfn2/Drp1 expression and mitochondrial morphometry. ERS were assessed through IRE1a-XBP1, PERK-eIF2α and ATF6 pathways. Cell apoptosis were determined by TUNEL assay and Caspase-3 activity.

Results: Succinate accumulated during hypoxia and SDH activity increased after reoxygenation. ROS production significantly increased in response to H/R and induced downstream of mitochondrial dysfunction(DY_m and ATP content decreased) and mitochondrial fission(Mfn2 and mitochondrial morphometry decreased while Drp1 increased). ERS were also activated by ROS. Apoptosis ratio increased in response to H/R. Malonate can attenuates H/R-induced renal tubular epithelial cells injury through inhibiting SDH activity.

Conclusions: Inhibition of SDH activity can attenuate hypoxia/reoxygenation induced ROS overproduction, mitochondrial dysfunction, ERS and apoptosis in RPTC. Our findings provide a new perspective in treating renal ischemia-reperfusion injury.

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TH-PO033

GSK3β Regulates Toxic Nucleophosmin (NPM)-T^{95} Phosphorylation During Ischemic AKI

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Background: GSK3β promotes regulated renal cell death partly by phosphorylating and activating Bax. Here, we document that GSK3β also phosphorylates and activates NPM, a key Bax chaperone, during ischemic renal injury *in vitro* and AKI *in vivo*. We hypothesize that: (1) antagonizing NPM phosphorylation is effective for ameliorating acute renal cell injury that contributes to organ failure during AKI and (2) phosphorylated NPM detects acute renal cell injury.

Methods: To determine the extent to which GSK3β mediates ischemia-induced NPM phosphorylation, constitutively active or inactive GSK3β mutant proteins were expressed in primary murine and human proximal tubule cells (PTEC). GSK3β was also subjected to pharmacologic inhibition by TDZD-8 or CRISPRi-mediated knockdown. GSK3β activity was estimated from steady state p-NPM-T^{95} content and correlated with intracellular NPM localization and cell survival.

Results: Transfection of primary PTEC with constitutively active, inactive or wild type GSK3β resulted in an expected increase in total GSK3β content compared with empty vector. In contrast, CRISPRi caused an 80% reduction in GSK3β expression. TDZD-8 decreased GSK3β kinase activity without affecting its content. Only active GSK3β promoted NPM T^{95} phosphorylation, NPM translocation from the nucleus to the cytosol and positively correlated with cell death during ischemia. Both TDZD-8 and CRISPRi–mediated GSK3β knockdown significantly reduced NPM T^{95} phosphorylation and cell death induced by constitutively active GSK3β. Furthermore, T^{95} NPM is detectable in both urine and cortical kidney homogenates harvested from humans and mice within hours after acute renal ischemia.

Conclusions: GSK3β promotes ischemia-induced renal cell death by phosphorylating an activating NPM, an essential partner for Bax during regulated cell death. Thus, manipulation of NPM phosphorylation is likely to be an effective therapeutic maneuver for ameliorating AKI and phosphorylated NPM is a novel marker of acute renal cell injury.

Funding: NIDDK Support

TH-PO034

SIRT5 Alleviates Ischemia-Induced Mitochondrial Dysfunction in Human Proximal Tubular Epithelial Cells

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Background: Acute kidney injury (AKI) is a major global health concern with a high mortality and poorly effective therapies. The most common cause of AKI is renal hypoperfusion, leading to ischemia/reperfusion injury (IRI). Mitochondria are highly dynamic organelles required for energy production that undergo constant fission and fusion to meet metabolic requirements. Accumulating evidence has identified excessive mitochondrial fragmentation causing mitochondrial dysfunction as a central pathologic feature of IRI. Recently, the mitochondrial NAD^+-dependent lysine-desuccinylase/demalonylase sirtuin 5 (SIRT5) has emerged as a key regulator of mitochondrial form and function, but its role in renal IRI is unknown.

Methods: Male C57Bl/6J mice underwent renal IRI or sham-surgery. Kidneys were screened for SIRT5 by immunohistochemistry. Human proximal tubular (PT) cells (HKC-8) were exposed to oxygen/nutrient-deprivation (OND; 1%O_2+HBSS), an *in vitro* model developed to mimic renal ischemia *in vivo*, and analysed by qPCR and Western blot (WB). A SIRT5 RNA interference (RNAi) strategy combined with OND was applied, followed by assessment of mitochondrial form and function using confocal/ transmission electron microscopy, ATP assay, Seahorse, FACS and WB.

Results: SIRT5 expression was increased in murine PTs after renal IRI and in HKC-8 cells exposed to OND. Knockdown of SIRT5 impaired glycolytic and mitochondrial ATP generation, reduced mitochondrial membrane potential and induced mitochondrial fragmentation. WB analysis of proteins involved in mitochondrial dynamics revealed that SIRT5 depletion disrupted the fission/fusion equilibrium by increasing pro-fission proteins (DRP1, DRP1-S616) and decreasing pro-fusion proteins (MFN1/2, OPA1), and that this effect was exacerbated by OND. Finally, combining the OND model with SIRT5 RNAi showed that SIRT5 reduced mitochondrial swelling and increased respiration (OXPHOS) to improve mitochondrial function in PT cells exposed to ischemia.

Conclusions: Our findings suggest SIRT5 is a central component of the endogenous stress response that alleviates ischemia-induced mitochondrial dysfunction in PTs and, therefore, may be a promising therapeutic target in AKI.

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TH-PO035

Effect of Calorie Restriction on Cisplatin-Induced Nephrotoxicity

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Background: Calorie restriction is associated with the resistance of mitochondria against stresses. Although cisplatin is a widely used and very effective anticancer drug, its nephrotoxicity limits its use. Cisplatin nephrotoxicity is associated with its mitochondrial accumulation following oxidative stress induction, so here, we investigated whether the control of food supply affects cisplatin nephrotoxicity.

Methods: C57BL6 male mice were subjected to a high-fat diet (HFD) supply, fasting, and refeeding after fasting. Afterwards, mice were administered with either cisplatin or 0.9% saline. Mitochondrial morphology and dynamics were evaluated by transmission electron microscope and mitochondrial fission and fusion regulating protein expression. ROS production and mitochondrial antioxidant enzymes were biochemically analyzed.

Results: Cisplatin increased blood urea nitrogen (BUN) concentration in mice. These increases were significantly greater in the HFD-feeding mice when compared with mice given a normal diet. In contrast, fasting and refeeding significantly reduced cisplatin-induced increase of BUN. Cisplatin increased mitochondrial reactive oxygen species (ROS) level, oxidative stress, and mitochondrial fragmentation in the kidney tubular cells. These increases were greatest in HFD feeding mice and least in fasting mice. After cisplatin injection, expression of Opa1, a mitochondria fusion protein, was most greatly decreased in HFD feeding mice and least in fasting mice. In contrast, expression of fis1, a mitochondria fission protein was highest in HFD feeding mice and lowest in fasting mice. In addition, the expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), a transcription coactivator for mitochondrial biogenesis, were most greatly decreased in the HFD feeding mouse kidneys.

Conclusions: These results indicate that fasting reduced cisplatin nephrotoxicity, whereas HFD feeding aggravated cisplatin nephrotoxicity, suggesting that the regulation of calorie restriction may be useful for the reduction of cisplatin nephrotoxicity.

TH-PO036

Sirt3 Modulates Fatty Acid Oxidation and Attenuates Cisplatin-Induced AKI in Mice

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Background: Acute kidney injury (AKI) induced by cisplatin is very common in the clinic. Fatty acid oxidative damage is an important mechanism of renal fibrosis. Sirt3 has been shown to alleviate AKI by improving mitochondrial function and was found to be involved in the regulation of fatty acid oxidation (FAO) in other disease models. However, it is not clear whether Sirt3 is involved in regulating FAO to improve the prognosis of AKI.

Methods: Male SV129 and Sirt3 knockout (KO) mice were administered a single intraperitoneal (i.p.) injection of cisplatin (20 mg/kg) with or without treatment with honokiol (5mg/kg/day). Additionally, cultured mouse renal tubule epithelial cells (mRTECs) were treated with cisplatin (5μmol/L). Then, FAO and renal injury were evaluated.

Results: Oil red O staining and free fatty acids(FFA) analysis of kidney tissues from WT cisplatin-treated mice showed fatty acid oxidative damage and extensive lipid deposition in the mice. Metabolomics analysis revealed decreased ATP production and the presence of disordered energy metabolism. Additionally, fatty acid accumulation induced the apoptosis of mRTECs. The expression of Sirt3 was decreased in mice with cisplatin-induced AKI compared to that in control mice. Sirt3 deletion aggravated FAO dysfunction, resulting in the increased apoptosis of kidney tissues and aggravated renal injury. The activation of Sirt3 by honokiol improved FAO and renal function and reduced fatty acid deposition. In vivo and in vitro experiments confirmed that Sirt3 regulates fatty acid oxidation by deacetylating LKB1 and activating AMPK. In addition, Sirt3 increased ATP production and reduced ROS and lipid peroxidation by improving mitochondrial function.

Conclusions: These findings indicated that activated Sirt3 could protect against cisplatin-induced acute kidney injury, possibly by improving FAO and mitochondrial function, and that improving FAO in AKI may be a potential therapeutic strategy in the future.

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TH-PO037

Sirtuin 3 Suppresses Ferroptosis in Cisplatin-Induced AKI

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Background: Sirtuin 3 (SIRT3) is a mitochondrial deacetylase that protects against acute kidney injury (AKI) by mitigating renal oxidative stress. Ferroptosis, a recently characterized form of regulated cell death triggered by massive lipid peroxidation, is known to play a critical role in the pathogenesis of AKI. However, the role of SIRT3 in regulating ferroptosis in cisplatin-induced AKI (Cis-AKI) is unclear. Therefore, we aim to determine whether SIRT3 protects kidney function by restraining ferroptosis in Cis-AKI.

Methods: Male 129 wild type (WT) and SIRT3 knockout (KO) mice received cisplatin by a single intraperitoneal injection with or without Fer-1 (a ferroptosis inhibitor) and honokiol (a SIRT3 activator). AKI was determined by serum creatinine (Scr), blood urea nitrogen (BUN), and tubular damage on PAS staining 72h after cisplatin injection. Ferroptosis was assessed by multiple indicators, including the extent of lipid peroxidation (4-hydroxynonenal (4-HNE), malondialdehyde (MDA), and glutathione/oxidized glutathione (GSH/GSSG) ratio), and the level of glutathione peroxidase 4 (GPX4) and xCT. The expression of SIRT3 was detected by qPCR, western blot and immunohistochemistry. In addition, the status of p53 acetylation was evaluated by immunoprecipitation.

Results: Both WT and SIRT3 KO mice developed AKI after cisplatin injection. In response to cisplatin treatment, sirt3 expression levels were markedly decreased. In AKI groups, kidney function (Scr and BUN) and tubular damage extent on PAS staining were more severe when SIRT3 was missing. Ferroptosis indicators, including the increased levels of 4-HNE and MDA, the reduced ratio of GSH/GSSG, and the decreased expression of GPX4 and xCT, were also had more significant changes in SIRT3 KO mice than in the WT mice after cisplatin treatment. In contrast, honokiol protects against Cis-AKI as demonstrated by improved renal dysfunction, attenuated renal pathological changes, and decreased ferroptosis. In addition, Fer-1 exhibited protection against AKI in WT mice, but not in SIRT3 KO mice. Mechanistic studies demonstrated that cisplatin treatment induced p53 acetylation, and the acetylation of p53 in SIRT3 KO mice was more pronounced than in WT mice.

Conclusions: These data indicate that ferroptosis might be modulated by SIRT3 through p53 acetylation and suggest that ferroptosis is an important death mechanism in Cis-AKI.

Funding: Government Support - Non-U.S.

TH-PO038

Impact of Mechanical Ventilation Time on Ferroptosis in Renal Ischemia-Reperfusion Injury in Rats

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Background: Prolonged mechanical ventilation was considered as a risk factor for acute kidney injury(AKI) in previous studies, while the underlying mechanisms remain unclear. Ferroptosis is a recently discovered form of programmed cell death that is characterized by iron-dependent accumulation of reactive oxygen species. The present study aimed to investigate the impact of mechanical ventilation (MV) time on ferroptosis in renal ischemia/reperfusion injury (IRI) in rats.

Methods: 32 Male-adult SD rats were divided into 4 groups: Group 1 (Sham operation); Group 2 (IRI: subjected to 45-min bilateral renal ischemia); Group 3 (IRI and underwent MV 4hours); Group 4 (IRI and underwent prolonged MV (12hours)). At 12hours after IRI, animals were euthanized. Kidney function was evaluated by Scr. Morphological changes associated with kidney injury and ferroptosis were assessed by HE staining and electron microscopy. Central regulator of ferroptosis GPX4, GSH, the lipid peroxidation markers 4HNE and SOD2 were measured in kidney tissue by Western blot analysis. The level of inflammatory cytokine (TNF-α) was assessed in plasma by ELISA.

Results: Scr was significantly higher in Group 4 than in Groups 1, 2 ($P<0.01$). Scr also increased in Group 3 than Groups 1,2, but with no statistical significance ($P>0.05$). By HE staining, Group 4 showed the most severe morphological kidney damage, characterized by increased interstitial edema and tubular dilatation than Group 1,2,3. Plasma TNF-α increased with the prolonged MV time, and Group 4 showed the highest level, achieving statistical significance when compared to Group 1 ($P<0.05$). In kidney tissue, protein expressions of GPX4, GSH and SOD2 progressively decreased from Groups 1 to 4, and Group 4 showed the lowest level, achieving statistical significance(GPX4 and GSH, $P<0.05$; SOD2, $P<0.01$). Protein expressions of 4HNE progressively increased from groups 1 to 4, and Group 4 showed the highest level, achieving statistical significance($P<0.05$). Electron microscopy also revealed abnormal mitochondrial morphology of ferroptosis in Group 4, which is characterized by the presence of smaller mitochondria and reuced/absent cristae.

Conclusions: Our present data showing that prolonged MV time may worsen kidney injury by ferroptosis, which is linked to the GPX4-GSH system, following lipid peroxidation. It may be mediated by stimulated inflammation.

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TH-PO039

Myeloid Ferritin Heavy Chain Protects Against Ferroptosis in Ischemic AKI

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Background: Ferritin is classically involved in iron storage and metabolism and is made up of 24 subunits of two distinct types: light chain (FtL) and heavy chain (FtH). The latter confers ferroxidase activity, allowing for storage of iron in a safe, bioavailable form in the ferritin shell. Iron metabolism is in part regulated by myeloid cells. Furthermore, acute kidney injury (AKI) causes perturbations in iron metabolism, both highlighting the importance of studying the importance of FtH in preventing oxidative damage during AKI.

Methods: Previously characterized mice deficient in myeloid-FtH ($FtH^{LysM-/-}$) and their floxed controls ($FtH^{fl/fl}$) were subjected to bilateral renal ischemia-reperfusion injury (IR; 20 minutes). We measured renal function, inflammatory response, cell death, and cell proliferation on days 1 and 2 post-IR.

Results: Though $FtH^{LysM-/-}$ and $FtH^{fl/fl}$ mice both experienced a similar rise in serum creatinine levels ($FtH^{fl/fl}$1.6 ± 0.11 mg/dL; $FtH^{LysM-/-}$ 1.3 ± 0.12 mg/dL) and structural damage on day 1 following IR, renal function and damage in myeloid-FtH deficient

mice continued to worsen (2.4 ± 0.38 mg/dL), which subsequently results in mortality. Interestingly, $FtH^{LysM-/-}$ mice also had lesser polymorphonuclear (PMN), natural killer, B, and T cell density post-IR compared to floxed controls, as well as significantly exacerbated cell death ($p<0.0001$) as early as 1-day post-IR. Myeloid-FtH deficiency also was associated with reduced cell proliferation after IR. Due do perturbations observed in iron metabolism in $FtH^{LysM-/-}$ mice, we hypothesized that treatment with ferrostatin-1 (Fer-1), a potent ferroptosis inhibitor, would ameliorate injury in the absence of myeloid FtH. Here, we report significant protection from AKI by serum creatinine in $FtH^{LysM-/-}$ mice treated with Fer-1 (0.97± 0.29 mg/dL), compared to vehicle controls (2.05 ± 0.36 mg/dL).

Conclusions: Our findings demonstrate for the first time a crucial role for myeloid FtH in protecting against ferroptosis in renal IR. This study highlights the significance of controlling iron metabolism during injury for AKI resolution and prevention of disease.

Funding: NIDDK Support

TH-PO040

Identification of Anti-Ferroptosis Drugs Functioning as Lipid Peroxyl Radical Scavengers and Its Protective Effect Against AKI

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Background: Ferroptosis, a lipid oxidation-dependent cell death mediated by free radical reactions, is a therapeutic target because of its role in organ damages including acute kidney injury (AKI). Ferroptosis-causing radicals that are targeted by ferroptosis suppressors have not been unequivocally identified. Because certain cytochrome P450 (CYP) substrate drugs can prevent lipid peroxidation via obscure mechanisms, we evaluated their anti-ferroptotic potential and used them to identify ferroptosis-causing radicals.

Methods: We screened of CYP substrate compounds by a cell-based assay to identify drugs with anti-ferroptotic activity, and investigated the mechanism. Radical scavenging activity was evaluated using ESR-spin trapping methods and NBD-Pen, a lipid radical probe that we established. We evaluated the therapeutic potency of the drugs in mouse cisplatin-induced AKI models.

Results: We identified clinically-available various drugs and hormones with anti-ferroptotic properties including rifampicin, promethazine, omeprazole, indole-3-carbinol, carvedilol, propranolol, estradiol, and thyroid hormones. The anti-ferroptotic effects of the drugs were closely associated with the scavenging activity of lipid peroxyl radicals and not much related to interactions with other radicals. The elevated lipid peroxyl radical levels were associated with ferroptosis onset, and known ferroptosis suppressors such as ferrostatin-1 were also lipid peroxyl radical scavengers. The drugs showed anti-ferroptotic effect in various types of cells including tubular cell, podocyte, and renal fibroblast. Moreover, the drugs suppressed tissue lipid peroxidation and ameliorated cisplatin-induced renal injury.

Conclusions: The elevated lipid peroxyl radical would be a trigger for onset of ferroptosis, whereas lipid peroxyl radical scavenging drugs can control ferroptosis-related disorders including AKI.

TH-PO041

Asparaginyl Endopeptidase Deficiency Protects Against AKI via Inhibition of Tubular Ferroptosis

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Background: Lysosomal endopeptidase AEP (Asparaginyl Endopeptidase) is required for the maintenance of normal kidney physiology and homeostasis; AEP knockout aggravates interstitial fibrosis in the mouse model of obstructive nephropathy. However, role and underlying mechanism of AEP in the acute kidney injury (AKI) is unclear.

Methods: AKI was induced by bilateral ischemia–reperfusion of renal arteries or folic acid treatment in $AEP^{+/+}$ and $AEP^{-/-}$ mice. We assessed the indexes of renal tubular injury, inflammatory infiltration and programmed cell death. Tubular injury markers Kim-1 and NAGL was measured as well. *In vivo*, ferroptosis was evaluated via assessment of MDA, 4-HNE and degradation of GPX4. *In vitro*, we compared hypoxia- or erastin- induced ferroptosis in the primary tubular cells isolated from $AEP^{+/+}$ and $AEP^{-/-}$ mice. Supplement of FAC and downregulation of GPX4 were used to evaluate the role of AEP in hypoxia- or erastin- induced ferroptosis. Further, we analyzed the lysosomal degradation of GPX4. Coimmunoprecipitation was used to determine the interaction between AEP and GPX4. For tentative treatment, a synthetic AEP inhibitor RR-11a delivered by AEP-targeted nanoparticles was used in the IRI model.

Results: AEP deficiency attenuated IRI-induced tubular injury, inflammation and programmed cell death compared with control. Ferroptosis, a regulated necrosis characterized with lethal lipid peroxidation was also inhibited in $AEP^{-/-}$ mice, manifested as decreased 4-HNE, MDA and degradation of GPX4. *In vitro*, ferroptosis induced either by hypoxia or by erastin was dampened in the primary $AEP^{-/-}$ tubular cells compared with $AEP^{+/+}$control. Supplement of FAC or downregulation of GPX4 rescued ferroptosis in $AEP^{-/-}$ *cells*. IP assay and immunofluorescence staining showed interaction between AEP and GPX4. Moreover, knockout of AEP prevented lysosomal degradation of GPX4. Administration of RR-11a-containing nanoparticles ameliorated renal injury induced by IRI.

Conclusions: Our data suggest that interaction of AEP and GPX4 contributes to the lysosomal degradation of GPX4, facilitating the process of ferroptosis. Therefore, Deficiency of AEP inhibits ferroptosis and attenuates IRI-induced AKI. Inhibition of AEP could be a potential strategy benefit for the treatment of AKI.

TH-PO042

Pretreatment with Roxadustat (FG-4592) Attenuates Folic Acid-Induced Kidney Injury by Decreasing Ferroptosis

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Background: Folic acid (FA)-induced kidney injury model is characterized by progressive tubular damage at early stage and interstitial fibrosis at later stage. Ferroptosis, has been thought to be one of the main causes for the acute kidney injury (AKI) by the iron-dependent accumulation of lipid peroxidation, therefore disrupting antioxidant defense system. FG-4592 is hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor (HIF-PHI) often used for improving anemia in patients with chronic kidney disease (CKD) through activating HIF-1a. What is more, precondition HIF-1a can enhance antioxidant capacity and iron mobilization through Nuclear erythroid 2 related factor 2 (Nrf2) signaling. Nrf2 is a key transcriptional factor which regulates almost all genes that are associated with ferroptosis. Given its anti-oxidant roles, FG-4592 was introduced in this study as a preconditionor to see if it had effects on FA-induced AKI and the mechanism.

Methods: Mice were divided into 4 groups, control group(n=12);FG-4592 group(n=12) pretreatment with FG-4592 for 2 days, mice were sacrificed 2 days (n=6 per group) or14 days later(n=6 per group); FA(folic acid-induced kidney injury) group(n=12); FA + FG-4592 group(n=12). In FA and FA+FG-4592 groups, mice were sacrificed 2 days (n=6 per group) or14 days(n=6 per group) after folic acid injection. Renal function, renal morphology, MDA, 4-HNE, GSH, Fe, HIF-1a, Nrf2, GPX4, HO-1, SLC7A11, ferroportion, IL-1β,TNF-α,F4/80, Fn, colIV,vimentin were assessed.

Results: pretreatment with FG-4592 improved kidney injury and inflammation in FA-induced kidney at early stage by upregulating antioxidant enzyme (GPX4 and HO-1) and GSH, meanwhile downregulating lipid peroxidation (MDA and 4-HNE) and iron. Furthermore, FG-4592 activated Nrf2 and upregulated antioxidant enzyme (GPX4 and HO-1), SLC7A11 (responsible for GSH synthesisthe) and ferroportin (an iron export protein), resulting in a reduction of ferroptosis. Further studies showed that Nrf2 was up-regulated by increased AKT and GSK-3βphosphorylation. Finally, pretreatment with FG-4592 ameliorated kidney fibrosis at later stage after FA-induced kidney injury.

Conclusions: pretreatment with FG-4592 plays an important role in the prevention of the transition from AKI to CKD through Nrf2-mediated anti-ferroptosis, and pretreatment with FG-4592 prevents FA-induced kidney injury partially via the AKT/GSK-3β-mediated Nrf2 activation.

TH-PO043

Effects of Paricalcitol on Ferroptosis in Cisplatin-Induced AKI

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Background: Ferroptosis is a newly defined form of non-apoptotic cell death characterized by the accumulation of iron-dependent membrane lipid peroxides. At present, ferroptosis is widely studied in rhabdomyolysis and ischemia/reperfusion-induced acute kidney injury (AKI), but the research on nephrotoxic AKI such as cisplatin is not deep enough. In this study, we explore whether ferroptosis occurs in cisplatin-induced AKI and the effect of paricalcitol on ferroptosis.

Methods: Twenty-five C57BL / 6 mice were randomly divided into control group, cisplatin + vehicle of Ferrostatin-1 (DMSO) group, cisplatin + Ferrostatin-1 (Fer-1) group, cisplatin + vehicle of paricalcitol (propylene glycol) group, cisplatin + paricalcitol group, 5 mice in each group. All drugs were injected intraperitoneally, and all mice were sacrificed 48 hours after cisplatin injection to collect serum and kidney tissue. The levels of serum creatinine and blood urea nitrogen were detected. The morphological changes of renal tubules were observed by HE staining. Cell death was observed and assessed by TUNEL fluorescence staining. The mitochondrial morphology was observed under electron microscope. Western blot was used to detect the expression level of glutathione peroxidase 4 (GPX4) in tissues, and the expression of 4-hydroxynonenal (4HNE) in renal cortex was observed by immunohistochemistry.

Results: Compared with the normal control group, the levels of serum creatinine and blood urea nitrogen were significantly increased in the cisplatin + DMSO group and cisplatin + propylene glycol group. At the same time, tubular damage and cell death were observed in the mouse tissues, the mitochondria volume was smaller and mitochondrial mites decrease or disappear, GPX4 expression decreases, and 4HNE expression increases in these two groups. Compared with the respective vehicle groups, the levels of serum creatinine and blood urea nitrogen were significantly lower in the cisplatin + Fer-1 group and the cisplatin + paricalcitol group, while renal tubular injury, cell death and mitochondrial morphological changes were significant relief, GPX4 expression was increased, and 4HNE expression was decreased.

Conclusions: Ferroptosis is involved in cisplatin-induced AKI. Paricalcitol inhibits ferroptosis by GPX4 to attenuate cisplatin-induced AKI.

Funding: Government Support - Non-U.S.

TH-PO044

Insights into the Pathophysiological Role of Gasdermin D: Assessment of Murine AKI and Human Biopsies

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Background: Regulated cell death (RCD) has been used synonymously to apoptosis for years; however, within the last decade it was discovered that necrotic cell death can be regulated as well. Some forms of RCD, namely necroptosis and ferroptosis, have been found to be critically involved in the pathogenesis of acute kidney injury (AKI) in vivo. Pyroptosis is another form of regulated necrosis, which depends on cleavage of Gasdermin D by inflammatory caspases, such as CASP-1 and CASP11. After cleavage, Gasdermin D N-terminal domains assemble and form pores in the cell membrane. As pyroptosis is highly immunogenic, we aimed to evaluate whether pyroptosis is involved in the pathogenesis of AKI.

Methods: We evaluated GSDMD-deficient mice in two commonly-used models of AKI: Ischemia-Reperfusion-injury (IRI) and Cisplatin-induced AKI. Additionally, we generated mice deficient for both necroptosis and pyroptosis (GSDMD-MLKL-dko mice) to test them in the same models. Furthermore, we stained human kidney biopsy samples immunohistochemically for cleaved GSDMD.

Results: We found GSDMD-deficient mice to be sensitive when AKI was induced by the chemotherapeutic agent cisplatin as assessed by serum markers of AKI (creatinin and urea) and histological damage 24h and 48h after cisplatin injection. In renal ischemia-reperfusion injury (IRI), and in contrast to the protective effects of necroptosis-deficiency or pharmacological ferroptosis inhibition, GSDMD-deficient mice were not protected in this model, but rather demonstrated slightly deteriorated functional values. Also, we evaluated our freshly-generated GSDMD-MLKL-dko mice in the above-mentioned models. The results have not been entirely read out by the time of abstract submission. Finally, we detected cleaved GSDMD in human biopsy samples; thus, demonstrating involvement of pyroptosis in human AKI for the first time.

Conclusions: In conclusion, the role played by Gasdermin D in AKI is unexpected: whereas inhibition of other forms of regualted necrosis is known to be beneficial, inhibition of pyroptosis increased kidney damage. This raises questions regarding the complex interplay between different forms of regulated necrosis in AKI.

Funding: Government Support - Non-U.S.

TH-PO045

Sodium Channel Alpha Subunit Deletion in the Endothelium Reduces Renal Ischemia-Reperfusion Injury

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Background: The epithelial sodium channel (ENaC) has a well described role in epithelia, however its role in endothelial cells remains to be further characterized. It has been suggested that endothelial ENaC modulates endothelial cell stiffness and this in turns regulates nitric oxide (NO) synthesis through the endothelial nitric oxide synthase (eNOS). The physiological relevance of endothelial ENaC in pathological conditions where reduced NO bioavailability plays an essential role remains largely unexplored. Renal ischemia/reperfusion (IR) injury is characterized by vasoconstriction, sustained decrease in renal perfusion and reduced oxygen supply causing tubular and endothelial cell injury. The decline of kidney blood flow is partly explained by a reduction in NO bioavailability. ENaC regulation of eNOS activity might have an influence in ischemic AKI. We aimed to explore if endothelial ENaC deficiency has an impact on the severity of renal injury induced by IR.

Methods: Male mice with specific alpha ENaC subunit gene inactivation in the endothelium (endo-αENaC^{KO}, n=26) and control littermates (n=26) were subjected to bilateral renal ischemia of 22 min or sham surgery. Kidney tissue hypoxia was evaluated at 3 hours by pimonidazole staining in 5 mice of each group. After 24 hours of reperfusion, kidney function and tubular injury was evaluated. Human endothelial cells (HMEC-1) in culture were used to study eNOS activation state under ENaC inhibition with amiloride 1mM for 24 hours, as compared to control cells.

Results: In control littermates, renal ischemia induced an increase in plasma creatinine (2-fold) and urea (1.7-fold), augmented Kim-1(100-fold) and NGAL (40-fold) mRNA levels and produced severe tubular injury as quantified by the tubular injury score. The absence of endothelial alpha ENaC subunit ameliorated renal tubular injury ($p<0.05$) and renal dysfunction ($p<0.001$). Moreover, endo-αENaC^{KO} mice recovered faster from renal hypoxia after the ischemia episode as compared to littermates as shown by reduced pimonidazole staining. In HMEC-1 cells, pharmacological ENaC inhibition promoted eNOS coupling and activation.

Conclusions: Our data suggest an important role for endothelial αENaC in renal IR, through improving eNOS activation and kidney perfusion.

Funding: Government Support - Non-U.S.

TH-PO046

Inhibition of the VE-PTP Phosphatase Protects the Kidney from Ischemia-Reperfusion Injury

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Background: The endothelial angiopoietin (ANG)–Tie2 signaling pathway is required for vascular development and homeostasis. Dysregulation of ang-Tie2 pathway has been implicated in diseases including venous malformation, glaucoma, diabetic nephropathy, and acute kidney injury (AKI). The endothelial-specific phosphatase VE-PTP/PTPRB is a crucial negative regulator of Tie2 phosphorylation status. We have previously shown that inhibition of VE-PTP is a promising therapeutic target for diabetic kidney injury in mice, but its role in acute kidney injury has not been studied. Here we hypothesize that inhibition of VE-PTP will protect the kidney from AKI due to ischemia-reperfusion injury (IR-AKI).

Methods: A bitransgenic doxycycline-inducible system (Veptp$^{flox/flox}$, Rosa26-rtTA$^{+/+}$, tetO-Cre$^{Tg/+}$) was used to knockout the VE-PTP gene from the vasculature of mice at postnatal day 0 (VE-PTPiKO). 3 month-old male VE-PTPiKO and littermate control mice underwent bilateral renal ischemia reperfusion injury (IRI) or sham surgery. Serum creatinine was measured on day1, day3 and day7 after surgery by HPLC method. Data were analyzed using two-way ANOVA. Kidney and lung tissues were harvested on day 7 for histology (H&E, PAS), immunohistochemistry and RNA/protein analysis.

Results: Genetic deletion of VE-PTP robustly enhanced Tie2 phosphorylation in vasculature of lung tissue and kidney tissue *in vivo*. Western blot analysis showed VE-PTP protein levels were increased in kidneys post-IRI and following hypoxia-inducible factor stabilization. While serum Creatinine was elevated 1day post-IRI in control mice, this increase did not occur in VE-PTP iKO mice ($p=0.0055$). A corresponding increase in fibrogenic factor and FOXO1 target gene CTGF was observed in control mice compared to VE-PTPiKO mice.

Conclusions: In sum, our data identify VE-PTP as a promising therapeutic target for renal protection following IR-AKI.

Funding: NIDDK Support, Private Foundation Support

TH-PO047

Hypoxic Renal Tubular Epithelial Cell-Derived Exosomes Promoted Peritubular Endothelial Cell Proliferation via Transfer of Vascular Endothelial Growth Factor A in Ischemic Kidney Injury

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Background: Acute kidney injury (AKI) is characterized by substantial injury of renal tubular epithelial cells (TECs) and peritubular capillaries(PTCs) rarefaction. Our previous studies revealed that increasing number of exosomes were secreted by hypoxic TECs during AKI. However, the effect of TECs exosomes on the injury and repair of the closely located PTCs remains unknown.

Methods: Ischemia-reperfusion (I/R) injury mice was established and sacrificed at Day 1, 3, 7. Tie2-GFP mice were treated with exosomes purified from hypoxia TECs labled with DII fluorescent via the renal parenchymainjection to track exosomes internalized by PTCs. *In vitro*, exosomes released by HK-2 were applied to HUVEC or a transwell co-culture system was conducted. Exosome secretion was inhibited by knockdown of Rab27a *in vivo* through lentiviral shRNA administration in I/R mice.

Results: Histologically, tubulointerstitial inflamation and microvascular rarefaction were observed in I/R treated kidneys at Day 3, 7. Tubular injury marker KIM-1, and kidney VCAM-1, ICAM-1 mRNA was induced significantly compared to sham mice. Increasing proliferation of TECs and PTCs were observed by PCNA staining. TEM and NTA showed typical morphology and size of exosome structures purified from TECs. WB showed the expression of exosome markers, Alix and CD63. I*n vivo*, DII labeled TECs exosomes were readily detected in glomerular and PTCs in Tie2-GFR mice. Besides, Knockdown of Rab27a reduced PTCs proliferation and aggravated PTC rarefaction after ischemic injury. *In vitro*, uptake of exosomes from hypoxia-treated TECs markedly enhance endothelial cell proliferation. Interestingly, VEGFA was significantly up-regulated in both cellular and exosomes fractions of TECs under hypoxic conditions. Exosomes from HK-2 cells with VEGFA siRNA attenuated cell proliferation induced by exosomes in HUVECs. Transwell co-culture study showed that exosomes travel through membrane and were internalized by HUVEC. Importantly, flow cytometry showed that internalization of exosomes significantly decreased when VEGFR was knock down in Endothelial cells.

Conclusions: Increasing release of exosomes from hypoxia TECs promoted PTCs proliferation via transfer of VEGFA, which may represent a novel protective response through which to ameliorate PTC rarefaction in AKI.

TH-PO048

A Powerful Anti-Angiogenic Activity in Extracellular Vesicles Isolated from Kidney Endothelial Cells

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Background: Acute kidney injury and chronic kidney disease are associated with capillary rarefaction, which promotes hypoxia and hastens renal fibrosis. The lack of renal vascular repair following injury is not clearly understood. We hypothesized that kidney

endothelial cells have intrinsic signaling properties that impair growth and angiogenesis, thereby contributing to poor vascular repair.

Methods: Rat or mouse primary kidney endothelial cells (rKEC or mKEC) were isolated using Dynabeads conjugated to CD45 (negative selection) and CD31 (positive selection) antibodies. Cells were grown in EGM2 (Lonza) on collagen-coated plastic to evaluate growth rates (MTT) or placed on Matrigel to quantify branching capacity.

Results: Previous studies demonstrated that rKEC grew slower than rat pulmonary EC (rPEC). rKEC consistently grew slower (<5% increase in cell number between day 1-4) than EC from brain, spleen or aorta (~60-100%, $p<0.01$ vs KEC). rKEC could not form branching structures on matrigel, but integrated into networks formed by rPEC when plated at a 1:100 ratio (KEC to PEC). Increasing ratios of rKEC:rPEC lead to a decline in branch formation with no rPEC branches at a ratio of 50:50. Co-culture of rKEC also inhibited branching of rat brain and aortic EC and human cord blood derived endothelial colony forming cells (ECFC), while EC from other tissues did not convey similar inhibitory activity. Increasing rKEC proliferation with hTERT overexpression did not attenuate rKEC's ability to disrupt branch formation of ECFC. We hypothesized that KEC secrete an anti-angiogenic factor which may impair cell growth. Conditioned media (CM) isolated from rKEC reduced growth of the highly proliferative human ECFC by ~ 40% ($p<0.001$). Similarly, CM isolated from primary mouse KEC decreased ECFC growth by ~50% ($p<0.001$). CM isolated from mouse heart or lung EC did not contain inhibitory activity. Specifically, only the extracellular vesicle (EV) fraction isolated from mKEC inhibited growth (40% decrease, $p<0.001$), while the EV depleted supernatant had no effect on ECFC proliferation.

Conclusions: Kidney endothelial cells possess an anti-angiogenic activity that is not observed in EC from other tissues. EV secreted from KEC may contain anti-angiogenic cargo that slow EC growth in vitro. Such activity may underlie impaired renal vascular repair following injury.

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TH-PO049

PAC-Mediated AKI Protection Is Critically Mediated but Does Not Exclusively Depend on Cell-Derived Microvesicles

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Background: Acute Kidney Injury (AKI) significantly worsens the prognosis of hospitalized patients. In recent years, cell-based strategies have been established as reliable option for improving AKI outcomes in experimental AKI. Own studies focused on so-called Proangiogenic Cells (PACs). Mechanisms that contribute to PAC-mediated AKI protection include production / secretion of extracellular vesicles (EV). In addition, the cells most likely act by paracrinic processes (secretome). The current study evaluated whether AKI may be preventable by the administration of either PAC-derived EV and / or the secretome alone.

Methods: AKI was induced in male C57/Bl6N mice (8-12 weeks) by bilateral renal ischemia (IRI - 40 minutes). Syngeneic murine PACs were stimulated with either melatonine, Angiopoietin-1 or -2, or with Bone Morphogenetic Protein-5 (BMP-5) for one hour, respectively. The four mediators were chosen since previous own studies showed improved PAC-mediated AKI protection after cell preconditioning with these substances. PAC-derived EV and the vesicle-depleted supernatant were subsequently collected and i.v. injected post-ischemia. Mice were analyzed 48 hours later.

Results: IRI induced significant kidney excretory dysfunction as reflected by higher serum cystatin C levels. The only measure that improved AKI was the injection of EV, collected from native PACs. The following conditions worsened post-ischemic renal function even further: EV+Ang-1, EV+BMP-5, EV+melatonin, and EV+secretome+Ang-1.

Conclusions: Together, our data show that PAC-mediated AKI protection substantially depends on the availability of cell-derived EV. The secretome, either collected from native or preconditioned cells does not prevent mice from ischemia-induced dysfunction. However, since previous data showed improved AKI-protection by PACs after cell preconditioning with certain mediators (Ang-1 and -2, melatonine, BMP-5), other than exclusively vesicle-dependent mechanisms must be involved in PAC-mediated AKI protection. We suggest, that the mere presence of intact cells in the post-ischemic tissue is necessary for improving functional and structural outcome parameters under certain conditions.

TH-PO050

Microparticles Released in Response to Oxidative Stress from the Renal Epithelium Carry Active Neprilysin

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Background: Acute kidney injury (AKI) is associated with significant morbidity, including remote organ dysfunction. In response to stress, cells release phenotypically and quantitatively distinct microparticles (MP). MP are microvesicles (1000 nm) derived from several cell types and released in response to stress or injury. Neprilysin (CD10), is a membrane-bound zinc activated endopeptidase, richly expressed in the renal proximal tubular epithelial cell (RPTEC) brush border. Neprilysin catalyzes the degradation of endogenous vasodilator/natriuretic peptides suggesting that its physiological action modulates the hemodynamic balance. Whether MP containing neprilysin released by renal epithelium can be mediators of biological activity is not known.

Methods: Human RPTEC immortalized cell line was used. Cells were exposed to 0.03 molar H_2O_2 for 1 hour and compared to controls in 3 or more different sets of experiments. We evaluated the levels of neprilysin using an ELISA assay and enzymatic activity with a fluorometric assay. Human samples (citrated plasma) were tested for the presence of biologically activity (Neprilysin levels and peptidase assay) derived from prospectively collected samples in AKI cases and controls.

Results: We have shown that neprilysin is present in RPTEC using immunofluorescence. We also reported that under conditions of oxidative stress the level of released MP is significantly different when compared to controls. To evaluate if the released MP are biologically active, we assessed the protease activity characteristic of neprilysin. The results showed that the maximal activity of neprilysin was in healthy cells and was 5-fold lower after treatment with oxidative stress. We then evaluated the protease activity in MP released from RPTEC under the same conditions. Our results showed that the peptidase activity was present and the activity correlated directly with the protein concentration. In a pilot of 30 cases and controls of AKI, we were able to measure the levels of plasma neprilysin using the ELISA assay as well as the confirm the peptidase activity in the MP derived from human samples.

Conclusions: The release of Neprilysin in microparticles derived from renal tubular epithelial cells are functionally active, and could serve as a biological link between epithelium and micro-vasculature

Funding: Clinical Revenue Support

TH-PO051

Long-Term Outcome of Biopsy-Proven Cholesterol Crystal Embolism

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Background: Cholesterol crystal embolism (CCE) causes renal damage, and there is an extremely high risk of end-stage renal disease. However, the time course of CCE-related renal deterioration varies and little is known about the subsequent risk of dialysis among patients with biopsy-proven CCE.

Methods: We performed a retrospective cohort study of 38 Japanese patients in whom a histological diagnosis of CCE was made from September 1992 to July 2005. Competing risk regression analysis was used to investigate the association between declining renal function (≥ 1.5-fold elevation of serum creatinine within 26 weeks after CCE) or its subtypes (acute [<1 week after CCE], subacute [1 to <6 weeks], and chronic [6 to <26 weeks]) and the risk of dialysis, with adjustment for age, baseline serum creatinine, and the precipitating event.

Results: During a median follow-up period of 25.9 weeks, 14 patients (35.9%) started dialysis. Multivariable analysis showed that patients with declining renal function had a higher risk of commencing dialysis than those without declining function (subdistribution hazard ratio [SHR]: 9.47; 95% confidence interval [CI]: 1.34-66.8). Patients with different renal presentations had a similarly increased risk of commencing dialysis, with the risk being significantly higher for the subacute and chronic patterns of declining renal function (adjusted SHR [95% CI] for acute, subacute, and chronic declining renal function[vs. no decline]: 7.36 [0.85-63.6], 11.9 [1.36-101], and 10.7 [1.49-77.0], respectively).

Conclusions: Declining renal function after CCE, even later than 6 weeks, was significantly associated with the subsequent risk of dialysis.

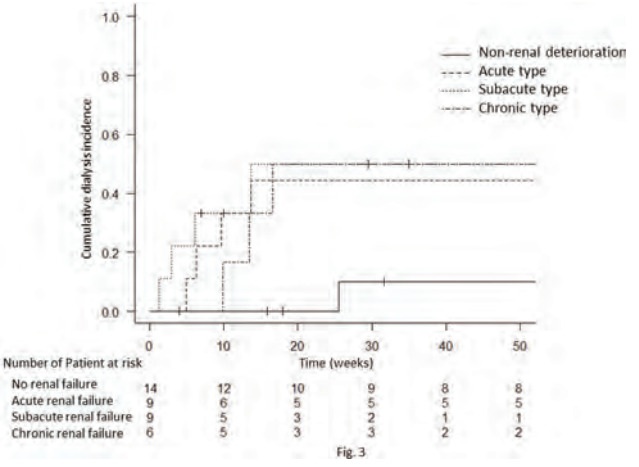

Fig. 3

TH-PO052

Urinary Neutrophil Gelatinase Associated Lipocalin Is Elevated in Neonates Who Develop AKI After General Surgical Procedures

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Background: Acute Kidney Injury (AKI) occurs commonly in critically ill neonates after surgery. AKI diagnosis by serum creatinine and urine output has significant limitations in this population. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) has been shown to predict AKI in many pediatric cohorts, but no study has assessed uNGAL performance to predict AKI in neonates after general surgical intervention.

Methods: Infants undergoing a surgical procedure were prospectively enrolled in this observational study. Urine was obtained pre-operatively and at 12, 24, 36, 48, 72 and 96 hours post-operatively. uNGAL was measured by The uNGAL Test™ (BioPorto, Denmark). AKI was defined by 2014 modified Kidney Disease Improving Outcomes (KDIGO) criteria. Mann-Whitney U tests were performed compare uNGAL levels of AKI and non-AKI groups.

Results: A total of 61 neonates had 70 surgical procedures at an average corrected gestational age of 41 weeks (*SD* ±8 weeks). AKI occurred in 18 (25%) patients. uNGAL levels above the published normative values occurred after 41 (58%) procedures - in 13 (72%) patients with AKI and in 28 (54%) patients without AKI. Post-op uNGAL values were elevated in infants with AKI with peak uNGAL values most commonly occurred approximately 48 hours after surgical intervention. (Table 1). The AUC-ROC for uNGAL to predict AKI at 48 hours was 0.74 (0.61-0.88).

Conclusions: Elevation of uNGAL occurs at 36-72 hours post-operatively in neonates who develop AKI after general surgical procedures. A substantial proportion of non-AKI patients had elevated uNGAL levels suggesting potential sub-clinical renal insult and this relationship should further be explored. Few patients were premature, however given that normative uNGAL values vary with gestational age, we intend to examine this relationship in the future.

Funding: Private Foundation Support

Table 1 – Median [IQR] uNGAL levels in patients with vs. without AKI after surgery

	12 hour uNGAL	24 hour uNGAL	36 hour uNGAL	48 hour uNGAL	72 hour uNGAL	96 hour uNGAL	Mean uNGAL for all timepoints	Peak uNGAL
All	(n=59)	(n=64)	(n=64)	(n=65)	(n=64)	(n=57)	(n=71)	(n=70)
No AKI (n=52)	30 [15-122]	20 [15-121]	41 [16-117]	32 [14-73]	30 [11-87]	31 [12-77]	45 [22-136]	73 [33-326]
AKI (n=18)	37 [19-718]	150 [28-275]	114 [35-267]	214 [42-463]	211 [31-434]	66 [14-195]	20 [40-549]	39 [111-1040]
p value	0.23	0.07	0.04	0.003	0.02	0.09	0.004	0.005

TH-PO053

Fibroblast Growth Factor 23, a Novel Biomarker for AKI in Patients with Acute Decompensated Heart Failure

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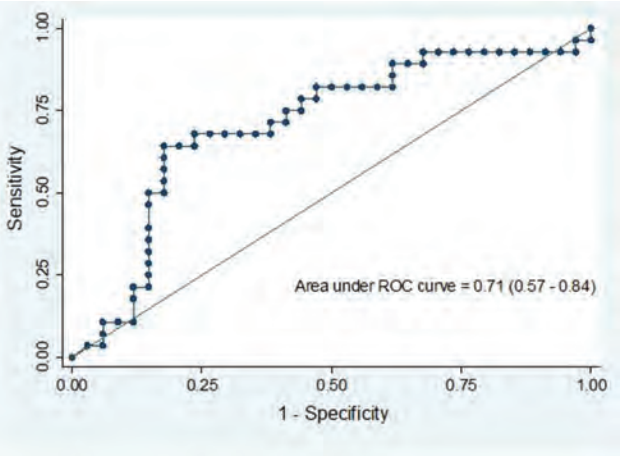
Background: Acute kidney injury (AKI) in acute decompensated heart failure (ADHF) is associated with poor prognosis. Recent evidences have proved that early rising of plasma Fibroblast Growth Factor 23 (FGF23) can predict AKI and adverse events in patients undergoing cardiac surgery and critically ill patients, but it remains unknown in ADHF patients. This study aimed to investigate the prognostic value of plasma FGF23 for predicting the occurrence of AKI.

Methods: A single center cohort study is performed in patients admitted for ADHF in Bhumibol Adulyadej hospital. Plasma c-terminal FGF23 (c-FGF23) was measured 2 times at baseline and 24 hours later after diagnosing ADHF. Serum creatinine was measured every other day or more frequently as appropriate according to general treating standards and AKI was assessed and defined using KDIGO criteria.

Results: The study enrolled 62 patients diagnosed with ADHF. The incidence of AKI is 45% and significantly increased risk of death. Patients who developed AKI had significantly higher levels of plasma c-FGF23 at baseline in comparison with AKI-free patients (median value 1,258.5 Ru/mL vs. 230.2 Ru/ml, p = 0.005). During the first 24 hours, plasma c-FGF23 levels in AKI-free group decreased more than AKI group, but the difference is not statistically significant. ROC analysis of both first time and second time of plasma c-FGF23 collecting yielded an AUC of 0.71 for prediction of AKI incident. With the cut-off point at 450 RU/ml, the sensitivity and specificity of plasma c-FGF23 at baseline for predicting AKI were 71.4% and 61.8% respectively.

Conclusions: Plasma c-FGF23 may serve as a novel biomarker for incident of AKI in patients with acute decompensated heart failure which should be measured immediately or within 24 hours after diagnosing ADHF.

Funding: Government Support - Non-U.S.



TH-PO054

Serum Cystatin C on Admission: A Potential Predictor for Hospital-Acquired AKI in Patients with an Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Background: Hospital-acquired acute kidney injury (HA-AKI) was associated with poor prognosis. In this study, we performed to determine whether serum Cystatin C on admission could predict AKI in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

Methods: This study was conducted from January 2014 to January 2017, and data from adult inpatients with AECOPD were analyzed retrospectively. A total of 1035 patients were included, 79 patients were identified with HA-AKI. Univariate and multivariate logistic regression analyses were used for investigating the predictors for HA-AKI in patients with AECOPD.

Results: Prevalence of HA-AKI was 7.6%. HA-AKI was also associated with poor prognosis, and was an independent risk factor for inpatient mortality for patients with AECOPD. Compared with patients without AKI, age, and the level of urea, Cystatin C, and platelet count on admission were four independent factors for HA-AKI in patients with AECOPD. Cystatin C (OR, 5.22; 95% CI, 2.49-10.95; $P < 0.001$) was the independent and significant predictor for AKI in patients with AECOPD. HA-AKI in patients with AECOPD could be identified with a sensitivity of 73.5% at specificity of 75.9% (AUC = 0.803, 95% CI 0.747 - 0.859) by Cystatin C (cut-off value = 1.3 mg/L). In addition, HA-AKI in patients with AECOPD could be identified with a sensitivity of 75.9% at specificity of 82.0% (AUC = 0.853, 95% CI 0.810 - 0.896) by the model.

Conclusions: Serum Cystatin C on admission may be adopted to predict the potential risk of HA-AKI in patients with AECOPD.

TH-PO055

Urinary Activin A: A Novel Biomarker for Monitoring the Severity of AKI

Izumi Nagayama, Akito Maeshima, Daisuke Nagata. *Jichi Medical University, Shimotsuke, Japan.*

Background: Acute kidney injury (AKI) is a common but complex condition that is associated with increased morbidity and mortality. There is a need for biomarkers to predict AKI development and severity in critically ill patients. We previously reported that activin A, a member of the TGF-beta superfamily, which was absent in normal kidney, was increased in the ischemic rat kidney and negatively regulates the repair process of the kidney after injury (Maeshima et al. J Am Soc Nephrol 2001). However, the dynamics and significance of urinary activin A have not been clarified in humans. To address this issue, we examined whether urinary activin A can be detectable in human AKI and may serve as a biomarker to predict AKI development and severity.

Methods: Thirty three patients with AKI (renal AKI 22, pre-renal AKI 11) were enrolled in this study approved by the institutional review board of the Jichi Medical University Hospital (Approved number A18-081, A18-089). Written informed consent was obtained from all participants. The Kidney Disease Improving Global Outcomes (KDIGO) classification was used to diagnose and classify patients developing AKI. Serum and urinary activin A was measured by ELISA. Correlations of urinary activin A with other clinical parameters were analyzed.

Results: Urinary activin A, which was almost undetectable in pre-renal AKI, was significantly increased in renal AKI (6.0 ± 3.17 vs. 204.8 ± 96.6 pg/mL, $p<0.05$). Urinary activin A level in patients with AKI stage III was significantly higher than that in patients with AKI stage I + II (199.4 ± 102.8 vs. 32.8 ± 16.3 pg/mL, $p<0.05$). There was a significant correlation of urinary activin A level with urinary NGAL, NAG, and alpha-1 microglobulin, but not with L-FABP, urinary protein, serum creatinine, and serum activin A. In one patient with drug-induced AKI who recovered renal function to normal, urinary activin A rapidly decreased before the normalization of serum creatinine, NGAL and L-FABP. In other patient with AKI due to contrast nephropathy, who did not recover renal function, urinary activin A remained at high level at 1 month after the initiation of hemodialysis therapy.

Conclusions: Urinary activin A can be detected in human with AKI and might be a useful and non-invasive biomarker for monitoring the severity of AKI.

Funding: Government Support - Non-U.S.

TH-PO056

Description of [TIMP-2] [IGFBP7] Significative Values at 72 Hours After Cardiac Surgery for Predicting AKI

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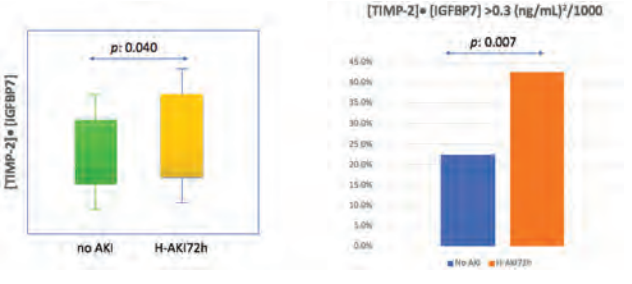
Background: AKI is common in critically ill patients and has been identified as an independent mortality predictor. Multiple biomarkers has been discovered in order to improve tools for AKI diagnosis. The aim of this study was AKI within the first 72 hours after cardiac surgery. Secondary endpoints were severity of AKI within 72 h, need for RRT, length of stay in the UCI and death during the ICU stay in relation with [TIMP-2] [IGFBP7]

Methods: Observational, prospective study. Patients 18Y, with or without AKI who underwent cardiac surgery, June to December 2016. A statistical analysis was performed. Urine samples for measurement of [TIMP-2] [IGFBP7] were collected 4 h after ICU admission. High risk for AKI was defined as urinary [TIMP-2] [IGFBP7] 0.3 (ng/mL)2/1000.

Results: 383 patients, 77 (20.1%) developed AKI within 72 h. At baseline (pre-ICU) age was AKI group [67 (58 – 74) vs74 (70 – 78); p=<0.0001]. The diuretic use [122 (41.5%) vs 42 (56.8%); p= 0.026]. Vancomycin during the surgery was significantly higher in the AKI group [122 (41.4%) vs 42 (56.8%); p=0.026]. The prevalence at 72 h of ICU admission was 77 (20.1%) patients and the severity AKI 1 60 (15.7%) patients, AKI 2 11 (2.9%) patients and AKI 3 6 (1.6%) patients. In those patients with AKI within 72 hours and [TIMP-2][IGFBP7] >0.3 (ng/mL)2/1000 had higher significantly FB in the first 6h [2.05 ± 933.84 vs 252.97 ± 761.26; p=0.016]. Cardiac arrest [1 (0.3%) vs (6 (8.2%); p=<0.0001], reintervention during the ICU stay [6 (2%) versus 6 (8.2%); p=0.017], LOS in ICU [7 (6 – 10) vs 9 (7 – 15.5); p=<0.0001] and death [52 (17%) vs 23 (29.9%); p=0.015] were significantly higher in the AKI group.

Conclusions: In high risk patients, [TIMP-2][IGFBP7] should be considered together with other clinical parameters to predict AKI and adverse outcomes (Cardiac arrest, Length of stay and death).



Variable		NC Negative <=0.3	NC positive >0.3	p Value
FB within 6 hours of ICU admission (mL, mean ± SD)		2.05 ± 933.84	252.97 ± 761.26	0.016
Norepinephrine max dose ICU (µg/kg/min, mean ± SD)		0.007 ± 0.06	0.009 ± 0.04	0.015
MAP (mmHg, mean ± SD)		78.48 ± 13.78	75.27 ± 12.97	0.043
Maximum AKI stage in the first 72h (n, %)				0.037
	AKI 1	36 (13.1%)	24 (22%)	
	AKI 2	6 (2.2%)	5 (4.6%)	
	AKI 3	3 (1.1%)	3 (2.8%)	

Outcomes between NC positive (>0.3) and negative (<=0.3) first 72h

TH-PO057

Urinary TIMP2 and IGFBP7 as Early Biomarkers of Nephrotoxicity

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Background: Elevated levels of urinary tissue inhibitor of metalloproteinases-2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7) predate severe AKI by >12 hours in critical illness; these biomarkers may help predate and predict drug-induced acute kidney injury (DI-AKI).

Methods: Prospective study involving serial urine collection in hospitalized patients, during course of therapy with nephrotoxic drugs. Absolute and normalized (against urine creatinine) levels of TIMP2 and IGFBP7 were examined in days leading up to study endpoint: onset of AKI by KDIGO criteria, or final day of nephrotoxic drug therapy in non-AKI patients.

Results: Twenty-two of 135 patients developed DI-AKI (16%), including 8 patients with KDIGO stage 2/3 AKI. Urinary biomarker analyses were performed for 21 AKI patients with available pre-AKI samples, and 28 non-AKI matched-controls. They were aged 57(±14) and 52(±15) years with baseline eGFR of 102(92-116) and 103(89-118) mL/min/1.73m^2, respectively, with corresponding drug therapy duration of 15(14-25) versus 14(10-21) days (all p=NS). Comparing biomarker trends at 4–6 days, 2–3 days, and 1–2 days before study endpoint; significantly higher TIMP2 and IGFBP7 levels ($p<0.05$) were observed in the absolute(ng/mL), normalized (µg/mmol) and composite ((ng/mL)^2/1000) of these markers as early as 2-3 days prior to AKI onset. The respective absolute and normalized TIMP2 levels (2-3 days prior) in AKI versus non-AKI patients were 4.9 versus 2.2 (p=0.02) and 1.2 versus 0.6 (p=0.005); corresponding levels for absolute and normalized IGFBP7 were 12.9 versus 1.2 (p=0.005) and 1.9 versus 0.3 (p=0.01); absolute [TIMP2]*[IGFBP7] level was 0.07 versus 0.005(p=0.007). Highest absolute and normalized TIMP2 levels at 2–3 days pre-AKI predicts AKI with an average AUROC of 0.75 and 0.81 respectively; correspondingly the average AUROC for both IGFBP7 values was 0.73. [TIMP2] *[IGFBP7] was able to predict AKI with 74% accuracy and the optimal biomarker cut-off level was determined to be 0.01(ng/mL) ^{2}/1000.

Conclusions: Elevated urinary TIMP2 or IGFBP7 predate and predict DI-AKI by 2–3 days during course of nephrotoxic drug therapy in hospitalized patients.

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

Urinary biomarkers levels (median (IQR)		4 to 6 days prior (14 versus 20)†	P value	2 to 3 days prior (19 versus 25)†	P value	1 to 2 days prior (18 versus 27)†	P value
TIMP2 (ng/mL)	AKI patients	3.6 (1.9-5.2)	0.70	4.9 (2.1-9.1)	0.02	4.4 (2.3-8.5)	0.02
	Non-AKI controls	2.6 (1.7-5.0)		2.2 (1.6-3.9)		2.0 (1.5-3.5)	
IGFBP7 (ng/mL)	AKI patients	3.9 (0.1-11.5)	0.65	12.9 (2.9-24.7)	0.005	7.0 (1.9-31.4)	0.02
	Non-AKI controls	2.7 (0.1-7.9)		1.2 (0.6-8.6)		1.5 (0.4-7.3)	
TIMP2 x IGFBP7 (ng/mL)²/1000	AKI patients	0.01 (0.0002-0.04)	0.44	0.07 (0.01-0.36)	0.007	0.03 (0.001-0.34)	0.01
	Non-AKI controls	0.006 (0.0005-0.02)		0.005 (0.0007-0.03)		0.004 (0.0004-0.02)	
TIMP2:Cr (µg/mmol)	AKI patients	0.9 (0.6-1.3)	0.20	1.2 (0.7-2.1)	0.005	1.1 (0.8-2.3)	0.005
	Non-AKI controls	0.7 (0.6-0.8)		0.6 (0.5-0.9)		0.6 (0.4-0.9)	
IGFBP7:Cr (µg/mmol)	AKI patients	1.6 (0.04-5.2)	0.23	1.9 (0.6-10.6)	0.01	1.9 (0.5-13.3)	0.03
	Non-AKI controls	0.5 (0.02-1.8)		0.3 (0.1-1.4)		0.4 (0.2-1.4)	

Table 1: Urinary biomarker levels at various time-intervals prior to AKI onset.
LEGEND: †: Number of patients (AKI versus non-AKI controls) with available urine samples analyzed at respective time-intervals.

TH-PO058

Time of Surgery Is Associated with Greater Increase in Urinary KIM-1 in Patients with Major Elective Abdominal Nonvascular Surgery-Associated AKI

Graziela R. de Souza. *Clinical, São Paulo University, São Paulo, Brazil.*

Background: Acute kidney injury (AKI) is a complex syndrome that occurs in a wide variety of surgical situations, and has been associated with the surgery time (ST). The aim of this study is to assess if the ST in patients (pts) developing AKI after major elective abdominal non-vascular surgeries (MEANVS) is associated with the intensity of urinary biomarkers (uBM) changes after surgery.

Methods: We studied a prospective cohort of MEANVS pts, which did the post-operatory (post-op) period in intensive care units (ICU) in a university hospital. AKI diagnosis was made by serum creatinine (SCr) or urinary output (UO) KDIGO criteria. SCr was analyzed in pre-operatory time, ICU admission and daily up to 7 days or ICU discharge. UO was evaluated hourly (mL/kg/h) trough 24 h every day. The uBMs (NGAL, KIM-1 and Nephrochek - NC) were analyzed in the immediate post-op (time 0, ICU admission) and 12 h after ICU admission. Diagnosis of chronic kidney disease stages IV/ V, nephrotoxic drugs use before surgery and ICU stay < 48 h were exclusion criteria. Statistical significance was $p < 0.05$.

Results: The sample was composed by 297 pts ≥ 18 y old. The most frequent surgeries were hepatectomy and gastrectomy. Among the 297 pts, 197 (66.3%) developed AKI, mostly KDIGO stage 1 (60% of 197). Using SCr criteria 71 pts were diagnosed, while the UO criteria diagnosed 126 pts (62 pts has simultaneous SCr and UO changes). Eight pts (2.6%) needed hemodialysis. Mortality in AKI pts was 9.1% and without AKI 1.9%, p = 0.0149. Among pts developing AKI 53.3% had ST ≥ 300 min. The values of all uBMs were similar at time 0, independently of the ST. At 12 h KIM-1 values were significantly higher em pts with ST ≥ 300 min as compared to < 300 min: 2.42 vs 1.62 ng/mL, p = 0.011. The values of NGAL and NC were higher at 12h in the ST ≥ 300 group, but did not reached statistical significance: 214 vs 147 ng/mL for NGAL, p = 0.387 and 18.9 vs 14.6 ng/mL, p = 0.223, for NC.

Conclusions: In conclusion, longer ST was associated with increased KIM-1 in MEANVS-associated AKI pts, suggesting an occurrence of more severe tubular injury.

TH-PO059

Hemoglobin Is a Strong and Independent Predictor of Major Adverse Kidney Events

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Background: Anemia is an established risk factor for acute kidney injury (AKI). However, most prior studies assessed anemia as a dichotomous variable, and were further limited by modest sample sizes, incomplete adjustment for confounders, and failure to account for dialysis and death as competing risks.

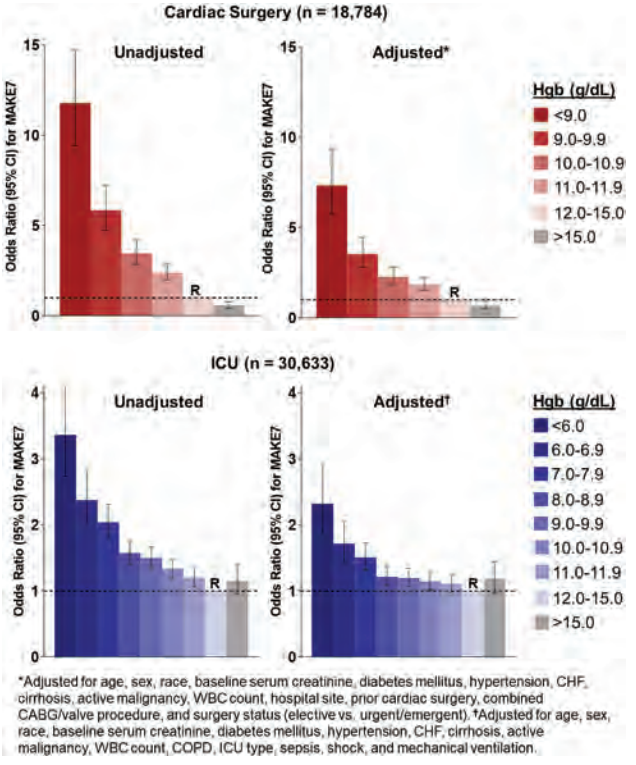
Methods: We performed a retrospective cohort study of patients who underwent cardiac surgery (CS) or were admitted to an ICU at two medical centers in Boston, MA, between 2005-2018. We excluded patients with ESRD and those who already had AKI. Our final cohort included 18,784 CS and 30,633 ICU patients. The primary exposure was the most proximal Hgb before surgery or ICU admission. The primary endpoint was any Major Adverse Kidney Event within 7 days (MAKE7) after CS or ICU admission. MAKE7 was defined as an increase of serum creatinine (SCr) ≥100%, dialysis, or death. We used multivariable logistic regression to adjust for potential confounders.

Results: The incidence of MAKE7 was 6% in the CS cohort and 14% in the ICU cohort. In both cohorts, we observed a monotonic increase in risk of MAKE7 with lower

Hgb values. Patients who underwent CS with a Hgb<9 vs. 12-15 g/dL had a 7.3-fold (95% CI, 5.7-9.4) higher risk of MAKE7 in a model adjusted for preoperative SCr, urgent/emergent surgery, and 11 additional key variables. Additionally, each 1 g/dL decrease in Hgb associated with a 1.6-fold higher risk of MAKE7 in adjusted models (95% CI, 1.5-1.7). ICU patients with a Hgb<6 vs. 12-15 g/dL had a 2.3-fold (95% CI, 1.9-2.9) higher risk of MAKE7 in a model adjusted for baseline SCr, sepsis, shock, mechanical ventilation, and 13 additional key variables.

Conclusions: Lower Hgb associates monotonically, independently, and strongly with higher risk of MAKE7 in patients undergoing CS and in those admitted to the ICU.

Funding: NIDDK Support



TH-PO060

Red Blood Cell Distribution Width and Risk for Contrast-Induced AKI After Percutaneous Coronary Intervention

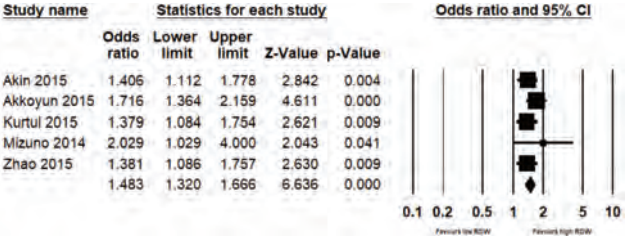
Takayuki Yamada,[1,3] Hiromichi Wakui,[3] Kouichi Tamura,[3] Alfred Burger,[1] Steven G. Coca.[2] *[1]Mount Sinai Beth Israel, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Yokohama City University, Yokohama, Japan.*

Background: Contrast-induced acute kidney injury (CI-AKI) is a major complication following percutaneous coronary intervention (PCI) and is associated with greater morbidity and mortality. Accumulating evidence suggests that inflammation and oxidative stress play an important role in the development of CI-AKI. Red blood cell distribution width (RDW) is a possible marker of oxidative stress and inflammation. In this study, we performed a systematic review and meta-analysis to investigate the association between RDW levels and CI-AKI after PCI.

Methods: We assessed clinical studies through Pubmed, Embase, and the Cochrane Library that investigated the association between RDW and a risk of CI-AKI in patients after PCI up to April 2019. The primary outcome was CI-AKI.

Results: A total of five observational studies met the inclusion criteria. The pooled population consisted of 2,432 patients. Using multivariable logistic regression analysis, increased RDW (cutoff between 13.25 to 15.2) was independently associated with greater risk for CI-AKI after PCI (pooled adjusted odds ratio (OR), 1.48; 95% confidence interval (CI), 1.32 to 1.67; I2 = 0%) (Figure). Subgroup analysis in patients with ST elevation myocardial infarction demonstrated a similar tendency (OR, 1.58; 95% CI, 1.35 to 1.85; I2 = 0%).

Conclusions: Increased RDW is associated with increased risk of CI-AKI after PCI. Further studies are needed to assess the utility of RDW as a risk-stratifier for CIN.



TH-PO061

Clinical Significance of Hypoalbuminemia for AKI in Patients with Scrub Typhus

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Background: The aim of this study is to investigate the clinical significance of hypoalbuminemia (HA) for acute kidney injury (AKI) in patients with scrub typhus.

Methods: From 2010 to 2017, 449 patients were diagnosed with scrub typhus. We divided the patients into two groups [normoalbuminemia (NA) vs. hypoalbuminemia (HA)] based on the serum albumin level of 3.5 g/dL, and compared the incidence, clinical characteristics, and severity of AKI based on RIFLE classification between two groups.

Results: Of the total 449 patients, 52 (11.6%) were categrized as HA group. Compared with patients in NA group, patients in HA group were older (74 ± 8 vs. 63 ± 13, P<0.01) and had higher total leukocyte counts (10.4 × 10^3/ mL vs. 6.9 × 10^3/mL, P<0.01). HA group showed significantly longer hospital stay (10.1 ± 4.7 vs 8.8 ± 4.5, p<0.01) and higher incidence of acute kidney injury (56% vs. 19%, p<0.01). The overall incidence of AKI was 22.9%; of which, 12.2%, 10.0% and 0.7% were classified as Risk, Injury and Failure, respectively. In a multivariate logistic regression analysis for predciting AKI, age, presence of chronic kidney disease, leukocytosis and hypoalbuminemia were significant predictors of AKI. Most patients recovered baseline renal function without renal replacement therapy following antibiotics therapy and supportive care.

Conclusions: Hypoabluminemia was closely associated with AKI in patients with scrub typhus.

TH-PO062

Prediction of AKI in ICU Using Routinely Collected Data by Machine-Learning Algorithms and Its Visualization

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Background: Acute kidney injury (AKI) is associated with high mortality, and occur frequently particularly in the intensive care unit (ICU), due to various conditions such as septic shock. It is clinically important to identify high-risk patients with AKI in advance and perform appropriate interventions. There have been many studies that predicted the onset of AKI using data like medication or laboratory data so far, but few studies have utilized time series vital data to predict AKI, and have assessed which time point is important for the prediction in each patient. In this study, we attempt to predict the onset of AKI by applying machine learning algorithms to vital data acquired routinely in most ICU patients from the publicly available dataset, followed by the visualization of the rationale behind the prediction.

Methods: We used publicly disclosed dataset named Medical Information Mart for Intensive Care three. AKI was defined based on KDIGO serum creatinine criteria. We included patients with stage 2 or higher AKI within 48 hours after admission to ICU. The onset of AKI was defined as when the high creatinine level was first detected. We included data of systolic, diastolic, and mean blood pressure, heart rate, respiratory rate, body temperature, and SpO2. In addition, age and the baseline serum creatinine level were collected. We utilized machine learning algorithm of XGBoost and 1-dimensional convolutional neural networks (1D-CNN). We predicted the onset of AKI in 24 to 48 hours using data collected in 0 to 24 hours after admission to ICU. We evaluated the performance of the model using area under receiver operating characteristic curve (AUROC), with five-fold cross-validation. We applied Grad-CAM to visualize the rationale behind the prediction in 1D-CNN.

Results: The highest performance was obtained by XGBoost when minimum, maximum and mean value of vital data and age, serum creatinine data was combined (AUROC: 0.793±0.34). Using only vital data, the performance was 0.666±0.046, 0.675±0.053 for XGBoost, 1D-CNN respectively. Using Grad-CAM to the 1D-CNN model, some visualization results suggested that the time period of lower blood pressure might contribute to the prediction.

Conclusions: It was suggested that XGBoost and 1D-CNN could predict the onset of AKI and visualize its rationale behind the prediction.

Funding: Government Support - Non-U.S.

TH-PO063

Predicting AKI After Cardiac Surgery by Using Machine Learning Methods

Po-Yu Tseng,[1] David Chih-Yu Yang.[2] *[1]Far Eastern Memorial Hospital, New Taipei, Taiwan; [2]Taipei Veterans General Hospital, Taipei, Taiwan.*

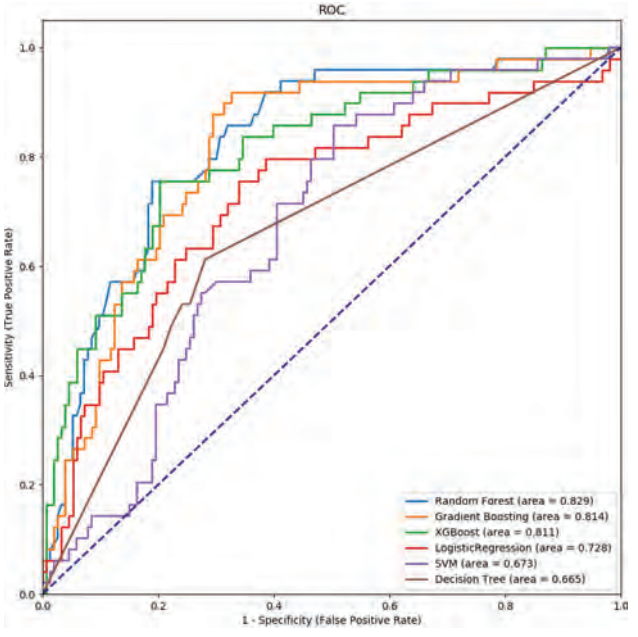
Background: Acute kidney injury (AKI) is an important complication of the cardiac surgeries. Small increases in serum creatinine (SCr) after cardiac surgery have been associated with a significant increase in 30-day mortality. A model that accurately estimates a patient's risk for AKI after cardiac surgery is important in clinical practice. Several risk models have been developed to predict postoperative AKI after cardiac surgery. However, there is less study analyzing clinical big data with the application of machine learning to predict AKI after cardiac surgery.

Methods: We retrospectively enrolled the patients undergoing cardiac surgery (coronary artery bypass graft or valve surgery) in Far East Memorial Hospital from August 2016 to August 2018. The primary outcome was the development AKI.The following machine learning techniques were used: decision tree, random forest, gradient boosting, and support vector machine. The performance of these techniques was compared with that of logistic regression analysis regarding the area under the receiver-operating characteristic curve (AUC). We also used importance matrix plot and shap value to determine the importance of each variables.

Results: A total of 671cases received cardiac surgery. AKI developed in 163(24.3%) patients during the first postoperative week. The highest AUC is 0.829 by the random forest with oversampling. The important matrix plot of random forest revealed that intraoperative urine output, pRBC transfusion during the surgery and and preoperative preoperative serum creatinine were the top three variables contribute to the model.

Conclusions: We successfully use the perioperative parameters to develop the predictive model for AKI after cardiac surgery by using machine learning method.

Funding: Other NIH Support - MOST, Taiwan (108-2633-B-009-001); Taipei Veterans General Hosptial (V106D25-003-MY3); National Yang-Ming University School of Medicine (107F-M01); MOE, Taiwan (Center for Intelligent Drug Systems and Smart Bio-devices)



Comparison of AUC among the different machine learning models

TH-PO064

Central Venous Pressure and the Risk of Diuretic-Associated AKI in Patients After Cardiac Surgery

Ian Mccoy, Maria E. Montez-Rath, Glenn M. Chertow, Tara I. Chang. *Stanford University School of Medicine, Stanford, CA.*

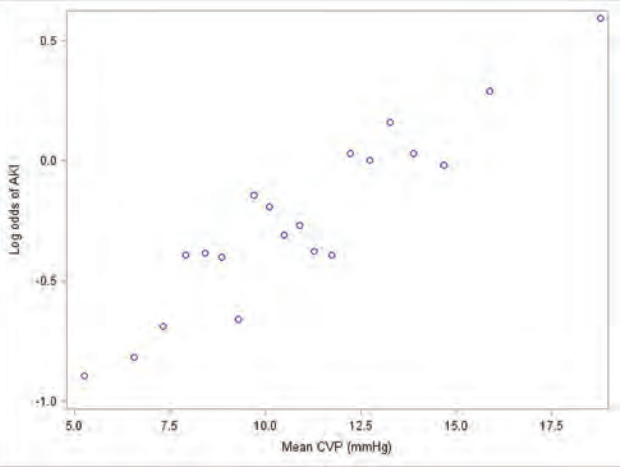
Background: Clinicians strive to weigh the benefits of diuretic therapy for treating and preventing fluid overload against the risks, including acute kidney injury (AKI) due to excessive or overly rapid diuresis. We hypothesized a lower risk of AKI after diuretic administration in patients with higher central venous pressure (CVP) following cardiac surgery.

Methods: We used the MIMIC-III database to study adults admitted to the post-cardiac surgical intensive care unit between 2001 and 2012, excluding those on maintenance dialysis, at an urban academic medical center. Multivariable logistic regression models included adjustments for demographics, comorbidities, admission diagnosis, procedures (cardiopulmonary bypass, coronary artery bypass grafting, left heart catheterization), medications, and severity of illness (mean arterial pressure, admission creatinine, vasopressor use, mechanical ventilation, and platelet count). Inverse probability treatment weighting estimated the risk of diuretic-induced AKI across tertiles of CVP.

Results: Among 4,164 patients receiving intravenous loop diuretics, in contrast to our a priori hypothesis, the adjusted odds of subsequent AKI were 1.11 (95% confidence interval [CI] 1.08-1.13) times higher per mmHg increase in mean CVP on ICU day 1. This association was log-linear across the entire range of CVP observed. The odds ratios were higher for more severe AKI (KDIGO Stage 1: 1.09 (95% CI 1.06-1.11), KDIGO Stage 3: 1.23 (95% CI 1.15-1.31). Among the 5,396 patients including those not on intravenous loop diuretics, the risk ratio for AKI with diuretic use was 1.59 (95% CI 1.39-1.82); results did not materially differ when examined by CVP tertile.

Conclusions: Higher rather than lower CVP is an independent marker of AKI risk. Further research should aim to identify better tools to assess volume status and to determine ICU patient groups for whom diuretics can be most safely administered.

Funding: NIDDK Support



TH-PO065

Relation Between Biomarkers of Decongestion and Kidney Function with Outcomes in Acute Decompensated Heart Failure

Wendy I. McCallum, Hocine Tighiouart, Marvin Konstam, James Udelson, Mark J. Sarnak. *Tufts Medical Center, Boston, MA.*

Background: In-hospital acute declines in kidney function occur in approximately 20-30% of patients admitted with acute decompensated heart failure (ADHF), but it remains unknown whether these declines are associated with improved or worse outcomes, and whether incorporation of markers of congestion modifies these associations.

Methods: Using data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, multivariable Cox regression models were used to evaluate the association between in-hospital changes in eGFR and changes in brain natriuretic peptide (BNP) with death and a composite outcome of death or rehospitalization. The association of eGFR decline with outcomes within subgroups of changes in other surrogate markers of congestion including N-terminal prohormone of brain natriuretic peptide, hematocrit, and weight was also examined.

Results: Among 3,988 patients over a median 8-month follow-up, in-hospital decline in eGFR was not significantly associated with outcomes (HR=1.09 [95% CI 0.96, 1.24] for death per every 30% decline in eGFR; 1.03 [95% CI 0.95, 1.12] for composite per every 30% decline in eGFR), whereas there was a 24% reduction in risk of death for every halving of BNP (HR=0.76 [95% CI 0.71, 0.83]). There was no significant interaction between decline in eGFR and change in BNP for either death (p-interaction =0.09) or the composite of death or rehospitalization (p-interaction =0.35) (Figure). Decline in eGFR was not found to be significantly associated with either improved or worse outcomes in any subgroups of either increasing or decreasing markers of congestion (p-interaction $\rangle$0.12 for all subgroups).

Conclusions: Achieving decongestion is an important goal for patients with ADHF and declines in BNP are associated with better prognosis. The prognostic significance of declines in eGFR, however, remains less clear, even if occurring in the setting of achieving decongestion.

Funding: Other NIH Support - NIH Training Grant T32 DK007777

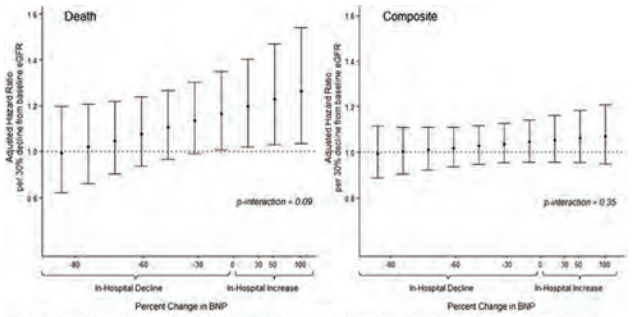


Figure. Adjusted hazard ratios for death (left) and for composite of death or rehospitalization (right) based on fixed estimated glomerular filtration (eGFR) decline of 30% and varying changes in brain natriuretic peptide (BNP).

TH-PO066

A Modified Renal Angina Index by Using the Kinetic Glomerular Filtration Rate for Predicting AKI

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Background: Reliable prediction of AKI has the potential to optimize its treatment. Recently Goldstein SL et al. proposed an empiric clinical model of renal angina to identify critically ill children who would be at higher risk of AKI. In children the combination of the renal angina index (RAI) and AKI biomarkers has an excellent diagnostic performance. The purpose of this study was to evaluate the performance of a modified RAI using kinetic glomerular filtration rate (*Ke*GFR) for the prediction of AKI in a cohort of critically ill adults.

Methods: We included 208 consecutive patients admitted to our medical ICU. Serum creatinine (sCr) was measure every 24 hours for 7 consecutive days following ICU admission. RAI was calculated 24 hours after ICU admission (day 1) using the following formula: **Risk level** (presence of sepsis, use of vasopressors and/or use of invasive mechanical ventilation, and presence of diabetes mellitus) ***x*** **Injury level** (changes in kidney function based on *Ke*GFR). *Ke*GFR was calculated from the change in consecutive values of sCr using the formula developed by Chen S. We used KDIGO AKI sCr criteria to diagnose AKI. In patients with no baseline sCr available we back calculated baseline sCr using MDRD equation (for an eGFR = 75 ml/m/1.73m^2). We analyzed if a modified RAI score ≥6 points could predict subsequent AKI (after 48 hours).

Results: From 208 patients enrolled in the study 101 patients developed AKI (48.6 %). Age, baseline sCr, and eGFR (CKD-EPI) we not different between patients with AKI and patients without AKI. At 24 hours post ICU admission patients with AKI had lower *Ke*GFR (47.7 ml/m vs. 81.1 ml/m; p < 0.0001). A renal angina index ≥6 points was able to identify individuals who developed AKI after 48 hours of ICU admission, with a ROC-AUC of 0.697 (95% CI 0.626-0.769), p < 0.0001. A Renal Angina Index of ≥6 points had an OR of 9.9 (95% CI 2.65 – 37.11; p < 0.0001) for subsequent development of AKI after 48 hours of ICU admission.

Conclusions: A modified renal angina index by using the *Ke*GFR provides a clinically feasible methodology to identify critically ill adults at high risk of developing AKI before a rise in serum creatinine occurs. This tool would permit the early identification of AKI to initiate preventive and treatment strategies minimizing extension of kidney injury.

TH-PO067

Using Kinetic eGFR to Predict AKI in Pediatric Intensive Care Unit

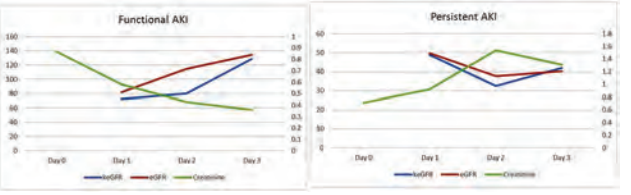
Shina Menon,[1] Stuart Goldstein,[2] Rajit K. Basu.[3] *[1]Seattle Children's Hospital, Seattle, WA; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [3]Children's Healthcare of Atlanta, Atlanta, GA.*

Background: Acute kidney injury (AKI) is common in intensive care unit (ICU). The ability to distinguish between functional and persistent AKI is important. Creatinine (Cr), commonly used for diagnosis is imperfect; combining it with urinary biomarkers may help differentiate the two. Kinetic estimated GFR (keGFR) has been used to predict AKI and likelihood of renal recovery. It uses creatinine values at two time points for a dynamic assessment of renal function. It can improve understanding of AKI trajectory and has been used to predict AKI. There are limited data on its use in pediatrics. We hypothesized keGFR would improve clinical and prognostic information beyond Cr or eGFR (modified Schwartz GFR)

Methods: We performed secondary analysis of data from Acute Kidney Injury in Children Expected by Renal angina and Urinary Biomarkers (AKI-CHERUB), a prospective, observational study of children 3months- 25 years age admitted to ICU. For this analyses, only those with complete data upto day 3 were analyzed. keGFR was calculated on Days 1-3. Functional AKI (fAKI) was defined as return to baseline Cr by Day 3 and persistent AKI (pAKI) was absence of recovery by Day 3. Primary outcome was pAKI and secondary outcomes were AKI stage 2/3 during the first 7 days and fAKI

Results: 169 patients were analyzed (50% female). AKI at admission was seen in 40 (23.6%). Of those, 23 had fAKI and 13 had pAKI. keGFR pattern was similar to that of eGFR (Fig 1) for both groups. Of those who did not have AKI at admission, 17 developed stage 2/3 AKI during the first 7 days in PICU. Median keGFR for these patients was 85.5 mL/min/1.73 m2 compared to eGFR of 79.5 mL/min/1.73m2

Conclusions: AKI diagnosis is mostly dependent on a rise in Cr which is an imperfect and late marker. The key to improving outcomes in AKI is early prediction of Cr trajectory and appropriate intervention. Although keGFR has been used in adults for this purpose, our analysis shows that it may not be ready for use in pediatrics. It can be used in conjunction with eGFR to identify AKI patterns but it is not superior to eGFR



TH-PO068

AKI and Long-Term Renal Dysfunction After Nonrenal Solid Organ Transplant

Shina Menon,[1] Ari Pollack,[1] Erin M. Sullivan,[1] Jodi M. Smith.[2] *[1]Seattle Children's Hospital, Seattle, WA; [2]Children's Hospital & Regional Medical Center, Seattle, WA.*

Background: Solid-organ transplantation (SOT) is the treatment of choice for end-stage organ disease. Improved long term survival after SOT has uncovered chronic morbidity including chronic kidney disease (CKD). AKI is common after SOT and associated with increased morbidity, mortality, long term CKD

Methods: Retrospective cohort study using PEDSnet database. We studied rates of AKI and CKD after non renal SOT and relationship between the two. First-time heart (n=109), liver (n=112) transplant recipients ≤21 years age included. Perioperative AKI (pAKI) was AKI ≤ 7days post transplant (txp); CKD was eGFR< 60 mL/min/1.73m2 for ≥ 3 months. Incidence of CKD calculated using Product-limit Kaplan-Meier estimates & compared with log rank test. Effect of txp, time since txp, age, pAKI &successive AKI in first year post txp on the slope of eGFR assessed using multivariate linear regression

Results: pAKI seen in 50.3% (112/221). pAKI after liver txp was more common in older children and those with acute liver failure. Among heart txp, it was more common in younger patients. It was associated with longer ICU and hospital length of stays, lower eGFR at follow-up, and higher incidence of CKD (Figures 1 and 2).

Conclusions: pAKI is common after NRSOT- particularly after heart txp. Cumulative incidence of CKD is higher after heart txp than liver. Post liver txp, incidence of CKD is higher in those with pAKI than those without. pAKI and subsequent AKI episodes are both associated with significant decreases in eGFR during follow up. Patients who develop AKI need close monitoring for CKD and may benefit from kidney sparing immunosuppression.

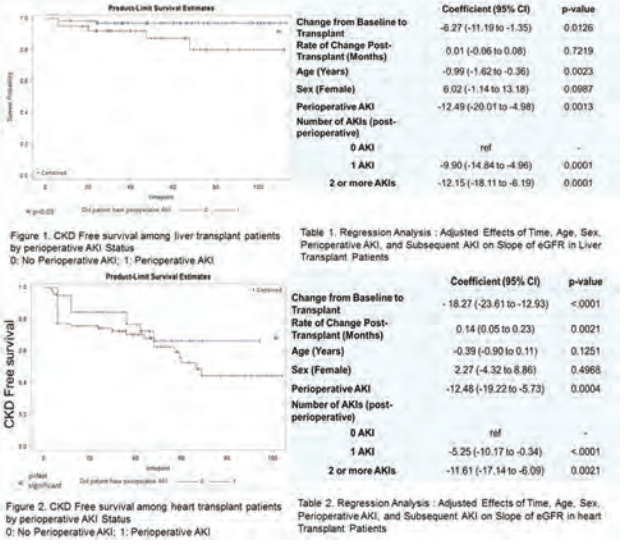
Demographics and Outcomes- Liver

	No Perioperative AKI (N=69)	Perioperative AKI (N=43)
Female (%)	36 (52.2%)	17 (39.5%)
Age (years)*	1.5 (0.7 - 7.9)	3.4 (0.9 - 13.7)
Weight (kg)*	9.5 (7.4 - 24.1)	18.0 (8.6 - 48.7)
Underlying diagnosis*		
Acute Liver Failure	7 (10.1%)	15 (34.9%)
Biliary Atresia	25 (50.7%)	12 (27.9%)
IEM	15 (21.7%)	6 (14.0%)
Other	12 (17.4%)	10 (23.3%)
Pretransplant AKI	6 (8.7%)	12 (27.9%)
eGFR baseline**	129.2 (15.9)	121.1 (23.2)
Periop RRT	-	7 (16.3%)
ICU LOS (days)*	4.3 (3.0 - 8.6)	12.5 (6.7 - 26.9)
Total LOS (days)*	17 (11 - 26)	30 (19 - 50)
Mortality*	0 (0.0%)	5 (11.6%)

Demographics and Outcomes- Heart

	No Perioperative AKI (N=40)	Perioperative AKI (N=69)
Female	18 (45.0%)	29 (42.0%)
Age (years)*	5.5 (0.4 - 13.0)	1.9 (0.6 - 11.7)
Weight (kg)*	15.9 (9.4 - 43.1)	10.3 (6.6 - 36.5)
Underlying diagnosis		
Congenital heart dis	22 (55.0%)	45 (65.2%)
Cardiomyopathy	18 (45.0%)	23 (33.3%)
Other	0 (0.0%)	1 (1.5%)
eGFR baseline**	120.0 (18.9)	116.5 (18.7)
Pretransplant AKI	18 (45.0%)	44 (63.8%)
Periop RRT		8 (6.0%)
ICU LOS (days)*	19.7 (7.6 - 40.7)	36.5 (13.0 - 94.7)
Total LOS (days)*	45 (20 - 79)	74 (27 - 158)
Mortality	1 (2.5%)	8 (11.6%)

Demographics & outcomes of liver & heart txp



CKD free survival and effect of variables on slope of eGFR post liver & heart txp

TH-PO069

Novel Algorithm for AKI Detection in Outpatient Settings

Chin-Chi Kuo. *Big Data Center, China Medical University Hospital, Taichung, Taiwan.*

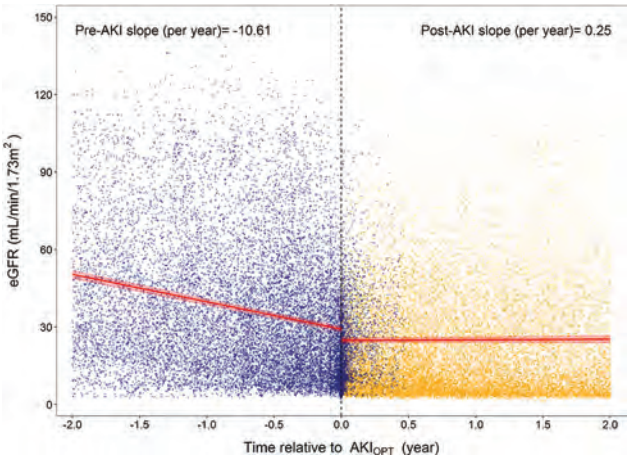
Background: Existing acute kidney injury (AKI) diagnostic criteria is restricted to inpatients. We proposed an AKI algorithm for outpatients(AKI_{OPT}) and evaluated how AKI_{OPT} modifies the course of chronic kidney disease (CKD).

Methods: The occurrence of AKI_{OPT} were analyzed retrospectively among CKD patients who were enrolled into the pre-dialysis care program in a tertiary hospital in Taiwan. AKI_{OPT} was detected by the definition of a 50% increase in serum creatinine (S-Cre) or a fall in eGFR by 35% in the 180-day period prior to pre-dialysis care program enrollment. Outcomes were progression to end-stage renal disease (ESRD) and all-cause mortality. The association analyses were performed using multiple Cox regression and coarsened exact matching (CEM) analysis.

Results: Among the total of 6046 patients, 31.5 % (1905 patients) had ever developed AKI_{OPT} within the 180-day period before the enrollment. The fully adjusted hazard ratios (aHRs) of the 1-year and overall risk of ESRD among patients with preceding AKI_{OPT} were 1.78 (95% CI, 1.50, 2.12) and 1.50 (1.32, 1.71), respectively, compared with those without history of AKI_{OPT}. For 1-year and overall risk of all-cause mortality, patients with AKI_{OPT} had respectively a 120% (95% CI 73-182%) and 74% (95% CI, 48-106%) higher risk than those without AKI_{OPT}. This statistical inference remained robust in CEM analysis. We discovered a complete reversal in the eGFR slope before and after the AKI_{OPT} from −10.61 ± 0.32 to 0.25 ± 0.30 mL/min/1.73 m^2 per year; however, the loss of kidney function is not recovered (Figure).

Conclusions: The new AKI_{OPT} diagnostic algorithm fits the outpatient setting and provides a prognostic significance in patients with CKD.

Funding: Government Support - Non-U.S.



eGFR slope (red line) with the light red shaded area representing 95% confidence intervals before and after the AKI_{OPT} event, modeled using the growth piecewise linear mixed model by incorporating random effects. Blue and orange points represent eGFR measurements before and after enrollment into pre-ESRD program.

TH-PO070

Development and Validation of a Risk Score for AKI After Cardiac Surgery

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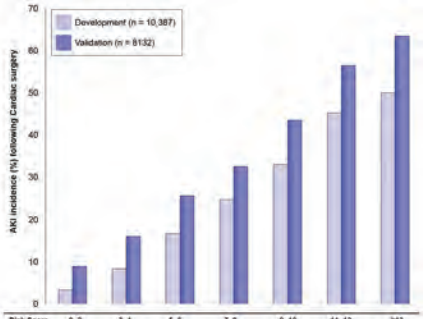
Background: AKI is a frequent and important complication of cardiac surgery. However, existing prediction models for cardiac surgery-associated AKI are limited by reliance on diagnostic and billing codes, lack of external validation, and inclusion of variables that can only be determined postoperatively (e.g., cardiopulmonary bypass time). Most importantly, existing models are mainly limited to prediction of severe AKI, whereas accurate risk stratification of more mild forms of AKI is crucial for enrichment of patients in early phase clinical trials.

Methods: We collected data from adults who underwent cardiac surgery between 2008 and 2018 at two major academic medical centers in Boston, MA. Data were obtained by querying the Society for Thoracic Surgeons National Database, along with electronic medical records. The primary exposures included clinically plausible demographics, comorbidities, laboratory values, and surgical characteristics, each of which was available preoperatively. The primary endpoint was AKI, defined according to KDIGO criteria as follows: an increase in serum creatinine ≥ 0.3 mg/dl within 48 hours, ≥50% in 7 days, or dialysis. We used forward selection, with a p value cutoff of 0.05, to develop the model, using a development (n=10,387) and external validation (n=8132) approach. The final model included 12 variables.

Results: The AKI event rate in the development and validation cohorts was 11% and 19%, respectively. A higher score monotonically predicted a higher risk of AKI in both cohorts (AUC 0.75 in the development cohort; AUC 0.71 in the validation cohort). The positive predictive value of a score >8 was 37% and 48% in the development and validation cohorts, respectively. The model was similarly predictive of more severe stages of AKI.

Conclusions: We present a 12-variable risk prediction score for AKI following cardiac surgery. We propose that this model could be used for both clinical prognostication and for research purposes.

Risk Factor	Points
Male gender	1
eGFR (ml/min/1.73m²)	
45–59 (REF to ≥60)	1
30–44 (REF to ≥60)	2
<30 (REF to ≥60)	3
Hemoglobin (g/dL)	
10–11.9 (REF to ≥12)	2
<10 (REF to ≥12)	3.5
White blood cell count (per mm³)	
<4 (REF to 4–12)	1
>12 (REF to 4–12)	2
Platelet count (10³/L)	
<150 (REF to 150–400)	1
>400 (REF to 150–400)	2
Albumin (g/dL)	
3.6-4 (REF to >4)	1
<3.6 (REF to >4)	2
Diabetes mellitus	1
Hypertension	1
CHF	1
Chronic liver disease	1
Prior cardiac surgery	1.5
Combined CABG/valve	1



Risk Score	0–2	3–4	5–6	7–8	9–10	11–12	≥13
Development	3673	3323	1870	914	418	155	34
Validation	2759	2692	1410	769	356	124	22
Total No.	6432	6015	3280	1683	774	279	56

TH-PO071

The Scoring Model for Prediction of Acute Renal Replacement Therapy in Intensive Care Unit Patients with AKI in a Limited-Resource Country

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Background: Acute kidney injury (AKI) is a common problem with high mortality in clinical practice, especially in the intensive care unit (ICU) patients. Making-a-decision of Acute Renal replacement therapy (ARRT) initiation has still been state-of-the-arts. This study aimed to generate and validate a scoring model for prediction of ARRT in ICU patients with AKI (ARRT score).

Methods: We performed a retrospective cohort study of ICU patients with AKI in a university hospital, Thailand. Risk factors of 7-day AKI requiring ARRT (7d-ARRT) were derived from the medical records between January 2013 and June 2015 (derivation cohort; der-cohort). We generate an ARRT score by the significant risk factors from the multivariate logistic analysis. To find the best model, we applied the area under the receiver operating characteristic curve (AUROC) analysis and Akaike information criterion (AIC). The ARRT score was validated by the data between June 2015 and December 2015 (validation cohort; val-cohort).

Results: The study included 292 patients in a der-cohort and 57 patients in a val-cohort. We found the best model to predict 7d-ARRT was oliguria (<0.5 ml/kg/hr after resuscitation), advanced CKD (eGFR < 45 ml/min/1.73m²) and severity of AKI at ICU admission [der-cohort: AUROC = 0.768, AIC = 201.02, val-cohort: AUROC = 0.845, AIC = 57.04]. These risk factors were used for generation of ARRT score by weighting their score from coefficients value of each risk factors (figure 1). At 4 points of the ARRT score, specificity was 84.2%, 81.6% and sensitivity was 55.8%, 73.7% for der-cohort and val-cohort respectively.

Conclusions: We strongly recommend that ARRT score ≥ 4 points could predict 7d-ARRT. We suggest further large prospective cohort study to validate our ARRT scoring.

Funding: Government Support - Non-U.S.

Figure 1 Demonstrate the ARRT score and the points of each risk factors (A). Sensitivity, specificity, PPV, NPV, and Youden index analysis of each cut-off value (B). AUROC and AIC analysis of the derivation cohort and validation cohort (C).

A	ARRT score			B	Derivation cohort				
Risk factors	Coefficients	Points		Cut-off	Youden index	Sensitivity	Specificity	PPV	NPV
eGFR < 45 ml/min/1.73m²	0.7833	1.6		1	0.360	0.84	0.52	0.39	0.90
UO < 0.5 ml/kg/hr	1.3350	2.7		2	0.384	0.78	0.61	0.41	0.88
AKI staging				3	0.370	0.58	0.79	0.50	0.84
-Stage 2	0.4888	1		4	0.400	0.56	0.84	0.56	0.84
-Stage 3	1.5020	3		5	0.359	0.43	0.93	0.69	0.82
C	AUROC	AIC		6	0.129	0.14	0.99	0.79	0.76
Derivation cohort	0.768	277.2		Validation cohort					
Validation cohort	0.845	57.0		4	0.553	0.74	0.82	0.67	0.87

A: The ARRT score was used for evaluation in patients with AKI at ICU admission by summary the points of 3 risk factors. Parameter defined as following: eGFR, the lowest baseline eGFR that calculate by CKD-EPI equation in past 12 months; UO, the amount of urine output after adequate fluid resuscitation in 1 hour; AKI staging, define by creatinine criteria as AKIN classification.
B: Analysis of sensitivity, specificity, PPV, NPV, and Youden index of each cut-off value showed ARRT score ≥ 4 points could predict ARRT within 7 days.
C: Comparison of AUROC, AIC for derivation cohort and validation cohort represented good accuracy of ARRT score.
Abbreviation: AIC, Akaike information criterion; AKI, acute kidney injury; ARRT, acute renal replacement therapy; AUROC, area under the receiver operating characteristic curve; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; NPV, negative predictive value; PPV, positive predictive value; UO, urine output.

TH-PO072

The Role of Concurrent Major Complications in the Association Between AKI and Survival After Coronary Artery Bypass Grafting Surgery

Dadi Helgason,[1,2] Sólveig Helgadóttir,[3] Runolfur Palsson,[1,2] Martin I. Sigurdsson,[1,2] Tomas Gudbjartsson,[1,2] Olafur S. Indridason.[1] *[1]Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland; [2]University of Iceland, Reykjavik, Iceland; [3]Uppsala University Hospital, Uppsala, Sweden.*

Background: Acute kidney injury (AKI) is associated with decreased survival following coronary artery bypass grafting (CABG). In this study, we evaluated the impact of AKI and concurrent major complications on short- and long-term survival after CABG.

Methods: A retrospective study of all isolated primary CABG cases in Iceland in 2001-2013. AKI was defined by the KDIGO criteria and major postoperative complications comprised myocardial infarction, reoperation, stroke, mediastinitis, sternum dehiscence, acute respiratory distress syndrome and multiple organ failure. Patients were divided into four groups: AKI with or without major complications and non-AKI with or without major complications. Survival was plotted by Kaplan-Meier method and 30-day mortality evaluated by logistic regression. Predictors of long-term survival were only evaluated for patients without concurrent major complications using Cox regression.

Results: Of 1710 patients, 184 (11%) developed AKI. Major complications occurred in 21% of the AKI patients compared with 10% non-AKI patients (p<0.001). Overall survival was lower in patients with AKI compared with non-AKI patients (p<0.001, **Figure 1**). In adjusted analysis, AKI patients with major complications (OR=30.3 [95%-CI, 9.1-105.8]) and non-AKI patients with major complications (OR=11.6 [4.2-34.9]) had higher risk of 30-day mortality than non-AKI patients without major complications, while the risk of death for AKI patients without major complications was not significantly increased (OR=3.4 [0.8-13.3]). AKI was not significantly associated with 5-year mortality (HR=1.4 [0.8-2.4]). However, when the entire follow-up time (median 6 years, range, 0-13.5) was included, AKI predicted higher mortality (HR=1.6 [1.1-2.2]).

Conclusions: AKI associated with decreased survival following CABG. However, this relationship can to a great extent be explained by concurrent major complications, particularly in case of early mortality.

Funding: Government Support - Non-U.S.

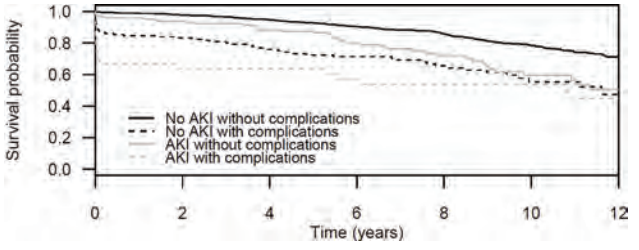

Figure 1. Overall unadjusted survival of AKI vs. non-AKI patients categorized based on whether they developed concurrent major complications or not.

TH-PO073

Incidence and Risk Factors of AKI After Total Knee Arthroplasty (TKA) or Revision (TKA-R) in Kidney Transplant Recipients (KTx)

Sorkko Thirunavukkarasu, Ziad Zoghby. *Mayo Clinic, Rochester, MN.*

Background: Kidney transplant recipients have an increased risk of complications following knee arthroplasties and revisions compared to non-transplant patients. The incidence of AKI is reported to be as high as 15.6 % and has been associated with increased mortality, morbidity, and length of hospital stays (LOS). Our AIM was to determine the incidence of AKI in KTx patients undergoing primary knee arthroplasty (TKA) or secondary revision (TKA-R), identify risk factors associated with AKI and evaluate its effect on allograft function at one year.

Methods: Using the orthopedic and transplant databases we designed a case-control study of 82 patients undergoing a total of 101 TKA and knee revisions between 2000 and 2018 at the Mayo Clinic. Information not available through the databases was obtained through chart review. AKI was defined per current KIDGO guidelines.

Results: The average age at surgery was 65 years (range 35-83); with 58% male and 98% white. The most common surgical indication was degenerative joint disease (80%). The incidence of AKI was 7 % in TKA and no patients developed AKI in the TKA-R group. All were stage 1 as per AKIN criteria. The LOS for those with AKI was 4.9 days compared to 3.5 days for those without AKI (p = 0.04). Mean anesthesia time was similar in patients with AKI (170 vs 189 min, p = 0.3). There was no significant difference between pressor requirements, estimated blood loss, need for transfusion, or amount of fluid administered between the AKI and Non-AKI groups. At one year, the mean eGFR change in the AKI group was (- 11.8 ml/min) compared to (-0.9 ml/min) in the Non-AKI group, p=0.065.

Conclusions: The incidence of AKI after total knee arthroplasty in KTx was 7 % and associated with longer hospitalization. All cases of AKI were mild, with renal function improving by hospital discharge. At one year, patients with AKI did have a lower eGFR compared to the non-AKI group but the difference did not reach statistical significance. Further larger studies are needed to assess the effect of TKA on allograft function.

TH-PO074

AKI Following Cardiac Bypass Surgery in Jamaica: Observations from a Low-Resource Country

Lori- Ann M. Fisher,[1] Sunil Stephenson,[2] Marshall K. Tulloch-Reid,[3] Simon G. Anderson.[2] *[1]University Hospital of the West Indies, Kingston, Jamaica; [2]University of the West Indies, Bridgetown, Barbados; [3]The University of the West Indies, Kingston, Jamaica.*

Background: AKI following cardiac surgery requiring cardiopulmonary bypass (CPB) is a common but serious complication with an incidence of 25-40%. It is associated with a 3 to 8 times increase in mortality, increased hospital length of stay and Chronic Kidney Disease. Little is known about the incidence and impact of AKI following CPB in the Caribbean. We describe the incidence and outcomes of AKI following CPB at a referral cardiac surgery centre in the Caribbean.

Methods: Medical records of adult patients with no prior ESRD or dialysis requirement who underwent cardiac surgery requiring CPB at the University Hospital from January 1, 2016 to December 31, 2017 were reviewed. All cause mortality was the defined end-point. Demographics, pre-operative status, intraoperative and post operative data were abstracted by two independent reviewers. AKI was based on KDIGO criteria using serum creatinine measurements obtained within 72 hours post-operatively. Multivariate logistic regression was used to examine the risk factors for and impact of AKI on all-cause mortality

Results: 125 patients (57% male) with mean age 57.4±12.9 years and mean pre-operative creatinine levels of 84.6 ± 33.7 μmol/L underwent cardiac surgery. The incidence of AKI was 31.2% (39/125), Of these 41% (16/39) were KDIGO I, 23% (9/39) KDIGO II and (14/39) 36% KDIGO III. Renal replacement therapy was required in 4% (5) of patients. In logistic regression analyses male sex (OR 0.46,95%CI: 0.2-0.9), and higher preoperative haemoglobin (OR 0.69,95% CI: 0.5-0.9) reduced the likelihood of AKI, whereas preoperative CKD (eGFR<60) (OR 8.6, [95% CI:1.7-43.6]) and prolonged bypass time (OR per 1 hour=2.9[95% CI 1.18-7.2]) increased risk. There was no association of age, cross clamp time or type of surgery (valve replacement or CABG) with AKI. Approximately 21%[26/125] of patients died in hospital. AKI was associated with four fold increased risk for death after adjusting for age and sex (OR[95% CI]=4.2[1.6-10.5])

Conclusions: The incidence of AKI following CPB is similar in our cohort to that reported in high income countries and significantly increases the risk of in hospital mortality. Larger multicentre prospective studies to predict risk, identify interventions to reduce mortality and assess long term complications of AKI following CPB in low resource countries are needed.

TH-PO075

Risks and Outcomes of Postoperative Dialysis-Requiring AKI in Patients Who Underwent Coronary Artery Bypass Grafting Surgery: A Large Retrospective Study

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Background: In-hospital acute kidney injury (AKI) has been linked to higher mortality and kidney disease progression. We aim to evaluate the associated factors and long-term outcome from patients underwent coronary artery bypass grafting (CABG) surgery, who developed dialysis-requiring AKI.

Methods: Data were collected by the National Health Insurance Research Database of Taiwan from 2002 to 2012. Individuals 18 and older, who underwent scheduled isolated CABG were identified (n=33790). Patients who were ESRD or received renal replacement therapy (RRT) within one year before surgery were excluded. AKI requiring dialysis was identified by the dialysis procedure code. The long-term mortality and ESRD were examined using multivariate Cox regression.

Results: The incidence of dialysis-requiring AKI after CABG is 7.6% (2,575). Patients with age 65 and older, history of Type 2 diabetes (T2DM), hypertension (HTN) and use of Angiotensin receptor blocker (ARB), erythropoietin (EPO) as well as on-pump CABG were the risk factors. And older age (>=65 y.o), T2DM and in-hospital RRT were associated with increased long-term mortality (HR 2.62, 1.49 & 4.47, p<0.0001). RRT also had a significantly increased risk of progression to ESRD (HR 17.16, p<0.0001). Neither on-pump nor off-pump CABG affects long-term mortality (HR 0.95, p=0.051), but on-pump CABG patients had a higher risk of developing ESRD (HR 1.19, p=0.001). While preoperative statin use linked to lower long-term mortality (HR 0.82), it caused a higher risk of ESRD progression (HR 1.23m)(p<0.0001). A similar observation was also seen in ARB use (HR 1.23, p< 0.0001). Furthermore, EPO use significantly increased the risk of progression to ESRD (HR 7.10, p<0.0001) despite no worsening effect on long-term mortality (HR 0.77, p=0.13)

Conclusions: We have identified the risk factors that increase the incidence of dialysis-requiring AKI after CABG; we further identified factors that affect the risk of mortality and ESRD progression. Statin appears to have protective effects in mortality and on-pump CABG showed higher risks in developing post-operative AKI and ESRD progression. Our finding may serve as a guideline for risk assessment and managing those who undergo CABG.

TH-PO076

Incidence and Prevention of Contrast-Induced Nephropathy in Percutaneous Coronary Intervention

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Background: Contrast induced nephropathy (CIN) has been reported in 20% of patients who undergo percutaneous coronary intervention (PCI). Contrast induces nephrotoxicity through direct tubule toxicity, capillary obstruction, vasoconstriction and hypoxia. Patients who have poor renal reserve with comorbidities are more susceptible, while the pleiotropic effects of statins may be nephroprotective. Prior studies have debated the role of contrast in the development of renal insufficiency. We hypothesize that while post-PCI acute kidney injury is multifactorial, the occurrence of CIN is likely understated. This is of clinical importance, because CIN is related to worse outcomes and longer hospital stays. Patient risk stratification can mitigate this risk.

Methods: Our study evaluates the incidence of CIN among 1521 patients at our hospital over 1 year. We used SAS 9.4 to perform logistic regression to assess the occurrence of CIN among patients with pre-PCI normal versus abnormal renal function (determined by GFR and Cr) in regards to underlying comorbidities. We also incorporated a CIN risk-calculator into our hospital EMR system and PCI practices.

Results: Our results showed that 15.3% of patients who underwent PCI developed CIN. Advanced age (OR 1.014, p = 0.02); race (blacks had OR 1.8, p = 0.01); underlying heart failure (OR 1.6 p = 0.004), especially among those with BNP > 400 (OR 4.5, p < 0.001) or EF < 40% (OR 1.47, p = 0.04); and diabetes (OR 2.0, p = 0.002) increased the probability of CIN. Patients with Cr > 1.2 were 3X more likely to get CIN (p < 0.001). GFR 30 – 60 and GFR < 30 increased the odds of CIN by 2.5 and 5 times, respectively (p < 0.01). By each unit decrease in hemoglobin, the odds of CIN increased by 5.5% (p = 0.002). Statin use reduced CIN by 42.9% (p = 0.001). Most notably, CIN also occurred in 9.1% of patients with normal baseline kidney function; among these patients, diabetes and age were the only contributory covariants.

Conclusions: Patients who undergo PCI are at significant risk of CIN. While baseline renal dysfunction and comorbidities are contributory, patients without these risk factors also developed CIN. Statins were renal-protective.

TH-PO077

Impact of Contrast Media Volume on the Onset of Contrast-Induced Nephropathy During Coronary Angiography: A Retrospective Study

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Background: Contrast media administration after coronary angiography can be complicated by a contrast-induced nephropathy (CIN). The toxicity threshold volume of contrast media remains undefined. The objective is to study (1) the relationship between the volume of injected contrast media and the occurrence of CIN and (2) the existence of a possible formula to calculate the threshold volume of toxicity of the contrast media for each patient after acute percutaneous coronary intervention.

Methods: We performed a retrospective study in 4773 patients who received percutaneous coronary intervention for acute coronary syndrome between 2012 and 2018. Contrast-induced nephropathy was defined as an increase of ≥ 0.5 mg/dL or ≥ 25% of serum creatinine compared to its baseline value between the 1st and 10th day following contrast media injection. Predictive factors independent of CIN adjusted to their observed mean was introduced into the formula calculate the threshold volume for renal toxicity.

Results: Of the 3073 patients analysed, 724 (23.6%) developed CIN. In our population, age, diabetes, PC volume, basal CrS and basal DFG are independent predictors of CIN, the risk of CIN is lower in men. Diabetes almost doubles the risk of NIC. A positive correlation was found between the volume of contrast media and the variation of basal serum creatinine. Patients receiving a higher amount of contrast media are significantly more likely to develop nephropathy (p<0.001). The volume of contrast media is an independent predictive factor of the occurrence of contrast nephropathy. We have developed a threshold volume prediction formula with a negative predictive value of 82%.

Conclusions: The volume of contrast media influences the occurrence of CIN. Therefore, there is an interest in reducing the amount of injected contrast during the intervention despite a weak relationship. A toxic PC volume threshold is difficult to establish given the different factors involved in the development of CIN. Nevertheless, the proposed formula could provide an additional tool for optimizing the prevention of renal toxicity.

TH-PO078

The Impact of Iodinated Contrast Media on Renal Outcomes in Diabetes and CKD

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Background: Iodinated radiocontrast media induced nephropaty (CI-AKI) is a major clinical problem accounting for 12% of all hospital-acquired cases of acute kidney injury (AKI), especially in patients with Chronic Kidney Disease (CKD) and Diabetes Mellitus (DM). Aim of this study was to estimate the influence of DM and CKD regarding the incidence of CI-AKI in rats. Renal function, global and renal hemodynamics were measured and the discriminating value of NGAL for assessing early renal injury was evaluated.

Methods: Wistar, adult, male rats were randomized into four groups: Sham (control); Citrate (citrate buffer, streptozotocin vehicle); CKD (5/6 nefrectomy); DM (streptozotocin, 65 mg/kg, iv); CKD+IC (CKD that received iodinated contrast-IC, 6ml/kg); DM+IC (DM animals that received IC, 4 weeks after DM, 6 ml/kg, ip). Renal function (inulin clearance), urinary neutrophil gelatinase (uNGAL), global and renal hemodynamics (systemic blood pressure, renal blood flow, renal vascular resistance) were evaluated.

Results: Renal hemodynamics showed an increase in renal vascular resistance in CKD and DM, while IC enhanced this damage. Also, CKD and DM rats presented lower inulin clearance and higher uNGAL levels. These paramethers were worsened when IC was associated.

Conclusions: Our results indicated that CKD and DM improves renal vulnerability to the toxicity of IC, once association between CKD or DM with CI predisposes to severe kidney injury by modulating renal hemodynamics in rats. NGAL showed to be a sensitive marker for CI-AKI when comorbidities are involved.

Funding: Government Support - Non-U.S.

Renal hemodynamics, renal function

Groups (n)	Blood pressure (mmHg)	Renal blood flow (mL/min)	Renal vascular resistence (mmHg/mL/min)	Inulin Clearance (mL/min)	Urinary neutrophil gelatinase (ng/mL)
Sham (5)	87±6	9.5±1.6	9.4±2.4	0.66±0.10	47.9±19.1
Citrate (5)	93±6	9.2±1.3	11.2±2.1	0.96±0.18	37.9±0.8
CKD (5)	132±13 *	8.7±2.3	16.1±4.8 *	0.28±0.04 *	76.7±31.3 *
DM (5)	96±4	5.3±1.7 &	23.9±8.3 &	0.55±0.08 &	53.8±17.8 &
CKD+IC	122±6 *	3.2±1.3 *#	37.9±15.0 *#	0.10±0.03 *#	153.5±70.0 *#
DM+IC	106±19 §	3.3±1.2 &§	38.4±9.3 &§	0.17±0.02 &§	99.8±18.7 &§

* p<0,05 versus Sham; # p<0,05 versus CKD; & p<0,05 versus Citrate; § p<0,05 versus DM

TH-PO079

Renal Events Following Iodinated Contrast Aggravate Diabetic Nephropathy

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Background: Iodinated contrast (IC) is a leading cause of AKI (CI-AKI) and occurs more frequently in individuals with increasingly common risk factors, including diabetes. IC-AKI has been growing in recent years faced with the more frequent diagnostic needs in old patients and with comorbid conditions such as diabetes. This complication is due to a number of factors, including the osmolality of the IC. The aim of this study is to evaluate the injury in kidneys of diabetic rats submitted to treatment with high- osmolar and low-osmolar iodinated contrast, evaluating the impact on hemodynamic and renal function in addition to oxidative profile.

Methods: Wistar rats, male and adult, weighing 250-290g were randomized into four groups: Citrate, Diabetes Mellitus (DM), Diabetes+low-osmolar iodinated contrast (DM+LIC) and DM+high-osmolar iodinated contrast (DM+HIC). Physiological parameters (body weight, water and food intake, glycemia and kidney/body weight ratio); renal function (Inulin Clearance; urinary neutrophil gelatinase/uNGAL); hemodynamics (arterial blood pressure; renal blood flow/RBF; renal vascular resistance/RVR) and oxidative profile (urinary peroxides/UP, urinary TBARS, renal tissue thiols and urinary nitric oxide/NO) were evaluated.

Results: Diabetic groups showed polyphagia, polydipsia, polyuria, high levels of blood glucose and reduction in body weight. DM group showed a reduced inulin clearance, elevated uNGAL, elevated RVR, reduced RBF, elevated UP, TBARS and NO and a consumption of antioxidant reserve. When IC was introduced, the parameters of renal function, renal hemodynamic and oxidative profile became worse, specially in the group DM+HIC.

Conclusions: The use of high and low osmolarity IC promoted additional deleterious action to renal function and hemodynamics with oxidative injury in diabetic rats, with a more expressive effect in the group submitted to high osmolality contrast treatment.

Funding: Government Support - Non-U.S.

Renal function, hemodynamics, oxidative

Group (n)	Serum creatinine (mg/min/kg)	Inulin clearance (mL/min/kg)	Neutrophil gelatinase-associated lipocalin (ng/mL)	Renal blood flow (mL/min)	Renal vascular resistance (mmHg/mL/min)	Urinary peroxides (nmol/g creatinine)	TBARS (nmol/g creatinine)	Thiols (nmol/mg potein)	Nitric oxide (μM/g creatinine)
Citrate (7)	0.30±0.06	0.94±0.23	41.41±4.63	8.19±0.76	15.05±2.00	2.15±0.85	0.16±0.04	30.92±7.44	25.06±4.05
DM (7)	0.80±0.25 *	0.58±0.05 *	57.25±14.44	3.96±0.70*	26.34±5.60 *	12.74±3.94 *	1.09±0.28*	15.75±1.17 *	53.72±5.31 *
DM+LIC	0.87±0.11 *#	0.34±0.11 *#	103.78±9.09 *#	3.06±0.42 *#	35.42±6.35 *#	18.94±7.54 *#	2.13±0.46 *#	12.50±3.64 *#	76.78±8.47 *#
DM+HIC	1.47±0.66 *#&	0.14±0.01 *#&	167.27±8.50 *#&	2.29±0.55 *#&	44.97±6.06 *#&	25.57±7.54 *#&	3.31±0.47 *#&	6.22±0.31 *#&	88.23±8.47 *&

* p<0.05 versus Citrate; # p<0.05 versus DM; & p<0.05 versus DM+LIC

TH-PO080

Beneficial Effect of Statin on Preventing Contrast-Induced AKI in Patients with Renal Insufficiency: A Meta-Analysis

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Background: Renal insufficiency is an important predictor of contrast-induced acute kidney injury (CI-AKI). We performed a meta-analysis to examine the effects of short-term statin therapy on the incidence of CI-AKI, particularly in patients with renal insufficiency.

Methods: A systematic search was conducted to retrieve randomized controlled trials (RCTs) that investigated the impact of statin pretreatment before administration of contrast media on the development of CI-AKI in patients with mild to moderate renal insufficiency. The primary outcome was development of CI-AKI. The secondary outcome was the incidence of AKI requiring hemodialysis.

Results: Data analysis from eight RCTs, which included a total of 2313 subjects in the statin-treated group and 2322 in the control group, showed that statin pretreatment was associated with significant reduction of the risk of CI-AKI (Relative Risk (RR) = 0.59; 95% Confidential Interval (CI) 0.44 to 0.79; $p = 0.0003$, $I^2 = 0\%$). A beneficial effect of statin on preventing CI-AKI was consistent, regardless of the dose of statin and use of N-acetylcysteine. The incidence of hemodialysis was low after contrast administration in the statin-treated group, but the reduction was not significant (RR = 0.28; 95% CI 0.05 to 1.70; $p = 0.17$, $I^2 = 0\%$). In subgroup analysis based on baseline estimated glomerular filtration rate (eGFR), patients with baseline eGFR < 60 ml/min/1.73 m^2 (RR = 0.63; 95% CI 0.41 to 0.98; $p = 0.04$, $I^2 = 0\%$) and 30 < eGFR < 90 ml/min/1.73 m^2 (RR = 0.56; 95% CI 0.39 to 0.82; $p = 0.003$, $I^2 = 0\%$) showed significant reduction of risk of CI-AKI.

Conclusions: Statin pretreatment is effective at preventing CI-AKI and should be considered in patients with pre-existing renal insufficiency.

TH-PO081

AKI Is a Rare Complication of Therapeutic Paracentesis Among Inpatients with Cirrhosis

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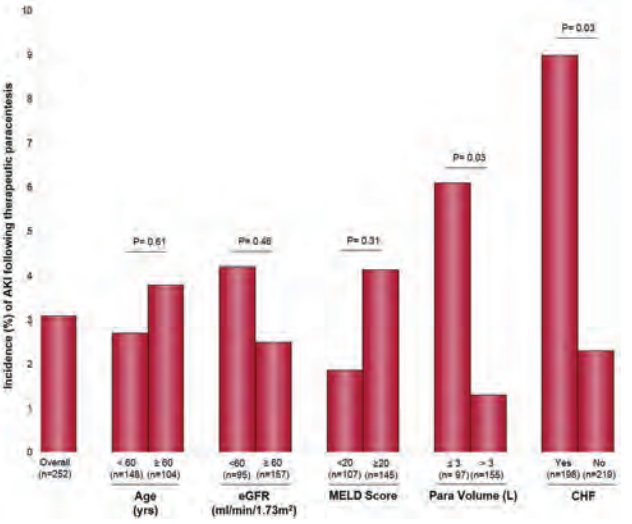
Background: AKI is a feared complication of therapeutic paracentesis. However, prior studies that assessed AKI incidence following paracentesis were limited by small sample sizes (most had <40 patients) and restricted generalizability (e.g., exclusion of inpatients).

Methods: We conducted a large, retrospective, "real-world" cohort study of all adult inpatients with cirrhosis who underwent a therapeutic paracentesis (>1L) while admitted to Massachusetts General Hospital between 2016 and 2018. We assessed the incidence and severity of paracentesis-associated AKI based on changes in SCr. AKI and its severity were defined based on KDIGO guidelines. We also performed stratified analyses to assess whether the incidence of AKI differed across subgroups.

Results: A total of 252 paracenteses were performed in 101 cirrhotic patients. IV albumin was administered in 77% of paracenteses. The overall incidence of AKI was 3%. AKI severity was as follows: 50% stage 1, 12.5% stage 2, and 37.5% stage 3. The incidence of AKI was similar when stratified by age (<60 vs. ≥60 years), baseline eGFR (<60 vs. ≥60 ml/min/1.73m²), and MELD score (<20 vs. ≥20). Patients who received lower compared to higher volume paracenteses (≤3L vs. >3L) had a higher incidence of AKI (6% vs. 1.3%; P=0.03), however, these patients were also less likely to have received IV albumin (65% vs. 84%; P<0.001). Patients with CHF had higher rates of AKI compared to patients without CHF (9% vs. 2.3%; P=0.03).

Conclusions: In a large cohort of inpatients with cirrhosis undergoing therapeutic paracentesis, we found that post-procedure AKI rates were low. This finding was consistent across multiple subgroups, with the notable exception of CHF. Therapeutic paracentesis with IV albumin replacement is a procedure that can generally be performed without significant concern for AKI.



TH-PO082

An Evaluation of the Prevalence of Kidney Diseases in Patients with Inflammatory Bowel Diseases in a Nationwide Analysis

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Background: Up to 40% of patients with Inflammatory bowel diseases(IBD) may have extra-intestinal manifestations, mainly involving liver, skin, and joints. Anecdotal reports suggest renal involvement, but there are no estimates of prevalence. Our aim was to examine the prevalence of kidney diseases among hospitalized patients with IBD, along with the prevalence of kidney disease among patient with collagen vascular diseases (CVD) and among patients without IBD and CVD

Methods: We analyzed 2000-2014 data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample database which captures annual hospital discharge data for 20% stratified sample of U.S.community hospitals. We used International Classification of Diseases, Ninth Revision, diagnosis codes to identify three subsamples. Kidney diseases include acute kidney injury, glomerular diseases and others. CVD included systemic lupus erythematosus, rheumatoid arthritis and others.

Results: Among 713,902 hospitalized IBD patients, we identified 69,049 individuals with kidney diseases(9.6%), representing a weighted national estimate of 341,946 individuals with kidney diseases. The prevalence of kidney disease among patients with IBD was 9.6%,11.9% in patients with CVD, and 8.5% in the general population (all p<0.001). Baseline characteristics of patients in three groups are given in Table1. Patients with IBD had a younger age distribution, higher distribution of white race, and a lower prevalence of hypertension, diabetes, and CHF when compared to patients with CVD or the general population without IBD or CVD

Conclusions: The burden of renal disease among patients with IBD is greater than that of the general population, which is notable given their lower traditional risk factors for kidney disease;and similar to CVD which is an immune-mediated systemic disorder. Coexisting renal disease should be considered among patients with a known diagnosis of IBD

Table	All IBD N=713,902	All CVD N=1,809,221	All pts - IBD- CVD N=94,215,528	p-value*
Age				<0.001
18-39	30.5%	10.7%	25.0%	
40-59	33.2%	28.1%	25.5%	
>60	36.2%	61.0%	48.6%	
Female	56.9%	78.8%	60.0%	<0.001
Race(White)	67.1%	59.2%	56.2%	<0.001
HTN	27.2%	44.9%	35.4%	<0.001
DM	13.3%	21.5%	21.3%	<0.001
CHF	6.3%	15.8%	13.0	<0.001
% with Kidney Diseases	9.6%	11.9%	8.5%	<0.001

* Chi-square testing, including pairwise comparisons with Bonferroni correction, was used for all evaluations. In pairwise comparisons of disease states, patients with IBD were compared to patients with CVD and those patients without IBD or CVD; patients with CVD were compared to patients with IBD and patients without IBD or CVD(all p<0.001).

Table1

TH-PO083

EPILAT-IRA Study: A Contribution to the Understanding of the Epidemiology of AKI in Latin America

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Background: Acute kidney injury (AKI) is a public health problem, due to its high and rising frequency, its association with increased morbidity and mortality, and the economical burden related to its care. Considering the limited data on AKI epidemiology in Latin America and the Caribbean, we performed a prospective observational study to determine risk factors, clinical profile, process of care and outcomes of AKI in the region

Methods: Participants were recruited by open invitation through the Latin American Society of Nephrology and Hypertension. Patients meeting the KDIGO AKI definition, during hospitalization, were included over a a 9-month period and designated as community or hospital acquired. De-identified clinical and lab data was entered in a specifically designed on-line platform. Co-variables potentially linked to AKI were recorded and correlated with mortality at hospital discharge and 90 days using a multiple logistic regression model

Results: A total of 57 participants from 15 countries provided data on 905 patients, the majority of them with acceptable coverage of basic needs. Median age was 64 (50-74) yrs. and 61% were male. Comorbidities were present in 77% of the patients. AKI was community-acquired in 62%. Dehydration, shock and nephrotoxic drugs were the most usual AKI causes. Seventy-seven percent of the patients were assessed by nephrologists. Renal replacement therapy was performed in 29% of cases. All-cause in-hospital mortality was 26.5% and was independently associated to older age, chronic liver disease, hypotension, shock and cardiac disturbance as etiologic factors, infection and sepsis as in-hospital complications, need of renal replacement therapy and mechanical ventilation. Mortality at 90-days follow up was 25%.

Conclusions: This study provides new information on the characteristics and outcomes of AKI patients in Latin America and Caribbean region. Notwithstanding, this study represents partially the AKI situation in the participant countries rather than the actual epidemiology of AKI in Latin America, a pending and needed task.

TH-PO084

Increased Mortality Among AKI Patients Attending the Emergency Department: A Retrospective Hospital-Based Cohort Study

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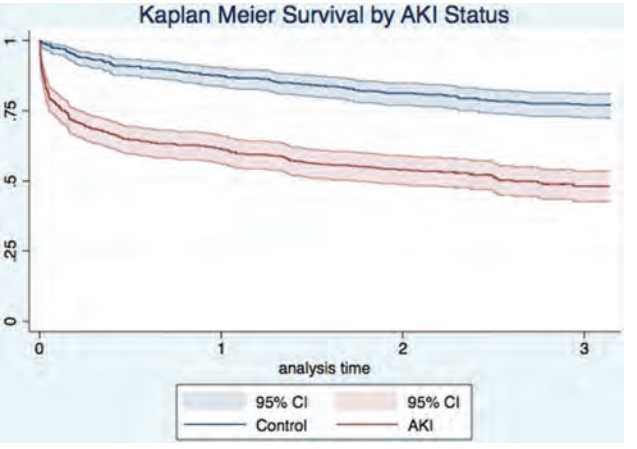
Background: It is well documented that acute kidney injury (AKI) is associated with increased inpatient mortality, but this association is poorly described in the emergency department (ED) setting.

Methods: Between April 2016 and March 2017, we randomly selected electronic records of 365 patients from 1695 presented to ED with AKI using an electronic AKI reporting system, and compared them to 379 randomly selected patients without AKI. The cohort was followed up till the end of April, 2019. Mortality as well as other demographic characteristics were compared.

Results: Incidence of AKI was 5.3%. AKI was associated with significantly higher risk of death 50.27% compared with 22.96% amongst those with no AKI (p< 0.001). Those whose AKI worsened while inpatients had a higher mortality risk of 63.6% compared to 49.09% in these whoms AKI did not progress to a higher stage, although it did not reach statistical significance (p=0.11). Risk of inpatient mortality was significantly higher amongst the AKI group (34.4% vs 0.0% P=<0.0001). Risk of readmission within 30 days did not significantly differ between the 2 groups (16.5% vs 21.4%, P=0.14). At 12 months, 71.9% of the AKI group developed CKD progression or de novo CKD compared to 54.6% in controls (P=<0.0001). Average follow-up time was 3.14 years. After adjusting for age, gender, ethnicity, 13 comorbidities, serum sodium and albumin, AKI was still independently associated with increased mortality (adjusted HR 1.93, CI 1.4-2.7). Hypoalbuminemia (HR 2.1 CI 1.5-2.9 P=<0.0001), being 75-84 years old (HR 1.7 CI 1.1-2.7 P=0.02), or over 85 years (HR 2.3 CI 1.5-3.5, P=<0.0001), as well as having at least one comorbidies (HR 1.5 CI 1.1-2.1, P=0.02) were all independently associated with mortality.

Conclusions: Presentation to ED with AKI is independently associated with inpatient deaths as well as overall mortality and morbidity.

Funding: Government Support - Non-U.S.



TH-PO085

Renal Failure After Knee Arthroplasty and Antibiotic Cement: Role of Dialysis

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Introduction: Two-step arthroplasty procedures have become the standard of care in the treatment of prosthetic joint infections. Antibiotic spacer placement is associated with renal failure requiring dialysis depending on the type and amount of antibiotics. We present a case of renal failure post-antibiotic cement placement. To our knowledge, our case reports one of the highest serum tobramycin levels post spacer impregnation

Case Description: A 65-year-old female with a history of left knee replacement presented with worsening pain and an inability to extend the knee. Bedside arthrocentesis was consistent with an infected prosthetic left knee. She underwent elective arthroplasty. She had no h/o CKD, DM, HTN. She underwent the first step of revision arthroplasty with successful fusion nail and placement of antibiotic cement. Intraoperatively she sustained hypotensive episodes requiring levophed for a brief period. Post-op she had hypoxic respiratory failure associated secondary to laryngeal swelling and stridor, which resolved with steroids On postoperative (POD) day 2 nephrology was consulted for oliguric renal failure with a serum creatinine of 3.06 mg/dl (Pre-op creatinine 0.7 mg/dl). Renal failure was speculated to be from nephrotoxic medications and Ischemic acute tubular necrosis. Surgery consisted of placing an antibiotic cement spacer, which contained a total of 12 grams of vancomycin and 15 grams of Tobramycin Drug levels obtained on POD 3 were 38mcg/ml of Vancomycin and 20 mcg/ml of Tobramycin. Her renal failure continued to worsen with a peak serum creatinine of 4.9 mg/dl, developed anuria. She was started on hemodialysis and received 5 sessions over the next 7 days. Dialysis sessions were extended to 4 hours to achieve drug clearance. POD day15, levels decreased to 6.6 mcg/ml of tobramycin and 18.3 mcg/ml of Vancomycin. She demonstrated renal function recovery with a reduction in Tobramycin levels. With an improvement in the renal function explantation of the antibiotic spacer was not required

Discussion: Arthroplasty procedures with antibiotic cement impregnation are associated with significant AKI with incidence varying from 4.8% - 26%. Early recognition of toxicity and timely hemodialysis sessions may help the recovery of renal function and avoid re-exploration and explanation of prosthetic joints and antibiotic spacers

TH-PO086

Incidence and Risk Factors of AKI After Total Hip Arthroplasty or Revision in Kidney Transplant Recipients (KTx)

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Background: Immunosuppressive regimens increase the risk of bone complications such avascular necrosis and osteoporosis in KTx. Treatment of choice is Arthroplasty but limited data show that adverse events, specifically AKI is higher in KTx (16-26.6%) compared to the general population (1.1%). AKI has been linked to increased morbidity and mortality. Our aim was to determine the incidence of AKI in KTx undergoing primary hip arthroplasty (THA)or revision (THA-R), identify risk factors associated with AKI and evaluate its effect on allograft function at 1 year.

Methods: Using the orthopedic and transplant databases, we designed a case-control study of 102 patients undergoing a total of 141 THA and THA-R between 2000 and 2018 at the Mayo Clinic. Variables of interest not available in the databases were obtained through chart review. AKI was defined per the current KIDGO guideline.

Results: The average age at surgery was 59 years (range 27-82); with 58% male and 96% white. The most common surgical indications for THA were degenerative joint disease (57%), avascular necrosis (27%), and fractures (12%); and for THA-R, loosening (28%), dislocation (22.7%) and Infection (9%). The incidence of AKI was 10.4% and 17% in THA and THA-R, respectively (p=0.36). All AKI were stage 1 per AKIN criteria. Anesthesia time was longer in patients with AKI (232 vs 196 min, p = 0.055) and in those undergoing THA-R compared to THA (256 vs 182 min <0.001). The length

of hospitalization for those with AKI was 5.1 vs. 4.3 days for those without AKI (p = 0.2). There was no significant difference between vasopressors use, blood loss, need for transfusion, crystalloid or colloid administration between the AKI and Non-AKI groups. At one year, mean change in eGFR was not different between the two groups (AKI: -1.7 ml/min; Non-AKI: -2.6 ml/min; p = 0.7).

Conclusions: The incidence of AKI after total hip arthroplasty in KTx was 10.4% (17% after revision arthroplasty) and associated with longer hospitalization. However, all cases of AKI were mild, resolved by hospital discharge and did not affect allograft function at 1 year.

TH-PO087

Risk Factors of AKI in Upper Urinary Tract Obstruction

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Background: Obstruction to urine flow occurs at any site in the urinary tract and development of post-renal acute kidney injury (AKI) depends on whether it is acute or chronic, unilateral or bilateral and presence of combined sepsis. However, incidence, etiologies, risk factors or prognosis of post-renal AKI in urinary tract obstruction are largely unknown due to paucity of extensive epidemiologic data.

Methods: We conducted a retrospective analysis of 1,784 patients who received percutaneous nephrostomy (PCN) due to upper urinary tract obstruction in 3 university hospitals in Korea from January 1, 2002 to August 16, 2018. AKI was diagnosed according to KDIGO AKI criteria and analyzed risk factors of AKI using multivariate logistic regression analysis.

Results: AKI developed in 79.9% of patients who underwent PCN. Patients with post-renal AKI were more likely to be male (50.4 vs 51.1%, p<0.01)), older (64 vs 57yrs, p<0.01) and associated with decreased baseline renal function (eGFR 72.88 vs 90.79 ml/min/1.73m2, p<0.01). Prevalence of hypertension (47.5 vs 35.5%, p<0.01)), ischemic heart disease (5.4 vs 2.3%, p=0.013), peripheral arterial occlusive disease (7.1 vs 3.9%, p=0.03), heart failure (4.5 vs 1.1%, p<0.01) or cancer (68.5 vs 53%, p<0.01) was significantly higher in patients with AKI compared with those without AKI. Mean hemoglobin level, protein, albumin and tCO2 level were significantly lower while uric acid, CRP and procalcitoning level were significantly elevated in patients with AKI. In multivariate logistic regression analysis, lower tCO2 (OR 0.835, 95% CI 0.716-0.975, p=0.022) and albumin level (OR 0.190, 95% CI 0.049-0.739, p=0.017), and high uric acid level (OR 2.004, 95% CI 1.252-3.208, p=0.004) were significantly associated with the development of AKI in these patients.

Conclusions: The incidence of AKI was very high (79.7%) in patients who underwent PCN due to upper urinary tract obstruction. Anemia, leukocytosis, hyperuricemia, and underlying hypertension are found to be independent risk factors for AKI with male predominancy.

TH-PO088

Risk Factors of AKI in Patients with Decompensated Cirrhosis

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Background: Acute kidney injury(AKI)is a common complication with high mortality and morbidity in decompensated cirrhotic patients. However, few studies concerning the risk factors of cirrhosis-associated AKI have been published. In our study, we aim to investigate the risk factors of AKI in patients with decompensated cirrhosis in our hospital from 2012 to 2016.

Methods: We performed a single-center retroperspective stuty. Clinical data of patients with decompensated cirrhosis were collected from Dept. of Liver diseases, Hwamei Hospital, University Of Chinese Academy of Sciences from 2012 to 2016. According to the KDIGO criteria, patients were divided into AKI group and non-AKI group. Risk factors for AKI were analyzed by univariate and multivariate analysis methods.

Results: 945 inpatients with decompensated cirrhosis (mean age was 55.42 and 65.3% were male.) were enrolled, with the incidence of AKI being 17.7%. The mean course of cirrhosis was (5.59±4.94) years and the average **length of stay** was (20.01±14.00) days. Multivariate Logistic regression analysis showed that increased age (OR=1.031, p=0.001), infection (OR=7.125, p<0.001), decreasing eGFR (OR=0.845, p<0.001), ascites (OR=5.012, p<0.001), and ACEI/ARB use (OR=7.882, p=0.003) were independently correlated with patients with decompression cirrhosis complicated with AKI.

Conclusions: There was high incidence of AKI in patients with decompensated cirrhosis, whose independent risk factors were associated with increasing age, infection, decreasing eGFR, ascites and using of ACEI/ARB.

Funding: Government Support - Non-U.S.

TH-PO089

AKI in Hospitalized Patients Who Underwent Percutaneous Kidney Biopsy

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Background: Performing a kidney biopsy is necessary to accurately diagnose diseases such as glomerulonephritis and tubulointerstitial nephritis, among other such conditions. These conditions predispose patients to chronic kidney disease, as well as acute kidney injury (AKI). Notably, most epidemiological studies describing AKI have not investigated this patient population.

Methods: Included patients admitted to the nephrology ward of a tertiary hospital who underwent percutaneous kidney biopsy. AKI was diagnosed based on the Kidney Disease: Improving Global Outcomes criteria.

Results: Of the 223 patients investigated, 140 (62.8%) showed AKI. Of these, 91 (65%), 19 (13.6%), and 30 (21.4%) presented with AKI classified as stages 1, 2, and 3, respectively. The primary indication for performing biopsy was nephrotic syndrome or nephrotic proteinuria (73 [52.1%] in the AKI vs. 51 [61.4%] in the non-AKI group, p=0.048). Focal segmental glomerulosclerosis was the most prevalent primary disease (24 [17.1%] in the AKI vs. 15 [18.0%] in the non-AKI group, p=0.150). Multivariate analysis of risk factors associated with AKI showed hemoglobin levels (odds ratio [OR] 0.805, 95% confidence interval [CI] 0.681–0.951, p=0.011), serum high-density lipoprotein cholesterol levels (HDL-c, OR 0.970, 95% CI 0.949–0.992, p=0.008), and baseline serum creatinine levels (OR 2.703, 95% CI 1.471–4.968, p=0.001) were significantly associated with AKI.

Conclusions: We observed a high incidence of AKI in hospitalized patients who underwent kidney biopsy to investigate their renal disease, particularly glomerulonephritis. Higher levels of hemoglobin and serum HDL-c were associated with a lower risk of AKI.

Funding: Government Support - Non-U.S.

TH-PO090

Incidence and Risk Factors of AKI and Tumor Lysis Syndrome in Patients with Multiple Myeloma Treated with Bortezomib

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Background: Nephrotoxicity of bortezomib, a proteasome inhibitor, has not yet been described frequently, while tumor lysis syndrome (TLS) associated with multiple myeloma (MM) has been increased after introduction of the drug. This study compared the incidence and risk factors of acute kidney injury (AKI) and TLS in patients with MM after bortezomib-based chemotherapy to investigate the drug-related nephrotoxicity.

Methods: From 2006 to 2017, 276 patients who underwent first cycle of bortezomib-based chemotherapy for MM were identified in single tertiary hospital. Laboratory TLS was defined according to the Cairo-Bishop definition. Development of AKI was assessed by AKI Network criteria within 7 days after first chemotherapy.

Results: The age was 65 [56-72] years old, and 47% (n=131) of participants were female and baseline estimated glomerular filtration rate (eGFR) was 61.3 [34.1-89.1] mL/min/1.73m^2. The incidences of AKI and laboratory TLS were 17% (n=47) and 13% (n=36), respectively. Ten (3.6%) subjects corresponded to the both AKI and TLS criteria. Multivariate analyses showed that lower eGFR category (30~59, odds ratio [OR]=3.063 [1.278-7.339]; 15~29, OR=3.417 [1.088-10.726]; <15, OR=10.080 [2.677-37.951] vs ≥ 60), lower serum albumin level (OR=0.491 [0.278-0.868], *P*=0.0144) and renal amyloidosis (OR=11.174 [3.974-31.420], *P*<0.0001) were predictors of development of AKI. MM stages and β2-microglobulin were not associated with AKI occurrence. Regarding laboratory TLS, MM stage and β2-microglobulin were higher in those with TLS. In multivariate analyses, β2-microglobulin levels (OR=1.194 [1.066-1.337], *P*=0.0021) and any chromosomes abnormalities at high risk (OR=0.115 [0.026-0.503], P=0.0041) were associated with higher risk of TLS.

Conclusions: Development of AKI was often observed without being accompanied by TLS in patients with MM after treatment of bortezomib. In addition, risk factors of AKI and TLS were widely different. These findings implicated the potential nephrotoxicity of bortezomib besides TLS in patients with decreased kidney function. The efforts to prevent the developments of AKI are needed in patients with risk factors, when initiating bortezomib treatment.

TH-PO091

Clinical Significance of AKI in Lung Cancer Patients

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Background: Acute kidney injury (AKI) in cancer patients is related to increased morbidity and mortality. Previous our exploration of AKI in cancer patients showed unexpectedly a higher incidence of AKI in lung cancer patients than those with other malignancy. This study aimed to evaluate the clinical significance of AKI in lung cancer patients.

Methods: The patients diagnosed as lung cancer from 2004 to 2013 in Seoul National University Hospital were enrolled. They were categorized into two groups by an occurrence of AKI, and the patients with AKI were categorized into three groups by AKI stage. AKI was defined according to KDIGO-AKI guideline. Demographic factors, co-morbidities, laboratory findings, count of contrast-enhanced computed tomography (CE-CT), pathologic types, and treatment options such as surgery and chemotherapy were included as covariates. We performed Cox proportional hazard modeling for mortality among patients who survived more than 1 year after cancer diagnosis.

Results: A total of 3,202 patients were included in the final analysis. Mean age was 63.8±10.34 years and 68.6% were male. AKI occurred in 1,783 (55.7%) patients during the follow-up period. Most AKI was mild AKI with stage 1 (75.8%). We found that the development of AKI were independently associated with older age, higher systolic blood pressure, diabetes mellitus, high initial serum creatinine, anemia, hyperkalemia,

hypophosphatemia, hyperuricemia, hypoalbuminemia, acidosis, frequent CE-CT, and chemotherapy. During follow-up duration (2.64±2.18 years), 21 (0.7%) patients reached end-stage kidney failure and all of them were experienced AKI. In the survival analysis, we found that not only AKI development but also AKI severity was an independent risk factors for mortality even after adjustment with cancer-specific variables including stage or pathologic type.

Conclusions: In this study, more than half of lung cancer patients experienced AKI during their diagnosis and treatment period. Moreover, AKI occurrence and more advanced AKI were associated with higher mortality risk. Further studies about risk factor analysis for AKI occurrence should be needed to prevent AKI in lung cancer patients.

TH-PO092

Characteristics and Outcomes of Hospitalized Homeless AKI Patients

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Background: Hawaii has the highest rate of homeless population per capita. Homeless people are a vulnerable group and prone to multiple health problems, including kidney diseases. Little is known about the characteristics and outcomes of acute kidney injury (AKI) in this population.

Methods: This is a retrospective study of homeless and domiciled patients who were admitted to a tertiary medical center in Honolulu, Hawaii between 2015-2016, with AKI diagnosis present on admission by ICD10 code and meeting 2012 KDIGO criteria for AKI.

Results: Between 2015 and 2016, we identified 324 patients who were admitted with AKI of which 6.48 % were homeless. Mean age of homeless patients was 56.9±8.75 compared to domiciled patients 65.85±17.59 with p<0.01. Homeless patients tended to be female (80.85%) compared to domiciled patients (52.81%), p<0.01. Caucasian race was a majority of the homeless patients, 47.62%, compared to 21.45% in domiciled patients. 71.43% of the homeless patients had a pre-renal cause of AKI compared to 38.61% in domiciled patients, p=0.06. There was no difference in percentage of underlying chronic kidney disease between homeless and domiciled patients, p=0.89. 38.10% of homeless patients visited the emergency room within 1 month prior to an index admission compared to 17.49% in domiciled patients, p=0.02. Homeless patients were more likely to be a substance user, current smoker, and alcohol abuser compared to domiciled patients, all p<0.01. Homeless patients were more likely to be discharged with a lower serum creatinine, p<0.01, and significantly shorter hospital stay, p=0.04.

Conclusions: Homeless AKI patients tended to be younger, more likely a substance user, current smoker, alcohol abuser, and with liver disease than domiciled patients. Caucasian race was the majority of homeless patients, whereas Asian race was the majority of domiciled patients. Although pre-renal cause was the most common cause of AKI in both groups, the rate of pre-renal cause in homeless patients was almost twice that of domiciled patients. There was no difference in admission serum creatinine, but the homeless were discharged with lower serum creatinine likely due to a higher rate of reversible kidney injury. There was no difference in mortality or dialysis rate.

TH-PO093

Incidence, Associated Factors, and the Survival After 1-Year Follow-Up in Patients with Community-Acquired AKI Admitted to the Emergency Room

Diego F. Argudo sanchez, L. M. Perez-Navarro, Maribel Merino, Rafael Valdez-Ortiz. *Hospital General de Mexico, Mexico City, Mexico.*

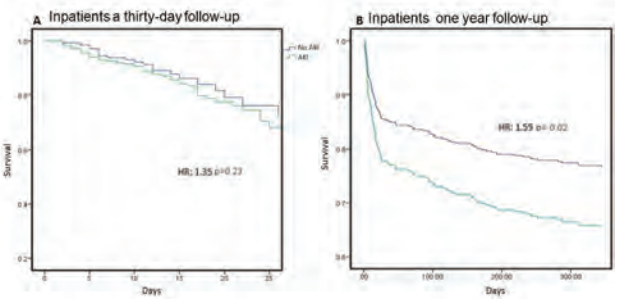
Background: Community acquired acute kidney injury (AKI-CA)is defined in patients who, at the time of admission to the hospital, present criteria for acute kidney injury diagnosis. The acute kidney injury (AKI) is frequent complication among inpatients in the emergency room (ER). Our aims were to know the incidence, associated factors and the one-year survival of patients with AKI-CA.

Methods: Prospective cohort of admitted patients in the ER. The AKI was defined according to KDIGO 2012 criteria. The groups were compared using the Student's t-distribution or the X2 distribution, logistic regression was performed for OR and a Cox regression for HR and survival with IC 95% and p≤0.05.

Results: Eight hundred thirteen patients with an average age of 52.4±18 years were included. The 55% (443) were men. The incidence of AKI-CA was 55%, where 32.5% was due to AKI-1, 15% AKI-2, and 7.5% AKI-3. The associated factors with the develop of AKI-CA were hypertension (OR: 1.5, IC95% 1.1-2), liver failure (OR: 3.5, IC95% 1.8-6.3), chronic kidney disease (OR:3.82, IC95% 1.7-8.3), sepsis OR:3.48, IC95% 2.3-5.1), and surgical pathology (OR:2.55, IC95% 1.7-3.8). According to the state of AKI the inpatients days increased (AKI-1:10.7, AKI-2:12.8, AKI-3:14.2 days, p< 0.001). The risk of death during the inpatients days did not exhibit significant differences among the patients with and without AKI (p=0.23, Figure 1). However, the analysis after a one-year follow up showed a mortality of 64% in patients with AKI-CA versus 36% in patients that did not suffer it (p<0.001), with increased mortality risk (Figure 1b).

Conclusions: A high incidence of AKI at the time of admission and with an impact on survival over one year of follow-up.

Figure 1. Survival of patients with Acute Kidney injury



TH-PO094

Community-Acquired AKI in Older Adults Admitted to the Emergency Medical Service: At 1-Year Follow-Up

Diego F. Argudo sanchez, L. M. Perez-Navarro, Ivan Rosero, Maria F. Garcia-Guevara, Rafael Valdez-Ortiz. *Hospital General de México Dr. Eduardo Liceaga, México, Mexico.*

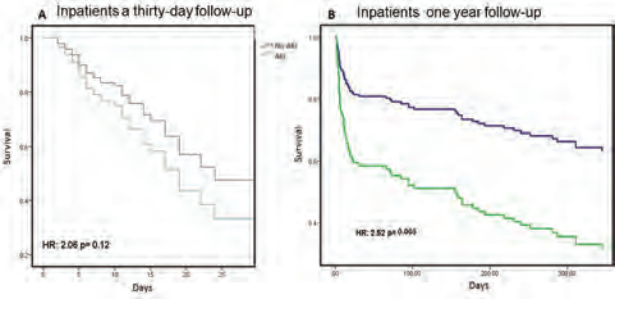
Background: Community acquired acute kidney injury (AKI-CA)is defined in patients who, at the time of admission to the hospital, present criteria for acute kidney injury diagnosis. Older adults are recognized as a vulnerable population for the development of AKI. The objective of this study was to determine the risk factors and the prognosis at one year follow-up of older adult's patients suffering from AKI-CA.

Methods: Cohort study in patients with ≥65 years old admitted in the emergency room, from March to May of 2018. The AKI-CA was according to the criteria of KDIGO 2012. The groups were compared using the Student's t-distribution or the X2 distribution depending on the type of variable, logistic regression was performed for OR, and a Cox regression for HR and survival with IC 95% and p ≤0.05.

Results: A total of 221 patients that satisfied the inclusion criteria, the average age was 75.1±7.6, the 44% (97) were men. The incidence of the AKI-CA was 58.8% being more common in patients with sepsis (p< 0.001), this was the principal associated factor with the development AKI-CA (OR: 3.52, IC95% 1.6-7.1). It was noticed that the highest stage of the AKI occurs in patients with previous chronic kidney disease (AKI1: 6.4% AKI2: 5.7% AKI 3: 41.2 % p< 0.001), or presence of sepsis (AKI1: 50.7% AKI2: 55.9% AKI 3: 57.1 % p= 0.009). It was not identified increase in risk of inpatient's mortality in patients with AKI-CA. In contrast, a relation between them was noticed after one year follow-up (Figure 1).

Conclusions: Older adults patients that suffer AKI-CA exhibit worst outcomes after one year follow up.

Figure 1. Survival of older adults patients suffering acute Kidney injury



TH-PO095

Differences on Outcomes Between AKI and AKI on CKD in Community-Acquired AKI

Rolando Claure-Del Granado,[1] Susana G. Ramirez-Yapura,[3] Emmanuel A. Burdmann,[4] Luis Yu,[5] Mauricio Younes-Ibrahim,[8] Alejandro Ferreiro,[6] Guillermo J. Rosa diez,[7] Raul Lombardi.[2] On behalf of EPILAT-IRA study group. AKI Committee of the Latin American Society of Nephrology and Hypertension (SLANH) *[1]Hospital Obrero #2 - C.N.S.; Universidad Mayor de San Simon, School of Medicine, Cochabamba, Bolivia, Plurinational State of; [2]Servicio Medico Integral, Montevideo, Uruguay; [3]Hospital Obrero #2 - C.N.S., Cochabamba, Bolivia, Plurinational State of; [4]University of Sao Paulo Medical School, Sao Paulo, Brazil; [5]University of Sao Paulo School of Medicine, Sao Paulo, Brazil; [6]School of Medicine, Montevideo, Uruguay; [7]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [8]University of Rio de Janeiro, Rio de Janeiro, Brazil.*

Background: AKI is a frequent disorder in community-based populations. Most studies have focused on hospital-acquired AKI and very few have explored characteristics and outcomes of patients with community-acquired AKI (CA-AKI). CKD may adversely affect kidney repair and recovery from AKI. We therefore aimed to explore characteristics and outcomes of CA-AKI in patients with and without CKD.

Methods: We conducted a prospective observational study (EPILAT-IRA) within the ER of a University Hospital, screening for any patient ≥16 years. We included patients meeting sCr KDIGO AKI definition over a 9-month period and designated as community acquired. De-identified clinical and lab data was entered in a specifically designed on-line platform. Co-variables potentially linked to AKI were recorded and we analized if there were differences in short and long-term outcomes between patients with and without CKD.

Results: During study period we screened 1,210 patients, CA-AKI incidence was 11.65% (n = 141) most patients were male (55.32%) and the mean age was 67,9±2 years. There were no differences in risk factors between patients with AKI and AKI on CKD. Nephrotoxic drugs were the most common cause of CA-AKI in both groups (AKI 92.2% vs. AKI on CKD 87.2%; p= 0.72) followed by dehydration (AKI 81.3% vs AKI on CKD 76.9%; p 0.65) and systemic disease (AKI 81.3% vs. AKI on CKD 82.0%; p = 0.64). Different outcomes are reported in table.

Conclusions: CA-AKI in developing countries is common and potentially preventable since the two main etiology factors were dehydration and nephrotoxins. Hospital, 90-day and one year mortality were not different between AKI and AKI on CKD; however, RRT requirement was higher and partial recovery of renal function was lower in patients with AKI on CKD which indicates that CKD may adversely affect kidney repair and recovery. Our study provides important information that contributes to a better knowledge of CA-AKI.

Table 1. Comparison of the different outcomes between CA-AKI with and without CKD.

Variable	AKI (N=102)	AKI on CKD (N=39)	*P* value
90-day renal recovery			
Complete renal recovery	11.7%	23%	0.30
Partial renal recovery	50.9%	20.5%	0.01
Non-recovery	17.5%	23%	0.34
Required RRT	7.8%	15.4%	0.041
Nephrology consultation	51.5%	64.1%	0.16
Hospital length of stay (days)	14.4±12.2	11.2±8.7	0.016
In-hospital mortality	14.7%	15.4%	0.34
90-day mortality	24.7%	30.7%	0.428
One-year mortality	36.1%	47.4%	0.181

TH-PO096

Comparison of Urinary Biomarkers in Critically Ill Children: Early Detection of AKI, Prediction of Mortality, and Confounding Factors

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Background: Most AKI biomarkers are susceptible to confounding factors in the prediction. We aimed to compare the performance of urinary biomarkers for early detection of AKI and the prediction of PICU mortality, and investigate the impact of confounding factors on these biomarkers in critically ill children.

Methods: Urine samples were serially collected in 123 children during the first 7 d of PICU stay for measurement of NGAL, KIM-1, TIMP2, IGFBP7, L-FABP, TIMP1, Renin, trefoil factor 3 (TFF-3), interferon-inducible protein-10 (IP-10). AKI diagnosis was based on KDIGO classification.

Results: Of the children, 35 developed AKI, including 12 with stage 1, 14 with stage 2 and 9 with stage 3, and 15 died during PICU stay. (1). The initial urinary biomarkers, associated with AKI stage 3 in univariate analysis, were TIMP1, KIM-1, NGAL, TIMP2, Renin and L-FABP; and achieved AUC of 0.75, 074, 0.74, 0.71, 0.70, and 0.68 for early detection of AKI stage 3. The initial TIMP1, TIMP2, NGAL, IP-10, KIM-1, L-FABP, TFF-3, Renin and IGFBP-7 achieved AUC of 0.84, 079, 0.78, 0.77, 0.76, 0.74, 0.73, 0.67 and 0.65 for predicting mortality. However, only initial TIMP1 remained associated with AKI stage 3 (P=0.016) and mortality (P=0.038) after adjustment for age, body weight and illness severity. (2). Peak urinary KIM-1 and TIMP2 remained associated with AKI stage 3; and peak KIM-1, NGAL, L-FABP, and IP-10 remained associated with mortality after adjustment. (3). Illness severity assessed by PRISM III was identified as an independent factor associated with all the initial and peak urinary biomarkers. Sepsis had an impact on initial and peak levels of NGAL, KIM-1 and IP-10 and peak Renin levels. Furosemide was independently associated with initial and peak levels of NGAL, L-FABP, TIMP1 and Renin and peak KIM-1, TIMP2 and TFF3 levels.

Conclusions: Although a higher initial urinary level of TIMP1, NGAL, KIM-1, TIMP2, Renin or L-FABP is predictive of severe AKI and mortality in critically ill children, these urinary biomarkers are significantly associated with illness severity and influenced by confounding factors. Sepsis has an impact on levels of NGAL, KIM-1, Renin and IP-10. Furosemide affects NGAL, FABP-1, TIMP1 and Renin. Sepsis appeared not to have impact on urinary TIMP1 and TIMP2, in contrast to NGAL and KIM-1, in critically ill children.

TH-PO097

Biomarkers in the Prediction of Contrast Media Induced Nephropathy: The BITCOIN Study

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Background: Subjects with chronic kidney disease (CKD) are at increased risk for the development of contrast-induced acute kidney injury (CI-AKI). It remains elusive, whether urinary biomarkers are able to identify subjects at increased risk as well. The present prospective trial examines the predictive value of urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), calprotectin, and Dickkopf-3 (DKK3) for the development of CI-AKI.

Methods: We enrolled 489 patients undergoing coronary angiography, 137 subjects had a CKD. An increase of serum creatinine concentration ≥ 0.3 mg/dl from baseline to day 2-3 was defined as CI-AKI and primary endpoint. Urinary calprotectin, NGAL, KIM-1 and DKK3 concentrations were assessed < 24h before coronary angiography.

Results: 30 (6.1%) patients suffered from CI-AKI (27 AKIN stage I, 3 AKIN stage II, none AKIN stage III). Those subjects with CI-AKI showed significantly higher concentrations of NGAL (p=0.001) and DKK3 (p=0.001) at baseline. No difference was obtained for KIM-1 (p=0.057) and calprotectin (p=0.36). Predictive accuracy was assessed by receiver operating characteristics (ROC) calculations yielding an area under the curve (AUC) of 0.69 each. CI-AKI was twice as prevalent in 137 patients with CKD (n=15, 11%; no AKIN III, 2 CIN AKIN II). The AUC of eGFR to predict CI-AKI in the overall study population was 0.59.

Conclusions: The present study is the largest prospective study so far, investigating the use of urinary biomarkers for the risk assessment before application of contrast-media. Urinary NGAL and DDK3 are able to identify patients at risk for CI-AKI, whereas KIM-I and calprotectin do not.

TH-PO098

Admission Plasma Uromodulin and the Risk of AKI in Hospitalized Patients with Cirrhosis

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Background: Acute kidney injury (AKI) is a common complication in patients hospitalized with decompensated cirrhosis. Current methods for identifying patients at risk for AKI are suboptimal. Uromodulin, a protein uniquely produced by the kidney and released both in the urine and circulation, has been shown to regulate AKI and is linked to tubular reserve. Although low levels of urine uromodulin are associated with an increased risk of AKI after cardiac surgery, it is unclear whether circulating uromodulin can stratify the risk of AKI, particularly in a susceptible population such as patients with cirrhosis.

Methods: Patients admitted with cirrhosis were monitored for subsequent hospital-acquired AKI (defined by a rise in serum creatinine more than 0.3mg/dL within 48 hours or 1.5 fold increase compared to baseline). Plasma levels of uromodulin were measured at the time of hospital admission. Multivariable logistic regression adjusted for significant clinical variables was used to evaluate the associations between admission uromodulin and odds of developing AKI.

Results: 98 patients [mean age 54 years, Model for Endstage Liver Disease Sodium score (MELD-Na) 19, and baseline creatinine of 0.95 mg/dl] were included, of which 13% (n=13) developed AKI. Median uromodulin levels were significantly lower in patients who developed AKI compared to patients who did not (9.30 vs. 13.35 ng/mL, p=0.02). After adjusting for age, sex, diabetes, hypertension, albumin, and MELD-Na score (which includes kidney function) as co-variates, uromodulin was independently associated with AKI [OR of 1.19 (95% CI 1.02, 1.37; p=0.02)].

Conclusions: Lower uromodulin levels on admission are associated with increased odds of subsequent AKI in hospitalized patients with cirrhosis. To our knowledge, this is the first study linking plasma uromodulin with AKI development, albeit in a unique population of patients with cirrhosis. If validated in larger studies, the measurement of circulating uromodulin on admission could enhance our clinical decision making for risk assessment of AKI in patients with liver disease.

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TH-PO099

Effect of 3% Saline and Furosemide on Biomarkers of Kidney Injury and Renal Tubular Function and GFR in Healthy Subjects: A Randomized Controlled Trial

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Background: Chloride is speculated to have nephrotoxic properties. In healthy subjects we tested the hypothesis that acute chloride loading with 3 % saline would induce kidney injury, which could be prevented with furosemide.

Methods: The study was designed as a randomized, placebo-controlled, crossover study. Subjects were given 3 % saline accompanied by either placebo or furosemide. Before, during and after infusion of 3 % saline we measured GFR, fractional excretion of sodium (FE_{Na}), urinary chloride excretion (u-Cl), urinary excretions of aquaporin-2 (u-AQP2), neutrophil gelatinase-associated lipocalin (u-NGAL) and kidney injury molecule-1 (u-KIM-1) as marker of kidney injury and vasoactive hormones: renin (PRC), angiotensin II (p-AngII), aldosterone (p-Aldo) and arginine vasopressin (p-AVP). Four days prior to each of the two examinations subjects were given a standardized diet and fluid intake.

Results: After 3% saline infusion u-NGAL and KIM-1 excretion increased slightly (u-NGAL: 17+/- 24 during placebo vs. -7 +/- 23 ng/min during furosemide, p=0.039, u-KIM-1: 0.21 +/- 0.23 vs -0.06 +/- 0.14 ng/ml, p<0.001). The increase in NGAL was absent when furosemide was given simultaneously, and the responses in NGAL were not significantly different from placebo control. Furosemide changed responses in KIM-1 where a delayed increase was observed. GFR was increased by 3 % saline but decreased when furosemide accompanied the infusion. U-Na, FE_{Na}, u-Cl, and u-osmolality increased in response to saline, and the increase was markedly pronounced when furosemide was added. FE_K decreased slightly during 3 % saline infusion, but simultaneously furosemide increased FE_K.U-AQP2 increased after 3 % saline and placebo, and the response was further increased by furosemide. 3 % saline significantly reduced PRC, p-AngII and p-Aldo, and responses were attenuated by furosemide. p-AVP was increased by 3 % saline, with a larger increase during furosemide.

Conclusions: This study shows minor increases in markers of kidney injury after 3% saline infusion Furosemide abolished the increase in NGAL and postponed the increase in u-KIM-1. The clinical importance of these findings needs further investigation.

Funding: Government Support - Non-U.S.

TH-PO100

Sarcopenia May Be a Protective Factor for Mortality in Severe AKI Patients Requiring Continuous Renal Replacement Therapy

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Background: Sarcopenia can be defined as degenerative loss of skeletal muscle, which has been associated with poor prognosis in patients with chronic kidney disease or end-stage renal disease. However, the clinical impact of sarcopenia in acute kidney injury (AKI) has not been studied extensively.

Methods: Among the patients diagnosed with severe AKI requiring continuous renal replacement therapy (CRRT) at multi-center from May 2017 to March 2018, Inbody, impedance body fat analyzer, was measured at the start of CRRT. We measured muscle mass, body fat mass, and water content using an inbody, and analyzed the long-term outcome including mortality.

Results: A total of 417 patients were enrolled. We calculated the dry weight of the patients using the Tahara edema index to rule out the possibility that the fluid overload would have caused the body weight to be higher than actually measured. The calculated dry body weight was used for the study. Sarcopenia was defined as an appendicular skeletal muscle mass (ASM)/body weight (ASM%) beyond two standard deviations below the gender-specific mean for healthy young adults according to nationwide health examinations of the Korean population (ASM% <29.0 in men or <22.9 in women was considered to indicate sarcopenia). Of these, 71 (17%) had sarcopenia. Patients diagnosed with sarcopenia were more males, older, with more diabetes and congestive heart failure. However, age-modified CCI, baseline renal function, APACHE II score, and SOFA score were not different between two groups. When mortality was defined as the primary outcome, mortality was significantly lower in the patients with sarcopenia (HR 0.47; 95% CI 0.24-0.91; P = 0.026).

Conclusions: In this study, muscle mass was directly measured in patients with AKI, and the relationship between sarcopenia and long-term outcome was investigated. Further studies on specific mechanisms and causes will be needed.

TH-PO101

Cell Cycle Biomarkers and Soluble Urokinase-Type Plasminogen Activator Receptor for the Prediction of Septic AKI Courses Requiring Renal Replacement Therapy: An Explorative Study

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Background: Sepsis-induced acute kidney injury (AKI) is the dominant AKI etiology in critically ill patients and is often associated with the need for renal replacement therapy (RRT). The timinig of RRT is an ongoing controversy. A major issue that persists is the early differentiation of patients with progressive AKI and need for RRT from those with autonomous renal recovery. We hypothesized, that the product of the two cell cycle arrest and tubular injury biomarkers tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 ([TIMP-2]*[IGFBP7]), and the soluble urokinase-type plasminogen activator receptor (suPAR) are of diagnostic value for the prediction of septic AKI courses requiring RRT.

Methods: 100 critically ill patients were enrolled prospectively after the fulfillment of Sepsis-3 criteria. Urinary [TIMP-2]*[IGFBP7] levels over time and serum suPAR levels once at inclusion were measured. The primary clinical endpoint was the occurrence of need for RRT within 7 days. Area under the receiver-operating characteristic curves (AUC-ROC), deLong's tests and logistic regression models were calculated.

Results: Nineteen patients developed need for RRT. Diagnostic performance of urinary [TIMP-2]*[IGFBP7] improved significantly over time with the highest AUC of 0.89 (95%CI 0.80-0.98) at 24h after study inclusion. SuPAR levels at inclusion showed an AUC of 0.83 (0.75-0.92). The best discrimination ability for the primary outcome measure was achieved for [TIMP-2]*[IGFBP7]24h by applying a cut-off value of ≥0.6 (ng/ml^2)/1000 (sensitivity 90.9, specificity 67.1). SuPAR at inclusion performed best by using a cut-off value of ≥8.53 ng/mL (sensitivity 84.2, specificity 82.7). The combination of newly tested biomarkers with cystatin C (CysC) resulted in a significantly improved diagnostic accuracy. CysC in combination with [TIMP-2]*[IGFBP7]24h outperformed all present standard renal parameters (AUC 0.93 [0.86-1.00]).

Conclusions: [TIMP-2]*[IGFBP7] levels after the initiation of therapeutic measures and suPAR levels at baseline are promising biomarker candidates for the risk stratification of septic AKI patients with the need for RRT.

TH-PO102

Assessment of Urinary Biomarkers for AKI in Major Elective Nonvascular Abdominal Surgeries

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Background: Data on the role of renal injury urinary biomarkers (uBMs) to predict AKI in patients (pts) submitted to major elective non-vascular abdominal surgeries (MENVAS) are scarce.

Methods: A total of 298 pts submitted to MENVAS were prospectively assessed and evaluated, pre, peri-operatively and from the ICU admission up to 7 days. Serum creatinine (SCr) was assessed before surgery and once a day up to 7d or until ICU discharge. Hourly urinary output (UO) (ml/kg/h) was measured. AKI was diagnosed by either SCr or/and UO (KDIGO definitions). Urine was collected 1d before surgery (baseline), 30 min, 12 and 24h after ICU admission. Monocyte chemotactic protein 1 (MCP-1), interleukin 18 (IL-18), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7) were assessed by Luminex x-MAP. Data are median (1st and 3rd quartiles) or frequency. AUC of ROC curves was assessed using non-AKI/AKI KDIGO I as controls and AKI KDIGO II/III as positive results. We assessed different combinations of uBMs to find the better performance. Statistical significance was p<0.05.

Results: Overall, age was 56±15y, 59.1% were female, hospital LoS was 17.7±16.2d, ICU LoS was 3.1±2.9d and 90d mortality was 6.4%. A total of 197 pts (60.1%) developed AKI, mostly KDIGO I (118 pts, 59.9%). The uBMs combination with the higher AUC was KIM-1 vs NGAL vs IGFBP-7 (baseline: 0.65; 30min: 0.72; 12h: 0.79; 24h: 0.72), which was better than any of the uBMs alone, or other combinations, including the product TIMP-2 vs. IGFBP-7(baseline: 0.62; 30min: 0.65; 12h: 0.75; 24h: 0.72).

Conclusions: We found a strikingly high incidence of MENVAS-associated AKI diagnosed by KDIGO criteria in patients admitted at the ICU. The uBM with the better performance to diagnose moderate and severe AKI was the combinations of KIM-1 vs. NGAL vs. IGFBP-7 12h after ICU admission.

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uBM	Baseline			30 min - ICU			12h - ICU			24h - ICU		
	Non-AKI	KDIGO I	KDIGO II/III	Non-AKI	KDIGO I	KDIGO II/II	Non-AKI	KDIGO I	KDIGO II/III	Non-AKI	KDIGO I	KDIGO II/II
MCP-1 (ng/mL)	0.1 (0.01 - 0.2)	0.1 (0.1 - 0.3)	0.1 (0.1 - 0.5)	0.3 (0.1 - 0.8)	0.5 (0.2 - 1.1)	1.1 (0.3 - 2.1)	0.6 (0.2 - 1.6)	0.78(0.3 - 1.6)	1.6 (0.7 - 4.1)	0.5 (0.2 - 1.3)	0.8(0.3 - 1.5)	1.41 (0.6 - 3.5)
IL-18 (pg/mL)	19.7 (8.0 - 30.0)	11.4 (8.0 - 19.0)	14.0 (12.1 - 42.00)	13.8 (8.0 - 65.5)	17.7 (10.3 - 56.9)	27.5 (12.5 - 125.1)	17.7 (9.3 - 71.6)	25.6 (11.4 - 97.7)	53.1 (19.6 - 137.7)	20.3 (9.2 - 87.4)	23.9 (11.4 - 71.6)	33.5 (14.3 - 106.5)
KIM-1 (ng/mL)	0.1 (0.1 - 0.4)	0.1 (0.1 - 0.4)	0.4(0.1 - 0.7)	0.2 (0.1 - 0.5)	0.4 (0.2 - 0.9)	0.7 (0.3 - 1.8)	0.6 (0.2 - 1.4)	1.0 (0.3 - 1.9)	1.9 (0.9 - 4.0)	0.6 (0.3 - 1.7)	1.0 (0.4 - 2.10)	2.1 (0.78 - 4.32)
NGAL (ng/mL)	21.0 (10.3 - 40.5)	19.8 (10.7 - 52.0)	27.6 (14.3 - 63.5)	21.3 (13.1 - 40.3)	32.8 (18.2 - 74.6)	47.25(18.1 - 208.8)	25.7 (13.8 - 51.3)	51.7 (16.3 - 60.5)	101.5 (27.1 - 238.3)	36.9 (17.9 - 96.5)	55.9 (21.1 - 132.2)	89.6 (30.8 - 421.7)
TIMP-2 (ng/mL)	4.3 (1.6 - 11.3)	4.9 (1.7 - 10.7)	5.8 (2.0 - 14.9)	6.3 (3.1 - 15.9)	13.6 (4.8 - 23.8)	15.6 (7.4 - 28.9)	6.3 (2.8 - 13.9)	8.7 (3.9 - 17.8)	17.7 (8.7 - 27.8)	8.3 (4.5 - 16.6)	11.3 (3.8 - 22.6)	19.3 (9.0 - 40.7)
IGFBP-7 (ng/mL)	31.4 (10.3 - 136.1)	51.0 (12.8 - 129.5)	102.0 (34.5 - 265.3)	133.5 (64.0 - 214.0)	215.6 (114.0 - 514.9)	379.1 (145.2 - 886.5)	141.7 (60.6 - 249.5)	204.1 (75.5 - 419.4)	474.0 (211.8 - 1566.0)	132.0 (70.6 - 244.4)	177.0 (91.2 - 373.1)	410.9 (182.0 - 1033.0)
TIMP-2 X IGFBP-7 (ng/mL)²/1000	0.4 (0.1 - 1.7)	0.2 (0.3 - 1.5)	0.7 (0.1 - 3.6)	0.9 (0.2 - 3.6)	3.3 (0.7 - 11.6)	6.1 (1.2 - 25.5)	1.1 (0.1 - 3.2)	1.6 (0.5 - 7.7)	10.6 (1.6 - 39.7)	1.2 (0.3 - 4.8)	1.6 (0.5 - 7.7)	8.6 (1.7 - 36.3)
IGFBP-7 X NGAL x KIM-1 (ng/mL)²/1000	0.4 (0.1 - 2.0)	0.1 (0.1 - 1.5)	0.6 (0.1 - 4.7)	0.6 (0.1 - 4.0)	3.7 (0.4 - 26.2)	9.0 (0.7 - 116.40)	1.7 (0.4 - 13.5)	7.2 (0.5 - 38.0)	80.0(9.2 - 535.3)	3.6 (0.5 - 21.5)	6.3 (0.3 - 87.6)	83.1 (2.5 - 672.7)

TH-PO103

Low Fractional Excretion of Urinary Sodium Is a Common Finding During Acute Tubular Injury Presenting with Abundant Muddy Brown Granular Casts

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Background: Fractional excretion of urinary sodium (FENa) remains the most widely utilized diagnostic test in clinical practice for the evaluation of acute kidney injury (AKI). A low FENa (<1%) is considered consistent with prerenal azotemia and not due to overt acute tubular injury (ATI). However, presence of muddy brown granular casts (MBGCs) during microscopic examination of the urinary sediment (MicrExUrSed) are deemed pathognomonic of ATI. We hypothesized a lack of concordance between the two tests.

Methods: We conducted a prospective observational study in patients seen in the inpatient nephrology consultation team with AKI stage ≥ 1 (AKIN) over a 1.5-yr period. On the day of the consult and 48 hrs later, MicrExUrSed was performed to determine the percentage of low power fields (lpf) containing MBGCs. FENa was calculated on the same day to compare it with MBGCs abundance. Outcome measure was ≥ 50% increase from baseline serum creatinine (sCr) at discharge.

Results: Both FENa and presence of MBGCs by MicrExUrSed was completed in 135 patients, 57 (42%) were female, median age was 59 (25 - 88). The median sCr at the time of AKI was 3.2 (2.5 - 4.6) mg/dL. The etiology of AKI (pure *de novo* AKI 57%, AKI on CKD 43%) was ischemic ATI (40%), toxic ATI (15%), ischemic/toxic ATI (19%) and others (27%). MBGCs were found in 71 patients (53%) in our cohort. Among those, 56 (42%) and 32 (24%) had >10% and ≥50% lpf with MBGCs, respectively. FENa was <1% in 24/56 (44%) and 13/32 (41%) of those with >10% and ≥50% lpf with MBGCs, respectively. Thus, the concordance between FENa and MicrExUrSed for ATI diagnosis was deemed poor (estimated kappa coefficient 0.3018). In addition, ≥50% lpf with MBGCs was associated with greater risk for ≥ 50% increase from baseline sCr at discharge [relative risk (RR) 1.5, CI 1.1 – 2.0, p = 0.012], whereas FENa >1% did not predict that outcome [RR 1.1, CI 0.8 – 1.5, p = 0.39].

Conclusions: Close to half of the patients in our cohort who exhibited abundant MBGCs during MicrExUrSed presented with FENa <1%. "Sheets" of MBGCs were associated with greater risk for more sustained elevation in sCr after AKI, whereas FENa >1% was not predictive. These data strongly suggest that sole reliance in low FENa to exclude ATI should be abandoned and MicrExUrSed should be pursued for AKI diagnosis.

TH-PO104

Urinary Tubular Epithelial Cells as a Tool for Diagnosis and Prognosis Estimation in AKI

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Background: Acute kidney injury (AKI) is a common clinical condition with serious short- and long-term consequences. Present classifications focus on serum creatinine (SCr) and urine output, though these are functional damage markers and only allow indirect conclusions about the actual structural damage taking place. In this project we quantified the amount of tubular epithelial cells (TECs) in urine as a marker for kidney damage at the cellular level.

Methods: Urinary samples were taken from inpatients with AKI according to the KDIGO classification (n=50) and from inpatients with cardiological disease but without AKI according to the KDIGO classification (n=8; control group). Samples were analyzed within 72 hours after the initial SCr increase using flow cytometry. A marker combination of cytokeratin, CD13 and CD10 was used to detect proximal TECs (pTECs) and a combination of cytokeratin, CD326 and CD227 was used to detect distal TECs (dTECs). The cell counts were calculated as cells per 100 ml urine. Patients with renal replacement therapy or with inflammatory cause of the AKI were excluded from this study.

Results: Both the amounts of pTECs and dTECs correlated with the relative increase of SCr from the baseline value to the maximum value within the AKI (pTECs: p=0,0006; dTECs: p=0,0004; Spearman). Samples of the control group contained significantly lower amounts of TECs compared to the AKI cohort (pTECs: p=0,0001; dTECs: p<0,0001; Mann-Whitney-Wilcoxon). Some donors (n=5) with a low relative increase of SCr showed very high amounts of urinary TECs. These donors either did not recover from the AKI or showed acute cardiovascular decompensation on the day of sample uptake. Furthermore, both the amounts of pTECs and dTECs correlated with the change of the eGFR stage according to KDIGO from baseline value to the value at hospital discharge (pTECs: p=0,0176; dTECs: p=0,0282; Spearman).

Conclusions: Urinary TECs are an innovative, non-invasive possibility to quantify structural kidney damage during an AKI. As a potential new biomarker for prognosis of AKI, TECs additionally allow predictions about the renal filter function during the course of the hospital stay. High amounts of urinary TECs in donors who only had a modest SCr increase may have detected severe structural kidney damage.

TH-PO105

Urinary Waxy Casts Are Associated with Greater Severity of Acute Tubular Injury

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Background: Waxy casts (WxCs) constitute a recognized finding during microscopic examination of the urinary sediment (MicrExUrSed) and they are classically linked to chronic kidney disease (CKD). It is less clear whether WxCs are a relevant finding in acute kidney injury (AKI). We hypothesized that identification of WxCs in AKI due to acute tubular injury (ATI) provides prognostic information.

Methods: We conducted a prospective observational study in patients seen in the inpatient nephrology consultation team with AKI stage ≥ 1 (AKIN) over a 1.5-yr period. On the day of the consult, MicrExUrSed was performed to determine the percentage of low power fields (lpf) with WxCs and to assess a validated score for ATI based on granular casts and tubular epithelial cells per lpf [Perazella score (PS): score ≥ 2 consistent with ATI]. The primary outcome measure was need for dialysis at 30 days (RRT).

Results: Urine specimens from 167 patients [median age 58 (25 – 88), 43% women] were assessed. The etiology of AKI (pure *de novo* AKI 56%, AKI on CKD 44%) was ischemic ATI (41%), toxic ATI (14%), ischemic/toxic ATI (17%) and others (28%). WxCs were found in 47 patients (28%), 33 (70%) of which had pure *de novo* AKI. Median serum creatinine for those with WxCs was 3.7 (2.8 – 4.9) mg/dL compared to 3.1 (2.4 – 4.6) mg/dL for those without WxCs (p = 0.087). Having >10% lpf w/ ≥1 WxCs was associated with greater risk for RRT [relative risk (RR): 2.3, CI 1.4 – 3.5, p = 0.0003). As reported by others, PS ≥ 2 was associated with increased risk for RRT (RR: 2.6, CI 1.1 - 6.6, p = 0.04). When presence of WxCs was added to a PS ≥ 2, the RR for need for RRT became stronger (RR: 6.0, CI 2.9 - 12.5, p< 0.0001). In addition, the greater the abundance of WxCs, the greater the need for RRT: need for RRT was 26% (31/120), 43% (20/47), 59% (13/22), and 60% (6/10) for those with none, >0%, >10% and ≥50% lpf w/ ≥1 WxCs, respectively (p = 0.0003 for chi-square for trend).

Conclusions: WxCs can be found in a significant proportion of patients with AKI, even among those without preexisting CKD. Among patients with ATI, the presence and abundance of WxCs are associated with a greater risk for need for RRT, suggesting that WxCs carry similar and potentially additive prognostic value to that of granular casts.

TH-PO106

Urinary Biomarkers Normalization by Urinary Creatinine in Patients Submitted to Major Elective Nonvascular Abdominal Surgeries: Is It Necessary?

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Background: There is no consensus regarding urinary biomarkers (uBM) performance using absolute and normalized by urinary creatinine concentration.

Methods: A total of 298 patients (pts) submitted to major elective non-vascular abdominal surgeries (MENVAS) were prospectively assessed. Serum creatinine (SCr) was assessed before surgery and once a day up to 7d post-op or ICU discharge. Hourly urinary output (ml/kg/h) was measured daily. AKI was diagnosed using either SCr or/and urinary output (UO) according to KDIGO definitions. Urinary samples were collected 1 day before surgery (baseline), and 30 min, 12 and 24h after ICU admission. Urinary Cr (uCr) and 7 uBMs were assessed: monocyte chemotactic protein 1 (MCP-1), interleukin 18 (IL-18), kidney injury molecule-1 (KIM-1), osteopontin (OPN), neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7) by Luminex x-MAP method. Data are presented as AUC from ROC curves. Statistical significance was p<0.05.

Results: A total of 197 pts (60.1%) developed AKI, mostly KDIGO I. Those developing AKI KDIGO II and III had significantly higher uBMs compared to AKI KDIGO I or non-AKI in all times. We used non-AKI and AKI KDIGO I as controls and AKI KDIGO II and III as positive results to develop of ROC curve. The uBMs' AUC results (w/ or w/o uCr) are presented in table 1. AUC w/o uCr normalization results were consistently higher for all uBMs. AUC normalized for uCr loses the AUC significance for NGAL at baseline and IL-18 at 24h.

Conclusions: uBMs had better performance w/o normalization for uCr in all periods after surgery and a similar performance in baseline. These results suggest that uBMs results should not be normalized for uCr after MENVAS.

Funding: Government Support - Non-U.S.

Difference in AUC of absolute and normalized uBMs concentrations

uBM	Baseline		30 minutes -ICU		12h -ICU		24h - ICU	
	uBM	uBM/uCr	uBM	uBM/uCr	uBM	uBM/uCr	uBM	uBM/uCr
MCP-1	0.60	0.60	0.67	0.64	0.69	0.63	0.64	0.59
IL-18	0.63	0.57	0.64	0.59	0.65	0.60	0.61	0.54 ns
KIM-1	0.63	0.64	0.70	0.70	0.72	0.67	0.67	0.63
OPN	0.58	0.59	0.66	0.64	0.66	0.61	0.64	0.59
NGAL	0.58	0.53 ns	0.64	0.61	0.71	0.67	0.63	058
TIMP-2	0.56 ns	0.55 ns	0.60	0.59	0.70	0.66	0.67	0.61
IGFBP-7	0.64	0.65	0.68	0.65	0.74	0.70	0.72	0.67

ns AUC not significant

TH-PO107

Prognostic Biomarkers of Kidney Function and Steroid Responsiveness After Acute Interstitial Nephritis

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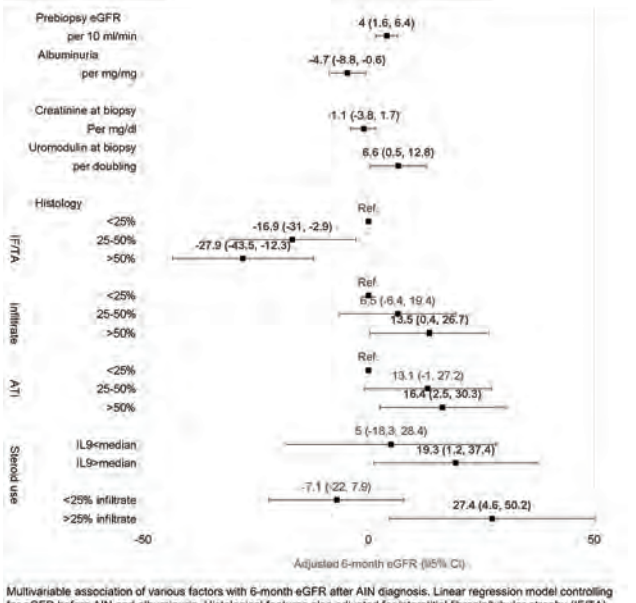
Background: Predictors of kidney injury, inflammation and function after AIN can guide therapeutic strategies.

Methods: In participants with adjudicated AIN, we examined the relationship of conventional and novel biomarkers of kidney structure and function (glomerular filtration rate [eGFR] before biopsy, histology), injury (urine uromodulin, NGAL, KIM-1, IL-18, microscopy) and inflammation (TNFa, IFNg, IL4, IL5, IL6, IL9, IL13) with eGFR measured 6 months (6m) after biopsy controlling for eGFR before biopsy and albuminuria. We also evaluated the impact of steroids on 6m eGFR.

Results: We ascertained 6m eGFR in 51 (93%) out of 55 participants. Mean (SD) eGFR before, during, and 6m after AIN was 41.6 (26.3), 15.6 (10.5), and 33.4 (24.3) ml/min, respectively. Urine uromodulin at time of AIN diagnosis was independently associated with 6m eGFR (Figure), whereas other novel biomarkers were not associated with 6m eGFR. Among the histological features, higher interstitial fibrosis/tubular atrophy (IF/TA) was associated with lower 6m eGFR, whereas interstitial infiltrate and tubular injury were associated with higher 6m eGFR. We noted that steroid use was associated with higher 6m eGFR in those with ≥25% inflammatory infiltrate on biopsy but not in those with <25% involvement, and in those with urine IL-9 level above the median (0.75 ng/mg) but not in those with IL-9 levels below the median.

Conclusions: Higher urine uromodulin level at the time of AIN diagnosis was associated with higher 6m eGFR independent of prebiopsy eGFR and albuminuria. Steroid use was associated with higher 6m eGFR in those with active inflammation at the time of biopsy. These findings could help prognosticate kidney function after AIN and guide initiation of steroid therapy.

Funding: NIDDK Support



Multivariable association of various factors with 6-month eGFR after AIN diagnosis. Linear regression model controlling for eGFR before AIN and albuminuria. Histological features also adjusted for interstitial fibrosis/tubular atrophy (IF/TA) score. Association of steroid use reported separately by degree of interstitial infiltrate (<25% vs. >25%; interaction P=0.048) and urine IL-9 level above or below median (interaction P=0.097).

TH-PO108

Risk Factors and Outcomes of AKI Subphenotypes Based on Serum Creatinine Trajectory After Vancomycin Exposure

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Background: Vancomycin-associated (VA) acute kidney injury (AKI) is poorly characterized. We hypothesized that the phenotyping of VA-AKI according to the time course of changes in serum creatinine (sCr 'trajectory') could identify different risk factors and prognosis.

Methods: Cohort study. We included all subjects (2017 to 2019) admitted to a tertiary referral hospital exposed to vancomycin IV ≥4 days without CKD G5 or dialysis treatment. We collected daily sCr and vancomycin serum concentrations, calculated the area under the concentration-time curve (AUC24h), and eGFR 30-days after hospital discharge.

Results: We included 361 subjects. In survivors (332/361,94%), we identified 4 phenotypes based on sCr trajectory: **1** ***No AKI-VA*** (n=229, 68%): subjects without AKI who did not have sCr changes during exposure; **2** ***Severe AKI-VA*** (n=19,6%): subjects with an accelerated rise in sCr not related to other clinical factors, with a median time of vancomycin exposure 10 days (IQR: 7-18) with tubular injury (biopsy in 2 cases); **3** ***non-severe AKI-VA*** (n=55, 17%): subjects who at the beginning of vancomycin prescription had AKI, which was improving but had slight and slow sCr increases during treatment, usually in context of other AKI risk factors (sepsis relapsed, nephrotoxic drugs, bleeding); **4** ***recovery of AKI*** (n=29, 9%): subjects with sepsis induced AKI who had improvement without relapses during treatment. In a multivariate analysis, risk factors for group 2 were the slope of the initial day 2-4 vancomycin drug levels (OR:2.0 95%IC 1.22-2.7) and baseline sCr (OR:1.7 95%IC 1.1-2.8). Risk factors for group 3 non-severe AKI-VA were vancomycin drug levels >15 ng/mL (OR 1.6 per each 10 ng/mL, 95%IC 1.1-3.5) and AUC24h target of ≥ 600 mg*h/L (OR 2.9 95%IC 1.6-5.9). After 30-d of discharge, severe AKI-VA was usually reversible (12% had CKD G3A1). Group 3 had a higher frequency of CKD (78% CKD G3) compared to other groups. Total daily vancomycin dose, accumulated dose, and duration of therapy were not risk factor for any group.

Conclusions: VA-AKI occurs in different clinical presentations. Abrupt and severe AKI-VA can be predicted according to slope change in first doses of vancomycin levels. Non-severe AKI-VA was multifactorial, had a higher risk of CKD, and had pre-AKI high vancomycin trough levels.

TH-PO109

Plasma Neutrophil Gelatinase Associated Lipocalin (NGAL) and the Prediction of Sustained AKI and Worsening Renal Function in Hospitalized Kidney Transplant Recipients

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Background: Neutrophil gelatinase-associated lipocalin (NGAL) and Calprotectin (CPT) have been validated as biomarkers of acute kidney injury (AKI) in multiple clinical settings. The utility of these biomarkers in post-transplant care of kidney transplant recipients (KTR) remains largely unclear. We hypothesized that NGAL and CPT levels, measured at the time of any unscheduled hospital admission after kidney transplantation, would be associated with episodes of sustained AKI (sAKI) and worsening renal function (WRF).

Methods: As part of a monocentric cohort study of 709 KTR, plasma and urinary NGAL and CPT levels were measured in 164 KTR at the time of hospital admission for any non-elective cause. sAKI was defined as an increase in creatinine by ≥0.3 mg/dl or by ≥1.5-fold compared to outpatient baseline that did not normalize within 72 hours (h). WRF was defined as an increase in creatinine by ≥0.5 mg/dl within 72 h after admission. ROC analyses, univariable and multivariable logistic regression analyses and net reclassification improvement (NRI) were assessed for the biomarkers in predicting sAKI and WRF.

Results: 33 KTR developed sAKI, 12 developed WRF. Plasma NGAL (pNGAL) had the highest diagnostic accuracy compared to urinary NGAL, urinary and plasma CPT. Median pNGAL levels at admission were significantly higher in patients with sAKI (332 [IQR 247.5-633] ng/ml versus no sAKI 275 [IQR 193-363] ng/ml, p<0.05) and WRF (395 [IQR 305-639] ng/ml versus no WRF 278.5 [IQR 193.5-378.8] ng/ml, p<0.05). ROC analyses for pNGAL showed an AUC ROC of 0.66 for sAKI and of 0.75 for WRF. A pNGAL level >410 ng/ml had positive likelihood ratios of 2.3 (95% CI 1.38-3.81) for sAKI and of 2.0 (95% CI 1.15-4.1) for WRF. In multivariable logistic regression, pNGAL was an independent predictor of sAKI when combined with other predictors (serum creatinine, coronary artery disease, congestive heart failure, p<0.05). Adding pNGAL to conventional predictors of sAKI resulted in an NRI of 20.5% (p<0.01).

Conclusions: Elevated pNGAL at the time of hospital admission may be useful in identifying KTR at risk of sustained or progressive acute kidney injury. Although test characteristics speak against its use as a single biomarker, it may contribute to prognostication.

Funding: Private Foundation Support

TH-PO110

Urinary Exosomal MicroRNA-21 as a Marker of Scrub Typhus-Associated AKI

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Background: Extracellular vesicles contain various molecules including DNA, mRNA, and microRNA (miRNA), and are involved in cell-to-cell communication. MiRNA-21 is reported to be a biomarker for detection of acute kidney injury (AKI). The aim of this study is to investigate the clinical significance of urinary exosomal miRNA-21 for AKI in patients with scrub typhus.

Methods: In a cross-sectional study, we collected 138 urine samples at the time of admission from 145 patients with scrub typhus. For 25 patients with scrub typhus-associated AKI and 25 age, sex-matched patient without AKI, we measured miRNA-21 in urinary exosomal fraction. Then, we investigated correlation between urinary exosomal miRNA-21 and clinical parameters.

Results: Compared with patients in the non-AKI group, patients in the AKI group had worse renal function (30 ± 13 vs. 56 ± 20 mL/min/1.73m^2, P<0.01) at admission and higher total leukocyte counts(10.4 × 10^3/ mL vs. 5.2× 10^3/mL, P<0.01). Serum NGAL (404 ± 269 vs. 104± 51 ng/mL, P<0.01) and urine NGAL/creatinine values (371± 672 vs. 37± 57 ng/mg, P<0.01) were higher in the AKI group than in the non-AKI group. The levels of urinary exosomal miRNA-21 (17.8 ± 1.8vs. 20.1± 1.2 ΔCt value of miRNA-21, P<0.01) were higher in the AKI group than in the non-AKI group, while those levels in urinary supernatant were not different between two groups. Urinary exosomal miRNA-21 levels correlated directly with total leukocyte counts and serum NGAL values and inversely with estimated glomerular filtration rate. The reciver operator characteristics curve analysis for urinary exosomal miRNA-21 showed good discriminative power for detectng scrub typhus-associated AKI, with area under the curved value of 0.887.

Conclusions: Urinary exosomal miRNA-21 could be a surrogate markers for the diagnosis of scrub typhus–associated AKI.

TH-PO111

Impact of Elevated Echocardiographic Index of Left Ventricular Filling Pressure on AKI After Aortic Valve Replacement

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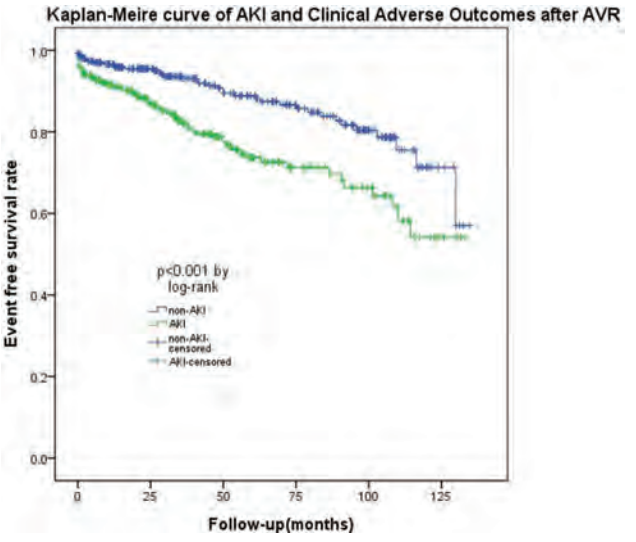
Background: Increased LV filling pressure was found to be associated with deterioration of renal function in patients with congestive heart failure. However, it remains unclear how to contribute to cardio-renal interaction in patients who underwent aortic valve replacement (AVR). We sought to evaluate the association between preoperative echocardiographic index of left ventricular (LV) filling pressure and postoperative acute kidney injury (AKI), and impact of AKI on clinical adverse outcomes after surgical AVR.

Methods: We conducted a retrospective study of 576 patients (292 males, mean age 68±10 years) who underwent surgical AVR. Patients were stratified according to E/e' ratio above and less than 15, and assessed for AKI using the KDIGO criteria, defined as either a serum creatinine rise >0.3 mg/dl, or an increase in serum creatinine ≥1.5 times baseline within 7 days after AVR. The clinical adverse outcomes were early and long-term mortality, and hospitalization due to heart failure.

Results: Patients with E/e'ratio ≥15 had more AKI complication after surgical AVR (52.1% vs. 38.2%, p=0.001), In multivariable analysis, E/e'ratio ≥15 was independently associated with AKI after surgical AVR (odd ratio [OR], 1.66; 95% confidence interval [CI], 1.17–2.34 p=0.005). The Cox hazard model reveals that AKI (hazard ratio [HR], 1.57; 95% CI, 1.03-2.39, p=0.037) and advanced age (HR, 1.07; 95% CI, 1.04-1.11, p<0.001), coronary artery disease (HR 1.54, 95% CI, 1.02-2.32, p=0.04) were poor prognostic factors for clinical adverse outcomes after surgical AVR.

Conclusions: Among patients who undergoing surgical AVR, preoperative elevated LV filling pressure is associated with increased risk for AKI, and AKI is related to postopearative adverse clinical outcomes.



TH-PO112

Endothelial Glycocalyx Shedding and Microcirculatory Impairment in Traumatic Haemorrhagic Shock Are Early Markers of AKI

Jennifer R. Joslin,[1] David N. Naumann,[2] Kate Bramham,[1] Sam Hutchings.[3] *[1]Renal Sciences, King's College London, London, United Kingdom; [2]University of Birmingham, Birmingham, United Kingdom; [3]King's College Hospital, London, United Kingdom.*

Background: Microcirculatory disruption is evident in the pathogenesis of many acute kidney injury (AKI) causes, and regulation of microvascular perfusion is dependent on the integrity of the endothelial glycocalyx (Glx). We hypothesised that systemic Glx shedding and microcirculatory impairment are associated with AKI. The MICROSHOCK study reported on multiple organ dysfunction syndrome; we report the association with Glx and microcirculatory changes and AKI outcomes for the first time.

Methods: Patients with traumatic haemorrhagic shock from two UK Major Trauma Centres underwent plasma sampling for Syndecan-1 (Syn-1, Glx constituent) and sublingual Incident Dark Field (IDF) microscopy on admission. IDF videos were analysed to quantify perfused vessel index (PVD) and microvascular flow index (MFI). Presence and stage of AKI within 7 days were recorded.

Results: 45 patients were included; 10 (22%) female and 35 (78%) male. Mean age was 45 (SD 26) years. 34 of 45 (76%) developed AKI within 7 days; 15 (44%) stage 1; 12 (35%) stage 2; and 7 (21%) stage 3. Syn-1 results were available for 17 patients. Admission Syn-1 concentration was significantly higher (representing increased Glx shedding) in patients who did (n=11) than did not (n=6) develop AKI within 7 days, p = 0.0183 (Figure 1). PVD and MFI results were available in all 45 patients. Both PVD and MFI were significantly lower (representing impaired microcirculatory perfusion) in patients who went on to develop stage 2 or 3 AKI (Table 1).

Conclusions: This novel study provides preliminary evidence that Glx shedding and impaired microcirculatory perfusion parameters can predict AKI. Further research in other and larger cohorts is needed and planned. We propose that Syn-1 may be a mechanistic biomarker for AKI.

Table 1: PVD and MFI in patients who did and did not develop AKI

	AKI	No AKI		Severe (stage 2 or 3) AKI	No severe AKI	
Median [IQR] PVD (mm/mm2)	10.2 [7.9,12.0]	10.5 [9.6,11.0]	NS	8.7 [7.6,10.9]	11.1 [10.3,12.5]	p=0.0102
Median [IQR] MFI	2.70 [2.57,2.85]	2.81 [2.64,2.88]	NS	2.62 [2.25,2.71]	2.82 [2.71,2.90]	p=0.0026

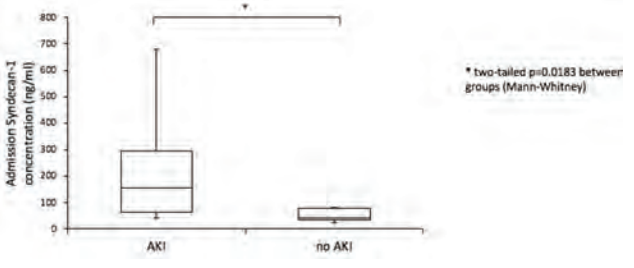


Figure 1: Syn-1 concentration in patients who did and did not develop AKI

TH-PO113

Serum α1-Antitrypsin Predicts Severe AKI After Cardiac Surgery

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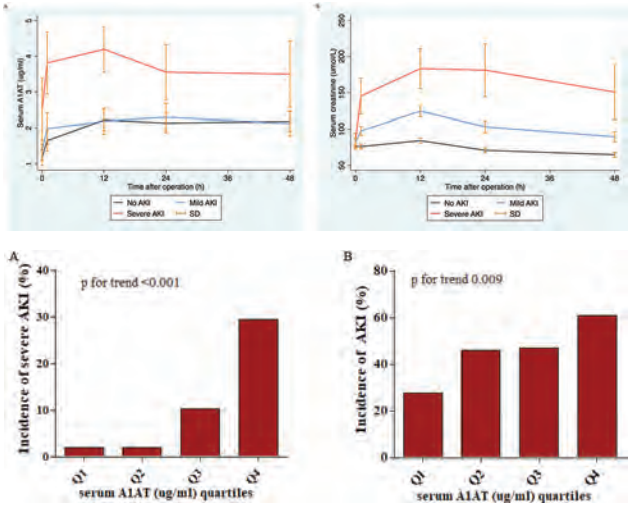
Background: Human α1-antitrypsin (A1AT), a binding protein with affinity to hemin, is an acute phase glycoprotein with broad anti-inflammatory properties. It is involved in the pathophysiologic processes underlying ischemic AKI and could exert dramatic renoprotective effects. Our objective is to assess the ability of serum A1AT (sA1AT) to predict AKI in adults undergoing heart surgery.

Methods: We conducted a prospective, single-center, cohort study in 201 patients undergoing cardiac surgery in our center since 1st July to 31st December 2017. We analyzed levels of sA1AT and other injury biomarkers during the perioperative period. Severe AKI was defined as Kidney Disease Improving Global Outcomes (KDIGO) stage 2 or 3. Overall AKI was defined as KDIGO stage 1.

Results: Of the 201 patients entered the final analysis, 69 (34.3%) developed mild AKI, and 22 (10.9%) developed severe AKI. sA1AT level increased immediately 1h after operation, maintained at the peak for 12 hours, and subsequently decreased in patients who developed severe AKI. After multivariate adjustment, sA1AT 1h after CPB independently associated with the development of severe AKI (OR, 1.46; 95% CI, 1.10-1.95; P=0.009) compared with mild AKI and no AKI, and the highest quartile of sMMP-7 level associated with 23-fold higher odds of severe AKI compared with the lowest quartile. For predicting severe AKI, sA1AT had an area under the receiver operating characteristic curve of 0.814, outperforming uTIM-1 and the clinical model. Elevated sA1AT level associated with longer stay in the intensive care unit and hospital.

Conclusions: sA1AT is a valuable potential predictor for severe AKI and poor in-hospital outcomes in patients after cardiac surgery.



TH-PO114

Incidence and Predictors of Nephrology Follow-Up After AKI in Critically Ill Patients

Emily J. See, David Ransley. *Austin Health, Melbourne, VIC, Australia.*

Background: Acute kidney injury (AKI) is a common complication of critical illness, and survivors are at increased risk of chronic kidney disease, end-stage kidney disease, and death. International guidelines have recommended that patients with AKI are evaluated after hospital discharge to assess for complications; however, follow-up rates have been reported to be low, and they have never been studied in critical care or Australian settings.

Methods: We conducted a retrospective study of all critically ill adults admitted with AKI between 1 January 2012 and 31 December 2016 to a single centre in Melbourne, Australia. Eligible patients were required to have a baseline eGFR >30 mL/min/1.73m^2 and to be alive and independent of renal replacement therapy at 30 days after hospital discharge. Logistic regression models were used to examine the primary outcome, which was nephrology review within the first year. Candidate predictors were screened for inclusion using univariable models and a backward stepwise elimination approach was used to remove covariates whose multivariable p value was >0.2.

Results: A total of 702 critically ill patients with AKI were included in the study (mean age 66 years, 64% male, baseline eGFR 78 mL/min/1.73m^2). Only 43 patients (6%) received nephrology follow-up in the first 3 months, while 63 patients (9%) were reviewed within a year. The median time to review was 41 days (interquartile range 23-136). Nephrology follow-up occurred more frequently in patients with a higher baseline creatinine (OR 1.02, 95% CI 1.01-1.03), a higher discharge creatinine (OR 1.01, 95% CI 1.01-1.02), and a greater severity of AKI (stage 3 OR 3.26, 95% CI 1.50-7.10). Traditional risk factors for chronic kidney disease, including older age and a history of hypertension, diabetes, or cardiovascular disease, did not prompt referral.

Conclusions: Despite international recommendations, few critically ill patients with AKI currently receive nephrology follow-up after discharge. The presence of other risk factors for chronic kidney disease was not associated with outpatient review. This represents a missed opportunity for the early detection of chronic kidney disease after AKI and prevents the timely implementation of preventative strategies to improve patient outcomes.

TH-PO115

A Modified Renal Angina Index Predicts Poor Outcomes After Pediatric Cardiac Surgery

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Background: Children undergoing congenital cardiac surgery are at high risk for poor outcomes including those related to acute kidney injury (AKI), prolonged mechanical ventilation and death. Early adjudication of risk for poor outcome may identify opportunities for early mitigative or preventative actions We hypothesized modification of the renal angina index (RAI), a composite score of patient risk and early signs of renal dysfunction, for use in patients following cardiac surgery would predict AKI related poor patient outcomes.

Methods: The cRAI, combining risk factors and clinical signs of kidney dysfunction [Figure] was studied in a multicenter derivation analysis to compare predictive performance for poor outcome to prediction by the individual cRAI terms. Poor outcome was defined as Day 3 AKI or ≥5 days of mechanical ventilation or death.

Results: 308 patients (64% male, med age 37 days (IQR:5-152 days) were analyzed. Half had single ventricle heart disease. The cRAI ≥10 outperformed individual and combination risk and injury factors for prediction of the composite outcome and demonstrated the optimal balance of sensitivity and specificity (AUC=0.77)[Table].

Conclusions: Derivation data indicates the cRAI, assessed soon after surgery, may optimize prediction for poor outcomes in children undergoing cardiac surgery. Future prospective studies are needed to validate the cRAI encompassing factors that may enhance its performance.

Table. Sensitivity analysis for individual and combination risk and injury factors

	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Youden
Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery (STAT) > 2	97.75 (92.1-99.7)	15.84 (11 .3-21.3)	31.87 (30.5-33.3)	94.59 (81.1-98.6)	13.59
Cardiopulmonary bypass (CPB) > 180 minutes	21.35 (13.3-31.3)	80.54 (74.7-85.6)	30.65 (21.5-41.7)	71.77 (69.2-74.2)	1.89
Vasoactive inotrope score at 8 hours (VIS-8) >15	33.71 (24.0-44.5)	92.76 (88.5-95.8)	65.22 (51.9-76.6)	77.65 (74.9-80.2)	26.47
CPB>180 minutes + VIS-8>15	28.09 (19.1-38.6)	97.29 (94.2-99.0)	80.65 (63.9-90.8)	77.06 (74.7-79.3)	25.37
Urine output (4-8 from ICU admission): <1 mL/kg/hr	37.08 (27.1-47.9)	69.68 (63.2-75.7)	33.00 (26.0-40.8)	73.33 (69.6-76.7)	6.76
Urine output (4-8): = 1-1.5 mL/kg/hr	64.04 (53.2-73.9)	39.82 (33.3-46.6)	30.00 (26.2-34.1)	73.33 (66.6-79.1)	3.86
Urine output (4-8): = 1.5-2 mL/kg/hr	79.78 (69.9-87.6)	23.08 (17.7-29.2)	29.46 (26.9-32.2)	73.91 (63.7-82.0)	2.85
Cardiac renal angina index positive (cRAI+) (10-40)	58.43 (47.5-68.8)	80.90 (75.2-85.9)	55.32 (47.2-63.1)	82.87 (78.9-86.2)	39.42

Figure. Cardiac Renal Angina = patient risk factors x early signs of renal dysfunction

Patient Risk Factors

Patient	Risk	Score
STAT 2-5	Moderate	1
CPB≥ 180 minutes **OR** VIS-8 ≥ 15	High	3
CPB≥ 180 minutes **AND** VIS-8 ≥ 15	Very High	5

X

Early signs of renal dysfunction: average urine output (UOP) from hours 4-8 from ICU admission in mL/kg/hour

Patient	Score
UOP(4-8): > 2	1
UOP(4-8): 1.5-2	2
UOP(4-8):1-1.5	4
UOP(4-8): < 1	8

= Cardiac Renal Angina Index (1-40)

STAT: Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery mortality categories 1-5; 5 = higher mortality)
CPB: cardiopulmonary bypass duration in minutes
VIS-8: Vasoactive inotrope score at 8 hours from intensive care unit admission
UOP (4-8): average urine output in mL/kg/hour from 4-8 hours after intensive care unit admission

TH-PO116

Creatinine-Cystatin C Ratio Is Associated with Mortality in ICU Patients Undergoing Continuous Renal Replacement Therapy

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Background: Development of acute kidney injury (AKI) in intensive care patients considerably increases the risk of mortality. Although several factors that are related to outcome have been recognized in this patient group, stratifying mortality risk still remains

a challenge. While serum creatinine levels are confounded by muscle wasting in critical illness, cystatin C is expected to be less modulated by muscle mass. Speculating that the ratio between serum creatinine and cystatin C may reflect muscle mass in critically ill AKI patients, we evaluated the association between creatinine-cystatin C ratio and mortality in patients requiring continuous renal replacement therapy (CRRT) in the intensive care unit (ICU).

Methods: Retrospective analyses were conducted on 443 ICU patients who underwent CRRT between August 2009 and October 2016 at Severance Hospital of Yonsei University Health System, Seoul, South Korea. The patients were divided into four groups based on creatinine-cystatin C ratio at the time of CRRT commencement. The primary outcome was 90-day mortality after CRRT initiation.

Results: The mean age was 64 ± 15 years, and 57.3% of patients were male. The most common cause of AKI was sepsis. The median and range of the creatinine-cystatin C ratio was 0.83 (0.13-6.20). The 90-day mortality rate for each creatinine-cystatin C ratio quartiles 1, 2, 3, and 4 were 76.6%, 73.9%, 61.3%, and 51.8%, respectively. Multiple Cox proportional hazard models revealed that the creatinine-cystatin C ratio was an independent predictor of 90-day mortality even after adjusting for confounding factors (Hazard ratio, 0.97; 95% confidence interval, 0.95-0.99, P<0.01). The prediction of mortality was significantly improved when creatinine-cystatin C ratio was considered compared to APACHE-II or SOFA scores alone.

Conclusions: Creatinine-cystatin C ratio is associated with mortality in ICU patients undergoing CRRT, and may be a practical marker in predicting survival among ICU patients with AKI.

TH-PO117

In the Aftermath of Hurricane Maria, a New Threat Arises

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Introduction: The 2017 Atlantic Hurricane Season was among the most active in history and on September 20th, Hurricane Maria struck the island of Puerto Rico. Human leptospirosis is endemic in Puerto Rico and reaches epidemic levels after natural disasters.

Case Description: A 51-year-old farmer presented after a 5-day history of cough with bloody sputum, yellow skin, fever, nausea, vomiting and myalgias. Symptoms began after consuming a banana found on the ground weeks after Hurricane Maria. Vital signs were unremarkable. Physical examination revealed lung rales, conjunctival suffusion and jaundice. Laboratories showed leukocytosis, anemia and thrombocytopenia; creatinine 6.27, BUN 123 and bilirubin 27.4 mg/dL; ALT 44 and AST 114 U/L. ABGs revealed hypoxemia. Chest CT scan without IV contrast was positive for diffuse bilateral ground glass opacities and interlobular septal thickening, worrisome for alveolar hemorrhage. Ultrasound revealed normal liver and bile ducts, and normal kidneys without obstruction. Leptospirosis was considered as a cause of illness and he was started on Ceftriaxone. Within the first 8 hours of admission, his respiratory function deteriorated requiring mechanical ventilation. Daily high-dose hemodialysis was prescribed. Serology was positive for Leptospirosis. Due to respiratory deterioration and rise in bilirubin levels, the decision was made to begin plasma exchange. Over the next 48 hours of admission, he underwent two 4-liter exchanges using fresh frozen plasma. After two plasma exchange sessions, there was a reduction of serum bilirubin to 7.6. Respiratory function improved and patient was extubated. He had recovery of renal function and hemodialysis was discontinued.

Discussion: Puerto Rico has reported at least 76 cases of suspected and confirmed leptospirosis in the aftermath of Hurricane Maria. Our patient presented the most severe form of leptospirosis, Weil's disease, that comprises jaundice, renal and respiratory failure and a high mortality rate. There are few case reports documenting the benefits of plasma exchange with severe leptospirosis. Given the dramatic recovery of our patient after plasma exchange, we conclude that more research is needed to define its role in patients with severe leptospirosis without clinical improvement after standard therapy.

TH-PO118

Intravenous Contrast on Continuous Renal Replacement Therapy: Does It Matter?

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Background: Acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) is commonly encountered in the intensive care unit (ICU). Clinicians caring for ICU patients are often forced to weight the risks of aggravating the AKI before using intravenous (IV) contrast agents when obtaining diagnostic imaging studies for patients on CRRT. We hereby describe the risk of dialysis dependency (DD) or persistent severe kidney dysfunction (SKD), defined as creatinine >4 mg/dL at discharge, among ICU patients receiving IV contrast while on CRRT for AKI.

Methods: All ICU patients at our institution who underwent a CT scan while on CRRT between 2013-2017 were identified. ESRD patients, those with baseline eGFR <15 mL/min per 1.73 m^2, and those without overnight ICU stay were excluded. Cases were grouped according to IV contrast exposure as contrast-enhanced (CECT) or unenhanced (UCT) groups. We compared baseline characteristics, mortality, and DD/SKD at discharge between the groups using Wilcoxon Rank-sum and Chi-square tests. We fitted a competing risk regression model for DD/SKD at discharge with death as a competing risk adjusted for demographics and known comorbidities.

Results: A total of 189 CECT and 644 UCT patients were included in the final analysis. Baseline characteristics were similar between groups including baseline creatinine and CKD stage as defined by the Kidney Disease Outcomes Quality Initiative cutoffs. The CECT group had significantly higher ICU length of stay (median 24 vs 17 days; p<0.001) and required more days on CRRT (median 10 vs 6; p<0.001). 58.7% of CECT and 51.6% of UCT died during hospitalization (p=0.08), while 27.5% and 27% had DD/SKD at discharge respectively (p = 0.89). Similarly, no significant difference was found in competing risk model for DD/SKD (SHR for CECT vs UCT: 0.81; 95% CI: 0.60-1.10; p=0.18)

Conclusions: Despite the apparently sicker CECT group, IV contrast administration while on CRRT for AKI was not associated with an increased risk of DD/SKD at discharge. This study suggests that contrast enhanced imaging need not be withheld from AKI patients on CRRT, particularly when valuable information can be gained from the contrast study with potential therapeutic implications.

TH-PO119

Incidence of Amoxicillin-Induced Crystal Nephropathy

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Background: Amoxicillin (AMX)-induced crystal nephropathy (AICN) has been considered as a rare complication of high dose intravenous AMX. However, in the recent years, its incidence seems to be increasing. Occurrence of AICN has been observed exclusively with intravenous (IV) administration and mostly under daily doses over 8 g/day. AMX cristalluria is a major diagnostic criterion but is rarely performed by practitioners. Thus, the real incidence of AICN may be underestimated. The objective the present study was to determine the incidence of AICN in the current practice.

Methods: We conducted a retrospective study between the 01/01/2015 and 01/01/2018 in Angers University Hospital. Inclusion criteria were admission in Angers University Hospital, age over 18 years-old, and administration of more than 8g/day of AMX using IV route for more than 24h. Patients admitted directly into the intensive care units were excluded. Medical records of patients that developed KDOKI stage 2-3 AKI were reviewed by a nephrologist and a specialist in pharmacovigilange in a blinded fashion. AICN was retained if temporality analysis was conclusive, after exclusion of other causes of AKI, in absence of other nephrotoxic drug administration and if evaluations were concordant.

Results: During the 3 -years period of the study, 1303 patients received IV AMX for at least 24h, 358 (27.5%) were exposed to AMX doses over 8g/day and were included in the study. Patients were predominantly males (68.2%) with a mean age of 69.1 years-old. AMX was administered in surgical context in 21.5% of cases and in a medical context in 78.5% of cases. Patients received a mean dose of AMX of 11.2 g/day, representing a mean dose of 153.9 mg/Kg/day. Seventy-four patients (20.7%) developed AKI, 42 (56.8%) of KDIGO stage 2 or 3. Among patients with KDIGO 2-3 AKI, AICN diagnosis was retained in 16 (38.1%) patients, representing an incidence of 4.47%. As compared to other AKI patients, female proportion was significantly higher in AICN group as compared to other AKI (p=0.013). As compared to non AKI patients, no prédictive factor of AICN could be identified.

Conclusions: This study suggests that AICN incidence is underestimated and may represent as much as one third of AKI developping under AMX treatment.

TH-PO120

AKI Is Not an Independent Risk Factor for Low Probability of Target Attainment (PTA) of Piperacillin

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Background: Infection is the leading cause of death in patients with acute kidney injury (AKI). Most antibiotics are renally cleared. Dose adjustments are based on imperfect estimates of renal function. We have shown that patients with severe AKI (e.g., continuous dialysis) are often underdosed. We hypothesize that piperacillin is underdosed in less severe AKI as well.

Methods: In a prospective study, patients admitted to the intensive care unit (ICU) had piperacillin concentrations measured in residual blood samples (RBS). Concentration-time curves for each patient were estimated from RBS values using nonlinear mixed-effects methods and a two-compartment model in NONMEM and R. AKI was assessed on each day of ICU admission based on modified KDIGO criteria. Patients were grouped according to the most severe AKI observed during their admission. Piperacillin PTA for patients with KDIGO classes 0,1,2, or 3 were estimated from concentration-time curves during the dosing period in which the first RBS was collected. PTA frequencies were compared using Pearson chi-square test. For this analysis, an MIC of 16μg/ml piperacillin was used, as it is the CLSI susceptibility breakpoint for clinical isolates of *Enterobacteriaceae*. PTZ was infused over 4 hours, per institutional protocol, to optimize pharmacodynamics.

Results: We measured piperacillin levels of 386 patients, of whom 86 were excluded due to incomplete data (74) or RRT for non-renal indications (12). Of the remaining patients, 113 met KDIGO 1-3 AKI criteria and 187 had no AKI. There were no significant differences in age, weight, or gender between groups. Most patients received 3.375 gm PTZ q8h; 28% of the AKI group received 3.375 gm q12h. 93% of the AKI group and 77% of the non-AKI group achieved a of fT>MIC > 50% (P < 0.001). These percentages decreased to 48% and 41% respectively for fT > MIC = 100% (P = 0.226).

Conclusions: ICU patients with AKI are not at increased risk of failing to achieve a commonly accepted PK target for piperacillin compared to patients without AKI. The biosample collection may not be synchronized to the AKI occurrence. However, given that fewer than 50% of critically ill patients attain a conservative target of ft > MIC = 100%, strategies to improve dosing and measure variation in exposure are urgently needed.

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TH-PO121

Use of Caplacizumab in Germany to Treat Acquired Thrombotic Thrombocytopenic Purpura in a Real-World Setting

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Background: Acquired thrombotic thrombocytopenic purpura (aTTP), a form of thrombotic microangiopathy, is a rare but life-threatening disease, which is characterized by microangiopathic hemolysis and thrombocytopenia with and without end-organ damage. It results from an autoantibody mediated inhibition of the metalloproteinase ADAMTS13 that is required for the degradation of ultra-large von-Willebrand-factor multimeres. Two recent seminal trials (HERCULES and TITAN) demonstrate the efficacy of the new nanobody caplacizumab for the treatment of this condition. To assess the utility and role of caplacizumab in the treatment of aTTP patients, we analyzed the first 22 German patients that had been treated with the new drug since Mai 2018.

Methods: Retrospective analysis of epidemiologic and treatment related data of the first 23 German aTTP patients undergoing caplacizumab treatment in 12 German medical institutions between Mai 2018 and April 2019.

Results: Between Mai 2018 and April 2019, 22 patients (age range 26-83 years) were treated with caplacizumab in addition to pulsed steroids, plasma exchange and rituximab. On average, patients received 32 daily doses of caplacizumab, and treatment was initiated on day 7 after disease onset. Patients received an average of 12 plasma exchanges. 36 percent of all patients relapsed, however, most patients received caplacizumab only as treatment of refractory disease or relapse and not as front-line therapy. This resulted in only 20% of patients being treated strictly according to the HERCULES trial protocol. One patient died from microangiopathic complications despite early caplacizumab treatment. One patient suffered major bleeding complications, one patient an allergic reaction to the drug; in general, minor bleeding complications were reported but scarce.

Conclusions: Caplacizumab appears to be efficacious and reduced the time to platelet normalization in a real-world setting. Caplacizumab augments therapy options for patients with aTTP. The data presented here and future experience will help address pending questions about patient selection for caplacizumab treatment, therapy monitoring, timing of treatment cessation, and drug safety.

TH-PO122

Acute Interstitial Nephritis After Treatment with the Human Anti-CD20 Antibody Ocrelizumab: First Case Report

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Introduction: Acute interstitial nephritis (AIN) is an important cause of acute kidney injury and is commonly caused by drugs. Ocrelizumab, a humanized anti-CD20 antibody, was recently approved as a treatment for primary progressive and relapsing multiple sclerosis. Here we report a patient who developed severe AIN requiring hemodialysis after receiving Ocrelizumab.

Case Description: A 64-year-old female with a history of diabetes and hypertension received the first infusion of Ocrelizumab 300 mg for multiple sclerosis. One week later she presented to the emergency room complaining of fatigue and generalized weakness. Laboratory findings were significant for a creatinine of 5.5 mg/dL (was 0.9 mg/dL a few days prior). Her creatinine continued to increase to 10 mg/dL on hospital day 4 requiring initiation of hemodialysis. Urinalysis showed moderate blood, +3 protein, 21 RBC's, 11 WBC's. Serologic work-up included a normal C3, C4, ANA, ANCA, anti-GBM, and SPEP/UPEP. Renal ultrasound was normal. A kidney biopsy was performed which demonstrated a moderate mixed interstitial infiltrate with many eosinophils, in a background of interstitial edema. The tubules were dilated and showed significant degenerative changes in tubular epithelial cells, with intratubular calcium oxalate crystals and intratubular degenerative debris. No viral inclusions were seen and there was minimal to mild interstitial fibrosis. The patient was started on oral prednisone 60 mg daily with a subsequent slow taper. Renal function significantly improved with the creatinine trending down to 2.4 mg/dL two weeks later on clinic follow-up.

Discussion: Ocrelizumab, a humanized anti-CD20 monoclonal antibody, was recently approved for the treatment of primary progressive and relapsing multiple sclerosis. To our knowledge, this is the first report of severe AIN associated with an anti-CD20 antibody. In this case, the patient responded well to treatment with high dose steroids. Our report highlights the need to monitor patients closely for potential renal toxicities that may be associated with such medications.

TH-PO123

Incidence and Risk Factors of AKI in Cancer Patients with Multi-drug-Resistant Infections Treated with Colistin

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Background: Developing countries have seen a resurgence in the use of Colistin in recent years, for treatment of multidrug resistant (MDR) gram-negative bacterial infections. Colistin is associated with increased risk of nephrotoxicity and consequently poor outcomes in high-risk patients. We studied cancer patients at our centre to determine incidence, risk factors and outcomes of acute kidney injury (AKI) associated with use of Colistin.

Methods: We reviewed patient medical records using electronic information system (eHIS), from January 2015 to December 2018, in this single centre cross-sectional study using secondary data analysis. Adults with solid organ or hematological malignancies with confirmed or suspected multi drug resistant gram-negative infections, who received colistin for at least 48 hours, were included. Outcomes of AKI including need for renal replacement therapy (intermittent or continuous), length of hospital stay and mortality were studied. Patients were followed for 3-6 months following an episode of AKI to review development of chronic kidney disease (CKD). AKI was defined according to Kidney Disease Improving Global Outcomes (KDIGO).

Results: A total of 115 patients were studied. Mean age was 42.6 ± 15.4 years and Mean weight was 60.3 ± 14 kilograms. Majority (68.7%) were male. In multivariable analysis, three independent variables including weight (adjusted odds ratio [AOR] 1.04; 95% confidence interval [CI] 1.01-1.10), underlying malignancy (solid versus hematological (AOR 3.39; 95% CI (1.15-9.98), 0.02) and need for admission to intensive care unit (ICU) (AOR 2.75; 95% CI (1.00-7.82), 0.05) were identified as significant independent risk factors for nephrotoxicity. In patients who had AKI (n=75, 65.2%), mean length of hospital stay was 21.7 ± 13.7 days, 20% required renal replacement therapy (RRT), 10.4% developed residual CKD and 60% died.

Conclusions: Increased weight, solid organ malignancy and ICU admission were significantly associated with increased risk of AKI in this cohort. Patients who required RRT had worse outcomes.

TH-PO124

A Case of Steroid-Dependent Interstitial Nephritis Related to Pembrolizumab Use

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Introduction: Pembrolizumab is a humanized monoclonal antibody belong to class of Immune check point inhibitor (ICI)used in cancer immunotherapy which targets the programmed cell death protein 1 receptor of lymphocytes. Ever since the FDA approval of ipilimumab in 2011 for Metastatic melanoma, there has been a rapid advancement in the use of ICI in various forms of cancer. Every year the use of ICI is rising so do adverse events related to the use of Immune check point inhibitors

Case Description: 77 y/o female with h/o metastatic lung cancer, on chemotherapy, transferred to ER from clinic after labs showed Creatinine of 8.95 and potassium: 7.4 compared to a baseline creatinine of 1.1 six weeks prior. Her Urinalysis showed 62 wbcs with rest of the labs unremarkable except for metabolic acidosis with a bicarbonate level of 16. She was managed supportively and subsequently a renal biopsy was done which showed diffuse severe acute tubulointerstitial nephritis with eosinophils consistent with a hypersensitivity reaction, marked interstitial fibrosis, marked arteriosclerosis and mild arteriolosclerosis. Her history is significant for biopsy proven adenocarcinoma of the lung diagnosed in June 2017 Started on chemotherapy with Carboplatin, pemetrexed initially. She had Left upper lobectomy and wedge resection in Oct 2017, followed by maintenance immunotherapy with Pembrolizumab only since Decmeber 2017. Considering the pathology finding patient was started on high dose prednisone for AIN. Eventhough creatinine improved to 1.71 on follow up visit she remained steroid dependent and her AKI progressed to CKD IV with recent EGFR of 27

Discussion: The presence of Acute interstitial nephritis (AIN) secondary to Immune check point inhibitors has been described before but usually with the cessation of drug and with high dose prednisone therapy for few weeks renal function improves. We present a case of Acute interstitial nephritis related to pembrolizumab use which presented a year after initiation of therapy and despite early initiation of steroids, she remained steroid dependent with progression of Acute Kidney injury (AKI) to Chronic Kidney disease (CKD). Our case emphasis on keeping AIN on top of differential diagnosis in patients treated with ICI even if ICI use is not recent and patient can develop steroid dependency with progression of AKI to CKD

TH-PO125

Spontaneous Late Acute Cholesterol Emboli with Acute Hydrophilic-Polymer Kidney Injury in a Renal Allograft

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Introduction: Hydrophilic coatings are used on intravascular devices to avoid thrombosis, and vasospasm during endovascular procedures. We report a very rare case of Acute Kidney Injury caused by this coating.

Case Description: 58 year old male underwent his second left sided renal transplant in March 2017. Prior to transplant he has mild- to moderate aortic stenosis. However subsequent to his transplant in October 2017 he was found to have critical aortic stenosis. For which he underwent a transcatheter -aortic valve replacement via right transfemoral percutaneous approach with the insertion of a bioprosthetic aortic valve. His renal function function remained stable at 1.4mg/dl range at the time of the aortic valve replacement. Three months in January 2018 later he presented with oliguric acute kidney injury with a creatinine of 5mg/dl. Urinalysis revealed microscopic hematuria and 1+ proteinuria. Doppler evaluation revealed elevated velocities within the proximal, midportion, the renal artery. with features suggestive of renal artery stenosis. The biopsy showed Acute tubular necrosis; Arteriole with isolated cholesterol embolus; Glomerular capillaries with intraluminal embolic material which was nonpolarizable which appeared weakly eosinophilic, periodic acid–Schiff (PAS)-negative, largely silver-negative with speckled granular positivity, and light blue-gray on trichrome stain. This was consistent with hydrophilic-polymer emboli per prior case reports. The biopsy was complicated by acute hemorrhage and the patient had to have angiogram showing a severe 90% stenosis at the origin of the renal transplant artery. The lower pole segmental artery had to be embolized along with a 5 mm self-expanding bare-metal stent with resultant brisk flow through the stent into the transplant kidney. After 6 weeks of needing dialysis he recovered from his acute kidney injury with a creatinine back down to 1.6mg/dl.

Discussion: To date, only 4 cases of hydrophilic polymer emboli have been reported to involve the kidneys, of which 2 were in a renal allograft.(Chen et al NEJM 2015). This case provides evidence that renal lesions may be induced by hydrophilic-polymer emboli due to the transcatheter aortic valve procedures in conjunction with spontaneous acute atherosclerotic cholesterol emboli.

TH-PO126

Focus on POCUS: Do Not Blindly Trust the Bladder Scanner in Patients with Ascites

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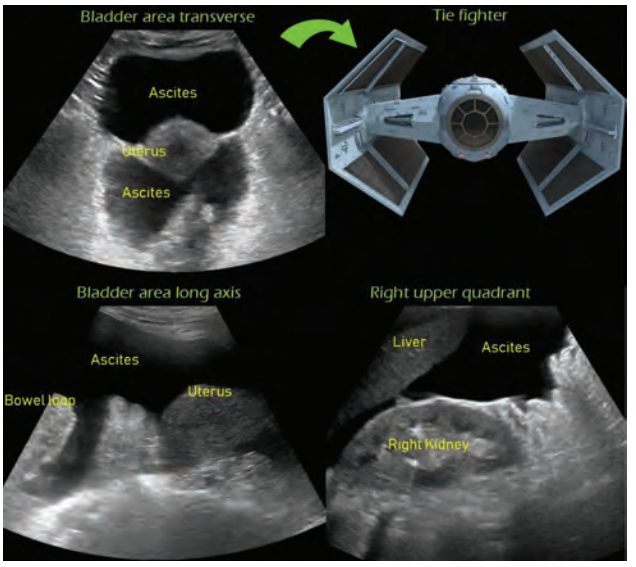
Introduction: Urethral catheterization, an invasive procedure with infection risk, was regarded as gold standard for measuring residual urine volume(UVol). It has now been superseded by portable automated bladder scanners(BS) performed by nurses at the patient's bedside. The benefits include fewer invasive catheterizations and increased patient comfort. However, caution has to be exercised when using BS to identify UVol in complex cases such as patients with ascites or other pelvic pathology. We report a case of pelvic ascites, where nephrologist-performed point-of-care ultrasonography (POCUS) has facilitated the correct diagnosis.

Case Description: A 45-year-old woman with history of liver cirrhosis was admitted for failure to thrive. Hospital course was complicated by decompensated cirrhosis, septic shock, and Acute Kidney Injury requiring renal replacement therapy. A routine BS to monitor renal recovery revealed UVol of ~800ml. However, there was no urine return on insertion of a urethral catheter. Urology consult was requested to assist with the catheter placement. Meanwhile, nephrology team performed POCUS, which demonstrated a large amount of anechoic fluid in the pelvis, which was 'continuous' with the peritoneal cavity in the longitudinal plane indicating that it is pelvic ascites and not the urinary bladder. In the transverse plane, uterus was seen floating in the pelvic ascites and together with ovarian ligaments, gave the appearance of a "TIE fighter" ('Star Wars' fictional Starfighter) [Figure]. A CT scan obtained later confirmed decompressed bladder deep in the pelvis.

Discussion: The blind nature of BS measurement does not allow differentiation of bladder from other fluid collections. Hence, nephrologists should perform POCUS and need to be aware of the pelvic anatomy in patients prone to ascites, which likely avoids unnecessary consultations and catheterizations.



TH-PO127

Acute Interstitial Nephritis Presenting with Isolated Glycosuria

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Introduction: Acute Interstitial Nephritis (AIN) is often induced by drugs and is a common cause of acute kidney injury. The classical triad of AIN consists of eosinophilia, rash, and fever. However, clinically diagnosing AIN can often be challenging as these signs and symptoms rarely present in concert. The inflammatory pathology of AIN leads to renal tubule dysregulation which can be clinically observed as glycosuria, eosinophilia, leukocytes or white blood cell casts and proteinuria. We present a case of AIN presenting with acute kidney injury and isolated glycosuria without pyuria.

Case Description: A 34-year-old female presented to our institution with nausea, vomiting and abdominal pain. She had been treated for tonsillitis with amoxicillin a month prior to presentation. She had a blood pressure of 169/104 mmHg without antecedent history of hypertension. She was afebrile. Her physical exam was significant for trace lower extremity edema. She had no rashes. On admission, her serum creatinine was 7.7 mg/dL with a potassium of 3.1 mmol/L, and hemoglobin of 11.7 g/dL. Her white blood cell count was 10.2 without eosinophilia. Urinalysis was significant only for glycosuria of over 500 mg/dL with a serum glucose of 119 mg/dL. Urine sediment examination was unremarkable. Hepatitis and HIV serologies were negative, complement levels were normal, and urine immunofixation was negative. Ultrasound of kidneys was normal. Throughout admission she sustained glycosuria with normoglycemia. She underwent renal biopsy which demonstrated acute interstitial nephritis. She was started on high dose prednisone that was tapered over the course of three months. Two months following presentation her glycosuria resolved, and four months following presentation her serum creatinine was 1.2 mg/dL.

Discussion: This patient had an atypical presentation of AIN that lacked classical diagnostic lab features and has been rarely reported. She had profound glycosuria in setting of normoglycemia, which resolved following a course of corticosteroids. Glycosuria was most likely due to proximal tubule damage from AIN. This case supports previous hypotheses that drug-induced AIN can cause SGLT dysfunction resulting in glycosuria in the absence of other identifiable proximal tubule dysregulations. We propose that resolution of AIN involves the repair and restoration of SGLT function.

TH-PO128

Sizzurp Joins the List: AKI from Recreational Drug Use

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Introduction: Synthetic cannabinoids and bath salts, both popular for their psychoactive effects have been associated with acute kidney injury (AKI). Another recreational drug "sizzurp" (also known as "purple drank", and "lean") was first used in the 1960s and made popular in the 1990s by the hip hop community. It consists of the antihistamine promethazine +/- codeine, typically mixed with a sweet soft drink, and ingested in higher than prescribed doses. Promethazine causes CNS depression, cholestatic jaundice and hypotension. Codeine can cause behavioral changes, respiratory depression, and cardiac arrest. Promethazine induces codeine metabolism to morphine via CYP2D6, potentiating a "high" and intensifying the sedative effects. Sizzurp is desired for creating euphoria accompanied by a "dissociative feeling". Often ingested with alcohol, its risk profile is magnified.

Case Description: We have a 39-y/o man with no PMH, who presented with abdominal pain after taking sizzurp for several days. He had scleral icterus and a BP of 150/96. Labs: WBC 25.4, Hgb 13.2 g/dl, Plt 367k, BUN 80 mg/dl, Cr 8.3 mg/dl. Total

bilirubin was 12 mg/dl with a mild transaminitis and a CK of 1500 units/L. The UA showed mild hematuria and proteinuria with urine P/C ratio of 1.2 g/g. The urine drug screen was positive for cannabinoids. Serologies, SPEP and UPEP were negative. The kidneys were normal in size and echogenicity and without hydronephrosis. Liver US showed fatty infiltration and liver biopsy revealed drug induced injury. A renal biopsy had 11 nl glomeruli with diffuse ATN, focal interstitial nephritis and a negative bile stain. IF was negative. He was oliguric and required dialysis for one month but had eventual renal recovery with a Cr of 1.3 mg/dl.

Discussion: Little is known about the mechanism of AKI in many recreational street drugs including sizzurp. It may be directly toxic (nephrotoxic ATN) or it may be associated with hypoperfusion leading to ischemic ATN. Sizzurp should be added to the list of recreational drugs associated with AKI.

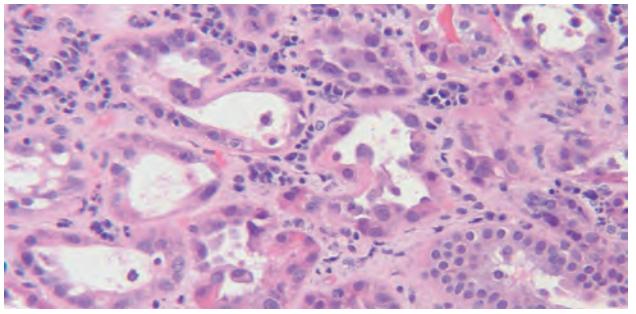

Figure 1. ATN with focal interstitial nephritis.

TH-PO129

An Unusual Case of Atypical Hemolytic Uremic Syndrome Triggered by Acute Infectious Mononucleosis Infection Presenting Without Thrombocytopenia

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is characterized by abnormal clotting with features of intravascular hemolysis, thrombocytopenia, and acute kidney injury. Athrombocytopenia has rarely been associated with aHUS. Approximately one half of patients with aHUS have pathogenic gene variants of the complement pathway and gene variants in the coagulation pathway of unclear pathogenicity have also been identified. We describe a patient with acute Epstein Barr virus (EBV) infection who developed aHUS without thrombocytopenia in the setting of gene mutations of both the complement and coagulation pathways.

Case Description: A 26-year-old female with acute infectious mononucleosis diagnosed a week before, presented with malaise, hypertension (148/98 mm) and oliguria. Laboratory data revealed hemoglobin 7.9 gm/dl, BUN 123 mg/dl, creatinine 11.3 mg/dl, UPCR of 5.6 mg/mg with a nephritic sediment. Moderate schistocytes were seen in the peripheral smear but platelets were normal. ADAMS13 was normal. Renal biopsy showed acute and subacute thrombotic microangiopathy. Other than a recent positive IgM Monospot, autoimmune and other infectious studies were unremarkable. She had elevated Ba fragment, Bb fragment and soluble level sMAC/C5b-9. Genetic panel found a likely pathogenic variant in the CFH gene and a novel variant of unknown significance in the PLG (plasminogen) gene. Treatment with eculizumab resulted in discontinuation of dialysis after 4 weeks. Follow up at 6 months showed improved UPCR to 1.5 mg/mg.

Discussion: aHUS is characterized by uncontrolled activation of the alternate pathway of complement at the cell surface. Mutations of the complement pathway are implicated in disease pathogenesis and coagulation pathway genetic variants have been associated. Our patient's finding of EBV-triggered aHUS has been rarely reported and even less commonly in association with athrombocytopenia. The patient has a rarely described combination of a likely pathogenic variant in the complement pathway CFH gene and a variant in the coagulation pathway PLG gene. Due to absence of causal relationships, these findings may be coincidental in this patient with EBV-triggered aHUS. Further research is needed to elucidate the pathophysiology of aHUS

TH-PO130

Diagnosing Atypical HUS in the Setting of Complement Amplifying Conditions (CAC): A Case Series

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Introduction: Diagnosing aHUS in the setting of complement amplification conditions (CAC'S) is challenging. We report 2 cases of aHUS which presented as treatment resistant Lupus, and unresolving sepsis from influenza in post partum period.

Case Description: **Case 1:** 20 Yr old African American woman with Lupus (diagnosed at age 16, chronically low complements, partially controlled with Azathioprine, Rituximab, Mycophenolate and recently started on Cyclophosphamide (CYC) for class IV lupus nephritis, received 3 doses) presented to hospital for confusion and seizures. Started on pulse dose steroids for possible Lupus cerebritis. Labs were significant for microangiopathic hemolytic anemia, thrombocytopenia and low complements. Considering her resistant lupus despite outpatient CYC and inpatient pulse dose steroids, she was started on plasmapharesis (TPE) after sending ADAMTS13 and genetic panel for aHUS. No clinical or lab improvement was noted after 5 sessions of TPE. Genetic panel for aHUS resulted equivocal with heterozygous missense mutations in *CFH, CFHR1-CFHR3* gene. Started on Eculizumab (ECU) for aHUS (900 mg/week for 4 weeks). Serum creatinine and hemolysis labs improved significantly. She was maintained on ECU (1200mg/ 2 weeks) for 8 months after which she suffered sudden death. **Case 2:** 38 Yr old African American woman with hypertension presented with headaches in her 3rd trimester (first pregnancy); underwent C-section at 27 weeks due to pre-eclampsia. Post-op she was transferred to ICU for hypoxic respiratory failure (ARDS) and sepsis. She was treated with antibiotics initially and changed to Oseltamivir due to positive Influenza PCR. She developed AKI requiring CRRT. Due to lack of clinical response, low complements and slowly declining platelet counts, further workup showed microangiopathic hemolytic anemia. TPE was started after sending ADAMTS13 and genetic panel for aHUS. Hemolysis labs and platelet levels partially improved after 10 sessions of TPE. aHUS genetic panel showed heterozygous missense mutation for *CFHR3*. Started on ECU 900 mg/week for 4 weeks, followed by 1200 mg/ 2 weeks for 3 doses. Her renal function and other lab parameters returned to normal, and remained stable for past 18 months.

Discussion: Clinicians should have low threshold for suspecting aHUS if CAC's do not respond to appropriate therapy.

TH-PO131

Don't Judge a Book by Its Cover: The Challenges of Diagnosing Nondilated Obstructive Uropathy

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Introduction: Nondilated obstructive uropathy (NDOU) is a rare and elusive cause of AKI since the diagnosis of obstructive uropathy (OU) depends on the demonstration of a dilated collecting system while the lack of rules it out. Reported in <5% of OU, NDOU has been associated with retroperitoneal malignancy, lymphadenopathy and fibrosis. The diagnosis requires a high index of suspicion and intervention despite normal radiographic screening studies. We present a case of AKI thought to be ATN where recognition and treatment of NDOU prevented irreversible ESRD.

Case Description: A 60-y/o woman with breast cancer complicated by metastasis to the retroperitoneal lymph nodes with a baseline serum creatinine (sCr) of 0.6 mg/dl was given zoledronic acid and one month later had a sCr of 1.3. She had decreased urine output and abdominal pain. Ultrasound and CT imaging showed no evidence of hydronephrosis. Her UA was benign. She became anuric and HD was initiated. Her AKI was postulated to be ATN from bisphosphonate use. A renal biopsy could not be performed because of DVTs requiring anticoagulation. She was discharged on HD. Despite normal imaging and a potential explanation for her AKI, there remained a clinical concern for NDOU. Bilateral retrograde pyelogram performed two weeks post-discharge showed no hydronephrosis. There were questionable areas of mild ureteral segmental narrowing and because her clinical course suggested obstruction, bilateral stents were placed. There was an immediate diuresis with an average output of about 300 ml/hr. Her sCr improved from 8.6 mg/dL to 0.8 mg/dL over the next 24 hrs (Fig.1).

Discussion: NDOU is a rare diagnosis that requires a high level of clinical suspicion. The lack of dilatation in NDOU has many pathophysiologic explanations, but is felt mainly to be secondary to the encasement of the collecting system. Direct visualization via retrograde or antegrade pyelography with empiric stent or nephrostomy tubes placement may be necessary when the concern for NDOU is high despite imaging lacking evidence of hydronephrosis.

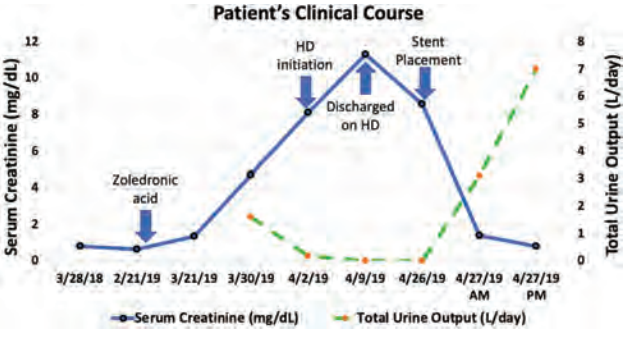

Fig. 1

TH-PO132

Benefits of Renal Artery Stenting in Select Cases with Severe Renal Artery Stenosis and AKI

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Introduction: Prevalence of RAS in US is estimated to be 7% in those >65 years. Two large RCTs demonstrated that RA stenting do not improve CV and renal outcomes. We present 2 cases of oliguric AKI 2º to RAS who had prompt improvement in renal function after RA stenting.

Case Description: Case 1: A 78-year-old WF with hx of uncontrolled HTN and baseline SCr 1.3-1.5 mg/dL presented with SOB, edema, and AKI. Admission SCr was

2.7 mg/dL and she developed oliguric AKI.Renal US with Doppler was consistent with bilateral RAS (Table1). Right RA stenting was performed, with immediate improvement in UO and SCr (Fig1&2A/B). At 6-mo f/u, her SCr is 3.3 mg/dL with BP of 114/62 mmHg on 3 meds, incl ACEI. **Case 2:** A 72-year-old WF with hx of uncontrolled HTN, CKD (baseline SCr 1.8-2.5 mg/dL) and recurrent hospitalizations for vol overload, presented with SOB and oliguric AKI.Renal US with Doppler revealed L RAS (Table 1). She developed oliguric AKI and left RA stenting was performed (Fig 1), with prompt improvement in renal function. At 5-mo f/u, her BP is 138/64 mmHg on 3 meds, including an ARB, and her SCr was 1.62mg/dL. She has not had any further hospitalizations for vol overload.

Discussion: After publication of 2 large RCTs (ASTRAL & CORAL), RA stenting has fallen out of favor in tx of RAS. However, it is important to note that these studies excluded patients with severe disease, pulm edema and renal failure. Thus, determination for risks and potential benefits of RA stenting needs to be individualized high-risk pts. RA stenting in our 2 pts with high CV risk averted imminent dialysis, improved BP and allowed use of RAAS blockade.

	Age	Sex	PMH	Tobacco use	AntiHTN meds	BP on admission	Admission SCr	Peak SCr	Renal sizes on US	Renal artery Doppler	Discharge SCr
Case 1	78	F	HTN CKD 3 HLD	Current smoker	Amlodipine Triamterene HCTZ	160/70 mmHg	2.7 mg/dL	4.07 mg/dL	RK 9.4 cm LK 8.6 cm	PSV R RA origin: 404 cm/sec PSV L RA origin: 271 cm/sec PSV aorta: 110 cm/sec	2.15
Case 2	72	F	HTN, DM, CKD 4, CAD, HLD	Former smoker	Amlodipine Carvedilol Clonidine Furosemide	156/58 mmHg	3.35 mg/dL	5.26 mg/dL	RK 6.6cm LK 10.0 cm	PSV R RA origin: 121 cm/sec PSV L RA origin: >400 cm/sec PSV aorta 138 cm/sec	1.8 mg/dL

FIGURE 1

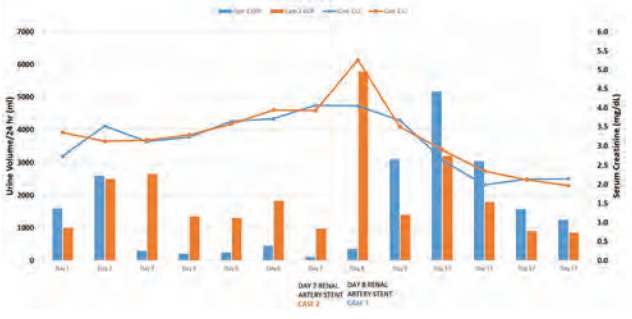

Figure 2 A

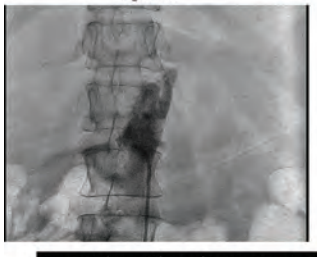

Figure 2 B

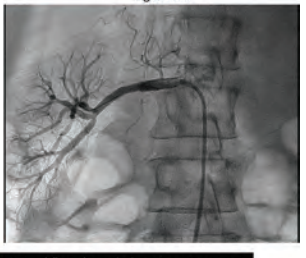

Figure 2 A shows evidence of R artery stenosis with minimal flow through the artery. Figure 2 B shows excellent renal blood flow after stent placement.

TH-PO133

Renal Amyloidosis and Intracranial Mucormycosis in an Intravenous Drug User

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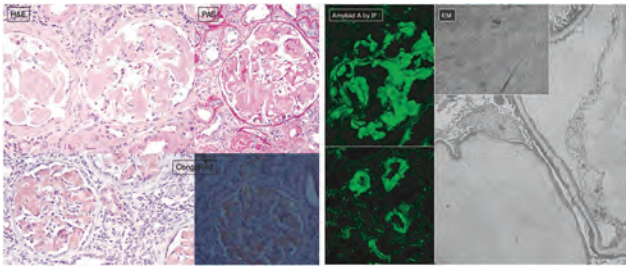
Introduction: Mucormycosis is a rare but fatal fungal infection commonly seen in immunocompromised states such as end-stage kidney disease and post-renal transplantation. Here we report a unique case of invasive mucormycosis associated with severe acidemia in a patient with impaired renal function and AA amyloidosis.

Case Description: A 37-year-old Caucasian man with a history of active intravenous drug use including heroin was admitted for one week of slurred speech, right-sided weakness and right facial droop. CTH showed a 2x3 cm lesion in the left deep frontal white matter with surrounding vasogenic edema. His labs showed a serum creatinine (SCr) of 15.04 mg/dL (estimated GFR: 4 mL/min/1.73m2), BUN of 120 mg/dL, and bicarbonate of 10 mmol/L. The pH and pCO2 of the first venous gas were 7.14 and 28 mmHg respectively. His urinalysis was positive for 3+ glucose with a pH of 8.0. A spot urine protein/creatinine ratio was 6.87. A brain biopsy confirmed the diagnosis of mucormycosis and a renal biopsy was subsequently performed. Outcomes: The patient received maintenance isotonic bicarbonate fluid with daily urine output about 3-4L. His SCr improved but plateaued at 7 mg/dL. A course of IV amphotericin B, IV micafungin, and oral posaconazole were implemented. Renal biopsy (Fig.1) demonstrated AA amyloidosis, with greater than 90% of glomeruli showing mostly global involvement by amyloid. There was also vascular and tubulointerstitial involvement, and approximately 70-80% interstitial fibrosis and tubular atrophy were noted. He was eventually started on peritoneal dialysis and remains on posaconazole.

Discussion: Invasive intracranial mucormycosis can occur in patients with profound acidemia. Therefore, aggressive bicarbonate repletion is essential to control the infection in addition to appropriate antibiotic treatment. Glucosuria and bicarbonate wasting in our patient may suggest proximal tubular injury from AA amyloidosis. A comprehensive history taking is pivotal to diagnose heroin-related AA amyloidosis, which results from chronic subcutaneous injections.



TH-PO134

Silicone Implant-Induced Granulomatosis and IgA Nephropathy in a Male-to-Female Transgender Person

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Introduction: Silicone implants, used in cosmetic procedures, induce local and systemic inflammatory reactions. We describe a case of silicone implant-induced granulomatosis (SIG) presenting with hypercalcemia and AKI.

Case Description: A 58-year-old male-to-female transgender was referred to nephrology for symptomatic hypercalcemia (11.7 mg/dl) and AKI (Cr 1.46 mg/dl; baseline 0.88 mg/dl). Her history included well-controlled HIV, HTN, gender reassignment surgery, breast augmentation, perineal/gluteal silicone implantation in the 1990s. Evaluation of hypercalcemia revealed a suppressed PTH (12 pg/mL), normal PTHrP and SPEP, and high ACE and 1,25 vitamin D levels, suggestive of granulomatous disease. There was no evidence of TB. Urine protein/Cr was 0.360 mg/g and urinalysis was bland. Other studies showed the following: CT scan, calcified granulomas on breasts and gluteal areas with portacaval and retroperitoneal lymphadenopathy; renal ultrasound, increased cortical echogenicity and non-obstructing left renal calculi; inguinal node biopsy, granulomatous inflammation and non-polarizable injectable material consistent with silicone implant. Renal biopsy showed acute mild tubular injury, mild focal interstitial calcification without significant scarring or granulomas; 2-3+ mesangial IgA deposits with 30% foot process effacement. Resection of the granulomas was impossible. Low-dose prednisone was initiated for chronic management of hypercalcemia with normalization of serum calcium (9.6. mg/dl) and Cr (0.9 mg/dl).

Discussion: Bioimplants, like silicone, trigger local and systemic immune reactions by acting as T-cell-directed antigens or as adjuvants – substances that enhance the antigen-specific immune response. The systemic inflammatory responses that ensue have been labeled autoimmune/inflammatory syndrome induced by adjuvants (ASIA). ASIA can present as granulomatous disease, lupus-like syndromes, or vasculitis weeks to decades following receipt of the bioimplant. Our patient presented with hypercalcemia mediated by SIG an unanticipated finding of IgA nephropathy on biopsy, but no evidence of renal granulomatous disease. It is unknown if IgA nephropathy is a manifestation of ASIA or a coincidental diagnosis in this case. With increasing prevalence of cosmetic procedures, nephrologists should be aware of potential latent complications of bioimplants.

TH-PO135

First Case of Leptotrichia goodfellowii Endocarditis-Associated Glomerulonephritis

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Introduction: Infective endocarditis is a well described cause of glomerulonephritis (GN), but can be difficult to diagnose. We present the first case of ANCA-associated immune complex GN from Leptotrichia goodfellowii endocarditis with initial diagnosis made by kidney biopsy.

Case Description: A 57 year old male with hypertrophic cardiomyopathy with an ICD was found to have an acute rise of his creatinine to 3.4 mg/dL from a baseline of 1.1 mg/dL prior to his left heart catheterization in preparation for a septal myectomy. He noted two weeks of lower extremity edema, chills, subjective fevers, and poor oral intake. Workup notable for a UPCR 1.9 mg/mg, 415 RBC/HPF with dysmorphic RBCs, low C3 and C4 at 35 and 8 mg/dL respectively, atypical ANCA staining with positive MPO and PR3, and type II cryoglobulinemia. Remainder of serologic workup was negative. Creatinine worsened so methylprednisolone 1 gram daily was started and a renal biopsy

was performed showing IgM dominant, predominantly mesangiopathic immune complex and necrotizing crescentic glomerulonephritis suggestive of endocarditis, as well as diffuse tubular injury. He developed acute severe mitral valve regurgitation due to a torn chordal tissue with vegetations seen on the mitral valve and an ICD lead. He was started on broad spectrum antibiotics and steroids stopped. Blood cultures grew Leptotrichia goodfellowii, likely from recent dental work, and antibiotics narrowed to ceftriaxone and metronidazole with subsequently cleared blood cultures. He required initiation of hemodialysis a week after his biopsy, but after completing antibiotic treatment, he had renal function recovery allowing stoppage of hemodialysis after two months with most recent creatinine 1.9 mg/dL.

Discussion: To our knowledge, this is the first reported case of endocarditis-associated GN from Leptotrichia goodfellowii, a gram negative fusiform bacteria found in oral flora. It highlights the importance of considering indolent infectious etiologies in patients with acute renal failure. Clues suggesting subacute endocarditis-associated GN include presence of cardiac devices, low C3 and C4, and ANCA positivity, though kidney biopsy is key in confirming the diagnosis. While the role of immunosuppression in these patients is unclear, renal recovery can be seen with antimicrobial therapy alone, underscoring the need for isolation of the pathogen.

TH-PO136

Bilateral Renal Infarction: An Uncommon Presentation of Multiple Myeloma

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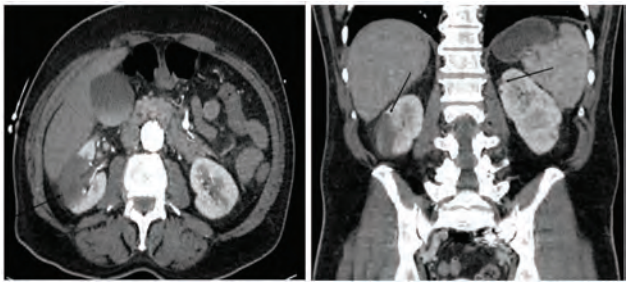
Introduction: We report on a case of bilateral renal infarction from disseminated intravascular coagulation, secondary to a previously undiagnosed multiple myeloma. This cause of acute renal infarction is uncommon and may have a misleading presentation, leading to diagnostic delays/misdiagnosis, reason for us highlighting it here.

Case Description: A 70-year-old male with coronary disease, hypertension, repaired abdominal aortic aneurysm, presented with acute onset severe abdominal pain, nausea and a 25 lbs weight loss (in 6 months). Blood pressure was 185/96 mm Hg. He had abdominal tenderness. Labs showed hyponatremia (normal plasma osmolality) and creatinine was 1.43. CBC showed leukocytosis, anemia and thrombocytopenia. Peripheral smear showed Rouleaux formation and plasma cells (plasma cell count was 1239/mm3). Also, there was an elevated LDH, D-Dimer, and low fibrinogen, haptoglobin. He had an elevated bilirubin, alkaline phosphatase and AST with normal ALT. Prothrombin time and INR were elevated. A CT scan showed wedge-shaped opacifications within the right kidney and the left renal cortex without thrombi. Procalcitonin was normal and factor 5 Leiden mutation was absent. A 2D-echo was negative for any valvular disease. EKG showed sinus rhythm. With concerns for multiple myeloma (age, creatinine, rouleaux formation, increased plasma cells), we observed a monoclonal protein in SPEP. SIFE showed monoclonal IgG-Lambda protein. Kappa/Lambda free Light chain ratio was 0.01. Bone marrow biopsy revealed 20% plasma cells. FISH showed an IgH/MAF rearrangement (seen in plasma cell disorders). Carfilzomib, cyclophosphamide and dexamethasone as well as anticoagulation were initiated. Partial remission was achieved within two cycles of chemotherapy. Creatinine came down to 1.0.

Discussion: Multiple myeloma is a hematological malignancy that similar to other malignancies, can lead to disseminated intravascular coagulation and infarction at unusual places. We want to bring to the clinicians' attention this relatively uncommon causes of renal infarction.



CT scan of Abdomen showing bilateral renal infarction

TH-PO137

Acute Tubulointerstitial Nephritis Associated with a Vaccination of Japanese Encephalitis Virus: A Case Study

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Introduction: Common causes of acute tubulointerstitial nephritis (ATIN) include infectious diseases, collagen diseases, sarcoidosis, or a reaction to certain drugs (e.g., nonsteroidal anti-inflammatory drugs, antibiotics). In Asia, according to frequency and severity, Japanese encephalitis virus (JEV) is the most important cause of viral encephalitis and vaccinations are recommended at ages 3, 9, and 17 years in Japan.

Case Description: A 17-year-old healthy Japanese male received the JEV vaccine in September, 2018. He was not on any previous medications. A few days after vaccination, he began to feel fatigue. He underwent a check-up at a local clinic and was diagnosed as having acute kidney injury (serum creatinine [Cr] 2.91=mg/dl). He was admitted to our hospital for further examination. Upon admission, laboratory tests revealed the following values: serum Cr=4.41 mg/dl, urinary protein=0.22 g/day, urine sediment erythrocytes=<1/HPF, and urinary β_2-microglobulin=12,034 ng/ml. Gallium scintigraphy showed uptake in the bilateral kidneys. Renal biopsy showed almost normal glomeruli. We observed inflammatory cells and the infiltrate was mainly composed of lymphocytes and a few eosinophils, with a granuloma formation in the interstitium. The proximal tubular epithelial cells also showed a moderate degree of atrophy and tubulitis. However, deposition of immunoglobulin and complements were not observed. Moreover, immunostaining showed a predominance of CD4-positive T cells in the interstitium. Finally, a drug lymphocyte stimulation test (DLST) for the JEV vaccination was positive. The patient received 500 mg methylprednisolone intravenously for 3 days, followed by oral prednisolone (40 mg/day). His serum Cr and urinary β_2-microglobulin levels decreased by 2.51 mg/dl and 1,116 ng/ml, respectively.

Discussion: In this case, our findings suggest that the JEV vaccine is the cause of ATIN associated with a Type IV allergy. To our knowledge, this is the first report of ATIN associated with JEV vaccination. We should be aware of ATIN as a reaction to the JEV vaccination, in addition to other well-known side effect, such as acute disseminated encephalomyelitis.

TH-PO138

A Case of Severe AKI from Cutaneous Contact with Cresol

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Introduction: Cresol is a hydroxytoluene of ortho-, meta-, and para-isomers that are precursors to various compounds including household pesticides, disinfectants, and dyes. Although cresol is harmless in low concentrations in the environment, it can be inadvertently absorbed through intact skin, respiratory, and gastrointestinal tracts causing multiple organ dysfunction.

Case Description: A 29-year-old man presented to the emergency department after an accidental spill of cresol to his upper body and thighs at an alcohol-manufacturing chemical plant. He had no history of prior kidney disease. Physical exam revealed sharply demarcated dark brown discolorations with first degree burns to the exposed areas. A small amount of green urine was produced after bladder catheterization. The serum creatinine on arrival was 1.7 mg/dL, and he was oliguric despite fluid resuscitation. Liver enzymes were normal. Over the next two days the creatinine increased to 9.63 mg/dL and hemodialysis was initiated. Abdominal ultrasound and computed tomography were normal. The patient continued to require thrice weekly hemodialysis during his two-week hospitalization. Although he became non-oliguric, he was discharged with scheduled outpatient dialysis because a 24-hour creatinine clearance at time of discharge was 11 mL/minute.

Discussion: Cresol exposure is a rare cause of acute kidney injury. Previous cases of cresol toxicity have focused on ingestions that report multiple organ dysfunction with a high prevalence of liver dysfunction. Only a handful of cases describe cutaneous absorption of cresol, usually associated with severe acute kidney injury without evidence of significant liver injury. This observation is likely because cutaneous cresol absorption bypasses the portal venous system and reduces the liver's exposure to the toxin. The cause of acute kidney injury in cases of cresol intoxication is acute tubular necrosis based on a limited number of biopsy and autopsy case studies. Treatment is supportive with the potential for requiring prolonged hemodialysis depending on extent of exposure.

TH-PO139

A Case of BK Nephropathy in a Newly Diagnosed HIV Patient

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Introduction: BK virus-related nephropathy has been reported more among post-transplant patients with immunosuppressive therapy but is less identified among non-transplant and HIV patients.

Case Description: We report at 52-year-old male, admitted due to chronic cough. He was incidentally found to be Human Immunodeficiency Virus (HIV) positive with CD4 254 cells/μL and was empirically treated for possible Pulmonary Tuberculosis (PTB) reactivation and Pneumocystis pneumonia (PCP). During his hospital stay, his serum creatinine (sCr) was noted to be increasing reaching level of 3.82 mg/dL (from baseline of 0.82 mg/dL one year prior). He was then dialyzed and underwent kidney biopsy which showed minor glomerular abnormalities, acute interstitial nephritis with acute tubular injury, mild interstitial fibrosis and tubular atrophy with 6% global glomerulosclerosis. Trial of steroids was given and was started on antiretrovirals (ARVs). His kidney function stabilized without dialysis support over the next two months. Persistence of non oliguric acute kidney injury incompatible with his seemingly stable clinical state prompted further investigation, trial of drug holiday (off ARVs), and a repeat kidney biopsy was done. Results showed acute interstitial nephritis with acute tubular injury, moderate interstitial fibrosis and tubular atrophy with 20% global glomerulosclerosis; additional SV 40 stain was requested and showed positive results – supportive of BK nephropathy (BKN). Previous biopsy tissue was reviewed and re-examined. SV40 stain was requested and patient was already positive for SV40 stain. BK virus load was at 262,577 copies/mL and was placed on trial of fluoroquinolone. Patient's renal function no longer recovered with peak sCr of 18.65 mg/dL, is currently maintained on intermittent hemodialysis, and ARVs were resumed.

Discussion: This is an interesting case of a biopsy-proven BK nephropathy in a native kidney of a newly diagnosed HIV patient with a CD4 count of more than 200 cells/μL. Most published data on BK nephropathy in HIV patients have CD4 of less than 50 cells/μL.

BKN may be considered as a differential diagnosis in HIV or immunocompromised patients with progressive renal failure.

TH-PO140

AKI Secondary to Thrombotic Microangiopathy (TMA) in a Myeloma Patient: Scleroderma Renal Crisis (SRC), A Paraneoplastic Phenomenon

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Introduction: AKI due to TMA in a myeloma patient is an uncommon presentation. Rheumatic paraneoplastic syndromes have atypical presentations and are typically a result of anti-tumor immune responses. These subsets of diseases occur simultaneously or in close temporal relation to the diagnosis of an underlying malignancy. Our case report describes scleroderma as a likely cause of AKI/TMA and a paraneoplastic manifestation of multiple myeloma.

Case Description: A 47-year-old man with no prior renal disease presented with peripheral neuropathy, hypertensive urgency, seizures, microangiopathic hemolytic anemia (MAHA), and acute renal failure. AKI work up revealed paraproteinemia and subsequent bone marrow biopsy confirmed multiple myeloma (MM). On examination, he was found to have findings suspicious for scleroderma including telangiectasia, limited cutaneous thickening, salt-and-pepper skin changes, and abnormal nailfold capillaroscopy. CT Abdomen revealed distal esophageal and rectal thickening and esophagram showed esophageal dysmotility. Worsening kidney function, new skin findings, and MAHA lead to a kidney biopsy, which demonstrated findings of severe thrombotic microangiopathy (TMA) with no evidence of cast nephropathy. Deep skin biopsy was compatible with papillary and mid dermal sclerosis. Although autoantibodies were negative, patient was diagnosed clinically with scleroderma with scleroderma renal crisis (SRC) which appeared to be a paraneoplastic presentation of MM. Patient was treated with captopril initially for SRC and subsequently Eculizumab. Interestingly, his skin findings have not progressed after treatment for MM but remains dialysis dependent.

Discussion: AKI due to TMA in a patient with MM and SRC is a diagnostic dilemma. Paraproteins are associated with mimics of rheumatic diseases; however, there are rare reports on the coexistence of MM and paraneoplastic scleroderma. TMA is known to be associated with both MM and SRC, and although the clinical presentation was suggestive of scleroderma, the negative serologies challenged the diagnosis. Further studies are required to determine whether MM can induce SRC and if chemotherapy can improve scleroderma outcomes in these patients.

TH-PO141

Rhabdomyolysis Associated with Aspirin-Mediated Hyperthermia

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Introduction: Salicylate toxicity and rhabdomyolysis are both potentially life-threatening conditions. Only 2 reports have previously described an association between salicylate toxicity and rhabdomyolysis. We present a case of non-traumatic rhabdomyolysis occurring after aspirin overdose.

Case Description: A 36-year-old male with a history of chronic aspirin use (~2,600 mg daily) presented to the emergency department with dyspnea. A few hours earlier, he had taken approximately 20 tablets of aspirin (325 mg each) to treat a headache. He denied trauma. Within an hour, he developed hypoxic respiratory failure requiring intubation and mechanical ventilation. His initial salicylate level was 76.1 mg/dL. Other laboratory values on presentation included serum creatinine 2.7 mg/dL, total CO2 18 mmol/L, arterial pH 7.22, and creatine kinase (CK) 436 U/L. Pressors were initiated for worsening hypotension. The patient became hyperthermic to 41.7°C. The aspirin overdose was initially treated with intravenous sodium bicarbonate, but when the patient became anuric on hospital day 2, continuous renal replacement therapy was initiated. Evaluation of stage 3 acute kidney injury (AKI) revealed that CK increased to 28,880 U/L by hospital day 3, and then slowly returned to normal limits over the next 2 weeks. Kidney function recovered sufficiently to stop hemodialysis on hospital day 27.

Discussion: Two cases, published in 1989 and 1994, describe rhabdomyolysis and AKI in patients presenting with acute aspirin overdose. Both cases describe patients with hyperthermia, attributed to aspirin-mediated mitochondrial toxicity, followed by rhabdomyolysis. A case report from 2016 describes a young patient presenting with temperature 41.1°C, CK 57,050 U/L, and AKI after use of K2, a synthetic cannabinoid. Exertional hyperthermia is a well-known cause of rhabdomyolysis, but drug-induced hyperthermia is less frequently described. High fever may be an important link between aspirin overdose and rhabdomyolysis.

TH-PO142

Atypical Multiorgan Disease Possibly Associated with IgG4RD

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Introduction: IgG4 related disease (IgG4RD) is associated with multi-system disease processes. Hallmarks include lymphoplasmacytic infiltration with a predominance of IgG4+ plasma cells with associated storiform fibrosis and elevated serum IgG4 levels. We report a patient with multiple yet atypical manifestations suspicious for IgG4RD.

Case Description: 38yo man with UC, T2DM, proteinuric CKD-2 (Cr-1.2) and hematuria was admitted for AKI and hyperkalemia. Chief complaints were chronic diarrhea and fatigue. Labs showed K-6.3, HCO3-9, Cr-2.6 and alk phos-861. U/A revealed hematuria and low-grade proteinuria. Renal u/s demonstrated right kidney-13cm and left-14cm. Abdominal u/s revealed dilated intrahepatic ducts. MRCP was unremarkable except for hepatomegaly and splenomegaly. CT abdomen/pelvis 3 months prior demonstrated enlarged retroperitoneal lymph nodes but no hepatomegaly/splenomegaly. Kidney biopsy revealed diabetic nephropathy and plasma cell rich interstitial infiltrate with 20% IgG4+ (>50/HPF) without storiform fibrosis. Serum IgG was 2424 (694-1618) with IgG1-1117 (382-929) and IgG4-338 (4-86). Liver biopsy revealed minimal plasma cell infiltrate with negative IgG4 staining and no sclerosing cholangitis. CT revealed increased retroperitoneal and inguinal lymphadenopathy. Prednisone 60 mg was initiated. He was subsequently re-admitted for brawny LE edema and SOB. Repeat CT demonstrated bilateral cavitary lung lesions and increased retroperitoneal/pelvic lymphadenopathy. Blood cultures were positive for MSSA, TEE revealed normal leaflets and no vegetations. Repeat kidney biopsy again revealed plasma rich interstitial infiltrate (>30 IgG4+ cells/HPF) and diabetic kidney disease. Lymph node biopsy was recommended but patient left prior to procedure.

Discussion: IgG4RD is challenging to diagnose due to multiple disease manifestations. In our patient, findings consistent with IgG4RD include those on kidney biopsy along with retroperitoneal lymphadenopathy and possible fibrosis. However, not all diagnostic criteria were met and he did not respond to a course of steroids. Other diseases potentially associated with IgG4+ plasma cells within tissues (drugs, sarcoidosis, syphilis, GPA) were excluded in our patient. Our case may represent an atypical case of IgG4RD or manifestation of a yet to be diagnosed disease.

TH-PO143

Urinary Ascites from Spontaneous Bladder Rupture: Rare Cause for Pseudo AKI

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Introduction: Spontaneous intraperitoneal bladder rupture is a rare entity. Diagnosis can be challenging. Symptoms are non-specific and misleading which delays the diagnosis and treatment of SUBR. In the pediatric population, the leading causes of rupture in reported cases are patients with neurogenic bladders, bladder diverticulum, bladder outlet obstruction, and history of bladder augmentation surgery. Symptoms of urinary leakage into the peritoneum include abdominal pain and distension, oliguria or anuria, and elevated serum creatinine. Elevation of the creatinine from resorption of peritoneal fluid results in elevation of serum creatinine, termed as pseudo-renal failure. Measuring the creatinine of the ascitic fluid can help aid in accurate diagnosis of an intraperitoneal bladder rupture. We present an interesting case of a 13 year old boy who presented with abdominal distension and pain with rapidly rising creatinine.

Case Description: 13 y.o. male with urachal cyst excision 6 years ago, presented with abdominal pain and elevated creatinine. Imaging studies revealed mild ascites. Liver morphology was reported normal. Elevation in creatinine was attributed to pre-renal etiology and was encouraged hydration. He presented back 3 months later with increasing abdominal distension and discomfort, rapid elevation of the creatinine with hematuria. With rapid rise in creatinine and positive urinary sediment, renal biospy was done. Biopsy was suggestive of MPGN with faint IgM and C3 deposits. He was started on urgent dialysis for elevated creatinine and steroids initiated. Peritoneal fluid creatinine was reported high consistent with urine leak in the peritoneum. CT Cystogram confirmed urinary leak. He was emergently taken up by urology for cystorraphy.

Discussion: This case highlights phenomenon of bladder rupture, urinary ascites and pseudo-renal failure. Bladder rupture can occur following trauma, irradiation, iatrogenic or spontaneous. Pseudo renal failure is the elevation of the creatinine from the resorption of the peritoneal fluid from urinary leak. If the ascitic fluid creatinine is significantly higher than serum levels, one should consider spontaneous bladder perforation as the etiology for the urinary ascites. CT cystogram is the gold standard imaging technique for diagnosis.

TH-PO144

Cocaine-Associated Atypical Haemolytic Syndrome in a Genetically Susceptible Individual

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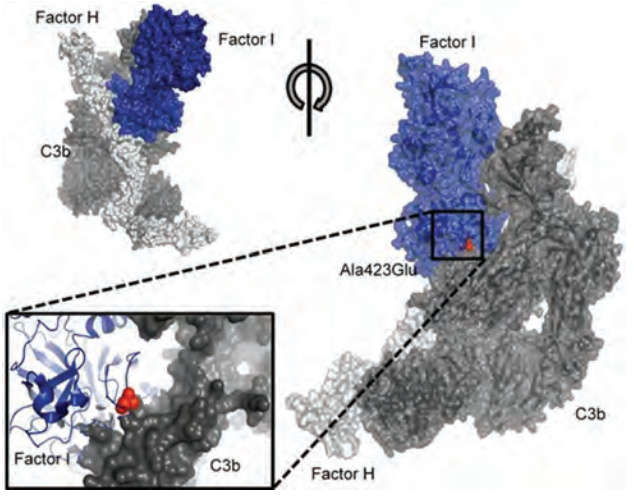
Introduction: Atypical haemolytic uraemic syndrome (aHUS) is characterised by thrombocytopaenia, renal impairment and non-autoimmune haemolytic anaemia that requires early recognition and urgent treatment. Genetic variants predispose to this condition when a trigger, or, 'complement amplifying condition', is supplied. Identification of new genetic variants and of lesser known complement amplifying conditions are crucial for furthering the understanding of this serious condition.

Case Description: A forty-seven-year-old man presented to the emergency department and was found to have an acute kidney injury, thrombocytopenia, non-immune haemolytic anaemia and hypertension (205/150mmHg). He had smoked cocaine for the first time two weeks prior. The patient was taken to the intensive care unit for urgent plasma exchange with fresh frozen plasma. An urgent ADAMTS13 demonstrated normal level (44.1% [40-130]). Treatment with eculizumab was commenced and the patient responded well. Six months following his initial presentation, the patient was weaned off haemodialysis. The patient was heterozygous for the c.1268C>A p.(Ala423Glu) variant in the *CFI* gene.

Discussion: This case highlighted several important points. Firstly, our patient was found to be heterozygous for a rare gene variant previously detected in only two aHUS

patients. Although genetic analysis can uncover definitively pathogenic mutations which predispose to aHUS, the interpretation of variants of unknown significance remains a challenge. Secondly, there are few reports of an association between cocaine and aHUS. In our case, it is unclear whether aHUS was triggered by cocaine or hypertension. It responded well to rapid treatment with eculizumab supporting the hypothesis of an underlying immunological complement-based pathogenesis. Furthermore, in the absence of gold standard diagnosis of aHUS in the acute setting, prompt treatment with eculizumab can be challenging and delayed.



TH-PO145

Immune-Complex Glomerulonephritis Following PD-1 and PD-L1 Therapy in Renal Cell Carcinoma

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Introduction: Inhibition of the Programmed cell death-1 (PD-1) pathway is associated with interstitial nephritis. Vascular endothelial growth factor (VEGF) inhibition via receptor tyrosine kinase blockade (RTKi) is associated with hypertension (HTN), proteinuria, thrombotic microangiopathy (TMA), and podocytopathies. Here we describe the development of Immune-complex glomerulonephritis (ICGN) in a patient who was treated with PD-L1 inhibitor, atezolizumab, and PD-1 inhibitor, nivolumab.

Case Description: A 49-year-old male with metastatic RCC and nephrectomy presented with worsening HTN and found with acute kidney injury (AKI). Initial treatment for RCC prior included bevacizumab (VEGF), pegylated interferon, and atezolizumab (anti-PD-L1). Following cycle 4, bevacizumab was held due to HTN and new proteinuria of 1.9 g/g. Despite this, proteinuria worsened to 5.2g/g and treatment changed to sunitinib and nivolumab. Following the initiation of this new regimen, he was admitted for AKI (with serum creatinine (SCr) increasing from 1.6 mg/dl to 2.6mg/dl), proteinuria of 9.2g/g, and a serum albumin that fell to 1.6g/dl from 3g/dl. Renal biopsy showed no interstitial infiltrate but one glomerulus displayed thickened. Electron microscopy showed segmental subepithelial, subendothelial, and numerous mesangial deposits with global foot process effacement. Immunofluorescence could not be obtained. These findings were consistent with an ICGN. Prednisone and a loop diuretic were initiated. Nivolumab was held and sunitinib was continued. At 1 month follow up, his NS improved along with serum albumin that rose to 2.3g/dl. Unfortunately, his RCC continued to progress and he subsequently passed away.

Discussion: PD-1 inhibition has become a cornerstone of many immunotherapeutic regimens for various malignancies. We describe a case of progressive proteinuria, AKI, and subsequent NS with biopsy proven ICGN following PD-L1 and PD-1 inhibition that responded to corticosteroids. This case describes a novel case of ICGN, seen rarely with anti-VEGF therapy, now seen with PD-L1 and PD-1 inhibition.

TH-PO146

Infliximab-Associated Focal Segmental Glomerulosclerosis in a Patient with Crohn Disease: A Case Report

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Introduction: Infliximab is a monclonal antibody against tumour necrosis factor alpha (TNFα) used for immune mediated disorders such as ulcerative Colitis, Crohn's Disease, ankylosing spondylitis. Renal effects of Infliximab are uncommon and are poorly understood. Effects mentioned in literature review include acute tubulo-interstitial nephritis, focal segmental glomerulosclerosis (FSGS) and membranous nephropathy. Herein we present a case of biopsy proven FSGS in the setting of Infliximab use in a patient with Crohn's disease.

Case Description: We present a case of a 36 years old male Caucasian patient with Crohn's disease on treatment with Infliximab for 20 months, who presented with a symptom of urinary frequency. His urinalysis demonstrated microhematuria and urine protein excretion was 2.1g with serum albumin level of 3.2 g/dL. He underwent a renal biopsy that showed FSGS tip lesion with acute tubular necrosis. His Infliximab dose was titrated off. Subsequently, he was started on an angiotensin receptor blocker losartan at 25 mg and the dose was increased as tolerated. His proteinuria and hematuria improved with this therapy and after 2 months a repeat urinalysis showed 0.3g of proteinuria and absence of microhematuria. This is only the third known case of biopsy proven FSGS reported with Infliximab use.

Discussion: Our case highlights an uncommon adverse effect of a commonly used medication. Contrary to the other two cases, which reported renal effects within first 6 months of infliximab therapy, we found renal involvement even after 20 months of infliximab suggesting possibility of delayed effects on kidneys. The possible mechanism responsible for the development of renal complications during anti-TNFα infliximab administration implicates an interaction of anti-TNFα antibodies with TNFα present on glomerular visceral epithelial cells. These effects of the TNFα inhibitors should trigger screening urinalysis in patients on these medications for early diagnosis and management of renal effects. Future research should elucidate the links behind the renal effects of infliximab.

TH-PO147

Membranous Glomerulonephritis as an Immune-Related Adverse Effect of Checkpoint Blockade Therapy

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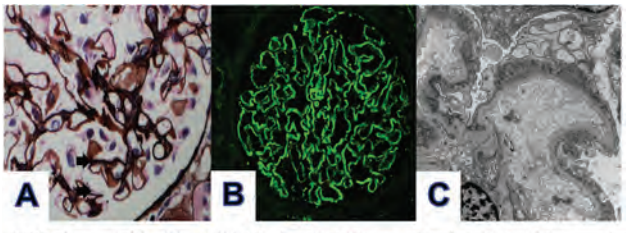
Introduction: Immune checkpoint inhibitors are being used more frequently to treat various cancers, leading to immune related adverse effects (irAE). Although data on checkpoint inhibitor-induced nephrotoxicity is limited, a link to tubulointerstitial nephritis has been previously documented. We present a case of a patient who received ipilipumab and nivolumab, who developed membranous glomerulonephritis (MGN).

Case Description: A 20-year old Caucasian male with fibrolamellar-variant hepatocellular carcinoma (HCC) treated with nivolumab for the prior 2 years and additional ipilimumab for the prior 2 months presented with shortness of breath and pedal edema. Vital signs were notable for a heart rate of 100. Exam revealed tachycardia with no murmurs, lungs had inspiratory crackles bilaterally at the bases, and abdomen was soft, non-tender, and non-distended. On initial labs, albumin was 1.2 g/dL. Urinalysis demonstrated 4+ protein, and urine protein/creatine (UPC) ratio was 14. He was found to have bilateral pleural effusions. Kidney biopsy demonstrated membranous glomerulonephritis negative for staining with PLA2R and THSD7A. Immune checkpoint inhibitors were discontinued and tacrolimus 2mg twice daily and prednisone 60mg daily were initiated. The patient was discharged home on lisinopril, rosuvastatin, and bumetanide. UPC ratio was 6.5 at discharge and 0.7 a month after discharge.

Discussion: This is a case of a patient with HCC on immune checkpoint blockade therapy developing membranous nephropathy. Although HCC may also cause MGN, the rapid improvement of MGN with cessation of therapy more strongly suggests that this was an irAE. Given the increased use of checkpoint inhibitors, nephrologists should be mindful of this complication.



A) Light microscopy (LM), ~600x: A) JMS stain: glomerulus with sparse capillary loop spikes and holes, suggestive of MGN (arrows). B) Immunofluorescence (IF), ~400x: IgG stain: positive, global granular pattern of glomerular capillary loop staining. C) Electron microscopy (EM), ~6,000x: Glomerular capillary loops with regularly distributed, subepithelial immune-complex mediated type electron dense deposits.

TH-PO148

Tocilizumab-Induced Immune Complex Glomerulonephritis in a Patient with Rheumatoid Arthritis

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Introduction: Anti-TNF-α inhibitors used in the treatment of rheumatoid arthritis (RA) often cause immune complex glomerulonephritis (IC-GN) as part of biologics-induced autoimmune renal disorder. However, similar effects due to anti-IL-6 receptor inhibitors are very rare. Here, we report a case of tocilizumab (TCZ)-induced IC-GN in a patient with RA.

Case Description: A 70-year-old Japanese man was admitted to our hospital due to acute nephritic syndrome. He was diagnosed with RA 14 years previously and had received methotrexate (MTX) and biologics. Three years ago, the biologic was switched from adalimumab to TCZ. RA had been in remission, and his serum creatinine (Cr) was 0.8 mg/dL. One month ago, after showing flu-like symptoms, he developed bilateral lower leg edema, renal dysfunction (Cr 1.3 mg/dL), hematuria, and proteinuria, indicating acute nephritic syndrome. On admission, renal dysfunction (Cr 1.77 mg/dL, eGFR 30.7 ml/min/1.73 m^2), urinary protein 0.75 g/gCr, urinary red blood cells 50–99/high power field,

and hypocomplementemia (C3, 24 mg/dL; C4, 1 mg/dL; CH50, 0 IU/L) were found. Anti-nuclear antibody, anti-dsDNA antibody, parvoviral B19DNA, and anti-streptolysin O were negative, whereas cryoglobulin was weakly positive. Renal biopsy revealed mesangial cell proliferation and endocapillary hypercellularity with partial crescent formation. Immunofluorescence analysis indicated IgG, IgA, IgM, C3, and C1q deposition in the mesangium, so a diagnosis of IC-GN was made. After discontinuing TCZ and MTX, intravenous methylprednisolone was administered at a dose of 500 mg/day for three days and then prednisolone (PSL) was initiated at 60 mg/day. His renal function and urinary abnormalities improved, and serum complement levels increased. After 5 months of treatment, his renal function has been maintained using PSL 10 mg/day.

Discussion: The anti-IL-6 receptor antibody, TCZ, may lead to the development of IC-GN, similar to anti-TNFα inhibitor. The mechanism remains unknown because only one case of TCZ-induced IC-GN has been reported to date. Rheumatologists and nephrologists should be aware of this lesion and similar cases should be collected in future.

TH-PO149

DAMPAned Methotrexate Levels: A Case Report of Acute Methotrexate Toxicity

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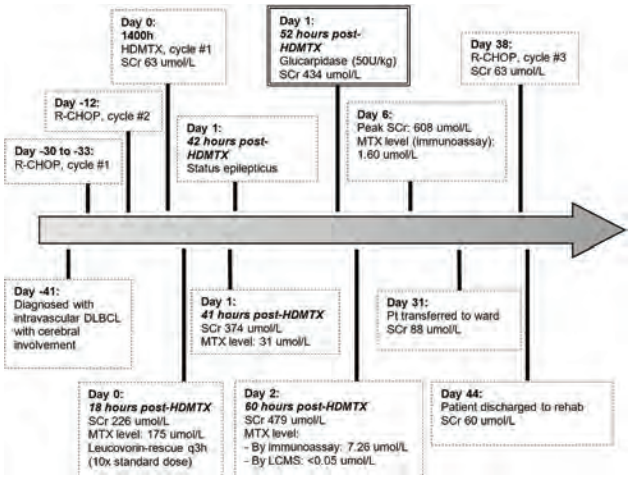
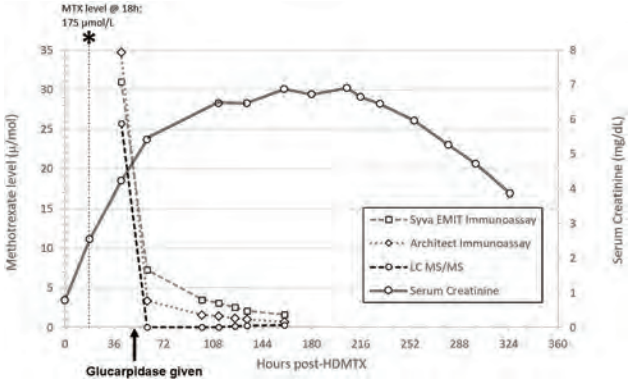
Introduction: New guidelines exist on the management of methotrexate-induced nephrotoxicity, focusing on the use of glucarpidase (Voraxaze®). We describe an application of these guidelines and highlight nuances around drug procurement and post-intervention laboratory monitoring.

Case Description: A 61-year old male with diffuse large B-cell lymphoma (DLBCL) with cerebral involvement was admitted for his first cycle of high-dose methotrexate (HDMTX). He previously received two cycles of R-CHOP chemotherapy. Baseline serum creatinine (SCr) was 63 μmol/L. Following HDMTX, his methotrexate level was 175 μmol/L. Despite extracellular volume expansion, urinary alkalinization, and leucovorin rescue, he developed severe acute kidney injury (SCr 374 μmol/L) and subsequently went into status epilepticus. He was given glucarpidase at 52-hours post-HDMTX. Methotrexate level 8 hours after glucarpidase was 7.26 μmol/L by immunoassay, but <0.05 μmol/L by mass spectrometry. Interference due to the DAMPA metabolite resulted in falsely elevated levels by immunoassay for > 5 days after glucarpidase administration. He remained non-oliguric. Serum creatinine peaked at 608 μmol/L then trended down. He ultimately avoided the need for dialysis and had full renal and neurologic recovery.

Discussion: Glucarpidase is an effective option for non-renal elimination of toxic methotrexate concentrations in patients with nephrotoxicity. Awareness of how to access the drug, protocolization of monitoring including specific laboratory requirements, and knowledge of alternative treatments is necessary for centres where HDMTX therapy is used.





TH-PO150

Azacitidine Inhibition of Creatinine Tubular Secretion: A Case Report

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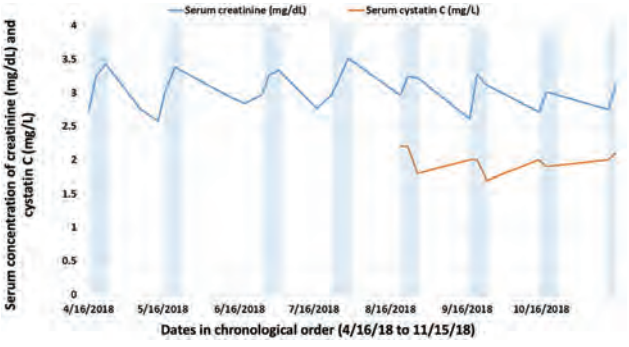
Introduction: It is well documented that a number of medications lead to mild to moderate and reversible elevations of serum creatinine (SCr) without affecting glomerular filtration rate. In many instances, the discovery of this effect is a result of clinical observation with high index of suspicion. Such as an observation is also illustrated in our case report on a patient who has been receiving azacitidine.

Case Description: A 63-y/o male with PMH of FLT3+ AML in remission and stage 4 CKD was referred for episodic worsening of SCr. The initial presentation of AML was with a blastic crisis and AKI due to tumor lysis syndrome requiring urgent hemodialysis (HD). He was continued on intermittent HD for an additional 2 months and was able to come off HD with a new baseline SCr of 2.5 mg/dL. Around the same time, he was initiated on chemotherapy with azacitidine 75 mg/m^2 of body surface area subcutaneously daily for 7 days every 4 weeks. Upon evaluation of the patient in our Clinic 9 months after his AML diagnosis, transient elevations in SCr were noted, as illustrated in figure 1. The sharp rise in SCr was noted at the dates during which azacitidine was administered. Following careful review of history, which was unrevealing as to the cause of fluctuating SCr, decision was made to monitor SCr concurrently with serum cystatin C during and after administration of azacitidine. Serum cystatin C did not follow the same trend, raising suspicion for inhibition of creatinine tubular secretion by azacitidine without affecting renal function per se.

Discussion: The current drug label for azacitidine recommends that if unexplained elevations of SCr occur, the next cycle of therapy to be delayed until values return to normal or baseline and the dose to be reduced by 50%. To our knowledge, inhibition of creatinine tubular secretion by azacitidine was not previously reported. This case calls for the effects of azacitidine on renal proximal tubular transporters to be defined with physiologic studies, as this would have important implications on the underlying diseases being treated.



TH-PO151

Membranous Nephropathy Associated with Immune Checkpoint Inhibitors: A Report of Two Cases

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Introduction: Immune checkpoint inhibitors (ICI) are novel cancer immunotherapies with recognized nephrotoxicities. The most common toxicity is acute tubulointerstitial nephritis, but cases of glomerular injury have been reported. We describe 2 patients with membranous nephropathy (MN) associated with pembrolizumab.

Case Description: Case 1: 52-year-old woman with stage III ovarian cancer, treated with pembrolizumab. She presented with frothy urine and edema. Urine sediment was bland. Investigations demonstrated albumin 3 g/dL, proteinuria 12 g/d and serum creatinine (sCr) 0.7 mg/dL. A biopsy showed thickened glomerular capillary walls. Immunofluorescence showed staining for IgG3(+), Anti-Phospholipase-A2-Receptor antibody [PLA2R](-) and Thrombospondin Type-1 Domain Containing 7A antibody [THSD7A](+). Electron microscopy (EM) showed subepithelial immune-type electron-dense deposits with diffuse effacement of the podocyte foot processes consistent with MN. Pembrolizumab was held and she received prednisone 1 mg/kg with remission of proteinuria. She was re-challenged with pembrolizumab with recurrence of proteinuria. Pembrolizumab was stopped and she received prednisone with resolution of proteinuria. **Case 2:** 39-year-old man with stage IV colon cancer, treated with pembrolizumab. He presented with proteinuria 2.2 g/d, sCr 1.1 mg/dL, albumin 3.3 g/dL and bland urine sediment. Biopsy revealed staining for IgG3(+2), Anti-PLA2R(-) and anti-THSD7A(+). EM showed subepithelial immune-type electron-dense deposits with diffuse podocyte effacement. The findings were consistent with MN. He received prednisone and pembrolizumab was held with resolution of proteinuria (0.3 g/d).

Discussion: These are the first reported cases describing the association of MN and pembrolizumab. Although MN is well-described in solid tumors, the timing of onset and remission of proteinuria in these cases is suggestive of immunotherapy-related glomerular

injury. Clinicians should be aware of the risk of this nephrotoxicity. Additional studies may elucidate patient and malignancy-related risk factors

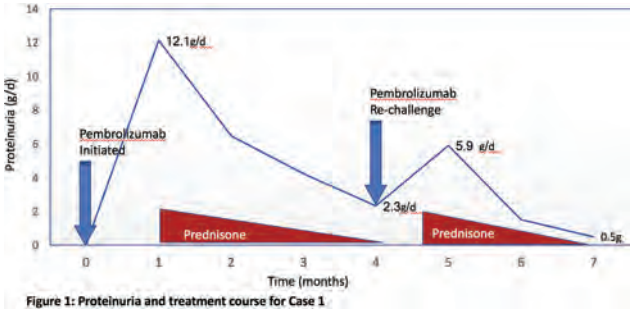

Figure 1: Proteinuria and treatment course for Case 1

Case 1

TH-PO152

Bevacizumab-Associated Thrombotic Microangiopathy Treated with Eculizumab

Rachel Hilburg, Matthew Palmer, Robert Burger, Elaine Chiang, Ashley Graul, Sonali Patankar, Abdallah Sassine Geara, Jonathan J. Hogan. *University of Pennsylvania, Philadelphia, PA.*

Introduction: Bevacizumab is a recombinant monoclonal antibody neutralizing VEGF-A that has demonstrated efficacy as an anti-neoplastic agent. Thrombotic microangiopathy (TMA) is a well-described complication of VEGF inhibitors. A previous case series described treatment of VEGF inhibitor-associated TMA with eculizumab. Here, we present two cases of bevacizumab-associated TMA with biopsy-proven kidney involvement who were treated with eculizumab.

Case Description: Case 1: A 68 yo woman with recurrent, metastatic ovarian high-grade serous carcinoma received pegylated liposomal doxorubicin (PLD) and bevacizumab. She developed new onset HTN, proteinuria (UPCR 0.6 from 0.1 g/g), and AKI (SCr 1.5 from 0.9 mg/dL). Her HTN and AKI improved with holding bevacizumab. Bevacizumab was restarted and she again developed HTN, proteinuria (UPCR 3.1 g/g) and AKI (SCr 1.5 mg/dL). Despite drug discontinuation for over two months, she developed hypertensive emergency, PRES, nephrotic syndrome, and microangiopathic hemolytic anemia (haptoglobin <30 mg/dL, LDH 282 U/L, schistocytosis) consistent with systemic TMA. A kidney biopsy showed severe chronic TMA. Eculizumab was initiated (900mg IV x 4 doses). Hemolysis and HTN resolved, and SCr improved to 2.7 mg/dL. Case 2: A 52 yo woman with HTN and stage IIIC poorly differentiated serous carcinoma was treated for progression of disease with PLD, atezolizumab, and bevacizumab. She had near complete response but developed palmar-plantar erythrodysesthesia attributed to PLD followed by worsening HTN, proteinuria (UPCR 1.6 from 0.1 g/g), and AKI (SCr 1.7 from 0.7 mg/dL). Bevacizumab was held, but SCr increased to 2.2 mg/dL. Further evaluation revealed evidence of systemic TMA (haptoglobin <30 mg/dL, LDH 425 U/L, schistocytosis). Kidney biopsy showed chronic TMA. Despite several months off bevacizumab, her TMA failed to improve. She received eculizumab, which was stopped after 2 doses for rash of unclear etiology. However, her hemolysis resolved, thrombocytopenia improved, and SCr stabilized at 1.6 mg/dL.

Discussion: We present two cases of severe bevacizumab-associated TMA with renal involvement who had evidence of disease improvement or stabilization with eculizumab treatment. The role of complement in VEGF inhibitor-associated TMA and treatment with complement blockade deserves further study.

TH-PO153

Nivolumab-Related ANCA-Negative Focal Necrotizing Glomerulonephritis

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Introduction: Immune checkpoint (ICP) inhibitors have revolutionized treatment options for many types of cancers. Adverse events associated with ICP inhibitors are mainly due to uninhibited immune system causing autoimmune diseases. Acute tubulointerstitial nephritis (ATIN) is the most commonly described kidney injury secondary to ICP inhibitors. Few case reports also identified glomerulonephritis (GN) induced by ICP inhibitors. Here we present a case of ICP associated focal necrotizing pauci-immune GN.

Case Description: Patient, 65-year-old man with aortic valve replacement, prior embolic stroke, was diagnosed with left lower quadrant de-differentiated liposarcoma on 7/21/2018, and treated with nivolumab on 9/6/2018. A month later he underwent excision of tumors, resection and anastomosis of small intestine and revascularization of femoral/popliteal/iliac arteries. His baseline Cr of 0.8-1.12 mg/dL. His course was complicated with infections and was treated with ciprofloxacin and developed an allergic reaction with a rash. Thereafter, he started having increase in creatinine with a peak of 7.53 mg/dL on 12/16/2018. His urine analysis was significant for hematuria and proteinuria of 2 grams. Renal ultrasound did not show hydronephrosis. ANA, dsDNA Ab, c/p-ANCA, anti-GBM Ab, C3 and C4, hepatitis A/B/C and HIV1/2 were all negative. Patient underwent a renal biopsy that revealed pauci- immune vasculitis with minor mesangial IgA and C3 positive staining. Patient was started on prednisone, Rituximab, and plasmapheresis with improvement in renal function and finally came off dialysis and creatinine stabilized at 2.0 mg/dL two months later.

Discussion: Use of ICP have resulted in improvement in patient survival compared to standard chemotherapy; however, there has been increasing appreciation for the adverse events associated. Therefore, obtaining a kidney biopsy and early recognition of ICP associated renal toxicity is essential to further optimize cancer patient's morbidity and mortality.

TH-PO154

Abiraterone Acetate: Enough of the S.A.M.E. Old Steroids

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Introduction: Abiraterone acetate is an androgen synthesis inhibitor, which suppresses testosterone production, utilized in the treatment of castrate-resistant prostate cancer. We report a case of syndrome of apparent mineralocorticoid excess (SAME) caused by abiraterone.

Case Description: A 82-year-old male, with a past medical history of metastatic prostate cancer on treatment with leuprolide, abiraterone, and prednisone, presented with progressive weakness and falls. Prednisone was discontinued two months prior due to concerns for steroid myopathy. On examination he was hypertensive, delirious, and had diffuse weakness. Labs illustrated hypokalemia (K 1.7 mg/dl) and metabolic alkalosis (HCO3 34 mmol/L, pH 7.62). Additionally, he had suppressed aldosterone and renin levels with an elevated aldosterone/renin ratio of 60, high ACTH level, and low serum morning cortisol. These findings are consistent with the SAME secondary to abiraterone. The patient was treated with resumption of prednisone and initiated on eplerenone.

Discussion: Abiraterone suppresses testosterone production by inhibiting the 17-alpha-hydroxylase and $C_{17,20}$-lyase enzymes. Consequently, cortisol production decreases, adrenocorticotropic hormone (ACTH) increases, and corticosterone increases, presenting as the SAME with hypokalemia, hypertension, and edema. Glucocorticoid administration with abiraterone inhibits ACTH and reduces corticosterone, thereby reducing the SAME risk. Eplerenone, a mineralocorticoid receptor antagonist, is the first-line treatment. Eplerenone avoids possible androgen receptor agonism, which can occur with spironolactone, and can be detrimental in treating metastatic prostate cancer. Conclusion: Abiraterone is an effective steroidal inhibitor for castrate-resistant prostate cancer, but can lead to the SAME, which clinicians should be able to recognize and treat.

TH-PO155

Renal Limited Anti-GBM Glomerulonephritis with Negative Serology in a Patient Following Immunotherapy with Checkpoint Inhibitors

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Introduction: A growing body of evidence implicates checkpoint inhibitor (CPI) immunotherapy as a cause of AKI. Two individual cases of CPI-induced anti-GBM glomerulonephritis (GN) have been reported. We now report the first case of diffuse linear IgG 3+, IgA 2+, Kappa 2+, lambda 1+ anti-GBM GN with negative serology in a patient following CPI exposure.

Case Description: A 58-year-old male undergoing immunotherapy for metastatic melanoma presented with AKI and proteinuria. He had been started on ipilimumab & nivolumab almost a year prior to presentation which was complicated by dermatitis, colitis & hepatitis leading to discontinuation of therapy 3 months later. Due to persistent bilateral lung metastases he was initiated on dabrafenib & trametinib for the next 6 months until he developed AKI with proteinuria. Serologic testing was negative for ANCA, PR-3, MPO, and anti-GBM antibody. Complement levels were normal. Renal biopsy showed focal crescentic (2 of 15 glomeruli with cellular crescents), proliferative and sclerosing GN with diffuse linear staining of glomerular capillary loops dominant for IgG (3+), IgA (2+), Kappa (2+) and lambda (1+). Repeat anti-GBM testing remained negative & the patient's creatinine eventually rose to a peak of 3.8 mg/dL. He had no signs of lung hemorrhage. Dabrafenib & trametinib were discontinued and he was initiated on oral cyclophosphamide (2 mg/kg/day) and pulse intravenous methylprednisolone (1000 mg daily for 3 consecutive days) followed by 1 mg/kg/day of prednisone. Immunosuppression with cyclophosphamide was discontinued after four months of therapy & he was weaned off of prednisone by 6 months. His renal function remained stable for the ensuing 12 months but it started to slowly decline & eventualy he was started on HD.

Discussion: This is a case of anti- GBM GN with negative serology & linear IgG 3+, IgA 2+, Kappa 2+, lambda 1+ anti-GBM likely secondary to treatment with CPI immunotherapy which has been linked to different GN including anti-GBM up to 10 months after therapy. BRAF inhibition only causes AIN or ATN within 2 months of therapy and is not consistant with the time course of renal injury in our case. Discontinuation of all immunotherapeutic agents and treatment with prednisone and cyclophosphamide stabilized our patient's GFR.

TH-PO156

Dasatinib Induced Thrombotic Microangiopathy

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Introduction: Treatment of chronic myeloid leukemia (CML) is complex. With the development of tyrosine kinase inhibitors (TKI), disease control is now possible. Dasatinib, a second-generation TKI, has proven to be effective for the long-term treatment of CML. Nephrotic range proteinuria has been reported with this agent, however a kidney biopsy is rarely performed. We present a case of a patient with CML who developed nephrotic-range proteinuria after initiation of dasatinib therapy that resolved after changing treatment to Imatinib.

Case Description: A 48-year-old female with CML was started on dasatinib. Three months into treatment, her dose was increased. Two months later, she developed worsening hypertension, nephrotic range proteinuria (6gm/24 hours) and hypoalbuminemia (2.4g/dl). Her urinalysis was otherwise unremarkable. She had no laboratory signs of microangiopathic hemolytic anemia. She had not been on any other chemotherapy or targeted therapy. A kidney biopsy was performed. Pathological findings of kidney biopsy specimen by light microscopy and electron microscopy were consistent with acute and chronic thrombotic microangiopathy. There were no signs of podocyte injury. These pathological findings were compatible with renal-limited thrombotic microangiopathy induced by dasatinib. After change of treatment to imatinib(gleevac), levels of proteinuria dropped to less than 1gm/24 hours and she was taken off her blood pressure medications. Her CML is responding to imatinib.

Discussion: We present a case of acute kidney injury, hypertension and proteinuria that developed during treatment with dasatinib for CML. Pathological findings revealed endothelial injury consistent with a renal-limited thrombotic microangiopathy. Patient's proteinuria and hypertension resolved after changing therapy from dasatinib to imatinib. These findings are suggestive of dasatinib as the culprit drug. We should be aware of this off-target adverse effects of dasatinib on the kidney.

TH-PO157

Bevacizumab-Associated IgA-Dominant Membranoproliferative Glomerulonephritis

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Introduction: Bevacizumab, a recombinant monoclonal antibody that blocks the vascular endothelial growth factor A (VEGF-A), is known to induce a renal-limited thrombotic microangiopathy (TMA), hypertension and proteinuria. A chronic bevacizumab-associated TMA can eventually lead to a glomerulopathy with membranoproliferative glomerulonephritis (MPGN) histology. We describe the unique case of IgA-dominant MPGN induced by bevacizumab in the absence of TMA.

Case Description: A 29-year-old male patient, with a history of neurofibromatosis type II and bilateral vestibular schwannomas treated with bevacizumab, is evaluated for nephrotic range proteinuria with preserved renal function eighteen months after initiation of therapy. Bevacizumab was initially held and the serologic evaluation for proteinuria was negative. The proteinuria was persistent and worsening (24h-urine protein: 6460 mg/24h) despite cessation of bevacizumab for 9 months and treatment with ACE Inhibitor eventually leading to a kidney biopsy. The kidney biopsy showed segmental endocapillary hypercellularity with thickening of the glomerular capillary walls and segmental double contours. The immunofluorescence was positive for IgG, IgM, IgA, Kappa and Lambda with IgA dominant pattern. The electron microscopy showed subendothelial and mesangial deposits. No TMA was seen. The final diagnosis was MPGN with IgA-dominant immune complex deposition. The patient was treated with Mycophenolate Mofetil with poor response after 4 months of therapy.

Discussion: VEGF-A secretion by the podocytes is essential in maintaining a healthy glomerular capillary endothelium. Disruption of this interaction by bevacizumab leads to a renal-limited TMA that is reversible after stopping the medication. Few previous case reports described IgA deposits in patients with bevacizumab-induced TMA. Previous reports of bevacizumab-associated TMA are well described, and a link between these two differing lesions may be possible but presently remain speculative. As the use of these agents is becoming more prevalent, further studies are needed to identify the mechanism and potential risk factors for renal disease to help guide treatment.

TH-PO158

Immune Checkpoint Inhibitor Use in a Patient with a History of Familial Anti-GBM Disease: A Clinical Dilemma

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Introduction: Immune checkpoint inhibitors (ICIs) have gained increasing use for the treatment of lung adenocarcinoma. Its utilization in patients with underlying autoimmune diseases is a challenge due to the fear of disease relapse or flare. Here, we present the case of a familial anti-GBM disease that received pembrolizumab for lung cancer.

Case Description: 71 -year-old lady was evaluated 6 years ago for worsening kidney function. A kidney biopsy led to a diagnosis of anti GBM-disease. Circulating anti-GBM antibodies were positive. She was treated with steroids, cyclophosphamide and plasmapheresis. Interestingly, her family history was significant for familial anti-GBM disease affecting 2 of her siblings. Her creatinine peaked at 12.7 mg/dl and with treatment nadired at 1-1.2 mg/dl, with anti-GBM undetectable after therapy. Three years later, she was diagnosed with left lung adenocarcinoma and underwent surgical resection, followed by external beam radiation and chemotherapy (carboplatin and paclitaxel). Unfortunately, her disease progressed and since she had positive Programmed Death-Ligand (PD L1) staining of her tumor cells; she was considered for starting on immunotherapy with pembrolizumab as a second line. She was evaluated by nephrology prior to initiation. Her baseline anti-GBM antibodies, ANCA antibodies and Anti-nuclear antibodies (ANA) were negative. Mutual decision with the patient was made to proceed with pembrolizumab with close monitoring of these tests and her serum creatinine. Seven months after treatment, her creatinine remains stable at 1.2-1.3 mg/dl with undetectable Anti-GBM, ANCA and ANA antibody titers.

Discussion: Checkpoint inhibitors are agents that unleash the immune system against cancer cells. Its use in patients with pre-existing autoimmune diseases pose a major clinical challenge. With cautious monitoring patients can use checkpoint inhibitors as a therapeutic option.

TH-PO159

Checkpoint Inhibitors: The Double-Edged Sword in Kidney Transplant Patients

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Introduction: Immunotherapy in the form of Checkpoint inhibitors (CPI) has significantly improved outcome and survival in patients with melanoma and its use has extended to multiple malignancies with good outcome. However around 50% allograft rejection is reported in patients with renal transplant who were treated with CPI with median time of 21 days from initiation of therapy

Case Description: 40-year-old man with deceased donor kidney transplantation 7 years ago was diagnosed with metastatic melanoma of the right scalp and underwent wide excision followed by Dabrafenib and Trametinib and then switched to Nivolumab and Ipilimumab. His baseline creatinine was1.8 mg /dl. After 2 cycles of immunotherapy, he was noted to have severe acute kidney injury with Creatinine of 8.5 mg/dl. Renal biopsy showed acute T cell mediated rejection Banff grade IIA and suspicioun for acute antibody mediated rejection with positive peritubular capillaries for C4d. patient was treated for acute rejection with IV Methylprednisolone, rituximab, plasmapheresis (3 sessions) and intravenous immunoglobulin. Patient didn't have renal recovery and a decision was taken to sacrifice the allograft and continue immunotherapy for Melanoma

Discussion: The complex mechanism for acute rejection in renal transplant patient with use of CPI is still under investigation. One suggested mechanism is related to the inhibition of programmed death ligand 1 (PDL1) that involved in increasing graft tolerance by increasing T regulatory (Treg) cells and limiting the function of effectors T cells. The current recommendation for treatment of malignancy in patients with renal transplant is to reduce the immunosuppression by stopping the anti-metabolites and possibly switching to mTOR inhibitors. However, these guidelines predated the era of immunotherapy for metastatic malignancy and need to be reevaluated. Currently there are no established guidelines to help guide the prevention and treatment of acute rejection in this population and no clear studies about the safety of anti-rejection therapy on tumor progression. With the reported high probability of graft loss, the nephrologist and oncologist should have an extensive discussion with the patient prior to starting CPI to guide with treatment decision that will impact patient lifestyle and cancer response

TH-PO160

Intravitreal Injection of Avastin over Time Can Be Associated with Thrombotic Microangiopathy in the Native Kidney

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Introduction: Avastin, an inhibitor of vascular endothelial growth factor, has been used for treating various metastatic cancers. Its side effects leading to renal thrombotic microangiopathy (TMA) has been well known. Intravitreal injection of Avastin (IIA) has been used to treat macular proliferation or degeneration in patients. A recent study of 69 patients with IIA showed no side effects, while there were two case reports suggested a link with IIA and native renal failure in 5 patients without proven biopsies. Whether IIA over time can lead to renal TMA in diabetic patients remain controversial. This case reports the presence of renal TMA after months of IIA in a diabetic patient.

Case Description: A 56 years old diabetic man received IIA for macular edema and proliferative retinopathy over the past few months was found to have deteriorated renal function (serum creatinine up to 2.47 mg/dl) with a nephrotic range of proteinuria (protein/creatinine ratio 4.7). All his serology tests were negative. A renal biopsy was performed to evaluate pathologic changes in the kidney (Light microscopy revealed mesangial nodular expansion, characteristic for diabetic nephropathy but with additional sub-endothelial expansion and lamination around the diabetic nodules. The acute tubular injury was present on PAS-stained sections. No thrombi formation was noted in glomeruli or vessels.

Immunofluorescent studies reveal moderate nearly linear IgM staining around diabetic nodules with positive fibrinogen staining. Electron microscopy showed double contoured glomerular basement membranes with subendothelial edema causing detachment of glomerular endothelial cells. Overall findings supported a diagnosis of chronic active TMA on top of diabetic nephropathy background and secondary acute tubular injury.

Discussion: Patient's ophthalmologist was informed of the result. A follow-up will be conducted (IIA may be discontinued). The finding of this case suggestive the link between repeat IIA and renal TMA, where a small leakage of Avastin from repeat IIA could be a thread to interact with glomerular podocytes and endothelial cells leading to chronic active TMA in the kidney, resulting in renal failure and proteinuria.

TH-PO161

Wiedemann-Steiner Syndrome Presenting as Bladder Outlet Obstruction

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Introduction: Wiedemann-Steiner syndrome is a rare autosomal dominant disorder associated with pathogenic variants in the *KMT2A* (Lysine Methyltransferase 2A) gene, which encodes a histone methyltransferase thought to regulate transcription via methylation of histone H3KA. This gene has targets in many human tissues, including multiple HOX and WNT genes. The disorder classically presents as prenatal and postnatal growth restriction with atypical facial features. While renal involvement has been seen in some cases, this has never been described as a presenting feature, as in this case.

Case Description: This late-preterm SGA newborn boy presented with anuria for the first 2 days of life and a distended bladder. There was a prenatal diagnosis of hydronephrosis later described as bilateral grade IV hydronephrosis with hydroureter on US and isolated left grade V reflux on VCUG, not due to PUV or ureterocele. SCr on DOL 2 was 1.9 with improvement to 1.2 after a suprapubic tube was placed for urine output. He was evaluated by genetics in the early newborn stage who appreciated hypertrichosis, upslanted palpebral fissures, and clinodactyly. After recurrent UTIs, a voiding cystourethrogram was performed and showed a severely distorted left upper tract collecting system. A skeletal survey showed no signs of skeletal dysplasia and a chromosome microarray was normal. Endocrine evaluation for his short stature (height and weight below the 3rd percentile) revealed no obvious hormone-mediated disease process. Whole Exome Sequencing (WES) identified a de novo autosomal dominant pathogenic variant in the *KMT2A* gene (p.R1151*, c. 3451 C>T), consistent with the diagnosis of Wiedemann-Steiner syndrome. He went on to develop stage III chronic kidney disease within his first year of life, and is expected to require kidney transplant by the age of 5 after vesicostomy closure and self-catheterization for renal protection.

Discussion: This case illustrates an atypical presentation of a rare genetic disorder and adds to the phenotype of Wiedemann-Steiner syndrome.

TH-PO162

Unraveling the Genotype to Phenotype Correlation: A Child with PH1 and a Novel Mutation Responsive to Pyridoxine Therapy

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Introduction: Primary hyperoxaluria type 1 (MIM 259900) is a rare genetic disease with an estimated prevalence of 1-3 cases per 1 million population worldwide. Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disorder, caused by a mutation in the *AGXT* gene, and characterized by an accumulation of calcium oxalate in various body tissues, particularly the kidney. Disease expression is variable, ranging from nephrocalcinosis during infancy to recurrent or infrequent nephrolithiasis in childhood or adulthood and renal failure in 20-50% of patients. Over 175 mutations have been identified to date. About 10 to 30% of patients with PH1, particularly those with p.Gly170Arg or p.Phe152Ile mutations, respond to pyridoxine therapy with a significant reduction of urinary oxalate excretion. We present a patient with PH1, found to have a previously undescribed mutation in the *AGXT* gene, who showed excellent response to pyridoxine therapy.

Case Description: AS, now a nine year old male, born in Afghanistan to consanguineous parents, initially presented with a history of flank pain, failure to thrive and bilateral nephrolithiasis at the age of five years. He underwent several rounds of extracorporeal shock wave lithotripsy (ESWL) for significant stone burden. Upon establishing care with nephrology in the U.S., his workup revealed hypocitraturia, elevated 24 hour oxalate level at 127mg/day (normal range 20-40) and a urine glycolate level of 249 mg/gram of creatinine (normal range <75), raising concern for PH. He was empirically started on vitamin B6, potassium citrate and advised to increase hydration. Genetic testing confirmed PH1 with a homozygous mutation in *AGXT* (c.352C>T; p.Arg118Cys), reported as a variant of uncertain significance. Follow up urine testing at 3 and 7 months showed a reduction in oxalate levels by 35% and 58%, respectively. He remains asymptomatic, has normal GFR, with no evidence of systemic oxalosis and stable right sided nephrolithiasis since last ESWL in 2017.

Discussion: We conclude that in this patient with classic PH1 phenotype, the finding of a homozygous variant in *AGXT* is not only pathogenic, but also responsive to pyridoxine therapy. We hope this case will add to the knowledge base of PH1 and help guide management in patients with a similar genotype. Pyridoxine therapy has been life changing for AS and his family.

TH-PO163

A Case of Childhood Bilateral Renal Artery Stenosis Not Seen on Angiography

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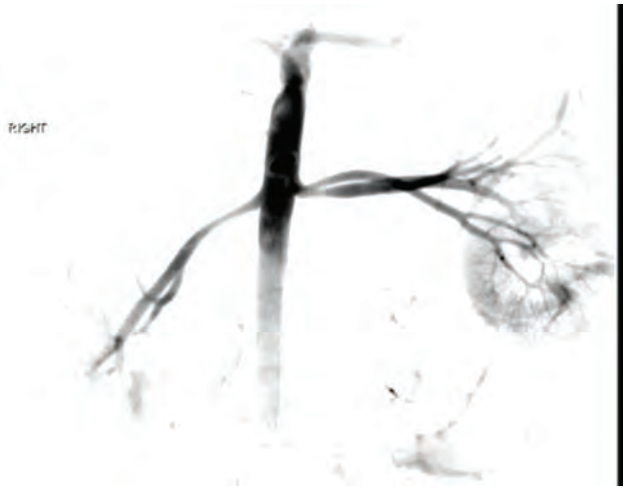
Introduction: Renovascular hypertension (HTN) is an important cause of secondary HTN in children. Multiple imaging modalities are considered for detection of renal artery stenosis (RAS) such as: duplex ultrasound, CTA, and MRA. However, the gold standard for detection is conventional angiography. We present a case of bilateral RAS that was undetected by angiography.

Case Description: A 12 year old previously healthy female presented to a well-child exam with a BP 180/111 mmHg. Her BMP was remarkable for a serum K+ of 3.2 mmol/L and normal eGFR. Renal US was unremarkable and UA demonstrated microscopic hematuria (5-10 RBCs/hpf). She also had left ventricular hypertrophy on echocardiogram. Hypertension work up included: plasma aldosterone, serum free metanephrines, ACTH, monogenic HTN panel, and serum cortisol levels. Work up was negative other than an elevated aldosterone. A CTA demonstrated "string of beads appearance of the bilateral renal arteries and lobar segments suggestive of bilateral fibromuscular dysplasia and focal moderate-severe stenosis of the proximal left renal artery." Angiography did not demonstrate RAS. She was started on captopril and elevation in creatinine was noted. She was then sent to a vascular surgeon for a second opinion. At that time, angiography was repeated and bilateral renal vein renin measurements were elevated. Via imaging, she had ostial left RAS and mid-right RAS. She is currently managed on clonidine, HCTZ, and lisinopril. She is scheduled for bilateral renal revascularization.

Discussion: This case illustrates the importance of multiple imaging modalities in the work up of renovascular HTN. Our patient underwent angiography by a skilled radiologist and bilateral RAS was not detected, thus we highlight the value of specialized vascular surgery centers for cases with a high index of suspicion.



Angiography showing pt's bilateral RAS.

TH-PO164

A Case of Pilsicainide Hydrochloride Toxicity That Relapsed After Discontinuation of Hemodialysis

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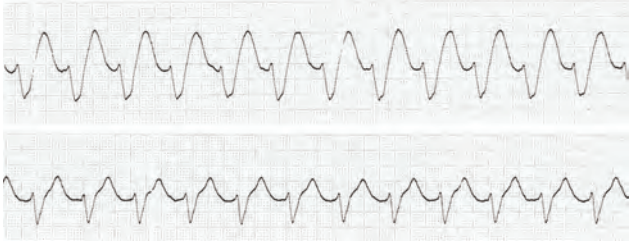
Introduction: Pilsicainide is a class I C sodium channel blocker known to be effective in treating atrial fibrillation (Afib). However, the high plasma concentration of pilsicainide can trigger ventricular tachycardia (VT) and ventricular fibrillation. We present a case of pilsicainide induced VT, which relapsed after discontinuation of hemodialysis (HD).

Case Description: An 84-year-old male with a history of hypertension, paroxysmal Afib on pilsicainide, and Parkinson's disease developed a cough and fever three days before admission. One day prior, he became lethargic and was brought to a local hospital. A 12-lead electrocardiography (ECG) showed VT. He was transferred to our hospital due to pilsicainide toxicity. His creatinine increased to 6.2mg/dL secondary to sepsis (baseline 0.9 mg/dL). We initiated emergent HD, which narrowed the QRS instantly (Figure). We performed 3 hours of HD. Two hours after ending HD his QRS prolonged again; we resumed HD followed by direct hemoperfusion. The QRS remained narrow after the 2nd HD session. He remained hemodynamically stable and was transferred to the initial hospital. Serum pilsicainide levels were: at previous hospital 3.47 μg/mL, on admission 2.61 μg/mL, after 1st HD 2.31 μg/mL, after 2nd HD 1.1 μg/mL, and after hemoperfusion 0.76 μg/mL.

Discussion: Pilsicainide is excreted by the kidney; therefore, elimination is prolonged in patients with chronic kidney disease (CKD). The mean clearance of this drug by HD is 32 %. Interestingly, the QRS was narrow during HD even though the serum pilsicainide level was high. The volume of distribution of this medication is 1.7 L/kg in CKD patients; most of the drug is distributed in the tissue. We infer that the drug in the tissue was re-distributed after HD. In conclusion, pilsicainide should be administered cautiously to elderly patients even if the serum creatinine is normal. Serum pilsicainide level may not correlate with EKG findings.



TH-PO165

Vedolizumab, a Monoclonal Antibody for Treating Crohn Disease, Can Cause T-Cell-Mediated Interstitial Nephritis and CKD

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Introduction: Vedolizumab (Vedo), a gut-selective humanized monoclonal antibody, binds specifically to the α4 β7 integrin as a lymphocyte homing antagonist. Previously, Bailly et al have reported the first case of Veldo induced acute interstitial nephritis (AIN) (*Am J Kid Dis* 2017), with good renal recovery after the standard steroid treatment. Here, we report another case of Vedo associated AIN which resulted in CKD despite the standard steroid treatment. She was subsequently received steroid treatment without significant improvement of renal function (serum creatinine 1.8 mg/dl at the 3nd month follow-up following the biopsy). The case indicates that Vedo associated T cell medicated AIN can lead to a substantial CKD.

Case Description: A 33 years old woman with Crohn's disease involving her small bowel and colon developed acute kidney injury with rising serum creatinine (from 0.7 to more than 2.0 mg/dl) after her receiving 3 standard doses of Vedo infusions over 2 months. Without signs of recovery after stopping the Vedo treatment, a renal biopsy was performed to evaluate her renal pathology. Light microscopy revealed AIN with only 10 % of B lymphocytes, 10% of CD8 positive macrophages, but 80% of T lymphocytes in the interstitium and mild tubulitis. Further stains showed 60% CD4 regulatory T lymphocytes and 40% of CD8 positive cytotoxic T lymphocytes. No eosinophils, neutrophils or granulomas were present. Kidney injury molecule-1 staining was positive in proximal tubules, consistent with an acute tubular injury secondary to AIN. Trichrome stained sections showed moderate interstitial fibrosis and tubular atrophy. Immunofluorescent studies and electron microscopy did not reveal additional specific findings.

Discussion: She has subsequently received steroid treatment without significant improvement of renal function (serum creatinine 1.8 mg/dl at the 3nd-month follow-up following the biopsy). The case indicates that Vedo associated T cell medicated AIN can lead to a substantial CKD.

TH-PO166

Cefepime-Induced Neurotoxicity in a Patient with ESRD

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Introduction: Cefepime causes neurotoxicity with an increased risk in patients with renal dysfunction.

Case Description: A 59-year-old male with ESRD on hemodialysis (HD) on Tuesday/Thursday/Saturday, hypertension and peripheral arterial disease was admitted with altered mental status of 2 days duration. Patient was admitted 1 month prior to presentation for elective amputation of right third/fourth toes due to dry gangrene of the right foot. His wound cultures grew Citrobacter and Serratia sensitive to ceftriaxone. He was discharged on oral cefpodoxime. He was transitioned to cefepime (2 gm IV on Tuesday/Thursday and 3 gm IV on Saturday following dialysis) after a wound culture grew Pseudomonas. He developed altered mental status presenting as disorientation with decreased consciousness and paranoid hallucinations one day after a single dose of 3 gm IV cefepime. On admission, BP was 213/123. Exam revealed bilateral myoclonic jerks involving all extremities. Head CT and brain MRI without contrast showed no acute process without any evidence of hypertensive encephalopathy. Cefepime was discontinued. His symptoms of hallucinations and delirium lasted for about a week. After 3 daily sessions of HD, his mental status eventually returned to his prior baseline with resolution of his myoclonus. Patient was discharged with close follow-up with nephrology.

Discussion: Cefepime causes neurotoxicity with an increased risk in patients with renal dysfunction, critical illness, advanced age and inappropriate dosage for renal function. It is postulated that neurotoxicity results from inhibition of GABA receptors in the CNS. Manifestations include decreased level of consciousness, myoclonus, agitation, seizures and non-convulsive status epilepticus. Median onset of neurotoxicity was observed 4 days after initiation (range 1 to 10 days) often with median resolution of symptoms within 2 days of appropriate therapy (range 1 to 4 days). Hemodialysis is an effective treatment option with a reported 60 to 70% decrease in cefepime level after a single session. Unique characteristics of our case include rapid onset of symptoms after a single high dose, longer duration of symptoms and prolonged dialysis needs to clear the antibiotic. Physicians should be aware of drug-induced neurotoxicity in patients taking cefepime and should be cautious with excessive dosing in patients with renal dysfunction.

TH-PO167

An Unexpected Complication After a Motor Vehicle Accident: Propofol Infusion Syndrome

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Introduction: Propofol is the most commonly used parenteral anesthetic in the United States due to its rapid onset and reversal of action. Propofol infusion syndrome (PRIS) is a serious complication associated with multiorgan failure. An incidence of less than 1% have been reported for this life-threatening complication, making its early recognition critical for a favorable outcome.

Case Description: A 59-year-old woman was admitted due to multiple body trauma after a motor vehicle accident. She was intubated for airway protection and propofol was used for sedation. Hospitalization complicated with acute kidney injury (AKI) and Nephrology service was consulted. Examination revealed a critically ill patient sedated with an intravenous infusion of propofol at a 0.83 mg/kg/hr rate and norepinephrine for hemodynamic support. Propofol drip was infused for more than 48 hours. Physical exam revealed adequate urine output, clear lungs and no edema. Laboratory tests with increased lactate levels from 37.4 to 54.8 mg/dl, bicarbonate 13.6 mEq/L and pH of 7.24. Anion gap (AG) was 17.9. Creatinine worsened from 0.55 to 1.12 mg/dl. Creatinine phosphokinase level of 3,421 U/L was observed. Triglyceride levels increased from 171 to 372 mg/dl. Laboratory findings were consistent with high AG metabolic acidosis, AKI, rhabdomyolysis and hypertriglyceridemia. Based on clinical course and risk factors for PRIS including critical illness, prolonged sedation and catecholamine infusion; propofol was discontinued and altered laboratories showed marked improvement.

Discussion: Our patient received a prolonged infusion of propofol and exhibited risk factors previously stated for developing this rare complication. He had a worsening metabolic acidosis with additional findings not explained by other causes of acidosis. Moreover, improvement of parameters after discontinuation of propofol infusion supports our diagnosis of PRIS. This syndrome should be suspected in any patient with prolonged infusion of propofol and the cardinal features of this syndrome, including cardiovascular collapse, lactic acidosis, AKI, rhabdomyolysis and hypertriglyceridemia. PRIS suspicion should prompt immediate propofol weaning, since this complication carries a high mortality risk. In our case, early recognition and proper management lead to a satisfactory outcome.

TH-PO168

Chondrodysplasia Punctata in a Baby Born to a Woman with Lupus Nephritis Who Received Belimumab

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Introduction: Belimumab is a human monoclonal antibody that inhibits B-cell activating factor, used to treat extrarenal systemic lupus erythematosus. Experience with belimumab in pregnancy is limited.

Case Description: A 28 year old presented for evaluation of lupus nephritis (LN) in pregnancy. She had been diagnosed with class 4 LN in 2008. She achieved remission after induction with mycophenolate mofetil (MMF). A 2013 relapse was treated with MMF (no response), cyclophosphamide (stopped due to neutropenia), and rituximab, with partial remission. In 2018 she had worsening renal function, and biopsy revealed class 4 LN with crescents, moderate activity, and severe chronicity. She was treated with cyclophosphamide but again developed severe leukopenia. She received no further induction therapy for LN, but was started on belimumab for extrarenal lupus symptoms. Shortly after her 3rd infusion of belimumab, pregnancy was diagnosed. She was maintained on azathioprine, hydroxychloroquine, nifedipine, and low-dose aspirin. Renal function and proteinuria remained stable (serum creatinine 2.0-2.2 mg/dl, proteinuria 3-5 g/day). Complement levels were slightly low, and anti-double stranded DNA antibody titer was negative. Fetal ultrasound at 17 weeks gestation showed absent nose and palate, hemivertebrae, brachycephaly, and shortened long bones. Amniocentesis showed no genetic or chromosomal abnormalities. At 30 weeks, she was delivered due to superimposed preeclampsia. Her infant was diagnosed with chondrodysplasia punctate based on morphologic features.

Discussion: Chondrodysplasia punctata (CDP) is a skeletal abnormality characterized by premature foci of calcification within the cartilage. Features include proximal shortening of the limbs and stippled epiphyses. CDP can be caused by inborn error of metabolism, disruption of vitamin K metabolism, chromosomal abnormalities, and maternal factors. There are 21 published cases of neonates with CDP born to women with autoimmune diseases, including SLE and Sjögren syndrome. Our patient was exposed to belimumab in early pregnancy. CDP has not previously been reported with belimumab exposure, and limited data do not suggest teratogenicity. It is unknown if our case of CDP was caused by belimumab or maternal lupus. Belimumab should be avoided in pregnancy until more safety data are available.

TH-PO169

DRESS to Impress: Unusual Case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) due to Epoetin Alfa

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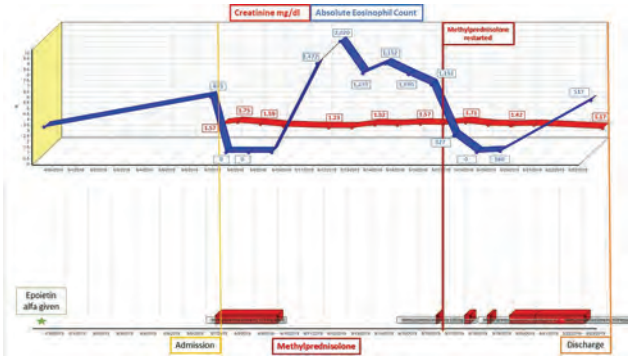
Introduction: DRESS syndrome is a severe life-threatening hypersensitivity reaction to medication or its active metabolites. It manifests with fever, rash & organ involvement, kidneys & liver most commonly. It has a 10% mortality rate. More frequently associated with DRESS are sulfonamides, anti-inflammatory medications & anticonvulsants. There is only one case report of epoetin alfa related DRESS syndrome in the literature, and herein we present the second.

Case Description: 92 y/o man with hypertension, A. fib. & CKD IIIa arrived at ED due to generalized pruritic skin eruption since 7 days ago. Physical exam: generalized non-blanching erythematous patches on lower extremities, torso & upper extremities. Few violaceous purpuric patches on extremities, petechias on palms & feet. Labs: WBC: 17.9 x10^3/UL, Plt: 270 10^3/UL, Eosinophils: 895. BUN: 50.7 mg/dL & Cr.: 1.8 mg/dl (base:1.2), ALT: 39, AST: 23 & CRP: 127.3. He was started on epoetin alfa 8 days prior, which was discontinued upon admission. Dermatology biopsied a lesion & recommended methylprednisolone (MP) IV for 2 days. Rash, eosinophils & creatinine improved. MP was discontinued as per derm. recc. but rash, eosinophils & creatinine again worsened. Biopsy: spongiotic dermatitis w/parakeratosis, pustules in stratum corneum, dermal perivascular lymphocytic infiltrate & scanty eosinophils. Allergist recc. restart MP for epoetin alfa related DRESS. See Fig 1 for data on MP, creatinine & eosinophils. He improved & was discharged on a steroid tapering

Discussion: The European Registry of severe cutaneous adverse reactions is a scoring system to help yield the diagnosis of DRESS, a score of 6 makes it definitive, as presented in this case. Only ~11% of patients with DRESS manifest with renal disease. After literature review, this is only the second case of epoetin alfa associated DRESS. **Epoetin alfa is a commonly used drug in patients with CKD & physicians should be aware of this potentially fatal adverse effect.**



Changes in eosinophilia and creatinine with methylprednisolone dose

TH-PO170

Fanconi Syndrome in an Elderly Patient with Membranous Nephropathy During Treatment with Immunosuppressant Mizoribine

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Introduction: Acquired Fanconi syndrome (FS) is often caused by drugs (antibacterial drugs, antiviral agents and anticancer agents), is sometimes caused by autoimmune diseases, monoclonal light chain associated diseases and heavy metal poisoning. Mizoribine (MZR) is an oral immunosuppressant inhibiting inosine monophosphate dehydrogenase, widely used in Japan for treatment of autoimmune diseases, nephrotic syndrome and renal transplantation. Recently several studies have shown that a combination of steroids and MZR is effective in patients with membranous nephropathy (MN). Furthermore, there is an interesting report that the addition of steroid after MZR monotherapy for two or three months may be beneficial for patients with MN.

Case Description: An 80-year-old man was referred to our hospital with FS, acute kidney injury (AKI) and severe proteinuria (15 g/gCr). Two months before this admission, he was diagnosed with primary MN by his renal biopsy. He and his wife chose outpatient treatment because of his mild dementia due to ageing. Oral administration of MZR was started prior to prednisolone administration. One month later, serum creatine was rapidly increased from 1.9 to 2.7 mg/dL with nephrotic-range proteinuria. In addition, serum albumin was decreased to 1.1 g/dL, and various abnormalities of laboratory data including glucosuria, hypokalemia, hypophosphatemia and hypouricemia were newly recognized. He had no history of exposure to heavy metals or administration of any other additional drug, including Chinese medicines. Hypokalemia, hypophosphatemia, glucosuria, hypouricemia and severe proteinuria were gradually improved by discontinued administration of MZR, additional oral administration of prednisolone followed by single intravenous injection of rituximab. He was finally diagnosed with MZR-induced FS from this clinical course and his typical laboratory data except proximal tubular acidosis.

Discussion: To the best of our knowledge, this is the first report demonstrating FS induced by MZR. Although the mechanisms induced proximal tubular dysfunction with MZR are unknown, nephrologists should pay attention to the onset of FS during treatment with MZR.

TH-PO171

Atazanavir Crystal-Induced Chronic Granulomatous Interstitial Nephritis

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Introduction: Atazanavir (ATZV) is a protease inhibitor used in the treatment of human immunodeficiency virus (HIV) infection. Highly active antiretroviral therapy (HARRT)-related nephrotoxicity is primarily linked to tenofovir (TFV) or to the no-longer-used drug, indinavir. We describe a case of biopsy-proven atazanavir crystal-induced chronic granulomatous interstitial nephritis (CGIN) and review previously reported cases.

Case Description: A 51-year-old black man with HIV infection presented to renal clinic for evaluation of worsening kidney function. He was asymptomatic. He denied NSAID use and was on ritonavir (RTV), ATZV, abacavir and lamivudine. Physical examination was unremarkable. Laboratory data showed a serum creatinine (sCr) 2.7 mg/dL (3 months prior 1.7 mg/dL; 9 months prior 1.2 mg/dL). CD4 count was 327 and HIV-1 RNA viral load was undetectable. Hepatitis B and C were negative. Complements, lupus serology and serum protein electrophoresis were within normal limits. Urinalysis showed 20-30 white blood cells/hpf. Urine protein-creatinine ratio (UPCR) was 450 mg/g. Urine culture was negative. Renal ultrasound was normal. One month later, sCr rose to 3.3 mg/dL. A kidney biopsy was performed and the specimen showed: interstitial mononuclear infiltrate with numerous eosinophils, a granulomatous process with central necrosis, crystal-like material and neutrophils, moderate interstitial fibrosis, and 9/15 obsolescent glomeruli. ATZV was stopped and prednisone was begun. After 8 months, sCr gradually improved to a new baseline of 2.0 mg/dL. Our case is only the 10th reported (see Table

Discussion: ATZV must be considered as a potential cause of chronic progressive nephropathy in patients on HAART and can present as CGIN and acute interstitial nephritis (AIN).

Comparison of ATZV nephropathy case reports

Case	Viglietti et al.	Izzedine et al.	Hara et al.	Kanzaki et al.	Coelho et al.	Brewster and Perazella	Schmid et al.	Schmid et al.	Schmid et al.	Varghese and Velez
sCr at biopsy (mg/dL)	2.2	3.6	2.2	2.0	7.1	11.1	10.3	3.4	7.0	3.3
UPCR (g/g)	N/A	0.3	0.25	0.38	N/A	N/A	0.75	0.5	1.0	0.45
Pyuria	+	-	-	-	+	+	-	+	-	+
ATZV duration	4.1 years	N/A	5.6 years	3.5 years	8 months	4 weeks	3 months	6 weeks	4 months	3.5 years
Select HAART	RTV	RTV	RTV	RTV, TFV	RTV, TFV	-	RTV, TFV	RTV, TFV	RTV, TFV	RTV
Pathology	CGIN	CGIN	CGIN	CGIN	AIN	AIN	AIN	AIN	AIN	CGIN

TH-PO172

Successful Treatment of Chronic Osteomyelitis with Avoidance of Amputation During PCSK9-inhibitor Treatment for Cardiovascular Diseases in Patients with Diabetes Mellitus and CKD

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Introduction: Management of DM patients with chronic osteomyelitis (OM) of the foot can be challenging. Even with targeted antimicrobial therapy tailored to culture and sensitivity results, due to micro-and-macrovascular ischemia, patients' conditions usually deteriorate leading to subsequent amputation. We present a case series of 5 patients whose chronic OM recovered during treatment with PCSK9(Proprotein Convertase Subtilisin Kexin type 9) inhibitor to reduce the risk of myocardial infarction, stroke, and coronary revascularization.

Case Description: The patients (age 65-91 years) have a common history of chronic DM-2 (20-35 years) and multiple comorbidities such as coronary artery disease, CKD, CHF, chronic diabetic complications, and peripheral artery disease(PAD). History of DM foot ulcer began as a minor injury, precipitated by DM peripheral neuropathy and atherosclerosis, worsened to cellulitis and subsequent OM. Appropriate antibiotics were used guided by wound culture and sensitivity results without improvement, instead deterioration of infection. Imaging studies of the foot revealed OM. Patients underwent surgical debridement and prolonged antibiotic courses without success, requiring amputation to avoid septicemia and death. However, one month after initiation of PCSK9-inhibitor treatment for cardiovascular co-morbidities, complete wound healings were achieved in those patients, avoiding all planned amputations.

Discussion: Patients with DM have a 10-fold increased risk for lower extremity amputation and almost twice as likely to require re-amputation compared to patients without DM. PCSK9-inhibitor is a human monoclonal IgG preventing PCSK9-mediated LDL-receptor degradation, and allowing LDL-receptor to recycle back to the liver cell surface, thus lowering serum LDL cholesterol. It is speculated that PCSK9-inhibitor may improve circulation, promoting antibiotic penetration into the wound, thus wound healing. We suggest that PCSK9-inhibitor should be used in all patients with PAD and chronic

nonhealing wounds as prevention of future amputation. It may also be advantageous to initiate PCSK9-inhibitor in all DM foot ulcer patients during treatment of chronic OM or even before the development of cellulitis or OM.

TH-PO173

Far Infrared Therapy May Improve Arterial Insufficiency and Joint Inflammation in CKD Stage 5 Patients

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Introduction: Far infrared (FIR) induces expression of endothelial heme oxygenase-1, reduces monocyte adhesion to endothelial cells, and provides a strong anti-inflammatory benefit to the vascular endothelium. It has been shown that FIR therapy improves dialysis fistula flow, maturation, and patency and leads to decreased pain and hematoma formation with needling in CKD stage 5 and 5d patients. It is also effective in relieving pain in patients with chronic pain syndromes like fibromyalgia and phantom limb after amputation through thermal and non-thermal effects. In the past we reported an improvement in graft stenosis and resolution of internal jugular vein thrombus associated with tunneled catheter insertion in two dialysis patients with FIR therapy. Now we report 3 CKD stage 5 patients with improvement of arterial insufficiency, frozen shoulder and partial rotator cuff injury using FIR therapy.

Case Description: Case 1. A 68 year old man with CKD 5 due to FSGS and HTN developed significant claudication on his right leg and discoloration of his second toe. An arteriogram showed substantial small arterial disease not amenable to bypass and below knee amputation was recommended by his surgeon. A trial of FIR therapy on his leg was done, and after three weeks, claudication and toe discoloration resolved. FIR therapy was stopped and he remained pain free after 2 years of follow-up. Case 2. A 67 year old man with CKD 5d due to HTN developed left shoulder pain with restricted range of motion. Analgesics and 3 weeks of physical therapy (PT) did not provide relief. A trial of 40 minutes of FIR therapy 3 times a week during dialysis was done. After 3 weeks, his frozen shoulder improved completely. Case 3. A 75 year old woman with CKD 5 developed right partial rotator cuff tear after a fall. Diagnosis was confirmed by MRI and surgery was recommended. She refused surgery and tried 2 months of PT, which did not provide relief. Trial of FIR therapy was done with complete resolution of pain and stiffness after 3 weeks.

Discussion: FIR therapy may have beneficial effect on arterial insufficiency and joint injury and inflammation and should be considered in CKD 5 patients suffering from these conditions. It is non-invasive and can be easily done as 40-minute sessions in the clinic or during dialysis treatments.

TH-PO174

Denosumab-Induced Severe Hypocalcemia and Hyperparathyroidism in a Peritoneal Dialysis Patient

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Introduction: Denosumab is increasingly used in the treatment of osteoporosis in patients with End Stage Renal Disease (ESRD). The safety of Denosumab in ESRD is unproven. We report a case of severe hypocalcemia and hyperparathyroidism after Denosumab use in ESRD.

Case Description: A 56-year-old woman with history of osteoporosis, secondary hyperparathyroidism and ESRD on peritoneal dialysis for the past eight years, presented to clinic with complaint of paresthesias of hands and feet for two weeks. Vital signs and physical exam were unremarkable. Laboratory work-up showed profound hypocalcemia (corrected calcium of 6.8 mg/dL) and markedly high intact PTH (iPTH) of 3448 pg/mL (Table 1), with normal phosphate (5.1 mg/dl) and alkaline phosphatase (193 U/L). Upon medication review, she notably received denosumab 60 mg subcutaneously for the first time, two weeks prior to her visit. Before the use of denosumab; calcium, phosphorus, and 25-vitamin D were normal, with mildly high iPTH (Table 1). We gave total daily doses of 3,000 mg oral calcium and 4,000 mg Renvela. With these drugs, her symptoms resolved with normalization of serum calcium six weeks later, and iPTH ten weeks later (Table 1). She was later closely monitored in clinic.

Discussion: Denosumab is a monoclonal antibody used to treat osteoporosis; it binds to receptor activator of nuclear factor-kappa B ligand, an osteoclast differentiating factor, to inhibit bone resorption and increase bone mineral density. Bisphosphonates are first line treatment for osteoporosis. However, bisphosphonates are contraindicated in ESRD due to impaired clearance. Denosumab is not renally cleared, hence seen as an alternative for treating osteoporosis in ESRD. Decreased phosphate clearance, reduced production of 1α hydroxylase, and elevated fibroblast growth factor-23 all predispose ESRD patients to hypocalcemia. Denosumab further increases this risk by downregulating osteoclast activity. Denosumab continues to be used in ESRD, with increasing reports of hypocalcemia. Our case outlines the life-threatening hypocalcemia that may occur, and highlight the need for closer monitoring in ESRD patients receiving denosumab.

Table 1. Changes in Calcium and iPTH levels after Denosumab.

	Before Denosumab	2 weeks after Denosumab	6 weeks after Denosumab	10 weeks after Denosumab
Corrected Calcium	9.7	6.8	8.7	10.6
iPTH	584	3448	3526	399

TH-PO175

Topical Vitamin A Ointment-Induced Hypercalcemia and Renal Stones in CKD

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Introduction: Hypervitaminosis A is a rare cause of hypercalcemia, possibly secondary to the effect of vitamin A on bone to stimulate osteoclastic resorption and/or inhibit osteoblastic formation. Since Vitamin A metabolites are renally excreted, patients with chronic kidney disease (CKD) are at high risk of developing hypercalcemia even with lower dose of vitamin A. We present an unusual case of hypercalcemia from topical vitamin A ointment in a patient with CKD.

Case Description: A 55 year old male with past medical history of intellectual disability and CKD 3A with baseline serum creatinine (S.Cr.) of 1.4mg/dL was admitted to the hospital for hypercalcemia and acute kidney injury on CKD. On presentation, his S.Cr. was 1.9mg/dL, calcium was 11.4 mg/dL, albumin was 4.4 g/dL and parathyroid hormone (PTH) was 5 pg/mL. Renal ultrasound demonstrated a 7 mm nonobstructive stone with mild to moderate hydronephrosis of the left kidney. Serum phosphorous, PTH related protein, 25-hydroxyvitamin D, 1,25-hydroxyvitamin D, serum protein electrophoresis and serum free light chains were within normal limits. Vitamin A level was elevated at 156 mcg/dL (reference range 38-98 mcg/dL). Medication review found that the patient was using a vitamin A and D topical ointment for perianal dryness as a preventative measure. The topical ointment was stopped and within a month his S.Cr. stabilized to 1.5mg/dL, calcium came down to 10.6 mg/dl and vitamin A level returned close to normal at 106 mcg/dL.

Discussion: Hypercalcemia is a rare but reported side effect of oral all-trans-retinoic acid, a vitamin A metabolite, used for acne treatment. It is also known to occur from over the counter vitamin A supplements. We present the first case of topical vitamin A induced hypercalcemia in CKD. Vitamin A toxicity should be considered in the differential diagnosis of hypercalcemia and clinicians should be aware of the potential of vitamin A containing preparations causing hypercalcemia, especially in CKD populations. Our case highlights the importance of a thorough review of medications, including over the counter and topical medications in workup of hypercalcemia.

TH-PO176

A Unique Case of Metformin-Associated Lactic Acidosis

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Introduction: Metformin intoxication with lactic acidosis may develop in diabetic patients when the drug dose is inappropriate or its clearance is reduced. Comorbid medical conditions can make the diagnosis difficult, especially in the critical care unit. In this case, we present a patient who presented with AMS, found to have severe acidemia, with co-existing myxedema coma and urosepsis.

Case Description: A 62 year-old female presented for altered mental status. She takes Metformin 1 gm BID and recently started Liraglutide 1.2 mg daily. EMS found her at home, notably hypoxic, hypotensive and hypothermic. On arrival, she was found to have dysarthria but was able to convey a 2-week history of non-bloody diarrhea. Vitals revealed T 93.3C, BP 89/49, HR 79, RR 20, SpO2 100%. VBG showed severe acidemia with pH 6.97, pCO2 22, HCO2 6. Labs revealed lactic acid 13.5, AKI (72/13.6 from baseline 16/0.9), K 6.3, Mg 0.7, Ca 5.8, PO4 13.1, glucose 13. UA positive for infection. TSH found to be >500.00 with free T4 <0.2. She was given stress dose steroids followed by IV levothyroxine, ceftriaxone and bicarbonate infusion. One hour after arrival, her lactate rose to 15.6 with levophed at 0.4 mcg/kg/min. At this point, metformin intoxication was suspected and intermittent hemodialysis with dialysate flow rate of 300mL/min was initiated. Both blood pH and lactate level showed dramatic improvement after 6 hours of IHD. After a 14-hour IHD session, CHD was conducted through day 2. Urine culture grew Enterococcus faecalis and Aerococcus urinae and the patient received 3 days IV ceftriaxone. Levothyroxine 200mcg daily was started and steroids were stopped with pre-treatment AM cortisol level 62.1. Temporary dialysis catheter was removed on day 5 and the patient was discharged home on day 6. She was started on Repaglinide 0.5mg TID and asked to avoid metformin for the rest of her life.

Discussion: MALA is generally treated with supportive therapy, including initiation of RRT. In our case, we initiated a prolonged course of sustained low-efficiency dialysis (SLED) followed by CHD for one additional day to prevent rebound acidosis. This case is meant to highlight the importance of the early initiation of RRT and prevention of mortality. Additionally, it is important to manage comorbid conditions, such as myxedema coma and urosepsis, which may predispose patients to acute kidney injury and development of MALA.

TH-PO177

Resolution of Intramuscular Calcifications on CT Scan Correlating with Severe Hypercalcemia in the Recovery of Rhabdomyolysis

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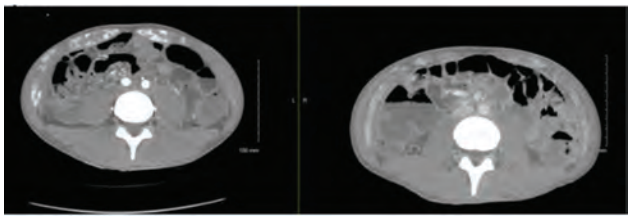
Introduction: Calcium homeostasis in rhabdomyolysis often follows a biphasic pattern of hypocalcemia during the oliguric phase followed by potentially life-threatening hypercalcemia during the non-oliguric phase. We present a case of sudden onset severe hypercalcemia corresponding with improved urine output and dissolution of intramuscular calcium deposits as identified on commuted tomography (CT).

Case Description: A 23-year-old male was admitted after drowning and subsequent cardiac arrest resulting in anuric AKI due to rhabdomyolysis. Initial lab work demonstrated

a creatinine kinase > 50,000 μ/L, hyperkalemia, hypocalcemia, and hyperphosphatemia. On the day the patient became non-oliguric his calcium began gradually rising to a peak ionized calcium of 1.91 mmol/L requiring multiple sessions of hemodialysis. Workup demonstrated depressed intact parathyroid hormone, Vitamin D 25-OH and 1-25$(OH)_2$ Vitamin D as well as ongoing hyperphosphatemia and a marginally elevated 24-hour urine calcium. Comparison of two CT scans obtained during the oligoanuric/hypocalcemic and non-oliguric/hypercalcemic phases of AKI demonstrated a clear reduction in intramuscular calcification. Calcium levels improved spontaneously after 11 days along with complete renal recovery.

Discussion: Sudden onset of severe hypercalcemia during the non-oliguric phase of AKI in the setting of rhabdomyolysis is due to mobilization of intramuscular calcium as evidenced by decreased intramuscular calcification observed on CT scan, a novel finding. Previous cases have described secondary hyperparathyroidism as the driving cause of hypercalcemia, although PTH was appropriately suppressed in this case, which is a unique finding. The temporal relationship between renal recovery and hypercalcemia could be explained by contemporaneous recovery of renal and skeletal tissue. Nephrologists must remain vigilant during the recovery phase of rhabdomyolysis and monitor for potentially life-threatening hypercalcemia.



CT abdomen on days 14 (L) and 29 (R) during the oliguric and non-oliguric phases of rhabdomyolysis induced AKI with improving intramucular calcification

TH-PO178

Survival After Severe Metformin-Associated Lactic Acidosis (MALA) with Aggressive Dialysis and Massive Bicarbonate Administration

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Introduction: MALA is a severe condition affecting fewer than 1 in 10,000 people. Mortality is often above 20%. We present a case of intentional metformin overdose surviving after combined dialysis modality use and massive parenteral sodium bicarbonate ($NaHCO_3$) administration.

Case Description: 52-year-old male with PMH: HIV on HAART, DM, HTN, Hep C and cocaine use who intentionally ingested 60g Metformin in the ED without staff knowledge. 12 hours later, patient was found lethargic with a blood glucose of <10 mg/dl. Arterial blood gas: pH 7.02, $PaCO_2$ 23.3mmHg, PaO_2 128mmHg. Serum chemistry: Na 144mmol/L, K 3.8mmol/L, Cl 98mmol/L, Cr 1.57mg/dL, HCO3 12mmol/L, ALT 64unit/L, AST 74unit/L, AG 32, lactic acid >25.0 mmol/L. Patient was intubated, hyperventilated and begun on 3 vasopressors for hypotension. No GI lavage performed. Next, simultaneously started 150meq $NaHCO_3$ infusion at 150mL/hr and intermittent HD (IHD) for 3 hours with O200, Qb 400mL/min and Qd 800mL/min, Bicarb bath: 40meq/L. He was transitioned directly onto CVVHD using Prismasate 4/2.5 with Qb 300mL/min and Qd 3L/hr, later increased to 5L/hr. The $NaHCO_3$ infusion was increased to 600mL/hr due to persistent pH <7.2. An additional 50meq of $NaHCO_3$ was added to each dialysate bag. The patient's pH remained <7.2 throughout renal replacement therapy (RRT). A Metformin level prior to any RRT was 67mcg/dL. 11.5 hours after IHD and CVVHD initiation, the Metformin level fell to 23mcg/dL. CVVHD was continued due to anuria and high fluid requirements. 24 hours after initiating RRT, pH and HCO_3 improved to 7.35 and 23mmol/L, respectively. Serum lactic acid fell from >25mmol/L to 13.7mmol/L. The patient was extubated, weaned off vasopressors and discharged after delayed renal recovery on hospital day 25 with Cr 3.41mg/dl.

Discussion: Metformin (molecular weight 129, minimal protein binding) is rapidly distributed into tissue compartments. The large volume of distribution (300-1000L) prevents complete clearance by conventional IHD resulting in prolonged toxicity. In our case, 11,780meq of $NaHCO_3$ was given IV over 24-hours. He also received additional $NaHCO_3$ from 3 hrs of IHD in a 40meq/L dialysate bath followed by CVVHD using 32meq/L bags, later increased to 42meq/L. High UF rate with RRT allowed massive delivery of IV $NaHCO_3$ in combo with dialysis for aggressive treatment of MALA.

TH-PO179

Mannitol Therapy for Choroidal Hemorrhage: A Nephrological Challenge

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Introduction: Mannitol is an osmotic diuretic that reduces intraocular pressure (IOP). Hyponatremia and acute renal failure are complications that can occur in high risk patients. We report a case of hyperosmolar hyponatremia and oliguria necessitating hemodialysis (HD) after mannitol infusion for choroidal hemorrhage.

Case Description: A 91 year old female with chronic kidney disease (CKD) stage 3 on angiotensin II receptor blocker, coronary artery disease, hypertension, and chronic hyponatremia presented to the hospital with left eye pain and redness concerning for choroidal hemorrhage after her ophthalmologist discovered elevated IOP. Laboratory testing revealed a serum sodium concentration [Na] of 128 mg/dL and a serum creatinine concentration [Cr] of 1.21 mg/dL, at her baseline. She was given 2 g/kg of 20% mannitol. Seven hours later, testing revealed serum [Na] 123 mg/dL, serum [Cr] 1.49 mg/dL, and serum osmolality gap (OG) of 19 mOsm/kg with improvement in IOP. The following morning, serum [Na] remained 123 mg/dL, serum [Cr] increased to 2.03 mg/dL with a serum OG of 19 mOsm/kg. Due to recurrent eye pain, a second dose of 2 g/kg mannitol was given. Three hours later, serum [Na] decreased to 111 mg/dL, serum [Cr] increased to 2.54 mg/dL, with a serum OG of 83 mOsm/kg and serum osmolality of 322 mg/dL. Nephrology was consulted and recommended normal saline 500 ml bolus followed by continuous infusion at 125 mL/hr. However, over the next 12 hours, urine output continued to decline with serum [Na] decreased to as low as 107 mg/dL with serum [Cr] 4.90 mg/dL. Though serum osmolality decreased to 296 mg/dL, serum OG remained 60 mOsm/kg. Given progressive oliguria, azotemia, and hyperkalemia, emergent HD was performed with repeat serum [Na] 117 mg/dL, serum OG 31 mOsm/kg, and improved urine output. After repeat HD, serum [Na] increased to 129 mg/dL with a normal OG. Oliguria resolved and mental status improved.

Discussion: Mannitol can be used to manage elevated IOP but high and frequent dosing can lead to oliguric renal failure with profound hyperosmolar hyponatremia, particularly in elderly patients with CKD. Our case highlights the importance of recognizing hyperosmolar hyponatremia as a distinct clinical entity and emphasizes reversibility of renal failure with early HD. It also raises thoughts regarding alternative therapies for elderly patients with CKD and increased IOP.

TH-PO180

A Case of Hyperosmolar Hyponatremia from Polyethylene Glycol (PEG)

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Introduction: N/A

Case Description: 69 year old man with pulmonary sarcoidosis presented to the ER with shortness of breath, diagnosed with acute pneumonia and treated with antibiotics, with gradual improvement in dyspnea. Hospital course was complicated by an ileus, for which increasing amounts of polyethylene glycol (PEG) was prescribed. On hospital day 10 the laboratory data revealed acute worsening of hyponatremia (123mmol/l), hyperkalemia (5.5mmol/l), and a mild non-oliguric AKI, prompting nephrology consultation.

Discussion: The measured serum osmolality of our patient was normal (277 mOsm/kg), and a low whole blood sodium (127mmol/L) ruled out pseudohyponatremia. The serum osmolar gap was elevated at nearly 20 mOsm/kg, indicating the presence of an unmeasured osmolyte. A negative correlation between the patient's serum sodium and potassium was observed, such that when $[Na^+]$ decreased, $[K^+]$ increased (Image 1). Searching the chart for known etiological agents that may act as an effective osmole and produce these series of events was unsuccessful. Our attention was focused on PEG, which was being administered in high doses (170 grams cumulatively) in the absence of a bowel movement. A dose-dependent temporal relationship between PEG administration and hyponatremia was observed, supporting the diagnosis of PEG-induced hyponatremia. A proposed mechanism is outlined and illustrated in Image 2. When PEG was discontinued by Nephrology, the electrolyte abnormalities corrected rapidly.

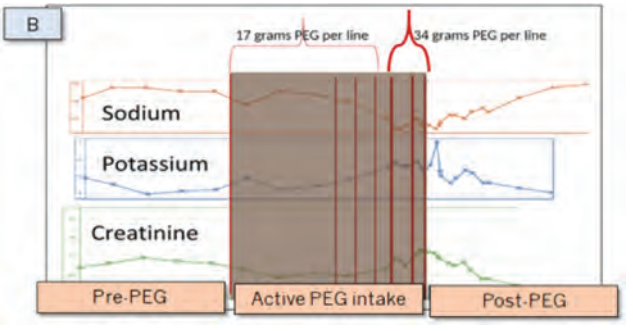
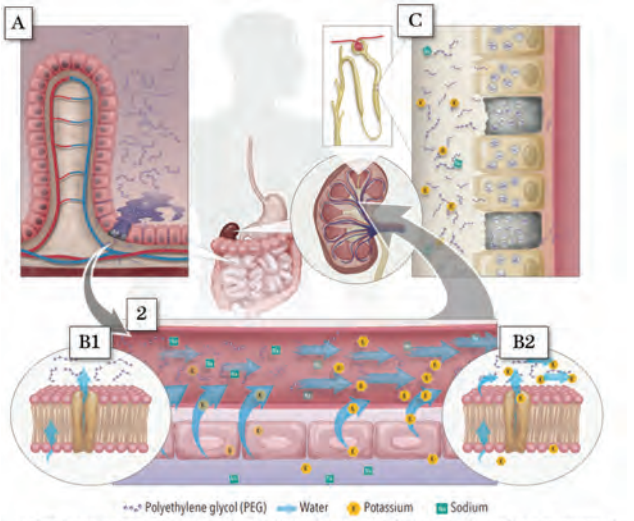


Figure 1. Lab Data relevant to PEG dosing



(A)Small intestine permeability: Ileus is a risk factor for increased PEG absorption, and due to increased contact with small intestinal mucosa and reduced function of cell-cell barriers more PEG can be absorbed..
(B1) Hyperosmolar hyponatremia: PEG exerts an osmotic force and pulls water into the intravascular compartment, causing dilutional hyponatremia
(B2) Solvent drag: Intracellular K^+ is dragged with intracellular water
(C) Osmotic nephropathy: Proximal tubular epithelial cells are unable to degrade PEG, and it builds up in intracellular lysozymes, leading to cellular death

TH-PO181

Severe Hypermagnesemia-Induced Ischemic Colitis in a Patient with AKI

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Introduction: Severe hypermagnesemia is a rare complication seen with laxative/antacid overdose, usually in patients with acute kidney injury(AKI). We present a case of marked hypermagnesemia leading to ischemic colitis with perforation, pancreatitis and multi system organ failure in a patient with AKI.

Case Description: A 54 year old female with hypertension, asthma, and chronic neurogenic bladder presented with abdominal pain and vomiting for one day. She was taking magnesium hydroxide 1200mg four times a day for constipation. She was hypotensive on arrival with blood pressure of 70/50mmHg. Labs were remarkable for AKI with serum creatinine of 6.8mg/dL (baseline 0.9mg/dL) and severe hypermagnesemia (>10mg/dL, baseline of 2.2mg/dL about one month ago). Other significant lab findings were microangiopathic hemolytic anemia (MAHA) and lactic acidosis. She was intubated, started on vasopressors and admitted to the intensive care unit. CT abdomen revealed free air suggestive of perforation, reactive pancreatitis and ischemic colitis. Emergent exploratory laparotomy was performed which showed cecal ischemia. She also received plasma exchange for for MAHA which was stopped after three treatments given normal ADAMTS13 activity. Continuous renal replacement therapy (CRRT) was started for hypermagnesemia and oliguria. Her renal function and hypermagnesemia improved and she was weaned off CRRT. The etiology of AKI was presumed to be multifactorial in the setting of obstructive uropathy from neurogenic bladder, acute tubular necrosis from hypotension and thrombotic microangiopathy. Severe hypermagnesemia was attributed to high dose oral magnesium supplementation in the setting of AKI. She showed significant improvement in her follow up labs in renal clinic two months later with magnesium level of 2.2mg/dL and serum creatinine of 0.9mg/dL.

Discussion: Hypermagnesemia is known to induce hypomotility of gut leading to ileus, colitis, intestinal perforation and toxic megacolon, especially in the setting of AKI. Our patient developed severe refractory hypermagnesemia requiring CRRT complicated by ischemic colitis, bowel perforation and reactive pancreatitis. High index of suspicion for these bowel complications is warranted if patients present with hypermagnesemia and abdominal symptoms.

TH-PO182

Noninvasive Left Ventricular End-Diastolic Pressure (LVEDP): A Novel Volume Assessment Tool

Eric Jia Yi Xu,[1] Harry A. Silber,[1] Surekha U. Mullangi,[1] Seungyoung Hwang,[1] Luis F. Gimenez,[1] Bernard G. Jaar,[1] Tariq Shafi.[2,1] [1]*Johns Hopkins University, Baltimore, MD;* [2]*University of Mississippi Medical Center, Jackson, MS.*

Background: Objective assessment of volume is a major barrier to improving volume management in dialysis patients. The Valsalva maneuver is a well-recognized bedside marker of central volume overload. We tested a novel non-invasive handheld device that combines Valsalva maneuver with finger photoplethysmography to reliably estimate LVEDP. The goal of our pilot study was to determine the associations of non-invasive LVEDP measurements with common volume-related hemodialysis parameters.

Methods: We assessed predialysis LVEDP in 67 patients undergoing maintenance hemodialysis at two dialysis units in Baltimore. Patients also underwent extracellular water measurement by bioimpedance (BIA), in addition to routine dialysis parameters. We assessed the association of these parameters with changes in systolic blood pressure during dialysis.

Results: Mean age of the participants was 57 years, 63% were male, and 76% black. Predialysis LVEDP was 16 ± 6 mm Hg (normal: <12 mm Hg) with a range of 5 mm Hg to 33 mm Hg. Among the parameters assessed, only LVEDP was associated with a significant fall in systolic blood pressure (SBP) during dialysis (Table). However, LVEDP was not associated with any of the commonly used definitions of intradialytic hypotension. R^2 was 47% for a model of change in SBP that included predialysis SBP, LVEDP, interdialytic weight gain (IDWG), extracellular water, ultrafiltration (UF) volume, UF rate, and treatment time, suggesting that >50% of the variability in the change in SBP during dialysis remains unaccounted for by these variables.

Conclusions: Non-invasive LVEDP is a novel parameter that can provide additional information to guide volume assessment in hemodialysis patients. However, 50% of the variability in the change in SBP remained unexplained, pointing to the need to fully understand the pathophysiology of fall in SBP during hemodialysis.

Funding: NIDDK Support

Predictors of change in SBP (adjusted for age, sex, and race)

Predictor	Mean ± SD	Change in SBP (Post – Pre) per 1 SD decrease in predictor [SE]	p
LVEDP, mmHg	**16.1 ± 5.6**	**-5.4 [2.6]**	**0.04**
IDWG, kg	2.0 ± 1.3	-2.2 [3.3]	0.52
Extracellular water by BIA, L	20.3 ± 7.2	-1.3 [3.3]	0.70
Ultrafiltration (UF) volume, L	2.4 ± 1.4	0.3 [3.0]	0.93
UF rate, mL/hr/kg	7.9 ± 4.8	-2.3 [2.8]	0.41

SD, standard deviation; SE, standard error

TH-PO183

Fluid Volume Overload and Vascular Stiffness in Hemodialysis Patients

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Background: Fluid overload (FO) and vascular stiffness are prominent features of end-stage renal disease patients. Although both are risk factors for cardiovascular events, the relationship between these two factors has not yet been fully elucidated. We hypothesized that FO is associated with high vascular stiffness which can only be partly corrected by ultrafiltration (UF) of fluid during the hemodialysis (HD). We aimed to determine whether vascular stiffness is higher in fluid overloaded (FO) vs. non-fluid overloaded (non-FO) HD patients. Also, we investigated the effect of fluid removal on vascular stiffness of a single HD run.

Methods: Fluid status and arterial stiffness were tested in 20 FO and 19 non-FO HD patients. 26 healthy subjects were evaluated as controls. Fluid status was assessed by bioimpedance spectroscopy device. Pulse wave velocity (PWV) and augmentation index (AIx), as markers of vascular stiffness, were measured using Arteriograph24™. The PWV and AIx were performed for 5 hours, starting 30 minutes before and ending 30 minutes after the HD run. All measurements were done during the mid-week HD session. In healthy controls, 5-hour measurement of PWV and AIx was performed as time control. HD subjects were divided into three tertiles according to the baseline PWV measurement.

Results: The median age of HD patients was 60 (29-56) and 49 (29-56) years in healthy subjects. Fluid status in healthy controls, FO and non-FO HD patients was 0.05 (-0.6-0.5), 2.9 (1.7-5.2), and 0.3 (-0.3-0.6), respectively. As anticipated, PWV and AIx were higher in HD patients vs. healthy controls. FO was not associated with a higher PWV (m/s) in FO 10.0 (9.2-11.1) vs non-FO 10.0 (8.8-11.4) HD groups. A significant positive linear relationship was observed between dialysis UF (L) and intradialytic PWV changes in the upper-tertile group (r^2= 0.223; P<0.05). The latter group showed significant changes in AIx (%) -20.0±55.5 compared to the lower-tertile 15.7±27.1 (P<0.05).

Conclusions: The PWV and AIx were higher in HD patients compared to healthy subjects. Surprisingly, there was no difference in PWV/AIx between the two HD groups. Dialysis treatment appears to be a detrimental factor in improving the vascular status of patients with higher PWV and/ or AIx. However, an additional interventional study would be needed to further delineate the relationship between fluid status and arterial stiffness.

TH-PO184

Calculation of Extracellular Fluid Volume from Regular Blood Test Results of Patients Undergoing Hemodialysis

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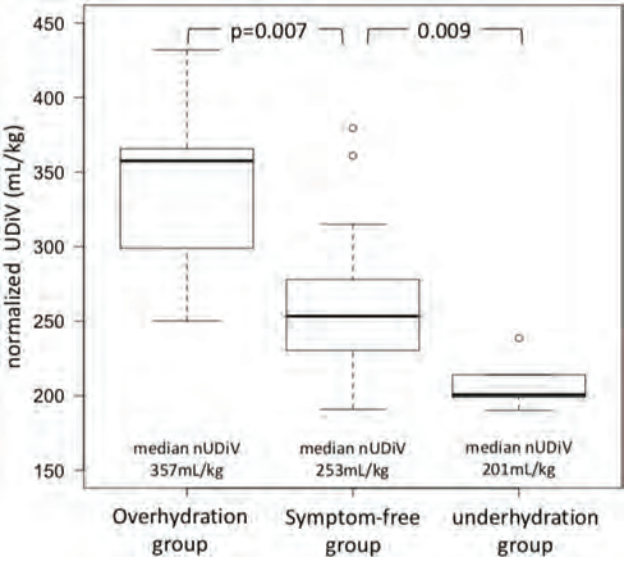
Background: Uric acid (UA) is a solute that cannot cross cell membranes in the general tissues via simple diffusion, facilitated diffusion, or active transport, indicating that the UA distribution volume (UDiV) is equal to the extracellular fluid volume (ECFV). At ASN 2018, we reported that UDiV is closely correlated with ECFV predicted using

the bioimpedance method (BIA-ECFV); however, whether UDiV is a useful tool for distinguishing different hydration statuses remains unclear.

Methods: We compared UDiV calculated from regular blood test results with BIA-ECFV of 53 patients undergoing hemodialysis (HD) predicted using BCM (Fresenius Medical Care). Further, we compared UDiV normalized with the post-HD body weight (nUDiV) in nine patients with pedal edema (overhydrated patients), five with intradialytic hypotension (underhydrated patients), and 24 without any clinical symptoms relating to hydration status (symptom-free patients).

Results: We observed a significant correlation between UDiV (x) and BIA-ECFV (y) ($y = 0.69\mathbf{x} + 3.25$; *r-square* = 0.61; $p < 0.0001$). The regression line substantially coincided with the line of identity. Bland-Altman analysis showed a systematic error for UDiV versus BIA-ECFV. In addition, we found a significant difference between UDiV and BIA-ECFV (mean difference = 0.94 L; 95% CI = 0.37-1.52 L). As shown in the figure, the nUDiV could help distinguish different hydration statuses.

Conclusions: UDiV is a plausible alternative marker of BIA-ECFV for the assessment of the hydration statuses of HD patients.



nUDiV and hydration statuses

TH-PO185

Overhydration Is an Independent Risk Factor for Postdialysis Hypertension and Predicts Mortality in Hemodialysis Patients

Hae Yeul Park,[1] Kwon soo Jung,[1] Moon hyoung Lee,[1] Hoon Young Choi,[1] Hyunwook Kim,[1] Jung eun Lee,[3] Hyung Jong Kim,[2] Hyeong cheon Park.[1] *[1]Gangnam Severance Hospital, Seoul, Republic of Korea; [2]Bundang CHA Medical Center, CHA University, Seongnam, Gyeonggi-do, Republic of Korea; [3]Yongin Severance Hospital, Gyeonggi-do, Republic of Korea.*

Background: Accurate volume assessment is important for hemodialysis (HD) patients because chronic fluid overload leads to increased cardiovascular morbidity and mortality. Postdialysis hypertension (PDHYPER) has been reported to occur commonly in HD sessions but the cause of PDHYPER remains to be determined. Our aim was to ascertain the association between volume status and PDHYPER and the influence of PDHYPER on mortality in HD patients.

Methods: A cross-sectional multi-center study enrolled clinically stable HD patients. All patients underwent a bioimpedance analysis (BIA) after a midweek HD session to assess volume status. PDHYPER was defined as an increase in systolic blood pressure (SBP) of 10mmHg or more after dialysis. Delta SBP was calculated by SBP difference between before and after HD.

Results: A total of 254 prevalent HD patients (158 men and 96 women) with a mean age of 59.0±12.8 years were included in this study. Patients were divided into 2 groups according to the SBP change after dialysis: the hypertensive group (29.1%), and the non-hypertensive group (70.9%), those with less than 10mmHg or no increase in SBP. The hypertensive group showed older age (64.3±11.9 vs 56.8±12.6, p<0.001), more use of diuretics (45.9% vs 29.4%, p=0.016), higher ECW(Extracellular water)/TBW(Total body water) (0.400±0.014 vs 0.389±0.015, p<0.001), lower phase angle (4.4±1.6 vs 5.3±1.4, p<0.001), higher BNP (1034.1±1122.4 vs 519.0±758.7, p=0.029), and lower albumin (3.77±0.42 vs 3.97±0.34, p=0.01) than non-hypertensive group. In Pearson correlation, delta SBP showed a significantly positive correlation with ECW/TBW (r=+0.334, p<0.001). In multiple logistic regression analysis, ECW/TBW was the only independent risk factor affecting PDHYPER. Ultrafiltration volume, however, was not significantly associated with PDHYPER. PDHYPER was also associated with 4-year all cause mortality (30.2% vs 15.9%, p=0.017).

Conclusions: Our data demonstrated that increased ECW/TBW is a potential risk factor of PDHYPER and such PDHYPER independently predicts 4-year all cause mortality in HD patients. HD patients who experience frequent increase in postdialysis SBP should be reassessed for their volume status and target dry weights, with emphasis on increased the ECW/TBW ratio.

TH-PO186

Thoracic Electrical Bioimpedance Measurement in Monitoring Cardiac Index and Thoracic Fluid Content During Hemodialysis

Jining Wu, Zhuo Xu, Hong Ye, Junwei Yang. *Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: Hemodynamic stress during hemodialysis (HD) results in recurrent segmental ischemic injury that drives cumulative cardiac damage. Thoracic electrical bioimpedance (TEB) has been shown to provide accurate, noninvasive, continuous, measurements of cardiac index (CI) and thoracic fluid content (TFC). We performed this study to evaluate the changes in TFC in comparison with fluid removal (FR) and to understand the trends in CI changes in HD patients.

Methods: In this observational study, we enrolled 114 patients from a single hemodialysis unit. Minute-by-minute changes in TFC and CI were collected using the TEB (BioZ) in HD patients. Change in body weight (DW) and amount of FR were measured.

Results: The TFC decreased in all patients by an average of 4.6±2.4 1/kΩ, weight decreased by 2.05±1.12kg, and FR averaged 2.5±0.98 L in HD session. There were good correlations between change in TFC and DW (R=0.74, P<0.001) and FR (R=0.82, P<0.001). A 1/kΩ change of TFC correlates with an 150mL change in total body water. The change in CI (-0.42 ±0.51L/min/m^2) during HD did not correlate with FR (R=0.14, P=NS). Changes in TFC represented the monitored variable most closely related to FR. Interestingly, during the first 5 mins of HD, CI and stroke volume index reduced obviously compared to the base lever before dialysis.

Conclusions: It suggested that thoracic electrical bioimpedance could monitor the acute cardiac effects of dialysis during hemodialysis treatment.

Funding: Government Support - Non-U.S.

TH-PO187

Change in Extracellular Fluid Volume (ECV) Calculated with a Plasma Uric-Acid Kinetic Model May Reflect True ECV Better Than That with Body Weight in Hemodialysis Patients

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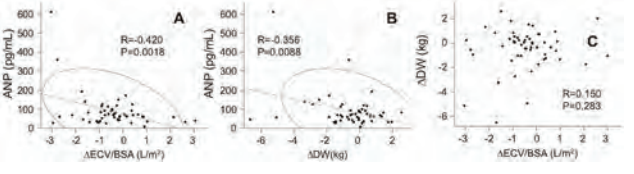
Background: In Kidney Week 2018 (SA-PO-867 and 868), we reported a novel method to calculate extra-cellular fluid volume (ECV) of hemodialysis (HD) patients, which is based on a kinetic model of plasma uric acid (UA) concentration. In this study, we compared annual change of clinically adjusted dry weight (DW) with that of ECV calculated by our method.

Methods: Among 79 Japanese HD outpatients who were enrolled in the previous study, 53 patients maintaining stable blood flow and ultrafiltration rates on the days of blood sampling both at April 2018 and at April 2019 were included in this analysis (64.8 ± 10.5 y, male 69.8%). They had no cardiac event at least for two years. DW of each patient had been adjusted throughout the period by a nephrologist-in-charge using cardio-thorax ratio and blood pressure. ECV values at post-HD were calculated by our method and were standardized by the body surface area (BSA). Demographic and biochemical data used below were obtained at April 2018. An annual increment is designated as Δ.

Results: DW and ECV/BSA values decreased during the period (-0.51 ± 1.71 kg and -0.42 ± 1.22 L/m^2, paired Wilcoxon P=0.0377 and 0.0078, respectively). Both were not associated with age, sex, total protein, albumin, creatinine, corrected-calcium, phosphate, urea nitrogen, hemoglobin, nPCR, and diabetic history. ΔECV/BSA was not associated with ΔDW at all (R=0.141, P=0.3133) (**Fig**). ΔECV/BSA correlated positively with dialysis vintage (R=0.307, P=0.0251) and negatively with Δalbumin (R=-0.402, P=0.0029), but ΔDW did not. ΔECV/BSA showed better correlation with plasma atrial natriuretic peptide concentration measured in 2018 (R= -0.420, P= 0.0018) than ΔDW (R=-0.356, P=0.0088) (**Fig**).

Conclusions: ΔECV, which is calculated with our plasma UA kinetic model, was consistent with clinical data better than ΔDW. Our results suggest that ΔECV/BSA rather than ΔDW reflects true change of ECV in HD patients.

Funding: Clinical Revenue Support



Although ΔECV/BSA (***A***) and ΔDW (***B***) from April 2018 to April 2019 negatively correlated with plasma ANP concentration measured at April 2018, both did not correlate with each other (***C***).

TH-PO188

Oxidative Stress Is Associated with Overhydration and Sarcopenia in Hemodialysis Patients

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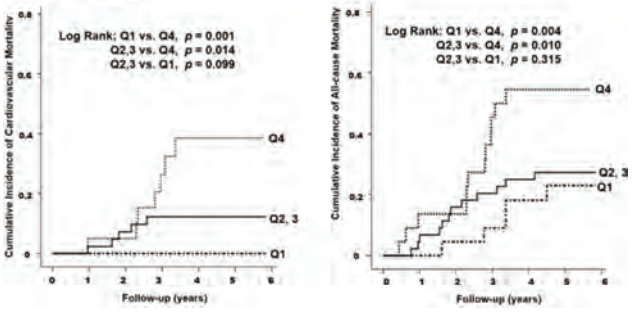
Background: Increased oxidative stress is regarded as an important nontraditional risk factor in patients undergoing hemodialysis (HD). However, studies examining the long-term effect of oxidative stress by direct measurement of these markers and its association with volume status and sarcopenia are limited.

Methods: In this longitudinal observational study, serum protein carbonyl levels were measured in 88 stable HD patients. Additionally, multifrequency body composition analysis and handgrip strength (HGS) and nutritional assessments were performed and followed prospectively for up to 6 years.

Results: The mean patient age was 60.6 ± 13.5 years, and the mean HD duration was 50.8 ± 41.3 months. In total, 16 patients (18.2%) were overhydrated, 49 (55.7%) had low HGS and 36 (40.9%) had low muscle mass. Serum protein carbonyl levels were associated with serum levels of albumin, prealbumin and transferrin, hydration status and low HGS. Overhydration, prealbumin, subjective global assessment score and sarcopenia were significant predictors for serum protein carbonyl levels in the highest quartile. Multivariate analysis showed that the serum levels of protein carbonyl, albumin, prealbumin, overhydration and sarcopenia were independent determinants of all-cause and cardiovascular mortality. (Figure 1.)

Conclusions: Serum protein carbonyl was significantly associated with overhydration, nutritional status and sarcopenia and could be an important predictor of long-term outcomes in patients undergoing HD

Figure 1. Cumulative incidence of Cardiovascular mortality and All-cause mortality according to quartile of serum protein carbonyl



TH-PO189

The Role of sCD146 in Assessing Hydration State of Hemodialysis Patients

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Background: sCD146 is a marker of endothelial cell injury and also a biomarker of systemic circulation congestion. There is no study on the relationship between sCD146 and water load hydration state in dialysis patients in Chinese dialysis patients. We will study the role of sCD146 and NT-proBNP in assessing hydration state in hemodialysis patients.

Methods: The maintenance hemodialysis patients of the First Affiliated Hospital of Zhengzhou University from September 2018 to January 2019 were screened. And 10 healthy people were enrolled to measure the level of sCD146 as control. Clinical data were collecting, including sex, age, height, type of dialysis pathway, systolic blood pressure (sBP), hemoglobin (Hb), serum albumin (Alb), blood urea nitrogen (blood Urea Nitrogen, BUN), uric acid (UA), creatinine (Serum Creatinine), total cholesterol (TC) were collected. Triglycerid (TG), potassium, phosphorus, dialysis effectiveness index Kt/V, parathyroid Hormone (PTH). The blood was taken in the morning to measure the concentration of sCD146. Body weight was measured before and after dialysis on dialysis day, and bioelectrical impedance was measured by Xitro4200 bioelectrical impedance meter. Total body water (TBW), Extracellular Fluid Volume (ECV) and excess water (M_{EXF}) were calculated. Ultrafiltration volume was recorded.

Results: Compared with 10 healthy controls, plasma sCD146 levels in hemodialysis patients increased before and after dialysis (275.58 [209.00, 370.80] VS. 187.03 [152.01, 214.09] ng/ml, P < 0.05), (233.00 [172.50, 442.59] VS. 187.03 [152.01, 214.09] ng/ml, P < 0.05). Pearson or Spearman correlation analysis showed that sCD146 before dialysis was positively correlated with M_{EXF} (r = 0.400, P < 0.05) before dialysis, negatively correlated with age (r = 0.394, P < 0.05), but not with pre-dialysis body weight (r = 0.030, P = 0.872), blood pressure (r =-0.085, P = 0.646), ECV/TBW (r = 0.269, P = 0.136).

Conclusions: sCD146 may be a new biomarker for the overhydration state in hemodialysis patients.

Funding: Government Support - Non-U.S.

TH-PO190

Relationship Between Interdialytic Weight Gain and Change in Whole Body Extracellular Resistance

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Background: Estimation of interdialytic fluid gain is essential to determine ultrafiltration volume (UFV) in routine hemodialysis (HD). The aim of this study was to evaluate the relation between interdialytic changes in whole body extracellular resistance (Re) and interdialytic weight gain (WG) to facilitate prescription of ultrafiltration volumes (UFV) and rate (UFR).

Methods: Ambulant patients were studied at ≥4 successive HD sessions. Whole body and calf bioimpedance were measured pre- and post-HD to obtain whole body extracellular resistance (Re) and calf normalized resistivity (CNR). Interdialytic weight change (ΔWt), change in Re (ΔRe), and CNR (ΔCNR) between pre- and post-HD (calculated as pre-HD minus post-HD of the preceding HD session), UFV, and UFR were recorded per HD session. Simple and multiple regression analysis were used to determine the relationship between ΔWt and ΔRe.

Results: Thirty-eight patients (age 54.3±14 years, 17 females, BMI 26.4±7.4 kg/m^2) were studied. We collected 387 measurements (10.2±6 per patient; table 1). UFV and UFR were 2.98±0.9 L and 0.78±0.24 L/h, respectively. ΔWt correlated inversely with ΔRe (average R^2=0.71; range 0.44 to 0.91) with a slope of -53.3 (range -182 to -18) kg/Ω and an intercept of -12.9 (range -110 to 99) kg. As an example, Fig 1 and 2 show the relationship between ΔRe to ΔWt and to ΔECV in the same patient. Multiple regression analysis indicated that the slope was determined by UFR (p<0.01) and pre-HD CNR (p<0.05).

Conclusions: This study demonstrates that interdialytic weight gain can be predicted in individuals by whole body extracellular resistance. This method may be useful in patients who cannot be weighed. Using ΔRe to predict fluid gain is based on the high correlation between extracellular resistance and extracellular volume. Once corroborated in an elderly, non-ambulant population, this method may provide guidance for UFV prescription, a problem encountered occasionally in patients undergoing dialysis at home or – more frequently - in nursing homes.

Table 1

	ΔWt kg	ΔECV L	ΔRe Ω	ΔCNR 10^{-2}Ωm^3/kg
Mean±SD	2.54±1.0	2.27±1.0	-131±72	-3.4±1.7
95% CI	2.2; 2.9	1.9; 2.6	-154; -107	-4.0; -2.8

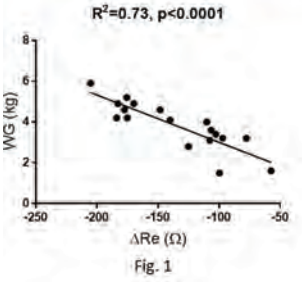

Fig. 1

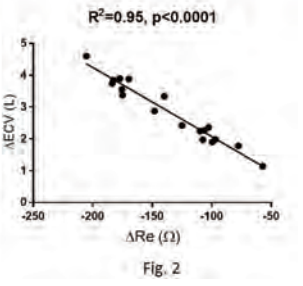

Fig. 2

TH-PO191

Lung Ultrasound for Fluid Status Assessment in Dialysis Patients: An Option to Consider

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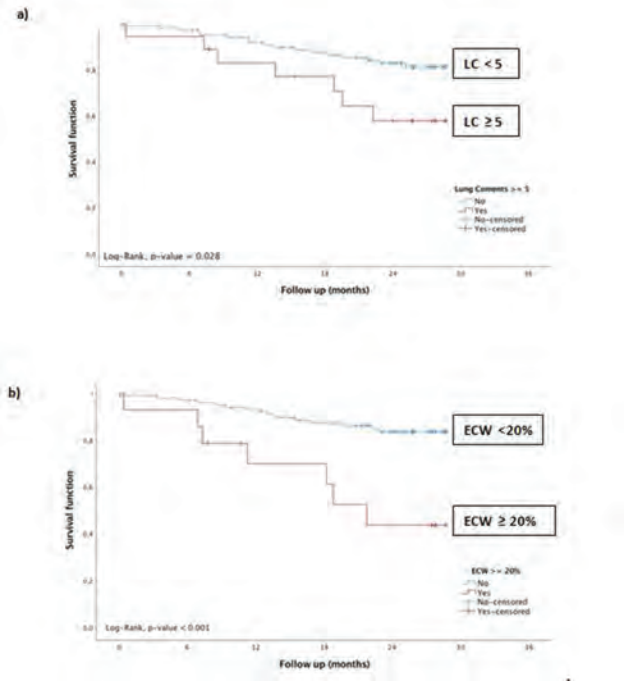
Background: Lung ultrasound (LUS) has been postulated as a possible tool to evaluate fluid status in dialysis. Objective:To verify if lung comets determination (LC), in comparison with Spectroscopic Bioimpedance-BCM and Blood volume monitoring-BVM could be a practical instrument for daily fluid status evaluation and its relationship with cardiovascular events and mortality

Methods: Two-year prospective follow-up study in 120 patients (84% hemodialysis, 16% peritoneal dialysis) 61.7±5.6 years. Two measurements were taken at the start of intermediate dialysis session: BCM to evaluate extracellular water excess(ECW%) and lung ultrasound (Philips CX50®, convex probe) to detect LC. BVM data and blood samples were also collected and an echocardiogram performed. Follow-up until death was also censored if patients moved dialysis center or received kidney transplant

Results: LC average was 3±1.3. Two groups were established according to LC number. Patients with ≥5 LC were mainly men (61.1%), younger (57.8±9.3 years), diabetic (89%), with higher CRP (1.75±1.3 mg/dL) and higher pulmonary arterial pressure (PSAP) estimated by echocardiography (37.9±2.4 mmHg) and more overhydrated by BCM(p <0.009). No differences observed in BVM. During the follow-up, 8 patients presented non-fatal cardiovascular events and 21 died. Mild pulmonary congestion (LC≥5)(p <0.028) and ECW≥20%(p <0.001) were associated with higher mortality risk (Figure 1), but not with a cardiovascular event.

Conclusions: Strengthen nephrologists' lung ultrasound skills could be appropriate for optimizing fluid status in patients with high PSAP in those departments with US device and the right probe available, since its predictive mortality value has been demonstrated even in patients with a low LC number.

Figure1. Kaplan-Meier analysis for all causes of mortality according to LC number (a) and ECW% (b)



TH-PO192

Lung Ultrasound: A New Technique for Fluid Status Assessment in an Asian Haemodialysis Cohort

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Background: Studies in non-Asian haemodialysis (HD) cohorts have shown that lung congestion is an insidious problem with negative impact on cardiovascular outcomes. However, assessment of extravascular lung water (EVLW) clinically is difficult. Markers such as plasma N-terminal pro-B-type natriuretic peptide (NT-pro BNP) and bioimpedance analysis (BIA) have uncertain correlations with EVLW. In recent years, point-of-care lung ultrasound (POCLUS) has emerged as a new technique to assess EVLW. However, there is a dearth of Asian studies. We compared the performance of a 28-point POCLUS protocol against clinical examination, NT-pro BNP and BIA in an Asian HD cohort.

Methods: We performed a prospective observational study of 20 HD patients undergoing dialysis at our institution. Patients were assessed pre- and post-HD using a 28-point POCLUS protocol, with physical examination for lung crepitations and pedal oedema, and with plasma NT-pro BNP and BIA. BIA was performed using the Bodystat Quadscan 4000 (BQ4000). Patients with active cardiac disease (angina and recent myocardial infarction in last 6 months), lung pathology (infection, interstitial lung disease or malignancy), cardiac devices and limb amputations were excluded.

Results: Pre-HD, 18 (90%) of the patients had moderate fluid overload, defined as ≥15 B-lines. However, 4 (22%) of this cohort had neither lung crepitations nor pedal oedema detected clinically. Pre-HD B-line score was positively correlated with pre-HD NT-pro BNP (rho=0.654, p=0.006), but not with pre-HD positive hydration status by BIA (p=0.051). B-line score significantly decreased post-HD (pre-HD 51.7 ± 32.5 to post-HD 24.9 ± 26.4, p<0.001). Reduction in B-lines from pre- to post-HD was associated with a corresponding reduction in NT-pro BNP (rho = 0.994, p<0.001). Post-HD, 2 out of 7 of patients who achieved weights within 0.5kg of dry weight still had ≥15 B-lines on POCLUS. Both patients did not manifest lung crepitations or pedal oedema post-HD.

Conclusions: In this cohort of patients, POCLUS showed good correlation with NT-pro BNP, but not with BIA. It also demonstrated significant promise in recognising asymptomatic pulmonary congestion. Further longitudinal studies are required to investigate for potential benefits of POCLUS in volume management of HD patients.

TH-PO193

Lung Ultrasonography in the Assessment of Volume Overload: An Extra Tool to Improve Patient Care and Clinical Skills in Nephrology Fellows

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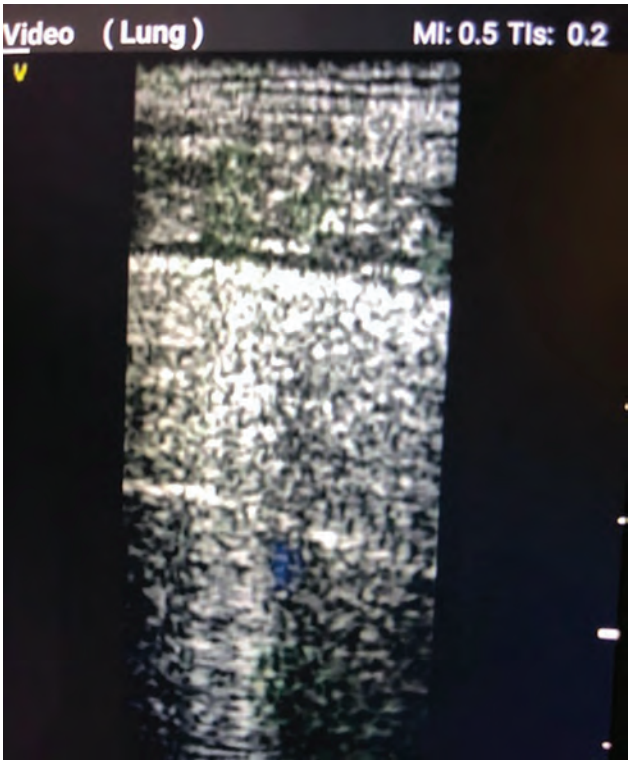
Background: Estimating euvolemia in patients with end stage renal disease (ESRD) is critical in their management. Nephrologists use their clinical judgment and skills to estimate the volume status. Lung ultrasonography (LU) is a tool that allows clinicians to have an objective evaluation of volume status. B-lines on lung ultrasound have been validated as a sign of pulmonary congestion and volume overload. This study evaluates the use of LU in the clinical assessment of volume status in the patient that is admitted to the hospital with ESRD.

Methods: Twenty patients with ESRD, admitted with volume overload were evaluated on admission with LU. Physical exam on all the patients didn't show physical signs of volume overload, on 9 patients the chest X-ray was clear, on 8 patients the CXR showed signs of congestion and on 3 patients the CXR showed mild-moderate pulmonary edema. A LU using a GE VScan portable ultrasound was done on all the patients.

Results: B-lines were found in the 20 patients, LU was suggestive of volume overload (B-lines present). Hemodialysis/Ultrafiltration was provided for all the patients, 10 patients needed extra ultrafiltration sessions in the following days for a complete resolution of the B-lines which was evidenced with subsequent use of LU.

Conclusions: LU guided fluid management protocol improves the clinical evaluation in ESRD patients. Clinical judgment and integrated lung ultrasonography for management of volume in hemodialysis patients improves outcomes and facilities the clinical management of hypervolemia. LU is an objective tool to assess volume overload in this patient population.



TH-PO194

Seeing the Volume for the Bs: Longitudinal Variation in Ultrasound-Guided Volume Assessment in Hemodialysis Patients

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Background: Ultrasound (US) studies in hemodialysis (HD) patients have demonstrated improvements in lung water from the beginning to the completion of HD. These studies, however, have focused primarily on the pre-, intra-, and immediate post-dialytic periods. There are no published studies examining how fluid shifts between the intravascular and interstitial compartments in the post-dialysis period. This study aimed to characterize this phenomenon.

Methods: In this single-center, prospective observational study, patients with acute kidney injury and end-stage renal disease receiving HD in an inpatient HD unit at an urban academic medical center were recruited to receive three US volume assessments: first within two hours before HD, second within an hour following HD conclusion, and third four hours

after HD conclusion. US volume assessment consisted of assessment of inferior vena cava (IVC) variability and 28-point lung ultrasound (LUS) with B-line scoring per zone (BLZ).

Results: In a preliminary analysis, IVC variability increased a mean of 21.1% in three of the four subjects (range 29.9 to 23.2%) between the pre-HD and post-HD period. At the extended post-HD period, the same three subjects demonstrated a mean decrease in IVC variability of 19.1% (range 10.9 to 23.2%), whereas a fourth subject experienced an increase in IVC variability of 19.9%. The BLZ results were mixed, without clear signal across the four patients.

Conclusions: In preliminary analysis, IVC variability appeared to decrease in the extended post-HD period compared to the immediate post-HD period. BLZ did not show a signal for increase or decrease in the same period. The study is continuing to recruit patients for further analysis.

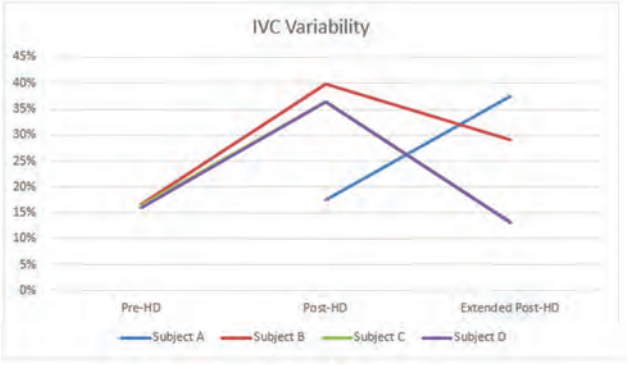

Fig. 1: IVC variability among study subjects against time.

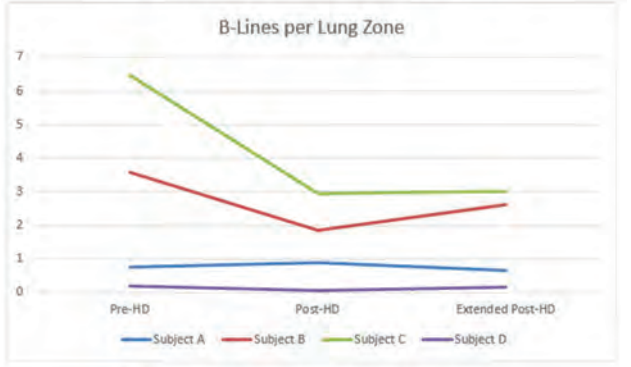

Fig. 2: B-lines per lung zone among subjects against time.

TH-PO195

Unilateral Pulmonary Edema in Dialysis Patients

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Introduction: Unilateral pulmonary edema (UPE) usually affects right upper lobe & is seen in less than 2% cases of cardiac failure. Severe mitral regurgitation (MR) is the commonest underlying cause. We report 4 cases of UPE in Hemo dialysis (HD) patients which resolved following dialysis.

Case Description: Four cases of Diabetic Nephropathy on MHD, presented with breathlessness. There was no preceding H/O chest pain/fever/hemoptysis. ECHO showed moderate MR in 2, mild & severe MR in one each. All had hypoalbuminemia (2.8-3.6 gm/dl). In view of Unilateral opacities on chest X-ray (Fig 1-4), patients were started on broad spectrum antibiotics. Following dialysis surprisingly there was clearance of opactites in all of them.(Fig 5-8)

Discussion: UPE is a rare manifestation of cardiogenic pulmonary edema. Severe MR associated regurgitant blood in right pulmonary vein, poor lymphatic drainage of the right lung & hypoalbuminemia are the main contributing factors. Our cases show that UPE can affect any zone of right lung. We feel that, in fluid overloaded dialysis patients even mild/moderate MR is enough to cause UPE of any zone. High index of suspicion for UPE and impressive clinical response following dialysis warrants repeat chest skiagram. Clearance on X-ray gives diagnosis avoids antibiotic therapy.

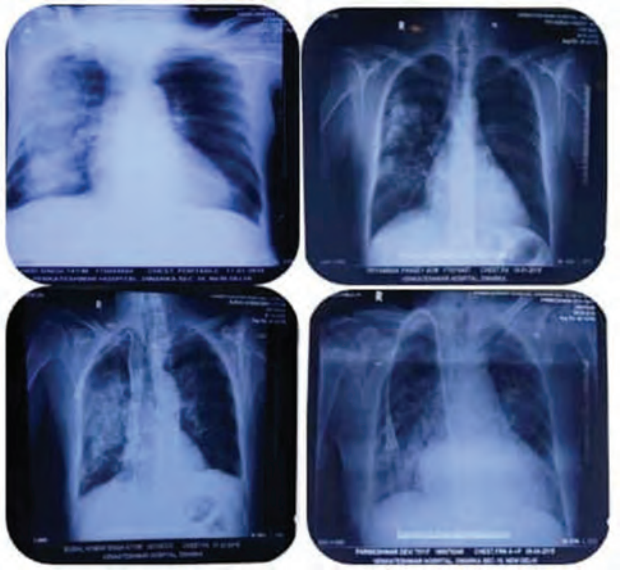

FIG 1-4 (X-ray at presentation of 4 cases)

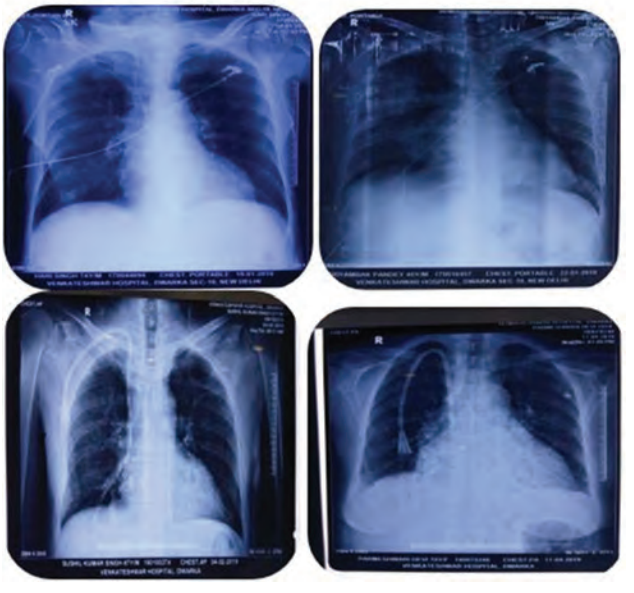

FIG 5-8 (Post dialysis X-rays)

TH-PO196

Lung Ventilation Abnormalities in Chronic Hemodialysis Patients with Hyperpolarized ^{129}Xe Gas Magnetic Resonance Imaging

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Background: Shortness of breath is common among chronic HD patients, usually attributed to congestive heart failure and volume overload. However, it may be the hallmark of an underlying lung airway disease, such as asthma or COPD, which are often undiagnosed and there may be unique pathomechanisms in dialysis patients (e.g. salt loading). In this study, we used inhaled hyperpolarized xenon-129 (^{129}Xe) gas magnetic resonance imaging (MRI) to directly measure lung ventilation abnormalities in prevalent HD patients.

Methods: Ten chronic HD patients underwent ^{1}H and ^{129}Xe lung MRI on a non-HD day. ^{129}Xe MRI was acquired during breath-hold at end-inspiration, after inhalation of a fixed volume of hyperpolarized ^{129}Xe, and co-registered with proton images with matching lung volumes. Patients were scanned before and after administration of salbutamol to evaluate reversibility. Static ventilation ^{129}Xe images were analyzed with a semiautomated software pipeline implemented in Matlab (2018b; Mathworks, Natwick MA) to calculate the ventilation defect percent (VDP).

Results: In the study sample, three main ventilation patterns were identified: Normal, Single Defect, Multiple Defects (Figure 1A). Partial ventilation improvement after salbutamol administration was also observed (Figure 1B).

Conclusions: Underlying lung airway diseases as detected by ^{129}Xe lung MRI are common and may help explain the pathophysiology of shortness of breath in prevalent HD patients.

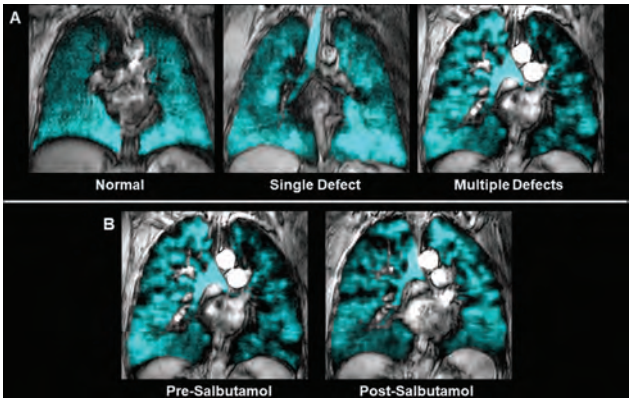

Figure 1. (A) ^{129}Xe MRI ventilation images showing three ventilation patterns: Normal, Single Defect and Multiple Defects. (B) ^{129}Xe MRI ventilation images showing partial improvement after salbutamol administration.

TH-PO197

Changes in Ultrafiltration Rate (UFR) with Relative Blood Volume Monitoring (RBV-M)

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Background: High UFRs during hemodialysis (HD) have been linked to increased risk of mortality, and avoidance of UFR ≥13 ml/hr/kg has been advised. However, limiting UFR may lead to volume overload. We examined the changes in UFR and related parameters among patients who were part of a one-year fluid management QI project with RBV-M at 20 Renal Research Institute clinics.

Methods: Patients included in the analysis were receiving HD at Baseline (BL; month before QI project) and at Month 12 of the QI project (M12). Crit-Line monitor (CLM-III, CLM-IV, or CLiC) was used to monitor relative blood volume during the QI project. All available data on ultrafiltration volume (UFV), HD treatment duration (TD), UFR, interdialytic wt gain (IDWG), and post-HD body weight (wt) were averaged monthly for each patient. Paired t-tests and McNemar's tests were used to test for differences between BL and QI month 12 (M12).

Results: Treatment parameters at BL and M12 stratified by BL UFR are shown in Table. Pts with UFR<10 ml/kg/h experienced an increase in UFR by M12 (0.43 ml/kg/h) along with decreases in Post-HD wt of -1.1 kg and -1.0 kg in pre-HD wt. Pts with UFR>13 ml/kg/h experienced an average decrease in UFR of -2.34 ml/kg/h accompanied by a decrease in IDWG with no change in post-HD wt or TD. A similar, but less pronounced, pattern was observed for pts with UFR 10-13 ml/kg/h.

Conclusions: During a one-year fluid management QI project utilizing RBV-M, pts with UFR<10 ml/kg/h at baseline experienced an increase in UFR with a decrease in post-HD wt. Patients with UFR>10 ml/kg/h at baseline experienced a decrease in UFR accompanied by improvements in IDWG with stable post-HD wts. Treatment duration remained unchanged for all groups.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

		UFR>13 (N=39)	UFR 10-13 (N=113)	UFR<10 (N=481)
UFR (ml/kg/h)	BL	15.89	11.05	6.67
	M12	13.55	10.46	7.10
	diff	-2.34*	-0.59*	0.43*
Treatment duration (min)	BL	206.33	211.63	226.71
	M12	206.68	212.82	226.82
	diff	0.35	1.19	0.11
IDWG (kg)	BL	3.32	2.70	2.22
	M12	2.74	2.53	2.30
	diff	-0.58*	-0.17*	0.08
UF volume (l)	BL	3.30	2.63	2.16
	M12	2.73	2.47	2.26
	diff	-0.57	-0.16	0.1
Pre/Post-HD wt (kg)	BL	63.86/60.58	69.92/67.32	89.08/86.91
	M12	63.18/60.46	70.29/67.87	88.05/85.81
	diff	-0.68/-0.12	0.37/0.55	-1.03*/-1.10*

* <0.01

TH-PO198

Decline in Hemodialysis Ultrafiltration Rate (UFR), 2012-2018

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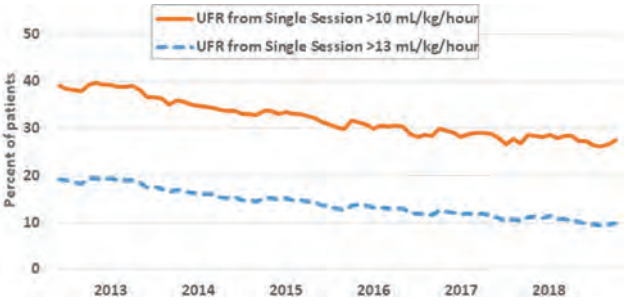
Background: UFR has received heightened attention due in part to several observational studies that reported higher mortality at UFRs above 10 to 13 ml/kg/hour. Several organizations have proposed quality measures to discourage high UFR. We examined national UFR trends for US patients.

Methods: We evaluated trends in UFR and its components (pre- and post-dialysis weight, dialysis session time) from 2012-18 as reported by dialysis facilities through the CROWNWeb system. Medicare-certified dialysis facilities began reporting UFR data for the last hemodialysis session of each month in 2012, and for a full week of sessions in 2018 in accordance with the ESRD Quality Incentive Program.

Results: Data for monthly UFR were submitted for 88-98% of patients. Average UFR declined steadily from 9.3 to 7.8 ml/hour/kg between 2012 and 2018. The percent of dialysis sessions with a UFR>13 ml/kg/hour declined from 19% to 10%. The percent of dialysis sessions with a UFR>10 ml/kg/hour fell from 39% to 26%. The decline in UFR was largely driven by interdialytic weight gain, which fell from approximately 3.3% to 2.8% of body weight (~2.6 to 2.2 kg). Dialysis treatment time and patient weight trended upward, but these made a relatively small contribution to the decline in average UFR.

Conclusions: The average UFR has declined from 2012 to 2018, largely driven by lower interdialytic weight gain. One possible explanation is that dialysis facilities provide patients with better education about fluid and dietary intake and patients follow such advice more carefully. However, we believe a more likely explanation comes from other studies reporting a secular decline in the average dialysate sodium concentration, which suppresses thirst and fluid intake. Although the strength of current evidence has not supported specific UFR guidelines, the changes responsible for the declining UFR were potentially motivated by published studies and expectations of forthcoming guidelines and incentives related to UFR management.

Funding: Other U.S. Government Support



Patients with UFR ≥ 13 and 10 mL/kg/hour, 2012-2018

TH-PO199

Electronic Health Record-Based E-Alerts for Ultrafiltration Rate in Prevalent Dialysis Patients: A Quality Improvement Project

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Background: Studies have shown an association between higher ultrafiltration rate and mortality in prevalent dialysis patients. Ultrafiltration rate exceeding 10mL per kg per hour has been associated with greater mortality even when calculations are normalized to various anthropometric measurements.

Methods: We recorded interdialytic weight gain (IDWG) for one week of thrice a week prevalent dialysis patients. Also baseline characteristics of study population were noted. Our dialysis data is recorded in AXIS renal data solution (electronic health record designed and conceptualized by Nephrologist). IDWG was calculated as predialysis weight minus the post dialysis weight of the previous hemodialysis session. The ultrafiltration rate was calculated by dividing the ultrafiltration volume (ml) by the target dry weight (kg) and length of time of the dialysis session (hours). Average ultrafiltration rate for all 3 sessions of hemodialysis and percentages of dialysis session where UF rate exceeded 10mL per kg per hour were calculated. After preliminary data collection, we are planning to introduce electronic alert (e alert) within AXIS system whenever ultrafiltration rate exceeds 10mL per kg per hour. This e alert will be sent to patient's caregiver as well as will serve as a teaching tool for dialysis nurse.

Results: Of the 387 subjects, 62% were males. The average age was 53.1± 13.6 years. The average dialysis vintage was 4.0 ± 3.4 years. 33.6 % had diabetes, 85.5 % had hypertension and 10.0 % had history of ischemic heart disease. Average UF rate of first session of week (after weekend) was 13.8 ± 5.7mL per kg per hour. Average UF rates of mid week and last session of week were 10.5 ± 10.5 and 10.0 ± 4.5mL per kg per hour respectively. About 75.7% of HD sessions after weekend had UF rate more than 10mL per kg per hour whereas 48.3 % and 47.8 % sessions of remaining week exceeded safe UF rate limits.

Conclusions: About 75% of dialysis sessions after weekend gap exceeded safe limits for ultra-filtration rates in prevalent dialysis patients. This calls for quality improvement initiative to improve knowledge and to monitor in change in behavior among dialysis patients, caregivers and providers regarding safe limits of UF rate.

TH-PO200

Ultrafiltration Does Not Correlate with the Difference Between Pre-Dialysis and Post-Dialysis Blood Pressure

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Background: Hypervolemia contributes to blood pressure (BP) elevations in hemodialysis (HD) patients and is addressed with ultrafiltration (UF). However, high UF rates (UFR) are generally avoided as it is associated with intradialytic hypotension. It is unknown whether the amount of UF or volume removed actually correlates with the change between pre and post dialysis BPs. We hypothesize that there is an inverse correlation, with higher UF resulting in larger decreases in post HD BP.

Methods: We reviewed the records of 24 ESRD patients receiving HD in a single outpatient center in Philadelphia over a 2 month period. Patients on midodrine were excluded, and treatments with missing pre and post HD BPs and without UF were not analyzed. Using Pearson r, we correlated intradialytic weight change (pre minus post HD weight) and achieved UF rate (UFR, ml/kg/hr) with changes in systolic BP, diastolic BP and mean arterial pressure during HD (post minus pre HD SBP, DBP and MAP). Patients were further stratified into those who received UFR < vs ≥ 10 ml/kg/hr and with intradialytic weight (IDW) changes < vs ≥ 3kg.

Results: Individual intermittent HD treatments were analyzed (n=363). We found no significant correlation between IDW change and change in SBP (r= -0.024), DBP (r= -0.012) and MAP (r= -0.019). IDW change ≥ 3kg correlated better with a decrease in SBP post HD, although it did not reach statistical significance (r= -0.24, p=0.08). There was also no correlation between achieved UFR and change in SBP (r= -0.061), DBP (r= -0.021) and MAP (r= -0.04). There was still no significant correlation even in patients who received high UFRs (≥ 10 ml/kg/hr).

Conclusions: Our study showed that UFR and IDW change did not correlate with the difference in pre and post dialysis BPs. This suggests that other factors, in addition to volume, play important roles in intradialytic BP regulation and should be explored. To our knowledge, only one other smaller study looked at similar parameters and reported a significant but weak correlation between UF and change in MAP (r=0.17, p=0.045, 136 treatments) (Kovacic, et al, 2003). Larger studies are necessary.

TH-PO201

Prevalence of Body Weight Variations in the Pre-Dialysis Period and the Effect of Hemodialysis Initiation: A Single-Centre Retrospective Observational Study

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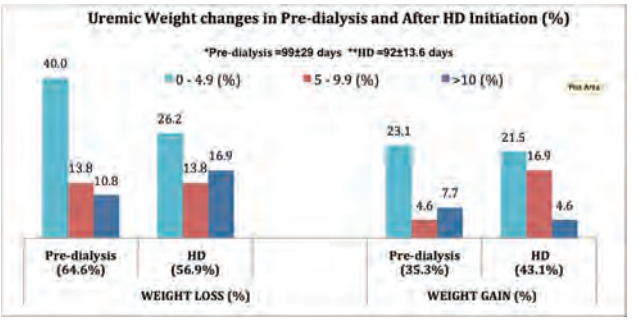
Background: Body weight(BW) changes rapidly during pre-dialysis(pre-D) period and is regularly monitored during pre-D clinics but less utilised as an indication for RRT initiation in isolation. Hemodialysis(HD) provides a target weight (TW). **Aims:**To 1) Assess prevalence and magnitude of BW changes during pre-D 2) Measure the effect of RRT initiation on BW 3 months(m) post HD

Methods: We retrospectively examined BW changes of a large cohort of incident HD patients who attended ***Pre-D clinics*** between 2012-2016 (n=103). ***Excluded:***Those with missing BW between 2-5 m in pre-D and 2-5 m after RRT initiation, previous PD, HD or fluid overload as indication for RRT initiation (n= 38). W0, W1and W2 are the corresponding BW at -3 m(Pre-D clinic), pre-weight at 1stHD initiation and post-HD TW after +3 m. Delta BW is calculated as absolute and % change for Pre-D(W0-W1) and HD period(W1-W2). Weight loss and Weight gain data analysed using Past.V3 software.

Results: n= 65**,** mean age 68±12 yr, M:F 44:21. HD was RRT in all. Pre-D and HD intervals were similar 99 ± 29 Vs. 92 ± 13.6 days. Post-weight and TW were within 0.5±0.4 Kg. Weight loss seen in both pre-D and HD; it slowed modestly after HD initiation (66.4% to 56.9%) mainly in 0-5% (40% Vs. 26%) ***(Fig 1)***. **Weight gain** was mostly 0 - 9.9% on HD as compared to pre-D (38.4 Vs 27.7). High weight gainers of >10% BW reduced from 7.7% in the pre-D period to 4.6% on HD, probably reflecting closer monitoring of TW. However, **group comparison** of pre-D and HD for % BW changes did not reach statistical significance for weight loss (difference between means 1.47, 95% CI -1.45 to 4.48, p=0.35) or weight gain (difference between means 0.12, 95% CI -2.86 to 3.11, p=0.93).

Conclusions: Uremic state is predominantly catabolic in both pre-D and HD period; RRT initiation can provide anabolic milieu. Increased recognition/incorporation of BW changes is needed as an added indication for RRT initiation. Body composition monitor use could well extend into pre-D clinics to guide bedside decisions.



TH-PO202

Impact of Extracellular Volume Overload on Ambulatory Blood Pressure in Hemodialysis Patients with and Without Intradialytic Hypertension

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Background: Hemodialysis (HD) patients with recurrent intradialytic hypertension (IH) have higher ambulatory blood pressure (BP) and atypical ambulatory BP patterns compared to HD controls. Recurrent IH is also associated with increased extracellular volume (ECV) and intradialytic vasoconstriction surges. We examined how these variables influence ambulatory BP in HD patients with and without IH.

Methods: In a case-control study of recurrent IH patients (systolic pre to post-HD BP increase >10 mmHg in 4/6 treatments) and hypertensive HD controls we obtained pre and post-HD ECV/weight with bioimpedance spectroscopy and total peripheral resistance index (TPRI) with a cardiac output monitor. Linear regression measured associations of peridialytic variables on 44-hr ambulatory BP measurements.

Results: There were 18 IH subjects and 57 controls. Those with IH had higher ECV than controls (0.27±0.04 L/kg vs. 0.23±0.04, p=0.002) and different intradialytic TPRI changes than controls (385±840 dyn/sec/cm^2/m^2 vs.-478±700, p=0.001). Mean ambulatory BP was nonsignificantly higher in IH subjects (147±13 mmHg vs. 142±14, p=0.1), and BP slopes were different in hours 1-24 (-0.14±0.9 mmHg/hr vs. 0.42±0.9, p=0.04) but not hours 1-44. ECV/weight was associated with mean ambulatory BP in IH subjects and ambulatory BP slope in controls (Table). Post-HD BP associated with ambulatory BP in both groups.

Conclusions: Chronic ECV overload is a primary factor associated with ambulatory BP in IH patients, but interdialytic weight gain and intradialytic vasoconstriction surges are not. In controls, ECV overload is associated with a blunted ambulatory BP rise. Intra- and interdialytic BP patterns may help guide diagnosis and management strategies of ECV in HD patients.

Funding: NIDDK Support, Veterans Affairs Support

Regression Coefficients and P-values for Variables Using Mean Ambulatory Blood Pressure and Ambulatory Blood Pressure Slope as Dependent Variables in Subjects With and Without Intradialytic Hypertension

	Dependent Variable: Mean Ambulatory Systolic BP				Dependent Variable: Ambulatory Systolic BP Slope (Hours 1-44)			
	Intradialytic Hypertension (n=18)		Controls (n=57)		Intradialytic Hypertension (n=18)		Controls (n=57)	
	β	p-value	β	p-value	β	p-value	β	p-value
Post-HD Extracellular Water/Body Weight (L/kg)	314	<0.001	49.4	0.5	0.03	0.9	-4.56	0.04
Intradialytic Change in Total Peripheral Resistance Index (dyn/sec/cm2/m2)	-0.002	0.2	0.004	0.3	-0.0002	0.2	0.00002	0.9
Post-HD Systolic BP (mmHg)	0.24	0.002	0.3	0.02	-0.005	0.5	-0.002	0.001
Interdialytic Weight Gain (% of dry weight)	-1.3	0.07	0.55	0.7	-0.13	0.2	0.09	0.1

TH-PO203

Aquapheresis: An Institutional Experience at Lenox Hill Hospital

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Background: Aquapheresis (AQ) is the extracorporeal extraction of plasma water from the vascular space across a semipermeable membrane in response to a transmembrane pressure gradient, which efficiently removes extravascular fluid from the patient without compromising electrolytes. It is primarily used in the management of patients (pts) with diuretic resistant heart failure (CHF). AQ is comparable to isolated ultrafiltration (UF) performed on those pts requiring dialysis, but utilizes a machine that is smaller, and easier to operate compared to traditional dialysis equipment. Three major

studies on the use of AQ compared to diuretics have shown mixed results: UNLOAD (2007), found that UF produced greater fluid loss and also a 53% reduction in the 90-day rehospitalization; in contrast, in CARRESS-HF (2012), the use of AQ did not relieve CHF and caused worsening of renal function; AVOID (2016), supported the use of AQ to lower re-hospitalization rates in CHF pts. There are no reports of the use of AQ in clinical studies outside of decompensated CHF.

Methods: A retrospective study of AQ utilization at Lenox Hill Hospital, a tertiary care hospital in NYC. Records of pts who received AQ therapy were reviewed. The patient list was generated by searching for keyword "Aquaph" in our EMR. Pts were categorized by indication for AQ and hospital location. Additional information includes duration of treatment (days), changes in creatinine, and total volume removed.

Results: The search generated 28 pts, 5 were excluded as they never actually received AQ. Indications for AQ went into 5 categories: cardiogenic shock including post cardiothoracic procedure (10); anasarca (5); ATN with volume overload (4); ESRD with bridge ultrafiltration between hemodialysis treatments (2); post-op volume overload (2). There were 16 pts from Cardiothoracic ICU, 5 pts from CCU, 1 pt from the Medical ICU and 1 pt from the Surgical ICU. The average duration per patient was 4.26 days. The mean aquapheretic volume per day was 1954 mls, and per encounter was 8323 mls with no significant change in creatinine.

Conclusions: We found that aquapheresis can be safely utilized in situations other than diuretic resistant heart failure. Also to consider, is the ease in which this less complicated aquapheresis machine can be operated compared to the more complex hemodialysis equipment.

TH-PO204

Over-Ultrafiltration May Increase the Risk of Ischemic Cerebral Small Vessel Disease in Hemodialysis Patients

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Background: Cerebral small vessel disease (CSVD) is an important cause and risk factor of stroke and dementia. Recently, CSVD in patients with end-stage renal disease and undergoing dialysis had attracted great attentions. A higher prevalence of CSVD in hemodialysis patients had been shown in others' and our previous studies. Hemodialysis is a complicated procedure with multiple factors that could affect cerebrovascular disease. Ultrafiltration could bring hemodynamic instability during the hemodialysis. The aim of this study is to discovery the relationship between ultrafiltration and ischemic CSVD

Methods: In this retrospective study, we collected a whole year's ultrafiltration information before the brain MRI scan of the HD participants in our dialysis cohort of 2013~2014 CSVD/CI study in which the CSVD were assessed by magnetic resonance imaging. We analyzed average ultrafiltration volume (UV mean), fluctuation of ultrafiltration volume (UV CV) and ultrafiltration volume over 6% dry weight (UV mean - 6%W), and their influence to ischemic CSVD findings (lacune and white matter hyperintensity) in MRI. Multivariable analysis was used to explore the relevance between ultrafiltration parameters and CSVD.

Results: In our 2013~2014 dialysis CSVD/CI cohort, 119 participants were on HD, and among them, 50.9% were male. The average age was 56.6yr, average dialysis vintage was 58 months. Median UV mean was 2.3 (0.2~ 4.6) L, UV CV was 21.4 (0.0 ~ 78.1) mL and "UV mean - 6%W" was -1.3 (-4.6 ~ 1.4) kg. The prevalence of lacune in MRI was 28.6% and WMH was 38.7%. By multivariable analysis, we found that UV and UV CV were not relative to both features of CSVD, but the "UV mean - 6%W" was relative to increased risks for lacune and WMH with OR1.74 (1.06, 2.87) and 1.89 (1.16, 3.08), respectively. In further analyzed, it showed that ultrafiltration mainly affected subcortical white matter lacune (OR 1.98 (1.09, 3.59)) and periventricular white matter hyperintensities (OR1.81 (1.08, 3.03)), rather than deep CSVD lesions.

Conclusions: Over ultrafiltration during hemodialysis procedure could increase the risk of ischemic CSVD, especially the risk of subcortical white matter lacune and periventricular white matter hyperintensities. "6% dry weight" could be considered as ultrafiltration cut-off values in hemodialysis therapy in order to avoid ischemic CSVD.

TH-PO205

Ultrafiltration Rate Correlates Better with Intradialytic Weight Change Indexed to Body Weight Than Absolute Weight Change

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Background: Intradialytic weight change (IDW change), ultrafiltration rate (UFR), and total ultrafiltration (UF) are used to quantify volume removal during hemodialysis (HD) treatments. These parameters are frequently used in clinical research to find associations between volume removal and outcomes like mortality and intradialytic complications. IDW change expressed as a proportion of body weight (indexed weight change) is rarely used both in the clinics and research. The objective of this study is to explore how indexed weight change correlates with the commonly used volume parameters during HD.

Methods: We reviewed records of 28 ESRD patients receiving HD in a single outpatient center in Philadelphia over a 2 month period. Treatments without UF were excluded from analysis. Correlations between absolute IDW change (pre minus post HD weight), achieved UFR (ml/kg/hour), and indexed weight change (IDW change divided by pre HD weight) were calculated using Pearson r. Range and mean of indexed weight change was also calculated and expressed as a percent of body weight lost (indexed weight change multiplied by 100).

Results: Individual intermittent HD treatments were analyzed (n=422). Absolute IDW change had a significant and strong correlation with achieved UFR (r=0.745, p<0.00001) and indexed weight change (r=0.824, p<0.00001). Interestingly, UFR correlated strongly and better with indexed weight change (r=0.963, p<0.00001) than with absolute IDW change. During treatments, patients lost an average of 2.13% ± 1.22% of their body weight with a range of 0.08 to 5.65%.

Conclusions: Our results show that UFR, absolute IDW change, and indexed weight change all correlate strongly. However, UFR correlates better with indexed weight change than absolute IDW change. Indexed weight change takes into account differences in body habitus of individual patients, and by transitivity, differences in their body surface area and total body water. Indexed weight change may be an important clinical parameter that could be used to guide UF prescriptions and more studies are needed to look into its association with hemodynamic changes during hemodialysis.

TH-PO206

Rise of Plasma Sodium Levels Is Followed by an Increase of Plasma Syndecan 1 in Hemodialysis Patients

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Background: In hemodialysis (HD) patients, endothelial dysfunction (ED) contributes to atherosclerosis. A major hallmark of ED is loss of glycocalyx evidenced by shedding of syndecan-1 into the blood stream. Release of syndecan-1 is seen in pro-inflammatory and pro-oxidative conditions such as in HD patients. HD by the Hemocontrol biofeedback system (HHD) is characterized by initially higher dialysate and plasma sodium levels. Using HHD as a model for an acute increase in plasma sodium, we investigated associations between courses of plasma sodium and syndecan-1 during HHD and standard HD (SHD).

Methods: Plasma syndecan-1 was measured by ELISA in blood samples obtained from a cohort of 29 prevalent HD patients before, during and after HHD and SHD (randomized sequence). Wilcoxon signed-rank test or paired student's t-test was used to compare syndecan-1 levels between SHD and HHD. Intradialytic shedding of syndecan-1 was determined by area under the curve analyses. Associations with the intradialytic course of syndecan-1 were analyzed with a mixed effects repeated-measures model.

Results: During HHD, plasma sodium increased early after the start of HD (predialysis 139,1 mmol/L; at 30 minutes of HD 142.3 mmol/L; P<0.0001) whereas sodium did not increase significantly during SHD. During HHD, plasma syndecan-1 increased after 120 minutes of HD (P=0.007). Plasma syndecan-1 also increased significantly during SHD (within 120 minutes; P=0.003) but at 120 minutes, the rise in syndecan-1 levels was significantly higher in HHD as compared to SHD (+42.9% vs. +17.2%; P=0.021). The total amount of shed syndecan-1 was higher during HHD than during SHD, albeit at borderline significance (P=0.05). Lower plasma sodium and osmolality before dialysis were independent predictors of syndecan-1 increase during dialysis (P=0.001 for both groups). In HHD, a higher cumulative UF volume was independently associated with more intradialytic syndecan-1 shedding (P=0.001).

Conclusions: Plasma syndecan-1 levels increased significantly during both HHD and SHD. In HHD, this rise was significantly greater and occurred earlier as compared to SHD. This may reflect ED resulting from increased sodium load. Further research to assess long term effects and clinical implications of high salt exposure is needed.

TH-PO207

Home vs. In-Center BP in Hypertensive Hemodialysis Patients

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Background: In hemodialysis (HD) patients, home blood pressures (HBP) are stronger than dialysis unit BP as predictors of adverse outcomes. In the BID pilot study, we assessed safety and feasibility of treating hypertensive HD patients to a standardized predialysis systolic BP (SDUBP) of 110-140 mm Hg vs. 155-165 mm Hg. Participants measured HBP according to American Heart Association guidelines twice on the day after the midweek HD. We assessed left ventricular mass index (LVMI) using MRI at baseline and at the end of the 1-year intervention. The present study assessed the differences between HBP and SDUBP within individuals.

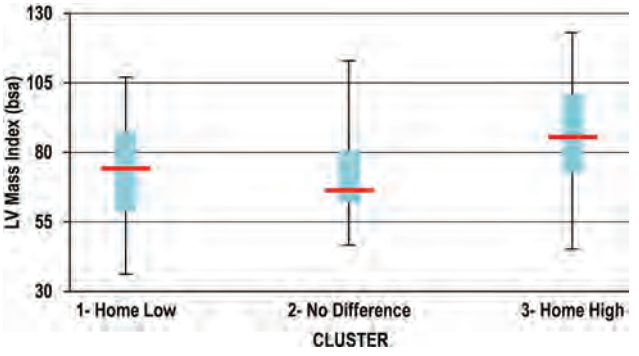
Methods: To be included patients had to have ≥ 6 pairs of standardized predialysis BPs from a midweek HD and a time-matched HBP the following day. Patients were assigned to one of 3 clusters, based on the average SDUBP to HBP differences and the variability of the difference within an individual, using cluster analysis in R.

Results: There were 97 patients with an average of 26 pairs of SDUBP and HBP who were included in the cluster analysis. This resulted in three clusters; (1) SDUBP > HBP (n=31); (2) no significant difference (n=36); and (3) HBP > SDUBP (n=30). LVMI in Cluster 3 (84.5, 95% CI 75.5, 93.6) were significantly higher than Cluster 1 (72.7, 95% CI 65.8, 79.6; p= 0.06) and 2 (71.5, 95% CI 65.3, 77.7; p=0.03). Within Cluster 3 there was no difference in LVMI by treatment arm. At baseline, the participants in Cluster 3 had higher LVMI than those in Clusters 1 and 2. Contrary to Cluster 1 and 2, systolic BP post-dialysis (151.7 mm Hg) was significantly higher than pre-dialysis (149.1 mm Hg) in Cluster 3 (p= 0.001). Variability was similar across clusters.

Conclusions: Patients in Cluster 3 (HBP higher than SDUBP) had higher LVMI at baseline and after the 12-month intervention than those in Clusters 1 and 2. Patients

in Cluster 3 frequently had an increase in SBP during HD. Monitoring home BP measurements may improve care of HD patients.

Funding: NIDDK Support, Commercial Support - Dialysis Clinic, Inc.



TH-PO208

Patient Engagement with a Digital Health Intervention (patientMpower) to Optimise Interdialytic Fluid Management in Ambulatory Hemodialysis Patients

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Background: Many aspects of a chronic illness rely heavily on patient self-care and engagement. While promising, studies on the use of digital medicine platforms to empower patients to self-manage have suffered from low patient engagement. This pilot-scale study (NCT03403491) evaluated a mobile digital health intervention+weighing scales+blood pressure (BP) meter [patientMpower intervention (pMp)] in ambulatory hemodialysis patients treated in a clinical setting. Patient-reported weight and BP were captured by wireless connection to pMp (cellular or Bluetooth).

Methods: 43 patients (28M/15F; age 51±14y) entered an open-label, randomised, random-order, 2 x 28-day crossover comparison of pMp vs. a sham intervention. Patients were asked to record weight, BP, symptoms, fluid intake & medicines adherence every day during the pMp period. pMp calculated and displayed weight gain relative to individualised target (dry) weight to each patient. An algorithm within pMp delivered tailored feedback messages (dependent on actual weight gain) to optimise fluid intake between dialysis sessions. Primary endpoint was patient engagement with pMp.

Results: Engagement was high. 35 patients (81%) recorded weight on ≥21 days of the pMp period. Engagement metrics in the 28-day pMp period are shown below. However, only 2 patients recorded medicines adherence on pMp. Patients were asked to complete an online survey to feed back opinion of pMp. 23 gave feedback. 19(83%) reported pMp gave them a greater sense of control & had positive impact on their well-being, 18(78%) wished to continue using pMp after study, 21(91%) rated pMp as easy to use and 15(65%) liked using pMp (score ≥8/10 on rating scale).

Conclusions: This study demonstrated that ambulatory hemodialysis patients are willing and engaged in using a mobile digital health intervention with connected devices to regularly monitor body weight and BP to help them optimise fluid intake. The high engagement by these patients suggests that this methodological approach could be useful in future studies of optimisation of dry weight estimation and/or fluid intake.

Funding: Commercial Support - patientMpower Ltd., Government Support - Non-U.S.

	weight	BP	symptoms	fluid intake
Patients recording data (n)	43	38	33	33
Days data recorded (n; mean±SD)	24±6	18±8	13±8	13±8
Days data recorded (n;range)	5-28	1-28	1-24	1-24

TH-PO209

Assessment of Hemodialysis Patients' Knowledge of Fluid and Blood Pressure Management

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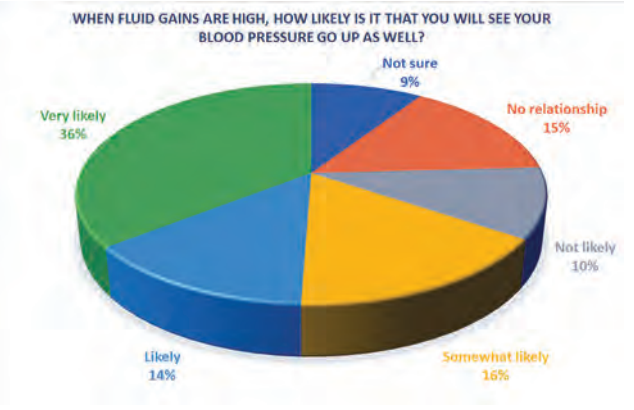
Background: Hemodialysis (HD) patients are expected to minimize interdialytic fluid gains and manage their blood pressure (BP) with antihypertensive (AHT) medications. Due to a paucity of data reporting patients' knowledge and understanding of fluid and BP management, we conducted a prospective cross-sectional survey with retrospective medical record review at three HD clinics in Illinois.

Methods: HD patients were consented and interviewed using a standardized cross-sectional survey consisting of 50 questions on fluid and BP management. Patients were paid $10 for their participation. Six months of retrospective data was collected from medical records.

Results: Ninety-two patients completed the survey, and 38/92 were not aware of the last time their dry weight (DW) was changed. Patients reported their last DW change was made 5.93 +/- 15.3 months ago on average. Of the 54 patients who reported knowing the last time their DW was changed, 31/54 reported it was raised, 17 lowered, and 6 were not sure what changes were made. Medical records indicated that patients were not aware of the majority of DW changes. Over 3 months, DWs were changed an average of 2.54 +/- 2.18 times. Twenty four patients (26%) could not list their current or any previous DWs, while those who listed a DW were on average 3.73 +/- 10.16 kg away from the DW listed within their medical record. Forty-six patients were currently on 1 or more AHT medications. Of these, the average time since AHT medications were last changed was 15.22 +/- 16.4 months. The majority of patients (78/ 92) patients were interested in (or already) measuring their BP at home. Figure 1 shows how patients rated the likeliness of a direct relationship of their interdialytic fluid gains and BP.

Conclusions: Despite a desire to learn, most HD patients lack an understanding of the basic principles of fluid & BP management. There is a need for a structured education program for those initiating dialysis that encompasses fluid and BP management.

Funding: Private Foundation Support



TH-PO210

Factors Influencing Hourly Hemodynamic Changes During Hemodialysis

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Background: The cardiovascular system adapts to maintain blood pressure during hemodialysis primarily by altering cardiac output and systemic vascular resistance. However, many dialysis patients develop intradialytic hypotension (IDH) or hypertension, both having serious consequences. While blood pressure is consistently monitored during dialysis, other hemodynamic variables are not. The purpose of our study is to examine changes in total peripheral resistance index (TPRI) and cardiac power index (CPI) during each hour of dialysis to determine the primary factors causing IDH and intradialytic hypertension throughout a dialysis session.

Methods: Intradialytic systolic blood pressure (SBP), mean arterial blood pressure (MAP), CPI and TPRI were evaluated hourly using peripheral bioimpedance (NiCaS, Inc) in 27 HD patients. Measurements were taken at baseline and after each hour of dialysis for a total of 198 hourly measurements. IDH was defined as a drop of hourly SBP ≥ 20 mmHg or drop of hourly MAP ≥ 10mmHg. Intradialytic hypertension was defined as a rise in hourly BP ≥ 15 mmHg. Measurements of blood pressure not meeting the definitions were defined as non-IDH or non-intradialytic hypertension time periods. Hourly changes in CPI and TPRI were compared.

Results: During the 1st hour of dialysis, neither SBP, CPI nor TPRI changed significantly. During the 2nd hour of dialysis, the average hourly TPRI changes in IDH and non-IDH groups were -211.5 ± 480.6 and 145.6 ± 572.1 (p=0.03). During the 3rd hour, the hourly CPI change was 0.12 ± 0.1 in the intradialytic hypertensive and -0.04 ± 0.1 in non-hypertensive groups (p= 0.02) whereas the average TPRI change was -476.6 ± 701.7 in IDH and 168.4 ± 812.5 in non-IDH groups (p=0.008). During the 4th hour, the hourly CPI change was -0.06 ± 0.07 in the intradialytic hypertensive group and 0.04 ± 0.1 in intradialytic non-hypertensive group (p=0.03).

Conclusions: The predominant change responsible for IDH in the 2nd and 3rd hour of dialysis appears to be reduction in TPRI. By contrast, intradialytic hypertension in the 3rd hour appears to be primarily mediated by increases in CPI. In the 4th hour, there was a paradoxical reduction in CPI in the intradialytic hypertensive group. More closely monitoring hemodynamic changes during dialysis may provide information that could be used to intervene medically to prevent these dialysis-associated complications.

Funding: Commercial Support - RRI

TH-PO211

Crit-Line Monitoring Decreases Intradialytic Hypotension

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Background: Published clinical studies on the use of blood volume monitoring to guide ultrafiltration in hemodialysis (HD) have had mixed results. We conducted a continuous quality improvement (CQI) project to assess the impact of Crit-Line monitoring during routine care in a chronic HD facility operated by a large, non-profit dialysis provider. We postulated that Crit-Line monitoring would decrease intradialytic hypotension & hospitalization due to fluid overload.

Methods: After a 6-month baseline period, we conducted 1 month staff training on Crit-Line use, followed by a 2nd 6-month period with Crit-Line monitoring with each HD. 29 HD patients contributed a mean of 62 & 61 treatments to the baseline & Crit-Line periods, respectively. Mean & 95% confidence intervals (95% CI) for age & vintage were 62.6 (57.6, 67.6) & 4.7 (2.2, 7.2) years, respectively. Males & diabetics comprised 72% & 38% of the patients, respectively. Hypotension was defined as systolic blood pressure (BP) < 100 mmHg or symptoms associated with a drop in BP. Dialysate temperature & composition did not change significantly between the 2 time periods. We used Poisson regression models, adjusted for sex, diabetes, vintage & BMI, to compare treatment related events including cramping, symptomatic hypotension, & leaving treatment > 1 kg from estimated dry weight (EDW) & hospitalization during the baseline period & the 6-months in which Crit-Line monitoring was used.

Results: Intradialytic hypotension was significantly lower during Crit-Line monitoring (OR 0.37, 95% CI 0.2, 0.7). Other adverse events including all-cause & cardiovascular hospitalization rates did not differ across the 2 time periods (see table).

Conclusions: Crit-Line use was associated with a statistically significant decrease in the frequency of intra-dialytic hypotension; however there was no association with hospitalization. Well trained staff are essential to the optimal use of Crit-Line monitoring.

Funding: Commercial Support - Dialysis Clinic, Inc.

Frequency of Dialysis Related Symptoms

Complication	Baseline n (%)	Crit-Line n (%)	Odds Ratio (95% CI)	*P*-value
Number of treatments	1855	1971	-	-
Cramps	121 (6.5)	128 (6.5)	1.1 (0.7, 1.8)	0.69
Hypotension	**38 (2.0)**	**17 (0.9)**	**0.4 (0.2, 0.7)**	**0.02**
IDWG >3% EDW	631 (34.0)	722 (36.6)	1.1 (1.0, 1.3)	0.24
Post weight >1 kg over EDW	273 (14.7)	271 (13.7)	0.9 (0.6, 1. 3)	0.57
Post weight >1 kg under EDW	52 (5.2)	71 (3.6)	1.4 (0.6, 3.3)	0.44
Shortened duration >10 min	71 (3.8)	91 (4.6)	1.2 (0.9, 1.8)	0.25
UFR > 13 ml/kg/hr	188 (10.1)	230 (11.7)	1.1 (0.8, 1.7)	0.56
Predialysis SBP >195 mmHg	131 (7.1)	109 (5.5)	0.8 (0.5, 1.4)	0.54
Post SBP >195 mmHg	32 (1.7)	28 (1.4)	0.8 (0.2, 2.5)	0.70

TH-PO212

Characterisation of Haemodynamic Responses to Haemodialysis Using Frequency Analysis

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Background: Intradialytic haemodynamic instability remains a significant problem, leading to ischaemic end-organ damage. Extrema points frequency analysis of blood pressure (BP) is a method of assessing beat to beat variation in BP, which may have relevance to end-organ perfusion. Our aim was to utilise this method to describe the patterns of individual cardiovascular response to haemodialysis (HD), study its variability and identify factors associated with higher BP frequencies.

Methods: 50 participants aged >18 years were recruited from our prevalent HD population. Participants' demographics, HD background, HD prescription and laboratory parameters at each session were recorded. All participants had continuous non-invasive haemodynamic monitoring using pulse wave analysis (Finapres NOVA) during the entirety of three consecutive dialysis treatments. The data generated were then analysed by identifying the frequency and amplitude of local extrema points for mean arterial pressure (MAP).

Results: In total, 44 participants completed all three dialysis sessions with continuous haemodynamic monitoring. 61% were males, mean age was 62.3±16yrs and 43% had diabetes. Analysis of intradialytic trends of haemodynamic measures demonstrated a gradual near-linear decline in BP, cardiac output, stroke volume; and a rise in total peripheral resistance. In frequency analysis, overall MAP frequency across the study population for the first monitored session was 0.54 Hz (IQR: 0.18). The frequency extracts varied through the dialysis sessions, generally rising and reaching peak in 3rd hour of dialysis. There was intra-individual variation between dialysis sessions, with Coefficient of Variation of average frequency values of 0.01-0.53. MAP frequencies correlated with dialysis vintage (r=0.307, p=0.043), pro-BNP levels (r=0.318, p=0.038), Baroreflex sensitivity (r=0.319, p=0.035) and average real variability of SBP (r=0.393, P=<0.0001), MAP (r=0.631, P=<0.0001) and DBP (r=0.512, p=<0.0001).

Conclusions: Frequency analysis of BP provides additional information regarding the variability in BP during HD, and this may be of importance when considering effects of HD on organ perfusion. Prospective follow up of participants in this study will allow us to establish the relationship of BP frequency analysis and patient outcomes.

TH-PO213

Blood Pressure Variability and Prognosis in Hemodialysis Patients: A Systemic Review and Meta-Analysis

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Background: As the prognostic value of blood pressure variability (BPV) in hemodialysis patients had previously been inconclusive, this work performed a systematic review and meta-analysis to assess the association between BPV and clinical outcomes in the hemodialysis population.

Methods: Pubmed/Medline, EMBASE, Ovid, the Cochrane Library, and the Web of Science databases were searched through March 5, 2019 for full text articles in English. Cohort studies on the association between BPV and prognosis in hemodialysis patients were selected. Study selection and data extraction were performed by two reviewers independently, with adjudication by a third reviewer. Hazard ratios and 95% confidence interval were pooled in a random-effects model for the primary outcomes of all-cause and cardiovascular mortality. Statistical analysis was performed using STATA 14.0 (STATA Corp., Texas, USA).

Results: A total of 13 studies (37,827 patients) were eligible. Systolic BPV was associated with higher all-cause mortality (HR: 1.12, 95% CI: 1.06-1.19, P < 0.001) and cardiovascular mortality (HR: 1.16, 95% CI: 1.10-1.22, P<0.001), while diastolic BPV was not associated with them (P = 0.14, 0.56). Long-term systolic BPV (inter-dialytic or inter-visit BPV) was shown to be a risk factor for all-cause (HR: 1.11, 95% CI: 1.05-1.17, P = 0.001) and cardiovascular (HR: 1.14, 95% CI: 1.06-1.22, P<0.001) mortality, but short-term systolic BPV (intra-dialytic or ambulatory) was only associated with cardiovascular mortality (HR: 1.19, 95% CI: 1.09-1.29, P < 0.001). The associations between systolic BPV and mortality events were not affected by region (North America-Europe vs. Asia), follow-up time (≤2.5 years vs. >2.5 years) or variable type (BPV as a categorical vs. continuous variable). Among the different BPV metrics, the coefficient of variation (CV) of systolic blood pressure was identified as predictor of both all-cause (P=0.012) and cardiovascular (P=0.002) death.

Conclusions: In the hemodialysis population, systolic BPV was associated with both increased all-cause and cardiovascular mortality, while diastolic BPV was not associated with the clinical outcomes. CV of systolic blood pressure was identified as a predictor for both all-cause and cardiovascular mortality, while the utility of other BPV metrics requires further investigation.

Funding: Government Support - Non-U.S.

TH-PO214

Comparison of Pressure-Independent Pulse Wave Velocity Between Haemodialysis Patients and Patients with Preserved Kidney Function

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Background: Chronic kidney disease (CKD) is associated with progressive arteriosclerosis and increased arterial stiffness (AS) – expressed as higher measured aortic pulse wave velocity (aPWV) – has been frequently described in dialysis patients. However, the intrinsic physiologic relationship between aPWV and prevailing arterial pressure complicates the direct comparison of aPWV values between different collectives. An individual pressure-independent expression of aPWV could be a possible solution.

Methods: Hemodialysis patients were age- and sex-matched with patients with preserved kidney function. Long-term measurements (24 hours for patients with preserved kidney function and 44 hours for haemodialysis patients) of blood pressure (BP) and aPWV were obtained. aPWV was then adjusted to 120 mmHg central systolic BP (PWV120) based on individually determined relationship and mean PWV120 was compared between the two collectives.

Results: 45 patients were included in each group. Haemodialysis group had significantly higher prevalence of diabetes mellitus and significantly more patients with hyperlipoproteinemia, history of coronary heart disease, stroke and peripheral artery disease, while patients with preserved renal function had significantly higher systolic and diastolic BP. PWV120 did not differ between the groups.

Conclusions: In our study, we used BP-adjustment for pressure-independent expression of aPWV. Our results show that pressure-independent aPWV did not differ between patients on haemodialysis and with preserved kidney function. This finding is in contrast to previous reports and prompts questions about association between AS and CKD. However, more data are needed to reproduce the results for further assessment.

Haemodynamic parameters

systolic blood pressure, mmHg	119.4±13.6	134.9±16.2
diastolic blood pressure, mmHg	67.8±10.5	78.3±8.6
heart rate, beats/min	68.3±9.3	69.7±10.0
central systolic blood pressure, mmHg	106.6±13.1	122.3±14.0
aortic Pulse wave velocity, m/s	11.0 [9.2-12.8]	10.9 [9.1-12.8]
PWV120, m/s	10.9±2.5	10.8±2.5

TH-PO215

Body Composition Analyzer Monitoring Improves Dialysis in Maintenance Hemodialysis Patients Role in Hypotension

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Background: Exploring the role of body composition analyzer (BCM) monitoring in improving dialysis hypotension in patients undergoing maintenance hemodialysis (MHD)

Methods: 51 patients with dialysis hypotension in our center, 27 females and 24 males, with an average age of (55±8.7) years old, were monitored and adjusted by BCM. The patients were re-evaluated and adjusted for 1 month before and after BCM monitoring. The incidence of hypotension and changes in mean arterial pressure.

Results: The average dry weight before BCM monitoring was (53.2±7.9) kg, and the average dry weight after BCM monitoring was (55.8±8.1) kg. The incidence of dialysis hypotension before BCM monitoring was 38%, and the incidence after monitoring was significantly reduced to 14%. The incidence of dialysis hypotension was significantly reduced after BCM was monitored and up-regulated ($P<0.001$). There was no significant change in the mean arterial pressure after BCM monitoring and up-regulation of dry weight ($P>0.05$).

Conclusions: BCM monitoring can improve the dialysis hypotension of patients with MHD without increasing the patient's water and sodium retention, and does not increase the blood pressure before transfusion. It can quickly and accurately regulate the patient's dry weight.

TH-PO216

Standing Blood Pressure Differentiates True and Pseudo Intradialytic Hypertension

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Background: Intradialytic hypertension (IH) is a blood pressure (BP) increase from pre to post-hemodialysis (HD). While IH occurs sporadically in nearly all HD patients, recurrent IH is clinically significant and associated with extracellular volume (ECV) excess, intradialytic vasoconstriction and mortality. We investigated if standing BP measurements from a single HD treatment with seated IH could distinguish patients with recurrent vs sporadic IH.

Methods: Among HD patients with increases in seated systolic BP from pre to post-HD in a single treatment, we compared ECV/weight (biompedance spectroscopy) and cardiac hemodynamics from that treatment and intradialytic BP trends in the prior 6 months between those with increases (true IH) or decreases (pseudo IH) in standing BP from pre to post-HD.

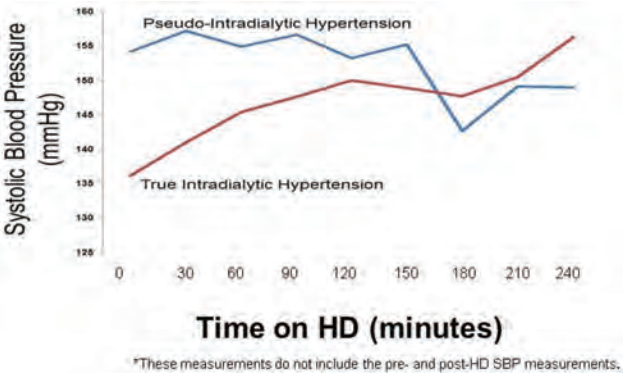
Results: There were 18 subjects with true IH and 7 with pseudo-IH with no differences in age or demographics. True IH subjects had higher post-HD ECV/weight, intradialytic TPRI increases, and more IH episodes in the past 6 months compared to pseudo IH(Table). The intradialytic BP patterns (excluding pre and post-HD seated measurements) are shown (Figure).

Conclusions: Patients with seated, but not standing, IH in a single treatment have a different physiologic phenotype than those with true-IH. The clinical significance of IH in an individual treatment can be assessed by determining the changes in standing SBP from pre to post-HD.

Funding: NIDDK Support, Veterans Affairs Support

Comparison of Subjects with Pseudo IH and True IH

	Pseudo IH (n=7)	True IH (n=18)	p-value
Seated pre-HD systolic blood pressure (mmHg)	146 (14)	137 (14)	0.6
Seated post-HD systolic blood pressure (mmHg)	167 (12)	155 (18)	0.07
Standing pre-HD systolic blood pressure (mmHg)	160 (17)	134 (14)	0.002
Standing post-HD systolic blood pressure (mmHg)	130 (19)	150 (14)	0.02
Post-HD ECV/body weight (L/kg)	0.23 (0.04)	0.27 (0.04)	0.02
Intradialytic Change in Total Peripheral Resistance Index	-491 (470)	577 (840)	0.005
Mean change in systolic blood pressure from pre to post-HD over prior 6 months (mmHg)	-10.4 (12)	4.6 (8)	0.005
Percentage of treatments with seated IH in prior 6 months	20 (14)	43 (15)	0.001



TH-PO217

Effect of Sodium and Ultrafiltration Modeling vs. Low-Temperature Dialysate on Prevention of Intradialytic Hypotension: Single-Center Study from India

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Background: Symptomatic intradialytic hypotension is the most frequent complication in patients receiving hemodialysis. It complicates 5 to 30 percent of all dialysis treatments. In our study, we aimed to compare the effect of sodium and ultrafiltration modeling versus low-temperature dialysate on the occurrence of intradialytic hypotensive episodes.

Methods: A total of 320 patients with chronic kidney disease (CKD) stage V on conventional hemodialysis (HD) for at least twice weekly for a minimum of 3 months were observed for the occurrence of ≥1 intradialytic hypotensive episodes per month. After full filling the inclusion and exclusion criteria, 60 patients were randomized into two groups based on computer-generated randomization numbers allotted to them by the dialysis coordinator. Group 1: Underwent dialysis with sodium and Ultrafiltration modeling (Linearly decreasing dialysate sodium from 141 mmol/L to 128 mmol/L and linearly decreasing ultrafiltration rate). Group 2: Underwent dialysis with low-temperature dialysate (36 degrees Celsius). Both groups underwent 240 sessions of hemodialysis.

Results: Intradialytic hypotension was found in 18.75 % of patients. Diabetic nephropathy (61.66%) was the leading cause of end-stage renal disease in these patients. There was no significant difference between the two groups in mean arterial blood pressure, hemoglobin, cardiac status, and serum albumin before dialysis. Both groups had a similar incidence of intradialytic hypotensive episodes ($P>0.05$). Interdialytic weight gain and ultrafiltration volume removed per session were also similar in both groups.

Conclusions: Sodium and ultrafiltration modeling and low-temperature dialysate were both equally effective in the prevention of intradialytic hypotensive episodes.

TH-PO218

True Arterial Stiffness Does Not Change Between Dialysis Sessions During 1 Week in Outpatients on Intermitted Hemodialysis

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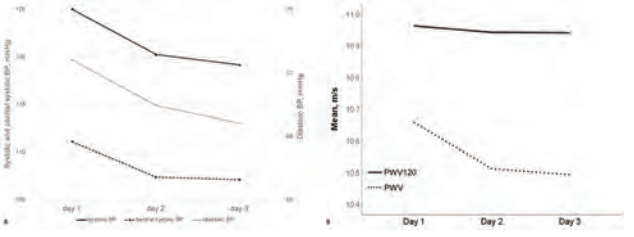
Background: End-stage renal disease (ESRD) is associated with exponentially elevated cardiovascular mortality. Higher pulse wave velocity (PWV) values are frequently observed in patients with ESRD. However, the intrinsic physiologic relationship between PWV and prevailing arterial pressure can deteriorate its cardiovascular predictive value making an individual pressure-independent expression of PWV essential.

Methods: Dialysis patients from a single outpatient unit obtained repeated measurements of blood pressure (BP) and pulse wave analysis during each dialysis session of one week. Aortic PWV was then adjusted to 120 mmHg central systolic BP based on individually determined relationship.

Results: 54 subjects were included. The median age was 75.5 years. Mean systolic/diastolic BP was 121.4/70.5 mmHg and the median heart rate was 64.6 beats/min. Mean PWV was 10.9 m/s and mean PWV120 was 11.3 m/s. PWV120 did not change across single dialysis session during one week, while systolic, diastolic BP, PWV and ultrafiltration volume differed significantly.

Conclusions: Our data suggest that true AS does not change in the short-term course in dialysis patients and observed changes in PWV are rather associated with BP change due to intrinsic pressure-dependence. Our analytical approach represents a novel method for this purpose, which is easy in performance and also applicable for large interventional trials and clinical practice.



Change in A- systolic, diastolic, central systolic blood pressure (BP) and B- pulse wave velocity (PWV) and PWV adjusted to 120 mmHg central systolic blood pressure (PWV120) between the dialysis days of one week

TH-PO219

Serum Fibroblast Growth Factor 21 Level Is a Risk Factor for Central Arterial Stiffness in Maintenance Hemodialysis Patients

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Background: Fibroblast growth factor 21 (FGF21) is a hepatic hormone in the regulation of glucose and lipid metabolism. Serum FGF21 levels were higher in patients with carotid atherosclerosis and in patients with coronary artery disease. The aim of this study was to evaluate the relationship between serum FGF21 levels and carotid-femoral pulse wave velocity (cfPWV) values in patients on hemodialysis (HD).

Methods: Blood samples and baseline characteristics were obtained from 130 HD patients. Serum FGF21 concentrations were determined by enzyme-linked immunosorbent assay kit. Central arterial stiffness was defined as carotid-femoral pulse wave velocity (cfPWV) values >10 m/s according to the ESH-ESC 2013 guidelines.

Results: Among 130 HD patients, 54 patients (41.5%) were in the central arterial stiffness group. When compared to those in control group, the central arterial stiffness group had high prevalence of diabetes mellitus ($P < 0.001$), hypertension ($P = 0.026$), and older age ($P = 0.036$), higher body weight ($P = 0.027$), body mass index ($P = 0.048$), systolic blood pressure ($P = 0.044$), C-reactive protein ($P = 0.040$), and higher serum FGF21 level ($P < 0.001$). Multivariable logistic regression analysis of the factors significantly associated with central arterial stiffness revealed that FGF21 levels (odds ratio (OR): 1.001, 95% confidence interval (CI): 1.000–1.001, $P = 0.001$), age (OR: 1.043, 95% CI: 1.002–1.085, $P = 0.042$), and diabetes mellitus (OR: 4.495, 95% CI: 1.703–11.867, $P = 0.002$) were the independent predictors of central arterial stiffness in HD patients. Multivariable forward stepwise linear regression analysis also showed that logarithmically transformed FGF21 level (log-FGF21, $\beta = 0.301$, adjusted R^2 change = 0.105, $P < 0.001$) was an independent predictor of cfPWV values in HD patients. The area under the receiver-operating characteristic (ROC) curve predicting central arterial stiffness by serum FGF21 level in HD patients was 0.693 (95% CI: 0.606-0.771, $P < 0.001$).

Conclusions: Serum FGF21 level positively correlated with cfPWV values and is also the independent predictor of central arterial stiffness among HD patients.

TH-PO220

Correlation Between Arterial Stiffness and Body Fat in Hemodialysis Patients

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Background: Arterial stiffness is common in chronic kidney disease. It has been known that the traditional risk factors such as ageing, hypertension and diabetes are linked to aortic elasticity. Few studies have focused on peripheral arterial elasticity. Some clinical trials have found a nonlinear relationship between body fat percentage and atherosclerosis in general population. Here, we explore the correlation between body fat and arterial elasticity in hemodialysis patients by measuring a variety of body fat indexes.

Methods: A total of 166 patients on maintenance were included in the study. All subjects underwent arterial elasticity examination and body fat assessment. Basic information of body fat was collected including height,weight,waist circumference, hip circumference, triceps skin fold thickness, and subscapular skin fold thickness. We used human body composition analyzer (Inbody S10) to assess body fat mass, body fat percentage and visceral fat area.

Results: The mean age were 49.9±11.2 years old. Median cfPWV and crPWV was 9.3±2.8 m/s and 9.6±1.7 m/s,respectively. After adjusted to age, sex and other confounding factors, only skin fold thickness(β=-0.041,p=0.022) was associated with cfPWV. Body fat indexes including triceps and subscapular skinfold thickness, BMI, body fat percentage, body fat mass, visceral fat area were significantly negative correlated with crPWV (all p<0.001). We performed a gender- stratified subgroup analysis and found that significant associations between triceps(β=-0.065,p=0.009), subscapular skinfold thickness(β=-0.063,p<0.001)and crPWV were observed in male patients.

Conclusions: The effect of body fat indexes on arterial elasticity was mainly concentrated in peripheral artery. The association between subcutaneous fat and peripheral arterial stiffness significant mainly in males rather than in females.

Funding: Government Support - Non-U.S.

TH-PO221

Post-Dialysis Orthostatic Blood Pressure Is Not Associated with Extracellular Volume in Hemodialysis Patients

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Background: Blood pressure (BP) measurements are obtained before, during, and after hemodialysis (HD) for safety monitoring. The pattern of intradialytic seated BP changes is becoming recognized as an extracellular volume (ECV) assessment tool. It is unknown if orthostatic BP changes after HD provide information on ECV.

Methods: In a cohort of 55 hypertensive HD patients, we identified those with and without orthostatic BP decreases, defined as a >10 mmHg decrease in systolic BP from seated to standing position (both post-HD). We compared post-HD ECV/body weight using bioimpedance spectroscopy between the groups. We also compared orthostatic BP changes among tertiles of post-HD ECV/weight.

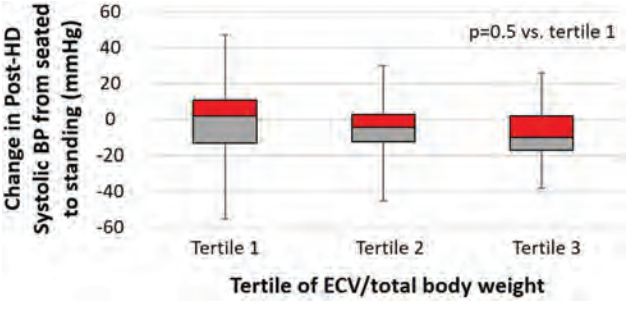
Results: Compared to those with orthostatic decreases (n=26), those without orthostatic BP decreases (n=29) were more likely to be African American. There were no differences in presence of diabetes or distribution of antihypertensive drug class. There were no differences in ECV/weight or cardiac hemodynamics between the groups (Table). There were no differences in orthostatic BP changes among tertiles of ECV/weight (Figure).

Conclusions: We found no associations between ECV/weight and post-HD orthostatic BP changes. Seated to standing BP changes should not be used to diagnose post-HD ECV overload or depletion in HD patients.

Funding: NIDDK Support, Veterans Affairs Support

Differences in Volume and BP Related Variables

Variable	Orthostatic Systolic BP Decrease >10 mmHg (n=26)	Orthostatic Systolic BP Increase or Decrease <10 mmHg (n=29)	p-value
Seated Pre-HD Systolic BP (mmHg)	151 (19)	155 (20)	0.5
Intradialytic Systolic BP Nadir (mmHg)	115 (20)	115 (21)	0.9
Seated Post-HD Systolic BP (mmHg)	151 (21)	133 (21)	0.003
Standing Post-HD Systolic BP (mmHg)	126 (21)	140 (21)	0.02
Change in post-HD Systolic BP from seated to standing (mmHg)	-24 (14)	6.7 (12)	<0.0001
Estimated Dry Weight (kg)	83 (22)	89 (18)	0.3
Ultrafiltration Rate (mL/kg/hr)	7.1 (3)	8.3 (4)	0.2
Pre-HD ECV/body weight (L/kg)	0.27 (0.05)	0.25 (0.05)	0.3
Post-HD ECV/body weight (L/kg)	0.25 (0.05)	0.23 (0.05)	0.2
Change in TPRI from pre to post HD (dyn sec/cm5)	-262 (860)	-218 (780)	0.8
Change in Cardiac Index from pre to post HD (L/min/m2)	0.09 (0.4)	0.04 (0.5)	0.7



TH-PO222

Oxygen Extraction Ratio (OER) and Intradialytic Hypotension

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Background: Intradialytic hypotension (IDH) worsens treatment tolerance, and outcome of hemodialysis (HD) patients. Attention has been given to the role of HD-induced hypoxia, evaluated by measuring arterial oxygen saturation (SaO2) and central venous saturation (ScvO2), in IDH prone patients. Oxygen Extraction Ratio (OER), the ratio between SaO2 and ScvO2, better than the two parameters alone theoretically describes intra-HD hypoxia. OER basal values and its changes occurring during HD (deltaOER) have been associated with mortality in Hd patients. A delta OER>40% seems to identify patients experiencing sub-clinical hypoxia and parenchymal stress. Aim of our study was to evaluate if delta OER could help identify patients at higher risk of IDH.

Methods: We enrolled clinically stable patients on HD since 3 months, with Central Venous Catheter. we sampled arterial SO2 (oxymeter) and ScvO2 (blood gas analysis) to calculate OER basally and at the end of HD, for three consecutive HD sessions. Average individual measurements were obtained to divide patients into two groups with delta OER > or <40 %. we recorded IDH in each subject, during a 24-months follow-up period.

Results: We divided patients into two group according to delta OER (threshold 40%). The group were not different for age, HD vintage, systolic (SBP) and diastolic blood pressure (DBP) and pulse rate. The group with delta OER >40% had a number of

IDH significantly higher than delta OER<40% group (30±20vs.10±20;p= .011), which was associated with lower pre-HD OER (30±4vs.36±8;p<.025) and similar post HD OER values.

Conclusions: Our study indicates that in HD patients, delta OER associate with IDH, with a threshold value set at >40% the basal value. We suggest that we could use OER to identify patients at higher risk of IDH, deserving more intensive intradialytic monitoring. Regrettably, it is applicable only in patients with CVC.

Patients, (n.)	Delta OER >40% (12)	OER <40% (16)	p<
Men/Females; n	7/ 5	7/9	
Age, yr	71±13	76±13	n.s
Vintage HD, months	53±34	41±33	n.s
SBP, mmHg	130±19	122±15	n.s
DBP, mmHg	71±8	66±13	n.s
Pulse rate, b/m	70±8	75±12	n.s.
V.E post HH	-10±4	-8.8±4	n.s
Diabetes, n (%)	7 (58%)	4 (25%)	n.s
Follow-up, months, (*range*)	12±2.2 (19-3)	12±5.7 (22-3)	n.s
IDH, N/1000 days/patients	**30±20**	**10±20**	**.011**
Pre-HD OER, %	30±4	36±8	.025
Post-HD OER, %	48±7	44±9	n.s
Delta OER, %	59±11	25±10	.001

TH-PO223

High Serum Calcium and Parathyroid Hormone Are Risk Factors of Intradialytic Hypotension in Hemodialysis Patients

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Background: Hypercalcemia and high serum intact parathyroid hormone(iPTH) are involved in the pathogenesis of vascular calcification. But the relationship between hypercalcemia and iPTH with intradialytic hypotension (IDH) is unclear.

Methods: This is a retrospectively cohort study, 922 HD patients were enrolled from 10 HD facilities in China. The patients were categorized into hypercalcemia group and hypocalcemia group according whether the serum corrected calcium levels ≥ 8.67mg/dl (the median of serum corrected calcium in all patients), which were further categorized into high PTH(serum intact PTH>300pg/ml) and low PTH(serum intact PTH≤300pg/ml) groups. Not only the clinic characters, especially the pre and post dialysis blood pressure were analyzed between the four groups, but also the risk factors of IDH were studied by multiple logistic regression in all HD patients.

Results: The prevalence of IDH was much higher in patients of hypercalcemia and high PTH than those of hypocalcemia and low PTH (21.1% vs. 9.6%, p<0.001). Adjusted with age, dialysis vintage, gender, diabetes mellitus, BMI, Kt/V, serum albumin, and hemoglobulin, logistic multiple regression analysis determined that hypercalcemia (OR:2.477, 95%CI: 1.632-3.758, P<0.001) (Model1), and hypercalcemia accompany with high PTH (OR:2.634, 95%CI: 1.378-5.031, P=0.003) (Model2) were risk factors of IDH. Furthermore, increasing ultrafiltration was also risk factor of IDH (Model1OR:1.409, 95%CI: 1.072-1.851, P=0.014; Model2 OR:1.397, 95%CI: 1.061-1.839, P=0.017). However, hemodiafiltration (HDF) was a protective factor of IDH in the patients (Model1 OR:0.441, 95%CI: 0.281-0.693, P<0.001; Model2 OR:0.442, 95%CI: 0.281-0.694, P<0.001).

Conclusions: Not only increasing ultrafiltration, but also high serum calcium and PTH are the risk factors of IDH. Furthermore, the hemodiafiltration will lower the risk of IDH compared with hemodialysis.

Funding: Other U.S. Government Support

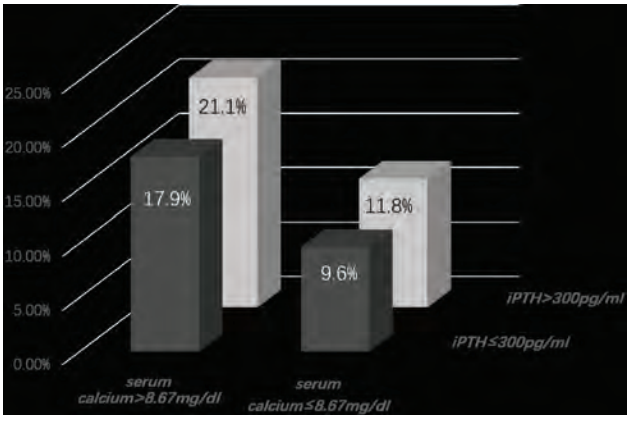

Fig.1 Associations between serum calcium, PTH levels, and the prevalence of IDH.

TH-PO224

Intradialytic Hypertension Increases Non-Access-Related Hospitalization and Mortality in Maintenance Hemodialysis Patients

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Background: Intradialytic hypertension, in patients on maintenance hemodialysis, is associated with increased morbidity and mortality. This study was aimed to determine the prevalence and outcome of intradialytic hypertension (IDH) in a tertiary care dialysis centre in India.

Methods: This was a prospective analytical study of 120 patients on hemodialysis. At screening phase, all patients were subjected to fluid optimization and adjustment in the antihypertensive medicines for appropriate control of blood pressure (BP). BP measurements during hemodialysis were recorded. The prevalence of IDH was noted. IDH was defined as increase in systolic BP of > 10 mmHg from pre to post hemodialysis or after 2nd hour of dialysis when significant ultrafiltration had occurred, on 3 consecutive sessions. Factors associated with IDH were evaluated and compared with cohort without IDH. The outcome of these patients in terms of morbidity and mortality over a follow up period of 12 months were recorded.

Results: The prevalence of IDH was 21.9%. The baseline demographic parameters of patients in both the groups (with and without IDH) including age, sex, dialysis access, duration of dialysis and comorbidities were similar. Laboratory parameters were similar except serum potassium and serum phosphorus, which were lower in patients with IDH. Out of all the variables studied, only low serum phosphorus was associated independently with IDH. During follow up, at 6 month, 19/71 (26%) non IDH and 12/20 (60%) IDH patients (p = 0.006) and at 12 month, 30/71 (42%) non IDH patients and 12/20 (60%) IDH patients required admission (p = 0.05). Mortality at 6 months was similar, 5/71 (7%) in non IDH and 4/20 (20%) in IDH (p = 0.10) patients, but was higher at 12 months, 11/71 (15.5%) in non-IDH and 8/20 (40%) in IDH (p = 0.028).

Conclusions: Incidence of intradialytic hypertension is high in India (21.9%) with increased morbidity in terms of hospitalization and increased mortality over a period of one year.

TH-PO225

Effect of Impaired Orthostatic Blood Pressure Homeostasis on Brain Network in Patients on Maintenance Hemodialysis

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Background: Patients with renal failure are at excessive risk of developing impaired orthostatic BP homeostasis. We have recently demonstrated that it is associated with memory deficit in dialysis patients. However, the neurobiological basis of this link remains poorly understood. The aim of this study was to evaluate the effect of impaired orthostatic BP homeostasis on brain network in ESKD patients leveraging the advances of graph-theory based network analysis and machine learning.

Methods: This is a data-driven analysis of the baseline neuroimaging data from an ongoing prospective cohort study which has enrolled 166 dialysis patients. Patients were excluded if they had a previous history of stroke or any other neurologic disease.

Results: Orthostatic BP reduction was defined as seated systolic / diastolic BP minus the minimum of three standing systolic / diastolic BPs. Functional, structural, and diffusion MRI data sets were obtained with a 3T scanner. After preprocessing, we constructed the whole-brain structural and functional networks using GRETNA software. We combine powerful MRI and machine learning to decode the relationship. Whole-brain structural connectivity (SC) and SC strength (SCs) were extracted as prediction features. After selecting significant features by Pearson coefficient from 141 participants, we use Extremely Randomized Tree model and the predict error is measured by Mean absolute error, Mean Square Error or corrections between actual and predicted values. By using the most accurate predicting model, we further investigate the biologic essence provided by

the predicting model. The data showed that the connections of BG-MTG and Amyg-FuG is stronger than other regions in predicting systolic orthostatic blood pressure reduction, while the connections strength in Amyg-pSTS holds the major contribution in predicting diastolic reduction.

Conclusions: Our analysis suggests that impaired orthostatic BP homeostasis has a significant effect on brain network in dialysis patients. These results provide further insight into the association between orthostatic hypotension and cognitive impairment and indicate that maintaining orthostatic homeostasis might be an effective strategy for the prevention of cognitive decline in the patients.

Funding: Government Support - Non-U.S.

TH-PO226

Pilot Study to Measure Indicators of Blood Flow in the External Auditory Meatus During Haemodialysis

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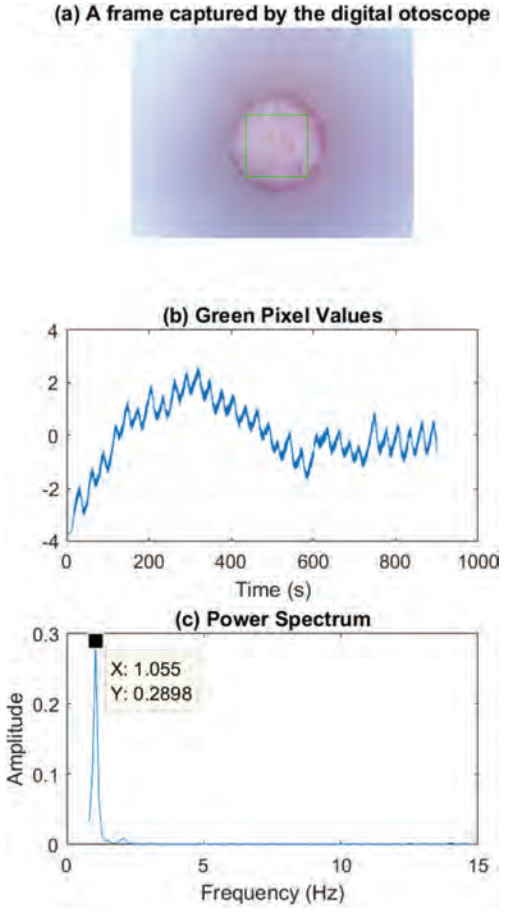
Background: Intradialytic hypotension remains the most common complication of outpatient haemodialysis (HD) sessions. As such, there is a need to develop non-invasive monitoring devices, which would then allow for therapeutic interventions to prevent hypotension. We report on a pilot study monitoring indicators of blood flow in the outer auditory meatus.

Methods: We measured the maximum pulse wave amplitude and indicators of blood flow by red and green pixel values in the outer auditory meatus from video recordings made using an otoscope fitted with a digital camera in adult patients undergoing haemodialysis treatments.

Results: We studied 61 patients, 43 (71.5%) male, mean age 64.9 ± 12.7 years during their dialysis session. Weight fell from 72.8±22.5 pre-dialysis to 71.5±22.1 kg post-dialysis ($p<0.001$). Blood pressure did not significantly change (pre-dialysis 142±29/67±18 to 143±25/68±17 mmHg post-dialysis). The maximum pulse wave amplitude in the external auditory meatus fell from 0.21 (0.1-0.55) to 0.14 (0.04-0.4) after 90 minutes, $p<0.001$, and remained low thereafter, and the change at the end of the dialysis session was associated with percentage weight loss ($r= -0.37$, $p=0.003$). Green and red pixel values did not change (pre-dialysis 0.339 (0.333-0.345) to 0.302 (0.291-0.33) post, and 0.301 (0.293-0.328) pre-dialysis to 0.339 (0.334-0.347), respectively).

Conclusions: This pilot study showed that the maximum pulse wave amplitude measured in the external auditory meatus fell during the dialysis session, and that the fall was associated with fluid removal. This could potentially lead to the development of a monitoring device which could fit in the ear and record during the dialysis session.

Funding: Private Foundation Support



TH-PO227

Uric Acid Distribution Adjusted by Urea Distribution Volume Is a Promising Marker of Hydration Status in Hemodialysis Patients

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Background: Hemodialysis (HD) patients are prone to developing volume disturbance. Bioelectrical impedance analysis (BIA) provides indices for evaluating volume status, although this requires a dedicated machine, which precludes it from other general clinical use. Uric acid (UA) barely crosses the cell membrane, while urea does so readily. The volume of distribution (Vd) of UA and urea can be considered markers of extracellular water (ECW) and total body water (TBW), respectively. We investigated whether the ratio of the Vd of UA and urea (V_{UA}/V_{UN}) can be a surrogate marker of ECW/TBW measured by BIA.

Methods: In total, 108 patients who were receiving HD at our facility and who underwent BIA in 2018 were included in this study. V_{UA}/V_{UN} was calculated using the single-pool model. We compared ECW/TBW values after dialysis measured by BIA (InBody S10; InBody, Tokyo, Japan). We investigated factors associated with residuals from regression. We also evaluated the predictive ability of overhydration (ECW/TBW ≥ 0.4) or dehydration (ECW/TBW < 0.38) in two randomly selected groups, the training group and the validation group.

Results: V_{UA}/V_{UN} and ECW/TBW were 0.646 ± 0.062 and 0.393 ± 0.014, respectively. ECW/TBW was highly correlated with V_{UA}/V_{UN} (ECW/TBW = 0.274 + 0.184* V_{UA}/V_{UN}). Multivariate analysis demonstrated that only creatinine and ECW/TBW were significantly associated with the regression residuals. The cut-off values of V_{UA}/V_{UN} for overhydration and dehydration were 0.666 and 0.579, respectively, in the training group. The corresponding area under the receiver operating characteristic curves were 0.872 and 0.898, respectively. The sensitivity and specificity values in the validation group were 0.571 and 0.868 for overhydration and 0.444 and 0.953 for dehydration, respectively.

Conclusions: V_{UA}/V_{UN} was not only associated with ECW/TBW but was also highly predictive of hydration status evaluated by BIA. We need only blood tests before and after the dialysis session for estimating V_{UA}/V_{UN}, so this measure is widely applicable, even in epidemiological studies, without the need for dedicated devices.

TH-PO228

Ambulatory Blood Pressure Monitoring and Other Blood Pressure Measures in the BID (Blood Pressure in Dialysis) Pilot Study

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Background: Ambulatory blood pressure monitoring (ABPM) is the gold standard for diagnosis and management of hypertension. However, poor adherence limits its use in clinical practice. In the BID pilot, we used predialysis standardized dialysis unit systolic blood pressure (SDUSBP) to drive BP management. We also compared this measure to ABPM, standardized home SBP (SHSBP), intradialysis SBP (IDSBP), and postdialysis SBP (PDSBP).

Methods: The BID protocol called for a 44-hour ABPM after the mid-week dialysis at baseline and quarterly in 5 geographic hubs, SDUSBP before each dialysis, SHSBP weekly the day after the mid-week HD treatment and also IDSBP and PDSBP with each treatment. Outcomes included the quantitative differences between these measures and their ability to predict left ventricular hypertrophy (LVH) on cardiac MRI at baseline and quarter four by analyzing the area under receiver operator characteristic (ROC) curves (AUC).

Results: Ninety-four out of 95 patients and 53 out of 84 patients eligible for ABPM, had both an ABPM and cardiac MRI at baseline and in quarter 4 respectively. The differences between average daytime SBP on ABPM vs. other measures in quarter 4 were as follows 1) SDUSBP – 3.36 (95% CI -8.72, 2.00) mm Hg; 2) IDSBP 1.63 (95% CI -2.73, 5.99) mm Hg and 3) PDSBP 1.40 (95% CI -2.90, 5.71) mm Hg. Forty-four patients in quarter 4 had ABPMs in addition to SHBP measurement. Mean difference between average day SBP on ABPM vs. SHSBP was 0.35 (95% CI -5.45, 6.16) mm Hg. The AUCs used to compare the ability of the different BP measures to predict LVH are shown.

Conclusions: Although difference between daytime SBP on ABPM and SDUSBP were higher than the other measures, the differences were modest. HSBP, IDSBP and PDSBP demonstrated similar values when compared to ABPM. ABPM was the strongest and SDUSBP the weakest predictor of LVH. Dialysis units should encourage adherence with ABPM and HBP measurements.

Funding: NIDDK Support, Commercial Support - Dialysis Clinic, Inc

AUC for relationship of different BP measurements with LVH

BP Measure	Systolic BP AUC (95% CI)	Diastolic BP AUC (95% CI)
ABPM at baseline	0.77 (0.65, 0.88)	0.70 (0.58, 0.82)
ABPM in quarter 4	0.71 (0.55, 0.87)	0.74 (0.57, 0.90)
HSBP	0.61 (0.44, 0.79)	0.69 (0.51, 0.86)
SDUBP	0.51 (0.32, 0.69)	0.64 (0.47, 0.82)
Intradialytic BP	0.62 (0.45, 0.79)	0.61 (0.44, 0.79)
Post Dialysis BP	0.67 (0.51, 0.84)	0.67 (0.50, 0.83)

TH-PO229

Higher Dialysis Dose and Less Intradialytic Hypotension Are Associated with Improvements in Longitudinal Changes in Dialysis Recovery Time

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Background: We studied if higher hemodialysis (HD) dose and less intradialytic hypotension (IDH) would associate with longitudinal improvements in dialysis recovery time (DRT).

Methods: We used data from adult HD patients at a large dialysis organization who responded to DRT survey ≤180 days from first date of dialysis (FDD) during 2014 to 2017. DRT survey asks: "How long does it take you to be able to return to your normal activities after your dialysis treatment?". Answers are: <0.5, 0.5-1, 1-2, 2-4, or >4 hours. A logistic regression model computed odds ratio for increased/maintained longer DRT (increase above DRT >2 hours) in reference to decreased/maintained shorter DRT (decrease below DRT <2 hours, or from DRT >4 hours). Changes in DRT were calculated from incident (≤180 days FDD) to prevalent (>365-to-≤545 days FDD) year. Model included/adjusted for incident DRT, age, comorbidities, HD with IDH episodes/month, Kt/V, and HD start before/after 1200 hours.

Results: Among 98616 incident HD patients (age 62.6±14.4 years), higher incident spKt/V associated with 13.5% (OR=0.865; 95%CI 0.801-to-0.935) lower odds of increased/maintained longer DRT in the prevalent year (Figure 1). A higher incident number of HD sessions with IDH episodes/month and change to a higher number associated with 0.8% (OR=1.008; 95%CI 1.001-to-1.015) and 2.2% (OR=1.022; 95%CI 1.015-to-1.028) higher odds of increased/maintained longer DRT in the prevalent year, respectively.

Conclusions: Incident patients who had higher spKt/V with a low number of HD sessions with IDH episodes had a lower likelihood of increased/maintained longer DRT in first year of HD. Dose optimization strategies with cardiac stability in fluid removal should be tested.

Funding: Commercial Support - Fresenius Medical Care North America

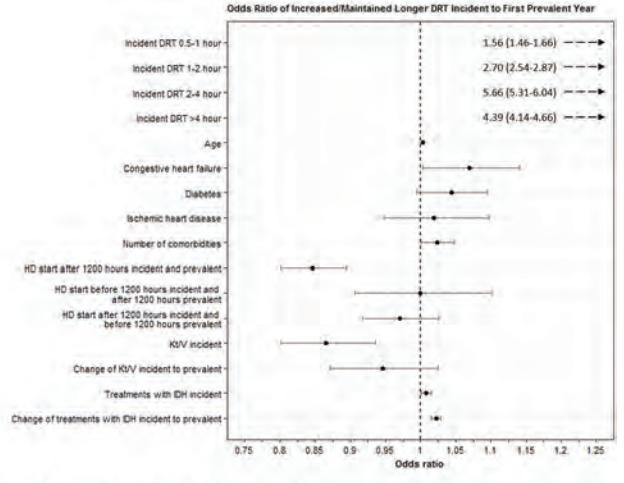

Figure 1: Forest plot of odds ratio and confidence intervals for variables associated to increased/maintained longer DRT from the incident to first prevalent year in reference to a decreased/maintained shorter DRT.

TH-PO230

Fluid Overload and Obstructive Sleep Apnea in Hemodiafiltration

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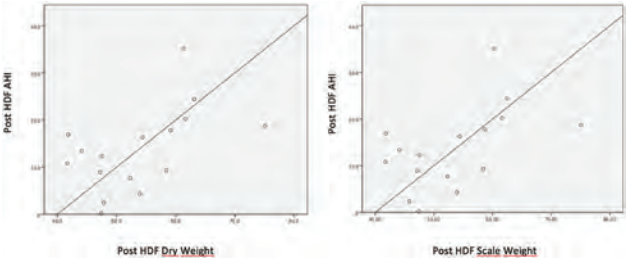
Background: Obstructive sleep apnea (OSA) seems to be more common in patients with end-stage renal disease (ESRD) than in the general population with a prevalence as high as 50 to 70%.Fluid overload leading to greater accumulation in the neck when supine may contribute to increased upper airway collapsibility. The aim of the study was to evaluate the impact of ultrafiltration on the apnea-hypopnoea index (AHI) in prevalent hemodiafiltration (HDF) patients.

Methods: We included patients from the HDF unit at the Instituto Nacional de Cardiologia from July 2018 to April 2019. Bioimpedance and overnight polysomnography were done the day before and the day after HDF. The primary outcome was AHI index. T test was used for within group comparisons (pre and post HDF) and Rho Spearman was used for correlations.

Results: 16 patients were included, 10 had mild AHI, 3 moderate AHI and 3 had severe AHI. After HDF, 11 patients improved the number of apnea/hyponea events. Patients with severe AHI significantly improved after HDF (38±6.4 to 25.2±9.4, p=0.03). Total body water/ extracellular relationship (TBW/ECW), thoracic TBW/ECW, scale and dry weight were all significantly associated with AHI improvement. There was a significant correlation between AHI and post HDF weight scale and dry weight (r = 0.56, p = 0.022 and r= 0-59, p = 0.016 respectively)(Figure).

Conclusions: AHI is improved with HDF, in particular in those with moderate and severe OSA. Volume overload appears to contribute to OSA in this population.



TH-PO231

Patient-Reported Quality of Life in Dialysis Compared with Non-Dialysis CKD Patients with Hyperkalemia in the United States and European Union 5: Results from the KDQOL

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Background: Patients with chronic kidney disease (CKD) have an increased risk of hyperkalemia (HK), which increases with CKD progression. Patients on hemodialysis report negative impact to quality of life (QoL), though evidence is limited. The increased risk of HK and associated morbidity and mortality may further add to patient burden.

Methods: Data from the 2015 and 2018 Adelphi CKD Disease Specific Programmes were pooled to create a cross-sectional dataset of patients, including data from physicians and their CKD patients across France, Germany, Italy, Spain, the UK and USA. Patients completed the KDQOL, a measure targeted at specific concerns of individuals with CKD. A multiple linear regression was performed, for each of the 5 KDQOL domains, to study the association between non-dialysis dependent (NDD) patients with HK (K^+ >5.0 mmol/L), DD patients without HK (K^+ 3.5-5.0 mmol/L) and DD patients with HK to a reference group of NDD patients without HK (and their interaction), adjusting for age, sex, eGFR level, and presence of heart failure and diabetes.

Results: Results from 1,242 patients showed an incremental decrease in QoL across each patient group for 2 of the 5 KDQOL domains. When compared to the reference group, NDD patients with HK experienced significantly poorer QoL across all 5 of the KDQOL domains. However, DD patients with HK experienced an additional significant deterioration in QoL across 4 of the 5 domains, compared with NDD patients without HK (Table 1).

Conclusions: This study highlights the negative impact that HK contributes to CKD patients, leading to further decrements in QoL, particularly among DD CKD patients. Innovative HK treatment approaches should be an important consideration by physicians to contribute to improved QoL in this patient population.

Funding: Commercial Support - AstraZeneca

Table 1: KDQOL values vs. CKD and Hyperkalemia Status

KDQOL domains, mean (n)	NDD without HK	NDD with HK	DD without HK	DD with HK
Burden of kidney disease	62.44 (774)	57.61 (178); p=0.030	44.78 (190); p=<0.001	46.96 (100); p=<0.001
Symptoms/problems	83.67 (760)	80.03 (177); p=0.012	78.60 (188); p=0.005	76.77 (101); p=0.002
Effect of kidney disease	78.42 (759)	69.68 (174); p=<0.001	68.29 (186); p=<0.001	61.26 (100); p=<0.001
SF-12 physical summary score	41.81 (741)	39.37 (171); p=0.002	38.30 (178); p=<0.001	38.39 (98); p=0.005
SF-12 mental summary score	47.42 (741)	45.53 (171); p=0.025	45.33 (178); p=0.050	45.85 (98); p=0.020

lower scores represent poorer quality of life; p-values show the comparison to the reference group

TH-PO232

Quality of Life in Caregivers of Patients Receiving Standard vs. Extended Hours Hemodialysis: The Co-ACTIVE Substudy of the ACTIVE Dialysis Trial

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Background: Caregivers of dialysis patients experience significant burden and lower quality of life (QOL) compared to the general population. Extended hours dialysis has benefits for the patient, however little is known about its effects on caregivers.

Methods: We evaluated QOL amongst caregivers of the ACTIVE Dialysis trial participants who were randomised for 12 months to receive extended (median 24 hours/week) or standard (12 hours/week) hemodialysis. Caregivers completed the EuroQOL-5 Dimension-3 Level (EQ5D-3L), Short Form-36 (SF-36) physical component summary (PCS), mental component summary (MCS) and SF-6D, and Personal Wellbeing Index (PWI). Primary outcome was change in QOL scores from study entry to follow-up.

Results: A total of 40 participated in this longitudinal study. Most caregivers were female (64%) and Asian (94%). At baseline, QOL scores in caregivers of patients randomised to standard and extended hours hemodialysis were similar (Table 1). At follow-up, there was a significant difference in the mean change in EQ5D-3L between those allocated to standard versus extended hours dialysis (-0.022±0.16 vs -0.197±0.30, p=0.04). There were no differences between standard and extended hours groups in mean change in PCS (-5.6±9.8 vs -1.2±9.8, p=0.2), MCS (-0.5±7.1 vs -4.1±11.2, p=0.4), SF-6D (-0.04±0.1 vs 0.03±0.12, p=0.8) or PWI (0.00±20.4 vs -2.3±17.6, p=0.9).

Conclusions: Our study found significantly poorer health utility amongst caregivers of patients randomised to extended hours dialysis, but no difference in QOL measures. This suggests extended hours dialysis may have a negative impact on caregivers, although our study has a number of limitations including small sample size and short follow-up, and the results should be regarded as exploratory. Further studies are needed to better understand the impact of dialysis on caregivers to inform the provision of support services.

Table 1. Baseline characteristics of caregivers in the Co-ACTIVE study

	Standard (n=16)	Extended (n=24)	p-value
Mean age, years (SD)	54.6 (10.3)	53.4 (13.0)	0.9
Sex, % Female Male	 71.4 28.6	 59.1 40.9	0.4
Marital status, % Married/defacto Single	 92.9 7.1	 100 -	0.4
Caregiver QOL score, mean (SD) EQ5D SF-36 PCS SF-36 MCS SF-6D PWI	 0.920 (0.12) 50.0 (7.3) 50.4 (10.0) 0.74 (0.1) 63.8 (21.1)	 0.911 (0.12) 47.9 (8.5) 48.3 (8.8) 0.71 (0.1) 62.5 (23.8)	 0.8 0.4 0.4 0.4 0.8

TH-PO233

Travel Arrangements in In-Center Hemodialysis: A Qualitative Study

Janewit Wongboonsin, Joseph R. Merighi, Paul E. Drawz. *University of Minnesota, Minneapolis, MN.*

Background: For people with end-stage renal disease, "travel" and "independence" are rated as 2 of the top 5 factors that inform their treatment modality choice. The limits imposed by in-center hemodialysis (IHD) treatment can present a variety of challenges for patients who wish to travel. This exploratory study investigated how IHD patients managed their travel and the role of dialysis social workers in executing travel arrangements for patients.

Methods: An interview-based, qualitative study was conducted with IHD patients being treated at a University-affiliated hospital and community-based dialysis social workers. Patients were screened from an inpatient nephrology consult panel and, after enrolling in the study, provided contact information for their dialysis social workers. Two coders used a grounded theory (constant comparative) approach to analyze the data from verbatim transcriptions.

Results: Sixteen patients and eight social workers were enrolled in the study. The patient sample included 8 women (50%), 13 whites (81.3%), and a mean dialysis vintage of 5 years. The social worker were all women and had a mean of 6 years of practice experience. Three overarching themes emerged from the interviews: the process, barriers, and facilitators of travel. The travel process subthemes included communication, dialysis schedule, and travel itinerary. The barrier and facilitator subthemes were categorized into patient, dialysis unit, and supporting factors. These subthemes addressed caregiver roles, being flexible, staff professionalism, and managing unanticipated situations. Overall, there was lack of uniform infrastructure and understanding regarding the travel process at the patient level, provider level, and system level.

Conclusions: This study identified multiple perspectives surrounding travel arrangements in chronic IHD patients. There is limited research on travel issues for chronic IHD patients and this investigation is among the first to articulate barriers and facilitators associated with travel from the perspective of patients and social workers. Promoting and supporting travel for IHD patients can serve to increase their sense of autonomy and provide opportunities to improve their quality of life.

TH-PO234

Hemodialysis Transportation, Compliance, and Quality of Life

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Background: A common reason for nonadherence to hemodialysis (HD) treatments is difficulty with transportation. This difficulty can also be the catalyst for mental stress surrounding getting to the dialysis unit on time. Health disparities reflect social, economic, and/or environmental disadvantages. As modality used for transportation is dependent on a patient's socioeconomic status, it can be related to health disparities. Identifying how transportation modality affects adherence to HD regiments and a patients perceieved quality of life can hopefully lead to improved strategies in HD transportation and improve clinical outcomes for all HD patients. We examined transportation modality, HD treatment compliance and its relationship with quality of life.

Methods: We reviewed the electronic charts of patients enrolled at our large hospital based non-profit dialysis network. We identified eligible patients that had documented transportation modality and Kidney Disease and Quality of Life (KDQOL-36) scores as well as health insurance information. HD compliance was calculated for the group between April 2014 to April 2018. The modes of transportation were designated as self/family (SF), ambulance/ambulette (AMB) and Taxi/AbleRide (TX). Health insurance was divided into three groups: Medicare (MCR), Medicaid (MCD) and private insurance/self-pay (PVT).

Results: The study population (n=249) was 46% white, 60% male, and had a median age of 62 years. The average compliance for the group was 91.6% with 76% of the patients at or above 90% compliance. 60%, 15% and 25% of the patients had MCR, MCD, or PVT insurance respectively. HD compliance by primary insurance varied at 93.3%, 92.14%, and 86.46%, for PVT, MCR and MCD, respectively (P<0.01). The average compliance was 92.7%, 90.8%, and 87.8% for travel by SF, AMB, and TX, respectively. There was a significant difference in the MCS component of the KDQOL-36 among the different modes of transportation with 48.4±10.4, 49.8±9.5, and 52.5±9.6, for travel by AMB, TX, and SF, respectively (p<0.02).

Conclusions: Our findings suggest that health insurance and transportation modality plays a significant role in hemodialysis treatment compliance. Transportation modatlity also plays a significant role in the mental health component of the KDQOL survey. Further prospective studies are required to confirm these relationships.

TH-PO235

Assessing the Impact of Hyperkalemia on the Quality of Life of Dialysis Patients Compared with Non-Dialysis Patients: Results from a Real-World Study in the United States and European Union 5

Eskinder Tafesse,[2] James Jackson,[1] Rebecca Moon,[1] Gary R. Milligan,[1] Jennifer Kim.[2] *[1]Adelphi Real World, Macclesfield, United Kingdom; [2]AstraZeneca, Gaithersburg, MD.*

Background: Patients with chronic kidney disease (CKD) are at increased risk for hyperkalemia (HK), which increases with CKD disease severity. Quality of life (QoL) may be impacted by the presence of HK, which is associated with greater risk of sudden cardiac death and hospitalization among hemodialysis patients. Only limited data exists on the impact of HK on the QoL of CKD patients who are dialysis dependent (DD) compared with non-dialysis dependent (NDD) patients, with and without HK.

Methods: Data from the 2015 and 2018 Adelphi CKD Disease Specific Programmes were pooled and analyzed. These real-world surveys collected data from physicians and patients with CKD in France, Germany, Italy, Spain, the UK and the USA. Patients completed the EuroQol-5D-3L (EQ-5D) questionnaire and the EuroQol visual analog scale (EQ-VAS). Physicians provided data on patient demographics, disease characteristics and comorbidities. A multiple linear regression was performed for EQ-5D utility and EQ-VAS to assess the association between NDD patients with HK (K^+ >5.0 mmol/L), DD patients without HK (K^+ 3.5-5.0 mmol/L), and DD patients; with HK to a reference group of NDD patients without HK (and their interaction), adjusting for age, sex, eGFR level, HF and diabetes.

Results: NDD patients with HK (n=176) had a significantly lower mean EQ-5D utility score than NDD patients without HK (n=766) (0.788 vs. 0.825; p=0.039). DD patients with HK (n=100) reported an additional deterioration in mean EQ-5D utility scores compared with NDD patients without HK (0.755; p=0.009) indicating poorer health status among this cohort. EQ-VAS mean scores also showed a significantly poorer QoL for NDD patients with HK (n=175) compared to NDD patients without HK (n=766; 64.7 vs. 67.5; p=0.048). Further reduction in QoL was observed for DD patients with HK (n=100) (62.3 vs. 67.5; p=0.015), compared with NDD patients without HK.

Conclusions: HK is associated with reduced EQ-5D health state utility scores in CKD patients. DD patients with HK experienced significantly greater negative impact on their QoL compared with NDD patients without HK. New therapeutic options and effective management of HK in DD CKD patients may positively improve QoL in this population.

Funding: Commercial Support - AstraZeneca

TH-PO236

How Does Starting Dialysis Impact Quality of Life in Patients and Their Partners? A Longitudinal Study

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Background: For patients and their families, quality of life (QOL) while on dialysis is of central importance. Despite this, limited research exists on how (QOL) changes as patients transition onto dialysis. The present study aimed to investigate changes in QOL in renal patients and their partners (spouses or significant others) during the critical period of preparing for dialysis and over the first 12 weeks on dialysis. We also aimed to determine whether psychosocial factors measured during pre-dialysis can predict QOL outcomes 12 weeks after starting dialysis.

Methods: 10 renal units in England took part in this observational, longitudinal study. 88 couples completed baseline questionnaires during pre-dialysis; 50 couples completed follow-up questionnaires at 6 weeks after starting dialysis; and 40 couples completed further follow-up questionnaires at 12 weeks after starting dialysis. At each time point patients and their partners completed a QOL questionnaire (WHOQOL-BREF), study specific questionnaires on psychosocial factors (Expectations, Accepting Dialysis, and Patient-Partner Relationship Characteristics), affect (HADS), and symptoms (POS-S Renal or Generic).

Results: Preliminary analyses show significant positive changes in QOL in patients from pre-dialysis to 6 weeks (b=0.3, p <0.001, 95% CI (0.17, 0.45). No significant differences were found in changes in partners' scores over this time period (b=0.2, p=0.134, 96% CI (-0.1, 0.6)). QOL remained steady over the subsequent 6 weeks (patients b=0.2, p=0.357, 95% CI (-0.2, 0.5); partners b=-0.1, p=0.793, 95 %CI (-0.5, 0.4)). Further analyses will be conducted once data collection concludes in June 2019. Multi-level modelling will be used to estimate the changes in QOL between patients and partners. Baseline scores on the psychosocial factor scales will then be tested as predictors of QOL outcomes at 12 weeks.

Conclusions: This research is one of the first to investigate QOL in patients and their partners as they transition onto dialysis and to explore the impact of psychosocial variables on QOL. These findings could assist renal clinicians in targeting couples who may need support and may suggest the key psychological and relationship factors which will facilitate better QOL during this stressful period.

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TH-PO237

Effectiveness of Decision Aids in Promoting Knowledge and Shared Decision Around Treatment for ESRD: A Systematic Review and Meta-Analysis

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Background: Renal replacement therapy (RRT) for end stage renal disease (ESRD) is a preference-sensitive decision yet patients do not perceive they have a choice. Guidelines have called for increased shared decision making in this space especially for higher risk patients for whom there is equipoise regarding the balance of benefits and harms. Decision aids have been proposed to ensure goal concordant care. We systematically reviewed the performance of decision aids for ESRD treatment choice.

Methods: Multiple databases were searched for comparative studies of using decision aids to help advanced kidney failure patients choose between different types of RRT from inception to January 30, 2018. PRISMA guidelines were followed with two reviewers independently screening abstracts, performing full text assessment of inclusion criteria and extracting study design, outcomes and risk of bias.

Results: Of 1083 articles screened and 90 reviewed in full text, 10 were included, tested in a total of 1114 patients (range 35-569). There was great heterogeneity of measured and reported outcomes and few used validated tools. Pre-planned meta-analyses of knowledge showed significant increase in standardized mean difference of 0.598 but with high heterogeneity I^2 61%.

Conclusions: Decision aids appear to increase patient knowledge in ESRD but their outcome reporting is heterogeneous which limits the strength of inferences. To move the field forward, international consensus is needed on the most meaningful outcome measures and best practices in future decision aid research.

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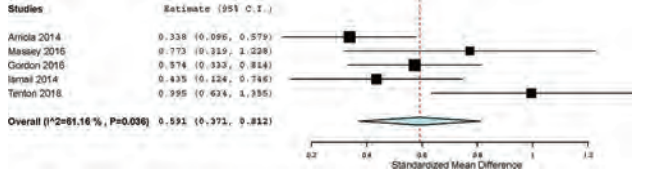

TH-PO238

Week-to-Week Variability of Dialysis Recovery Time

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Background: Fatigue is identified by patients as a priority for research. Post-dialysis fatigue is common and associated with poor outcomes. Unpredictability of symptoms worsens the impact of these symptoms on patients. In a previous study, we prospectively recorded weekly dialysis recovery time (DRT) for four weeks in patients with prolonged DRT at baseline [Duggal et al. HDI. 2019]. Here, we report on the weekly variability of DRT in these patients.

Methods: Patients with DRT data from all four weeks were included in this study. We hypothesized that a change in DRT of four hours or more from the previous week was a significant fluctuation to impact symptom predictability and patient's ability to plan activities after dialysis. We report on the proportion of patients who had at least two such fluctuations during the follow-up period. In addition, we report on within-patient week-to-week variability using within-patient ranges, standard deviations (SD), coefficients of variation and mean absolute differences (MAD).

Results: Seventy-four patients were included in this analysis; median age 64 years (IQR: 59 - 75), 32% female. During the follow-up period, 26% of patients had at least two recorded DRTs that were four hours or more different from the prior week. Median within-patient week-to-week DRT range, SD and MAD were 525 (180-960), 230 (77 – 464) and 209 (80 – 440) minutes respectively, and the coefficient of variation was 0.48 (0.22 – 0.87).

Conclusions: Among patients with long recovery time at baseline, we report substantial variability in week-to-week DRT. These fluctuations in symptoms increase the burden on hemodialysis patients. More attention is needed to study the variability of symptoms and its burden in terms of extent and effect.

TH-PO239

The Impact of Extended Hours Haemodialysis on Quality of Life, Vascular Access, Mortality, and Residual Renal Function: Systematic Review and Meta-Analysis

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Background: Patients with end-stage renal failure on conventional haemodialysis (CHD) experience significant morbidity and mortality. There is increasing evidence that extending weekly haemodialysis (HD) time is associated with improvements in quality of life (QoL), biochemical and cardiovascular parameters, and mortality. However, there is concern that increasing HD duration or frequency accelerates the loss of residual renal function (RRF) and increases vascular access adverse events. This systematic review aims to determine the impact of extended HD in comparison to CHD on QoL, vascular access events, mortality and RRF.

Methods: Randomised and non-randomised controlled trials of adult prevalent HD patients comparing extended hours HD (> 12 hours of HD in 1 week) to CHD were eligible. Outcomes of interest were quantitative measures of QoL, vascular access adverse events, all-cause mortality and RRF. Data from randomised and non-randomised trials were pooled separately using a random-effects model.

Results: 476 patients from 6 trials were eligible. The number of trials available for meta-analysis varied for each outcome. There was no significant change in QoL when comparing extended HD to CHD (SF-36 PCS standardised mean difference 0.61, 95% CI -0.10 to 1.31, *P*=0.09, SF-36 MCS standardised mean difference -0.04, 95% CI -0.61 to 0.54, *P*=0.90). There was no significant change in vascular access adverse events (relative risk ratio 1.25, 95% CI 0.88 to 1.77, *P*=0.21) or mortality (relative risk ratio 2.29, 95% CI 0.60 to 8.71, *P*=0.22). RRF was only assessed in one report which demonstrated a potential reduction over 12 months with extended HD, however, RRF was not a pre-specified secondary outcome. All trials had a high risk of bias.

Conclusions: In this systematic review, we demonstrated no significant difference between extended HD and CHD on QoL, adverse vascular access events and mortality. There was only a single trial with data regarding the changes in RRF. The majority of the included trials were either low or very low in quality. This supports the need for further adequately powered randomised controlled trials.

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TH-PO240

Comparison of Approaches to the Identification of Symptom Burden in Hemodialysis Patients Utilizing Electronic Health Records

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Background: Symptoms are common in patients on maintenance hemodialysis (HD), however identification within the electronic medical record (EMR) is challenging. Natural language processing (NLP) can be utilized to identify symptoms from narrative clinical documentation by physicians and other providers.

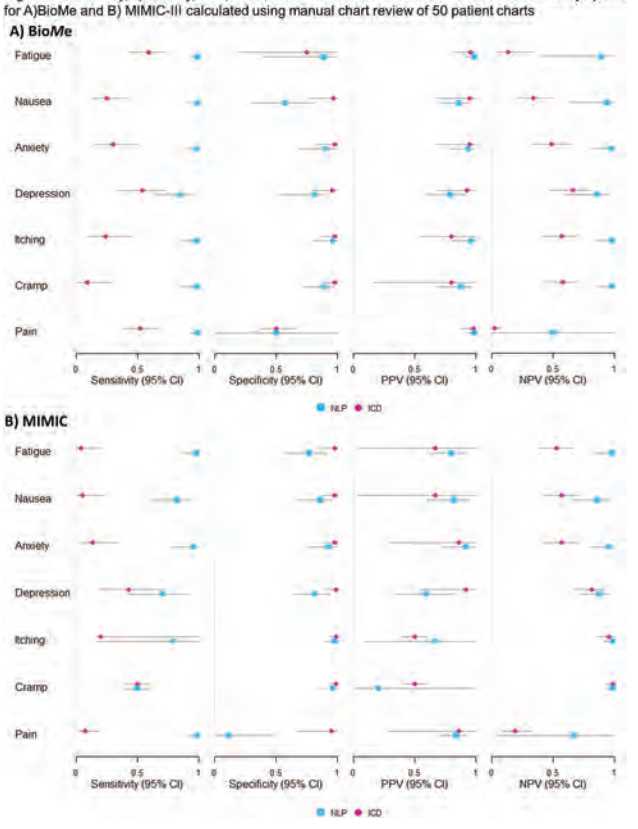
Methods: We utilized NLP to identify 7 patient symptoms from clinical notes of HD patients from the Bio*Me* Biobank and validated our findings using the MIMIC-III database. We compared NLP performance with ICD codes and validated the performance of NLP and ICD codes vs. manual chart review.

Results: We identified 1034 and 519 HD patients from Bio*Me* and MIMIC-III, respectively. In Bio*Me*, the most frequent symptoms identified were pain (NLP 93% vs. ICD 46%, P<0.001), fatigue (NLP 84% vs. ICD 41%, P<0.001), and nausea and/or vomiting (NLP 74% vs. ICD 19%, P<0.001). Sensitivity for NLP ranged from 0.85 (95% CI 0.65-96) for depression to 0.99 (95% CI 0.93-1) for fatigue while sensitivity for ICD ranged from 0.09 (95% CI 0.01-0.29) for cramps to 0.59 (95% CI 0.43-0.73) for fatigue. Results were similar in MIMIC-III. ICD codes were significantly more specific for nausea and/or vomiting in Bio*Me* and for fatigue, depression, and pain in MIMIC-III. A majority of patients in both cohorts had ≥4 symptoms. Patients with more symptoms identified by NLP, ICD, and chart review had more clinical encounters. Results were similar in a subgroup of 608 patients who had ≥2 years of follow up with only 1 year of notes reviewed.

Conclusions: NLP had higher sensitivity compared to ICD codes for identification, with comparable specificity for most symptoms and may be useful for the high-throughput identification of patient-centered outcomes.

Funding: NIDDK Support

Figure 1: Sensitivity, specificity, PPV, NPV, and F1 score of NLP vs. ICD for identification of symptoms for A)BioMe and B) MIMIC-III calculated using manual chart review of 50 patient charts



TH-PO241

Symptom Burden in Renal Patients Under the Care of Single United Kingdom Center

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Background: Renal patients suffer from a high and variable symptom burden, irrespective of the standard of care provided. We assessed the symptom burden of a cohort of renal patients under our care to understand the extent of the problem in our center.

Methods: NHS England health survey questionnaire was used to evaluate symptoms suffered by patients with chronic kidney disease (CKD) stage 4/5 and those receiving renal replacement therapy (RRT). Age, Urea clearances, Charlson comorbidity index (CCI), eGFR and RRT vintage were noted.

Results: 290 patients completed the questionnaire. Median age was 64.5 (IQR: 21), 60.3% were males with median CCI of 3.5 (IQR: 6). The whole cohort experienced a median of 3.5/17 symptoms (IQR: 6). Weakness (53.45%), poor mobility (40.69%) and difficulty sleeping (33.96%) were the top 3 symptoms complained. Table 1 summaries the distribution and top 3 symptoms suffered by patients with CKD and those on RRT. Symptom burden was significantly less in the transplant cohort. Age, renal clearances (eGFR in CKD and tranplant cohorts; Kt/V in dialysis cohorts) did not correlate with symptom burden, however CCI score statistically (r=0.193, p=0.001) correlated to the symptom burden.

Conclusions: Renal patients experience multitude of symptoms and symptom burden is similar in CKD and those on RRT. The standards of care provided to renal patients should include symptom assessment and management where possible.

Table 1

	CKD N=63	Haemodialysis N=111	Home therapies N=49	Transplant N=67
Median number of symptoms experienced*	4 (IQR: 7)	5 (IQR: 6)	4 (IQR: 5)	1 (IQR: 4)
1st most common Symptom and % experiencing	Weakness 50.8%	Weakness 63.96%	Weakness 55.10%	Weakness 37.31%
2nd most common Symptom and % experiencing	Poor Mobility 38.1%	Poor Mobility 57.66%	Poor Mobility 40.81%	Difficulty Sleeping 31.34%
3rd most common Symptom and % experiencing	Difficulty Sleeping 38.1%	Difficulty Sleeping 43.24%	Difficulty Sleeping 40.81%	Feeling anxious & Shortness of Breath 20.9%

*Questionnaire explored 17 symptoms in total

TH-PO242

Symptom Burden with Calcium Carbonate Compared to Sevelamer in Haemodialysis Patients

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Background: Patients with CKD frequently experience a considerable symptom burden which interferes with quality of life. Gastrointestinal tract (GIT) symptoms, including nausea, vomiting, constipation and diarrhoea, affect 10-40% of CKD patients. Medications, including phosphate binders (PB), often contribute to this symptom burden. We compared symptoms on the calcium-based phosphate binder, calcium carbonate (CC) therapy with those on sevelamer in a clinical trial.

Methods: Prevalent haemodialysis (HD) patients were recruited into a randomised study (*n*=37). Total study duration was 37 weeks, including 1 week of PB 'washout'. Participants were randomised to either i) 36 weeks of CC therapy or ii) 12 weeks of CC, followed by 24 weeks of sevelamer therapy. Patient symptoms were assessed with the Palliative Care Outcome Scale-Renal Version (POS) and analysed according to total scores and individual scores for specific GIT symptoms.

Results: 26 participants completed the study, and were analysed according to intention-to-treat analysis. 10 participants were randomised to the CC only arm, whilst 16 to the CC/sevelamer arm. There were no statistically significant differences in baseline demographics or co-morbidities between the groups. At baseline, median total POS scores were 10 (interquartile range: [IQR] 7-14) in the CC only arm vs. 13 (IQR 3-19) in the CC/sevelamer arm. At study completion, median POS scores were 12 (IQR 7-13) in the CC only arm, vs 8 (IQR 2-13) in the CC/sevelamer arm, with no statistically significant differences between groups at any timepoint. With regards to GIT symptoms, the proportion of patients experiencing improvement in nausea from baseline to study end were 30% and 44% in the CC only and CC/sevelamer arms respectively, and for vomiting, 10% vs 25% experienced improvement in the respective groups. 20% of CC only patients had more severe constipation at study end vs 31% in the CC/sevelamer group; and for diarrhoea, 30% of CC only vs 35% of CBPB/sevelamer patients reported increased symptoms. None of the changes in specific GIT symptoms were statistically significant.

Conclusions: Symptom burden of patients on HD did not change significantly with different PB therapy in our study, with similar changes in GIT symptoms over time comparing CC and sevelamer therapy.

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TH-PO243

Pruritus and Mortality in Hemodialysis Patients: Results from the International DOPPS

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Background: Chronic kidney disease-associated pruritus (CKD-aP) has been previously associated with poorer quality-of-life and increased risk of depression and death in hemodialysis (HD) patients. We sought to assess the association between pruritus and mortality in a large, contemporary, international cohort of HD patients.

Methods: We analyzed 25,916 HD patients from 21 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS) phases 4-6 (2009-2018) who self-reported the degree to which they were bothered by itchy skin (5-category ordinal scale from "Not at all" to "Extremely"). We used Cox regression to investigate the association between pruritus and all-cause mortality, adjusted for confounders.

Results: The proportion of patients who were at least moderately bothered by pruritus was 37% overall, and ranged from 27% in Germany to 47% in the UK. The groups with more severe pruritus had lower mean hemoglobin and albumin, a higher proportion of catheter use, and a higher prevalence of cardiovascular comorbidities, diabetes, and psychiatric disorders. The death rate was 0.106/year over a median (IQR) follow-up of 17 (9, 27) months (4,063 deaths). Compared to the reference group of patients not at all bothered by itching, the adjusted mortality HR (95% CI) was 1.02 (0.93, 1.11) for somewhat bothered, 1.13 (1.03, 1.24) for moderately bothered, 1.08 (0.98, 1.21) for very much bothered, and 1.30 (1.15, 1.48) for extremely bothered (Figure).

Conclusions: Analyzing these recent data, survival was shorter for HD patients who were moderately-to-extremely affected by pruritus. These results underscore the importance of diagnosing, evaluating possible causes of, and treating CKD-aP, with the goal of reducing symptom severity, in hopes of improving patient outcomes.

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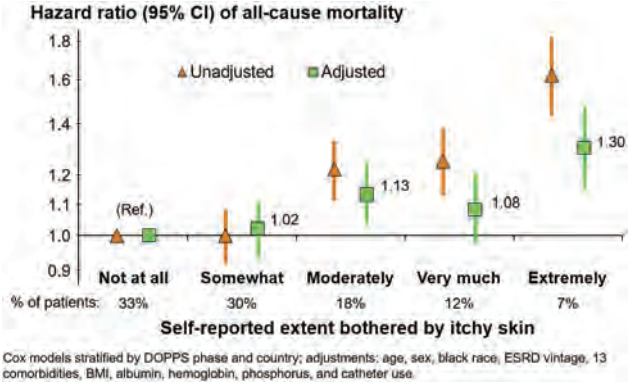

Cox models stratified by DOPPS phase and country; adjustments: age, sex, black race, ESRD vintage, 13 comorbidities, BMI, albumin, hemoglobin, phosphorus, and catheter use.

TH-PO244

Pruritus and Patient-Reported Outcomes (PROs): Associations Between the Skindex-10 and PROs in Hemodialysis Patients

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Background: Chronic kidney disease-associated Pruritus (CKD-aP) is a prevalent and distressing symptom in hemodialysis (HD) patients that affects Health Related Quality of Life (HR-QoL), but remains poorly characterized.

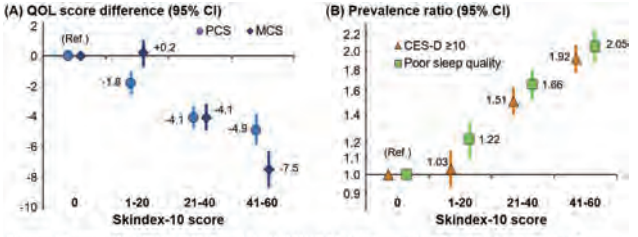
Methods: We analyzed 5418 HD patients from 17 countries in phase 5 (2013) of the Dialysis Outcomes and Practice Patterns Study (DOPPS) who self-reported being bothered by itchy skin (yes/no). "No" responses were assigned a Skindex-10 (SK-10) score of 0. Patients responding "Yes" then answered 10 questions about the frequency (0-6 scale) they were distressed by various aspects of CKD-aP. We investigated the association between SK-10 score (0-60 range; higher = more bothered) and 4 outcomes: (1) Physical and (2) Mental Component Summary (PCS; MCS) scores from the SF-12 (higher score = better HR-QoL) using linear mixed models; (3) Center for Epidemiologic Studies-Depression (CES-D) score ≥10 (indicative of depressive symptoms) and (4) Poor sleep quality (≥3 nights/week of restless sleep), both using modified Poisson regression.

Results: Mean SK-10 score was 12.2 overall and 27.4 among those affected by CKD-aP (Yes responders); 45% of patients had SK-10 score >0, including 17% with 1-20, 19% with 21-40, and 9% with 41-60. In adjusted models, lower PCS and MCS scores, poorer sleep quality, and greater likelihood of CES-D ≥10 were observed with increasingly higher SK-10 scores (Figure). SK-10 was highly correlated (r=0.71) with a separate summary question about the extent patients were bothered by itchy skin in the past 4 weeks.

Conclusions: Pruritus severity, reflected by the SK-10, was clearly and monotonically associated with other PROs including physical and mental HR-QoL, depression, and sleep quality, further emphasizing the importance of identifying and treating CKD-aP. Given its strong correlation with the SK-10 score, the single summary question could make routine assessment of pruritus in HD patients more concise and efficient.

Funding: NIDDK Support, Commercial Support - This analysis was supported by Vifor, Relypsa, and Cara Therapeutics. The DOPPS Program is supported by Amgen (since 1996, founding sponsor), Kyowa Hakko Kirin (since 1999 for Japan DOPPS), and Baxter Healthcare Corp. Additional support for specific projects and countries is provided by Akebia Therapeutics, AstraZeneca, European Renal Association-European Dialysis

& Transplant Association (ERA-EDTA), Fibrogen, Fresenius Medical Care Asia-Pacific Ltd, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGfN), Italian Society of Nephrology (SIN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Otsuka America, Proteon Therapeutics, the Association of German Nephrology Centres, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Belgian Federal Public Service of Public Health in Belgium, Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN) in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN), and Kidney Research UK (KRUK) in the United Kingdom, and the Agency for Healthcare Research and Quality (AHRQ) and National Institutes of Health (NIH) in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health and not to Mr. Karaboyas directly., Private Foundation Support, Government Support - Non-U.S.



Skindex-10 score calculated as in Mathur et al. (*CJASN 2010*); Linear mixed models (QOL) and modified Poisson regression (≥3 nights/week of restless sleep; CES-D ≥10) models adjusted for age, sex, black race, ESRD vintage, 13 comorbidities, BMI, albumin, hemoglobin, phosphorus, catheter use.

TH-PO245

Difelikefalin Improved Quality of Life (5-D Itch Scale-Domains) in Hemodialysis Patients with Pruritus in an 8-Week Phase 2 Randomized, Placebo-Controlled Study

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Background: Among patients with chronic kidney disease (CKD) undergoing hemodialysis (HD), >40% have moderate-to-severe pruritus, which is associated with poor quality of life (QoL). Difelikefalin (DFK; CR845) is a selective kappa opioid receptor agonist that acts peripherally with a dual anti-inflammatory/antipruritic effect and to date has negligible abuse potential. In a Phase 2 study of HD patients with CKD associated pruritus, it was previously reported that DFK significantly reduced itch intensity. Itch reduction, assessed by the Worst Itching Intensity Numerical Rating Scale (WI-NRS) score correlated with significant improvements in itch-related QoL measures, as measured by the Skindex-10 and 5-D Itch scales. To further characterize the impact of itch reduction on patient QoL, we present results using the 5-D Itch scale domains.

Methods: Patients were randomized 1:1:1:1 to receive an IV bolus of DFK 1.5, 1.0, 0.5 mcg/kg or placebo (PBO), at the end of each dialysis over an 8-week (Wk) treatment period. The 5-D Itch scale domains were used to measure Degree, Duration, Direction [change over time of itch], Disability [sleep, leisure/social, housework/errands, work/school], and Distribution [body location of itch] – each ranked on a 5-point increasing severity scale. This analysis focused on the 0.5 mcg/kg dose that was advanced into Phase 3 studies.

Results: Patients treated with DFK 0.5 mcg/kg (n=44) exhibited a clinically meaningful improvement in 5-D Itch total scores vs PBO (n=45) at Wk 8 (-5.7 vs -2.8 LS mean [p<0.001 vs PBO]), with a significant correlation between WI-NRS and 5-D total scores (r= 0.71, p<0.0001). Except for Distribution (-0.6 vs -0.4 [p=0.368]), significant improvements from baseline were reported across all subdomains in DFK vs PBO groups at the end of Wk 8; Degree: -1.1 vs -0.5 [p<0.001 vs PBO]; Duration: -1.2 vs -0.6 [p=0.003]; Direction: -1.6 vs -0.7 [p<0.001]; Disability: -1.2 vs -0.5 [p=0.004].

Conclusions: This analysis further characterized the impact of itch severity reduction with DFK indicating significant improvement in QoL as measured by the 5-D Itch multidimensional questionnaire. Results demonstrate itch intensity reduction with DFK is associated with improved QoL.

Funding: Commercial Support - Cara Therapeutics, Inc.

TH-PO246

Moisturizer Improves Pruritus in Dialysis Patients by Increasing Water Content in the Stratum Corneum: A Multicenter, Randomized, Confirmatory Study

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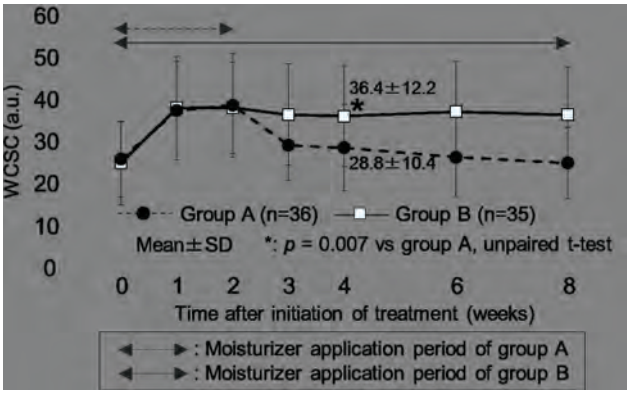
Background: Dialysis patients often have skin dryness and pruritus that are treated with moisturizers without sufficient evidence. We had reported an exploratory study on the efficacy of a heparinoid moisturizer for asteatosis in dialysis patients at Kidney Week 2017. In this confirmatory study, the efficacy and safety of additional 4-week treatment was evaluated in a larger population.

Methods: This study was an open-label, randomized, before-after, parallel group comparison, multi-center study conducted after approval by the Institutional Review Board. The study was funded by Maruho Co., Ltd., and registered at the University Hospital Medical Information Network (ID: UMIN000029360). In total, 71 Japanese chronic renal failure patients on dialysis with asteatosis applied a topical heparinoid (Maruho) twice a day on dryness/pruritus areas, including the lower ribs where water content in stratum corneum (WCSC) was measured using a Corneometer (Courage+Khazaka, Cologne, Germany), at proper dose by finger-tip unit for 2 weeks in Group A and 8 weeks in Group B. The primary endpoint was WCSC at Week 4 and secondary were trends in WCSC, pruritus visual analogue scale (VAS), dryness symptoms and dermatology life quality index (DLQI). Safety endpoint was adverse events (AEs).

Results: WCSC at Week 4 of group B (n=35) was significantly higher than Group A (n=36). WCSC, pruritus VAS and dryness symptoms improved until Week 2 in both groups. After Week 2, improvement sustained in Group B, but exacerbated in Group A. DLQI showed the same trend, especially in "symptoms and feelings" subscale. AEs occurred in 51 patients (107 events); 1 patient had treatment-related rash/eruption.

Conclusions: Heparinoid moisturizer increased WCSC, which subsequently improved pruritus and QOL. Continuous treatment at proper dose is necessary to maintain efficacy for asteatosis and pruritus in dialysis patients.

Funding: Commercial Support - Maruho Co., Ltd.



TH-PO247

Difelikefalin Significantly Reduced Sleep Disturbance in Hemodialysis Patients with Moderate-to-Severe Pruritus in an 8-Week Phase 2, Randomized, Placebo-Controlled Study

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Background: Patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) often have CKD-associated pruritus (CKD-aP), a debilitating chronic systemic itch. More than 40% of CKD patients suffer from moderate-to-severe itch with associated poor quality of life (QoL) and sleep disturbance.[4] Sleep disturbance in CKD is associated with an increased mortality risk.[5] Difelikefalin (DFK, CR845) is a selective kappa opioid receptor agonist that acts peripherally with dual anti-inflammatory and antipruritic effects. In an 8-week Phase 2 study in HD patients with moderate-to-severe pruritus, DFK demonstrated significant efficacy in reducing itch intensity and improved itch-related QoL measures. To further characterize the impact of itch reduction with DFK, we report results regarding changes in sleep disturbance.

Methods: Patients were randomized 1:1:1:1 to receive an intravenous bolus injection of DFK 1.5, 1.0, or 0.5 mcg/kg, or PBO at the end of each dialysis over an 8-week treatment period. The sleep disturbance subscale is part of the MOS sleep scale (MOS-S) and focuses on trouble falling asleep, sleep restlessness, awakening during sleep, and time to fall asleep during the past week. The MOS-S was administered on Day 1 (predose) and at Week (Wk) 4, Wk 8, and at the end of treatment (EOT, Day 57). This analysis focused on the DFK 0.5 mcg/kg dose, which was advanced into Phase 3 studies.

Results: Patients treated with DFK exhibited a significant reduction in sleep disturbance compared with PBO, with a mean change from baseline in DFK 0.5 mcg/kg (n=44) and PBO (n=45) groups, respectively, of -8.6 vs 2.2 [p=0.013] at Wk 4; -9.8 vs -2.2 [p=0.077] at Wk 8; -13.8 vs -1.3 [p=0.006] at EOT.

Conclusions: Significantly improved MOS-S sleep disturbance scores were obtained after DFK treatment, indicating a clinically sustained improvement in sleep through Wk 8 that was associated with a robust and sustained reduction in itch intensity. The effects of DFK on sleep, as well as long-term efficacy and safety of DFK, are currently under investigation in patients with CKD-aP in ongoing Phase 3 studies. **Reference:** [4]Shirazian S et al. *Int J Nephrol Renovasc Dis* 2017;10:11; [5]Benz R et al. *Am J Kidney Dis* 2000;35:1052

Funding: Commercial Support - Cara Therapeutics, Inc.

TH-PO248

Arterial Pulse Enhancement Technology (A-PET) Therapy Using VascuPump for Relief of Symptoms in Restless Legs Syndrome (RLS) in Patients on Dialysis

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Background: Restless legs syndrome (RLS) occurs in 25% to 40% patients on hemodialysis. In patients on dialysis poly-pharmacy and pill burden is a significant risk factor and there is a need for treatment which is noninvasive, non-pharmacologic, time efficient and has long lasting response. Arterial Pulse Enhancement Technology (A-PET) therapy delivered using VascuPump is noninvasive, non-pharmacologic treatment given during dialysis for 15 minute on both legs (no extra visit). VascuPump device uses inflatable cuffs, placed around calf, to rhythmically compress the limb with each heartbeat to enhance blood flow down the limb.

Methods: Open labelled treatment for patients on maintenance hemodialysis thrice per week. Six treatments were given during consecutive dialysis sessions. Patients with DVT, aortic insufficiency, leg wound or ulcer, acute thrombophlebitis and medically unstable patients were excluded. Baseline Doppler study was done to exclude DVT. To assess RLS, International RLS Study Group Rating Scale (IRLSSG) was used, range 1-40. Wong Baker Pain Scale (WBPS) was used before and after treatment, range 0-10.

Results: 52 patients with mean age 58.4 yr (range 26-77), male 32 (62%), diabetes 40 (77%). RLS score at start of the treatment was 27.1 (17-39) which dropped to 20 (14-34) at the end of the last treatment. WBPS before and after treatment was 7.6 (2-10) and 3.3 (2-8) respectively. The acute response after cumulative 270 treatments was a 41% decrease in pain. There was a trend towards consistent decrease in the baseline WBPS of individual patients with multiple treatments. Average Relief lasted for an average of 55 hours (range 0-172 hrs) after individual treatment. A total of 14 patients did not complete the six treatments due to unstable clinical condition or no response. One patient had worsening cramps in the legs. There were no other complications observed after 270 cumulative treatments in these patients on dialysis. A total of 73% (38/52) patients benefitted from the treatment.

Conclusions: A-PET therapy during dialysis is an effective non pharmacologic therapy for RLS patients on maintenance hemodialysis. Further randomized controlled studies are needed in larger population.

TH-PO249

Effective Analysis of Electroacupuncture Treatment for Restless Legs Syndrome in Maintenance Hemodialysis Patients

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Background: Restless legs syndrome (RLS) is a common complication in patients with end stage renal disease. Current study was conducted to analysis the effect of electroacupuncture in the treatment of RLS.

Methods: A total of 7 regular hemodialysis (HD) patients (5 Male and 2 Female) in our center were enrolled to conduct before and after self-control study. Demographic, clinical, and pretreatment laboratory data were collected. After one month of pharmacological washout period, patients received 12 sessions of electroacupuncture on three acupoints (Zusanli (ST36), Sanyinjiao (SP6) and Taichong (LR-3)) during HD. Changes of RLS were rated by International Restless Legs Syndrome Study Group rating scale (IRLS) pre-, post- and one month after the therapy.

Results: The average age of enrolled patients was 53.0±9.6 years, with median dialysis duration of 3.0 years. The hemoglobin level were 125.9±22.9 g/l. The IRLS score was significantly lower after electroacupuncture treatment (9.4±3.9) than that before treatment (17.3±4.3) (P=0.0004). One month after the end of treatment, the quantitative IRLS score was 9.7±1.2, which was still significantly lower than that before treatment (P=0.0068). Both the frequency (2.9±0.6 days/week pre-treatment vs. 1.9±1.0 days/week post-treatment, P=0.02) and severity (1.7±0.7 points vs. 1.0±0 points, P<0.05) of RLS were significantly improved after electroacupuncture. These improvement trends were able to maintain after the treatment was discontinued for one month.

Conclusions: Electroacupuncture on the acupoints in the legs during HD was as an effective treatment for attenuating the symptoms of RLS in hemodialysis patients, and the therapeutic effect maintain for at least one month.

TH-PO250

Frailty, Age, and Post-Dialysis Recovery Time in an Incident Hemodialysis Population

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Background: Frailty, a phenotype characterized by an inability to recover from a stressor, may help identify incident hemodialysis patients at risk for longer recovery time. Recovery time has been associated with downstream outcomes including quality of life and mortality. We characterize post-dialysis recovery times in incident in-center hemodialysis patients and quantify the association of frailty and recovery time.

Methods: In 285 incident hemodialysis patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study, frailty was classified by the Fried phenotype as non-frail, intermediately frail, or frail. Post-dialysis recovery time was assessed by asking, "How long does it take you to recover from a dialysis session?" We estimated the association of frailty and post-dialysis self-reported recovery time using negative binomial regression after adjusting for clinical confounders.

Results: Mean age was 55 years, 24% were >65 years, and 73% were African American. Median recovery time was 20 min (IQR: 10, 120). Age <65 was independently associated with longer recovery time (IRR 2.36; 95%CI: 1.44-3.85). Intermediate frailty and frailty were associated with 2.56-fold (95%CI: 1.45-4.52) and 1.72-fold (95%CI: 1.03-2.89) longer recovery times. In particular, frail participants <65 were more likely to report longer recovery times (IRR 2.55; 95%CI: 1.46-4.43).[Figure] In non-frail participants, however, age was not associated with recovery time.

Conclusions: In adults initiating hemodialysis, frailty was independently associated with prolonged post-dialysis recovery. Future studies should assess the impact of frailty-targeted interventions on recovery time to improve clinical outcomes.

Funding: NIDDK Support

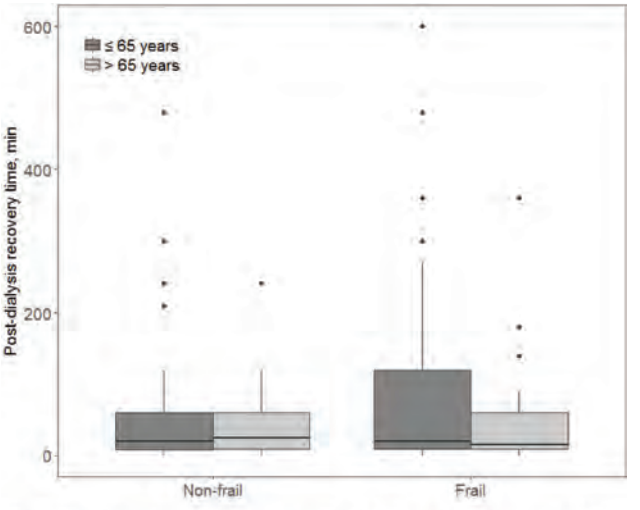

Figure. Distribution of post-dialysis recovery time by frailty status and age among adults initiating hemodialysis.

TH-PO251

Frailty in Prevalent Hemodialysis Patients: Regina Frailty Study

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Background: Frailty is characterized by accumulating physiological deficits in patients across many domains and puts individuals at a higher risk of poor health outcomes. The prevalence of frailty is disproportionately increased in patients on Hemodialysis (HD) when measured either at entry to the dialysis unit or once stabilized on HD. However, trajectory of frailty on serial measurements and its relationship to level of independence, cognition, quality of life (QoL) and mood has not yet been explored.

Methods: We conducted a prospective longitudinal study amongst 100 prevalent HD patients at the Regina General Hospital, Canada from Jan 2015 to Jan 2016. Patients were reevaluated one year after the initial assessment. Four levels of dependence were defined: independent, independent with family support, requiring home care assistance, and long-term care home resident. Frailty was measured using the Fried Criteria (score of ≥3/5), cognitive function was assessed with Montreal Cognitive Assessment, mood was assessed using the Geriatric Depression Scale and QoL was measured with EuroQol-5D at each assessment. To determine associations, chi square and McNemar's tests were used.

Results: At baseline, the mean age was 62.86 ± 15.44 years, 58% were men, and majority (73%) were Caucasian. 68% were frail, 53% screened positive for depressive symptoms and 69% had impaired cognitive function. After one year, the % of independent patients decreased (81.5% vs. 63.1%), and more patients required additional support at home

(17% vs. 31%). Higher proportion of patients experienced challenges with mobility (67.7% vs. 83.1%, p= 0.02), as well as with self– care (6.2% vs. 18.5%, p=0.02). Non–frail patients had more favorable cognition scores in comparison to the frail cohort [24 (21–26) vs. 21 (15–24), p=0.006]. Of the 21 patients who died at one year follow up, 62% were frail.

Conclusions: Two thirds of established dialysis patients met the criteria for frailty. Frail patients are more likely to be dependent on their family members and need greater number of support systems in place. The collective impact of multiple comorbidities, depression, cognitive impairment, reduced QoL and frailty on HD patients, and its consequent impact on health care delivery will have to be proactively addressed in a multidisciplinary manner. We suggest sequential frailty measurements in HD units to improve care delivery of patients.

TH-PO252

Fall Risks in Chronic Hemodialysis and Peritoneal Dialysis Patients in the United States (2006-2016)

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Background: Patients with end stage kidney disease (ESKD) have a substantially higher risk of falls, but the burden of fall events has not been sufficiently characterized in this population. We compared trends in minor and major fall rates in both hemodialysis (HD) and peritoneal dialysis (PD) patients in the US between 2006 and 2016.

Methods: Analysis included 4,766,341 dialysis patients (HD: 4,343,752; PD: 422,589) in the US Renal Data System database (2006-2016). ICD-CM diagnosis codes were used to identify major and minor falls. Major falls included those in combination with fractures, brain injuries, or joint and ligament dislocation. Minor falls included falls without these complications. Fall rates expressed per 1000 patient-years (py) were calculated and patient characteristics compared for both types of falls by dialysis modality.

Results: Overall, HD patients were older and more likely to be male compared with PD patients (mean age: 63.6 vs 57.5 years, male: 56.3% vs 54.7%). Over the past decade, patients on HD experienced higher rates of both major and minor falls than those on PD (Figure 1). The rate of major falls gradually decreased from 2006-2014, and grew substantially after 2014 among both populations (HD vs PD: 227 vs 157 per 1000 py in 2016). There was a notable increase in the rate of minor falls among both populations during the period from 2006-2016 (HD: 125 to 190 per 1000 py; PD: 66 to 119 per 1000 py). Patients who were female, white, age >45 years and prevalent dialysis patients had a higher risk of falls than their counterparts who were male, other ethnicity origins, age ≤45 and incident dialysis patients.

Conclusions: Fall risk is high for the ESKD population, especially among those undergoing HD, aged >45years, white, female and prevalent dialysis. Falls are a safety issue can cause serious injuries with resultant complications along with increased resource utilization. Further research and implementation projects designed to lower fall risk among ESKD patients are urgently warranted.

Funding: NIDDK Support

Figure 1 Unadjusted fall rate (per 1,000 patient year) by ESKD modality and type of fall

TH-PO253

Physical Activity in Patients on Hemodialysis and Its Relation to Fatigue and Depression

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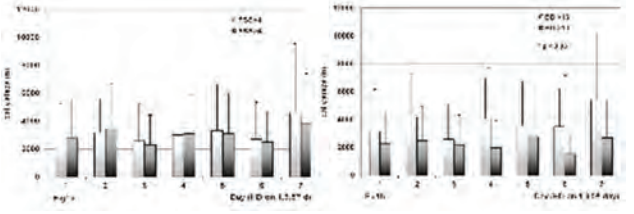
Background: Hemodialysis (HD) patients are less active than healthy sedentary adults. Fatigue and depression are considered main reasons for physical inactivity in HD patients and are associated with impaired quality of life (QOL). A better understanding of the relation between fatigue, depression and physical activity (PA) is crucial in order to develop effective therapies and improve QOL. Measurement of PA is however challenging, as it is usually assessed by subjective self-report questionnaires. Recently, objective assessment of PA with motion sensors has gained interest. Therefore, we aimed to objectively measure HD patients' daily PA and to explore its relation with fatigue and depression.

Methods: PA was assessed in 37 HD patients (mean age 61 years) based on the daily step count measured with the SenseWear™ Armband for 7 days. The Fatigue Severity Scale (FSS) and Beck Depression Inventory-II (BDI) were administered to evaluate fatigue and depressive mood.

Results: Median physical activity was 2247 steps a day, [IQR:614-4363], and no significant differences in PA were observed between treatment and non-treatment days. PA per measurement day did not correlate with fatigue experience (r_s=0.04, p=0.499), and did not significantly differ between patients that were categorized as fatigued (n=23, FSS≥4) or not (n=14, FSS<4) (Fig.1a: p's 0.745-0.988; Cohen's d's <0.20). In contrast, PA per measurement day significantly though inversely correlated with depressive mood (r_s=-0.22, p<0.001) and significantly differed between high-depressed (n=18, BDI>13) and low-depressed subjects (n=19, BDI≤13) (p=0.004), who made on average 1.7 times more steps a day than their high-depressed counterparts. The main differences in PA were observed on non-treatment days (Fig.1b: p's 0.017-0.105; Cohen's d's 0.57-0.90).

Conclusions: Objective assessment of PA with motion sensors is feasible in HD patients. Depressive mood, in contrast to fatigue experience, seems to be associated with PA. These findings may help to increase awareness about the need for intervention trials to assess the effect on PA in HD patients by improving their mood, or vice versa.



TH-PO254

Psychosocial Interventions for Preventing and Treating Depression in Dialysis Patients: A Cochrane Review and Meta-Analysis

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Background: People with end-stage kidney disease treated with dialysis are frequently affected by major depression. Psychological and social support are potential treatments for depression, although a Cochrane review in 2005 identified zero eligible studies. This is an update of the Cochrane review published in 2005 to evaluate the available evidence for using psychosocial interventions to prevent and treat depression in patients treated with dialysis for end-stage kidney disease (ESKD).

Methods: The specialized register of Cochrane Kidney and Transplant was searched for randomized trials (RCTs) reporting psychosocial interventions for prevention and treatment of depression among adults treated with long-term dialysis. Two authors independently screened citations for eligibility, extracted data, and assessed risk of bias using the Cochrane tool. Evidence certainty was evaluated using GRADE.

Results: Thirty-one studies (1820 participants) were eligible. Twenty-four new studies were added to this 2018 update. Seven studies originally excluded from the 2005 review were included as they met updated review eligibility criteria. Trial duration ranged between three weeks and one year. Median study age was 50.8 years. Methodological reporting was incomplete for most studies. Cognitive-behavioural therapy probably improves depression symptoms (mean difference [MD] -6.10, 95% confidence interval [CI] -8.63 to -3.57; moderate certainty) and health-related quality of life (standardized MD [SMD] 0.51, 95% CI 0.19 to 0.83; moderate certainty). Exercise probably improves depression symptoms (MD -7.61, 95% CI -9.59 to -5.63; moderate certainty) and health-related quality of life (MD 3.06, 95% CI 2.29 to 3.83; moderate certainty). Counselling and relaxation techniques probably reduce depressive symptoms (MD - 3.84, 95% CI -6.14 to -1.54; moderate certainty and MD -5.77, 95% CI -8.76 to -2.78; moderate certainty, respectively). In very low certainty evidence, the effects of acupressure, telephone support, and meditation were uncertain. Data on adverse events were sparse.

Conclusions: Cognitive-behavioural therapy, exercise, counselling, or relaxation techniques probably reduce depressive symptoms for adults with ESKD treated with dialysis. Evidence for other psychosocial interventions is uncertain.

TH-PO255

Effects of Intravenous L-Carnitine (LC) Administration in Improving Muscle Strength in Hemodialysis (HD) Patients

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Background: Several clinical studies have suggested that LC, a naturally occurring compound involved in bioenergetic processes, may improve muscle function of HD patients. In this study, our aim was to evaluate the effect of intravenous administration of LC on muscle strength measured by isometric handgrip strength (HGS) in HD patients.

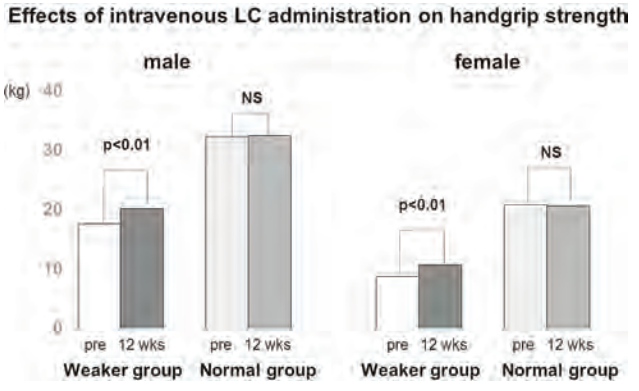
Methods: After appropriate IC 172 HD patients on HD were enrolled in this study. Intravenous L-carnitine (1000 mg) was administered after each HD session. HGS was measured using a dynamometer before and 12 weeks after LC administration in female

(n=56) and male (n=116) patients of different ages (median age: 68.2±33.3 years) as well as various clinical parameters were determined. Using the Asian Working Group for Sarcopenia criteria the subjects were divided into 2 groups by initial HGS: cut-off score of 18 kilograms (kg) for female and 26 kg for male.

Results: As shown in Figure, significant increase was obtained both in female and male among weaker HGS groups, but not normal HGS groups. There was no significant difference in nutrition parameters such as serum albumin or cholinesterase between weaker and normal HGS groups in females or males.

Conclusions: In our study the administration of intravenous LC has potentially contributes to muscle strength in patients on maintenance HD. LC can be one of the candidates for improving sarcopenia in patients on HD.

Funding: Private Foundation Support



TH-PO256

A 6-Month Program of Intradialytic Cycling Results in a Reduction in Associated Healthcare Costs in Patients Receiving Prevalent Hemodialysis

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Background: Individuals receiving hemodialysis have complex medical needs. Interventions that reduce health care utilization can improve patient outcomes, and therefore decrease the financial burden. The aim of this health economic analysis is to investigate the effect of a 6-month program of intra-dialytic cycling exercise (IDE) on health care costs.

Methods: This is a retrospective complete case analysis of a 100 participants enrolled in CYCLE-HD, an open-label, blinded end-point, cluster randomised control trial investigating the benefit of IDE. Participants were randomised to either a 6-month progressive program of IDE (30 minutes of thrice weekly, moderate intensity cycling at RPE 12-14) or standard care (control). Data on hospital admissions, length of stay, clinic appointments, A&E attendances, primary care appointments and prescribed medications were extracted from medical records for the 6-months before, during and after the IDE intervention. Costs of healthcare utilization were calculated using the National Health Insurance National Tariff Payment System, and prescribed medications were calculated using the British National Formulary. Data are presented as mean difference (95% confidence interval) or mean (95% confidence interval).

Results: Data from a 100 participants (control *n*=49 and IDE *n*=51) were included in our complete case analysis. Time-series with incomplete data sets were excluded. There was no difference between groups for the before (£284.30 (-£4550.24 to £5118.83), *P*=0.9075) or during (-£2124.67 (-£6466.69 to £2217.35), *P*=0.3342) periods. However following the IDE program there was a significant reduction in cost of -£8199.438 (-£15137.43 to -£715.4473, *P*=0.0227) per participant between IDE and control groups. Similarly, post IDE number of admissions (IDE; 0.8 (0.4-1.2), control; 1.2 (0.8-1.6)) and length of stay (IDE; 3.1 (0.2-6.0) days, control; 4.4 (2.4-6.3) days) were also reduced.

Conclusions: These data show a 6-month of program IDE can reduce associated health economic costs. The overall reduction appears to be driven by a reduction in hospital admissions and length of stay. These results strengthen the argument that IDE programs should be routinely offered and are of crucial importance to commissioners of dialysis care.

TH-PO257

Intradialytic Isometric Handgrip Training Seems to Be Safe: A Pilot Study on Hemodialysis Patients

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Background: Cardiovascular capacity of chronic kidney disease (CKD) patients tends to decline with the natural progression of the disease. In this sense, resistance training is an important non-pharmacological tool in the control of cardiovascular (CDV) parameters. However, there is no evidence of isometric handgrip training (IHT) protocols in this population. Thus, the aim of this study was to verify the safety of two isometric RT protocols on CDV variables in hemodialysis (HD) patients.

Methods: This was an experimental study, with acute intervention, cross-over design and sample of 8 patients, mean age 56.63 ± 12.66 years, who undergoes HD at a private clinic in the city of Brasília – DF. The participants were randomly assigned to three different moments to analyze the response of the variables heart rate variability (HRV) and blood pressure (BP), being: 1) control; 2) low-intensity; 3) moderate-intensity. Variables were collected at the beginning of session 5, 15, 30, 40, 60 minutes and immediately after the end.

Results: IHT protocols, regardless of intensity, did not show a significant change for both HRV and BP variables during their performances, nor when compared to the control moment. When the moments immediately before and after exercise were analyzed, a significant increase was observed for SBP (120,3±4,6 vs 126,7±4,6, p<0.05) and DP (8634,5±398,5 vs 9419,1±545,3, p<0.05) in the protocol of moderate-intensity, but returning to normal values 10 minutes later.

Conclusions: Therefore, we conclude that the intradialytic IHT seems to be a safe therapeutic tool for the intradialytic control of cardiovascular parameters in this population.

Funding: Government Support - Non-U.S.

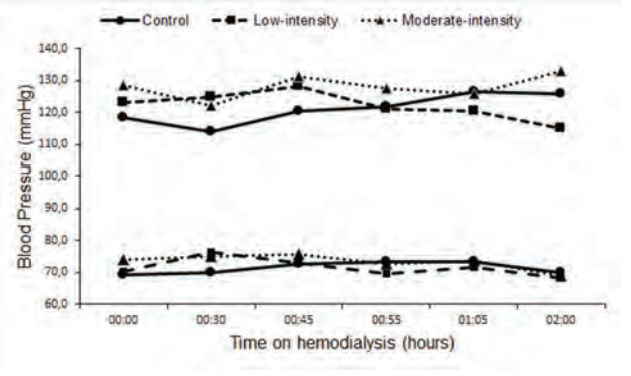

Figure 1. BP during HD with and without isometric handgrip training

TH-PO258

L-Carnitine Supplementation Enhances Physical Activity and Improves Muscle Quality in Hemodialysis Patients

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Background: Carnitine plays a central role in the activation of fatty acid b-oxidation and energy production by transporting long-chain fatty acids from the cytoplasm to mitochondria. We previously reported that serum carnitine levels are significantly decreased in hemodialysis (HD) patients and thereby involved in muscle atrophy and decreased quality of life. Moreover, recent evidence has suggested that ergometer exercise can be effective against sarcopenia and frailty in HD patients. However, whether L-carnitine supplementation or ergometer exercise can improve HD-related impairment of physiological activity and muscle quality is yet to be elucidated. Here we prospectively examined this issue.

Methods: Twenty patients undergoing HD were divided into two groups: L-carnitine group (n = 10) and exercise group (n = 10). Patients were treated with L-carnitine supplementation (1000 mg intravenously) for 3 months. Muscle and fat mass were measured using impedance methods. Physical activity was evaluated using indices, including grip strength, lower limb extension strength, chair stand up time, 10 m walking times (10 mWT), functional reach test, time up & go test, and the Borg Scale. We further evaluated muscle mass quality using magnetic resonance imaging.

Results: Total and free carnitine levels in the serum significantly decreased in HD patients than in healthy subjects (both p < 0.001). At baseline, muscle mass and the Borg scale were positively associated with free carnitine levels; however, the other variables were not. L-carnitine supplementation significantly increased muscle mass (p = 0.023) and thigh circumstance (p = 0.019), decreased fat mass (p = 0.007), and improved chair stand up time (p = 0.003) and 10 mWT (p = 0.004). Ergometer exercise did not improve any physical activity. Notably, the intramuscular fat fraction significantly decreased with L-carnitine supplementation (p = 0.023), suggesting the improvement of muscle quality.

Conclusions: Compared with ergometer exercise, L-carnitine supplementation had superior effects on physical activity and muscle quality in HD patients. These observations suggest that L-carnitine supplementation may be a novel therapeutic strategy for HD-related sarcopenia and frailty.

TH-PO259

Use of a Wrist-Based Monitoring Device Among Hemodialysis (HD) Patients: A Feasibility Study

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Background: Pervasive sensing technologies allow healthcare providers to gain insights into patients' status outside the clinical setting. To adopt widespread use of remote monitoring devices we must first study their feasibility. We aim to quantify how long patients will use a wearable device before requiring an intervention to maintain use of the device.

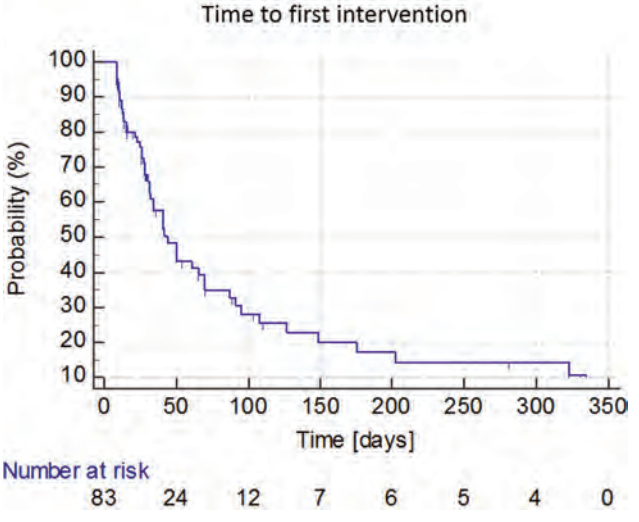
Methods: HD patients were enrolled from 3 clinics in New York City starting in May 2019. Patients ≥18 years, on HD ≥3 months, able to walk, owning a smartphone, tablet or PC were enrolled and provided with a wrist-based monitoring device (Fitbit Charge 2). Participants were instructed on how to use the device. If a patient failed to sync data for 7 consecutive days, a text message or email reminder was sent. We evaluated time to first notification using Kaplan Meier analysis. Patients were censored at 5/15/2019.

Results: 89 patients were enrolled into our study with 6 patients screen-failed. At enrollment patients were 55±12 years old with a dialysis vintage of 5.8±6.3 years. 36% lived alone, 54% were single, 57% unemployed, 68% were African-American, and 49% had an education level of some college or higher. 61% of the patients required a notification to continue using the device. Mean and median time to first notification were 95 days (95%CI 66 to 125) and 44 days (95%CI 32 to 70 days), respectively. The probability of being on the study without intervention is shown in Figure 1.

Conclusions: We found that most patients will require some counseling to maintain the use of a wrist-based wearable device for remote monitoring. While most patients require an intervention before 90 days into wear, the patients who can maintain use independently after that point are likely to do so for longer.

Funding: Commercial Support - Fresenius Medical Care

Figure 1. Kaplan Meier curve of time to first intervention



TH-PO260

The Relationship Between the Patient Activation Measure and Changes in Patient Self-Efficacy on In-Center Hemodialysis

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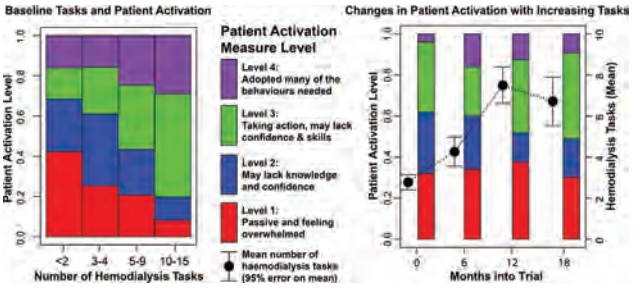
Background: The patient activation measure (PAM) assesses the knowledge, skills and confidence to manage their health condition. Low PAM is associated with worse outcomes and increased healthcare cost, and is increasingly seen as an endpoint for complex interventions in chronic diseases. PAM includes many domains applicable to in-center (ICHD) and home (HHD) hemodialysis but its sensitivity to change in more objective measures of self-efficacy in ICHD and HHD patients is unknown.

Methods: A stepped wedge randomised trial involving 12 centers supported patients to learn and undertake ICHD-related tasks over 18 months. PAM and how many of 15 ICHD tasks patients were undertaking was measured on 4 occasions. The relationship between within-patient changes in PAM (scored 0-100%) and the endpoints of numbers of ICHD tasks and moving to HHD were assessed using mixed-effects linear regression models, adjusting for patient characteristics.

Results: 534 patients completed 1611 PAM questionnaires during the study. The proportion of patients doing 5+ tasks increased from 44.3% to 52.3% (P=0.01), with 10.3% performing HHD or ICHD independently by the end of the study. At baseline (left figure) performing 5+ tasks was associated with a 10.7% difference in PAM score (95% CI 6.8 – 14.6). During the study (right figure) moving from <5 to 5+ tasks was associated with a 4.3% change in PAM (95% CI 2.3 – 6.4%) and 4.8% (95% CI 0.4 – 9.2%) moving to independent ICHD or HHD.

Conclusions: This supported learning intervention was effective at increasing patient participation in ICHD-related tasks. Despite a strong baseline relationship between PAM and ICHD tasks, the longitudinal change in PAM with increased ICHD tasks, independent ICHD and HHD only just exceed the minimum clinically meaningful difference (4%). The relationship between PAM and self-efficacy is complex and greater understanding of their measurement is needed to avoid potential underestimation of benefits of complex interventions.



TH-PO261

Natural Killer Cell Activity Contributes to Development of Sarcopenia in Hemodialysis Patients

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Background: Sarcopenia, a syndrome of reduced skeletal muscle mass and function, is associated with decrease immune system responsiveness. Decreased natural killer (NK) cell activities have been suggested in hemodialysis (HD) patients. The aim of this study is to determine the relationship between NK cell activity and sarcopenia in HD patients.

Methods: We enrolled 116 clinically stable HD patients (62 male) and clinical data such as age, sex, height, weight, dialysis duration, and comorbidities were collected. Biochemical parameters, including white blood count, hemoglobin, albumin, C-reactive protein, and iron profiles were determined before the dialysis session. Muscle mass was evaluated by bioimpedance analysis (Inbody S10, Biospace Co., Korea) and hand grip strength was assessed using digital hand grip dynamometer. The diagnosis of sarcopenia was made according to the guidelines of Asian Working Group for Sarcopenia. Cytotoxic activity of NK cells was determined using commercial blood test assay (NK Vue, ATGen, Seongnam, Korea) that uses serum of ex vivo stimulated whole blood to detect interferon (IFN)-γ secreted from NK cells as an indicator of NK cell activity. IFN-γ levels were further quantitated by ELISA. Univariate and multivariate binominal logistic regression analyses were used to determine the association between clinical variables including NK cell activity and sarcopenia in HD patients.

Results: A total of 29 patients (25%) were diagnosed as sarcopenia among 116 HD patients. The sarcopenic HD patients were significantly older (70.1 ± 8.1 vs. 61.1 ± 11.3 years, P<0.001) and had longer HD vintage (63.1 ± 54.0 vs. 38.5 ± 38.9 months, P=0.029), whereas showed lower body mass index (BMI) (20.7 ± 3.8 vs. 23.4 ± 6.2 kg/m2, P<0.01), lower appendicular lean muscle mass (ALM, 8.26 ± 2.8 vs. 9.83 ± 4.5 kg/m^2, P<0.01), and lower activity of NK cell (392 ± 517 vs. 876 ± 667 pg/mL, P=0.001). Low NK cell activity had a very significant correlation with sarcopenia, and the statistical significance was maintained even after adjustment for age, sex, BMI, ALM in multivariate regression analysis [Exp(B) 0.104(0.033, 0.324), P<0.001].

Conclusions: Our results show that the NK cell activity of sarcopenic HD patients is significantly decreased and such low NK cell activity may contribute to development of sarcopenia in HD patients.

TH-PO262

Skeletal Muscle Chaperone and Co-Chaperone Proteins Are Elevated in Maintenance Hemodialysis Patients

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Background: Various chaperone and co-chaperone proteins are required for the assembly and maintenance of the sarcomere to allow for maintenance of muscle tissue. We have previously established that both myofibrillar protein synthesis rates and markers of proteolysis are elevated in patients on maintenance hemodialysis (HD) when compared to BMI-matched controls. This result potentially underpins poor structural integrity that ultimately leads to poor physical performance in HD patients. Therefore, we aimed to determine whether HD patients have a higher abundance of chaperone and co-chaperone proteins involved in sarcomere integrity as compared to age- and BMI-matched controls.

Methods: Six HD patients (sex: 83.3% male; age: 58±13 y; BMI: 32±7 kg/m^2) and six controls (sex: 66.7% male; age: 51±7 y; BMI: 31±4 kg/m^2) received biopsies from the

vastus lateralis after an overnight fast on a non-dialysis day to assess the relative protein content of Unc45b, Smyd1, Stub1, MuRF1, Hsp40, Hsp70, Hsp90α, and αβ-crystallin by Western blotting. We also determined plasma C-reactive protein (CRP) concentrations by ELISA. Pearson's correlation coefficient or the Spearman correlation coefficient were used to test the associations between systemic inflammation and sarcomere integrity.

Results: The skeletal muscle protein contents of Stub1 (P=0.032), MuRF1 (P=0.025), Hsp40 (P=0.039), and αβ-crystallin (P=0.019) were all elevated in HD patients when compared to controls, but the protein expressions of Unc45b (P=0.073), Smyd1 (P=0.922), Hsp70 (P=0.636), and Hsp90α (P=0.434) were not different. Among the four chaperones and co-chaperones whose protein expressions increased in HD patients, Stub1 (r_s=0.833, P=0.010) and Hsp40 (r=0.896, P=0.003) were positively correlated with plasma CRP concentrations. However, neither MuRF1(r_s=0.450, P=0.224) nor αβ-crystallin (r_s=0.417, P=0.265) were associated with plasma CRP concentrations.

Conclusions: We demonstrated that the protein expression of several chaperones and co-chaperones in skeletal muscle were upregulated and positively correlated with the level of systemic inflammation in HD patients. Future studies are required to identify if dampening the inflammatory and uremic milieu can restore the regulation of muscle mass to a more 'normal-state' in HD patients.

Funding: Commercial Support - American Egg Board/Egg Nutrition Center

TH-PO263

Reliability of Appendicular Muscle Mass Assessment by Bioelectrical Impedance Analysis vs. Dual-Energy X-Ray Absorptiometry in Hemodialysis Patients

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Background: Loss of skeletal muscle mass(MM) increases the risk for morbidity and mortality in hemodialysis (HD) patients. Dual energy X-ray absorptiometry (DXA) is a valid tool for assessing skeletal MM but limited by cost and radiation exposure. In contrast, bioelectrical impedance analysis (BIA) is cheap and has no radiation exposure risk. Aim of this study was to assess the concordance between MM measured by BIA and DXA in HD patients.

Methods: We enrolled 55 clinically stable HD patients. Body composition, including appendicular lean muscle mass (ALM), was evaluated by BIA (Inbody S10) and whole body DXA (HOLOGIC®). Hand grip strength (HGS) was performed to evaluate muscle performance. Agreement between tools was assessed by means of the Bland Altman method. Multiple linear regression was used to develop an ALM value by BIA closed to that by DXA.

Results: The mean age was 63.4±11.29 years (range 39 to 88 years) and 65.5% were men. The prevalence of diabetes and hypertension was 54.5% and 94.5%, respectively. There was a significant association between muscle mass index which determined via DXA and BIA. The mean value of ALM divided by the height^2 (AMMI) was found to be 5.98±0.90 kg/m^2 and 7.90 ±1.39 kg/m^2 by DXA and by BIA, respectively, indicating overestimation of ALM in BIA method. BIA overestimated total body lean mass in 98% of participants. Bland-Altman plots for differences in AMMI between BIA and DXA showed large bias (Mean= 1.92kg/m^2), with significant mean differences ([0.29, 3.55], P<0.001). After adjusting for sex, age and BMI, AMMI by BIA was significantly correlated with those measure by DXA (R2=0.643, P<0.001). Using the formula, we can estimate the AMMI by DXA with AMMI by BIA (DXA=0.859+0.452BIA+0.068BMI, R2=0.709, P<0.001). Mean HGS was 24.6±7.90 kg and AMMI showed no correlation with the HGS.

Conclusions: Our results showed that AMMI measured by BIA is reliable but overestimated in HD patients. Further reinfinement of adaptation formula for use BIA is needed to obtain accurate measurement of AMMI close to that measured by DXA.

TH-PO264

Wrist-Based Accelerometry and Physical Function in Dialysis Patients

Sonia Kotwani,[4] Lovepreet S. Randhawa,[4] Samhitha Munugoti,[4,3] Solomon Dalezman,[1] Kate Nam,[2] Antonio C. Elters,[4] Sandheep Venkataraman,[3] William Paredes,[4] Nitin Ohri,[4,3] Matthew K. Abramowitz,[4] Jose S. Ibarra.[4] *[1]Island Nephrology Services, Flushing, NY; [2]Albert Einstein Medical School, Scarsdale, NY; [3]Montefiore Medical Center, Bronx, NY; [4]Albert Einstein College of Medicine, Bronx, NY.*

Background: Poor physical function is a powerful predictor of adverse outcomes in dialysis patients. Whether daily activity monitoring can detect patients with lower levels of physical function is unknown.

Methods: We conducted a prospective study of wrist-based accelerometry in a single outpatient dialysis unit. Fifty patients receiving thrice-weekly hemodialysis were enrolled and wore a commercial fitness tracker for 6 months. Physical function was assessed by usual gait speed, grip strength, and the Short Physical Performance Battery (SPPB, range 0-12, higher is better). Information on the composite outcome of emergency department (ED) visits or hospitalizations was obtained from monthly patient questionnaires, dialysis unit records, and our hospital electronic medical record. Mixed effects models were created to examine the association of daily step counts with each functional outcome. Poisson regression using generalized estimating equations was used to examine associations with the composite outcome. Models were adjusted for age, sex, race, BMI, and diabetes status.

Results: Data were excluded for 3 patients who did not perform physical function testing. Daily step counts at baseline averaged 4538 +/- 3001. The mean age of the cohort was 60+/-13, 49% were women, 40% were black, 47% had diabetes, and the mean BMI was 28+/-7 kg/m^2. For each 1000 steps more per day, gait speed was 1.2 cm/sec faster (95%CI 0.1-2.3); dominant hand grip strength was 0.6 kg higher (95%CI: 0.1-1.1) and SPPB was 0.13 (95% CI: 0.02- 0.23) points higher. Neither SPPB, gait speed, nor grip strength was associated with the composite outcome. However, step counts were associated with the composite outcome even among patients with high SPPB scores: among patients with SPPB>8, every 1000 steps more per day was associated with 50% decreased risk (IRR 0.5, 95% CI 0.39- 0.63); among those with SPPB≤8, there was a 14% decreased risk (IRR 0.86, 95%CI 0.73- 1.00).

Conclusions: Lower step counts are associated with poorer performance on several measures of physical function in dialysis patients and are associated with the risk of hospitalization and ED visits even among patients with preserved physical function.

Funding: NIDDK Support

TH-PO265

Dialysis Recovery Time and Physical Activity Levels

Lovepreet S. Randhawa,[4] Sonia Kotwani,[4] Samhitha Munugoti,[4,3] Solomon Dalezman,[1] Kate Nam,[2] Sandheep Venkataraman,[3] William Paredes,[4] Nitin Ohri,[4,3] Matthew K. Abramowitz,[4] Antonio C. Elters,[4] Jose S. Ibarra.[4] *[1]Island Nephrology Services, Flushing, NY; [2]Albert Einstein Medical School, Scarsdale, NY; [3]Montefiore Medical Center, Bronx, NY; [4]Albert Einstein College of Medicine, Bronx, NY.*

Background: Longer post-dialysis recovery times are associated with an increased risk of mortality. Factors accounting for this finding have yet to be elucidated. We examined whether lower physical activity levels could be one explanation.

Methods: We conducted a prospective study of wrist-based accelerometry in a single dialysis unit. Fifty patients receiving thrice-weekly hemodialysis were enrolled and wore a commercial fitness tracker for 6 months which provided daily step count data. Average monthly post-dialysis recovery times were assessed by asking **"**How long does it take you to recover from a dialysis session?" Mixed effects models adjusted for age, sex, race, BMI, diabetes status, and ultrafiltration volume, with random coefficients for follow-up time, were created to examine the association of recovery time with daily step counts.

Results: Only the 48 patients who had at least a month of step-count data available were included in the analysis. The cohort consisted of 51% women, 40% African-Americans and 47% were diabetic. Patients who reported recovery time of <15 minutes walked 5576(+/-427) steps per day in comparison to patients who reported recovery time of > 12 hours and walked 3260(+/- 573) steps. After adjustment, compared with patients in the <15 min recovery time group, those in the 15min-2 hr group took 271 fewer steps(95% CI, -1038 to 496), 2-6 hours recovery took 1635 fewer steps(95% CI,-2456 to-812), 6-12 hours recovery time group took 2129 fewer steps(95% CI,-4417 to 170) and >12 hours recovery time took 2367 fewer steps (95% CI, -3397 to -1336). In comparison, 10 years older age was associated with 1060 fewer steps per day (95% CI,-1350 to -770). Diabetes, gender, race and ultrafiltration amount were not associated with step counts.

Conclusions: Longer recovery time after dialysis is strongly associated with lower physical activity level. This is not explained by the amount of ultrafiltration. Studies should examine the effectiveness of increasing physical activity to improve outcomes in these patients.

Funding: NIDDK Support

TH-PO266

Wrist-Based Accelerometry and Risk of Emergency Department Visit or Hospitalization

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Background: Sedentary behavior has been associated with poor outcomes in dialysis patients. Whether changes in physical activity yield additional prognostic information is unknown.

Methods: We conducted a prospective study of wrist-based accelerometry in a single outpatient dialysis unit. 50 patients receiving thrice-weekly hemodialysis were enrolled and wore a commercial fitness tracker for 6 months which provided daily step count data. Information on emergency department (ED) visits and hospitalizations were obtained from monthly patient questionnaires, dialysis unit records, and our hospital electronic medical record. Each patient's baseline activity level was defined as the mean step count during the 2 weeks following study entry. Poisson regression using generalized estimating equations and adjusted for age, sex, race, BMI, diabetes status, and follow-up time was conducted to examine the association of step counts with the composite outcome of ED visit or hospitalization, and with hospitalization alone.

Results: Data were excluded for 2 patients who wore the device <1 month. Daily step counts at baseline averaged 4538 +/- 3001. The mean age of the cohort was 60+/-13, 49% were women, 40% were black, 47% had diabetes, and the mean BMI was 28+/-7 kg/m^2. Compared with participants in the highest step count tertile, those in the lowest step count tertile were older but did not differ by other baseline characteristics. There were 38 occurrences of the composite outcome in 17 patients. After adjustment, each 1000-step reduction in daily step count was associated with 28% increased risk of both the composite outcome (incidence rate ratio (IRR) 1.28, 95% CI 1.07-1.53) and hospitalization alone (IRR 1.28, 95% CI 1.21-1.61). Each 10% reduction from an individual's baseline activity level was associated with a 17% increased risk of the composite outcome (IRR: 1.17, 95%CI: 1.02-1.34).

Conclusions: Step count monitoring using a wearable device identifies changes in activity that are associated with increased risk of hospitalization or ED visit. Future studies should examine whether this approach could provide a real-time prediction of adverse events.

Funding: NIDDK Support

TH-PO267

Dialysis Recovery Time as a Predictor of Hospitalization Among Incident Hemodialysis Patients

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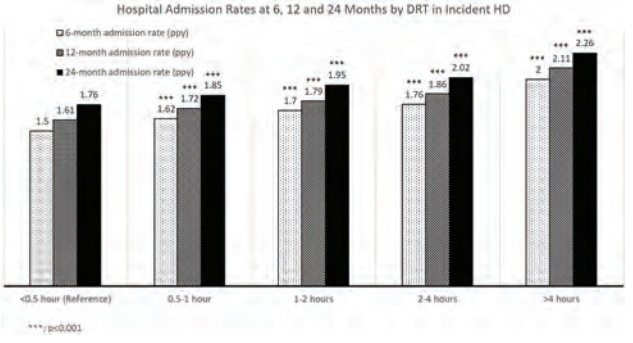
Background: Dialysis recovery time (DRT) is the perceived time it takes patients to recover their ability to undertake daily activities after hemodialysis (HD). DRT is a meaningful variable to assess health related quality of life (HRQOL) in HD patients. As such, DRT as a predictor of hospitalization could be looked at as an early indicator of treatment success or impending morbidity. We characterized the hospital admission rates based on DRT categories among incident HD patients treated at a large dialysis organization (LDO).

Methods: We used data at an LDO during 2014 through 2017 for patients who completed a DRT survey ≤180 from first date of HD. DRT survey was administered as part of KDQOL questionnaire. DRT survey asks: "How long does it take you to be able to return to your normal activities after your dialysis treatment?". Categorical answers were: <0.5, 0.5-1, 1-2, 2-4, >4 hours. Hospital admission rates were compared by DRT category (DRT <0.5 hour reference) via unadjusted Poisson models.

Results: We included data from 98616 incident HD patients (age 62.6±14.4 years; 57.8% male). There were 25.2%, 19.1%, 17.3%, 15.5%, and 22.9% of HD patients reporting a DRT of <0.5, 0.5-1, 1-2, 2-4, and >4 hours, respectively. We observed 6-, 12-, and 24-month crude admission rates of patients rose with each longer DRT category (all p<0.001), as compared to patients with a DRT <0.5 hour (Figure 1).

Conclusions: Findings suggest longer DRTs in incident HD may associate with progressive increases in crude short- and long-term admission rates. DRT is an important marker of how well the patient feels and tolerates HD therapy. Optimizing the HD treatment around DRT in the incident period may have the ability to improve HRQOL and outcomes.

Funding: Commercial Support - Fresenius Medical Care North America



TH-PO268

Perspectives of Pakistani Patients Receiving Maintenance Dialysis on End-of-Life and Dialysis Decision-Making

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Background: There is a paucity of literature on end-of-life care (EoLC) and treatment preferences of Pakistani patients receiving maintenance dialysis. Most of the literature on these issues report beliefs of Western dialysis patients; however, both patient populations may differ in their cultural and religious beliefs about EoLC issues.

Methods: Using a convenient sampling method, we surveyed 522 dialysis adult patients from 7 different dialysis units across 4 cities of Pakistan from March through June 2015. The survey was adapted from the previous literature and translated in the Urdu language.

Results: The majority of the patients wanted detailed information about their disease (67.6%), and prognosis (54.4%). However, 81% reported not having prognostic discussions with their nephrologists. Only a small percentage of patients' self-reported knowledge about services such as hospice (5%) and palliative care (8%). Nearly forty-seven percent of the respondents said that they would choose a course of treatment focused on relieving pain rather than extending life (19%). The decision to initiate dialysis over conservative management was made by doctors in 54% of the respondents. Almost 35% of the patients were not satisfied with their decision to start dialysis.

Conclusions: Pakistani patients receiving maintenance dialysis wish to receive better education on their prognosis and end-of-life care issues. Interventions to improve dialysis decision-making processes and uptake of hospice and palliative care services are needed in this population.

TH-PO269

The EDITH Kidney Patient Survey on Modality Choice Among More Than 8000 European Dialysis and Transplant Patients

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Background: Renal replacement therapy (RRT) modality selection may be challenging for both patients and nephrologists. Within the EDITH project we surveyed adult European dialysis and kidney transplant patients on factors influencing modality choice and their satisfaction with the modality choice made.

Methods: The EDITH kidney patient survey (online and on paper) was translated into 30 languages. European adults with end-stage kidney disease treated by dialysis or kidney transplantation were eligible to participate between November 2017 and November 2018.

Results: 8133 patients from 40 European countries participated. Age, gender and modality characteristics (56% male, mean age 59 years (SD 14), 66% on haemodialysis (HD), 6% on peritoneal dialysis (PD), 29% on transplantation (Tx)) reflected the European RRT population in the ERA-EDTA Registry. A quarter of the patients did not receive any information on any modality before the start of RRT. 44% received no information on home haemodialysis (HHD), 24% nothing on PD and resp. 23% and 20% nothing on living and deceased kidney donor Tx. The majority of those who received information, were (very) satisfied with the information (range 57% for HHD to 86% for deceased kidney donor Tx). Two-thirds of the patients reported that decision making was shared with their doctor and most patients (83%) were satisfied with way the decision was made. The main reasons for patients not having a particular treatment are listed in Table 1. Most important factors influencing modality choice were quality of life, survival and safety (resp. 97.3%, 96.6% and. 92.2% rated as (very) important). Results were similar by age group, sex, educational level and start of RRT time period.

Conclusions: Though most patients seem to be satisfied with the information provision and modality choice, there remains room for improvement as a quarter of all patients did not receive any information on treatment modalities before start of RRT. Better education may also influence patients to choose a home-based form of dialysis or empower them to find a living donor.

Funding: Government Support - Non-U.S.

Table 1 Main reasons not to have a certain treatment

HHD
Don't want treatment at home (34%)
Treatment is not available in my hospital (26%)
Discomfort with no supervision (24%)
PD
Don't want treatment at home (34%)
Dislike of abdominal catheter (23%)
Fear of peritonitis (22%)
Living Tx
No living kidney donor available (37%)
Don't want to ask potential donors (31%)
Concerns about the health of the donor (18%)
Deceased donor Tx
Not healthy enough (25%)
Currently on waiting list (22%)
Too old (18%)

TH-PO270

Functional Status Index Directed Care in the Patient-Centered Supportive Care Pilot

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Background: A large dialysis organization (LDO) developed a functional status index (FSI) that can identify hemodialysis (HD) patients who are experiencing a lower level of functional status. The LDO performed Patient Centered Supportive Care (PCSC) pilot that identified HD patients with a decreasing/diminished FSI and provided targeted interventions based on identified barriers. We assessed if the FSI-directed intervention was associated with improvements in the FSI score.

Methods: We used data from 8 PCSC pilot clinics between 04/13/2018 to 10/30/2018. The FSI uses an array of clinical data and is computed via Z scores and weighted assignments of parameters. In the PCSC pilot, FSI-directed intervention was provided over 28 weeks to patients with a low and decreasing trend in their FSI score. This intervention included targeted clinical recommendations related to treatment adherence, weight management, nutrition, financial assistance, medications and comorbidities, as well as, external referrals to specialists. We calculated the percent of patients who had an increase in their FSI score from baseline in the FSI-directed intervention (FSI positive) versus standard of care (SOC) group who did not have an intervention (FSI negative).

Results: We analyzed data from 497 HD patients at the 8 PCSC pilot clinics. FSI-directed intervention was provided to 42 patients. Patients with a low/decreasing FSI score had a higher mortality rate (14% FSI positive and 6% FSI negative SOC). Over the course of the pilot, 58% of the survivors with FSI-directed intervention had an increase in their FSI score compared to baseline. In the SOC group, 47% of survivors without the intervention had an increase in their FSI score.

Conclusions: The FSI-directed intervention was associated with >10% higher proportion of patients having an improvement in their FSI score. As anticipated, the FSI score identifies patients with higher mortality rates. Additional testing of the FSI-directed intervention is needed to confirm these observations.

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TH-PO271

"I Didn't Know Better": Family Members' Unexpected Negative Experiences with ESKD Treatments

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Background: Understanding the extent to which family members feel prepared for what to expect from patients' end-stage kidney disease (ESKD) treatment could guide the development of family-centered interventions that enhance their treatment preparedness. We examined unexpected negative experiences with ESKD treatments among family members of dialysis and post-transplant patients to inform family-centered research and clinical care.

Methods: Forty-nine family members of patients receiving medical care in the Baltimore, Maryland metropolitan area participated in eight focus groups stratified by their self-reported race (African American or non-African American) and patients' treatment experience in the past year (in-center hemodialysis, home hemodialysis, peritoneal dialysis, or live donor kidney transplantation). Focus group discussions were analyzed thematically. Themes present in discussions from multiple treatment groups were highlighted to provide insight into common experiences. Exemplar quotes are provided for each theme.

Results: Four themes were identified. *Becoming a caregiver* reflected family members' unpreparedness for caregiving responsibilities ("I didn't expect to have to be involved") and related consequences ("I couldn't even sleep"). *Psychological responses* captured family members' negative reactions to treatment ("The anxiety") as well as their perceptions of patients' reactions ("I think he's depressed"). *Treatment delivery and logistics* depicted treatment situations family members considered problematic ("Why can't they just use layman's terms?"), challenging ("We had so many medications, it's constantly juggling that"), or inconvenient ("The space it takes to store 3,000 cases of stuff is unbelievable") for themselves and patients alike. *Morbidity* encompassed family members' perceptions of patients' experiences with dialysis-related health problems ("More illnesses since dialysis") and fatigue ("My son was so tired").

Conclusions: Findings suggest patients' family members are unprepared for non-clinical, logistical, and clinical aspects of ESKD treatments. Efforts to prepare families for ESKD treatments through more family-centered care, early and tailored education, and interventions targeting caregiver preparedness are needed.

Funding: NIDDK Support

TH-PO272

Patients' Unexpected Adverse Experiences with Dialysis and Transplantation

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Background: Patients with end-stage kidney disease (ESKD) desire better education about what to expect from treatment, and preparatory information is associated with positive outcomes for chronic disease patients. Yet, knowledge about the expectedness of ESKD patients' treatment experiences is limited. We studied unexpected adverse treatment experiences among dialysis patients and transplant recipients to understand how providers and pre-treatment interventions can better prepare ESKD patients for treatment experiences.

Methods: Fifty-five patients receiving medical care in Baltimore, Maryland participated in focus groups stratified by their treatment in the past year (in-center hemodialysis, home hemodialysis, peritoneal dialysis, or live donor kidney transplantation) and race (African American or non-African American). Discussions were analyzed thematically. Themes present in discussions from multiple groups were highlighted; exemplar quotes are provided.

Results: We identified five themes. *Psychological responses* reflected patients' negative psychological reactions to treatment, which ranged from feeling different from healthy peers ("I want to be like everybody else who's not on dialysis") to feeling suicidal ("I'm going to kill myself"). *Constrained freedom of choice* captured losses or limitations in recreational ("The only thing I can get on now is the treadmill") and work ("I can't work anymore") activities. *Treatment delivery and logistics* characterized patients' perceptions of painful ("I dislike sticking needles in my arm"), problematic ("I felt like a number in the center"), challenging ("It was hard for me to stay focused on the diet plan"), and inconvenient ("It's not always convenient to dialyze five days a week") treatment situations. *Morbidity* described patients' experiences with treatment complications ("I've had a lot of operations") and comorbidities ("I've had two asthma attacks"). *Finances* pertained to treatment-related expenses, financial strain from unemployment, and hiring caregivers to assist with treatment delivery.

Conclusions: Patients felt unprepared for non-clinical, logistical, and clinical aspects of ESKD treatments. Findings underscore the need for pre-treatment interventions to help patients know what to expect from and feel psychologically prepared for ESKD treatment.

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TH-PO273

Patient and Caregiver Experiences and Perspectives on Access to Kidney Replacement Therapy in Rural and Remote Communities: Thematic Synthesis of Qualitative Studies

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Background: Patients with chronic kidney disease requiring kidney replacement therapy in rural and remote communities are at higher risk of mortality when compared with those in urban areas, and encounter many barriers in accessing care. We aimed to describe patient/caregiver perspectives on access to dialysis and kidney transplantation in rural/remote communities. Access is defined as the opportunity to reach and obtain appropriate health care services and includes the right to seek information concerning health issues.

Methods: Medline, Embase, PsycINFO and CINAHL were searched to February 2019. Studies that where qualitative in nature, provided perspectives of patient and/or caregivers who resided in rural/remote communities, patients over 18 years of age and required Kidney replacement therapy were included. Thematic synthesis was used to analyze the findings.

Results: From 18 studies (n= 540 participants) conducted across 8 countries (Australia, Canada, United Kingdom, New Zealand, Ghana, United States, Tanzania, and India), we identified six themes: uncertainty in navigating healthcare services (inadequacy of absorbing information, without familiarity and exposure to options, lacking trust in clinicians and yearning for cultural safety at a local level); fearing separation from family and country (devastating homesickness, unable to fulfil family roles, preserving sense of belonging in community and grieving former roles); intense burden of travel and cost (poverty of time, exposure to risks and hazards, taking a financial toll and tedious pre-transplant testing processes and workup expenses); suffering hardship and loss (making life changing sacrifices, relocation with no return and inadequacy of transitional accommodation); grief, guilt and worry in receiving care (shame in resource usage and harboring concerns for living donor) and; coping and managing in isolation (hesitation about capacity to do home dialysis).

Conclusions: Patients with CKD in rural/remote areas face profound challenges of displacement, financial burden, separation from family in accessing kidney replacement therapy; which can have severe consequences on wellbeing and outcomes. Strategies are needed to improve access for those patients in rural/remote communities.

TH-PO274

Patient Driven Video-Educational Tool in ESRD

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Background: Eeach year, of the ~ 110,000 incident incident end stage renal disease (ESRD) patients in the U.S., ~ 46% have not received pre-ESRD nephrology care. Pre-ESRD patient education improves outcomes and quality of life. There are limited options to incorporate patient experience into pre-ESRD education.

Methods: In a large academic program we designed a educational tool comprised of a patient interview video, in a patients-teaching-patients model. A planning committee (trainees, physicians, nurse educator and patient surveys) determined the components of this tool. The open-ended patient interviews focused on domains pertaining to experience with dialysis modality, preparation towards dialysis/transplant, lifestyle changes, and journey of accepting life after ESRD. After obtaining informed consent patients were interviewed for ~ 4 hours, edited by three reviewers into a 50 min video, and viewed by faculty and trainees to obtain provider feedback.

Results: There were 6 patients with ESRD (3 Women; 1 White and 5 Black); [3 hemodialysis (HD), 2 home dialysis (HD and peritoneal dialysis), and 1 transplant recipient]. Patients had varying degrees of pre-ESRD education, and had different journeys prior dialysis; and were eager to share their experiences with their peers. The patient reported themes included: their pre-determined fear of dialysis was misplaced; they appreciated the value of adherence to life-sustaining therapies; adjustment to diet and lifestyle modifications was a big component in accepting ESRD care; and they did not realize the available flexibility of dialysis care which may allow them to travel, continue employment, and maintain quality of life. As for provider feedback, 100% found this video to be a critically important educational tool. A shorter shorter duration and including more discussion on transplantation was recommneded. Interestingly, patients felt that although they preferred a peer-driven educational component, it cannot replace the healthcare professionals education.

Conclusions: We successfully demonstrated that patient experience can be incorporated into a succinct video-based educational tool. Key peer-driven components may allay fears of dialysis, improve adherence to dietary and lifestyle changes, and

compliment provider education. Future steps include incorporating this tool prospectively, and assess its effectiveness in pre-ESRD educational programs.

Funding: Clinical Revenue Support

TH-PO275

Shared Care in Haemodialysis: A Path to Independence

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Background: Most dialysis patients spend many hours every week in hospital, which can leave patients feeling exhausted. Shared care haemodialysis programmes can improve patient satisfaction and may reduce costs. The Queens hospital dialysis unit is a satellite is one of the satellite units of Royal London Hospital, United Kingdom. In order to promote more control of dialysis care to be delegated to patients we aimed to offer shared care programme to all suitable patients coming to the unit which enabled the patients to manage their care with nursing support. Shared haemodialysis care is when patients at dialysis units are supported to undertake tasks involved in their own treatment to the extent that they wish, which would range from performing selected tasks to complete independence in performing haemodialysis in the unit also named as self-care haemodialysis which is suitable for patients with housing issues.

Methods: All patients transferred to the unit were assessed for suitability for shared care. A dedicated link nurse for shared care offered these patients the list of performing 15 different dialysis related tasks. The performance data was collected from January 2018 to April 2019 and 3 monthly progress was noted in patients' capability to perform specific tasks related to haemodialysis care. All these patients were also offered to sign up to "Patient View" a web based system which enabled patients to review there blood results and physician's letters.

Results: In January 2018, at the start of the programme 72 out of 100 (72%) patients were offered to perform the tasks. Only 19% were able to perform 5 or more tasks including 1 patient who could needle fistula independently. By April 2019, 97 out of 105 (92.4%) patients were offered to perform dialysis related tasks and 49.5% were performing 5 or more tasks with 2 patients needling their fistulas independently.

Conclusions: Shared care in haemodialysis is a good way of involving patients in the dialysis care which provides feeling of achievement and independence to patients. It provides dialysis space for patients who cannot perform home haemodialysis due to housing related issues. Achieving complete self care is a daunting task for both the patients as well as responsible health care providers as it was a slow progress to do more complicated tasks. Identifying barriers to achieve these tasks will help in implementation of shared care programme.

TH-PO276

Reasons for Referral to Kidney Supportive Care Clinic and Outcomes in Haemodialysis Population

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Background: In Australia, 32-40% of deaths in the dialysis population are due to treatment withdrawal. Withdrawal from dialysis is usually triggered by failure to thrive on dialysis, high symptom burden, and its associated accelerated chronic comorbid illness. The role of a dedicated multidisciplinary kidney supportive care (KSC) clinic for those on dialysis is not only in managing these symptoms but also providing support surrounding dialysis cessation where appropriate. We aim to analyse the reasons for referral of chronic haemodialysis patients to a KSC clinic and assess decision-related outcomes following the clinic.

Methods: Retrospective analysis of all persons on haemodialysis referred to KSC clinic in the 3 years from inception (February 2016). Reason(s) for referral to clinic, documented advanced care planning, number of visits, potential change of pathway and timing of death were extracted from medical records and analysed descriptively.

Results: Of the total of 364 people referred to KSC clinic, 118/364 (32%) were receiving haemodialysis. Of these, 58% were male with a median age of 69 years (range 27-89 years). Reason for referral were: control of symptom burden (65%), resolve decision-making conflict (25%), advance care planning (50%), education surrounding cessation of dialysis (30%) although some had more than one reason. Post KSC review, 72% had documented advance care plan. Number of visits ranged from 1-12 with a median of 2 clinic reviews. 59/118 (50%) have died at the time of analysis. 38/59 (64%) opted to change pathway from receiving haemodialysis to conservative management pathway before death due to deteriorating health.

Conclusions: Access to KSC is vital in the journey of a patient with chronic kidney disease. A key role of KSC is the discussions on future planning which is usually started by the treating nephrologists and then further elaborated in KSC leading to advanced care planning. This offers tailored, patient-centred care that aligns their beliefs and preferences with their goals, aiming to not only improve quality of life, but quality of death.

TH-PO277

Numeracy Relates to Communication and Clinical Outcomes in ESKD

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Background: Numeracy is assessed subjectively via confidence in numerical tasks or objectively via computation. Low numeracy is associated with poor communication with providers and disease control in chronic illness. Understanding kidney function requires interpretation of numerical values, yet numeracy is unexplored in end-stage kidney disease (ESKD). We tested whether numeracy associates with increased confidence in communicating with nephrologists and phosphorus control.

Methods: In a cross-sectional study we recorded demographics, clinical data, and validated surveys. Subjective and objective numeracy were measured via the Subjective Numeracy Scale (SNS) and Wide Range Achievement Test (WRAT), and communication via Patient Perceived Efficacy in Patient Physician Interactions. Pearson's correlations tested associations, and regression models tested associations adjusting for age, sex, race, income, education, cognition, dialysis vintage.

Results: In 150 patients on hemodialysis, subjective and objective numeracy associated with higher income, education, and white race ($p<.01$) (Table). Subjective numeracy associated with confidence in communication ($r=.25, p<.01$) even after covariate adjustment ($\beta=.25, p<.05$), but not with phosphorus ($p=.58$). Objective numeracy did not associate with confidence in communication ($p=.27$) and associated with phosphorus ($r=-.18, p<.05$) but not in adjusted models.

Conclusions: Poor numeracy is common in vulnerable ESKD patients. Supporting efficacy in numeracy may improve communication with nephrologists, but medication and diet control may be more influenced by computation. Numeracy in ESKD education and counseling may enhance patient engagement.

Funding: NIDDK Support

Numeracy, Demographics, Outcomes with Median, IQR

		SNS r(p)	WRAT r(p)
SNS s3.5	3.4[2.8-4.1]		
WRAT s93	89[78-98]		
Age	52[42-63y]	-.09(.3)	.13(.1)
Male	49%	3.4[2.8-4.1] (.2)	92[80-98] (.4)
Black	74%	3.3[2.6-4.1] (<.05)	86[76-96] (<.01)
Income <29K	69%	3.2[2.6-4.2] (<.01)	84[74-96] (<.01)
Education	12[12-14y]	.32(<.01)	.34(<.01)
Literacy(3-15)	12[10-14]	.37(<.01)	.25(<.01)
Communication(22-50)	42[38-48]	.25(<.01)	.1(.3)
Phosphorus -mg/dL	6[5-7]	.05(.6)	-.18(<.05)

IQR=interquartile range; s=standardized; y=years; K=,000

TH-PO278

Concerns About and Impacts of Treatment for Kidney Failure from the Perspectives of African American Family Members

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Background: Understanding African American families' experiences with treatment for kidney failure is necessary for informing the delivery of family-centered care and the design of appropriate interventions. This qualitative study explored treatment-related questions, concerns, and positive and negative family impacts from the perspectives of African American family members of pre-kidney failure and kidney failure patients.

Methods: Thirty-five African American family members of kidney disease patients receiving medical care in Baltimore, Maryland participated in five focus groups stratified by patients' treatment status in the past year (progressive kidney disease, hemodialysis, peritoneal dialysis, evaluated for living-donor kidney transplantation, or underwent living-donor kidney transplantation). Discussions were analyzed thematically. Themes present in discussions from multiple groups were highlighted to provide insight into common experiences. Exemplar quotes are provided.

Results: Family members raised *questions* and *concerns* about patients' "high risk of" infections, "mental breakdowns," constrained freedom of choice ("Dialysis would just bust her goals"), "the financial aspect" of treatment, and treatment delivery and logistics, specifically inconveniences ("The tube bothers her"), patients' treatment adherence ("Sneaking around and getting the chocolate"), and care quality ("They should have better training"). *Positive family impacts* included improvements in patients' well-being ("He's a lot more compassionate"), "good" patient and family quality of life, strengthened family relationships ("rallying" around the patient), greater freedom of choice ("Going to work again"), and family members' "chance to give life" to patients via transplantation. They identified decrements in patients' well-being ("Her being down on herself"), family members' adverse psychological treatment reactions ("I'm scared"), strained family relationships ("My son and I are not speaking"), and caregiving difficulties ("You as family member need support too") as *negative family impacts*.

Conclusions: Findings underscore the importance of addressing African American family members' perspectives on kidney failure treatment through additional research, early and tailored education, and supportive interventions.

Funding: NIDDK Support

TH-PO279

Challenges to Hemodialysis Care and Solutions: Qualitative Analysis of the Can-SOLVE CKD Triple I Study

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Background: Part of the Can-SOLVE CKD program, 'Triple-I' is a pan-Canadian study that aims to identify top priorities and test solutions for improving patients' hemodialysis (HD) experience in three areas: a) **Information** patients receive b) **Interactions** between provider and patient c) **Individualization** of care. Triple-I follows Can-SOLVE's guiding principles to involve patients in all phases of research as co-creators of knowledge and solutions. In Phase 1, using focus groups and interviews, we identified challenges in HD care and potential solutions in the areas of *information, interaction* and *individualization*.

Methods: From July 1, 2017 to July 31, 2018, we performed focus groups and interviews with HD patients, their caregivers and healthcare providers in 5 academic centres (Edmonton, Calgary, Winnipeg, Ottawa and Halifax). Subsequently, 3 members of the research team conducted a pragmatic categorical analysis to code the data from de-identified transcripts of these sessions. Data were classified by respondent type (patients/caregiver or health care providers).

Results: A total 113 people (64 HD patients, 18 caregivers, 31 health care providers) participated in 8 focus groups or individual interviews, of which 41% were women. Mean age of patients and caregivers was 61 years and mean time on HD was 4.6 years. After accounting for redundancy, a total of 45 recurring challenges in HD care were identified (information n=18; interaction n=16; and individualization n=11). Highly prevalent challenges included *information* on modality/access, transplant and first day of HD; *interactions* with nephrologists, nurses and inconsistency of care with different healthcare providers; and, insufficient *individualization* of session set-up, transportation arrangements and ways to address socio-economic and emotional well-being. Although there were some differences in responses between patients/caregivers and health care providers, many of the challenges coded were identified by both groups.

Conclusions: Although a deeper qualitative analysis of this data is ongoing, the codes/challenges identified in this phase of the study will be used to prioritize challenges and identify and test potential solutions to these challenges in further phases of the study.

Funding: Government Support - Non-U.S.

TH-PO280

A Cross-Sectional Study of Insomnia in Chronic Hemodialysis Patients

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Background: The most frequent complaint in chronic hemodialysis(CHD) patients(pts) is insomnia yet little research has identified all of the causes of this disorder in CHD pts.(Flythe, CJASN,14:150, 2018)

Methods: We conducted a review of sleep patterns in 103 CHD pts on the first & second shifts in our 2 largest dialysis units using these tools: the National Sleep Foundation Survey, the Sleep Diary, Insomnia Severity Index(>8 abnl), Stop-Bang-8 for sleep apnea(SA, 5-8 high risk), Epsworth Sleepineess Scale, Restless Leg(RL) Survey & the International RL Severity Score(>8 abnl).

Results: 25 CHD pts (24%) including 4 with SA had normal sleep patterns averaging 8.1 hours of sleep/nite & <1 awakening from the Sleep Diary & scores of < 7 on the Insomnia Severity Index, 0-3 on Epsworth & 3 or < on Stop Bang-8. Insomnia occurred in 78 CHD pts(76%). Mean duration of sleep ws 3.9 hrs with 2.5 awakenings from the Sleep Diary, p<.001 vs normal CHD pts. The National Sleep Foundation Survey & Epsworth Scale were inconsisitent in identifying these pts. There were no differences in age, duration of dialysis, sex, or causes for ESRD between groups. 24 CHD pts had known SA & in all 24 the STOP Bang-8 was 4 or >, mean 6.2 which is a high risk score for SA. 13 other CHD pts had a Stop Bang-8 of 4 or > & have been sent to sleep medicine. RL occurred in 19 CHD pts with a mean severity score of 25. 14/19 RL pts had iron deficiency vs 22/78(28%) of all other CHD pts with insomnia(p<.01) The levels of serum iron & saturation did not correlate with the RL Severity Score. They are receiving iv iron therapy & will be re-scored. 5 CHD pts had both SA and RL. 13 CHD pts had newly reported causes for insomina : painful neuropathy 9, cramps 2, pruritus, 1 & arthrits 1. Only 13 CHD pts had primary insomnia. Cognitive behavioral therapy(CBT) has started for these pts.

Conclusions: Insomnia occurs in up to up to 75% of CHD pts from diverse causes. The most useful tools to identify insomnia are the Sleep Diary, Insomnia Severity Index & the Stop Bang-8 which correctly identifed all 24 SA CHD pts. RL in CHD pts was associated with iron deficiency. We found 4 new insomnia causes in CHD pts including painful neuropathy, cramps, pruritis & arthritis. Algorithms to treat each cause of insomnia have been developed especailly for safe sedatives for primary insomnia if CBT fails.

Funding: Clinical Revenue Support

TH-PO281

Association of Illness and Disability with Elective Withdrawal in Hemodialysis

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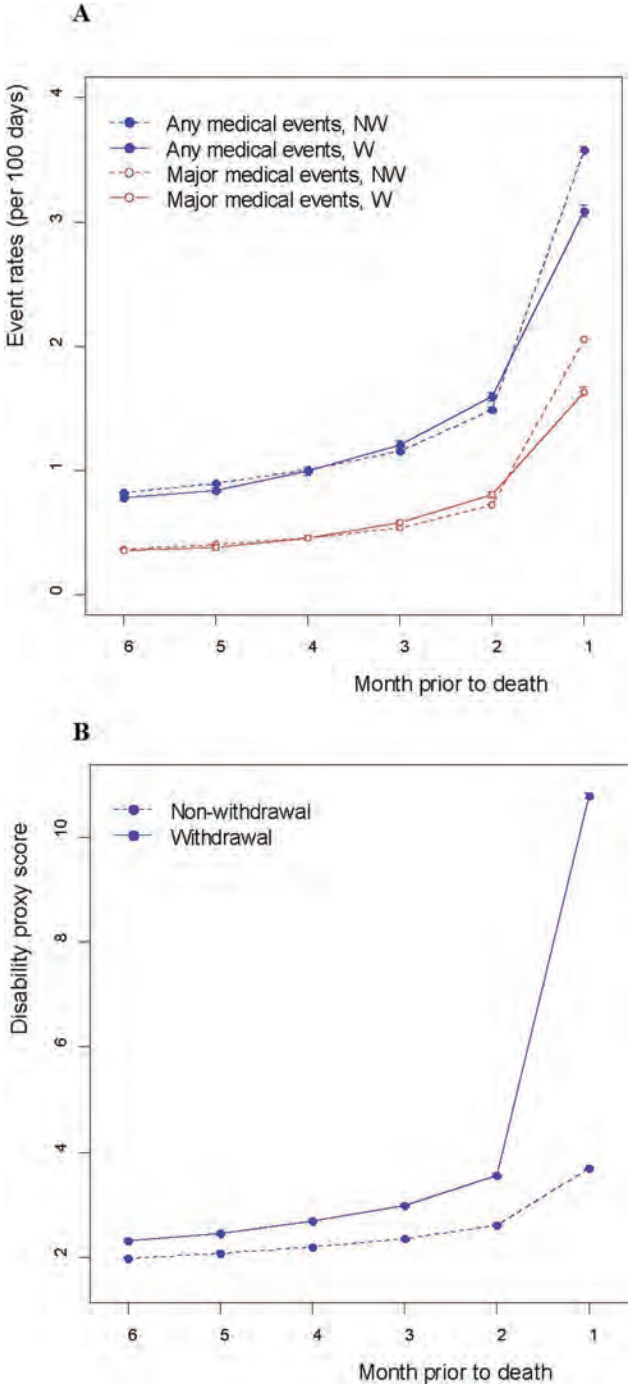
Background: Few studies have contrasted elective withdrawal with non-withdrawal death by examining factors immediately prior to death.

Methods: Using USRDS data, we performed a retrospective analysis of hemodialysis patients who died 2010-2015. Deaths were divided into withdrawal versus non-withdrawal. A claims-based disability proxy score was used to characterize disability. Logistic regression was used to identify characteristics associated with type of death and death setting. Trajectory models were used to characterize trajectories of medical illness and disability prior to death. Factors associated with in-hospital death were examined.

Results: We identified 14,571 (9.2%) patients who withdrew and 144,305 (90.8%) who died of a non-withdrawal cause. Women were more likely to withdraw (odds ratio [OR] 1.19, 95% confidence interval 1.15-1.24). The most rural patients were more likely to withdraw than the most urban ones (OR 1.37, 1.25-1.50). Medicaid coverage (a marker for impoverishment) was associated with less withdrawal (OR 0.90, 0.86-0.94). Disability proxy score was strongly related to withdrawal: the OR for patients in the highest disability score category was 31.16 (28.40-34.20), vs. a score of 0. While trajectories of traditional medical events did not appear to differ between those who withdrew and those who otherwise died, the trajectory of the disbility score was markedly worse for those who withdrew (Figure). Women and whites (as opposed to blacks) were relatively over-represented in the worse, as opposed to better, trajectory of proxy disability score. In-hospital death was more common in women and minorities than in men and whites, but less common in rural patients.

Conclusions: Worsening disability may be a particularly important marker for elective dialysis withdrawal.

Funding: NIDDK Support



NW, non-withdrawer; W, withdrawer.

TH-PO282

The Effect of Extracorporeal Shock Wave Therapy in Hemodialysis Patients: A Randomized Controlled Trial

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Background: Muscle wasting is a common feature in the hemodialysis (HD) patients and associated with comorbid complications, poor quality of life, frailty and premature death. Extracorporeal Shock-Wave Therapy (ESWT) is able to relief pain, as well to positively regulate inflammation (probably as immunomodulator), to induce neoangiogenesis and stem cells activities, thus improving tissue regeneration and healing, and has the advantages of easy application, and minimal risks for these patients. This study aimed to evaluate the effects of intradialytic ESWT.

Methods: This was a single center, prospective, randomized controlled trial. Seventeen HD patients were randomly assigned to either the ESWT group or the control group. The ESWT group received intradialytic ESWT over a 12-week period. Measurement of body composition using a dural energy X-ray absorptiometry, the handgrip strength test, gait speed test, five time sit to stand test, and the timed up and go test for physical function assessment, and blood tests were performed before and after the intervention period.

Results: The ESWT group demonstrated significant improvement compared with the control group in main functional parameters: decreased time in gait speed test (5.5 ± 13.3 vs. -0.5 ± 1.3 sec), five time sit to stand test (3.9 ± 10.7 vs. -1.4 ± 2.8 sec), and the timed up and go test (6.9 ± 17.8 vs. -3.1 ± 4.2 sec). After treatment, lipopolysaccharide concentrations were reduced, and glutathione peroxidase concentrations were increased significantly in ESWT group. However, there was no significant difference in muscle mass and other blood tests.

Conclusions: The ESWT group showed improvement after intervention in physical function test, and oxidative stress parameters. ESWT could be an effective treatment tool for HD patients with either muscle wasting, weakness, or sarcopenia.

TH-PO283

Physical Activity Levels In Hemodialysis Patients: The Fitbit Prospective Study

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Background: Physical decline in end stage kidney disease is associated with morbidity and mortality. The aim of this study was to quantify physical activity (PA) in hemodialysis (HD) patients using the Fitbit. We hypothesize that PA measured as by the number of daily steps will be lower in older patients, and those from a rural HD unit.

Methods: In this prospective study, 52 chronic HD patients were recruited from outpatient HD units in urban San Diego and rural Imperial County, CA between March 2018 and April 2019. Key inclusion criteria included: 1) Receiving HD for ≥3 months 2) age ≥18 years and 3) able to walk without assistance or assistive devices. All HD patients wore Fitbit Charge 2 (Fitbit, San Francisco, CA) for 4 weeks. The display of the Fitbit was covered to minimize participation bias. The primary outcome was number of steps per day.

Results: Of 52 enrolled patients, 7 HD patients dropped out before completing 4 weeks study duration. The remaining 45 HD participants (urban=25; rural= 20) were included in the analysis. The mean age was 61 years, 42% were women and 64% were hispanic. The mean dialysis vintage was 4.4 years. On average, HD subjects walked 3687 steps per day. Elderly walked fewer steps compared to younger (age < 65 yrs) HD patients (1359 vs. 4387 steps, p=0.02). Although, not statistically significant average daily steps for participants from rural HD clinic (3141 vs. 4123 steps, respectively) and on dialysis days (3272 vs. 4070 steps, respectively) were less compared to participants from urban HD clinic and non-dialysis days. We found no difference in physical activity levels by gender and dialysis shift (Figure 1). Only about 10 percent of HD participants found activity tracker not comfortable to wear.

Conclusions: Participants on HD were found to be less PA on dailysis days and from rural dialysis clinic. Difference was more pronounced between younger and elderly individuals. Future studies should focus on patient-centered adaptive interventions to sustain and improve PA among HD patients.

Funding: Private Foundation Support

Figure 1. Physical Activity Stratified by Patient Characteristics (N=45)

TH-PO284

Framingham's Cardiovascular Disease (CVD) Risk Score (FRS) and Its Components as Predictors of Mortality in Peritoneal Dialysis (PD) Patients

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Background: Non-traditional risk factors (e g inflammation and oxidative stress) contribute to the high mortality risk due to CVD in patients (pts) with chronic kidney disease (CKD). However, the impact of traditional risk factors represented by FRS, and its components age, sex, hypertension, diabetes mellitus (DM), smoking and hyperlipidemia, is less well documented. We analyzed the associationof FRS with mortality in PD pts.

Methods: In 1276 incident PD pts (median age 50 years, 56 % males), FRS andmetabolicbiomarkers linked to CVD were analysedat baseline. Associations of FRS and its components with all-cause and CVD-related mortality during follow up of up to 60 months (median 44 months) was analysed using regression models with transplantation as competing risk.

Results: Pts in the high tertile of FRS were predominately older men with DM, CVD and high BMI, and low serum creatinine, albumin and parathyroid hormone (iPTH). In linear regression model, FRS associated with CVD, BMI, Hb, iPTH, alkaline phosphatase (ALP), calcium and albumin after adjustments for confounders. *All-cause mortality risk* (expressed as crude sHR) associated with 1-SD higher FRS (sHR 1.50), and its components, higher age (sHR 2.63), female gender (sHR 0.67), and DM (sHR 2.40), and crude *CVD-mortality risk* with 1-SD higher FSR (sHR 1.64), and age (sHR 2.89), DM (sHR 3.41) andcholesterol(sHR 1.08). In competing-risks regression analysis, high vs low tertile of FRS, independently associated with all-cause, sHR 3.65(95% CI 2.07 - 6.44) and CVD, sHR 3.28 (95% CI 1.45 - 7.11) mortality risk after adjusting for CVD, year of recruitment, and 1-SD higher: BMI, creatinine, uric acid, calcium, phosphate, ALP, iPTH, triglycerides, glucose, Hb, ASAT and ALAT.

Conclusions: FRS is independently associated with mortality risk in PD pts, underlining the importance of traditional risk factors in CKD. FRS is a useful risk assessment tool for predicting clinical outcomes in PD pts.

TH-PO285

Relationship of Short-Term and Long-Term Blood Pressure Variability with Death and Cardiovascular Events in Peritoneal Dialysis Patients

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Background: Blood pressure (BP) variability is associated with increased cardiovascular risk, not only in hypertensive patients but also in patients with chronic kidney disease. However, little is known about this association in peritoneal dialysis (PD) patients. This study aims to investigate the relationship of short-term (within 24-hour) and long-term (visit to visit) BP variability with death and cardiovascular events in patients on PD.

Methods: A total of fifty two prevalent PD patients were enrolled and underwent 24-hour ambulatory BP monitoring. Short-term BP variability was assessed with the weighted standard deviation (w-SD) of 24-hour ambulatory systolic BP monitoring and long-term BP variability was assessed with the SD of systolic BP across clinic visits. We assessed the associations of short-term systolic BP variability and long-term systolic BP variability with a composite outcome of death and cardiovascular events.

Results: The average short-term systolic BP variability was 13.3±2.9 mmHg, and average long-term systolic BP variability was 20.6±5.9 mmHg. In unadjusted Cox regression analyses, higher short-term systolic BP variability was significantly associated with increased risk of death and cardiovascular events (HR, 1.437; 95% CI, 1.146-1.801; *P*=0.002). The significant association of short-term systolic BP variability with the composite outcome was also maintained, in adjusted multiple Cox regression model (HR, 1.342; 95% CI, 1.025-1.756; *P*=0.033). However, long-term systolic BP variability was not related to the composite outcome in both the unadjusted (HR, 1.067; 95% CI, 0.958-1.188; *P*=0.239) and adjusted (HR, 1.083; 95% CI, 0.955-1.229; *P*=0.214) models.

Conclusions: In patients on PD, increased short-term systolic BP variability is related to higher risk of death and cardiovascular events, whereas long-term systolic BP variability is not.

TH-PO286

The Beneficial Role of Peritoneal Dialysis on Cardiac Functional Parameters in Patients with Congestive Heart Failure: A 3.5-Year Follow-Up

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Background: Peritoneal Dialysis (PD) applied in patients (pts) with congestive heart failure (CHF), resistant to diuretic therapy, results in significant improvement of their condition. We examined the effect of PD on extended time period, as a continuous ultrafiltration treatment to pts with CHF (NYHA class IV) and renal disease stage > IIIb on cardiac functional parameters. We performed a detailed Cardiac Ultrasound (CU) in an effort to identify markers to distinguish population that might benefit of early PD application.

Methods: We enrolled 28 pts (mean age 78.3 years) in PD over 42 months (mo). Inclusion criteria were CHF (NYHA class IV) symptoms, resistant to diuretics, and deterioration of renal function. Assessment of cardiac function by CU on the initiation of PD, 6 and 12 mo later. We recorded and evaluated the Ejection Fraction (LVEF), Relative Wall Thickness (RWT), Left Ventricular Mass Index (LV), E/E', Left Atrium Volume Index (LA), Pulmonary Artery Systolic Pressure (PASP), Tricuspid Annular Plane Systolic Excursion (TAPSE).

Results: Mean time on the method was 21 ± 10.16 (7 - 42) mo. Remarkably, significant reduction of all CU parameters, was noted, during period 0 – 6 mo and 6 – 12 mo for every patient. In contrast, no important changes were observed in period 6 – 12 mo. Also, there was substantial decrease of diuretics, as well as elimination of hospitalizations due to CHF decompensation and noteworthy improvement of NYHA class. As it was expected we observed significant body weight decrease in period 0 – 6 mo as well as in 0 – 12 months. But, no important changes in period 6 – 12 mo.

Conclusions: The gradual and continuous removal of excess fluid resulted in clinical improvement of the living status of all our pts. Furthermore, there was a long term improvement of the left and right cardiac functional parameters in CU. Thus, dramatically diminishing hospitalizations, due to decompensation of CHF, and restoring pts autonomy. The application of PD can be an important choice in the management of CHF NYHA class IV. The outcome of this prospective study supports the use of PD in selected pts of this cohort.

TH-PO287

Cardiovascular Effects of Peritoneal Dialysis in a Uremic Rat Model

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Background: In the US more than 700,000 people suffer from end stage renal disease (ESRD) of which 97.5% are reliant on dialysis. Among dialysis patients, cardiovascular (CV) related events are the leading cause of death. Despite therapeutic advancements the continued CVD following the onset of dialysis poses an interesting clinical challenge that necessitates further studies into the effects and effectiveness of dialysis. Based on clinical outcomes, we hypothesized that peritoneal dialysis (PD) would have no effect on CV outcomes in the 5/6 nephrectomy (5/6Nx) rat model.

Methods: We performed 5/6Nx (n=13), or sham surgery (n=10), on 10 week old male Sprague-Dawley rats. Peritoneal catheters were implanted 6 weeks post-surgery. PD was initiated 2 days later in some of the 5/6Nx (n=6) and sham (n=5) animals (15ml [Baxter PD-2 2.5%] 1-hour dwell 3x/day x7days). Echocardiography was performed at baseline, 6, and 7 weeks post-surgery. At week 7 pressure volume analysis was performed prior to serum and tissue collection. Statistical significance was determined by two-way ANOVA.

Results: Blood urea nitrogen (BUN) was increased by 5/6Nx (5/6Nx 41.57±2.78 vs. sham 20.25±0.48; p<0.05). PD had no effect on BUN in sham animals, but decreased BUN in 5/6Nx (5/6Nx 41.57±2.78 vs. 5/6Nx+PD 31.5±1.48; p<0.05). PD had no effect on serum sodium, potassium, or bicarbonate levels, nor did it effect serum cholesterol. PD had no effect on albumin excretion in both sham and 5/6Nx animals. PD did not alter kidney weight in sham animals, but reduced remnant kidney weight in 5/6Nx (5/6Nx 0.49±0.03 vs. 5/6Nx+PD 0.39±0.01; p<0.05). 5/6Nx increased heart weight (5/6Nx 0.42±0.02 vs. 0.35±0.01; p<0.05). PD had no effect on heart weight in sham animals, but attenuated the increase in 5/6Nx (5/6Nx 0.42±0.02 vs. 0.39±0.02; p=0.08). PD had no effect on CV functional parameters in sham animals and in 5/6Nx neither improved nor worsened CV outcomes.

Conclusions: These data combined suggests that PD may reduce renal pathology by reducing stress on remaining functional nephrons. Importantly, we did not observe an improvement in CV parameters with PD, which is consistent with persistent CV risk in the PD population. These findings indicate this is an appropriate model for future studies focused on improving dialysis efficacy and CV outcomes for ESRD patients.

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TH-PO288

Prognostic Value of Soluble ST2 and Soluble LR11 on Mortality and Cardiovascular Events in Peritoneal Dialysis Patients

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Background: Because end-stage renal disease (ESRD) patients are at high risk of cardiovascular (CV) disease, developing a biomarker for CV risk stratification has clinical importance. Soluble form of suppression of tumorigenicity 2 (sST2) and soluble low-density lipoprotein receptor relative with 11 ligand-binding repeats (sLR11) are emerging CV biomarkers, however, to date, the prognostic value of those has not been investigated in patients undergoing peritoneal dialysis (PD).

Methods: We determined serum sST2 and sLR11 concentrations using enzyme-linked immunosorbent assay, and evaluated the association of those biomarkers with all cause mortality and major adverse cardiac and cerebrovascular event (MACCE) in 74 prevalent PD patients.

Results: The median (interquartile range) concentrations of sST2 and sLR11 were 70.9 (57.8-89.8) ng/mL and 15.2 (12.3-19.6) ng/mL, respectively. During a median follow-up of 38.5 months, 13 (17.6%) patients died and MACCE was observed in 23 (31.3%) patients. When patients were dichotomized by the median value of sST2 and sLR11, Kaplan-Meier analyses showed that higher sST2 group was significantly associated with lower event-free survival rates (log-rank test; P=0.002 for all-cause death; P=0.01 for MACCE). In multivariable Cox analyses, higher sST2 was independent risk factor for all-cause mortality (per 1 standard deviation [SD] increase; hazard ratio [HR]=1.947; 95% confidence interval [CI]=1.124-3.371) and MACCE (per 1 SD increase; HR=1.647; 95% CI=1.079- 2.516). In contrast, sLR11 did not have a significant association with all-cause mortality or MACCE. Furthermore, only sST2 provided a significant predictive value for all-cause mortality (AUC=0.699; P=0.03).

Conclusions: sST2, not sLR11, was independently associated with greater risk of all-cause mortality and CV outcome in prevalent PD patients. Additional studies are needed to confirm these findings and examine underlying mechanism between new biomarkers and CV disease in ESRD populations.

TH-PO289

Incremental Peritoneal Dialysis and Clinical Outcomes: A Propensity Score Matching Study

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Background: Incremental peritoneal dialysis (iPD) can be useful in selected patients with higher residual renal function, needing lower financial cost, or wanting less time burden of PD treatment. In addition, patients on iPD would have a reduced risk of peritonitis or peritoneal glucose exposure. However, the long-term effects of iPD on patient survival and PD survival are not clear compared to conventional PD (cPD). The aim of this study to evaluate the patient survival and PD survival in iPD compared to cPD.

Methods: Clinical data was retrospectively collected from a single center between January 2007 and December 2018. We included 303 patients percutaneously inserted PD catheter by surgical methods. An analysis was performed using propensity score matching for age, gender, and the presence of DM. Finally, 96 cPD patients and 48 iPD patients were included. IPD was defined as starting PD with 3 or fewer peritoneal exchanges per day.

Results: Median duration of iPD was 31.2±22.5 months and mean PD duration of iPD was longer than cPD. Initial blood urea nitrogen and serum creatinine levels (7.3±2.7 vs. 9.7±3.7 mg/dL, p <0.001) were significantly lower in iPD patients than cPD patients. Mortality as well as rates of peritonitis and hospitalization was significantly lower in patients with iPD than those with cPD (log-rank, p=0.034, p=0.001 and p=0.023). Mortality and hospitalization rate were prominent in cPD patients with diabetes. However, there was no significant difference in PD survival between iPD and cPD.

Conclusions: Incremental PD may be not only safe PD modality but also has better clinical outcome in less uremic patients to initiate and maintain PD. Further prospective studies are necessary to confirm these benefits in diabetic patients treated with PD.

TH-PO290

Excessive Salt Intake Increases Peritoneal Local Production of Interleukin-6 and Baseline Peritoneal Solute Transport Rate in Subtotal Nephrectomized Mice

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Background: Baseline peritoneal permeability varies between patients before exposure to peritoneal dialysis fluid. Dialysate interleukin (IL)-6 was an indicator of peritoneal transport function. Besides, we previously reported upregulation of peritoneal IL-6 level in uremic mice with salt loading. The present study aims to investigate the peritoneal transport and the role of IL-6 in uremic mice with salt loading.

Methods: Sham-operated (Sham) and subtotal nephrectomized (Nx) mice were randomly given tap water or 1% salt (NaCl)-containing water. After 8 weeks, 4.25% glucose-based peritoneal equilibration test was performed to evaluate peritoneal function. Locally overexpressed IL-6 was functionally blocked by rat anti mouse IL-6 receptor antibody (MR16-1) in another study to examine the role of IL-6 in this process.

Results: A significant elevation of D/P Cr and a decrease of D/D0 glucose were observed in Nx+salt group. There was also enhanced angiogenesis and macrophage infiltration in the peritoneum of Nx+salt mice, along with elevated VEGF-A and MCP-1 concentration in the dialysate. Compared to Nx+water group, the increased concentration of effluent but not serum IL-6 and soluble IL-6 receptor α suggested a strong local production in Nx+salt group. IL-6 was expressed in mesothelial cell layer and CD68-positive macrophages in peritoneum of Nx+salt mice. Elevation of peritoneal phosphorylated stat3 indicated an increment of IL-6 signaling. Blockade of IL-6 signaling by MR16-1 alleviated macrophage infiltration and angiogenesis as well as rescued peritoneal transport function in Nx+salt mice. In mesothelial cells, incubation with additional 40mM NaCl in the medium upregulated the expression of IL-6, along with the translocation into the nucleus of transcription factor tonicity-responsive enhancer binding protein (TonEBP), the only known transcription factor responding to high tonicity. Upregulation of IL-6 under hypertonicity induced by NaCl was also observed in mouse peritoneal-derived macrophages and bone marrow-derived M1 macrophages.

Conclusions: These findings suggest that high salt intake under uremic condition could increase peritoneal local IL-6 production leading to higher peritoneal solute transport rate.

TH-PO291

Safety and Efficacy of a Zero Sodium Peritoneal Solution

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Background: Sodium (Na) removal with conventional peritoneal dialysis solutions, which have a Na concentration similar to serum, primarily occurs by means of convective clearance. Zero Na peritoneal solution with a high osmolarity may offer more effective Na removal given the large Na concentration gradient to serum. This solution could have clinical application as an intermittent therapy for venous congestion.

Methods: This was a randomized open label crossover study in 10 established peritoneal dialysis patients comparing zero Na dialysis solution (10% dextrose, ~505mOsm/L) to standard 4.25% dextrose solution (485mOsm/L). Patients underwent a 1liter dwell for 120 minutes with both solutions at two separate study visits. Serum and dialysate sodium were monitored every 15 minutes, and intraperitoneal volume was determined using indicator dilution technique with I-131 albumin. (NCT03801226; IND141103)

Results: Total Na removal and ultrafiltration were significantly greater with the zero Na solution, and Na removal rate was highest in the first 30 minutes (figure 1). There was a small decrease in serum Na of 1meq/L after 120 minutes with the zero Na solution. There were no significant differences between the two solutions in non-Na plasma electrolytes at 120 minutes. While serum glucose increased with both solutions, this increase was not significantly different between the two solutions at 120 minutes. There were no significant differences in blood pressure trends.

Conclusions: Despite similar osmolarities, zero Na peritoneal solution results in more effective Na clearance and higher UF volume. The solution was well tolerated without significant adverse changes in blood pressure or off target electrolytes.

Funding: Commercial Support - Sequana

TH-PO292

Peritoneal Sodium Removal Technique with Salt-Free Solution in Pigs

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Background: Over time, interest in the concept of sodium and fluid removal via non-renal routes in heart failure (HF) has grown significantly. One approach to removing sodium and fluid without diuretics is peritoneal dialysis (PD). Traditional PD, however, is ineffecient in that it requires large intraperitoneal volumes with long dwell times while only offering limited sodium and fluid removal. Utilization of salt free peritoneal solution will result in removal of a clinically significant amount of sodium and fluid.

Methods: Eighty kg anesthetized pigs (N=15) underwent surgical implantation of PD catheters. In 5 pigs, we allowed a 6 hour dwell and the intraperitoneal volume was determined serially using indicator dilution technique with I-131 radiolabeled albumin. 10 pigs underwent a 2 hour dwell with fluid volume measured by manual removal. To understand the effects of higher peritoneal solution volumes, 4 of these pigs then underwent 4 cycles of 2.5 L of 10% dextrose with 90 minute dwell times, for a total of 11 L cycled. These 4 animals had plasma volume measured with I-131 radiolabeled albumin prior to and after cycling was complete. Serial plasma and peritoneal fluid samples were obtained and glucose and electrolyte concentrations were determined.

Results: In the 5 animals with a 6 hour dwell, ultrafiltration approached 1.5 L and 5.1 +/- 0.4 grams of sodium was removed. In the 10 pigs that underwent a 2 hour dwell, an average of 0.9 +/- 0.2 L of ultrafiltration occurred with a corresponding 3.9 +/- 0.5 g of sodium removed. Despite a large sodium removal, the average decrease in serum sodium concentration following the 2-hour dwell was only 2.2 +/- 0.3 mmol/L ($P < 0.0001$). In the pigs that underwent fluid cycling, an average of 22.5 +/- 3.5 g of sodium was removed and plasma volume decreased dramatically in these animals.

Conclusions: Peritoneal sodium removal with salt free solution is capable of removing large quantities of fluid and sodium with relatively small intraperitoneal volumes. Additional research is required to understand the safety/tolerability of this

approach in humans, development of optimal solutions and protocols for fluid instillation and removal from the peritoneum.

Funding: Commercial Support - Sequana

TH-PO293

Is There a Place for Peritoneal Dialysis in Treatment of Refractory Heart Failure?

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Background: Ultrafiltration techniques have shown promise in the treatment of diuretic-resistant heart failure (HF). The aim of this study was to describe a single-center experience in the treatment of refractory HF patients with PD.

Methods: Retrospective study of 14 patients presenting symptoms and signs of severe refractory congestive HF despite optimal pharmacological therapy. Baseline characteristics and laboratory data were recorded. Charlson score and Doppler-echocardiogram results were collected at the beginning and end of follow-up period. PD adequacy was evaluated through peritoneal equilibrium test (PET) results.

Results: We followed a cohort of 14 patients with HF, all excluded as candidates for heart transplantation. 12 were males (85.7%) and 2 females (14.3%), with a median age of 72.13 (IQR 42.5 - 75.38) years. The mean following time was 52.5 ± 25.3 (range 18 – 95) months. Seven patients (50%) had hypertension, 7 (50%) were diabetic and 2 (14.3%) had hepatitis C infection. The etiology of HF was arterial hypertension in 7 patients (50%), ischemic cardiopathy in 3 (21.4%), valvular cardiopathy in 3 (21.4%) and in 1 patient (7.1%) congenital cardiopathy. Three patients (21.4%) had been previously treated with intermitent hemodiafiltration, which was suspended due to hemodynamic instability; the other 11 patients started PD *ab initium*. Symptoms of HF improved in 35.7% (N=5) of patients, with an upgrade of New York Heart Association (NYHA) Functional Classification and improvement in ejection fraction (EF). At the beginning of PD treatment the mean Charlson score value was 5.7 ± 2.3, wich reduced to 5.3 ± 2.6 by the end of observation time. There was a positive correlation between the first and the last Charlson score acessed (r=0.984; n=12; p<0.001). Six patients presented 1 episode of decompensated heart failure needing hospitalization, with a median length of stay of 2 (IQR 0 - 6.75) days. During the observation period seven patients were transferred to HD. In 3 cases this was lead by peritonitis episodes and in 4 by ultrafiltration failure. Two patients died, one from an acute hemorrhagic stroke and the other with a septic shock.

Conclusions: PD treatment in refractory HF, in addition to optimal pharmacological therapy, seems to be effective, since it improves quality of life and functional class.

TH-PO294

Follow -Up and Survival in Refractory Congestive Heart Failure Patients Treated with Peritoneal Dialysis

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Background: Data on survival rates of patients (pts) suffering from Refractory Congestive Heart Failure (RCHF) treated with Peritoneal Dialysis (PD) are limited. We have previously reported the beneficial effect of PD application for RCHF for a period of 12 months. According to our results body weight, use of diuretics and hospitalisations were decreased, while clinical status and their New York Heart Association (NYHA) class were improved along with cardiac function parameters on Cardiac Echo. We followed this cohort and evaluated the mortality over a 48 months observational period.

Methods: We had enrolled 18 pts (mean age 82.6 years). Inclusion criteria were NYHA IV symptoms for a 6 months interval with deterioration of renal function. Mean time on PD was 26.7 (6 - 48) months.

Results: Overall, while on PD, 10 pts died (55.5 %) during the 4 year period. Cardiac arrest was the main cause of death (6/10), infections being the second (4/10). Two pts died of complicated urinary tract infection and one of respiratory infection. One patient developed fungal peritonitis, had the PD catheter removed, was transferred to hemodialysis and later died. One patient suffered from Encapsulating Peritoneal Sclerosis and had the PD catheter removed, transferred to hemodialysis and doing well. 7 pts still remain in PD, on good clinical condition and stable body weight. During this period, no hospitalisation was recorded due to RCHF decompensation, in any of the pts. Mean survival time in PD was 32 months ± SE 4 months.

Conclusions: Cardiac arrest is still the major cause of death in this cohort, however, 40 % of pts died of non cardiovascular causes. According to literature < 50 % pts with NYHA class IV RCHF, survive 6 months. Impressively in this cohort mean survival time was 5 times longer indicating that PD not only contributes to life elongation, but also offers better quality.

TH-PO295

Peritoneal Dialysis for Refractory Heart Failure; Decongestion, Cardiac Function, and Functional Status: A Reappraisal

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Background: Congestion is an integral component of heart failure (HF) syndrome. Growing evidence points to peritoneal dialysis (PD) as an efficient therapeutic modality for management of fluid overload in refractory HF. Improvement in left ventricular ejection fraction (LVEF) is a frequently reported benefit of PD in this setting. We sought to explore whether the observed salutary impact of PD on cardiac function and functional status is due to efficient decongestion (i.e. Frank-Starling law).

Methods: Available data from contemporary clinical trials of PD in HF (performed between January 2010 and May 2019) that included more than 20 patients were selected and reviewed. Those studies evaluating the impact of PD on LVEF and volume status (assessed through changes in weight) in patients without end-stage kidney disease were included. Pertinent data were extracted and using Pearson product-moment correlation, the degree of linear dependence and correlation between these two variables was determined.

Results: Out of 11 clinical studies meeting the criteria, 1 was a duplicate and 3 did not have the needed data; 7 studies (4 retrospective and 3 prospective) with a total of 399 participants were included. The mean age was 71 years, and the mean baseline LVEF and weight were 35.1% and 76 Kg respectively. The median follow up was 14 months. There was substantial variation in the reporting of time point for cardiac function, functional status, and weight. LVEF changes ranged from -1.4 to +6.0 % (mean 1.51 ± 2.71) and weight changes ranged from -8.3 to +3.3 Kg (mean 2.09 ± 3.95). No correlation was observed between changes in LVEF and weight (r= 0.39, p= 0.37). All studies that evaluated functional status reported on its improvement after PD therapy.

Conclusions: While PD therapy for management of refractory HF is associated with improvement in cardiac function and functional status, data from contemporary trials suggests that changes in LVEF and weight do not have a strong correlation. Therefore, it is unlikely that efficient decongestion could fully explain the beneficial impact of PD on cardiac function. Since these studies did not included nutritional indices, an alternative explanation is that the relationship between weight and volume status in HF may be confounded by changes in in muscle mass after initiation of PD therapy.

TH-PO296

The Effect of Dialysis Modality Choice on Cognitive Functions in Patients with ESRD: A Meta-Analysis

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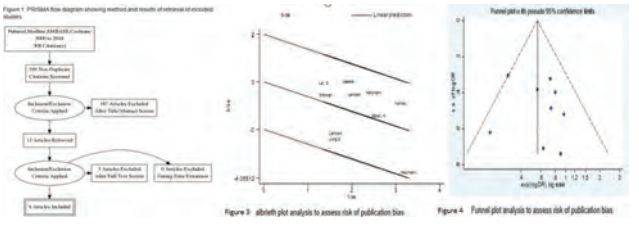
Background: Cognitive dysfunction is a major debilitating co-morbidity of end-stage renal disease, affecting up to 80% of the dialysis population. However, differential effect of hemodialysis (HD) versus peritoneal dialysis (PD) on cognitive dysfunction remains debated.

Methods: We performed a systematic review in different databases including Pubmed, Medline, Embase and Cochrane to identify studies that assessed effect of different dialysis modalities on cognitive functions. Inclusion criteria for our meta-analysis were all studies that compared effect of PD to intermittent HD on cognitive function. Studies were included with reviewing the journal title, year of publication, name of the first author, country of study and the number of enrolees in the PD and HD arms and the methods of assessment of cognitive functions were reported. A fixed effects model was used for the meta-analysis. Publication bias was assessed using a Funnel plot and Galbreith plot analysis.

Results: Out of 200 abstracts reviewed, 11 papers as well as registry studies were identified for this meta-analysis with a total of 219,320 subjects included (Figure 1). Forest plot analysis for the rate of cognitive impairment in different dialysis modalities showed less cognitive impairment in PD population compared to HD patients (Relative Risk = 0.49, 95% Confidence Intervals: 0.46 - 0.52). There was no evidence of heterogeneity in the forest plot analysis (I^2 = 0.00%, P = 0.58, Figure 2). Moreover, there was no evidence of publication bias among the studies included (Figure 3 and 4).

Conclusions: Patients on PD show less cognitive dysfunction compared to those on HD.



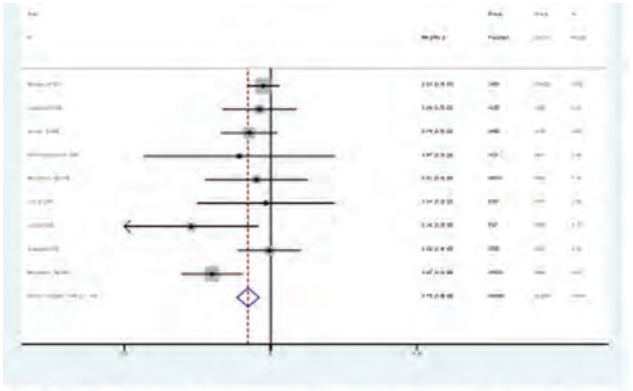
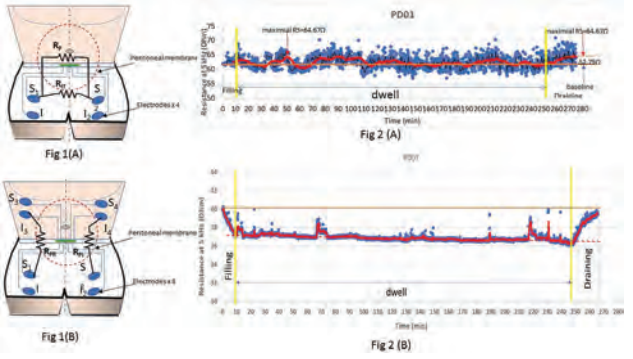


Figure 2: Forest plot analysis for assessment of cognitive impairment in hemodialysis versus peritoneal dialysis



TH-PO297

The Predictive Value of Neutrophil-to-Lymphocyte Ratio in Peritoneal Dialysis

Roberto C. Marques, Eduarda C. Carias, Ana T. Domingos, Anabela M. Guedes, Idalécio Bernardo, Pedro L. Neves. *Centro Hospitalar Universitário do Algarve, Faro, Portugal*.

Background: Neutrophil-to-lymphocyte ratio (NLR) may reflect a shift on immune response towards a pro-inflammatory pattern (i.e. high value of neutrophils) balanced with a depression of cell-mediated immunity (i.e. low values of lymphocytes). It has been used as prognostic factor in cardiovascular and oncologic diseases. In dialysis studies are scarce. The aim of this study was to evaluate NLR as a predictor of mortality in peritoneal dialysis (PD) patients.

Methods: In this longitudinal study, incident PD patients with a peritoneal equilibration test (PET) between 2004 and 2018 were included. Demographic, clinical and laboratory data were collected. Univariate and multivariate Cox regression analysis were performed to determine the association of NLR with survival.

Results: We included 122 PD patients (55.0 ± 17.5 years, 31,1% diabetic, Charlson Comorbidity Index (CCI): 5.0±2.5) with a mean follow-up of 30.2±24.0 months. Our population was dialysed with a mean Kt/V 2.75±0.94, and the mean evaluated parameters were: nGFR 6.7±4.7 ml/min/1.73m2, prealbumin 39.3±11.3 mg/dL, neutrophils 5.6±2.5x10^9/L, lymphocytes 1.8±2.3x10^9/L, NLR 3.99±2.6. Using the Cox model we found that higher CCI (HR=1.650, 95%CI 1.174-2.320), higher NLR (HR=1.662, 95%CI 1.117-2.472) and lower nGFR (HR: 0.706, 95%CI 0.554-0.900) were associated with higher mortality, when adjusted for nutritional status (n.s.).

Conclusions: In dialysis inflammation is associated with global cause mortality. The neutrophil-to-lymphocyte ratio is a simple calculation and it predicted survival in our PD patients.

TH-PO298

Continuous Measurement of Intraperitoneal Volume Using Bioimpedance: Importance of Electrode Placement Sites

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Background: Continuous monitoring of intraperitoneal volume (IPV) may benefit peritoneal dialysis (PD) patients, e.g. by determining the peak ultrafiltration volume (UFV). The aim of this study was to optimize the placement sites of bioimpedance electrodes.

Methods: Six PD patients (age 61.3±7.6 years, 5 males, weight 87.3±25 kg) were studied with two different electrode placement sites. In group A, we used 4 and in group B 8 standard ECG electrodes (3M Red Dot Electrode; locations shown in Fig. 1 A and B). Measurements were done with the patients in a sitting position and their legs placed horizontally. We used the Hydra 4200 bioimpedance device (Xitron Technologies) for continuous measurement during the PD session. The PD sessions comprised three phases: filling (dialysate volume 2 L), dialysate dwell time (4 hours), and draining. The drain volume was weighted; we assumed that 1 kg equals 1 L.

Results: The average drain volume was 2.3±0.3 L. 5 kHz resistance data were extracted to assess intraperitoneal fluid changes. While in group A the 3 treatment phases are not obvious (Fig. 2 A), they can be clearly discerned in group B (Fig. 2 B).

Conclusions: These results show that electrode placement is key to successful continuous IPV measurements. In setup A (Fig. 1 A), 2 resistors are in parallel and the interstitial resistance (R_{IT}) is smaller than the peritoneal resistance (R_p); hence the measurement provides information only about the interstitial space. In setup B (Fig. 1B), the current travels through the peritoneal cavity so that IPV changes translate into resistance changes. If corroborated in larger studies, setup B has the potential to evolve into a future standard.

TH-PO299

Dietary Potassium Intake and Hypokalemia in Peritoneal Dialysis Patients in Thailand

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Background: Poor dietary intake might account for the high prevalence of hypokalemia in peritoneal dialysis (PD) patients in Thailand but the clinical evidence is still lacking.

Methods: A cross-sectional study was performed in stable prevalent PD patients at 4 PD centers in Thailand. Hypokalemia was defined if the average serum potassium level during the last 3 consecutive visits was <3.5 mEq/L, while the patients were considered normokalemic if the average serum potassium was 3.5 to 5.5 mEq/L. Patients were asked to perform 3-day dietary food record and take pre- and post-meal pictures of all foods they had taken following the provided instruction. Daily dietary nutrients including dietary potassium of all eligible patients were then estimated by a dietician using INMUCAL-N software. Total potassium excretion was determined by 24-hour PD effluents and urine collection. Intra- and extra-cellular water status were also assessed by electrical bioimpedance assay to explore the role of intracellular potassium shift and serum potassium status.

Results: Among 60 consecutive eligible PD patients, 19 (31.0%) had hypokalemia. Mean dietary potassium and total calories intake were 28.6±10.3 mEq/day and 1,088.0±335.4 Kcal/day, respectively. Dietary potassium intake was significantly lower in hypokalemic patients compared to normokalemic patients (24.4±11.1 vs. 30.5±9.4 mEq/day, p=0.031). Surprisingly, total potassium excretion was significantly lower in patients with hypokalemia (28.5±8.4 vs. 36.7±11.2 mEq/day, p=0.006). There was no significant correlation between serum potassium and daily PD exchange volume, total Kt/Vurea, urine volume, residual glomerular filtration rate, concurrent medications (insulin, ACEI/ARB, beta blocker, and spironolactone) or intracellular water (ICW). Low dietary potassium was an independent risk factor for hypokalemia after adjustment for insulin therapy, diuretic use, and peritoneal membrane transport. The risk of hypokalemia decreased by 15% for every 10 mEq increase in daily potassium intake.

Conclusions: Low dietary potassium intake, rather than increased potassium excretion or intracellular shift, is the major contributing factor to hypokalemia in Thai PD patients. Dietary intervention or potassium supplement protocol should be implemented.

Funding: Private Foundation Support

TH-PO300

Dental Care Decreased the Risk of Not Only Cardiovascular Events but Peritonitis for the Patients on Peritoneal Dialysis

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Background: Oral disease may be increased in people with end stage renal disease (ESRD) and associated with inflammation, cardiovascular disease and mortality. We had the patient who had severe gingivitis and suffered from sepsis due to oral Streptococcus Salivarius, and followed splenic abscess and peritonitis on January 2010. Hence we noticed the importance of dental care, and after Jan. 2010, we have been recommended to patients on peritoneal dialysis to have dental care, including 3 and more times tooth brushing, oral hygiene, more frequent dental visit and prophylactic antibiotics treatment before scaling or caries treatment.

Methods: We evaluated the difference of the incidence between two groups; peritoneal dialysis (PD) treatment from January 2000 to December 2009 (Group A), and January 2010 to May 2019 (Group B). We compared the admission rate of peritonitis, especially Streptococcus peritonitis, congestive heart failure (HF), acute coronary syndrome (ACS), cerebrovascular disease (CVD), and pneumonia. And the causes of death were also evaluated.

Results: The cumulative annual peritoneal dialysis patients in group A and B were 342 and 65 (mean age; 61.8 vs 65.9 years : $p < 0.01$) respectively, and PD treatment were 3404 vs 6219month·person($p < 0.01$). According to the cause of disease, diabetes was same, but glomerulonephritis was decreased, and nephrosclerosis was increased after 2010.

The incidence of peritonitis (0.275 vs 0.179/person·year:$p < 0.001$), Streptococcal peritonitis (0.081 vs 0.046/person·year : $p < 0.05$), HF (0.159 vs 0.089/person·year: $p < 0.005$), ACS (0.109 vs 0.025/person·year: $p < 0.001$), CVD (0.060 vs 0.029/person·year: $p < 0.05$), Pneumonia (0.078 vs 0.041/person·year:$p < 0.05$) were lower in group B than in group A. Moreover, according to the cause of death, the data were the same fashion as above.

Conclusions: Dental care was beneficial for not only CVD, but also peritonitis, especially Staphylococcal peritonitis. Considering, peritonitis and CVD may provide poor QOL and mortality, dental care (3 and more times tooth brushing, oral hygiene, more frequent dental visit and prophylactic antibiotics treatment before scaling or caries treatment) is important for better QOL and treatment survival and mortality.

TH-PO301

The Value of Geriatric Nutritional Risk Index in the Prognosis of Patients with Maintenance Peritoneal Dialysis

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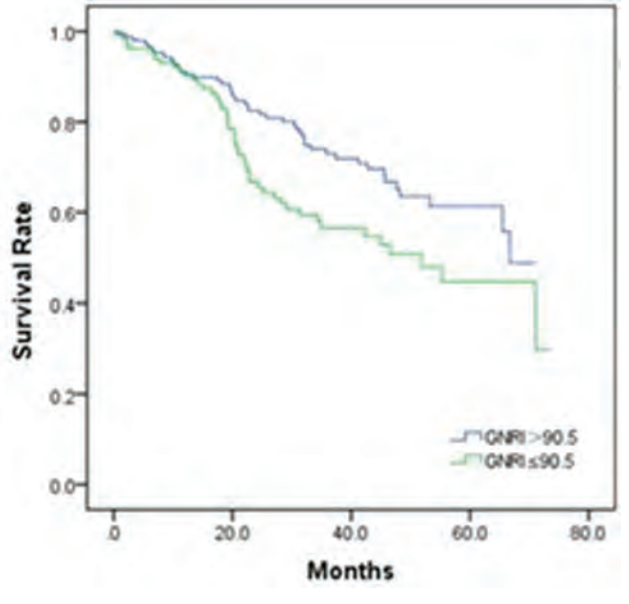
Background: Geriatric Nutritional Risk Index (GNRI) has been reported related to the prognosis and medical expenses of dialysis patients, but there are few related studies about Chinese patients, especially in terms of peritoneal dialysis (PD). The aim of this study was to explore the value of the GNRI in patients with end-stage renal disease at beginning of PD treatment.

Methods: Retrospectively analyze the medical records of patients undergoing peritoneal dialysis catheterization and starting peritoneal dialysis in the First Affiliated Hospital of Zhengzhou University from January 1, 2013 to December 30, 2018. Collect basic data and biochemical indicators of these patients in the first hospitalization for peritoneal dialysis catheterization. Follow-up these patients until March 1, 2019, and using death or turning to hemodialysis as endpoints, divide the patients into two groups according to the GNRI cutoff based on the ROC curve. Compare the clinical data and laboratory test results between the two groups, Kaplan-Meier analysis was used to observe the difference during follow-up,and the relevant factors affecting effect of peritoneal dialysis were estimated by binary logistic regression.

Results: The GNRI cut-off value was determined to be 90.5 according to the ROC curve, and the drop-out rate of GNRI≤90.5 group was significantly higher than the GNRI>90.5 group(35.9% VS 21.6%,*P*=0.003), and Kaplan-Meier survival curves showed a higher rate of peritoneal dialysis in the higher GNRI group during follow-up (*P*=0.021). Logistic univariate regression showed that male, GNRI and Alb were protective factors for PD patients, and after multi-factor correction, male and GNRI were also shown to be protective factors for PD patients.

Conclusions: The baseline GNRI can be used as a prognostic indicator for peritoneal dialysis patients.

Funding: Government Support - Non-U.S.



TH-PO302

Elderly Patients in Peritoneal Dialysis: Concerns Regarding Albumin Loss

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Background: Albumin loss in peritoneal dialysis is associated with morbidity and mortality among patients on peritoneal dialysis (PD). Since elderly patients had a higher risk of protein-energy wasting, there has been a concern of further impairment of nutritional status in this population.

Methods: This is an observational prospective study that included patients >65 years (elderly group, N=18) compared to patients <65 years (younger group, N=73). Patients were followed for a median period of 21.8 months after PD initiation in a single center.

Results: Patients >65years (50% diabetic, 78% men) started PD with a residual diuresis of 1.4± 0.5L, which did not differ from the young group (1.5± 0.7L); p=0.778. Elderly patients had lower serum creatinine (p=0.0001), serum phosphate (p=0.010), total protein (p=0.010), and higher bicarbonate (p=0.003), denoting impaired nutritional status. Serum 25(OH)-vitamin D at PD initiation was similar between groups (p=0.705). During follow-up, there was a slightly reduction of serum albumin in young patients (from 3.76±0.5 to 3.62±0.6mg/dl, p=0.0001), which did not reach statistical significance in the elderly population (from 3.67±0.4 to 3.57±0.4mg/dl, p=0.335), with a median change overtime of 0.14 and 0.10mg/dl in young and elderly patients, respectively (p=0.834). As expected, there was a weight increase over time, although not different comparing young and elderly patients (p=0.579). In addition, loss of residual renal function, and changes in hemoglobin, serum ferritin, iron saturation, β-2 microglobulin, and parathormone were similar between groups (all p>0.05).

Conclusions: Our findings suggest that there is no medical concern to avoid PD therapy in elderly patients with end-stage renal disease, at least in those who start therapy with no critical nutritional condition.

TH-PO303

Effects of Initial Hypoalbuminemia on the Longitudinal Changes of Residual Renal Function and Peritoneal Membrane in Incident Peritoneal Dialysis Patients: A Single-Center, Long-Term Follow-Up Study

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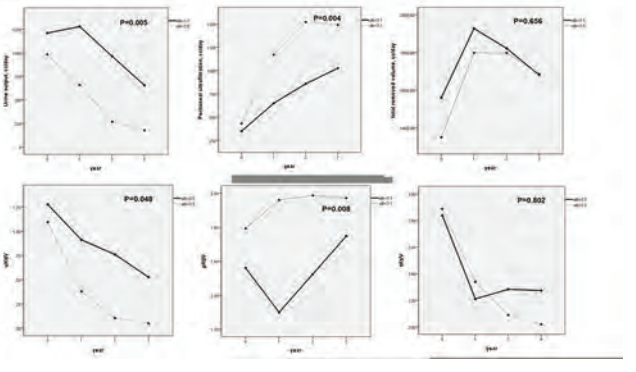
Background: Hypoalbuminemia was reported closely associated with increased patients' mortality and technical failure rate in PD patients. However, there were little studies that compared longitudinal changes of residual renal function or peritoneal membrane function according to the serum albumin level.

Methods: We retrospectively included patients who started PD between January 2010 and December 2015. We divided patients into two groups according to the initial serum albumin level. Hypoalbuminemia was defined as the serum albumin level lower than 3.5 g/dL. To compare longitudinal changes of residual renal function and peritoneal membrane status between two groups, we repeatedly collected data for urine output, uKt/V, peritoneal ultrafiltration, pKt/V, 4hr DPcr ratio per 1 year. We also checked technical failure rate and all-cause mortality rate of them.

Results: A total of 153 patients were included and 36.6% of them had hypoalbuminemia. During the median follow up period of 42.5 months, 9.8% of the patients were dead, 30.3% of the patients received kidney transplantation and the other 30.3% of the patients changed modality to hemodialysis. All-cause mortality rate was significantly higher in the hypoalbuminemia group (log rank 0.001). In both groups, residual renal function showed decreasing trend, peritoneal UF and pKt/V showed increasing trend and their changing rates were more rapid in hypoalbuminemia group (Figure 1).

Conclusions: Initial hypoalbuminemia was associated with rapid decline of residual renal function and increased all-cause mortality rate in incident PD patients. Thus, patients with hypoalbuminemia needed to be closely monitored.



TH-PO304

The Associations of Serum Uric Acid and All-Cause Mortality in Peritoneal Dialysis Patients

Shanfang Qiu. *The first affiliated hospital of xiamen university, Xiamen, China.*

Background: The relationship between serum uric acid and prognosis in diabetic peritoneal dialysis (PD) patients is unclear. This study was investigate whether baseline uric acid (UA) is an independent predictor of all-cause mortality in chronic renal failure patients (CRF) with peritoneal dialysis (PD)

Methods: A retrospective cohort study was designed. A total of 140 patients onstable continuous ambulatory peritoneal dialysis (CAPD) treatment for more than 3 months

were collected and follow up at First affiliated hospital of Xiamen University Peritoneal Dialysis Center during the January 1st,2001 to the December 31st,2017. All demographic and laboratory data were recorded at baseline. The subjects were divided into three groups based on the tertile of UA valu(M1:UA<387umol/L,M2:UA387~519umol/L,M3:UA >519umol/L). Multivariate Cox regression and Kaplan-Meier method was used to calculate the hazard ratio (HR) of all-cause mortality.

Results: A total of 140 CAPD patients were enrolled in this study, including 63 cases of male (45%),77 cases of female (55%). The average age was 57 (range: 44-65) years. The median follow-up time was 31.9 (IQR:19.6,66.0)months. The average UA of all participants was 450.1±146.1 umol/L. No significant differences of baseline characteristics between patients with Age, sex ratio, body mass index, duration of dialysis, proportion of patients with hypertension, diabetes mellitus and cardiovascular diseases. Compared to M1 group, the levels of serum creatinine, urea nitrogen, blood phosphorus and blood potassium were higher in M3 group ($P < 0.05$). Univariate COX regression analysis suggested a positive correlation between all-cause mortality and baseline uric acid (UA HR=1.04,95%CI: 1.00-1.08, P=0.048). Multivariate COX regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients(HR=1.04, 95%CI: 1.00-1.09, p=0.032).

Conclusions: UA was positively correlated with all-cause mortality in patients undergoing maintenance peritoneal dialysis. The increase of baseline UA elevation was an independent risk factor for all-cause mortality in those patients. Thecontrol of UA level may be helpful to prolong the survival time of patients with Peritoneal Dialysis.

Funding: Clinical Revenue Support

TH-PO305

Prognostic Role of Platelet-to-Lymphocyte Ratio in Peritoneal Dialysis

Roberto C. Marques, Ana T. Domingos, Eduarda C. Carias, Anabela M. Guedes, Idalécio Bernardo, Pedro L. Neves. *Centro Hospitalar Universitário do Algarve, Faro, Portugal*.

Background: Platelet-to-lymphocyte ratio (PLR) has been introduced as useful inflammatory marker to predict the outcome for a wide spectrum of diseases such malignancies and cardiovascular pathologies. Since platelets are active players in inflammatory response, both thrombocytosis and high PLR are probably part of the same pathophysiological process. In dialysis studies are scarce. The aim of this study was to evaluate PLR as a predictor of mortality in peritoneal dialysis (PD) patients.

Methods: In this longitudinal study, incident PD patients with a peritoneal equilibration test (PET) between 2004 and 2018 were included. Demographic, clinical and laboratory data were collected. Univariate and multivariate Cox regression analysis were performed to determine the association of PLR with survival.

Results: We included 122 PD patients (55.0 ± 17.5 years, 31,1% diabetic, Charlson Comorbidity Index (CCI): 5.0±2.5) with a mean follow-up of 30.2±24.0 months. Our population was dialysed with a mean Kt/V 2.75±0.94, and the mean evaluated parameters were: nGFR 6.7±4.7 ml/min/1.73m2, prealbumin 39.3±11.3 mg/dL, platelet 269.6±86.5x10^9/L, lymphocytes 1.8±2.3x10^9/L, PLR 195.5±101.7. Using the Cox model we found that higher CCI (HR=1.827, 95%CI 1.284-2.600), higher PLR (HR=1.010, 95%CI 1.004-1.015) and lower nGFR (HR: 0.673, 95%CI 0.513-0.883) were associated with higher mortality, when adjusted for nutritional status (n.s.).

Conclusions: Inflammation is a known risk factor for global cause mortality in dialysis. In this study platelet-to-lymphocyte ratio, which is quite simple and cheap method, was validated as an inflammatory marker in PD patients.

TH-PO306

Impact of Residual Renal Function (RRF) on Phosphate Clearance (PhCl) in Peritoneal Dialysis (PD)

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Background: Hyperphosphatemia is common in ESRD & is independently associated with increased risk of death among dialysis patients. In PD, the relationship between PhCl & D/P Cr or D/P PO4 is not well established. There is a suggestion that Low(L)&Low Average(LA) transporters have better PhCl with CAPD than APD. Our aim is to study the effects of RRF on PhCl in patients on APD and if its loss is compensated by adjusting dialysis dose.

Methods: 55 patients on APD were retrospectively reviewed. 30 patients qualified for the study.15 had loss of RRF(Group 1), defined as UOP ≦ 200 cc/24 hr &15 who did not lose RRF(Group 2). PhCl was calculated from the combined 24hr collection of peritoneal effluent and urine.

Results: Patients in both groups were all male & on APD. Most common etiology for ESRD in both groups was diabetes (60%). Group 1 cohort had an average age of 65.2±12.2, body weight 80 kg±18.7 & BMI 26.5 ±5.2. Prevalence of hyperphosphatemia (> 5.5mg/dl) was 53% at the initiation of PD & 60% at loss of RRF with an average follow up of 36 months. PhCl dropped from 61.4L/wk to 41.9L/wk with loss of RRF(Table 1). Group 2 cohort had an average age of 61.7±10.62, body weight 91.33±14.3 & BMI 28.45 ±4.0. Hyperphosphatemia prevalence was 40% at the beginning of PD and 60% at the end of the study period of 36 months while PhCl decreased from 96.5L/wk to 68.5L/wk. In both groups D/P PO4 and D/P Cr remained low throughout the study. Weekly Kt/V decreased significantly but remained adequate for PD treatment (Table 1). There was stronger correlation between PhCl & D/P PO4 than with D/P Cr(R=0.53 vs 0.36), although in multivariate analysis the relationship between D/P PO4 and PhCl was not statistically significant (P=0.6)

Conclusions: Overall prevalence of hyperphosphatemia was no different in the two groups. PhCl correlated better with D/P PO4 than with D/P Cr as in prior studies. Since the numbers in our study are small, effect of transporter status on PhCl was not analyzed. These results need validation in a larger prospective study.

Table 1

	Group 1			Group 2			InterGroup
	Baseline	End of Study	P-Value	Baseline	End of Study	P-Value	P-value
Hyperphosphatemia(%)	53	60	0.11	40	60	0.99	0.50
Total PhCl(L/wk)	61.4	41.9	0.04	96.5	68.5	0.02	0.003
D/P Cr	0.46	0.41	0.39	0.46	0.45	0.78	0.63
D/P PO4	0.29	0.37	0.30	0.26	0.33	0.06	0.54
Renal Kt/V	1.03	0.14	0.0009	1.56	0.78	0.0013	< 0.001
Total Kt/V	3.47	1.94	0.05	4.46	2.94	0.006	0.016

TH-PO307

Use of a Remote Monitoring System to Evaluate Adherence to Peritoneal Dialysis Prescription

Ramón Paniagua. Chronic Kidney Disease Reasearch Network of Instituto Mexicano del Seguro Social *Instituto Mexicano del Seguro Social, Mexico City, Mexico*.

Background: Remote Monitoring (RM) has been incorporated in the new machines for home Peritoneal Dialysis (PD); RM facilitates a more close and personalized surveillance and take proactive behavior about preventable complication. One important advantage of RM is the objective evaluation of the adherence to treatment and medical and non-medical risk factors for non-adherence.

Methods: A cohort of 222 patients starting PD with RM system was analyzed about adherence to the treatment, these mean days per week without connection and incomplete daily schedule. Information from RM was obtained blind for patients and compared with patient self-reported adherence.

Results: With the use of RM, it was detected than 105 (52.7%) of patients loss at least one day/month of treatment, 25.7% loss 4 or more days/month, this means a loss of 15% of the treatment or more. In 20.7% of patients the difference between RM and self-reported adherence was of ≥2 days/month, higher with RM. Among risk factors for lower adherence, low serum albumin level, higher economic income, and lack of couple were significant.

Conclusions: Rate of non-adherence to PD prescription was found higher than other reports. Lack of couple, low albumin level, and high income were risk factors for non-adherence.

Funding: Commercial Support - Baxter

TH-PO308

Use of a Remote Monitoring System to Know the Peritoneal Dialysis Prescription Patterns

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Background: Remote Monitoring (RM) is a new tool recently incorporated in the follow-up of Peritoneal Dialysis (PD) patients; it facilitates a more close and personalized surveillance of patients and take proactive behavior about preventable complication of the treatment. RM also can be used to know how Nephrologist prescribes PD and if prescription is appropriate for the clinical characteristics of patients.

Methods: A cohort of 227 patients starting PD with RM system were analyzed for prescription, this includes dray or wet day, time of nocturnal dialysis, number of exchanges, volume per dwell, and effective time of dialysis.

Results: Total dialysis volume was <10L in 34.4%, 10L in 34.8%, and >10L in 30.8%. Time of dialysis was ≤8hr in 2.6%, 9hr in 79.7%, and ≥9hr in 27.6%. Volume of nocturnal exchanges was ≤3 in 1%, 4 in 61.7%, and ≥5 in 37.4%. Volume/exchange was <2.0L in 11.9%, 2.0L in 57.7%, and >2.0L in 30.4%. Effective time of dialysis increased with the hours of dialysis, however, for the same number of hours it did not increase with more than 5 cycles.

Conclusions: Prescription patterns tend to a uniform schedule; however, the use of more than 5 cycles/night does not offer advantages since it does not increase the effective time of dialysis.

Funding: Commercial Support - Baxter

TH-PO309

Using a Logic Model to Systematically Evaluate an Initiative to Improve Patient Transition to Home Dialysis Therapies (HDTs)

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Background: The transition from choosing to initiating HDTs is not clearly defined or standardized for patients and staff. This may cause increased anxiety and unaddressed self-management for CKD patients, and lack of confidence in staff who support them. These factors may also lead to delays in transition. To address some of these concerns at BC Renal, a "Transition to HDTs" guidebook (the Guide) was designed, outlining a step-wise approach to transitioning to HDTs for patients. Assessment of this intervention required a structured and practical evaluation strategy. We used the Logic Model evaluation

framework to assess whether having the Guide can improve patient and staff experience with transitioning to HDTs.

Methods: The study ran over a 6-month period at 2 pilot and 3 control sites. The intervention strategies included: 1)Training of front-line staff to use the Guide and 2) Dissemination of the Guide to patients. Evaluation tools measuring data at baseline and at the 6-month point include: 1)Qualitative patient interviews, 2)Quantitative patient surveys, 3)Qualitative staff surveys, 4)Structured feedback session with renal care staff, and 5)Documented transition time between choosing and starting PD.

Results: 43 patients were enrolled in the pilot sites; 9 completed the study (6 PD and 3 HHD). Transition time was improved in pilot vs. control (54.4 vs. 73 days). Patients' anxiety, illness knowledge, and activation of resources improved after PD/HHD training at both pilot and control sites. During interviews, patients confirmed that the Guide was effective and helped retain knowledge. The staff felt that the intervention did not increase their workload and that the Guide was a good communication tool, but used inconsistently.

Conclusions: We present a systematic framework to evaluate a multi-intervention strategy to improve patients' transition to HDTs, which may be applicable to other complex healthcare initiatives. The Guide may help reduce transition time while improving patient anxiety and illness knowledge through enhanced communication between patients and health care providers. Future work is required to standardize the Guide's utilization.

TH-PO310

Use of Peritoneal Dialysis in Urban Boroughs of New York City

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Background: Peritoneal Dialysis (PD) is currently underutilized in the United States. Barriers to initiating PD such as geographical limitations, access to catheter care or trained personnel are less relevant in urban metropolitan cities, which may harbor heretofore unknown barriers to PD. We sought to describe the epidemiology of PD utilization within New York City in comparison to Boston, New York State (NYS) and the United States (US).

Methods: From the 2010-2016 US Renal Data Service, we estimated the odds of starting PD compared to hemodialysis (HD) in Brooklyn, Bronx, Queens, and Manhattan in comparison to Boston, NYS and the US. Next, we analyzed whether factors known to influence PD utilization such as diabetes mellitus (DM) as the primary diagnosis, age >65 years, gender and race played a role here. Statistical analysis was performed using SPSS 24.

Results: Between 2010 and 2016, the odds of starting PD vs HD in NYS compared to the rest of the US was 0.49 (95% CI:0.47-0.52; p<0.0001). The odds of starting PD vs HD in Brooklyn, Bronx, Queens and Manhattan in comparison to NYS were 0.30 (0.25-0.36; <0.0001), 0.56 (0.47-0.67; <0.0001), 0.66 (0.54-0.80; <0.0001) and 0.61 (0.52-0.71; <0.0001), respectively. In 2016, the odds of starting PD in Brooklyn, Bronx, Queens, Manhattan and Boston in comparison to the US were 0.14 (0.08-0.22; <0.0001), 0.39 (0.27-0.56; <0.0001), 0.32 (0.23-0.45; <0.0001), 0.54 (0.36-0.79; 0.002) and 0.89 (0.58-1.4; 0.624), respectively. Analysis of factors that influence PD initiation showed the following for Brooklyn: male sex (p=0.18) black race (0.06), age> 65 years (<0.0001) and DM (0.07) and Boston: male sex (0.45), black race (0.36), age> 65 years (<0.001) and DM (0.17). The percentage of residents in Brooklyn and Boston age >65 years in 2018 were 13.5% and 11%, respectively.

Conclusions: Our study demonstrated low odds of PD utilization for ESRD patients in NYC. There were segmental disparities suggesting borough-specific factors, perhaps socioeconomic and cultural. Brooklyn has the highest ESRD rates but lowest PD use. Similar findings were not seen in Boston. Commonly cited factors that influence PD usage such as DM as the primary diagnosis, gender and race were not statistically significant, while age seems to be an important factor. A concerted effort to identify and overcome barriers to PD amongst the elderly is needed

TH-PO311

Impact of a Renal Quality Program in the Peritonitis Rate in a Dominican Republic Continuous Ambulatory Peritoneal Dialysis Program

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Background: Peritonitis is a frequent complication in the management of peritoneal dialysis (PD), is one of the main cause of hemodialysis transfer with direct impact on a patient's quality of life and healthcare related costs. Also associated with loss of Residual Renal Function, peritoneal sclerosis and adequacy problems (1). Recently, the ISPD Guidelines recommends that regular monitoring of infections associated with peritoneal access should be part of the Continuous Quality Improvement program (CQI). The applications of these programs have shown an impact not only on the reduction of peritonitis events but also an improvement in patients and technique survival.

Methods: In 2015, a CQI program was implemented in 7 PD centers in the Dominican Republic. Lack of structured training and retraining program, home-visit and peritonitis treatment protocols, absence of local scientific committees, lack of standardized registries and key performance indicators were identified as the main problems. After this analysis, nurse activities were defined; structured training and retraining program, home-visit and peritonitis treatment protocols were implemented, a standardized registry was developed, and quality indicators were defined. A multicenter retrospective longitudinal analysis was performed on peritonitis events and outcomes between January 1st, 2015 to December 31st, 2018 were recorded. All patients were in CAPD and used Ultrabag system during all study period. Peritonitis was diagnosed according to the ISPD criteria. A two-time period was considered for technique and patient survival: 1st, 2015-2016 and 2nd, 2017-2018.

Results: During the study period, a total of 1801 patients were analyzed. The mean age was 57± 17 years, 65% were male, diabetes (48%) was the main cause of kidney disease. The median peritonitis rate for 2015: 0.8, 2016: 0.20, 2017: 0.14, 2018 0.12 year at risk, the percentage of patients free of peritonitis were: 75% in 2015, 95% in 2016, 90% in 2017 and 96% in 2018. Cure response rate was: 2015: 63%, 2016 83%, 2017: 90%, 2018: 92%. The mean technique survival was 331 days in period 1 vs 399 d in period 2 p <0.0001.

Conclusions: The use of CQI has proven to be an effective tool to reduce peritonitis in Dominican Republic PD program and improve technical and patient survival.

Funding: Commercial Support - Macrotech, Baxter

TH-PO312

Regionalization of Peritoneal Dialysis Services in an Era of Health Reform, 2006-2013

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Background: Over the last 15 years, Medicare has adjusted payment policy to promote peritoneal dialysis (PD) provision and use. Facility PD provision has grown modestly despite notable growth in patient PD use. A potential explanation underlying this trend is possible regionalization of PD services among dialysis chains. Regionalization may improve facility finances while maintaining patient access because: (1) consolidation into fewer chains allows for economies of scale and (2) as a home-based modality, PD requires minimal travel and impacts from regionalization of services. This study is the first to empirically assess the extent of PD program regionalization among dialysis chains.

Methods: We conducted a retrospective cohort study of non-federal US outpatient dialysis chains 2005-2013 with data from the US Renal Data System and Medicare Provider of Service files. Two outcomes were observed at the chain-hospital referral region level in 3-year time periods 2005-2013: - PD regionalization – decrease in PD facilities without decreasing PD patients - PD expansion – increase in PD patients without increasing PD facilities Generalized estimating equations with a logit link identified correlates of PD regionalization and expansion adjusting for chain and market characteristics.

Results: During the study, there were 2,799 market-chains; 49% large dialysis organizations ([LDOs] DaVita or Fresenius). We observed PD regionalization 103 market-chains and PD expansion in 728. Regionalization increased from 29 market-chains in 2005-2007 to 44 in 2011-2013. Expansion also increased from 175 market-chains to 293. In adjusted expansion increased over time (odds ratio [OR] 1.33; 95% confidence interval [CI] 1.18-1.49). Overall, LDOs had higher odds of regionalization (OR 3.92, CI 2.39-6.42) and expansion (OR 1.79; CI 1.48-2.17).

Conclusions: We provide early evidence that chains are expanding PD services and that LDOs are more likely to regionalize PD services. Dialysis chains have not regionalized PD services in response to reforms 2005-2013; but continued monitoring of PD care patterns will inform long-term effects of dialysis payment reform on dialysis industry service strategies and identify important implications for patient care.

Funding: NIDDK Support

TH-PO313

The Feasibility of Using Computerized Adaptive Testing (CAT) to Assess PD Patients' Quality of Life and Symptom Burden

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Background: Dialysis pts complain of myriad symptoms that negatively impact on their HRQOL and are often not appreciated by health care providers (HCP). How best to document these symptoms and their impact on pts and then incorporate the information into rx plans is challenging. Recent work has suggested that using CAT could provide a useful way for HCP to better understand difficulties experienced by pts.

Methods: This study was undertaken as a feasibility study. 20 questions, incorporating common symptoms reported by ESRD pts, were incorporated into a CAT program developed by the authors and Owl Insights. Questions dealing with pain, depression, anxiety, and sleep would expand from 1-2 items into more robust assessments if responses indicated domains were problematic. For example, depression screening was done with the PHQ2 which expanded to the PHQ9 if PHQ2 scores were ≥3. If pts reported problems with anxiety, then the Generalized Anxiety Disorder (GAD)7 questionnaire was administered. Pts were also given the option to free text any domains they wanted to discuss with their HCP. Questionnaires were given on an iPAD just prior to a clinic visit; results were printed and given to the HCP at the visit. The study was performed over 6 months with pts being asked to complete the questionnaires q 2 mths

Results: All 48 English speaking pts in our inner-city PD program were assked to participate. The mean +/-SD age was 60 +/-14. 55% were male, 43% AA, 33% white, 20% Hisp, 5% Asian. 92% completed the initial questionnaire; 86% completing this questionnaire completed the 2nd. The mean time to complete the questionnaire was 11 +/-2 min. 75% asked for assistance with the questionnaire. 75% complained of restless legs. 47% had PHQ2 scores of ≥3 and completed the PHQ9. 50% reported significant sleep problems and completed the sleep questionnaire. 30% were troubled by anxiety and completed the GAD7. Other problems frequently reported included fatigue, loss of energy, pain, and pruritis. HCPs (4 nurses, 2 dieticians, 7 MDs, 1 sw, and 2 PAs) uniformly

found the questionnaires helpful with their clinic visits, enabling them to focus on reported problem areas.

Conclusions: The present study demonstrates that using CAT questionnaires is feasible and is a useful way to capture PD pt perceptions of their symptoms and HRQOL and can enable HCP to perhaps better address pt domains of difficulty.

Funding: Commercial Support - Renal Research Institute

TH-PO314

Implementing the PD Easy Application in Mobile Phones, Enhancing Self-Management and Communications: Pilot Study

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Background: Since implementing Thai PD First Policy, we now take care 880 patients, biggest center in Thailand. Our center developed many retraining styles to capture our patient's diversity. Now, we develop our own mobile phone application, called PDeasy. The objective is to monitor, communicate, self-educate and promote self-management. We try with first 52 volunteer patients, exploring the barriers to implement the application.

Methods: The education level and the past experiences using any other IT device, were collected. The duration before using this fluently, problems and usefulness of this application were asked. We also compared baseline and 6-month self-management score by Wilcoxon signed rank test.

Results: There were 41 patients who completed the questionaire. The average age is 54 (min 23, max 74). The percentage of patients who use the application by themselves is 61% and 39% by their caregivers. Education level, less than 6 years, is 47%. Past experiences of using IT device is 88%. The duration to learn to use this application fluently, less than 3 days, is 83% and most can use it immediately. The self-management score comparing baseline and 6- month, is not different, as shown. 92% of the users give good satisfaction and the most useful part are the self-education and the warning system.

Conclusions: Our mobile phone PDeasy application, is user-friendly and helpful in terms of promoting self-care.

Self-Management score

Self-Management score	Points	Baseline	6-month	P-value
Exchange Procedure	40	36.04 ±4.13	36.31 ±03.73	0.217
Salt and water balance Nutrition management	16	12.38 ± 2.39	12.33 ±2.01	0.115
Drug adherence	12	10.10 ± 2.40	10.12 ±2.15	0.468
Self-assessment	16	13.04 ± 2.10	12.71 ±2.38	0.099
Management of complication	12	9.35 ±2.24	9.56 ±2.15	0.153
Overall	96	80.90 ±10.27	80.84 ±8.87	0.488

TH-PO315

Impact of the Implementation of Management Protocols Using Priority Signals in Automated PD Patients Using Remote Patient Monitoring

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Background: The recent introduction of a two-way Remote Patient Monitoring (RPM) for the management of Automated Peritoneal Dialysis (APD) patient has made it possible to assess patient's adherence to the therapy, as well as dialysis treatment-related complications. This system was introduced in this hospital 2 years ago. The purpose of the study is to assess the impact on the adherence and lost treatment times after the implementation of protocols using the signals provided by the RPM system.

Methods: This is a retrospective study in a cohort of patients receiving APD. 183 patients in the APD program of the Hospital Belisario Dominguez under remote monitoring were included. On the basis of the messages provided by the system, a program was developed in order to prioritize patient care and interventions according to the type and number of flags shown; then, signals were categorized into treatment-related signals and system-related signals. Based on this, protocols of care and management strategies were established, and change in the number medium priority signals (MPS) and High priority signal (HPS), impact on lost treatment times and adherence to treatment were assessed.

Results: Signals from 203 patients provided by the system throughout one week were assessed and dedicated protocols were implemented afterwards. Patients were reassessed 6 months after the implementation of the protocols. Patients without MPS improve 20% ($p<0.001$) and patients with more than 6 MPS reduce 67% (0.0001). Patient without HPS signals improve 36% ($p<0.0001$) and patients with more than 6 HPS decrease 73% ($p<0.0001$). Patients with not loss of treatment time increase 6% and patients with more than 300 minutes lost reduce 20% ($p<0.004$), adherence improve 29% (0.001)

Conclusions: Remote monitoring makes it possible to differentiate treatment-related complications and to establish specific processes of care, allowing for more effective treatment times and enhanced patient's adherence to his/her treatment.

TH-PO316

Factors Associated with Discordance in Initial ESKD Treatment Decision and Eventual Dialysis Modality

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Background: Pre-Dialysis counselling (DC) prepares patients with ESKD for renal replacement therapy (RRT). However, the eventual RRT modality may differ from the initial decision made at DC, making a prepared start on dialysis challenging. We study the distribution of treatment decisions made after DC and factors associated with a change in the eventual RRT modality at initiation.

Methods: This prospective cohort study included patients who underwent DC from APR 2010 to DEC 2015, and followed till 30 APR 2019 for their eventual RRT modality. All data were collected prospectively, with the study population grouped according to the initial treatment decision and stratified by eventual RRT modality (Table 1). Multivariate logistic regression was performed, examining factors that influence discordance in treatment decision and eventual modality. Variables were included in the model if univariate analysis has p-value<0.20.

Results: 1644 patients (63.3±13.1 years, 57% males, 77% DM) were included in the study, after excluding 47 without any decision and 42 who had not initiated RRT. HD (65.6%) was the most common choice of RRT after DC, while patients who chose PD were less likely to be actualized on their chosen therapy (PD 50.4%, HD 96.9%; $p<0.001$). Patients who chose PD were also more likely to die before needing RRT (PD 12.3%, HD 3.0%; $p<0.001$). Multivariate analysis showed that failure to actualize the decision for PD was associated with factors that suggested greater frailty or potential challenges to PD (Table 2).

Conclusions: Patients who chose PD were less likely to receive this RRT modality. These patients were older and frail, with a high proportion who died before requiring RRT. Difficulties with PD such as obesity, poor diabetic control and lack of home storage space for PD solutions may also influence a subsequent switch to HD.

Table 1: Distribution of Initial Treatment Decision and Eventual RRT Modality

Initial RRT Decision	Eventual RRT Modality					Total
	Death W/O RRT	HD	PD	Palliative	Transplant	
HD	32 (3.0%)	1,045 (96.9%)	0 (0%)	2 (0.2%)	0 (0%)	1,079 (100%)
PD	41 (12.4%)	110 (33.1%)	167 (50.3%)	12 (3.6%)	2 (0.6%)	332 (100%)
Palliative	0 (0%)	1 (0.4%)	0 (0%)	232 (99.6%)	0 (0%)	233 (100%)
Total	73	1,156	167	246	2	1,644

Table 2: Adjusted Factors Associated with Non-Actualization of PD when made as Initial Treatment Decision

Factors	Odds Ratio	95% CI	p-value
Associated with Frailty			
Age	1.020	1.004, 1.037	0.017
Mobility	0.530	0.338, 0.833	0.006
ADL Assistance	2.240	1.270, 3.950	0.005
Charlson Score	1.149	1.044, 1.265	0.005
Serum Albumin	0.945	0.912, 0.978	0.001
Challenges to PD			
Public Housing	2.350	1.111, 4.970	0.025
Obesity	4.128	1.628, 10.467	0.003
Diabetes Mellitus	2.051	1.188, 3.541	0.010

TH-PO317

Incremental Peritoneal Dialysis in Incident ESKD Patients

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Background: Incremental peritoneal dialysis (Incre-PD) has been an underused strategy in treating end stage kidney disease (ESKD). This retrospective study analyzed the characteristics and outcomes of ESKD patients undergoing Incre-PD in a large academic center.

Methods: ESKD patients initiating PD with a contact PD volume ≤6 L/day between 2013 and 2017 inclusive were followed up until death, PD cessation, or the end of 2018.

Results: 175 Incre-PD patients were identified, accounting for 85% of the incident patients of that period,and were followed up for 352.6 patient-years. Compared to those with initial PD dose >6 L/day, there were more Asians (24.0% vs. 6.7%, p=0.033) but fewer of African descent (13.7% vs. 36.7%, p=0.002) among the Incre-PD patients. The two cohorts were comparable in comorbidity status except for peripheral vascular disease, which was more common in Incre-PD patients (14.3% vs. 0.0%, p=0.030). The baseline urine volume (1.5±0.7 L/day vs. 1.0±0.9 L/day, p=0.001) and residual kidney function (RKF, 8.3±3.4 mL/min/1.73m^2 vs. 5.5±3.2 ml/min/1.73m^2, $p<0.001$) were greater in Incre-PD patients, and they were less likely to have undergone hemodialysis (HD) prior to PD (19.4% vs. 50.0%, $p<0.001$). The baseline daily contact PD volume was 4.5 (IQR 4.3-6) L, and it was 5.4 (4.5-6.0) L, 6.0 (4.5-7.0) L, 6.0 (4.8-8.0) L, 7.0 (5.7-9.8) L, and 8.0 (6.0-9.8) L at 1 to 5 years on PD, respectively. Fifty-seven (32.6%) patients increased PD dose to

>6 L/day at a median time of 10.3 (6.2, 15.7) months. The unadjusted 1 to 5-year patient survival rate was 90%, 80%, 65%, 63%, and 49%, respectively, and the corresponding PD technique survival rate was 95%, 89%, 89%, 82%, and 77%. The average peritonitis rate and hospitalization rate was 0.12 and 0.65 episodes per patient-year, respectively. The length of hospitalization was 5.9 days per patient-year. Greater initial daily contact PD volume (HR=1.608, 95% CI 1.089-2.375) was associated with death after adjusting for age, Charlson comorbidity index, HD prior to PD, assisted PD and baseline RKF, likely as a result of residual confounding. It was not a factor related to technique failure. Male sex, greater body mass index and lower serum albumin at PD initiation were risk factors for increasing PD dose to >6 L/day within 1 year.

Conclusions: In the largest reported series to date, Incre-PD is a successful and patient-oriented strategy to treat ESKD patients.

TH-PO318

Standardized Outcomes in Nephrology-Peritoneal Dialysis (SONG-PD) Consensus Workshop with Patients, Caregivers, and Health Professionals to Establish a Core Outcome Set for Trials in PD

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Background: Outcomes reported in peritoneal dialysis (PD) trials are very diverse, measured inconsistently and may not be important to patients, families and clinicians. We aimed to establish a core outcome set based on the shared priorities of all stakeholders to improve the consistency and relevance of outcomes to patients and healthcare providers to inform decision-making.

Methods: We convened an international Standardized Outcomes in Nephrology-Peritoneal Dialysis stakeholder consensus workshop in May 2018 in Vancouver, Canada. In facilitated breakout groups, participants discussed the development and implementation of core outcomes for trials in PD.

Results: Nineteen patients/caregivers and 51 health professionals attended the workshop. Participants confirmed that *"life participation" was a main goal of PD,* which reflected the need for flexibility and freedom. Participants regarded life participation to be as important as key clinical outcomes (such as cardiovascular disease, infection or mortality) for indicating treatment success. *Severity and immediacy of symptoms* encompassed the debilitating impact of symptoms such as fatigue, which was identified as a key contributing factor to reduced life participation. *Empowered for preparation and planning* was about ensuring that patients were informed about the status of their membrane function, enabling them to be mentally and physically equipped to deal with potential PD failure. *Demarcating distinct outcomes for clarity* was suggested as participants recognized the conceptual overlap among outcomes, such as membrane function and PD failure. Participants also discussed the importance of the core outcome set to be *measurable and feasible for implementation*, including the need for simple, standardized and validated measures, particularly for life participation.

Conclusions: Patients, caregivers and health professionals supported the inclusion of PD failure, mortality, cardiovascular disease, PD-infection and the patient-reported outcome of life participation as core outcome domains for PD. Recommendations from this workshop will be integrated into the establishment of a core outcome set for use in trials and other research to ensure that research evidence can better inform decision-making.

TH-PO319

Can Cardiovascular Risk Score Calculators Be Used for Nondiabetic Peritoneal Dialysis Patients?

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Background: Cardiovascular diseases caries a significant burden upon peritoneal dialysis (PD) patients. Despite overwhelming data regarding the usefulness of cardiovascular risk score calculators in the general population, only very few studies addressed this issue in PD.

Methods: We performed a prospective study. Three risk score calculators were evaluated at inclusion in the study: SCORE chart, Framingham and simplified Framingham risk score calculators. We excluded diabetic patients since they are already at increased cardiovascular risk. Predictive power for cardiovascular diseases was assessed using *Receiver Operating Characteristic curve* analysis by *IBM SPSS ver. 20.0.*

Results: We included 246 non-diabetic patients (118F), mean age 56.3 ± 15.7 years in stable PD for at least 6 months. Mean follow up time was 6.2 years. All the three risk scores where significantly higher in patients with renal hypertensive disease, compared to patients with glomerulonephritis, tubular interstitial diseases and other end stage renal disease etiologies (Table 1). The two Framingham risk scores were also significantly higher in patients with subclinical atherosclerosis as appreciated by an intima-media thickness (IMT) ≥0.9 mm at carotid ultrasound and the best predictive value for an IMT ≥0.9 mm was obtained by Framingham risk score (Tables 2 and 3). The best predictive value for developing acute coronary syndrome (ACS), heart failure (HF) and cardiovascular death (CvD) during the follow up period was obtained by Framingham risk score (AUC 0.887 for ACS, 0.731 for HF, and 0.809 for CvD), and by simplified Framingham risk score for ischemic stroke (AUC 0.883).

Conclusions: Risk score calculators, especially the Framingham one, may be useful in non-diabetic PD patients to both predict subclinical atherosclerosis and established cardiovascular disease and thus improve patients' management. Our results need to be validated in larger multi-center studies.

Table 1. Risk score calculators and renal disease etiologies

	Renal hypertensive disease	Glomerulonephritis	Tubular interstitial diseases	Other	p
Framingham mean ± SD	38.3 ± 2.3	11.2 ± 2.6	19.7 ± 6.6	16.1 ± 4.8	<0.001
Simplified Framingham mean ± SD	39.7 ± 4.5	11.4 ± 1.8	23.9 ± 3.5	14.1 ± 3.7	<0.001
SCORE mean ± SD	6.3 ± 4.8	2.2 ± 2.4	3.9 ± 3.2	2.1 ± 1.1	0.02

Table 2. Risk score calculators and IMT

	IMT<0,9	IMT≥0,9	p
Framingham mean ± SD	15.0±4.8	32.5±9.5	0.001
Simplified Framingham mean ± SD	16.1±5.6	34.2±7.6	0.001
SCORE mean ± SD	3.3±1.5	4.9±2.6	NS

Table 3. Predictive value for IMT ≥ 0.9 mm

Risk score	AUC
Framingham	0.773
Simplified Framingham	0.759
SCORE	0.622

TH-PO320

Mouse Model of Venous Stenosis

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Background: A response of the vein wall to balloon angioplasty results in post-angioplasty restenosis (PARS). PARS impedes normal blood flow leading to a spectrum of complication and morbidities that exacerbates the outcome of vascular diseases, and remains a limiting factor for successful vascular intervention. Previous studies have indicated that mice of different inbred backgrounds have differences in arterial remodeling response, however, have not assessed the venous remodeling response.

Methods: To objectively evaluate the influence of uremia on venous remodeling, we utilized a CKD mouse model and developed a surgical technique that mimics the vascular damage of angioplasty. We recapitulated renal failure by inducing chronic renal function insufficiency via partial nephrectomy (2/3-nephrectomy) model with a high protein diet, and model venous restenosis via wire injury to the external jugular vein (EJV). To provide the basis for a genetic analysis of venous remodeling, we subjected 3 different inbred strains of mice; chosen based on their remodeling response to arterial injury (C57BL6, FVB, and SJL/J), to EJV wire injury to evaluate the cellular response involved in venous remodeling influenced by uremia.

Results: We developed a model that mimics venous stenosis in mice. Our model was validated via assessing vascular composition by immunological and histological staining and geometrical analysis (i.e., the evaluation of the lumen, intimal and medial area) by microscopy of the injured vein.

Conclusions: Our model helps us elucidate and further understand the pathophysiology of venous remodeling that occurs in hemodialysis vascular access dysfunction.

Funding: NIDDK Support

TH-PO321

Uremia Induces Functional and Histological Changes in a Mouse Model of Arteriovenous Fistula (AVF) Stenosis

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Background: Arteriovenous Fistula (AVF) stenosis is responsible for a very significant morbidity, mortality and economic cost. Despite the magnitude of the clinical problem there are currently no effective therapies for AVF stenosis. The focus of this project was therefore to identify uremia specific functional and histological differences in AVF stenosis in a mouse model.

Methods: Mice were made uremic through the removal of the upper and lower poles of one kidney followed by a nephrectomy of the contralateral kidney. AVFs were created through an end (vein) to side (artery) anastomosis using standard techniques. Functional parameters included flow mediated dilation (FMD) and the area enclosed within the elastic lamina at 100 micron intervals x 12 from the AV anastomosis. The histological end point was the ratio of thrombus area/perimeter at 100 micron intervals x 12 from the AV anastomosis (with the first 600 microns being considered proximal and the second 600 microns as distal).

Results: A total of 22 mice were used in these experiments. The mean +/- SE for BUN in the uremic animals was 109+/-4.8 mg/dL as compared to 17.4 +/- 1.0 mg/dL in the control animals ($p<0.05$). FMD at 60 seconds was decreased significantly in uremic animals (13.4 +/- 1.5%) as compared to the control animals (19.5 +/- 1.1%), although there was no difference at the 90 second peak. There was a trend towards a smaller area enclosed by the elastic lamina (an indicator of inward remodeling) in the uremic animals,

although this achieved statistical significance only in the distal segments (at 1000-1200 microns beyond the AV anastomosis). Finally, uremic animals had significantly more attached thrombus (thrombus area/perimeter) in the distal portions of the AVF (9414.7 +/- 7187.5) as compared to the proximal portions (1055.0 +/- 529.5).

Conclusions: These data document impairment of endothelial linked, functional (FMD and inward remodeling) and histological (thrombus formation) pathways in a mouse model of AVF stenosis. Further elucidation of the uremia specific mechanistic pathways responsible for these differences, could result in the development of novel drugs and devices for the treatment of AVF stenosis in patients with CKD and ESRD.

TH-PO322

Hemodynamic and Geometrical Characteristics of Rat Arteriovenous Fistula: Effect of Nitric Oxide Treatment

Hannah M. Northrup,[1] Yan-Ting Shiu,[1] Daniel Pike,[1] Isabelle D. Falzon,[1] Maheshika S. Somarathna,[2] Lingling Guo,[2] Timmy C. Lee.[3] *[1]University of Utah, Salt Lake City, UT; [2]University of Alabama at Birmingham, Birmingham, AL; [3]Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Nitric oxide regulates endothelial function and promotes vascular health. Overexpression of endothelial nitric oxide synthase has been shown to improve arteriovenous fistula (AVF) maturation in mice. AVF maturation is dependent on hemodynamics and remodeling of the vessel wall. Here we investigate the impact of localized delivery of nitric oxide on AVF lumen hemodynamics and geometry in rats.

Methods: Femoral AVFs were created in 12-16 week old male Sprague-Dawley rats. At the time of creation AVFs were treated with NO releasing nanomatrix gel therapy (treatment gels) (n=4). Gels without nitric oxide (placebo gels) were used as a control (n=3). 7 days post creation, animals were subject to non-contrast MRI scans, and the MR images were used for reconstruction of the AVF lumen and computational fluid dynamic simulations of the AVF blood flow. Hemodynamic parameters (velocity, fluid wall shear stress (FWSS), and vorticity) and geometrical analysis (anastomosis angle (AA), tortuosity, and nonplanarity angle (NA)) were calculated.

Results: As shown in Fig. 1, AVF vein velocity, FWSS, and vorticity of placebo gels were significantly higher than treatment gels ($p<0.05$). AA were not significantly different between placebo and treatment gels. Tortuosity of the AVF showed a higher trend in treatment gels than control gels, with NA showing a slight decrease in treatment gels.

Conclusions: The NO treatment leads to significantly lower hemodynamics than the placebo, suggesting the return of velocity, FWSS, and vorticity to the pre-surgery baseline levels in the native vein by NO. However, localized treatment of NO releasing nanomatrix gels does not result in significant differences in AVF lumen geometry.

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

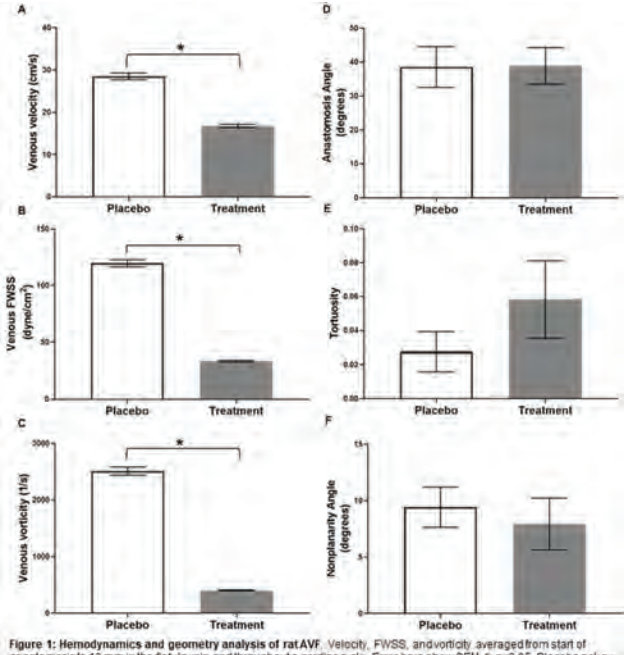

Figure 1: Hemodynamics and geometry analysis of rat AVF. Velocity, FWSS, and vorticity averaged from start of anastomosis to 10 mm in the flatula vein and throughout a cardiac cycle. Error bars show SEM. *: $p<0.05$. Placebo gel n= 3. Treatment gel n=4.

TH-PO323

Effect of Endothelial Nitric Oxide Synthase on Geometrical Parameters of Murine Arteriovenous Fistulas

Isabelle D. Falzon,[1] Yan-Ting Shiu,[1,2] Daniel Pike,[1] Hannah M. Northrup,[1] Maheshika S. Somarathna,[3] Lingling Guo,[3] Timmy C. Lee.[3,4] *[1]University of Utah, Salt Lake City, UT; [2]VASLCHCS, Salt Lake City, UT; [3]University of Alabama at Birmingham, Birmingham, AL; [4]Veterans Affairs Medical Center, Birmingham, AL.*

Background: Arteriovenous fistula (AVF) maturation failure is a significant clinical issue. Endothelial nitric oxide synthase (NOS3) leads to the production of nitric oxide, a vasodilator, which contributes to successful AVF maturation in mice. Previous small clinical studies have reported the association between the AVF geometrical parameters and AVF maturation. Here we investigated the effect of NOS3 on AVF geometry in mice.

Methods: Carotid-jugular AVFs were created in NOS3 over expression (OE) and NOS3 knock out (KO) mice on C57BL/6 background, with C57BL/6 mice as wild type (WT) control (n=1 per strain). Black-blood MR images were taken at Day 7 and Day 21 post AVF creation and used to reconstruct AVF lumen geometries. Geometrical analysis (Fig. 1A) quantified the anastomosis angle (AA), nonplanarity angle magnitude (NA), and tortuosity of the AVF vein.

Results: The AVF lumen area was bigger in the NOS3 OE mice than in NOS3 KO and WT mice. Lumen reconstructions are shown in Fig. 1B. Overexpression of NOS3 led to a reduced AA and NA by 16° and 10°, respectively, from Day 7 to Day 21, indicating that the AVF vein remodeled to align more parallel with and on the same plain of the feeding artery. In contrast, NOS3 KO increased NA by 14° and decreased AA by 0.3° from Day 7 to Day 21. WT increased AA and NA by 17° and 5°, respectively, from Day 7 to Day 21. While OE and KO decreased in tortuosity by 0.15 and 0.14, respectively, WT increased tortuosity by 0.08 from Day 7 to Day 21.

Conclusions: Geometrical parameters differ with varying NOS3 expression and over time. More research is needed to understand how these geometrical parameters affect AVF maturation and the mechanisms leading to geometrical changes.

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

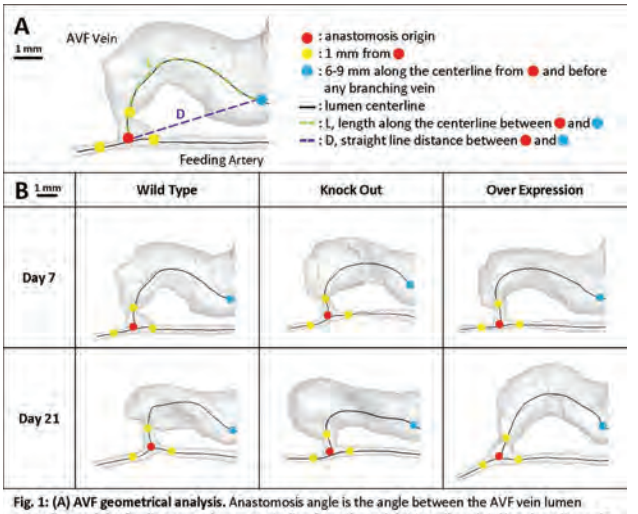

Fig. 1: (A) AVF geometrical analysis. Anastomosis angle is the angle between the AVF vein lumen centerline and the feeding artery lumen centerline from the red dot to yellow dot. Nonplanarity angle is the angle between D and a plane created with the 3 yellow dots. Tortuosity of the AVF vein is L/D−1. **(B) AVF Geometry Over Time.** Scale bar in (B) applies to all geometries in (B).

TH-PO324

Activation of Formyl Peptide Receptor 1 Causes Arteriovenous Fistula Failure in Rats

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Background: Formyl peptide receptor 1 (FPR1) is a recognition receptor for damage-associated molecular patterns. It is best known for mediating myeloid cell chemotaxis and activation to bacterial formylated peptides. However, it can also recognize mitochondria-derived proteins from apoptotic/necrotic cells due to the evolutionary origins of mitochondria. In a recent transcriptomics analysis of human arteriovenous fistulas (AVFs) that matured or failed after creation, higher expression of FPR1 in the native vein was associated with non-maturation. Immunohistochemistry analyses demonstrated that FPR1 was expressed in smooth muscle cells (SMCs) in the media, where it possibly sensed apoptotic/necrotic cells as a result of vascular trauma after AVF creation. In this study, we tested the effects of FPR1 activation in the maturation of experimental fistulas. **We hypothesized that activation of FPR1 at the time of AVF creation would increase the frequency of fistula failure.**

Methods: AVFs were created in Sprague Dawley rats (n=16) by anastomosing the superficial epigastric vein to the nearby common femoral artery. Twenty nanograms

(20 ng) of the FPR1 agonist fMLF were applied perivascularly to eight AVFs in 200 uL of Matrigel at the time of fistula creation. The remaining eight fistulas received Matrigel plus vehicle (control group). AVFs were harvested at 21 days after creation.

Results: Five out of eight AVFs (62.5%) failed to mature in the fMLF-treated subgroup, compared to one out of eight (12.5%) in control animals. Blood flow decreased from 19.2 [8.5-32.4] mL/min in control AVFs to 0.0 [0.0-6.6] mL/min in fMLF-treated fistulas (P=0.018). Venous distensibility was also significantly lower in the latter than in control AVFs, both in the juxta-anastomotic area and in the distal fistula (P<0.05).

Conclusions: Together with the human transcriptomics data, these results suggest that FPR1 activation is implicated in AVF maturation failure.

TH-PO325

Decreased Jagged1 Expression in Vascular Smooth Muscle Cells Delays Maturation of Arteriovenous Graft

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Background: It is well-known that endothelial dysfunction promotes activation of vascular smooth muscle cell (VSMC). Whether decreased accumulation of VSMCs affects endothelial regeneration and functions in arteriovenous graft (AVG) remodeling has not been studied. We plan to identify mechanisms by which the Notch ligand, Jagged1, in VSMCs regulates EC functions in AVGs.

Methods: AVGs were created in transgenic mice bearing VSMC-specific knockout (KO) or overexpression of Jagged1. VSMC migration, EC regeneration and its barrier functions as well as AVG remodeling were evaluated.

Results: Jagged1 expression was induced in VSMCs of neointima in the AVGs. Jagged1 KO in VSMCs inhibited the accumulation of extracellular matrix as well as VSMC migration. Fewer α-SMA-positive VSMCs were found in AVGs created in Jagged1 KO mice vs. results in WT mice. Decreased VSMCs in AVGs were associated with deteriorated the EC functions. In AVGs created in transgenic mice bearing Jagged1 KO in VSMCs exhibited delayed EC regeneration and impaired EC barrier function. Barrier dysfunction of ECs increased the inflammatory cell infiltration and dysregulation of AVG arterialization. In contrast, AVGs created in mice with overexpression of Jagged1 in VSMCs exhibited improved EC regeneration plus decreased macrophage infiltration. This led to AVG remodeling and arterialization. In co-cultures of ECs and VSMCs, Jagged1 deficiency in VSMCs suppressed N-cadherin and integrin β3 expression in ECs. Inhibition of integrin β3 activation delayed EC spreading and migration. Notably, Jagged1 overexpression in VSMCs stimulated the expression of N-cadherin and integrin β3 in ECs. Jagged1-induced responses were blocked by inhibition of Notch signaling.

Conclusions: our results demonstrate that Jagged1 expression in VSMCs maintains EC barrier functions and blocks infiltration of macrophages. These responses promote remodeling and arterialization of AVGs.

Funding: NIDDK Support

TH-PO326

p-Cresyl Sulfate Induced Oxidative Stress and Inflammation on Endothelial and Vascular Smooth Muscle Cells

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Background: Vascular access dysfunction affects negatively patient morbidity and mortality. The most common problem in AVF and AVG is venous stenosis, resulting from a neointimal hyperplasia development. Recent study reported that p-Cresyl sulfate was related to the outcome of vascular access in hemodialysis patients. p-cresyl sulfate (p-CS), poorly removed by conventional dialysis, has been known to exhibit pro-oxidant properties in renal tubular cells by enhancing NAD(P)H oxidase activity and induce reactive oxygen species(ROS) production in endothelial cells. However, the mechanism of vascular toxicity induced by p-CS was poorly understood. The aim of the study was to determine whether p-CS enhances the production of ROS in vascular endothelial cell and proliferation of smooth muscle cell resulting in neointimal hyperplasia. Additionally, we aimed to determine whether p-CS induces the expression of ICAM-1 and MCP-1 by ROS induced activation of NK-KB in endothelial cell.

Methods: Aortic smooth muscle cells (SMCs) were treated with p-CS (10-1000 μmol/L), and aortic SMC proliferation was measured Bromodeoxyuridine cell proliferation assay. Western blot analysis was done for ERK1/2 and p38 MAPK. Human umbilical vein endothelial cells (HUVEC) were also treated with p-CS (1000 μmol/L). The productions of NF-κB, ICAM-1, MCP-1 and eNOS in HUVEC were assessed using RT-PCR and ELISA.

Results: p-CS stimulated the proliferation of aortic SMCs in a dose dependent manner, and promoted the phosphorylation of ERK1/2 and p38 MAPK. In HUVEC, p-Cresyl sulfate induces ROS production by enhancing NAD(P)H oxidase and upregulates the expression of ICAM-1 and MCP-1 by ROS-induced activation of NF-kB. However, NO synthase seemed not to be involved in p-cresyl sulfate induced oxidative stress in HUVEC.

Conclusions: Our data confirmed that p-CS was attributed to vascular SMC proliferation and inflammation and oxidative stress in HUVECs in vitro. Further evaluation will be needed to clarify the role of p-CS in vascular access stenosis and neointimal hyperplasia.

TH-PO327

Human Arteriovenous Fistula Wall Thickness in the First 6 Months After Creation

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Background: Previous studies of the arteriovenous fistula (AVF) maturation process have focused almost exclusively on enlargement of the AVF lumen to allow increases in AVF blood flow. There is a lack of information regarding AVF wall thickness. Here we assess the change in AVF wall thickness, in conjunction with AVF lumen area, during the first 6 months after creation. We hypothesize that during AVF development, the wall thickens in response to lumen enlargement to maintain the structural strength and integrity of the wall.

Methods: Non-contrast black-blood magnetic resonance imaging (MRI) scans were performed on newly-created AVFs at 3 post-operative time points (1-3 days, 6 weeks and 6 months) in 10 ESRD patients at the University of Utah Hospital. MRI images were used to reconstruct 3D geometries of the AVF veins, from which the lumen area and wall thickness were calculated for the cross sections perpendicular to the lumen centerline at 1 mm intervals for 20 mm along the AVF length starting from the anastomosis.

Results: Fig. 1A-B shows the lumen area and wall thickness of each AVF at 3 sequential MRI scans. The lumen area increased from 14.26±5.40 mm^2 at 1-3 days to 21.91±8.79 mm^2 at 6 weeks to 30.62±12.78 mm^2 at 6 months (p=0.0005 by ANOVA for 3 time points), while the wall thickness increased from 0.76±0.09 mm at 1-3 days to 1.05±0.23 mm at 6 weeks to 1.21±0.18 mm at 6 months (p<0.0001 by ANOVA for 3 time points). During this 6-month period, the lumen area change was positively associated with the wall thickness change (p=0.0369) (Fig. 1C).

Conclusions: In ESRD patients, AVF wall thickened as their AVF lumen area enlarged. More rigorous validation of this observation using a larger cohort is necessary.

Funding: NIDDK Support, Veterans Affairs Support

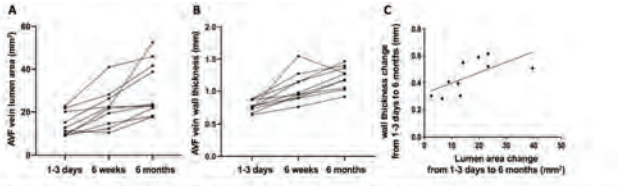


Figure 1. The time course of lumen area (A) and wall thickness (B) of individual AVF. Each connected line represents one patient. (C) Association between the lumen area change and the wall thickness change.

TH-PO328

Secondary Hyperparathyroidism Stimulates Neointimal Hyperplasia of Arteriovenous Fistula in Mice

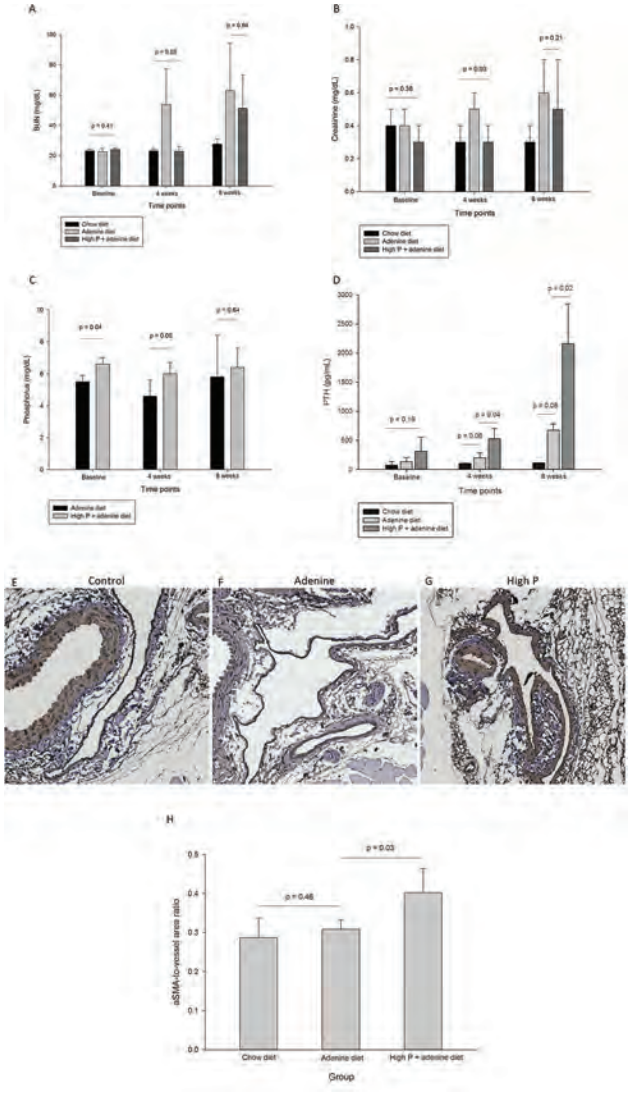
Chung-te Liu. *Division of Internal Medicine, Wanfang Hospital, Taipei Medical University, Taipei, Taiwan*.

Background: Arteriovenous fistula (AVF) is the preferred vascular access due to superior patency and lower infection rates. Nonetheless, its suboptimal maturation rate remains to be resolved. Previous clinical studies had shown that elevated parathyroid hormone (PTH) associated with AVF maturation failure. In thisstudy, we try to repeat this finding in a mice model of secondary hyperparathyroidism and AVF.

Methods: Chronic kidney disease (CKD) and secondary hyperparathyroidism were induced by feeding diet containing 0.2% adenine (adenine group) or 0.2% adenine and additional 2% phosphorus (high P group) in C57BL/6 mice. After 8 weeks of induction, AVF was created by aortocaval puncture. AVF was resected 6 weeks later. AVF was stained for α-smooth muscle actin (αSMA) to show neointimal hyperplasia. The severity of neointimal hyperplasia was expressed by ratio of area of αSMA/entire AVF.

Results: At the 8th week, renal function CKD was induced in adenine group and high P group (Figure 1A-B). Serum phosphorus level was insignificantly higher in high P group (Figure 1C). Compared with control group, serum PTH level was insignificantly higher in adenine group, while it was significantly higher in high P group (Figure 1D), indicating successful induction of secondary hyperparathyroidism in high P group. The severity of AVF neointimal hyperplasia was similar between control group and adenine group, while it was significantly more severe in high P group (Figure 1E-H). The above findings showed that secondary hyperparathyroidism may stimulate neointimal hyperplasia in AVF and play a role in AVF maturation failure.

Conclusions: The deleterious effect of PTH on AVF maturation shown will be confirmed by pharmaceutical suppression of PTH to reverse neointimal hyperplasia.



TH-PO329

Far Infrared Ray Irradiation Inhibits Platelet Aggregation Pathway Through Increasing ADAMTS13 Production to Cleave Length of von Willebrand Factor on Cell Surface and Decreasing Platelet Adhesion to Human Umbilical Vein Endothelial Cells

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Background: Far-infrared Ray (FIR), wavelength between 3-1000 μm, bears multiple effects on cardiovascular system and thrombogenesis. The von Willebrand factor (vWF), a large multimeric plasma glycoprotein as crucial player in arterial thrombus formation, can be cleaved by metalloprotease ADAMTS13 at its A2 domain cryptic in normal circulating vWF. We hypothesized FIR may induce ADAMTS13 release and decrease platelet adhesion to endothelial cells.

Methods: Cultured HUVECs treated with FIR irradiation for 30 minutes. Extracted mRNA and protein were measured by real time PCR, western blot, or ELISA. Supernatants were subjected to nonreducing gel electrophoresis to assess vWF multimer patterns by western blot. Platelet-HUVEC interactions were done by labeling platelet with calcein AM and co-cultured calcein AM-labeled platelet with FIR-treated or controlled HUVECs, followed by fluorescence microscopy analysis. Peripheral blood samples from 14 healthy volunteers before and after FIR irradiation were measured for ADAMTS13 by immunoassay and multimeric vWF pattern by SDS-agarose gel western blot.

Results: The mRNA level of ADAMTS13 after FIR irradiation showed a time-duration dependent effect. FIR also stimulated ADAMTS13 but not vWF protein expressions in HUVECs. The levels of ADAMTS13 and vWF D4-CK domain in culture media measured showed increased after FIR irradiation. These findings reflected the possibility of vWF been cleaved from cell surface into medium, and it was demonstrated by the significantly reduced vWF D4-CK terminal expression on the surface of endothelial cells after FIR irradiation. The vWF multimer patterns in supernatants showed less presence of higher molecular weight forms, and binding of platelets to HUVEC cells was significantly reduced in FIR-treated cells. In healthy subjects, FIR irradiation increased blood levels of ADAMTS13 and reduced higher molecular weight forms of multimers of vWF.

Conclusions: We concluded FIR irradiation may inhibit platelet adhesion to endothelial cells via induction of ADAMTS13 which cleaves vWF on cell surface and results in decrease of platelet adhesion to endothelial cells. Our results provide information for further exploring the mechanisms of FIR in prevention of thrombus formation.

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

TH-PO330

Perivascular Administration of Sirolimus During Arteriovenous Access Surgery: Delivering Therapeutic Outcomes Minimizing Risk of Systemic Side Effects

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Background: Unmitigated cell proliferation at and around the vascular anastomosis resulting in flow limiting stenosis is an important cause of access dysfunction. *m*TOR (mammalian target of rapamycin), controls cell growth, proliferation and survival. *Oral* sirolimus is an immunosuppressant. Sirolimus (cytostatic) delivered *locally* to site(s) of vascular injury downregulates *m*TOR and inhibits cell proliferation by causing cell cycle arrest between G1 & S phases. *Perivascular delivery* of sirolimus is a novel method of harnessing its anti-proliferative effect with the intent of improving access outcomes. A prior Paclitaxel (cytotoxic; anti-mitotic) perivascular AVG study was prematurely terminated because of excessive infections.

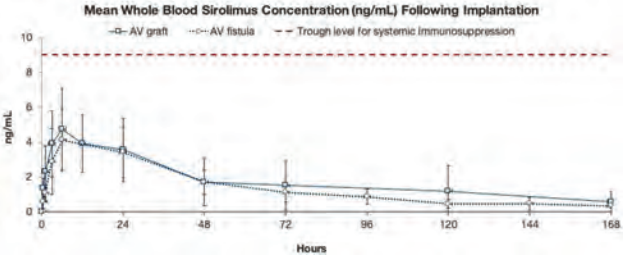
Methods: Data from 56 AVF pts (includes open label subset of a US Phase 3 randomized, *data safety monitored* study; 55 ESRD) and 12 AVG pts (Paulson NDT 2012) treated with perivascular sirolimus at & around the anastomosis (AVF) & venous anastomosis (AVG) delivered from a collagen matrix (Sirogen™ Vascular Therapies, Cresskill NJ) were analyzed. Access functional outcomes were evaluated using 2 needle cannulation for dialysis. Blood drawn at protocol specified time points yielded pharmacokinetic (PK) data.

Results: One AVF wound dehiscence required secondary suturing & local treatment with subsequent healing & preserved 12 mo. fistula primary functional patency; no cases of local infection. PK: Sirolimus levels peak ~6 hrs. after start of drug delivery (4-5ng/ml), declines to <1ng/ml by 96 hrs. PK profile for AVF and AVG are similar. Key efficacy metrics are tabulated.

Conclusions: 1. Perivascular sirolimus delivery with targeted high local concentrations of sirolimus achieves therapeutic effectiveness without increasing risk of problems with wound healing and infection. 2. Systemic release of sirolimus is negligible and levels are sub-therapeutic for systemic immunosuppression. 3. The US Phase 3 study is nearing enrollment completion.

Funding: Commercial Support - Vascular Therapies, Inc.

Access Type	N	Maturation	Primary Patency		Suitability for Dialysis	
			6 mos.	12 mos.	6 mos.	12 mos.
AVF	56	86%	62%	52%	78%	72%
AVG	12	-	82%	73%	82%	73%



TH-PO331

A Pilot Study to Measure Distensibility Using Open-Source Software

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Background: Arteriovenous fistulas (AVF) are the preferred access for hemodialysis. Yet, they often fail to mature. Doppler ultrasound has been employed for enhancing the preoperative examination of the patient prior to AVF construction. Blood vessel distensibility may be useful in predicting fistula maturation. This pilot study reports on the feasibility of measuring distensibility using conventional ultrasound data and an open-source ultrasound software program that our group developed based on ultrasound speckle tracking.

Methods: Ten patients were enrolled for this study after obtaining informed consent. Demographics and clinical data were collected. Ultrasound scanning of the brachial and radial artery were performed. Conventional digital imaging and communications in medicine (DICOM) format data were collected from the ultrasound exam. The distensibility of arteries were computed from the DICOM data using our open-source software to track the frame to frame displacement of user selected pixels located at the near

and far field edge of the vessel wall. Exploratory relationships between baseline brachial and radial artery distensibility and clinical covariates are also reported.

Results: Of the total 10 patients, there were 10 males, 8 had history of diabetes, 9 had hypertension. The mean age was 70.2 ± 5.4 years, BMI 28.0 ± 5.0 kg/m2, systolic pressure 128 ±26 mmHg, diastolic pressure 65 ±8 mmHg. The baseline distensibility of the branchial artery and radial artery were 2.8% ± 1.1% and 1.8% ± 0.8% respectively. Distensibility of both arteries increased with increases in systolic and diastolic blood pressures. Plots of distensibility versus peak systolic velocity and baseline vessel diameter are shown.

Conclusions: This study demonstrates that distensibility measurement using an open-source automated ultrasound software program is feasible.

Funding: Veterans Affairs Support

TH-PO332

Effectiveness of Flow Volume Measurement Training Using Custom-Made Doppler Flow Simulator

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Background: The purpose of this paper was to present the effectiveness of custom-made Doppler ultrasound (DU) flow simulator, vascular phantom, and Doppler test fluid in training dialysis staffs on the flow volume (FV) measurement for arteriovenous (AV) access of hemodialysis (HD) patients.

Methods: A DU flow simulator was constructed using a continuous renal replacement therapy machine. Vascular phantoms were made with a rubber enema tube and keyboard cleaning gel. Doppler test fluid consisted of freeze-dried instant coffee granules and 0.9% saline. This easy and affordable simulator was applied to the training DU flow volume measurement on 12 dialysis staffs who had never experienced DU examination. After 3 days of theoretical education, dialysis staffs performed DU on AV access of HD patients. Thereafter, they underwent a 3-day training course using the simulator and then measured FV of AV access again. Each dialysis staff assessed FV 3 times, and the mean values of measurements between pre and post-training were analyzed by paired t-test.

Results: The difference in mean value of FV measurements from the reference value decreased from 131.6 ml/min to 62.5 ml/min (95% CI 30.0-108.0, P = 0.002), and the standard deviation of FV measurements were decreased from 96.9 ml/min to 47.0 ml/min (95% CI 7.9-91.8, P = 0.023) after DU training with the simulator.

Conclusions: The accuracy and reproducibility of FV measurement by dialysis staffs were markedly improved after training using the current simulator, and it may be helpful to medical practitioners participated in the management of AV access and HD treatment.

TH-PO333

Performance Characteristics of Criteria for Hemodialysis Arteriovenous Fistula Clinical Maturation

Jia Hwei Ng, Wei Yang, Sidney M. Kobrin, Laura M. Dember. *University of Pennsylvania, Philadelphia, PA*.

Background: A barrier to conducting and interpreting clinical studies of interventions for improving fistula outcomes is the lack of standardized and readily ascertainable criteria for defining fistula maturation. Using data from the multicenter, prospective NIDDK Hemodialysis Fistula Maturation (HFM) study, we determined performance characteristics of more readily ascertainable alternatives to the HFM clinical maturation criteria.

Methods: We included the 544 participants for whom clinical maturation was ascertained during the HFM study. The HFM criteria for maturation required fistula use for ≥75% of dialysis sessions within any 4-week period with either a) dialysis machine blood pump speed ≥300 ml/min or b) spKt/V ≥1.4. The criteria had to be met within 9 months of fistula creation or 8 weeks of dialysis initiation, whichever was later. For the current analysis, we developed alternative maturation criteria that incorporated one or more of the following domains: 1) # of sessions of fistula use, 2) dialysis machine blood pump speed, 3) small solute clearance, 4) no use of an alternative access, and 5) time from fistula creation.

Results: Mean age was 56 years, 69% were men, 45% were Black, and 64% had diabetes. 396 (72%) had successful fistula maturation (either assisted or unassisted) by HFM criteria. Performance characteristics of our alternative criteria are shown in the Table. All criteria had high specificity (93-100%), but criteria that require only 3 months for ascertainment had low sensitivity (36-67%).

Conclusions: Several alternatives to the HFM maturation outcome that are easier to ascertain have high predictive utility and, thus, could potentially simplify the conduct of research studies. However, an ascertainment period that extends beyond 3 months after fistula creation is required for adequate sensitivity.

Funding: NIDDK Support

Table. Performance characteristics of alternative criteria for fistula maturation using the HFM criteria for maturation (either assisted or unassisted) as the reference

	Met within 3 months of fistula creation			Met within 6 months of fistula creation		
	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
HFM criteria within earlier time points	43% (39-49)	99% (96-100)	0.71 (0.69-0.74)	86% (82-90)	98% (94-100)	0.92 (0.90-0.94)
Fistula use for ≥75% of dialysis sessions within a 4-week period	67% (62-72)	96% (91-99)	0.81 (0.79-0.84)	94% (91-96%)	93% (87-96)	0.93 (0.91-0.96)
4 consecutive uses of fistula with dialysis machine pump speed ≥300ml/min	40% (35-45)	100% (98-100)	0.72 (0.68-72)	84% (80-88)	99% (95-100)	0.90 (0.89-0.93)
4 consecutive uses of fistula	55% (49-59)	96% (91-99)	0.75 (0.72-0.78)	91% (88-94)	93% (88-96)	0.92 (0.90-0.95)
No use of alternative access for ≥4 weeks	36% (32-41)	95% (91-98)	0.66 (0.63-0.69)	83% (80-87)	93% (87-96)	0.88 (0.85-0.91)

TH-PO334

Proving the Value of the Bluedop™ Device in the Renal Unit

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Background: Static Pressure Ratio *SPR*, showed early promise as a monitoring device in prediction of Arteriovenous Fistula Failure. 'Arterial' needle pressure is monitored with dialysis pump switched off. Blood pressure on the venous outflow will rise towards central arterial level in the presence of a 'blood flow limiting' venous stenosis. The method is not widely used, possibly due to difficulties in compensating for hydrostatic height difference between needle and mean blood pressure *MAP* measured on the contralateral arm. We suggest a simpler alternative using identical principles solves many of the practical problems associated with the earlier technique.

Methods: The Bluedop™ device is intended to measure mean blood pressure non-invasively, without the use of needles, is unaffected by pump speed and can be applied at any suitable part of the AVF without any requirement for hydrostatic height correction. We have named our parameter 'Non Invasive Static Pressure Ratio' *SPRn*. A Doppler Ultrasound probe is used to sample blood flow waveforms from the distal brachial artery. A patented function based on blood velocity waveform shape calculates non-invasive intra AVF mean perfusion pressure *MPP* [2]. This is comparable to the needle pressure measured directly in the *AVF*. *SPRn* is calculated as *SPRn = MPP/MAP*. The complete measurement takes approximately 5 minutes. and can be carried out by regular Renal Unit Staff without significantly interfering with their normal duties.

Results: The range of SPRn values in normally functioning AVF was established in 479 dialysis patients. Following this 340 prospective measurements were made on 73 patients over a 10 week period. SPRn in 27 AVF rose above the +2SD normal limit. Of these 23 had 60% or greater focal stenosis shown on Duplex scanning, 2 were maturing AVF and 2 had no significant stenosis. A review of clinically identified 'failing' AVF in the same unit showed that 48% were found to be 'false alarms' in Duplex studies. Bluedop™ reduced the number of false alarms to 18%.

Conclusions: Bluedop™ offers a practical solution to the perennial problem of unheralded AVF failure. It also has the desirable property of indicating AVF status during the maturing phase References: 1 A Besarab et al, Vol.47, no.5, pp 1364-1373, 1995 2 D H King et al, J Vasc Access, 2015, 16 (3):211-217, DOI: 10.5301/jva.5000324

TH-PO335

Algorithmic Estimation of Vascular Access Dysfunction from Serial Bruit Recordings

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Background: Hemodialysis vascular access dysfunction accounts for a large fraction of hospital visits for dialysis patients and has significant implications on cost of care, morbidity and mortality. This study examined if mathematical analysis of serially-recorded bruits could detect changes in bruit pitch indicative of imminent vascular access dysfunction.

Methods: An algorithm was developed to detect bruit pitch shifts between recording locations along the vascular access. The algorithm produced a single value for each location which monotonically increased with bruit pitch caused by turbulent blood flow. Algorithm performance was validated on a phantom vascular access at flows of 80-1,200 mL/min and stenoses ranging from 10-85%. Prognostic value in predicting vascular access dysfunction was tested longitudinally in 24 patients at an outpatient Veteran's Affairs HD unit. Bruit recordings were made using a digital stethoscope (Littman 3200) 1-4 times per month just prior to HD. In each evaluation, 10-s bruit recordings were obtained at 5-9 serial locations, 3 cm apart along an upper extremity arteriovenous fistula (AVF) or graft (AVG). Recordings were made from the arterial anastomosis to beyond the cannulation zone (for AVF) or to the venous anastomosis (for AVG). True positive detection of access dysfunction was counted when the algorithm value exceeded a fixed threshold at one or more recording sites and when clinical evidence of access dysfunction occurred within 30 days after the recording date. Evidence of access dysfunction included prolonged post-HD bleeding or access rupture, access pain, radiologic intervention, non-functional access, or unexplained KT/V below 1.3.

Results: 3,441 bruits were recorded for 24 Veterans (age 67 years, HD vintage 51 months, 96% male, 83% Black) over an average of 13 months per patient. 71 instances of access dysfunction were observed in 18 patients (median 3 per patient). Use of the algorithm showed 89% sensitivity, 83% specificity, and 92% accuracy at predicting access dysfunction up to 30 days in advance.

Conclusions: Prospective use of serial bruit recordings and algorithmic analysis positively identified at-risk patients up to 30 days before clinical evidence of access dysfunction. This technique may help prevent emergency interventions or hospital admissions for access dysfunction.

TH-PO336

The Use of Doppler Ultrasound in Hemodialysis Patients for Vascular Access Surveillance: Arguing the Revised Hemodialysis Vascular Access Guidelines

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Background: The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for the management of vascular access (VA) in hemodialysis (HD) is currently in external review process. Only clinical monitoring is being clearly suggested for VA surveillance. Our experience implies a promising role for the use of diagnostic methods like Doppler ultrasound (US) in daily practice. The aim of this study is to explore the use of Doppler US audit in HD patients with arteriovenous fistulas (AVF) and grafts (AVG), performed by nephrologists.

Methods: This is a single centre study with prospective evaluation of AVF or AVG in stable HD patients. Patients' VA was assessed by the same nephrologist with the use of a color Doppler US in a twelve-month monitoring period. Basic VA anatomical and functional parameters like mean volume flow (MVF) and percentage of change in mean volume flow (ΔMVF), stenosis and other abnormalities were recorded. Demographic and clinical characteristics were assessed, while cumulative secondary survival (CSS) and secondary patency rate (SPR) along with abnormality rates were calculated and further analysed.

Results: A total of 43 patients (30 male), 21% diabetic, age 61.5±13 years, enrolled in the study. 76.7% of patients had an AVF while 23.3% had an AVG. At baseline, 18.6% of patients had a MVF<600 ml/min, while 18.3% appeared to have significant stenosis in the access circuit. ΔMVF was categorized as stable or reduced in the event of a change in mean VF>30%. At the end of the study, SPR for all VA was 76.74%, (81.82% for AVF and 40% for AVG). Cumulative secondary survival was 65±26 months for the above study population, and when comparing AVF and AVG, CSS was 78.61±24 months and 21.80±13 months respectively (p=0.001). In univariate analysis, age, the presence of diabetes, ΔMVF, and the presence of stenosis were correlated with CSS. In a multivariate model only age and the presence of stenosis in the access circuit retained correlation with CSS.

Conclusions: In a hemodialysis unit where VA assessment with an US by nephrologist is available, frequent audit seems to offer an additional benefit for patients' VA survival to clinical surveillance.

TH-PO337

Vascular Access Surveillance: Impact of an Intensive Ultrasound Surveillance Protocol in Arteriovenous Fistulae and Arteriovenous Grafts Patency Rates

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Background: Impact of an intensified monthly ultrasound surveillance protocol for vascular access (VA) in the patency rates of native arteriovenous fistulae (AVF) and arteriovenous grafts (AVG) for hemodialysis.

Methods: Prospective observational study that involved hemodialysis patients receiving treatment from either an AVF or an AVG in an in Center Hemodialysis facility in Greece, from January 2016 to December 2018. Patients were assigned to an intensified VA surveillance protocol, according to which were followed monthly by Color Doppler ultrasound. When was needed, patients were referred to for pre-emptive corrective procedures. The number of procedures, frequency of primary repair, percentage of primary assisted patency (APP), secondary patency (SP) and failure rates of VA were all reviewed.

Results: Two hundred twenty-three patients completed the study (243 VA, 192 AVF and 51 AVG). In total, 56 pre-emptive corrective interventions were performed (0.13 procedures per 12 months) from which 34 involved AVF patients (0.09 procedures/12 months) and 22 patients with AVG (0.40 procedures/12months). Totally observed were 33 VA failures (0.06 failures/12 months), 17 in patients with AVF (0.04 failures/12 months) and 16 in AVG (0.20 failures/12 months). Percentages of APP and SP for all VA were 83% and 93% in 12 months of follow-up, respectively, whereas for 24 months was 75% and 88% and for 36 months 72% and 83%. The percentage of APP and SP among patients with AVF was 89% and 96% in 12 months follow-up period, 81% and 93% in 24 months and 80% and 89% in 36 months, respectively. On the contrary, the percentage of APP and SP among patients with AVG was 56% and 80% in 12 months follow-up, 44% and 65% in 24 months and 39% and 54% in 36 months, respectively.

Conclusions: The use of an intensive monthly ultrasound surveillance protocol for VA is positively associated with a significantly improved cumulative survival of VA for hemodialysis. By offering the advantage of a timely diagnosis of VA dysfunction enables physicians to perform pre-emptive access corrective procedures improving thus VA patency rates. The establishment of firm conclusions requires the conduction of randomized controlled trials to address to the gap of knowledge and debate regarding VA surveillance.

TH-PO338

The Possibility of Ionic Dialysance as an Index to Predict the Dysfunction of Vascular Access

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Background: Vascular access dysfunction (VAD) in hemodialysis (HD) results in insufficient dialysis dose represented by low Kt/V_{urea} calculated using the serum levels of BUN. If Kt/V_{urea} declines by more than 0.2 without any specific cause, VAD accounts for 70% of the causes. However, the measurement of Kt/V_{urea} in every session of HD is very cumbersome in clinical practice. Ionic dialysance, Kt/V_{ID} calculated by on-line monitoring of conductivity, is easy, non-invasive, able to be measured in every session without cost. Although Kt/V_{ID} was not the same value as Kt/V_{urea}, it was highly correlated with Kt/V_{urea}. The aim of this study is to investigate whether Kt/V_{ID}, instead of Kt/V_{urea}, could be used as an index for the detection of VAD by analyzing the change of Kt/V_{ID} before and after intervention.

Methods: We conducted a retrospective study in 23 patients (M:F=13:10, median of age 71 (IQR 63~80) years, HD duration 80 (43~128) months, AVF:AVG=7:16, DM:non-DM=12:11) underwent 29 times of intervention for VAD between Jan 2017 and Apr 2018. We gathered demographic data and available Kt/V_{ID} in our subjects for 14 days just before and just after intervention by reviewing electronic medical records.

Results: The median age of vascular access was 48 (IQR 20~60) months in this study. The main intervention for VAD was percutaneous transluminal angioplasty (96.5%). Thrombectomy (10.3%) or the insertion of peripheral stent (6.9%) was combined, if needed. Although the change of arterial static intra-access pressure ratio (SIAPR) was not significant, venous SIAPR significantly decreased after intervention (0.613 ± 0.194 vs. 0.399 ± 0.159, $p < 0.01$). The intervention for VAD showed the significant increase in Kt/V_{urea} (1.66 ± 0.29 vs. 1.75 ± 0.28, p=0.044) and in Kt/V_{ID} (1.26 ± 0.30 vs. 1.31 ± 0.30, p=0.038).

Conclusions: Considering the significant increase of Kt/V_{ID} before and after intervention, the reduction of Kt/V_{ID} could be used as an index to require the intervention for VAD. In the future, the analysis of prospectively collected Kt/V_{ID} at every HD session is necessary to define the degree of decrement in Kt/V_{ID} to suggest critical VAD.

TH-PO339

A Noninvasive Method for Assessing Arteriovenous Access Recirculation Using the Crit-Line® Monitor in Hemodialysis Patients: An In Silico Analysis

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Background: The arteriovenous vascular access is the Achilles' heel of hemodialysis (HD). Access malfunction, often caused by stenosis or thrombosis, results in reduced access flow, increased access recirculation (AR), and lower Kt/V_{urea}. Measurement of access recirculation is a common method to detect fistula problems; however, existing methods are either invasive, costly, or labor intensive. We propose a novel method to measure AR using the Crit-Line® Monitor (CLM), which is non-invasive and free for existing CLM users.

Methods: The proposed method is based on an abrupt increase in ultrafiltration rate (UFR) for a brief period, which will increase the hemoglobin (Hgb) concentration at the dialyzer outlet. When a fraction of this venous return recirculates in the access, we will observe increased Hgb concentration on the CLM. We developed a mathematical model of an extracorporeal dialysis circuit. We perturb the UFR from 10 mL/min (assumed baseline) to 50 mL/min during HD. In the simulations, we start with a known AR and observe the effect of UFR perturbation on CLM-reported Hgb.

Results: At the baseline UFR of 10 mL/min and assumed AR of 10%, when systemic Hgb concentration is 10 g/dL, the CLM Hgb concentration will be 10.04 g/dL. An increase in UFR to 50 mL/min increases the CLM Hgb concentration to 10.23 g/dL. If AR is 20%, the CLM Hgb concentration will be 10.52 g/dL (Figure 1). Per our model, the time required to observe the change in Hgb concentration is less than 3 min. These changes in Hgb concentration can be discerned by the CLM. Systemic Hgb concentration is assumed constant during the simulation period. Based on the described principle, the mathematical expression in Figure 1 can be used to calculate AR.

Conclusions: With a simple UFR perturbation, AR may be measured in every HD session. Our simulation results warrant validation in a clinical study.

$$AR\,[\%] = \frac{(Hgb_1 - Hgb_2)}{Q_b\left(\frac{Hgb_1}{Q_b - Q_{uf,1}} - \frac{Hgb_2}{Q_b - Q_{uf,2}}\right)} \times 100;$$

$Q_{uf,1}$ – Baseline ultrafiltration rate
$Q_{uf,2}$ – Perturbed ultrafiltration rate
Hgb_1 – Baseline hemoglobin concentration
Hgb_2 – Perturbed hemoglobin concentration
Q_b – Arterial blood flow rate

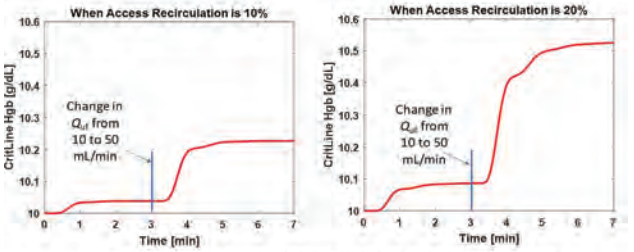

Figure 1: Effect of ultrafiltration perturbation on the hemoglobin concentration.

TH-PO340

Ultrasound-Guided Percutaneous Transluminal Angioplasty for Stenosis and Occlusion in Juxta-Anastomosis Arteriovenous Fistula: A Single Center Research Study

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Background: Arteriovenous fistula (AVF) is the preferred access for hemodialysis. Percutaneous transluminal angioplasty(PTA) has become a choice for AVF stenosis and ultrasound has been used in PTA more and more frequently.

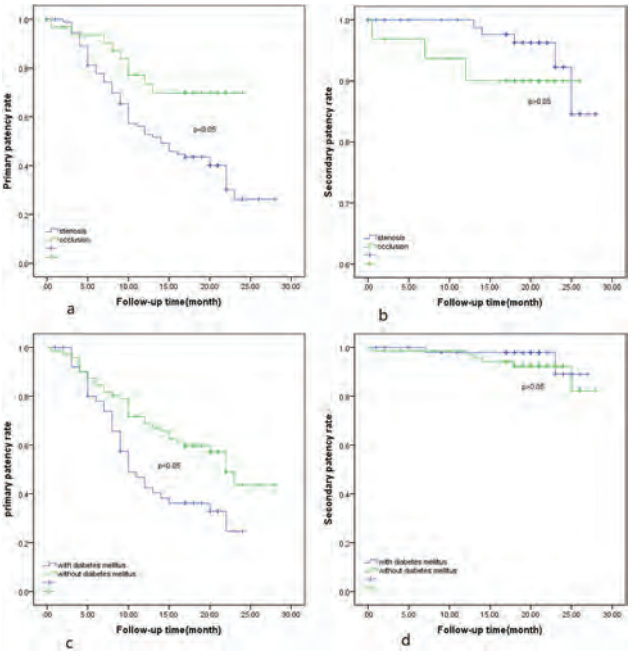
Methods: In 2016,192 patients underwent PTA in our hospital. Angioplasty was performed using a non-compliant high pressure balloon. The process was visualized by duplex scan. Our inclusion criteria were:1)Stenosises or occlusions were located at juxta-anastomosis:the first 5cm of vein distal to the anastomosis;2)Stenosis was confirmed with conditions:*a*.flow rate is<500ml/min in brachial artery and<200ml/min in fistula during dialysis;*b*.diameter of stenosis is<1.7mm.

Results: 129 patients with 76 males were analyzed.104 of them have AVFs on left arm, and there is one Ulnar-basilic AVF while others are Radial-cephalic AVF. The comparasion of variables are presented in the table. We use Kaplan-meier curve to show the primary and secondary patency rates of patients with stenosis and occlusion respectively. The primary patency rates are better in occlusion(P<0.05), while secondary patency rates have no difference. The primary patency rates are better in patients without diabetes mellitus(P<0.05)while the secondary patency rates had no difference.

Conclusions: For the juxta-anastomosis's stenosis or occlusion, PTA can be used to obtain satisfactory results.

variables comparison

	Before the procedure	After the procedure	p
Diameter of brachial artery(mm)	5.28±0.73	6.11±0.72	0.00
Flow rate in brachial artery(ml/min)	334.59±187.24	1026.19±268.46	0.00
Diameter of feeding artery(mm)	3.47±0.83	4.00±0.88	0.00
Diameter of stenosis(mm)	1.08±0.32	3.54±0.71	0.00
PSV in stenosis(cm/s)	417.96±168.73	271.46±100.42	0.00
Diameter of draining vein(mm)	3.91±0.93	4.32±0.87	0.00
Flow speed in draining vein(cm/s)	57.17±48.85	150.71±58.98	0.00



KM curve

TH-PO341

Comparison of Peripheral Cutting Balloon vs. Conventional Balloon Angioplasty for Hemodialysis Vascular Access Stenosis: Prospective Randomized Controlled Trial

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Background: Adequate vascular access is essential for undergoing hemodialysis treatment. Even though clinical success rate of PTA is high, the patency of conventional PTA is relatively low. The cutting balloon which has small blades to create sharp incisions into neointimal hyperplasia is designed to minimize vessel damage. Although few randomized trials have evaluated cutting balloon angioplasty for vascular access, larger study are needed.

Methods: This prospective, randomized single-center clinical trial included patients who had a hemodynamically significant vascular access stenosis within 6 months after the previous procedure. The study was designed to evaluate the efficacy and safety of cutting balloon (cutting balloon group) as compared with conventional balloon angioplasty (conventional balloon group) for the short-time patency cases in the previous treatment. The Kaplan-Meier method was performed to assess the primary and secondary patency of treatment lesion and whole access circuit. A log-rank test was used to evaluate the differences of patency between each group.

Results: One hundred fifty-seven patients provided informed consent and were randomly assigned to undergo cutting balloon angioplasty or conventional balloon angioplasty from December 2012 to November 2017. The clinical success rate was 100% in the both groups. The anatomical success rates were 64.0% in cutting balloon group and 53.9% in conventional balloon group. The primary patency of target lesion was significantly better in the cutting balloon group (28.3%) than in the conventional balloon group (14.1%) at 6 months (P=0.009). The mean pain scale measured using Visual Analogue Scale during the cutting balloon dilation (38.8±25.1) was much lower than the conventional balloon (57.5±28.5) (P<0.001). The average percent stenosis decreased significantly after PTA using the cutting balloon (Δ-49.1%) compared with the conventional balloon (Δ-40.9%) (P=0.0007). Access flow measured by the duplex doppler ultrasonography improved after PTA in both groups. Change in access flow in the cutting balloon group (Δ+308±221) was greater than conventional balloon group (Δ+240±152) (P=0.027).

Conclusions: Our data suggest that cutting balloon angioplasty is effective for patients whose vascular access were short-lived.

TH-PO342

Drug Eluting Balloon Angioplasty in Dialysis Access

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Background: Recurrent stenosis is responsible for less than 50 percent patency at 6 months. Neo-intimal hyperplasia (NIH) is driven by hemodynamic factors and barotrauma from angioplasty. Paclitaxel has been shown to reduce NIH. In a RCT, paclitaxel-coated

balloon (Lutonix®) angioplasty compared to conventional angioplasty in AVFs showed better target lesion primary patency (TLPP) at 24 months. We present our data using Lutonix® in the treatment of recurrent stenosis in dialysis accesses.

Methods: This is a retrospective review of all angioplasties from June 1, 2017 to December 31, 2018 done at our hospital. A total of ten patients who underwent Lutnonix® angioplasties after successful conventional balloon angioplasties (< 30% residual stenosis) were included in the study. The target lesion angioplasty free periods before and following Lutnonix® angioplasty were reviewed. Re-interventions requiring angioplasty were clinically driven.

Results: Technical success of target lesion angioplasty was 100% for all angioplasties. The Lutonix® application following conventional angioplasty had a twice longer angioplasty free period compared to conventional angioplasty alone (mean of 320 versus 166 days, respectively) which represents a difference of 154 days, p = 0.04, 95% CI (11, 297). The 6-month TLPP (the index lesion) following Lutonix® angioplasty was 80%. No complications were reported with its use.

Conclusions: Lutonix® application following successful conventional angioplasty appears effective in delaying dialysis access clinically-driven re-stenosis requiring angioplasty. Further longer term studies are required to confirm the effectiveness of the Lutonix® angioplasty and see it is a suitable alternative for stent placement.

TH-PO343

No Increase in All-Cause Mortality from Paclitaxel Coated Balloons (DCB) Used in an Arteriovenous Circuit in Dialysis Patients

Prabir Roy-Chaudhury,[1] Theodore F. Saad,[2] Scott O. Trerotola.[3] on behalf of the Lutonix AV IDE investigators and the Medical Advisory Board *[1]University of North Carolina, Chapel Hill, NC; [2]Nephrology Associates, PA, Newark, DE; [3]University of Pennsylvania, Philadelphia, PA.*

Background: Recent data have suggested an increased mortality in patients treated with paclitaxel balloons (DCB) in the femoropopliteal circulation. In order to assess this issue, in the setting of hemodialysis patients, a post-hoc analysis was performed to describe short (6 month), medium (12 month) and long term (24 month) mortality, in a randomized study on the use of DCB in failing arteriovenous fistulae (AVF).

Methods: 285 patients were enrolled at 23 centers. Patients in both arms received vessel pre-dilatation followed by treatment with either a DCB or a control balloon of similar design to the DCB but without drug (PTA group). Endpoints included 3, 6, 9, 12, 18 and 24 month target lesion primary patency (TLPP), number of interventions required to maintain target lesion patency, and safety endpoints. A special focus of this presentation is a comparison of survival at 6, 12 and 24 months in the two arms of this study.

Results: The DCB and Control (PTA) groups were evenly matched with regard to age, sex, hypertension and smoking. 6 month post intervention primary patency was 71.4% for DCB and 63% in the control (p=NS). There were, however 31.3% fewer interventions at 6 months at the target lesion for the DCB group. A post-hoc analysis documented that there were no significant differences in all cause mortality (see Table) between the DCB and control (PTA) groups at 6 months (6.4% vs 4.2% mortality respectively), 12 months (12.8% vs 9% mortality) and 24 months (23.4% vs 18.1%). p = NS for all analyses.

Conclusions: These data (from the first large prospective randomized trial on the use of DCB in failing AVF) document that the use of DCB in the arteriovenous circuit (failing AVF) does not result in a statistically significant increase in mortality at the short (6 months), medium (1 year) and longer term (2 years) endpoints.

Funding: Commercial Support - BD

Summary Time Point	DCB Subject (N=141)	PTA Subject (N=144)	P value
Subjects Discontinuing from Treatment to Day 180, n(%)			
Evaluable subjects	137 (97.2%)	144 (100.0%)	
Died by Day 180	9 (6.4%)	6 (4.2%)	n/s
Subjects Discontinuing from Treatment to Day 365, n(%)			
Evaluable subjects	135 (95.7%)	142 (98.6%)	
Died by Day 365	18 (12.8%)	13 (9.0%)	n/s
2 Year Subject Disposition, n(%)	141 (100.0%)	144 (100.0%)	
Completed the Study	96 (68.09%)	111 (77.08%)	
Died by 2 years	33 (23.4%)	26 (18.1%)	n/s

TH-PO344

Abstract Withdrawn

TH-PO345

Post-Dialysis Bleeding from AV Fistula (AVF) or Graft (AVG)

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Background: AVF is the the preferred access for hemodialysis, and AVG is considered the second best choice. Bleeding from the puncture site after withdrawal of needles is a frequent event in the dialysis unit. The duration of "normal" bleeding time is not well defined. Usually bleeding lasts for up to 10 min, but if this bleeding persists for more than 30 min is considered as prolonged. The purpose of this study was to understand what is considered a normal bleeding time among patients and staff.

Methods: This was a cross-sectional study using a convenient cohort. In this setup, we conducted an anonymous survey in 4 dialysis units (3 hospital based and 1 community located), asking patients, nurses and physicians about issues related with bleeding after needles are removed: the average bleeding time, the difference time between AVF/AVG, the effect of Heparin use on postdialysis hemorrhage, the use of device for bleeding control and the influence of high venous pressure on bleeding.

Results: A total of 92 persons (patients 50%, nurses 38%, physicians 12%) answered the survey. The average bleeding time after a puncture of AVF recorded by patients was 11±7 min and 14±6 with an AVG. This bleeding time was not significantly different from the time defined by nurses (9±7 and 14±4 min) or physicians (8.5±2 and 12±5min). In terms of differences between AVF/AVG, 32% of patients, 26% of nurses and 10% of physicians estimated that there was no difference. Around 30% of the interviewed stated that bleeding may be related to the heparin administration. Use of an hemostatic device was registered by patients in 37%, nurses in 77% and physicians in 90%. Fifty percent of patients thought that bleeding may be related to high venous pressure, as opposed to 88% of the nurses and 100% of the physicians.

Conclusions: Bleeding from the puncture site concern patients, nurses and physicians. Differences of understanding and expectations were appreciated between these groups, showing how much more education must be provided in this field.

TH-PO346

An Endovascular Treatment System for Occluded Native Arteriovenous Fistula

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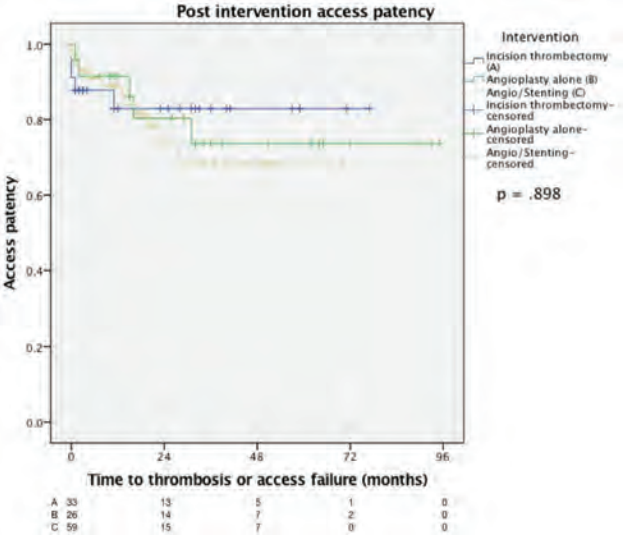
Background: Westmead Hospital looks after a high number of patients on haemodialysis and because of the superior outcomes achieved with our endovascular techniques in occluded fistulas, from 2005 onwards, all patients who presented with an occluded native arteriovenous fistula (nAVF) to the Western Renal Area institution, were referred to our unit. We have also developed minimally invasive techniques to mature and repair dysfunctional nAVF including techniques to reestablish the flow through a thrombosed nAVF. The aim of this study is to present the techniques and results of the Endovascular Treatment System that we have developed for managing the occluded nAVF.

Methods: The current study is a retrospective chart review on all patients who presented with an occluded nAVF and underwent attempted resuscitation between the 1st January 2005 to 31st of December 2014.

Results: 130 patients were included in the study. Post intervention primary access patency was 83.8% at 6 months, 78.7% at 12 months, 64.6% at 2 years and 59.6% at 3 years. Post intervention assisted access patency in fistulas-in-use was 86.5% at 6 months, 81% at 12 months, 66.8% at 2 years and 61.2% at 3 years. Post intervention secondary patency for all cases was 84.7% at 6 months, 80.2% at 12 months, 66.1% at 2 years and 62% at 3 years. Post intervention secondary patency in fistula-in-use was 91.1% at 6 months, 90% at 12 months, 85% at 2 years and 74.6% at 3 years. Neither access survival nor patency differed significantly when incisional thrombectomy was compared to angioplasty with or without stenting with access survival of 91.2% and 92.5% at 12 months and access patency of 82.9% and 89.7% at 12 months (p = .834 and p =.898 respectively).

Conclusions: In autologous arteriovenous thrombosed fistulae the use of purely endovascular techniques to revive the access is a viable and safe technique to employ in most cases.



TH-PO347

Primary Patency of Single-Needle Puncture for Arteriovenous Fistula Stenosis Resistant to High-Pressure Balloon

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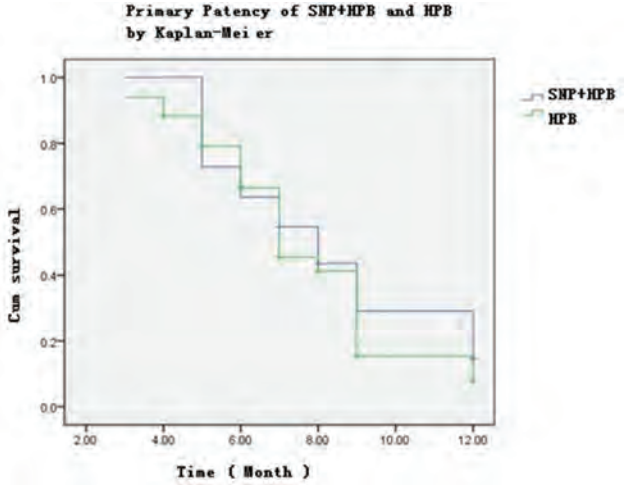
Background: To evaluate primary patency, safety and Doppler ultrasound data of single-needle puncture (SNP) treatment for AVF stenosis resistant to high-pressure balloon (HPB).

Methods: A retrospective study were conducted from June 2017 to August 2018 that included 83 patients who received PTA for AVF stenosis. Patients were allocated to SNP if AVF stenosis were resistant to HPB. Data collection included AVF stenosis location, stenosis length, percent stenosis, resident inner diameter, balloon pressure,intima thickness, mean access blood flow before and after intervention, complication and primary patency determined by Kaplan-Meier analysis.

Results: I type AVF stenosis (55.4%) were the most in 83 enrolled patients. Sixty-eight patients(81.9%) got technical success with HPB. The remaining 15 patients were allocated to SNP. Ten of 15 patients(88.0%)resistant to HPB got technical success with SNP. There were no significant difference in AVF stenosis location, stenosis length, residual inner diameter and percent stenosis between SNP and HPB. Balloon inflation pressure and inflation times during operation in SNP group (21.9±2.1 atm and 4.4±2.1 times) were higher compared with HPB (15.6±4.5 atm and 1.9±0.6 times). The mean increases in access blood flow after PTA were 578.9±150.8ml/min with SNP and 487.2±100.5ml/min with HPB (p=0.006). Primary patency were similar with SNP and HPB (63.6% v.s.66.5% in the 6th month and 14.5% v.s.7.7% in the 12th month, p=0.65). Intima were thicker in SNP group than HPB group before PTA(1.2±0.3 vs 1.0±0.3,p=0.029), but were similar 6 months after PTA(1.5±0.3 vs 1.3±0.4,p=0.24). No uncontrolled complication endangered AVF occurred.

Conclusions: SNP is a safe option for AVF stenosis resistant to HPB with satisfied primary patency and no more financial burden.

Funding: Government Support - Non-U.S.



TH-PO348

Risk Factor Profile for Thrombophilia in Patients with ESRD on Maintenance Hemodialysis with Recurrent Arteriovenous Fistula Clotting

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Background: Vascular access is critically important for hemodialysis patients, being both a lifeline and an Achille's heel. Failure of arteriovenous fistula (AVF) has a substantial impact on the patient in terms of economic burden, morbidity and all-cause mortality. Thrombosis is the leading cause of AVF failure accounting for 80-85% of AV access loss. Since limited number of well-established risk factors for access thrombosis are known, in the present study we evaluated the relation between hereditary and acquired thrombotic factors contributing to recurrent AVF thrombosis. We also studied the association between recurrent AVF thrombosis with thrombotic factors in comparison with well-functioning fistulas and its association with ABO blood group, age, gender and diabetes.

Methods: This is a cross-sectional observational study with a total of 100 hemodialysis patients. 50 patients with recurrent AVF failure secondary to access thrombosis served as cases and 50 patients with well working AVFs as controls. Parameters studied are hereditary thrombotic factors- Factor V leiden (G1691A), Factor XIII (val34leu), Prothrombin (G20210A), MTHFR (C677T) by DNR isolation and PCR products and acquired thrombotic factors - Lipoprotein (a), Fibrinogen using immunoturbidimetry, Homocysteine by enzyme recyclic and Anticardiolipin antibody(IgG and IgM) by ELISA method.

Results: In our study hereditary factors were not significantly different between the two groups but acquired factors Lipoprotein (a), Fibrinogen, Homocysteine, Anticardiolipin Antibody IgG and IgM were found to be elevated in patient with recurrent AVF thrombosis when compared to controls (P 0.001). There was significant association between recurrent vascular access thrombosis and non O blood groups (P 0.047). Anemia (Hb < 10 gm/dl) was observed in patients with recurrent vascular access thrombosis when compared to well working fistulas. We did not find a significant association between age, gender and presence of diabetes contributing to recurrent vascular access thrombosis (P 0.826).

Conclusions: Acquired thrombotic factors contribute to recurrent AVF clotting in patients on maintenance hemodialysis. Recurrent AVF thrombosis is more common in non-O blood group and in patients with anemia.

TH-PO349

Coagulation Differences in Dialysis Vascular Access Failure

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Background: Vascular access failure in hemodialysis patients is often caused by access stenosis or thrombosis. Neointimal proliferation and abnormal coagulation play important pathogenetic roles. Currently, no biomarker is available for prediction of access failure leading to stenosis and thrombosis. Sonorehometry is a novel tool assessing blood clot elasticity. We hypothesize blood clot elasticity can be a valuable tool to diagnose vascular access complications in hemodialysis.

Methods: In a cross-sectional study, conventional markers of coagulation including Fibrinogen, platelet count, PT/INR, and aPTT were measured in 21 patients on chronic hemodialysis (for over 3 months). 6 patients had recurrent vascular access failure caused by concurrent thrombosis and stenosis, 9 patients had recurrent access stenosis without thrombosis and 6 patients had functioning access without complications. For each patient, QPlus Cartridge was run on Quantra analyzer to measure coagulation parameters, including Clot Stiffness (CS). Kruskal – Wallis Test was used for in group comparisons and Pearson / Spearman analysis for correlation of fibrinogen level, platelets count and CS.

Results: There was no statistical differences in stiffness parameters in the 3 subpopulations. However, the patients with recurrent vascular access complications caused by Thrombosis/Stenosis had high CS values (figure 1). Numerically higher fibrinogen values were found in patients with vascular access complications.

Conclusions: Hemodialysis patients with recurrent vascular access complications due to thrombosis/stenosis might have higher clot stiffness and signs for a hypercoagulable state explained by the renal failure. A larger cohort needs to be examined to confirm findings and demonstrate that clot stiffness can be utilized to monitor dialysis patients for vascular access complications.

TH-PO350

Antiphospholipid Antibodies Significance in Hemodialysis Patients: A Single-Center Cohort Study

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Background: Antiphospholipid syndrome (APS) is an autoimmune disease caracterized by arterio-venous thrombotic manifestations and persistently positive antiphospholipid antibodies (APAb) as reported in the revised Sapporo classification criteria. The prevalence of APAb in haemodialysed patients is higher compared to the general population. Their role in the occurrence of vascular access thrombosis remains controversial. This study aims to determine the prevalence of APAb and APS and to evaluate their association with vascular access thrombosis and quality of extrarenal purification in haemodialysis patients.

Methods: This is a singler-centre crosse sectional study including 145 haemodialysis patients with available demographic, clinical, biological and immunological parameters (APAb) as well as haemodialysis characteristics. Antiphospholipid biology was defined as persistently positive antibodies (at least 12 weeks apart) without history of clinical manifestation.

Results: The prevalence of antiphospholipid biology (APB) and APS were respectively 17.7% (12/ 117) and 10.3% (6/117). Those patients were younger. Antiphospholipid biology is significantly associated with arterial hypertension and diabetes while the antiphospholipid syndrome with dyslipidaemia. Antiphospholipid biology is a significant risk factor for lower Kt/V independently of type of membrane or haemodialysis modality (conventional haemodialysis versus hemodiafiltration). The APS is associated with vascular access thrombosis. Interestingly, patients with one positive APAb at the screening that were controlled negative during the follow-up were still expose to an increased risk of arterial thrombosis (however this did not reach statistical significance, p = 0,054). These patients were not at risk for vascular access thrombosis.

Conclusions: Despite a small sample size, we report that antiphospholipid syndrome increases the risk of vascular access thrombosis and is an independent risk factor of a lower Kt/V. Our observation underlines the importance of antiphospholipid antiboidies screening in hemodialysis patients and needsmerits to be validated by prospective studies.

TH-PO351

Quantified Vascular Calcification of Vascular Access: Correlation with Coronary Artery Calcium Score and Survival Analysis of Access and Cardiovascular Outcome

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Background: Vascular calcification (VC) is the major contributor to mortality and morbidity in end-stage renal disease (ESRD) patients. We investigated whether there is a correlation between Coronary artery calcium score (CACS) and quantified vascular calcification score (VCS) of the arm including vascular access and whether VC increases the incidence of intervention and major adverse cardiac and cerebrovascular events.

Methods: ECG gated, non-contrast arm CT scan including vascular access and the coronary vessel was taken. Later, CACS and VCS were measured by using Aquarius Ver. 4.4.12 simulating the Agatston Method. We examined if the subjects with CACS>400 was higher in the group of VC>500, a cutoff of the highest 40% of VC. Survival analysis according to VCS groups was also performed.

Results: In the total 77 patients, there were 44 males (57.1%), and the mean age was 63.9 years. The median vintage of hemodialysis was 49.4 [31.5, 99.2] months. When dividing the patients into two groups based on VCS 500 (lower VCS vs. higher VCS), there were no differences between the 2 groups in sex, age, ESRD etiology, and type of vascular access. However, the HD vintage was significantly older in higher VC group. Median VC and CACS were higher in the higher VC group (VC, 144[75,264] vs. 1058 [713, 3355]; CACS, 21 [0, 171] vs. 552 [93, 2430], P<0.001), and the ratio of the subjects with CACS>400 was higher (17.4% vs. 61.3% P<0.001). Since interventions can occur multiple times in one patient and each intervention is not independent, the Prentice, Williams and Peterson Total Time survival analysis model was used. Intervention Hazard ratio (HR) of the higher VCS group increased by 3.2 times. Additionally, longer duration of hemodialysis and higher magnesium (>2.5 mg/dL) had the lower HR of intervention. Moreover, in the higher VCS group, the HR of MACCE increased 2.3 times.

Conclusions: We quantified the VC and found for the first time that it is associated with CACS. Considering that CACS is closely related to the cardiovascular outcome, VC may also be suggested as a new biomarker to predict the outcome of ESRD patients. Higher vascular calcification increased the risk of access intervention and MACCE.

Funding: Other NIH Support - NRF-2016R1D1A1B03934173

TH-PO352

Severe but Not Mild Hand Ischemia Is Associated with Poorer Survival in Hemodialysis Patients

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Background: Some hemodialysis (HD) patients develop hemodialysis access-induced distal ischemia (HAIDI) of the hand that is caused by loss of blood pressure along the heart-hand axis. Anecdotal data suggest that the presence of hand ischemia is associated with poorer patient survival. We hypothesized that patients with severe HAIDI have a worse survival compared to patients with mild or no HAIDI.

Methods: Two patient groups were studied between January 2006 and December 2018 in one Dutch hospital. A control group consisted of patients on stable HD without symptoms or signs of hand ischemia. The experimental group (HAIDI) reported pain and coldness in the dialysis hand in the presence of low digital brachial indices DBIs (normal >0.8, now <0.6). HAIDI patients were graded as mild (Grade I-IIa) or severe (IIb-IV) as suggested by a 2016 consensus meeting. Access flows (Qa) were obtained and potential factors associated with 4-year overall survival were calculated using standard statistical testing.

Results: Age and time on HD tended to be higher in controls (n=45, 24 males; age 73yrs ±12, HD 34months ±26) compared to the HAIDI group (n=49, 26 males; age 68yrs ±16, HD 23months ±28; 0.05<p<0.09). Controls displayed lower Qa and higher DBI (Qa: 1.2L/min ±0.1 vs 1.8L/min ±0.2; DBI 0.80 ±0.2 vs 0.34 ±0.03; both p≤0.001). Interestingly, both Qa and DBI were higher in mild HAIDI (n=26) compared to severe HAIDI (n=23; Qa: 2.4L/min ±0.2 vs 1.1L/min ±0.1; DBI 0.42 ±0.02 vs 0.26 ±0.05; both p=0.005). A total of 43 patients (47%) died during the 4-year follow-up. Overall 2 and 4-year survival were similar in controls and grade I-IIa HAIDI (2-year 79% ±5; 4-year 55% ±6) but lower in grade IIb-IV HAIDI (2-year 58% ±10; 4-year 34% ±10; p<0.028). Following correction for age (HR 1.04 [1.01 - 1.07]), presence of diabetes (HR 2.11 [1.13 - 3.04]) and cardiovascular disease (HR 2.74 [1.48 - 5.09]), low DBI displayed some predictive value for 4-year mortality (HR .99 [.98 - .99], p=0.05)

Conclusions: Severe hand ischemia is associated with poorer survival in HD-patients. Moreover, lower DBI-values have some predictive value for overall mortality, even when correcting for known risk factors.

TH-PO353

Excessively High Fistula Flows in Hemodialysis Patients Possibly Result in an Irreversible Loss of Arterial Remodelling Capacity

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Background: Longstanding high flows in hemodialysis access (high flow access, HFA, >2L/min) likely harm hemodialysis patients due to cardiac overload. Flow reduction is advised, especially if hemodialysis access-induced distal ischemia (HAIDI) is also present. Revision using distal inflow (RUDI) effectively reduces flow but high flows often recur. We hypothesized that RUDI would result in shrinking of the brachial artery and dilatation of both the radial artery and greater saphenous (GSV) interponate.

Methods: HFA-patients with a brachial-artery based arteriovenous fistula with high flows (>2L/min) who underwent RUDI between 2011 and 2016 in two Dutch hospitals underwent serial Duplex sonography prior to and 2 and 12 months following RUDI. Volume flow (L/min), diameter (mm) and peak systolic velocity (PSV, cm/s) of the brachial artery, radial artery and GSV were measured. HFA-patients were grouped according to concomitant presence of hand ischemia (HFA-HAIDI), or absence (HFA).

Results: Fifteen patients (54 yr ±16, 10 males; HFA-HAIDI, n=6; HFA, n=9) with a brachial artery HFA undergoing RUDI were studied. Despite an initial decrease in brachial arterial flow followed by a slight increase (preoperative 2.7L/min ±0.3; two months 1.2L/min ±0.2; twelve months 1.5L/min ±0.2; p<.001), brachial artery diameters remained unchanged (7.4mm ±0.5). Proximal radial artery diameters doubled (overall 2.6mm ±.2 to 5.4mm ±1.0, p<.001), albeit less prominent in the HFA-HAIDI-group (+80%) than in the HFA-group (+130%, p=.019). Neither dilatation nor aneurysmatic degeneration were found in the GSV-interponate.

Conclusions: Revision using distal inflow (RUDI) for high flow access (HFA) reduction does not reverse brachial artery dilatation suggesting irreversible structural arterial wall damage possibly contributing to recurrent high flow. Radial artery remodelling is attenuated in HFA-patients previously reporting concurrent hand ischemia, diminishing the likelihood of high flow recurrence in this subgroup. The greater saphenous vein does not dilate within one year following RUDI.

TH-PO354

An Online Ultrafiltration Rate Calculator to Empower Home HD Patients

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Background: Despite a 3 decade solute clearance focus, hemodialysis (HD) outcomes correlate more closely with volume factors, especially the rate of change of blood volume. A high ultrafiltration rate (UFR) induces hypotension, hypoperfusion, and functional organ stunning.(1) Thus, a low sessional UFR is critical for circulatory stability. As salt and fluid restriction often manifestly fail to limit interdialytic weight gain**,** HD sessional duration becomes the governing variable to assure a low, safe UFR. While the ideal safe mean maximum per treatment UFR remains in debate, clinical risk increases as the UFR exceeds 6-8 ml/kg/hr, (2) although US guidelines currently recommend a UFR <13ml/kg/hr. Since home HD (HHD) patients can self-adjust their treatment time to ensure a low UFR, we devised an on-line UFR calculator to display the impact of UFR and encourage patients to safely use this flexibility.

Methods: Using the interdialytic weight gain (IDWG), pre-dialysis weight (pre-DW), and intended upcoming treatment time (t), the mean treatment UFR (ml/kg/hr) can be calculated by UFR = (IDWG ÷ pre-DW) ÷ t. This (1) informs impending treatment UFR safety and (2) allows treatment time adjustment to the desired UFR maximum. On-line since 2/2017, an open-access calculator https://www.homedialysis.org/ufr-calculator on the Home Dialysis Central website has facilitated UFR (ml/kg/hr) and 't' flexibility. We have interrogated the site analytics for patterns of use.

Results: Key data (25/2/2016 - 5/5/2019) are shown (attached diagram: Analytics Overview). Rising through 2017–2018, regular use has stabilised in 2019 at 2000–2250 pageviews/week and 0.36 minutes/view. User feedback is uniformly positive. Many HHD patients now routinely use the calculator to adjust their upcoming sessional duration.

Conclusions: HHD patients and professionals can now be empowered to regulate the UFR by durational adjustments based on the UFR calculator. The calculator encourages and empowers flexibility in treatment time and a safer, gentler rate of volume change. McIntye et al: CJASN 2016; 11(4):549-551 Charra et al: Blood Purif 2017; 44:89-97

Analytics Overview

TH-PO355

Vancomycin and Teicoplanin Clearance During an In Vitro Model of Continuous Venovenous Hemofiltration Using Different Hemofilters

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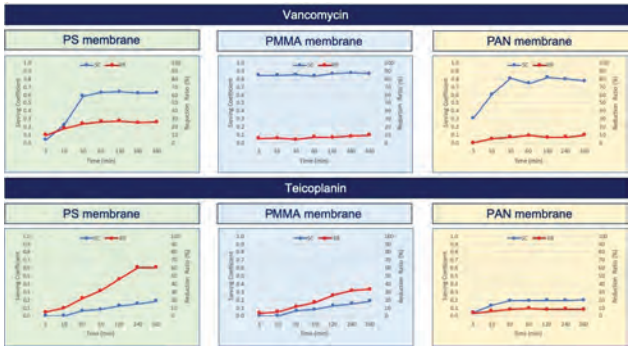
Background: Continuous renal replacement therapies (CRRT) can affect pharmacokinetic behavior of antibiotics. The factors that need to be considered are related to the drug characteristics, CRRT features and patient status. Particularly, the type of membrane can play a major role in drug removal. The aim of this study was to evaluate in an *in vitro* system the convective and adsorptive drug clearance of vancomycin (VAN) and teicoplanin (TEC) during continuous venovenous hemofiltration (CVVH) with polysulfone (PS), polymethylmethacrylate (PMMA) and polyacrylonitrile (PAN) filters.

Methods: VAN and TEC clearance was assessed *in vitro* in blood from healthy donors. Closed circuit simulating CVVH was performed using PS, PMMA and PAN mini-filters at 10ml/min ultrafiltrate and 50 ml/min blood flow rates. The duration of the experiment was of 360 min. Samples were collected at 5, 10, 30, 60, 120, 240 and 360 minutes from in-flow, out-flow and ultrafiltrate line; antibiotic concentrations were measured with biochemistry analyzer. Convective clearance was evaluated in terms of sieving coefficient (SC), and adsorptive clearance was calculated using mass balance analysis.

Results: VAN and TEC blood SC are shown in Fig 1, as well as the reduction ratio of plasmatic concentrations for each membrane. During CVVH using PS, PMMA and PAN membranes, the estimated total adsorbed mass per surface area for VAN was 36.52mg/m2, 11.33mg/m2 and 6.97mg/m2, and for TEC was 98.17mg/m2, 51.33mg/m2 and 9.77 mg/m2, respectively.

Conclusions: Our findings show that during CRRT both convective and adsorptive mechanisms have a role in antibiotics clearance. When dosing patients on CRRT, physicians should take into account not only CRRT flow rate settings and modality but also drug-membrane interaction.



TH-PO356

Application of Individualized Physiologically Based Pharmacokinetic Modeling of Rate Data (iPBPK-R) to Estimate the Effect of Hemodialysis on Nonrenal Clearance Pathways

Yoko Franchetti, Thomas D. Nolin. *University of Pittsburgh, Pittsburgh, PA.*

Background: We previously developed an individualized physiologically-based pharmacokinetic modeling approach using rate data (iPBPK-R) to differentiate contributions of nonrenal metabolic and transport pathways to the disposition of the non-specific probe drug erythromycin. The objectives of the current work were (1) to differentially estimate contributions of nonrenal clearance pathways to erythromycin in patients with ESRD, (2) to investigate the effect of hemodialysis (HD) on these pathways, and (3) to explore the relationship between parameter estimates and uremic toxin concentrations.

Methods: Twelve patients with ESRD received ^{14}C-erythromycin (0.074 mmol IV) pre- and again post-HD and 11 breath samples were collected over 2 hours after each dose. iPBPK-R was applied to measured $^{14}CO_2$ production rates. Eight PBPK parameters were co-optimized between pre- and post-HD periods within patients while activity of CYP3A4 clearance was independently estimated. Inhibitory coefficients of uptake transporters (i.e., OATP) were also estimated. Nonrenal clearance parameter estimates were compared pre- vs post-HD and by gender. As exploratory analysis, the parameter estimates were correlated with uremic solutes and used in hierarchical cluster analysis (HCA). Optimizations were run on the Bridges supercomputer (PSC via NSF XSEDE).

Results: Seven compartments with OATP uptake and CYP3A4 clearance were modeled. Mean relative increase in CYP3A4 clearance pre- vs post-HD within individual patients was 12% which was not statistically significant (p=0.06). However, males had 16% and 19.3% lower median CYP3A4 activity than females pre- (p=0.001) and post-HD (p=0.005), respectively. The estimated inhibition coefficient of uptake transport did not differ between pre- and post-HD (p=0.129). A sub-cluster of two patients with more improved CYP3A4 activity at post-HD (9.4% increase) was identified compared to the other patients (0.59% increase). β-2 microglobulin was inversely correlated with CYP3A4 activity in males pre- (Spearman r=-0.79, p=0.04) but not post-HD.

Conclusions: iPBPK-R is a novel tool to estimate nonrenal clearance parameters within individuals and to explore the effect of HD and uremic toxins on drug disposition in patients with ESRD. Further work is required to validate the i-PBPK-R based results.

Funding: Other NIH Support - National Institute of General Medical Sciences, Other U.S. Government Support, Government Support - Non-U.S.

TH-PO357

Characterization of Metoprolol and Metabolite Concentrations Pre and Post Hemodialysis: Potential Implications for Intradialytic Hypotension and Post-Dialysis Fatigue

Michael C. Dean, Gabrielle M. Costello, Ernane Souza, Jeremy A. Felton, Balazs Szamosfalvi, Manjunath P. Pai, Amy B. Pai. *University of Michigan, Ann Arbor, MI.*

Background: Previous pharmacokinetic (PK) studies of metoprolol succinate (MPL) were conducted before high-flux HD and did not evaluate post-HD rebound or parent:metabolite (P:M) ratios. Intercompartmental redistribution of antihypertensives may contribute to intradialytic hypotension and post-dialysis fatigue. The aim of this study was to characterize the PK of MPL and α-hydroxymetoprolol during and post-HD.

Methods: Eligible patients were >18 years, on HD 3 days a week for 3.5-5 hours (h), daily dose of MPL 25-200mg, and hemoglobin >9.5 g/dL. Arterio-venous (AV) paired samples were collected prior to HD initiation, 0.5h, 2h, and end of treatment. Post-HD sampling occurred at 0.5, 2, and 4h. Serum samples were assayed by liquid chromatography-tandem mass spectrometry and a non-parametric population PK model was used (PMetrics™ LAPK). T0 samples were analyzed for CYP2D6*4.

Results: Eight patients (5 male, 3 female; Age 59±17 years) were enrolled. The MPL PK data were best fit with a linear, 2-compartment model with absorption rate and fraction absorbed fixed to known values from literature. The model predicted MPL clearance (CL) was relatively unchanged on- and post-HD with a mean (CV) of 46.5 (17.4%) and 41.9 (54.4%) L/h, respectively. AV-dialytic CL was minimal (13.1±8.8% of total CL). The mean volume of distribution (Vd) in central compartment (Vc) decreased: 119.7 (103.2%) L on-HD to 18.4 (128.7%) L post-HD. Mean peripheral compartment Vd (Vp) increased: 17.7 (252.2%) L on-HD to 160.0 (0.0%) L post-HD. Vd changes resulted in significant MPL flux from Vp to Vc on-HD driven by redistribution and from Vc to Vp post-HD due to hemoconcentration. Higher MPL concentrations were seen at 2h on-HD and 4h post-HD. The P:M ratios were variable suggesting phenotypic differences in CYP2D6 activity. Three CYP2D6*4 heterozygotes were identified, but only one showed decreased metabolism based on P:M ratio.

Conclusions: Large changes in Vd due to ultrafiltration drive fluctuating MPL concentrations during and after HD, resulting in highly variable MPL serum concentrations. This may contribute to intradialytic hypotension and/or post-dialysis fatigue. Dialytic CL does not appear to contribute significantly to varying MPL concentration profiles.

TH-PO358

Effect of CKD on the Ex Vivo Metabolism of Δ9-THC into 11-OH-Δ9-THC

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Background: Over 40% of chronic kidney disease (CKD) patients experience adverse drug reactions. Cytochrome P450s (CYPs) are major contributors to drug disposition, as they mediate drug metabolism to help facilitate clearance. Rodent models of CKD have shown reduced CYP expression and drug metabolic activity. The use of cannabis for both medicinal and recreational purposes has increased recently and cannabis has been legalized in several regions of the world. While CKD is known to impact the disposition of many drugs, there have been no studies investigating the impact of CKD on the hepatic metabolism of cannabis. This study utilized a rat model of CKD to investigate the impact of CKD on the metabolism of the psychoactive component of cannabis (Δ9-THC) to its primary metabolite 11-OH-Δ-THC. It was hypothesized that CKD would decrease Δ9-THC metabolism.

Methods: CKD was induced in male Wistar rats (n=13) by feeding chow supplemented with 0.5% adenine (n=7) for a total of 42 days while controls (n=6) received standard chow. Blood and organs were collected, and plasma creatinine concentrations were measured utilizing ultraperformance liquid chromatography coupled to mass spectrometry (UPLC-MS). Hepatic microsomal fractions, isolated by differential centrifugation, were incubated with THC (10mM and 20 mM) for 4 minutes, and 11-OH-Δ9-THC concentrations were measured by UPLC-MS, and the metabolite formation rate (pmol/min/mg protein) was calculated.

Results: Plasma creatinine was significantly elevated eleven-fold in adenine-fed rats compared to controls ($p < 0.05$). Metabolite formation rate of 11-OH-Δ9-THC (pmol/min/mg protein) was 30% and 45% higher in CKD samples, when microsomal fractions were incubated with 10 mM and 20 mM, respectively ($p < 0.01$; $p < 0.05$).

Conclusions: Contrary to our hypothesis, this data suggests that CKD results in increased metabolism of Δ9-THC into 11-OH-Δ9-THC. Further analysis, performing Michalis-Menten kinetics will better elucidate the effect of CKD on THC metabolism.

Funding: Government Support - Non-U.S.

TH-PO359

Association Between CYP3A5 SNP rs776746 and Tacrolimus Dose: Single Transplant Center Experience in Southern Chile

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Background: Tacrolimus (TAC) is a common immunosuppresor used in renal transplant (RTx) that requires monitoring to minimize risks. The best marker of TAC exposition is 24 hrs-AUC, but only Co is typically monitored. TAC is metabolized by CYP3A5 that contains a SNP (rs776746 A>G) associated in worldwide cohorts to slow (GG), intermediate (AG) or rapid (AA) TAC metabolism. The aim of this study was 1) to determine the association between rs776746 and TAC doses, 2) to establish if Co had a good correlation with AUC, 3) to analyze the genotype frequencies in Chile and their relationship with the Mapuche (Native Amerindian) ancestry.

Methods: A retrospective study was performed in 57 RTx adults of a single center using TAC of prolonged liberation for more than 3 months. The SNP rs776746 was analyzed by PCR Taqman/sequencing. AUC was determined in 16 patients with the three genotypes (GG/AG/AA). Mapuche ancestry in association to the genotypes was analyzed with the DNA repository in ChileGenómico.

Results: The mean age of the patients was 43 yrs [17-71 yrs], 51% female, 81% RTx with cadaveric donor, median time of RTx was 2.7 yrs. At the time of recruitment, 60% presented C0 between 5-10 ng/ml. We identified 58%, 26% and 16% of subjects with the GG, AG or AA genotype, respectively. The dose/weight (mg/kg) resulted GG=0.06±0.03, AG=0.12±0.05 and AA=0.15±0.05 (mg/kg) that were statistically different between GG-AA and GG-AG ($p<0.001$). The highest correlation between Cx and AUC was C12 ($r=0.97$) and C0 ($r=0.96$), independently of the genotype. The Mapuche ancestry percentage resulted 26% 30% and 37% for GG, AG and AA, respectively ($p<0.0001$).

Conclusions: A high prevalence of the GG genotype was identified, associated to lower requirements of TAC doses, but carriers of at least one A allele duplicated TAC dose. Chilean population has a mixed genetic ancestry and Mapuche ancestry appears to be associated with higher TAC doses, because of higher A allele frequency. Co turns to be an optimal marker of drug exposition. Our results demonstrate the potential clinical value of the CYP3A5 genotype to personalize therapy in Chile, to facilitate post-RTx monitoring, as well as improve credibility of patients TAC adherence. Grants *FONDECYT 111-40242, FONDECYT 116-0465.*

Funding: Government Support - Non-U.S.

TH-PO360

Mycophenolate Mofetil vs. Cyclophosphamide as Induction Treatment and Mortality in a Series of Cases from the Colombian Caribbean Region with Lupus Nephritis

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Background: Lupus nephritis (LN) is the most severe complication of systemic lupus erythematosus and induction therapy defines the prognosis of the disease. The type of immunosuppressive therapy (Mycophenolate Mofetil; MMF and Cyclophosphamide; CP) is chosen according to clinical and histological criteria. The objetive was to assessing response to induction therapy with MMF vs CFM and mortality in a number of cases from the Colombian Caribbean region with LN.

Methods: A retrospective analytical study. 423 patients with diagnosis of LN between 2008-2018 were included. Two regimens of immunosuppressive therapy for induction were evaluated in LN: MMF (n = 331); (Dose 2 g / day for 6 months) vs CP (n = 92) (500 mg IV every 15 days for 3 months). Patients were classified according to the criteria of clinical response of ACR (American College of Rheumatology) at: Complete remission (CR), partial remission (PR) and no remission (NR). Furthermore, the mortality associated with MMF vs CFM to 500 weeks (9 years) by Kaplan-Meier estimator was calculated.

Results: All patients, 87% were women, the mean age was 36 ± 13 years. The most common clinical presentation was nephrotic syndrome (70%). Histological class was predominantly proliferative class IV (66%), followed by Class III (23%). Statistically significant proteinuria in 24 hours and creatinine in both treatment groups (MMF vs CFM) ($p <0.05$) difference was found. Regarding the response to induction therapy, 225 (49%) cases NR, 123 (29%) were made and RC 91 (22%) RP. CFM mortality rate (68%) VS MMF (30). There were no statistically significant differences in clinical response and mortality among patient groups, as well as the values of C3, C4 and anti-dsDNA.

Conclusions: In our population, the clinical response in the induction and the mortality rate is similar between the two treatment groups (MMF vs CFM), although the MMF was superior in terms of averages, in response and decreased mortality, but this does not he reached for a statistical difference.

TH-PO361

Fosfomycin Trometamol Administration Enhances Cyclosporine Nephrotoxicity

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Background: Urinary tract infection (UTI) is very frequent in renal transplant immunosuppressed patients and the clinicians face the growing increase in antibiotic resistance. Fosfomycin trometamol (Fos) has emerged as a potential UTI treatment, however its influence on calcineurin inhibitors nephrotoxicity (CIN) has not been explored. This study was designed to evaluate the effect of Fos in combination with cyclosporine (CsA) on CIN in the rat.

Methods: Twenty-four male Wistar rats were included and divided into four groups: 1) Control, 2) CsA 15 mg/kg s.c., 3) CsA+Fos 62.5 mg/kg and 4) CsA+Fos 500 mg/kg. Cyclosporinr was daily administered for 14 days, whereas, fosfomycin was starting on day 9 with three doses every 48 h. At the end of the study, functional studies were performed, and tissue samples were obtained.

Results: Table 1

Conclusions: CsA nephrotoxicity was characterized by a significant decrease in RBF and GFR, as well as with a reduction in eNOS, AGT, and AT1R mRNA levels. In CsA+Fos group, greater hypoperfusion, oxidative stress, and increased mRNA levels of pro-inflammatory cytokines were observed. This study shows that Fos increases CsA nephrotoxicity through increasing renal inflammation and alerts us to the combined use of these drugs in the clinical scenario.

Funding: Government Support - Non-U.S.

Group	Control	CsA 15 mg	CsA+Fos 62.5 mg	CsA+Fos 500 mg
RBF (mL/min)	6.6 ± 0.2	3.2 ± 0.4*	3.6 ± 0.4*	2.5 ± 0.2*
GFR (mL/min)	2.3 ± 0.5	1.0 ± 0.1*	1.1 ± 0.1*	0.9 ± 0.1*
Urinary H2O2(μM)	219.2 ± 10.6	304.9 ± 70.5	234.1 ± 27.4	401.7 ± 46.5*
Endothelin	1.0 ± 0.1	3.1 ± 0.8	2.5 ± 0.5	3.4 ± 0.7
ETA	1.0 ± 0.1	1.3 ± 0.3	1.6 ± 0.2	1.6 ± 0.2
ETB	1.0 ± 0.1	0.8 ± 0.1	1.1 ± 0.2	1.3 ± 0.2
eNOS	1.0 ± 0.1	0.5 ± 0.2*	0.5 ± 0.1	0.6 ± 0.1
Nrf2	1.0 ± 0.1	2.0 ± 0.3*	1.7 ± 0.2	1.9 ± 0.2
Catalase	1.0 ± 0.1	0.9 ± 0.1	0.7 ± 0.1	0.8 ± 0.1
SOD1	1.0 ± 0.1	0.7 ± 0.1	0.5 ± 0.1*	0.7 ± 0.1
Gpx1	1.0 ± 0.1	1.0 ± 0.3	1.1 ± 0.2	0.9 ± 0.2
AGT	1.0 ± 0.1	0.3 ± 0.1*	0.5 ± 0.1*	0.6 ± 0.1*
AT1R	1.0 ± 0.1	0.2 ± 0.1*	0.3 ± 0.1*	0.4 ± 0.1
AT2R	1.0 ± 0.1	3.8 ± 1.0	6.2 ± 0.8*	5.0 ± 1.4
MCP-1	1.0 ± 0.1	3.4 ± 0.4	3.4 ± 0.7*	4.3 ± 0.7*
TNF-α	1.0 ± 0.1	1.4 ± 0.3	2.3 ± 0.4	2.6 ± 0.8
IL-6	1.0 ± 0.1	1.8 ± 0.3	3.7 ± 0.6*	3.2 ± 0.8*
IL-10	1.0 ± 0.1	7.4 ± 1.9*	12.1 ± 2.4*	9.6 ± 1.8*

TH-PO362

Improved Early Treatment Response of Eculizumab with a Patient-Friendly Dosing Scheme in Adult Patients with Atypical Hemolytic Uremic Syndrome

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Background: With the currently approved dosing schedule of eculizumab in adult aHUS patients (900mg weekly, followed by 1200mg in the fifth week and every 14 days thereafter), exposure is often sub-therapeutic after the first dose, while being supra-therapeutic when starting the maintenance phase. We aimed to develop a dosing strategy to improve early treatment response.

Methods: Pharmacokinetic (PK) and pharmacodynamic (PD) data from 30 aHUS patients were available, consisting of 647 eculizumab time-concentration data and 504 classical pathway (CP) activity levels. PK-PD modeling was performed by means of non-linear mixed effects modeling. The final model was used to investigate alternative dosing strategies through Monte Carlo simulations in 1000 virtual patients to develop a dosing strategy with a higher percentage of patients with a CP activity <10%, without increasing the dose during the initial phase.

Results: A PK-PD model with parallel first order and Michaelis-Menten elimination rates best described the data. The estimates of the model were CL 0.167 L/day (RSE 6%), Vd 7.11 L (RSE 8%), V_{max} 27.7 mg/day (RSE 6%), K_m 20.8 mg/L (RSE 28%). The PK-PD relation was described with an inhibitory Emax model, with an IC50 of 21.3 mg/L (RSE 17.1%). A weight-based loading dose of eculizumab (<60kg: 1500mg, 60-<90kg: 1800mg, 90-<120kg: 2100mg and ≥120kg: 2400mg) on day 1, followed by 1200mg on day 14 and 28 was found to improve treatment. In total, 96.6% of the patients reached the CP target on day 7, compared to 81.3% with standard dosing (Figure 1). This also resulted in a dose reduction of 12.5% compared to the first 28 days of the approved dosing regimen.

Conclusions: A patient-friendly weight-based dosing strategy of eculizumab results in better treatment response during the initial phase at lower costs.

Funding: Government Support - Non-U.S.

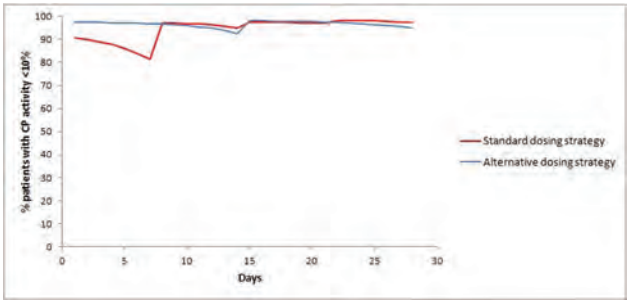

Figure 1: Predicted percentage of patients with a CP activity <10% for standard and improved dosing

TH-PO363

Darunavir Localizes to Cytoplasmic Stress Granules in Human Proximal Tubular Cells

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Background: HIV protease inhibitors (PI) have off-target effects on many cellular pathways data from our laboratory demonstrated that darunavir (DRV), the most commonly used PI, protects renal epithelial cells from HIV-induced injury and inflammatory responses via mechanisms independent of HIV protease. Since the mechanism by which DRV protects kidney cells from injury is poorly understood, we performed studies to identify cellular protein targets of DRV in human renal epithelial cells.

Methods: We used the Direct Magnetic IP/Co-IP Kit to covalently link DRV to NHS-activated magnetic beads. DRV bound– and unbound– beads were incubated with HPT1b whole cell lysate from immortalized human proximal tubular cells (HPT1b). Bound proteins were eluted and analyzed by mass spectrometry. DRV was also covalently linked to NHS-AlexaFluor 488, and cellular localization of DRV-AF488 and stress granule protein G3BP1 were analyzed by fluorescence microscopy.

Results: 52 proteins were identified in all 3 samples from DRV-bound beads at 100-fold or greater abundance than control samples. 23 of the 52 proteins are RNA-binding proteins, most of which are components of cytoplasmic stress granules (SG), including canonical SG proteins G3BP1, G3BP2, and Caprin1. DRV-G3BP1 interaction was confirmed by western blotting of protein eluted from DRV- and control-conjugated beads. To determine if DRV colocalizes with G3BP1 at SG, SG formation was induced in HPT1b cells by incubation with NaAsO2. Fluorescence microscopy localized G3BP1 and DRV-AF488 in the cytoplasm and in cytoplasmic punctae, consistent with SG localization. HIV transduction of HPT1b cells increased G3BP1 punctate staining, demonstrating that HIV induced SG formation. We examined phosphorylation of G3BP1, which promotes SG disassembly. A reduction in p-G3BP1 (Ser149) was observed in HIV transduced HPT1b cells treated with DRV, suggesting that DRV prevents SG disassembly.

Conclusions: These data demonstrate that DRV localizes preferentially to SG in renal epithelial cells. Since SG are intracellular domains that regulate response to stress, DRV may attenuate renal epithelial injury via novel effects upon SG dynamics. Additional studies are needed to determine the role of SG proteins in mediating the protective effects of DRV against kidney injury.

Funding: NIDDK Support

TH-PO364

Tenofovir Alafenamide Fumarate (TAF) and Tenofovir (TFV) Have a Different Impact on the Proteome of Proximal Tubular Cells (PTCs)

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Background: TAF, a new produg of TFV was developed to be less nephrotoxic than Tenofovir Desproxil Fumarate (TDF), by releasing less TFV in the blood. First clinical studies confirmed the low renal toxicity of TAF. However, TAF and TFV respective effects on renal tubular cells have never been compared. The aim of this study was to study the effects of TFV, TAF and ABC (as control nucleosidic inhibitor) on PTC.

Methods: iTRAQ differential proteomic strategy was used to analyse the effects of TFV (287 ng/mL), TAF (215 ng/mL), ABC (4200 ng/mL) or vehicle (water) on LLC-PK1. Cells were exposed for 24h to the different drugs before protein extraction. After proteins digestion by trypsin, peptides were tagged with iTRAQ reagents, then seperated into 12 different fractions by isoelectrofucusing. Generated fractions were analysed using triple TOF 5600+ mass spectrometer (ABSciex).

Results: One hundred sixty-nine proteins were identified in all 5 independent experiments. Among them, 17 were modified by TFV (11 up-regulated and 6 down-regulated), 21 by TAF (10 up-regulated and 11 down regulated) and 17 by ABC (9 up-regulated and 8 down-regulated). Only few proteins were similarly modified by the 3 drugs. ATP synthase-coupling factor 6 and Electron transfer flavoprotein-ubiquinone oxidoreductase were reduced by the 3 drugs whereas testin was increased. TAF and TFV commonly affect the expression of Ras-related protein Rab-1A, U1 small nuclear ribonucleoprotein A, and alter in opposite way the expression of Thymosin beta-10, Polypyrimidine tract-binding protein 1. TFV specifically increased 5 proteins and decreased 3 proteins among them the V-type proton ATPase catalytic subunit A, which is involved in the acidification of cytoplasmic vesicles during membrane trafficking. TAF alone decreased 5 proteins and increased 7 proteins among them megalin, the major protein involved in endocytosis in PTC.

Conclusions: Our results confirmed the different impact of TFV, TAF and ABC on PTC. If the 3 drugs modified the electron chain transport explaining their potential mitochondrial toxicity, TFV seemed to negatively affect the endocytic capacity of PTC whereas TAF may maintain it through the upregulation of megalin. These results are in accordance with clinical data showing a decrease in tubular proteinuria after the switch from TDF to TAF.

TH-PO365

Metabolomics Analytic Approach Reveals Global Metabolic Influences by Xanthine Oxidoreductase Inhibitors in a Rat Model of Unilateral Renal Ischemia-Reperfusion Injury

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Background: Xanthine oxidoreductase (XOR) inhibitors are clinically applied as anti-gout drugs to inhibit the conversion of xanthine to uric acid by XOR. They reportedly exert an organ-protective effect, especially the potent and selective XOR inhibitors, febuxostat and topiroxostat. We aimed to verify the hypothesis that preservation of tissue high-energy phosphate concentrations contributes to these positive effects in a rat model of unilateral renal ischemia-reperfusion (I/R) injury through global metabolic pathway analysis.

Methods: Six-week-old male Sprague–Dawley rats were orally administrated either 10 mg/kg of febuxostat, 10 mg/kg of topiroxostat, 50 mg/kg of allopurinol, or vehicle 60 min before they were subjected to 30 min of unilateral renal I/R injury. Kidney samples were collected at three time points; before I/R injury (stationary group), 30 min left renal ischemia (ischemic group), 30 min after I/R injury (reperfusion group). Metabolites in kidney lysates were analyzed by HPLC and CE-TOFMS metabolomics.

Results: Metabolomics analysis revealed global impact of I/R injury on metabolic pathways. In XOR-selective-inhibitor-treated groups, tissue concentrations of high-energy phosphates were higher before and after I/R injury, and renal adenine compounds were better preserved throughout I/R injury than in vehicle and allopurinol groups. The XOR-selective inhibitors were also shown to uniquely influence glycolysis, glycogenesis, and the tricarboxylic acid cycle metabolic pathways.

Conclusions: These findings were well in accordance with the proposed hypothesis that the recomposition of high-energy phosphates, such as ATP and ADP, is promoted by the XOR-selective inhibitors via the salvage pathway through blockade of hypoxanthine catabolism, whereas non-specific inhibitory effects of allopurinol on purine/pyrimidine enzymes impede this re-synthesis process. The unique global metabolic alterations by the XOR-selective inhibitors, presumably by a change in the ATP/AMP ratio, acting as an allosteric effector, remained further to be investigated. This study revealed novel findings of the XOR inhibitors' influences on global metabolic pathway, and sheds light on the undetermined physiology of the organ-protective effects of XOR inhibitors.

TH-PO366

Renoprotective Effects of Phosphodiesterase 5 Inhibitor in Models of CKD with Hypertension and Nephrotic Syndrome

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Background: Phosphodiesterase (PDE) 5 inhibitor has a renoprotective effect. PDE5 expression in glomeruli is confirmed, but its role has been unclear. In this study, we assessed the effects of tadalafil (Tad), a PDE5 inhibitor, using two renal dysfunction models, chronic kidney disease (CKD) with hypertension and nephrotic syndrome.

Methods: ***1) CKD model.*** We used Dahl salt-sensitive rats with hypertension and CKD induced by a high-salt diet. The rats were divided into normal salt, high salt, and Tad 1- and 10-mg/kg treatment groups. After 8 weeks of treatment, we analyzed kidney function, blood pressure, and histopathological changes. ***2) Nephrotic syndrome model.*** A nephrotic syndrome model was created with Wistar-ST rats by adriamycin (ADR) injection. The rats were divided into control, ADR, and ADR+Tad 10 mg/kg groups. After 2 or 4 weeks of treatment, urinary protein and serum albumin levels were evaluated.

Results: ***1) CKD model.*** High-salt diet induced kidney dysfunction and severe hypertension. Tad 10 mg/kg treatment prevented increases in serum creatinine (SCr) and urinary protein levels and hypertension (Fig. 1). Tad 1 mg/kg treatment significantly prevented the increase in SCr and urinary protein levels, but not hypertension. Histopathological analysis revealed that Tad treatment attenuated glomerular injury. ***2) Nephrotic syndrome model.*** ADR injection induced high urinary protein level and low serum albumin level. Tad treatment attenuated proteinuria at 2 and 4 weeks and reduction of serum albumin level at 4 weeks.

Conclusions: This study suggests that Tad treatment is effective for both CKD and nephrotic syndrome. The improvement might be induced by the effects against glomerular impairment, particularly podocyte injury.

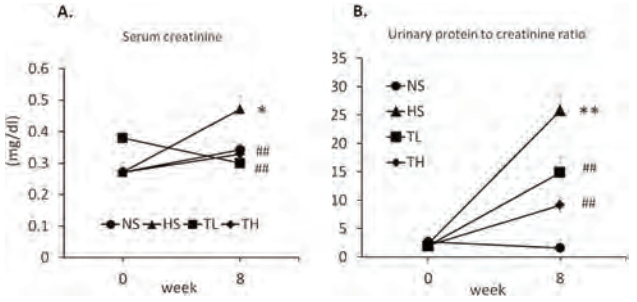

Fig. 1 SCr (A) and urinary protein to creatinine ratio (B) in CKD model. NS, normal salt; HS, high salt; TL, HS+tadalafil (1 mg/kg/day); TH, HS+tadalafil (10 mg/kg/day; n=5–7). *P<0.05; **P<0.01, versus NS; #P<0.05; ##P<0.01, versus HS.

TH-PO367

SNF472 Is More Efficacious In Vivo Than Its 4,6-bisPEGylated Derivative in Inhibiting Vascular Calcification in Rats

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Background: Vascular calcification (VC) is a major contributor to increased morbidity and mortality in Chronic Kidney Disease patients undergoing dialysis. Although VC is a multifactorial process, the final common pathway is deposition of solid hydroxyapatite (HAP) within the arteries. SNF472, salt of InsP6, is a selective calcification inhibitor that interferes in the formation and growth of ectopic HAP. SNF472 is currently being developed for the treatment of calciphylaxis in patients on dialysis. Inositol-1,2,3,5-tetraphosphate-4,6-bisPEG$_{100}$ (InsP4bisPEG) is an inositol phosphate derivative resulting from the PEGylation of inositol tetraphosphate (InsP4) with polyethylene glycol (PEG) 100. The aim of this study was to compare the relative bioavailability and *in vivo* efficacy in the inhibition of calcification of subcutaneous (s.c.) InsP4bisPEG and SNF472 at equimolar doses in rats.

Methods: S.c. pharmacokinetics (PK) of InsP4bisPEG and SNF472 were assessed in male Sprague Dawley rats after a single administration. Plasma samples were obtained and analyzed. The *in vivo* efficacy was evaluated in 24 male Sprague Dawley rats, divided into three groups of eight rats receiving placebo (NaCl 0.9%) or equimolar doses (36 μmol/kg) of SNF472 or InsP4bisPEG. Vascular calcification was induced by 3 consecutives daily s.c. administrations of 150 kIU/kg vitamin D3, starting on day 1. Rats were sacrificed 5 days after induction of calcification, and aorta was collected for calcium analysis.

Results: The plasma C_{max} of InsP4bisPEG was 9.8 μM, at a t_{max} of approximately 30 minutes. AUC_{0-t} was 13.1 μmol/h/L and the terminal half-life ($t_{1/2}$) was 46 min. SNF472 showed a plasma C_{max} of 7.4 μM at around 15 min, with an AUC_{0-t} of 2.5 μmol/h/L and a terminal $t_{1/2}$ of 17 min. SNF472 treated animals presented significantly lower calcium levels in aorta, which were 38% and 55% lower than placebo and InsP4bisPEG treated animals, respectively.

Conclusions: InsP4bisPEG is more bioavailable than SNF472 and presents a longer plasma half-life. However, SNF472 is more efficacious inhibiting aorta calcification than this InsP6 PEGylated derivative in an *in vivo* vitamin D3 rat model at 36 mmol/kg. This is probably due to the larger affinity of SNF472 for HAP crystals.

Funding: Commercial Support - Sanifit Therapeutics

TH-PO368

An Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Effects of Renal Impairment on the Pharmacokinetics of ELX-02: Results from Subjects with Mild and Moderate Renal Impairment

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Background: ELX-02 is an investigational synthetic eukaryotic ribosomal selective glycoside (ERSG) that induces read-through of nonsense mutations through interaction with the ribosome resulting in full-length functional proteins. ELX-02 is being developed as a therapy for genetic diseases caused by nonsense mutations such as nephropathic cystinosis and polycystic kidney disease. It is well established that kidney disease is characterized by multiple physiologic effects, which induce clinically significant changes in pharmacokinetics.

Methods: Eloxx Pharmaceuticals, Inc. is presently conducting a Phase 1 study designed to determine the effect of various severities (i.e., mild [eGFR 60-89 mL/min/1.73m^2], moderate [eGFR 30-59 mL/min/1.73m^2], and severe eGFR [<30 mL/min/1.73m^2, not requiring dialysis] of renal impairment, compared to a control group with normal renal function [eGFR ≥ 90 mL/min/1.73m^2) on the PK of ELX-02 after a single dose of 1 mg/kg. Six subjects are planned to be enrolled in each category of renal failure, and 6-8 subjects enrolled in the control group.

Results: To date, treatment of subjects with mild and moderate renal impairment has been completed. In subjects with mild renal impairment the mean eGFR at baseline was 74.7 mL/min/1.73m^2, C_{max} was 2,993 ng/mL, T_{max} was 1.1 hr, AUC_{0-inf} was 16,999 ng*h/mL, $t_{1/2}$ was 3.3 hr, and Cl/F was 4.4 L/h. In the moderate group the mean baseline eGFR was 41.7 mL/min/1.73m^2, C_{max} was 3,688 ng/mL, T_{max} was 1.3 hr, AUC_{0-inf} was 35,172 ng*h/mL, $t_{1/2}$ was 6.5 hr, and Cl/F was 2.4 L/h. These results indicate that the degree of renal impairment has effects on the PK of ELX-02, with an increase in C_{max}, T_{max}, AUC, and $t_{1/2}$ and a decrease in Cl/F in subjects with moderate renal impairment when compared to subjects with mild renal impairment. No adverse events have been reported in this study.

Conclusions: Results from the severe and control groups will be available at the meeting. Based on the preliminary results available to date, ELX-02 can be used safely in patients with renal dysfunction and dose adjustments may be considered for patients with varying degrees of renal impairment. These results support the continued development of ELX-02 for the potential treatment of nonsense mutation mediated kidney diseases.

Funding: Commercial Support - Eloxx Pharmaceuticals, Inc

TH-PO369

Effect of Moderate Hepatic Impairment on Pharmacokinetics of Vadadustat, an Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI)

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Background: Vadadustat is an oral HIF-PHI in development for the treatment of anemia due to chronic kidney disease. Vadadustat is primarily metabolized to O-glucuronide by UPD-glucuronosyltransferases (UGTs). The predominant UGT involved in the metabolism of vadadustat is UGT1A9, which is expressed in the liver and kidney. Therefore, the role of hepatic impairment in vadadustat clearance was evaluated.

Methods: This phase 1, open-label, parallel-group, single-dose study evaluated pharmacokinetics (PK) of 450 mg vadadustat in adults (18-70 y) with moderate hepatic impairment (Child-Pugh Class B) versus those with normal hepatic function. Blood samples were collected pre-dose and up to 72 h post-dose. Primary endpoints were area under the curve from dosing to last concentrations (AUC_{last}) and to infinity (AUC_{inf}) as well as maximum concentration (C_{max}); additional PK parameters included time to C_{max} (T_{max}) and half-life ($t_{1/2}$). Safety and tolerability were assessed throughout the study.

Results: All 16 enrolled participants completed the study (hepatic impairment, n=8; normal, n=8). Demographics were similar between groups (overall: 100% white, 62.5% female, mean age 59.2 y). Vadadustat plasma exposure (AUC) was slightly higher in the hepatic impairment group, whereas C_{max} was generally similar between groups (Table). Point estimates of the hepatic impairment:normal geometric mean ratios (90% CI) for AUC_{last}, AUC_{inf}, and C_{max} were 1.05 (0.82-1.35), 1.06 (0.82-1.36), and 1.02 (0.79-1.32), respectively. Mean elimination half-life was 5.8 h in the normal group and 7.8 h in the hepatic impairment group. Treatment-emergent adverse events (TEAEs) were reported by 1 participant in the hepatic impairment group and 2 in the normal group. Most TEAEs (86% [6/7]) were mild in severity; none were severe.

Conclusions: In this study, moderate hepatic impairment did not significantly impact vadadustat systemic exposure. A single dose of 450 mg vadadustat was generally well tolerated by participants with both normal and moderately impaired hepatic function.

Funding: Commercial Support - Akebia Therapeutics, Inc.

Hepatic Function Status	$AUC_{0\text{-}last}$ (h*μg/mL)	$AUC_{0\text{-}inf}$ (h*μg/mL)	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)
Moderate Impairment (n=8)	432 (35.4)	436 (35.6)	52.9 (22.2)	2.0 (1.0-4.0)	7.8 (32.6)
Normal (n=8)	395 (18.2)	397 (18.1)	52.6 (28.0)	2.5 (1.5-6.0)	5.8 (24.5)

Values=arithmetic mean (% coefficient of variation) except Tmax, shown as median (range)

TH-PO370

A Systematic Meta-Analysis on Interspecies Differences in Renal Drug Clearance

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Background: Various animal models are used to study drug efficacy and safety prior to approval for human use. Renal clearance (CLr) is a standard pharmacokinetic measure, for which animal data is extrapolated to humans by allometric scaling, using exponents of 0.55-0.75. It is worth noting that the physiological system of waste removal is designed to exactly meet the demand set by metabolic rate, which in turn scales with body weight to the power of 0.75 (Kleiber's law). Thus, human CLr should be predictable based on body weight by scaling with 0.75. The exponents used in literature aim for best fit, thus deviations from 0.75 might result from biological interspecies differences. Using the allometric exponent of 0.75, our study aimed at quantifying interspecies differences in renal drug clearance. To find possible mechanistic explanations for these differences, we related them to the physicochemical properties of drugs.

Methods: Using PubMed and EMBASE, we systematically reviewed literature on human and animal CLr measures for 20 renally excreted drugs. Based on the human data and simple allometric principles, we calculated the CLr value expected for the respective animal body weight. Subsequently, average fold errors (AFEs) were calculated as the ratio between the literature-derived CLr values and the expected CLr values. Finally, we quantified mean differences (MDs) in AFEs between animals and humans.

Results: Based on 264 included studies, we calculated AFEs ranging from 0.45-3.05 for mice, 0.77-3.34 for rats, 0.28-1.61 for rabbits, 0.27-3.4 for dogs, 0.57-1.78 for monkeys and 1.01-1.31 for humans. Comparing animal to human AFEs, we determined for all drugs an average MD [95% CI] of 0.01 [-0.23, 0.26] for mice, 0.47 [0.17, 0.77] for

rats, 0.17 [-0.12, 0.45] for rabbits, 0.23 [-0.13, 0.56] for dogs and -0.08 [-0.33, 0.16] for monkeys. Only for rats, the overall effect size was significantly different from humans. Subgroup analyses showed no clear relation to physicochemical drug properties.

Conclusions: In general, animal models are good predictors for human drug clearance using simple allometry. However, rats (the most popular animal model) significantly overestimate human CLr, which could explain the exponent deviation in literature and suggest that rat models should be used with caution.

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TH-PO371

Drugs Applied to Kidney Patients May Interact with Uremic Toxins for Renal Excretion

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Background: Organic anion transporters (OATs) are involved in the tubular secretion of protein-bound uremic toxins (PBUT). In CKD, excretion of PBUTs is compromised leading to their accumulation, exacerbating CKD and contributing to uremic complications. Recently, we showed that conditionally immortalized proximal tubule epithelial cells (ciPTECs) expressing OAT and cultured on biofunctionalized membranes, actively secrete PBUTs [1,2]. However, OAT1 also handles a wide range of drugs. Here, we investigated the interaction between drugs commonly prescribed to CKD patients and PBUTs for OAT1-mediated transport, using indoxyl sulfate (IS) as prototype PBUT.

Methods: A panel of 9 drugs was screened for interactions in ciPTECs-OAT1 monolayers in the presence (+) and absence (-) of IS, at a uremic concentration (110 μM). To evaluate OAT1 function, fluorescein was used as substrate and its uptake was measured using a multi-plate reader.

Results: Our results show that ACE-inhibitors and cimetidine have either no or a slight effect at non-therapeutical concentrations on OAT1-mediated fluorescein uptake. On the contrary, ATII-inhibitors, statins and furosemide significantly reduced fluorescein uptake, with the highest potency for ATII-inhibitors. This trend was maintained in presence of IS, suggesting that these drugs could negatively influence secretion of PBUTs by ciPTECs (**Table 1**).

Conclusions: Drugs commonly used by kidney patients may compromise endogenous waste product clearance. Further studies should address the transepithelial excretion of PBUTs in the presence of drugs. A similar evaluation in CKD patients would validate our findings. 1. Jansen J, *et al*, Sci. Rep. 6:26715, 2016; 2. Nieskens TTG, *et al*, AAPS J. 18: 2, 2016

Funding: Government Support - Non-U.S.

Table 1. OAT1-mediated fluorescein uptake: IC50 (μM) in the absence (-) and presence (+) of IS *

Drug	IC50 - IS	IC50 + IS	Drug	IC50 - IS	IC50 + IS
	ACE inhibitors			Statins	
Captopril	NT	NT	Simvastatin	21.3 ± 3.8	71.8 ± 27.3
Enalaprilate	NT	NT	Pravastatin	23.2 ± 8.3	40.9 ± 9.2
Lisinoprol	No effect	No effect		Others	
	ATII inhibitors		Furosemide	28.1 ± 9.1	44.7 ± 12.4
Losartan	8.6 ± 2.5	13.9 ± 4.9	Cimetidine	NT	No effect
Valsartan	11.5 ± 3.5	16.1 ± 3.6			

* Values are given as mean of two independent observations. NT=non-therapeutical concentration.

TH-PO372

Kidney-Targeted Drug Delivery via Chitosan-Modified Liposome

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Background: Regarding kidney disease therapy, extra-renal effects, the inactivation of drug before reaching kidney or altered distribution due to the pathophysiology of diseases limit some medication widely use. The specific delivery or selective activation in kidney maximizes therapeutic effectiveness and minimizes toxic side effects. The improvement of the pharmacokinetic profile should be accomplished by drug targeting strategies. Liposome is single-layer or multi-layered vesicles composed of ordered lipid bilayers with an aqueous phase inside. Selective delivery of drugs in liposomes has been used clinically to treat some diseases because of their excellent biocompatibility, wide range of drug loading and low toxicity. They can increase the stability and solubility of the drug, give drug delivery and sustained release drug characteristics, and effectively improve the drug bioavailability. In this study, we evaluated the safety and effectiveness of chitosan-modified liposome as a kdiney-trageted delivery system.

Methods: To establish chitosan-modified liposome delivery system, liposomes were prepared by thin-film methods and post-insertion technology was performed to achieve chitosan modification. The morphology was confirmed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). To study the safety of this system, the cellular viability of human renal tubular epithelial cells, HK-2, was evaluated by cell proliferation kit. Drug release from the nanocomplex was analyzed at pH 7.4,6.8 and 5.0 using the dialysis method. To investigate the specific kidney-targeted delivery, the vector and its modified liposome was injected into mice and the distribution was analyzed by fluorescence imaging.

Results: Zeta potential of liposome pre- and post- chitosan modification confirmed the success of the reaction. The drug-loading system was spherical-like nanoparticles with an average particle size of (48.49±0.61) nm. The *in vitro* release results showed the nanoparticles had no burst release under physiological pH conditions. Near-infrared fluorescence imaging indicated that the system could be effectively distributed to the kidney. Furthermore, this system had no obvious toxicity to renal tubular epithelial cells.

Conclusions: The chitosan-modified liposome is expected to achieve renal targeted drug delivery and the drug-loading system is safe and stable.

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TH-PO373

Screening for Effective Components of Tripterygium wilfordii Hook F for the Treatment of Diabetic Nephropathy Based on Computer Simulation

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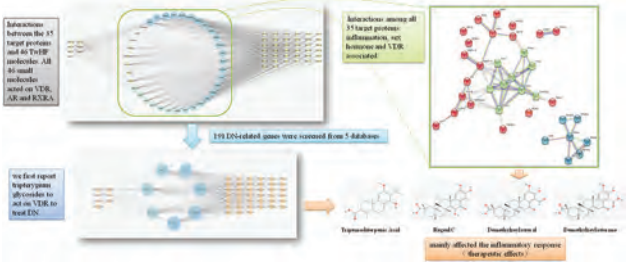
Background: Triptergium wilfordii Hook F (TwHF), is commonly used in the management of many renal diseases through antiinflammation and immunosuppressive in traditional Chinese medicine. How to reduce the toxicity of TwHF without affecting its efficacy has always been an important research issue. In this study, we used evidence-based research to detail the natural ingredients isolated from TwHF, referenced a gene library when screening for components effective in the management of diabetic nephropathy (DN) and provide a scientific foundation for the development of novel drugs for treatment of this condition.

Methods: CNKI, Wanfang, VIP, Pubmed and relevant databases were used to retrieve and summarize the components of TwHF. All data analyses were carried out using the Discovery Studio 4.5 System, and the Systemdockonlinedockingmethod platform to find active small molecules and effector proteins, and then using online big data to screen for genetic information relevant to DN.

Results: A total of 370 compounds classed into 4 main categories(36 sesquiterpenes, 93 diterpenes, 133 triterpenes and 106 alkaloids) obtained. A total of 46 small molecules were found to be biologically active constituents of TwHF in the setting of DN, mainly affecting the inflammatory response through PI3K-Akt and Jak-STAT pathways. 4 small molecules (Triptonoditerpenic Acid, Regeol C, Demethylzeylasteral and Demethylzeylasterone) mainly affected the inflammatory response. Through screening DN genes, 7 target proteins(VDR, JAK1, JAK2, JAK3, PPARG, MARK14, TGFBR1) were found to have high correlation scores.

Conclusions: The emergence of network pharmacology has completely altered the research approach towards novel drug development and has greatly compensated for a lack of experimental capabilities. We first report tripterygium glycosides to act on VDR. Further experimentation can confirm the accuracy of target and molecular networks as well as effective components of TwHF.



TH-PO374

Additive Renoprotective Effects of Angiotensin Converting Enzyme Inhibition and Nitro Fatty Acid (CXA-10) Combination

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Background: Underlying pathogenic mechanisms in chronic kidney disease (CKD) include chronic inflammation, oxidant stress, and matrix remodeling associated with dysregulated NF-κB, NRF2 and SMAD signaling pathways, respectively. During CKD progression these pathogenic mechanisms overwhelm endogenous cytoprotective mechanisms mediated by nitro fatty acids (NO_2-FA) that act through posttranslational protein modification to limit inflammation and oxidant stress.

Methods: To restore cytoprotective balance, we evaluated the effects of chronic treatment with CXA-10 (10-nitro-9(E)-octadec-9-enoic acid), a nitro fatty acid, in a reduced renal mass (RRM) – high salt rat model of progressive CKD. Five treatment groups were examined (Control, CXA-10 (1.25 and 3.75 mg/kg, p.o.), enalapril and enalapril + CXA-10), for a 3-week dosing period that commenced 4 weeks following RRM.

Results: Enalapril significantly attenuated the increase in mean arterial pressure (MAP) and mildly blunted proteinuria, non-significantly. Similarly, the low dose of

CXA-10 non-significantly attenuated proteinuria but had no effect on the increase in MAP. In a two-factor analysis model, both CXA-10 and enalapril treatment significantly blunted the increase in proteinuria (p= 0.048 and 0.045, respectively). The combination of enalapril and CXA-10 (1.25 mg/kg) did not further alter MAP more than enalapril alone, but significantly reduce proteinuria after 3 weeks of treatment when compared to Control (-12% vs. 30%). Treatment with CXA-10 alone (1.25mg/kg & 3.75 mg/kg) maintained renal blood flow (RBF) at pretreatment levels. Based on a histopathologic analysis, none of these short-term treatment regimens (3 weeks) altered the moderate glomerulosclerosis and mild renovascular injury observed in the model.

Conclusions: The results suggest that the combination of enalapril and CXA-10 may exert additive MAP-dependent (enalapril) and MAP-independent (CXA-10) effects to limit increases in proteinuria without compromising renal perfusion.

Funding: Commercial Support - Complexa

TH-PO375

Rhein Reverses miR-34a-Mediated Autophagy in D-Galactose-Induced Renal Aging Rats via the Regulation of Gut Microbiome

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Background: The alterations of gut microbiota in composition, diversity and functional features have a close relationship with aging-associated pathologies, including renal aging. microRNAs (miRNAs)-mediated autophagy also has an important role in aging. Recently, traditional Chinese herbal medications have been reported to possess potent anti-aging activities. Rhein is a bioactive constituent of rhubarb, derived from the root of *Rheum palmatum* with the anti-aging pharmacological effect. But the characteristics of gut microbiome and its relationship with miRNAs-mediated autophagy of rhein in anti-renal aging are unknown.

Methods: Forty rats were divided into Normal (N), Model (M), Rhein (R) and Vitamin E (VE) groups. D-galactose (D-gal) was used to induce renal aging. The appropriate doses of rhein, VE and distilled water were administrated with oral, respectively. All rats were sacrificed after 8 weeks treatments. Blood serum, fecal samples and kidneys were collected for the detection of various indicators. The characteristics of gut microbiome were determined by 16S rDNA Sequencing. Serum concentrations of uremic toxins indoxyl sulfate (IS), p-cresol sulfate (pCS) and trimethylamine oxide (TMAO) were detected by ELISA. miR-34a expression level was detected by RT-PCR. The senescence-associated-β-galactosidase (SA-β-gal) staining was observed. The aging-related protein expressions of Klotho, p53 and p21, as well as the protein expressions of autophagy markers, Beclin-1, LC3 I/II, p62, and Atg12 were detected by Western Blot.

Results: Results showed that, the structure and diversity of gut microbiota in 4 groups were different. Rhein and VE could reverse the abundance of some genus changed significantly in M group when compared with N group. Rhein and VE could notably decrease the increased IS, pCS and TMAO in M group. Rhein and VE markedly alleviated the up-regulation of miR-34a in M group. In addition, rhein and VE could attenuate strong positive staining for SA-β-gal, and reverse the significantly changed aging-related protein expressions and autophagy markers in M group.

Conclusions: This study proved rhein, similar to VE, could alleviate renal aging via regulating gut microbiome and miR-34a-mediated autophagy. Thus, targeting gut-kidney axis and miRNAs-mediated autophagy may provide new strategies in age-associated renal damage of the elderly patients.

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TH-PO376

Hyperoside Ameliorates Renal Tubular Epithelial Cells Ageing Induced by D-Galactose via Regulating m^{6}A Modification of TFEB mRNA

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Background: The kidney is a typical organ that undergoes age-related tissue injury, however, there is little information on therapeutic effects underlying age-associated renal damage. Hyperoside (HYP), a component of *Abelmoschus manihot*, is reported to be useful for preventing premature ageing induced by D-galactose (D-gal). But its potential mechanisms remain unclear. N6-methyladenosine (m^{6}A) mRNA modification plays a critical role in transcription factor EB (TFEB) discovered as a master regulator of autophagic function. We thereby aimed to determine whether HYP alleviates D-gal-induced renal ageing by targeting autophagic activity and m^{6}A modification of TFEB mRNA, compared to vitamin E (VE).

Methods: Renal proximal tubular epithelial cells of rats (NRK-52E cells) were divided into the normal, the D-gal model, the low dose of HYP, the high dose of HYP and the VE groups, and treated by the different measures, respectively. More specifically, NRK-52E cells in each group were separately treated by 1% FBS or D-gal (100 mM) or D-gal (100 mM) + HYP (5 mg/L) or D-gal (100 mM) + HYP (10 mg/L) or D-gal (100 mM) + VE (50 mg/L). After intervention for 24 h, firstly, effects of D-gal on the mRNA levels of m^{6}A and TFEB; the ageing-related protein expression levels of Klotho, P27, P16, IL-1, TGF-β and MCP-1; SA-β-gal staining and LC3 Lentiviral transfection in NRK-52E cells were detected, respectively. Secondly, effects of D-gal, HYP and VE on activation of NRK-52E cells proliferation were investigated. Finally, effects of HYP and VE on the mRNA levels of m^{6}A and TFEB; the ageing-related protein expression levels; SA-β-gal staining and LC3 Lentiviral transfection in NRK-52E cells exposed to D-gal were examined severally.

Results: For NRK-52E cells, D-gal induced the low mRNA levels of m^{6}A and high mRNA levels of TFEB, and caused ageing and autophagy. The co-treatment of HYP at the high dose and D-gal significantly ameliorated the ageing-related protein expression levels and LC3 protein expression. In addition, the co-treatment of HYP at the high dose and D-gal obviously increased the mRNA level of m^{6}A and decreased the TFEB level. The VE group has the similar changes as HYP at the high dose.

Conclusions: We clarified that HYP and VE could improve D-gal-induced renal tubular cellular ageing by reducing autophagic activity and increasing m^{6}A modification of TFEB mRNA.

Funding: Government Support - Non-U.S.

TH-PO377

5-HT$_{1F}$ Receptor Mediates Renal Vascular Homeostasis and Mitochondrial Biogenesis

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Background: Acute kidney injury (AKI) is a disease with no treatment options. After AKI, there is a marked reduction in renal vasculature. Thus, promoting vascular recovery following AKI could facilitate renal repair as the vasculature is responsible for carrying oxygen and nutrients to extravascular tissues. Our laboratory has shown that stimulating mitochondrial biogenesis (MB) through the 5-HT$_{1F}$ receptor stimulates recovery from AKI. In contrast, 5HT$_{1F}$ receptor knockout mice have decreased MB, vascular content, and poor renal recovery. Importantly, induction of MB has been linked to increased angiogenesis. Thus, we hypothesized that the 5HT$_{1F}$ receptor mediates MB and plays a role in vascular homeostasis in renal endothelial cells.

Methods: Primary human glomerular endothelial cells (HEC) and mouse glomerular endothelial cells (MEC) were treated with the 5-HT$_{1F}$ receptor agonists 300nM LY344864 or 100 nM lasmiditan for 24 or 72h. Branching morphogenesis and wound healing were assessed via matrigel and scratch migration assays, respectively. Mitochondrial biogenesis was assessed by enumerating mitochondra via electron microscopy analysis.

Results: Treatment of HEC and MEC with LY344864 or lasmiditan induced MB, as evidenced by increased mitochondrial number in comparison to vehicle treated cells. HEC that were treated with lasmiditan or LY344864 exhibited increased migratory capacity, as evidenced by increased endothelial branching (matrigel migration assays) and increased would healing (scratch closure).

Conclusions: Stimulation of 5-HT$_{1F}$ receptor with LY344864 and lasmiditan induces MB in HEC and MEC, and 5-HT$_{1F}$ receptor mediates angiogenic pathways. We propose that inducing MB in endothelial cells after AKI could restore vascular function and stimulate renal repair and recovery.

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TH-PO378

Activation of the Keap1/Nrf2 Pathway Increases GFR by Increasing Glomerular Effective Filtration Area Without Affecting the Afferent/Efferent Arteriole Ratio

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Background: The Keap1/Nrf2 pathway regulates various cytoprotective, anti-inflammatory, and antioxidant genes. Nrf2 activator, Bardoxolone methyl (BARD), increases the estimated glomerular filtration rate (eGFR) in patients with diabetic kidney disease (DKD). Moreover, BARD improved renal function in DKD patients, as revealed through the assessment of inulin clearance, the gold standard for measuring the GFR. These findings indicate that the Keap1/Nrf2 pathway is largely involved in the regulation of the GFR; however, the precise underlying mechanisms are yet unclear. This study aimed to pharmacologically and genetically investigate the mechanisms underlying the regulation of the GFR by the Keap1/Nrf2 pathway via multiphoton microscope (MPM) imaging in vivo.

Methods: C57BL/6 (Control), Nrf2-knockout (Nrf2-KO), and Nrf2-activated Keap1-knockdown mice (Keap1-KD) were used herein and treated with the synthetic terpenoid RTA dh404 (RTA, 10 mg/kg/day by gavage) for 1 week. Single-nephron GFR (SNGFR), the diameter of the afferent/efferent arterioles and glomerular permeability were evaluated using MPM. Intracellular calcium in response to ATP and angiotensin II stimulation and the effect of RTA on [Ca2+]i were evaluated using Fluo 4 and Fura red in cultured mesangial cells and podocytes. Production of reactive oxygen species and nitric oxide (NO) availability were assessed using CellROX® Deep Red and diaminofluorescein-FM diacetate (DAF-FM DA) upon the exposure to these stimuli.

Results: SNGFR was significantly higher in Keap1-KD mice than in the control group (9.13±0.55 vs 4.40±0.39 nl/min, p<0.05). RTA administration increased the SNGFR in the control mice but not in Nrf2-KO mice (6.00±0.40 vs 4.66±0.35 nl/min, p<0.05). The glomerular afferent/efferent arteriole ratio was not altered significantly in all groups. RTA treatment did not affect the glomerular permeability of albumin and 40 kDa dextran. RTA treatment inhibited calcium influx into cultured podocytes and mesangial cells induced by angiotensin II or ATP, thereby affecting contractile responses. Oxidative stress and NO bioavailability were also ameliorated with upon RTA treatment.

Conclusions: The Keap1/Nrf2 pathway plays a pivotal role in regulating GFR and presumably mediates the effects of BARD on GFR.

Funding: Commercial Support - Reata Pharmaceuticals

TH-PO379

PEGylation of Inositol Hexaphosphate (InsP6) Decreases Its Binding Affinity for Hydroxyapatite and Its Capacity to Inhibit Plasma Calcification In Vitro

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Background: Vascular calcification (VC) is a major contributor to increased morbidity and mortality in Chronic Kidney Disease patients undergoing dialysis. Although VC is a multifactorial process, the final common pathway is deposition of solid hydroxyapatite (HAP) within the arteries. SNF472, a salt of InsP6, is a selective calcification inhibitor that interferes in the formation and growth of ectopic HAP. SNF472 is currently being developed for the treatment of calciphylaxis in patients on dialysis. Inositol-1,2,3,5-tetraphosphate-4,6-bisPEG$_{100}$ (InsP4bisPEG) is an inositol phosphate derivative resulting from the PEGylation of inositol tetraphosphate (InsP4) with polyethylene glycol (PEG) 100. Our aim was to study the binding affinities of SNF472, InsP4bisPEG and InsP4 for the HAP surface, and its relationship with their *in vitro* efficacy by inhibiting calcium phosphate crystallization.

Methods: To evaluate the adsorption binding affinity (E_{ads}) of SNF472, InsP4bisPEG and InsP4 to the HAP crystal surface, computational studies were performed using Density Functional Theory calculations with DMOL3 (MS2016). The in vitro efficacy of InsP4bisPEG and InsP4 was evaluated using a pharmacodynamic assay to measure the plasma calcification potential using a previously validated spectrophotometric method, and compared to SNF472 in the 0-100 μM range.

Results: Molecular modelling revealed that SNF472 binds to the HAP surface with higher affinity than InsP4bisPEG, as revealed by their relative energies of absorption taking InsP4 as reference (ΔE_{ads}=-110 kcal/mol for SNF472 and ΔE_{ads}=-41.1 kcal/mol for InsP4bisPEG). These results are correlated with the inhibition potencies observed in the human plasma HAP crystallization assay. EC_{50} was 2.2 μM, 3.8 μM and 8.5 μM, for SNF472, InsP4bisPEG and InsP4, respectively.

Conclusions: SNF472 shows the highest binding affinity and the highest in vitro potency in the inhibition of HAP crystallization in human plasma, which is concordant with the larger electrostatic interactions between SNF472 and HAP, since it is a more charged molecule.

Funding: Commercial Support - Sanifit Therapeutics

TH-PO380

Antisense Oligonucleotides Target Proximal Tubular Epithelial Cells in Kidney

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Background: Developing, refining and deploying new drugs to target specific molecules in cell types and tissues of interest is crucial for advancing towards precision medicine. Antisense oligonucleotides (ASO) are chemically synthesized, short DNA oligomers that can be applied to target specific mRNAs via hybridization and degradation, thus resulting in a reduced synthesis of related proteins. Recent data suggest that newer, more stable and effective generations of ASO may be of therapeutic value, including in humans. However, our understanding of the biodistribution and efficacy of systemically delivered ASO in organs is insufficient.

Methods: Here, we investigated the distribution, cell incorporation and gene knockdown efficiency of ASO specifically in kidney cells *in vitro* and *in vivo* using an unbiased approach.

Results: First, we designed and generated several eGFP-specific LNA Gapmer-type ASO and tested for eGFP knockdown potency *in vitro*. Promising candidates were amplified and then used in two transgenic mouse models of ubiquitous, constitutive eGFP-expression. EGFP-mice were i.p. injected with ASO directed against eGFP or control ASO for five to ten days, sacrificed and organs harvested for analyses. Comprehensive immunohistological studies in kidney using cell-specific staining techniques found distinct and robust eGFP suppression in proximal tubular epithelial cells (PTEC) but not in other renal cell types including the TAL, collecting duct, interstitium and endothelial cells. To study the biodistribution and dynamics of systemic ASO in more detail, we administered fluorophore-labeled ASO to wildtype mice and found overwhelming ASO enrichment in PTEC, suggesting highly preferential ASO incorporation in this segment of the nephron. In line, temporary exposure of mammal PTEC to labeled ASO *in vitro* resulted in rapid and sustained increases in intracellular fluorescence, indicating efficient ASO uptake by PTEC.

Conclusions: In summary, our data provide strong evidence for a differentiated biodistribution and cellular internalization of ASO in renal tissue with systemic delivery, implicating important differences in ASO-mediated knockdown efficacy and favoring, overall, PTEC as potential target cells. This disparity in ASO accessibility and hence expectable impact needs to be considered when defining therapeutic targets in kidney.

Funding: Government Support - Non-U.S.

TH-PO381

Application of the Kidney Failure Risk Equation to an Electronic Health Record-Based CKD Registry

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Background: The Kidney Failure Risk Equation (KFRE), utilizes age, sex, estimated glomerular filtration rate (eGFR), and urine albumin to creatinine ratio (UACR), to predict progression to End Stage Renal Disease (ESRD). Application of the KFRE to an electronic health record (EHR)-based chronic kidney disease (CKD) registry enables ESRD risk stratification across a CKD population.

Methods: Cross-sectional study of 57,385 patients included in the Partners Healthcare System (PHS) CKD registry (dialysis and transplant patients were excluded). Multivariate logistic regression analyses were conducted to identify factors associated with: UACR testing; arteriovenous fistula (AVF) and placement; kidney transplant referral; and completion of advance directives.

Results: 17,266 (30%) patients had all variables required for KFRE; 40,119 (70%) patients lacked UACR. Factors associated with UACR testing were diabetes, hypertension, obesity, and being seen by an in-network nephrologist. In the highest KFRE risk stratum (≥ 40% risk of ESRD within two years; N=515), 35 (6.8%) patients had an AVF; 64 (12.4%) patients had been referred for transplantation; and 61 (11.8%) patients had advanced directives. Factors associated with not having an AVF were older age, female sex, and fewer visits to an in-network nephrologist. Factors associated with lack of transplant referral were older age, higher eGFR, and not having a PHS nephrologist. Factors associated with lack of advance directives were younger age, male sex, not having a PHS Primary Care Provider, and KFRE stratum of lowest (<3% risk) or low (3-9.9% risk).

Conclusions: The KFRE stratifies risk of ESRD; however, 70% of our patients with CKD lack UACR testing. Institution-wide UACR testing will facilitate care optimization. Our findings enable targeted care of sub-populations to improve care delivery and transition to ESRD.

Funding: NIDDK Support

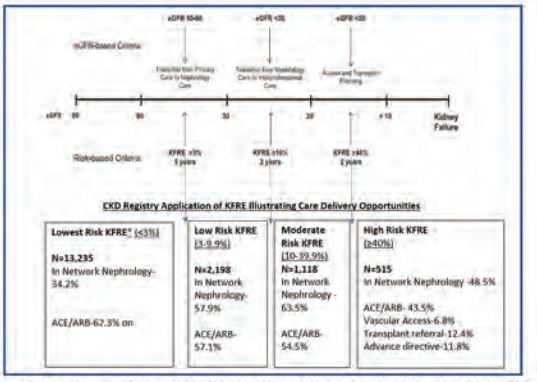

Figure 1: Risk stratification adapted from Tangri NDT 2017, with performance on metrics per stratum applied to PHS CKD Registry. *2 year risk of ESRD from Kidney Failure Risk Equation (KFRE). Abbreviations. ACE/ARB: angiotensin converting enzyme inhibitor / angiotensin receptor blocker.

Risk stratification adapted from Tangri NDT 2017, with performance on metrics per stratum applied to PHS CKD Registry.

TH-PO382

A Predictive Model for Progression of CKD to Kidney Failure Using an Administrative Claims Database

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Background: To develop and validate a predictive model to identify patients (pts) with chronic kidney disease (CKD) Stage 3 or 4 at high risk for progression to kidney failure (KF) over a 24-mo period.

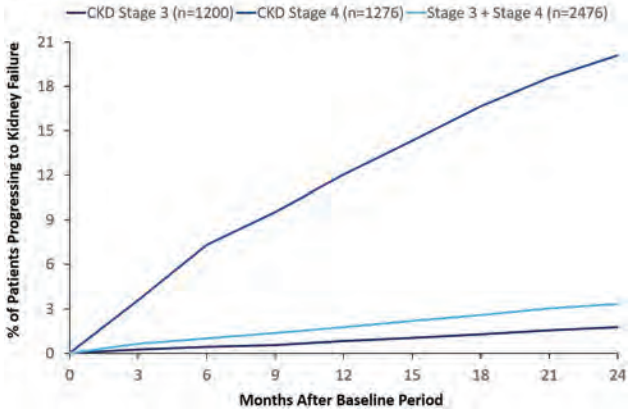
Methods: A predictive model was developed and validated utilizing a retrospective claims database of CKD Stage 3 or 4 patients from a large US payer. The study covered 36 mo with a 12-mo (2015) baseline period and 24-mo (2016–2017) prediction period. All pts were ≥18 yrs of age without dialysis or kidney transplant and had 36 months of enrollment. KF was defined as: eGFR <15 mL/min/1.73 m^2; or dialysis; or kidney transplant; or one diagnosis (ICD-10-CM: N18.5, N18.6) in prediction period. Multivariate logistic regression was used to develop a model estimating the 2-yr probability of KF as a function of baseline covariates. Area under receiver operating characteristic (ROC) curve (AUC), calibration, gain and lift charts of the validation sample were used to assess the predictive model performance.

Results: Of the 74,114 pts studied, 2476 (3.34%) had incident KF in the prediction period (**figure**). The predictive model included age, gender, CKD Stage, hypertension (HTN), diabetes mellitus (DM), congestive heart failure (CHF), peripheral vascular disease (PVD), anemia, hyperkalemia (HK), and poor RAAS inhibitors adherence. The strongest predictors were CKD Stage (4 vs 3), HTN, DM and HK. The ROC curve and calibration analyses in the validation sample showed good predictive accuracy (AUC=0.834) and good calibration.

Conclusions: This predictive model provides a good level of accuracy in identifying CKD pts at high risk of progressing to KF up to 2 yrs in advance in a national health plan with over 10 million lives. Early identification using this model could potentially lead to improved health outcomes and reduce health care expenditure.

Funding: Commercial Support - Funded by Relypsa, Inc., a Vifor Pharma Group Company

Figure. Time to Progression for Kidney Failure (Kaplan-Meier curve)



TH-PO383

Prognostic Score for Chronic Renal Disease in Patients with Lupus Nephritis

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Background: There is currently a prognostic score of progression to chronic kidney disease (CKD) in patients with lupus nephritis (LN), this tool evaluates: cellular and fibrous crescents; activity and chronicity index; glomerular sclerosis; interstitial fibrosis; nephrotic syndrome and glomerular filtration rate. The resulting data divides the population at low risk; moderate; and severe risk. The objective of this study was to apply this score to Mexican patients with LN and to predict their progression to CKD.

Methods: Study of ambilective cohort of patients with NL of the HGM from August 2012 to August 2017, in which the prognostic score was applied. Descriptive statistics and survival analysis were performed with Cox regression, with 95% CI, considered a value of $p < 0.05$ as statistically significative.

Results: 141 patients were analyzed; we found a mean age of 32.01±10.95 years, 73% (103) women. According to the ISN/RPS class IV (38%) and class IV+V (34%) were identified and classes II, III, III+IV and V were presented with frequency of 11% or less. The score stratified 54% (76) patients in the low risk; 43% (60) moderate; and 3% (4) severe. During the follow-up at 6 months, 29 patients (26%) presented total remission (RT); 42% (48) partial remission (PR); and 32% (36) without remission (SR). Progression to CKD was observed in 19% of patients with (RT), in 37% with (RP) and in 44% (SR), ($p < 0.05$). For terminal CKD (ERCT) no significant differences were observed (patients with RT 20%, RP 27% and SR 53%, $p = 0.15$). According to the score, 15 (22%) of the patients with low risk presented progression to CKD, unlike 33 (73 %) of those with moderate risk, and 4 (100%) with high risk ($p < 0.001$). Progression to ERCT was observed in 3 (4%) patients with low risk, 27 (45%) moderate risk and 1 (20%) patient with high risk ($p < 0.001$).

Conclusions: The results show that the application of this prognostic score in Mexican patients with LN is useful to predict the progression to CKD and ESRD regardless of the response to treatment.

TH-PO384

Prediction Model from Big Data for Rapid GFR Decline in CKD Patients by Machine Learning Technique

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Background: Recent studies have focused on kidney function trajectory because it might be related to the incidence of cardiovascular (CV) disease and all-cause mortality. We aimed to investigate risk factors for rapid GFR decline and create a machine learning-based predictive model by using one big hospital database.

Methods: We used a database derived from the Fujita Health University Hospital. Medical data were available for 120,689 eGFR-recorded patients in this study. Among them, 21,198 patients met the CKD criteria. Rapid GFR decline in patients with CKD was defined as eGFR decline of ≥30% per 2 years; we used average eGFR of past 90 days to avoid temporal spikes of measurements. We then selected unique 5,818 CKD patients with rapid GFR decline, from which 10,093 samples of rapid GFR decline were obtained. We built a prediction model to classify rapid GFR decline using machine learning algorithms including logistic regression, decision tree, and random forest. We used explanatory variables including 90-day past data of eGFR, proteinuria, serum creatinine (Cr), blood pressure, body mass index, sex, and age. Among those longitudinal data, we used average, standard deviation (SD), and exponentially smoothed average (ESA) to form explanatory variables for the prediction model. Contribution to rapid GFR decline was examined by weight of each variable.

Results: We used serial 10,093 data each from 5,818 CKD patients with rapid GFR decline and without rapid GFR decline for the prediction model. There were no significant differences in age and sex between the two groups. Mean proteinuria, ESA of proteinuria, SD of serum Cr, ESA of serum Cr, and SD of Hematocrit were associated with rapid GFR decline in the random forest model. Moreover, the random forest model predicted rapid GFR decline with an accuracy of 0.75 (area under the curve). Meanwhile, area under the curves for predicting rapid GFR decline were 0.69 and 0.69 in the logistic regression and decision tree models, respectively. By the decision tree analysis, the incidence of rapid GFR decline was 90% if the following criteria were fulfilled: 4+ or more of mean urine protein; ≤1.33 ESA of serum Cr; ≤1.03 SD of hemoglobin.

Conclusions: The random forest model by machine learning could be useful to identify patients with rapid GFR decline in real world clinical setting.

TH-PO385

Discovery of CKD Patient Subgroups by Consensus Clustering: The CRIC Study

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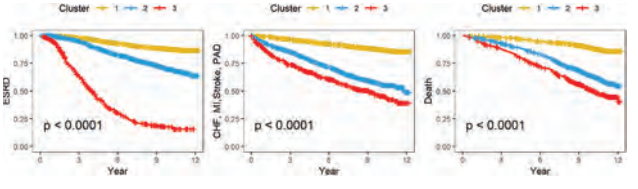
Background: CKD is a heterogeneous condition with multiple underlying causes, risk factors, and outcomes. Consensus clustering may reveal CKD subgroups with different risk profiles of adverse outcomes.

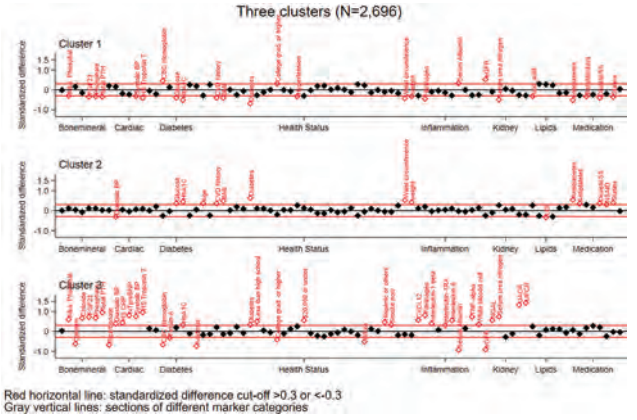
Methods: Among 2696 participants in the prospective CRIC Study, we performed unsupervised consensus clustering with K-means, without using outcome information, on 72 baseline characteristics of traditional and novel factors to discover patient subgroups. We calculated the standardized difference of all predictors across subgroups, and used the cut-off of ±0.3 to show key features. We examined the associations of each subgroup with ESRD, cardiovascular diseases (composite of heart failure, MI, stroke and PAD), and death.

Results: Three unique CKD subgroups, identified using only baseline factors, were associated with low (Cluster1, N=1203), medium (Cluster2, N=1098), and high (Cluster3, N=395) risks of the outcomes (**Fig 1**). Patients in cluster 1 (lowest risk) had lower bone & mineral, diabetes, cardiac, and obesity markers, greater eGFR, and used fewer medications. Patients in cluster 2 had higher diabetes and obesity markers, and used more medications. Patients in cluster 3 (highest risk) had higher bone & mineral (except for lower serum calcium), cardiac (except for lower serum CO_2), inflammation (except for lower serum albumin), and kidney markers (except for lower eGFR) (**Fig 2**).

Conclusions: Consensus clustering discovered distinct subgroups of CKD patients with distinguishing patterns of baseline clinical and laboratory factors yielding markedly different risks of important clinical outcomes. Specific biomarkers featuring high-risk CKD subgroup could provide potential treatment targets.

Funding: NIDDK Support





TH-PO386

Optimizing Machine Learning Methods for Clinical Outcome Prediction

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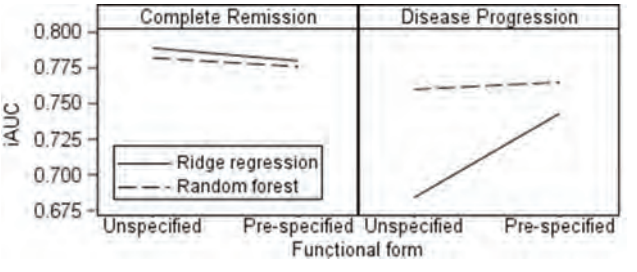
Background: Machine learning (ML) is useful to identify novel biomarkers and predict clinical outcomes, especially when predictors outnumber patients, but model building procedures are underutilized. We compared two ML methods and the impact of pre-specifying covariate functional forms on predictive accuracy and variable importance using data from NEPTUNE, a prospective cohort study of glomerular disease patients.

Methods: The sample was split into training (70%) and validation (30%) sets. Ridge regression and random forest models were developed in the training set to predict time to two clinical outcomes: disease progression (ESRD or ≥40% eGFR decline with last eGFR <60) and complete remission of proteinuria (UPCR <0.3), with and without categorizing continuous covariates to accomodate non-linear associations with outcomes. Predictors included 56 demographic/clinical characteristics, which were ranked by variable importance. Discrimination was estimated in the validation set using integrated area under the curve (iAUC).

Results: Using pre-specified covariate functional forms in ridge regression increased iAUC from 0.68 to 0.74 for the progression outcome, but had little impact for remission (0.79 vs. 0.78; Fig) or the random forest method for both outcomes. iAUCs from random forest were higher than those from ridge for progression but not remission. After pre-specifying functional forms in ridge regression, variable importance ranks increased for some known risk factors: rank of UPCR for predicting remission rose from 48 to 5 and rank of eGFR for predicting progression rose from 52 to 1. Other important predictors were disease diagnosis, age, and immunosuppression use for remission and disease diagnosis, race, and hypertension for progression.

Conclusions: For ML methods assuming linear associations, like ridge regression, pre-specifying covariate functional forms is important for predictive accuracy and detecting important predictors. Different ML methods may improve prediction for different outcomes. Higher ranking of known risk factors improves face validity in prediction models and may have positive implications for external validation performance.

Funding: Other NIH Support - National Center for Advancing Translational Sciences



TH-PO387

Study on Glomerular Filtration Rate Equation Using Ensemble Learning and Linear Regression

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Background: Accurate estimating glomerular filtration rate (GFR) is crucial both in clinical practice and epidemiological survey. We incorporated semi-supervised learning technology to improve GFR estimation performance.

Methods: Data from patients with CKD and healthy people who were examined by radionuclide renal dynamic imaging or dual plasma DTPA in the Tianhe and Lingnan districts of The Third Affiliated Hospital of Sun Yat-sen University from January 2012 to April 2018 including baseline indicators, laboratory indicators, Kidney color Doppler ultrasound results, medication status. A total of 1,732 CKD patients and healthy people who had ECT examinations were included, of which 932 patients in Tianhe District used data as modeling data, and other 400 patients in Tianhe District as an internal validation data set, 400 patient data from Lingnan districts and outpatient department was used as the external validation data set. In the modeling group, the conventional data is modeled by linear regression and ensemble learning method, and then the verification group data is imported into the model to judge the prediction performance. We use internationally accepted bias, precision and accuracy comprehensively evaluate the predictive the model effectiveness and use the bootstrap method to calculate the 95% confidence interval and select the optimal model.

Results: A total of 1,732 CKD patients and healthy people were included in the study. The mean age was 57.15±13.56 years, and the mean GFR (mGFR) was 87.01±37.63 ml/min/1.73 m^2. The newly revised CKD-EPI equation using smooth linearity (N-Spline technique) is superior to the equations modeled by traditional linear regression methods in terms of precision ($p < 0.001$). In terms of accuracy and precision, the XGboost model equation is superior to the linear regression equation of the same variable ($p<0.05$). Compared with the 4-variable revision CKD-EPI model, the 15-variable, 3-variable XGboost model improved in bias, but it was not statistically significant; it was better in accuracy and precision ($P<0.05$). Compared with the widely used eGFR model (4 and 6 variable MDRD models), the bias, accuracy and precision of the 4-variable revision CKD-EPI model were better ($P<0.05$).

Conclusions: The ensemble learning model can optimize the predictive performance of the GFR model.

Funding: Government Support - Non-U.S.

TH-PO388

Improving Glomerular Filtration Rate Estimation by Semi-Supervised Learning: A Development and External Validation Study

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Background: Accurate estimating glomerular filtration rate (GFR) is crucial both in clinical practice and epidemiological survey. We incorporated semi-supervised learning technology to improve GFR estimation performance.

Methods: Databases of AASK, CRIC and DCCT studies were pooled together for model development, whereas MDRD and CRISP studies for model external validation. The pooled development data set contained 2,719 participants, whereas the pooled external validation data set contained 1,952 participants. 4,829 participants only without GFR records but all other information available were pooled into an unlabeled data set for semi-supervised learning. New Predictors & Established Predictors : Serum creatinine, Age, Sex, Black race, Diabetes status, Hypertension and Body Mass Index. GFR measured as the urinary clearance of ^{125}I-iothalamate. The revised CKD-EPI creatinine equations was selected as benchmark for performance comparisons. The proposed semi-supervised model was essentially an artificial neural network developed by Ladder Network algorithm. Head-to-head performance comparisons were conducted between revised equations and semi-supervised models from 4-variable to 7-variable.

Results: In each independent variables combination, the semi-supervised models consistently achieved superior results in all 3 performance indicators compared with corresponding revised CKD-EPI equations in the external validation data set. When selecting one representative revised equation and semi-supervised model for further comparison, compared with revised 4-variable CKD-EPI equation, the 7-variable semi-supervised model performed less biased (mean of difference: 0.03 [-0.28, 0.34] vs 1.53 [1.28, 1.85], $P < 0.001$), more precise (interquartile range of difference: 7.94 [7.37, 8.50] vs 8.28 [7.76, 8.83], $P = 0.1$) and accurate (P30: 88.9% [87.4%, 90.2%] vs 86.0% [84.4%, 87.4%], $P < 0.001$.

Conclusions: The superior performance of the semi-supervised models during head-to-head comparisons supported the hypothesis that semi-supervised learning technology could improve GFR estimation performance. The semi-supervised model still requires extra and careful validation, and further improvement is expected by integrating more cohort data.

Funding: Government Support - Non-U.S.

TH-PO389

Development of the Deep Neural Network for Estimating Glomerular Filtration Rate

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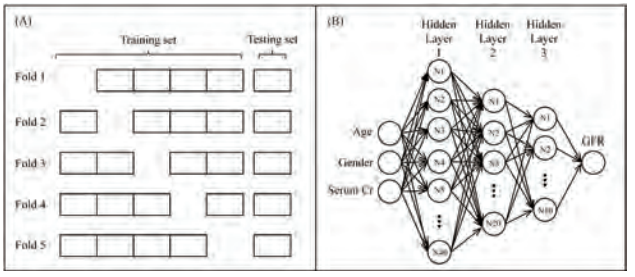
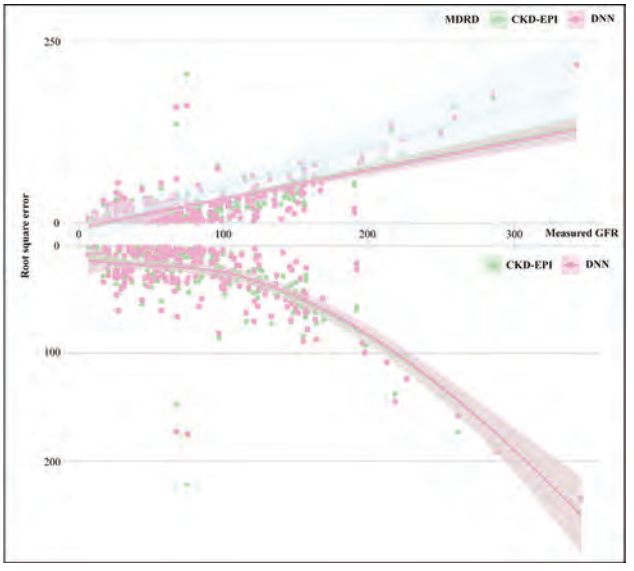
Background: A variety of calculation formulas to estimate glomerular filtration rate (GFR) have been developed for decades. Recently, modern clinical medicine has been trying to use a deep neural network (DNN) in various clinical fields. Thus, we aimed to use DNN model for estimating GFR in the study.

Methods: A total of 241 patients with chronic kidney disease were enrolled in the study. All participants had technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) renogram to obtain the standard value of GFR. We measured serum creatinine levels from all participants and calculated GFRs using various formulas such as MDRD and CKD-EPI. Furthermore, we developed a DNN model with three hidden layers. The first, second, and third hidden layers included 40, 20, and 10 nodes respectively. We compared GFR values of MDRD, CKD-EPI, and DNN model against standard GFR values from renogram in various statistical ways.

Results: The mean differences of GFR value from MDRD, CKD-EPI, and DNN methods with standard GFR were 2.35, 2.86, and 1.87 mL/min respectively. The mean root-mean-square-error values of MDRD, CKD-EPI, and DNN methods against standard GFR were 19.45, 18.9, and 16.78 (mL/min)^2 respectively suggesting that the GFR values of DNN model are closest to standard GFR values. When estimating the accuracy in classifying CKD stages, the degree of accuracy of MDRD, CKD-EPI, and DNN methods were 83.0, 84.3, and 85.1% respectively suggesting that the DNN model is the most accurate method in classifying CKD stages.

Conclusions: GFR measurement using DNN model is believed to be useful and accurate.





TH-PO390

Comparison of Standard and Age-Adapted GFR Criteria for Determination of CKD Prevalence

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[1]Landspitali - The National University Hospital of Iceland, Reykjavík, Iceland; [2]University of Iceland, Reykjavík, Iceland; [3]deCODE genetics, Reykjavík, Iceland.

Background: Inclusion of age-adapted GFR criteria in the definition of chronic kidney disease (CKD) has been proposed to avoid overdiagnosis in the elderly and underdiagnosis in the young. The aim of this study was to estimate the prevalence of CKD based on age-adapted glomerular filtration rate (GFR) criteria compared with a standard cut-off GFR value of 60 mL/min/1.73 m^2.

Methods: In this retrospective study, we obtained all serum creatinine (SCr) values and urine protein measurements from every clinical laboratory in Iceland in 2008-2016. Clinical information, including ICD-10 diagnosis codes, was retrieved from nationwide electronic medical records. Estimated GFR was calculated from SCr using the CKD-EPI equation. CKD was defined as presence of kidney damage, either proteinuria or ICD-10 diagnosis codes indicating kidney disease, or reduced eGFR for ≥3 months. The definition of reduced eGFR was <60 mL/min/1.73 m^2 according to the standard KDIGO criteria, whereas the age-adapted eGFR definition was <75 mL/min/1.73 m^2 for age <40 years, <60 mL/min/1.73 m^2 for 40-65 years and <45 mL/min/1.73 m^2 for age ≥65 years.

Results: We obtained 2,120,232 SCr values for 218,437 individuals. The median age was 46 (range, 18-107) years; 47% were men. The age-adjusted mean annual prevalence of CKD per 100,000 men and women, respectively, was 4420 (95%CI, 4370-4470) and 5500 (95%CI, 5440-5550) using standard GFR criteria, compared with 2844 (95%CI, 2805-2883) and 3232 (95%CI, 3190-3274) using age-adapted criteria. In men, the prevalence per 100,000 using standard vs age-adapted GFR criteria was 505 vs 591 in the age group 18-44 and 54,454 vs 31,958 in the age group 85+. In women, the prevalence per 100,000 was 908 vs 1078 and 48,868 vs 26,157 for the same age groups, respectively (Figure 1).

Conclusions: Compared with the conventional GFR cut-off, age-adapted GFR thresholds for definition of CKD yield a slightly higher prevalence in the young age groups, but a markedly lower prevalence among older people.

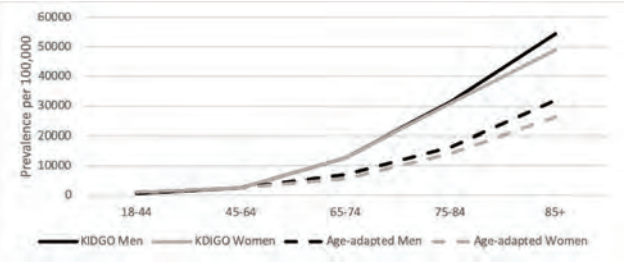

Figure 1. *Prevalence of CKD per 100,000 by sex (men black, women gray), age groups and diagnostic criteria.*

TH-PO391

Normalizing Urine Albumin to Urine Creatinine, Osmolality, or Not at All: Insights from NHANES

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Background: The concentration of urinary metabolites and proteins such as albumin is influenced by water excretion and urinary concentration, which varies across individuals and diurnally within individuals. To account for this variability, measures like albuminuria are often reported as normalized ratios. We hypothesized that the method of expressing urinary albumin – whether as a raw concentration or normalized to urine creatinine or osmolality – would influence observed associations with mortality due to confounding from determinants of urine creatinine excretion and osmolality, such as muscle mass, solute intake, and concentrating ability of the kidney.

Methods: We used data from the National Health and Nutrition Examination Survey 2009-2010 to model associations of albuminuria with mortality using Cox proportional hazards models. We used measurements on spot urine samples from 5,641 adults (age 42 ± 17 yrs) who had follow-up information on vital status (377 deaths) over 6 years.

Results: Median estimated glomerular filtration rate was 97 (range, 7-170) ml/min/1.73m^2, and median albumin:creatinine ratio was 5.9 (range 0.3-13,788) mg/g. The Table shows the associations of albuminuria with the risk of death. The strongest association was observed with urine albumin after multivariable adjustment for urinary creatinine.

Conclusions: While all methods of modeling urine albumin showed that elevated levels were independently associated with mortality, we found that associations were stronger when *adjusted* rather than *normalized* for urine creatinine and osmolality. Normalizing urinary biomarkers to urine creatinine may not be the optimal approach to distinguish urinary biomarker associations with health outcomes.

	Q1	Q2	Q3	Q4
Urine albumin	-	1.78 (1.06-2.98)	1.68 (1.12-2.51)	2.12 (1.33-3.37)
Urine albumin:creatinine ratio	-	1.24 (0.74-2.07)	1.62 (1.08-2.43)	2.51 (1.60-3.92)
Urine albumin:osm ratio	-	0.82 (0.53-1.27)	1.53 (0.94-2.50)	1.85 (1.23-2.79)
Urine albumin, adjusted for urine creatinine	-	2.30 (1.33-3.99)	2.42 (1.50-3.91)	3.14 (1.86-5.30)
Urine albumin, adjusted for urine osm	-	2.10 (1.22-3.62)	2.19 (1.34-3.56)	2.80 (1.68-4.65)

Multivariable-adjusted (MV) hazard ratios (95% confidence intervals) for different measures of urinary albumin quartiles and the risk of death. Models were adjusted for age, sex, race/ethnicity, hypertension, cardiovascular disease, diabetes mellitus, body mass index, and estimated glomerular filtration rate.

TH-PO392

Conversion of Urine Protein-Creatinine to Albumin-Creatinine Ratio for Use in CKD Risk Equations

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Background: Urine albumin-creatinine ratio (ACR) is a core component of CKD staging and used in equations to predict adverse outcomes. However, many cohorts and health systems preferentially measure urine protein-creatinine ratio (PCR) rather than ACR. These assays measure different protein components and the degree to which levels of PCR may be convertible to ACR is untested.

Methods: Cohorts in the CKD Prognosis Consortium with outpatient measures of PCR and ACR performed <90 days apart were included in the development of an equation for conversion of PCR to ACR using linear regression. Analyses were performed using all available data within individual cohorts, accounting for multiple records per person. Data were then meta-analyzed using random effects and linear splines to model log-PCR with a knot at 500 mg/g.

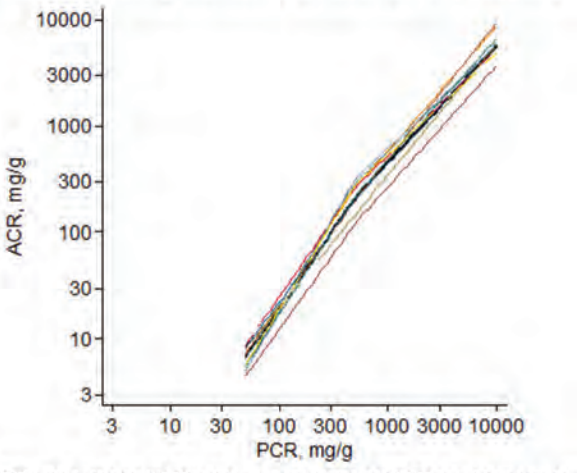
Results: There were 11 cohorts (2 general population, 3 high cardiovascular risk, 6 CKD cohorts) with 34,708 participants included from North America, Europe, and Japan. Average age was 58 years (SD, 16), 50% were female, and 7.4% were black. Median ACR was 181 mg/g (IQR, 51-304), and median PCR was 373 mg/g (152-654). There was no relationship between ACR and PCR at PCR <50 mg/g; thus, these values were excluded in the development of the equation. Above PCR 50 mg/g, there was a log-linear relationship with a slightly shallower slope at PCR >500 mg/g (p<0.001; footnote of figure; median

RMSE 0.83). Relationships between PCR and ACR were similar across cohorts (Figure), as well as demographics, and hypertension, cardiovascular disease, and diabetes status.

Conclusions: Guidelines recommend measurement of ACR. However, when ACR is not available, we developed an equation to convert PCR levels >50mg/g to ACR for use in risk equations. Lower levels of PCR were not amenable to harmonization.

Funding: NIDDK Support, Private Foundation Support

Figure: Relationship between PCR and ACR in 11 cohorts



ACR=EXP(1.486702*LN(MIN(PCR,500)/200)+1.105372*LN(MAX(PCR,500)/500)+3.99156)

TH-PO393

High-Normal Albuminuria Is Strongly Associated with Incident CKD in a Nondiabetic Population with Normal Kidney Function

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Background: Several studies have reported that high albuminuria within the normal range (high–normal albuminuria) is associated with chronic kidney disease (CKD). This study aimed to clarify the association between high–normal albuminuria and the risk of incident CKD, particularly in a nondiabetic population with normal kidney function.

Methods: A 10–year follow–up, retrospective cohort study was preformed involving 317 Japanese men (mean age, 42 years) with an eGFR ≥ 90 mL/min/1.73 m^2 and urine albumin-to-creatinine ratio (UACR) < 30 mg/gCr. Patients were free of diabetes mellitus. We calculated the cut–off value of the UACR from receiver–operating characteristic curves, and the value of ≥ 7.0 mg/gCr was defined as high–normal albuminuria. Multivariate stepwise analysis and logistic regression approaches were used to assess independent predictors of the incidence of CKD.

Results: Twenty–nine (9%) participants developed CKD through 10 years of follow–up. At the baseline examination, blood pressure, the UACR, and BUN values were higher in participants who developed incident CKD than in those with normal renal function. After adjustment for confounders, high–normal albuminuria was associated with an increased risk of incident CKD. Logistic regression analyses showed that subjects with a UACR ≥ 7.0 mg/gCr had an increased risk of new–onset CKD 10–years later compared with a UACR < 7.0 mg/gCr (odds ratio, 16.61; 95% confidence interval, 6.45–42.78; $P < 0.01$]. This difference persisted after adjustment for age, BMI, hypertension, smoking status, and dyslipidemia.

Conclusions: High–normal albuminuria is associated with incident CKD in a nondiabetic population with normal kidney function.

TH-PO394

eGFR Trajectory in Old Age

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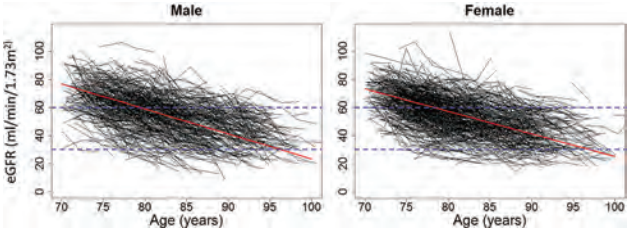
Background: Longitudinal data about the natural course of estimated glomerular filtration rate (eGFR) among older adults over several years are scarce. The Berlin Initiative Study (BIS) aims to fill this gap by evaluating repeat assessments of eGFR over time and potential risk factors for GFR decline in older adults.

Methods: The BIS is a prospective population-based cohort study initiated in 2009 whose participants are members of a German insurance company with the biggest fraction of older adults. Participants were interviewed face-to-face biannually using a standardized questionnaire recording clinical, laboratory and patient reported outcomes. eGFR was calculated with the $BIS2_{(crea/cysC)}$ formula. The course of eGFR was analyzed with a linear mixed-effects model, comprising age, sex, diabetes mellitus (DM), smoking status, body mass index (BMI), systolic blood pressure (sysBP), albumin-creatinine ratio (ACR), serum creatinine, cystatin C, ACE inhibitors, AT1 antagonists, NSAID, number of regular drugs, and myocardial infarction (all time-dependent), applying multiple imputation for missing data.

Results: As of May 06, 2019, 2,069 participants (47.4% male, mean age 80.4 years at inclusion) were followed for a median of 6.0 years. Of those, 1,699 (82%) had at least 2 eGFR assessments. We observed higher eGFR values in men. Crude linear regression lines of the eGFR course suggested a continuous decline, which decreased with rising age. In the mixed linear effects model, age, sex, BMI, myocardial infarction, current smoking, sysBP, use of sartanes and the number of regular drugs had a significant impact on eGFR.

Conclusions: Taking into account the potential impact of clinical, therapeutically and behavioral variables, we still observed an age-dependent decrease of eGFR, suggesting a naturally declining course in older age. The mixed model reveals that the expected mean eGFR for men aged ≥79 and women ≥78 is below 60, defining deficient kidney function when using the current classification system.

Funding: Private Foundation Support



TH-PO395

Sex Differences in the Risk of ESKD and Death Among Patients with Moderate to Advanced CKD Followed Up in Renal Clinics

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Background: Data on sex-specific differences in the epidemiology of CKD may help nephrologists to better tailor treatments for their patients. However, studies evaluating the association of sex with CKD progression have provided conflicting results.

Methods: We pooled four observational cohort studies including consecutive CKD patients (not dialysis/transplant) under stable Nephrology care for >6 months. Out of 3,212 unique patients, we selected 1,311 men and 1,024 women with eGFR<45 mL/min/1.73m^2. Primary outcome was ESKD (chronic dialysis or renal transplantation); all-cause mortality and eGFR decline were secondary outcomes. We used multivariable Cox proportional hazard analysis to estimate relative risk of ESKD and all-cause mortality, and linear mixed models to estimate the rate of eGFR decline.

Results: Age (67±14 y), systolic BP (139±20 mmHg), use of RAS inhibitors (69%), antihypertensive drugs (2.3±1.2) and statins (30%) were similar in men and women. Compared to men, women had lower eGFR (26±11 vs 28±10 mL/min/1.73m^2, P<0.001) and lower proteinuria (0.45 g/d IQR 0.14-1.10 vs 0.69 g/d, IQR 0.19-1.60, P<0.001). During a median follow-up of 4.2 years, 757 developed ESKD (307 women) and 471 died (196 women). Table reports the adjusted risk (HR and 95%CI) of ESKD and all-cause mortality overall and by CKD stages. We found a significant interaction between sex and proteinuria with the risk of ESKD in men becoming significantly greater at a level of proteinuria ≥0.5 g/d. Rate of eGFR decline (mL/min/year) was greater in men than in women (2.1 95%CI 2.0 -2.2 vs 1.8, 95%CI 1.7-1.9, P<0.001) with no difference across CKD stages (P=0.28). The difference in slopes between men and women was progressively larger with proteinuria levels ≥0.5 g/d (P=0.04).

Conclusions: Our study highlights an excess of renal risk in men possibly related, at least in part, to the higher levels of proteinuria in men compared to women.

	Overall	CKD stage 3B (eGFR 30-45)	CKD stage 4 (eGFR 15-29)	CKD stage 5 (eGFR<15)
ESKD: Women	Reference	Reference	Reference	Reference
Men	1.50 (1.27-1.77)	1.52 (1.03-2.24)	1.58 (1.25-1.99)	1.41 (1.09-1.83)
Mortality: Women	Reference	Reference	Reference	Reference
Men	1.32 (1.07-1.62)	1.49 (1.09-2.02)	1.19 (0.89-1.60)	1.27 (0.72-2.26)

Adjusted for age, smoking, BMI, cause of CKD, history of CVD, LVH, systolic BP, cholesterol, phosphate, albumin, hemoglobin, GFR, proteinuria, use of RAS inhibitors and stratified by cohort

TH-PO396

Performance of Creatinine-Based GFR Estimates in Patients on Ritonavir-Boosted Protease Inhibitors

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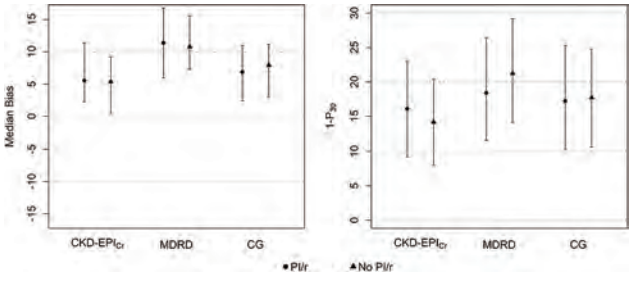
Background: The pharmacoenhancer ritonavir has been shown to inhibit tubular transport of creatinine *in vitro*. We aimed to determine whether use of ritonavir-boosted protease inhibitors (PI/r) affects the performance of creatinine-based GFR estimates.

Methods: We previously measured GFR (mGFR) in 200 HIV-positive adults on stable antiretroviral therapy using plasma iohexol clearance. We evaluated performance of the CKD-EPI creatinine equation (CKD-EPI$_{cr}$), MDRD Study equation, and Cockcroft-Gault creatinine clearance (indexed to 1.73m^2 body surface area) versus mGFR. We compared bias (median difference between mGFR and estimated GFR) and accuracy (percent of estimates within 30% of mGFR, with large errors indicated by 1-P$_{30}$). Statistical significance of the differences in bias and accuracy were tested by Wilcoxon two-sample test and chi-square test, respectively.

Results: 73% of the population was male, 52% of Black race, and 34% over the age of 50 years. 61% were virologically suppressed and 44% were on a PI/r. No participants were taking other antiretrovirals known to inhibit creatinine secretion. The CKD-EPI$_{Cr}$ equation performed better than other equations. There were no clinically or statistically significant differences in the performance of any equation between the PI/r and no-PI/r groups (Figure).

Conclusions: Use of PI/r did not have a significant impact on the performance of creatinine-based GFR estimates as compared to mGFR. Declines in eGFR with the use of PI/r may reflect real changes in kidney function.

Funding: Other NIH Support - Supported by the National Center for Research Resources; the National Center for Advancing Translational Sciences, National Institutes of Health Grant UL1 RR025752 (Tufts Medical Center) and UL1 RR029887 (Mount Sinai School of Medicine); the Center for Clinical and Translational Sciences Grant UL1 RR025777 (University of Alabama at Birmingham)., Commercial Support - Supported by Gilead Sciences, Inc under an investigator-initiated protocol NCRR L1RR025752



Performance of creatinine-based estimating equations in patients on PI/r versus no PI/r Left: Bias; Right: Accuracy; PI/r, ritonavir-boosted protease inhibitor; GFR, glomerular filtration rate; CKD-EPI$_{cr}$, GFR by CKD-EPI creatinine equation; MDRD, GFR by MDRD Study equation; CG, creatinine clearance by Cockcroft-Gault equation indexed to 1.73m^2 body surface area. Error bars represent 95% confidence intervals.

TH-PO397

CKD Prevalence in the US Military Health System (MHS) by Laboratory vs. ICD-9 Coding

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Background: Epidemiological analysis of CKD is limited by variable definitions of CKD and accuracy of the diagnosis in the medical record. We report here on CKD prevalence by laboratory and coding data in the MHS Data Repository (MDR), a large database for a universal system of coverage of US active-duty military, retirees, and family members, with demographics similar to that of the US general population.

Methods: Patient data for age ≥ 18 from Fiscal Year (FY) 2006-15 were extracted from the MDR. CKD diagnosis was based on either ICD-9 codes or from labs (CKD-EPI eGFR < 60 mL/min/1.73m^2, uPCR ≥ 0.15 g/g, or uACR ≥ 30 mg/g). Code+ was defined as ≥ 1 inpatient or ≥ 2 outpatient CKD codes during the FY. Two definitions of Lab+ were used: 2Lab+ (gold standard) was defined as the most recent labs in the FY being persistently abnormal over ≥ 3 months. 1Lab+ was defined as any abnormal lab during the FY. Code+ and 1Lab+ were compared to 2Lab+ by sensitivity/specificity, chi-square, Cohen's kappa, and McNemar's test.

Results: For FY2015, data from 3,360,305 patients were analyzed (mean age = 37.6±15.6). 969,873 (28.9%) had labs. Among patients with labs, 2Lab+CKD prevalence was 2.5% overall and increased to 9.7% for age ≥ 60. 1Lab+CKD prevalence was 9.9% overall and increased to 31.5% for age ≥ 60. Code+CKD prevalence was 2.8% overall and 4.8% in patients with labs. Only 54.8% of 2Lab+ were also Code+. 1Lab had a Positive Predictive Value (PPV) = 0.25 and a Negative Predictive Value (NPV) = 1.0 for 2Lab (Table). Code had a PPV = 0.28 and a NPV = 0.99 for 2Lab. For age ≥ 60, PPVs were higher for both 1Lab+ (0.31) and Code+ (0.47).

Conclusions: Based on ICD-9 codes, provider awareness of CKD in the MHS is low. Use of a single lab value significantly overestimates CKD prevalence and has a poor PPV compared to repeat measures. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Departments of Army/Navy/Air Force, Department of Defense, Department of Health and Human Services, or the US Government.

Funding: Other U.S. Government Support

OVERALL	2Lab+	2Lab–	
1Lab+	24,281	71,827	96,108
1Lab–	0	873,765	873,765
	24,281	945,592	969,873
Sensitivity =1.0, Specificity=0.92			
PPV=0.25, NPV=1.0, κ=0.38			

OVERALL	2Lab+	2Lab–	
Code+	13,303	33,503	46,806
Code-	10,978	912,089	923,067
	24,281	945,592	969,873
Sensitivity =0.55, Specificity=0.96			
PPV=0.28, NPV=0.99, κ=0.35			

AGE ≥ 60	2Lab+	2Lab–	
1Lab+	19,422	43,270	62,692
1Lab–	0	136,534	136,534
	19,422	179,804	199,226
Sensitivity =1.0, Specificity=0.76			
PPV=0.31, NPV=1.0, κ=0.38			

AGE ≥ 60	2Lab+	2Lab–	
Code+	10,393	11,892	22,285
Code-	9029	167,912	176,941
	19,422	179,804	199,226
Sensitivity = 0.54, Specificity=0.93			
PPV=0.47, NPV=0.95, κ=0.44			

TH-PO398

State-Level Kidney Disease Surveillance Using Medicaid Data in Michigan and California

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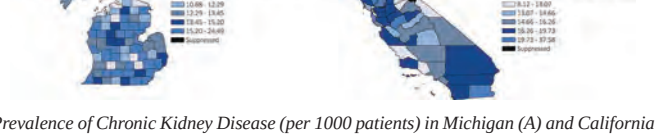
Background: Medicaid provides health insurance for low-income individuals, including children. Coverage varies by state. We examined the feasibility of using state-level Medicaid data for chronic kidney disease (CKD) surveillance in a disadvantaged, low income, and younger US population.

Methods: The 2012 Medicaid Analytic eXtract data for the states of Michigan (MI) and California (CA) were evaluated. Patients with >3 months of Medicaid eligibility ≥1 claim were included. CKD was defined by two outpatient or one inpatient ICD-CM diagnosis codes. Descriptive analyses were conducted for children (age <22) and adults (age ≥ 22).

Results: The study population for MI (n=1,700,044) included 989,834 (58%) children and for CA (n=7,457,920) included 3,661,569 (49%) children. CKD was diagnosed in 0.9% of children (9,160) and 3.7% of adults (26,580) in MI, and 0.7% of children (24,090) and 3.0% of adults (114,183) in CA. There was geographic variation in prevalence of diagnosed CKD (Figure 1). Higher proportions of diabetes (DM) and hypertension (HTN) were seen in those with CKD (vs. non-CKD) in MI (DM: children 3.9% vs. 0.7%, adults 41.3% vs. 11.7%; HTN: children 7.6% vs 0.6%, adults 62.4% vs 17.2%) and CA (DM: children 2.2% vs. 0.4%, adults: 40.6% vs. 7.9%; HTN: children 6.6% vs. 0.2%, adults 47.7% vs. 11.1%). Emergency department use was higher among CKD patients (vs. non-CKD) in both MI (children 59.4% vs. 40.5%; adults 65.9% vs.40.9%) and CA (children 49.8% vs. 28.8%; adults 41.6% vs. 21.4%).

Conclusions: We demonstrate the feasibility of utilizing Medicaid data from two states for CKD surveillance efforts. There is substantial geographic variation of diagnosed CKD in both MI and CA with higher prevalence mostly in urban areas. Children and adults with CKD had a higher prevalence of comorbidities and ED use compared to those without CKD. This work serves as a foundation for future analyses of other state and longitudinal data to guide upstream disease prevention and management for a young and socioeconomically disadvantaged population.

Funding: Other U.S. Government Support



Prevalence of Chronic Kidney Disease (per 1000 patients) in Michigan (A) and California (B), by county

TH-PO399

Forecasting Future Growth in CKD in the Irish Population: 2005-2024

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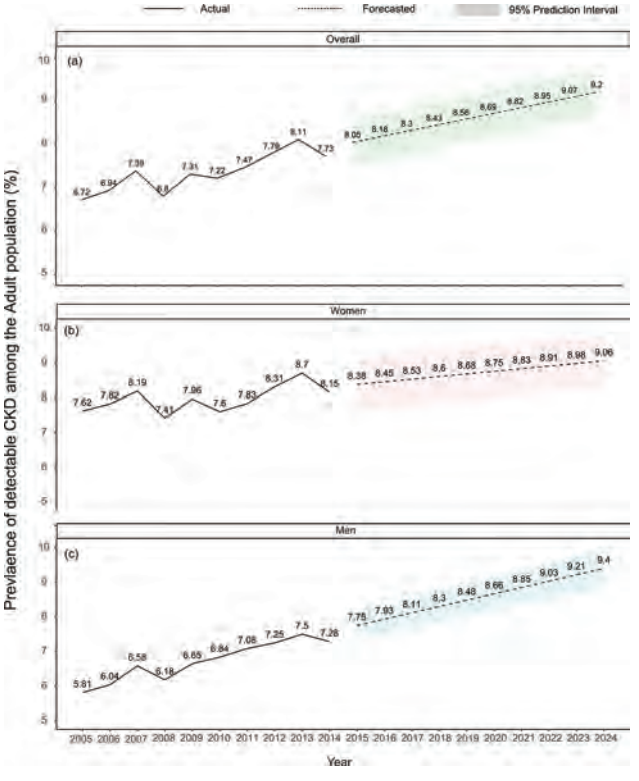
Background: Although chronic kidney disease (CKD) is common in the Irish health system, few data exist on longitudinal trends and future growth. To better inform strategic planning of renal services, we determined future trends in CKD burden in the Irish population.

Methods: Data from the National Kidney Disease Surveillance System (NKSS) determined age and sex standardised prevalence of CKD among adults > 18 yrs, in Midwest and Northwest regions from 2005-2014. CKD was defined as eGFR <60 ml/min per 1.73 m^2 using the CKD-EPI equation. Four forecasting models (naive with trend, exponential smoothing, Holt's linear trend, and autoregressive integrated moving average (ARIMA)) estimated future prevalence of CKD beyond 2015 to 2024. The population at risk was derived from national census data in 2006 and 2011.

Results: Study included 478,251 participants, average age 55.5 (18.8) years with 53% female. From 2005 to 2014, overall prevalence increased significantly from 6.72% (95% CI 6.71-6.74%) to 7.73% (7.71-7.46%), with significantly greater increases for men [5.81 (5.78,5.85) to 7.28 (7.25,7.32), p< 0.001)] than for women [7.62% (7.59,7.66%) to 8.15 (8.12,8.19)]. The largest growth occurred in the elderly age 75+, p-value <0.001, while prevalence fell in all other age groups, p value <0.001 for each. By 2024, overall prevalence was predicted to increase to 9.20 % (95% PI 8.66, 9.75); men 9.40% (95% PI: 8.81, 9.99); and women 9.06 % (95% PI: 8.31, 9.80).

Conclusions: In line with current trends, we forecast continued growth in CKD burden up to 2024. These are driven principally by increases in the elderly. Given the risk implications on rates of kidney failure, morbidity and mortality, actionable policies that promote better CKD prevention and treatment strategies should be vigorously pursued.

Funding: Government Support - Non-U.S.



TH-PO400

The Prevalence, Awareness, and Treatment of CKD in Korean Adults

Kyeong Min Kim. *Eulji medical center, Daejeon, Republic of Korea.*

Background: Chronic kidney disease (CKD) is a global public health problem, and its prevalence has dramatically increased with an increasing old aged and their chronic diseases. It is known that the rate of recognition and treatment of chronic renal failure is very low. But there is a lack of data on prevalence, awareness, treatment of CKD that is representative of the Korean population. Our objective was to investigate the prevalence, awareness and treatment in Korean CKD patients.

Methods: Among adults aged ≥19 years who participated in the Korea National Health and Nutrition Examination Survey (KNHANES) between 2013 and 2014, a total of 15,568 subjects were analyzed. CKD prevalence was defined as an eGFR < 60mL/min/1.73m2 or spot urine albumin to creatinine ratio ≥ 30 mg/g.

Results: A total of 9,550 incident CKD patients between 2013 and 2014 were included in the analysis. The prevalence of CKD was 8.66%. Of the total patients, 341 patients (3.78%) were in the stage 1 of CKD, 316 patients (2.52%) in the stage 2, 311 patients (2.15%) in the stage 3, 15 patients (1.16%) in stage 4 and 4 patients (0.04%) in the stage 5. The rate of awareness and the treatment of CKD were 2.19% and 1.35%, respectively.

Conclusions: In this nationally representative KNHANES data, very low awareness and treatment observed for Korean patients with CKD. And we analyzed the prevalence of chronic kidney disease in Korean adults using the most up-to-date data available. The present findings provide meaningful epidemiological data.

Table 1. Awareness of CKD in South Korea

Diagnosis of CKD by Doctor	Non-CKD	CKD	Total
None	8029(96.5)	906(94.28)	8935(96.27)
Yes	9(0.11)	21(2.19)	30(0.32)
Unknown or unresponsive	282(3.39)	34(3.54)	316(3.4)
Total	8320(100)	961(100)	9281(100)

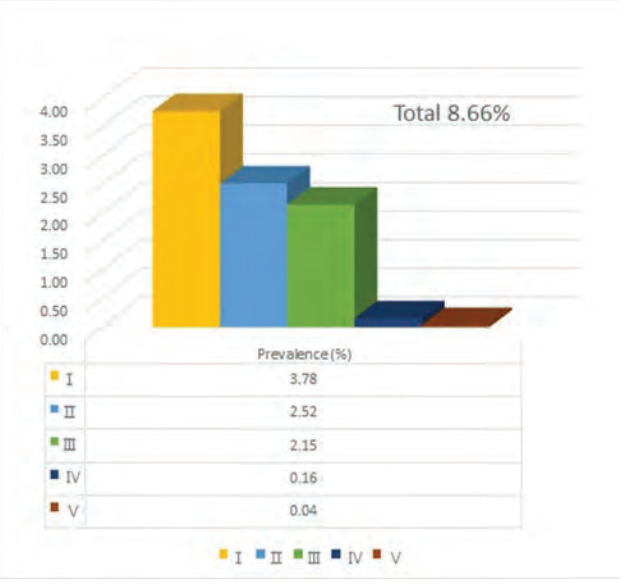


Figure 1. Prevalence of CKD in South Korea

TH-PO401

Histopathologic and Demographic Features Associated with ESRD and Death

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Background: The ability to stratify risk for developing end-stage renal disease and death in those who undergo a kidney biopsy allows us to better prognosticate patients who are at higher risk. We hypothesize that histopathologic features in kidney biopsy specimens augment risk stratification for ESRD and death over and above a fully adjusted demographic and clinical model.

Methods: Data from 2,720 individuals who underwent a kidney biopsy from 2001 to 2015 from the Biobank Biopsy Cohort of Indiana were obtained. Natural language processing facilitated annotation of histopathologic features and discrete clinical data was added using bioinformatics methods. Primary outcome was defined as time to ESRD or death, whichever occurred earlier. Censoring was done at 5 year follow up. Using Cox proportional hazard models, we studied relationship between demographic variables, comorbidities, baseline clinical features, primary diagnosis, and histopathologic features.

Results: Within 5 years of biopsy, 625 (23.0%) patients reached the primary endpoint of ESRD or death. Survival analysis with demographic and clinical variables as covariates and stratification by baseline renal function, showed following histopathologic features stratifying risk for the primary outcome, glomerular obsolescence (Hazard Ratio 1.81, 95% CI, 1.42 to 2.32, Pvalue < 0.001), interstitial fibrosis and tubular atrophy (HR 1.61, 95% CI, 1.30 to 2.0, Pvalue < 0.001), arteriolar hyalinosis (HR 1.46, 95% CI, 1.15 to 1.85 Pvalue < 0.01), and nodular mesangial sclerosis (adjusted HR 1.44, 95% CI, 1.15 to 2.82 Pvalue <0.01).

Conclusions: Histopathologic features on kidney biopsy specimens further augmented risk prediction for ESRD and death when compared to models with demographic and clinical variables alone. Inclusion of histopathologic features in ESRD and death risk models facilitates improved prognostication.

Funding: NIDDK Support

TH-PO402

The Histological Spectrum of CKD in HIV-Infected Black Patients: A Single-Centre Experience

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Background: HIV infection has become one of the world's most serious health and developmental challenge affecting 36.9 million people. Kidney disease is the 4th most common cause of death among HIV-infected patients. HIV-Associated Nephropathy (HIVAN) has been documented as the most common cause of chronic kidney disease (CKD) in HIV-1seropositive patients. Although 9% of world's HIV-infected patients live in Nigeria, data on spectrum of kidney diseases affecting HIV-infected patients are still paltry. The study was undertaken to determine the histological spectrum of CKDs in HIV-infected patients.

Methods: Fifty-eight adequate biopsy samples from 72 adult HIV- infected patients with ≥stage 3 CKD who underwent real time ultrasound guided kidney biopsy between April 2016 and August 2018 were studied using light microscopy and immunohistochemistry. Patients having diabetes mellitus, other viral infections, obstructive uropathies, other systemic diseases with renal involvement and malignancies were excluded.

Results: There were 25 (43.1%) males and 33 (56.9%) females. Participants were aged 21-65 years. Mean age was 43.86± 9.83years. Forty-three (74.1%) patients had WHO clinical asymptomatic disease. Only 9/58(15.5%) patients had CD4 cell count < 200 cells/mm^3. Histology showed 13(22.4%) HIVAN, 8(13.8%) normal histology and 37(63.8%) non-HIVAN lesions including: 12(20.7%) FSGS (NOS), 7(12.1%) focal global glomerulosclerosis, 6(10.3%) chronic interstitial nephritis, 4(6.9%) minimal chronic damage, 4(6.9%) arterionephrosclerosis, 3(5.2%) FSGS (cellular variant) and 1(1.7%) BK-virus nephropathy.

Conclusions: Although HIVAN remains the predominant histology finding in HIV-infected patients with CKD, its prevalence in this study is less than previous reports emphasizing the need for kidney biopsy for accurate diagnosis of CKD in HIV-infected patients.

Funding: Private Foundation Support

TH-PO403

Clinical and Pathological Characterization of Patients with ESKD from a Potential Mexican CKD of Undetermined Etiology (CKDu) Hotspot

Sofía De Arrigunaga,[1] Marco A. Ascencio Martinez,[1] Laura Crespo Ortega,[1] Gregorio Villarreal,[1] Gregorio T. Obrador,[1] Antonio Villa,[1] Diego J. Aguilar-Ramirez,[2] Magdalena Madero.[3] *[1]Universidad Panamericana, School of Medicine, Mexico City, Mexico; [2]University of Oxford, Oxford, United Kingdom; [3]Instituto Nacional de Cardiologia, Mexico, Mexico.*

Background: Mesoamerican nephropathy (MeN) – the chronic kidney disease of unknown etiology (CKDu) identified in Central American hotspots – affects mostly young, male farmers without traditional risk factors (TRF) for kidney disease. To date, CKDu hotspots have not been described in Mexico. Between 1991 and 2018, 57 patients from a sugarcane region in Tierra Blanca, Veracruz (Mexico) were referred to our Institution for kidney transplantation. The aim of this study was to identify the clinical characteristics and risk factors for CKDu in these patients and compare their histopathological findings with others previously reported.

Methods: Sociodemographic, clinical, laboratory and pathological data were collected from medical records. Patients were categorized as having TRF for CKD (diabetes mellitus and/or hypertension) or not (CKDu). Descriptive statistics were used and multivariate logistic regression models were built to identify CKDu associated risk factors.

Results: The mean age of the 57 patients was 26.9 ± 9.7 years, 70% were male, and 44% farmers. Mean BMI was 23.0 ± 4.17, and 39% had a positive family history for CKD. Thirty (53%) patients met CKDu criteria. In the multivariate logistic regression model, agricultural work and family history of CKD were independent risk factors for CKDu, while high BMI conferred protection. Of the six patients who underwent kidney biopsy, 5 showed atrophy, mild sclerosis, tubulointerstitial nephritis, and inflammatory infiltrate, all compatible with previously reported MeN findings.

Conclusions: The clinical and pathological characteristics of this group of patients suggest that Tierra Blanca, Veracruz (Mexico) may be a potential CKDu hotspot. This conclusion is further supported by another study done by our group that showed a high prevalence of CKDu in this region. Further research is needed to confirm our findings.

Characteristic	OR (CI 95%)	p
Age in years	0.99 (0.9 - 1.0)	0.75
Sex	0.96 (0.2 - 4.5)	0.96
BMI (kg/m^2)	0.81 (0.8 - 1.0)	0.03
Agriculture work	4.61 (1.0 - 21.3)	0.05
Family History of CKD	4.56 (1.2 - 17.7)	0.03

Table 1. Logistic regression model for CKDu

TH-PO404

Biomarkers and CKD Progression: Avoiding Pitfalls in Methodology

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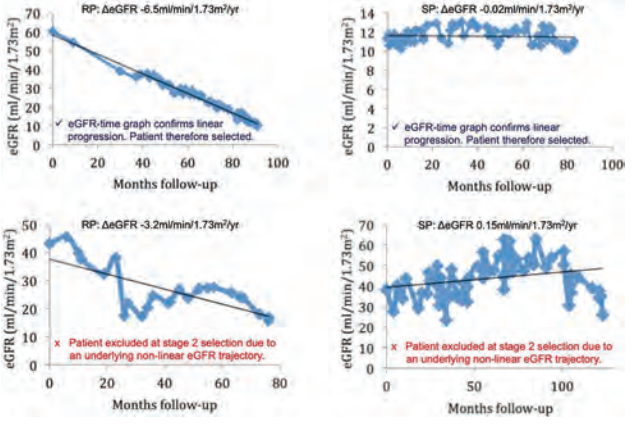
Background: Many studies that report biomarkers predictive of CKD progression share a key pitfall: poor characterisation of patients' progression, due to a lack of eGFR values and a short follow-up time. We apply a 2-stage method to robustly categorise patients with linear CKD progression for an upcoming biomarker study.

Methods: We included 2038 CKD patients in the Salford Kidney Study, with a total of 66455 outpatient eGFR values. Stage 1: Delta (Δ) eGFR (±ml/min/1.73m^2/yr) for each patient was calculated by linear regression. ΔeGFR ≤-3ml/min/1.73m^2/yr defined rapid progressors (RP); -0.5 to +1m/min/1.73m^2/yr defined stable progressors (SP). Stage 2: We assessed the eGFR-time graphs of RP and SP using our hospital e-records. Patients were selected if they had a clear, linear pattern of progression. To validate our method, we analysed plasma levels of KIM-1 and NGAL, biomarkers shown to be predictive of ESRD, in RP and SP, expecting higher levels in RP at stages 1 and 2.

Results: By linear regression alone, there were 388 RP and 458 SP. Stage 2 refined this group by unmasking non-linear progression, excluding 22% of RP and 33% of SP in the process (see figure). Median ΔeGFR in the final RP group was -4.69ml/min/1.73m^2/yr (IQR -5.86 to -3.65) and 0.09ml/min/1.73m^2/yr (IQR -0.53 to 0.93) in SP; p<0.001. Median number of eGFR values per patient was 23 in both groups (IQR 15-35 in RP; 15-39 in SP). Median follow-up was 52months (IQR 36-73) in RP and 78months (IQR 56-112) in SP. KIM-1 and NGAL levels were higher in RP than SP in stage 1 (p<0.001), and also higher in the refined stage 2 group, but significant for only NGAL, p=0.02.

Conclusions: We believe we are the first to combine linear regression and eGFR-time graphs to precisely stratify patients based on their ΔeGFR. Our method, aided by a cohort with multiple eGFR values and long follow-up, should help yield improved insights between measured biomarkers and specific, linear patterns of CKD progression.



Illustrative graphs of the stage 2 process

TH-PO405

Evaluation of Kidney Fibrosis Based on Imaging and Histologic Analysis

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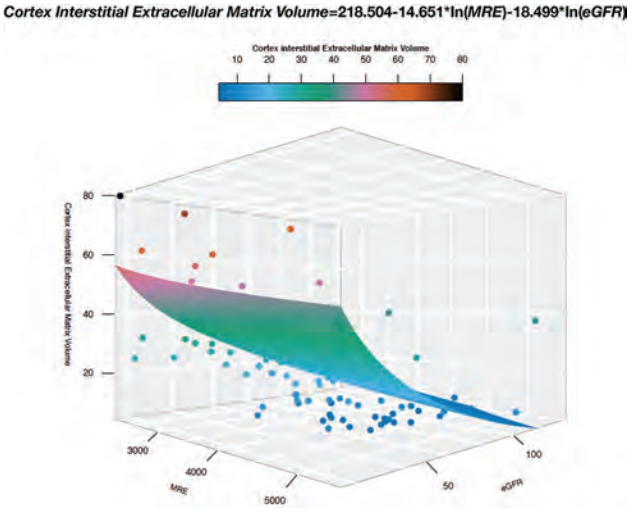
Background: Increased institial extracellular matrix (EM) and peritubular capillary (PTC) dropout are two key pathologic features of the fibrosing kidney. There is absence of multiple dimensional pictures to show fibrotic kidney from function, imaging and morphology.

Methods: We derived a represented model for EM ratio and PTC densities using intravoxelincoherent motion diffusion weighted imaging (IVIM-DWI), magnetic resonance elastography (MRE) and glomerular filtration rate (estimate GFR). 97 patients with chronic kidney diseases from stage 1 to 4 were studied. EM ratio and kidney microcirculation were evaluated by pathology. A multi-dimensions perspective and relationship of kidney fibrosis based on histology, imaging and GFR were established. Multiple linear regression models were performed.

Results: The cortex EM ratios were linear with the nature logarithm of MRE and eGFR, which were both negatively associated with EM ratios. The best fitted model was as below: EM ratio=218.504-14.651×In(MRE)-18.499×In(eGFR) The lower of eGFR and MRE, there were higher of CEMR (Figure 1). The PTC densities were linear with DWI-Fraction and eGFR, which were both positively related with PTC. The best fitted model was as below: PTC density=17.914+9.403×(DWI-Fraction)+0.112×eGFR The lower of eGFR and DWI-Fraction, there were lower of PTC (Figure 2).

Conclusions: Our study firstly provides histological evidences to support that IVIM-DWI and MRE can effectively evaluate the EM ratio and PTC density. These findings delineate the multi-dimensional picture of kidney fibrosis.



TH-PO406

Reproducibility of the SOMAscan Proteomic Assay in CKD: A Pilot Study in the Chronic Renal Insufficiency Cohort (CRIC) for the CKD Biomarkers Consortium

Ruth F. Dubin,[1] Rajat Deo,[2] Yue Ren,[2] Haochang Shou,[2] Harold I. Feldman,[2] Eugene P. Rhee,[3] Josef Coresh,[6] Paul L. Kimmel,[4] Peter Ganz.[5] *[1]UCSF, San Francisco, CA; [2]University of Pennsylvania, Philadelphia, PA; [3]Massachusetts General Hospital, Newton, MA; [4]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [5]University of California, San Francisco, San Francisco, CA; [6]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD.*

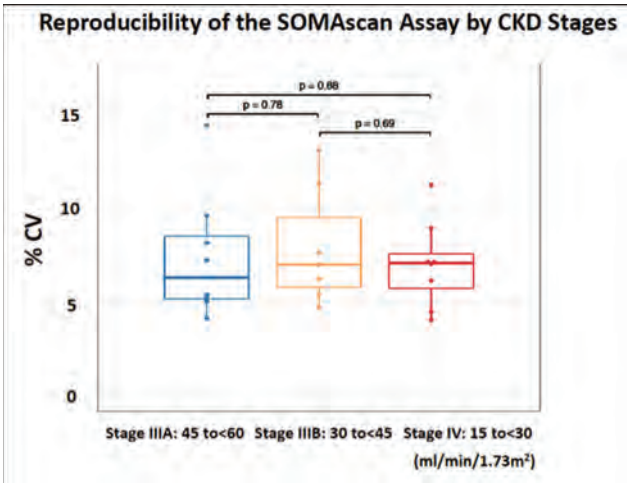
Background: The Slow Off-rate Modified Aptamer proteomic assay (SOMAscan) is a transformative tool used increasingly in medical research as it affords the opportunity to measure 4,933 unique proteins in 150µl of plasma. In prior studies, mostly outside of the setting of chronic kidney disease (CKD), these assays have low levels of analytical variability, with median inter- and intra-assay coefficients of variation (CV) of 4–6%. Whether the biochemical alterations present in CKD impact the assay's precision is unknown. We examined the reproducibility of these assays in participants with CKD.

Methods: Cryopreserved blinded split duplicate plasma samples from 24 CRIC participants were assayed at SomaLogic (Boulder, CO). Among these 24, 8 were from each of CKD Stages IIIa, IIIb, and IV. Within each stage, 4 had diabetes, and 4 had history of CVD. Using the SOMAscan v.4, 4933 unique proteins were quantified in each paired sample in fluorescent units.

Results: Prior to unblinding, 1 sample was excluded for having a technical error. For the remaining 23 paired samples, the median intra-assay CV for all proteins was 7%; 95.6% of all 4,993 proteins had CV ≤10% and 99.8% had a CV ≤20%. The distribution of CV's did not differ by CKD stage (Figure).

Conclusions: Measurement of 4,993 unique proteins with SOMAscan in plasma samples of patients with CKD was achieved with low levels of analytical variability. These data demonstrate that the SOMAscan assay is suitable for large-scale proteomic studies of individuals with CKD.

Funding: NIDDK Support



TH-PO407

The Association Between FIB-4 Index and the Prevalence of CKD: The Fukuoka Kidney Disease Registry Study

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Background: Growing evidences have shown that non-alcoholic fatty liver disease (NAFLD) associates with chronic kidney disease (CKD). Liver biopsy is the gold standard for assessing the severity of NAFLD. However it is difficult to be used as a routine screening tool due to its possible risk. Therefore non-invasive assessments to evaluate NAFLD by combining clinical and routine laboratory parameters have been developed. One of such assessments, Fibrosis-4 (FIB-4) index, defined as as [age (years) × AST (U/L)/[platelet count (10^9/L) × √ALT (U/L)], has shown a good correlation with historical severity of NAFLD. However, it is still unclear whether FIB-4 index associates with CKD.

Methods: In this cross-sectional study, we included 3,197 CKD patients who participated in an ongoing prospective study, the Fukuoka Kidney disease Registry Study. We evaluated the association between FIB-4 index and either the prevalence of estimated glomerular filtration rate (eGFR)<60 ml/min/1.73 m² or urinary albumin creatinine ratio (UACR)≥30 mg/g. Patients were divided into quartiles according to their baseline FIB-4 index levels: quartile (Q) 1, <1.12; Q2, 1.12–1.66; Q3, 1.67–2.30; and Q4, ≥2.31. The association between FIB-4 index levels and the prevalence of eGFR<60 ml/min/1.73 m² or UACR≥30 mg/g was estimated using the logistic regression analysis.

Results: In this study, 2464 (77.0%) patients were eGFR<60 ml/min/1.73 m², and 2433 (76.1%) showed UACR≥30 mg/g. FIB-4 index was negatively correlated with eGFR levels (r = -0.38, P<0.001), whereas there was no correlations with UACR levels (r = 0.014, P = 0.42). The multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for prevalence of eGFR<60 ml/min/1.73 m² were 1.25 (0.92–1.71), 1.50 (1.04–2.16), and 1.85 (1.18–2.89) in Q2, Q3, and Q4, respectively, compared with patients in the lowest category (Q1) (P for trend = 0.005). Every 0.1 increment in FIB-4 index was associated with a 1.03-fold (95% CI 1.01–1.05) increased prevalence of eGFR<60 ml/min/1.73 m² after adjusting for the potential confounding factors.

Conclusions: Higher FIB-4 index was associated with higher ORs of eGFR<60 ml/min/1.73 m². Further follow-up study is needed to determine whether FIB-4 index predicts the development and progression of CKD.

TH-PO408

Association of Serum Uromodulin with Mortality, Cardiovascular Disease, and Kidney Function Decline in CKD Patients: The GCKD Study

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Background: Uromodulin is exclusively produced by tubular cells and released into both urine and serum. Lower sUMOD has been associated with end-stage renal disease (ESRD) in Chinese chronic kidney disease (CKD) patients and with higher risk for mortality in patients undergoing coronary angiography. The association of sUMOD with mortality, cardiovascular (CV) events and ESRD in Caucasian CKD patients is unknown.

Methods: We measured sUMOD in 5143 participants enrolled in the German Chronic Kidney Disease (GCKD) study. The associations of baseline sUMOD with all-cause mortality, major adverse CV events (MACE; a composite of fatal CV event, non-fatal myocardial infarction or stroke, or incident peripheral vascular disease) and ESRD (dialysis or transplantation) were evaluated using multivariable Cox regression analysis, adjusting for demographics, estimated glomerular filtration rate (eGFR), albuminuria, CV risk factors and medication.

Results: The mean age was 60±12 years, 60% were male. sUMOD level was 98±60 ng/ml, eGFR was 47±17 ml/min/1.73 m^2 and 78% had eGFR<60 ml/min/1.73 m^2. Patients in the lower sUMOD quartiles had lower eGFR and higher albuminuria. Prevalent diabetes, hypertension, coronary artery disease and stroke at baseline were more frequent in lower sUMOD quartiles. During a follow-up of 4 years, 319 patients died, 398 developed MACE and 216 ESRD (Table 1). In multivariable analysis, higher sUMOD was significantly associated with lower hazard for mortality (HR 0.572, 95%-CI [0.377-0.869] for the highest versus lowest quartile), MACE (HR 0.632 [0.445-0.898]) and ESRD (HR 0.238 [0.103-0.547], Table 1).

Conclusions: Higher sUMOD is independently associated with lower risk for mortality, CV events and ESRD in Caucasian CKD patients. A better understanding of the underlying mechanisms may lead to therapies offering both renal and CV protection in CKD patients.

Table 1: Associations of serum uromodulin (sUMOD) with mortality, end-stage renal disease and cardiovascular disease

	N/o events	Univariate	Plus adjusted for demographics[a]	Plus adjusted for eGFR and ACR[b]	Plus adjusted for CVD HF, prevalent disease and medication[c]
All-cause mortality					
Q1	319/4953	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2		0.61 (0.48-0.82)	0.69 (0.53-0.90)	0.76 (0.57-1.01)	0.80 (0.60-1.07)
Q3		0.48 (0.36-0.62)	0.53 (0.39-0.71)	0.62 (0.45-0.86)	0.70 (0.50-0.97)
Q4		0.31 (0.22-0.44)	0.40 (0.28-0.57)	0.50 (0.34-0.75)	0.57 (0.38-0.87)
End-stage renal disease					
Q1	216/4953	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2		0.50 (0.37-0.68)	0.50 (0.37-0.68)	0.73 (0.53-0.99)	0.73 (0.52-1.01)
Q3		0.27 (0.19-0.40)	0.28 (0.19-0.42)	0.63 (0.43-0.96)	0.65 (0.43-0.99)
Q4		0.07 (0.03-0.14)	0.08 (0.03-0.13)	0.27 (0.12-0.59)	0.24 (0.10-0.55)
Cardiovascular disease					
Q1	398/4953	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2		0.73 (0.57-0.93)	0.75 (0.59-0.96)	0.76 (0.59-0.99)	0.85 (0.66-1.11)
Q3		0.61 (0.47-0.79)	0.64 (0.49-0.83)	0.70 (0.53-0.93)	0.78 (0.58-1.03)
Q4		0.35 (0.26-0.48)	0.43 (0.32-0.59)	0.49 (0.35-0.69)	0.63 (0.45-0.90)

95%-confidence intervals for the hazards ratios are given in parentheses. Cardiovascular disease defined as myocardial infarction, stroke or death myocardial infarction. Abbreviations: CVD=cardiovascular disease; HR=hazard ratio; SD=standard deviation; eGFR=estimated glomerular filtration rate; ACR=urinary albumin/creatinine ratio; RF=risk factors. Quartile distribution: Quartile 1 (Q1)<55.4 ng/ml, Quartile 2 (Q2)=55.6-83.4 ng/ml, Quartile 3 (Q3)=83.4-125.3, Quartile 4 (Q4)>125.3 ng/ml.
[a] adjusted for age, sex, body-mass-index
[b] adjusted for * + eGFR & ACR
[c] adjusted for * + pre-ident CVD, diabetes and hypertension at baseline, systolic blood pressure, diastolic blood pressure, serum high and low density lipoprotein concentration, serum C-reactive protein and phosphorus concentration, prescription of diuretics, lipid and blood pressure lowering medication

TH-PO409

Association Between Urinary A Megalin and Metabolic Syndrome in Japanese Adults

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Background: Metabolic syndrome (MetS) is a risk factor for chronic kidney disease (CKD). Megalin is an endocytic receptor in proximal tubule epithelial cells that mediates the endocytosis of glomerular-filtered toxic substances and is recognized as a potential therapeutic target for MetS-related CKD. Although microalbuminuria is a well-known marker of MetS-related CKD, markers for its early detection remain unestablished. Thus, in this study, we assessed the association of urinary biomarkers including ectodomain (A-megalin) and full-length (C-megalin) forms of megalin with MetS in Japanese adults.

Methods: Among 348 subjects (184 men; average age 61.3 years old) with urine albumin-to-creatinine ratio (ACR) < 300 mg/g on health check examination, urine biomarkers including A-megalin, C-megalin, ACR, α_1-microglobulin (a1M), β_2-microglobulin, *N*-acetyl-β-D-glucosaminidase, and podocalyxin were assessed cross-sectionally. MetS scores were adopted from National Cholesterol Education Program (third revision) of the Adult Treatment Panel criteria modified for Asians; subjects with ≥3 components were diagnosed as having MetS.

Results: Subjects included 97 patients with MetS, 20 with diabetes, and 134 with hypertension; median body mass index, estimated glomerular filtration rate (eGFR) and ACR were 22.6 kg/m^2, 74.4 mL/min/1.73 m^2, and 7.5 mg/g, respectively. MetS scores were positively correlated with urinary A-megalin, ACR, and a1M in Spearman's partial correlation analysis, adjusted for sex and age (r = 0.12, 0.25, and 0.13, respectively). In multivariable logistic regression analysis, higher urinary A-megalin was positively associated with MetS even after adjustment for age, sex, diabetes, hypertension, ACR and eGFR (adjusted odds ratio of MetS for elevated quartile of A-megalin: 1.37, 95% CI: 1.06-1.77, P = 0.01).

Conclusions: Urinary A-megalin was independently associated with MetS in a Japanese adult population. Further longitudinal studies are needed to confirm the association of urinary A-megalin with the development and progression of MetS-related CKD.

Funding: Commercial Support - Denka Seiken Co., Ltd.

TH-PO410

The Association Between Urinary Neutrophil Gelatinase-Associated Lipocalin and Renal Prognosis in Patients with CKD

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Background: Urinary neutrophil gelatinase-associated lipocalin (uNGAL) is a new biomarker for renal tubular damage. Significant associations between uNGAL and renal prognosis have been reported in many papers; however, it may often be affected by urinary tract infection (UTI), and its cut-off value in patients with chronic kidney disease (CKD) has not been well established. The aims of our study were to investigate the association between uNGAL and renal prognosis in CKD and to explore the cut-off value specific for patients with CKD.

Methods: This was a retrospective observational cohort study at a single hospital in Japan. We included adult patients with the estimated glomerular filtration rate (eGFR) of 10 to 70 mL/min/1.73m^2 from Jan 2017, who had at least one measurement of uNGAL. We used baseline uNGAL adjusted for urinary creatinine (Cr) as an exposure variable and divided the patients into quartiles. The renal outcome was defined as a 30% increase in serum Cr from baseline values. UTI was determined by baseline urinalysis. We performed survival analyses for the renal outcome, by using the Cox proportional hazards model including restricted cubic spline (RCS) curves. We also performed longitudinal analyses for eGFR decline using the mixed effects model. All statistical analyses were done using STATA 13.1.

Results: In total, 195 patients with CKD were included. Mean age and eGFR at baseline were 70.6 years and 32.3 mL/min/1.73m^2, respectively. The median [interquartile range (IQR)] of baseline uNGAL and urinary protein to Cr ratio (uPCR) were 71 [21 - 219] ug/gCr and 0.71 [0.18 - 2.53] g/gCr, respectively. Patients with UTI showed significantly higher uNGAL at baseline than those without (226 [90 - 429] vs. 42 [15 – 123]). During the mean follow up of 171 days, there were 59 renal events. The Kaplan-Meier curve indicated a gradual risk escalation towards the upper quartiles of uNGAL. The adjusted hazards ratios of uNGAL quartiles were 2.8 [0.8 - 10.2], 4.9 [1.3 - 18.7], and 4.2 [1.0 - 17.2] in Q2, Q3, and Q4, respectively. The RCS curves suggested a significantly higher risk at 73.6 ug/gCr or greater. The eGFR slope, however, was comparable among Q1-4, while proteinuria was significantly associated with a greater reduction in eGFR.

Conclusions: A single measurement of uNGAL greater than 73.6 was associated with poor renal outcome. UTI may partially explain its limited prognostic value in clinical practice.

TH-PO411

Plasma Biomarkers and the Association with Kidney Outcomes in African Americans with High-Risk Apolipoprotein L1 Variants

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Background: The high-risk Apolipoprotein L1 (*APOL1*) genotype is associated with incident and progressive chronic kidney disease (CKD) in people of African ancestry. Previous studies have demonstrated that suPAR is associated with CKD in individuals with the APOL1 high-risk genotype. We assessed the associations of suPAR and other plasma biomarkers with CKD in this population.

Methods: We measured plasma suPAR, IL-18, MCP-1 and YKL-40 in 498 Bio*Me* Biobank participants with a high-risk *APOL1* genotype. Using multivariable Cox Regression, we determined the association of these biomarkers with a composite kidney outcome of ESRD or ≥ 40% sustained decline in eGFR during the follow-up period using sequentially adjusted models.

Results: Among 498 participants, median age was 56 years, 67.7% were female and baseline eGFR was 83.3 ml/min/1.73 m^2. 80 of the 498 (16.1%) experienced the composite outcome over a median of 5.9 years. After adjusting for demographics, comorbidities, medications, and eGFR, suPAR (adjusted HR 1.9 per doubling, 95% CI 1.2-3), IL-18 (adjusted HR 1.4 per doubling, 95% CI 1.1-1.9), MCP-1 (adjusted HR 1.6 per doubling, 95% CI 1.1-2.1), and YLK40 (adjusted HR 1.3 per doubling, 95% CI 1.1-1.5) were associated with increased risk of the composite kidney outcome (**Figure** left panel). After adjustment for 3 previously measured biomarkers (plasma TNFR1, TNFR2 and KIM-1), however, the independent associations between all 4 biomarkers and the kidney outcome were attenuated (**Figure** right panel).

Conclusions: Plasma suPAR, IL-18, MCP-1 and YLK40 were individually associated with kidney function decline or ESRD in individuals with high-risk *APOL1* genotype. However, the relevance of these biomarkers in the setting of other commonly measured biomarkers is unclear.

Funding: NIDDK Support

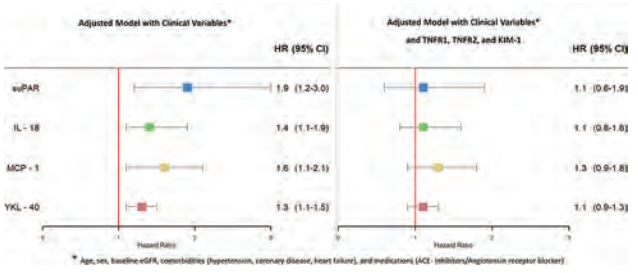

Figure. Adjusted Hazard Ratio for the Kidney Endpoint per Doubling in Plasma Biomarkers

TH-PO412

Attenuation of Estimated Glomerular Filtration Rate Decline After Arteriovenous Fistula Creation in Pre-Dialysis

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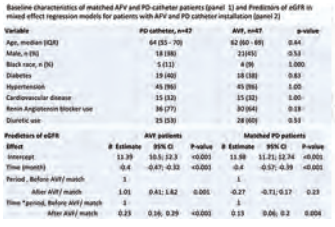
Background: Arteriovenous fistula (AVF) placement has been associated with potential attenuation of eGFR decline. Uncertainty remained as to whether this association is specifically related to AVF or rather involves confounding such as natural change in eGFR decline. We sought to assess CKD-EPI eGFR changes before and after AFV creation using a comparator group of peritoneal dialysis (PD) oriented patients.

Methods: This observational study included incident patients followed in a CKD clinic between 2000 and 2017. Patients with AVF placement were matched 1:1 (using age, sex, race, diabetes and eGFR) with patients who underwent PD catheter installation. Time zero/match-point was defined by AVF creation date (AVF group) or date when eGFR was closest to their 'AVF-pair' eGFR at time of AVF creation (PD-matched group). Mixed effect linear regression models were built to predict eGFR in the AVF and PD-matched groups. Estimated-GFRs were calculated using the CKD-EPI equation.

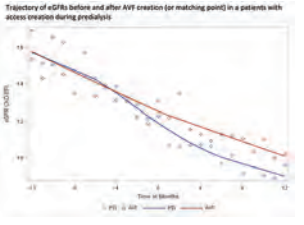
Results: Baseline characteristics of the 47 patients with AVF and 47 patients with PD catheter installation were globally similar. Median eGFR at time of AVF creation was 11.4 ml/min/1.73m^2 (and 11.9 ml/min/1.73m^2 in matched PD group). Predicted eGFR decreased by 0.4 ml/min per month in both groups. There was an attenuation in eGFR decline each additional month after AVF creation/match-point (*B* 0.23, p<0.001 AVF group, *B* 0.13, p<0.001 PD matched group). However, the period after AVF creation (or match-point) was associated with a fixed increase in predicted eGFR only for the AVF group (*B* 1.01, p<0.001).

Conclusions: In this matched cohort study, placement of AVF was associated with an increase in predicted eGFR in the AVF group only. There was however, an attenuation of monthly eGFR decline in both groups with progression of advanced CKD. Overall, this study supports other findings suggesting a contribution of AVF in the stabilisation of eGFR decline.


Baseline characteristics of matched AFV and PD-catheter patients (panel 1) and Predictors of eGFR in mixed effect regression models for patients with AFV and PD catheter installation (panel 2)

Variable	PD catheter, n=47	AVF, n=47	p-value
Age, median (IQR)	64 (55 - 70)	62 (60 - 69)	0.64
Male, n (%)	18 (38)	21(45)	0.53
Black race, n (%)	5 (11)	4 (9)	1.000
Diabetes	19 (40)	18 (38)	0.83
Hypertension	45 (96)	45 (96)	1.00
Cardiovascular disease	15 (32)	15 (32)	1.00
Renin Angiotensin blocker use	36 (77)	30 (64)	0.19
Diuretic use	25 (53)	28 (60)	0.53

Predictors of eGFR	AVF patients			Matched PD patients		
Effect	β Estimate	95% CI	P-value	β Estimate	95% CI	P-value
Intercept	11.39	10.5; 12.3	<0.001	11.99	11.21; 12.74	<0.001
Time (month)	-0.4	-0.47; -0.32	<0.001	-0.4	-0.57; -0.39	<0.001
Period , Before AVF/ match	1			1		
After AVF/ match	1.01	0.41; 1.62	0.001	-0.27	-0.71; 0.17	0.23
Time * period, Before AVF/ match	0			0		
After AVF/ match	0.23	0.16; 0.29	<0.001	0.13	0.06; 0.2	0.004



TH-PO413

Prevalence of Kidney Failure Among Adult Population in Madagascar

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Background: Kidney Failure becomes a public worldwide health problem mainly in a developing country. Few data is available in most of countries in Africa to specify the prevalence of CKD. We assessed the prevalence and risk factors of kidney failure among population in Madagascar.

Methods: We conducted a randomized, multicenter, cross sectional study among four provinces in the Island. It includes Tananarive, Majunga, Fianarantsoa and Tamatave. Kidney function was evaluated by capillary creatinine using strip test and creatinine meter. We defined kidney failure if the glomerular filtration rate calculated with the Equation of Chronic Kidney Disase Epidemiology was under than 60ml/mn/1,73m2. Cluster sample was used to characterise the study population.

Results: A total of 808 patients were included. Prevalence of kidney failure was 12.5%. Mean age was 38 years old (+/-15). Sex-ratio was 0,84. Patients were aged 25-55 years old in 62,1%. Normal socioeconomic class was found in 64% of the cases. Hypertension and diabetes were identified respectively in 30,3% and 7,7% in studied population. During screening, mean creatinine level was 99µmol/l (+/-25) and mean post prandial glycemia was 1,16g/dl (+/-0,3). According to KDIGO classification, patients were classified in Stage 3, 4 and 5 of CKD respectively in 10,76%(N=87), 0,7 % (N=6) and 1% (N=8). In mono variable analysis, kidney failure was related with gender (p =0,078), age(p =0,0001), socioeconomic class (p=0,005), familial back ground of hypertension (p =0,04), personnel back ground of hypertension (p <0,0001) and diabetes (p =0,05), the level of blood pressure during examination (p=0,088), glycemia (p = 0,003) and body mass index (p = 0,003). In Multiple variable analysis, it was related with female gender (OR =0,57; IC =0,35-0,92), age > 54 years old (OR =14,04; IC =5,25-37,5), rich socio economic class(OR =2,8; IC =1,03-7,81), overweight (OR =2,5; IC =1,08-4,92) and obesity (OR =2,5; IC =1,13-5,73)

Conclusions: This is the first study in Africa which evaluates the kidney failure by using creatinine strip test. The prevalence is high compare another african countries. Almost of the patients were seen lately over Stage 3 of CKD requiring a specialized medical follow-up. Prevention of all risk factors should be first of all the best solution.

TH-PO414

Estimated Glomerular Filtration Rate and Incidence of Major Surgery: A Population-Based Cohort Study

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Background: Approximately 1 in 9 Canadian adults have a surgical procedure each year, however whether the rates of major surgical procedures vary by level of estimated glomerular filtration rate (eGFR) is unknown. We aimed to quantify the incidence of major surgery by varying degrees of impaired kidney function.

Methods: We identified 1,455,565 adults in Alberta, Canada that had at least one outpatient serum creatinine measure or were in receipt of chronic dialysis between 2008 and 2009. As in prior studies, incident major surgical procedures were identified and categorized into 13 major surgical subtypes using procedure codes and physician claims; major surgery was defined by requiring hospital admission for at least one day. Surgical subtypes included musculoskeletal, intra-abdominal, lower urologic/gynecologic, head and neck, vascular, skin and soft tissue, cardiac, breast, neurosurgery, retroperitoneal, thoracic, anorectal, and ophthalmologic. Only the first event per surgical subtype was included. Patients were followed from January 1 2010 to December 31 2016, and were censored at kidney transplantation, outmigration or death. Incidence rates by eGFR strata were estimated using negative binomial regression and adjusted for age, sex, income, location, proteinuria, and comorbidity.

Results: The median age of the cohort was 51.6 years (IQR 39.4, 63.4) with the majority female (57.0%). Most patients had an eGFR ≥60mL/min/1.73m^2 (92.2%), with 0.1% having an eGFR <15mL/min/1.73m^2 not on dialysis. Over a median follow up of 7.00 years, musculoskeletal surgeries were the most common across all eGFR strata, with adjusted incidence rates between 9.48 per 1000 person-years (95%CI: 9.39, 9.56) for those with eGFR ≥60mL/min/1.73m^2 and 74.81 per 1000 person-years (95%CI: 65.60, 85.32) for dialysis patients. Similar trends of increasing surgical incidence for those with lower eGFR were noted for all surgical types except for breast and lower urologic/gynecologic.

Conclusions: In a large population-based cohort, incidence rates of major surgical procedures increased with decreasing eGFR, and were highest among dialysis-dependent patients. Further research is needed to investigate whether differences exist in perioperative outcomes and costs for those with varying degrees of kidney function.

TH-PO415

Clinical Significance of Creatinine Variability and Its Impact on Cardiovascular Outcomes in the General Population

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Background: Linear decline of glomerular filtration rate (GFR) is associated with aggravating the patient outcomes. Serum creatinine, which is commonly used for estimating GFR, often fluctuates throughout the serial measurement. The clinical significance of creatinine fluctuation among the general population whose renal function is prior to chronic kidney disease (CKD) development had not been demonstrated yet. Thus, we investigated the study to evaluate the impact of creatinine variability on patient outcomes.

Methods: A nationwide retrospective cohort study was performed using the database of Korean National Health Insurance System. Adult patients who received national health screening program and measured creatinine for ≥3 times between 2012 and 2016 were considered. Those who previously developed CKD were excluded. The variability of creatinine values were presented with variability independent of mean (VIM). The patients were classified into quartiles of the VIM and Q4 presented highest variability of creatinine. Then, the risks of myocardial infarction (MI), stroke and death were assessed according to the extent of variability.

Results: During the median follow up of 3.27 years, 3,509,899 participants were examined for association of creatinine variability and cardiovascular outcomes.

Participants with higher creatinine variability were significantly associated with elevated risk of MI (hazard ratio (HR) (95% confidence interval (95% CI)) 1.11 (1.04-1.18), stroke (HR (95%CI) 1.06 (1.00-1.13)) and death (HR (95%CI) 1.15 (1.09-1.21)), compared to those with the lowest quartile of creatinine variability.

Conclusions: Increased creatinine variability exhibited association with elevated risk of MI, stroke and death. In general population, whose renal function is prior to CKD development, monitoring of creatinine variability needs to be considered as the parameter of predicting the adverse outcomes, in addition to the decline of GFR.

TH-PO416

Progressive Kidney Failure: An Overlooked Feature of Down Syndrome

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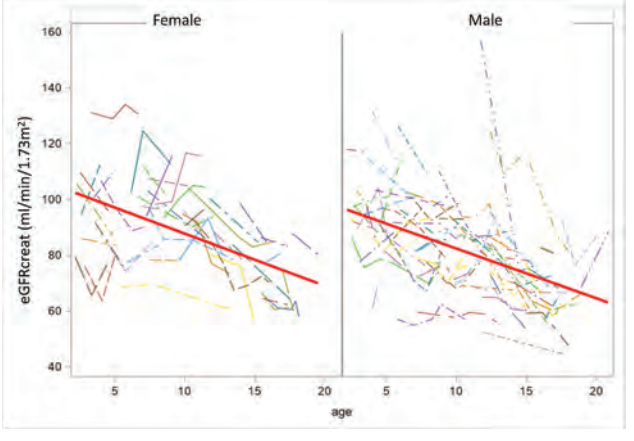
Background: Life expectancy of patients with Down syndrome (DS) has increased significantly in the last decades. DS is associated with a fourfold risk of urinary tract abnormalities, still data on renal dysfunction in DS patients are conflicting. The present study was set out to assess kidney function in a large pediatric tertiary DS clinic.

Methods: Retrospective analysis of data collected during routine visits at the DS clinic of VU medical center. All patients aged between 2 and 18 years in whom serum creatinine had been measured were eligible for inclusion. Exclusion criteria were glucocorticosteroid use, neuromuscular disease or primary referral to a nephrologist or urologist. Kidney function was assessed using the full-age spectrum equations, i.e. $eGFR_{crea}$= (107.3/[sCr (mg/dL)/Q (age- or height-based normal value)]) and $eGFR_{cys}$= (107.3/sCys (mg/L)/0.82). In a subgroup of 74 patients, a total of 374 serial creatinine measurements were analyzed by linear mixed modelling.

Results: Serum creatinine was available in 189 patients (63% boys), aged 10.8 ± 5.0 years, cystatin C in 143 (64% boys). Mean $eGFR_{crea}$ was 83.6 ± 16.7 mL/min/1.73m^2, mean $eGFR_{cys}$ 87.3 ± 12.0 mL/min/1.73m^2. Based on $eGFR_{crea}$, 32% of patients had CKD stage 1, 62% stage 2 and 6% stage 3. There was no relation between kidney function and co-morbidity (i.e. celiac disease, congenital heart disease, hypothyroidism and history of leukemia). Serial measurements showed a significant decline of $eGFR_{crea}$ (slope -2.01ml/min/1.73m^2/yr [95%CI -2.99 to -1.04] (p = 0.0001).

Conclusions: Mildly to moderately impaired renal function is a common finding in children with Down syndrome. The progressive loss of GFR is troublesome and calls for regular monitoring of kidney function both in children and in adults with DS to identify potentially treatable risk factors for disease progression such as hypertension and microalbuminuria.



Serial measurements of $eGFR_{crea}$

TH-PO417

Incidences of ESKD and Death Before ESKD Among US Veterans with New-Onset CKD

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Background: Epidemiologic data on competing-risk events of progressing to ESKD or dying before ESKD are mixed due to prevalent cohorts used. Using a recently constructed national incident CKD cohort, we report the 5-year incidence of these two events following new CKD onset by demographics, kidney function and comorbid conditions.

Methods: The cohort included 534,972 subjects with new onset CKD (stage 3-5) between 2002 and 2011 in the U.S. Veteran Affairs database. CKD onset was determined by two eGFRs (based on CKD-EPI equation) <60 mL/min/1.73 m^2 at >90 days apart. We excluded subjects in the database who had <2 years before the first eGFR<60 or had prior ESKD. As such, the index date identified was very close to new onset CKD. All subjects were followed for 5 years.

Results: The three groups had similar mean eGFRs at onset (range 49-50 ml/min/1.73m^2) and gender distributions (97-98% male). Blacks had younger onset age (mean 67 yrs) than Hispanics (71 yrs) and whites (74 yrs). Over the course of 5 years after onset, approximately two-thirds of the initial cohort remained alive in pre-ESKD, with Blacks having a lower percentage (65%) than Hispanics and Whites (68%). Among the one-third who progressed, Blacks and Hispanics had greater percentages who progressed to ESKD than Whites (10%, 7%, and 2%, respectively), whereas they had smaller percentages of dying before ESKD (25%) than Whites (30%). Males were more likely than females to develop these two events. The relative likelihood of the two events also varied by age and eGFR stage (Table), as well as comorbidities such as diabetic and hypertensive status and cardiovascular diseases (not shown).

Conclusions: Improving outcomes for patients with CKD could be more effective by identifying risk factors associated with differential risks of developing ESKD and dying before ESKD.

Funding: NIDDK Support

Percentages of events within 5 years of CKD onset

	Black (n=56,949)			Hispanic (n=17,414)			White (n=460,609)		
Group	Alive in pre-ESKD	ESKD	Death before ESKD	Alive in pre-ESKD	ESKD	Death before ESKD	Alive in pre-ESKD	ESKD	Death before ESKD
Overall	65.1	10.2	24.7	67.7	6.7	25.6	68.1	2.3	29.6
Male	64.8	10.2	25.0	67.5	6.8	25.8	67.9	2.3	29.8
Female	77.9	9.3	12.8	81.5	4.4	14.0	77.5	1.2	21.3
Age 18-55	61.9	25.0	13.1	62.5	23.7	13.8	75.1	9.3	15.6
Age 56-75	70.3	9.3	20.4	73.2	7.4	19.4	75.9	3.0	21.1
Age >75	55.1	2.4	42.5	60.4	1.7	37.9	60.2	1.1	38.7
eGFR 30-59	68.0	7.4	24.6	69.9	4.8	25.3	69.4	1.5	29.1
eGFR <30	23.8	51.1	25.1	28.9	40.4	30.7	34.9	22.1	43.1

TH-PO418

Survival of Patients with CKD Stages 1-5 in Iceland

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Background: Studies on survival of patients with chronic kidney disease (CKD) employing the KDIGO definition and classification system with repeated serum creatinine (SCr) and proteinuria measurements are scarce. The purpose of this study was to estimate hazard ratio (HR) for death in patients with CKD stages 1-5 in Iceland.

Methods: In this retrospective study, we obtained all SCr values and urine protein measurements from every clinical laboratory in Iceland in 2008-2016. Clinical information, including ICD-10 diagnosis codes, was retrieved from nationwide electronic medical records. Estimated glomerular filtration rate (eGFR) was calculated from SCr using the CKD-EPI equation. CKD was defined as presence of kidney damage, either ICD-10 diagnosis codes indicating kidney disease or proteinuria, or as eGFR <60 mL/min/1.73 m^2 for ≥3 months. Cox regression was used for survival analysis with CKD stage as a time-dependent variable and adjustments for age at study entry, sex, number of SCr measurements, initial eGFR, multiple co-morbid conditions and by CKD detection criteria, i.e. proteinuria, kidney specific diagnosis or reduced eGFR, either by a single criterion or various combinations.

Results: We obtained 2,120,232 SCr values for 218,437 individuals and information on proteinuria for 84,364 individuals. A total of 4972 had persistent proteinuria, 5286 had kidney disease diagnoses and 20131 had eGFR <60 mL/min/1.73 m^2. The median age was 46 (range, 18-107) years and 47% were men. Compared with individuals without CKD, the hazard ratios (95%CI) for patient survival were 10.39 (7.62-14.17), 3.92 (3.18-4.85), 1.43 (1.31-1.56), 2.00 (1.83-2.20), 3.15 (2.78-3.57) and 11.18 (8.96-13.95) for CKD stages 1, 2, 3a, 3b, 4 and 5, respectively.

Conclusions: This nationwide study on survival of patients with CKD, incorporating kidney disease diagnoses and numerous urine protein and SCr values over time, suggests increased risk of death for all CKD stages. While this finding supports current criteria for definition of CKD, a more detailed analysis of the influence age is needed.

TH-PO419

eGFR Decline in Patients with CKD and at Risk for CKD by Age, Gender, and Race/Ethnicity in Two Large Health Systems

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Background: Comparisons in eGFR decline in patients with CKD and At-risk for CKD have not been described. We completed an analysis of eGFR trajectories (eGFR-T) in CKD and At-risk for CKD patients from the UCLA-PSJH CKD Registry.

Methods: The cohort: >2.6 million adults (2006-2017) based on labs and/or diagnoses of CKD, hypertension (HTN), diabetes mellitus (DM), or pre-DM from administrative codes. We analyzed CKD (N=84,150) and At-risk CKD (N=807,211) patients with ≥3 eGFRs ≥15ml/min/1.73m^2 followed for an average (SD) of 5.4±2.4years. We identified non-decliners, moderate and severe decliners (<2mL; 2-5mL and >5mL/min/1.73m^2/year), by least-squares fit for individual eGFR-T. Linear mixed effects (LME) models compared eGFR-T in moderate and severe decliners across gender and race/ethnicity groups, stratified by CKD vs. At-risk for CKD.

Results: Most patients were 45-64 yrs (41%), female (56%) and White Non-Latino (83%). CKD vs. At-risk CKD patients were ≥65years (72% vs 36%), and had more DM (18% vs 106%) and HTN (25% vs 18%), p<0.001. Severe (vs. non- and moderate-) decliners had higher baseline eGFR and 27% of At-risk CKD progressed to eGFR <60ml/min/1.73m^2). eGFR-T were steepest for CKD 18-44 yrs: -5.22 (95%CI= -5.38, -5.11) and At-risk patients 18-44 yrs: -4.16 (95% C= -4.18, -4.14) vs. other age groups, p<0.001. In LME bivariate analyses, eGFR slopes differed by age, gender and race/ethnicity for all decliners. Specifically, annual change in eGFR was lowest in patients >45 yrs (p<0.001) and declined in female>male CKD (p=0.025) and At-risk CKD (p<0.001) patients. eGFR-T were steepest for CKD American Indian/Alaska Native (p=0.007) and At-risk Native Hawaiian/Pacific Islander (p<0.001) vs. White Non-Latino. Similar results were obtained in fully adjusted LME models.

Conclusions: Patients with CKD are older, have more DM and HTN, lower baseline eGFR and more rapid renal function decline compared to At-risk CKD patients. CKD and At-risk CKD severe decliners were youngest, with the highest baseline eGFR. The study results suggest a subset of young patients with high baseline eGFR may be important to target to prevent rapid renal function decline.

Funding: Private Foundation Support

TH-PO420

Progression of Kidney Disease in Patients with CKD of Undetermined Etiology in Sri Lanka: Disease Natural History and Association with Water Source

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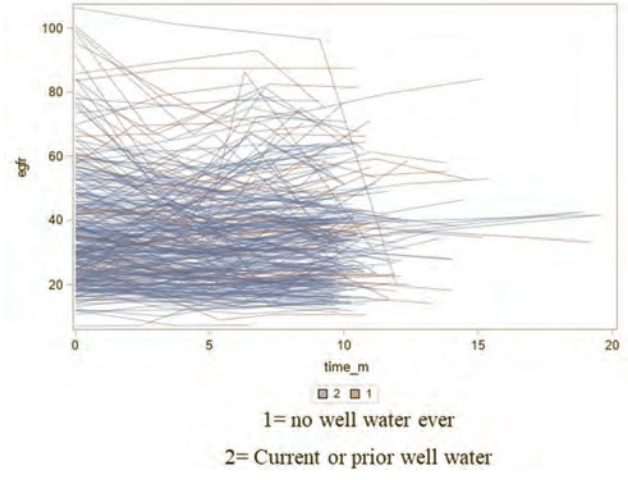
Background: Chronic kidney disease of unknown etiology (CKDu) is occurring at high rates in Sri Lanka, without an identified cause or risk factors for progression. Prior GIS mapping and case-control studies have implicated shallow water well use as potentially causative, since water here could communicate with irrigated fields. We recruited a cohort of patients with CKDu from an endemic region in Sri Lanka to determine 1) natural history of disease, and 2) identify any modifiable risk factors for disease progression, with the hypothesis that persons experiencing faster progression may have ongoing or higher dose exposure to the putative causative agent(s).

Methods: We recruited 302 persons with CKDu, with the clinical criteria: CKD-EPI eGFR < 60 ml/min/1.73m2 on two tests at least 3 months apart, none to trace proteinuria on urine dipstick, and no self-reported diagnosis of diabetes. In addition to extensive baseline questionnaire and groundwater sampling, we undertook quarterly IDMS-calibrated serum creatinine testing. We used linear mixed models to test the association of three putative risk factors with eGFR decline over time, accounting for age and sex.

Results: Over a median follow up 9.8 (25th-75th percentile 9.6, 10.7) months, 293 participants provided at least one serum test for eGFR assessment, with median eGFR slope -0.68 (25th-75th percentile -3.14 to 1.00) ml/min/1.73m2/year. 48 (16.4%) participants experienced eGFR decline > 5 ml/min/1.73m2/year. Participants who had never used water from a dug well had slower decline (eGFR slope 6 ml/min/1.73m2 higher (95%CI: 0.3-12.3 ml/min/1.73m2, p value: 0.04) (Figure 1).

Conclusions: Kidney function decline in surviving patients with CKDu in Sri Lanka is slow. No exposure to dug well water was associated with slower decline, and could be investigated as potential cause(s) or disease modifiers.

Funding: Other NIH Support - NIH grant number- grant 12102751



TH-PO421

Urinary Molybdenum Levels and CKD: National Health and Nutrition Examination Survey (1999–2016)

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Background: Molybdenum is both a metal and a micronutrient needed for enzymatic reactions in the carbon, sulfur, and nitrogen metabolism. However, their effects on kidney functions are not well investigated. We aimed to investigate the association of urinary molybdenum levels with chronic kidney disease (CKD) according to increased urinary albumin-to-creatinine ratio (ACR), decreased glomerular filtration rate (GFR), and composite outcomes.

Methods: Population-based cohort study. A total of 16,294 adult aged above 18 years old participants, who participated in the NHANES surveys over 18 years, were enrolled. We used multivariable linear regression adjusting age, sex, ethnicity, diabetes mellitus, hypertension, and body mass index to analyze the association between log-transformed standardized (standard deviation converted to 1) urinary molybdenum levels and urinary ACR and GFR. The association between log-transformed standardized urinary molybdenum levels and CKD was investigated by multivariable logistic regression methods. CKD was defined as three categories; urinary ACR above 30 mg/g (CKD_ ACR30), GFR below 60 ml/min/1.73m2 (CKD_GFR60), and composite of CKD_ACR30 or CKD_GFR60 (CKD_ACR30GFR60).

Results: Mean age of participants was 47.1 ± 19.3 years old, and male participants were 7,978 (49.0%). Mean urinary ACR was 42.6 ± 326.5 mg/g and GFR was 94.4 ± 24.7 ml/min/1.73m^2. Diabetic patients were 2,162 (13.3%) and participants with hypertension were 6,314 (38.8%). Number of patients with CKD_GFR60, CKD_ACR30, and CKD_ ACR30GFR60 was 1,401 (8.6%), 1,983 (12.2%), and 2,922 (17.9%). Log-transformed standardized urinary molybdenum levels were significantly associated with the GFR (β = 3.093, P-value < 0.001), but not with urinary ACR (β = 2.761, P-value = 0.289). Prevalence of CKD_GFR60 and CKD_ACR30GFR60 decreased significantly according to the increased urinary molybdenum levels (P-value < 0.001 and 0.03, respectively).

Conclusions: Urinary molybdenum levels are positively correlated with GFR, risk of CKD (CKD_GFR60 and CKD_ACR30GFR60) decreased according to the increased urinary molybdenum levels.

TH-PO422

A Newly Recognized Endemic Region of CKD of Undetermined Etiology in South India: The Tondaimandalam Nephropathy

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Background: There are some regions with high incidence of unexplained CKD, referred to as CKD of Undetermined etiology (CKDu), predominantly affecting underprivileged farming populations in tropical climates in Sri Lanka & Latin America. Similar CKD cluster was reported from Andhra Pradesh, India. Many patients exhibiting characteristics of CKDu seek treatment at our tertiary care center in South India & we explored whether a similar burden of CKDu exist in our region as well.

Methods: All consecutive incident adults with CKD per KDIGO criteria presenting to the renal clinic between 1st January 2015 and 31st December 2018 were prospectively recruited in this observational study. Case definition of CKDu by WHO was used.

Results: Among 2440 patients with CKD, 75.3% were male & mean age 50.8 (±13.6) yrs. 56% patients were from Villupuram & Cuddalore districts of Tamil Nadu state (Figure 1). Approx. 50% patients reported working on sugarcane, peanut & rice paddy farms. 65.7% had family income < INR 5000 (USD$77) per month. Diabetic Nephropathy was the cause of CKD in 21.7%, Hypertensive Nephrosclerosis in 14.5% & Chronic Glomerulosclerosis in 3.1%. The single largest diagnostic category was CKDu - 56.2%. CKDu contributed a significantly higher proportion of kidney disease among farmers, agricultural & other unorganized laborers; the proportion of CKDu was significantly higher among the uneducated patients & in the lower income group.

Conclusions: We define a new endemic area of CKDu (Tondaimandalam) in Tamil Nadu, India, accounting for 56.2% of CKD.

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

District-wise Distribution of Patients

District	N = 1900 (%)
Villipuram	674 (35.5)
Cuddalore	392 (20.6)
Pondicherry	216 (11.3)
Thiruvannamalai	118 (6.2)
Ariyalur	91 (4.8)
Kanchipuram	35 (1.8)
Nagapattinam	35 (1.8)
Thanjavur	27 (1.4)
Salem	24 (1.4)
Others	288 (15.2)

Comparison of CKDu and non-CKDu patients

Distribution by	CKDu (%)	Non-CKDu (%)
Education status		
Illiterate	735 (54.5)	480 (45.9)
Primary	265 (19.6)	232 (22.2)
Secondary	267 (19.8)	242 (23.2)
Graduation	70 (5.2)	77 (7.4)
Post-graduation	12 (0.9)	14 (1.3)
	1349 (100)	1045 (100)
Income group		
< INR 5000	1190 (91.8)	436 (83.8)
INR 5000-20000	99 (7.6)	76 (14.6)
>INR 20000	8 (0.6)	8 (1.5)
Hypertension	737 (54.6)	863 (82)
Stages of CKD		
Stage 1	42 (3.2)	55 (5.4%)
Stage 2	15 (1.2)	14 (1.4)
Stage 3	227 (17.5)	150 (14.9)
Stage 4	305 (23.5)	218 (21.6)
Stage 5	708 (54.6)	574 (56.8%)

TH-PO423

Associations Between Long-Term Ambient $PM_{2.5}$ Exposure and Prevalence of CKD: An Analysis Based on the China National Survey of CKD

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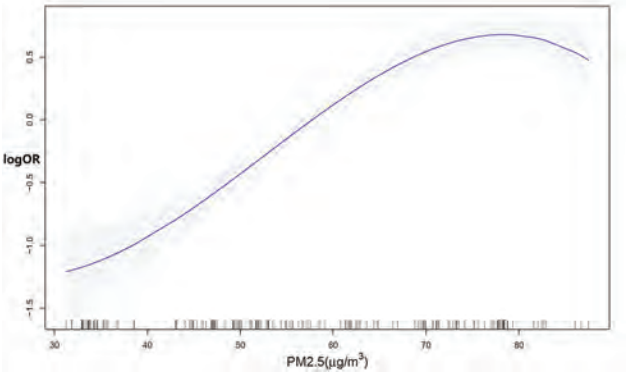
Background: Our aim is to explore the associations between long-term exposure to ambient $PM_{2.5}$ and prevalence of chronic kidney disease (CKD) based on the China National Survey of CKD.

Methods: A sample of 47,204 people representing general adult population in China were recruited from January 2007 to October 2010. Annual exposure to satellite derived $PM_{2.5}$ (obtained from the Aerosol Optical Depth Database) prior to the survey date (2 years range) was estimated at each participant's address using validated satellite-based spatiotemporal model with 10km×10km resolution. Participants with estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or urinary albumin creatinine ratio≥30mg/g were defined as CKD. Generalized additive mixed effects models were used to estimate the associations, and the influence of the potential modifiers were also analyzed.

Results: The overall prevalence of CKD was 10.8%. Two-year mean $PM_{2.5}$ concentration was 57.41 μg/m^3, with a range from 31.25 to 87.49 μg/m^3. Per 10 μg/m^3 increase in $PM_{2.5}$ was positively associated with the prevalence of CKD with adjusted OR of 1.33 (95%CI: 1.25, 1.41). The exposure-response curve showed relatively steep at low levels of exposure and flattened out at higher exposures (Figure). Similar findings were detected for albuminuria. Stratified analyses indicated the associations were stronger in the smokers than non-smokers, in the young people versus the elderly, and were stronger in participants without comorbid diseases than those with comorbid diseases including diabetes, hypertension, obesity, and cardiovascular history.

Conclusions: This study showed a significant association between long-term $PM_{2.5}$ exposure with broad range and increased prevalence of CKD in the national representative general population.

Funding: Government Support - Non-U.S.



The exposure-response curve between long-term exposure to ambient $PM_{2.5}$ and prevalence of CKD

TH-PO424

Incident CKD over 4 Years in a Population-Based Study of Apparently Healthy Young Adults at Risk of Mesoamerican Nephropathy (MeN)

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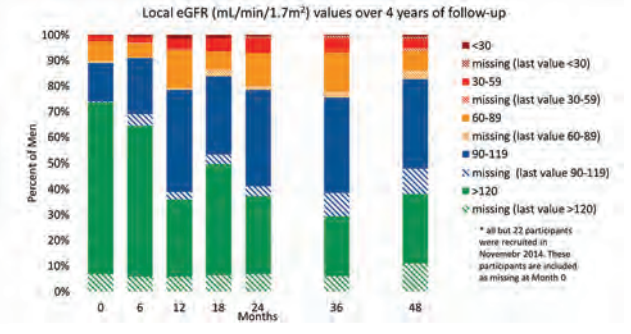
Background: MeN has led to the death of tens of thousands of young adults across rural Central America. We recently reported eGFR decline of over 30mL/min/1.7m^2 over 2 years among substantial numbers of apparently healthy young adults from rural communities in northwest Nicaragua[1]. The consequences of this early loss of eGFR is not known.

Methods: The original 350 participants (a rural, population-based sample, aged 18-30 years, male:female ratio 3:1, without reported diabetes, hypertension or CKD) from the study have been followed-up annually for a further 2 years. An additional 417 men and women (ratio 1:1) were recruited in October 2018. Serum creatinine was measured at UNAN-León after each study visit and eGFR was calculated by CKD-EPI formula. *de novo* CKD was defined as those participants from the original cohort with an eGFR≥60mL/min/1.7m^2 at baseline who developed an eGFR <60mL/min/1.7m^2 on at least two serial measurements without recovery.

Results: Across all participants (mean age 24.8 years) at baseline 87% of men and 95% of women had an eGFR≥90mL/min/1.7m2, but despite excluding those self-reporting CKD, 2.9% of males had an eGFR<60mL/min/1.7m^2. In the original cohort, 90% participants attended ≥2 of the 7 study visits. eGFR varied substantially visit-to-visit such that 42% of men (Figure) and 54% of women had an eGFR<90mL/min/1.7m^2 at some point during the 4-year follow-up. Furthermore, among men (but not women), 11% had an eGFR<60mL/min/1.7m^2 (at ≥1 visit), 3.8% developed *de novo* CKD, and 0.8% (n=2) died from kidney failure over the follow-up.

Conclusions: Within person eGFR varies substantially in this population at high-risk of MeN. This likely reflects important biological effects, as well as analytical variation, making longitudinal studies critical for disease insight. Nonetheless there is both a substantial loss of eGFR and unprecedented rates of incident CKD among young men in the region. 1. Gonzalez-Quiroz et al. *JASN* 2018

Funding: Private Foundation Support



Local eGFR measurements over the study period in men

TH-PO425

Electron Microscopic Description of a Sensitive Diagnostic Proximal Tubular Lysosomal Lesion in Patients with CINAC/CKDu/MeN and Calcineurin Inhibitor Nephrotoxicity

Benjamin A. Vervaet,[2] Cynthia C. Nast,[1] Gerd Schreurs,[2] Channa Jayasumana,[3] Frank Roels,[9] Chulani A. Herath,[4] Nika Kojc,[5] Anne S. Rodrigo,[4] Swarnalata Gowrishankar,[6] Christiane I. Mousson,[10] Rajeewa T. Dassanayake,[7] Carlos M. Orantes,[8] Patrick C. D'Haese,[2] Marc E. De Broe.[2] *[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]University of Antwerp, Antwerp, Belgium; [3]Faculty of Medicine, Anuradhapura, Sri Lanka; [4]Sri Jayawardenepura General Hospital, Colombo 5, Sri Lanka; [5]Medical faculty Ljubljana, Ljubljana, Slovenia; [6]Apollo Hospitals, Hyderabad, Hyderabad, India; [7]General hospital Polonnaruwa Sri Lanka, Polonnaruwa, Sri Lanka; [8]National Direction of Non-communicable diseases of Ministry of Health, San Salvador, El Salvador; [9]Ghent University, Gent, Belgium; [10]University Hospital Dijon, Dijon, France*.

Background: In Sri Lankan CINAC patients, we observed a constellation of proximal tubular cell findings including cellular/tubular atrophy, cell fragment shedding and the presence of an increased number of enlarged lysosomes. Here we define the EM lysosomal phenotype and evaluate its presence in CINAC/MeN/CKDu cases and controls.

Methods: Renal biopsies (18 Sri Lanka, 10 El Salvador, 1 India, 3 France) of patients with a diagnosis of CINAC (CKD 1-3A, 3B) were examined by electron microscopy (EM) in comparison to renal biopsies of normal kidneys at implantation, patients with calcineurin inhibitor (CNI) toxicity (n=17), proteinuric nephropathies (n=15), light chain disease (n=4), cases on nephrotoxic drugs (lomustine, clomiphene, lithium, tenofovir, cisplatinum) and patients with reduced renal function of various causes (n=20).

Results: The aberrant lysosomal phenotype can be defined as enlarged (>1.2μm) and dysmorphic with a light-medium electron-dense matrix containing dispersed dark electron-dense non-membrane bound "aggregates". Clusters of 4-6 smaller lysosomes with the same features could be observed. No cristae or other features of mitochondria, autophagic vacuoles, lipofuscin/ceroid droplets, peroxisomes, myeloid bodies or laminated inclusions were observed. Patients with CNI nephrotoxicity and several nephrotoxic cases (lomustine, clomiphene, lithium) and a subset light chain disease patients, all conditions directly or indirectly linked to calcineurin inhibition, presented the same lesions. We present an image set of the consistency of the diagnostic lysosomal lesion versus similar non-diagnostic features.

Conclusions: A rather sensitive constellation of lysosomal lesions in renal proximal tubular cells was detected associated with CINAC/CKDu/MeN and CNI nephrotoxicity in several countries, suggesting a common pathomechanistic paradigm where CINAC patients are experiencing a tubulotoxic mechanism similar to CNI nephrotoxicity.

Funding: Government Support - Non-U.S.

TH-PO426

MicroRNA Profiling of Urinary Exosomes to Identify Appropriate Housekeeping Genes and Early Biomarkers of CKD in Humans

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Background: In the last decade or so the CKD mortality increased by almost 30%, with diabetic kidney disease increased by 40% throughout the globe. Regular screening for kidney disease onset can lessen this burden. The potential of urinary exosome (UE) as a non-invasive source for kidney disease biomarkers has gained enormous research attention. However, the lack of optimal endogenous control for normalizing gene-expression in UE limits its translation into clinical practice.

Methods: Using microarray, we compared the microRNA profile of UE from early kidney disease subjects [with and without diabetes, serum creatinine < 2.0 mg/dl) with matched healthy controls. taqman-based RT-PCR was done for validation

Results: Around fifteen hsa-miRs were found constitutively expressed across the three groups. Out of these, four abundant miRs were validated by TaqMan-based RT-PCR (n=10-20/group). Also, we found twenty-seven differentially expressed miRs in the UE among the three groups. Pathway analysis revealed VEGF signaling, focal adhesion, and cytokine-cytokine receptor interaction pathways as major targets of the differentially expressed miRs. Among the the differentially expressed miRs, miR-200c-3p, let-7b-3p, miR-6812 and miR-320 were validated by TaqMan-based RT-PCR (n=10-20/group). Also, the target gene prediction of ten novel miRs, identified in the UE, was done using the bioinformatic approach.

Conclusions: In conclusion, we have identified miRs in UE with the potential to serve as 1) kidney disease biomarkers and, 2) endogenous controls, for normalizing miRNA expression in urinary exosomes in kidney disease subjects. Funded by ICMR

Funding: Government Support - Non-U.S.

TH-PO427

Clinical Considerations Surrounding CKD of Undetermined Etiology (CKDu): Expert Consensus from the Third International Workshop on CKDu

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Background: CKDu is a term that describes a pattern of endemic, non-diabetic, non-hypertensive kidney diseases characterized by reduced GFR without nephrotic range proteinuria or features of glomerulonephritis. It has been described most extensively in rural communities in Mesoamerica, Sri Lanka, and India, although the global extent is unknown. The underlying etiology or etiologies of CKDu remains incompletely understood, and there are no consensus guidelines for CKDu management.

Methods: The Third International Workshop on CKDu was held March 20-22, 2019 in San Jose, Costa Rica. Our working group, comprised of clinicians who care for CKDu patients in Sri Lanka, India, and Mesoamerica as well as CKDu researchers, developed an expert consensus on the on clinical features and management of the disease.

Results: While there are many similarities in the clinical aspects of CKDu in India, Sri Lanka, and Mesoamerica, there are notable differences as well. Individuals affected in Mesoamerica are younger (aged 20-40 as opposed to 20-60). Both regions show a high male-to-female ratio, and familial concordance. Affected individuals largely live in poverty. Most work in agriculture and live in rural areas, although not all. Hypokalemia, hyponatremia, minimal proteinuria, and sterile pyuria are highly prevalent. Individuals in Central America but not India or Sri Lanka can have hyperuricemia and urate crystalluria. Early biopsies demonstrate tubulointerstitial nephritis with a lymphocytic infiltrate. Both regions describe AKI episodes which may or may not be associated with CKDu. Clinical management in early stages of CKDu focuses on appropriate hydration with clean water, minimization of exposure to heat and agrichemicals, and correction of electrolyte disturbances. Timely diagnosis and establishment of nephrology care appears to improve outcomes.

Conclusions: More studies on the clinical aspects and management of CKDu are desperately needed; to date there is little published guidance for clinicians and health care policymakers. Nevertheless, based on our experience there are concrete actions which can be taken by both healthcare providers and governments to care for people affected by CKDu.

Funding: NIDDK Support

TH-PO428

Association of Urine Biomarkers of Kidney Tubule Health with Incident CKD in the REGARDS Cohort

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Background: Novel biomarkers have been identified that associate with the onset or progression of CKD in specific populations. Within the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, we evaluated whether 5 proteins, measured in stored urine specimens, were associated with the subsequent development of CKD among persons without diabetes at baseline.

Methods: The REGARDS Study recruited Black and White participants from the continental US with emphasis on the Southeast US stroke belt. Candidate participants for this ancillary study had a baseline estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73m2, had a stored urine specimen from baseline, and eGFR repeated at the follow-up visit 9 years later. Incident CKD was defined as the onset of an eGFR <60 ml/min/1.73m2 and a ≥40% decline in eGFR. The case-cohort design included a subcohort of 493 individuals, among whom 57 developed incident CKD, and 431 additional cases of incident CKD. Weighted multivariable proportional hazards analyses modeled biomarkers both as continuous variables (log2) and in quartiles.

Results: The mean age of the subcohort was 63±8 years, 58% were women, and 30% were Black; mean (SD) eGFR was 89±14 ml/min/1.73m2 and median (IQR) albumin-to-creatinine ratio was 6.1 (4.2- 9.7) mg/g. In unadjusted models, only higher urine EGF was associated with incident CKD (HR per two-fold increment 1.20; 95% CI: 1.02-1.41); this

association was attenuated after adjustment. No other biomarker approached statistical significance in any analysis (Table).

Conclusions: Among REGARDS Study participants without diabetes or CKD at baseline, none of the 5 urine biomarkers studied was independently associated with incident CKD

Funding: NIDDK Support

Quartiles of Urine Biomarkers and Incident CKD in REGARDS

Urine Biomarker	Q1 HR (95% CI)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)
KIM-1	1.00 (ref)	0.97 (0.59, 1.59)	0.80 (0.47, 1.37)	0.71 (0.40, 1.28)
MCP-1	1.00 (ref)	0.96 (0.57, 1.61)	0.76 (0.41, 1.38)	0.86 (0.43, 1.71)
EGF	1.00 (ref)	0.93 (0.58, 1.48)	1.35 (0.84, 2.18)	1.49 (0.91, 2.42)
YKL-40	1.00 (ref)	1.11 (0.71, 1.74)	1.36 (0.86, 2.13)	1.07 (0.67, 1.72)
α-1 microglobulin	1.00 (ref)	0.84 (0.53,1 .34)	0.98 (0.61, 1.59)	1.30 (0.77, 2.20)

Adjusted for age, sex, race, education, urine creatinine, BMI, SBP, HTN meds, smoking, CHD, stroke, urine albumin & eGFR.

TH-PO429

Longitudinal Follow-Up and Outcomes for Patients with CKD in China: Results from the C-STRIDE Study

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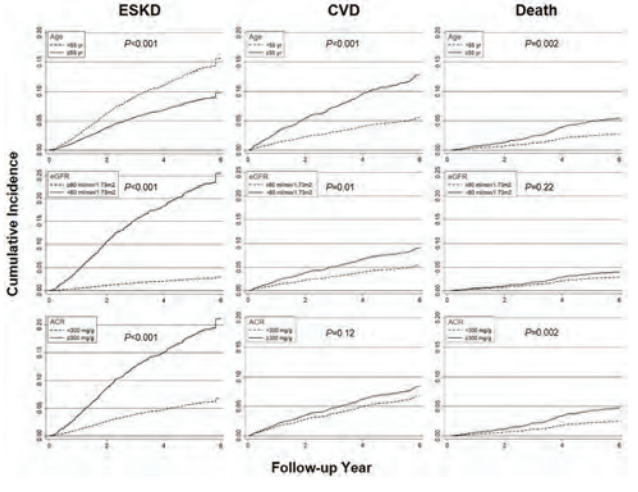
Background: We aimed to evaluate the longitudinal prognosis of chronic kidney disease (CKD) in China by comparing incidence rates of end-stage kidney disease (ESKD), cardiovascular disease (CVD) and death.

Methods: Totally, 3,700 participants of the C-STRIDE study, an ongoing cohort study with stage 1-4 CKD, were included. The outcomes were occurrence of ESKD, CVD, and death. Crude incidence rates were computed and expressed as the number of events per 100 patient-years. Cumulative incidence curves were depicted for the outcomes and stratified by age, eGFR and ACR, with the adjustment for other risk factors. Fine and Gray model was used in computing the cumulative incidence of ESKD and CVD.

Results: The participants were 49.9±14.3 years, with 58.2% of male, 70.6% with eGFR<60ml/min/1.73m2 and 55.5% with ACR≥300mg/g. After a median follow-up of 5 years, the crude incidence rate of ESKD was about two times that of CVD (3.14/100 patient-years vs. 1.77/100 patient-years) and three times that of death (3.14/100 patient-years vs. 0.92/100 patient-years). The cumulative incidence of ESKD was significantly higher among those aged<55 years than the counterparts, while adverse situations were observed for CVD and death (all p-values<0.05). Higher cumulative incidence rate of ESKD was observed in those with eGFR<60ml/min/1.73m2 and ACR≥300mg/g, while much smaller gaps were detected for cumulative incidence rates of CVD and death (Figure).

Conclusions: Our study found a higher rate of ESKD than CVD or death in a prospective cohort study of patients with CKD in China. Advanced age was shown as protective factors for the risk of ESKD, while reduced eGFR and presence of albuminuria exacerbate the risk of ESKD, compared with their effect on the risk of CVD and death.

Funding: Government Support - Non-U.S.



Multivariable adjusted cumulative incidence of ESKD, CVD and death stratified by age, eGFR and ACR categories

TH-PO430

Associations of Plasma YKL-40 with Kidney Disease Progression, Mortality, and Histopathologic Lesions in Native Kidney Biopsies

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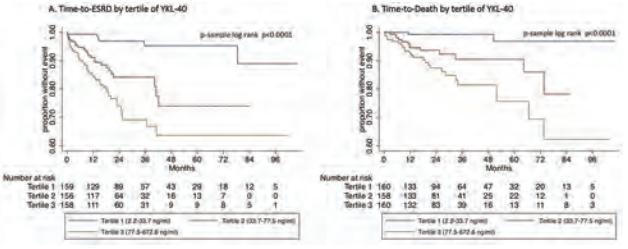
Background: YKL-40 is a chitinase-like protein and important regulator of renal tissue injury and apoptosis. We evaluated the association of plasma YKL-40 with progression to ESRD and all-cause mortality among patients with diverse kidney diseases. Furthermore, we tested whether YKL-40 is associated with specific clinicopathologic diagnoses and histopathologic lesions in human kidney biopsies.

Methods: We measured plasma YKL-40 levels in 490 participants of the Boston Kidney Biopsy Cohort—a prospective cohort study of patients undergoing native kidney biopsies. Biopsies were reviewed by renal pathologists and adjudicated for histopathologic findings. Cox proportional hazard models tested the association between YKL-40 and the risks of progression to ESRD and all-cause mortality. Multivariable linear regression models were used to assess the relationship between YKL-40, histopathologic lesions, and clinicopathologic diagnoses. Models were adjusted for age, race, sex, diagnosis, proteinuria, and eGFR.

Results: YKL-40 correlated positively with proteinuria and inversely with eGFR (r=0.27, r=-0.51; p<0.0001, respectively). During a median follow-up time of 25 months, higher YKL-40 levels were independently associated with an increased risk for progression to ESRD (adjusted HR per 1-SD increase of natural log-transformed YKL-40=1.59, 95%CI (1.10-2.31)) and all-cause mortality (adjusted HR=2.28, 95%CI (1.44-3.62)). YKL-40 levels were significantly higher in non-proliferative glomerulopathies (adjusted β=0.48 [ref=normal or thin basement membrane], 95%CI (0.16-0.79), p=0.003) and significantly associated with more severe arterial sclerosis (adjusted β=0.16 [ref=no sclerosis], 95%CI (0.005,0.32), p=0.043).

Conclusions: YKL-40 is independently associated with increased risks of all-cause mortality and progression to ESRD in patients with a diverse spectrum of kidney diseases. Higher levels of YKL-40 were seen in non-proliferative glomerulopathies and biopsies with more severe arterial sclerosis.

Funding: Other NIH Support - R01DK093574



TH-PO431

Urinary Calprotectin, Neutrophil Gelatinase Associated Lipocalin (NGAL), and KIM-1 in the Differentiation of Inflammatory vs. Noninflammatory CKD

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Background: It has been demonstrated that urinary neutrophil gelatinase-associated lipocalin (NGAL) and calprotectin are helpful biomarkers in the differentiation of intrinsic and prerenal acute kidney injury. The present cross-sectional study investigates, whether urinary biomarkers are able to differentiate primarily inflammatory from non-inflammatory entities in chronic kidney disease (CKD).

Methods: Urinary calprotectin, NGAL and kidney injury molecule-1 (KIM-1) concentrations were assessed in a study population of 143 patients with stable CKD and 29 healthy controls. Stable renal function was defined as an eGFR fluctuation 5ml/min/1.73m2 in the past 12 months. Pyuria, metastatic carcinoma and renal transplantation were regarded as exclusion criteria. Diabetic nephropathy, hypertensive nephropathy, and polycystic kidney disease were categorized as "non-inflammatory renal diseases", whereas glomerulonephritis and vasculitis were regarded as "inflammatory renal diseases".

Results: Urinary calprotectin and NGAL concentrations significantly differed between CKD and healthy controls (p<0.05 each), whereas KIM-1 concentrations did not (p=0.84). Urinary calprotectin concentrations were numerically highest in glomerulonephritis/vasculitis (155.7 ng/ml), NGAL concentrations in diabetic and hypertensive nephropathy (18741 pg/ml), and KIM-1 concentrations in polycystic kidney disease (1556 pg/ml). However, the three biomarkers did neither show significant differences in-between the individual entities, nor the two categories of inflammatory vs. non-inflammatory renal diseases (calprotectin 155.7 vs. 96.99 ng/ml; NGAL 14896 vs. 11977 pg/ml; KIM-1 1388 vs. 1009 ng/ml; p>0.05 each).

Conclusions: The urinary biomarkers calprotectin, NGAL and KIM-1 have no diagnostic value in the differentiation of inflammatory vs. non-inflammatory etiologies of CKD.

TH-PO432

A Phase 1 Randomized, Double-Blind, Placebo-Controlled, Cohort Dose-Escalation Study of a Human Monoclonal Antibody to IL-6 in Patients with CKD

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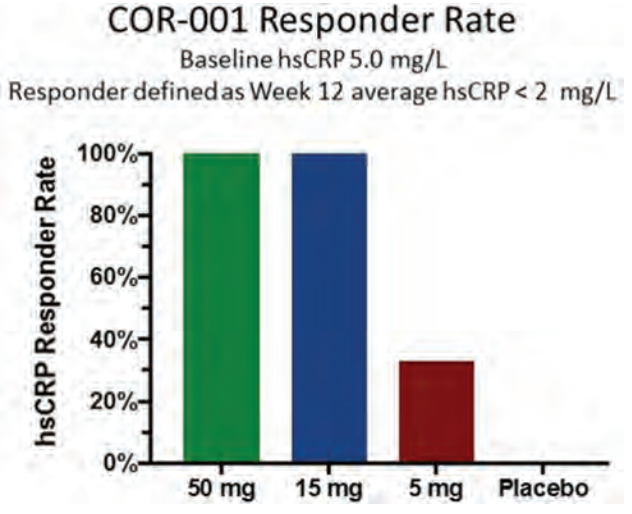
Background: Chronic systemic inflammation is highly prevalent in patients with CKD (measured as an elevated high-sensitivity C-reactive protein [hsCRP]) and independently associated with cardiovascular events and mortality. Use of an interleukin-6 (IL-6) blocker to suppress inflammation represents a potential new paradigm to reduce cardiovascular risk in patients with CKD.

Methods: COR-001 is a fully human monoclonal antibody against IL-6. A phase I trial of COR-001 was conducted in patients with moderate-to-severe non-dialysis dependent CKD (estimated glomerular filtration rate [eGFR] 20-60 ml/min/1.73 m^2) and evidence of chronic inflammation (hsCRP] level >2 mg/L over two consecutive measurements). Three cohorts of n=4 (3:1 active vs. placebo) were randomized in a blinded fashion to a single dose of COR-001 (5 mg, 15 mg, and 50 mg subcutaneous injection) and followed for 12 weeks for safety, and pharmacokinetic and pharmacodynamics assessments.

Results: Participants were 67±11 years with a baseline eGFR of 40±13 ml/min/1.73 m^2 and hsCRP of 5.1±2.6 mg/L. Throughout the 12-week study period, dose escalation was approved and all adverse events were within the expected range for a CKD population selected based on the presence of inflammation. hsCRP levels were substantially reduced with COR-001 treatment. 100% of participants achieved suppression of hsCRP to < 2mg/L with the 15 mg and 50 mg dose, and several subjects had undetectable levels of hsCRP with the 50 mg dose (Figure). No SAEs were reported in any cohort. The pharmacokinetic data suggested a half-life of 38-52 days in these patients.

Conclusions: IL-6 inhibition with COR-001 was safe and highly effective at suppressing hsCRP over a long period with a single injection, in adults with moderate-to-severe CKD and evidence of chronic inflammation.

Funding: Commercial Support - Corvidia Therapeutics, Inc.



TH-PO433

A Meta-Analysis of Placebo-Controlled Randomized Clinical Trials of Octreotide-LAR in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal Dominant polycystic kidney disease (ADPKD), is the most common hereditary disease of the kidneys, characterized by tubular epithelial cell proliferation (ECP) and fluid secretion (FS) leading to cystic kidney enlargement and progressive renal failure in most cases. Cyclic adenosine monophosphate (cAMP) pathway has been clearly implicated in both ECP and FS. Somatostatin and its synthetic analogues have shown to inhibit invitro adenyl cyclase activity in vitro and slow cyst growth both in few underpowered studies in either early or more advanced stages of ADPKD. This project aimed to evaluate the efficacy of Octreotide-LAR on disease progression based on a meta-analysis of published literature, across all stages of CKD due to ADPKD.

Methods: All placebo-controlled randomized trials (RCT) of Octreotide-LAR (OLAR) in ADPKD were identified through a search using the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases. A meta-analysis of efficacy (rate of cyst growth and kidney function decline) and safety outcomes was performed. Participants in those trials were adults, with clinical and ultrasound diagnosis of AKPKD with glomerular filtration rate (GFR) of ≥15 ml/min/1.73 m2, with exclusion of diabetics and poorly controlled hypertension (BP> 180/110 mmHg). Outcomes were mean Total kidney volume (TKV) and decrease in Gfr (Ideally you want an annualized rate of eGFR decline) and were compared by using Standard mean difference (SMD).

Results: Four RCTs fulfilled the inclusion criteria, yielding 445 patients. Compared to placebo, OLAR showed a significant reduction of TKV, SMD -0.41 [95% confidence intervals CI -0.69 to -0.12], p=0.005 but a comparable mean reduction in Gfr SMD 0.01 [95% CI -0.17 to 0.20], p=0.90 and rate of adverse events RR (risk ratio) 1.46 [0.82 to 2.61], p=0.20.

Conclusions: OLAR delays the cyst growth across all stages of kidney disease in ADPKD, without a clear beneficial effect on kidney function, or a significant difference in adverse outcomes. Longer follow up is required to elucidate a potential beneficial role of OLAR on kidney function.

RCTs	OLAR group TKV (Mean+ SD)	Number of paticats OLAR group	Placebo group TKV (Mean + SD)	Number of patients Placebo group	SMD	OLAR group eGFR (Mean+ SD)	Number of patients OLAR group	Placebo group eGFR (Mean+SD)	Number of patients Placebo group	SMD
Caroli et al (ALADIN)	220.1±290.479	35	454.3±478.019	35	-0.59	-4.06±6.32	36	-4.73±7.52	31	0.10
Hogan et al	0.25±7.53	28	8.61±10.07	14	-0.97	-5.1±15.46	21	-7.2±13.21	9	0.14
Meijer et al (DIPAK1)	-4.16±4.68	125	5.51±4.90	132	-0.28	-3.58±6.95	140	-3.45±6.95	140	-0.02
Perico et al (ALADIN2)	742.1±1208.69	37	916.75±1237.80	39	-0.14	-4.85±3.93	35	-4.9±4.94	35	0.01
Total		225		220	-0.41		232		215	0.01

TH-PO434

Protein-Bound Uremic Toxins Lowering Effect of Sevelamer in Pre-Dialysis CKD Patients with Hyperphosphatemia: A Randomized Controlled Trial

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Background: P-cresol (pCS), the protein-bound uremic toxins, is strongly associated with cardiovascular events and mortality in chronic kidney disease(CKD). However, effectively therapeutic reduction of this toxin is still limited. This is the first study to evaluate the pleiotropic effects of sevelamer on decreasing of pCS in predialysis CKD patients with hyperphosphatemia.

Methods: This was a randomized controlled trial comparing sevelamer with calcium carbonate in predialysis CKD patients with persistent hyperphosphatemia. After 2 weeks of run-in period, patients were randomly assigned to receive either daily 2,400 mg of sevelamer (n=12) or 3,000 mg of calcium carbonate (n=12) for 12 weeks. Plasma pCS, high sensitivity C-reactive protein (hs-CRP), lipid profiles and renal function were evaluated at baseline and 12 weeks after treatment. The study was registered with the Thai Clinical Trials Registry (TCTR20181018003).

Results: The baseline characteristics were not different. The significant reduction of log plasma pCS, hs-CRP, LDL-cholesterol, and serum phosphate were demonstrated in sevelamer group, whereas non-significant changes were observed in calcium carbonate group (Table1). Interestingly, there was significantly greater renal function progression in calcium carbonate group comparing with sevelamer group (mean difference of eGFR -2.71±1.04 mL/min/1.73m^2, p=0.018).

Conclusions: This is the first study to demonstrate benefit effect of sevelamer on decreasing pCS and retarding renal impairment in predialysis CKD patients with hyperphosphatemia. These effects of sevelamer might be considered as treatment for slowing CKD progression and decreasing the risk of cardiovascular events in CKD patients.

Funding: Private Foundation Support

Table1

Variable	Calcium carbonate		Sevelamer	
	Baseline	Week 12	Baseline	Week 12
Primary outcome				
Log plasma p-cresol	0.80±0.36	0.65±0.72	1.14±0.24	0.83±0.32*
Secondary outcomes				
Plasma high sensitivity-C reactive protein (mg/L)	1.64±1.58	1.84±2.14	1.84±2.22	1.04±1.72*
Serum low density lipoprotein cholesterol (mg/dL)	95.80±41.99	83.50±40.49	94.6±30.61	60.00±30.63*
Serum Calcium (mg/dL)	8.83±0.89	9.09±0.89	9.09±0.65	9.28±0.66
Serum Phosphate (mg/dL)	5.36±0.65	5.04±0.64	5.59±1.00	5.07±1.07*
estimated glomerular filtration rate (ml/min/1.73m2)	18.35±6.45	15.04±5.42*	16.23±6.76	15.64±5.40**

* p<0.05 vs baseline,** p<0.05 difference between group

TH-PO435

Utility of D-Serine in the Estimation of GFR and the Diagnosis of Kidney Diseases

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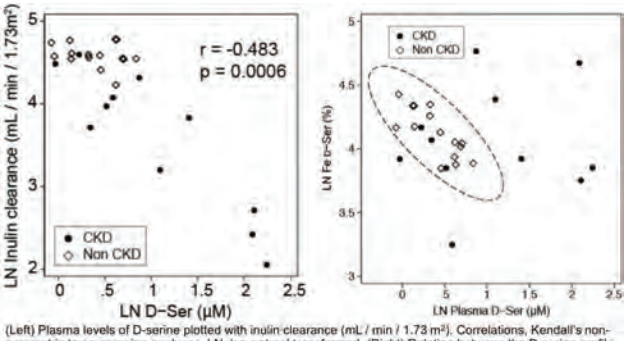
Background: Glomerular filtration ratio (GFR), measured by inulin clearance, is rarely used in clinics due to its methodological complexity. As a replacement, estimated GFR (eGFR), calculated from either serum creatinine or serum cystatin C, is widely used currently, but it has some limitations such as the accuracy. D-Amino acids, long-term undetected enantiomers of L-amino acids, is now emerging as a potential biomarker

especially in kidney diseases. Here we investigated the potential of D-serine as a biomarker for kidney function and diseases.

Methods: Inulin clearance and chiral amino metabolomics were simultaneously performed in 11 CKD patients and 15 non-CKD participants. The association between chiral amino acids and clinical parameters was analyzed using either unsupervised principal component analysis (PCA) or supervised orthogonal partial least squares (OPLS) analysis. Additionally, D-serine was monitored in one patient with systemic erythematous lupus nephritis during its recovery phase.

Results: The plasma level of D-serine correlated well with the actual GFR, and this correlation was compatible with those of serum creatinine and cystatin C. Fractional excretion (Fe) of D-serine in non-CKD was much higher than those of L-serine, but its variance was maintained within a certain limited range. Although Fe of D-serine was uncorrelated with GFR, it reflected the presence of CKD. The combination of plasma and Fe of D-serine effectively separated the CKD from non-CKD participants. This concept was exemplified in a patient with SLE, in which the combination of plasma and Fe of D-serine well-reflected its recovery phase.

Conclusions: D-serine would benefit patients with kidney diseases via accurate estimation of GFR and estimation of disease activities.



(Left) Plasma levels of D-serine plotted with inulin clearance (mL / min / 1.73 m²). Correlations, Kendall's non-parametric tau regression analyses. LN, log-natural transformed. (Right) Relation between the D-serine profile (plasma level and Fe) and CKD. The dotted-eclipse represents 95% confidence interval of non-CKD.

TH-PO436

High Serum Adiponectin Is Associated with Renal Outcome in CKD: Results from the KNOW-CKD Study

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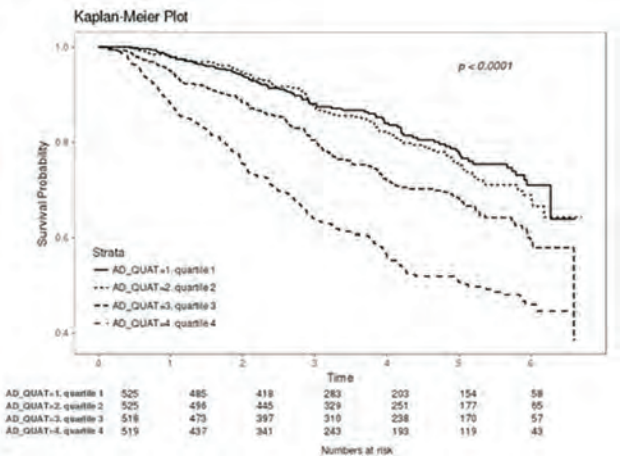
Background: Adiponectin, a peptide hormone secreted from adipocytes, exerts anti-inflammatory, anti-diabetic, anti-atherogenic properties. Paradoxically, serum adiponectin levels are increased in patients with end-stage renal disease, and those patients are featured with chronic inflammation, increased insulin resistance and increased cardiovascular risk. We aimed to determine the relationship between serum adiponectin levels and renal outcome in chronic kidney disease (CKD) patients.

Methods: This prospective longitudinal study included 2087 CKD patients from the KNOW-CKD study (KoreaN Cohort Study for Outcomes in patients With Chronic Kidney Disease). Patients were divided into quartiles according to their serum adiponectin levels. The composite renal outcome was defined as one or more of the followings: initiation of dialysis or transplantation, a two-fold increase in baseline serum creatinine level, or a 50% decline in the estimated glomerular filtration rate (eGFR) during the follow-up period. A Cox proportional hazard ratio model was applied to analyze the relationship between composite renal outcome and serum adiponectin levels.

Results: Mean patient age was 53.5 ± 12.2 years, and 1273 (61%) were men. The eGFR was 50.4 ± 30.2 ml min^{-1} 1.73 m^{-2}. Mean values of each quartile of serum adiponectin were 2.9 ± 1.4, 7.2 ± 1.2, 12.7 ± 2.0 and 26.1 ± 9.6 μg/ml. Serum adiponectin level was inversely associated with body mass index and eGFR. In multivariate regression models, an association was found between the highest quartile of serum adiponectin and increased risk of composite renal outcome (HR, 1.336; 95% CI 1.029-1.734).

Conclusions: A high serum adiponectin level is independently associated with poor renal outcome, which suggests the potentially adverse role of adiponectin in CKD progression.



Kaplan-Meier survival curve according to serum adiponectin quartile groups.

TH-PO437

Deoxycholic Acid and Mortality, ESRD, and Cardiovascular Events in Patients with CKD

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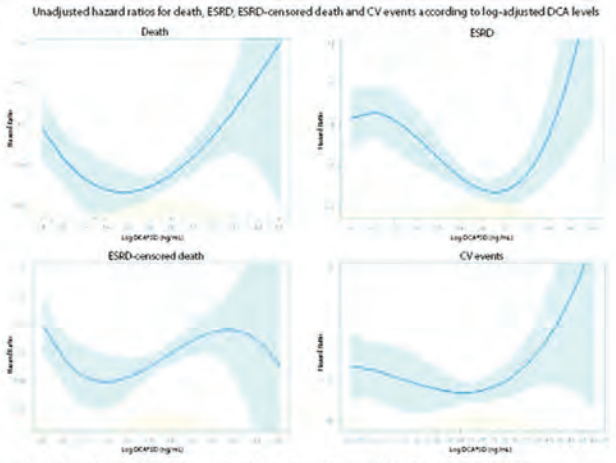
Background: Deoxycholic acid (DCA), a secondary bile acid, is elevated in patients with chronic kidney disease (CKD) and has been linked to vascular calcification in this population. There have not been studies examining the relationship between DCA and adverse events in CKD patients.

Methods: Using data from the prospective Chronic Renal Insufficiency Cohort Study, we analyzed the association between fasting serum DCA levels and death, end-stage renal disease (ESRD), ESRD-censored death and cardiovascular (CV) events in 3147 participants with CKD. We used Tobit regression to determine predictors of high DCA and Cox regression to determine the association between DCA and outcomes.

Results: The average age of participants was 58.9 ± 10.7 years, 40.6% were black, 48.0% had diabetes, and the mean eGFR was 42.5 ± 16.0 ml/min/1.73m^2. The independent predictors of elevated DCA were increased age and non-use of statins. Cox regression showed a U-shaped association between log-transformed DCA levels and outcomes. After adjustment, DCA values above the transition points were significantly associated with death, ESRD and ESRD-censored death (HR 1.23, 95% CI 1.04-1.45; HR 1.73, 95% CI 1.13-2.66; HR 1.23, 95% CI 1.00-1.50 respectively). DCA values below the transition points were significantly associated with ESRD (0.87, 95% CI 0.78-0.96). There was no association between DCA and CV events.

Conclusions: DCA is associated with death, ESRD and ESRD-censored death in a U-shaped distribution. DCA levels above the transition points are associated with death, ESRD-censored death, and ESRD in CKD patients, while values below the transition points are associated with ESRD.

Funding: NIDDK Support



Association of fasting DCA level with clinical end points, HR per 1 standard deviation of log DCA

Outcome	N	Median follow up time (years)	Events (%)	Log DCA x SD levels (pg/ml)	Unadjusted HR	*Adjusted HR model 1	**Adjusted HR model 2
Death	3147	8.8	819 (26.0%)	< 1.9	0.82 (0.64 - 1.04)	0.86 (0.67 - 1.10)	0.90 (0.69 - 1.18)
				≥ 1.9	1.24 (1.06 - 1.45)	1.20 (1.03 - 1.41)	1.23 (1.04 - 1.45)
ESRD	3147	8.1	829 (26.3%)	< 2.9	0.85 (0.78 - 0.93)	0.86 (0.79 - 0.94)	0.87 (0.78 - 0.96)
				≥ 2.9	1.51 (1.06 - 2.15)	1.54 (1.07 - 2.22)	1.73 (1.13 - 2.66)
ESRD-censored death	3147	8.1	495 (15.7%)	< 1.75	0.79 (0.53 - 1.19)	0.81 (0.53 - 1.22)	0.92 (0.58 - 1.45)
				≥ 1.75	1.23 (1.02 – 1.48)	1.16 (0.96 – 1.40)	1.23 (1.00 - 1.50)
CV events	3147	6.8	686 (21.8%)	< 2.5	0.92 (0.80 - 1.05)	0.94 (0.82 - 1.07)	0.97 (0.83 - 1.12)
				≥ 2.5	1.17 (0.90 - 1.51)	1.12 (0.85 - 1.44)	1.16 (0.88 - 1.54)

* Model 1 adjusted for: age, sex, black race, Hispanic ethnicity, and center

** Model 2 adjusted for: model 1 + eGFR, urinary protein, diabetes, SBP, number of antihypertensive medications, current smoking, history of cardiovascular disease, total cholesterol, statin use

TH-PO438

Differences in Urinary Potassium and Acid-Base Handling in African American vs. Non-African American CKD Patients

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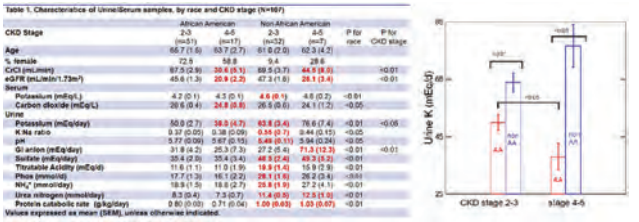
Background: African American (AA) patients with chronic kidney disease (CKD) have faster progression to end stage renal disease (ESRD) than non AA CKD patients. The underlying etiology is multifactorial related to genetics (APOL1), renal disease pathology, co-morbidities or underlying physiologic differences. Physiologic differences include potassium (K+) and acid/base metabolism within the CKD population, specifically racial differences between AA and non AA patients with CKD. Correction of metabolic acidosis in CKD patients has shown to slow progression of CKD, but few studies have examined differences between acid/base metabolism in AA and non AA. No studies have examined differences in urinary K+ excretion in these populations but studies that have shown AA CKD patients maintain lower serum K+ compared to non AA CKD patients. Our object is to identify differences in K+ handing and acid/base metabolism in AA vs non AA CKD patients

Methods: We studied a cohort of 107 patients with CKD Stage 3-5 who had collected 24-hr urine and serum studies as part of routine clinical care between 2009-2018

Results: Urinary K+ excretion in AA patients was much lower (50±3 mEq and 38±5 mEq, early and late CKD respectively; p<0.05) compared to non AA patients (64±3 mEq and 77±7 mEq, early and late CKD respectively; p value <0.01). Examination of acid/base metabolism using "GI anion", a measure of net dietary alkaline load, found late stage CKD non AA male patients had more urinary alkali excretion (71±12, p value <0.01) compared to early stage non AA patients (27±5) and all stages of AA patients (32±4 and 25±7 mEq, early and late CKD respectively). Also, within each CKD stage, protein catabolic rate (PCR) in non AA patients was much higher (1.00±0.03 and 1.03±0.07, early and late CKD respectively; p value <0.01) than AA patients (0.8±0.03 and 0.71±0.04, early and late CKD respectively).

Conclusions: AA patients with CKD handle K+ excretion and acid/base metabolism differently than non AA patients. The mechanism and impact of these racial disparities in CKD warrant further investigation.

Funding: NIDDK Support



TH-PO439

Association Between Income Disparities and Risk of CKD: A Nationwide Cohort Study of 7 Million Adults in Korea

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Background: Income disparities may have bearing on public health problems. However, longitudinal studies of the relationship between income level and incident chronic kidney disease (CKD) are scarce.

Methods: To examine the association between income level and incident CKD in healthy adults with normal baseline kidney function, we studied the association between income level categorized into deciles and incident CKD in a national cohort comprised of 7.4 million adults who underwent National Health Insurance Service health examinations between 2009–2015 with baseline estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2. Incident CKD was defined as *de novo* development of eGFR <60 mL/min per 1.73m^2 (model 1) or ≥25% decline in eGFR from the baseline values accompanied by eGFR <60 mL/min/1.73m^2 (model 2).

Results: During a median follow-up of 4.8 years, there were a total of 122,032 (1.65%) and 55,779 (0.75%) incident CKD events based on model 1 and 2 definitions, respectively. Compared with income levels in the sixth decile, there was an inverse association between lower income level and higher risk of CKD up to fourth decile, above which no additional reduction (model 1) or slightly higher risk of CKD (model 2) was observed at higher income levels. The multivariable-adjusted hazard ratios (95% confidence interval) from the lowest to fourth deciles were 1.30 (1.26-1.33), 1.16 (1.13-1.19), 1.07 (1.05-1.10), and 1.06 (1.03-1.09) in model 1 and 1.32 (1.27-1.37), 1.18 (1.14-1.22), 1.08 (1.04-1.13), and 1.05 (1.01-1.09) in model 2, respectively. These associations persisted across various subgroups of age, sex, and comorbidity status.

Conclusions: In this large nationwide cohort, lower income levels were associated with higher risk of incident CKD.

TH-PO440

Implications of Different Methods for Calculating Time to Percentage in eGFR Decline Outcomes

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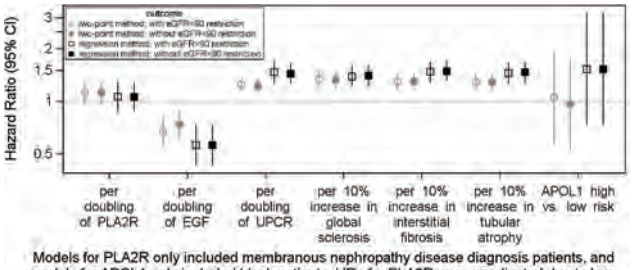
Background: Multiple methods for calculating time to 40% eGFR decline outcomes may differentially characterize kidney disease progression. We compared the traditional "two-point method" (using baseline eGFR to determine the decline threshold and first subsequent eGFR lower than the threshold for the event time) to a "regression method" (fit a regression line to all eGFRs to calculate the threshold and event time), with and without an additional restriction that eGFR<90 at the event time.

Methods: NEPTUNE is a multi-site observational cohort study of patients with glomerular disease. Based on subsets of N=605 patients with available data, we used Cox models to estimate effects of morphologic damage (interstitial fibrosis, tubular atrophy, global sclerosis), urine biomarkers (epidermal growth factor [EGF], urine protein creatinine ratio [UPCR]), serum anti-Phospholipase A2 receptor (PLA2R), and apolipoprotein L1 (APOL1) genotype on time to 40% eGFR decline (or end-stage renal disease) across different methods, adjusted for patient demographic and clinical characteristics.

Results: The regression method and additional restriction of eGFR<90 yielded lower event rates, the latter especially for patients with high eGFR at study enrollment. Effect estimates using the regression method were similar or greater in magnitude (i.e., away from the null) for most predictors [Fig]. Effect estimates with and without the eGFR<90 restriction were similar.

Conclusions: The regression method can facilitate detection of smaller exposure effects. Given a previous study showing increased accuracy of the regression method over the two-point method, we recommend the regression method for calculating time to percent eGFR decline to increase accuracy of effect estimates. The eGFR<90 restriction can capture at least mild loss of kidney function at the event time, which may be needed when hyperfiltration at baseline is a concern.

Funding: NIDDK Support



Models for PLA2R only included membranous nephropathy disease diagnosis patients, and models for APOL1 only included black patients. HRs for PLA2R were unadjusted due to low number of outcome events. HRs for others were adjusted for patient age, race, sex, disease diagnosis, eGFR, UPCR, and medication use (immunosuppression and RAAS blockade), unless the number of events was limited, in which case backward selection was used to select adjustment variables.

TH-PO441

Aldosterone Antagonists for Preventing the Progression of CKD: An Updated Cochrane Review

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Background: Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) reduce proteinuria and retard the progression of chronic kidney disease (CKD), though resolution of proteinuria may be incomplete. We evaluated whether addition of an aldosterone antagonist may further prevent progression of CKD.

Methods: We searched the Cochrane Kidney and Transplant Register of Studies through to 3 September 2018 for randomized controlled trials comparing aldosterone antagonists to standard care or placebo in patients with proteinuric CKD. Two independent authors extracted data for end-stage kidney disease (ESKD), major cardiovascular events, mortality, proteinuria, glomerular filtration rate (GFR), blood pressure, hyperkalemia, acute kidney injury (AKI), and gynecomastia. Risk of bias was assessed using the Cochrane tool. Evidence certainty was evaluated using GRADE.

Results: Forty-three studies (5171 participants) were eligible. Risk of bias in the evaluated methodological domains was unclear or high risk in most studies. Aldosterone antagonists had uncertain effects on risk of ESKD (2 studies, 84 participants, risk ratio [RR] 3.00, 95% confidence interval [CI] 0.33 to 27.65, *very low certainty evidence*), mortality (3 studies, 421 participants, RR 0.58, 95%CI 0.10 to 3.50, *low certainty evidence*), cardiovascular events (3 studies, 1067 participants, RR 0.95, 95%CI 0.26 to 3.56, *low certainty evidence*) and GFR (12 studies, 861 participants, MD -2.25 ml/min/1.73 m^2, 95%CI -4.76 to 0.25, *low certainty evidence*); may reduce proteinuria (14 studies, 910 participants, standardized mean difference [SMD] -0.53, 95%CI -0.86 to -0.19, *very low certainty evidence*) but probably increases risk of hyperkalemia (17 studies, 2683 participants, RR 2.10, 95%CI 1.42 to 3.13, *moderate certainty evidence*), AKI (4 studies, 1088 participants, RR 2.02, 95%CI 1.02 to 4.02, *moderate certainty evidence*) and gynecomastia (4 studies, 281 participants, RR 5.14, 95% CI 1.14 to 23.23, *moderate certainty evidence*) compared to standard care or placebo.

Conclusions: Aldosterone antagonists when added to ACEi or ARB (or both) may reduce proteinuria but have uncertain effects on death, major cardiovascular events or ESKD and may incur excess hyperkalaemia, acute kidney injury and gynecomastia.

TH-PO442

Comprehensive Profiling of the Clinical Nephropathies in Participants of the H3Africa Kidney Disease Research Network Project Cohort Study

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Background: It is estimated that more than greater than 50 million African Blacks have Chronic Kidney Disease (CKD) due to clinically defined nephropathies. A significant fraction of these will progress to ESRD. Despite the high rate of CKD progression among individuals of African ancestry, the molecular and clinical factors underlying this high burden is not completely understood. The ongoing H3Africa Kidney Disease Cohort study aims to evaluate the independent contribution of risk variants in the *APOL1* genes to the progression of clinically defined nephropathies among 3,000 African Blacks. This abstract described the baseline characteristics of the participants of the study

Methods: A longitudinal study of 3,000 African black with clinical defined nephropathies. It involves baseline and follow up visits. At the baseline, relevant clinical information was obtained while blood and urine specimens were collected for the assays. Biological specimens were processed, stored, packaged and shipped to the central repository for analysis. Information obtained from participants were demographics, contact information and medical history and blood was collected for DNA, RNA, whole blood, serum creatinine, full blood count and anthropometric measures. Where clinically indicated a kidney biopsy was performed and kidney tissue examined histologically.

Results: A total of 2,192 participants were included in this analysis, and the clinical nephropathies include hypertensive nephropathy 1194 (54.5%), diabetic nephropathy 558(25.5%), sickle cell nephropathy 63(2.9%) and CKD of unknown aetiology 377(17.2%). The mean age among participants were 53.84±14.41, 58.92±11.46, 35.24 ±13.67 and 37.08 ±15.97years for hypertyensive, diabetic and sickle cell nephropathies and CKD of unknown aetiology respectively. Albumin-Creatinine Ratio was higher among participants with CKD of unknown aetiology (165.09±302.49mg/Mmol) and sickle cell nephropathy (109.13±111.18mg/mMol) compared to hypertensive nephropathy 62.68±184.32mg/mMol) and diabetic nephropathy (78.71± 144.61mg/mMol)

Conclusions: Hypertensive nephropathy, diabetic nephropathy and CKD of unknown aetiology are the leading clinically defined nephropathies among the sub-Saharan African population

Funding: NIDDK Support

TH-PO443

Design and Patient Characteristics of a Study to Assess the Renoprotective Effects of the SGLT2 Inhibitor Dapagliflozin in Non-Diabetic Proteinuric Kidney Disease (DIAMOND)

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Background: Sodium glucose co-transporter 2 (SGLT2) inhibition decreases albuminuria and reduces the risk of kidney disease progression in patients with type 2 diabetes. These beneficial effects are likely mediated by activation of tubuloglomerular feedback by natriuresis, leading to decreased intraglomerular hypertension. Since non-diabetic kidney diseases are also characterized by glomerular hypertension, we tested the hypothesis that in patients with non-diabetic proteinuric kidney disease, SGLT2 inhibition with dapagliflozin reduces proteinuria and acutely and reversibly reduces glomerular filtration rate (GFR).

Methods: We designed a multicenter double-blind randomized placebo controlled 6-week cross-over study to assess the change from baseline in 24-hour proteinuria with dapagliflozin 10 mg/day in patients with proteinuric kidney disease without diabetes (ClinicalTrials.gov identifier: NCT03190694). The secondary endpoint was the change in iohexol-derived GFR. The main inclusion criteria were: urinary protein excretion >500 mg/24hr and ≤3500 mg/24hour, eGFR ≥25 mL/min/1.73m^2; stable dose of RAAS inhibitors.

Results: Patients with non-diabetic kidney disease were enrolled between November 2017 and April 2019. A total of 58 patients were screened of whom 53 patients were randomized in this ongoing study. The mean age at screening was 51 (SD 13) years and 32% were female. Mean screening eGFR was 59 (29) ml/min/1.73m^2 and median proteinuria 1074 (25th to 75th Percentile 810 -1400) mg/24hr. Overall, blood pressure was well controlled (SBP/DBP 128 (15) /78 (8) mmHg) and mean body weight was 83.0 (20) kg. Mean HbA_{1c} was 5.6 (0.4) % and mean hemoglobin level 138 (20) g/L. All patients were using a RAAS inhibitor.

Conclusions: This is the first placebo controlled clinical trial to examine the effects of an SGLT2 inhibitor in a non-diabetic population at risk for progressive kidney function loss. Final study results are expected in December 2019.

Funding: Commercial Support - AstraZeneca

TH-PO444

Effect of Bardoxolone Methyl on Kidney Events in Patients with CKD Stage 4 and Type 2 Diabetes at High Risk of Adverse Kidney Outcomes

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Background: Increases in kidney function, including increases in inulin clearance and estimated glomerular filtration rate (eGFR), have been observed with bardoxolone methyl (Bard) in 11 studies enrolling approximately 3,000 patients with chronic kidney disease (CKD). The largest of these studies was Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes (BEACON), a multinational, randomized, double-blind, placebo-controlled phase 3 trial, which enrolled patients with type 2 diabetes and stage 4 CKD. We performed a *post-hoc* analysis of BEACON to characterize changes

in kidney function induced by Bard in subgroups of patients at particularly high risk of adverse kidney outcomes, including those with baseline eGFR below 22 mL/min/1.73 m^2 or with a urine albumin to creatinine ratio (UACR) > 300 mg/g.

Methods: Patients in BEACON (n=2185; NCT01351675) were randomized 1:1 to receive once-daily bardoxolone methyl (20 mg) or placebo. For the subsets of patients with baseline eGFR < 22 mL/min/1.73 m^2 (n=503 for Bard, n=514 for placebo) or baseline UACR > 300 mg/g (n=540 for Bard, n=578 for placebo), we compared the effects of Bard and placebo on a *post-hoc* composite kidney endpoint consisting of a sustained ≥30% decline from baseline in eGFR, sustained eGFR <15 mL/min/1.73 m^2, and end-stage kidney disease events.

Results: Patients with baseline eGFR < 22 mL/min/1.73 m^2 randomized to Bard were significantly less likely to experience the composite kidney endpoint than patients randomized to placebo; 45/503 (9%) Bard patients experienced an event compared to 111/514 (22%) placebo patients (hazard ratio 0.39; 95% CI, 0.28-0.55; p<0.001). For patients with baseline UACR > 300 mg/g, 58/540 (11%) Bard patients experienced an event compared to 105/578 (18%) placebo patients (hazard ratio 0.58; 95% CI, 0.42-0.80; p<0.001).

Conclusions: In the subsets of patients enrolled in BEACON who were at greatest risk for progression to kidney failure, the increases in eGFR with Bard were associated with a significant reduction in the likelihood of an end-stage kidney disease composite endpoint.

Funding: Commercial Support - Trial sponsored by Reata Pharmaceuticals Inc.

TH-PO445

Effect of Aspirin on Cardiovascular Events, Mortality, and Bleeding Outcomes in Older Individuals with CKD

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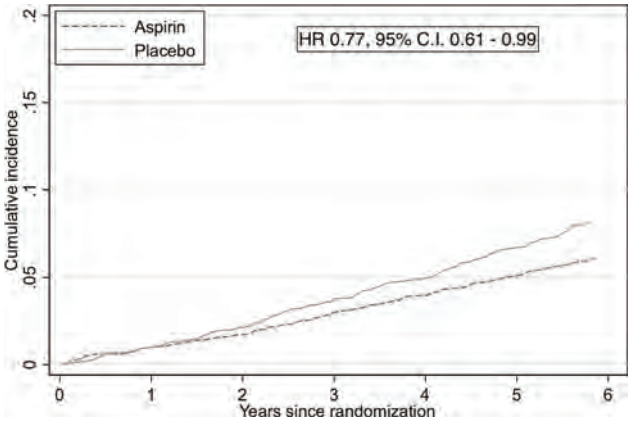
Background: The primary efficacy and safety of aspirin (ASA) in older people with chronic kidney disease (CKD) is unclear. ASPirin in Reducing Events in the Elderly (ASPREE), a large binational (Australia, US) RCT in elderly participants free of diagnosed CVD or disability, found no benefit of aspirin for primary prevention. The ASA To Target Arterial Events In CKD (ATTACK) trial is underway with a primary endpoint of major adverse cardiovascular events (MACE) in patients with CKD. To provide insights into whether ATTACK should consider exclusion of individuals aged >70 years, we examine the effects of daily 100mg ASA on outcomes in ASPREE participants with CKD.

Methods: ASPREE participants with eGFR <60, or ≥60mL/min with urine albumin creatinine ratio (UACR) ≥3mg/mmol, were included in these analyses. MACE was defined as a composite of fatal coronary heart disease, non-fatal myocardial infarction (MI), and fatal and non-fatal ischemic stroke. Other endpoints included all-cause mortality and major hemorrhage. In intention-to-treat time-to-event analyses, Cox proportional hazards models were used to compare the ASA group with the placebo group.

Results: Of 19,114 ASPREE participants, 4,758 had baseline CKD. Median eGFR was 56.2 mL/min/1.73m2 (IQR 50.2, 67.1), median UACR was 1.8 mg/mmol (0.6, 4.8). Sex, age, CVD risk factors, eGFR, and uACR were well-balanced between ASA and placebo groups. Participants with CKD randomized to ASA had a lower risk of MACE (HR 0.77, [95% C.I. 0.61, 0.99], figure), higher rate of major hemorrhage (HR 1.28, [0.98, 1.68]) and similar rate of mortality (HR 1.08, [0.89, 1.32]) compared to placebo.

Conclusions: The balance ofbenefit and harms of treatment with ASA in older people with CKD are unclear and merit ongoing investigation.

Funding: Other NIH Support - National Institute on Aging and the National Cancer Institute



Cummulative incidence MACE.

TH-PO446

Oral Adsorbent AST-120 Improves Microcirculatory Impairment in Patients with CKD

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Background: Microcirculatory impairment plays an important role at an earlier stage for peripheral arterial disease (PAD) in patients with chronic kidney disease (CKD). To treat PAD as early as possible is mandatory to avoid lower limbs' amputation. Therefore, we evaluated whether uremic toxin-lowering therapy could improve microcirculatory impairment in patients with CKD.

Methods: Oral charcoal adsorbent AST-120 (Kremezin, Kureha Corporation, Tokyo, Japan) adsorbs indole, a precursor of indoxyl sulfate (IS), in the gastrointestinal tract so that IS does not accumulate in the body. We performed a prospective interventional clinical trial whether AST-120 could improve atherosclerotic surrogates in CKD patients (UMIN no. 000013577). As a primary endpoint, skin perfusion pressure (SPP) of lower limbs, and flow mediated dilation (FMD) were evaluated as surrogate of microcirculatory and macrocirculatory status, respectively. They were evaluated at baseline, 3, 6, and 12 months after AST-120 administration. Serum levels of total IS (free IS and protein-binding IS) and renal function (serum creatinine (sCr), 1/sCr) were also evaluated at baseline, 3, 6, and 12 months after AST-120 administration. Total IS was evaluated using HPLC method and expressed as μM.

Results: We enrolled 30 non-diabetic CKD patients (CKD stage; G3a (n=4), G3b (n=9), G4 (n=14), and G5 (n=3)), and AST-120 6 gram/ day was orally administered for 12 months. Serum creatinine (sCr) levels and 1/sCr at baseline were 2.03±0.85 mg/dL and 0.578±0.226 dL/mg (mean±SD), respectively. Monthly decline in renal function (slope of 1/sCr) after AST-120 administration did not change compared to that in pre-treatment period. However, serum total IS significantly decreased at 3 months after AST-120 administration (baseline: 11.7±8.6 μM to 3 months: 6.9±5.0 μM, p<0.01). Serum IS levels continued to be decreased for 12 months (p<0.01). Although FMD did not change during study period, SPP values in lower limbs constantly elevated, and was significantly improved at 12 months after AST-120 administration compared to baseline values (69.7 ± 14.6 vs. 78.8 ± 18.9 mmHg, p<0.05).

Conclusions: IS-lowering therapy significantly improved micro-circulatory impairment in non-diabetic pre-dialysis CKD patients.

TH-PO447

AST-120 Can Delay the Decline of Renal Function in Patients with CKD

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Background: AST-120 (KREMEZIN®, Kureha Chemical, Tokyo, Japan) consists of oral spherical carbonaceous adsorbent, which was approved for use in delaying the initiation of dialysis and ameliorating the symptoms of uremia in patients with progressive chronic kidney disease (CKD). It adsorbs the precursor of indoxyl sulfate in the intestines and prevents indoxyl sulfate production. Indoxyl sulfate, initially identified as a major uremic toxin that causes uremic symptoms, contributes to CKD progression. Although international multicenter prospective trials of AST-120 did not slow progression of CKD in patients with moderate to severe CKD, present study evaluated the efficacy of AST-120 in preventing the progression of CKD and its indication in our Japanese cohort.

Methods: Antihypertensive therapy using renin-angiotensin-aldosterone inhibitor (RAS-i) and a low-protein diet is conventionally used to treat patients with CKD. We retrospectively recruited 225 patients with CKD treated with AST-120 from 2014 to 2016. Changes of serum levels of blood urea nitrogen (BUN) and eGFR were analyzed for 4 years, from 1 year before medication. Moreover, we elucidated the recommended timing of initiation of AST-120 administration.

Results: The mean eGFR and BUN at the baseline were 25.7 ml/min/1.73m^2 and 33.1 mg/dL, respectively. Decline of eGFR before AST-120 treatment was -5.4 ml/min/1.73m^2/year. After 1-year and 3-year medication with AST-120, the decline of eGFR was significantly improved to -1.1 and -2.3 ml/min/1.73m^2/year, respectively. AST-120 treatment was effective to decline the eGFR slope even in patients with diabetes mellitus as well as patients with high amount of proteinuria (over 1.0g/gCr). We next divided patients into 3 groups depending on baseline eGFR, *i.e.*, >50 eGFR ≥40, >40 eGFR ≥30 and eGFR<30 ml/min/1.73m^2 groups. The effect of AST-120 to prevent progression of CKD was the highest in >50 eGFR ≥40 group in which decline of eGFR was -7.8 to -2.0 ml/min/1.73m^2/year during intervention period.

Conclusions: Present study suggests that treatment with AST-120 may delay the decline of renal function in patients with CKD. Especially, AST-120 administration is recommended to initiate relatively maintained renal function (>50 eGFR ≥40). AST120 is useful for management of CKD patients.

Funding: Government Support - Non-U.S.

TH-PO448

Randomized Controlled Trial of Long-Term Safety and Efficacy of Veverimer for Treatment of Metabolic Acidosis

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Background: Metabolic acidosis in CKD is associated with accelerated GFR decline, augmented muscle catabolism and increased mortality. Veverimer, an oral, non-absorbed, counterion-free, polymeric drug candidate, selectively binds and removes HCl from the GI lumen.

Methods: We report a multicenter, randomized, blinded, placebo-controlled, 40-wk extension (n=196) of a 12-wk parent study (n=217) in patients with CKD (eGFR 20-40 mL/min/1.73m^2) and metabolic acidosis (serum bicarbonate 12-20 mEq/L) randomly assigned (4:3) to veverimer or placebo. The primary endpoint was safety; secondary endpoints were effect on bicarbonate level, patient-reported physical function (Kidney Disease and Quality of Life Physical Functioning Domain [KDQOL-PFD] and objectively measured physical function (repeated chair stand [RCS] test). A pre-specified time to event analysis for the composite outcome of death, RRT or eGFR decline ≥50% was also performed.

Results: Fewer patients on veverimer than placebo discontinued treatment prematurely (2.6% vs 9.8%) or experienced a serious adverse event (1.8% vs. 4.9%). No patients on veverimer died (vs. 2 on placebo) or discontinued due to an adverse event (vs. 1 on placebo) and the frequencies of common adverse events were comparable between groups. More patients on veverimer than placebo had an increase in bicarbonate (≥4 mEq/L or normalization) at Week 52 (62.7% vs. 37.8%, p=0.001) and higher bicarbonate levels were observed on veverimer at all time points (p<0.001). The KDQOL-PFD score improved on veverimer vs. placebo, with a mean placebo-subtracted (SE) change at end of treatment of 12.1 (3.3) points (p<0.0001). Veverimer specifically improved ability to climb 1 flight of stairs (p<0.0001) and all measures of walking (p<0.01) on the KDQOL-PFD. Time to perform the RCS test decreased by 4.3 (1.2) sec on veverimer vs. 1.4 (1.2) sec on placebo (p<0.0001). Veverimer was associated with longer time to the kidney composite endpoint (annualized incidence rate 4.2% [veverimer] vs. 12.0% [placebo], p=0.022).

Conclusions: Veverimer safely and effectively improved metabolic acidosis in patients with CKD. Our multicenter, randomized, controlled trial adds to the evidence that treating metabolic acidosis slows progression of CKD and improves physical function.

Funding: Commercial Support - Tricida, Inc. San Francisco, CA, USA

TH-PO449

PHYOX: A Safety and Tolerability Study of DCR-PHXC in Primary Hyperoxaluria Types 1 and 2

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Background: Primary Hyperoxaluria (PH) is characterized by hepatic overproduction of oxalate due to three distinct genetic mutations. DCR-PHXC is an investigational RNAi therapeutic targeting the LDHA enzyme, which is involved in the final step of hepatic oxalate production.

Methods: Preliminary data from the ongoing PHYOX study (ClinicalTrials.gov: NCT03392896), a two-part, single-ascending dose study conducted in 25 Healthy Volunteers (HVs, Group A) and 18 PH patients (Group B, reported here). Eligible PH patients have PH1 or PH2, urinary oxalate (Uox) ≥0.7mmol/24Hr, and eGFR ≥30 mL/min/1.73m2. Group B is open label and has three PH1 Cohorts dosed at 1.5, 3, and 6 mg/kg DCR-PHXC and a 4th PH1/PH2 cohort (1.5 and 3 mg/kg DCR-PHXC). The primary objective is safety. Change in 24Hr Uox from baseline (the mean of two screening 24Hr urine collections) was assessed.

Results: Safety Results: Group A is complete with no clinical meaningful safety signals and no serious adverse events (SAEs). Two mild injection site reactions (ISRs) occurred. Group B: Fifteen adult and three adolescent participants have been dosed. Four SAEs have occurred in three participants. Two SAEs of reoccurring fever, both unrelated to study drug, occurred in one participant. An SAE of ureteral stone occurred in a different participant and was unrelated to study drug. A fourth SAE of appendicitis was reported in another patient, also unrelated to study drug. All four SAEs are resolved. Seven participants experienced mild or moderate ISRs and all resolved within 96 hours. **Efficacy Results:** Group B: Preliminary results following a single administration of DCR-PHXC are captured in table 1. At 6mg/kg one participant experienced undetectable levels of Uox at Days 57 and 85.

Conclusions: Observed reduction of 24Hr Uox following a single administration of DCR-PHXC in both PH1 and PH2 participants is a promising sign of DCR-PHXC's potential potency and duration of action.

Funding: Commercial Support - Dicerna Pharmaceuticals

Table 1

Dose	N	Day 57 Reached	Max Reduction. Mean (range)	Max Reduction Time. Mean (range)	Near-normalization (> 0.46 and < 0.6 mmol/24Hr) N (%)	Normalization (< 0.46 mmol/24Hr) N (%)	Follow-up in Weeks. Mean (range)
1.5 mg/kg	6 (1 PH2)	6	47 (28-59%)	57 (Day 43 –85)	2 (33.3)	1 (16.7)	10.8 (8.1-14.1)
3.0 mg/kg	8 (2 PH2)	8	64 (22-80%)	60.5 (Day 29 – 141)	1 (12.5)	5 (62.5)	Ongoing
6.0 mg/kg	4 (4 PH1)	4	66 (35-100%)	46.5 (Day 43 – 113)	2 (50)	1 (25)	Ongoing

TH-PO450

Levothyroxine in Proteinuric CKD Patients Decreases Proteinuria and Improves Kidney Function: A Randomized, Double-Blind, Clinical Trial

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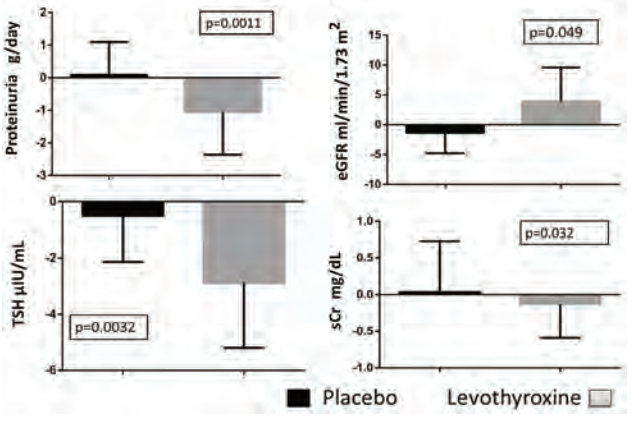
Background: Thyroid hormomes can affect kidney function. Elevated levels of TSH in CKD patients is associated to proteinuria, decrease in GFR, and progression to ESRD. We hypothesized that the use of levothyroxine (LTX) in proteinuric CKD patients with TSH levels between 2.5- 9.9 μIU/mL and normal FT4, decreases proteinuria and improves kidney function. Clinical trial registration number: NCT03898622

Methods: A double-blind, phase 2 randomized clinical trial, in proteinuric CKD patients, stage 3-5, not on dialysis, with TSH levels between 2.5-9.9 μIU/mL, and FreeT4 in a range of 0.7-1.8 ng/dL. All patients were already on ACE inhibitors or ARBs. Patients were randomized 1:1 to receive LTX (25-50mcg/day) or placebo for 12 weeks. The main outcomes were change in proteinuria, sCr, eGFR, TSH, and tolerability and safety of LTX.

Results: 163 patients were assessed for eligibility; 119 were excluded; 32 patients were randomized. Demographic and clinical characteristics between groups were similar. At 12 weeks, mean change in proteinuria (LTX vs placebo) was –1.1 (-4.1 to +0.9) g/day vs +0.20 (-0.4 to +2.1) g/day (p= 0.001); sCr –0.20 (-0.7 to +0.5) mg/dL vs +0.05 (-0.5 to +1.49) mg/dL (p=0.32); eGFR +4.04 ((+9.8 to -2.0) ml/min/1.73m^2 vs -1.96 ((-5.0 to +3.0) ml/min/1.73m^2 (p=0.049); and TSH -3.2 (-6.8 to +1.6) μIU/dL vs -0.4 (-3.09 a +1.87) μIU/dL (p=0.003), respectively (Fig 1). Adverse events were similar betwwen groups (7.14% vs 11.11%, p=1.0). No patient abandoned treatment because of adverse events.

Conclusions: LTX in proteinuric CKD patients decreased proteinuria and improved kidney function. Further studies are needed to determine the long-term impact of exogenous thyroid hormone treatment on proteinuria and CKD progression.



Mean change in proteinuria, sCr, eGFR, and TSH after 12-week treatment with LTX.

TH-PO451

Efficacy and Safety of Oral Ferric Maltol in Treating Iron-Deficiency Anemia in Patients with Non-Dialysis-Dependent CKD

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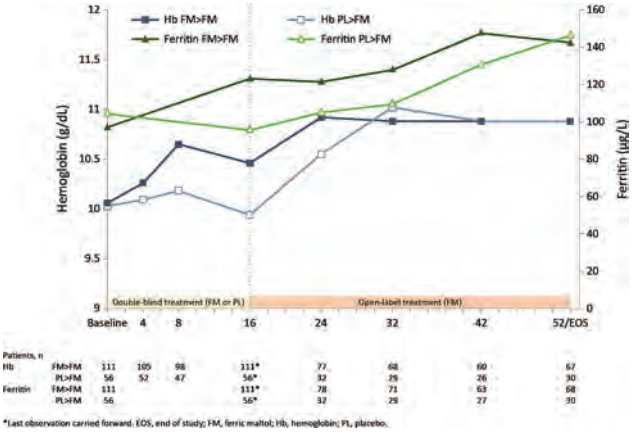
Background: Iron-deficiency anemia (IDA) is a major cause of morbidity/mortality in CKD. Ferric maltol (FM) is an oral iron replacement therapy formulated to improve absorption and reduce adverse events (AEs). FM significantly increased hemoglobin (Hb) and iron indices from baseline to week 16 vs placebo (PL) in a phase 3 trial in patients with stage 3/4 CKD (Kopyt ASN 2018). We present 52-week data from that trial.

Methods: Patients aged ≥18 years with stage 3/4 CKD and IDA [Hb 8.0–11.0 g/dL + either ferritin <250 μg/L with transferrin saturation (TSAT) <25% or ferritin <500 μg/L with TSAT <15%] were randomized 2:1 to oral FM 30 mg or PL twice daily for 16 weeks, followed by open-label (OL) FM for a further 36 weeks. Changes from baseline to Week 52 in Hb, ferritin, and TSAT were assessed in the intent-to-treat population.

Results: Of 167 patients randomized (FM 111, PL 56), 125 started open-label FM, and 92 completed 52 weeks. Improvements in Hb and iron indices with FM during double-blind treatment were maintained with OL FM to Week 52, while changes in Hb and iron indices for those moving from PL to FM mirrored the changes seen with FM during double-blind treatment (Figure). Drug-related AEs (mostly gastrointestinal) were recorded in 24 patients in the OL phase. Eleven patients discontinued treatment because of AEs during the OL phase.

Conclusions: Long-term treatment with FM was associated with sustained and clinically meaningful increases in Hb and iron indices, further confirming efficacy of oral FM for treating IDA in patients with stage 3/4 CKD. There were no new safety signals with up to 52 weeks' treatment.

Funding: Commercial Support - Shield Therapeutics plc



TH-PO452

The Effect of Proton Pump Inhibitor Use on the Development of Metabolic Acidosis and Decline in Kidney Function in Patients with CKD Stages G3a to G4

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Background: Proton Pump Inhibitors (PPI) block H+, K+ - ATPase and are widely used for the treatment of GERD and PUD. H+-K+ ATPase is present in other organs, including the kidneys. Metabolic acidosis (MA) can hasten progression of kidney disease. We evaluated the relation between chronic PPI use in patients with CKD Stages G3a to G4, the development of MA, and the rate of decline in renal function. We hypothesized that CKD patients who have been on PPI for at least one year would have a higher prevalence of MA and faster progression of CKD compared to patients not on PPI therapy.

Methods: We extracted data of patients from the VA Informatics and Computing Infrastructure national database system. We included adult patients with CKD (eGFR <60 ml/min1.73m2) and a record of receiving care for at least 5 yrs at the VA starting on January 1, 1999, through May 31, 2018. We excluded patients on dialysis, patients that transitioned to renal transplant, or death. Our outcome measures included mean serum bicarbonate and progression of CKD, measured by the decline in GFR determined by the MDRD formula. We applied Propensity Score Matching to match the PPI group and the control group on age, sex, race, and Charlson Comorbidity Index. Kaplan-Meier curve & Cox regression were performed to analyze the associations of PPI use with MA, dialysis, all-cause mortality, and CKD progression (defined as a 10 unit decrease of eGFR from the baseline eGFR).

Results: The final sample included 1406 patients (age: 62.07±7.82, 62.02% of white) in PPI cohort with a median 4.7 yrs follow-up, and 573 patients (age: 63.25±7.00, 70.33% of white) in no-PPI cohort with a median 4.2 yrs follow-up. When compared to the no-PPI cohort, the PPI group had a significantly increased risk of CKD progression and dialysis (aHR, 1.43; 95% CI, 1.17 to 1.74; and aHR, 1.69; 95% CI, 1.03 to 2.77, respectively). Patients on PPI also had a higher risk of MA (aHR, 1.83; 95% CI, 0.88 to 3.82) and all-cause mortality (aHR, 1.25; 95% CI, 0.96 to 1.64), but these differences were not statistically significant.

Conclusions: The data suggest that chronic PPI accelerates progression of kidney disease in CKD patients. Chronic PPI use should be discouraged in this population.

Funding: Private Foundation Support

TH-PO453

A Metabolome-Wide Association Study of Kidney End Points in CKD Patients: Results from the GCKD Study

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Background: Chronic kidney disease (CKD) affects >10% of the adult population and is associated with increased risk of end-stage kidney disease (ESKD) and mortality. The underlying mechanisms are incompletely understood. A comprehensive screen of metabolites whose levels in urine are associated with kidney endpoints can identify novel biomarkers for CKD progression and may provide pathophysiological insights.

Methods: We performed Cox Proportional Hazards analyses relating incident kidney endpoints to levels of 1487 urinary metabolites quantified in 5088 participants of the German Chronic Kidney Disease (GCKD) study in a randomly selected discovery (N=3392) and replication (N=1696) sample adjusted for age, sex, eGFR and UACR at baseline. Main endpoints were time to ESKD (dialysis or transplantation) or renal death ("ESKD", N_{events}=241) and a composite endpoint that additionally included acute kidney injury AKIN stage 3 ("Composite", N_{events}=382). Urinary metabolites were measured using the Metabolon HD4 platform, $\log_2$-transformed and analyzed when quantified in at least 30 patients with an event. Cause-specific hazard (CSH) regression as well as subdistribution hazard (SH) analyses with death of other causes as a competing event were performed. Statistical significance was defined using a Bonferroni correction for the number of tested metabolites in both the discovery (p≤4e-05) and replication setting.

Results: Median follow-up time was 4.0 years. CSH analyses of the Composite and the ESKD event identified and replicated 20 and 8 significant metabolites, respectively. For the Composite event, there were both protective and harmful metabolites, with cause-specific hazard ratios ranging from 0.63 to 2.75 per doubling of metabolite levels. Many replicated metabolites have not yet been implicated in ESKD. They belong to different biochemical classes, with evidence for enrichment in one sub-pathway. Most associations remained after adjusting for additional clinical covariates. SH analyses showed almost identical results.

Conclusions: We identified 20 urinary metabolites significantly associated with adverse kidney events in a cohort of CKD patients, potentially providing new insights into the mechanisms of kidney disease progression.

Funding: Government Support - Non-U.S.

TH-PO454

A Randomized Controlled Trial of the Effects of Febuxostat Treatment on Markers of Endothelial Dysfunction and Renal Progression in Patients with CKD

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Background: Hyperuricemia relates to chronic kidney disease (CKD) progression, systemic inflammation and impaired endothelial function. Febuxostat, a novel nonpurine selective xanthine oxidase inhibitor, is potent and effective for decreasing serum uric acid levels. The study aimed to evaluate the effect of oral febuxostat on markers of endothelial dysfunction and renal function in CKD patients.

Methods: A total of 84 CKD stage III-IV patients with asymptomatic hyperuricemia were randomly assigned to either the febuxostat (40 mg/day, N=40) or the matching control (N=44) for 8 weeks. Serum uric acid, estimated glomerular filtration rate (eGFR), urine albumin, serum asymmetric dimethylarginine (ADMA), and high sensitivity C-reactive protein (hsCRP) were measured at baseline and at the end of study.

Results: Febuxostat administration significantly reduced the serum uric acid concentration in patients with CKD when compared with control [-3.40 (95% CI -4.19 to -2.62) vs. -0.35 (95% CI -0.76 to 0.06) mg/dL; P<0.001, respectively]. No significant difference in the changes in serum ADMA, hsCRP, eGFR and albuminuria, was identified between the two groups. Subgroup analysis in patients with decline serum uric acid after treatment, mean eGFR showed a significant increase in the febuxostat group (P=0.022), but no significant change in the palcebo group (P=0.802). The difference GFR change between groups was 1.97 ml/min/1.73 m^2 with 95%CI 0.15 to 4.64 at 8 weeks (P=0.03). Adverse events specific to febuxostat were not observed.

Conclusions: Febuxostat effectively reduced serum uric acid in the population of CKD without effect to endothelial dysfunction and systemic inflammation. It was able to preserve renal function in subgroup CKD patients with lower serum uric acid level after treatment.

TH-PO455

Long-Term Impact of Bariatric Surgery on Renal Outcomes at a Community-Based Publicly Funded Bariatric Program

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Background: Obesity is recognized as an independent risk factor for chronic kidney disease (CKD) through multiple direct and indirect biological pathways. Bariatric surgery is a proven, effective method for sustained weight loss. However, there is a relative paucity of data on the impact of bariatric surgery on renal outcomes.

Methods: 471 consecutive obese adult patients who underwent bariatric surgery between 2008-2015 were included in this observational retrospective cohort study. The patients were followed for two years post surgery at the Provincial Bariatric Surgery Clinic, Regina General Hospital, Saskatchewan. The primary objective was to evaluate the change in urine albumin/creatinine ratio (ACR) at the time of surgery and at 12 months post procedure. Secondary objectives were to determine the changes in ACR at (6 and 24 months), estimated glomerular filtration rate (eGFR) (6, 12 and 24 months), and HbA1c (12 and 24 months) post procedure. The change in body mass index (BMI), and metabolic outcomes (fasting glucose, total cholesterol, LDL, triglycerides, HbA1c) were also measured.

Results: Patients were predominantly female (81%) with a mean age (±SD) of 46 ± 10 years. The majority of patients (87%) had a BMI >40 kg/m2 and 81 % of the patients underwent Roux-en-Y gastric bypass. The mean BMI decreased from 47.7 ± 7.8 kg/m2 at baseline to 37.1 ± 7.9 kg/m2 at 6 months and 34.8 ± 8.8 kg/m2 at 12 months. In patients with microalbuminuria, ACR showed an improvement from a median [IQR] value of 5.1 [3.7-7.5] mg/mmol at baseline to 2.3 [1.2-3.6] mg/mmol at 6 months (p=0.007), to 1.4 [0.9-3.7] mg/mmol at 2-year follow-up (p < 0.001). Similarly, eGFR increased in patients with microalbuminuria from 109 ± 10 mL/min/1.73m2 at baseline to 120 ± 36 mL/min/1.73m2 at two-year follow-up (p=0.013). There were statistically significant reductions in triglycerides, fasting glucose, and HbA1c.

Conclusions: The results of our study suggest bariatric surgery significantly decreased weight and consequently improved renal outcomes. There was a significant improvement in albumin excretion rates and improvement in filtration rates. An improvement in metabolic outcomes was also seen (fasting glucose, cholesterol, and triglycerides) in patients with elevated BMI.

TH-PO456

Advanced CKD Is Associated with Higher and Not Lower Insulin Use

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Background: As kidneys metabolize insulin, it is commonly held that insulin use is lower with more advanced CKD. On the other hand, more advanced CKD might result in progressive loss of beta cell function, increase in peripheral insulin resistance and contraindications to other antidiabetic medications, all of which might increase the need for insulin.

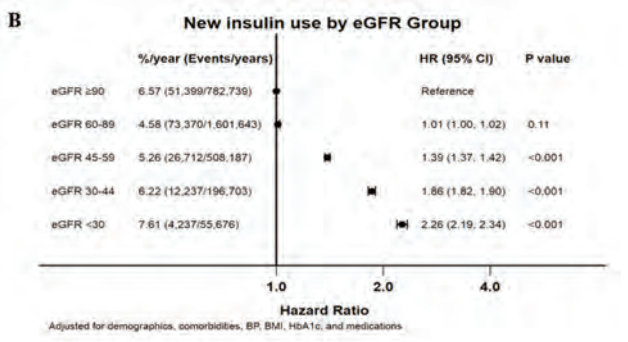
Methods: We related baseline level of kidney function with baseline and subsequent incidence of insulin use in 944,891 veterans in the VA system with a ICD-9 diagnosis of type 2 diabetes mellitus and at least one outpatient serum creatinine drawn between Jan 1, 2008 and Dec 31, 2010. Baseline and subsequent insulin use was identified by pharmacy data and tracked until Dec 31, 2013.

Results: There were 212,040 (22%) on insulin at baseline. Baseline characteristics by insulin use are summarized in Table. In a multivariable logistic regression model (adjusted for demographics, comorbidities, blood pressures, BMI, HbA1C and other anti-diabetic medications), compared to eGFR≥90, the odds ratios for baseline insulin use in those with eGFR of 30 to <45 and < 30 were 1.86 (95% CI 1.82 to 1.90) and 2.62 (2.19 to 2.34), respectively. Results were similar for incident insulin use in a Cox model adjusted for above (Fig).

Conclusions: Insulin use increased with more advanced CKD. Given the availability of newer anti-diabetic agents, the safety of insulin use in more advanced need to be evaluated in randomized controlled trials.

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

	Insulin (N=212,040)	No Insulin (N=732,851)
Age (years)	65 ± 11	67 ± 11
Male (%)	97	97
Black (%)	21	17
Diabetes Duration (years)	5.6 ± 3.2	3.9 ± 3.0
HbA1C (%)	8.4 ± 2.0	7.0 ± 1.4
BMI (kg/m^2)	32.7 ± 6.9	31.4 ± 6.2
Sulfonylurea (%)	36	42
Metformin (%)	44	50
TZD (%)	7	5
Other Meds (%)	2.0	1.3



TH-PO457

Proximal Tubular Secretory Clearance Is Associated with the Progression of CKD: The CRIC Study

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Background: The secretion of organic solutes by the proximal tubules is an essential intrinsic kidney function. The clinical significance of tubular secretory clearance is uncertain.

Methods: We evaluated 3,416 participants from the Chronic Renal Insufficiency Cohort (CRIC) Study. We estimated the kidney clearances of 11 endogenous secretory solutes based on their measured concentrations in paired 24-hour urine and plasma samples at baseline using targeted mass spectrometry. CKD progression was defined by a 50% decline in the estimated glomerular filtration rate (eGFR), initiation of maintenance dialysis, or kidney transplantation. We used Cox proportional hazards regression to test associations of secretory solute clearances with CKD progression and all-cause mortality, adjusting for eGFR, albuminuria, and other potential confounders.

Results: There were 1,206 CKD progression events and 1,004 mortality events over a median follow-up of 6.0 and 9.6 years, respectively. After adjustment for eGFR, albuminuria, and other risk factors, lower kidney clearances of six secretory solutes (cinnamoylglycine, indoxyl sulfate, isovalerylglycine, kynurenic acid, pyridoxic acid, and xanthosine) were associated with greater risks of CKD progression (11%-21% greater risk per 50% lower secretory clearance; Table). Lower clearances of four solutes (hippurate, isovalerylglycine, tiglylglycine, and trimethyluric acid) were associated with all-cause mortality after adjustment.

Conclusions: Lower proximal tubular secretory solute clearance is associated with greater risks of CKD progression and all-cause mortality independent of eGFR and albuminuria. These findings suggest that estimates of tubular secretory clearances may provide complementary information to existing measures of glomerular filtration and integrity.

Funding: NIDDK Support

Table. Adjusted associations between secretory solute clearances and outcomes.

	CKD progression			All-cause mortality		
	HR[a]	95% CI	P-value[b]	HR	95% CI	P-value
Hippurate	1.01	0.97-1.05	0.738	1.07	1.02-1.11	0.002*
Cinnamoylglycine	1.11	1.06-1.17	<0.001*	1.06	1.01-1.12	0.019
Indoxyl sulfate	1.15	1.06-1.24	<0.001*	1.06	0.97-1.15	0.219
p-cresol sulfate	1.08	1.01-1.16	0.020	1.01	0.93-1.08	0.869
Isovalerylglycine	1.13	1.05-1.21	0.001*	1.23	1.14-1.32	<0.001*
Kynurenic acid	1.21	1.10-1.32	<0.001*	1.13	1.03-1.24	0.011
Pyridoxic acid	1.18	1.10-1.26	<0.001*	1.10	1.02-1.19	0.010
Tiglylglycine	1.06	1.00-1.13	0.049	1.19	1.11-1.28	<0.001*
Dimethyluric acid	1.03	0.99-1.07	0.206	1.02	0.97-1.06	0.472
Trimethyluric acid	1.03	0.99-1.07	0.118	1.06	1.02-1.11	0.004*
Xanthosine	1.13	1.08-1.19	<0.001*	1.06	1.01-1.12	0.025

[a] Hazard ratio expressed per 50% lower secretory solute clearance.

[b] * denotes statistical significance after correction for multiple comparisons using the Hommel method.

TH-PO458

Therapeutic Drug Monitoring Is Associated with Better Survival in Hospitalized Nondialysis CKD Patients Treated with Vancomycin

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Background: Vancomycin is widely used to treat patients infected by Gram-positive bacteria. Therapeutic drug monitoring (TDM) is routinely recommended for all patients treated with vancomycin to avoid underdoing and minimize the risk of toxicity. There are few studies, however, investigating the relationship between the TDM and clinical outcome in patient with chronic kidney disease treated with vancomycin.

Methods: We conducted a nationwide, observational population-based cohort. Claim data from Longitudinal Health Insurance Databases 2010 (LHID2010) which randomly chose one million beneficiaries from Taiwan's National Health Insurance Research Database are used. From LHID2010, all hospitalized non-dialysis chronic kidney patients (ND-CKD) who were more than 20 years old, less than 85 year old, and received vancomycin treatment were recruited. All subjected are grouped according to whether the application of TDM or not. Cox regression was performed to assess the relationship between vancomycin TDM and mortality within 90 days.

Results: There were 3434 patients enrolled for analysis. There were 762 patients (22.2%) received TDM. There was no significant difference between these two groups with the aspect of demographic and comorbidity(gender, age, hypertension, diabetes mellitus, heart failure, coronary artery disease, cerebrovascular accident, peripheral arterial disease, chronic obstructive pulmonary disease, liver disease, and malignancy), except that patients in medical centers received more TMD than those in non-medical centers(27.3% vs. 19.4%; p <0.001). Cox regression model indicated that TDM was associated with decreased risk for 90-day mortality (adjusted hazard ratio: 0.46; 95% confidence interval: 0.34-0.63; p <0.001). Moreover, age, male, heart failure, liver disease, and malignancy were also associated with increased mortality risk.

Conclusions: This is the first study to evaluate the importance of TDM in ND-CKD patients received vancomycin. In real practice, the application of TDM of vancomycin was even unexpectedly low in ND-CKD patients. Our results show ND-CKD patient with TDM of vancomycin is associated with reduced risk of mortality. The TDM of vancomycin in ND-CKD patients cannot be overemphasized.

TH-PO459

Frequency of eGFR and Albuminuria Measurement in Patients with Diabetes and/or Hypertension in 27 Health Care Organizations

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Background: Clinical guidelines for diabetes recommend screening for chronic kidney disease annually with spot urinary albumin-to-creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR). For hypertension, measures are recommended at diagnosis to establish a baseline for medication use, and to screen for secondary causes of hypertension, with eGFR listed as a basic test, and uACR optional.

Methods: Using a large, geographically diverse clinical dataset from 27 health care organizations (HCOs), 580,950 patients with diabetes and 1,558,525 patients with hypertension were identified, among a population aged 18-85, with ≥ 1 face-to-face ambulatory encounter with a primary care provider in 2018, and no prior evidence of end stage renal disease. Measurement rates were described in 1-year (2018), 2-year (2017-2018), and 3-year (2016-2018) periods, overall and for HCOs at the 5th and 95th percentile. Measurements were limited to quantitative values recorded in a structured field in the HCOs' electronic health records.

Results: Overall, 89.1% of patients with diabetes and 85.1% with hypertension had eGFR measured in the 1-year period. Measurement rates for uACR were 45.2% for diabetes and 16.5% for hypertension in the 1-year period, and increased to 65.3% and 24.8% using the 3-year measurement period. Rates varied considerably across HCOs for uACR (e.g., 5th and 95th percentiles for the 3-year period were 25.3% and 79.6% among patients with diabetes). When limiting to patients with hypertension but no diabetes, uACR measurement rates were very low, even with eGFR < 60 (i.e., CKD G3+).

Conclusions: Most patients with diabetes or hypertension have eGFR measured, consistent with recommendations from clinical guidelines. uACR measurement rates were moderate and variable across HCOs among patients with diabetes, demonstrating an opportunity for improvement in clinical practice. Measurement rates for uACR were very low for hypertension without diabetes, even in the presence of reduced eGFR.

Lab	Measurement Period	Diabetes (DM)	Hypertension		
		All Patients (n = 580,950) Overall (5th - 95th percentile)	All Patients (n = 1,558,525) Overall (5th - 95th percentile)	No Diabetes (n = 1,096,955) Overall (5th - 95th percentile)	No DM, and eGFR < 60 (n = 161,242) Overall (5th - 95th percentile)
estimated GFR (eGFR)	1 year	89.1% (78.5 - 93.7%)	85.1% (74.4 - 89.5%)	82.7% (71.9 - 87.3%)	
	2 year	94.9% (84.4 - 97.9%)	93.1% (82.3 - 96.6%)	91.9% (80.7 - 95.7%)	
	3 year	96.0% (85.9 - 98.6%)	94.7% (84.2 - 97.8%)	93.9% (82.8 - 97.2%)	
Urine albumin to creatinine ratio (uACR)	1 year	45.2% (17.8 - 60.5%)	16.5% (5.9 - 23.7%)	3.7% (0.6 - 7.0%)	6.0% (0.8 - 10.9%)
	2 year	59.3% (23.1 - 75.0%)	22.1% (7.6 - 30.0%)	5.6% (1.3 - 9.5%)	8.7% (1.6 - 14.7%)
	3 year	65.3% (25.3 - 79.6%)	24.8% (8.4 - 32.6%)	6.9% (1.8 - 11.5%)	10.6% (2.6 - 18.2%)

Overall rates are patient weighted across all health care organizations (HCOs). Percentiles are calculated among the individual HCOs. Standard errors were <2.0% for each HCO and measure shown.

TH-PO460

Anti-Inflammatory Therapy in CKD Using Drug-Delivery Technology: Mechanisms and Effects of Renal NFkB Inhibition

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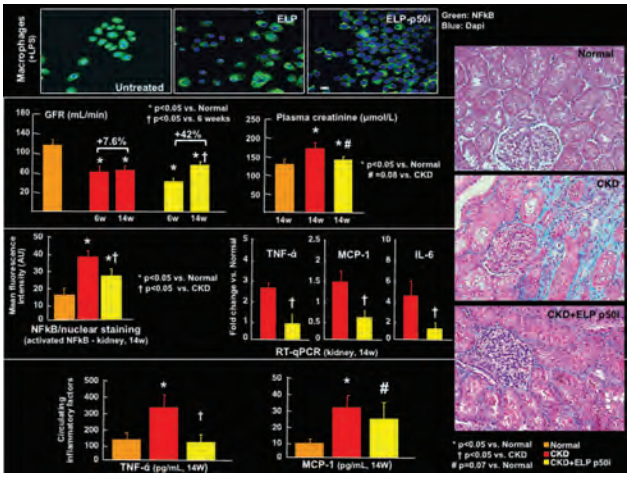
Background: The NFkB pathway mediates chronic inflammation in chronic kidney disease (CKD). The NFkB p50/p65 heterodimer, once activated, translocates into the cell nucleus to stimulate inflammation via defining macrophage phenotype and production of inflammatory cytokines. We designed a construct of an inhibitor of the NFkB-p50 subunit (p50i) fused to a drug carrier (elastin-like polypeptide, ELP) equipped with a cell-penetrating peptide. We hypothesize that ELP-p50i therapy will inhibit production of inflammatory cytokines, ameliorate renal inflammation and injury in CKD

Methods: We first exposed LPS-stimulated macrophages to ELP-p50i to confirm its NFkB inhibitory activity. Next, CKD was induced in 10 pigs (bilateral renal artery stenosis+dyslipidemia). After 6 weeks of CKD, pigs were treated with single intra-renal ELP-p50i therapy (10 mg/kg) or placebo (n=5 each). Glomerular filtration (GFR) was quantified using multi-detector CT before and 8 weeks after treatment. Pigs were then euthanized and renal expression of NFkB, downstream mediators of NFkB signaling, circulating inflammatory cytokines, and renal morphology were quantified

Results: ELP-p50i inhibits nuclear translocation of NFkB in vitro. Fourteen weeks of CKD increased renal NFkB nuclear expression and renal mRNA expression of downstream mediators (TNF-α, MCP-1, and IL-6), accompanied by blunted GFR, increased plasma creatinine, and renal fibrosis. All these changes were improved after ELP-p50i therapy. Notably, intra-renal therapy also reduced circulating TNF-α and MCP-1 in CKD (Figure)

Conclusions: Our study provides mechanistic support, *in vitro* and *in vivo*, to the therapeutic potential of a targeted anti-inflammatory strategy using a novel drug-delivery technology. It also suggests that the kidney in CKD is both a source and target of inflammation that could be offset via specific molecular inhibition of NFkB signaling

Funding: Other NIH Support - NHLBI



TH-PO461

Proximal Tubule Activation of B-Catenin Ameliorates Chronic Kidney Injury in Mice

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Background: Tubulointerstitial fibrosis (TIF) is the hallmark of chronic kidney disease (CKD), and growth factors play an important role in injury and TIF. The Wnt/b-catenin pathway has been shown to be protective in acute kidney injury (AKI), but is thought to promote CKD progression, likely mediated by b-catenin signaling in mesenchymal cells. However, the cell-autonomous effects of b-catenin signaling on chronically injured tubules remains unknown.

Methods: To address how proximal tubule (PT)-specific b-catenin alters the response to chronic injury, we generated conditional mice with constitutive activation of b-catenin in the PT (gGT-Cre;Ctnnb1$^{ex3fl/fl}$). We injured these mice and their floxed littermates using two models of AKI to CKD: aristolochic acid nephropathy (AAN) and ischemia reperfusion (IRI) plus delayed contralateral nephrectomy. We used murine PT cells for in vitro studies.

Results: Surprisingly, 6 weeks after AAN, injury score, KIM-1 transcript, cortical fibrosis and BUN levels were decreased in conditional mice compared to their controls, suggesting that b-catenin signaling in the PT is protective. Cortical tubular apoptosis was decreased in the conditional mice. Consistently, stabilizing b-catenin in vitro (Wnt3a or GSK-3 inhibitor) also reduced aristolochic acid (AA)-induced apoptosis. Oxidative stress reportedly switches b-catenin transcriptional binding partners from LEF/TCF to FoxO, but this has not been examined in PT cells. We found that oxidative stress, present in CKD, reduced LEF/TCF-dependent transcription in PT cells (Topflash and Axin2 mRNA)

and augmented FoxO3 activity. Co-IP studies showed that oxidative stress plus Wnt3a significantly increases nuclear FoxO3/b-catenin interactions. In the AAN model, injured conditional b-catenin mice have augmented nuclear FoxO3 expression in proximal tubules. Furthermore, FoxO3 was required for b-catenin's protective effect as mice with PT-specific b-catenin stabilization and FoxO3 deletion (using gGT-Cre) lost the protective effect in AAN. RNAseq on PT cells was performed and identified 19 novel b-catenin and FoxO3 targets.

Conclusions: In conclusion, b-catenin signaling within the proximal tubule mitigates AKI to CKD transition through its interaction with FoxO3. Ongoing efforts are examining this b-catenin effect in the IRI and validating novel targets in vivo.

Funding: Veterans Affairs Support

TH-PO462

Inhibition of Nα-Acetyltransferase Attenuates Renal Interstitial Fibrosis via Modulation of Epithelial-to-Mesenchymal Transition and Inflammation

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Background: Nα-acetyltransferase 10 (Naa10), the catalytic subunit of N-acetyltransferase A, has been reported to be involved in the regulation of telomerase activity, DNA damage response, cytokinesis, microtubule reorganization and histone acetylation. This study was designed to investigate whether the pharmacological inhibition of Naa10 could affect the progression of renal tubulointerstitial fibrosis.

Methods: Remodelin 1mg/kg, a Naa10 inhibitor, was administered to the mice for 3 or 7 days following unilateral ureteral obstruction (UUO).

Results: Renal Naa10 expression after UUO was significantly enhanced but reduced by the Naa10 inhibitor remodelin. Masson trichrome and Sirius red staining demonstrated that Naa10 inhibition led to a decrease in renal interstitial fibrosis induced by UUO. In addition, the α-SMA- or TUNEL-positive cells were apparently decreased in obstructed kidneys with administration of remodelin. Furthermore, remodelin inhibited the increase in the mRNA levels of α-SMA, fibronectin, MMP-2, IL-1β, IL-6, TNF-α, TGF-β1 and ColIV without significant changes in mRNA levels of vimentin, E-cadherin and VE-cadherin and protein expressions of Nox1, Nox2, Nox4, SOD1, HO-1, NQO1 and catalase in obstructed kidneys. All these findings were apparent at day 7 after UUO. Collectively, these results indicate that longer treatment of remodelin mitigates UUO-induced renal interstitial fibrosis by affecting epithelial-to-mesenchymal transition (EMT) and inflammation.

Conclusions: Current study suggests that Naa10 inhibition could attenuate renal fibrosis through regulation of certain EMT- and inflammation-related factors.

Funding: Government Support - Non-U.S.

TH-PO463

Proximal Tubule-Derived Amphiregulin Amplifies and Integrates Profibrotic EGFR Signals in Kidney Fibrosis

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Background: Sustained activation of epidermal-growth-factor-receptor (EGFR) in proximal-tubule-cells (PTCs) is a hallmark of progressive kidney fibrosis after acute-kidney-injury (AKI) and in chronic-kidney-disease (CKD), but the molecular mechanism(s) and particular EGFR ligands involved are unknown.

Methods: We studied EGFR activation in PTCs and in primary tubular cells isolated from injured kidneys *in vitro.* To determine the role of amphiregulin (AREG), a highly injury-upregulated low-affinity EGFR ligand *in vivo*, we used ischemia-reperfusion-injury (IRI) or unilateral-ureteral-obstruction (UUO) in AREG PTC-KO mice, or injection of soluble AREG (sAREG) into mice with PTC-KO of its releasing enzyme, a-disintegrin-and-metalloprotease-17 (ADAM17), and into ADAM17 hypomorphic mice. Serum AREG was measured by ELISA in a CKD patient cohort.

Results: We show that Yes-associated-protein-1 (YAP1)-dependent upregulation of AREG transcript and protein amplifies AREG signaling in a positive feedback loop and integrates signals of other moderately injury-upregulated low-affinity EGFR ligands (epiregulin, epigen, TGFα), which we show also require sAREG and YAP1 to induce sustained EGFR activation in PTCs *in vitro*. *In vivo*, sAREG injection sufficed to reverse protection from fibrosis after IRI in ADAM17 hypomorphic mice, and to reverse the corresponding protective PTC phenotype in injured ADAM17 PTC-knockout mice. AREG was necessary for the development of fibrosis, as AREG PTC-knockout mice were protected from fibrosis after IRI or UUO. In a nephrectomy cohort (n=78) of CKD patients, serum sAREG negatively correlated with kidney function.

Conclusions: Our results identify AREG as a key player in injury-induced kidney fibrosis and suggest therapeutic or diagnostic applications of sAREG in kidney disease.

Funding: NIDDK Support

TH-PO464

Graphene Quantum Dots Suppress Kidney Fibrosis After AKI by Affecting the Pericyte-Myofibroblast Transition

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Background: Renal pericytes are important in the pathogenesis of kidney disease. They are key to vascular survival can contribute to glomerular and interstitial fibrosis. Graphene quantum dots (GQDs) are novel nanomaterials with excellent biocompatibility. They have anti-oxidative, anti-inflammatory and immune regulatory effects. The purpose of this study is to demonstrate that GQDs can inhibit pericyte activation and reduce the conversion of pericytes into myofibroblasts, thereby suppress kidney fibrosis after acute kidney injury.

Methods: Unilateral ischemia-reperfusion injury (UIRI) was induced in 7- to 8-wk-old male wild-type C57BL6 mice. GQDs were injected in kidney fibrosis models through the tail vein and the animals were observed for 6 wk. Histopathological examination was performed on the kidneys using Masson's trichrome staining, and pericyte detection in tissue by Immunofluorescence technique. rhTGF-β1 was used in vitro experiments to induce pericyte-myofibroblast transition. Western blot analysis was used to detect the expression of fibrotic markers.

Results: At 6 wk after UIRI, GQDs treatment significantly attenuated interstitial fibrosis in UIRI models. GQDs administration significantly reduced the expression of α-smooth muscle actin, collagen I, and fibronectin, vimentin,TGF-beta1, Bax, and increased the expression of E-cadherin, smad7, and bcl2. In addition, the expression of PDGFR in the URI group was significantly increased compared with the control group, only a small part overlapped with NG2, and the overlap was significantly less than that of the normal group and away from the endothelial cells. Compared with the UIRI group, the expression of PDGFR was significantly decreased after GQDs treatment, and the overlap of PDGFR and NG2 was increased, and the signs of pericytes away from endothelial cells were improved. rhTGF-β1 was used in vitro experiments to induce pericyte injury, and the expression of NG2, a-SMA and collagen 1a1 was increased compared with the control group, and the dose-dependent decrease was observed after treatment with various concentrations of GQDs

Conclusions: We found that non-toxic doses of GQDs protect pericyte damage and inhibit the transformation of pericytes into myofibroblasts, there by plays an important role in anti-fibrotic processes after acute kidney injury.

TH-PO465

The Deletion of Akt1 Exacerbates the Renal Fibrosis via Transforming Growth Factor β1 Induction

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Background: Renal fibrosis is the hallmark of all progressive kidney disease. However, the mechanisms of renal fibrosis are poorly understood. Previous studies have found the increased Akt activity in experimental renal fibrosis. In this study, we investigated the role of Akt1, one of the three Akt isoforms, in renal fibrosis using the murine model of unilateral ureteral obstruction (UUO).

Methods: In vivo, we subjected the wild type and *Akt1*$^{-/-}$ mice to UUO. In vitro, gene silencing of Akt1 was achieved using the short hairpin RNA delivered by the lentiviral vector in immortalized human proximal tubular cells (HK2 cells) and rat kidney fibroblasts (NRK-49F cells). Western blot and immunohistochemical stain were used to investigate the mode of action of Akt1 in vivo and in vitro.

Results: In immunohistochemical stain, the expression of Akt1 was significantly higher in obstructed kidneys of wild type mice compared with control sham kidneys and increased gradually as UUO progressed. The fibronectin, type I collagen, and heat shock protein 47 (HSP47) were markedly more expressed in obstructed kidneys of *Akt1*$^{-/-}$ mice than in those of the wild type mice. Transforming growth factor β1 (TGFβ1) was highly induced within 1 day of UUO in obstructed kidneys of *Akt1*$^{-/-}$ mice and the expression of TGFβ1 was significantly higher in the *Akt1*$^{-/-}$ mice than in the wild type mice as UUO progressed. Western blot showed that silencing of Akt1 increased the expression of TGFβ1, which was enhanced by angiotensin II stimulation in HK2 cells, but not in NRK-49F cells. Immunohistochemical stain demonstrated that the expression of cleaved caspase-3 in renal tubules was significantly higher in the *Akt1*$^{-/-}$ mice than in the wild type mice. Western blot showed that silencing of Akt1 increased the expression of cleaved caspase-3 in HK2 cells, but not in NRK-49F cells.

Conclusions: TGFβ1 was induced in vivo and in vitro by the genetic deletion of Akt1. Our findings suggest that deletion of Akt1 might contribute to renal fibrosis and tubular apoptosis via TGFβ1 induction.

TH-PO466

Knockout of Interleukin-36 Receptor Ameliorates AKI-to-CKD Transition via Prevention of Fibrosis and Inflammasome

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Background: IL-36, a newly named member of the IL-1 cytokine family, includes 3 isoforms, IL-36α, IL-36β, and IL-36γ, all of which bind to a heterodimer containing IL-36 receptor (IL-36R). Little is known about the role of the IL-36 axis in fibrosis during AKI to CKD transition. We examined IL-36 function using mice AKI to CKD models and clinical samples.

Methods: We evaluated IL-36 function in two models of AKI to CKD transition by using IL-36R knockout (KO) and wild-type (WT) mice. First model, left renal ischemia was performed for 35min and right kidney was removed 21days later, and left kidney analyses at 28 days (IRI). Second model, we used aristolochic acid toxic nephropathy (AAN) in mice at 28 days. We evaluate the renal function and histological analysis of KO and WT mice in both models. Fibrotic changes and inflammasome were evaluated by RT-PCR, Western blot analysis. Immunohistologial analysis of collagen type IV, CTGF, and Masson trichrome staining were performed. In clinical study, we performed immunohistological examination of IL-36α in AKI to CKD patients renal biopsy sample.

Results: IL-36R was found to be expressed in the kidney mainly in proximal tubules in WT mice. IL-36R KO mice had significantly lower Cr and BUN at 28 days compared to WT mice in both models. Immunohistological examination showed mild tubular injury and fibrotic change in IL-36R KO mice compared to WT mice in both models. IL-36α/β/γ levels were increased after IRI and AAN, and IL-36α was expressed in lymphocytes and renal tubular cells. Immunohistologial analysis of collagen type IV and CTGF, and Masson trichrome staining revealed that massive fibrotic changes were observed in WT mice compared to KO mice. Protein expression of collagen type IV, CTGF, and inflammasome proteins(NLRP3, IL-1b, caspase 1) were also increased in WT mice compared to KO mice. IL-36α staining in renal-biopsy samples of AKI to CKD patients was enhanced.

Conclusions: Our results demonstrate that IL-36α is up-regulated in renal tissues in both mouse and human AKI to CKD transition, and that IL-36α stimulates collagen type IV, CTGF, and inflammasome in AKI to CKD transition models. Thus, IL-36α/IL-36R blockage could serve as a potential therapeutic target in AKI to CKD transition.

TH-PO467

The Novel NQO1 Donor Reduced Renal Fibrosis in Unilateral Ureteral Obstruction Mice

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Background: Reactive oxygen species (ROS) are thought to be a major factor in the development of acute renal injury and renal fibrosis in unilateral ureteral obstruction (UUO). NAD(P)H:quinone oxidoreductase 1 (NQO1) is a well-known antioxidant protein that regulates ROS generation. We generate the NQO1 donor, KL1333 and investigate whether KL1333 modulates the renal injury in UUO mice.

Methods: in vivo, 10 weeks old C57BL/6 male mice were divided 4 groups as following, sham, sham with KL1333, UUO, UUO with KL1333. KL1333 was treated oral route, 10mg/kg, daily. UUO were generated by tying left ureter, and after 7 days, the mice were sacrificed and kidney tissue were collected. in vitro, TGF beta treated HK2 cell were used. We analyzed renal injury using various stains, oxidative stress and tubular apoptosis using western blot and immunohistochemical stains.

Results: UUO mice kidney showed increased alpha SMA, collagen, masson trichrome stained area, and renal inflammation, compared to sham kidney. the KL1333 treatment decreased alpha SMA, collagen, masson trichrome stained area, and renal inflammation in UUO mice kidney. In addition, KL1333 increased the levels of HO-1, catalase, UCP2 in UUO mice kidney. Also, KL1333 increased NQO1, p-sirt1, and NAD+/NADH ratios in UUO mice. These finding indicate that KL1333 decreased UOO-induced oxidative stress and renal fibrosis.

Conclusions: NQO1 activation using KL1333 might be beneficial for ameliorating renal injury induced by UUO mice.

TH-PO468

Regulation of Renal Fibroblast Functions by Myocardin-Related Transcription Factor Focal Adhesion in Response to TGFβ$_1$

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Background: Renal fibrosis is a common pathway resulting in end-stage renal disease regardless of their etiologies. As pathological findings, tissue fibrosis is characterized by the accumulation of fibroblasts and the excessive deposition of extracellular matrix (ECM). In general, cells can contact with ECM via multiprotein structures called focal adhesion composed of various cytoskeletal proteins and integrins. We have previously found the lipid mediator lysophosphatidic acid (LPA) and one of its receptors, LPA$_1$, contributes to the development of renal fibrosis through connective tissue growth factor (CTGF) expression, at least in part, via myocardin-related transcription factors (MRTFs; MRTF-A and MRTF-B). Recently, TGFβ$_1$ has also been reported to be involved in MRTFs pathway, however, the precise mechanisms how TGFβ$_1$-MRTFs signaling contributes to the regulation of renal fibroblast activities through focal adhesion remain to be investigated.

Methods: In this study, we focused on the effects of TGFβ$_1$ signaling on the activities of renal fibroblasts, especially through MRTFs signaling. Cultured renal fibroblasts were used to examine the activation of MRTFs signaling using promoter assays and the expressions of molecules in response to TGFβ$_1$. Renal fibroblasts were transfected with either siRNA targeting MRTFs or focal adhesion components to determine the impact of MRTFs-focal adhesion on renal fibroblast biologies.

Results: Promoter assay showed the activation of MRTFs signaling by TGFβ$_1$ in a dose- and a time-dependent manner in renal fibroblasts. The stimulation of renal fibroblasts with TGFβ$_1$ increased CTGF expression, while siRNA treatment targeting MRTFs suppressed it. In addition, TGFβ$_1$ enhanced fibronectin, various integrins (αv, β1 and β5) and cytoskeletal proteins such as zyxin and talin, all of which were MRTFs-dependent. The treatment of renal fibroblasts with integrin αv siRNA or integrin-linked kinase inhibitor attenuated CTGF expression in response to TGFβ$_1$. Finally, TGFβ$_1$ stimulated the proliferation of renal fibroblasts, however, CTGF siRNA treatment suppressed it.

Conclusions: Our results suggest that MRTF signaling mediates renal fibroblast biologies through focal adhesion formation in response to TGFβ$_1$.

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TH-PO469

Macrophage IRF4 Deletion Protects Against Renal Fibrosis as a Result of Decreased Macrophage Recruitment and Activation

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Background: Macrophage infiltration and polarization plays a key role in recovery from acute kidney injury (AKI). Previous studies have indicated that persistent and aberrant presence of M2 macrophages leads to renal fibrosis after AKI. Interferon regulatory factor 4 (IRF4) plays an important role in macrophage M2 polarization. We examined the role of macrophage IRF4 in renal macrophage polarization and development of fibrosis after AKI.

Methods: Wild type (WT, IRF4$^{f/f}$) or LysM-Cre; IRF4$^{f/f}$ (macrophage IRF4$^{-/-}$) mice (male, 3 months, C57BL/6) were uninephrectomized, immediately followed by 32 min ischemia-reperfusion injury. Renal macrophages were isolated with a mixture of CD11b and CD11c microbeads. Bone marrow derived monocytes (BMDMs) were isolated and used for *in vitro* transwell migration and *in vivo* PHK26-labeled BMDM migration into injury WT kidneys. Peritonitis was induced by peritoneal injection of 3 ml of 4% thioglycolate.

Results: Compared to WT mice, LysM-Cre; IRF4$^{f/f}$ mice developed less renal fibrosis 4 weeks after severe AKI, as indicated by Sirius red staining and decreased profibrotic and fibrotic components including TGF-β1, TGF-β2, CTGF, α-SMA, fibronectin, and collagens I, III, IV. LysM-Cre; IRF4$^{f/f}$ mice had significantly fewer renal macrophages with less activation, as indicated by decreases in both Th1/M1 proinflammatory cytokines (TNF-α, MCP-1, IL-1α, IL-6, and IL-23α) and Th2/M2 pro-fibrotic cytokines (FIZZ1, CD206, CD209, B7-H4, IL-4Rα, and arginase 1). Flow cytometry and qPCR also determined low number and less activated renal macrophages (low levels of both Th1/M1 and Th2/M2 cytokines) in LysM-Cre; IRF4$^{f/f}$ compared to WT mice at 1 and 5 days after AKI. An *in vitro* migration assay showed that IRF4-/- BMDMs had decreased migratory ability. IRF4-/- BMDMs also had decreased ability to infiltrate into injured kidney as indicated by fewer renal PKH26 and F4/80 double positive cells. Finally, LysM-Cre; IRF4$^{f/f}$ mice had attenuated peritoneal macrophage infiltration in thioglycolate-induced peritonitis.

Conclusions: Macrophage IRF4 deletion protects against renal fibrosis after severe AKI, at least due in part to attenuated macrophage recruitment and activation in response to kidney injury, leading to decreased renal pro-fibrotic M2 macrophages.

Funding: NIDDK Support

TH-PO470

LOXL4 Promotes Renal Fibrosis via Triggering Col1 Production

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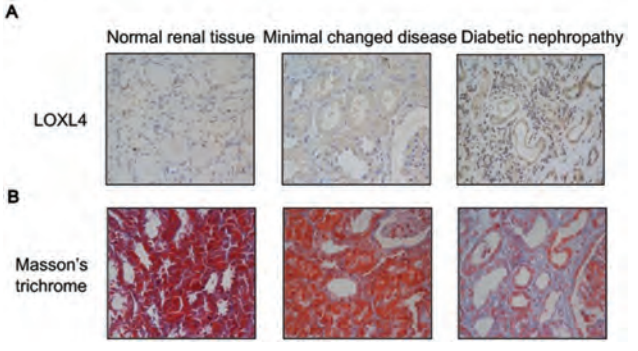
Background: Renal fibrosis characterized by excessive deposition of extracellular matrix (ECM) represents a feature of end stage of kidney disease. ECM consists of collagen, fibronectin, elastin and so on. Over crosslinking of extracellular matrix acts as a key role in the process of fibrosis. Lysyl oxidase (LOXs) facilitates the crosslinking of collagen and elastin. Lysyl oxidase-like protein 4(LOXL4) is the latest member of the LOXs family. Till now, there is no report about the pathogenesis of LOXL4 during renal fibrosis. The aim of the current study is to uncover the role of LOXL4 in renal fibrosis.

Methods: Human renal specimens were obtained from renal biopsy and normal renal tissues adjacent to renal cancer after nephrectomized kidneys. Fibrosis in the kidney specimens was assessed by Masson's trichrome staining, and LOXL4 expression was examined by using IHC staining. We used unilateral ureteral ligation (UUO) kidney *in vivo* and used a cell line of rat fibroblast (NRK-49F) *in vitro* to demonstrate the underlying mechanism of LOXL4 with renal fibrosis by realtime-PCR and western blot analysis. We investigated the biological role of LOXL4 after over-expression or silencing its expression in NRK-49F.

Results: LOXL4 deposited in the fibrotic renal tissue in patients with diabetic nephropathy,which were significantly higher compared with that in renal tissues adjacent to renal cancer after nephrectomized kidneys and minimal changed disease. Compared with sham group, the expressions of LOXL4 and Col1 in the kidney of UUO group were extremely upregulated ($p<0.05$, n=5). TGF-β1 significantly increased the expression of LOXL4 and Col1 ($p<0.05$, n=5) in NRK-49F. After transfecting with LOXL4 overexpression plasmid, the Col1 expression was significantly increased. There was sharply reduction of Col1 in NRK-49F cells after transfected with LOXL4 siRNA.

Conclusions: LOXL4 was significantly increased in human and rat fibrosis, and TGF-β1/Smads promotes the expression of LOXL4. This indicates that LOXL4 is closely related to the renal fibrosis.



LOXL4 expression in human kidney tissues

TH-PO471

Macrophages Mediate Renal Fibrosis via C5AR1 Signaling

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Background: Macrophages regulate innate immunity, inflammation, metabolism and tissue repair. We reported increased expression of intracellular complosome components, C1q, C3, C5 and anaphylatoxin receptors C3aR1 and C5aR1 in macrophages isolated from kidney tissue of mice receiving folic acid (FA) or unilateral ureteral obstruction (UUO). Recently, single cell transcriptomic study performed in UUO mice identified new proximal tubule sub clusters, but also increased expression of C5aR1 in UUO macrophages. We hypothesized that deletion of C5aR1 in macrophages reduces kidney fibrosis

Methods: C5aR1GFP$^{fl/fl}$ mice were generated by inserting LoxP sites flanking exon 2 as previously reported. C5aR1GFP$^{fl/fl}$ mice were crossed with mice expressing Cre-recombinase under control of the LysM promoter to generate LysM-Cre-C5aR1GFP$^{fl/fl}$ mice. LysM-Cre-C5aR1GFP$^{fl/fl}$ mice and C5aR1GFP$^{fl/fl}$ (control mice) received intraperitoneal injections of either vehicle (sodium bicarbonate) or FA in sodium bicarbonate. Two weeks later kidney tissue was harvested for analysis. Macrophages expressing C5aR1 and C5aR1 negative control macrophages were isolated from C5aR1GFP$^{fl/fl}$ mice by flow cytometry following UUO-injury and we performed RNA seq analysis of their trancriptome

Results: Flow studies and confocal microscopy using C5aR1GFP$^{fl/fl}$ reporter mice confirmed that macrophages are the dominant expressors of C5aR1 in both models of fibrosis. RNAseq analysis of GFP^{+} macrophages isolated from C5aR1GFP$^{fl/fl}$ mice subjected to UUO confirmed increased expression of *C5aR1* mRNA, as well as increased transcripts encoding markers of inflammation, including *Tlr4* and *Cxcl13*. GFP^{+} macrophages also exhibit increased expression of iron homeostatic genes, iron transporters and iron-recycling transcription factors. Immunohistochemistry, flow cytometry, qRT-PCR and western blots demonstrated reduced inflammation and fibrosis in whole kidney tissues from mice with selective deletion of C5aR1 in macrophages (LysMCreC5aR1GFP$^{fl/fl}$) compared to control mice treated with FA.

Conclusions: Increased expression of C5aR1 in macrophages represents an important pathophysiologic mechanism leading to increased tissue inflammation and organ fibrosis. We propose that increased iron-recycling and overload in C5aR1+ macrophages represents an important cellular mechanism leading to kidney fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO472

Ferroptosis Is Activated by TGF-β/Smad3-Driven Renal Fibrosis Both In Vivo and In Vitro

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Background: Ferroptosis is a novel non-programmed cell death driven by iron-based lipid peroxidation and its role in renal fibrosis is unknown. In this study, we hypothesized that ferroptosis is activated by TGF-β/Smad3-drivend renal fibrosis both *in vivo* and *in vitro.*

Methods: The morphology of ferroptosis and expression of ferroptosis indexes such as glutathione peroxidase 4(GPX4) and solute carrier family 7 member 11(SLC7A11) were detected both in TGF-β-stimulated rat tubular epithelial cells(rTEC) and unilateral ureteral obstruction(UUO) mouse model by electron microscopy(EM), IHC, western blot(WB) and quantitative real-time polymerase chain reaction(qRT-PCR). In addition, the ferroptosis was induced or inhibited by ferroptosis specifically agonist Erastin and inhibitor Ferrostatin in rTEC. Renal fibrosis markers of fibronectin(FN), collagen I(Col I) and α-smooth muscle actin(α-SMA) were detected by WB and qRT-PCR. Moreover, GXP4 was observed in SIS3 specifically inhibited Smad3 rTEC and Smad3 conditional knock out (KO) UUO mice by WB or IHC. The co-expression of P-Smad3 and GPX4 were detected by confocal and CO-IP in TGF-β-stimulated renal fibrosis in rTEC.

Results: The ferroptosis morphological changes including the shrucked volume of mitochondria, a reduced number of cristae and an increased density of bilayer membrane were observed in TGF-β-stimulated rTEC and renal tissue of UUO by EM. The expression of ferroptosis negatively indexes of GPX4 and SLC7A11 was significantly decreased in renal fibrosis both *in vivo* and *in vitro*. After ferroptosis induced by Erastin, the renal fibrosis markers of FN, Col I and α-SMA were significantly enhanced after TGF-β treatment for 24 hours, while renal fibrosis was decreased by Ferrostatin. In SIS3 specifically inhibited Smad3 rTEC and Smad3 KO UUO mice, GPX4 expression was significantly up-regulated. Confocal and CO-IP results suggested that the P-Smad3 and GPX4 was co-expressed in rTEC and physically combined with each other after TGF-β1 stimulated for 24h.

Conclusions: Ferroptosis is expressed in renal fibrosis both *in vivo* and *in vitro*. The intervention of ferroptosis by agonist and inhibitor has effect on the renal fibrosis in TECs. GPX4-mediated ferroptosis is dependent on TGF-β/Smad3 signaling in renal fibrosis. These data indicates that the potential role and mechanism of ferroptosis in TGF-β/Smad3-driven renal fibrosis.

Funding: Government Support - Non-U.S.

TH-PO473

Grape Seed Proanthocyanidin Extract Alleviates Renal Fibrosis by Inhibiting the Activation of the C3/HMGB1/TGF-β Pathway

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Background: Grape seed proanthocyanidin extract (GSPE) has been reported to exhibit a variety of protective effects, such as antioxidant, anti-tumor, anti-aging, hypoglycemic, anti-atherosclerosis and other pharmacological effects. Kidney disease is usually a pathogenic immune response to the kidney's autoantigen or local autoimmune response. As a member of the complement system, complement component 3 (C3) deposited in the kidney is now recognized as an important causative mediator of various human kidney diseases. In this study, we aimed to identify the effect of GSPE on C3 in the chronic kidney fibrosis and evaluate the possible mechanism.

Methods: Eight-week-old C57bl/6 mice were subjected to unilateral ureteral occlusion (UUO) with or without GSPE administration. Pathological damage, collagen deposition, interstitial inflammation and renal fibrosis were detected by histological staining, immunofluorescence and Western Blot. For the in vitro studies, mouse primary renal tubular epithelial cells (PTECs) and NRK-49F were used. In order to find possible inhibition targets for GSPE, we used complement C3 (C3a), HMGB1 and TGF-β1 to stimulate PTECs or NRK-49F, then the fibrosis-related proteins and inflammatory factor were analyzed by immunofluorescence, Western Blot or rt-PCR.

Results: In vivo, we observed that administration of GSPE relieves inflammation and chronic renal fibrosis in mouse models of UUO (unilateral ureteral obstruction). Our data indicated that GSPE inhibited C3 secreted by macrophages to relieve renal interstitial inflammation. In vitro, we found that C3 could stimulate HMGB1 translocation form nucleus to cytoplasm and promote the expression of pro-inflammatory cytokines including TGF-β1 in primary renal tubular epithelial cells (PTEC), which could be inhibited by GSPE. Meanwhile, GSPE could also decreased HMGB1-induced EMT of PTEC through suppresses the HMGB1/TLR4/p65/TGF-β1 pathway. In addition, the myofibroblast

activation was inhibited by GSPE via TGF-β1 /Smad2/3signaling pathways in normal rat kidney fibroblast (NRK-49F) cells.

Conclusions: Taken together, these observations provide that GSPE alleviates renal fibrosis by inhibiting the activation of C3/ HMGB1/ TGF-β pathway and could thus lead to find the potential therapy for the suppression of renal fibrosis.

TH-PO474

A Water-Soluble Extract from Actinidia arguta (PG102) Can Inhibit Kidney Fibrosis

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Background: PG102 is a water-soluble extract of hardy kiwifruit *Actinidia arguta*. We aimed to investigate whether treatment with PG102 can attenuate kidney fibrosis.

Methods: Male C57BL/6 mice (7-week-old, n = 14) were purchased. Treatment group (n = 7) was administered with PG102 per oral using Zonde needle at dosage of 100 mg/kg daily for 10 days. Control group (n = 7) was fed with distilled water. After this pre-treatment, unilateral ureteral obstruction operation performed, and mice were administered with PG102 or distilled water at the same dose for 10 days. After 10 days, mice were sacrificed. In addition, human kidney proximal tubular cells were cultured and challenged with TGF-β (2 ng/ml) with or without PG102 (2.5 and 5 μg/ml).

Results: Mice in both groups showed similar body weight and similar serum creatinine levels between groups. In the histopathologic specimen of Masson's trichrome stain, areas of kidney interstitial fibrosis attenuated in the treatment group (3.6 ± 0.9 % area vs. 8.7 ± 3.0 % area, P = 0.03). In the western-blot analysis, protein abundance of α-smooth muscle actin (50.6% of control), fibronectin (47.8% of control), p53 (20.8% of control) decreased, and protein abundance of e-cadherin increased (325.1% of control) in the treatment group. In immunohistochemical stain of phospho-p38, PG102 treated group showed decreased tissue expression of phosphorylated p38. In vitro experiment, human kidney proximal tubular cells treated with TGF-β and PG102 showed significantly decreased protein expression of α-smooth muscle actin (47.8% of control), and phospho-p38 (51.5% of control).

Conclusions: PG102 attenuates kidney fibrosis in the unilateral ureteral obstruction mice model and TGF-β-treated human kidney proximal tubular cells, p38 MAPK pathway is inhibited after treatment of PG102.

TH-PO475

Suppression of Transcription Factor OASIS Ameliorated Kidney Fibrosis

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Background: Old astrocyte specifically induced substance (OASIS), a transcription factor, was originally identified as an ER stress transducer. We found that there was a correlation between OASIS mRNA expression and the severity of tubular atrophy and interstitial fibrosis in patients with kidney diseases, analyzed by Nephroseq database. However, the pathophysiological roles of OASIS in kidney remain to be elucidated. The aim of this study is to determine the functional roles of OASIS in the development of kidney fibrosis.

Methods: OASIS expression was investigated by immunohistochemistry, immunoblotting and quantitative PCR. To assess the functions of OASIS in (myo) fibroblast, NRK49F cells, rat renal fibroblasts, were transduced with the lentivirus encoding OASIS shRNA, followed by TGF-β1 treatment. Twenty-four hours after TGF-β1 treatment, wound healing assay and proliferation assay were performed. To examine the effects of OASIS on kidney fibrosis, OASIS knockout (KO) mice were subjected to unilateral ureteral obstruction (UUO). At day 7 after UUO, Masson's trichrome stain and hydroxyproline assay were performed. To explore the downstream molecules of OASIS, DNA microarray was performed on OASIS KO myofibroblasts. Anti-bone marrow stromal antigen (Bst2) antibody was injected into mice at day 1 after UUO.

Results: The protein level of OASIS was increased in human fibrotic kidney. Consistently, mRNA and protein levels of OASIS were upregulated in UUO-induced murine fibrotic kidney. In addition, the number of OASIS-expressed myofibroblasts were elevated after UUO. OASIS expression was induced by TGF-β1 in NRK49F cells. OASIS knockdown suppressed TGF-β1-induced migration and proliferation of NRK49F cells. Moreover, kidney fibrosis was attenuated in OASIS KO mice (HP content (μg/mg): Wild type-UUO; 0.48±0.08, OASIS KO-UUO; 0.38±0.05, n=7, $p<0.05$). DNA microarray revealed that Bst2 was a candidate downstream molecule of OASIS. Finally, antibody blockade of Bst2 ameliorated kidney fibrosis after UUO (HP content (μg/mg): control IgGκ; 0.60±0.08, anti-Bst2 antibody; 0.49±0.09, n=6, $p<0.05$).

Conclusions: OASIS exacerbated kidney fibrosis in part by increased Bst2 expression. Suppression of OASIS could be a novel therapeutic strategy against chronic kidney disease.

TH-PO476

Investigation of the Role of Renal Tubular NFAT5 in Renal Fibrogenesis Caused by Unilateral Ureteral Obstruction

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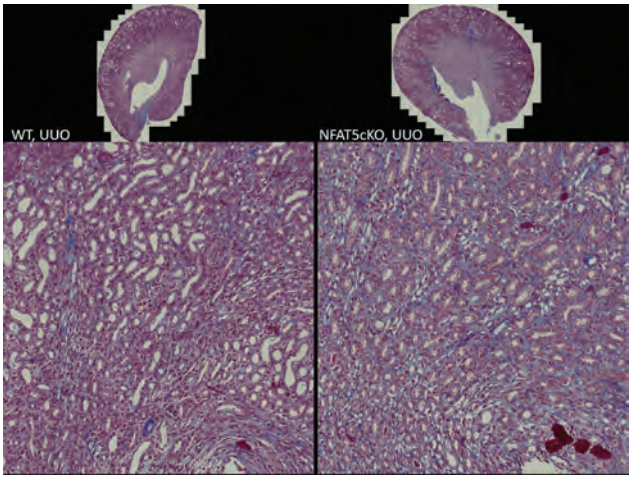
Background: NFAT5 (nuclear factor of activated T-cells 5) is a transcription factor that stimulates the expression of osmoprotective genes in response to extracellular hypertonicity, contributing to cell survival even in extreme hypertonic conditions. Not only hypertonicity but also hypoxia, oxidative stress, and toll-like receptor signaling, which promote fibrogenesis in the kidney, have been suggested to increase the NFAT5 activity. In the present study, we investigated the role of NFAT5 in renal fibrogenesis using renal tubular cell-specific NFAT5 conditional knockout (cKO) mice.

Methods: We generated renal tubular cell-specific NFAT5 cKO mice by crossing NFAT5 floxed mice with Pax8-rtTA/LC-1 mice, in which Cre recombinase was specifically expressed in renal tubular cells by the treatment with doxycycline. Wild-type (WT) mice and NFAT5 cKO mice were subjected to unilateral ureteral obstruction (UUO) or sham-operation. After 7 days, mice were sacrificed and kidneys were collected for analysis. The mRNA expression levels of NFAT5 and markers for fibrogenesis (TGF-β, α-SMA, CCL2, Col1, Col3, KIM-1, NGAL) in the kidney were examined by real-time PCR. Renal fibrosis was evaluated by Azan staining.

Results: In WT mice, the expression of NFAT5 mRNA was two times greater in the kidney from UUO mice than that from sham-operated mice. Fibrogenesis-related mRNAs were significantly increased in the kidney from UUO mice compared with that from sham-operated mice. In the UUO groups, the expressions of NGAL, TGF-β and collagen 3α1 tended to be higher in the kidney from NFAT5 cKO mice compared with that from WT mice. Azan staining showed a progression of fibrosis in the kidney from NFAT5 cKO mice.

Conclusions: NFAT5 in renal tubular cells may contribute to protective action against the development of renal fibrosis caused by UUO.



TH-PO477

CCN2 Module IV-Derived Decoy Peptides Attenuate Renal Fibrogenesis Through Inhibition of FAK Pathway in the Tubular Epithelium

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Background: CCN2 mediates the renal fibrotic action of TGF-b. We focused on CCN2 module-IV (M4) and its contribution to fibrogenesis. We previously demonstrated that M4 activated FAK (Focal Adhesion Kinase), PI3K, Akt, GSK-3b (Glycogen Synthase Kinase-3b) and b-Catenin using knock-in mice bearing M4-deleted, mutant CCN2 gene (mCCN2 mice). Furthermore, Erk1/2 and p38 were also phosphorylated by M4. Since FAK is directly activated by integrin, we considered that M4 interacts with integrin. Thus, we created decoy peptides (DCs) that mimic partial sequences of M4 and tested their anti-fibrotic effects.

Methods: Six types of DCs were designed as unmodified peptides that divide M4 into 10-14 aa and purified by HPLC. Each DCs was administered to wild-type mice with unilateral ureter obstruction (UUO) model, and histological examination and immunohistochemistry (IHC) were performed. Next, the human proximal tubular cell line, HK-2, was cultured for 24 hours in Ham's F-12/DMEM supplemented with 5% FCS, after which the medium was replaced with serum free medium, and added dissolved DCs directly to the medium. Activation of signal pathways was assayed with Western blots.

Results: Two of six DCs, DC2 and DC5, inhibited the progression of renal fibrosis in the UUO model. IHC revealed that accumulation of p-FAK in tubular epithelium cells (TECs) was suppressed in the DC2- and DC5-groups. Next, DC5 was selected for the in-vitro experiment because its aa sequence has been conserved in mouse and human. The levels of p-FAK were significantly lowered in the DC5-treated TECs compared to the control (p-FAK/FAK: 1.0+/-0.1 vs. 0.5+/-0.1, $p<0.01$). The levels of p-Akt, and p-GSK-3b

were also lowered (p-Akt/ Akt: 7.0+/-1.4 vs. 2.5+/-0.3, p<0.05), (p-GSK-3b/ GSK-3b: 3.2+/-0.3 vs. 1.6+/-0.6, p<0.05). Among MAPKs, only the levels of p-p38 were lowered by DC5.

Conclusions: DCs likely suppressed FAK-mediated renal fibrogenesis in mice. This finding is the same as that observed in the mCCN2 mice, suggesting that these DCs may have inhibited the interaction between M4 and integrin in TEC. The in-vitro experiments showed that down-stream signals activated by CCN2M4-Integrin-FAK pathway were PI3K-Akt-mediated phosphorylation of GSK-3b and p38 in TECs. The CCN2M4-Integrin-FAK pathway seems to be a promising, therapeutic target for attenuating renal fibrogenesis.

TH-PO478

Suppression of the Hippo Pathway in Tubular Cells Leads to Renal Fibrosis in Mice

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Background: The Hippo pathway controls organ size and tumorigenesis. The core components of the Hippo pathway consist of Mammalian Ste20-like kinases 1/2 (MST1/2) and their scaffold protein SAV1, large tumor suppressor 1/2 (LATS1/2) and their scaffold proteins MOB1A/1B, and two downstream effectors YAP/TAZ. Several components of the Hippo pathway, including SAV1, LATS1/2, and YAP/TAZ, have been found to be critically involved in embryonic kidney development or kidney disease. However, the role of MST1 and MST2 in kidney remains unknown.

Methods: We generated tubular cell specific Mst1/Mst2 double knockout mice by intercrossing floxed Mst1/Mst2 mice with Ksp-Cre transgenic mice. The Hippo pathway is restrained in renal tubular epithelium in Mst1/Mst2 mutant mice.

Results: We showed for the first time that MST1 and MST2 were highly expressed in all nephron segments and collecting ducts in mouse kidneys. Deletion of Mst1/Mst2 ($Mst1^{f/f}$;$Mst2^{f/f}$;Ksp-Cre) in mouse renal tubular epithelium resulted in increased kidney sizes starting from 4 weeks of age, coupled with increased YAP activity and cell proliferation in renal tubules. The Mst1/Mst2 mutant mice developed chronic kidney disease as indicated by progressive increases in tubular damage, inflammation, fibrosis and functional impairment. Deletion of Yap prevented kidney overgrowth and tubular damage in Mst1/Mst2 mutant mice and rescued the expression of many inflammatory factors measured at 4 weeks of age. More importantly, ablation of Yap prevented fibrosis development in Mst1/Mst2 mutant mice at 8 weeks of age.

Conclusions: We found that suppression of the Hippo pathway in renal tubular epithelium results in renal fibrosis via activation of YAP.

Funding: Government Support - Non-U.S.

TH-PO479

The Association Losartan/Erlotinib Is More Effective in Attenuating Renal Fibrosis Formation by Blocking TACE-Dependent EGF Receptor Activation in 5/6-Nephrectomized Rats Under Vitamin D Deficiency

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Background: Hypovitaminosis D has been described as a risk factor for the progression of kidney disease. Among others, overactivity of renin-angiotensin system and renal fibrosis formation (RFF) are hallmarks of CKD. In an alternative RFF pathway, angiotensin II can mediate the activation of tumor necrosis factor-α converting enzyme (TACE), leading to release of TGF-α, which binds to and activates the epidermal growth factor (EGF) receptor (EGFr). Although many studies have focused on the mechanisms underlying RFF, novel anti-fibrotic therapies need to be evaluated in order to retard the progression of CKD. We evaluated the effects of losartan (L) and erlotinib [EGFr inhibitor (E)] in 5/6-nephrectomized rats under vitamin D deficiency.

Methods: Male Wistar rats were fed a vitamin D-free diet (D) for 90 days and submitted to 5/6 Nx (N) on day 30. We studied four groups: **DN**; **DNE** (6 mg/Kg/day IP for 53 days); **DNL** (50 mg/Kg/day in water for 53 days); **DNEL** (dual treatment). We performed immunohistochemistry for TACE, TGF-α, fibronectin, vimentin and α-SM-actin; ELISA in renal tissue for EGF and collagen 3 (col3); and immunoblot for p-EGFr.

Results: The dual treatment was more effective in blocking the TACE-dependent EGFr activation pathway demonstrated by lower expression of TACE, TGF-α, EGF and p-EGFr. In addition, we observed decreased expression of fibronectin, col3, vimentin and α-SM-actin in renal tissue.

Conclusions: Our results indicate that the dual treatment L+E may represent a novel anti-fibrotic strategy for attenuating CKD. Financial support: FAPESP 2018/12297-1, 2018/04930-6; CNPq 302599/2018-5.

Funding: Government Support - Non-U.S.

Table 1

	DN	DNE	DNL	DNEL
TACE (%)	3.98±0.54	2.49±0.24c	2.82±0.29c	1.37±0.17afi
TGF-α (%)	3.07±0.43	1.62±0.34a	0.84±0.15af	0.20±0.04adi
p-EGF receptor (%)	100.0±2.0	88.0±4.0c	71.0±3.0ad	59.0±3.0adi
EGF (pg/µg protein)	2.13±0.18	1.59±0.24	1.44±0.28	1.06±0.07b
Fibronectin (%)	7.41±0.50	3.33±0.15a	3.67±0.32a	2.49±0.14afi
Collagen 3 (ng/µg protein)	6.37±0.31	5.62±0.21	4.98±0.41b	3.82±0.26aei
Vimentin (%)	3.86±0.30	2.73±0.23b	3.26±0.23	1.95±0.15afg
α-actin (%)	4.09±0.29	2.71±0.21a	2.33±0.15a	1.19±0.07adg

Data are expressed as mean±SEM. a p<0.001, b p<0.01, c p<0.05 vs DN; d p<0.001, e p<0.01, f p<0.05 vs DNE; g p<0.001, i p<0.01 vs DNL.

TH-PO480

Sphingosine Kinase 2 Deletion in Kidney Pericytes/Fibroblasts Protects Against Kidney Fibrosis via Suppression of Local Interstitial Inflammation

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Background: Sphingosine 1-phosphate (S1P), which is produced by two different kinases, sphingosine kinase (SphK) 1 and 2, is a sphingolipid involved in myriad cell functions. We recently showed that *Sphk2*$^{-/-}$ mice were protected from renal fibrosis when compared to wild type or *Sphk1*$^{-/-}$ mice; bone marrow chimera experiments suggested that *Sphk2* deletion in non-hematopoietic cells contributed to the protection (PMID: 27799486). We hypothesized that *Sphk2* deletion in renal pericytes/fibroblasts confers the protection from progressive kidney fibrosis.

Methods: Folic acid (250 mg/kg) was given i.p. to male *Foxd1Cre*$^{+}$ *Sphk2*$^{fl/fl}$ (perivascular (pv) *Sphk2KO*) mice and *Foxd1Cre*$^{-}$ *Sphk2*$^{fl/fl}$ (WT) mice. For unilateral ischemia-reperfusion injury (IRI), left kidney was clamped for 30 min; right nephrectomy was performed at day 13. For bilateral IRI, both kidneys were clamped for 30 min. Mice were euthanized at day 14 to evaluate kidney fibrosis (folic acid and unilateral IRI) and at day 1 to evaluate the extent of acute kidney injury (folic acid and bilateral IRI). Primary renal pv cells were isolated from kidneys of pv*Sphk2KO* mice and WT mice.

Results: In both folic acid and unilateral IRI models, pv*Sphk2KO* mice demonstrated better kidney function (pCr, BUN), less kidney fibrosis (histology) with less macrophage infiltration, and suppressed expression of fibrosis-related genes (*Acta2, Col1a1, Col3a1*) in the kidneys compared with WT mice. In contrast, there was no difference between pv*Sphk2KO* mice and WT mice in kidney function, kidney *Kim-1/Ngal* expression, and histology at day 1. In *in vitro* studies, the expression level of *Sphk2* was much higher than that of *Sphk1* in WT pv cells. *Sphk2* KO pv cells expressed less inflammatory cytokines, such as *Ccl2, Il6, Cxcl1*, after LPS stimulation compared with WT pv cells. Furthermore, treatment with a selective Sphk2 inhibitor (SLM6031434) recapitulated the phenotype of *Sphk2* KO pv cells.

Conclusions: *Sphk2* deletion in renal pericytes/fibroblasts was protective against kidney fibrosis. *In vitro* studies suggested that suppressed production of S1P in *Sphk2* KO pericytes/fibroblasts contributes to suppressed expression of inflammatory cytokines when injury occurs, leading to less immune cell infiltration into the kidneys and ameliorated kidney fibrosis.

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TH-PO481

Profiling Histone Modifications in the Normal Mouse Kidney and After Unilateral Ureteric Obstruction

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Background: Post-translational modification of nucleosomal histones has emerged as a major determinant of chromatin structure and gene activity. In this study, we hypothesised that unilateral ureteric obstruction (UUO), a widely used model of tubulointerstitial injury, would be associated with a distinct pattern of histone (H) modifications (marks) in the kidney.

Methods: Mass spectrometry (MS) was used to profile 63 different histone marks, and their corresponding unmodified amino acid, in normal mouse kidneys and those after 10 days of UUO. A subsequent histochemical analysis further examined examples of specific marks that changed significantly after UUO, for which antisera are available. The distribution of marks was compared with markers of pathology and transcription.

Results: Histone marks were much more widely distributed and abundant in the normal kidney than usually appreciated. Although aggregate analysis of the MS results revealed net differences between control and UUO groups, residue-specific variations were subtle. Of 16/63 significant changes (P<0.05), only 8 were quantitatively different by more than 5%. Nevertheless, we identified several not usually examined in the kidney including marks in the globular domain of core histones (H3K79), linker histones (H1.4) and histone variants (H3.1K27, H3.3K27). In several cases there were complementary changes in different marks on the same amino acid. In situ staining showed compartment specific differences in the distribution of individual marks. Using H3K79Me2 as an example, mark enrichment was heterogeneous, but largely co-localised with tubular hypoxia and transcription, but not proliferation, apoptosis or interstitial pathology.

Conclusions: Our study highlights the importance of unbiased screening in examining histone marks. Simultaneous changes in multiple marks on the same amino acid are indicative of a coordinated histone mark signature. The heterogeneous enrichment of marks, even within the same tubule, highlights the importance of regulatory context.

Funding: Government Support - Non-U.S.

TH-PO482

Diabetic Glomeruli Stiffen as They Scar

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Background: Glomerulosclerosis is an important manifestation of diabetic glomerular injury. Studies of mesangial cells (the main producers of scar in the glomerulus) have mostly focused on biochemical stimuli (eg. high glucose, TGF-β). However, increasing evidence suggests that biomechanical stimuli such as extracellular matrix stiffening can also activate mesenchymal cells. In particular, the mechanosensory transcription co-factors YAP and TAZ appear to link matrix stiffness to fibrogenesis. Our goal was to study changes in glomerular stiffness as diabetic injury progresses.

Methods: We studied male Akita$^{+/-}$ Ren$^{+/-}$ mice at early (8 wk old, n = 8) and late (26 wk old, n = 6) time points. These mice develop diabetes and renin-mediated hypertension, resulting in progressive glomerulosclerosis that mimics human diabetic kidney disease. Male non-diabetic, normotensive Akita$^{-/-}$ Ren$^{-/-}$ mice served as healthy controls. Parameters of glomerular stiffness (atomic force microscopy, AFM) and histology (picrosirius red, type 1 collagen, and YAP/TAZ immunostaining) were measured and correlated. Glomerular stiffness was measured in a minimum of 30 glomeruli per kidney.

Results: Mean glomerular stiffness and glomerulosclerosis values increased with age in both the diabetic, hypertensive Akita$^{+/-}$ Ren$^{+/-}$ mice and their non-diabetic, normotensive Akita$^{-/-}$ Ren$^{-/-}$ controls, although at each time point, diabetic, hypertensive Akita$^{+/-}$ Ren$^{+/-}$ glomeruli were significantly stiffer and more scarred than glomeruli in healthy Akita$^{-/-}$ Ren$^{-/-}$ controls (Table 1). At both early and late stages of diabetic kidney injury, stiffness increased with glomerulosclerotic burden. Reflecting this increased stiffness, glomerular cell YAP/TAZ activity was increased in Akita$^{+/-}$ Ren$^{+/-}$ mice at 26 weeks compared to wild type controls, as evidenced by increased YAP/TAZ nuclear localization.

Conclusions: As glomerulosclerosis progresses in diabetes, the stiffness of glomeruli, as well as the activation of the mechanosensitive, pro-fibrotic transcription co-factors YAP and TAZ, increases. Taken together, our data suggest a novel biomechanical stimulus for glomerulosclerosis progression in diabetes.

		Plasma glucose (mmol/L)	Body weight (g)	Systolic blood pressure (mmHg)	Urinary albumin (ug/day)	Right kidney/tibia length (mg/mm)	Right kidney/body weight (mg/g)	Glomerula stiffness (kPa)
8 weeks	Akita-/- Ren-/-	10.85±1.4	23.2±1.8	76±7.4	167.8114	9.96±3.78	7.78±2.2	1.6±0.5
	Akita+/- Ren+/-	27.75±5.0	24.4±2.1	123±23.0	1989.9125	13.54±1.08	10.27±0.4	6.4±1.6
26 weeks	Akita-/- Ren-/-	9.03±1.5	43±2.9	58±6.2	180.5073	12.7±1.05	6.08±1.0	5.8±0.9
	Akita+/- Ren+/-	30.1±2.3	35±2.6	134±15.8	3440.7175	62.4±11.09	19.24±5.5	12.2±4.1

TH-PO483

The Protective Effect of Prostacyclin in Renal Fibrosis

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Background: Progressive decline of renal function is a hallmark of CKD, the mechanism of which is incompletely understood. Inadequate repairing process to injury has been reported to play an important role. Mounting evidence suggests that prostaglandins are important in serving as a "buffer"in response to physiological changes or pathophysiologic insults to tissues including the kidney. Importantly, under certain conditions such as aging and hypertension, prostacyclin (PGI_2), an active production of COX/PGI_2 Synthase (PGIS), is reduced. The present study provides data showing that PGI_2 plays an important role in response to renal injury to maintain adequate injury and repairing process. Low levels of PGI_2 are associated with enhanced renal fibrosis.

Methods: Mice with global PGIS gene deletion were obtained by crossing the floxed PGIS mice with the EIIA-Cre mice. The endothelial-specific PGIS-deficient mice were generated by mating the floxed PGIS mice with the TEK-CRE (Tie2-CRE) mice. Unilateral ureteral obstruction (UUO)was used as a renal fibrosis model. At days 10 after UUO, the mice were sacrificed, and the kidneys were collected.

Results: Immunohistochemistry showed that PGIS is primarily expressed in endothelial cells and vascular smooth muscle cells. The expression of PGIS was markedly induced following AKI and fibrotic kidney. Enhanced PGIS expression is associated with increased PGI_2 level. Losing one allele of PGIS (PGIS$^{+/-}$) significantly aggravated UUO -induced renal fibrosis, showing increased fibronectin, collagen I and α-SMA, and more extracellular matrix deposition in the section at 10 days after UUO comparing to their wild type littermates. Kidney thromboxane synthase expression is not significantly different between PGIS$^{+/-}$ mice and wild type littermates after UUO. Loss of one allele of PGIS did not change blood pressure. To examine the role of specific cells that express PGIS in renal fibrosis, we specifically deleted PGIS in endothelial cells. Endothelial-specific PGIS-deficient mice had normal blood pressure and renal function. Endothelial PGIS gene deletion also significantly aggravated UUO -induced renal fibrosis. Furthermore, the level of phosphorylated PKA substrates in the kidney of deficient mice was significantly reduced.

Conclusions: PGIS/PGI_2 plays an important role in protecting the kidney from fibrosis. Lack of PGIS enhances kidney damage. PGIS/PGI_2 is a potential target for CKD.

Funding: Government Support - Non-U.S.

TH-PO484

Plant Homeodomain (PHD) Finger Protein 14 (PHF14) Inhibits Renal Fibrosis via Repressing Connective Tissue Growth Factor Induced by Hypoxia-Inducible Factor 1 Alpha

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Background: Renal fibrosis is the final common pathological manifestation of chronic kidney diseases progressing to ESRD, while no effective way has been found to reverse it. Chronic hypoxia was thought to play an important role in renal fibrosis. PHF14, a novel histone binding protein, was discovered in our previous studies to be an innate inhibitor of renal fibrosis. However, the mechanism of PHF14 is not unraveled. We hypothesized PHF14 may be induced by hypoxia-inducible factor 1 α (HIF-1α), and repress the over-expression of connective tissue growth factor (CTGF) by regulating histone methylation.

Methods: We confirmed the biological function of PHF14 in PHF14 conditional knockout mice following aristolochic acid administration. Relationship between hypoxia and PHF14 has been explored in NRK52E cells. We detected the interactions of PHF14 with H3K4me3 and H3K27me3 using Chromatin Immunoprecipitation (ChIP) and Co-immunoprecipitation (Co-IP). We also generated PHF14-KO cell via CRISPR/Cas9 system.

Results: 1. Compared with controls, PHF14 conditional knockout mice presented aggravated renal fibrosis and worse renal function (Figure 1A-1C). 2. PHF14 was induced in hypoxia environment *in vitro*. And PHF14 was upregulated by HIF-1α stimulant DMOG and repressed by HIF-1α inhibitor KC7F2 (Figure 1D). ChIP detected HIF-1α binding on the promoter of PHF14 and CTGF. 3. PHF14 knockdown enhanced CTGF expression following DMOG stimulation *in vitro* and PHF14 could bind on the promoter of CTGF, which was proved by ChIP. 4. The enrichment of histone methylation in CTGF promoter induced by HIF-1 α was changed in PHF14-KO cells. Co-IP validated PHF14 could interact with H3K4me3 and H3K27me3.

Conclusions: Lack of PHF14 deteriorated aristolochic acid nephropathy in mice. PHF14, which was induced by HIF-1α, inhibited CTGF expression via regulating histone methylation in CTGF promoter.

Funding: Government Support - Non-U.S.

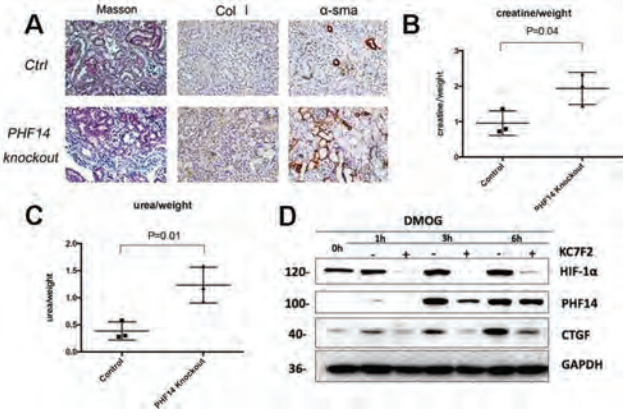

Figure 1

TH-PO485

High Throughput Sequencing of Human Kidney Tissue Implicates FRMD3 as Important in the Pathogenesis of Progressive CKD

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Background: The global health concern of Chronic Kidney Disease (CKD) is enhanced by the struggle to predict future disease events, particularly progression to End Stage Kidney Disease (ESKD). We examined the transcriptional profile of human kidney biopsies, aiming to provide insight into the mechanisms of progressive CKD. We evaluated the potential role of the candidate gene *FRMD3*in CKD progression.

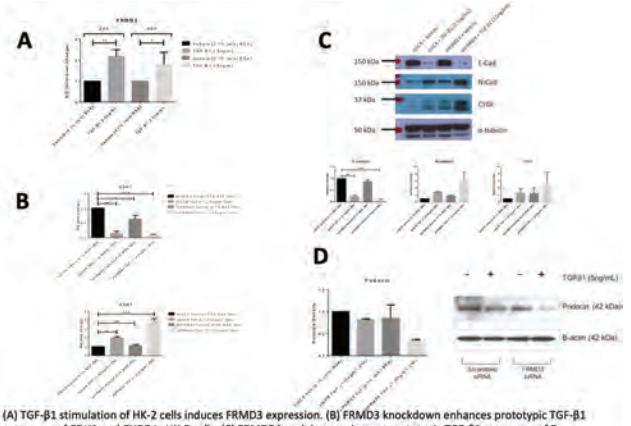
Methods: RNA extracted from kidney biopsy tissue was sequenced using high throughput techniques and gene expression correlated with clinical variables, eGFR and percentage tubulointerstitial fibrosis (%TIF) on kidney biopsy. We identified genes which were differentially expressed in patients experiencing progressive CKD (doubling of serum creatinine or reaching ESKD). Analyses were adjusted for age and sex of the patients, and

with a FDR cut-off of <0.05. Using established cellular models we examined the impact of knock-down of the gene *FRMD3*in human kidney epithelial cells and podocytes.

Results: We examined gene expression in discovery (n=24) and validation cohorts (n=23) and identified a subset of genes which correlated with the clinical variables, eGFR and %TIF, and were associated with CKD progression. Pathways of inflammation and immune system function are heavily represented in our dataset. *FRMD3* expressionwas consistently associated with worse kidney disease, with lower expression seen in patients with higher %TIF and lower eGFR, and in patients with progressive CKD. FRMD3 knockdown enhances the fibrotic responses to TGF-β1, including loss of E-cadherin, upregulation of N-cadherin and CTGF in human kidney epithelial cells, and exaggerated loss of podocin in immortalised human podocytes.

Conclusions: Inflammatory cell signaling pathways are driving forces in CKD progression. Loss of FRMD3 is associated with more severe kidney disease and CKD progression.

Funding: Private Foundation Support



(A) TGF-β1 stimulation of HK-2 cells induces FRMD3 expression. (B) FRMD3 knockdown enhances prototypic TGF-β1 responses of CDH1 and CHD2 in HK-2 cells. (C) FRMD3 knockdown enhances prototypic TGF-β1 responses of E-cadherin, N-cadherin and CTGF in HK-2 cells. (D) FRMD3 knockdown exacerbates the loss of Podocin following TGF-β1 treatment of human podocytes.

TH-PO486

Collecting Duct-Specific Deletion of Renin Attenuates Obstruction-Induced Renal Fibrosis and Inflammation

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Background: Increasing evidence demonstrates that renin is synthesized and secreted by the collecting duct (CD) as a component of the intrarenal renin-angiotensin system (RAS). The intarenal RAS is well known to contribute to the pathogenesis of chronic renal disease (CKD) in addition to hypertension. However, the precise mechanism of how intrarenal RAS is activated in the disease process is poorly characterized.

Methods: The goal of the present study was to examine the impact of CD-specific deletion of renin on renal fibrosis and inflammation in a mouse model of unilateral ureteral obstruction (UUO). CD-specific renin deletion was generated by crossing aquaporin-2-Cre mice with renin floxed mice (CD renin KO). UUO was performed by ligation of the left ureter near the renal pelvis in flox mice and CD renin KO mice.

Results: After 3 days of UUO, the renal medullary renin content, renin activity and renin mRNA in obstructed kidneys of flox mice were increased by 4.7-, 2.2- and 7.8-fold, respectively, which were all blocked by CD renin KO mice. In contrast, renal cortical renin was largely unaffected by UUO, irrespective of the genotype. Meanwhile, CD renin KO decreased the α-SMA (51.3±10.9%) and fibronectin (60.4±7.2%) protein expression and increased E-cadherin (2.1-fold) protein expression in obstructed kidneys. The content of hydroxyproline, a major component of the protein collagen, in obstructed kidneys of CD renin KO mice showed a significantly reduced generation compared with obstructed kidneys of flox mice. (KO+UUO: 7.7±0.9 versus flox+UUO: 12.3±1.6 ug/mg tissue; P<0.05). The Masson's trichrome staining (MST) data also showed that CD renin KO significantly attenuated UUO-induced collagen deposition and histological damage in the kidney. In parallel, CD renin KO reduced α-SMA (48.2±4.3%), fibronectin (38.6±7.4%), TGF-β (32.9±6.7%), IL-6 (20.6±6.1%) and TNF-α (47.2±5.2%) mRNA expression in obstructed kidneys.

Conclusions: Overall, these results suggest that overactivation of renal CD renin plays an essential role in driving local RAS to promote renal fibrosis induced by obstruction.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO487

Major Vault Protein Contributes to Tubulointerstitial Fibrosis in CKD

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Background: Chronic kidney disease (CKD) is a major global issue leading to much morbidity and mortality. Tubulo-interstitial fibrosis is the final pathogenic pathway in the progression of CKD to end-stage renal failure. There is currently no effective treatment for kidney fibrosis. We previously reported that major vault protein (MVP), a key component in the vault complex, contributed to fibrogenesis in HK-2 cells in lupus nephritis. We extended our investigations to other causes of CKD.

Methods: MVP expression in renal biopsies from patients with CKD due to various causes was examined with cytochemical staining. Animal studies were carried out using unilateral ureteral obstruction (UUO) model in wild-type (WT) and MVP knockout (KO) mice, with the contralateral unobstructed kidney serving as control. Mice were sacrificed 14 days after UUO, and the kidneys were harvested and examined. The effect of MVP overexpression in HK-2 cells was investigated.

Results: Kidney biopsies from patients with IgA nephropathy, diabetic nephropathy, or idiopathic membranous glomerulonephritis with CKD showed markedly increased MVP expression, predominately in proximal tubular epithelial cells, compared with normal kidney specimens. MVP gene expression was negligible in normal mice. UUO significantly induced MVP mRNA expression, accompanied by tubular atrophy, increased tubulo-interstitial inflammatory cell infiltration, and matrix protein accumulation including fibronectin and collagen III. MVP KO in UUO mice was associated with reduced immune cell infiltration and decreased tubulo-interstitial collagen III and fibronectin expression compared with WT. Further data showed that MVP regulated collagen III at transcription level, whereas its effect on fibronectin expression was at the post-transcriptional level. MVP gene editing using CRISPR-Cas9 in HK-2 cells was accompanied by decreased MCP-1 secretion and fibronectin expression.

Conclusions: Our data show increased renal tubulo-interstitial MVP expression in CKD irrespective of original cause, which may contribute to inflammatory and fibrotic processes in CKD progression.

Funding: Government Support - Non-U.S.

TH-PO488

Upregulation of miR-382 Contributes to AKI to CKD Transition via the PTEN/AKT Signaling Pathway

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Background: Acute kidney injury (AKI) is recently considered as a critical factor for the development of chronic kidney disease (CKD). But mechanisms driving AKI to CKD transition remain unclear. Previously we have discovered miR-382 as a novel target in TGF-β1-induced epithelial-mesenchymal transition and the development of tubulointerstitial fibrosis after AKI was accompanied with an overwhelmed activation of miR-382.

Methods: In our recent study of aristolochic acid nephropathy (AAN), we exam the effects of genetic absence or pharmacologic inhibition of miR-382 on the expression of NF-κB/PTEN/AKT signaling pathway and renal pathological changes.

Results: Renal fibrosis developed at 14 days after a single dose of aristolochic acid (AA, 10mg/kg,ip) and renal fibrotic lesions getting even more severe at 28 days after AA treatment. Renal abundance of miR-382 was detected increasing until 28 days post AA administration while inhibition of miR-382 partly reversed renal tubulointerstitial fibrosis. The protective effects of anti-miR-382 treatment against fibrosis was also verified in miR-382 KO mice. Protein expression of phosphatase and tensin homolog (PTEN), a target of miR-382, was down-regulated and subsequently its downstream phosphorylated protein kinase B (AKT) signaling pathway was activated during AA induced AKI to CKD transition. Furthermore, we found the up-regulation of miR-382 of renal epithelial cells was in part mediated by activation of NF-kB signaling secondary to AA exposure, with substantial elevation of pro-inflammatory cytokines such as interlukin-1β and tumor necrosis factor-α. In vivo study revealed that either miR-382 knockdown or miR-382 knockout was pivotal for inflammatory suppression. In vitro experiment confirmed that up-regulation of miR-382 in cultured HK-2 cells under AA exposure could be remarkably reversed by NF-kB siRNA.

Conclusions: These data supported a novel mechanism in which AA induced miR-382 up-regulation via NF-kB activation, therefore targeting PTEN/Akt signaling, contributing to the development of renal fibrosis secondary to acute AA related renal toxicity.

Funding: Government Support - Non-U.S.

TH-PO489

Kinin in Hypertensive Kidney Disease: A Novel Therapeutic Target

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Background: Hypertensive kidney disease is the second leading cause of end-stage renal disease (ESRD) following diabetes. While inhibition of the renin-angiotensin system remains the current management of hypertensive kidney disease, we are still spending billions of dollars for hemodialysis and the incidence of ESRD is projected to increase in upcoming years. Thus, elucidating the pathogenesis of hypertensive kidney disease, particularly if there is any non-angiotensin pathway involved is important to formulate newer treatment strategies. Recently, a growing body of evidence suggests a role for kallikrein-kinin system in hypertension and kidney diseases. The effects of kinins are exerted through two G-protein coupled receptors- B1R and B2R. It has been recently shown that B1R regulates neurogenic hypertension in mice. However, the role of B1R in hypertension induced end-organ damage, particularly in the kidney has not been studied. This study examines the significance of B1R induced inflammation and fibrosis in the kidney.

Methods: Human kidney sections were used to study the expression pattern of B1R in kidneys by immunohistochemistry. Deoxycorticosterone acetate (DOCA)-salt hypertension model coupled with a whole body B1R knockout (B1RKO) mice were used to study the effect of kinin B1R blockade on hypertensive kidney disease. Hypertension induced renal damage was assessed by measuring the mRNA and protein expression of

fibrosis markers (collagen I/III, fibronectin, TGF-β). Renal inflammation was studied by assaying inflammation markers (TNFa, IL6, IL1b) and inflammatory cell infiltration.

Results: B1R is expressed in human kidneys predominantly in proximal tubular cells. Treatment with DOCA-salt significantly increased blood pressure ($p<0.001$) in wild-type mice, which was attenuated in B1RKO mice. B1R blockade decreased DOCA-salt-induced renal fibrosis. Moreover, DOCA-salt-induced increase in renal inflammation was significantly blunted in B1RKO mice.

Conclusions: Our data provide evidence that kinin B1R is expressed in human kidney and may have an important role in the pathogenesis of hypertensive kidney disease. In an animal model, B1R knockdown reduces hypertensive renal damage by decreasing inflammation and fibrosis. Kinin B1R offers a potential therapeutic target for the treatment of hypertension and hypertensive kidney disease.

TH-PO490

TGFBI and Kidney Disease Progression

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Background: TGFBI was identified as one of the genes whose hypomethylation is associated with chronic kidney disease (CKD) progression. Increased expression of TGFBI is reported in patients with diabetic kidney disease (DKD) and was considered to play a central role in a novel pathway that promotes DKD. However, the molecular mechanism of TGFBI in kidney disease progression remains to be determined.

Methods: Bioinformatic analysis was performed to investigate the association of TGFBI expression with kidney disease association in human and mouse models for kidney disease. Single cell RNAseq analysis, in situ hybridization and IHC were used to determine the cellular localization. Expression of key pathway genes was evaluated in TGFBI treated-human mesangial and podocyte cells by qRT-PCR and IHC.

Results: Higher expression of TGFBI is associated with increased kidney disease severity in transforming growth factor-β1 transgenic mice (Albumin/Tgfb1 Tg), developing focal segmental glomerular sclerosis and tubulointerstitial injury. In patients with various CKD etiologies, TGFBI expression is reversely correlated with glomerular filtration rate (GFR), including DKD and SLE. Single cell RNAseq analysis demonstrated that TGFBI is enriched in immune cells, followed by mesangial cells. In vitro mesangial cells can produce TGFBI and knock down reduces pathogenic proliferation. Treatment of podocytes with TGFBI leads to actin cytoskeletal rearrangement and fibrotic gene expression, suggesting that increased *Tgfbi* expression by mesangial cells may cause the podocyte injury. This is supported by the observation that Tg*fbi* mRNA is reversely associated with podocyte density ($r=-0.66$, $p<0.01$) in Tgfb1 Tg mice.

Conclusions: TGFBI is an important player in CKD/DKD progression by initiating podocyte injury which will lead to proteinuria.

Funding: Commercial Support - AstraZeneca

TH-PO491

The Role of Renal Uric Acid Crystal Granulomas on CKD Progression in Mice and Humans

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Background: Tophaceous uric acid (UA) deposits are occasionally found on diagnostic kidney biopsies. Whether UA crystal granulomas are a cause or bystander of CKD is subject of debate. We hypothesized that renal UA granulomas associate with more severe interstitial fibrosis; therefore contribute to CKD progression. UA granulomas are mainly comprised of M1-macrophages. We thought to target a phenotype switch from M1- to M2-macrophages by activating adenosine receptor signaling in a mouse model of CKD with UA granulomas.

Methods: We screened 81,200 diagnostic kidney biopsies for the presence of UA granulomas to determine the prevalence and performed a case-control study to compare biopsies with and without granulomas for morphological abnormalities. Alb-creERT2/Glut9$^{lox/lox}$ (ki/ki) or Glut9$^{lox/lox}$ control mice were fed either a high-fat or chow diet with inosine. We assessed UA crystal deposits, GFR and the extent of kidney damage (MALDI-FTICR MS imaging, immunostaining, flow cytometry). Adenosine therapy was started after renal fibrosis had established.

Results: 84 out of 81,200 kidney biopsies showed UA granulomas, which revealed significantly more glomerulosclerosis and interstitial fibrosis compared to control biopsies. Ki/ki mice on chow diet with inosine developed only hyperuricemia (HU), whereas ki/ki mice on high-fat diet with inosine developed HU + CKD compared to control mice. Indeed, urate nephropathy caused a significant GFR decline compared to HU or control mice. MALDI-FTICR MS imaging confirmed UA crystal deposits that were associated with tubular atrophy, interstitial fibrosis and macrophage infiltration. Histological analysis showed that UA granulomas occur after renal fibrosis had established. Adenosine therapy significantly reduced the number of renal UA granulomas due to less M1- but more M2-macrophages, a process that attenuated CKD progression.

Conclusions: Renal UA granulomas are found in 0,1% of diagnostic kidney biopsies and associated with more renal fibrosis and tubular atrophy. Our *in vivo* data revealed that UA granulomas form after renal fibrosis had established. M1-macropages are essential for UA granuloma formation, and interfering with a switch from M1- to M2-macrophages prevents CKD progression. Together, UA granulomas develop secondary to renal fibrosis but contribute to accelerated kidney atrophy and dysfunction.

Funding: Government Support - Non-U.S.

TH-PO492

Dual Disruption of Endothelial Nitric Oxide Synthase and ApoE Gene Accelerates Kidney Fibrosis and Aging After Injury

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Background: Medical advances have made it possible to control diseases such as cancer, autoimmune diseases and infectious diseases, extending life for affected patients worldwide. On the other hand, CKD has become a lifestyle-related disease and lifestyle management is necessary to extend healthy life span. In this study, we clarify the effect of interaction between hypertension and atherosclerosis on renal fibrosis and aging.

Methods: Wild type (WT) mouse, apolipoprotein E$^{-/-}$ (ApoE KO) mouse, and endothelial nitric oxide synthase (eNOS)$^{-/-}$; ApoE$^{-/-}$ (WKO) mouse were obtained by crossing eNOS$^{+/-}$ mouse and ApoE$^{+/-}$ mouse. Unilateral ureteral obstruction (UUO) was performed on 8-10 weeks old male mice after blood pressure and lipid profile were measured. Mice were sacrificed 10 days after UUO. The degree of renal tubular injury, fibrosis and kidney aging were evaluated among the three groups.

Results: ApoE KO mice had higher total cholesterol and lower HDL cholesterol than WT mice. WKO mice manifested elevated blood pressure, higher total cholesterol and lower HDL cholesterol than WT mice. Compared with WT mice, ApoE KO and WKO mice showed sustained kideny injury molecule-1 expression and increased α-smooth muscle actin protein expression was found in WKO mice after UUO. mRNA expression of transforming growth factor-β, connective tissue growth factor and type 1 collagen was increased both in ApoE KO and WKO mice and the highest in WKO mice with statistical significance. The picro-sirius red positive stained kidney area was significantly higher in ApoE KO mice and WKO mice. The antioxidant, heme oxygenase-1 was significantly decreased in WKO mice. Furthermore, mRNA expression of p53, p21 and p16 were increased both in ApoE KO and WKO mice and the highest in WKO mice among three groups with significance. A significant increase in senescence associated β-gal positive tubule area was observed in WKO mice.

Conclusions: Mice at high risk for cardiovascular disease developed kidney fibrosis and aging even in the young mice after injury. Vulnerability to oxidative stress promotes fibrosis and aging. Managing lifestyle-related diseases from a young age is important for CKD prevention. This mouse model could be a good tool for elucidating the relationship between bad lifestyle and kidney fibrosis and aging.

Funding: Government Support - Non-U.S.

TH-PO493

Paraoxonase 1 Regulation of Renal Inflammation and Fibrosis in CKD

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Background: Paraoxonase1 (PON1) is a hydrolytic lactonase enzyme which is synthesized by the liver and circulates attached to high density lipoproteins. Clinical studies have demonstrated an association between diminished PON1 and progression of CKD however whether decreased PON1 is mechanistically linked to renal disease is unknown. We tested whether absence of *PON1* is mechanistically linked to progression of renal injury in a Dahl salt-sensitive model of hypertensive renal disease.

Methods: Experiments were performed on Dahl salt-sensitive rats (wild) and PON1 knock-out rats (*PON1* KO). Ten week old, male rats were maintained on high salt diet (8% NaCl) for up to 5 weeks to initiate renal disease.

Results: Early mortality was observed in 5 out of 12(41.6%) Pon1 KO rats (mean time until death=33 days), while no mortality was observed in wild type rats. At 4 weeks, Pon1 KO and wild type rats developed similar degrees of hypertension however Pon1 KO demonstrated significantly decreased renal function compared to the wild type rats as assessed by FITC-Sinistrin glomerular filtration rate as well as increases in cystatin C and urinary protein excretion. Upon histological examination, kidneys from Pon1 KO rats showed significant evidence of increased renal injury compared to the wild rats as noted by increased renal fibrosis, glomerular sclerosis, and tubular ischemia. Pon1 KO rats also showed significant increases in renal inflammation vs wild type, as measured by increased recruitment of CD68 positive immune cells in the renal interstitium. Further, expression of the key inflammatory genes (Timp-1, MCP-1, IL-6, COL1A1, and TGF-β) was significantly higher in renal tissue from Pon1 KO rats compared to the wild type rats. Also, Pon1 KO rats had significantly increased renal oxidative stress demonstrated by increased renal staining of the oxidative stress marker 8-OHdG as well higher urinary excretion of 8-OHdG vs. wild type. Finally, as activation of Src kinase has been shown to act as a common integrator of multiple pro-fibrotic signals we noted that, compared to wild type rats, renal tissue from Pon1 KO showed increased activation of Src kinase

Conclusions: Our data suggest a new role for PON-1 in regulating renal inflammation and fibrosis in the setting of hypertensive renal disease

Funding: Other NIH Support - Grant 1RO1HL137004

TH-PO494

TNFα Inhibition Decreases Fibrosis After Ischemia-Reperfusion Injury

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Background: Renal fibrosis is a frequent complication of acute kidney injury (AKI) and sustained EGFR activation in tubule cells is a hallmark of this process. We have previously shown that injury-induced a disintegrin and metalloproteinase 17 (ADAM17) drives maladaptive repair and kidney fibrosis after injury, but the implicated ADAM17 substrates are unknown. At least two of the main physiological substrates of ADAM17 are upregulated by kidney injury, pro-TNFα and pro-EGFR ligands. ADAM17 releases the active forms of these molecules from the cell surface. We examined the individual contribution of TNFα and EGFR-dependent pathways using FDA-approved drugs in mice: (murine) Etanercept and erlotinib.

Methods: FVB-N mice were subjected to severe bilateral ischemia-reperfusion-injury (IRI) and assigned to 4 treatment groups: (1) vehicle, (2) murine Etanercept (soluble TNFα inhibitor scavenger), (3) Erlotinib (EGFR kinase inhibitor), (4) Erlotinib plus Etanercept. Treatments were started Day 0. Sham surgeries were performed as additional controls. Kidney injury and fibrosis were assessed by biochemical parameters and kidney tissue stains (Fibronectin, α-SMA and picrosirius red). GFR was measured by transdermal monitoring of FITC-sinistrin clearance. Phospho-EGFR levels were detected in kidney lysates by western blotting.

Results: All groups showed the same degree of initial kidney injury. Etanercept or Erlotinib individually significantly decreased renal fibrosis by approximately 40% compared to vehicle-treated mice, but there was no additive protective effect when the drug combination was used. In kidney lysates, Erlotinib (alone or in the combination) decreased EGFR phosphorylation, while Etanercept alone had no effect on p-EGFR.

Conclusions: Etanercept treatment significantly reduced fibrosis after AKI without affecting EGFR activation, and additional EGFR inhibition in combinatorial drug treatment did not further improve outcomes. This suggests that TNFα in the context of AKI-induced fibrosis acts downstream of EGFR. This opens a potentially new therapeutic window for etanercept, a well-tolerated FDA-approved drug, in human AKI.

Funding: NIDDK Support

TH-PO495

The Competing Endogenous RNA Network in Renal Aging

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Background: It is well known that aging is a continuous and gradual process that causes the physiological functions of all organ systems in the human body to gradually decline. The kidney, which is a metabolically active organ, is extremely susceptible to aging, but the mechanism of kidney aging is unclear. MicroRNAs (miRNAs) are a highly conserved small non-coding RNA of 18-25 nucleotides in length that inhibits protein expression at the post-transcriptional level or degrades target genes to regulate gene expression. Long-chain non-coding RNA (lncRNA) is a non-coding RNA consisting of 200 nucleotides. It is generally considered that they do not encode proteins, but are expressed in various forms at the RNA level. In ceRNA networks, lncRNAs bind to miRNAs via miRNA response elements (MREs), and miRNAs can also bind to the corresponding mRNA 3'UTR through specific binding sites, inhibiting the level of protein expressed.

Methods: Analyse the lncRNA expression profiles in different ages mouse using a microarray array. And predicted miRNAs and mRNAs that interact with lncRNAs. SA-β-gal staining and immunohistochemistry were operated for the detection of the p53, p16 expression in different ages. Then we use Masson and PAS staining to assess the degree of fibrosis in the kidney.

Results: Bioinformatics analysis results show that the expression of some lncRNAs decreased with age, and the corresponding miRNAs expression increased accordingly. With the increase of age, we detected that the expression of senescence-associated galactosidase gradually increased, the expression of p16 and p53 gradually increased, and the renal fibrosis gradually worsened.

Conclusions: With the increase of age, the expression of senescence-associated galactosidase gradually increased, the expression of p16 and p53 gradually increased, and the renal fibrosis gradually worsened. ceRNA network plays an important role in kidney aging.

TH-PO496

Impairment of CPT-1α and Fatty Acid Metabolism Aggravates Renal Fibrosis During Aging

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Background: Defects in renal fatty acid metabolism (FAM) pathway have been implicated in the development of renal fibrosis. Aged kidneys show significantly increased fibrosis with impaired kidney function. The mechanisms underlying the effects of FAM on renal aging and fibrosis have not been investigated. In this study, we investigated carnitine palmitoyltransferase-1α (CPT-1α) and FAM pathway as regulators of age-associated renal fibrosis.

Methods: Renal biopsy samples from 126 patients were examined by masson trichrome staining, oil red O staining and immunohistochemical staining for CPT-1α. To evaluate the effects of CPT-1α deficiency on age-associated renal fibrosis, age-matched tubular cell specific CPT-1$\alpha^{-/-}$ mice and their wild-type littermates were used.

Results: In patients, fibrosis and lipid accumulation in tubulointerstitial spaces were associated with the age of patients. After been followed up for 5 years, age and lipid accumulation were risk factors for the progression of renal fibrosis. As compared with wild-type litermates, renal dysfunction measure by blood urine nitrogen and serum creatinine, tubular damage evaluated by urinary KIM-1, NGAL and NAG, urinary albumin and protein excretion were all more severe in mice with tubular specific deficiency of CPT-1α at the age of 1-year-old. Meanwhile, more lipid accumulation, tubulointerstitial fibrosis, extracellular matrix deposition were observed in CPT-1$\alpha^{-/-}$ mice at the age of 1-year-old. The increased expression of aging proteins (p21, p53, PCNA), inflammatory factors (NF-κB, CD3, IL-1, IL-18) and apoptosis molecule (cleaved caspase3) and decreased expression of autophagy (Atg12, Beclin-1, LC3β, p62) in kidney of CPT-1$\alpha^{-/-}$ mice were accompanied by the dysregulated expression of FAM proteins, including PPARα, CD36, ACADL, ACOX1, FASN and ACLY. In primarily cultured tubular cells, down-regulation of CPT-1α resulted in increased ROS and decreased mitochondrial energy production.

Conclusions: Impairment of CPT-1α and fatty acid metabolism in tubular cells aggravates renal aging and fibrosis.

Funding: Government Support - Non-U.S.

TH-PO497

Protective Role of Kallistatin Against Renal Fibrosis in Unilateral Ureteral Obstruction

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Background: Kallistatin is an endogenous serine protease inhibitor, which exerts anti-oxidative and anti-inflammatory function against kidney injury in animal models. However, it remains unknown whether kallistatin plays any protective effect in renal fibrosis, the final common pathway of all chronic kidney diseases.

Methods: Unilateral ureteral obstruction (UUO) was used to investigate the effect of kallistatin on renal extracellular matrix (ECM) protein expression and fibrotic signaling pathways. Renal kallistatin was either overexpressed by ultrasound-mediated microbubble kallistatin gene transfer or depleted by injection of anti-kallistatin antibody.

Results: Endogenous kallistatin expression was reduced in renal cortex of UUO kidneys. Kallistatin treatment significantly suppressed macrophage accumulation and the increase in ECM proteins including collagen type I and III as well as α-SMA. In contrast, injection with anti-kallistatin antibody aggravated renal fibrosis as evidenced by a further increase in ECM proteins. Moreover, depletion of endogenous kallistatin exacerbated UUO-induced Wnt4, β-catenin and Axin2 overexpression in the kidneys, while treatment with kallistatin reduced both Wnt4 and TGF-β over-expression in UUO kidneys.

Conclusions: Our results suggest a therapeutic role for kallistatin against renal fibrosis. Kallistatin exerts its anti-fibrotic effect in the kidney via modulating TGF-β and Wnt/β-catenin pathways, thereby offering a novel potential target of treatment for chronic kidney disease. **Fund support:** Research Grants Council of Hong Kong (GRF grant number 17151716, CRF grant number C7018-16G), Hong Kong Society of Nephrology and Hong Kong Kidney Foundation Research Grant (2017).

TH-PO498

Semaphorin 3A Inhibitor Ameliorates Renal Fibrosis in Unilateral Ureter Obstruction Mice

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Background: Renal fibrosis is the common pathological pathway of progressive renal diseases. Semaphorin3A (SEMA3A) is a secreted protein involves in angiogenesis, cell motility and immune cell regulation. Previous reports suggest SEMA3A accelerates renal injury. However, it is unclear whether SEMA3A signaling is associated with renal fibrosis. Here we examined the role of SEMA3A on renal fibrosis using unilateral ureter obstruction (UUO) mouse model and examined the effects of SEMA3A-inhibitor (SEMA3A-I: provided from Dainihon Sumitomo Pharm).

Methods: 10-week old wild-type male C57BL/6N mice were assigned into three groups (n=5 / each): UUO group (UUO+daily saline injection), UUO+SEMA3A-I group (UUO+daily SEMA3A-I injection) and sham group. All the mice were sacrificed 2 weeks after UUO surgery. We analyzed the effect of SEMA3A-I *in Vivo* and *in Vitro*, using mouse proximal tubular cells (mProx24 cells). In addition, human samples of urine, serum and kidneys from biopsied patients (n=36) were collected to analyze the involvement of SEMA3A in renal diseases.

Results: The expressions of SEMA3A and the receptor, neuropilin-1 (NRP1) increased in renal fibrotic area in UUO group while SEMA3A-I significantly ameliorated UUO-induced renal fibrosis in Masson staining as well as tubular cell apoptosis in TUNEL staining. The expression of phospho-c-Jun, a downstream of c-Jun N-terminal kinase (JNK) signaling, known as the target of SEMA3A-NRP1 signaling, increased in UUO group compared to sham group. *In vitro* study, the treatment with SEMA3A in

mProx24 cells caused Epithelial-Mesenchymal Transition (EMT) with the increase of Vimentin/E-cadherin ratio as well as apoptosis, while SEMA3A-I treatment partially attenuated cisplatin-induced tubular cell apoptosis and TGFβ1-induced EMT. JNK inhibitor decreased SEMA3A-induced tubular apoptosis and EMT. These data suggest that SEMA3A causes renal injury via JNK signaling. The analysis of human data revealed the positive correlation between urinary SEMA3A and N-acetyl-β-D-glucosaminidase (r=0.531, p=0.007). In addition, the higher expression of SEMA3A in tubulointerstitial area were seen in human kidneys with severe renal fibrosis, confirming SEMA3A signaling is associated with tubular injury and fibrosis.

Conclusions: SEMA3A-I ameliorates UUO-induced renal fibrosis and tubular injury through the inhibition of JNK signaling.

Funding: Government Support - Non-U.S.

TH-PO499

Disturbed Phosphate Metabolism Facilitates Kidney Damage in Dahl Salt-Sensitive Hypertensive Rats

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Background: Several lines of evidence indicate that hypertensive end-organ damage is associated with altered phosphate metabolism. Here, we evaluated the effects of intestinal phosphate binding by sucroferric oxyhydroxide (SF) on renal damage in Dahl salt-sensitive rats, a model of hypertensive kidney disease.

Methods: Control rats received a normal diet containing normal (0.3%) phosphate. High salt (HS) group received a diet containing 8% NaCl and 0.3% phosphate for four weeks. A subgroup of HS rats received SF (HS+SF). We also evaluated the effects of phosphate loading in NRK-52E, a proximal tubule cell line.

Results: Compared with control, HS showed progressive increase in BP. Although urinary Na^+ and BP levels were similar between HS and HS+SF groups, albuminuria was significantly ameliorated in the latter. In PAS staining, SF attenuated glomerulosclerosis and tubulointerstitial injury in this model. Moreover, upregulation of inflammatory cytokines in renal tubules was significantly ameliorated by SF. Reduced inflammatory response in the tubulointerstitium of HS+SF rats were confirmed by quantitative evaluation of CD68 staining. In the heart, HS group showed myofiber hypertrophy and macrophage infiltration. However, only the latter was attenuated in HS+SF. We then evaluated phosphate metabolism in this model. Although plasma phosphate levels were not significantly different among three groups, fractional excretion of phosphate and plasma FGF23 levels were significantly elevated in HS group, which was attenuated by SF. In NRK-52E cells, phosphate loading significantly increased the expression of MCP-1. Removing calcium-phosphate crystals by centrifugation, but not the knockdown of sodium-dependent phosphate transporter Slc34a1, abolished the effect of phosphate.

Conclusions: Phosphate loading to renal tubules can aggravate renal inflammation likely through calcium-phosphate nanoparticle formation. These data support the pathological role of latent phosphate accumulation in hypertensive kidney damage.

Funding: Government Support - Non-U.S.

TH-PO500

Agonistic cMet Antibody Prevents Kidney Fibrosis in Acute Kidney Disease Mice Model

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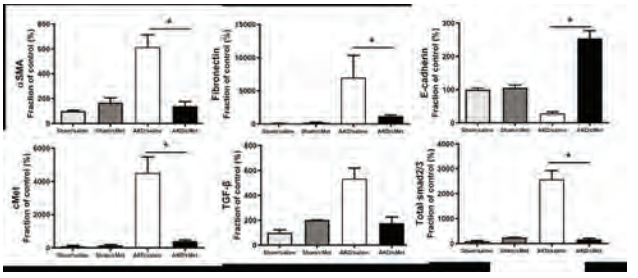
Background: HGF/cMet signaling pathway plays important roles in kidney development and maintenance of normal adult kidney structure, and cMet activation is expected to prevent kidney fibrosis. We aimed to investigate whether treatment with agnostic cMet antibody can prevent kidney fibrosis in the acute kidney disease mice model.

Methods: Unilateral ischemic-reperfusion injury at left kidney was introduced in 7-week-old male C57BL/6 mice (n = 14) and raised for up to 28 days to induce acute kidney disease model. Agnostic cMet antibody (20 mg/kg) was injected via tail vein at a schedule of day -1, 0, 1, 3, and twice weekly thereafter in the treatment group (n = 7). Vehicle (saline) was injected via tail vein at the same schedule in the control group (n = 7).

Results: Kidney weight (left) per total body weight was significantly higher in the treatment group (0.63 ± 0.21% vs. 0.43 ± 0.22%, P = 0.022). In the histopathologic specimen of Masson's trichrome stain, areas of kidney interstitial fibrosis attenuated in the treatment group. In the western-blot analysis, protein abundance of α-smooth muscle actin (22.5% of control, P = 0.03), fibronectin (16.4% of control, P = 0.03), TGF-β (33.3% of control, P = 0.05), total (6.6% of control, P = 0.03) and phospho-smad2/3 (10.1% of control, P = 0.03) decreased significantly, and protein abundance of e-cadherin increased (912.4% of control, P = 0.03) significantly in the treatment group. In the real-time PCR analysis, mRNA expression of α-smooth muscle actin (11.5% of control, P = 0.006), collagen 1 (11.6% of control, P = 0.01), fibronectin (11.2% of control, P = 0.01), TGF-β (21.3% of control, P = 0.01) decreased significantly in the treatment group.

Conclusions: Agonistic cMet antibody attenuates kidney fibrosis in the mice unilateral ischemic reperfusion induced acute kidney disease model, and TGF-β and smad2/3 pathway involved in the kidney fibrosis are effectively suppressed in the treatment of agonistic cMet antibody.



Western Blot Results after Agonistic cMet Antibody Treatment

TH-PO501

Lysine Deacetylase Inhibition Attenuates Tubulointerstitial Injury and Fibrosis in a Model of Proteinuric CKD

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Background: There is a paucity of effective treatments for tubulointerstitial fibrosis associated with progressive CKD. Previously, we derived a CKD progression signature composed of differentially expressed genes based on aging and disease in *Col4a3*$^{-/-}$ mice, a model associated with proteinuria and progressive loss of kidney function. Through drug repurposing with the progression signature and the Connectivity Map we identified vorinostat, a lysine deacetylase (KDAC) inhibitor, as a potential therapy for CKD progression. Here, we examine effects of vorinostat treatment on tissue fibrosis in *Col4a3*$^{-/-}$ mice.

Methods: Male *Col4a3*$^{-/-}$ mice on a congenic 129/SvJ background were treated with vorinostat (50 mg/kg/day) or vehicle from 4 to 7 weeks of age by oral gavage. Mice were euthanized at 7 weeks of age. Plasma, urine, and kidney samples were collected. Kidney histological, function, inflammation, and fibrosis analyses were performed. Separate groups were followed for survival assessment. Finally, albumin-stimulated human proximal tubule epithelial (HK-2) cells were treated with vorinostat (5 μM) and used to assess mechanisms.

Results: Vorinostat treatment did not improve kidney function and had no effect on glomerulosclerosis scores, but significantly reduced tubular injury markers, KIM-1 and NGAL. This was associated with a significant increase in the lifespan of *Col4a3*$^{-/-}$ mice. *Col1a1, Fn1, Serpine1,* and *Tnf* mRNA levels were reduced in the kidneys of vorinostat-treated mice. Vorinostat administration lowered TGF-β1 and α-SMA protein levels in kidneys and urine, respectively. Treatment attenuated JNK phosphorylation in *Col4a3*$^{-/-}$ mouse kidneys. *In vitro*, vorinostat reduced albumin-induced activation of JNK, p38, and ERK in HK-2 cells. Vorinostat also attenuated the activation of activator protein 1 transcription factor *in vitro*.

Conclusions: Our findings suggest that KDAC inhibition and blockade of MAPKs may be effective treatment approaches to CKD associated with proteinuria and progressive tubulointerstitial injury.

TH-PO502

Lysine Methyltransferase SMYD2 Inhibition Ameliorates Renal Fibrosis Through Suppression of Renal Fibroblast to Myofibroblast Transition

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Background: Although SMYD2, a SET and MYND domain protein with lysine methyltransferase activity, has been reported to mediate tumorgenesis and cystic growth, its roles in the pathogenesis of renal fibrosis has not been explored.

Methods: We investigated whether pharmacological inhibition of SMYD2 attenuates renal fibrosis in a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO). We also used cell culture, immunoblot analysis, staining, and other techniques to study the mechanism by which SMYD2 mediates renal fibrosis and renal fibroblast activation and proliferation.

Results: SMYD2 was upregulated in interstitial fibroblasts and renal tubular epithelial cells of the kidney after urethral obstruction. Targeting inhibition of SMYD2 with AZ505, a highly selective inhibitor of SMYD2, protected mice from activation of renal interstitial fibroblasts and development of renal fibrosis. Mechanistic studies showed that AZ505 treatment reduced obstructive injury –induced arrest of epithelial cells at G2/M phase of cell cycle, phosphorylation of Smad3, ERK1/2, AKT, STAT3 and AKT as well as upregulation of transcriptional factors Snail and Twist. In vitro cultured renal interstitial fibroblasts, treatment with AZ505 or silencing of SMYD2 using specific siRNA also inhibited serum or TGF-b1-induced activation of and proliferation of renal interstitial fibroblasts.

Conclusions: These results implicate that SMYD2 is a key mediator of renal fibroblast activation and renal fibrosis. Given the availability of potent SMYD2 inhibitors, SMYD2 might be a potential therapeutic target for the treatment of chronic fibrotic kidney disease.

Funding: NIDDK Support

TH-PO503

Selective Inhibition of Histone Deacetylase 8 Suppresses Renal Fibroblast Activation and Mitigates Renal Fibrosis

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Background: Histone deacetylase 8 (HDAC8), a unique class I zinc-dependent HDAC, is implicated in the pathogenesis of various rumors, however, its role in renal fibrogenesis remains poorly understood.

Methods: In this study, we examined the effect of HDAC8 inhibition on the activation of cultured renal interstitial fibroblasts and. the development of renal fibrosis in a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO).

Results: Treatment of cultured renal interstitial fibroblasts with PCI34051, a selective HDAC8 inhibitor, or small interfering RNA-mediated silencing of HDAC8, inhibited their activation as indicated by decreased expression of alpha smooth muscle actin, fibronectin and type I collagen. In a mouse model of obstructive nephropathy, HDAC8 was up-regulated in renal epithelial cells of the injured kidney. Administration of PCI34051 immediately after UUO injury reduced the deposition of extracellular matrix proteins and inhibited activation of renal fibroblasts. Moreover, HDAC8 inhibition suppressed activation of several signaling pathways associated with the progression of renal fibrosis, including Smad-3, beta-catenin, signal transducer and activator of transcription 3 (STAT3), whereas increased expression of klotho and bone morphogenetic protein 7, two renoprotecive proteins, in the injured kidney.

Conclusions: Our results indicate that selectively targeting HDAC 7 can inhibit development of renal fibrosis and activation of renal fibroblasts by inactivation multiple profibrotic molecules and increasing expression of antifibrotic proteins. Thus, HDAC8 may be a druggable target.

Funding: NIDDK Support

TH-PO504

Critical Role of lincRNA-p21 in Mediating Lipotoxicity-Induced Kidney Injury

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Background: Ectopic lipid accumulation in kidney is a key factor in the etiology of lipotoxicity-induced kidney lesion. Emerging evidence unravels that long intergenic non-coding RNA p21 (lincRNA-p21) plays a pivotal role in diverse biological processes and diseases. However, little is known about the role of lincRNA-p21 in kidney diseases. We aim to identify the functional role of lincRNA-p21 in lipotoxicity-induced kidney injury.

Methods: Expression of lincRNA-p21 in kidney from mice (C57BL/6J) fed with normal diet (ND; 10 kcal%) or high-fat diet (HFD; 60 kcal%), as well as in palmitic acid (PA)-treated human proximal tubular epithelial cells line (HK-2 cells) was determined by qRT-PCR. Antisense locked nucleic acids (LNA) GapmeR technique was utilized to silence lincRNA-p21 expression in HK-2 cells, followed by evaluation of cellular inflammation, endoplasmic reticulum (ER) stress and apoptosis by qRT-PCR after PA exposure. Western blot and ELISA were performed to investigate the associated signaling cascades.

Results: Compared with ND-fed mice, a significantly increase in the expression of lincRNA-p21 was found in kidney biopsy from HFD-fed mice. Consistently, markedly upregulated expression of lincRNA-p21was observed in PA-treated HK-2 cells. By contrast, silencing lincRNA-p21significantly counteracted PA-induced gene expression associated with inflammation (IL6), ER stress (BiP, sXBP1 and CHOP) and apoptosis (BCL2). Additionally, PA suppressed PI3K/Akt/mTOR/Mdm2 signaling cascades and subsequently led to enhanced p53 activity, which consequently drove lincRNA-p21 expression in HK-2 cells.

Conclusions: PA acts through PI3K/Akt/mTOR/Mdm2 signaling pathway to up-regulate lincRNA-p21 expression in a p53-dependent manner, thereby contributing to lipotoxicity-induced pathological process in HK-2 cells. **Funding:** National Natural Science Foundation of China (81870496), Hong Kong Research Grants Council Collaborative Research Fund (C7018-16G) and Hong Kong Society of Nephrology Research Grant (2018)

Funding: Government Support - Non-U.S.

TH-PO505

Dicer Promotes Renal Recovery and Limits Interstitial Fibrosis Following Kidney Injury

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Background: Renal tubulointerstitial fibrosis is the histopathological hallmark observed in chronic kidney disease; and activated fibroblasts, myofibroblasts, are the dominant extracellular matrix-producing cells that contribute to fibrosis development. Dysregulation or deletion of Dicer, a ribonuclease involved in microRNA (miRNA) generation, impacts kidney health and function. Since fibroblasts are key cells responsible for renal fibrosis, we investigated whether Dicer might effect myofibroblast and fibrosis formation by deletion of Dicer from myofibroblasts *in vivo*.

Methods: $Dicer^{fl/fl}$ mice were crossed with α-smooth muscle actin promoter (αSMA^{Cre}) mice, a marker of activated fibroblast, to generate WT (αSMA^{Cre-};$Dicer^{fl/fl}$) and Dicer conditional knock-out mice (αSMA^{Cre+};$Dicer^{fl/fl}$, hereafter $Dicer^{cKO}$). Mice were challenged to three different kidney injury models. MiRNAs from primary kidney fibroblasts were analyzed.

Results: Isolated human and mouse fibroblast from fibrotic kidneys demonstrated increased Dicer hypermethylation. $Dicer^{cKO}$ mice had no overt renal abnormalities. To determine whether deletion of Dicer in myofibroblast might impact the development of tubulointerstitial fibrosis, both WT and $Dicer^{cKO}$ mice underwent unilateral ureteral obstruction, nephrotoxic serum nephritis, and folic acid kidney injury. $Dicer^{cKO}$ mice displayed increased collagen deposition and tubulointerstitial fibrosis compared to WT animals in all three models. Furthermore, loss of Dicer resulted in an increase of proliferating, Ki67 positive, αSMA^{+} myofibroblasts. MiRNA array analysis of primary mouse fibroblasts from the UUO kidneys of $Dicer^{cKO}$ and WT mice revealed a differential expression of several miRNAs, including upregulation of miR-451, a Dicer-independent miRNA, in the $Dicer^{cKO}$ mice.

Conclusions: Renal tubulointerstitial fibrosis is the pathological sequelae observed in chronic injury. Dicer is critically involved in kidney homeostasis, and here we show that Dicer deletion in myofibroblasts resulted in differential miRNA expression and pathologic myofibroblast proliferation perpetuating fibrogenesis. Depletion of Dicer and associated miRNAs is pathogenic in various kidney injury models and accelerates kidney failure.

TH-PO506

The Transcription Factor STAT3 Plays Key Roles in the Development of Kidney Fibrosis by Increasing Proliferation and Differentiation of Pericytes into Myofibroblasts

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Background: STAT3 is a key transcription factor, which plays important roles in inflammatory diseases. STAT3 has been shown to transcribe genes important for the acute and chronic phase of various malignant. There is little information regarding the function of STAT3 in stromal cells.

Methods: Phosphorylation of STAT3 was evaluated in 5 patient biopsy samples using immunofluorescence. In mice, stromal cell-specific STAT3 deletion was performed by breeding STAT3 floxed mice with FoxD1 Cre mice. Kidney fibrosis was induced by administering 300 mg/kg folic acid (FA) or 5 mg/kg body weight aristolochic acid (AA). Cell migration was evaluated with wound scratch assays. RT-PCR, immunostaining and western blotting were performed to measure changes in STAT3-dependent genes and to quantitate pro-fibrotic cytokines.

Results: STAT3 phosphorylation was increased in tubular epithelial cells and interstitial cells of 5 human subjects with chronic kidney disease. Deletion of STAT3 from stromal cells protects mice from FA or AA-induced kidney fibrosis at 7- and 14-days post-treatment respectively. Fibrotic markers, including fibronectin, collagen1a1, and α-SMA were reduced in STAT3 KO mice. STAT3 KO mice show similar acute injury {shown by histopathology and mRNA levels of TNFa and KIM-1 (Kidney Injury Molecule-1, acute kidney injury marker)}. KIM-1 expression was decreased at 7 and 14 days in STAT3 KO mice. In human primary pericytes in vitro, STAT3 was phosphorylated after treatment with IL-6 or Colivelin (a small peptide activator of STAT3). Inhibition of IL-6-induced STAT3 phosphorylation significantly decreased the proliferation, production of profibrotic cytokines and differentiation of pericytes into myofibroblasts.

Conclusions: STAT3 plays key roles in the development of kidney fibrosis by increasing proliferation and differentiation of pericytes into myofibroblasts. Thus, STAT3 may be a potential therapeutic target for kidney fibrosis.

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TH-PO507

Sodium Thiosulfate Improves Renal Function and Oxygenation in L-NNA Induced Hypertensive Rats

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Background: Sodium thiosulfate (STS, $Na_2S_2O_3$), a H_2S donor, a vasodilator and anti-oxidant, is an attractive agent for alleviating the damaging effects of hypertension. In experimental setting, nitric oxide synthase (NOS) inhibition by L-NNA induces hypertension, renal dysfunction and damage. We hypothesized that 1) STS attenuates renal injury and improves renal function, hemodynamics and oxygen efficiency in hypertensive renal disease and that 2) STS on top of RAS inhibition will further improve aforementioned variables in comparison to RAS inhibition alone.

Methods: NOS was inhibited in male Sprague Dawley rats by administering L-NNA (40 mg/kg/day) in the food for 3 weeks. After one week of NOS inhibition, rats were split in 2 groups for the remaining 2 weeks, 1) L-NNA only and 2) L-NNA with STS (2 g/kg/day) in the drinking water. In a parallel study, rats were divided in 2 groups, 1) L-NNA with lisinopril (1mg/kg/day) mixed in the food and 2) L-NNA with both lisinopril and STS. After weekly systolic blood pressure measurements and 24h urine collection, hemodynamics and sodium reabsorption efficiency (TNa/QO_2, sodium reabsorbed per oxygen consumed) were assessed under isoflurane and kidneys were collected for glomerulosclerosis and mesangial matrix expansion scores.

Results: STS increased 24h excretions of sodium 3.5-fold and sulphate 30-fold, alleviated hypertension (165±5 vs. 228±5 mmHg, P<0.001), reduced plasma urea (11±1 vs. 21±4 mmol/L, P<0.05) and improved terminal GFR (503±25 vs. 260±45 µl/min/100 g BW, P<0.01), effective renal plasma flow (919±64 vs. 532±97 µl/min/100 g BW, P<0.01) and TNa/QO_2 (14.3±1.1 vs. 8.6±1.4 µmol/µmol, P<0.01). Combining STS with lisinopril further reduced renal vascular resistance (43±4 vs. 63±7 mmHg/ml/min/100 g BW, P<0.05) vs. L-NNA+lisinopril. Additionally, glomerulosclerosis was completely prevented (P<0.001) and mesangial matrix expansion (P<0.01) was markedly reduced in L-NNA+lisinopril+STS vs. L-NNA+lisinopril.

Conclusions: Our results suggest that supplementing H_2S has therapeutic potential in hypertensive renal disease and might be of additive value in already existing antihypertensive regimens despite the increase in sodium load.

Funding: Private Foundation Support

TH-PO508

Pemafibrate Exerts Renoprotective Effects by Activation of PPARα in Murine Kidneys

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Background: Recently, free fatty acid (FFA) toxicity accompanying proteinuria was identified as a main cause of tubular damage, which was aggravated by an insufficiency of peroxisome proliferator-activated receptorα (PPARα). We have reported that strongly PPARα agonistic fibrate drugs exert renoprotective effects by PPARα activation in proximal tubular epithelial cells with FFA-overload nephropathy (FAON) tubular injury model mice. In the clinical setting, however, there have been no safe PPARα agonists for patients with chronic kidney disease (CKD) since fibrate drugs have severe dose-related adverse effects, including a decrease in kidney function. Pemafibrate (PMF) was approved in Japan in 2018 as the first selective PPARα modulator (SPPARMα). PMF has much more potent and specific PPARα-activating efficacy as compared with other fibrates and is excreted in the bile. Thus, the drug can achieve greater improvements in fatty acid metabolism with a highly reduced risk of diminished kidney function and other adverse effects. Although PMF can be safely prescribed for CKD patients, it is uncertain whether it activates PPARα in the kidneys or has renoprotective effects.

Methods: We examined the above possibilities using the kidneys of wild type mice and FAON model mice with and without 0.25 mg/kg/day PMF administration for 14 days.

Results: PPARα target gene expression in the kidneys was significantly decreased in FAON model mice and it was improved by PMF treatment. The PMF treated animals also exhibited decreased levels of tubular injury, urinary protein excretion, oxidative stress (OS), and pro-inflammatory apoptosis-stimulating responses, as well as stable fatty acid metabolism. Moreover, expression of the PPARα gene and its target mRNA-encoding proteins involved in OS, pro-inflammatory responses, apoptosis, and fatty acid metabolism were maintained with PMF treatment.

Conclusions: This study's results suggest that PMF activates renal PPARα, increases PPARα signaling, and imparts renoprotective effects.

TH-PO509

Calcineurin Inhibition but Not Dehydration in Rats Mimics Human Renal Histopathology of Patients with Chronic Interstitial Nephritis in Agricultural Communities (CINAC)

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Background: CINAC patients present a newly discovered constellation of proximal tubular lysosomal lesions which is also observed in patients experiencing calcineurin inhibitor (CNI) nephrotoxicity, suggesting that CINAC is a toxin-induced nephropathy involving calcineurin inhibition. An alternate hypothesis advocates chronic heat stress/dehydration as the major etiological factor for CINAC. Here, we evaluated in rats to what extent heat stress/dehydration versus CNI exposure reflects proximal tubular CINAC histopathology.

Methods: Wistar rats were divided in 3 groups. Group 1 (n=6) was given water ad libitum (control group). Group 2 (n=8) was water deprived for 10 hours per 24h, 5 days/week and were placed in an incubator (37°C) for 30 min/hr of water deprivation. Group 3 (n=8) underwent daily oral gavage with cyclosporine (50mg/kg body weight). Animals were weighed daily and urine was collected at day 3, 17 and 28. After 28 days, rats were sacrificed. Kidneys were collected for light (LM) and electron microscopic (EM) histopathological analysis as well as for cortical renal tissue proteomics.

Results: Cyclosporine rats developed focal cortical lesions mimicking those of CINAC patients: i.e. atrophic proximal tubuli with thickened basement membranes and associated tubulo-interstitial fibrosis, PASM staining demonstrating enlarged argyrophyllic granules in the affected proximal tubuli, LAMP1 immunofluorescent staining identifying a subset of these granules as lysosomes, and EM confirming the presence of enlarged lysosomes, some dysmorphic approaching CINAC lysosomes. In dehydrated rats, confirmed by urinary osmolality and fluctuating body weight associated with water deprivation, none of the cyclosporine features were observed. Proteomic analysis confirmed cellular toxicity by cyclosporine, whereas the dehydration group lacked any markers of such.

Conclusions: The histopathological analogy between CNI nephrotoxicity in rats and humans and CINAC suggests a toxicological etiology for CINAC. In rats, dehydration/heat stress alone does not lead to the constellation of proximal tubular lesions as observed in CINAC patients.

Funding: Government Support - Non-U.S.

TH-PO510

Renoprotective Effect of Astragalus Root in a Rat Model of CKD

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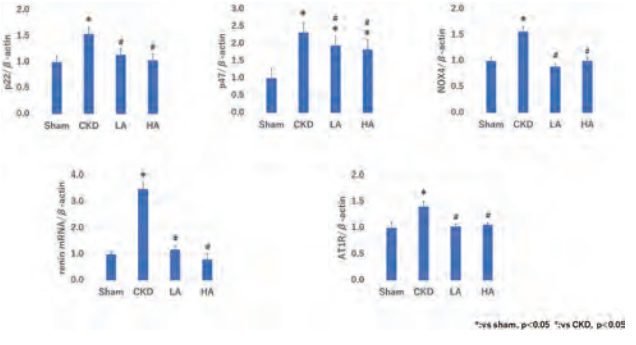
Background: Astragalus root is a commonly used herb in traditional Chinese medicine. Although it has been reported to have a renoprotective effect in clinical and animal studies, the pathophysiological mechanism remains unknown. In the present study, we examined the details of the renoprotective property of astragalus root using a rat model of chronic kidney disease (CKD).

Methods: CKD was induced by 5/6 nephrectomy using male Sprague Dawley (SD) rats. At 10 weeks, rats were classified into four groups and were orally administered vehicle (CKD), low-dose astragalus (LA, 400 mg/kg), and high-dose astragalus (HA, 800 mg/kg) once a day, except in the sham group (the sham, CKD, LA, and HA group). At 14 weeks, the rats were sacrificed for the evaluation of blood and urine samples and mRNA expression and histopathology in the kidney.

Results: At 14 weeks, the progression of kidney dyfunction was significantly slowed by administration of astragalus root (creatinine clearance: sham group; 3.8±0.3 mL/min, CKD group; 1.5±0.2 mL/min, LA group; 2.5±0.3 mL/min, HA group; 2.7±0.1 mL/min). Blood pressure and proteinuria also decreased in the astragalus root-treated groups. The urinary 8-OHdG excretion, which is an oxidative stress marker, decreased in the astragalus root-treated groups (sham group; 451.6±29.6 ng/day, CKD group; 1173.2±91.9 ng/day, LA group; 768.3±68.5 ng/day, HA group; 745.1±40.8 ng/day), and astragalus also decreased the oxidative stress score in the kidney, which was evaluated by immunostaining. In addition, mRNA expression of NADPH p22 and p47, renin and AT1R in the kidney decreased in the astragalus root-treated groups compared to the CKD group (Figure 1).

Conclusions: Our study suggested that astragalus root slowed the progression of CKD possibly through the suppression of oxidative stress.



TH-PO511

Treating CKD-Related Anemia with Erythropoietin and HIF- Prolyl Hydroxylase Inhibitors Improves FGF-23-Dependent and -Independent Outcomes

Megan L. Noonan,[1] Erica Clinkenbeard,[1] Pu Ni,[1] Samantha P. Tippen,[2] Rafiou Agoro,[1] William R. Thompson,[3] Matthew R. Allen,[1] Kenneth E. White.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]IU School of Medicine, Indianapolis, IN; [3]Indiana University, Indianapolis, IN.*

Background: In chronic kidney disease (CKD), high blood concentrations of the phosphaturic hormone FGF23 are associated with increased odds for patient mortality (>6-fold). Our lab has identified anemia as a potent driver of FGF23 expression. Patients with CKD ultimately develop anemia as the kidneys lose the ability to produce erythropoietin (EPO), in parallel with mineral metabolism alterations. We hypothesized that mitigating anemia through treatment with either recombinant EPO or HIF-PHi (hypoxia inducible factor-prolyl hydroxylase inhibitors), currently in clinical trials that elevate endogenous EPO, would reduce circulating bioactive, 'intact' FGF23 ('iFGF23'), thereby improving the pathogenic manifestations of CKD.

Methods: Using a novel murine inducible stem cell line (MPC2), we showed that the HIF-PHDi FG-4592 (Roxadustat) directly induced Fgf23 mRNA when differentiated into osteoblast-like cells (8-16 fold, $p<0.01$). Additionally, FG-4592 injection dose-dependently increased iFGF23 2-9 fold ($p<0.05$) in wild type (WT) mice with normal renal function. To determine the effects in CKD, mice were placed on a casein control or adenine diet to induce CKD, which resulted in markedly elevated iFGF23, hyperphosphatemia, hyperparathyroidism, and anemia. Separate cohorts were treated with either recombinant EPO or FG-4592.

Results: iFGF23 was significantly elevated (70-fold, $p<0.01$) in saline-treated CKD mice compared to controls. In CKD mice, EPO treatment improved total serum iron, and FG-4592 treatment led to marked induction of serum EPO ($p<0.01$). Importantly, circulating iFGF23 was significantly attenuated (>70%; $p<0.05$) in the CKD mice with EPO or FG-4592 administration, demonstrating that anemia is a primary driver of FGF23 in CKD. As expected with elevated iFGF23 in CKD mice, *Cyp24a1* mRNA increased ($p<0.01$), favoring low 1,25D. In contrast, both EPO and FG-4592 significantly enhanced *Cyp27b1* ($p<0.05$) and suppressed *Cyp24a1* ($p<0.01$) mRNAs in CKD mice, suggesting improved 1,25D synthesis. Indeed, EPO injection significantly increased serum 1,25D in control and CKD mice ($p<0.05$).

Conclusions: Collectively, these results support that treatment for anemia, via EPO or HIF-PHDi, leads to improved FGF23-dependent and -independent outcomes.

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

TH-PO512

Fibroblast Growth Factor 23 Produces Arterial Stiffness Through Changes in Vascular Smooth Muscle Cell Phenotype

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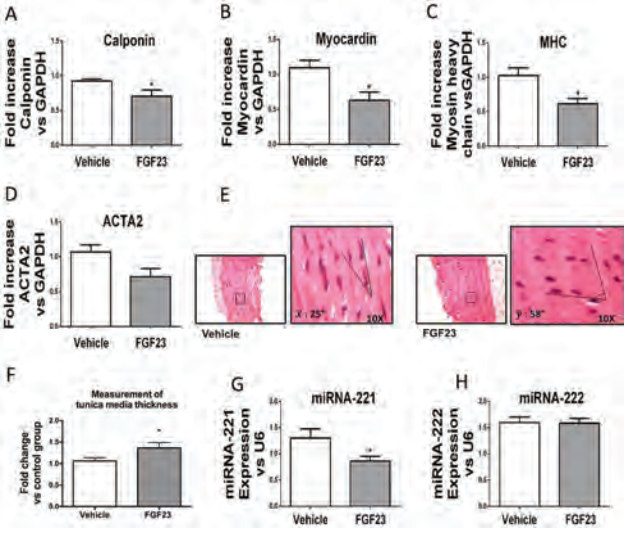
Background: In patients with chronic kidney disease (CKD), high levels of c-terminal fibroblast growth factor 23 (FGF23) are associated with cardiovascular disease and mortality. Vascular smooth muscle cells (VSMC) may present two differentiated functional phenotypes, contractile and synthetic. An excess of synthetic VSMC has been associated with vascular dysfunctions. It is unknown whether FGF23 may promote phenotypic transition causing vascular stiffness.

Methods: The expression of VSMC markers, miR-221 and miR-222 was determined in VSMC treated with high recombinant FGF23. *In vivo*, the VSMC markers were analyzed in aorta of rats receiving recombinant FGF23 for 14 days. Furthermore, the relationship between FGF23 and arterial stiffness was investigated in CKD patients stages 2-3.

Results: High levels of FGF23 promoted VSMC transition from a contractile to a synthetic phenotype. These effects were mediated through FGFR1 and Erk1/2 phosphorylation. Inhibition of both pathways enhanced contractile phenotype of VSMC. The pro-contractile microRNAs miR-221 and miR-222 were reduced by FGF23 and miR-221 transfection recovered the contractile phenotype of VSMC decreased by FGF23. In rats, exogenous infusion of FGF23 increased tunica media thickness and promoted synthetic phenotype reducing plasma levels of miR-221. In a group of CKD 2-3 patients it was observed an association between FGF23 and pulse pressure, reflecting vascular stiffness together with low plasma levels of miR-221 and miR-222.

Conclusions: FGF23 favors the transition of VSMC from contractile to synthetic phenotype causing vascular dysfunction and arterial stiffness. This may be a mechanism by which FGF23 contribute directly to the development of vascular disease in CKD patients.

Funding: Government Support - Non-U.S.



TH-PO513

FGF23-Mediated Activation of RAAS Contributes to Cardiac Hypertrophy and Fibrosis

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Background: Patients with CKD develop LVH accompanied with LV fibrosis. One of the main causes are the increased FGF23 serum levels, which were shown to induce the calcineurin/NFAT pathway in cardiomyocytes. Additionally, CKD patients show a systemic activation of RAAS and FGF23 is discussed to stimulate RAAS activation, which could be an alternative mechanism for the progression of FGF23-mediated cardiac pathologies. However, underlying molecular mechanisms are unknown.

Methods: We evaluated LVH and fibrosis in association with cardiac FGF23 and the local activation of RAAS in heart tissue of 5/6 nephrectomized (5/6Nx) rats compared to sham-operated animals. In order to distinguish between FGF23-mediated LVH and fibrosis via calcineurin/NFAT or RAAS, we stimulated isolated neonatal rat ventricular myocytes (NRVM) and fibroblast (NRCF) with FGF23 in the presence and absence of cyclosporine A, losartan and spironolactone, and investigated hypertrophic and fibrotic pathways by qPCR, Western blot and functional analysis.

Results: Uremic rats showed increased relative heart weight accompanied with enhanced cardiomyocyte size and LV fibrosis compared with sham. The cardiac expression of *Fgf23* and RAAS genes were significantly increased in 5/6Nx rats and correlated with the degree of LV fibrosis. FGF23 stimulated the expression of RAAS genes in cardiac cells *in vitro* and induced NGAL indicating mineralocorticoid receptor activation. The FGF23-induced hypertrophic growth of NRVM was attenuated by pre-treatment with cyclosporine A, losartan and spironolactone. In addition, the FGF23-mediated induction of pro-hypertrophic NFAT target genes was blocked by inhibition of calcineurin, AT1R and mineralocorticoid receptor. In NRCF, FGF23 phosphorylated Smad2/3 and induced Tgf-b and Ctgf, which were only suppressed by pre-stimulation with losartan and spironolactone but not with cyclosporine A. Interestingly, FGF23 increased the proliferation of NRCF independent of calcineurin/NFAT and RAAS activation.

Conclusions: The FGF23-induced cardiac hypertrophy is mediated by both the activation of RAAS and calcineurin/NFAT. Moreover, FGF23 impact on cardiac fibrosis primarily via RAAS-mediated activation of Tgf-b/Smad pathway.

TH-PO514

FGF23 Does Not Induce Left Ventricular Hypertrophy in Female Mice with CKD

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Background: Increased levels of fibroblast growth factor 23 (FGF23) in chronic kidney disease (CKD) are associated with development of left ventricular hypertrophy (LVH) and mortality. Men progress more rapidly to end stage renal disease and have an increased risk of cardiovascular death compared to women. We assessed whether delayed onset of CKD and/or delayed elevations of FGF23 levels in females could explain better cardiovascular outcomes than in males.

Methods: We studied B6 wild-type (WT) and Col4a3^{null} male and female littermate mice with progressive CKD at 4, 8, 12, 16, and 20 weeks of age. At each time point, we analyzed parameters of kidney and heart morphology and function, and we measured serum FGF23 levels. In parallel, we assessed the lifespan in separate groups of mice.

Results: As previously described, Col4a3^{null} males display impaired kidney function, increased serum FGF23 levels, development of LVH and reduced lifespan. Both Col4a3^{null} males and females showed signs of proteinuria at 4 weeks (albumin to creatinine ratio

(ACR); p<0.05 vs. sex- and age- matched WT). Progressive decline in kidney function resulted in increased levels of blood urea nitrogen (BUN) after 8 weeks of age in Col4a3^{null} females, and only after 12 weeks in Col4a3^{null} males (p<0.05 vs. sex- and age- matched WT). By 20 weeks, elevations of BUN, ACR and hypertension were similar in Col4a3^{null} males and females. Serum FGF23 levels increased in both Col4a3^{null} males and females after 8 weeks (p<0.05 vs. sex- and age- matched WT). Interestingly, Col4a3^{null} females displayed higher FGF23 levels at all timepoints and steeper elevations of FGF23 levels during CKD progression than Col4a3^{null} males, resulting in 50% higher FGF23 levels at 20 weeks (p<0.05 vs. Col4a3^{null} males). Unlike Col4a3^{null} males, and despite earlier onset of kidney disease and higher elevations of FGF23 levels, Col4a3^{null} females did not develop LVH and lived 1.5 week longer than Col4a3^{null} males in average.

Conclusions: In this well-established model of progressive CKD, absence of LVH in female mice may represent a survival advantage compared to males. The earlier onset of CKD and higher FGF23 levels in females suggest a role for female-specific cardioprotective mechanisms that remain to be determined.

Funding: NIDDK Support

TH-PO515

INS-3001 Efficiently Inhibits Severe CKD-Induced Cardiovascular Calcifications by Directly Targeting Hydroxyapatite Growth and Deposition

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Background: Prevention of cardiovascular calcification (CVC) in CKD patients currently is based on controlling CKD-specific risk factors such as hyperphosphatemia. A new therapeutic approach with potential higher efficacy consists in the use of molecules that directly interfere with the calcification process in the vessel wall, such as INS-3001. In this study we evaluated the efficacy of INS-3001, an inositol phosphate analog in a rat model of CKD-induced CVC.

Methods: CVC was induced in 48, 8 weeks old, male Wistar rats by the administration of an adenine (0.75%) and phosphate (0.92%) supplemented diet for 4 weeks, followed by a diet with 1.02% phosphate for 1 week until sacrifice. Rats were randomly assigned to 1 vehicle, and 3 INS-3001 groups (n=12 each) and treated with INS-3001 (5, 15 and 50 mg/kg) or vehicle (distilled water) by subcutaneous administration via osmotic minipumps during the last 4 weeks before sacrifice. CKD development was evaluated by measurement of serum creatinine and phosphate levels. CVC was evaluated on Von Kossa stained thoracic aorta tissue sections and by measurement of the total Ca content of the heart, abdominal aorta and a. carotis by atomic absorption spectrometry. Bone samples were analyzed by quantitative bone histomorphometry.

Results: Mortality rate was limited (≤1 animal/group). CKD developed to a similar extent in all groups. In the thoracic aorta, significantly lower Von Kossa positivity (area%) was measured in the INS-3001 group (50mg/kg) compared to the vehicle group (2.7±6.0 vs 14.5±15.1 %). Total Ca content of the abdominal aorta was also significantly lower in the INS-3001 (50mg/kg) group compared to the vehicle group (1.7±1.8 vs 14.5±13.9 mg/g tissue). Similar reductions in total Ca content were seen in the a. carotis and the heart. Quantitative bone histomorphometric analysis in vehicle treated rats showed a tremendously increased (not quantifiable) bone turnover. INS-3001 treated animals showed a significant increase in the bone area % (of total tissue area) compared to vehicles (42.3±14.6 vs 15.5±7.0 %). Neither osteoclast nor osteoblast morphology was affected.

Conclusions: In conclusion, INS-3001 is a promising molecule for the treatment of CKD induced CVC. Effects on bone have to be further investigated in a model with physiological bone turnover.

Funding: Commercial Support - Inositec AG, Switzerland

TH-PO516

Intravenous FGF-23 Loading Exacerbates Heart Failure with Preserved Ejection Fraction

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Background: The fact that FGF23 has an association with cardiovascular disease raises the question of whether it may not only be a biomarker of altered mineral metabolism and cardiovascular disease, but a therapeutic target. Herein, we studied the effect of continuous intravenous loading of FGF23 on mice of heart failure with preserved ejection fraction (HFpEF) model.

Methods: We used the deoxycorticosterone acetate (DOCA)-salt mouse model, which demonstrates mild hypertension and HFpEF. At the post-DOCA implantation day 7 mice were divided into two groups that received vehicle (DOCA+V) or FGF23 (DOCA+F) solution intravenously via a microinfusion pump for 10 days. Wild type mice were used as a control.

Results: Serum creatinine levels were comparable between the DOCA+F and the DOCA+V. Serum phosphorus levels were slightly increased in the DOCA+V compared with the control, whereas the levels remained normal in the DOCA+F. Serum FGF23 levels were slightly increased in the DOCA+V (249 pg/ml) compared with the control (51 pg/ml) and this increase was further amplified in the DOCA+F (1416 pg/ml). The heart weights were equal and significantly increased in the DOCA+V and the DOCA+F compared with the control. The DOCA+V (EF, 56%, E/A 1.0) showed HFpEF pattern, which was exacerbated in the DOCA+F (EF, 52%, E/A 0.7) assessed by echocardiography. Cardiac type I and type III collagen mRNA expressions were significantly increased in the DOCA+F compared with the control. Myocardial diameter was comparable between the DOCA+V (0.27 μm) and the DOCA+F (0.26 μm), whereas cardiac fibrosis was obvious in the DOCA+F (13,2 %) compared with the DOCA+V (7.0 %).

Conclusions: These results suggest that extremely high FGF23 levels have a crucial role in cardiac fibrosis which exacerbates HFpEF.

TH-PO517

The New RANKL Receptor LGR4 Regulates Vascular Smooth Muscle Cell Calcification in CKD

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Background: PTH is a main regulator of RANKL and OPG in bone remodeling. These 3 molecules have a well-known role in vascular calcification (VC). Due to controversies in the direct role of PTH in VC and the discovery of leucine-rich repeat-containing G-protein-coupled receptor 4 (LGR4) as a new RANKL receptor, we analyzed LGR4 involvement in VC in chronic kidney disease (CKD).

Methods: *In vivo*: We analyzed LGR4, RANK, RANKL and OPG gene expression and aortic calcium content ijn CKD rats fed for 14 weeks a normal phosphorus (0.6% -NP-) or a high phosphorus(0.9% -HP-) diet with or without parathyroidectomy (PTX) and PTH 1-34 supplementation aiming to normalize PTH. Rats with normal renal function fed a NP diet were used as reference. *In vitro*: We analyzed LGR4, RANK, RANKL and OPG expression and calcium content in vascular smooth muscle cells (VSMC) from rat aortas exposed to 3 different culture media (control, calcifying or calcifying plus 10-7/10-9M PTH). To characterize the pathways involved in calcification, the same parameters were examined in VSMC upon silencing of LGR4 or PTH1R (main PTH receptor) or after incubation with specific protein kinase (PK) A or PKC inhibitors, or with forskolin, a specific PKA agonist.

Results: CKD significantly increased aortic LGR4 and RANKL mRNA expression and decreased OPG, increasing aortic calcium content. These changes were greater in the group with higher PTH (CKD-HP) and were prevented by PTX. There were no changes in RANK expression under any of the experimental conditions. In VSMC, 10-7M PTH, but not 10-9M PTH, increased LGR4 and RANKL, reduced OPG expression with increases in calcium content. LGR4 and PTH1R silencing significantly attenuated the increases in calcium content induced by 10-7M PTH. Furthermore, silencing of PTH1R and PKA inhibition, but not PKC inhibition, prevented the increases in RANKL and LGR4 and OPG reduction. Exposure to forskolin corroborated these results.

Conclusions: In CKD, high PTH increases the aortic expression of LGR4 receptor and its ligand RANKL and decreases OPG inducing VC. These PTH actions in VSMC involve binding to PTH1R and PKA activation. Thus, LGR4 was identified for the first time as a pro-calcifying factor of VSMC in CKD.

Funding: Government Support - Non-U.S.

TH-PO518

Increases in Osteocyte RANKL Correspond with Elevated Cortical Porosity in Adenine-Induced CKD

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Background: Chronic kidney disease (CKD) increases bone fragility and fracture incidence. Bone loss in CKD preferentially occurs within the cortical bone through the development of porosity. For cortical pores to form, osteoclasts must be recruited into the cortex to locally induce bone resorption. Receptor activator of nuclear factor KB ligand (RANKL) is a key osteoclastogenesis regulator that is released by various cells within bone including osteocytes. We hypothesized that elevated cortical osteocyte RANKL coincides with the development of cortical pores in adenine-induced CKD.

Methods: Female C57BL/6J mice (8-wk-old) were fed a casein-based diet (0.9% P, 0.6% Ca) with 0.2% adenine (Ad) to induce CKD. Age-matched controls (Con) were fed the same casein-based diet without adenine. Mice were terminated after 2, 6, and 10 weeks.

Results: Serum blood urea nitrogen was elevated at all time points in Ad vs. Con confirming the induction of kidney disease. MicroCT of the distal 1/3 shaft of the femur demonstrated that Ad mice had porosity not different from Con at 2 weeks, mild cortical porosity at 6 weeks (1.9%; p<0.001 vs Con), and a greater average porosity at 10 weeks (4.1%, p=0.01 vs Con). At 2 weeks, the percentage of cortical osteocytes in the femoral shaft that stained positive for RANKL (%RANKL+) was 20% higher in Ad vs. Con while at 6 and 10 weeks %RANKL+ osteocytes were 115% higher and 277% higher, respectively, compared to Con. A time-by-treatment statistical analysis indicated significant impact of Ad treatment and a time-by-treatment interaction effect whereby Con groups had decreasing %RANKL+ osteocytes with age and Ad groups maintained high %RANKL+ osteocytes with age. This indicates adenine-induced CKD increased osteocyte RANKL in younger animals as well as prevented age-related declines in osteocyte RANKL as animals age in the presence of disease.

Conclusions: In conclusion, we determined that both osteocyte RANKL and cortical porosity are elevated over time in adenine-induced CKD. We hypothesize in CKD osteocytes release RANKL signaling osteoclasts into the cortical bone leading to the development of cortical porosity. Future research should address the factors altered in CKD, such as elevated parathyroid hormone, which are responsible for stimulating osteocytes to produce RANKL.

Funding: Veterans Affairs Support

TH-PO519

Effect of Acute Peritonitis on Serum Fibroblast Growth Factor 23 in a Rat Model of CKD: Possible Interaction Between FGF-23 and Inflammation

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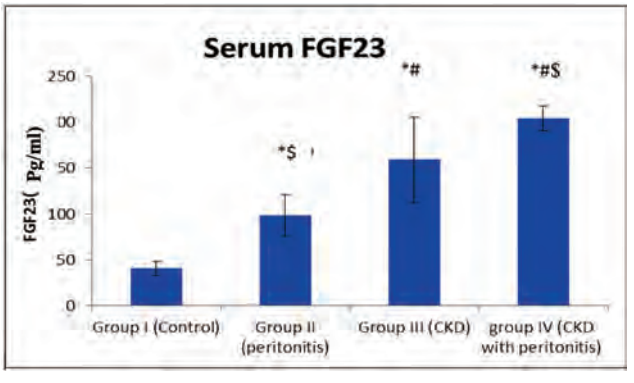
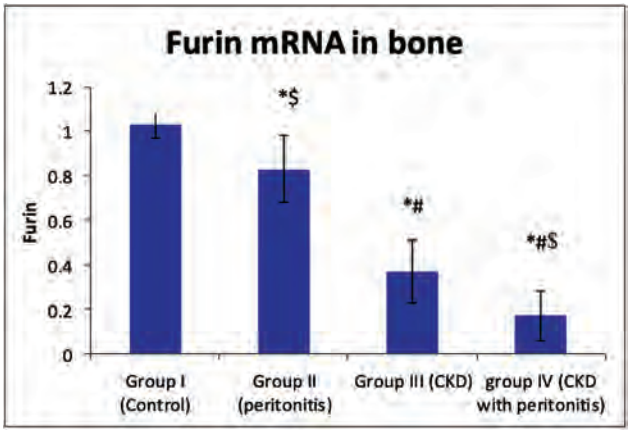
Background: Cardiovascular diseases are the leading cause of death among patients with chronic kidney disease (CKD). Fibroblast Growth Factor 23 (FGF- 23) has been associated with mortality among those patients and was found to correlate with different parameters of inflammation among them. The interaction between FGF- 23, uremia and inflammation is still under investigation.

Methods: 40 rats assigned to 4 groups: Control sham-operated, Acute peritonitis, CKD and CKD + acute peritonitis. Acute peritonitis and CKD were experimentally induced. Serum creatinine, phosphorus, iFGF23,Vit.D, TNFa, HsCRP and bone furin mRNA were compared between groups.

Results: Compared to the control group; FGF- 23 was significantly higher in both the CKD & the acute peritonitis groups. FGF 23 reached the highest level in the CKD with induced acute peritonitis group. Furin mRNA was significantly lower in both the CKD and the acute peritonitis groups compared to the control group and it reached its lowest levels in the group with induced CKD and peritonitis. FGF- 23 was positively correlated to serum creatinine, phosphorus, TNFa&CRP while it was negatively correlated to serum Vit.D & Furin mRNA.

Conclusions: Inflammation is a potent upregulator of iFGF23 and could be a main promoter of FGF23 excess early in CKD. Acute peritonitis on top of CKD amplifies the inflammatory states which could contribute to worsening the clinical outcomes. Increased serum iFGF23 in inflammation could be due to decrease its cleavage by furin pro-protein convertase enzyme.





TH-PO520

The Role of Mitochondrial Dysfunction in Matrix Vesicles (MV)-Induced Calcification of Recipient Vascular Smooth Muscle Cells (VSMC)

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Background: Oxidative stress is increased in patients with CKD and associated with vascular calcification. We have previously demonstrated that cellular derived MV, but not media derived MV, increase calcification of recipient normal rat VSMC in association with activation of mitogen activated protein kinase (MAPK), increased intracellular calcium $[Ca]_i$ derived from the endoplasmic reticulum (ER), and increased NADPH oxidase (NOX) 1 expression. We hypothesized that cellular MV induced generation of reactive oxygen species (ROS) from mitochondrial dysfunction in the recipient VSMC.

Methods: Ten ug of MV were co-cultured with recipient VSMC in calcification media (high phosphorus) for up to 7 days and alteration of ROS production examined by CellRox using confocal microscopy. Mitochondrial superoxide generation was determined by MitoROS. Direct mitochondrial respiration was measured by Seahorse XF Analyses. Mitochondrial contents of respiratory complexes was determined using total OXPHOS by Western blot. Some cultures were incubated with the NOX1/4 inhibitor GKT137831.

Results: MV increased ROS production by 146% at 24 h and continued to increase by 106% at day 7 in recipient VSMC during calcification. Incubation with GKT137831 reduced ROS production and decreased $[Ca]_i$ in recipient VSMC. We then determined if mitochondria dysregulation was the source of the increased ROS production in recipient VSMC. Adding MV had no effect on mitochondrial superoxide production or mitochondrial contents in recipient VSMC. Seahorse experiments demonstrated that there was no effect of MV on basal oxygen consumption (OCR), ATP production, maximal respiratory capacity or reserve respiratory capacity in recipient VSMC. These results suggest that MV-induced cytosolic ROS production is not due to mitochondrial dysfunction in recipient VSMC.

Conclusions: Cellular MV induce ROS production in recipient VSMC during calcification. However, this increased ROS is not mediated via mitochondrial dysfunction and thus likely represents a response to increased $[Ca]_i$ release from the ER and/or other cell signaling pathways. Further understanding the mechanism by which MV induce calcification of normal VSMC to propagate calcification is needed to facilitate the development of targeted therapies.

Funding: Other NIH Support - NIAMS, Veterans Affairs Support

TH-PO522

The Effect of PKD Gene Mutation on Bone

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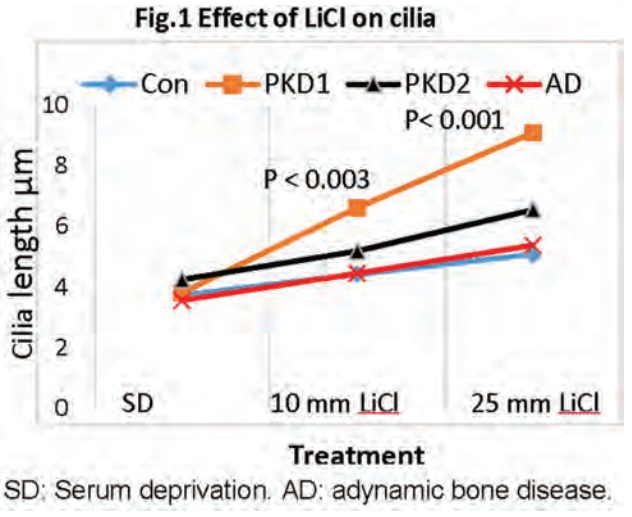
Background: Kidney cysts are an invariant feature of autosomal dominant polycystic kidney disease (ADPKD). However, patients with *PKD2* vs. *PKD1* mutations typically have milder disease. We showed previously that ADPKD patients with normal kidney function have a low turnover bone defect. The goal of the current study was to determine whether PKD gene mutations cause differential changes on osteoblast primary cilium structure or gene expression in osteoblasts.

Methods: Primary osteoblast cultures were established from human bone obtained by iliac crest bone biopsy. In order to visualize the primary cilium, cells were serum deprived to suppress cell division and treated with LiCl. The primary cilium was stained with anti-acetylated tubulin and the base with anti-pericentrin. Cilia length was measured on 200 -300 cells from each individual. RNAseq analysis was performed on RNA extracted from trabecular bone.

Results: Cilia on osteoblasts from ADPKD patients elongated more than those on healthy control osteoblasts in response to LiCl exposure and longer cilia were associated with PKD1 gene mutations (Figure 1). Elongation of osteoblast cilia from patients with other causes of adynamic bone disease did not differ from control cells, indicating that the gene mutation is responsible for the cilia abnormality in ADPKD. RNAseq analysis of bone from patients with PKD1 (N=12) or PKD2 (N=3) revealed decreased expression of several genes including COL1A2 and aggrecan proteoglycan (ACAN) in PKD1 compared to PKD2 bone.

Conclusions: PKD genotype affects both primary cilium structure and gene expression in bone from patients with ADPKD. Cilia structural abnormalities appear to be a result of the primary gene defect as they do not occur in patients with adynamic bone disease due to other causes.

Funding: NIDDK Support, Private Foundation Support



TH-PO523

Effect of Reduction of Bone Advanced Glycation End Products (AGE) Accumulation on Bone Mechanical Properties in a Rat Model of CKD-Mineral Bone Disorder (CKD-MBD)

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Background: Reduced bone quality is a key determinant of skeletal fragility in CKD. We have previously demonstrated that treatment with an AGE breaker ALT-711 decreased serum FGF23, reduced aorta expression of receptor for AGE (RAGE) and calcification in a rat model of CKD-MBD. We hypothesized that reduction in AGE accumulation and/or RAGE activation in bone will improve CKD-induced bone fragility.

Methods: Using a slowly progressive rat model of CKD, the Cy/+ rat, we compared four groups of animals [1: Normal (NL); 2: CKD; 3:CKD+ALT-711(3mg/kg); and 4: CKD+ 3% calcium in drinking water (Ca, lowering PTH and reducing bone remodeling). Treatment was started at 25 weeks of age (~50% kidney function) and ended at 35 weeks (~15% function). Bone AGE content was determined in demineralized femur shaft using fluorescence plate reader, normalized by collagen (hydroxyproline) content. Bone marrow (BM) were collected and RAGE expression determined by real time PCR. Bone geometry/architecture were determined with microCT. Bone mechanical properties were assessed by 4-point bending.

Results: There was increased AGE accumulation in bone and RAGE expression in BM in CKD rats vs. NL. Treatment with ALT-711 or calcium normalized both bone AGE levels and BM RAGE expression in CKD. MicroCT assessment of proximal tibial bone demonstrated lower trabecular bone volume fraction (BV/TV) in CKD rats. Calcium but not ALT-711 treatment increased trabecular BV/TV in CKD rats. CKD rats also had higher cortical porosity compared to NL and ALT-711 or calcium treatment each significantly reduced the cortical porosity in CKD rats. Bone mechanical analysis demonstrated that while several properties were lower in CKD rats, calcium, but not ALT-711 treatment, normalized these mechanical properties in CKD rats.

Conclusions: There is increased AGE accumulation in bone and RAGE expression in BM from CKD rats. Treatment with the AGE breaker ALT-711 early in the course of CKD decreased bone AGE levels and RAGE expression in BM in association with reduction in cortical porosity but without improvement of bone mechanics. Calcium treatment (which lowers PTH) showed similar bone efficacy to ALT-711 but increased serum levels of calcium and FGF23.

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TH-PO524

Bone Assessment by High-Resolution Peripheral Quantitative Computed Tomography in Premenopausal Stone-Forming (SF) Women

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Background: Nephrolithiasis has been associated to low bone mineral density (BMD). Bone assessment by Dual-energy X-ray absorptiometry (DXA) is widely used in clinical practice but has limitations as it only measures areal BMD (aBMD). New non-invasive technologies such as high-resolution peripheral quantitative computed tomography (HR-pQCT) provides additional information regarding bone quality and microarchitecture.

Methods: Forty-four (44) stone-forming (SF) premenopausal women (33.4±9.2 years old) and 202 age-matched healthy premenopausal women (33.7±9.0 years old) were included. aBMD was analyzed by DXA and volumetric BMD (vBMD), structure and biomechanical parameters of the distal radius and tibia were assessed by HR-pQCT.

Results: SF presented a trend for lower aBMD versus controls at L1-L4 (0.979±0.115 vs 1.013±0.111 p=0.06) and significant lower aBMD at femoral neck (0.787±0.11 vs 0.826±0.118 p=0.02), total hip (0.896±0.116 vs 0.932±0.12 p =0.04) and distal radius (0.668±0.049 vs 0.686±0.047 p=0.03). As shown in Table 1, trabecular number (Tb.N) was significantly lower and trabelcular separation (Tb.Sp) was significantly higher in SF compared to controls at both sites. Trabecular vBMD at distal radius was also significantly lower in SF versus controls.

Conclusions: Premenopausal SF women presented lower areal BMD than controls. HR-pQCT further disclosed that the trabecular compartment possibly accounts for this finding, due to lower trabecular volumetric BMD at distal radius, lower trabecular number and increased trabecular separation at both distal radius and tibia. The underlying mechanism for these important alterations of bone quality in this population deserves further investigation.

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	TIBIA		DISTAL RADIUS	
HR-pQCT	Controls (N=202)	Stone-formers (N=44)	Controls (N=202)	Stone-formers (N=44)
Tt.vBMD (mgHA/cm³)	319 ±50	311 ±47	335 ±63	344 ±51
Tb.vBMD (mgHA/cm³)	162 ±35	153 ±25	173 ±31	163 ±27 *
Ct.vBMD (mgHA/cm³) (#)	1017 ±32	1016 ±26	1024 ±37	1034 ±33
Tb.N (1/mm)	1.78 ±0.33	1.69 ±0.28 *	2.05 ±0.27	1.88 ±0.23 **
Tb.Th (mm)	0.077 ±0.014	0.076 ±0.012	0.071 ±0.011	0.073 ±0.013
Tb.Sp (mm)	0.506 ±0.116	0.531 ±0.09 *	0.427 ±0.07	0.466 ±0.064 **
Ct.Th (mm) (#)	1.26 ±0.19	1.25 ±0.20	0.87 ±0.17	0.89 ±0.13

Tt.vBMD: total vBMD; Tb.vBMD: trabecular vBMD; Ct.vBMD: cortical vBMD; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation; Ct.Th: cortical thickness; (#) Advanced cortical analyses (N=96 controls); SF vs Controls: (*) p<0.05 (**) p<0.001

TH-PO525

Total Flavonoids of Astragalus Ameliorates Renal Injury-Related Mineral and Bone Metabolic Disorder in the CKD-MBD Model Rats by Regulating FGF23-Klotho Signaling Axis, Compared with Calcitriol

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Background: Recently, chronic kidney disease-mineral and bone disorder (CKD-MBD) has become one of serious complications occurring in the CKD patients. Hence, the development of a new treatment for CKD-MBD is very important in clinics. FGF23-Klotho signaling axis is a pivotal regulator of MBD in the CKD-MBD patients. Targeting FGF23-Klotho signaling axis in response to renal injury-related MBD has been thereby identified as the multi-targets in the treatment of CKD-MBD. In China, total flavonoids in the flower of *Abelmoschus manihot* (TFA), a natural extract has been frequently used to improve renal dysfunction in the CKD patients. But the potential mechanisms *in vivo* of TFA on renal injury-related MBD remained unclear. Here, we verified whether TFA could ameliorate renal injury-related MBD in the CKD-MBD model rats by targeting FGF23-Klotho signaling axis in the kidney, compared to calcitriol (CAL).

Methods: Twenty-eight rats were divided into 4 groups, the Sham, the Vehicle, the TFA and the CAL groups. The appropriate doses of TFA, CAL and distilled water were administrated with oral for 3 weeks after the induction of CKD-MBD by adenine-administration and mononephrectomy, respectively. The changes in parameters of renal injury and bone abnormality in urine, blood, bone and kidneys were analyzed. The kidney and femur bone were isolated for histomorphometry, immunohistochemistry and Western blot at sacrifice.

Results: For the CKD-MBD model rats, renal injury and bone abnormality were significantly revealed, and there was a potential connection between renal injury and bone abnormality. Moreover, TFA alleviated renal dysfunction and tubulointerstitial pathological changes, improved calcium-phosphorus metabolic disorder and bone lesion, and regulated FGF23-Klotho signaling axis and ERK1/2-SGK1-NHERF-1-NaPi2α pathway in the kidney. Notably these beneficial actions *in vivo* of TFA were markedly different from CAL.

Conclusions: We clarified that TFA, different from CAL, can improve renal injury and bone abnormality, and that, more importantly, these ameliorative effects on renal injury-related MBD are closely associated with the regulation of FGF23-Klotho signaling axis and ERK1/2-SGK1-NHERF-1-NaPi2α pathway in the kidney. This study provided the first evidence that TFA directly contributes to the prevention of CKD-MBD.

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TH-PO526

Increases in Circulating Granulocyte Neutral Sphingomyelinase 2 Expression in Dialysis Patients Correlate Directly with the Propensity for Vascular Calcification

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Background: Systemic inflammation is a risk factor for atherosclerosis and vascular calcification in the general population and in chronic kidney disease (CKD) patients. Because increases in neutral sphyngomyelinase 2 (nSMase2) are essential for the severity of age-induced inflammation in health and atherosclerosis in the ApoE null mouse and contribute to initiate medial calcification in uremia, this study evaluated whether leukocyte gene expression of nSMase2 and its inducer in the vasculature, TNFα, could estimate the propensity for vascular calcification.

Methods: Peripheral blood mononuclear cells (PBMC) and granulocytes, from 28 peritoneal dialysis (PD) patients and 16 normal adults, matched for age and gender, were obtained from fresh blood using Fycoll gradient. A lumbar X-ray measured Kauppila index (KI) to estimate subclinical (KI<5) or clinical (KI>5) risk for vascular calcification (VC).

Results: In adults older than 40 with normal renal function, PBMC TNFα mRNA levels correlated directly with age ($r=0.61$; $p<0.05$; $n=10$), a risk factor for vascular damage. Furthermore, PBMC TNFα increased by 52% in peritoneal dialysis patients ($p<0.03$) compared to controls and, similar to the vasculature, PBMC nSMase2 gene expression increased in parallel with the elevations in TNFα in both healthy adults ($r=0.57$; $p<0.02$; $n=16$) and PD patients ($r=0.56$; $p<0.01$; $n=28$). In circulating granulocytes, TNFα was also 2-fold higher in PD patients, but with levels 2.2-fold lower than those in PBMC, even in normal controls. Significantly, the increases in granulocyte nSMase2 correlated directly with KI>5 ($r=0.65$; $p<0.05$; $n=11$), a recognized biomarker of the clinical risk for vascular calcification, but not with TNFα.

Conclusions: While in PBMC, the higher TNFα mRNA levels correlating with increases in nSMase2 may estimate the degree of systemic inflammation, the increased granulocyte nSMase2 gene expression appear sufficient to reflect VC risk.

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TH-PO527

Analysis of Cortical Bone Transcriptome Reveals Suppression of Bone Formation Pathways by Iron Therapy in Experimental CKD

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Background: Iron has been implicated in bone physiology and bone disorders. Most anemic patients with CKD require iron therapy. Iron excess has been shown to cause loss of bone mass in patients without CKD. However, the effects of iron therapy on the pathways underlying development of CKD-MBD remain largely unknown.

Methods: CKD was induced in mice by a 0.2% adenine diet, starting at 3 weeks of age. Femurs, kidneys, and blood were harvested at 3- and 8-week time-points in 4 groups of mice: - CTR: controls without CKD - CKDnoFe: untreated CKD - CKDPOFe: CKD + 0.5% carbonyl iron diet - CKDIPFe: CKD + weekly intraperitoneal injections of iron dextran, 0.5g/kg Femurs were analyzed by micro-CT and histology. RNA was extracted from femur diaphyses harvested at 3 weeks. RNA sequencing was performed on Illumina HiSeq4000 with single-end 50 bps and analyzed using STAR (V2.5.2) and DESeq2 package.

Results: By 3 weeks of experimental period, CKDnoFe mice developed renal injury and fibrosis and were mildly anemic. CKDPOFe and CKDIPFe mice did not have anemia at 3 weeks. No changes in bone microarchitecture were yet detected at 3 weeks in any group. At 8 weeks, CKDnoFe mice displayed progression of anemia and loss of the cortical bone volume. Compared to the CKDnoFe group, CKDPOFe and CKDIPFe mice had milder anemia, but more severe bone loss at 8 weeks. The expression of genes implicated in both bone formation (*Wnt16*, *Wnt2b*, *Dmp1*, *Mmp13*, *Spp1*, *Ank*) and bone resorption (*Ctsk*, *Acp5*, *Calcr*, *Clcn7*, *Slc4a2*) was higher in CKDnoFe than in CTR, consistent with increased bone turnover. In CKDPOFe and CKDIPFe groups, the expression of genes implicated in bone formation was lower than in CKDnoFe. At the same time, the expression of osteoclast genes associated with bone resorption was similar between CKDnoFe, CKDPOFE, and CKDIPFe groups.

Conclusions: In this model of CKD, both oral and parenteral iron therapy affected bone transcriptome before changes in bone microarchitecture. These transcriptional effects of iron, consistent with the suppression of bone formation pathways, without a corresponding effect on bone resorption pathways, likely represent early events in the process of bone loss associated with iron therapy in CKD. Our findings warrant attention to the potential unrecognized effects of iron on bone health in patients with CKD.

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TH-PO528

$25(OH)D_3$ Alone Stimulates Expression of $1,25(OH)_2D_3$-Responsive Genes, Calbindin-D9K, and Megalin in mpkDCT Cells Where the Cyp27b1 Gene Was Deleted by CRISPR-Cas9

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Background: During vitamin D synthesis, $25(OH)D_3$ (25D3) is converted to the active form, $1,25(OH)_2D_3$ (1,25D3), by CYP27B1 in the proximal tubule of the kidney, then the latter exerts its function via vitamin D3 receptor (VDR). In the kidney, the 1,25D3-VDR axis is responsible for the increase in calcium reabsorption. Recently, it has been reported that 25D3 has bioactivity in certain tissues derived from *Cyp27b1* knockout mice. On the other hand, others reported that 25D3-fed *Cyp27b1* knockout mice produced normal level of 1,25D3 in the plasma. Such 1,25D3 might have been brought about by the other unknown enzyme(s) and it would be difficult to prove the direct cell-intrinsic activity of 25D3 (but not 1,25D3) using the *Cyp27b1* knockout mouse models.

Methods: We used CRISPR-Cas9 system to knock out *Cyp27b1* gene in the mouse kidney distal tubule cell line, mpkDCT cells. We then investigated the 25D3 function in these cells.

Results: *Cyp27b1* knockout mpkDCT cells did not produce any measurable 1,25D3 after 25D3 administration to the cells. We found that 10^{-7} M of 25D3 translocated VDR into the nucleus and promoted expression of the positive control *Cyp24a1* gene in the *Cyp27b1* knockout mpkDCT cells. Microarray analysis also revealed that the exhaustive target gene profiles of 25D3 showed results similar to those of 1,25D3. Subsequently, we confirmed that 25D3 induced the expression of calcium reabsorption-related genes, Calbindin D9K (*S100g*) and Megalin (*Lrp2*), in the way analogous to 1,25D3.

Conclusions: In this study, we showed that a high dose(s) of 25D3 exerted vitamin D3 activity directly in the kidney cells without the aid of CYP27B1 function. We surmise that the ability to induce VDR target genes may provide a novel benefit with 25D3 in certain tissues. In the case of decreased CYP27B1 activity in advanced CKD, high concentrations of 25D3 may have a promising effect to maintain the serum calcium level.

TH-PO529

Increased Subset of Low-Density Granulocytes in Dialysis Patients Associated with the Degree of Abdominal Aorta Calcification

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Background: Although systemic inflammation increases the risk for adverse vascular outcomes in chronic kidney disease (CKD), the exact players remain unclear. The emerging evidence of the relevance of low density granulocytes (LDGs) in inflammatory conditions led us to evaluate whether LDGs may be associated with inflammatory/pro-calcifying features in CKD.

Methods: LDGs subsets were identified by flow cytometry in peripheral blood mononuclear cells (PBMCs) from 33 CKD patients undergoing peritoneal dialysis and 15 healthy controls (HC). An additional cohort of 16 CKD patients undergoing hemodialysis and 6 HC was recruited for replication. Defensin3a (DEF3a, a marker of early granulopoiesis) gene expression on PBMCs was quantified by qPCR.

Results: Total LDGs (CD15+) and both CD14lowCD16+ and CD14-CD16- subsets were increased in CKD. The relative frequency of the CD14-CD16- subpopulation among the total CD15+ pool was increased in CKD. Both LDG subsets differed in origin and maturation status as demonstrated by their CD11b, CD31, CD62L, Interferon receptor 1 (IFNAR1) and CD68 expression and size/granularity (FSC/SSC) features. LDGs subsets were not associated with parameters of bone and mineral metabolism, time on dialysis, serum cytokines or treatments. The increased CD14-CD16-CD15+ correlated directly with Kauppila scores and DEF3a expression in PBMCs, whereas no association was found with CD14lowCD16+CD15+.

Conclusions: CKD is associated with elevated LDGs, showing a skewed distribution towards a CD14-CD16-CD15+ enrichment in blood which correlated with vascular calcification. DEF3a expression in PBMC could be a marker of LDG expansion. These findings support an unprecedented role for LDGs in CKD immunopathogenesis.

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TH-PO530

Macrophage Migrasomes Is a Crucial Determinant of Subcutaneous Microvascular Calcifications in Patients with Calciphylaxis

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Background: Calciphylaxis is rare syndrome in hemodialysis patients who typically manifest as subcutaneous microvascular calcifications. Macrophage has been proposed to a prime mediator of calciphylaxis. However, the pathogenesis remains unclear. Here, we document that macrophage produce a previously unrecognized nanostructures called "migrasomes" (M-mig), which involve in microvascular calcifications in calciphylaxis.

Methods: Skin biopsy specimens from patients with calciphylaxis (n=34) were collected. The possible relation between M-mig and subcutaneous microvascular calcifications was studied. The stray artery from experimental mice were treated with M-mig under high Ca/P stimulation or hemodialysis patient· serum. The calcifying M-mig were assessed by TEM, Energy dispersive spectroscopy and Fluo-3 staining.

Results: Ultrastructural analysis revealed that macrophage produce a previously unrecognized nanostructures called M-mig (A. arrow) that originate from the filament like fibers (A. triangle). Pathology of skin biopsy surprisingly showed that macrophages infiltration (C. brown) was adjacent to the calcium deposition (D. green) in subcutaneous arteries which were rich in M-mig. Subsequently, TEM imaging revealed that mineral deposit in or on membrane of M-mig (B. asterisk). In murine model, when the stray artery incubated with M-mig under high level Ca/P or hemodialysis patient· serum, notablely, some mineral crystal enveloped M-mig and penetrated into inner lumen of the vascular wall, where microcalcifications deposition were observed by fine Fluo-3 staining. The microcalcifications were approved to correlation with calcific M-mig. In vitro, calcific M-mig showed a shift to larger size over time under high level Ca/P. Our study strongly suggests that M-mig could serve as the nucleating foci for mineralization and calcific M-mig initiates the microcalcification.

Conclusions: Our study documents that macrophages produce a formerly unrecognized nanostructure M-mig which involves in vascular microcalcifications. The discovery highlights the contribution of macrophages to vascular calcifications via M-mig and provides clues to the pathogenesis of calciphylaxis.

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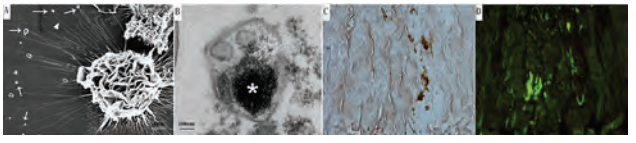

TH-PO531

Evidence of Circadian Rhythm of Plasma Activin A, Its Disturbance by CKD, and Contribution of Activin A Secreted from Injured Kidney

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Background: Activin A is an interesting new factor in CKD-MBD. It is a member of the TGF-β family, essential in kidney development and repair. Increased systemic activin A might be a biomarker of CKD-MBD that can be targeted for CKD-MBD prevention and therapy. Disrupted circadian rhythm (CR) causes detrimental health effects and CRs are observed in mineral metabolism. Our hypothesis is that increase in circulating levels of activin A is associated with disruption of circadian rhythm of plasma activin A, and parameters of mineral homeostasis in CKD.

Methods: CRs of activin A (pg/ml), FGF23 (pg/ml), PTH (pg/ml) and P (mM) were measured every 6th hour in control (Ctr) and CKD rats (5/6 nephrectomy) on low (LP), standard (SP), and high phosphate (HP) diet (N=8-26). Isolated renal vein and artery sampling was performed in kidney injury rats (14 days unilateral ureter obstruction, UUO) and healthy Ctr.

Results: Activin A was 2.5-fold higher in renal vein compared to artery in UUO (V:246±22, A:100%, $p<0.05$) but unaltered in Ctr (V:100±6, A:100%, ns) indicating renal secretion in kidney injury. Plasma activin A exhibited CR in Ctr ($p<0.01$ by cosinor analysis) with 300% higher values at acrophase (437±59) compared to nadir (106±7) ($p<0.05$). CKD obliterated the CR of activin A. Plasma FGF23 showed CR in Ctr ($p<0.05$) with peak at 14:00 (877±42), while the CR was obliterated in CKD rats on LP and SP even though FGF23 was suppressed in CKD LP ($p<0.05$). In CKD HP FGF23 was increased ($p<0.01$) and the CR was disturbed with shift in acrophase to 09:00 (4173±316). Plasma PTH exhibited CR in Ctr ($p<0.0001$), while the rhythm was disturbed in CKD ($p<0.05$) despite prevention of sHPT in CKD LP ($p<0.05$). Plasma P showed CR in all groups ($p<0.05$). However, the CR was disturbed in all CKD groups with shift in acrophase from 16:00 in Ctr to 19:00 (LP), 17:00 (SP), and 00:00 (HP).

Conclusions: Existence of a circadian rhythm of circulating activin A is established for the first time. The rhythmicity of activin A is disturbed in CKD rats and is associated with disturbed circadian rhythms of P and P regulating hormones PTH and FGF23. In injured kidney activin A is induced and secreted to venous effluent which can contribute to the disturbed circadian rhythm of activin A in uremia.

TH-PO532

An Internal Molecular Circadian Clock Operates in the Parathyroid Gland and Is Disturbed in CKD

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Background: Parathyroid hormone (PTH) secretion exhibits a well-known circadian rhythmicity (CR) which is disturbed in secondary hyperparathyroidism (sHPT). The mechanism behind the CR of PTH is, however, unknown and not correlated to the CRs of calcium (Ca) and phosphate (P). Furthermore, the parathyroid gland is not controlled by a superior "hypothalamic-pituitary axis". The possible existence of a molecular circadian clock in the parathyroid cell has not previously been examined.

Methods: Normal male Wistar rats were kept in 12h:12h light:dark cycle and fed *ad libitum*. Parathyroid glands were harvested with 4 hours interval for 24 hours, along with plasma samples for PTH (pg/ml), P (mM), total Calcium (mM), Urea (mM) and Creatinine (μM). (N=38; 6 per timepoint). Gene expression was examined by qPCR analysis. sHPT was induced by 5/6 nephrectomy and high phosphorus diet for 24 weeks. (N=10 and 16 age-matched controls).

Results: Parathyroid glands showed clear expression of core molecular clock genes: *Bmal1*, *Clock*, *Per1-3*, *Cry1-2* and *Rev-Erbα*. The circadian rhythmicity was examined by cosinor analysis fitted to a period of 24h and was significant for *Bmal1* ($p<0.0001$), *Per2* ($p<0.0001$), *Per3* ($p<0.0001$), *Cry1* ($p<0.0001$), *Cry2* ($p=0.002$) and *Rev-Erbα* ($p<0.0001$). Significant rhythmicity was also found for the cell cycle gene *Cyclin D1* ($p=0.003$). In parathyroid glands from uremic rats, downregulation of *Clock* (1.61±0.38 vs. 4.19±1.21, $p=0.041$) was found, as well as circadian clock output gene *CSNK1ε* (1.05±0.24 vs. 2.27±0.34, $p=0.047$). Also cell cycle gene *Cyclin D1* was downregulated in uremic rats (1.20±0.24 vs. 3.36±0.73, $p=0.041$).

Conclusions: The existence of a parathyroid molecular circadian clock is demonstrated for the first time. The expression of the parathyroid circadian clock genes is disturbed in uremic parathyroid glands, which potentially can contribute to the disturbed circadian rhythmicity of circulating PTH and to the development of parathyroid hyperplasia in uremia.

TH-PO533

Possible Clinical Relevance of Growth Hormone-Stimulated α-Klotho Upregulation

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Background: An aging suppressor protein, α-Klotho, known as a key factor for calcium-phosphorus homeostasis, is believed to have diverse physiological properties, because its global genetic deletion animal model shows short-stature and multi-organ dysfunction, resulting in early death. Interestingly, recent studies suggest that pituitary function plays an intriguing role, because growth hormone (GH)-producing pituitary adenoma significantly upregulates systemic α-Klotho levels. In end stage kidney disease (ESKD), growth spurt of pediatric patients is disturbed and often GH-resistant, whereas adult bone mineral disorder remains an unsolved clinical entity.

Methods: To elucidate the magnitude of GH/α-Klotho axis on both pituitary and bone-mineral reaction, we performed experiments involving GH administration to wild-type mice and adenine-induced kidney failure mice. GH was intraperitoneally given to 4-week-old male mice (C57BL/6J). We examined α-klotho mRNA expression, quantified by RT-PCR, in the pituitary gland and cancellous bones of mice with or without kidney dysfunction. Additionally, we performed immunohistochemistry (IHC) analysis of α-Klotho expression, surgically obtained from patients with pituitary adenomas.

Results: Exogenous GH increased α-klotho mRNA levels in the pituitary, and more robustly in cancellous bones. Strikingly, kidney failure cancelled GH-induced α-klotho expression in the pituitary and trabecular bones. Unexpectedly, GH administration induced modest α-klotho mRNA expression and markedly increased urinary excretion of soluble α-Klotho in wild-type mice, suggesting that GH triggers systemic circulation of α-Klotho in the bloodstream. IHC results indicated that pituitary GH-producing adenomas expressed α-Klotho more strongly than other (ACTH-producing, TSH-producing, or non-functioning) adenomas.

Conclusions: Established chronic kidney disease causes bone mineral disease, possibly by disrupting GH/α-Klotho axis. GH supplementation alone fails to catch up bone growth in juvenile patients with ESKD partly because of disrupted GH-triggered α-Klotho upregulation. Its stimulation might be a treatment option for patients with refractory bone and mineral disorders in ESKD. Organ-specific activation of GH/α-Klotho pathway might be a therapeutic target for restoring each organ function, leading to ideal organ rejuvenation and longevity.

Funding: Private Foundation Support

TH-PO534

Pin1 Isomerase Activity Determines PTH Gene Expression in Uremic Secondary Hyperparathyroidism

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Background: Secondary hyperparathyroidism (SHP) is a common complication of CKD that correlates with morbidity and mortality. In experimental SHP there is increased PTH secretion, gene expression and parathyroid cell proliferation. The high PTH gene expression is due to increased PTH mRNA stability mediated by the balanced protein-PTH mRNA interaction of AUF1 (AU-rich binding protein 1) that stabilizes and KSRP (K-homology splicing regulatory protein) that destabilizes PTH mRNA. Pin1 binds to and isomerizes phosphorylated Ser/Thr-Pro motifs in target proteins, including mRNA binding proteins. Pin1-KSRP interaction leads to dephosphorylation of KSRP at Ser181 that then binds to PTH mRNA with higher affinity to induce PTH mRNA decay. In SHP, Pin1 isomerase activity is decreased and phosphorylated KSRP fails to bind PTH mRNA, resulting in increased PTH mRNA stability and levels. Pin1 activity is regulated by phosphorylation at Ser16 and Ser71 that disrupts its interaction with target proteins and catalytic isomerase activity.

Methods: We performed proteome and phospho-proteome analysis of parathyroids from normal and adenine high phosphorus induced CKD rats. Pin1 phosphorylation was demonstrated by immunofluorescence staining. The PKA activator forskolin or PKA inhibitor H89 were added to mouse thyroparathyroid glands in culture or HEK293 cells transfected with a PTH expression plasmid. Secreted PTH was measured by Elisa and mRNA levels by qRT-PCR.

Results: Phospho-proteome analysis confirmed KSRP hyper-phosphorylation in parathyroids of SHP rats, that would prevent PTH mRNA-KSRP binding and decay. It also identified new Pin1 targets and signaling pathways. Phosphorylation of both Pin1 Ser16 and Ser71 was increased in parathyroids of SHP rats, correlating with the decreased Pin1 activity. Accordingly, parathyroid extracts from SHP rats showed increased in vitro phosphorylation activity towards recombinant GST-Pin1. PKA activation, that leads to Pin1 Ser16 phosphorylation, increased PTH secretion in parathyroid organ cultures and PTH mRNA in transfected HEK293 cells. PKA inhibition had the opposite effect.

Conclusions: Pin1 activity is central to the pathogenesis of SHP by orchestrating PTH mRNA-protein interaction and thus mRNA decay. The resulting increased PTH mRNA stability leads to the high serum PTH levels in SHP.

Funding: Government Support - Non-U.S.

TH-PO535

Novel Calcimimetic and Calcilytic Activity of Dietary Plant Polyphenols

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Background: Plant-derived polyphenols have diverse medicinal effects involving multiple signaling pathways. With grapes reportedly improving human bone mass and associated with hypercalcemia in certain dogs, we hypothesized a new mechanism involving the calcium sensing receptor (CaSR): some compounds being calcilytic, others calcimimetic. We study CaSR and species-specific effects of plant-derived polyphenols in human and canine cells.

Methods: CaSR modulation by polyphenols was studied in pCMV-human-CaSR plasmid transfected human HEK293T cells and canine MDCK Type II cells using dual luciferase reporter (DLR) and Fura-2AM ratiometric calcium dye assays, respectively, for grape seed and pomace extracts (GSE, GPE) and plant-derived polyphenols cyanidin-3-sophoroside (C3S), cyanidin-3-glucoside (C3G), delphinidin-3-O-glucoside, procyanidin B2, kaempferol 3-β-D-glucopyranoside and resveratrol. DLR assays in HEK293T cells used 1μg/mL GSEs, GPEs or polyphenols over 65h. Live intracellular MDCK calcium imaging via Fura-2AM was studied over six minutes with 5μM of each polyphenolic compound in 1.0 then 3.0 mM Ca^{2+} media to assess calcimimetic or calcilytic activity. Cinacalcet was a positive calcimimetic control and was tested to rescue grape calcilytic activity. YM-254890 was a control for blocking the CaSR pathway.

Results: In HEK293T cells 1μg/mL GSE and GPE were calcimimetic (raising intracellular Ca^{2+}), while the individual polyphenols C3G and C3S were calcilytic in both species. Cinacalcet inhibited the polyphenol-induced calcilytic effects. Surprisingly NPS-2143, a human calcilytic, was a calcimimetic in dogs.

Conclusions: This is the first evidence that polyphenols found in common foods affect calcium signaling by CaSR modulation and have species-specific calcimimetic or calcilytic properties. From preliminary data for grape extracts and individual polyphenolic compounds, we conclude that 1) these mechanisms explain how naturally-derived nutraceutical compounds may influence both human and canine medicine; 2) may provide the, heretofore, unexplained mechanism of lethal grape toxicity in dogs which 3) could lead to the development of antidotes that target the CaSR. In addition, elucidation of the active chemical moieties could guide therapeutic nutraceutical development for human bone mineral metabolism disorders.

TH-PO536

Cell Cycle Acceleration in Parathyroid Glands Is Caused by the Combination of CKD Environment and High-Phosphorus Diet in the Adenine Rat Model Because of Suppression of CDKN1B Expression

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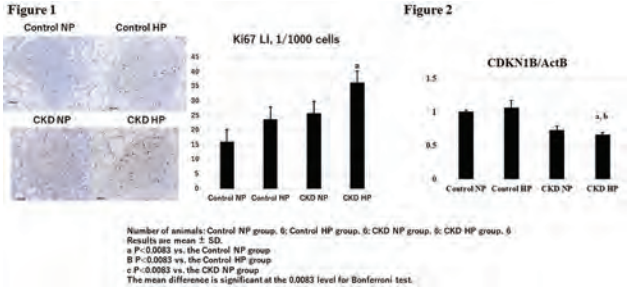
Background: Chronic kidney disease (CKD) disrupts mineral homeostasis and is characterized by secondary hyperparathyroidism (SHPT). SHPT is characterized by abnormally increased proliferation of parathyroid cells, although the underlying mechanism remains largely unknown. Previously, we reported that an increase in Ki67 immunohistochemical expression was observed in 5/6 nephrectomy rats fed the high phosphorus diet. The aim of this study was to investigate the role of the CKD environment with and without high-phosphorus diet in SHPT progression, particularly cell cycle acceleration in the parathyroid glands.

Methods: CKD was induced by a diet containing 0.75% adenine. For 2 weeks, few CKD rats and few control rats were fed diets containing 0.9% phosphorus (normal phosphate diet); other CKD rats and control rats were fed diets containing 1.3% phosphorus (high-phosphate diet). In a gene expression analysis related with cell cycle, such as *CDKs*, *CKIs* and *cyclins*, TaqMan probes were used to conduct quantitative polymerase chain reactions. Ki67 and cyclin-Dependent kinase inhibitor 1B (CDKN1B) protein expressions were analyzed immunohistochemically.

Results: Among the CKD rats, there was no significant difference in severity of CKD status between those fed the normal phosphorus diets (CKD NP rats) and those fed the high-phosphorus diets (CKD HP rats); however, the increase in Ki67 immunohistochemical expression in cells was observed in only CKD HP rats (Figure 1). Thus, SHPT and severe CKD-mineral and bone disorder status were induced only by high-phosphorus diets in CKD rats. CDKN1B expression, which plays an important role in the G1/S checkpoint, was significantly decreased only in CKD HP rats (Figure 2).

Conclusions: Only CKD HP rats showed a significant reduction in *CDKN1B* gene and protein expression. Our data indicated that CDKN1B plays a major role SHPT progression and cell cycle acceleration and is an important target in SHPT therapy.



TH-PO537

Dicer and MiRNA Deletion Leads to Ectopic Parathyroids

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Background: Ectopic parathyroid glands are a diagnostic and operative challenge in patients with hyperparathyroidism and are attributed to abnormal embryonic parathyroid migration. miRNA have vital roles in biology and development. The final step of miRNA maturation is mediated by Dicer. We have generated parathyroid specific Dicer knockout (PT-*Dicer*$^{-/-}$) mice to specifically delete parathyroid Dicer and miRNAs. The PT-*Dicer*$^{-/-}$ mice had normal basal serum PTH levels but an impaired increase in PTH in response to acute and chronic hypocalcemia and uremia. Parathyroid glands develop from the parathyroid-thymus common primordia and migrate to their adult location adjacent to the thyroid. We now show that in addition to parathyroid stimulation, Dicer and miRNA are central to parathyroid embryonic development.

Methods: We generated by cre lox recombination mice with parathyroid-specific Dicer knockout (PT-*Dicer*$^{-/-}$) and parathyroid specific YFP (PT-*YFP*), where the parathyroids can be identified under a fluorescence microscope. Mouse thyro/parathyroid histological slides were stained for PTH.

Results: Surprisingly, the parathyroid glands were absent in most thyroid sections of the PT-*Dicer*$^{-/-}$ mice, despite normal basal PTH. We identified ~75 % of parathyroids in control mice (n=45) but only ~20 % in PT-*Dicer*$^{-/-}$ and heterozygote PT-*Dice*$^{+/-}$ mice (n=63 and 14), most of which were small, some showing atypical follicular structures. Heterozygote PT-*Dicer*$^{+/-}$ mice also had an impaired increase in serum PTH after a low calcium diet, like homozygote PT-*Dicer*$^{-/-}$ mice, indicating that *Dicer* haplo-insufficiency abrogates the position of the parathyroid glands and parathyroid stimulation by hypocalcemia. To identify ectopic parathyroids in the PT-*Dicer*$^{-/-}$ mice, we generated parathyroid specific YFP (PT-*YFP*) mice. Unlike control PT-*YFP* mice, 80% of the PT-*Dicer*$^{-/-}$; *YFP* mice had no detectable parathyroid glands. Instead, there were small clusters of ectopic parathyroid cells scattered on the trachea. 20% of the PT-*Dicer*$^{-/-}$ mice had a single parathyroid gland

in the anterior mediastinum or adjacent to the thyroid. These findings explain the absence of parathyroids in thyroid sections of *Dicer*$^{-/-}$ mice and indicate that Dicer and miRNA are required for parathyroid differentiation and morphogenesis.

Conclusions: Parathyroid Dicer and miRNA are essential for development, migration, localization and function of the parathyroids.

Funding: Government Support - Non-U.S.

TH-PO538

Dietary Protein and Branched Chain Amino Acids Protect the Kidney from Phosphate Burden

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Background: Phosphate homeostasis is critically important for the maintenance of health. High phosphate intake has been reported to be harmful for the kidney. Although levels of dietary phosphate intake closely correlate with dietary protein intake, effects of dietary protein on phosphate toxicity remain uncertain.

Methods: Phosphate-induced chronic kidney disease (CKD) model were prepared by feeding a diet containing 2% phosphate to male Wistar rats for 6 weeks. Rats were randomly divided into 3 groups based on concomitant feeding of 12.5%, 25%, or 37.5% casein. Similar models were prepared by feeding ovalbumin instead of casein. We also analyzed effects of dietary branched chain amino acids (BCAA) on phosphate-induced kidney injury.

Results: Dietary casein suppressed serum levels of creatinine and phosphate, but elevated serum urea nitrogen, in a dose dependent manner. Dietary casein did not affect levels of food intake nor fecal phosphate. Although dietary casein elevated urinary protein in normal Wistar rats without phosphate burden, dietary casein did not increase urinary protein in phosphate-fed CKD rats. Both real time PCR and histological analyses revealed that dietary casein protected the kidney from phosphate-induced toxicity. Dietary casein maintained the mitochondrial integrity in tubular cells, and thereby suppressed oxidative stress. Ovalbumin showed even better renoprotective effects with unchanged serum urea nitrogen and suppressed urinary protein. To investigate underlying mechanisms of renoprotection by dietary proteins, we measured plasma amino acid levels and found that both dietary casein and ovalbumin elevated plasma valine, leucine, and isoleucine. Dietary supplementation of BCAA abrogated the toxic effects of phosphate to the kidney in a manner similar to that observed in ovalbumin-fed rats. Although dietary casein and ovalbumin increased water intake and urinary volume, BCAA affected neither of them.

Conclusions: Dietary protein protects the kidney from phosphate burden. BCAA supplementation may be even better way to suppress phosphate toxicity to the kidney.

Funding: Private Foundation Support

TH-PO539

Do You Know What Your Experimental Animals Eat?

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Background: Autoclaved diet use has been increasing in research animal facilities due to its ability to reduce infection. The high heat generated through autoclaving could have various effects on a diet. Our goal was to determine how autoclaved-induced increases in dietary advanced glycation end products (AGE) affect properties in a model of chronic kidney disease-mineral and bone disorder (CKD-MBD).

Methods: Cy/+ (CKD) rats and normal (NL) littermates were assigned to 1 of 3 diets: autoclaved 0.7% phosphorus grain-based diet for 28 wks (**AGEs**), autoclaved diet for 17wks followed by non-autoclaved 0.7% bioavailable phosphorus casein-based until 28 wks (**AGEs + Casein**), or a non-autoclaved diet for 17wks followed by a non-autoclaved casein-based diet (**non-AGEs+Casein**) until 28 wks. We examined kidney function, plasma biochemistries, and intestinal gene expression (phosphate transporters, the receptor for AGE (RAGE), and NADPH-oxidases). We assessed the effects of disease (CKD vs NL), diet, and the interaction by two-way ANOVA.

Results: Autoclaved diet contained 3.5-fold more of the AGE carboxymethyllysine and 2.5-fold more methylglyoxal than the non-autoclaved diet. There was a disease-by-diet interaction on the plasma DNA oxidation marker 8-OHdG, driven by differences between the NL and CKD rats fed the AGEs and AGEs + Casein diets. AGEs diet led to increased progression of CKD that was further augmented by the casein diet ($P_{interaction}$=0.03). There was a disease-by-diet interaction on phosphorus, PTH, and FGF23 driven by the higher values in the CKD rats fed the AGEs + casein diet ($P_{interaction}$<0.05 for all). At the intestinal level, NaPi2b was 2-fold higher in the rats fed the non-AGEs + casein diet (P_{diet}<0.0001). Intestinal RAGE was 2- to 4-fold higher in the rats fed the AGEs and AGEs + casein diets (P_{diet}<0.0001). This was mimicked by a higher expression of DUOX2 (P_{diet} = 0.0019).

Conclusions: Autoclaved diet contains higher levels of AGE and leads to increased systemic oxidative stress and more rapid progression of CKD-MBD phenotype if combined with a bioavailable phosphorus diet. Eating an autoclaved diet also altered intestinal transporters regulating AGE, NADPH-oxidases, and phosphate. These studies highlight the critical importance of dietary aspects, including autoclaving, in the study of CKD-MBD.

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TH-PO540

Intestinal Environmental Control and Renal Protection by Intestinal Alkaline Phosphatase (IAP)

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Background: Hyperphosphatemia is an independent risk factor for mortality, and prevention and correction of it is a major goal of the treatment of chronic kidney disease (CKD). Inorganic phosphate (Pi) balance is maintained by intestinal absorption, renal excretion, and bone accretion. Especially, the regulation of intestinal Pi absorption is an important target for the treatment of hyperphosphatemia. Intestinal alkaline phosphatase (IAP) is a brush border phosphomonoesterase that catalyzes the hydrolysis of nonspecific Pi ester bonds at an alkaline pH, and a plasma membrane-bound glycoprotein that dephosphorylates several substrates, including Pi additives. The relationship between IAP and Pi metabolism is not clear. We investigated whether intestinal alkaline phosphatase 3(Akp3), the enzyme that hydrolyzes dietary Pi compounds, is a target for the treatment of hyperphosphatemia in CKD.

Methods: We analyzed Pi homeostasis in Akp3 knockout mice (Akp3$^{-/-}$), and studied the progression of renal failure, and intestinal environment in an Akp3$^{-/-}$ renal failure model.

Results: In humans, rats, and mice, intestinal alkaline phosphatase (IAP, AKP3) is expressed throughout the gastrointestinal tract with the highest expression in the duodenum. Akp3$^{-/-}$ mice have high luminal ATP concentrations, which affects bacterial growth in the gut. Changes in the extracellular ATP concentration affected Pi transport. In the renal failure model, genetic deletion of Akp3 suppressed abnormal mineral homeostasis, progression of renal failure and inflammation of the intestinal and whole body in Akp3$^{+/+}$. As a result, Akp3$^{-/-}$ extended the life span compared to Akp3$^{+/+}$. In the Akp3$^{-/-}$ renal failure model, hyperphosphatemia was alleviated by suppression of intestinal Pi absorption via paracellular mechanisms as well as transcellular Pi transport.

Conclusions: Elucidation of the mechanism of suppression of renal disease progression confirmed by Akp3$^{-/-}$ could contribute to the development of a new CKD treatment.

Funding: Government Support - Non-U.S.

TH-PO541

PiT-2 Is the Main Transporter Responsible for Intestinal Phosphate Absorption in Human

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Background: In chronic kidney disease (CKD) patients, adequate management of hyperphosphatemia is critical. Phosphate is absorbed in the small intestine via passive and active transports. NaPi-IIb is thought to be the main transporter for the active route, but a selective NaPi-IIb inhibitor failed to ameliorate hyperphosphatemia in patients with CKD. Transporters besides NaPi-IIb are thought to contribute to active phosphate transport in humans.

Methods: We examined the protein expression levels of NaPi-IIb, PiT-1, and PiT-2 in the small intestine of humans and rats by mass spectrometry (LC-MS/MS). To evaluate the influence of kidney disease, these 3 transporters were also assessed in CKD/dialysis patients and CKD rat models. Phosphate metabolism including intestinal phosphate uptake was evaluated, and protein expression levels were compared in rats.

Results: In humans, intestinal NaPi-IIb protein expression was low and PiT-2 protein expression dominated. PiT-2 protein was mostly expressed in the duodenum and jejunum where most of the phosphate is absorbed. PiT-2 expression levels were similar in CKD or dialysis patients and normal subjects. Compared to humans, in normal rats NaPi-IIb was predominantly expressed in the upper small intestine. Expression levels significantly decreased with age, and this correlated with lower serum phosphate concentration and the velocity of phosphate uptake in intestinal brush border membrane vesicles (BBMV). In rat CKD models, NaPi-IIb protein expression decreased significantly and low-affinity sodium-dependent phosphate transport dominated in intestinal BBMV. The nature of this transport remains unknown, as PiT-1 or PiT-2 protein expression in these animals remained undetectable by LC-MS/MS.

Conclusions: Major species differences in the intestinal phosphate absorption system were identified between humans and rats. Unlike in rats, PiT-2 appears to be the dominant intestinal phosphate transporter in humans and its expression was unaltered in patients with CKD. Thus, we identify PiT-2 as a promising pharmacological target for the treatment of hyperphosphatemia in dialysis and/or CKD patients.

TH-PO542

Inhibition of Sodium Phosphate Transporter Npt2a Increases Urinary Phosphate Excretion and Improves Experimental Vascular Calcification in Rats

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Background: A dysregulated phosphate homeostasis is strongly associated with mortality, cardiovascular events and vascular calcification, particularly in patients suffering from CKD. Inhibition of the tubular phosphate transporter Npt2a provides a novel and unique mechanism to address phosphate homeostasis imbalance.

Methods: Npt2a activity was measured in a cell based assay, using a stable CHO cell line with inducible Npt2a expression. Male Wistar rats were used for all experiments. Healthy rats were treated orally with BAY 767, a potent Npt2a inhibitor developed at Bayer AG. Vascular calcification was induced by administration of a pan-FGFR inh. (25mg/kg) for 10 days.

Results: BAY 767 was identified as potent Npt2a inhibitor, with an IC_{50} of 2.9/6 nM on rat/ human Npt2a, respectively, selective over Npt2b, Npt2c and Pit-1. Single dose treatments of healthy rats resulted in a significant, dose-dependent increase in urinary phosphate excretion within 16h. Multiple dose treatments (3d) significantly reduced plasma phosphate levels from 2.0 mmol/ L to 1.6 mmol/ L at the highest tested dose. Congruent levels of FGF-23 as well as PTH were decreased to 46% and 43% as compared to untreated controls, respectively. In an experimental vascular calcification model, treatment with the Npt2a inhibitor significantly inhibited vascular calcification and normalized plasma phosphate levels in comparison to untreated rats that developed massive vascular calcification and hyperphosphatemia. In the same model 2.2% lanthanum carbonate was not beneficial with respect to vascular calcification.

Conclusions: Our results show for the first time that treatment with a Npt2a inhibitor improves vascular calcification by addressing urinary phosphate excretion and phosphate homeostasis in rats. Npt2a inhibition may provide a new therapeutic principle for patients suffering from disbalanced phosphate homeostasis and vascular calcifications, including CKD patients.

Funding: Commercial Support - Bayer AG

TH-PO543

High Phosphate-Inducing Valvular Interstitial-Endothelium Cross-Talk Through mir-382/SOD2 Axis in CKD with Valve Injury

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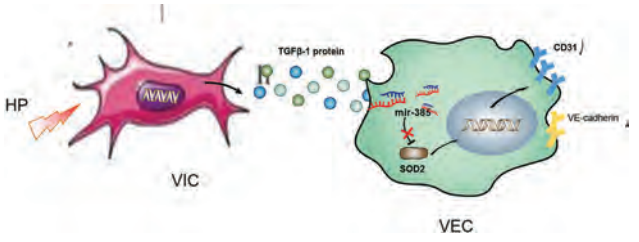
Background: CKD valve injury is the main cause of CVD among CKD patients, but it underlying mechanisms are still unknown. Previous studies demonstrated valve interstitial cells (VICs) participate in valve injury to produce excessive quantities of the valvular ECM. Recent findings suggested valve interstitial-endothelium crosstalk are closely related to valve homeostasis and injury. Hence, we want to investigate the mechanism between VECs and VICs upon high phosphate (HP) stimulation.

Methods: We used c57/b mouse and HP-stimulated VIC as in vivo and in vitro model of CKD, respectively. Transwell migration were performed to determine VIC could aggravate valve endothelial cell(VEC) EndMT upon HP stimulation by qPCR, WB and immunofluorescence. ELISA were performed to detect the expression of TGFβ-1 in VIC cell supernatant. The expression of key factors involved in EndMT process, such as CD31, VE-cadherin, α-SMA, FSP1 were evaluated by western blotting and immunofluorescence. qRT-PCR was used to measure levels of miR-382 in VEC.

Results: TGFβ-1were significantly increased in VIC upon HP stimulation. Transwell migration were proved VIC could aggravate VEC endothelial-to-mesenchymal transition (EndMT) upon HP stimulation, with the up-regulation of mesenchymal markers (FSP1 and α-SMA) and stem cell markers (CD44 and CD10) and down-regulation of the endothelial marker (CD31, VE-cadherin), consistent with CKD aortic valve samples. Knockdown of EC miR-382, which was up-regulated by TGFβ1, could attenuate TGFβ1-induced loss of the endothelial marker VE-cadherin and CD31. miR-382 was confirmed by 3'-untranslated region reporter assay to target superoxide dismutase 2 (SOD2) that were downregulated at the protein level by TGFβ1. Knockdown of miR-382 attenuated TGFβ1-induced downregulation of SOD2. Overexpression of SOD2 ameliorated loss of the endothelial marker and CKD aortic leaflets thickening.

Conclusions: VIC could secret TGFβ-1 upon HP stimulation, which lead to EndMT through mir-382/SOD2 axis. This could cause CKD aortic leaflets thickening and aggravate valve injury.



Pattern diagram

TH-PO544

A Crossover Study of Continuous Intake of the Different Phosphorus Bioavailability Meal in Healthy Japanese

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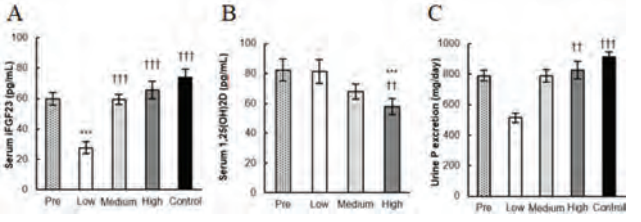
Background: Dietary phosphorus (P) management based on its bioavailability is crucial to prevent and treat the risk of cardiovascular disease and mortality in both general population and chronic kidney disease (CKD) patients. Our previous study has demonstrated that P bioavailability in various independent foods as the relative value of sodium P supplement. However, it reminds unclear that P bioavailability in mixed meal. Thus, we conducted the short-term dietary intervention study that ingested mixed meal consisting of different P bioavailability foods.

Methods: We conducted an open-label crossover study of 4 different test meals consumed for 5 days by 5 men and 5 women healthy young subjects, aged 20-30 years old. We obtained multiple points of blood and 24 h urine samples at before and after each intervention. Each meal was designed to have the same amount of P (1,200 mg/d) and only a half of P (600 mg/d) sources varied as test foods: soybean and tofu, pork and ham, milk and process cheese, and sodium P supplement for low, medium, high, and control P bioavailability test food, respectively.

Results: After continuous ingestion of high P bioavailability meal, fasting serum intact fibro blast growth factor 23 (iFGF23) levels increased, accompanied with decrease in serum 1,25-dihydroxyvitamin D levels and urinary P excretion [Figure 1]. Additionally, serum P and iFGF23 levels were lower in low P bioavailability meal compared with other test meals throughout the day. These results indicate consuming higher P bioavailability food results higher increase of iFGF23 which reflect more severe P burden.

Conclusions: Habitual ingestion of low P bioavailability food decreases P burden despite equivalent amount of P and may contribute to reduce the risk of disease and mortality in CKD patients.

Funding: Private Foundation Support



TH-PO545

Extracellular Matrix Stiffness Modulates Calcification of Vascular Smooth Muscle Cells via Phosphate Uptake

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Background: In patients with chronic kidney disease (CKD), stiffening and calcification of blood vessels are common and predict mortality and adverse cardiovascular events. Our preliminary data suggests that stiffening occurs early in CKD and could be independent of calcification. Stiffness of the extracellular matrix (ECM) has also been shown to influence differentiation of pluripotent stem cells. Thus, we hypothesize that stiffness of the ECM will increase phosphate mediated osteoblastic transformation and calcification of vascular smooth muscle cells.

Methods: Human aortic smooth muscle cells (HASMCs) were plated on polyacrylamide gels of varying stiffness: 8kPa, 50kPa, or plastic (~10,000kPa). Cells were cultured in either control or calcification medium (3.0mM phosphate and 2.7mM calcium). After 7 days in culture, alkaline phosphatase activity (ALP), intracellular phosphate and calcium content in cells were measured and normalized to total protein content.

Results: There was a 4-fold increase in calcium in HASMCs plated on 8kPa (243 ± 124 μg/mg of protein) compared to those on 50kPa (954 ± 59 μg/mg of protein, $P<0.05$) and a 9-fold increase from 50kPa to plastic (8246 ± 1324 μg/mg of protein, $P<0.05$) (Fig 1). HASMCs on plastic had a near 2-fold increase in ALP activity when cultured in calcification medium (0.58 ± 0.12 vs 0.33 ± 0.05 mU/μg of protein, $P<0.05$), while cells on 8kPa (0.36 ± 0.02 vs 0.35 ± 0.04 mU/μg of protein, $P>0.05$) and 50kPa (0.33 ± 0.03 vs 0.39 ± 0.05 mU/μg of protein, $P>0.05$) showed no appreciable increase in ALP activity. Similar to ALP data, phosphate uptake was increased in cells plated on plastic (2.21-fold increase, $p<0.05$) but not for the 8kPa and 50kPa gels in calcification media (Fig 2).

Conclusions: Our study showed that ECM stiffness increases calcification of HASMC. Osteoblastic transformation was abolished on soft gels. The decrease in osteoblastic transformation appears secondary to downregulation of phosphate uptake. Targeting molecular pathways that mediate stiffness induced upregulation of phosphate uptake might decrease calcification and improve cardiovascular outcomes in CKD.

Funding: Other NIH Support - NHLBI, K-08HL130945

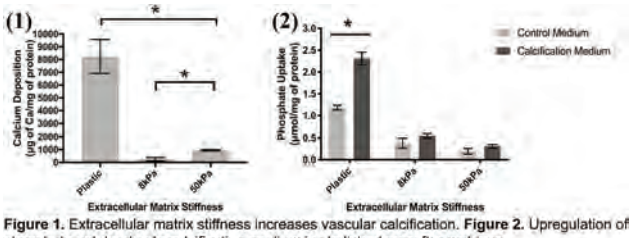

Figure 1. Extracellular matrix stiffness increases vascular calcification. **Figure 2.** Upregulation of phosphate uptake due to calcification medium is abolished on softer matrices.

TH-PO546

ASARM Peptide Reverses Hyperphosphatemia; Prevents Calciphylaxis-Like Lesions; and Corrects Renal, Bone, Brain, and Cardiovascular Calcification in a Rat Model of CKD

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Background: Abnormalities in mineral metabolism, bone and vascular calcification occur in Chronic Kidney Disease (CKD-MBD). Cognitive function also declines as the disease progresses. Bone ASARM peptides are strong inhibitors of mineralization and induce hypophosphatemia by inhibiting phosphate uptake from the gut. We hypothesize treatment of CKD-MBD rats with ASARM peptides will reverse hyperphosphatemia, correct mineralization defects and improve mortality.

Methods: To test our hypothesis, we used a rat 5/6 Nephrectomy experimental model (NEPHREX) and sham operated rats (SHAM) as controls. Male rats (16 wk, 250 gm) were fed a high phosphate diet to worsen mineral metabolism defects (2% P, 2000 IU Vit D and 0.8% Ca; TEKLAD 170496). ASARM peptide was infused continuously for 4 weeks using subcutaneous implantation of Alzet osmotic pumps. Sera collections were taken at the beginning and end of the study.

Results: NEPHREX rats treated with ASARM-peptide showed major reductions in hyperphosphatemia, and improved renal, bone, brain and cardiovascular calcification compared to controls treated with vehicle (Figure 1). Also, the high phosphate diet NEPHREX rats developed sub-dermal medial blood vessel calcification and calciphylaxis like lesions. The subdermal blood vessel calcifications did not occur in 56-NEPHREX rats treated with ASARM-peptide.

Conclusions: In summary our study shows ASARM peptides infused into a rat model with CKD corrects hyperphosphatemia and improves bone and renal mineralization abnormalities. These findings also confirm our hypothesis and supports the utility of ASARM peptide treatment in patients with CKD-MBD.

Funding: NIDDK Support

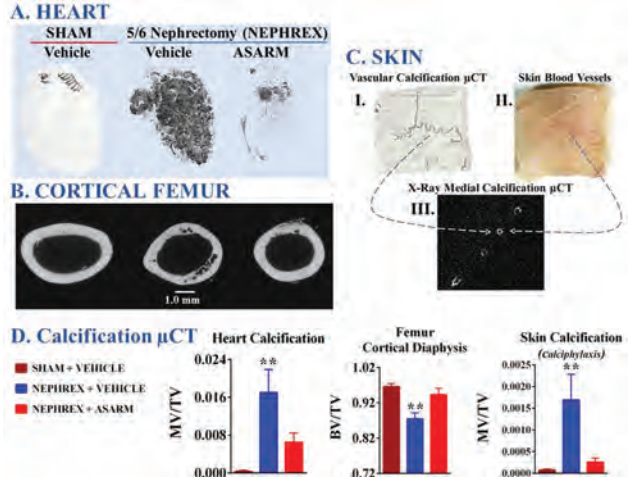

Figure 1: ASARM peptide corrects CKD-MBD mineralization abnormalities as measured using µCT: A. Heart, B. Cortical femur diaphysis, C. Skin, and D. graphical representation of MV/TV (mineral volume/total volume) and BV/TV (Bone /Total volume).

TH-PO547

Effect of PARP Inhibition on the Development of Vascular Calcification (VC) in CKD Rats

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Background: A new therapeutic approach for VC consists in the use of molecules directly interfering with the calcification process. Potential candidates for this are Poly ADP Ribose Polymerase (PARP) inhibitors. Through the understanding of PARP/PAR processes that occur in new bone formation, it has recently been discovered that VC is also mediated by PARP/PAR processes that release PAR from dying cells in the vascular wall. We evaluated the effect of the PARP inhibitor minocycline (MC) on the development of VC in a rat model with adenine-induced CKD.

Methods: 56 male Wistar CKD rats were randomly assigned to 4 study groups (n=14 each) and treated daily during 6 wks with either tap water (CKD-Veh) or MC at doses of 5, 10 or 50 mg/kg respectively. MC treatment was initiated 1 wk after the start of adenine dosing (0.75% in diet during 4 wks). VC was evaluated by measuring arterial calcium (Ca) content as well as area % Von Kossa positivity. Bone status was evaluated by quantitative histomorphometric analysis of static and dynamic bone parameters.

Results: Mortality was limited as only 1 animal died before the study end. MC did not impact renal dysfunction nor did it affect PTH, phosphorus, Ca or FGF-23 levels. Arterial Ca content as well as area % Von Kossa positivity, indicated MC treatment to dose dependently decrease calcification in the aorta, carotid and femoral arteries which became significant in the 50 mg/kg group. Compared to CKD-Veh rats MC treatment went along with a tendency towards a lower bone area which however, was inversely associated with the MC dose and was abolished when the mineralized area over bone area was considered. Similar patterns were observed for the bone formation and mineral apposition rates respectively. No significant effect of MC treatment on the number of osteoblasts and osteoclasts was observed.

Conclusions: MC treatment reduced VC without affecting renal function and associated mineral disturbances, suggesting a direct and local action on the arterial wall. The beneficial effects on the vasculature reveal that PARP inhibition might be a promising, safe and effective treatment of VC. Further studies are warranted to get a more profound insight in the potential effects of MC on bone.

Funding: Commercial Support - Cycle Pharma

TH-PO548

Inorganic Polyphosphate Amplifies the Macrophage-Inflammatory Response Induced by Lipopolysaccharide

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Background: Recent studies have revealed that inorganic polyphosphate (polyP), a linear polymer of orthophosphate, is involved in various physiological events like blood clotting, inflammation and energy metabolism. Infection, particularly sepsis, is a major cause of death in patients with chronic kidney disease (CKD) and is associated with high levels of phosphate in the serum. However, the role of phosphate in the induction of an inflammatory response during CKD is largely unknown. In this study, we examined the effect of polyP on lipopolysaccharide (LPS)-induced macrophage proinflammatory signaling *in vitro*.

Methods: A reaction of THP-1 derived macrophages with LPS (1.0 ng/mL) from *Escherichia coli* and polyP of various chain lengths (1, 2, 3, 15, 65, 100, 700 mer) and concentrations (1-200 µM, calculated as an orthophosphate monomer) was carried out. The levels of inflammatory cytokines released into the culture medium were measured using ELISA. The expressions of proinflammatory cytokine mRNAs of IL-1β, TNFα and IL-6 and signaling proteins like NF-κβ and MAPK were analyzed by real-time PCR and western blotting, respectively. The effect of polyP on LPS binding to the Toll-like receptor (TLR) 4 on cells and its structure was examined by quartz crystal microbalance (QCM), flow cytometry and fluorescence microscopy visualization, and isothermal titration calorimetry (ITC) and dynamic light scattering spectroscopy (DLS), respectively.

Results: PolyP amplified the inflammatory cytokine production induced by LPS (IL-1β, 50 µM polyP-65: 23.0 ± 2.9 pg/mL; 1 ng/mL LPS: 440.8 ± 45.7 pg/mL; 1 ng/mL LPS + 50 µM polyP-65: 1666.6 ± 162.4 pg/mL, $p<0.05$) in a dose- and chain length-dependent manner, whereas orthophosphate had no such effect. It also enhanced the expression levels of proinflammatory cytokine mRNAs, LPS-induced macrophage signaling (indicated by an increased expression of NF-κβ, MAPK) and LPS micelle formation. Results of QCM, flow cytometry and fluorescence microscopy showed that polyP bound directly to LPS, enhancing its interaction with TLR4.

Conclusions: This study suggests that polyP may be important in promoting an LPS-induced inflammatory response in macrophages and could be a form of phosphate associated with acute inflammation in patients with CKD.

TH-PO549

Resveratrol Ameliorates High-Phosphate-Induced VOT and AMC in CKD Through Regulating Wnt/β-Catenin Signaling

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Background: Vascular smooth muscle cells (VSMCs) to osteoblast-like cells transdifferentiation (VOT) induced by high-phosphate is a crucial step in the development of arterial medial calcification (AMC) in patients with chronic kidney disease (CKD). Our previous study demonstrated that Wnt/β-catenin signaling played an important role in promoting VOT and calcification in VSMCs induced by high-phosphate. Studies in cancer field have confirmed that resveratrol, a natural polyphenol, could regulate Wnt/β-catenin signaling. However, the potential effect of resveratrol on VOT and AMC through Wnt/β-catenin signaling remains to be elucidated.

Methods: An animal model of chronic renal failure with AMC was established by feeding rats a diet containing 0.75% adenine and 0.9% phosphorus. VOT and AMC in arterial ring was induced by placing isolated thoracic aortic rings from mice in culture medium containing 10 mM β-glycerophosphoric acid (β-GP). VOT and calcification of cultured VSMCs was also induced by 10 mM β-GP. The effect of resveratrol on VOT and/or calcification was observed in the *in vivo*, *ex vivo* and *in vitro* models mentioned above. The regulation of resveratrol on Wnt/β-catenin signaling in VSMCs was also examined.

Results: Resveratrol ameliorated AMC in chronic renal failure rats fed with high-phosphate diet and calcium deposition in arterial rings and VSMCs cultured in a high-phosphate environment. Resveratrol suppressed the induction of Runx2, osteocalcin and osteopontin and restored the expression of SM22α in arterial rings and VSMCs treated with high-phosphate. *In vitro*, resveratrol inhibited the upregulation of two forms of active β-catenin, dephosphorylated on Ser37/Thr41 and phosphorylated on Ser675 sites, and β-catenin nuclear translocation, stimulated by high-phosphate. Furthermore, porcupine and wntless was induced in VSMCs treated with high-phosphate in a time-dependent manner, which could be inhibited by resveratrol. Resveratrol also inhibited the phosphorylation of LRP6 induced by high-phosphate. However, it seemed that resveratrol couldn't inhibit the expression of Runx2 induced by Wnt3a.

Conclusions: The results presented in our study suggest that through targeting Wnt/β-catenin signaling, which in turn impeding VOT induced by high-phosphate, resveratrol possesses an effect on retarding AMC in CKD.

Funding: Government Support - Non-U.S.

TH-PO550

Increased Basal Tone and Impaired Smooth Muscle Cell Contractility of the Carotid Artery in a CKD Rat Model

Geoffrey Van den bergh, Patrick D'Haese, Anja Verhulst. *University of Antwerp, Antwerp, Belgium.*

Background: Increased arterial stiffness (AS) is linked to aging and accelerated in patients with CKD. Traditionally, CKD has been closely associated with the development of arterial media calcifications (AMC), which together with changes in extracellular matrix composition are typical examples of passive stiffening. AS, on the other hand also has cellular, active components. Endothelial induced relaxation and vascular smooth muscle cell (VSMC) contractility, in response to pressure changes, are crucial to maintain a proper vessel tone. Using a CKD rat model this study aims to unravel the passive and active mechanisms underlying CKD related AS.

Methods: Eight Wistar rats were administered an adenine supplemented/phosphate rich diet for a period of 8 wks to induce CKD-related AMC, and compared to 8 age-matched control rats with normal renal function. Serum creatinine and phosphate were determined to follow up CKD development. AMC was investigated by measuring bulk Ca content in the aorta. AS was evaluated *in vivo*, using echo evaluation of the abdominal aorta pulse wave velocity (PWVa). An in house *ex vivo* organ bath setup to mimic cyclic stretch, was used to evaluate endothelial and VSMC functionality and to quantify the Peterson's elastic modulus (Ep, measure of AS).

Results: As could be concluded from serum creatinine and phosphate levels, severe CKD developed in the adenine fed rats. Significantly higher Ca content in the aorta ($p<0.01$) of adenine rats confirmed AMC development. After 8 wks, adenine fed animals showed increased AS, both *in vivo* and *ex vivo*: significantly higher PWVa ($p<0.01$) and Ep ($p<0.01$) compared to controls. Furthermore, adenine rats have increased, pressure dependent, basal tone and diminished VSMC contractility ($p<0.01$).

Conclusions: The adenine rat model is suited to investigate the progressive character of AS. We observed an interplay between active and passive components. The reduction in VSMC contractility is detrimental for the arterial system to buffer pulsatile flows at higher pressures, further promoting AS. A logical next step would be to include earlier time points to study endothelial contribution and VSMC shift towards a pro-calcifying phenotype. Discovery of early mechanisms underlying AS will contribute to the development of novel AS preventive treatments.

Funding: Government Support - Non-U.S.

TH-PO551

The Inhibitory Effect of Zinc Chloride on Phosphate-Induced Calcification via Suppression of HIF1a Expression in Human Vascular Smooth Muscle Cells

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Background: Vascular calcification is a life-threatening pathophysiological abnormality in CKD. It was demonstrated that phosphate (P), a main inducer of vascular calcification, enhances oxidative stress and its resultant inflammation, leading to osteochondrogenic differentiation and calcification in cultured vascular smooth muscle cells (VSMCs). Because plasma Zn levels are low in CKD patients and Zn has anti-inflammatory effects, we examined effects of $ZnCl_2$ on P-induced inflammation, osteochondrogenic differentiation, and calcification in human VSMCs.

Methods: Human VSMCs were cultured in DMEM plus 10%FCS and 2.0mM P with 0, 0.5, 1, 5, 10, 50, or 100 mM $ZnCl_2$ for 3, 7 or 14 days. The precipitated calcium contents and expression of inflammatory mediators, osteochondrogenic differentiation markers and its inducers, including HIF1a and VEGF, were evaluated.

Results: At 14 days, $ZnCl_2$ inhibited calcification in a concentration-dependent manner, and high concentrations (>=10mM) of $ZnCl_2$ reduced calcification by almost 90% ($p<0.01$). Moderate to high concentrations (>=5mM) of $ZnCl_2$ suppressed expression of osteochondrogenic differentiation markers (SOX9, MSX2, and RUNX2) and inducers (BMP2, PiT1, and MMP2) ($p<0.01$). Moreover, moderate to high concentrations of $ZnCl_2$ suppressed IL-1b expression at earlier time points (3 and 7 days, $p<0.01$) and also inhibited expression of HIF1a and VEGF, a downstream gene of HIF1, through the period ($p<0.01$). Expression of both HIF1*a* and VEGF positively correlated with IL-1b expression, precipitated Ca content, and expression of BMP2, SOX9, MSX2, RUNX2, PiT1, and MMP2, respectively ($p<0.01$).

Conclusions: $ZnCl_2$ can directly inhibit P-induced inflammation and HIF1a expression, leading to suppression of osteochondrogenic differentiation and calcification in human VSMCs.

Funding: Government Support - Non-U.S.

TH-PO552

M2 Macrophages Promote Mouse Aortic Smooth Muscle Cells Calcification by the SGK1-TGFβ1 Axis

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Background: Macrophages play an important role in vascular calcification (VC). Recent researches show that SGK1 is a highly attractive candidate for developing vascular smooth muscle cells (VSMCs) calcification. Importantly, TGFβ1 induces VC through regulating osteo-/chondrogenic transdifferentiation of VSMCs. However, whether macrophages promote VSMCs osteo-/chondrogenic transdifferentiation via SGK1 and the associated mechanisms is unknown.

Methods: Mouse aortic smooth muscle cells (MAoSMCs) with the supernatant from diverse stimutited-macrophages (M0-CM, M2-CM, M2-EMD-CM; EMD: SGK1 inhibitor) were treated with or without TGFβ1 receptor inhibitor. Calcium deposition was evaluated by alizarin red and von Kossa staining. Intracellular calcum contents were measured via calcium quantification kit. Expressions of specifc-osteogenic markers, SGK1 and TGFβ1 were examined by RT-qPCR, western blotting, immunofluorescence staining or Elisa kit.

Results: MAoSMCs produced significant calcium deposits in M2-CM. Furthermore, M2-CM promoted MAoSMCs transdifferentiation, which was characterized by expression of osteo-/chondrogenic markers (Runx2, ALPL, FGF23) or decrease of the MAoSMCs marker (SM22α). Exploring the mechanism of the above phenomenon, we found that the expression of SGK1 and TGFβ1 were significantly increased in M2 group compared with M0 group ($P<0.05$). Interestingly, when blocking SGK1 expression, the expression of TGFβ1 was down-regulated in M2. In addition, inhibiting expression of SGK1 or TGFβ1 can partially blocked MAoSMCs osteo-/chondrogenic transdifferentiation and calcification. Subsequent analyses by using calcium quantification kit, alizarin red and von kossa staining showed that recombinant mouse TGFβ1 increased calcium content in MAoSMCs and promoted MAoSMCs transdifferentiation, which the expression of osteo-/chondrogenic markers obviously increased($P<0.05$), while MAoSMCs marker markly decreased($P<0.05$).

Conclusions: M2 macrophages SGK1-TGFβ1 axis contribute to promote MAoSMCs osteo-/chondrogenic transdifferentiation.

TH-PO553

Combining Phosphate Binder Therapy with High Vitamin K2 Diet Inhibits Vascular Calcification in an Experimental CKD Animal Model

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Background: Hyperphosphatemia may contribute to cardiovascular disease and mortality. Therefore, phosphate binders (PB) are widely used, but a proof of risk reduction is lacking. By binding vitamin K PB may offset beneficial effects of phosphate reduction on vascular calcification (VC). Here we tested whether high vitamin K2 supplementation in combination with PB can inhibit VC in an experimental animal model for CKD.

Methods: Description of the model (Figure 1). Blood chemistry was analyzed to verify the CKD model. Aortic arch, abdominal aorta and cartilage was analyzed for calcification using high resolution micro CT scan (in parafin embeded aortas and formalin fixed tibia's) and by inactive ucMGP using conformation specific antibodies.

Results: 3/4Nx resulted in increased circulating creatinine (mmol/L) and urea (mmol/L) ($p < 0.01$ for both). PB combined with low vitamin K2 diet resulted in significant vascular and cartilage calcification. On the contrary, PB combined with high vitamin K2 revealed significantly less ectopic calcification. Immunohistochemical staining of tissues for ucMGP revealed that ucMGP was present at sites of vascular calcification, mainly in the low vitamin K2 treated groups, indicating severe vascular vitamin K deficiency (Figure 2).

Conclusions: These experiments demonstrate that PB therapy in CKD cannot prevent VC, but that the combination with high vitamin K2 did. The inhibitory effect on vascular and cartilage calcification of combined phosphate binder with vitamin K2 therapy lies in the synergy of phosphate control and correction of vitamin K deficiency.

Funding: Private Foundation Support

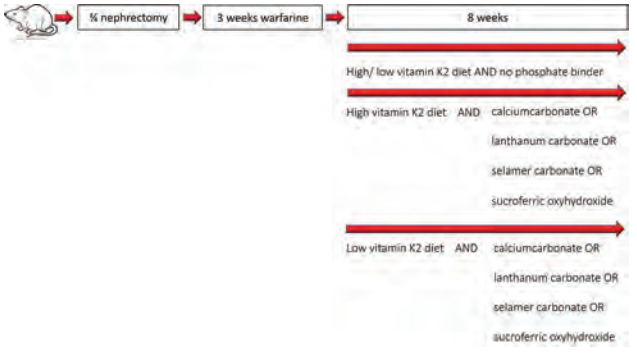

Figure 1

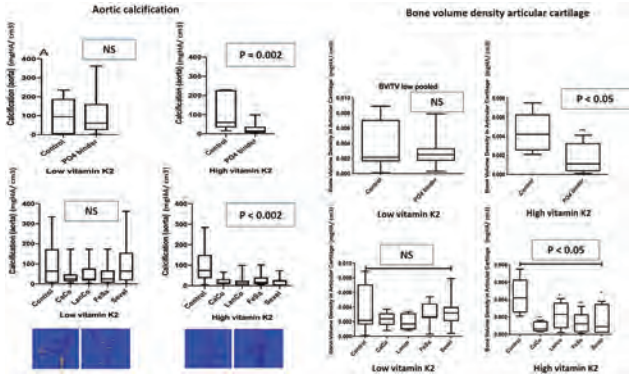

Figure 2

TH-PO554

Evidence for Disordered Acid-Base Balance in Calcium Stone Formers

Kristin J. Bergsland, Elaine M. Worcester, Fredric L. Coe. *University of Chicago, Chicago, IL.*

Background: Normal women (W) have higher urine pH (UpH) than normal men (M). Thus W are predisposed to urine calcium phosphate (CaP) crystallization which occurs at higher UpH, and CaP stones are more common in W; M are more likely to form calcium oxalate (CaOx) stones due to lower UpH. In a General Clinical Research Center, we investigated whether W CaOx stone formers (SF) and M CaP SF, who are atypical for their sex, have abnormal acid-base balance or renal acidification and if so, what components of acid-base metabolism are responsible for the altered UpH.

Methods: We measured UpH and determinants of acid-base regulation in 25 normal subjects (13 M), 18 CaOx SF (12 M) and 17 CaP SF (9 M). We collected 15 urines and 20 blood samples over a 15 hour day; diet was fixed. Gastrointestinal anion excretion (GIAE) = [(Na + K + Ca+ Mg) - (Cl + P)] in urine.

Results: Ammonia (NH_4) excretion was higher in CaP SF of both sexes and W CaOx SF vs same sex normal (N) even after adjustment for sulfate and GIAE (Table). Urine citrate (U Cit) and fractional excretion of citrate (FE Cit) were lower than N in M CaP SF. Net acid excretion (NAE) was high in all M SF vs normal M. W CaOx SF had lower GIAE than W CaP SF or W N (1.50 ± 0.26 mEq/hr vs 2.48 ± 0.22 or 3.11 ± 0.18 resp., $p<0.05$).

Conclusions: CaP SF of both sexes and women CaOx SF have different but clear disorders of acid-base handling, the former seemingly localized to abnormal renal proximal tubule acidification and the latter to aspects of food anion absorption.

Funding: NIDDK Support

	Women			Men		
	N	CaP	CaOx	N	CaP	CaOx
U TCO2	0.73±0.06	0.86±0.60	0.80±0.08	0.96±0.85#	0.97±0.06	0.84±0.05
U TA	0.52±0.02	0.53±0.02	0.56±0.03	0.56±0.02$	0.64±0.03#+	0.56±0.02
U NH4	1.09±0.04+$	1.41±0.05+	1.24±0.07	1.05±0.04$	1.41±0.05*+	1.16±0.04
U NAE	0.88±0.07	1.04±0.08	1.05±0.1	0.65±0.06#+$	1.07±0.08+	0.85±0.07
U Phos	0.98±0.04	1.04±0.04	0.97±0.05	1.08±0.04$	1.31±0.04#+	1.06±0.03
U Cit	0.18±0.01	0.17±0.01	0.16±0.01	0.14±0.01#$+	0.11±0.11#+	0.18±0.01
FE Cit	11.6±0.5	10.3±0.6	11.6±0.6	10.1±0.4#$	6.8±0.5#+	10.3±0.4
UpH	6.31±0.04	6.40±0.04+	6.19±0.05	6.26±0.03	6.32±0.04	6.35±0.04#

Mean±SE. Fed period, adjusted for sulfate and GIAE. TCO2, total CO2; TA, titratable acidity. All urine excretions are mmol/hour/1.73m2. Symbols: #, differs from W, same stone type; +, differs from CaOx, same sex; $, differs from CaP, same sex; all comparisons $p<0.05$.

TH-PO555

Regulation of Claudins by Metabolic Acidosis via Calcium-Sensing Receptor in Rat Kidney

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Background: Metabolic acidosis (MA) may present with nephrocalcinosis and nephrolithiasis because of hypercalciuria. Most of the calcium reabsorption paracelluarly occurs through tight junctions in the proximal tubule (PT) and thick ascending limb (TAL) whereas the distal convoluted tubule and connecting tubule are the major regulatory sites of active calcium transport. However, the regulatory contribution of paracelluar calcium transport in the PT and TAL to hypercalciuria in MA remains to be elucidated.

Methods: Male Sprague-Dawley rats were randomly divided into four groups to see the effects of calcium-sensing receptor (CaSR) stimulation (using cinacalcet) and inhibition (using NPS-2143) in the presence of MA: controls (n=6), cinacalcet-treated (n=6), NH_4Cl-loaded (n=6), and NH_4Cl/NPS-2143-cotreated rats (n=6). After seven days' animal experiment, renal claudin expressions were examined by semiquantitative immunoblotting, qPCR analysis, and immunofluorescence microscopy.

Results: Urinary calcium excretion was insignificantly increased by cinacalcet treatment, and it is significantly elevated by NH_4Cl loading and reversed by NPS-2143 coadministration. Renal claudin-2 protein/mRNA were not altered by cinacalcet treatment, and they were suppressed by NH_4Cl loading and recovered by NPS-2143 coadministration. Claudin-16 protein/mRNA and claudin-19 protein/mRNA were not altered by cinacalcet treatment, and they were also downregulated by NH_4Cl loading and reversed by NPS-2143 coadministration. Consistently, claudin-14 protein/mRNA were upregulated by NH_4Cl loading and reversed reversed by NPS-2143 coadministration. Furthermore, CaSR protein/mRNA were upregulated by NH_4Cl loading and reversed by NPS-2143 coadministration. The effects of acid loading were confirmed by immunofluorescence microscopy.

Conclusions: In metabolic acidosis, not only claudin-2 in PT but also claudin-16/19 in TAL are downregulated to produce hypercalciuria. The CaSR in rat kidney appears to have a regulatory role in MA-induced hypercalciuria.

Funding: Commercial Support - Myoungpoom Medical Co.

TH-PO556

Familial Hypocalciuric Hypercalcemia (FHH) Induced by Gene Deletion of Transient Receptor Potential Canonical 1 (TRPC1) Channels Is Independent of Gender, Like Ca Sensing Receptor (CaSR) Mutations

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Background: Previously in TRPC1 null males, we reported the mouse phenotypes of FHH, causally related to reduced cell free [Ca] & hyperparathyroidism, like human FHH induced by haploid loss-of-function mutations in the CaSR gene. But haploid TRPC1 deletion induces only hypercalcemia, no hypocalciuria or hyperparathyroidism. Here we tested the hypothesis that phenotypes in TRPC1 null mutation are gender non-specific, like CaSR mutations.

Methods: In age-matched female mice, we performed classical metabolic balance studies & measured blood & urine Ca & Mg.by standard methods. We analyzed creatinine by HPLC & calciotropic hormones by mouse ELISA.

Results: Similar to null males, 7 mon old TRPC1 null females also exhibited hypocalciuria, whether expressed as mean 24 h urine Ca (1 ± 0.1 [SE] vs 1.6 ± 0.1 mg/d, p<0.03), as urine Ca:creat ratio (2 ± 0.2 vs 3 ± 0.1, p<0.02), or as Ca clearance (13 ± 2 vs 22 ± 1 µl/min, p< 0.01). Like null males, TRPC1 null females were also hypercalcemic, whether fasted (9.8 ± 0.3 vs 8.1 ± 0.4 mg%, p<0.005) or fed ad lib (9.6 ± 0.2 vs 8.5 ± 0.2 mg%, p<0.005). Mean fasting serum PTH in TRPC1 null females (609 vs.461 pg/ml) was numerically higher, but shy of statistical significance which we found in null males. But the hypercalcemia in null females failed to suppress PTH, suggesting similar dysregulation in PTH secretion by TRPC1 deficiency like the null males. Indeed, over the same range of serum Ca (9.6 - 10.8 m%), PTH was 35% higher in null females (652 ± 45 vs 484 ± 42 pg/ml, p<0.04). In contrast to the disturbed Ca homeostasis, there was no difference between null & wild type females in serum or urine Mg, again, similar to comparable data on Mg metabolism between null & wild type males. Mean fasting serum calcitriol (353 vs 332 pg/ml) & calcitonin (2.1 vs. 2.1 pg/ml) were similar between female genotypes, like comparable data between male genotypes.

Conclusions: We conclude that deletion of the gene encoding TRPC1 channels produces the phenotypes of hypocalciuric hypercalcemia in females as in males though hyperparathyroidism is milder. Our data support the current concept that alongside CaSR, by mediating store-operated Ca entry, TRPC1 plays a key role in intracellular Ca homeostasis & in regulating PTH secretion.

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

TH-PO557

Deletion of the Proton Receptor OGR1 in the Osteoclast Impairs Metabolic Acidosis-Mediated Bone Resorption

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Background: Metabolic acidosis (Met) induces bone resorption. Using mice with a global deletion of OGR1 we demonstrated that loss of OGR1, a G protein-coupled H^+ sensing receptor, impairs H^+-induced bone resorption. OGR1 activity in both osteoblasts (OB) and osteoclasts (OC) was altered by Met. To determine if Met directly activates OGR1 in OC, rather than indirectly through the OB, we generated a conditional knockout with an osteoclast-specific deletion of OGR1 (OC-cKO). We tested the hypothesis that the lack of OC OGR1 would lead to increased bone mass in actively growing mice which generate large amounts of metabolic acid.

Methods: OC-cKO mice were generated from a LysM-cre mouse and OGR1flox/flox mouse. We examined bones from 3 month old female mice using micro-computed tomography (µCT) and immunohistochemistry. Mesenchymal stem cells (MSC) from femurs of OC-cKO and control (ctl) mice were differentiated to OC. Mature OC were detected by TRAP staining. Mature OCs grown on cover slips were incubated in neutral (pH 7.4) or Met (pH 7.1) medium for 45 min and then stained for NFATc1 to define active OCs.

Results: µCT demonstrated increased bone in OC-cKO (Bone Volume / Total Volume: 34.9±4.6 % (OC-cKO) vs 11.3±0.7 % (ctl); Trabecular (Tb) Thickness: 0.07±0.006 mm (OC-cKO) vs 0.05±0.001 mm (ctl); Tb. Number: 6.3±0.1/mm (OC-cKO) vs 4.3±0.1/mm (ctl); all p<0.05). TRAP staining of tibia sections indicated a decrease in OC number / bone surface from OC-cKO (4.6±0.7/mm (OC-cKO) vs 7.4±0.2/mm (ctl)) and OC surface area / bone surface (13.8±5.3% (OC-cKO) vs 26.6±2.2% (ctl)). We observed that OC derived from MSC of OC-cKO have less TRAP staining in OC / well (10.7±2.1 (OC-cKO) vs 38.9±9.7 (ctl)) and decreased OC surface area (mm^2/well: 0.05±0.01 (OC-cKO) vs 0.19±0.02 (ctl)). OC-cKO OC in response to Met had decreased nuclear translocation of NFATc1, a master transcriptional regulator of OC differentiation and proliferation, compared to ctl (17.0±2.6% (OC-cKO) vs 29.7±3.3% (ctl) p<0.05) but no difference at pH 7.4.

Conclusions: Our results indicate that OC OGR1 is directly regulated by Met and important in acid-induced bone resorption. Characterization of the direct role of OGR1 in acid-induced bone resorption may assist in understanding bone loss associated with the metabolic acidosis in patients with chronic kidney disease.

Funding: Private Foundation Support

TH-PO558

Subdued, an Anoctamin 4 Homolog, Changes Calcium Oxalate Crystal Formation in Drosophila Renal Structures Revealing Potential Roles in Mammals

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Background: Anoctamins function as Ca^{2+} activated Cl^- channels (CaCC) or as phospholipid scramblases. Using a miniature schnauzers GWAS, we discovered a risk locus for recurrent calcium oxalate (CaOx) stones harboring an *anoctamin 4 (ANO4)* variant. Human stone formers have decreased *ANO4* protein in urinary vesicles. In *Drosophila* Malpighian tubules (MTs) the ANO4-homolog, *subdued*, functions as a CaCC and scramblase. *Subdued* also functions in bacterial defense, so we knocked it down to determine if bacterial infection changes crystal growth.

Methods: *Subdued* knockdown (KD) in MT principle cells was used a MT-promotor and a *subdued*-RNAi. CaOx crystallization experiments were conducted on ex-vivo MTs by 1h addition ofsodium oxalate (NaOx); while prolonged feeding (4d) assays used food with NaOx. With DIC optics, we imaged CaOx birefringence then counted crystals using ImageJ. Uropathic *E. coli* (UPEC) were fed to flies or added to NaOx solution before an overnight time-lapse.

Results: The canine *ANO4* variant has a 0.01 allele frequency at a conserved residue (humans, canines and *Drosophila*). Rapid crystallization experiments show that *subdued-KD* MTs have less CaOx crystals than controls. However, feeding assays showed that MT *subdued-KD* produces enlarged crystals. These assays also show clustering and biofilms that change crystal appearance with patterning similar to human kidney stones. UPEC facilitates CaOx crystal aggregates.

Conclusions: The *Drosophila* avatar illustrates that *subdued* (ANO4) aggregates CaOx. An apparent pathogenic variant is conserved in mammals and flies; *subdued*'s role in fly bacterial infection indicates a possible additional role of ANO4 in kidney stones. Examining antibacterial treatments or other aspects of CaOx crystal formation with UPEC may allow an antibiotic approach to more efficiently eliminate kidney stones. Future experiments will determine the localization of ANO4 in mammalian kidneys to better understand the cell specific pathology. Finally, these studies indicate that this simple kidney stone avatar- the fly – continues to provide new insights to the mechanistic role of specific genes and infection.

Funding: NIDDK Support, Private Foundation Support

TH-PO559

Spatial Mapping of Cell Populations in the Human Kidney Papilla Using 3D Tissue Cytometry

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Background: Kidney stone disease or nephrolithiasis affects 10% of US population with estimated healthcare cost of more than $10 billion. To date, no clear mechanisms have been identified for the initiation and progression of kidney stone disease. A contributing factor to this knowledge gap is a poor understanding of the various cell types comprising the nephronal segments and the surrounding interstitium in the papilla. To fill this gap, we developed a novel methodology to classify cell types of the papilla based on spatial and morphological features, lectin binding properties which reflects carbohydrate content and staining with Aquaporin 1 (AQP1, detects thin descending limbs and descending vasa recta). The long-term goal is to link subpopulations of cells with other assays such as transcriptome and proteome profiling, and advance our understanding of the renal papillary micro-environment.

Methods: Papillary biopsies were obtained at the time of percutaneous nephrolithotomy or from reference nephrectomy tissues. Fifty-micron thick sections of papilla were stained with fluorescently labelled DBA (*Dolichos Biflorus*), PNA (Peanut Agglutinin), and/or AQP1. Large scale 3D imaging was performed with confocal microscopy, followed by 3D tissue cytometry analysis using our software tool Volumetric Tissue Exploration and Analysis (VTEA).

Results: With this strategy, VTEA analysis deconvolved all the cells in the papillae into specific subpopulations, which were directly visualized within the tissue. Various subtypes of $AQP1^+$ thin descending limb cells or $AQP1^-$ thin ascending limb cells were classified based on the presence of co-labeling with DBA and/or PNA. Collecting ducts and ducts of Bellini, which are easily identified by morphological features, stained predominantly with PNA. AQP1 weak staining cells that did not stain with any lectins were identified as vascular cells of the vasa recta.

Conclusions: Using a straightforward fluorescence based staining strategy, we can distinguish subpopulations of epithelial and vascular cells in the papilla. Implementing this strategy to link cell subtypes with "omics" signatures will define the biological significance of these subpopulation, and advance our understanding of the complex homeostasis within the papilla and its perturbance by stone disease

Funding: NIDDK Support

TH-PO560

Antibiotics Affect the Intestinal Microbiome and Alter Kidney Stone Formation in Genetic Hypercalciuric Stone-Forming Rats

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Background: There is growing evidence that antibiotic exposure is associated with incident stone disease. The intestinal microbiome (IMB) can rapidly shift in response to outside stimuli such as antibiotics. We utilized genetic hypercalciuric stone-forming (GHS) rats, whose pathophysiology parallels that of human hypercalciuria and who spontaneously form calcium phosphate (CaP) stones, to determine the effect of antibiotics on the intestinal microbiome, urine ion excretion and stone formation.

Methods: 116th generation GHS rats were fed a fixed amount of a normal Ca (1.2%) and P (0.65%) diet, housed in metabolic cages and divided into 3 groups (n=10): control (CTL) diet, or supplemented with ciprofloxacin (Cipro, 5 mg/d) or Bactrim (250 mg/d). Urine and fecal pellets were collected at 6, 12 and 18 wks for analyses. Fresh fecal pellets were stored at -80oC and then prepared for analysis by DNA extraction and amplification of the 16S rRNA V4 region using barcoded primers on an Illumina platform. QIIME was used for analysis. At 18 wks kidney stone formation was determined by Faxitron analysis and assessed by 3 blinded reviewers.

Results: After 18 wks, urine Ca decreased with Bactrim (CTL=13.7± 0.4, Bactrim=12.1±0.4 mg/d, p<0.05) as did urine oxalate (CTL=1.2±0.04, Bactrim=0.8±0.02 mg/d, p<0.05). CaP supersaturation increased with Bactrim (CTL=6.8±0.4,

Bactrim=8.4±0.5, p<0.05) while CaOx supersaturation fell (CTL=16.2± 0.6, Bactrim=12.0±0.4, p<0.05). Calcification was increased by Bactrim (CTL=1.0±0.2, Bactrim=2.98±0.3, p<0.05). Cipro was not different from CTL for any parameter. Analysis of the GHS IMB shifted substantially and principal component analysis showed the Bactrim group and controls clustered separately (p=0.001). Microbial diversity negatively correlated with urinary oxalate in all animals (R=-0.46, p=0.006), and positively correlated with urinary pH in the Bactrim treated group (R=0.76, p=0.01).

Conclusions: Bactrim altered the IMB of GHS rats and also caused a fall in urine Ca, increased CaP supersaturation and increased calcification while Cipro did not change urine ion excretion or calcification. Whether the alteration in the IMB is mechanistically related to the changes in urine ion excretion and calcification remains to be determined.

Funding: NIDDK Support, Private Foundation Support

TH-PO561

Cystathionine-Gamma-Lyase Deficiency Protects Against Calcium Oxalate Nephropathy

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Background: Cystathionine-gamma-lyase (CSE), along with cystathionine-beta-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (3-MPST) contribute to the production of the gazotransmitter hydrogen sulfide (H_2S) in various tissues. In the kidney, CSE is expressed in the cortex and in the outer stripe of the outer medulla, but its role remains elusive. Recent studies using pharmacological inhibition of CSE, or CSE deficient mice, have suggested a pro-inflammatory role of H_2S in various inflammatory mouse models. Moreover, administration of H_2S donor worsened the inflammation in these models. Here, we explored the role of CSE in a recently established mouse model of renal calcium oxalate crystallopathy.

Methods: CSE-deficient ($Cse^{-/-}$) mice were obtained from Dr. Ishii (Showa Pharmaceutical University, Tokyo, Japan). Eight-week old $Cse^{+/+}$ or $Cse^{-/-}$ male mice were allocated to either 1.5% calcium plus 1.5% hydroxyproline-enriched diet or to control diet for 3 weeks. Mice were kept in metabolic cages for 24h urine collection before termination of the experiments. Indirect methylene blue method was used to measure H_2S producing capacity of renal tissue. Crystal deposits were assessed by Pizzolato staining, and fibrosis and inflammation by trichrome staining. Fibrosis and inflammation parameters were further evaluated by qPCR.

Results: At baseline, *Cse*$^{-/-}$ mice have suppressed *Cse* mRNA expression, but unaffected levels of *Cbs* and *3-Mpst* in kidney tissue. Kidneys of *Cse*$^{-/-}$ mice had reduced H_2S producing capacity compared to *Cse*$^{+/+}$ littermates. Renal morphology and function were normal at baseline in both genotypes. After three weeks exposure to calcium-hydroxyproline-enriched diet, *Cse*$^{+/+}$ mice displayed significantly higher serum creatinine and blood urea nitrogen levels, while *Cse*$^{-/-}$ mice had normal renal function. *Cse*$^{-/-}$ mice had decreased crystal deposits, lower inflammation and fibrosis, as assessed by histomorphology and qPCR. Crystal-adherent proteins were less expressed in *Cse*$^{-/-}$ mice and in primary culture of proximal tubules exposed to calcium-oxalate crystals.

Conclusions: CSE deficiency protects from inflammation and fibrosis in a model of renal calcium oxalate crystallopathy, and preserves renal function. Collectively, our data show that H_2S-producing enzymes might be suitable pharmacological targets for calcium-oxalate nephropathy.

Funding: Government Support - Non-U.S.

TH-PO562

Chlorthalidone Plus Potassium Citrate Decreases Calcium Oxalate Stone Formation Better Than Either Agent Alone While Also Improving Bone Quality in Genetic Hypercalciuric Stone-Forming Rats

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Background: To study human idiopathic hypercalciuria (IH) we developed an animal model, genetic hypercalciuric stone-forming (GHS) rats, whose pathophysiology parallels that found in human IH. All GHS rats spontaneously form calcium oxalate stones when the oxalate precursor, hydroxyproline is added to the diet. Here we tested the hypothesis that CTD and KCit combined would effectively reduce CaOx stone formation and improve bone quality in the GHS rats better than either agent alone.

Methods: 113th generation GHS rats were fed a fixed amount of a normal Ca (1.2%) and P (0.65%) diet with 5% hydroxyproline added, housed in metabolic cages and divided into four groups. Diets were supplemented with KCl (4 mmol/d) as a control, KCit (4 mmol/d), CTD (4-5mg/kg/d)+KCl, or KCit+CTD. Urine (u) was collected at 6, 12, and 18 wks for analyses and kidney stone formation and bone parameters were determined at 18 weeks.

Results: Compared to the KCl control, KCit reduced uCa (KCl=17.2±0.3 mg/d, KCit=14.4±0.3), CTD reduced it further (CTD=13.0±0.6) and KCit+CTD reduced it even further (KCit+CTD=9.3±0.4). The combination of KCit+CTD decreased uOx compared to all other groups. There were no significant differences in CaOx supersaturation in any group. Compared to KCl (stone formation with a range of 0-4: KCl=2.1±0.1), KCit did not alter stone formation (2.0±0.3), while there was less stone formation in the GHS rats fed with CTD alone (CTD=1.6±0.2). The combination of KCit+CTD (0.8±0.2) resulted in significantly fewer stones than CTD or KCit alone. Vertebral trabecular bone was increased by both CTD (38.5±3.2% vs CTL=26.8±5.1%) and KCit+CTD (34.7±3.4%), p<0.05 for both. Cortical bone area was increased by CTD (7.3±0.3 mm2 vs CTL=6.9±0.2 mm2) but not altered with KCit+CTD or with KCit alone. Mechanical properties of trabecular bone were improved by CTD alone, but not the combination.

Conclusions: Thus in GHS rats, when fed a diet that results solely in CaOx stone formation, the combination of KCit+CTD prevented stone formation better than either agent alone. The improvements in bone quality were principally due to CTD alone; adding KCit provides no additional benefit.

Funding: NIDDK Support

TH-PO563

Understanding the Pathogenesis of Human Kidney Stone Disease by Spatially Mapping Its Proteome

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Background: Nephrolithiasis affects approximately one-in-eleven people in the United States. A detailed hypothesis of the mechanisms of stone disease etiology remains elusive, and thus difficult to treat and prevent. The present study aims to advance the understanding of the pathogenesis of stone disease by determining the pattern of protein organization within the matrix of human kidney stones.

Methods: The approach of this work relies on an innovative technique to perform histological sectioning of calcium oxalate (CaOx) stones following demineralization. Multi-photon imaging and label-free proteomics were used on laser micro-dissected (LMD) specific regions to assess proteome identity and signaling across spatial coordinates within the stone-matrix.

Results: The average area of LMD samples for proteomic analysis was $1.64x10^6 \mu m^2$, and these samples yielded an average of 629 distinct proteins. Dissection of broad regions of CaOx stone by LMD yielded similar proteins as found in larger specimens of pulverized CaOx samples. Proteins identified in LMD and pulverized samples included those involved in cell injury and repair as well as important mediators of the immune system (e.g. fatty acid synthase, osteopontin-D, complement C3). More recent results show brilliant autofluorescence of decalcified CaOx stones, which will allow LMD of distinctive regions of the stone without staining.

Conclusions: Utilization and optimization of these techniques will pave the way for a deeper understanding of kidney stone formation. Future investigation of the stone-matrix proteome will provide insight into underlying events that could become therapeutic targets to prevent stone growth.

Funding: Other NIH Support - P01 DK056788

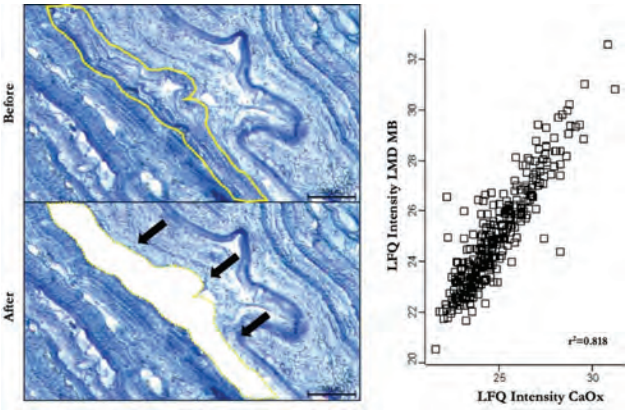

Figure 1 LMD of human kidney stones. Demineralized stone-matrix on LMD slides were stained with methylene blue (before). Dissection of broad regions of CaOx stone by LMD (after) yielded similar proteins as found in larger specimens of pulverized CaOx stone powder (right).

TH-PO564

Exploring Mechanisms of Protein Influence on Calcium Oxalate Kidney Stone Formation

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Background: Calcium oxalate monohydrate (COM) crystals are the primary constituent of most kidney stones, but urine proteins in stone matrix are believed to be critical to binding crystals into stones. Recent data have shown that hundreds of proteins appear in stone matrix with no explanation for inclusion of these various proteins. We have proposed a stone formation model with protein stimulated COM aggregation based on polyanion-polycation aggregation, which is supported by finding that matrix is highly enriched in strongly anionic and strongly cationic proteins. Many proteins are likely drawn to such aggregates due to their limited solubility in water. Finding similar protein

enrichment in both polyarginine (pR) induced aggregates of urine proteins and COM stone matrix would support this hypothesis.

Methods: Purified proteins (PP) were obtained from random urine samples from six healthy adults by ultradiafiltration. Protein aggregation was induced by adding pR to PP solutions at each of two concentrations; 0.25 and 0.5 μg pR /μg of PP. The resulting protein aggregates were separated by centrifugation, yielding aggregate (pRB) and supernatant fractions. Samples of each fraction and the original PP mixture were lyophilized and sent to the Proteomics Core Laboratory at Mayo Clinic for analysis.

Results: SDS gel electrophoresis revealed selective inclusion of urine proteins in pRB, which was shown to mimic COM matrix protein distributions by mass spectrometry analysis. Notable differences include enrichment of albumin and uromodulin in the pRB at the 0.5 μg pR addition compared to relative exclusion from COM matrix, while at 0.25 μg pR, albumin stayed in solution likely due to its weaker anionic charge, suggesting that aggregation was "overdriven" at the 0.5 μg pR addition. Many intracellular or nuclear proteins, that were prominent in COM matrix, were not observed in pRB, likely reflecting their absence in PP.

Conclusions: Aggregates induced by pR addition to PP samples collected a protein mixture that mimicked the protein distribution observed in COM matrix, supporting our hypothesis. The apparently discordant behavior of uromodulin may simply reflect its anionic character in this overdriven model. Future experiments will need to include observations of selective protein binding to COM crystal surfaces for comparison with these data.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO565

TRPV5 Surface Expression Contributes to Glucose-Induced Hypercalciuria

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Background: Lemann et al. showed that feeding normal (N) patients a glucose bolus increases fractional excretion of calcium (FECa). In addition, our group has shown that general feeding caused a significantly increased FECa of idiopathic hypercalciuric stone formers vs N patients. These observations imply a post prandial effect in calcium handling, with clinical implications for stone formers. We sought to identify transporter protein targets that mediate the effect of glucose induced hypercalciuria.

Methods: 5 N women were placed on a low salt (65 mEq/d) diet for 3 days. Patients then fasted overnight, and reported to the Clinical Research Center for serial blood and urine collections for 5 hours, consuming 100 grams of glucose at 2 hours. Endogenous lithium clearance was measured to calculate distal delivery. Urine was filtered, spun and ultracentrifuged to isolate urinary exosomes from selected time points. Resulting samples were assayed by ELISA for transporter protein abundance of TRPV5. Student's T-Tests were used to compare the last fasting period to periods of maximal change for metabolic parameters. A generalized linear model (GLM) was used to model the fractional excretion of distally delivered Ca (FEDCa).

Results: FECa rose with glucose feeding (p=0.02). Distal delivery of calcium did not differ significantly between the final fasting and any of the fed periods. FEDCa rose in parallel with FECa and rises significantly from the fasting period (p=0.015). TRPV5 expression decreased significantly after glucose feeding (p=0.047). A GLM (Table) with FEDCa as dependent, revealed TRPV5 and its known effector parathyroid hormone as significant predictors of FEDCa, with the overall model accounting for half the variation in FEDCa (R^2=0.503).

Conclusions: We have recreated the hypercalciuric effect of glucose feeding, and have localized it to the distal nephron in a cohort of young women. The finding of reduced TRPV5 in urinary exosomes implies protein trafficking away from the apical membrane, and thus identifies TRPV5 as a key mediator of FEDCa in this setting.

Funding: NIDDK Support

Effect	Coefficient	95% CI	P-Value
Constant (FEDCa)	41.8	[28.8, 54.9]	<0.001
TRPV5	-2.7	[-4.2, -1.3]	0.001
Serum PTH	-0.41	[-0.77, -0.05]	0.028

Constant coefficient is in %. TRPV5 effect is in %/pmol/mg Cr. PTH effect is in %/pg/mL.

TH-PO566

Matting Calcium Crystals by Melamine Improves Stabilization and Prevents Dissolution

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Background: Kidney stone recurrence has been shown to be as high as 50% within 10 years of stone elimination with renal stone recurrence rate among individuals who have received some form of intervention being as high as 40%. Recent studies have implicated melamine, a nitrogen-rich crystalline compound used in making plastics in nephrotoxicity. Our previous findings show that melamine induces calcium crystal formation and growth in a concentration dependent manner, however melamine's impact on recurrences remain unclear. We therefore investigated whether melamine's role in crystal stabilization/ retention could be contributing to the increased rates of kidney stone recurrence.

Methods: To examine the role of melamine, oven dried preformed CaOx and CaP crystals incubated with melamine were analyzed under an SEM/EDS microscope; morphological and elemental composition of samples were collected and analyzed. Time dependent dissolution and stabilization studies were performed using Alizarin red pH 4.3 and 6.8 to identify CaOx, CaP respectively remaining in solution. Dissolution experiments were conducted in the presence of known crystal inhibitors.

Results: We show here that the presence of melamine increases crystal retention/ stability even with the added presence of an inhibitor. Again ammeline, a similar triazine compound does not induce crystal growth. Similarly, our SEM/EDS analysis showed that melamine in the presence of calcium crystals acts as a nucleation site allowing for crystal deposition and ultimately crystal growth.

Conclusions: Together, our results highlights the mechanism utilized by melamine in calcium crystal growth as well as the pathological stabilization and retention of these crystals in the presence of known inhibitors of crystallization such as citrates, commonly used to alleviate the calcium stone conditions.

Funding: NIDDK Support, Other NIH Support - National Institute of Biomedical Imaging and Bioengineering (EB021483)

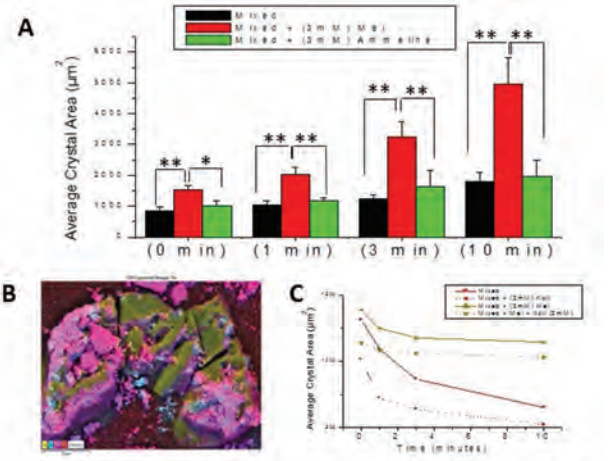

Figure 1. Increased Melamine -Calcium crystal interactions augments the size of crystals compared to the control.
To determine the mechanism utilized by melamine in inducing crystal formation and growth A. Rate of calcium crystal growth in the presence of melamine and another triazine compound ammeline B. SEM/EDS image showing the morphological interactions between melamine and Mixed (CaP+CaOx) crystals C. Dissolution experiments showing melamine increasing crystal retention in the presence of Potassium citrate (3mM).

TH-PO567

Expression of an Anti-Fibrotic Molecule, Smad Anchor for Receptor Activation (SARA), Is Significantly Decreased in Kidneys of Patients with CKD

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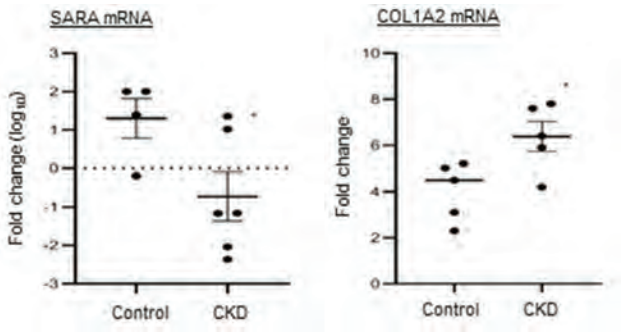
Background: Fibrosis is a final common characteristics of chronic kidney disease regardless of the primary injury. Many means to prevent cellular fibrotic processes have been explored with little success to date. We recently reported at previous ASN meetings, that overexpressing SARA in pericytes, one of the progenitor cells for fibroblasts in fibrosing kidney, prevents them from transdifferentiating to fibroblasts, hence inhibits fibrosis in chemically-induced interstitial fibrosis model in mouse. These findings suggest a novel approach in preventing fibrosis at a step where a progenitor cell acquires scar forming phenotype. Here, we evaluated relevance of the findings in human patient samples.

Methods: Kidney sections were freshly cut from archived, formalin-fixed paraffin-embedded biopsy samples. Biopsy samples include 5 with focal and segmental glomerulosclerosis (FSGS), 5 with diabetic nephropathy and 5 non-fibrosing controls. Sections were stained with Alexa 647 conjugated anti-SARA antibody and DAPI and evaluated with Nikon A1 confocal microscope. Thereafter, tubulointerstitial area of the sections were dissected using Zeiss PALM laser-capture microdissection system, and total RNA was extracted following digestion with proteinase K. RNAs were pre-amplified for SARA and β-microglobulin with Bio Rad prime PCR system, and mRNA levels were quantified with real-time PCR.

Results: SARA was highly expressed in proximal tubular epithelial cells and cells in the interstitium in non-fibrosing controls. In contrast, it was barely detected in samples from patients with FSGS or diabetic nephropathy. Consistant with the findings with immunostaining, SARA mRNA levels were significantly lower in samples from patients with FSGS or diabetic nephropathy ($P < 0.05$, Fig 1).

Conclusions: These results, consistent with our animal models, suggest that loss of SARA is pathogenic in fibrosis. SARA could be a novel therapeutic target in human CKD

Funding: NIDDK Support



TH-PO568

Are Bone Biopsies Needed Only in Patients with PTH Results Outside the KDIGO Target Range?

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Background: The 2017 KDIGO guideline update for chronic kidney disease - mineral bone disorder (CKD-MBD) in CKD-5D recommends that parathyroid hormone (PTH) levels be maintained 2 to 9 times upper normal for the assay (150-600pg/mL). There is no information on histologic bone abnormalities within vs. outside the KDIGO target PTH range.

Methods: We analyzed 142 bone biopsies done between 2004-2019 on CKD-5D patients performed for a variety of indications (fracture, hypercalcemia, osteoporosis, calciphylaxis and prior to parathyroidectomy (PTX)). The objective was to examine to what degree bone biopsies are helpful in management of patients with PTH levels outside or within the KDIGO target range.

Results: Mean age was 49±15 years, 46% were male and 63% white. Median (IQR) PTH was 776 (333-1348) pg/mL; there was a weak inverse relationship with age (r=-0.2, p<0.05), but no difference by race. Most of the biopsies (56%) were performed in patients with PTH levels >600 pg/mL (PTH>600 group); 33% of the biopsies were done in patients within the target KDIGO range (KDIGO target PTH group) and 11% in patients with PTH<150 pg/mL (PTH<150 group). The KDIGO target PTH group showed severe hyperparathyroid bone disease (HPTBD) with high to very high bone turnover (BTO) in 69%, mild to moderate HPTBD in 21% and low turnover bone disease (LTBD) in 10%. The PTH<150 group showed either LTBD or mild to moderate HPTBD. Patients within and below the KDIGO guideline were over twice as likely to show low bone volume on their biopsy (OR 2.2 95%CI 1.03-4.7). Anti-resorptive treatment was recommended in 7 patients in the KDIGO target PTH group, and anabolic therapy in 4 patients in the PTH<150 group. In the PTH>600 group, the concordance with severe HPTBD and high to very high BTO on biopsy was 92%, with moderate HPTBD in 8%; 44% subsequently underwent PTX.

Conclusions: Patients with PTH levels within the KDIGO target range show heterogeneity in their bone abnormalities with both HPTBD and LTBD, and bone loss. Contrary to current practice, these patients may be a unique risk group needing bone biopsy for targeted management of CKD-MBD. While bone biopsies are clearly also needed in patients with PTH levels below target, the procedure adds relatively little information in patients with levels above target.

TH-PO569

Magnesium Exposure Increases Fracture Risks in Patients with CKD

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Background: Bone fracture is a serious complication in CKD patients, which may lead to disability and reduced survival. In advanced CKD patients, blood magnesium (Mg) concentrations are usually above the normal range due to reduced kidney excretion of Mg. Excessive bone Mg may play a role in mineralization defects, leading to renal osteodystrophy. The present study aims to examine the relationship between Mg-containing antacid exposure and risk of incident hip fracture of CKD patients in a large, nationwide database.

Methods: Patients aged above 20 years old and diagnosed with CKD were identified from the National Health Insurance Research Database (NHIRD). From these eligible participants, study subjects in the case group were patients who were diagnosed with hip fracture, whereas the control group were selected randomly and matched to a case-patient by age, month and year of cohort entry, and Charlson comorbidity index score. The antacid usage, including Mg, aluminum, calcium, and other demographic characteristics, were analyzed.

Results: We enrolled 10,361 CKD patients with hip fracture, among which the mean age was 69.7 years old, and 54.7% was non-dialysis CKD. As compared to non-users, Mg-containing antacid users were significantly more likely to experience hip fracture (Adjusted odds ratio (OR) 1.15, 95% CI, 1.08 to 1.23; p < 0.001). Also, subgroup analysis showed that such risk exists in both non-dialysis CKD patients and long-term dialysis patients. In contrast, aluminum or calcium containing-antacid use did not reveal such association in our cohort. Next, we examined the influence of Mg-containing antacid dosage on hip fracture risk, the adjusted OR in the first quantile (Q1), Q2, Q3 and Q4, were 1.11 (95% CI, 1.02 to 1.20; p = 0.016), 1.23 (95% CI, 1.13 to 1.35; p < 0.001), 1.33 (95% CI, 1.21 to 1.46; p < 0.001), and 1.20 (95% CI, 1.09 to 1.33; p = 0.001), respectively, showing that such risk exists regardless of the antacid dosage.

Conclusions: Our findings indicated that there is a strong link between Mg-containing antacid exposure and incident hip fracture risk in both non-dialysis CKD and dialysis patients, suggesting that Mg-containing antacid should be cautiously prescribed in the CKD population.

Funding: Government Support - Non-U.S.

TH-PO570

Increase in Fat Mass Has Protective Effect on Bone Mineral Density Loss After Initiation of Dialysis Therapy

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Background: In contrast to general population, increased fat mass (FM) was reported to have a beneficial effect on mortality risk in dialysis patients. However, the effect of FM on bone status is unclear. We investigated the association between bone loss after initiation of dialysis and changes of fat mass during 1-year of dialysis therapy.

Methods: 246 patients initiating hemodialysis (HD; n=105) or peritoneal dialysis (PD; n=141) were investigated at initiation of dialysis and after 1 year on dialysis. Measurements included: whole body dual-energy X-ray absorptiometry (DXA) for assessment of bone mineral density (BMD) and body composition; nutritional status by subjective global assessment (SGA) and handgrip strength as percentage of controls (HGS%); and, various biochemical biomarkers including insulin growth factor-1 (IGF-1).

Results: During 1-year of dialysis therapy, T- and Z-scores decreased significantly compared to baseline (both p<0.05). Whereas there was no statistically significant change in body weight during 1-year dialysis therapy, total FM, trunk FM and peripheral FM increased significantly compared to start of dialysis, while lean body mass (LBM) decreased. In multivariate linear mixed model, changes of total FM, trunk FM, peripheral FM and LBM were positively associated (all p<0.05) with changes of BMD at all sites except head after adjusting for several confounders (sex, age, height, smoking, physical activity, SGA, HGS%, parathyroid hormone and dialysis modality. Furthermore, changes of serum IGF-1 levels were positively associated with changes of total FM, trunk FM and peripheral FM (p<0.05), but not LBM.

Conclusions: An increased fat mass, central as well as peripheral, appears to have a protective effect on bone loss 1 year after initiation of dialysis. We speculate that the observed effect - which might be one contributor to the beneficial effect of FM on mortality risk in dialysis patients - could be partially explained by enhancement of IGF-1.

Funding: Commercial Support - Baxter Healthcare

TH-PO571

Association Between Normalized Protein Catabolic Rate (nPCR) and the Risk for Bone Fracture in Patients Undergoing Hemodialysis: The Q-Cohort Study

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Background: Normalized protein catabolic rate (nPCR) is used as a surrogate of daily protein intake and nutritional status in patients receiving maintenance hemodialysis (HD). It remains unknown whether nPCR affect the incidence of bone fracture in HD patients.

Methods: A total of 2,869 patients registered to the Q Cohort Study, a multicenter, prospective, observational study, were followed up for a median of 4 years. The primary outcome was bone fracture at any site. The main exposure was nPCR level at baseline. Patients were divided into four groups based on their baseline nPCR levels (Q1: <0.85, Q2: 0.85-0.95, Q3: 0.95-1.05 [reference], Q4: ≥1.05 g/kg/day). We examined the relationship between nPCR levels and the risk for bone fracture using a Cox proportional hazards risk model.

Results: During the follow-up period, 136 patients experienced bone fracture at any site. In the multivariable analyses, the risk for bone fracture was significantly higher in the lowest (Q1) and highest (Q4) nPCR groups compared with Q3 group (hazard ratio [95% confidence intervals]: Group 1, 1.93[1.05-3.66]; Q2, 1.27[0.68-2.44]; Q3 1.00 (reference); Q4, 2.21[1.27-4.02]. Even when analyses were limited to those whose dialysis vintage was longer than 2 years, the association remained unchanged.

Conclusions: Our results suggest that both lower and higher nPCR values increase the risk for bone fracture in HD patients. Further studies are necessary to confirm our observation and elucidate the underlying mechanisms on the association between nPCR level and bone fracture in HD patients.

TH-PO572

Five-Year Changes in Quadriceps Muscle Properties and Risk of Hip Fractures in Older Adults with Reduced and Normal Kidney Function: Nine Years of Follow-Up of the AGES-Reykjavik Study

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Background: Chronic kidney disease (CKD) is associated with poor muscle and bone health, as well as an increased risk of fractures. However, the prediction of fractures from muscle-related parameters in older adults with impaired kidney function remains unknown. Therefore, this study aimed to determine the association of accelerated worsening of muscle properties over 5 years and incident hip fracture among older adults with reduced (estimated glomerular filtration rate < 60 ml/min/1.73 m^2)and normal kidney function.

Methods: A total of 2311 older adults (33.1% CKD stage 3-4), aged 66-91 years at baseline from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, who had completed data on baseline serum creatinine and potential covariates, and valid thigh quantitative computed tomography (QCT) scans and isometric testing at baseline and 5-years later were studied. Fracture predictors included: cross-sectional area (CSA, cm^2), attenuation (Hounsfield unit), and maximum rate of torque development (RTD, N*m/s). Analyses employed Cox-proportional hazard regression models adjusted for potential covariates.

Results: During the median follow-up of 5.7 years, 202 (8%) hip fractures occurred. Having reduced kidney function was associated with an increased risk of hip fracture (HR= 1.6, 95% CI 1.2 – 2.1) compared to having normal kidney function. Adjusted for confounders, an accelerated decline (highest tertile of decline) in quadriceps muscle CSA was associated with higher hip fracture risk (HR =1.62, 95% CI= 1.03–2.54) only in reduced kidney function older adults, while an accelerated decline in muscle attenuation and RTD were not significant predictors of hip fracture in both normal and reduced kidney function subjects.

Conclusions: Our findings support that monitoring quadriceps muscle quantity changes and implementing exercise regimens may be two essential and clinically feasible steps to prevent functional decline and fracture risk, particularly in older adults with reduced kidney function.

Funding: Other NIH Support - contract N01-AG-1-2100

TH-PO573

Trabecular Bone Score Predicts Osteoporotic Fracture in CKD Patients

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Background: Chronic kidney disease and mineral bone disease (CKD-MBD) is a common complication of CKD and this is associated with higher risk of fracture, morbidity and mortality. Current guidelines recommend measurement of bone mineral density (BMD) in CKD patients. However, the focus is only on bone turnover and bone density, and there is no guideline for trabecular bone score (TBS) for trabecular bone microarchitecture in CKD patients. We aim to evaluate the role of TBS in predicting osteoporotic fracture in CKD patients.

Methods: We retrospectively enrolled 125 patients with CKD between 2016 and March 2019. Lumbar spine TBS was extracted from dual-energy X-ray absorptiometry, and we categorized the TBS into three groups as lowest (≥ 1.31), moderate (1.31-1.23), and highest risk group (≤ 1.23). The logistic regression analysis was used to assess osteoporotic fracture risk.

Results: Of 125 patients, mean age was 65.9 ± 14.2 years, 49.6% were on dialysis, 11.2% was highest risk group by TBS. Patients with highest risk group by TBS were significantly older, had lower height, weight, serum 25-OH vitamin D, serum sodium level, BMD *T*-score (lumbar spine, femur neck and total hip) than lower risk group. TBS significantly correlated with BMD *T*-score (lumbar spine, femur neck and total hip), height, weight and serum creatinine level (P <0.001). Osteoporotic fracture was identified in 20 (16.0%) patients. In univariate analyses, old age, women, lower weight, TBS tertile group, lower potassium level were significantly associated with osteoporotic fracture. In multivariate analyses, only highest risk group by TBS was significantly associated with increased osteoporotic fracture risk after adjustment for demographic, comorbid, medication use, and previous fracture.

Conclusions: Lumbar spine TBS significantly correlated with BMD *T*-score and predicts osteoporotic fractures in patients with CKD.

TH-PO574

Usefulness of Trabecular Bone Score and Central Quantitative CT for Assessment of Bone in CKD Patients

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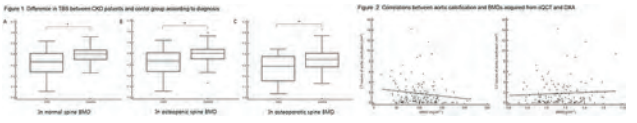
Background: The aims of this study are to propose the usefulness of central quantitative computed tomography(cQCT) and trabecular bone score(TBS) in bone assessment and to show the characteristics of diagnostic discordances in patients with chronic kidney disease(CKD) compared with healthy control.

Methods: This retrospective study included 135 patients (M : F, 73 : 62) with CKD that bone mineral density (BMD) was checked with both cQCT and dual energy absorptiometry (DXA) at the lumbar spine (LS) and femur neck (FN) area. Healthy control included 380 participants who visited hospital of a health check-up (M : F, 170 : 210). The discordancy refers to the diagnostic difference between two sites of DXA or between two modalities of DXA and cQCT. TBS was calculated from DXA images. The volume of abdominal aortic calcification (AAC) was measured using HU threshold (above 130HU) of CT images for cQCT. We classified bone state into three categories such as normal BMD, osteopenia and osteoporosis.

Results: The diagnosis rate for osteoporosis using T-score of FN was not significant different between two groups. Using T-score from only LS, osteoporosis was less common in CKD group compared with control (6.7% vs. 11.8%, P = 0.024). In CKD patients, the results of cQCT showed more osteopenia or osteoporosis among subjects with normal BMD in LS of DXA: osteopenia (n = 49, 31.9 %), osteoporosis (n = 12, 8.9%). Also, CKD patients had significantly lower value of TBS than control group within the same diagnostic category based on DXA (Figure 1). Furthermore, evaluating the discordancy between FN and LS in DXA, the rate of higher BMD of LS was more common than that of FN in CKD patients (85.7% vs. 14.3%; P < 0.001) compared with control group (49.4% vs. 50.6%). The volume of AAC has significant positive correlation with BMD from cQCT (r = -0.188, P = 0.031) whereas that showed negative correlation with BMD from DXA (r = 0.046, P = 0.456, Figure 2).

Conclusions: TBS and cQCT should be proper diagnostic method for the accurate assessment of bone in CKD patients because DXA may overestimate LS BMD. Probably, the AAC would contribute to increase the unexpected increase of LS BMD unlike actual bone status.



TH-PO575

A Novel Magnetic Resonance Imaging Biomarker of Tibial Bone Quality in CKD

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Background: The assessment of uremic bone disease remains a challenge, with available blood-based markers correlating poorly with gold standard histological assessment of bone. Novel quantitative imaging biomarkers with potential for standardization are needed to avoid the need for bone biopsy studies. Our objective is to initially explore the clinical associations of a novel MRI-based biomarker of bone quality of the tibia in healthy controls, CKD stage 3-5 and HD patients.

Methods: 10 healthy controls, 38 CKD stage 3 to 5 patients and 15 HD patients underwent MR with $^1H^+$-weighted imaging of the right calf. Acquired images were analyzed as shown in Figure 1 and the tibial cortical-trabecular bone ratio (CTR) was calculated for each subject. CTR values were compared between groups with Student's t-test for independent samples. Correlation analyses plotting CTR values in different groups against standard blood biomarkers were also run and standard curves interpolated as appropriate.

Results: Refer to Figures 1 and 2.

Conclusions: Worsening renal function is associated with significant reduction in directly image CTR. This may represent a promising imaging biomarker of CKD-MBD and identifies erythropoiesis as being associated with bone quality in CKD patients.

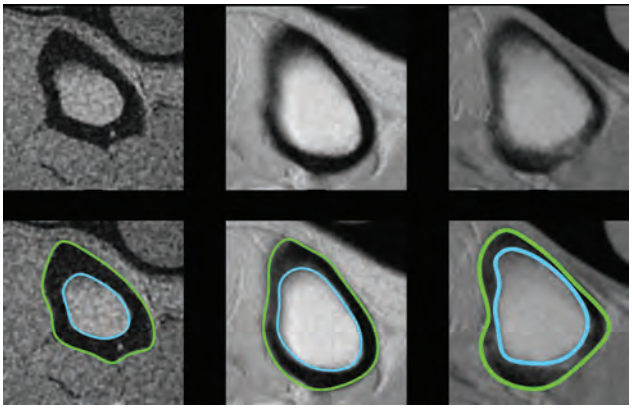

Figure 1: Sample raw and segmented images of the right tibia in a healthy control (A, B), CKD (C, D) and HD patient (E, F).

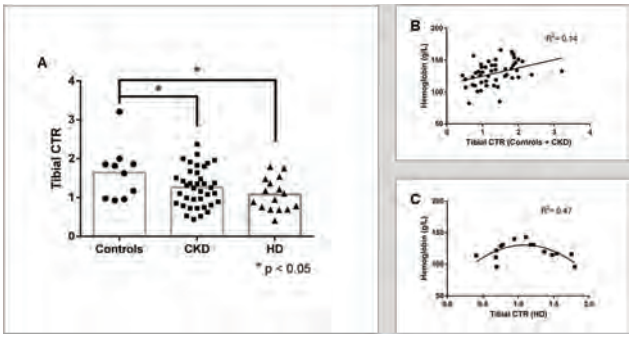

Figure 2: A decrease in CTR was observed in CKD and HD patients when compared to Controls (A). A weak linear relationship was observed between CTR and Hemoglobin levels in Controls+CKD patients (B) and a polynomial-quadratic relationship was observed in HD patients (C).

TH-PO576

Can a New ^{18}F-NaF PET/CT Scan Replace Bone Biopsy to Determine Bone Turnover in Patients with CKD-MBD?

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Background: CKD-MBD is an enormous problem in dialysis patients. Before optimal treatment can be accomplished, bone turnover has to be established. The golden standard, double tetracycline-labeled transiliac bone biopsy, has many disadvantages and is seldom performed. Bone biopsy is cumbersome, expensive, painful, and invasive. It would therefore be of outmost interest to develop an alternative method to establish bone turnover. The purpose of this ^{18}F-NaF PET/CT trail is to implement a new method for several region determination of bone turnover in patients with CKD-MBD.

Methods: A pilot study was conducted in which 17 dialysis patients underwent the new dynamic/static ^{18}F-NaF PET/CT scan. This scan method is initiated with a 60 min. thoracic dynamic scan followed by a 30 min. whole-body static scan. Venous blood samples are drawn at -5, 40, 50, 60 and 90 minutes after a 150 MBq ^{18}F-NaF intravenous injection. A 3-tissue compartment model is used to estimate regional bone ^{18}F-NaF clearance (K_i). K_i is an expression for bone turnover. One cardiac (left ventricle) volume-of-interest (VOI) and four thoracic vertebrae VOIs are placed. Time activity curves are generated. The software PMOD is used for this analysis. Moreover multi-point Patlak analysis is conducted. The PMOD analysis and the Patlak analysis are compared. Finally, the patients underwent double tetracycline-labeled transialic bone biopsy. As a control of the new method, the scan-bone turnover was then compared with the biopsy-bone turnover.

Results: To date, data have been obtained from 9 of 17 included patients. Preliminary results of PMOD analysis demonstrated a vertebral mean K_i-value of 0.041 ±0.01 ml/min/cm^3. The corresponding value by multi-point Patlak analysis was 0.035 ±0.01 ml/min/cm^3. Ki-values present the same range as previously published data for diverse patient groups. We are looking forward to compare results from this new method with results from the bone biopsies and hopefully we get the pleasure of presenting the full dataset at Kidney Week 2019.

Conclusions: The ^{18}F-NaF PET/CT seems feasible for measurement of bone turnover in CKD-MBD. The next step will be to appraise the clinical value to determinate changes in K_i (bone turnover) after medical intervention.

Funding: Private Foundation Support

TH-PO577

Associations Between Body Composition on Cortical Bone Quality in CKD

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Background: Obesity is considered beneficial to bone health due to well-established positive effects of mechanical loading of weight on bone formation. However, studies have reported that excessive fat mass may not protect against osteoporosis: high fat mass was associated with low total bone mineral density. Renal osteodystrophy (ROD) is associated with impaired cortical bone quality due to hyperparathyroidism, but the effects of fat and muscle mass on cortical bone in ROD are unclear. We hypothesized that body composition independently affects cortical bone and that muscle and fat mass have opposing effects on the cortex.

Methods: In 77 patients with mean +/- SD age of 59+/-10 years and with CKD stages 3-5D, we scanned the distal radius and tibia by high-resolution peripheral quantitative CT to measure cortical density, thickness and porosity. We measured total fat, muscle mass and percent body fat by whole body dual-energy X-ray absorptiometry. Cortical measures were correlated with age, sex, BMI, percent body fat, fat free muscle index, PTH, calcium, phosphorus and 25(OH)D. Linear regression models adjusted for age, sex and PTH determined whether muscle and fat mass were independent predictors of cortical bone quality.

Results: At the radius, higher muscle mass was associated with thicker cortices and higher percent body fat was associated with thinner cortices that had fewer and smaller pores (Table). At the tibia, higher muscle mass was associated with thicker, while higher fat content was associated with thinner cortices. In MV regression, higher muscle mass was associated with thicker cortices at the radius and tibia while higher fat mass was associated less porous cortices at the radius. Older age was associated with more severe cortical porosity at the radius (p=0.03) and tibia (p<0.001).

Conclusions: In CKD 3-5D, muscle and fat mass independently predicted, and had opposing effects, on cortical bone quality. Further studies evaluating underlying mechanisms linking muscle and fat to cortical bone quality are needed.

Funding: NIDDK Support, Private Foundation Support

Associations between cortical parameters and body composition adjusted for age and sex from MV linear regression

	Radius				Tibia			
	Cortical Mineral Density [mg HA/ccm]	Cortical Thickness [mm]	Cortical Porosity [1]	Cortical Pore Diameter [mm]	Cortical Mineral Density [mg HA/ccm]	Cortical Thickness [mm]	Cortical Porosity [1]	Cortical Pore Diameter [mm]
BMI	-2.40	0.0003	-0.00002	-0.00007	-0.54	0.01*	0.000006	-0.001
Body Fat %	0.45	-0.0004	-0.0002*	-0.0008	-0.41	-0.003	0.00004	-0.0006
Fat Free Muscle Index	-6.13	0.016*	-0.000003	-0.0003	-0.21	0.03*	-0.000005	-0.0009

*p<0.05

TH-PO578

Poor Correlation of Static Markers of Bone Turnover at the Iliac Crest vs. Greater Trochanter in Autopsy Specimens

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Background: Iliac crest bone biopsies and histomorphometry are the gold standard in the diagnosis of abnormalities within the Chronic Kideny Disease - Mineral and Bone Disorder (CKD-MBD), yet fractures more frequently occur around the greater trochanter of the hip. We compared bone turnover markers between these 2 anatomical sites in autopsies.

Methods: We collected bone tissue samples from the ipsilateral iliac crest and greater trochanter in 10 deceased individuals undergoing autopsy at University of California, San Diego between March-August 2018. Because post-mortem osteoblasts last <48 hours, we used osteoclast surface relative to bone surface (Oc.S/BS), eroded surface relative to bone surface (ES/BS), and osteoid volume relative to bone volume (OV/BV) as markers of bone turnover. We evaluated the correlation of these markers between the iliac crest and greater trochanter using Pearson correlations.

Results: Average age of these individuals was 57±16, 30% were women, and average time from death to autopsy was 3±2 days. We found that the Pearson correlation of Oc.S/BS at the iliac crest vs. greater trochanter was 0.44, p=0.37. Similarly, Pearson correlation of ES/BS and OV/BV were 0.30, p=0.44, and 0.003, p=0.99, respectively.

Conclusions: We found poor agreement of static measures of bone turnover between the iliac crest and greater trochanter. These data suggest that bone histomorphometric measures of the iliac crest may not provide reliable information about bone turnover at other anatomic sites.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO579

Hyperparathyroidism Helps to Explain the Disagreement Between Bioimpedance and Dual-Energy Absorptiometry in the Analysis of Nutritional Status

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Background: Body composition is critical in the evaluation of patients with CKD and can be obtained from multifrequency bioelectrical impedance analysis (BIA) or from the gold standard dual-energy absorptiometry (DXA). Previous studies have shown disagreements between these two methods, mainly regarding the bone mineral content (BMC). We hypothesized that secondary hyperparathyroidism, which is associated with bone loss, is the main responsible for this discrepancy.

Methods: We studied 20 pre-dialysis CKD patients (CKD) and 29 on hemodialysis (18 with severe hyperparathyroidism (HD-SHPT) and 11 already submitted to parathyroidectomy at least 1 year before our analysis (HD-PTX). The total-body composition was determined using DXA and BIA.

Results: HD-SHPT patients tended to be younger (CKD = 52.5 ± 14.3 ys.; HD-SHPT = 41.6 ± 14.9 ys.; HD-PTX 44.9 ± 13.4 ys.; p = 0.06), but had lower BMC measured through DXA (CKD = 2,266 ± 565 g; HD-SHPT = 1,808 ± 522 g; HD-PTX 2,301 ± 658 g; p = 0.04). This difference was not found in BMC measured by BIA (CKD = 3,011 ± 596 g; HD-SHPT = 2,896 ± 711 g; HD-PTX 2,650 ± 467 g; p = 0.30). The highest disagreement between DXA and BIA was found in HD-SHPT group (CKD = -711 g; HD-SHPT = - 915 g; HD-PTX -688 g; p = 0.004). There was a significant correlation between the difference of BMC obtained from DXA and BIA with parathormone (PTH; r = -0.394; p = 0.006) and alkaline phosphatase (AP; r = -0.489; p < 0.0001).

Conclusions: Our results confirm that BIA should be interpreted cautiously in patients with SHPT since higher PTH and AP lead to a greater disagreement between these methods. Moreover, the recovery of bone mass and the decrease of the disagreement after PTX support our hypothesis. BIA loss of accuracy occurs because BMC is not measured, but obtained from an algorithm derived from normal individuals, using the fat-free mass values. Therefore, BMC overestimation is associated with an underestimation of lean mass. This misinterpretation might compromise the management of the nutritional status, as well as of the bone disease, in SHPT patients.

Funding: Government Support - Non-U.S.

TH-PO580

Female Sex Enhances the Association of Secondary Hyperparathyroidism with Increased Bone Turnover Marker in Aged Patients Receiving Hemodialysis

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Background: Female patients undergoing dialysis are at higher risk of fracture than male patients, suggesting the involvement of postmenopausal osteoporosis. However, little is known about the impact of menopause on altered bone metabolism associated with secondary hyperparathyroidism in this population.

Methods: We analyzed data from a cohort of 654 patients receiving maintenance hemodialysis. We examined the hypothesis that female sex is associated with elevated levels of bone-specific alkaline phosphatase (BAP) and enhances the association between intact parathyroid hormone (PTH) and BAP in aged hemodialysis patients.

Results: Females had significantly higher levels of BAP compared to males in patients aged ≥50 years, but not in patients aged <50 years (*P* for interaction by age <0.001). This difference observed in the aged population remained significant after adjustment of age, diabetes, dialysis vintage, body-mass index, and PTH. In the overall cohort or in either of the age subgroups, increased PTH was significantly associated with increased BAP independently of age, diabetes, dialysis vintage, and body-mass index. Among patients aged ≥50 years, the association between PTH and BAP was pronounced in females compared with males (*P* for interaction by sex <0.001), but such effect modification by sex was not observed among patients aged <50 years.

Conclusions: Our results show that female sex enhances the increased bone turnover associated with secondary hyperparathyroidism in aged hemodialysis patients, highlighting the involvement of postmenopausal osteoporosis in high-turnover renal osteodystrophy.

Funding: Government Support - Non-U.S.

TH-PO581

Treatment with Lanthanum Carbonate (LC) May Reduce Bone Mineral Density (BMD): Six-Year Observation in Hemodialysis (HD) Patients

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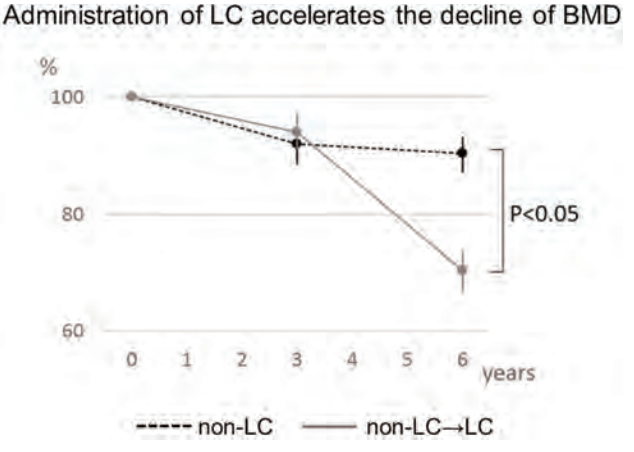
Background: LC is one of the most powerful phosphate binders (PB) for the treatment of hyperphosphatemia in HD patients. However, whether LC can increase BMD or not is still controversial. This study was performed to examine the effects of LC on alteration of BMD in HD patients.

Methods: Subjects were divided into 2 groups and compared. Group 1: Twenty-two HD patients who were treated with non-LC PB for 6 years (14 males and 8 females; mean age, 66.7±7.4 years old; mean HD duration, 11.4±7.6 years). Group 2: Fourteen HD patients who were treated non-LC PB for 3 years, then were converted to receive LC for 3 years (5 males and 9 females; mean age, 62.7±5.5 years old; mean HD duration, 9.7±6.6 years). BMD in these patients were estimated by digital image processing (DIP).

Results: As shown in Figure, the alteration ratio in BMD for group1 was -1.6% / year over 6 years, whereas the alteration ratio was -2.0% / year in the former 3 years, then declined to -7.9% / year in the latter 3 years in group 2. The decrease ratio of BMD for group 2 at 6 years was significantly lower than that of group 1 (p<0.05).

Conclusions: The decline of BMD was constant through 6 years in group 1; whereas the decline of BMD was accelerated after the treatment was converted from non-LC PB to LC in group 2. These observations suggest that administration of LC may reduce BMD in HD patients for some mechanisms.

Funding: Private Foundation Support



TH-PO582

Polymorphism in the Human Matrix Gla Protein Gene Is Associated with the Progression of Osteoporosis in Hemodialysis Patients

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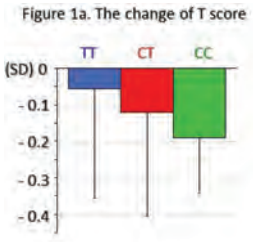
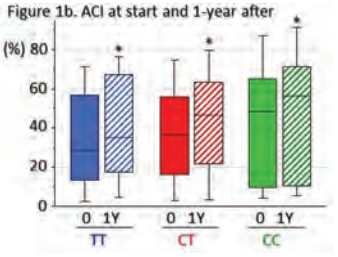
Background: Matrix Gla protein (MGP) is an important protein related osteoporosis and vascular calcification. Single nucleotide polymorphisms (SNPs) coding regions of the MGP gene affect the transcriptional activity. We investigated the relationship between the SNPs and progression of osteoporosis and vascular calcification in patients undergoing hemodialysis (HD).

Methods: This is a prospective and single center study. Using blood samples, SNPs on the MGP gene promoter T-138C (rs1800802, direct sequencing) was investigated. Bone mineral density (femoral, DEXA, T score) and vascular calcification index (ACI, abdominal CT) were examined at start and 1-year after. Several factors related bone: fibroblast growth hormone, bone-type alkaline phosphatase (BAP), and tartrate-resistant acid phosphatase (TRACP5b), uremia: Ca, P, parathyroid hormone-intact, and 25(OH) vitamin D, and inflammation: high-sensitivity CRP, tumor necrosis factor-α, interleukin-6 were measured. The change of T score and ACI were investigated.

Results: The distribution of the T-138C genotype was TT (47.5%), CT (40.0%) and CC (12.5%,). T score of all participants (n=80) at 1-year after was lower than that at start. T score for the CT and CC genotype were significantly decreased. The changes of T scores for the CC, CT, and TT genotype were shown (Figure 1a). The multiple regression analyses revealed that the change of BAP, TRACP-5b, and ACI were the independent predictors of T score change (standardized regression coefficients were -0.443, -0.276, and 0.400, respectively, R^2=0.659). ACI for each genotype were increased (Figure 1b), and there were no differences of ACI change among 3 genotypes.

Conclusions: The MGP-138C genotype may be associated with decrease in T scores in HD patients. The genotype of the MGP gene might be a genomic biomarker that is predictive of osteoporosis.





TH-PO583

Effects of Diuretics Furosemide and Hydrochlorothiazide on CKD-MDB: A Prospective Randomized Study

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Background: Diuretics are often prescribed to patients with CKD to control fluid overload and hypertension. Diuretics may affect CKD-MBD since thiazides are associated with reduced calciuria, reduction/maintenance of PTH levels and increased bone density while loop diuretics have the opposite effect. These effects are still debatable and not fully elucidated in patients with CKD. **Objective**: To evaluate the effects of furosemide (FURO) and hydrochlorothiazide (HYDRO) on CKD-BMD in patients with stage 3 CKD in a regular follow-up.

Methods: This was a RCT comparing HYDRO (25mg/day) and FURO (40mg/day) on urinary and biochemical variables including parathyroid hormone (PTH), alkaline phosphatase (AP), calcium (Ca), CTx and P1NP. After a washout period, patients were randomized to either the HYDRO or FURO group and followed for 1 year, by the same observer, blinded to randomization. Bone effects were also evaluated by Dual X-ray absorptiometry (DXA).

Results: 40 patients with a median of 62 years were included, 20 were randomized to each group, which presented similar characteristics after randomization (for age, gender, eGFR, weight, PTH, Ca, 25(OH)Vitamin-D, and AP). There was a reduction of urinary Ca in the HYDRO group and an increase in the FURO group ($p=0.02$), in addition to a tendency of a higher total serum Ca in the HYDRO group ($p=0.06$). There was no difference in PTH and 25(OH)Vitamin-D levels, albeit there was an annual percentage increase of 1,25 (OH)2ViTD in the FURO group (12.7 ± 32%) and a reduction in the HYDRO group (-13.6 ± 21%), $p=0.048$. CTX, P1NP, and AP increased in the FURO group and reduced in the HYDRO group (all $p<0.05$). No significant difference was found in the percentage change of bone density measured by DXA, only a tendency to greater loss in the proximal 1/3 of the distal radius, more pronounced in the FURO group ($p=0.06$).

Conclusions: Furosemide and hydrochlorothiazide had opposite effects on the CKD-MBD in a 1-year follow-up study. Furosemide seems to be associated with an increase and hydrochlorothiazide with reduced bone remodeling, a fact not evidenced by PTH change. Whether PTH would change in more advanced CKD or in a bigger sample size warrants further investigation.

TH-PO584

Associations of Bone-Related Markers and Cognitive Function in Hemodialysis Patients

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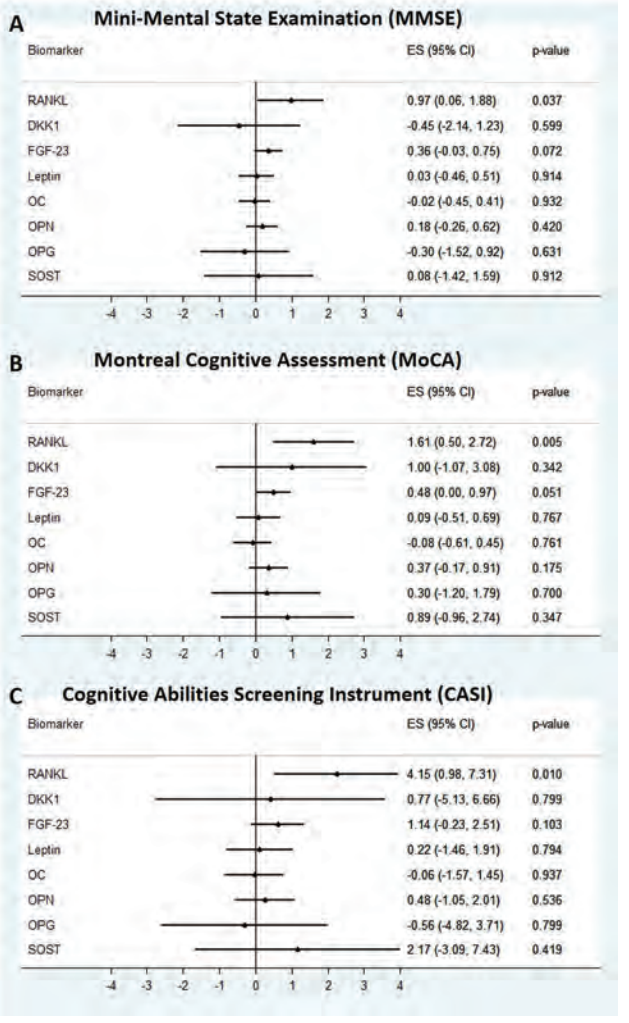
Background: Patients undergoing hemodialysis (HD) have a higher risk of cognitive impairment than the general population but limited data elucidated the biomarkers on this. We evaluate the association of bone turnover markers on cognitive function among 251 prevalent HD enrollees in a cross-sectional study.

Methods: 251 HD patients (median age=57.8; 55% men) without a prior stroke or dementia diagnosis were enrolled. Circulating levels of 8 bone markers (receptor activator of nuclear factor kappa-B ligand [RANKL], dickkopf-related protein 1 [DKK1], fibroblast growth factor 23 [FGF23], leptin, osteocalcin [OC], Osteopontin [OPN], osteoprotegerin [OPG], sclerostin [SOST]) were analyzed by a multiplex immunobead assay (Millipore, St Charles, MO, US). The association between bone-related markers and cognitive function test (Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA], and Cognitive Abilities Screening Instrument [CASI]) were investigated in a linear regression model.

Results: Among 8 bone-related markers, RANKL was the only bone markers found associated with cognitive function (MMSE, MoCA, and CASI test) in HD patients (Figure). In stepwise multiple linear regression analysis, the positive association remained statistically significant in MoCA (β=1.14, 95% CI 0.17 to 2.11) and CASI (β=3.06, 95% CI 0.24 to 5.88). Short-term memory (β=0.52, 95% CI 0.01 to 1.02), mental manipulation (β=0.51, 95% CI 0.05 to 0.96), and abstract thinking (β=0.57, 95% CI 0.06 to 1.09) were significant domain in CASI score.

Conclusions: Serum RANKL levels were found potential associated with higher cognitive function test in HD patients. Further large scale and prospective studies are needed to confirm our findings.

Funding: Government Support - Non-U.S.



TH-PO585

Bone Phenotype in Patients with ESKD Treated with Proton Pump Inhibitors

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Background: Proton pump inhibitors (PPIs) are suspected of having a negative impact on the skeleton and possibly increasing the risk of osteoporosis in the general population and patients with chronic kidney disease. Underlying pivotal pathophysiological mechanisms include calcium malabsorption, gastrin-mediated parathyroid gland stimulation, vitamin B12 deficiency, and impaired function of osteoblasts and osteoclasts. The present cohort study aimed to map the impact of PPI use on the bone phenotype in end stage kidney disease (ESKD) patients.

Methods: Bone mineral density (BMD, by dual energy x-ray absorptiometry, DXA) both at the lumbar spine and hip (total hip and femoral neck) and bone turnover markers (BTMs; bone alkaline phosphatase, tartrate-resistant acid phosphatase 5b, procollagen type I N-terminal propeptide) were assessed in 308 patients with ESKD (53.7 ± 13.1 yrs, male 64%), with bone histomorphometry data available in 69 patients. On-hundred and three patients (33%) were treated with PPIs (cases). Laboratory parameters of mineral metabolism including calcium, phosphate, magnesium, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23) and sclerostin, parameters of inflammation (C-reactive protein, Interleukin-6), vitamin B12 levels, and nonphosphorylated-uncarboxylated isoform of MGP (dp-ucMGP), as a proxy of vitamin K status were assessed in all patients.

Results: ESKD patients on PPI therapy showed lower BMD at the hip, while BTMs and bone histomorphometry were not different from controls. PPI users, furthermore, were characterized by older age, more cardiovascular morbidity, lower serum magnesium, lower phosphate and FGF23, and higher serum dp-ucMGP levels and parameters of inflammation. PTH and vitamin B12 levels did not differ between PPI users and non-users. PPI use associated with BMD at the femoral neck, independent of classical (age, gender, BMI) and non-classical (vitamin K status, cardiovascular disease, inflammation) determinants.

Conclusions: PPI use in patients with ESKD independently associated with low BMD at the hip. Our data argue against an important role of PTH, vitamin B12 or dysfunctional osteoblast and osteoclast in the pathophysiology of PPI-related osteoporosis in ESKD. The link between PPI use and poor vitamin K status needs further investigation.

TH-PO586

Proton Pump Inhibitor Use and Risk of Major Fractures in Kidney Transplant Recipients

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Background: Fracture is a significant problem among kidney transplant recipients (KTRs). Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs in KTRs and have been associated with a higher risk of fractures in the general population. This study aimed to determine how PPIs use is associated with the incidence of major fractures in KTRs.

Methods: Using the Wisconsin Allograft Recipient Database (WisARD), we identified 155 major fracture events that occurred at least 12 months after transplantation between 2000 and 2015. Each eligible case was matched using incidence density sampling with five controls on age, sex, race, transplantation year (±3 years), living versus deceased donor and prior transplantation. PPI and histamine 2-receptor antagonists (H2RA) use during the year prior to the index date were identified. The association between prior PPI/H2RA use and incidence of major fractures were assessed by conditional logistic regression.

Results: A total of 155 cases were matched to 685 controls. A higher proportion of cases had a history of diabetes and cardiovascular disease. During the year prior to the index date, cases had lower serum albumin, higher phosphorus, higher iPTH, and higher alkaline phosphatase. A higher proportion of cases ever used corticosteroid and bisphosphonate. 67.7% of cases and 51.5% of controls ever used a PPI, and 15.5% of cases and 11.3% of controls ever used an H2RA. PPI use was associated with higher incidence of major fractures in unadjusted analysis (OR=2.4, 95% CI: 1.6-3.5). The association remained similar when adjusting for demographic and transplant-related covariates (OR=2.3, 95% CI: 1.5-3.6); and further adjusting for use of corticosteroid, bisphosphonate, vitamin D and calcium supplement (OR=1.9, 95% CI: 1.2-3.1). H2RA use was not associated with higher incidence of major fractures in adjusted analysis (OR=1.0, 95% CI: 0.5-1.8). The associations between PPI use and major fractures remain similar in participants who never used a bisphosphonate in the prior year.

Conclusions: PPI use may be associated with a higher risk of major fractures among KTRs. Clinicians should carefully evaluate the risk factors for fracture, weight the risk versus benefit before prescribing PPI, and have interval assessment of continued PPI use in KTRs.

TH-PO587

Follow-Up of Bone Mineral Density Changes in De Novo Kidney Transplant Recipients Treated with Two Doses of the RANKL Inhibitor Denosumab

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Background: Studies in women with post-menopausal osteoporosis have shown that discontinuation of treatment with denosumab leads to an increased risk of vertebral fractures because of rebound bone turnover and rapid loss of bone mineral density (BMD).

Methods: In an extended analysis of a randomized clinical trial examining the effect of denosumab on BMD we analyzed the effect of denosumab withdrawal on BMD changes. A group of 25 *de novo* kidney transplant recipients (KTR) which were treated for 1 year with two six-monthly doses of denosumab (D) on top of standard treatment (daily calcium and vitamin D) were compared to a control group of 29 KTR which received standard treatment alone. BMD changes were analyzed by repeated DXA shortly after transplantation (baseline), after 6 and 12 months (active treatment phase) and once or twice after 2 to 6.5 years (follow-up phase).

Results: Figure 1 shows the change of total lumbar BMD (g/cm^2) over time by randomisation group. The BMD at the lumbar spine declined markedly (arrow) after discontinuation of treatment with denosumab (D) but increased again thereafter. Thus, the average monthly change in lumbar spine BMD from month 12 onward was only 0.1±2.8‰ in the denosumab group but 1.5±1.9‰ in the control group (p=0.021). The average monthly change in lumbar spine BMD from baseline to follow up was similar in the control and denosumab group (1.1±1.2‰ vs 1.5±2.4‰, p=0.788). Similar results were seen at the total hip.

Conclusions: In *de novo* KTR treated with two doses of denosumab, we detect a marked decrease in lumbar spine and hip BMD when denosumab is discontinued. To prevent the decline in BMD after denosumab discontinuation, bisphosphonate treatment might be considered to antagonize the enhanced bone turnover.

Funding: Clinical Revenue Support

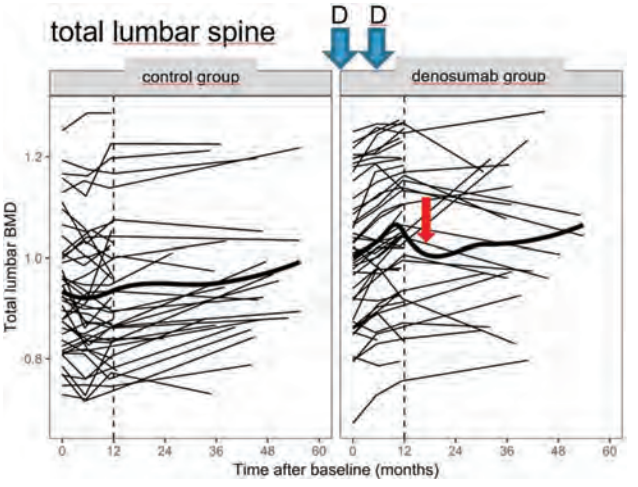

Figure 1: Total lumbar BMD over time

TH-PO588

The Effect of Increasing Dialysate Magnesium on Calciprotein Particles, Inflammation, and Bone Markers in Subjects with ESKD: Post Hoc Analyses from a Randomized Controlled Trial

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Background: The formation of fetuin-A-laden mineral-containing nanoaggregates, calciprotein particles (CPP), act as an important component of the humoral defenses against ectopic calcification. Magnesium (Mg) has been shown to delay the transition of amorphous calcium/phosphate-containing primary CPP to crystalline apatite-containing secondary CPP *ex vivo*, but the effects of increasing dialysate Mg on the endogenous CPP load is unknown.

Methods: *Post-hoc* analyses from a randomized double-blind parallel-group controlled clinical trial of 28 days treatment with high dialysate Mg of 2.0 mEq/L versus standard dialysate Mg of 1.0 mEq/L in 57 subjects undergoing maintenance hemodialysis for end-stage kidney disease. CPP particle load, markers of systemic inflammation and bone turnover were measured in serum at baseline and follow-up.

Results: After 28 days of treatment with high dialysate Mg, serum total CPP (–52%), primary CPP (–42%), and secondary CPP (–68%), were all lower in the high Mg group ($p < 0.001$), but were unchanged in the standard dialysate Mg group. Concentrations of tumor necrosis factor-alpha (–20%) and interleukin-6 (–22%) were also reduced with high dialysate Mg treatment ($p < 0.01$). With respect to effects on bone turnover markers, high dialysate Mg resulted in higher levels of bone-specific alkaline phosphatase (a marker of bone formation) (+17%) but lower levels of tartrate-resistant acid phosphatase 5b (a marker of bone resorption) (–33%) ($p < 0.01$). Inflammatory cytokines and bone turnover markers were unchanged in the standard dialysate Mg group over the same period. Correlation analyses between changes in the various parameters suggest that increasing serum Mg reduces CPP release from bone and thus lowers systemic inflammation related to CPP particle load.

Conclusions: Increasing dialysate Mg reduces CPP particle load and systemic inflammation, while also increasing markers of bone formation and decreasing markers of bone resorption.

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

TH-PO589

Plasma Osteopontin Levels Directly Correlate with Intact Parathyroid Hormone and Alkaline Phosphate Levels in ESRD

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Background: Bone turnover disorders and reduction in bone mineral density are commonly observed in end stage renal disease (ESRD) patients. Osteopontin (OPN) is a glycol-phosphoprotein that stimulates osteoclast adhesion to bone. OPN may play a significant role in the pathways involved in bone turnover disorders. The objective of this study was: (1) to identify plasma levels of OPN in ESRD and normal populations, and (2) to elucidate if relationships exist between OPN and iPTH, and OPN and alkaline phosphatase.

Methods: Plasma levels of OPN were measured via commercially available enzyme linked immunosorbent assays (ELISAs) in ESRD patients (n=92). A chart review was conducted on these patients to identify levels of intact parathyroid hormone (iPTH)

andalkaline phosphatase at time of plasma draw. Additionally, levels of total calcium, albumin, calcium corrected for albumin, phosphorus, ferritin, white blood cell count (WBC), and platelet count (PLT CT) were identified at time of plasma draw via the chart review. OPN levels were also measured in normal control patient plasma (n = 49) purchased from George King Bio-Medical, Inc., Overland Park, KS.

Results: The ESRD cohort showed a statistically significant elevation of OPN plasma levels ($p < 0.0001$, Mann-Whitney t-test) compared to the normal group. Spearman correlation tests revealed a significant positive correlation of OPN with iPTH ($p < 0.0001$; $r = 0.5606$, 95% confidence interval = 0.3968 to 0.6898) and OPN with alkaline phosphatase ($p < 0.0001$; $r = 0.4381$, 95% confidence interval = 0.2494 to 0.5948) in the ESRD cohort. No statistically significant correlations were identified between OPN and total calcium, calcium corrected for albumin, albumin, phosphorus, ferritin, WBC, and PLT CT ($p > 0.05$).

Conclusions: OPN levels are significantly elevated in ESRD patients. Furthermore, OPN levels were also found to be positively correlated with the bone turnover biomarkers iPTH and alkaline phosphatase. These studies suggest that hyperparathyroidism secondary to ESRD increases circulating iPTH, stimulating osteoblast and osteoclast activation and differentiation that increases alkaline phosphatase and OPN production, ultimately resulting in increased bone turnover.

TH-PO590

Infilling of Individual Cortical Pores in the Setting of CKD

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Background: Cortical porosity is the most prominent skeletal phenotype in the setting of chronic kidney disease (CKD), and likely contributes to the increased fracture risk in CKD. Reducing cortical porosity is likely to confer improved bone mechanical properties yet data on this topic are limited. Although strategies aimed at prevention of cortical porosity development would be ideal, a more likely clinical scenario would require that existing cortical porosity be reduced through pore infilling. The purpose of this work was to test the hypothesis that cortical porosity can be reversed indicating porosity infilling.

Methods: Skeletally mature male rats (n=6) with established CKD (BUN > 2x normal age-matched animals and PTH values of ~500-2500 pg/mL) were scanned with high resolution CT before and after 5 weeks of 3% calcium drinking water to suppress PTH.

Results: Baseline imaging showed cortical porosity of the distal tibia ranging from 0.5% to 10.1% across the six animals. After 5 weeks of treatment PTH values ranged from ~30-80 pg/mL, BUN was unchanged, and cortical porosity was < 1% in all animals. Using a newly developed MATLAB program that allows tracking of individual pores, the overwhelming majority of pores (93%) completely filled in over the 5 week period while 6% of pores became smaller and only 2% of pores newly developed. Preliminary analysis on kidney transplant patients (n=2), using high-resolution peripheral CT scans of the distal tibia, show that that over 60% of the pores either completely infill or get smaller one year following kidney transplant. This was offset by newly formed pores or pores that got larger over the year, resulting in overall porosity being unchanged.

Conclusions: These data confirm that in the setting of CKD, cortical pores can fill in and that analysis methods that tracking individual pores over time provides a unique view of the dynamic changes to cortical bone porosity.

TH-PO591

Evaluation of Provincial Initiatives in Integrated Renal Palliative Care: A Baseline Assessment of Pre-Implementation Patient Perspectives

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Background: Early goals of care (GOC) conversations show improved patient outcomes and reduced health care costs. However, content and timing of these conversations have been variable. BC Renal has recently implemented a province-wide multipronged approach to improve palliative care in nephrology, which requires systematic evaluation to demonstrate efficacy as part of ongoing quality improvement. Patient perspectives are presented here as part of a larger evaluation framework. Our objectives were to assess baseline advanced directives experiences and perspectives in patients with advanced renal disease (CKD, peritoneal dialysis, home hemodialysis and in-center HD) across 5 health authorities in British Columbia (BC).

Methods: Interventions include: 1)Serious illness conversation guide (SICG) workshops at regional meetings and implementation of a "train the trainer" SICG program, 2)Online best practice guidelines to GOC and renal disease symptom management, and 3)Online patient resources. Pre-implementation telephone interviews (~15 minutes each) were conducted with 30 randomly selected patients across BC. Interviews were analyzed quantitatively for patients' involvement in GOC and qualitatively for common themes. Following baseline assessment, a 1 year follow up across all jurisdictions in BC will be undertaken to evaluate improvements to the palliative care approach.

Results: 67% of patients interviewed have advanced directives and living wills; this is more common in patients on dialysis (75%) than in patients with CKD (50%). Only 30% of patients had detailed discussions with their health providers about life-sustaining therapy or palliation in case of a life-threatening condition; this varied across health authorities. While most patients did not find GOC discussions to be difficult, they would prefer if providers initiated discussion at multiple time points and had more time to provide information.

Conclusions: This baseline patient perspective assessment informs strategies for improvement in the quality, quantity, timing and frequency of GOC discussions. The provincial integrated palliative nephrology initiative targeting these identified gaps in care will be evaluated in 1 year as part of a holistic evaluation framework.

TH-PO592

Evaluation of Provincial Initiatives in Integrated Renal Palliative Care: A Baseline Assessment of Pre-Implementation Clinician Practices

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Background: Early goals of care (GOC) conversations show improved patient outcomes, enhanced quality of life, and reduced health care costs. However, content and consistency of these end of life discussions have been variable. Based on a recent needs assessment from renal care providers, BC Renal has implemented a multipronged approach to improve palliative care in nephrology. This large-scale project requires systematic evaluation to demonstrate efficacy as part of ongoing quality improvement. Our objective was to assess baseline quantity and quality of GOC directives and discussions documentation in patients with advanced renal disease across 5 health authorities in British Columbia (BC).

Methods: This study has a one year duration, and includes all renal units in health authorities across BC. Interventions include: 1)Serious illness conversation guide (SICG) workshops at regional meetings and implementation of a "train the trainer" SICG program, 2)Online best practice guidelines to GOC and renal disease symptom management, and 3) Online patient resources. A pre-implementation chart audit was conducted on 30 randomly selected charts from CKD and dialysis clinics. The contents of the chart audit included: 1) Presence and location of GOC directive and GOC discussion, 2) Correlation between chart data and provincial renal database (PROMIS), and 3)Evaluation of GOC as per the SICG framework.

Results: The chart audit showed the majority of patients had GOC directives documented (80%), most within the last year (57.6%). GOC discussions were less commonly documented (47%); wide variability across health authorities (0-100%) existed. Documentation regarding GOC was sparse in PROMIS (23%). Prognosis and patients' level of understanding was frequently documented during GOC discussions (92.3% & 69%), patients' goals and involvement of family was less frequent (53% & 46%).

Conclusions: Our pre-implementation baseline assessment informs that room for improvement in the quantity of GOC discussions as well as consistency in documentation across health authorities and in PROMIS exists. Documenting family involvement and patient goals can be improved. This baseline data will guide further quality improvement initiatives.

TH-PO593

Artificial Intelligence Hospitalization Risk Model-Guided Selection for Enhanced Psychosocial Care

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Background: A large dialysis organization (LDO) leverages an artificial intelligence (AI) risk model to help guide screening for a Social Work Intensive (SWI) program in value-based care (VBC) settings. SWI provides enhanced psychosocial care to improve quality of life, thereby reducing hemodialysis (HD) non-adherence/hospitalizations. In conventional models, patients are screened for SWI based on team identification of non-adherence or difficulty achieving outcome goals. We assessed if AI-directed SWI enrollment in VBC yielded comparable benefits to conventional clinician-based paradigms. The statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of the Centers for Medicare & Medicaid Services (CMS). The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Methods: We used data from patients enrolled in SWI in 2017. In VBC, a 12-month hospital admission risk model guided SWI screening. In conventional care, SWI screening was based on clinician evaluation of risk. Patients screened positive for barriers in depression, stress, and sleep were enrolled into SWI and provided tailored weekly interventions for 8 weeks. We calculated admission and HD non-adherence 3 months before and after SWI enrollment in VBC and conventional settings.

Results: Among 6425 patients (conventional n=4646, VBC n=1779) enrolled in SWI program, hospital admission rates were similar before SWI enrollment between care settings, but HD non-adherence rate was lower in VBC settings. Admission and HD non-adherence rates were consistently lower 3 months after SWI enrollment in both a VBC and conventional setting (Figure 1A & B).

Conclusions: AI-directed SWI screening and enrollment in VBC appears to have consistent improvements in outcomes compared to clinician-based identification of risks in conventional settings. Use of this AI technology may help streamline efforts and allowing more time to focus on patient care.

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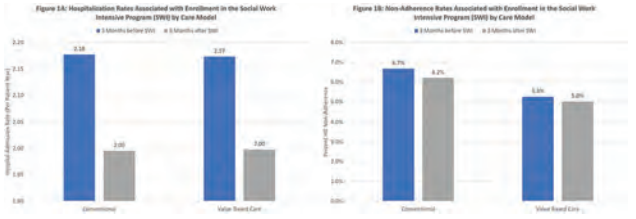

TH-PO594

A Qualitative Exploration of Treatment Burden and Its Impact on Quality of Life Among CKD Patients in Qatar

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Background: Chronic kidney disease (CKD) patients typically experience comorbidities and complications resulting in complex treatments. Treatment-related burden ultimately impair adherence and quality of life (QoL). Quantifying treatment-related burden and QoL using quantitative measures may not provide an in-depth understanding of this phenomenon. We performed a study to qualitatively explore and describe treatment-related burden and its impact on QoL among CKD patients in Qatar.

Methods: One-to-one semi-structured interviews with CKD patients were conducted. An interview guide was developed based on literature review, conceptual model and discussions among the research team members. The interview questions addressed several components including facing life limitations and stressors (physical, psychological, social, financial and nutritional). The interviews were audio-recorded, transcribed verbatim, and analyzed thematically.

Results: Randomly selected twenty-four CKD patients (10 pre-dialysis and 14 hemodialysis) of diverse characteristics were interviewed. Two themes related to the factors that reduce perceived treatment burden and improve patients' QoL emerged: (1) religion and faith in God; (2) quality of the care provided (including health care providers and facility quality and establishing family-like environment). On the other hand, five themes related to the factors that increase perceived treatment burden and worsen patients' QoL emerged from the interviews: (1) medication burden (polypharmacy, side effects, medication formulation, and non-adherence); (2) lifestyle changes imposed on CKD patients; (3) challenges with international travels; (4) financial burden and; (5) empathy.

Conclusions: Qualitative Thematic analysis has yield two factors that reduced perceived treatment burden and improved patients' QOL; religion and faith in God, and quality of the care provided. Medication burden, life style changes, challenges with international travelling, financial burden, and empathy were factors that worsen perceived treatment-related burden and HR-RQOL. Our study suggests that identified factors that increase treatment-related burden should be considered when designing healthcare interventions directed toward CKD population

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TH-PO595

Profiles and Determinants of Dialysis Recovery Time in Incident Hemodialysis

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Background: Hemodialysis (HD) is lifesaving, yet can associate with symptoms (e.g. nausea, cramping and fatigue). Dialysis recovery time (DRT) surveys capture the perceived time after HD to return to performing regular activities. We characterized the profiles and determinants of DRT in incident HD treated at a large dialysis organization (LDO) in the United States.

Methods: We used data at an LDO during 2014 through 2017 for patients who completed a DRT survey ≤180 from first date of HD. DRT survey was administered as part of KDQOL questionnaire. DRT survey asks: "How long does it take you to be able to return to your normal activities after your dialysis treatment?". Categorical answers were: <0.5, 0.5-1, 1-2, 2-4, >4 hours. Distinctions in demographic and clinical variables were assessed between DRT categories, with <0.5 hours as a reference.

Results: We analyzed data from 98616 HD patients who completed the DRT survey in the first 180 days of HD. Patients were 62.6±14.4 years old, 57.8% male, 69.1% white race, 64.7% used a catheter. Incident HD patients typically had a DRT <1 (19.1%) or >4 hours (22.9%). All demographic and clinical variables had some association with longer DRT categories compared to a DRT <0.5 hour, with exception of HD treatment time, interdialytic weight gain, and phosphate levels. Select variables are noted in Table 1.

Conclusions: More than 20% of incident HD patients report a DRT >4 hours. Longer DRTs are associate with most demographic and clinical variables. Remarkable factors associated with longer DRTs include: catheter use; lower albumin, sodium and iPTH levels; lower Kt/V, ultrafiltration volume by body weight, ultrafiltration rates, and treatment frequency. Patient centered strategies to optimize the HD therapy need to be tested and may have potential to improve how patients feel from HD and enhance their quality of life.

Funding: Commercial Support - Fresenius Medical Care North America

Parameter	Description	Dialysis Recovery Time ≤180 Days from First Date of HD (hours) Mean (SD), Column %, or Rate PPY				
		<0.5 (Reference)	0.5-1	1-2	2-4	>4
Patient	Percent of patients	25.2%	19.1%	17.3%	15.5%	22.9%
Treatment	Kt/V	1.609 (0.313)	1.630*** (0.319)	1.632*** (0.321)	1.627***	1.625*** (0.322)
	Normalized UFV by body weight (nUFVbw) (mL/kg)	26.9 (10.8)	27.1 (10.9)	26.6 (10.8)*	26.5 (10.9)***	25.9 (10.8)***
	UFR (mL/hour/kg)	7.14 (2.90)	7.19* (2.93)	7.07* (2.92)	7.03*** (2.93)	6.87*** (2.91)
	Number of treatments ±30 days of DRT survey (n)	24.71 (3.85)	24.61* (3.84)	24.62* (3.65)	24.61**(3.94)	24.23*** (4.20)
Clinical	Catheter (%)	63.4%	64.2%	65.3%***	64.8%**	65.8%***
Laboratories	Albumin (g/dL)	3.71 (0.41)	3.68*** (0.41)	3.67*** (0.42)	3.66*** (0.42)	3.64*** (0.43)
	iPTH (pg/mL)	396.1 (291.1)	390.7 (290.0)	389.5* (292.9)	383.7*** (283.7)	372.1*** (280.0)
	Sodium (mmol/L)	138.0 (3.1)	137.9*** (3.1)	137.8*** (3.1)	137.8*** (3.1)	137.7*** (3.2)

*Differences in means/proportions/rates with DRT of <0.5 hours as the reference: *, p<0.05; **, p<0.01; ***, p<0.001*

TH-PO596

Impact of Elobixibat on Chronic Constipation in Patients on Hemodialysis Assessed Using the Patient Assessment of Constipation-Quality of Life Questionnaire

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Background: Hemodialysis patients are prone to constipation caused by fluid restriction, water removal, food restriction, complications, and drugs among other causes, and their quality of life (QOL) is adversely affected. Elobixibat is a highly selective inhibitor of an ileal bile acid transporter, leads to the augmentation of bile acid levels in the colon, and subsequently enhances colonic motility and secretion. Administration of elobixibat to hemodialysis patients with chronic constipation may improve QOL by a novel mechanism of action. However, the impact of elobixibat on chronic constipation in patients on hemodialysis has not been reported to date. This study aimed to evaluate the effect of elobixibat on the QOL of hemodialysis patients with chronic constipation.

Methods: This was a multicenter study. We used the Japanese version of the Patient Assessment of Constipation-Quality of Life (PAC-QOL) questionnaire. Altogether, 26 patients (18 males and 8 females) aged from 47–90 years, who satisfied the Rome 3 diagnostic criteria for functional constipation were enrolled. These patients were additionally administered elobixibat 10 mg/day and responded to the PAC-QOL questionnaire at baseline and after 4 weeks. Bayesian statistics were used to confirm our results.

Results: The number of spontaneous bowel movements per week increased significantly from 2.5 ± 1.2 to 4.0 ± 2.0 ($p < 0.001$). The Bristol Stool Form Scale score significantly improved from 1.8 ± 0.8 to 3.6 ± 0.7 ($p < 0.001$). The physical discomfort score decreased significantly from 1.92 ± 0.82 to 0.99 ± 0.74 ($p < 0.001$). The psychosocial discomfort score decreased significantly from 1.19 ± 0.95 to 0.64 ± 0.60 ($p < 0.001$). The worries/concerns and satisfaction scores also decreased significantly from 1.87 ± 0.75 to 1.28 ± 0.61 ($p < 0.001$) and 2.80 ± 0.62 to 1.94 ± 0.79 ($p < 0.001$), respectively. The total PAC-QOL score showed a significant decrease from 1.85 ± 0.69 to 1.18 ± 0.58 ($p < 0.001$). Bayesian statistics confirmed the significance of these results.

Conclusions: Administration of elobixibat to hemodialysis patients with chronic constipation reduced the scores of PAC-QOL and improved the patients' QOL. Elobixibat may therefore serve as a new option for the treatment of constipation in hemodialysis patients.

TH-PO597

Dietary Patterns Associated with Kidney Function Decline and Incident CKD in the General Population: The LifeLines Cohort Study

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Background: Nutrition strongly impacts the incidence and progression of chronic kidney disease (CKD). Recently, reduced rank regression (RRR) has emerged as a method that identifies dietary patterns in an exploratory way while using prior knowledge to select a set of response variables. The aim of this study was to identify a specific dietary pattern associated with renal function using RRR, and to evaluate its association with CKD incidence.

Methods: We included 78,350 participants from the LifeLines population-based cohort in the Northern Netherlands. All participants were free of CKD (defined as $eGFR_{CKD\text{-}EPI}$ <60 mL/min/1.73 m^2) at baseline and completed a second visit four years later. Dietary intake was ascertained with a 110-item food frequency questionnaire. The dietary pattern, stratified by sex, was constructed cross-sectionally by RRR, with eGFR as a response variable. Multivariable logistic regression was used to study the association between dietary patterns score and CKD incidence or an eGFR decline of ≥20%, adjusted for potential confounders.

Results: Among women, the eGFR-associated dietary pattern was characterized by high intake of eggs, low-fat and high-fat cheese, and legumes and low consumption of sweetened dairy drinks, desserts, cake and cookies, sweet sandwich toppings, white meat,

and commercially prepared dishes. The male dietary pattern was characterized by high consumption of high-fat and low-fat cheese, bread, full-fat milk, fruits, vegetables, beer, and low consumption of white and red meat. After a mean follow-up of 3.9 years, 7,612 participants experienced a >20% eGFR decline and 2,072 participants developed CKD. The eGFR-based diet was associated with a lower risk of eGFR decline (OR 4th vs 1st quartile, women: 0.84 [95% CI 0.76-0.92]; men: 0.74 [0.65-0.84] and of incident CKD (women: 0.60 [0.50-0.73]; men: 0.52 [0.41-0.66]).

Conclusions: The results provide support for potential diet interventions to prevent renal function decline and CKD. RRR may be a useful tool for identifying dietary patterns that affect renal function and CKD development.

TH-PO598

The Impact of Eating During Hemodialysis Treatment on Nutritional Measures in In-Center Hemodialysis Patients

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Background: Poor nutritional status is common among patients receiving hemodialysis (HD) treatment. Providing nutrition during HD treatment may improve nutritional status and outcomes, but remains controversial. This has led to the adoption of different in-center dialysis unit nutrition policies. Therefore, we sought to examine the relationship between policies on food intake during treatment and nutrition-related measures.

Methods: We analyzed data from Phase 5 of the Dialysis Outcomes and Practice Patterns Study (DOPPS) to look at the relationship between baseline nutrition-related measures (serum levels of albumin, phosphorus, potassium, and body mass index (BMI)) and clinic policy related to eating during HD (not allowed, patients may eat food provided by clinic, patients may bring food from home, or patients may eat food provided by clinic and/or brought from home). We limited our analysis to only countries with clinics utilizing all four policies on eating during HD. Nutritional measures were compared by ANCOVA with individual differences determined by least square difference post-hoc. Additionally, the odds of having an albumin >3.4 g/dl were determined by multivariable logistic regression.

Results: Among 5,358 HD patients (61% male, age 66±15 years, vintage 4±6 years) included in the analysis, serum albumin and potassium were highest and phosphorus the lowest in patients dialyzing at clinics that provided food during HD ($p<0.05$). Body mass index (BMI) was highest among patients dialyzing at clinics that allowed patients to bring their own food. Compared to patients who dialyzed at clinics where they were not allowed to eat, the odds of having an albumin above 3.4g/dl was higher in those dialyzing at clinics where food was provided by the clinic (Adjusted OR=2.0, 95% CI 1.6-2.6) and those with food provided by the clinic and also allowed to bring their own food (Adjusted OR=1.6, 95% CI 1.3 – 2.0).

Conclusions: Patients who dialyze at clinics that provide food during HD treatment exhibit higher serum albumin, higher potassium, and lower phosphorus levels than patients who dialyzed at other clinics. Whether in-center nutrition and eating policies contribute to differences in other clinical outcomes including quality of life, hospitalizations, and mortality warrants additional studies.

TH-PO599

Improved Diet, Sleep, and Strength Among CKD Patients Following 6-Week App Intervention with Personalized Mentoring

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Background: CKD is a long-term condition which affects approximately 14% of the general population in the United States. CKD influences circulatory dysfunction, anaemia, malnourishment, strength degeneration, muscle integrity, glucose imbalance, and decreased bone thickness. Additionally, up to one third of CKD patients have depression. For CKD patients, adherence to the CKD diet is critical for maintaining quality of life, yet few studies have focused on methods to improve and maintain patients' adherence

Methods: In our trial 6-week "Remote Chronic Disease Management" Programme, nine (9) patients at various stages of CKD consented to participate and were provided with a smartphone app called RenalMate. The app allows for daily monitoring of self-reported data (Food log, Sleep, Stress and Activity Level), as well as a remote connection to fitness, dietician, and health mentors. Importantly, the social community and mentoring team provided accountability for the self-reported data tracking and diet/exercise adherence. In addition to daily feedback from coaches and other patients, participants were given weekly progress reports during individualized teleconference sessions with their coach

Results: By the end of the 6-week program, 78% of participants lost weight, and of those 14% lost 17-20 pounds and 72% lost 3-6 pounds. 89% of participants improved their strength during the programme. 71% of participants reduced their stress level from high/very high to medium/ low. 89% either increased their nightly hours of sleep or maintained a healthy 7-8 hours. These improvements were also seen by the participants. 89% felt more restful with higher levels of energy by the end of the programme. 72% felt they improved their diet overall. And most importantly, 100% said they would recommend the programme to a friend

Conclusions: This combination of self-reporting, comprehensiveness of data tracking, as well as the use of a specialized social app and weekly teleconferences with coaches represents a novel and scalable approach to CKD management. Participants improved in both quantitative and qualitative measures of health. Future studies should expand on the role of education and the long-term impact of such programmes, involving wider multidisciplinary teams (MDT) for example, healthcare scientists to provide CKD patients education surrounding laboratory parameters

TH-PO600

Development of an International Standard Set of Nutritional Priorities for Patients with Non-Dialysis CKD

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Background: Protein energy wasting is common in CKD and associated with poor outcome. Many studies have been conducted to improve nutrition in CKD, but outcomes may not be relevant to patients / clinicians and are variable. These problems can diminish the value of interventions as means to improve patient's lives. This project aims to identify areas of intervention and improvement in nutritional management of non-dialysis CKD based on shared priorities of stakeholders.

Methods: This Delphi consensus project involved 4 phases: systematic review to identify topics reported in studies involving nutritional outcomes (domains, measures) in non-dialysis CKD; review round of topics by 10 expert nephrologists in nutritional care; second review round by 105 Stakeholders (dietitians, nurses, patients) to refine the international Delphi survey to be distributed worldwide (Dec.2018 – May.2019) to patients, caregivers, clinicians, researchers, to develop consensus on clinical and research priorities in nutrition in non-dialysis CKD. The survey included 60 topics grouped in 5 categories, 11 sub-categories. Participants were invited to rate topics priority (importance) by 9-point Likert scale. Consensus for topic prioritization was defined as the combination of median ≥7 and ≥70% participants scoring 7-9 and <15% scoring 1-3 on the Likert.

Results: 1.224 subjects completed the survey; 43% were physicians, 25% dietitians, 16% patients, 8% nutritionists and 8% nurses; 62% were female and 87% from Europe. 30 topics reached priority consensus by health-care providers; patients gave priority to only 15 topics. All stakeholders agreed with prioritizing topics supporting patients to choose and personalize of diet; patients gave low priority to common issues of research interest, low-protein, low-sodium, renal progression (<65%), energy, quality proteins, malnutrition (<55%), or no priority, very-low, vegetarian, DASH, Mediterranean diets (<25%).

Conclusions: This project emphasizes agreements and disagreements among stakeholders in what matter the most regarding nutritional care management of patients with non-dialysis CKD. These differences should be considered in research and clinical practice; establishing targets to prioritize will enhance the relevance and impact of research and patient care.

TH-PO601

Clinical Significance of Nutritional Predictors in Prevalent Hemodialysis Patients

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Background: Nutrition has been consistently important in end stage renal disease patients. However, it is difficult to obtain adequate nutritional status while avoiding fluid overload, hyperphosphatemia and hyperkalemia in hemodialysis patients. We studied the clinical significance of serum albumin and other nutritional markers in maintenance hemodialysis patients.

Methods: We retrospectively enrolled patients who received hemodialysis for more than 3 months from 2016 to March 2019, excluding patients who died within 30 days. We evaluated the factors associated with all-cause mortality and major adverse cardiovascular events (MACE). In addition, we investigated factors related with sarcopenia defined as skeletal muscle mass index (SMI) ≤10.75 kg/m^2 (men) or ≤6.75 kg/m^2 (women) by using a BIA machine (InBody S10; Biospace, Korea).

Results: Of 284 patients, 63.7% were men, mean age was 64.2 ± 12.4 years, mean body mass index (BMI) was 23.7 ± 6.9 kg/m^2, and the most common underlying disease were hypertension and diabetes. During a median follow up of 16.7 months, 13.7% (n=39) patients experienced a MACE, 12.3% (N=35) patients died. In multivariate Cox analyses, lower albumin, higher CRP level and history of CVD were significantly related with all-cause mortality even after adjustment for covariates. SMI had a significant positive correlation with BMI, serum phosphorus, BUN, creatinine and uric acid level. SMI was not predicted all-cause mortality in total group, but was significantly predicted all-cause mortality in diabetes subgroup. In the logistic regression analyses, older, lower BMI, diabetes and male sex were significantly associated with sarcopenia. In addition, higher serum calcium, phosphorus level, history of CVD, cerebrovascular accident (CVA) were significantly associated with MACE.

Conclusions: In prevalent hemodialysis patients, nutrition, inflammation and precious CVD are the major risk factors for all-cause mortality. SMI might be an important predictor for all-cause mortality in diabetic patients. In patients with history of CVD or CVA, management of serum calcium and phosphorus is particularly important in aspect of MACE.

TH-PO602

Association of Inflammation with Dynapenia and Sarcopenia in Hemodialysis Patients: A Pilot Observational Study

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Background: Chronic inflammation is directly related to an increased cardiovascular mortality in hemodialysis patients. Low muscle strength (dynapenia) and low muscle strength in addition to decreased skeletal muscle mass (sarcopenia) often coexist with obesity in chronic hemodialysis patients. The main aim was to study the association of inflammation with sarcopenic obesity (SO) and dynapenic obesity (DO) in chronic hemodialysis patients.

Methods: High sensitivity C-reactive protein (hs CRP) was estimated using Nephelometry. hsCRP >10 mg/L was considered positive for inflammation. Body Composition Analysis through bioelectrical impedence was utilized to assess body fat and lean tissue index (LTI). Muscle strength was determined using handgrip strength (HGS) analysis. Dynapenia was defined by HGS <26 kg for men and < 18 kg for women. Sarcopenia was defined as LTI <10.7 kg/m^2 in men and <6.7 kg/m^2 in women. Obesity was defined as percent body fat > 25% in men and > 35% in women. Prevalence of inflammation in patients with DO and SO was reported.

Results: Of 81 patients, 49 were males. Their average age was 56.9± 16.1 years and average dialysis vintage was 2.9±2.4 years. All patients were on thrice a week hemodialysis. The etiology of kidney disease was diabetic kidney disease in 49%, hypertension in 31%, chronic tubulo interstitial disease in 7%, chronic glomerulonephritis in 4% and others in 9% patients. Mean hsCRP of was 12.4±11.9 mg/L. The overall prevalence of DO was 20.9% and SO was 16%. The prevalence of inflammation in patients with DO was 52.9% and without DO was 47.0%. The prevalence of inflammation in patients with SO was 46.1% and without SO was 37.1%. The prevalence of inflammation in diabetic patients with DO was 66.5% and that in diabetic patients with SO was 59.8%.

Conclusions: The prevalence of inflammation was higher in patients with both DO as well as SO, especially in diabetic population. Further long term studies are needed to assess the relationship between DO, SO and inflammation and their outcomes in hemodialysis population.

TH-PO603

Simultaneous Use of Bioimpedance Vectors Analysis (BIVA) for Dry Weight Adjustment and Oral Nutritional Supplementation in Hemodialysis Patients

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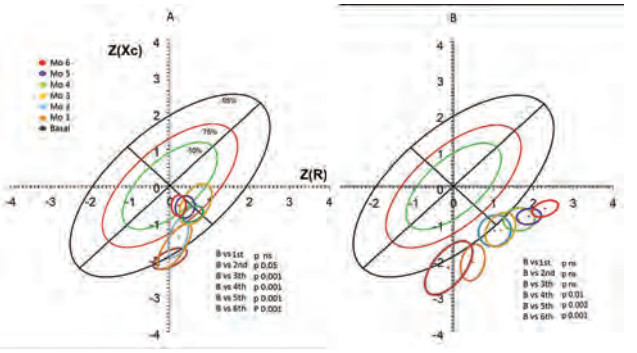
Background: Protein energy wasting and overhydration are two complications present in renal patients that must be treated simultaneously. The objective of this study was to compare the effectiveness of the simultaneous use of BIVA and oral nutritional supplementation against the exclusive use of BIVA on the nutritional status and body composition of patients on hemodialysis

Methods: Patients were randomized in two groups for 6 months intervention. In both groups, dry weight was adjusted by BIVA as necessary to reach euhydration. Group A (n=17) an individualized diet plus one can of nutritional supplement was given daily to patients. Group B (n=15) only the specific diet was provided. Nutritional status was evaluated with the Malnutrition Inflammation Score (MIS) and handgrip strength was measured at the beginning and the end of the study

Results: Mean age was 55.76 ± 17.6 years for group A and 53.71 + 11.8 for group B, dialysis vintage 24.47 ± 5.08 months and 18.88 ± 11.04 respectively. No significant baseline differences between groups were found and any patient was well nourished. After intervention, nutritional status improved significantly in group A, from 47 to 83% for mild undernutrition and from 53 to 17% for moderate undernutrition ($p<0.05$), while in group B, nutritional status worsened from 53 to 27% for mild undernutrition and from 47 to 73% for moderate undernutrition ($p<0.05$). Handgrip strength was increased in 58% of patients in group A and 21% in group B ($p < 0.03$). Dry weight was achieved in 100% of patients in both groups. At the end of the study, group A vectors indicated less body fluid and better nutritional status, unlike to the vectors of group B which indicated less body fluid but a worse nutritional status. ($p<0.007$ A vs. B)

Conclusions: Conjunctive use of oral nutritional supplementation and bioelectrical impedance vectors analysis, to determine dry weight, improves nutritional status and body composition in patients undergoing hemodialysis



TH-PO604

A Simplified Protein-Energy Wasting Scoring System for Survival Prediction in Korean Incident Hemodialysis Patients

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Background: Even though protein-energy wasting (PEW) is a crucial risk factor for survival in end-stage renal disease (ESRD) patients, a convenient and reliable assessment method to determine PEW in ESRD patients has not been established. However, a recent study proposed a simplified PEW scoring system based on the PEW diagnostic criteria, which was predictive for European ESRD patients' survival. This study aimed to validate the prognostic significance of the simplified PEW score in Korean incident hemodialysis patients.

Methods: Data were retrieved from a prospective cohort study from the Clinical Research Center for ESRD in Korea. The simplified PEW scoring system is graded from 0 (the worst) to 4 (the best), which consists of four components: serum albumin, body mass index, serum creatinine/body surface area, and normalized protein nitrogen appearance. Since the number of patients in the PEW score 0 group was too small (n=14), the PEW score 0 and 1 groups were combined into a same group. The survivals of the four groups (PEW score 0~1, 2, 3, and 4) were compared by Kaplan-Meier plot, and multiple Cox regression analysis was performed to identify the association between the PEW score and patients' survival.

Results: A total number of 430 patients were included in this study. The numbers of patients in the four score groups were 77 (score 0~1), 158 (score 2), 145 (score 3), and 50 patients (score 4). The mean age was 61.1 years and male was 59.8%. Kaplan-Meier plot revealed that the lowest PEW score group had the worst cumulative survival or there was a significant difference in patient survival across the groups (log-rank test, $P<0.001$); 2-year mortality rates of 15.6% in the score 0~1 group, 8.2% in the score 2 group, 1.4% in the score 3 group, and 2.0% in the score 4 group. In multiple Cox regression analysis, moreover, PEW score was a significantly independent factor for mortality even after adjusting for confounding variables (PEW score 0~1 as a reference; PEW score 2, hazard ratio [HR] 0.450, 95% confidence interval [CI] 0.262–0.772, $P=0.004$; PEW score 3, HR 0.165, 95% CI 0.070–0.385, $P<0.001$; and PEW score 4, HR 0.101, 95% CI 0.013–0.760, $P=0.026$).

Conclusions: A simplified PEW scoring system is a practical and reliable method for predicting mortality in Korean incident hemodialysis patients.

TH-PO605

Malnutrition and Protein Energy Wasting in Pediatric CKD

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Background: Malnutrition (malnut) predisposes CKD patients (pts) to poor growth through hormonal & metabolic derangements, decreased appetite & inflammation. Protein energy wasting (PEW) describes a state of decreased protein stores, associated w/ impaired growth and poor outcomes in peds. Few studies investigate the relationship between malnut, PEW & CKD progression in peds pts.

Methods: Retrospective chart review of pts 0 – 25 yrs with CKD stages 1-5 seen in peds renal clinic from 2013 - 2018. Diagnosis of malnut based on the Consensus Statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition. eGFR calculated by revised Schwartz equation. PEW scores (PEWS) assigned based on peds criteria (Abraham A, et al, 2014). Minimal PEW definition requires any positive test in ≥2 of PEWS categories. Linear regression was performed to determine effect of z-score for height (HZ), weight (WZ), BMI (BMIZ), weight-for-length (WLZ) or PEWS on eGFR. Mixed-effects models performed to determine effect of diagnosis of malnut and PEW on change in eGFR. $P < 0.05$ was significant.

Results: Of 135 pts, 68 (50.3%) were classified as malnut & 50 (37%) met minimal PEW criteria during a median 1.8yrs [0.9-3.5] follow-up. Majority diagnosed w/ malnut were male (65%), white (36%), w/ a median age of 14.2yrs [7.4-17.6], w/ CKD Stage 3 at time of 1st visit (50%) and a congenital anomaly of kidney and urinary tract diagnosis (46%). Majority were diagnosed with malnut based on Decline in Weight/Height Z-score (38%) using 2 data points as indicators. Linear regression showed no significant effect of

HZ, WZ, BMIZ, WLZ or PEWS on eGFR. Mixed-effects analysis of eGFR in pts w/ & without diagnosis of malnut demonstrate a significant worsening decline in eGFR for pts w/ malnut (-2.44 vs -1.41ml/min/1.73m^2/yr, p<0.001). Mixed-effects analysis of eGFR w/ diagnosis of malnut showed no significant difference in eGFR decline before or after diagnosis of malnut. Pts who met minimal PEW criteria had a significant worsening decline in eGFR compared to those who did not (-2.44 vs -1.72ml/min/1.73m^2/yr, p<0.001).

Conclusions: Malnutrition and PEW are common in peds with CKD. Our preliminary data demonstrate a trend in mild/moderate CKD for worse eGFR decline in pts with malnut and PEW. Future study will further characterize relationship between malnutrition, PEW and peds CKD outcomes.

TH-PO606

The Effect of Oral Pioglitazone on Muscle Protein Breakdown in Peritoneal Dialysis Patients: A Randomized Controlled Trial

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Background: Insulin resistance which occurs common in patients on chronic continuous ambulatory peritoneal dialysis (CAPD) plays an important role in decreasing available glucose and protein for muscle anabolism. Thiazolidinediones is a PPAR receptor agonist with a high ability to increase insulin sensitivity and possibly their anabolic effects on improve sarcopenia.

Methods: A randomized, placebo-controlled trial, 31 CAPD patients (age 57.0±15.2years in pioglitazone group and 60.5±15.4years in placebo group) were randomly allocated into two groups: pioglitazone (15 mg/day) and placebo for 16 weeks. Sarcopenia biomarkers include serum myostatin level and body composition by Dual-energy X-ray absorptiometry (DXA) were determined before and after the intervention.

Results: At baseline, serum myostatin level was 6.40±3.14 ng/mL in pioglitazone group and 5.12±3.53 ng/mL in placebo group and relative skeletal muscle index was 7.14±1.18 kg/m^2 in pioglitazone group and 6.52±1.33 kg/m^2 in placebo group. Serum myostatin level significantly decreased in the pioglitazone group compared to the placebo group at 8 weeks (-1.32 (95%CI -1.98 to -0.66) vs. 0.56 (95%CI -0.48 to 1.61) ng/mL; P=0.003) and at 16 weeks (-2.32 (95% CI -3.11 to -1.53) vs. 0.10 (95% CI -0.71 to 0.92) ng/mL; P<0.001). However, relative skeletal muscle index, fat mass and body weight did not change significantly in the both groups. No significant changes were observed in blood pressure, fasting plasma glucose, hemoglobinA1C, and serum creatinine compared with baseline in either group. No serious side-effects including hypoglycemia and heart failure was detected.

Conclusions: The study indicates that 16-weeks of pioglitazone treatment reduced the serum sarcopenia biomarkers but showed no effect on the muscle mass in no diabetic CAPD patients.

TH-PO607

Muscle Quality Assessment by Texture Analysis on ^{1}H-Magnetic Resonance Images in CKD Patients

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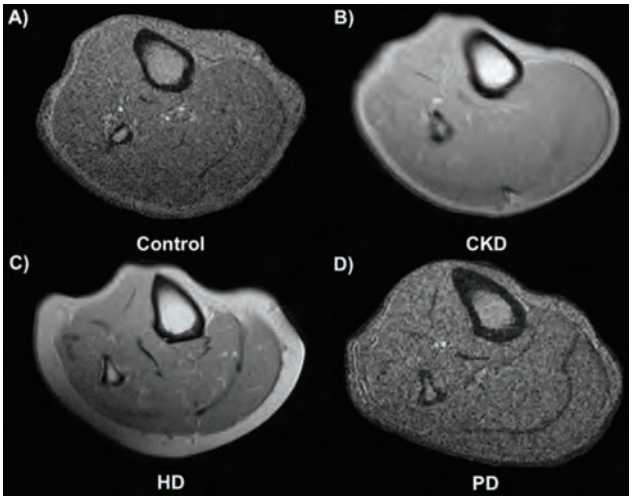
Background: Chronic kidney disease (CKD) is associated with reduction in skeletal muscle quality from the interplay of inflammation and malnutrition, resulting in reduced exercise capacity. Muscle quality can be assessed by texture analysis of images acquired by ^{1}H-Magnetic Resonance Imaging (MRI). The study objective is to compare muscle quality using MR images between healthy controls, CKD, hemodialysis (HD) and peritoneal dialysis (PD) patients. We hypothesize that progressive CKD and dialysis therapy are associated with muscle quality changes that can be detected by texture analysis.

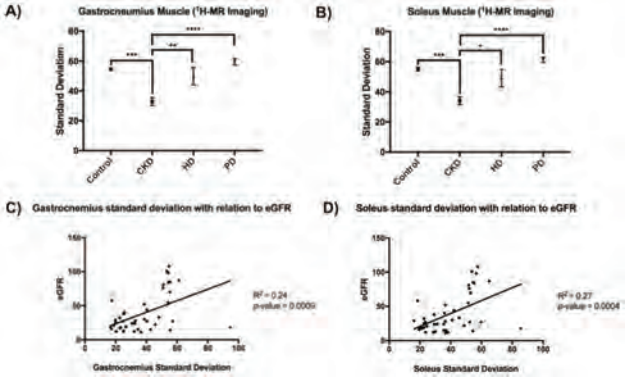
Methods: ^{1}H T1-weighted images of the calf were acquired on control, CKD, HD, and PD patients. Mid-slice was used to delineate the gastrocnemius and soleus muscle. Heterogeneity of the muscle was quantified by the standard deviation (SD) within the regions. One-way ANOVA was used to assess significance between groups. Pearson correlation analysis was completed between estimated glomerular filtration rate (eGFR) and SD of the muscles at CKD stages 1-5 (HD and PD cohort excluded).

Results: Refer to Figures 1 and 2.

Conclusions: Homogeneous characteristics seen in CKD cohort may be indicative of muscle wasting and fibrosis. MRI based quality assessment may provide potential non-invasive evaluation of the uremic state on skeletal muscle structure and function.



Proton T1-weighted MR image of the calf



Mean SD and standard error bars of (A) gastrocnemius (B) soleus muscle in control, CKD, HD, PD. Pearson correlation of SD and eGFR in (C) gastrocnemius (D) soleus muscle.

TH-PO608

Skeletal Muscle Index from CT Scans Can Predict Muscle Strength in CKD

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Background: Sarcopenia is associated with poor clinical outcomes in chronic kidney disease, but is often under-recognized during clinical encounters. Muscle mass and intramuscular fat are measures of muscle quantity and quality but requires DXA and extremity MRIs or CTs. We hypothesize that muscle quantity and intramuscular adiposity, measured on abdominal CT scans done for clinical care, can be used to predict grip strength in patients with CKD stage 5-5D and in healthy patients.

Methods: We studied 19 patients with CKD stages 5-5D and 12 healthy individuals who had measures of grip strength. Records were reviewed for abdominal CT scans performed as part of their clinical care. The regions of interest were muscles at the level of the L3: psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques and rectus abdominus. Skeletal muscle index (SKMI) and intra-muscular adipose tissue index (IMATI) were calculated as cross-sectional areas, corrected for height (cm^2/m^2) using Hounsfield unit ranges (skeletal muscle: -29 to 150 and adipose tissue: -190 to -30). We used linear regression to determine the independent relationship between SKMI and IMATI respectively with grip strength in univariate analyses and adjusted for covariates.

Results: Mean age was 48.5+/-12.5 y, BMI was 29.2+/-8.1kg/m^2, 55% white and 52% were male. Mean SKMI was 48.9+/-9.1 cm^2/m^2 and was not significantly different between those with CKD and without CKD. On univariate analysis, age, presence of CKD, sex and SKMI were significantly associated with grip strength (all p<0.05). Using multivariate linear regression SKMI, adjusted for sex and presence of CKD was associated to be a significant predictor of grip strength (p=0.014), with the model containing these 3 variables explaining 68% of the variability in grip strength. IMATI was not a signficant predictor of grip strength in univariate or multivariate models.

Conclusions: Incidental CT scans can be used to assess skeletal muscle cross-sectional area which is a useful predictor of hand grip strength. Poor handgrip strength or weakness

is a criteria for detecting sarcopenia in clinical practice and is associated with disability and frailty. Identifying those with probable sarcopenia during routine care provides an opportunity to attempt to intervene to regress or prevent worsening of sarcopenia.

Funding: NIDDK Support, Private Foundation Support

TH-PO609

Hypercatabolism, Body Composition, and Physical Function in Advanced CKD

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Background: It has been hypothesized that impaired physical function in CKD is the result of a hypercatabolic state leading to protein and energy wasting. We tested whether basal metabolic rate (BMR) is higher and accounts for impaired physical function in more advanced CKD.

Methods: We examined baseline data in 99 participants of an ongoing physical activity intervention trial (NCT 02970123) expected to be completed in Sep, 2019. Results will be updated with follow-up data for ASN presentation. Standardized protocols were used to measure BMR with indirect calorimetry (MedGem, Microlife Medical, Inc. Golden, CO) and body composition including fat free mass (FFM) and body fat% (BF%) with bioelectrical impedance analysis(Quantum X,RJL Systems, Clinton Township, MI) and physical function with 6-minutes walk distance (6-min WD).

Results: Demographic and clinical data by CKD stages are summarized in Table. Median(IQR) for BMR was 16.3 (14.8,18.2)kcal/kg/day. Mean values for FFM, BF% and 6-min WD in the entire cohort were 61±15kg, 31±10%, and 385±66m respectively. In separate multivariable linear regression models (adjusted for age, gender, race, ethnicity and diabetes), more advanced CKD was not associated with BMR or BF%, had non-significant, negative association with FFM and significant, negative association with 6-min WD (Table). The association of advanced CKD with lower 6-min WD persisted with further adjustment for BMR, FFM and %BF (Table).

Conclusions: Impaired physical function in CKD was not explained by BMR in the current study. Further studies are needed to test whether lack of anabolism rather than hypercatabolism plays a significant role in wasting and frailty in CKD.

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

	Stage 2/3A N=45	Stage 3B N=39	Stage 4/5 N=15
Clinical Characteristics			
eGFR(mL/min/1.73m^2)	55.0±8.4	36.7±4.0	17.3±9.0
Age(yr)	70±10	73±9	62±18
Women(%)	40	46	33
White(%)	98	92	67
Hispanic(%)	2	5	13
Diabetes(%)	33	38	40
Multivariate linear regression models			
BMR (kcal/kg/d)*	Reference	-0.06(-1.74,1.62)	0.03(-2.36,2.43)
FFM(kg)*	Reference	1.67(-2.20,5.56)	-2.20(-7.73,3.32)
BF(%)*	Reference	0.53(-2.61,3.68)	0.14(-4.34,4.63)
6-min WD(m) Model 1*	Reference	-18.6(-46.4,9.3)	-53.1(-93.5,-12.7)
6-min WD(m) Model 2**	Reference	-18.9(-48.3,10.5)	-55.8(-96.6,-15.0)

*Adjusted for age, gender, race, ethnicity and diabetes

**Adjusted for above plus BMR, FFM, BF(%)

TH-PO610

Grip Strength at Dialysis Initiation Predicts Hospitalization over Time

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Background: Patients new to dialysis are frequently hospitalized. Currently, prediction models for risk of hospitalization use clinical and demographic factors. Grip strength is an objective measure of muscle weakness that is easily measured in dialysis units and is associated with mortality in prior studies. We hypothesize that grip strength is an independent predictor of the total number of hospital days over 2 years of follow-up in incident dialysis patients, after adjusting for demographic and clinical variables.

Methods: This is a prospective cohort study of 195 incident dialysis patients with grip strength testing at enrollment with a median of 647 days of follow-up. Outcome data from all hospitalizations > 48 hours were collected by patient self-report, and verified in the electronic record. We examined the longitudinal relationship between baseline grip strength as a continous variable with total number of days spent in the hospital in the follow-up period using zero-inflated Poisson regression. Univariate relationships were initially studied, followed by grip strength adjusted for clinical/ demographic variables in multivariate models.

Results: The baseline study population was 53% men with mean age of 54.3±13.3 yrs who were enrolled a median of 92 days after dialysis initiation. Mean grip strength was 27.9±12.8 kg. 60.5% of subjects had at least 1 hospitalization in the follow-up period. The median (IQR) number of hospital days was 6(0-17). 74.6% of hospitalizations were ≤ 8 days in duration. Age, black race, dialysis vintage and modality, diabetic nephropathy as primary kidney disease, residual kidney function and comorbidities (diabetes, cardiovascular disease) and grip strength were univariately associated with increased number of hospital days (all p<0.05). In multivariate models, a 5kg higher grip strength at baseline was associated with a rate ratio of 0.96 (95% CI of 0.94-0.99) or a 4% decrease in total days in the hospitalization in the follow-up period (p=0.0009).

Conclusions: In our cohort of 195 incident dialysis patients, we show that grip strength independently predicts total days in the hospital when added to known predictors of hospitalization in patients on dialysis. Routine measurement of grip strength in those newly starting dialysis may help identify those most at risk of hospitalizations over time.

Funding: NIDDK Support

TH-PO611

Association Between Vitamin D Level and Muscle Strength in Patients Undergoing Hemodialysis

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Background: Considering conflicting results or heterogeneity in study design, further investigations are needed to identify the definite association between vitamin D level and muscle health. Our study aimed to address these issues and to evaluate the association between vitamin D level and muscle mass indices, strength, or physical performance through comprehensive measurements in patients undergoing hemodialysis.

Methods: This study was performed in a tertiary medical center. We included patients undergoing hemodialysis with age ≥20 years. A total of 84 patients were enrolled. The patients were divided into tertiles based on the 25-hydroxy (25-OH) vitamin D level as follows: lowest tertile (Lowest T, n = 28), middle tertile (Middle T, n = 28), and highest tertile (Highest T, n = 28). We evaluated the association between the tertiles and clinical outcomes including nutritional status, muscle mass, muscle function, handgrip strength (HGS), physical performance, and health-related quality of life scales (HRQoL).

Results: There were no significant differences in the muscle mass indices and nutritional markers according to tertiles of 25-OH vitamin D level. However, 25-OH vitamin D level as a continuous variable or the tertile of 25-OH vitamin D level as a categorical variable was positively associated with HGS. Logistic and linear regression analyses showed a consistent superiority of the Highest T in HGS compared with the Lowest or Middle T. Although the statistical significance was weak, the scores of various physical performance tests and the HRQoL scales were the highest in the Highest T, among the 3 tertiles.

Conclusions: The present study demonstrated that serum vitamin D level is associated with HGS in patients undergoing hemodialysis regardless of muscle mass indices or nutritional status.

TH-PO612

Exploration of Dietary Protein Intake and Skeletal Muscle Mass and Function in Non-Dialysis CKD

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Background: CKD patients are characterized by skeletal muscle wasting and poor physical function. Poor nutritional intake (of protein and energy) contributes to muscle wasting and loss of physical function in ESRD. However, the role of dietary protein in non-dialysis CKD remains topical. In healthy older adults, higher protein intake protects against sarcopenia and improves physical function. Recent studies suggest restricted protein intake is associated with loss of muscle mass in CKD but these are limited and the non-dialysis CKD population remains insufficiently researched. This study evaluated the relationship between protein intake, muscle mass, and physical function.

Methods: Average daily protein intake (g/kg) for 30 non-dialysis CKD patients (50% male, age 62.8±10.8, eGFR 36.9±20.5) was assessed using a food frequency questionnaire. Participants were categorised as having low protein intake defined by WHO and KDIGO recommendations (<0.8g/kg/day). Total skeletal muscle mass % was measured by bioelectric impedance analysis and rectus femoris muscle size by ultrasound cross-sectional area (CSA). Physical function was assessed using gait speed, handgrip strength, and the short physical performance battery (SPPB). Differences between groups were explored using linear regression (adjusted for age, sex, and ethnicity).

Results: Higher protein intake (≥0.8g/kg/day) was associated with a 15% greater muscle mass, 24% larger rectus femoris CSA, and 11-20% greater lower limb physical function in non-dialysis CKD (see Table 1).

Conclusions: This work suggests a higher dietary protein intake protects against muscle wasting which, in turn, preserves physical function in this group. Further research is required to confirm these findings which suggest efforts to increase protein intake in this group may confer favourable effects on muscle and functional preservation.

Funding: Private Foundation Support

Results

	<0.8g/kg/day	≥0.8g/kg/day	P Value
Body mass (kg)	94.0 (±23.2)	81.5 (±17.8)	.002*
Skeletal muscle mass (%)	33.6 (±5.4)	38.7 (±6.0)	.008*
Rectus femoris CSA (cm2)	7.5 (±2.7)	9.3 (±3.2)	.050
Gait speed (m/s)	1.0 (±0.2)	1.2 (±0.3)	.042*
Handgrip strength (kg)	27.4 (±12.0)	32.0 (±11.0)	.417
SPPB (score)	9.8 (±1.8)	10.9 (±1.7)	.014

Table 1

TH-PO613

Uremic Dysbiosis Causes Sarcopenic Phenotype Through Reduction in Muscle Mitochondria and Attenuation of Insulin-Stimulated Muscle Protein Synthesis

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Background: Chronic kidney disease (CKD) leads to clinically relevant sarcopenia, defined as reduced exercise endurance and muscle atrophy, which are novel risk factors associated with morbidity and mortality in CKD patients. However, the pathophysiology of uremic sarcopenia remains incompletely defined. Recent reports have shown alterations in the gut microbiota to be associated with the etiology of CKD. Using germ-free (GF) mice, we aimed to determine whether and how uremic dysbiosis causes uremic sarcopenia.

Methods: CKD was induced in specific-pathogen-free mice via an adenine-containing diet; control mice were fed a normal diet. Fecal microbiota transplantation (FMT) into GF mice was performed by oral gavage using cecal samples obtained from either control mice (control-FMT mice) or CKD mice (CKD-FMT mice). Vehicle mice were gavaged with sterile phosphate-buffered saline. Sarcopenic phenotype was evaluated after 2 weeks.

Results: Compared with control mice, CKD mice had sarcopenic phenotypes, including significant decrease in running distance, handgrip strength, and skeletal muscle mass. Sarcopenic phenotypes were reproduced in CKD-FMT mice as compared with control-FMT mice and were associated with reduced muscle mitochondria and attenuation in insulin-stimulated phosphorylation of S6 kinase beta-1, indicating reduced muscle protein synthesis. In addition, serum concentrations of indoxyl sulfate, phenyl sulfate, and hippuric acid among uremic solutes as well as fecal concentrations of indole and phenol among bacterial fermentation products were increased in CKD-FMT mice as compared with the concentrations in control-FMT mice. Gut microbiome analysis using 16S rRNA genes sequences revealed decrease in *Lactobacillus* and *Lactonifactor* and increase in *Allobaculum*, *Clostridium cluster IV*, and *Alistipes* in CKD mice as compared with those in control mice. All of these alterations in gut microbiome remained in CKD-FMT mice as compared with those in control-FMT mice.

Conclusions: Uremic dysbiosis can directly contribute to sarcopenic phenotypes even in the absence of the host CKD condition. Increased concentrations of microbiota-derived fecal putrefaction products, serum uremic solutes, and resultant insulin resistance can mediate the effects of uremic dysbiosis.

TH-PO614

A Pilot Study on Association of Arterial Stiffness with Dynapenia and Sarcopenia in Hemodialysis Patients

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Background: Low muscle strength (dynapenia) and low muscle strength plus low skeletal muscle mass (sarcopenia) are often found to be coexisting with obesity in chronic hemodialysis patients. As arterial stiffness is directly related to cardiovascular mortality, it was of interest to study its association with dynapenic obesity (DO), sarcopenic obesity (SO) in this population.

Methods: Arterial stiffness was estimated from brachial cuff-based oscillometric device Mobil-O-Graph. Body Composition Analysis through bioelectrical impedence was utilized to assess body fat and lean tissue index (LTI). Muscle strength was determined using handgrip strength (HGS) analysis. Dynapenia was defined by HGS <26 kg for men and < 18 kg for women. Sarcopenia was defined as LTI <10.7 kg/m^2 in men and <6.7 kg/m^2 in women. Obesity was defined as percent body fat > 25% in men and > 35% in women.

Results: Of 206 patients, 124 were males. Their average age was 55.3± 15.4 years and average dialysis vintage was 2.8±2.7 years. All patients were on thrice a week hemodialysis. Of 206 patients, 44% were diabetic, 58% were hypertensive and 29% had ischemic heart disease. The prevalence of dynapenia was 87.8% and that of sarcopenia was 42.7%. Prevalence of DO and SO was 19.4% and 14.5% respectively. The prevalence of arterial stiffness in patients with DO was 72.5% and that in patients with SO was 70%.

Conclusions: Prevalence of arterial stiffness is high in patients with DO and SO. Further studies are needed to evaluate interventions for reducing dynapenic and sarcopenic obesity and their impact on reduction in arterial stiffness inorder to reduce cardiovascular mortality.

TH-PO615

Lower Kidney Function Is Associated with Impaired Leg Skeletal Muscle Mitochondrial Oxidative Capacity

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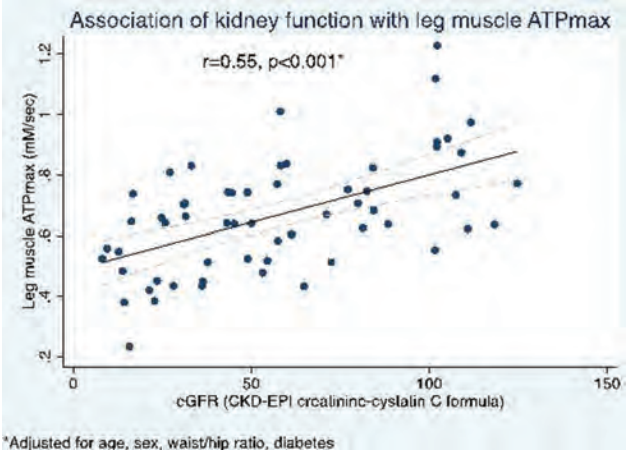
Background: Evidence suggests abnormal uremic environment may contribute to mobility limitation by impairing muscle mitochondrial function. We tested the association of kidney function with in vivo muscle mitochondrial oxidative capacity among patients with CKD.

Methods: The Muscle Mitochondrial ENergetics and Dysfunction (MEND) study was designed to evaluate determinants and consequences of skeletal muscle mitochondrial functioning in CKD. We recruited 57 participants (38 CKD and 19 controls) from a clinic-based population. We measured mitochondrial oxidative capacity of the tibialis anterior leg muscle (ATPmax) during exercise recovery using 31Phosphorus magnetic resonance spectroscopy. We determined associations of GFRcrcysc with ATPmax by using multivariable linear regression adjusting for age, sex, waist/hip ratio, and diabetes.

Results: Participants were 62 ±14years old with 32% female and 32% prevalence of diabetes (33% in controls). GFRcrcysc in the CKD group was 38 +19ml/min compared to 98 ±15 in controls. Mean ATPmax was 0.6 ±0.16mM/sec in CKD group and 0.8 ±0.18 in controls. After adjustment, CKD was associated with 0.18mM/sec lower (95% CI 0.27, 0.09; P<0.001) ATPmax. Diabetes was associated with 0.12mM/sec lower (95%CI 0.23, 0.02; P=0.02) ATPmax compared non-diabetes after adjustment. In continuous analysis, each 10ml/min/1.73m2 lower eGFRcrcysc was associated with a 0.03mM/sec lower ATPmax (95% CI 0.04, 0.01; P<0.001) (Figure). Among those with GFRcrcysc<60, correlates with ATPmax included bicarbonate level (r=0.39, p=0.02), C-reactive protein (r=-0.31, P=0.07), albuminuria (r=-0.33, P=0.05), and phosphorus (r=-0.21, p=0.2).

Conclusions: Lower kidney function and diabetes are associated with direct in vivo measurements of leg muscle mitochondrial oxidative capacity.

Funding: NIDDK Support, Private Foundation Support



TH-PO616

Impaired Leg Muscle Mitochondrial Oxidative Capacity by Phosphorus-31 Magnetic Resonance Spectroscopy (^{31}P MRS) Is Associated with Lower Physical Functioning in CKD

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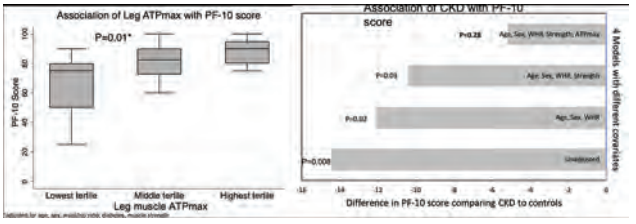
Background: Maintaining functional independence is the top health priority reported by patients living with CKD. Impaired mitochondrial function is hypothesized to be a key mechanism underlying mobility limitation in CKD.

Methods: The Muscle Mitochondrial ENergetics and Dysfunction (MEND) study was designed to evaluate determinants and consequences of skeletal muscle mitochondrial functioning in CKD. We measured mitochondrial oxidative capacity of the tibialis anterior leg muscle (ATPmax) during exercise recovery using ^{31}P MRS in 57 participants (38 CKD and 19 controls). We evaluated physical function by self-reported physical functioning-10 (PF-10 of the KDQOL) and performance on the Timed Up and Go (TUG) test. Statistical models adjusted for age, sex, waist/hip ratio, and maximal leg strength.

Results: Participants were 62 ±14years old and 32% had diabetes. GFRcrcysc in the CKD group was 38 ±19ml/min compared to 98 ±15 in controls. Among participants with CKD, lower muscle ATPmax correlated with slower TUG performance (r=-0.42; p=0.009) and lower PF-10 score (Figure). Results did not change after adjustment. Addition of ATPmax to the adjusted model weakened the association of CKD with physical functioning (PF-10) score by 50% (Figure) and TUG performance by 46% compared to controls.

Conclusions: Direct measurements of leg skeletal muscle mitochondrial capacity are associated with objective and subjective measures of physical functioning in patients with CKD. Mitochondrial impairment may contribute to mobility limitation in CKD.

Funding: NIDDK Support, Other NIH Support - Northwest Kidney Centers and Dialysis Clinics Incorporated



TH-PO617

Indoxyl Sulfate-Induced Apoptosis in C2C12 Cells

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Background: Indoxyl sulfate is a well-known uremic toxin and associated with skeletal muscle atropy in chronic kidney disease. However, there are few studies regarding precise molecular mechanism. The aim of the study was to identify indoxyl sulfate induced apoptosis as a molecular mechanism.

Methods: Mouse C_2C_{12} myoblast were purchased and cultured in Dulbecco's modified eagle medium. After cell adhesion, cultured medium was changed containing with uremic toxins and cultured. Reactive oxygen species (ROS) production and CCK assays were performed. Tunnel staining, phase contrast microscopy, and flowcytometry were also performed.

Results: ROS production was increased as dose of indoxyl sulfate increased. Apoptosis was increased as dose of indoxyl sulfate increased. In addition, tunnel stained cell count increased as dose of indoxyl sulfate. Cell confluence decreased as dose of indoxyl sulfate. Flowcytometry using Annexin V and PI showed that proportion of double positive cell increased as dose of indoxyl sulfate.

Conclusions: Our results demonstrate that indoxyl sulfate is associated with apoptosis of myoblast through ROS production.

TH-PO618

β2-Receptor Agonism Averts Indoxyl Sulfate-Induced Sarcopenic Phenotype of Mouse Skeletal C2C12 Myotube

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Background: Sarcopenia is a condition characterized by loss of skeletal muscle mass and function. In patients with chronic kidney disease, sarcopenia is recently attracting attention because of its strong association with increased morbidity and mortality. However, the direct association with uremia and sarcopenia is not fully elucidated yet. The aim of this research was to investigate the mechanism and therapeutic intervention for sarcopenia induced by uremia.

Methods: The mouse myogenic cell line C2C12 (ATCC®CRL-1772) was treated with indoxyl sulfate (IS) and evaluated as to cell viability (MTS assay), cytotoxicity (LDH assay, Trypan blue), cell morphology (measure the length and diameter of C2C12 myotubes), the expression of muscle atrophy related genes (quantitative-PCR) and protein levels of myosin heavy chain (MyH) and fast/slow twitch muscle fibers (Western blot). Moreover, clenbuterol and salbutamol as β2-stimulants were assessed for effect on the IS induced myocyte phenotypic changes.

Results: IS blunted C2C12 myoblast cell proliferation and reduced myotube length and diameter. IS treatment up-regulated mRNA expression of muscle atrophy related genes (MuRF-1 and Atrogin-1), and reduced protein levels of MyH and fast twitch muscle fiber, but not slow twitch muscle fiber. On the other hand, clenbuterol and salbutamol partially attenuated IS-induced upregulation of MuRF-1 and Atrogin-1, and prevented the degradation of MyH and fast twitch muscle fibers.

Conclusions: β2-agonist has a therapeutic potential for preventing IS induced muscle atrophy, predominantly fast twitch muscle fiber atrophy.

TH-PO619

Mitochondrial Dysfunction/NLRP3 Inflammasome Axis Contributes to Angiotensin II-Induced Skeletal Muscle Wasting via PPAR-γ

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Background: Although the angiotensin II (Ang II) level is elevated in patients with chronic kidney disease or heart failure, and directly causes skeletal muscle wasting in rodents, the molecular mechanisms of Ang II-induced skeletal muscle wasting and its potential as a therapeutic target are unknown.

Methods: We investigated the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome-mediated muscle atrophy response to Ang II in C2C12 myotubes and *Nlrp3* knockout mice. We also assessed the mitochondrial dysfunction (MtD)/NLRP3 inflammasome axis in Ang II-induced C2C12 myotubes. Finally, we examined whether a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist could attenuate skeletal muscle wasting by targeting the MtD/NLRP3 inflammasome axis *in vitro* and *in vivo*.

Results: We demonstrated that Ang II increased NLRP3 inflammasome activation in cultured C2C12 myotubes dose dependently. *Nlrp3* knockdown or *Nlrp3*$^{-/-}$ mice were protected from the imbalance of protein synthesis and degradation. Exposure of C2C12 to Ang II increased mitochondrial ROS (mtROS) generation, accompanied by MtD. Strikingly, the mitochondrial targeted antioxidant not only decreased mtROS and MtD, it also significantly inhibited NLRP3 inflammasome activation and restored skeletal muscle atrophy. Finally, the PPAR-γ agonist protected against Ang II-induced muscle wasting by preventing MtD, oxidative stress, and NLRP3 inflammasome activation *in vitro* and *in vivo*.

Conclusions: This work suggested a potential role of MtD/NLRP3 inflammasome pathway in the pathogenesis of Ang II-induced skeletal muscle wasting, targeting the PPAR-γ/MtD/NLRP3 inflammasome axis may provide a therapeutic approach for muscle wasting.

Funding: Government Support - Non-U.S.

TH-PO620

Skeletal Muscle Mitochondrial Response to Wheel Running in a Rat Model of CKD

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Background: We have previously found that treadmill running had detrimental effects upon mitochondrial pathways, while wheel running had multi-system beneficial effects in CKD rats. We hypothesized that wheel running would have beneficial effects on skeletal muscle mitochondria.

Methods: We used the $Cy/+_{IU}$ rat model of naturally occurring CKD (n = 12-14/group) to compare muscle bioenergetics in CKD rats versus NL littermates, and CKD versus CKD rats that performed 10 weeks of wheel running (from 25(~stage 2 CKD) to 35 weeks (~ESRD)). 1) Muscle protein lysates of the extensor digitorum longus (EDL, fast fiber type) and soleus (slow fiber type), were directly assessed for protein content of the mitochondrial respiratory subunit complexes by OXPHOS. 2) These muscles were permeabilized with direct assessment of mitochondrial respiration (Oxygraph-2k, Oroboros) in the presence of different substrates ((5Mm pyruvate, 2Mm malate; 25um-10mM ADP; 5mM glutamate; 20mM succinate).

Results: *EDL*: no difference in mitochondrial complex protein content or respiration in CKD vs NL. Wheel running reduced complexes I-IV subunit protein content (CKD-W vs CKD, $p<0.05$), but no difference respiration. *Soleus:* mitochondrial complex I was reduced in CKD vs NL, while complex III was reduced in the CKD-W vs CKD (both $p<0.01$). Respiration rates were increased in CKD (vs NL) for 300 and 500uM ADP ($p<0.01$), but not for state II (pyruvate, malate). In contrast, wheel running increased state II (i.e. pyruvate, malate) and 25uM ADP (compared to CKD; both $p<0.01$)) respiration.

Conclusions: Skeletal muscle from CKD rats did not demonstrate dramatic changes in mitochondrial content or respiration. Wheel running in CKD rats, compared to no wheel running, reduced isolated mitochondrial respiratory subunit content particularly in the EDL. Given there was no difference in respiration with lowered mitochondrial content there was a compensatory response. These data support that the systemic benefits of wheel running may not be due to direct changes in mitochondrial function in skeletal muscle, suggesting a more indirect effect.

Funding: NIDDK Support

TH-PO621

Correlates of Physical Inactivity Across Kidney Disease Stages: An Observational Multicentre Study

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Background: The importance of physical activity (PA) in the health and management of CKD is well established. Understanding causes of PA behaviour is essential for the development of potential interventions and promotional initiatives. We aimed to determine the prevalence and individual correlates of PA behaviour across the spectrum of kidney disease.

Methods: 5258 patients across 17 geographically diverse sites were stratified into CKD stages 1-2, 3, 4-5, haemodialysis (HD), peritoneal dialysis (PD) and renal transplant recipients (RTRs). Physical activity was assessed using the GP Physical Activity Questionnaire. Potential correlates of PA included clinical, co-morbidity and demographic data, self-efficacy, stage of change (Transtheoretical Model) and cardiorespiratory fitness (VO_2 peak estimated using Duke Activity Status Index). Multi- and bi-nominal generalized models were used to explore differences and correlates of PA. Unless stated, data expressed as odds ratio (OR).

Results: Prevalence of physical inactivity was high and worsened with disease progression (Fig 1). Overall, being older (OR=1.03), female (OR=1.27), having additional co-morbidities (OR=1.17), lower Hb (OR=.93) and lower VO_2 peak (OR=.92) were associated with being inactive. Patients in a receptive stage of change (OR=.35) and with higher self-efficacy (OR=.70) were more likely to be active. Stage of disease modified the interactions of age, sex, and VO_2 peak with PA.

Conclusions: In the largest cohort of its kind, we established that physical inactivity is highly prevalent across all stages of renal disease, reaching a nadir in those requiring dialysis and 'recovering' in those with a transplant. Our study emphasises the urgent need

to evaluate and implement strategies that can effectively support individuals in changing their PA behaviour. In particular, approaches to promote self-efficacy may increase the likelihood that patients will engage and continue with PA.

Funding: Private Foundation Support

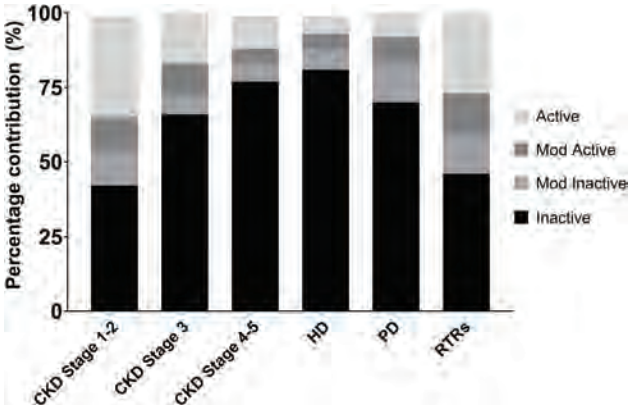

Fig 1

TH-PO622

A Multicenter Exercise Intervention for Persons Transitioning to Dialysis Using the "Exercise Is Medicine" Framework

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Background: Physical activity is associated with improvement of cardiovascular health, physical function, transplant outcomes and survival in persons with CKD. Yet at the time of dialysis initiation, 44% of individuals cannot walk one block and 56% cannot climb 12 stairs.

Methods: We are conducting a pilot and feasibility randomized controlled trial (NCT03311763) using the American College of Sports Medicine 'Exercise is Medicine' framework in patients with eGFR < 45 ml/min/1.73m^2 not on dialysis, in racially and ethnically diverse regions (San Jose, CA and Atlanta, GA). Group 1 receives a wearable activity tracker and exercise counseling; Group 2 additionally receives 8 weeks of twice-weekly group exercise sessions from a fitness professional trained in CKD related concerns (high/ low blood pressure and glucose, dialysis access precautions). Physical activity questionnaires (i.e. SF-12, IPAQ) and measurements [6-minute walk test (6MWT), handgrip strength, anthropometrics] are obtained at baseline, 8 and 16 weeks. Fitness trackers record daily step totals.

Results: 51 patients were recruited (23 San Jose, 28 Atlanta). 82% of participants were non-white, 55% have diabetes and mean baseline eGFR was 30.9 ± 9.7. 6MWT means were 399 ± 118m (Group 1) and 433 ± 118m (Group 2), compared with 571 ± 90m previously reported in pooled analyses of healthy individuals. 7 individuals were hospitalized and 3 transitioned to dialysis during the study. Complete data will be available Fall 2019.

Conclusions: We successfully integrated recruitment, physical activity assessment and group exercise into diverse clinical settings servicing minority patients with advanced CKD. At baseline patients have poor capacity and experience a high burden of hospitalizations.

Funding: NIDDK Support, Private Foundation Support

Participant Characteristics at Baseline

	Group 1 (n= 27)	Group 2 (n=24)
Age	61 (37-74)	58 (32-72)
Female	52	54
Hispanic Ethnicity	15	13
Race Black Caucasian Other	 48 15 37	 50 21 29
Diabetes	52	58
eGFR (ml/min/1.73m^2)	30 (7-46)	33 (15-46)
BMI (kg/m^2)	31 (16-54)	32 (17-45)
6MWT (m)	383 (193-574)	451 (193-719)
Handgrip strength (kg)	24 (9-54)	25 (11-55)

Data presented as Median (range) and %

TH-PO623

Exercise with Blood Flow Restriction Is Safe and Tolerable and Enhances Strength Adaptations Among Dialysis Patients

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Background: Haemodialysis (HD) patients have reduced exercise capacity, impaired muscle structure and function, and reduced exercise capacity. Intradialytic exercise interventions can improve subsequent declines in physical function associated with higher mortality with good adherence. Blood flow restriction (BFR) exercise enhances muscle strength and size adaptations to low-intensity exercise, thought to be insufficient for such adaptions. This technique appeals in ESKD but is yet to be evaluated in this population. The aim of this research was to assess haemodynamic safety and tolerability of BFR aerobic exercise in HD patients and the efficacy of a 6 week intervention.

Methods: In study 1, HD patients underwent a 3-phase program of supervised aerobic low-intensity exercise. Phase 1: 2 short bouts of cycling during 2 HD sessions. Phase 2: 2 short bouts of cycling with BFR whilst off HD on 2 separate days. Phase 3: 2 short bouts of cycling with BFR during 2 HD sessions. Participants with severe cardiovascular disease or known haemodynamic instability on HD were excluded. Outcome measures were haemodynamic (heart rate (HR) and blood pressure (BP)) and perceptual responses (exertion (RPE) and discomfort (RPD)) during exercise sessions. Study 2, a 6 week intervention, included a BFR group, undergoing 2 bouts of cycling with BFR during HD sessions, a non-BFR cycling group did 20 min continuous cycling during HD sessions, a usual care control group did no exercise. Outcomes included 3-rep maximum leg strength, and the 30-second sit-to-stand (30STS).

Results: There were increases in HR, systolic BP and mean arterial BP ($P<0.05$) post exercise for both exercise groups, with a delayed mean arterial BP reduction of 11.0 ± 1.3 mmHg ($P<0.01$). Adjusted for age and baseline, leg strength increased by 16±5% with BFR, compared with 9±5% in the non-BFR group, and no change in controls; 30STS increased only with BFR ($P < 0.05$). Across 452 sessions there were 6 minor adverse events, all episodes of self-resolving pre-syncope (4 after BFR exercise, 2 after non-BFR exercise).

Conclusions: Comparing BFR aerobic exercise to standard aerobic exercise during HD, haemodynamic safety and tolerability is comparable while strength and related physical function is increased with BFR aerobic exercise after 6 weeks exercise training.

TH-PO624

Lysosome: At the Crossroads Between Na^+-K^+-ATPase and NLRP3 in Hyperuricemia-Induced Renal Tubular Injury

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Background: We previously demonstrated the impairment of Na^+-K^+-ATPase (NKA) and NLPR3 signaling in hyperuricemia (HUA)-induced renal tubular injury and NKA was degraded in lysosomes. Here, we investigated the role of lysosome in NKA and NLRP3 signaling under HUA induce renal tubular injury.

Methods: Proximal tubular epithelial cells (PTECs) were incubated with different concentrations (50 μg/mL~200μg/mL) of UA for different times (6h~48 h), and the expression of NLRP3, lysosomal-associated membrane protein 2 (LAMP2), cathepsin B (CB) and interlukin-1β (IL-1β) were detected. CB inhibitor (Ca-074 methyl ester, Ca-074 Me) 10Mm or hydroxychloroquine (HCQ, 50 μM) was added to PTECs for 2h in advance, with the inhibition of NKA by its α subunit siRNA for 48h with or without the UA stimulation, NLRP3, LAMP2 and CB as well as mitochondrial function were detected. In vivo, SPF SD rats were divided (n=4 in each group) into control, HUA group [oxonic acid (OA) 750 mg/kg/d gavage for 8 weeks]; HCQ group (HCQ, with OA 750mg/kg/d for 8 weeks and HCQ 25 mg/kg/d gavage since the 5th week and for 4 weeks); and febuxostat group (Feb, with OA 750mg/kg/d for 8 weeks and Feb 3 mg/kg/d gavage since the 5th week for 4 weeks). Renal cortex NKA activity, its expression, CB, LAMP2, NLRP3, IL-1β and uncoupling protein 2 (UCP2) were examined.

Results: UA time and dose-dependently increased the expression of LAMP2 and CB. Ca-074 Me or HCQ alleviated the expression of NLRP3, LAMP2 and CB, mitochondrial dysfunction caused by UA and/or NKA siRNA. OA significantly increased serum UA levels in SD rats and developed reduced urinary UA excretion, renal cortex NKA activity and its expression, increased the expression of NLRP3, Il-1β, CB, LAMP2, and UCP2 expressions, compared with control. HCQ, but not Feb treatment, significantly increased urinary UA excretion. HCQ demonstrated similar effects with Feb in enhancing renal cortex NKA activity and expression, reducing the expression of NLRP3, Il-1β, CB, LAMP2, and UCP2 expressions, compared with HUA group.

Conclusions: UA induces lysosomal damage to release lysosomal contents and activate NLRP3 inflammasome. Lysosomal function protection could alleviate NKA-NLRP3 signaling pathway and effectively improve mitochondrial function *in vitro* and *in vivo*, suggesting that lysosome function plays an important role in HUA-induced renal tubular epithelial cell injury.

TH-PO625

The Influence of an Elevated Serum Uric Acid Levels for Cardiovascular Events in the General Population with Normal Renal Function

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Background: The significance of an elevated serum uric acid (SUA) level as a risk factor for the onset of cardiovascular events (CVEs) remains controversial. Since the SUA level is affected by the impaired renal function, we evaluated the association between the SUA level and the incidence of CVEs in the Japanese general population without chronic kidney disease (CKD).

Methods: The baseline survey items were the SUA level, age, sex, body mass index (BMI), blood pressure, blood sugar, hemoglobin A1c, serum creatinine, estimated glomerular filtration rate, urinary albumin/creatinine ratio, total cholesterol, and electrocardiogram findings (existence of atrial fibrillation). Baseline data were measured in participants of annual health checkups from a community-based population. After the exclusion of CKD, the subjects were stratified into sex-specific quartiles of SUA (n = 15,036, mean age 63.2 ± 10.0 years in men and 60.6 ± 9.6 years in women, men 33.5%, including 5,038 men and 9,998 women). The endpoint was determined as the composite of CVEs (stroke, myocardial infarction, and sudden cardiac death). A Cox regression analysis was performed to examine the sex-specific relationship between the baseline SUA level and the onset of CVEs.

Results: During a mean follow-up period of 8.8 years, we confirmed 611 CVEs (304 in men, 307 in women). After adjusting for traditional risk factors (age, BMI, hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation), the hazard ratio for the onset of CVEs did not differ among the quartiles in men (q1 (2.1≤SUA(mg/dl)≤4.8) = reference, q2 (4.9≤SUA(mg/dl)≤5.6) = 0.80, q3 (5.7≤SUA(mg/dl)≤6.4) = 1.01, q4 (6.5≤SUA(mg/dl)≤12.0) = 0.99; p = 0.447). In contrast, in women, a significant trend was observed (q1 (2.0≤SUA(mg/dl)≤3.7) = reference, q2 (3.8≤SUA(mg/dl)≤4.3) = 1.28, q3 (4.4≤SUA(mg/dl)≤4.9) = 1.58, q4 (5.0≤SUA(mg/dl)≤10.3) = 1.58; p = 0.035).

Conclusions: In the Japanese general population with normal renal function, an elevated SUA level is considered an independent risk factor for the onset of CVEs in women but not in men.

TH-PO626

Nifedipine Modulates Renal Lipogenesis and Fibrosis via the AMPK/SREBP Transcriptional Pathway: An In Vivo CKD Model and Translational Study

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Background: Overproduced free fatty acid induces inflammation and renal fibrosis. Weight reduction therapy including calcium loading method may decrease the above renal damage. However, calcium channel blocker affects lipid accumulation in extra-adipose tissue is in debate. Therefore, we want to initiate study on CKD animal and patients to realize effect of nifedipine on lipogenesis and renal toxicity.

Methods: 39 SD rat were divided in four groups including control, Doxorubicin (DR) treated, DR+nifedipine treated and high fat diet (HFD). In addition, nineteen renal transplant patients were also enrolled for the examination of graft fibrosis and lipid content via transient elastography. Lipogensis related enzymes including Sterol regulatory element-binding proteins (SREBPs), acetyl-coa carboxylase (ACC), fatty acid synthase (FAS), 5' AMP-activated protein kinase (AMPK) were tested.

Results: Hypertension and proteinuria were observed in DR, DR+Nifedipine and HFD group. However, TNF-α was expressed in DR group compared with control, and higher in DR+nefidipine group. ($p<0.05$) Renal fibrosis on pathology obviously occurred in DR and DR+nifedipine groups but not expressed in HFD group compared with control. ($p<0.05$) Immunohistochemistry of CD36 also significant higher in nifedipine treated group but not high fat diet group. ($p<0.05$) Western blot showed higher SREBP-1/2, ACC, and lower FAS. ($p<0.05$) P-AMPK/AMPK was lower in study groups. Low density cholesterol level was strongly correlated with graft kidney fibrosis and lipid accumulation. ($p<0.05$)

Conclusions: Nifedipine may potentiate renal fibrosis and lipid accumulation through SREBP-1/2 activation and lower AMPK activity in this in vivo study, similar results was observed in our previous in vitro study. Interestingly, hypercholesterolemia may correlate with renal fibrosis on graft kidney in CKD patients.

TH-PO627

The Histone Deacetylase (HDAC) Inhibitor Belinostat Attenuates H_2O_2-Induced Senescence-Like State by Regulation of HDAC7 in the Human Renal Proximal Tubular Epithelial Cells

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Background: Oxidative stress causes cell injury, disease, and aging. Renal aging is associated with decreased glomerular filtration rate, glomerulosclerosis, tubular atrophy, and fibrosis. HDAC7 modulates the cell cycle and induces cell senescence. We investigated the effect of HDAC inhibitor, belinostat on the H_2O_2-induced renal tubular senescence, and its underlying molecular mechanisms.

Methods: The effects of belinostat in H_2O_2-induced cell senescence was determined using human renal proximal tubular epithelial (HK-2) cells. H_2O_2-induced premature cellular senescence was detected by senescence-associated (SA)-β-gal staining and galactosidase activity, and the fluorescent dye 2',7'-dichlorofluorescein diacetate was used to measure intracellular reactive oxygen species (ROS). Cell cycle progression was measured by flow cytometry and immunoblotting, and the knock down of histone deacetylases 7 was induced by HDAC7 siRNA.

Results: We observed the effect of belinostat on cell cycle regulation of HDAC7 in H_2O_2-induced senescence-like cells. H_2O_2 increased SA-b-gal staining and increased protein expression of HDAC7, p-caveolin-1, p-Rb, p-P53, p-P21 and P27. It also increased phosphorylation of p-AKT, p-ERK1 / 2, p-JNK, and induced ER stress. In contrast, pretreatment of belinostat reduced protein expression of HDAC7 and p-caveolin-1 and cell cycle-related protein expression and the phosphorylation of p-AKT, p-ERK1 / 2, and p-JNK and reduced ER stress expression. SiRNA treatment of HDAC7 inhibited the expression of p-caveolin-1 and decreased SA-b-gal staining.

Conclusions: Treatment of belinostat may exert anti-senescence effect by controlling p-AKT, p-ERK1/2, p-JNK, and ER stress signal pathways via inhibition of HDAC7 in H_2O_2-treated HK-2 cells.

Funding: Government Support - Non-U.S.

TH-PO628

Transcriptional Regulation of Kidney Autophagy by Farnesoid X Receptor

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Background: Autophagy is an evolutionarily conserved catabolic process that removes damaged organelles and maintains cellular energy homeostasis. Acute regulation by nutrient-sensing of autophagy and long-term transcriptional regulation by nuclear hormone receptor farnesoid X receptor (FXR) is well known. Also, kidney autophagy regulates TGFβ expression and suppresses kidney fibrosis. However, the functional role of FXR on TGFβ-induced kidney autophagy is relatively unknown.

Methods: Expression levels of LC3 protein and autophagy related genes were measured on treatment with TGFβ and FXR agonists, GW4064 and WAY-362450, in human proximal tubule cells (HK2 cells). Also, we tested expression levels of autophagy related proteins and genes in overexpression or downregulation of FXR in cells. Expression levels of protein and autophagy related genes were measured in the sham and UUO model of WT and FXR knock-out mice.

Results: Treatment with TGFβ (5 ng/ml) in HK2 cells resulted in an increase in the level of LC3 protein and autophagy related genes, along with an increase in fibrosis markers. Activation of FXR by agonists in TGFβ-induced HK2 cells regulates expression levels of LC3 I/II and Becn1. Autophagy related genes were decreased in FXR agonists treated HK2 cells. Also, autophagic flux was further increased on co-treatment with GW4064 and TGFβ in HK2 cells. Autophagy related genes have no GW4064 effects on down-regulation of FXR by siRNA in HK2 cells. Autophagy related genes were regulated by fasting/feeding in WT mice. Protein levels of LC3 and fibrosis markers were increased in FXR-KO UUO mice model compared to those of WT UUO mice model.

Conclusions: These data reveal a functional role of FXR for kidney autophagy regulator in TGFβ-induced HK2 cells and suggest that FXR may play an important role in the suppression of renal fibrosis through transcriptional regulation of kidney autophagy.

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TH-PO629

Rhein Attenuated Palmitic Acid-Induced Renal Tubular Cell Injury by Regulating AMPK-mTOR-Autophagy

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Background: Rhubarb is one of the widely used Chinese medicine herbs in the treatment of some kidney diseases. Rhein is an important monomer composition of Rhubarb which has multiple biological effects. Our previous studies have found that Rhein suppressed autophagy to protect renal cells. However, the underlying mechanism is still unclear. Metabolism disorder, especially dyslipidemia, attracts more and more attentions in recent years. In current study, we evaluated the protective effects of Rhein and the underlying mechanisms in palmitic acid (PA)-induced cell injury.

Methods: To study the toxicity of lipid, we use different concentrations of PA to induce HK2, human proximal tubular cell, injury. CCK8 cell viability detection, Tunel staining, FITC/PI flow cytometry and western blot were employed to analyze the protective effects of Rhein in PA-triggered HK2 impairment. Western blot and Fluorescence microscope were used to evaluated autophagy. Oil O stanning and Bodipy Probe were used to detect lipid in the cell.

Results: PA induced HK2 cells detatchment from the bottom, morphological changes and loss of cell viability after 24h incubation. The Rhein obviously reduced the cell damage elicited by PA, improved morphological changes, attenuated the loss of cell viability. Western blot analysis indicated that Rhein inhibited PA-induced autophagy as evidenced by the change of LC3 I to LC3 II bands. In addition, the fluorescence optical microscopy observation showed that PA activated autophagy. Moreover, autophagy inhibitor, chloroquine, did not affect autophagy flow in western blot analysis. These reuslts

indicated that PA did not influence lysome function. PA increased autophagy upstream by upregulating AMPK-mTOR possiblelly in western blot analysis. And the Rhein might prohibit AMPK to regulate mTOR - ULK1 pathway.

Conclusions: Rhein attenuated the PA-induced renal tubular cell injury by regulating AMPK-mTOR-Autophagy pathway.

Funding: Government Support - Non-U.S.

TH-PO630

Sodium Glucose Co-Transporter 2 Inhibitor Ameliorates Autophagic Flux Impairment on Renal Proximal Tubular Cells in Obesity Mice

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Background: Obesity is supposed to cause to renal injury, and sodium glucose co-transporter 2 inhibitors (SGLT2-I) are reported to have possibilities to protect renal disorders. However, the SGLT2-I direct protective mechanism has been unclear. In this study, we investigated SGLT2-I effects focused on autophagic flux impairment in proximal tubular cells in obesity mice.

Methods: 5-week-old C57BL/6J mice were divided to normal diet (ND) fed group or 40 kcal % fat diet (HFD) fed group. After 9 weeks, we separated the mice, administrated 10.0 mg/kg/day SGLT2-I (empagliflozin provided from Boehringer-Ingelheim) group or solvent, hydroxypropyl methylcellulose (HPMC) group to each feeding group mice for 1 week. After total 10 weeks, urine was harvested for 24 hrs with ND. The mice were sacrificed, and serum plasma and kidneys were harvested. We investigated pathological analysis and protein expression focused on autophagy.

Results: The weight of HFD mice gained significantly than that of ND mice. HFD-SGLT2-I mice showed significant decrease of urinary N-acetyl-β-D-glycosaminidase (NAG) compared with HFD-HPMC group ($p < 0.05$). In oil red O staining, lipid accumulations were observed on proximal tubular cells in HFD-HPMC treated mice, however lipid accumulations were observed significantly decrease in HFD-SGLT2-I fed mice. HFD-HPMC mice showed significantly increase of p62 positive proximal tubules compared to ND-HPMC group. Interestingly, HFD- SGLT2-I showed significant decrease compared to HFD-HPMC group ($p < 0.05$). In electron microscopy, multilamellar bodies (MLBs), which shows the autophagosome or autolysosome storing lipids, appeared in proximal tubular cells of HFD-HPMC mice, however MLBs decreased in HFD-SGLT2-I group. In addition, abnormal formation of mitochondria was observed in proximal tubular cells of HFD-mice, and several mitophagosomes were observed in those treated with SGLT2-I.

Conclusions: SGLT2-I might have renal protective effects against obesity via improving autophagic flux impairment in proximal tubular cells by promoting autophagosomal degradation of lipids and damaged mitochondrias.

TH-PO631

Examining Transcriptional Coordination Among Pathways Using Single Cell Transcriptomics

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Background: Recent evidence suggests that the intracellular activity of certain immune pathways, such as the complement, engages in novel cross-talk with metabolic pathways. This pathway-pathway interaction is critical in directing a catered cellular response. Single cell RNA sequencing (scRNA-seq) provides an unprecedented opportunity to understand whether certain biological pathways act in synchrony.

Methods: Using single cell transcriptomics data from five different T cell subtypes (CD4+ naïve, memory, helper and regulatory T cells, and CD8+ cytotoxic T cells), we developed a model for assessing the canonical correlation between two pathways. We examined the significance of the correlation using a modified permutation null distribution that accounts for technical covariates. Complement dysregulation is a hallmark of several kidney diseases, so we used the complement as a *bait* immune pathway to detect which metabolic pathways it is correlated with, and how that correlation differs across T cell subtypes.

Results: Using canonical correlation analysis, we detect pairwise coordination among biological pathways, and explore how the complement pathway might interact with various metabolic pathways in different T cell subtypes. We found that complement-metabolism crosstalk varies substantially by T cell subtype. For instance, while the complement pathway demonstrated a significant canonical correlation with the arachidonic acid and NAD metabolism pathways in CD4+ memory T cells, we did not find evidence for the same in CD4+ naïve T cells. Further, in the latter naïve T cell type, glycolysis and the pentose phosphate pathways showed evidence for transcriptional coordination with complement.

Conclusions: Our method is a widely applicable approach that can be used to assess the differences in pathway cross-talk between cell-types, as well between a healthy and disease state.

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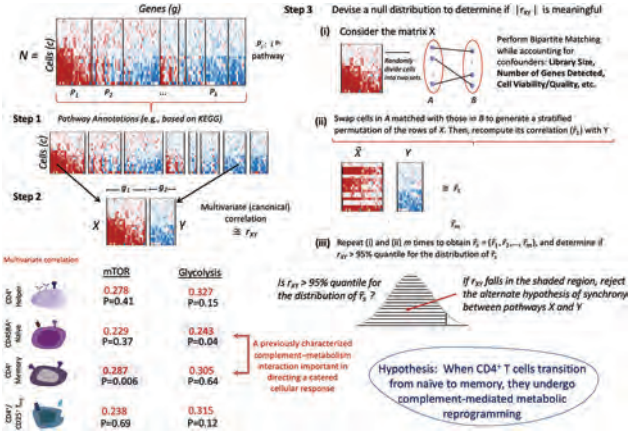

Examining the complement-metabolic axis using single cell RNA sequencing

TH-PO632

A Uremic Toxin, 3-Carboxy-4-Methyl-5-Propyl-2-Furanpropionate, Induces Cell Ferroptosis in Human Proximal Tubular Epithelial Cells via Reduced Glutathione Peroxidase 4 and Glutathione

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Background: 3-Carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF) was a uremic toxin metabolite of furan fatty acid that causes oxidative stress and accelerates the progression of renal failure. Ferroptosis is a form of cell death induced by accumulation of iron-dependent lipid-reactive oxygen species and inhibition of glutathione peroxidase 4 (GPX4). We investigated whether uremic toxin, CMPF affects renal proximal tubular cell damage by ferroptosis, a non-apoptotic form.

Methods: The fluorescent dye 2¢, 7¢-dichlorofluorescein diacetate was used to measure intracellular reactive oxygen species (ROS) following CMPF administration in human renal proximal tubular epithelial (HK-2) cells. The effects of CMPF on cell viability was determined using EZ-CyTox assays, and level of glutathione were determined by luminescence using the GSH/GSSH assay. glutathione peroxidase 4 (GPX4) proteins was determined by semiquantitative immunoblotting.

Results: Treatment of CMPF in HK-2 cells promoted the production of ROS. In addition, treatment with CMPF not only reduced the level of GSH but also decreased the expression of GPX4 protein. The ferroptosis inhibitor, lipophilic antioxidant, Fer-1, inhibited CMPF-induced ferroptosis, and iron chelators, DFO, also attenuated CMPF-induced ferroptosis in HK-2 cells.

Conclusions: The results of this study show that CMPF in HK-2 cells promoted the production of reactive oxygen species (ROS) and reduced the levels of GSH and GPX4 expression, resulting in cell death due to ferroptosis.

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TH-PO633

Donor-Recipient Gut Microbiota Similarity and Allograft Function Early After Kidney Transplantation

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Background: Gut microbiota affects the development and maintenance of innate and adaptive immune function. However, the effect of microbial composition similarity between recipient and donor on graft function after kidney transplantation (KT) remains unknown.

Methods: We prospectively enrolled living donor KT cases at two centers. Stool samples were obtained before KT. Microbiota composition was analyzed using extracted metagenomic DNA from the feces, using the Illumina MiSeq system. Gut microbiome difference between donor and recipient was calculated by weighted Unifrac distance. Clinical outcome was defined as 6 month post-transplant graft function.

Results: The microbial distance was estimated from 55 donor-recipient pairs. The recipients were 47.7 ± 13.0 years old; donors, 47.5 ± 11.2 years old. Among 26 related, 25 spousal and 4 unrelated donor transplants, couples showed lesser microbial composition difference than genetically related pairs. Spousal donors more frequently sharing meals with their recipients. The number of meals eating together in a day was significantly correlated with microbial distance. In terms of graft outcome, eGFR at 6 month after KT

was significantly correlated with microbial distance (P=0.014). In addition, patients with the farthest quartile of microbial distance suffered from more rejection events in 6-month after KT.

Conclusions: In this study, we found that intestinal microbiome similarity between donor and recipient might affect allograft function early after KT.

TH-PO634

Gut Microbiome and Circulating Uremic Solutes in Patients with CKD

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Background: The relationship between gut microbiome and renal function through the gut-kidney axis comes into the spotlight. However, the changes of microbiome according to the stages of chronic kidney disease (CKD) and the dynamics of uremic toxins produced by gut microbiome are not yet known.

Methods: We prospectively enrolled 149 CKD patients with various renal functions and healthy kidney donors as controls. We collected fecal samples of all participants and the microbial profiling was performed by 16S rRNA sequencing. Also, we measured the level of 4 uremic toxins including p-cresyl sulfate, indoxyl sulfate, p-cresol glucuronide, and trimethylamine N-oxide in serum of all participants by Liquid chromatography–mass spectrometry.

Results: Among the 149 participants, control, CKD stage 1 to 2, CKD stage 3 to 5 without dialysis, CKD stage 5 with dialysis were 46, 36, 32 and 35, respectively. The four uremic toxins were significantly increased with elevation of CKD stage. In microbial analysis with fecal samples, the abundances of genera *Prevotella, Lachnospira and Dialister* significantly decreased as the stage of CKD advanced. While, the abundances of genera *Alistipes* and *Oscillibacter* significantly increased as the stage of CKD advanced. Then, the uremic toxin-related microbiota was identified, and all four uremic toxins were associated with *Alistipes, Oscillobacter* and *Lachnospira*. These three genera showed significant correlations with both renal function and metabolite production.

Conclusions: We found that the composition of gut microbiota changed according to the stage of CKD. Especially, genera *Alistipes, Oscillobacter* and *Lachnospira* were correlated with levels of major uremic toxins. These results shows that gut microbiota might be a crucial factor for progression of CKD.

TH-PO635

Gut-Derived Uremic Retention Solutes in Patients with CKD and Healthy Adults

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Background: Elevated serum levels of the uremic retention solutes (URS), indoxyl sulfate (IS), p-cresol sulfate (PCS), and trimethylamine N-oxide (TMAO), have been observed in patients with late stage CKD/dialysis and have been associated with poor health outcomes. Diet is known to impact the production of these URS, yet no study to date has compared patients with mild/moderate CKD vs healthy adults on a controlled diet.

Methods: This secondary analysis aimed to determined serum and urine URS (sURS and uURS) in patients with mild/moderate CKD vs controls participating in a controlled feeding study. Patients with CKD (N=7, eGFR=29-55 mL/min/1.73m^2) were studied vs controls (N=7) matched for sex, age, and race. Subjects ate a diet controlled for macronutrients (protein 0.8g/kg/d), fiber (25g/d), P (1500mg/d), Ca (1400mg/d), K (3500mg/d), and Na (2400mg/d) content for 1 week. Fasting serum and urine were collected at the end of the study and IS, PCS, and TMAO were measured by LC/MS-MS. Differences between CKD and control were determined by paired comparisons, and associations were made by Pearson's correlations.

Results: Fasting sURS were higher in CKD vs controls (p<0.02). Fasting uURS (ratio to urine Cr) tended to be higher in CKD vs control, but only uIS reached significance (p<0.05). eGFR was inversely related to each sURS and uURS (r=-0.54 to -0.71, p=0.01-0.07). When correlations of eGFR with each sURS and uURS were evaluated by group (CKD or control), the inverse correlations persisted in CKD for sURS (r=-0.69 to -0.77, p=0.04-0.09), uTMAO (r=-0.79, p=0.03) and uIS (r=-0.77, p=0.04), but no associations remained in controls (p>0.30). There were strong correlations among the three sURS (r=0.82-0.95, p<0.001), which were strongest within CKD but still evident in controls. There were also strong correlations between the sURS and corresponding uURS (r=0.62-0.91, p<0.02), and these persisted within CKD and control groups.

Conclusions: These results show that URS are elevated in serum and urine in CKD vs matched healthy adults on a controlled diet. In the CKD patients, lower eGFR corresponded to higher serum and urine URS. Further studies are needed comparing different diets in patients with CKD to reduce the adverse health outcomes associated with URS production and retention.

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TH-PO636

Parathyroid Hormone Enhances Gluconeogenesis via the PKC/FoxO1 Pathway in Proximal Tubules

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Background: Parathyroid hormone (PTH) has been reported to enhance gluconeogenesis in proximal tubules (PTs), which may be comparable to that in liver. PTH is known to activate both cAMP/PKA and PLC/calcium/PKC pathways. In this study, we tried to determine the detailed mechanism of stimulatory effect of PTH on PT gluconeogenesis.

Methods: Freshly isolated rat and human PTs were incubated overnight in DMEM with 0.2 mM dibutyryl-cAMP (cAMP) or 1 nM PTH, and subsequently incubated with 10 nM insulin for 4 hours. Total RNA was extracted from the PTs. The mRNA expression of gluconeogenic enzymes (phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6P)) was determined by quantitative PCR. To clarify the signaling pathway of PTH, PTs were also treated with protein kinase A (PKA) inhibitor H89, protein kinase C (PKC) inhibitor Gö6983, or siRNA against FoxO1. In addition, we performed western blotting in the kidney cortex tissue to analyze the Akt phosphorylation. To examine the effect of PTH on hepatic gluconeogenesis, similar experiments were performed using primary cultured rat hepatocytes.

Results: In rat and human PTs, cAMP and PTH increased the mRNA expression of PEPCK and G6P by 5 and 3 times, respectively. Insulin almost completely abolished the stimulatory effect of cAMP, but failed to attenuate that of PTH. H89 completely abolished the stimulatory effect of cAMP without affecting that of PTH. By contrast, Gö6983 completely abolished the stimulatory effect of PTH without affecting that of cAMP. siRNA against FoxO1 inhibited the stimulatory effects of both cAMP and PTH. Insulin-induced Akt phosphorylation was preserved after incubation with PTH in the kidney cortex. In rat hepatocytes, cAMP, but not PTH, increased the mRNA expression of PEPCK and G6P.

Conclusions: Our results, for the first time to our knowledge, revealed that PTH enhances gluconeogenesis in PTs via PKC/FoxO1 pathway. We also found that insulin was able to induce the Akt phosphorylation but failed to suppress gluconeogenesis in the presence of PTH. PTH-enhanced gluconeogenesis as well as insulin resistance in PTs may at least partially contribute to altered glucose homeostasis reported in patients with hyperparathyroidism and/or pseudohypoparathyroidism.

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TH-PO637

The Effects of Dietary Glucose on Urinary Exosomal MicroRNA Expression in an Insulin-Resistant Mouse Model

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Background: Exosomal microRNAs provide a unique entry point to elucidate the molecular mechanisms of several metabolic processes and disease, including glucose metabolism and diabetic kidney disease. In addition, these miRNAs hold promise as attractive early non-invasive markers of disease. However, one limitation to the use of miRNAs as novel therapeutic interventions and early markers of disease is the influence of environmental and dietary factors on its expression. The goal of this study was to determine the effects of dietary glucose (ingestion) on the excretion of urinary exosomal miRNAs in an insulin-resistant mouse model.

Methods: 8 TALLYHO/Jng male mice were divided into three treatment groups with normal access to normal or 10% glucose drinking water for three-weeks. 24-hour urine was collected at baseline and week 3. Urinary exosomes were isolated using commercially available miRCURY Exosome kits and confirmed by western blotting.

Results: A diabetes pathway specific miRNA array revealed that 12 UE miRNAs were differentially expressed from baseline and week-3. UE miR-34a-5p, miR-320-3p, miR-26a-5p, miR-26b-5p, miR-23a-3p, miR-21a-5p, miR-194-5p, miR-1907, miR-185-59, and miR-126a-5p were increased 2-fold or greater, while miR-361-5p and let-7e-5p were decreased 2-fold or greater from baseline to week-3 in glucose-treated mice.

Conclusions: These findings suggest that these miRNAs play important roles in regulating processes associated with the development of diabetes and its complications, including diabetic kidney disease, and have potential as early markers and therapeutic targets for improving insulin sensitivity and renal senescence.

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TH-PO638

Ezrin Regulates Multiple Solutes Reabsorption via the Regulation of Membrane Protein Localization in the Proximal Tubules

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Background: Ezrin is a member of ERM (ezrin-radixin-moesin) proteins and works as a cross-linker between membrane protein and actin cytoskeleton. In kidneys, intense expression of ezrin is observed in proximal tubules, and it is postulated that ezrin plays important roles in tubular solute reabsorption via the regulation of apical membrane localization of several transporters. We previously reported that ezrin knockdown (*Vil2$^{kd/kd}$*)

mice show hypophosphatemia due to mislocalization of Na^+ dependent phosphate transporters and its scaffold protein, Na^+/H^+ exchanger regulatory factor 1 (NHERF1). However, we haven't investigated the influence of loss of ezrin on the membrane localizations of other transporters.

Methods: We performed a comprehensive proteomic analysis of renal brush border membrane vesicles (BBMVs) of proximal tubules from Wild type (WT) and *Vil2*$^{kd/kd}$ mice in this study. We also measured the plasma concentration and urinary excretion of nutrition including amino acids, glucose, and low molecular weight protein.

Results: We identified totally 1,412 proteins including 18.8 % of membrane integral proteins from WT and *Vil2*$^{kd/kd}$ mice. Scaffold proteins including NHERF1 and PDZK1 were significantly decreased in *Vil2*$^{kd/kd}$ mice. Several transporters including Slc5a1, Slc5a11, Slc22a4 and Slc22a5 showed marginally significant reduction ($0.05 < p < 0.1$). We also found that BBMV localizations of several other solute transporters associated with the reabsorptions of amino acids, glucose, and organic anions were totally decreased in *Vil2*$^{kd/kd}$ mice, suggesting that *Vil2*$^{kd/kd}$ mice exhibit the phenotype of Fanconi syndrome, which is accompanied with massive urinary solute waste. On the other hand, expressions of several proteins associated with actin remodeling, and endocytosis were increased in *Vil2*$^{kd/kd}$ BBMVs. *Vil2*$^{kd/kd}$ mice showed defective endocytosis of FITC-labeled β_2-microglobulin similar to Fanconi syndrome model mice.

Conclusions: These results suggest that ezrin plays important roles in the regulation of several membrane transporter localizations in the proximal tubules.

Funding: Government Support - Non-U.S.

TH-PO639

Relationship Between Plasma Concentration of Adiponectin and Kidney Function in the Elderly Subjects: Results of the PolSenior Study

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Background: Adiponectin is an adipose tissue hormone involved in the regulation of glucose metabolism and fatty acid breakdown. Based on meta-analyzes, it was documented that higher plasma adiponectin concentrations in CKD patients are associated with lower risk of cardiovascular complications. As adiponectin is mostly metabolized in the kidneys it is important to establish the relationship between glomerular filtration rate (GFR) and adiponectinemia. The aim of this study was to assess the plasma concentration of adiponectin in relation to GFR in the older population-based PolSenior study cohort.

Methods: The PolSenior study was a multicenter study which assessed the health and socio-economic status of older adults in Poland. In 3913 subjects aged 65 years or above (2041 male and 1872 female, BMI 28.1±5.1 kg/m^2, mean age 79±9 years) plasma adiponectin concentration (ELISA; B-Bridge International) were measured. GFR was estimated using a short MDRD formula. The results are presented as means with standard deviations.

Results: In studied subjects eGFR was 76 ml/min/1.73 m^2. eGFR below 60 ml/min/1.73 m^2 was observed in 842 (22%) subjects. Plasma concentration of adiponectin was 11.9±6.4 μg/ml. In subjects with eGFR < 60 ml/min/1.73 m^2 significantly higher plasma adiponectin concentrations were observed compared to subjects with eGFR ≥ 60 ml/min/1.73 m^2 (12.5±6.7 vs. 11.8±6.3, p=0.01). In the elderly subjects plasma adiponectin concentration depends strongly on BMI (R= -0.28; p<0.001) and marginally on the kidney function (R=-0.05; p=0.005). Multivariate regression analysis including plasma adiponectin concentration, BMI, eGFR, occurrence of diabetes and hypertension, showed that BMI and prevalence of diabetes (b=-0.24, p<0.001, b=-0.11, p<0.0001, respectively) but not eGFR explain variability of plasma adiponectin concentration.

Conclusions: In the older subjects from general population plasma adiponectin is weakly affected by kidney function.

TH-PO640

RNA Sequencing Analysis of Experimental Uremia and Compensated Pancreatic Exocrine

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Background: Malnutrition is a common problem in patients with chronic kidney disease (CKD). About 30 years ago, several studies showed that more than half of patients with end-stage renal disease (ESRD) suffered from exocrine pancreatic insufficiency. Recent years, some studies also reported this phenomenon. But it's not clear that if there is compensatory mechanism to help relieve the symptom.

Methods: Sprague-Dawley rats were divided into two groups: sham (group NC) and uremia (group U). Uremia group rats were processed with 5/6 nephrectomy for chronic renal failure. All rats were fed for 24 weeks. High-throughput sequencing technology was used to detect all gene expression differences in jejunum tissue samples of all rats. Differentially expressed genes were screened out and through functional annotation and enrichment analysis, gene expression signaling pathways of sham group rats and uremia group rats were screened out.

Results: The results showed that 95 up-regulated genes and 18 down-regulated genes were screened in uremia group compared with sham group. Analysis of GO function and KEGG signaling pathway enrichment showed that the above differentially expressed genes were mainly enriched in protein digestion and absorption, pancreatic secretion, fat digestion and absorption and other functions and pathways. The pancreatic secretion signaling pathway was related to our aim. RNA expressions of many genes increased including prss1, prss2, prss3, cpa1, cpa2, cpb1, cela3b, cela2a, ctrl, ctrb1, pla2g1b, pnlip, pnliprp1 and cel and these genes all code digestive enzymes like trypsin, carboxypeptidase, pancreatic elastase, chymotrypsin and phospholipase. Except trypsin, the enzymes above are usually detected by pancreatic secretion while their RNA expressions increased in the jejunum.

Conclusions: Patients with ESRD suffered from exocrine pancreatic insufficiency but we found that some pancreatic secreted enzymes increased RNA expressions in the jejunum of experimental uremia rats. So we can deduce that the jejunum could more or less compensate for exocrine pancreatic insufficiency of ESRD patients. However, the exact mechanism still needs to be studied further.

TH-PO641

The Pitfalls of Nephrology Care: Are Older Patients and Their Caregivers Getting What They Need?

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Background: Older patients with advanced chronic kidney disease lack knowledge and information regarding disease treatment and advance care planning. It is unclear whether clinicians and older patients have the same goals with regards to communication of treatment decisions and goals of care. We sought to explore perceptions of clinician behavior and patient preferences via interviews with nephrologists, primary care physicians, patients and caregivers regarding treatment for end-stage renal disease and advance care planning.

Methods: Between March 2017 and May 2018, we conducted individual semi-structured interviews with nephrologists, primary care physicians, older patients (age ≧ 65), and their caregivers. Transcripts were transcribed using TranscribeMe and reviewed in an iterative process. Using Nvivo 11, we coded all transcripts utilizing two codebooks (clinicians and patients/caregivers) and identified key themes. Three independent coders conducted thematic content analyses and discrepancies in coding were resolved through consensus coding.

Results: We interviewed 16 clinicians (nephrology, n = 8; primary care, n= 8), 10 patients, and 5 caregivers. We identified three key findings: 1) nephrologists felt their primary responsibility was to discuss dialysis and other treatments for kidney disease including conservative kidney management, 2) primary care clinicians felt that they should take the lead in helping patients navigate their disease management and also lead advance care planning discussions, and 3) patients' and caregivers' perspectives about dialysis, quality of life and planning ahead for their care were not adequately addressed by clinicians.

Conclusions: Our findings highlight the differences in opinions and expectations between clinicians, patients, and their caregivers regarding treatment decisions and advance care planning in nephrology. Importantly, patients and caregivers do not feel that their needs are being met. Further research is needed to test feasible models of patient-centered education to ensure all stakeholders feel valued.

Funding: NIDDK Support

TH-PO642

Palliative Care Consultation for Hospitalized Patients with Advanced CKD and Its Impact on Goals of Care

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Background: Chronic kidney disease (CKD) is a complex disease associated with high morbidity and mortality. Prognosis is even worse when these patients require hospitalization and identifying their goals of care is crucial. Palliative care (PC) is a comprehensive patient-centered approach that can help guide future care. Scarce data is available assessing frequency of PC consultation (PCC) for these patients and its impact on goals of their care. We aimed to assess frequency of PCC in hospitalized patients with advanced CKD/ESKD and its impact on advance directive (AD) and do not resuscitate (DNR) ordering.

Methods: We retrospectively studied all patients with CKD with eGFR<60 ml/min / ESKD hospitalized at UVA between 1/1/2015-6/30/2017. Number of PCC, AD and DNR orders were recorded as well as patients' demographic and comorbidity data.

Results: 8653 patients with eGFR<60 ml/min were hospitalized 13,321 times during the study period. PCC was obtained in 1274/8653 (14.7%) patients. Patient consulted for PC were significantly older, sicker, with less BMI and more advanced kidney disease (all with P<0.0001) compared with patients who did no get PCC. AD was obtained in 157/8653 (1.8%) patients. While AD was obtained in 12.1% with PCC, it was obtained in 0.04% with no PCC. DNR were signed in 2055/8653 (23.7%). While DNR was signed in 70.5% with PCC, it was signed in 15.7% with no PCC. Patients signing DNR orders were significantly older (73.0 ± 13.8 vs 67.7 ± 14.6), sicker (Charlson 4.6 ± 3.8 vs 3.3 ± 3.1) with less BMI and more advanced kidney disease (eGFR <30 ml/min 39.4% vs 27.1%). There was a trend to have more blacks signing DNR compared to whites (P =0.059)

Conclusions: PCC are underutilized in the care of hospitalized patients with advanced CKD/ESKD. PCC plays a significant role in guiding patients' goals of care.

PCC versus No PCC

	PCC (n=1274)	No PCC (n=7379)
Percentage	14.7%	85.3%
Age (years)	69.9+/-14.4	67.0+/-14.7
Charlson score	5.0 +/- 4.0	3.3 +/- 3.1
Sex (F)	46.5%	47.6%
Race (W)	80.5%	79.7%
BMI <25 >40	41.2% 7.0%	25.2% 9.7%
eGFR 30-60 ml/min <30 ml/min	58.8% 41.2%	71.9% 28.1%
AD	12.1%	0.04%
DNR	70.5%	15.7%

TH-PO643

The Oldest Dilemma: Dialysis or Conservative Treatment?

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Background: In comorbid elderly patients with stage 5 renal disease (ESRD) and functional impairment benefit of dialysis is not clear. The objective of this study is compare survival, characteristics and outcomes of patients who choose conservative palliative care management from those who decide dialysis after a shared decision meeting.

Methods: Prospective observational cohort study in patients with ESRD (CKD-EPI <12 ml / min, or CKD-EPI <15 ml / min in diabetics) who: 1. Prefer conservative palliative care management or 2. Meet the following criteria: > 75 years with comorbidity (Charlson Comorbidity Index (CI) > 5) or functional impairment (Barthel Index <95 or Palliative performance score (PPS) <60). The decision between dialysis (D) vs conservative management (CV) was taken after a reception meeting with patient, closest family and multidisciplinary team (nephrologists, nursery, palliative care physician, psychologist). Nephrology and Palliative Care team drove follow-up until death.

Results: One hundred two patients were included with no differences in ESRD etiology. Seventy eight (76.5%) chose CV, 24 (23.5%) D, 16 hemodialysis and 8 peritoneal dialysis. 55% were male although females chose mostly CV (p=0.015). Average age was 83.4±5.5 ys, statistically significant in CV vs D (84,5±5.9 vs 80.8±3.1ys; p=0,033), no differences in CI. Functional status was statistically lower measured by Barthel Index (77.3±20.3 vs. 94.48±10.8; p<0,0001) and PPS score (64.26±15.5 vs. 84.1±1.7; p:0.000) in CV vs D groups. Follow-up time was greater in D vs CV (median 25.2±17.1 vs 9.75±10 mo; p=0.000). Only 4 patients of CV group changed their decision to dialysis. Forty patients (39%) from CV required visits from home palliative care team (median 5, mean 7.83±9.9 visits). Sixty six died, 62 from CV and 4 from hemodialysis (p=0,0000). Survival was 43% at one year and 20% at 2 years in CV vs 96% at one year and 91% at 2 years in D group (p=0,0000). Places of death were, in frequency: Palliative care unit (n=25), hospitalization (n=20), home (n=17), medical residence (n=5) and ER (n=3).

Conclusions: ESRD patients who decide conservative treatment are oldest, with decreased functionality and mostly women. Despite a lower survival the decision remains firm which would indicate a probable stability in quality of life throughout their last days.

TH-PO644

Early Outcomes from an Ambulatory Kidney Palliative Care Program

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Background: Patients with advanced kidney disease have an elevated symptom burden, increased mortality, and poor quality of life. While palliative care can address these issues, nephrology patients infrequently receive such care. To address this, we implemented an ambulatory kidney palliative care program. We describe our initial outcomes.

Methods: Utilizing chart abstractions, we characterized the clinic population and symptom burden for patients seen from May 6, 2016-July 6, 2018.

Results: Ninety-four patients were referred; 74 (78.7%) patients seen. Forty (54.1%) had follow-up appointments (range 2-13). Mean patient age was 72.7 ±16 years with 32 (43.2%) on dialysis. The mean symptom burden (n=65) was 12 (± 4.9) symptoms (out of 17) with mean severity of 2 (range 0-4), representing moderate severity. The most common physical symptoms were nausea (78%), dyspnea (72%), pain (68%) and itch (66%). Eighty-seven percent reported anxiety and 73% reported depression. There was no difference in symptom burden between patients on dialysis and those on conservative management (n=22). Patients on conservative management were significantly older and had more comorbidities. By visit two, there was a significant reduction in global symptom score (21.9 vs 19.0, p=0.01) in addition to a reduction in anxiety (2.1 vs 1.7, p=0.03), vomiting (0.8 vs 0.2, p=0.04), and restless legs syndrome (1.3 vs 0.8, p = 0.02).

Conclusions: Patients with serious kidney disease treated in a kidney palliative care clinic have a high symptom burden regardless of treatment choice. The decision to pursue conservative management is more prevalent in older patients with more comorbidities. Follow up visits to the clinic demonstrated a decrease in symptom burden, suggesting that a dedicated kidney-palliative care clinic may be successful in managing symptoms and addressing unmet need.

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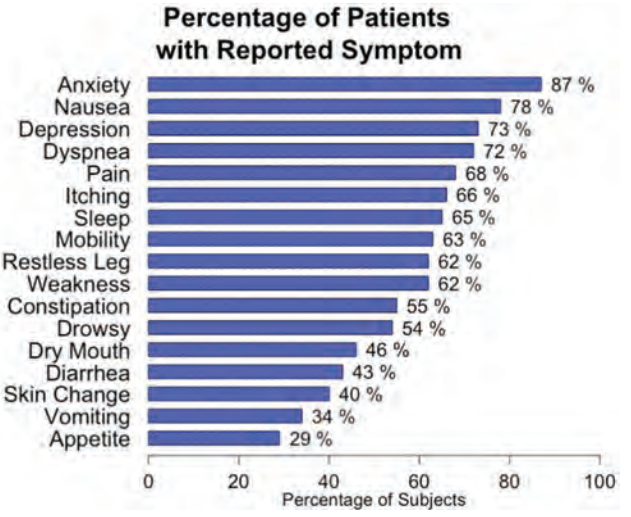

TH-PO645

Redefining End-of-Life Care in Dialysis: A Concurrent Hospice and Dialysis Program for Terminal Dialysis Patients

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Background: End of life for patients with end stage kidney disease (ESRD) is defined by increased health care utilization with limited access to hospice services. Financial and regulatory barriers within the Hospice Medicare Benefit often require patients to stop dialysis to receive hospice services. Unsurprisingly 40% of dialysis patients on hospice receive these services for three or less days. We developed a concurrent hospice and dialysis program with the goal to increase hospice utilization and improve patient, family and provider experience.

Methods: The ESRD Concurrent Care Program is a quality improvement initiative developed through partnership between Dialysis Clinic, Inc.'s Independence ESCO and UPMC Family Hospice in Pittsburgh, PA. The program offers concurrent hospice and palliative dialysis (10 sessions with weekly assessment) to terminal dialysis patients with an expected prognosis of two months or less and whose goals are comfort-focused. Palliative dialysis includes adjustment in the timing, frequency and delivery of dialysis to address symptoms and end of life goals. Outcomes measured include hospice length of stay (LOS), number of dialysis treatments provided and place of death.

Results: Since the program was initiated in January, 2018, 10 patients were offered the concurrent program. One patient elected to stop dialysis at enrollment. Of the remaining nine patients who elected the concurrent program, six survived to receive planned dialysis session(s). Among these six patients, 50% were female and all but one was Caucasian. Five of six patients received hemodialysis, and one patient received peritoneal dialysis. Hospice length of stay was almost 2 weeks (13.8 days, range of 7 to 28 days). The average number of dialysis treatments was 3.3 (range of 1 to 8 treatments). All patients died in a home-like environment. End of life goals attained included attending planned celebrations, spending time with family, and acheiving a sense of control.

Conclusions: Our concurrent hospice and dialysis program led to longer hospice LOS compared to general care trends. By allowing up to ten additional treatments, patients and families were able to achieve their end of life goals. Future direction involves expansion of the program within DCI with the goal to inform policy change in hospice delivery for dialysis patients at end of life.

TH-PO646

Survival of Elderly Patients with ESKD Managed Without Dialysis

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Background: Shared decision making (SDM) is important when considering whether an elderly patient ESKD should be managed with dialysis. Research has shown that physicians find these conversations difficult because of the relative paucity of data on survival of patients managed without dialysis.

Methods: We conducted a prospective observational study of 580 patients with CKD stages 4-5, aged ≤ 65 years between March 2009-August 2018 in our renal unit where SDM is actively implemented and conservative management is supported by a specific Renal Supportive Care (RSC) program. 148 dialysis patients attended the Pre-dialysis education clinic (PEC), 82 had not (non-PEC), and 280 patients were managed conservatively (CM) with RSC, an embedded multidisciplinary renal palliative care clinic. Survival was evaluated from: (1) Clinical pathway decision date; (2) eGFR ≤ 15; and (3) eGFR ≤ 10. Cox models were used to estimate survival adjusted for potential confounders identified as significant after multivariate regression analysis.

Results: CM patients were significantly older than PEC and non-PEC dialysis patients (mean±SD: 84±6 vs. 74±6 vs. 76±6; p<0.01) and had greater comorbidity (<0.01). From decision date, median survival was 6.0 years (Interquartile range [IQR] 2.5-9.5) in PEC compared with 3.3 (IQR 0.7-5.0) in non-PEC dialysis and 1.1 yrs. (IQR 0.4-1.7) in CM; p <0.01. From time eGFR ≤ 15, median survival was 7.8 years (IQR 3.5-12.6) in PEC, 5.6 (IQR 0.8-6.5) in non-PEC and 1.3 (IQR 0.5-2.0) in CM; p <0.01. From eGFR ≤ 10, median survival was 6.4 years (IQR 2.4-10.4) in PEC, 2.4 (IQR 0.5-6.0) in non-PEC and 0.7 (IQR 0.2-1.4) in CM; p <0.001. Non-PEC patients had lower eGFR than PEC at time of first visit (9±4 vs. 16±5 ml/min/1.73m^2, p<0.01). In the CM group, at least 51 (18%) patients did not reach eGFR ≤ 15 and the cause of death was mainly non-renal (41 out of 51; 92%). Older age reduced survival from decision date (HR 1.03, 95% CI 1.01-1.049; p<0.01).

Conclusions: The median survival of elderly patients managed conservatively was 15.4 and 8.5 months from the time of eGFR ≤ 15 and ≤ 10 respectively. Elderly patients who did not attend dialysis education prior to initiation had worse survival. This data should assist physicians with SDM discussions.

TH-PO647

Why Do Older Patients Choose Conservative Management?

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Background: Although many older patients with end-stage renal disease and limited prognoses prefer conservative management (CM), it is not widely offered in the US. Moreover, there is a dearth of US-based literature reporting clinical experience with shared decision-making regarding CM of advanced chronic kidney disease (CKD).

Methods: We describe the experience of 13 patients who opted for CM at the University of Rochester Medical Center's CKD clinic. Their reasons for choosing CM were categorized into four broad categories based on a review of their electronic medical records. A retrospective chart review conducted by two reviewers determined the status of advance care planning, hospice referral, and place of death.

Results: During the year 2016-2017, 13 patients opted for CM. The mean and median age of these patients was 81.8 years (standard deviation 7.3) and 83 years (interquartile range 11), respectively. Their reasons for choosing CM included: poor prognoses; a wish to maintain their quality of life; their desire for a dignified life closure; and the intention to protect family members from having to see them suffer, based on their own memory of having witnessed a relative on dialysis previously. A total of seven patients died: all received hospice services, five died at home, one at a nursing home and one at a hospital. Advance care planning was completed in 100% of the cases. Symptoms were managed in collaboration with primary care physicians.

Conclusions: Patients' decisions to forego dialysis and engage in CM were influenced by their values and previous experience with dialysis, in addition to co-morbidities and limited prognoses. Promoting the choice of CM in the US will require training of clinicians in competencies, including communication and decision-making skills, as well as basic symptom management.

TH-PO648

Racial Differences in End-of-Life Care Among Older Veterans with Non-Dialysis-Dependent CKD

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Background: Previous studies of veterans receiving dialysis demonstrated more intensive end-of-life (EOL) care among racial minorities than non-minorities. Little is known about racial differences in EOL care for older veterans with non-dialysis dependent chronic kidney disease (CKD).

Methods: We conducted a retrospective cohort study of veterans with incident stage 4 CKD from 2003-2014, age ≥70 years, and death before 1/18/17. Outcomes were a composite of intensive care (initiation of dialysis, invasive mechanical ventilation, cardiopulmonary resuscitation, or artificial nutrition) in the final month of life, and palliative care or hospice use in the final 6 months of life.

Results: 21,165 decedents met inclusion criteria. Non-Hispanic Whites were more often married and less often had hypertension, diabetes, and dementia compared to Non-Hispanic Blacks or Hispanics. In adjusted analyses, Non-Hispanic Blacks (OR 1.69, 95% CI 1.46-1.95) and Hispanics (OR 2.23, 95% CI 1.87-2.67) had a higher likelihood of intensive care compared to Non-Hispanic Whites. There was a significant interaction between death year and race with regard to hospice or palliative care use (p<0.01): compared with Non-Hispanic Whites, minorities had a similar likelihood of palliative care or hospice use before 2010, but higher use in recent years (Figure).

Conclusions: Historically, Non-Hispanic Black and Hispanic older veterans with CKD experienced more EOL intensive care and similar hospice or palliative care use compared with Non-Hispanic Whites. Following recent Veterans Health Administration investments in palliative care, minorities were more likely than non-minorities to use palliative care or hospice. More research is needed to assess how health system factors contribute to racial differences in EOL care.

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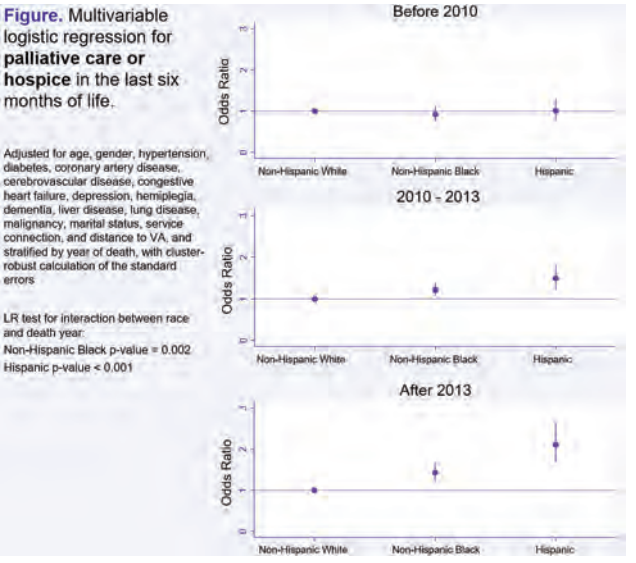

TH-PO649

Retrospective Cohort Study of Patients Seen in a Specialized Renal Supportive Care Clinic

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Background: Palliative care is underutilized in advanced kidney disease care despite similar mortality and symptom burden as other life-limiting illnesses. Patients are less likely to engage in advance care planning (ACP) and often begin dialysis without an informed conversation about conservative care. As a result, patients with advanced renal disease are more likely to receive invasive, burdensome treatments at the end of life compared to those with other serious illnesses. We describe outcomes of a Renal Supportive Care Clinic (RSCC) at UPMC, staffed by dually trained nephrology and palliative medicine physicians.

Methods: We reviewed the medical records of all patients seen in RSCC during 2015, with follow-up through February 2019. We recorded documentation of ACP and whether patients had chosen a conservative care (CC) pathway without dialysis. Additional data collected included demographics, comorbid conditions, date that eGFR fell below 20 mL/min/1.72m^2, and death date (when available).

Results: A total of 48 patients were seen in RSCC in 2015. Mean age at first visit was 74 (± 8.7) years. Over half (60%) were female, and 14 (29%) were Black. Eight (17%) were receiving dialysis at the time of RSCC visit. Mean creatinine at presentation was 2.4 (± 1.5) mg/dL (excluding dialysis patients). ACP was performed with 43 patients (90%), and a surrogate decision maker was documented for 41 (85%). Seventeen patients (35%) had a documented goals of care conversation indicating a CC pathway. Of these patients, only 2 (12%) started dialysis. Among the 15 patients who remained on CC, 9 survived until the end of the study period. Six of these patients had an eGFR that never fell below 20. Of the remaining three patients, an average of 1500 (± 283) days elapsed between eGFR <20 and the end of the study period. Of the patients who died, mean length of time between eGFR <20 and death was 376 days (± 340).

Conclusions: Advance care planning conversations occurred frequently in RSCC, and a significant minority of patients chose conservative care without dialysis. Of CC patients, a majority survived the 4-year follow-up period (including several with eGFR<20). Among patients who died, mean survival after eGFR fell below 20 was greater than 1 year. Further research is necessary to determine how palliative care can be efficiently integrated into care delivery for advanced kidney disease.

TH-PO650

A Brief End-of-Life Screening Module Improves Knowledge About End-of-Life Desires in CKD Patients

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Background: There are currently no published screening tools regarding end of life (EOL) care. An EOLmodule was developed and used by a nephrologist over the last decade. The module included three questions: 1) Whom would the patient like to make health care decisions in the event the patient is unable? 2) Is this the patient's next of kin? 3) In case of a medical catastrophe that resulted in severe changes in health and mentation that would be highly unlikely to be reversible, the patient would/would not want to be kept alive by artificial means, including dialysis. The checklist in general requires approximately 5 minutes for completion.

Methods: A retrospective review was performed on 398 patients seen in the outpatient clinic by the nephrologist who used the EOLM over ten years and a control group of 299 patients seen by other nephrologists at the same clinic. The following data were collected

from the electronic medical record: demographic data, information regarding EOL, patient comorbidities, and outcomes. All statistical analyses were conducted using SAS software.

Results: The EOLM was completed in 167 of 398 patients (42%) by the nephrologist using the EOLM. EOL was discussed in 17/299 (5.7%) patients seen by other nephrologists ($p<0.0001$). The mean age of patients using the EOLM was 63 years, 63% male, 55% with ESRD, 62% white, 31% African American. 89% of patients wanted comfort care in the event of a health catastrophe, with 6% desiring full care, and 5% undecided. 16 of 182 individuals (8.8%) identified an individual who was not their next of kin as the person that they would like to make healthcare decisions for them. 10/12 (83%) EOLM patients vs 19/37 (51%) control patients died during hospital admission and had documentation in the chart that EOL wishes were met ($p=0.089$).

Conclusions: An EOLM identified that the vast majority of CKD patients desire comfort care in the event of a health catastrophe. Nine percent of patients desired a surrogate decision maker who was not their next of kin and needed further documentation. Over ten years, only 12/167 patients died during a hospitalization. Patients with an EOLM were more likely to have EOL goals met (83% vs. 51%), though this was not significant due to lack of power.

Funding: Clinical Revenue Support

TH-PO651

A Pilot Study of a Supportive Care Video Decision Aid on Knowledge for Elderly Patients with Advanced CKD

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Background: The benefits of dialysis remain uncertain for elderly and frail patients with advanced chronic kidney disease (CKD). Although non-dialytic supportive kidney care (SKC) is an option for this patient population, there have been a lack of studies on patient-facing decision aids that specifically include this treatment approach. We performed a randomized controlled trial to test the efficacy of a video decision aid on knowledge of SKC among elderly patients with advanced CKD. We also assessed preferences for SKC and satisfaction and acceptability of the video.

Methods: Eligible patients were: age ≥ 65 years, English-speaking, had Stage 4 or 5 CKD, and were referred by their primary nephrologists at two academic centers in the US. Patients were randomized to receive education via a short verbal script or video. The video included images of patients undergoing hemodialysis, peritoneal dialysis or SKC. Patients received a knowledge questionnaire before and after receiving the verbal or video education.

Results: Among 100 enrolled participants, the mean age was 76 ± 6 years. Many were female (49%), White race (66%), and had completed high school education (85%). Knowledge of SKC increased in both arms after receiving education ($p < 0.01$); there was no difference in knowledge improvement between groups (Table 1). There was not a significant increase in those who preferred SKC after receiving either type of education ($p = 0.20$). The majority of patients who viewed the video felt comfortable watching it (96%), felt the content was helpful (96%) and would definitely recommend the video to others (72%).

Conclusions: Compared to an ideal verbal educational script, a video decision aid was not different in improving knowledge of SKC. Patients who received video education also reported high satisfaction and acceptability ratings. Future research will determine the effectiveness of a SKC video decision aid on patient preferences for treatment in real-world settings.

Table 1. Knowledge and preference for supportive care

	Total (N=100)	Verbal script (N=50)	Video (N = 50)	P-value
Pre-education correct knowledge of supportive care (%)	41	38	44	0.54
Pre-education preference for supportive care (%)	21	26	16	0.22
Post-education knowledge of supportive care (%)	61	58	64	0.54
Post-education preference for supportive care (%)	26	30	22	0.36

TH-PO652

Rapid eGFR Decline Is Not Associated with Cognitive Impairment

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Background: Cognitive impairment (CI) is underdiagnosed in patients with CKD. Unidentified CI may explain non-adherence to renal diet, fluid, medication and dialysis regimens. Determining if speed of eGFR decline is a significant risk factor for CI may help identify patients suffering from CI in CKD.

Methods: Patients enrolled into a UK longitudinal epidemiological non dialysis CKD cohort study without previously diagnosed CI underwent cognitive assessments. These included; Montreal Cognitive Assessment (MoCA) and Trail Making A and B (TMTA and TMTB). eGFR decline was measured by linear regression and percentage fall in eGFR prior to cognitive assessment. Multivariate logistic regression was performed for comorbidity and lifestyle values to determine factors predictive of CI. CI was defined as < 26 on MoCA and relative CI (rCI) defined by >-1.34SD of any cognitive Z score.

Results: 250 participants completed the MoCA and 239 participants underwent the MoCA and TMT. 44% and 17% of participants were diagnosed with CI or rCI using MoCA score (adjusted for education) and the Z score respectively. Fast eGFR decline (>-3mL/min/yr), measured over median 58 antecedent months was not associated with CI (Odds Ratio (OR) 0.589 95%CI 0.313-1.109) or rCI (OR 0.864 95%CI 0.369-2.021) in unadjusted analysis. >50% and >20% egfr drop over study period was not associated with CI or rCI. Older age and previous stroke were associated with CI after comorbidity adjustments. Only age was associated with rCI after same adjustments (Image 1).

Conclusions: Cognitive impairment is common in patients with CKD. Speed of eGFR decline is not a significant risk factor for CI in patients with CKD.

	Cognitive Impairment					Relative Cognitive impairment				
Variable	Unadjusted	Model 1	Model 2	Model 3	Model 4	Unadjusted	Model 1	Model 2	Model 3	Model 4
eGFR (per ml/min/1.73m^2 increase)	**0.984 (0.970-0.999)**	0.988 (0.973-1.003)	0.988 (0.973-1.003)	0.989 (0.972-1.006)	X	**0.954 (0.931-0.978)**	**0.960 (0.934-0.987)**	**0.960 (0.934-0.987)**	0.977 (0.948-1.007)	X
Age (per year)	**1.037 (1.017-1.057)**	X	**1.035 (1.015-1.055)**	**1.027 (1.003-1.050)**	**1.035 (1.009-1.062)**	**1.108 (1.066-1.151)**	X	**1.096 (1.056-1.138)**	**1.094 (1.047-1.142)**	**1.142 (1.07-1.210)**
Stroke	**5.543 (1.830-23.389)**	**5.461 (1.491-20.001)**	**5.351 (1.452-19.716)**	**4.946 (1.286-19.025)**	**6.430 (1.257-32.888)**	2.138 (0.712-6.421)	1.216 (0.359-4.114)	1.096 (0.314-3.823)	0.828 (0.202-3.398)	0.643 (0.129-3.215)
Myocardial infarction	**3.775 (1.668-8.544)**	**2.896 (1.251-6.704)**	**2.806 (1.209-6.515)**	1.933 (0.764-4.886)	1.547 (0.582-4.108)	1.416 (0.569-3.521)	0.666 (0.246-1.801)	0.614 (0.221-1.708)	0.656 (0.200-2.154)	0.723 (0.209-2.505)
Heart failure	**2.653 (1.280-5.495)**	1.857 (0.866-3.983)	1.738 (0.804-3.754)	1.516 (0.655-3.511)	1.280 (0.532-3.079)	**2.912 (1.323-6.412)**	0.589-3.317 (1.398)	1.212 (0.497-2.954)	1.050 (0.387-2.844)	1.183 (0.399-3.508)
Atrial Fibrillation	**2.497 (1.102-5.656)**	1.532 (0.642-3.660)	1.447 (0.602-3.480)	1.284 (0.493-3.345)	1.176 (0.422-3.278)	**5.547 (2.403-12.803)**	2.150 (0.862-5.359)	1.960 (0.760-5.054)	1.965 (0.703-5.489	1.463 (0.470-4.557)
Peripheral Vascular Disease	**2.559 (1.043-6.278)**	2.045 (0.814-5.135)	2.151 (0.836-5.534)	1.732 (0.627-4.788)	1.430 (0.462-4.427)	2.321 (0.892-6.044)	1.456 (0.510-4.151)	1.016 (0.452-2.284)	1.077 (0.315-3.688)	0.722 (0.158-3.302)
Diabetes	1.47 (0.821-2.632)	1.049 (0.584-1.953)	0.956 (0.506-1.805)	0.780 (0.393-1.548)	0.764 (0.366-1.594)	1.048 (0.339-3.238)	1.307 (0.6015-2.825)	1.016 (0.452-2.284)	0.905 (0.384-2.136)	1.081 (0.425-2.748)
UPCR >70	1.254 (0.743-2.116)	1.385 (0.804-2.386)	1.208 (0.672-2.169)	1.287 (0.686-2.415)	1.649 (0.877-3.102)	**2.459 (1.261-4.795)**	**3.258 (1.530-6.937)**	**2.335 (1.030-5.296)**	2.094 (0.881-4.979)	1.808 (0.709-4.609)
Anaemia	1.315 (0.791-2.184)	1.078 (0.633-1.835)	0.921 (0.520-1.625)	0.836 (0.459-1.524)	0.869 (0.471-1.601)	**3.227 (1.222-8.518)**	**2.245 (1.065-4.732)**	1.647 (0.749-3.622)	1.802 (0.798-4.071)	1.470 (0.607-3.556)
Psychodynamic medication	1.914 (0.872-4.199)	2.006 (0.889-4.527)	1.972 (0.869-4.476)	1.473 (0.602-3.605)	1.391 (0.55-3.487)	1.635 (0.650-4.113)	1.819 (0.645-5.129)	1.627 (0.559-4.738)	1.988 (0.628-6.294	2.221 (0.624-7.908)
Fast Progression (>-3ml/s/min/yr)	0.589 (0.313-1.109)	0.820 (0.418-1.608)	X	X	0.730 (0.350-1.522)	0.864 (0.369-2.021)	**3.151 (1.063-9.345)**	X	X	2.539 (0.720-7.725)

The table shows OR for CI and rCI in unadjusted and models 1-4. Model 1 adjusted for age, model 2 adjusted for age and eGFR, model 3 adjusted for all variables listed except fast progression. Model 4 is adjusted for all variables listed except eGFR.

TH-PO653

Intradialytic Cerebral Perfusion and Cognitive Outcomes in Older Adults on Hemodialysis

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Background: End-stage renal disease affects over 600,000 Americans; with the majority of patients treated with hemodialysis (HD). Over two thirds of HD patients have significant cognitive impairment. Although causes of cognitive impairment may be multifactorial, there is some evidence that HD-process may lead to cognitive decline through cerebral ischemic disease from HD related hemodynamic fluctuations. We hypothesize that, at baseline white matter integrity will be associated with change in intradialytic cerebral perfusion and cognitive performance.

Methods: Participants are over the age of 50 who have been on HD fewer than 2 years. Our predictor variable is change in intradialytic cerebral oximetry (ScO2). We include three cognitive outcome measures; patient-reported cognition survey, neuropsychological assessment, and white matter integrity on MRI.

Results: Currently 25 participants are enrolled, with 20 completing all baseline measurements (5 unable to do MRI). The mean (SD) age was 65.4 (6.6) years. Majority were males (72%) and Caucasian (64%). Most had diabetes (64%) and hypertension (80%). Overall cerebral oximetry declined during HD session with a mean drop of 7.0 (2.9) %. Participants reported overall no cognitive issues with mean PROMIS cognition score of 55.3 (9.8) against normative score of 50 for the general population. This contrasts with the neuropsychological scores showing deficits in test of executive function (39.8 (7.6)) and processing speed (40.0 (9.1)), again against normative score of 50. Correlational analysis demonstrates that greater intradialytic drop in ScO2 was associated with lower FA scores in some white matter tracts.

Conclusions: In our interim analysis we see that HD patients have cognitive deficits in key domains of executive function and processing speed and worse white matter integrity compared to healthy controls. Our results also show that cerebral oximetry does fluctuate during routine HD sessions. Our preliminary analysis demonstrate a trend of greater intradialytic cerebral oximtery decline being associated with lower white matter integrity in certain tracts, but the currently small sample size shows variability in results. Enrollment is ongoing and future analysis will include more participants.

Funding: NIDDK Support

TH-PO654

Association of CKD Markers with Dementia Markers on Brain MRI: The ARIC Study

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Background: Urine albumin-creatinine-ratio (UACR) and estimated glomerular filtration rate (eGFR) define chronic kidney disease (CKD) and are associated with an increased risk of dementia and cognitive impairment. Such pathologies are accompanied with damage to the structural integrity of the brain, which can be seen using magnetic resonance imaging (MRI). We therefore examined the association of ACR and eGFR with MRI structural brain abnormalities in participants in the Atherosclerosis Risk in Communities (ARIC) study.

Methods: We studied 1,525 ARIC participants aged 67-90 years who attended visit 5 (2011-2013), and had a brain MRI scan performed, and eGFR based on cystatin C and UACR measured. We analyzed the association of UACR and eGFR with reduced brain volume, increased white matter hyperintensity (WMH) volume, micro-hemorrhages and brain infarcts using linear and logistic regression models, adjusted for age, sex, race, education, Apolipoprotein E4 level, smoking, body mass index, total cholesterol level, hypertension, diabetes, stroke and intracranial volume (only for volume measurements). Effect sizes for eGFR and ACR were normalized to their interquartile range (IQR).

Results: Higher levels of UACR and lower levels of eGFR were associated with reduced brain volume in regions typically affected by Alzheimer's Dementia (AD), such as the hippocampus, and in non-AD related regions. Higher UACR and lower eGFR were also associated with increased WMH volume, and higher number of micro-hemorrhages and infarcts. The magnitude of the observed associations with MRI brain pathologies was similar between UACR and eGFR.

Conclusions: Higher UACR and lower eGFR are strongly associated with brain structural MRI abnormalities. These abnormalities include white matter lesions, infarcts, microhemorrhages and signs of brain atrophy, which manifest globally in regions typical for AD as well as other brain regions.

Funding: Other NIH Support - NHLBI

Pathology in brain MRI	Cystatin-based eGFR per 1-IQR decrease		Log UACR per 1-IQR increase	
	Standardized beta coefficient (95%CI) [1]	p-value	Standardized beta coefficient (95%CI) [1]	p-value
Brain volume, AD signature region	-0.10 (-0.14 to -0.05)	<0.001	-0.07 (-0.11 to -0.04)	<0.001
Brain volume, non-AD signature region	-0.05 (-0.08 to -0.02)	0.003	-0.05 (-0.07 to -0.02)	0.001
Log WMH volume	0.11 (0.04 to 0.17)	0.001	0.10 (0.05 to 0.16)	<0.001
	Odds ratio (95%CI) [2]		Odds ratio (95%CI) [2]	
Brain micro-hemorrhages	1.14 (0.96 to 1.36)	0.14	1.22 (1.07 to 1.40)	0.003
Brain infarcts	1.21 (1.02 to 1.45)	0.033	1.33 (1.16 to 1.52)	<0.001

Table: Adjusted estimates for associations of eGFR and ACR with MRI brain pathological changes
AD: Alzheimer's disease
WMH: White matter hyperintensity
[1] Estimates from linear regression models including age, sex, race, education, Apolipoprotein E4 level, smoking, body mass index, total cholesterol level, hypertension, diabetes, stroke and intracranial volume as covariates
[2] Estimates from logistic regression models including age, sex, race, education, Apolipoprotein E4 level, smoking, body mass index, total cholesterol level, hypertension, diabetes and stroke as covariates

TH-PO655

Renal Function Does Not Have a Graded Inverse Association with Cognition in the Elderly

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Background: Studies have shown a graded relation between estimated glomerular filtration (eGFR) and cognition. However, these studies are limited by inadequate matching at baseline, poor selection of neuropsychological tests (use of tests meant for screening to assess cognition) or low numbers of older participants. In this study we used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a NIH funded, longitudinal multicenter study for the early detection and tracking of cognitive impairment and dementia, to explore the association between eGFR and cognition in older adults.

Methods: We compared previously validated composite scores for memory and executive function in ADNI participants with and without cognitive impairment to assess the association with eGFR. We used CKD-epi equation for calculating eGFR. We divided the groups with and without cognitive impairment by baseline eGFR into <45, 45-60, 61-90 and >90 ml/min and analyzed differences in cognition between these groups. We also performed a linear multivariable analysis taking memory and executive function as the dependent variable and eGFR as a continuous independent variable.

Results: There were 1181 ADNI participants, 805 with cognitive impairment and 376 without (with available creatinine values at baseline). The mean ages were 73.3±7.7 and 74.5±5.6 respectively (p=0.006). Those with cognitive impairment were more likely male (58.6% vs 51.3%, p=0.018), and married (79.3% vs 68.6%, p=0.001). Race and ethnicity did not differ between the two groups (p>0.2). Mean eGFR was higher in the group with cognitive impairment (66.1±14) compared to the group with no cognitive impairment (63.9±14.8) (p=0.014). 6% of the participants had a eGFR<45, 22% eGFR 45-60, 51% eGFR 60-90, and 21% eGFR>90. In our multivariable model, memory scores decreased by 0.177 (p<0.001) and executive scores by 0.32 (p<0.001) for every 10 years increase in age in the entire cohort. Lower education was associated with lower memory and executive scores (p<0.001). There was no association between eGFR and memory (p=0.598) or executive scores (p=0.223) in the entire cohort.

Conclusions: We did not find an inverse relationship eGFR and cognitive impairment in the elderly in the ADNI Study.

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TH-PO656

The Effects of Testosterone Replacement Therapy (TRT) in Patients Established Dementia

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Background: Testosterone deficiency is common in both chronic kidney disease (CKD) and dementia. We have previously shown that dementia is associated with a faster progression of CKD, increased vascular disease and mortality. Here we examined the effect of TRT in patients with dementia and testosterone deficiency on progression of CKD progression, vascular disease and mortality.

Methods: Data from a large cohort of veterans diagnosed with low total testosterone (n=57,985) were used to determine the effect of TRT on the progression of CKD, cardiovascular events and all cause mortality in patients with dementia. Increase in serum creatinine to >1.5 mg/dl was taken as a measure of progression of CKD. Data were extracted using the Veterans Administration Informatics and Computing Infrastructure (VINCI), and analyzed using SAS. Propensity matching was used to adjust for age, vascular disease and follow up time. Results were compared using means tests, frequency tables, and odds ratios. P values ≤0.01 were considered significant.

Results: Of the 1,792 patients with dementia, 1,317 received TRT. Of the 57,985 controls without dementia, 44,434 received TRT. Baseline creatinine was similar in the dementia and control groups (1.06 mg/dl). TRT slowed the progression of CKD in patients with dementia (OR 0.63, 95% CI 0.51-0.79) and in controls (OR 0.89, 95% CI 0.88-0.91), and decreased all-cause mortality in patients with dementia (OR 0.61, 95% CI 0.49-0.75) and in controls (OR 0.85, 95% CI 0.84-0.87). TRT also decreased incident cerebrovascular accident (CVA) in dementia (OR 0.57,95% CI 0.41-0.79) and controls (OR 0.88, 95% CI 0.81-0.95), but incident myocardial infarction (MI) was decreased in controls only (OR 0.76, 95% CI 0.67-0.85). TRT did not reduce new diagnosis of retinopathy or nephropathy. Prior cardiovascular disease was more common in patients with dementia (% difference dementia/control), coronary artery disease (117), congestive heart failure (92), CVA (496), hypertension (67), MI (140), peripheral artery disease (129). Average follow up was 6.1 years.

Conclusions: TRT decreases the progression of CKD, CVA and all-cause mortality in patients with dementia. This finding is important, as dementia is associated with increased CKD progression, vascular disease and mortality.

Funding: Other NIH Support - NIA

TH-PO657

The Association of Depression with Geriatric Conditions in Older Adults with CKD

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Background: Depression is common in CKD and is associated with increased mortality. Geriatric conditions are constellations of signs and symptoms that are usually multifactorial in origin. Many geriatric conditions are associated with increased mortality. Examples of geriatric conditions include cognitive impairment or dizziness. Given depression and geriatric conditions both impact mortality, the presence of both may have additive or synergistic effects in CKD. Our goal was to examin e if depressive symptoms were cross-sectionally associated with the frequency of geriatric conditions in older adults with CKD.

Methods: Baseline data from the Aerobics, Weights, and Renal Disease Study, a randomized trial of exercise in community-dwelling adults 55+ years with stage 3b-4 CKD, were used. The independent variable was depressive symptoms, defined as Beck Depression Inventory score ≥ 10 points (range 0 to 63). The dependent variable was number of geriatric conditions (cognitive impairment, poor physical function, dizziness, fatigue, and chronic pain). Cognitive impairment was defined as Montreal Cognitive Assessment < 26; poor physical function as Short Physical Performance Battery ≤ 7; dizziness as reported on the Memorial Symptom Assessment Scale; fatigue if responded ≥ "good bit of time" to feeling worn out on Short Form-36 (SF-36); and chronic pain if answered ≥ "moderate" pain on SF-36. A generalized linear regression model adjusting for age, sex, race, study site, BMI, diabetes, hypertension, and eGFR was used.

Results: Of 99 persons (25% female, 61% African-American, mean age 68.0±8.2 years, mean BMI 31.1±6.6 kg/m^2, mean eGFR 33.1±9.2 ml/min/1.73m^2), mean BDI score was 7.2±6.1 points (range 0 to 31) points. Mean number of geriatric conditions was 1.7±1.0 (median 1, IQR 1). After adjustment, depressive symptoms were associated with more geriatric conditions (β coefficient = 0.5129 (95% CI 0.0468, 1.000, p value = 0.03).

Persons with depressive symptoms had 1.9 geriatric conditions (least square means), while those without depression symptoms had 1.4 geriatric conditions (least square means).

Conclusions: In older adults with CKD, depressive symptoms correlated with the frequency of geriatric conditions. Future studies should investigate how geriatric conditions may worsen poor health outcomes in CKD patients with depression.

Funding: NIDDK Support, Other NIH Support - 1UL1TR001430, K23AG057813, Other U.S. Government Support

TH-PO658

Benzodiazepines, Opioids, and Mortality Among Hemodialysis Patients

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Background: Mortality from benzodiazepine/opioid interactions is a growing concern in light of the opioid epidemic. HD patients suffer from a high burden of conditions which are treated with benzodiazepines and are 3-times more likely to be prescribed opioids than the general population. Therefore, they are at risk of mortality resulting from benzodiazepine/opioid interactions.

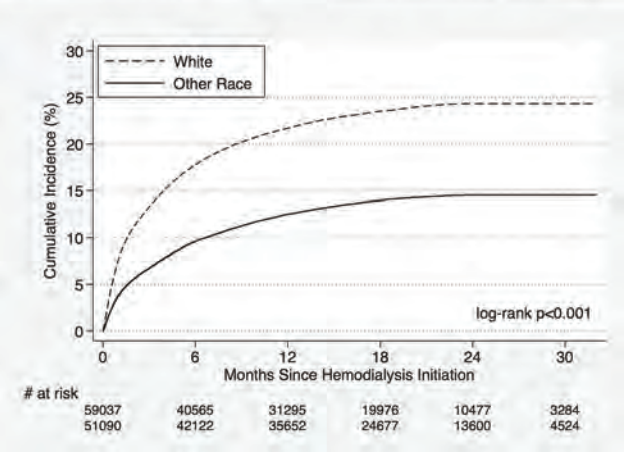
Methods: A cohort of 110,127 adults initiating HD (1/2013-12/2014) was assembled by linking USRDS/Medicare claims. Using adjusted Cox regression, we estimated the mortality risk associated with benzodiazepine prescribing (time-varying) and tested whether this risk differed by opioid prescribing.

Results: Within 1 year of HD initiation, 17.3% were prescribed a short- and 5.5% were prescribed a long-acting benzodiazepine. Co-prescribing of opioids and short- (78.7%) and long-acting benzodiazepines (81.8%) were common. Opioid prescribing was associated with short- (aHR=2.07,95%CI:2.00-2.14) and long-acting benzodiazepine prescribing (aHR=2.30,95%CI:2.15-2.47). Patients prescribed a short-acting benzodiazepine were at 1.53-fold (95%CI:1.45-1.61) increased mortality risk; this risk was exacerbated to 1.78-fold (95%CI:1.63-1.94) increased mortality risk with opioid co-prescribing ($p_{interaction}$=0.01). In contrast, long-acting benzodiazepine prescribing was inversely associated with mortality (aHR=0.85,95%CI:0.75-0.96) and there was no differential risk by opioid prescribing ($p_{interaction}$=0.57).

Conclusions: Patients initiating HD are commonly co-prescribed short-acting benzodiazepines and opioids which was associated with a 1.8-fold increased mortality risk. High-risk co-prescribing of short-acting benzodiazepine/opioids should be recognized by physicians caring for this vulnerable population.

Funding: NIDDK Support

Figure 1. Cumulative incidence of time to first short-acting benzodiazepine prescription among patients initiating hemodialysis (n=110,127) between 2013-2014, by race. Approximately 17.7% of white vs. 9.6% of non-white patients have used a short-acting benzodiazepine within six months of initiating dialysis.



TH-PO659

Time Trends in Opioid Prescribing and Uncontrolled Pain in the Last Month of Life Among Patients with ESRD, 2010-2018

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Background: Most patients with ESRD experience frequent, uncontrolled pain near the end of life. Opioids have long been a core component of pain management near the end of life. In response to the opioid crisis, organizations including the Veterans Health Administration (VA) and the Centers for Disease Control have developed guidelines intended to reduce opioid overuse at the population level. Little is known about how these efforts may have impacted opioid prescribing and pain among patients with ESRD near the end of life.

Methods: Using data from the VA, we identified all 3,370 patients with ESRD who died in a VA facility between 2010-2018 whose next-of-kin completed the Bereaved Family Survey. Using survey and pharmacy data, we assessed the mean daily opioid dose (in morphine equivalents) and the proportion with proxy-reported frequent uncontrolled pain, both focused on the last month of life. We used generalized estimating equations to assess time trends in these two outcomes after adjustment for patient demographics and medical comorbidity.

Results: From 2010 to 2018 mean daily opioid dose in the last month of life (in morphine equivalents) decreased by 1.4 mg per year (p=.006) (see Figure for mean doses by year). From 2010 to 2018 the percentage of patients with frequent, uncontrolled pain in the last month of life increased by 1.9% per year (p<.001) (see Figure for percentages by year). These differences persisted after adjustment for patient characteristics.

Conclusions: Decreases in opioid prescribing among patients with ESRD over the last decade have been accompanied by increases in uncontrolled pain near the end of life, highlighting potential unintended consequences of opioid safety initiatives.

Funding: Other NIH Support - National Institute on Aging, Veterans Affairs Support, Other U.S. Government Support

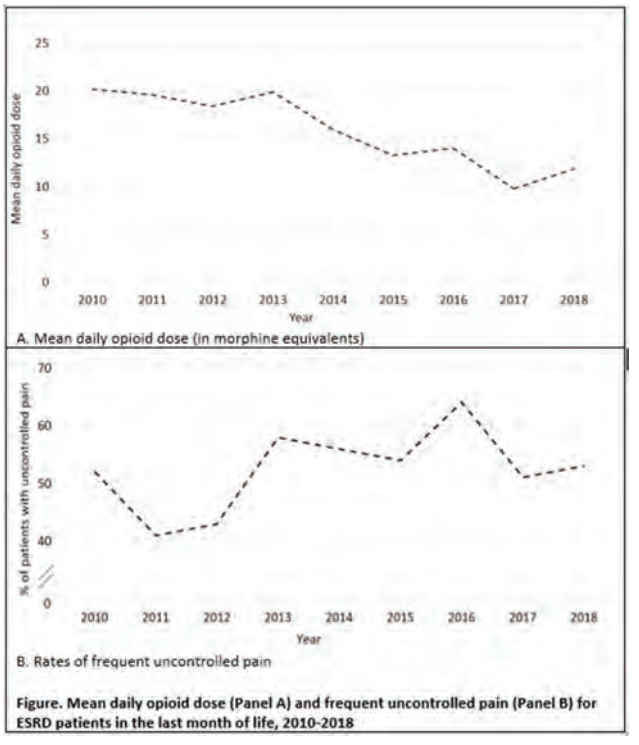

Figure. Mean daily opioid dose (Panel A) and frequent uncontrolled pain (Panel B) for ESRD patients in the last month of life, 2010-2018

TH-PO660

Kidney Biopsy in Elderly Chinese Patients

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Background: High-quality epidemiologic data on the spectrum of biopsy-proven kidney diseases among elderly patients are limited in China. This study aimed to examine the clinical characteristics and spectrum of kidney diseases in elderly patients who underwent native kidney biopsy.

Methods: We previously conducted a nationwide kidney biopsy survey including 178,803 patients from January 2002 to April 2018. A total of 10,597 native kidney biopsy performed in patients aged ≥65 years from 1590 hospitals across China were included in this study. The composition of kidney diseases and clinicopathologic correlations in different sexes, age groups, different period and regions were assessed.

Results: The most common indication for kidney biopsy in elderly patients was nephrotic syndrome (62.1%). Membranous nephropathy (MN) was the most frequent histological type (48.8%), followed by minimal change disease (9.8%) and IgA nephropathy (8.0%). We observed a increasing trend in the proportion of MN over the study period which was contemporaneous with a fall in the proportion of focal segmental glomerulosclerosis. There was no significant difference in major glomerular diseases between patients aged 65-79 years and ≥80 years after adjusting for sex, region, indication of biopsy, the level of the hospital that performed the biopsy and the time of kidney biopsy. Our study showed that the proportion of non-diabetic kidney disease (NDKD) is up to 62.7% in elderly diabetic patients underwent kidney biopsy, and the most common type of NDKD was MN. Compared with the patients aged 18-64 years underwent kidney biopsy over the same period, the proportion of renal artery injury (65.4% vs. 92.5%, p<0.001) was significantly higher, while phospholipase A2 receptor-positive MN (80% vs. 63.4%, p<0.05) was significantly lower in the very elderly patients (age≥80 years).

Conclusions: The spectrum of kidney diseases among elderly Chinese patients varied across sexes, age groups and regions and changed substantially from 2002 to 2018.

Renal biopsy diagnoses by clinical syndrome in the elderly

NS n(%)	Proteinuria (without NS) n(%)	CKD n(%)	AKI n(%)	NS+AKI n(%)	Hematuria n(%)
MN 4250(63.6)	MN 862(36.1)	IgAN 198(19.4)	AAV 81(22.1)	MCD 113(34.9)	MsPGN 15(34.9)
MCD 862(12.9)	IgAN 352(14.8)	DKD 111(10.9)	ATIN 71(19.4)	MN 59(18.2)	IgAN 13(30.2)
Amyloidosis 321(4.8)	MsPGN 243(10.2)	AAV 109(10.7)	ATN 33(9)	FSGS 44(13.6)	TBMN 3(7)

MsPGN, mesangial proliferative glomerulopathy; DKD, diabetic kidney disease; AAV, ANCA-associated vasculitis; ATIN, acute tubulointerstitial nephropathy.

TH-PO661

The Difference Between eGFR by Cystatin C vs. Creatinine Provides Clinical Information About Frailty in SPRINT

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Background: In prior studies, the discrepancy between the glomerular filtration rate (eGFR) estimated using either creatinine [$eGFR_{Cr}$] or cystatin C [$eGFR_{Cys}$] has been treated as measurement error related to kidney function. We propose instead that clinical information about frailty and muscle strength is contained in these differences. We examined the difference between eGFR by cystatin C and creatinine and its relationship to frailty, in cross-sectional and longitudinal analyses.

Methods: 9092 SPRINT participants had baseline measures of serum creatinine and cystatin C. $eGFR_{Cr}$ and $eGFR_{Cys}$ were calculated using CKD-EPI equations, and eGFRDiff was defined as $eGFR_{Cys}$ - $eGFR_{Cr}$. A 37-item frailty index (FI) included questionnaires, past medical history, cognitive tests and laboratory data (excluding albuminuria and eGFR). As defined in prior studies, frailty was FI > 0.21.

Results: Average (SD) was 68 (±9) years for age and was 73 (±23) for $eGFR_{Cys}$, 72 (±20) for $eGFR_{Cr}$, and 0.45 (±15) mL/min/1.73m^2 for eGFRDiff. Compared to participants with minimal difference in eGFR, those with a substantially positive difference eGFRDiff (≥20 mL/min/1.73m^2) were younger (64 vs. 68 years) and more likely to be male (77% vs. 64%). Those with a substantially negative eGFRDiff (≤ -20 mL/min/1.73m^2) were more likely to be frail (OR=1.34 95%CI [1.11; 1.61], p<0.01 in fully adjusted model, Table 1), and were at higher risk for death (HR=1.64 95%CI [1.14;2.36] p=0.008).

Conclusions: In SPRINT, an $eGFR_{Cys}$ estimate that was substantially less than an $eGFR_{Cr}$ estimate was associated with underlying frailty. The difference between $eGFR_{Cys}$ and $eGFR_{Cr}$ may provide important information on functional status and prognosis that should be incorporated into clinical reasoning when evaluating these measures.

Funding: Other NIH Support - T32 Institutional grant

Association of eGFRDiff groups with frailty at baseline

Outcome: Frailty	Negative eGFRDiff (< - 20 mL/min/1.73m2) (n=226)		eGFRDiff Reference (-20 to +20 mL/min/1.73m2) (n=1796)		Positive eGFRDiff (≥ 20 mL/min/1.73m2) (n=103)	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Unadjusted	1.43 (1.20; 1.70)	<0.001	0 (ref)		0.54 (0.43; 0.67)	<0.001
Fully adjusted *	1.40 (1.15; 1.72)	0.001	0 (ref)		0.76 (0.60; 0.97)	0.028

*adjusted for age, gender, race, education, body mass index, randomization arm, albuminuria, cardiovascular risk factors, chronic kidney disease stage

TH-PO662

The Difference Between eGFR by Cystatin C vs. Creatinine Provides Clinical Information About Frailty in CHS

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Background: Kidney function is typically assessed using serum creatinine. Cystatin C is an alternative marker of kidney function. The clinical significance of having a difference in estimated glomerular filtration rate (eGFR) by these 2 measures is unknown. We hypothesized that the magnitude of this difference is associated with frailty.

Methods: In 4101 community-dwelling older adults from the Cardiovascular Health Study (CHS) cohort, we investigated the cross-sectional association of the difference in eGFR by cystatin C vs. by creatinine (eGFRDiff) at baseline with prevalent frailty, using logistic regression, and the longitudinal association of eGFRDiff with incident frailty and mortality at 5 years, using Poisson regression. eGFR was calculated using CKD-EPI equations based on either measure ($eGFR_{Cr}$ and $eGFR_{Cys}$ respectively), and eGFRDiff was $eGFR_{Cys}$ - $eGFR_{Cr}$. Frailty was assessed based on the Fried frailty score.

Results: Mean (±SD) age was 72 (±5) years, $eGFR_{Cr}$ was 73 (±17) and mean eGFRDiff was -1.4 (range -68.0 to 70.6) mL/min/1.72m^2. 39% were males, 5% African-American, 72% non-diabetics. Per 10-point increment in eGFRDiff, the prevalence of moderate frailty was 19% lower, and that of severe frailty was 36% lower, in fully adjusted model (Table 1). Higher eGFRDiff (per 10 mL/min/1.73m^2) was associated with lower incidence rate ratio for moderate (IRR 0.93, 95%CI [0.87; 0.99]) and severe (IRR 0.59, 95%CI [0.47; 0.74]) frailty, as well as lower risk of mortality (IRR 0.65, 95%CI [0.57; 0.76], p<0.0001).

Conclusions: Those with a lower $eGFR_{Cys}$ than $eGFR_{Cr}$ were more likely to have prevalent frailty and were at higher risk for incident frailty and mortality. Considering eGFRDiff as a marker of patients' functional status may be a useful clinical tool to assess important geriatric outcomes.

Funding: Other NIH Support - T32 Institutional grant

Association of eGFRDiff (per 10-point increment) with frailty at baseline

Outcome: Frailty (n = 2084)	Moderately Frail (n=1832)		Severely Frail (n=252)	
	OR (95% CI)	p value	OR (95% CI)	p value
Unadjusted	0.78 (0.74; 0.82)	<0.0001	0.64 (0.58; 0.71)	<0.0001
Fully adjusted *	0.81 (0.76; 0.85)	<0.0001	0.64 (0.57; 0.72)	<0.0001

*adjusted for age, gender, race, body mass index, hypertension, diabetes, anti-hypertensives at baseline, cholesterol, smoking, chronic kidney disease stage by eGFRCr

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Which Factors Explain the Difference Between Measured and Estimated GFR?

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Background: Estimated GFR (eGFR) based on serum creatinine (SCr) is frequently reported by clinical laboratories, despite a certain degree of imprecision. The aim of this study was to examine factors that could explain the difference between eGFR and measured GFR (mGFR) in an elderly population.

Methods: We analyzed data from the AGES-Kidney Study, in which 805 individuals above the age of 70 (mean (SD) age 79 (3.9) years) had mGFR values available with simultaneous measurement of SCr and cystatin C. The CKD-EPI equation was used to calculate eGFR based on SCr (eGFRcr) or combination of SCr and serum cystatin C (eGFRcr-cys). The absolute difference between mGFR and eGFR (mGFR – eGFR) was determined and multivariable linear regression used to estimate the association of numerous variables with this difference, including age, sex, medication use, body composition, muscle strength and comorbidities.

Results: Mean (SD) mGFR in the study group was 62.4 (16.4) mL/min/1.73 m^2, whereas mean eGFRcr was 65.7 (17.1) mL/min/1.73 m^2 and mean eGFRcr-cys 64.7 (17.9) mL/min/1.73 m^2. The difference between mGFR and eGFR ranged from –36 to 46 mL/min/1.73 m^2 for eGFRcr and –35 to 26 mL/min/1.73 m^2 for eGFRcr-cys. In the multivariable linear regression model, significant predictors of the difference between mGFR and eGFRcr were age (p=0.047), thigh muscle mass (measured by computed tomography) (p<0.001), results of timed up and go test (p<0.001), mGFR (p<0.001) and urinary albumin/creatinine ratio (p=0.013). Significant predictors of the mGFR and eGFRcr-cys difference were age (p<0.002), sex (p<0.001), thigh muscle mass (p<0.001) and mGFR (p<0.05).

Conclusions: These preliminary results suggest that several variables, in particular those pertaining to muscle mass and strength, associate with the difference between mGFR and both eGFRcr and eGFRcr-cys. Incorporation of these variables into eGFR equations might yield more precise GFR estimates in the elderly than current equations. In addition, age and sex may not be adequately accounted for in these equations.

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Albuminuria and eGFR in Midlife and Older Age as Risk Factors of Dementia: The ARIC Study

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Background: Urine albumin-creatinine-ratio (UACR) and estimated glomerular filtration rate (eGFR) define chronic kidney disease (CKD) and are related to microvascular disease and endothelial damage. We extend previous studies by examining UACR and eGFR measured at midlife and older age as risk factors for dementia. Furthermore, we compare eGFR based on creatinine with eGFR based on cystatin C and beta 2 microglobulin.

Methods: We studied 9,967 participants aged 54-74 years in the Atherosclerosis Risk in Communities (ARIC) study who attended visit 4 (1996-1999) and had creatinine, cystatin C, beta 2 microglobulin and UACR measured with follow-up to December 31st, 2017. We evaluated the hazard of incident dementia associated with eGFR (based on creatinine, cystatin C and beta 2 microglobulin) and log UACR adjusted for age, sex, race, education and apolipoprotein E4 level (Model 1) and additionally for smoking, body mass index, diabetes and antihypertensive medication (Model 2). We compared eGFR and UACR associations to those observed among visit 5 participants (N=4,626, age 70-90, 2011-2013). Effect sizes for each measure of CKD were normalized to the interquartile range (IQR) at Visit 4.

Results: We observed 1,821 incident dementia cases over 16 years of follow-up (438 after visit 5). Risk of dementia was higher with higher levels of albuminuria and lower levels of eGFR but only when GFR estimation was based on cystatin C or beta 2

microglobulin (Table). There was no substantial difference in risk of dementia associated with eGFR or UACR between the two baseline visits.

Conclusions: Higher albuminuria is strongly related to dementia incidence. Lower eGFR shows similar associations but only when the estimation is based on cystatin C or beta 2 microglobulin. This could be explained by newer biomarkers being less influenced by muscle mass. The results are similar in midlife compared to older age.

Funding: Other NIH Support - NHLBI

Measure of CKD per V4 interquartile range, IQR	Baseline Visit 4, ages 54-74 years		Baseline Visit 5, ages 70-90 years	
	Model 1:	Model 2:	Model 1:	Model 2:
eGFR CKD-EPI, creatinine per 19.4 ml/min decrease	0.98 (0.92 – 1.04)	0.98 (0.91 – 1.05)	1.11 (0.99 - 1.24)	1.03 (0.91 – 1.17)
eGFR CKD-EPI, cystatin C per 24.3 ml/min decrease	**1.16 (1.07 – 1.25)***	**1.12 (1.03 – 1.21)***	**1.33 (1.16 - 1.53)***	**1.23 (1.05 – 1.44)***
eGFR CKD-EPI, creatinine and cystatin C per 20.7 ml/min decrease	**1.08 (1.01 – 1.16)***	1.06 (0.98 – 1.14)	**1.23 (1.09 - 1.38)***	1.13 (0.99 – 1.30)
eGFR CKD-EPI, beta 2 microglobulin per 18.3 ml/min decrease	**1.18 (1.11 – 1.27)***	**1.14 (1.06 – 1.23)***	**1.36 (1.20 - 1.54)***	**1.30 (1.12 – 1.50)***
Log urine albumin-creatinine ratio per 4.2 fold increase	**1.19 (1.13 – 1.25)***	**1.15 (1.09 – 1.21)***	**1.32 (1.18 - 1.46)***	**1.32 (1.17 – 1.49)***

Table: Adjusted HRs (95% CIs) for dementia incidence after midlife and after older age, by measure of CKD
Model 1: adjusted for age, sex, race, education and Apolipoprotein E4 level
Model 2: adjusted for age, sex, race, education, Apolipoprotein E4 level, smoking, body mass index, diabetes and antihypertensive medication.
*p < 0.05

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Predictors for 1-Year Mortality Among Elderly Patients with CKD Stage 4 and 5 Initiated on Hemodialysis at Divine Word Hospital, Tacloban City, Philippines, 2014-2016

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Background: Chronic kidney disease (CKD) prevalence among the elderly patients is increasing. This study aimed to describe the clinical and demographic profile of the elderly patients with CKD Stages 4 and 5; to determine the 1 year outcomes after HD initiation as to survival, death and its causes of mortality and to identify the predictors for 1 year-mortality among elderly CKD patients.

Methods: A descriptive retrospective study involving all elderly patients diagnosed with CKD Stage 4 and 5 initiated on hemodialysis at Divine Word Hospital in the year 2014 to 2016. Patients' demographic and clinical data, and the outcomes on hemodialysis in the form of 1-year survival or death were identified. Data were analyzed with the use of frequency distribution and percentages for categorical variables, and mean and standard deviation for continuous variables. Univariate cox regression was employed to identify the predictors of mortality.

Results: Eighty three participants were included in the study. The mean age was 73 years old, females comprised 56%, Dabetic Kidney Disease accounted to 58%, cardiovascular and metabolic co-mobidities were present in 91% and 65% of cases, respectively; and majority had no presume pre-HD nephrology care at 56%. Seventy five percent survived after 1 year from HD initiation. Female gender and hemoglobin level of <10 g/dL were significant predictors of mortality.

Conclusions: The predictors for 1 year-mortality among elderly patients with CKD stage 4 and 5 initiated on hemodialysis were female gender and anemia (hemoglobin of <10g/dL). Specific measures to address these risk factors must be implemented to improve survival in these patients.

Table 1

Univariate Cox Regression Predicting Mortality of Elderly CKD Patients on HD

Characteristic	Hazard Ratio	95.0% CI		p-value
		Lower	Upper	
Age	1.08	0.72	1.64	0.71
Sex (Female)	5.20	1.39	19.39	0.01*
Cause of CKD				
Diabetic Kidney Disease	0.04	0.00	7.87	0.24
Number of Comorbid Conditions	1.26	0.88	1.82	0.21
Estimated Glomerular Filtration Rate	1.58	0.02	136.07	0.84
Presume Pre-HD Care (None)	25.35	0.72	888.87	0.07
Hemoglobin Level (<10g/dL)	35.62	2.47	512.87	0.01*
Access at Initiation				
AVF	0.40	0.00	379.39	0.79
AVG	0.66	0.05	9.64	0.76

*Significant at 5% level

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Walking While Talking in Older Adults with CKD

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Background: Divided attention tasks predict falls in older adults. Adults with chronic kidney disease (CKD) have an increased risk of falling compared with people without CKD; however, it is unknown whether they have greater divided attention task interference.

Methods: Three hundred thirty nondisabled adults ≥65 years of age from the community participated in quantitative and clinical gait assessments, including a validated cognitive-motor dual task measure (Walking While Talking [WWT] Test). Multivariable linear regression that adjusted for demographics, body mass index, comorbidities, and medications was performed to examine the relationship between estimated glomerular filtration rate (eGFR) and WWT gait markers. CKD was defined as an eGFR <60 ml/min/1.73m^2.

Results: One hundred thirty-four subjects (41%) had CKD. During WWT, participants with CKD had 5.8 cm/s (95% CI 0.6-11.0) slower gait speed, 2.4 cm (95% CI 0.05-4.7) shorter step length, and 2.0% (95% CI 0.2-3.8) greater time in the double support phase of the gait cycle compared with those without CKD. These abnormalities were related to severity of CKD: among participants with CKD, every 10 ml/min/1.73m^2 lower eGFR was independently associated with 3.3 cm/s (95% CI 0.4-6.1) slower gait speed, 2.0 cm (95% CI 0.7-3.2) shorter step length, 4.0 cm (95% CI 1.5-6.4) shorter stride length, 1.2% (95% CI 0.7-1.8) less time in the swing phase, and 1.6% (95% CI 0.7-2.5) greater time in the double support phase. To better capture the multidimensional characteristics of gait, factor analysis was performed using the principal component method and produced 3 independent gait domains: Rhythm, Pace, and Variability. Every 10 ml/min/1.73m^2 lower eGFR was associated with 0.2 standard deviation (95% CI 0.1-0.3) poorer performance in the Rhythm domain. There was no significant association between eGFR and the Pace or Variability domains.

Conclusions: CKD is associated with quantitative gait abnormalities while performing WWT tasks. Future studies should examine whether poorer performance on WWT tasks contributes to fall risk and is an early indicator of cognitive dysfunction in CKD.

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Risk Factors for Early Mortality Among Elderly Filipino Patients with Indications for Initiation of Hemodialysis: A Comparative Study

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Background: The worldwide incidence of kidney failure is rising. Globally, 5-10 million people die annually from kidney disease. In 2015, the Philippines reported a mortality rate of 3.9 per 100,000 population for kidney diseases. Of the 32,077 Filipinos on dialysis in 2015, 18,603 were initiated within the same year. Most are 60 years old and older, diabetic, and have other co-morbid conditions. Because, dialysis is a high-cost treatment, the Philippines enforced the Universal Health Coverage Bill. However, Filipinos continue to bear the financial burden of hemodialysis. These issues along with the Filipino cultural context question the practicality of initiating hemodialysis among the elderly. This study aims to identify factors significantly associated with early mortality and obtaining the early mortality rates among elderly Filipino patients initiated on hemodialysis and those who were not. To our knowledge, this is the first study of its kind on Filipinos.

Methods: This is a prospective, observational, cohort study. Dialysis-naïve elderly patients admitted from January to April 2019 in a tertiary hospital in the Philippines and were advised to initiate hemodialysis were enrolled. Demographic data and the presence of the following risk factors were obtained: diabetes mellitus, congestive heart failure, peripheral arterial disease, dysrhythmia, active malignancy, severe behavioral disorder, unplanned dialysis, hypoalbuminemia, ischemic heart disease, ventilator dependency, coma, sepsis, hepatic failure, COPD, BMI <18.5 kg/m^2, and total dependency for transfers. Individual outcomes (death against survival) between the two groups (initiated on hemodialysis against those were not—refused or consented for but were not initiated on hemodialysis) will be followed until four months after their attending nephrologists advised hemodialysis.

Results: 52 patients were enrolled in the study—52% initiated hemodialysis while 48% did not. Preliminary data shows more deaths among those initiated on hemodialysis (37%) than those who were not (32%). Risk factors identified among those initiated on hemodialysis and died include unplanned dialysis (100%), total dependency for transfers (83%), diabetes mellitus (67%), and hypoalbuminemia (67%).

Conclusions: The study is currently on its follow-up phase and will end by August 2019.

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Poor Outcomes in Kidney Transplant (KT) Candidates and Recipients with History of Falls

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Background: In patients with ESKD, serious falls resulting in hospitalization/fractures lead to lower chance of listing or KT. While it is likely that candidates and recipients have high frequency of injurious and noninjurious falls, it is unclear if less serious, noninjurious falls also lead to lower access to KT and if these risks extend to poor outcomes post-KT.

Methods: Using a 2-center cohort of KT candidates (n=3,666) and recipients (n=769), we assessed time to listing (Cox), waitlist mortality (Cox), and KT rate (Poisson) for KT candidates by history of falls (self-report, past 6 months) and recurrent falls (≥2 falls); for recipients, we assessed risk of mortality (Cox), all-cause graft loss (ACGL) (Cox), and length of stay (LOS) (Poisson).

Results: In candidates, 16.3% had history of falls; 6.5% had recurrent falls. Candidates with recurrent falls had lower chance of listing (aHR=0.7, 95%CI:0.6-0.8); those with single fall had a lower KT rate (aIRR=0.7, 95%CI:0.5-0.9). Single and recurrent falls were associated with greater mortality risk at evaluation and 1-year after evaluation; this risk declined over time. In KT recipients, 12.5% had a history of falls; 5.1% had recurrent falls. Single falls were associated with greater mortality risk (aHR=9.2, 95%CI:3.4-25.1) and ACGL (aHR=7.3, 95%CI:2.9-18.6) at KT and at 1-year post-KT; these risks declined thereafter. KT recipients with recurrent falls were at increased risk of a longer LOS (aHR=1.1, 95%CI:1.0-1.3).

Conclusions: Candidates (6.5%) and recipients (5.1%) had recurrent falls which were associated with decreased chance of listing and increased risk of waitlist mortality, post-KT mortality/ACGL, and longer LOS. Centers should consider employing falls prevention strategies as part of a comprehensive prehabilitation intervention.

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Table 3. Access to KT and Risk Adverse Outcomes Among Kidney Transplant (KT) (n=3,666) and Recipients (n=769) by Falls. Hazard Ratios and 95% Confidence Intervals are presented from Cox Regressions unless otherwise indicated. Associations that are statistically significant at p<0.05 are bolded.

	No Falls	Fall = 1 HR (95% CI)	Fall ≥ 2 HR (95% CI)
KT candidates			
Chance of Listing	REF	0.90 (0.77, 1.04)	**0.68 (0.56, 0.83)**
Risk of Waitlist Mortality			
Time of KT Evaluation	REF	**6.74 (3.11, 14.60)**	**31.20 (11.33, 85.93)**
1 year post-evaluation	REF	**3.25 (1.80, 5.87)**	**15.03 (6.68, 33.80)**
2 years post-evaluation	REF	1.56 (0.96, 2.55)	**7.24 (3.78, 13.87)**
3 years post-evaluation	REF	0.75 (0.45, 1.26)	**3.49 (1.97, 6.16)**
4 years post-evaluation	REF	**0.36 (0.19, 0.69)**	**1.68 (0.92, 3.06)**
Transplantation Rate (IRR)	REF	**0.68 (0.52, 0.90)**	0.94 (0.68, 1.30)
KT recipients			
Risk of Mortality			
Time of KT	REF	**9.17 (3.35, 25.09)**	**51.43 (16.00, 165.43)**
1 year post-KT	REF	**5.83 (2.47, 13.75)**	**32.67 (11.91, 89.57)**
2 years post-KT	REF	**3.70 (1.78, 7.72)**	**20.75 (8.73, 49.28)**
3 years post- KT	REF	**2.35 (1.23, 4.50)**	**13.18 (6.24, 27.82)**
4 years post- KT	REF	1.49 (0.80, 2.77)	**8.37 (4.29, 16.33)**
Risk of all-cause graft loss			
Time of KT	REF	**7.34 (2.90, 18.57)**	**33.57 (11.25, 100.21)**
1 year post-KT	REF	**4.66 (2.11, 10.30)**	**21.34 (8.33, 54.69)**
2 years post-KT	REF	**2.96 (1.49, 5.88)**	**13.57 (6.06, 30.39)**
3 years post- KT	REF	**1.88 (1.01, 3.51)**	**8.63 (4.28, 13.37)**
4 years post- KT	REF	1.20 (0.65, 2.21)	**5.48 (2.90, 10.36)**
Longer length of stay	REF	1.07 (0.98, 1.17)	**1.13 (1.03, 1.25)**

For KT candidates, models were adjusted for age, sex, race, dialysis time, body mass index (BMI), and cause of ESRD. For transplant recipients, models were adjusted for age, sex, race, dialysis time, body mass index (BMI), cause of ESRD, and donor types.

TH-PO669

Geriatric Renal Transplantation in India: A Single-Centre Experience

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Background: Kidney transplantation is a deterrent all over the world in the elderly due to higher cardiovascular mortality and infections. Death censored allograft survival appears to be similar in elderly and young.

Methods: Data of elderly (age ≥60 years) patients who underwent renal transplant was assessed. Changes in renal function, complications, graft rejection and mortality over 12 months post-transplant were determined.

Results: In 71 patients, mean age was 63.3±3.5 years and 88.7% were females. Diabetic kidney disease (40.8%) was most common aetiology for renal failure. Serum creatinine (SrC) in immediate post-transplant period was 1.2±0.8 mg/dl. In follow-up, no significant change in SrC was observed at 3 months (1.2±0.7 mg/dl, p=0.458), 6 months (1.4±0.9 mg/dl, p=0.234), 9 months (1.4±0.9 mg/dl, p=0.148) and 12 months (1.5±1.0 mg/dl, p=0.105) in comparison to baseline value. Proportion of patients with SrC ≥ 2 mg/dl increased from 5.6% at baseline to 12.7% at 12 months. Overall, 39.4% patients developed one or more infections of which urinary tract infections (22.5%) were most common. Cytomegalovirus (CMV) and lower respiratory tract infections were observed in three (4.2%) patients each. Acute graft rejection occurred in three (4.2%) patients. Six (8.5%) patients died during the 12 months follow-up period. Among non-survivors, two patients died during hospital stay and infections were major cause for mortality.

Conclusions: In the elderly patients who underwent renal transplant, graft function was well maintained over 12 months. Urinary infections are of common occurrence. Rates of acute rejection and mortality were comparable to the literature from India.

TH-PO670

Geriatric Nephrology Patients Deteriorating and Dying in Acute Care: How Do They Die?

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Background: Older patients with advanced kidney disease have complex medical and psychosocial needs, and providing comprehensive end of life care (EOLC) within acute healthcare settings is a challenge increasingly encountered by nephrologists. Data relating to the practice of EOLC within the inpatient nephrology setting is required to better inform and improve service provision. This study aims to review current care practices for deteriorating and dying patients admitted to the nephrology unit at St Vincent's Hospital Melbourne (SVHM), Australia.

Methods: Retrospective cohort study of patients aged >60years who died while admitted to the Nephrology unit at SVHM between 1/1/2013 and 31/12/2018.

Results: During the study period, 56 patients died while admitted to the Nephrology unit (average age 73years), and 84% were receiving long term dialysis (55% haemodialysis, 29% peritoneal dialysis). The average length of admission was 13 days, and patients had more than 2 admission in their final year of life. On average four invasive interventions were performed in the final 48 hours of life, including dialysis, intubation, parenteral feeding, intravenous fluids or antibiotics. Patients were admitted to the intensive care unit (ICU) in 42% of cases, and one third (32%) died in the ICU. At the time of admission only two patients had a formal advance care directive in place. During the admission, on the majority of occasions (75%) a documented discussion regarding goals of care (GOC) was held between a physician and the patient or caregiver, on average 3 days prior to death. Consultation by palliative care services occurred on one third (33%) of occasions, and in the final 24 hours an average of two uncontrolled symptoms were documented for each patient, including pain (52%), dyspnoea (41%), drowsiness (32%), and nausea (23%).

Conclusions: The majority of geriatric nephrology patients who died in the acute setting were receiving long term dialysis, and had a high burden of uncontrolled symptoms. One third of these deaths occurred in the ICU, and very few had advance care directives. This study illustrates opportunities for the clinician to improve care for older renal patients through earlier recognition of the dying patient, enhanced communication during EOLC planning, and greater emphasis on symptom control.

TH-PO671

Hemodialysis Patients Who Receive Physical Therapy: An Opportunity to Modify the Frailty Trajectory?

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Background: Frailty markers, physical activity and gait speed (and muscle strength to a lesser extent), show decline over time among hemodialysis (HD) patients (J Gerontol 2019), but whether these patterns vary in association with receipt of physical therapy (PT) has not been investigated. In Medicare claims, we identified dates and types of outpatient PT services received by HD patients during their participation in the USRDS ACTIVE-ADIPOSE Study (AAS). We examined frailty measures assessed before and after receipt of PT that included therapeutic exercises (CPT code 97110) "to develop strength and endurance, range of motion and flexibility."

Methods: The AAS included a multi-center cohort of 771 prevalent HD patients aged 20-92 and was conducted 2009-2013 at 14 outpatient dialysis clinics in the Atlanta GA and San Francisco areas. Institutional review boards (Emory University; UCSF) approved the study and all participants provided written informed consent. At baseline and two annual follow-up assessments, trained study coordinators administered the Minnesota Leisure Time Activity (LTA) instrument to estimate kcal/week physical activity, and the Short Physical Performance Battery (SPPB) that includes chair stand, balance, and walk (gait speed) tests. Consistent with prior research, individuals with LTA-assessed kcal/week <500 were considered sedentary and 500+ non-sedentary, and total SPPB score (0-12) was categorized into three ordinal groups (<6, 7-9, 10-12).

Results: Medicare claims for outpatient PT were identified for 32 AAS participants: ages 32-82, 57% women, 81% black. Patient-reported reasons for PT emphasized mobility issues. At their post-PT follow-up evaluation: (1) Half had LTA scores = 500+ (non-sedentary), and kcal/week activity had increased from <500 pre-PT to 500+ post-PT for half of the non-sedentary group; (2) Although measured gait speed for most participants post-PT was consistent with values that characterize "limited community ambulators" (0.4-0.8 m/sec), two-thirds of participants either maintained SPPB scores > 7 pre-post PT or achieved SPPB scores > 7 post-PT.

Conclusions: Continued study of the role of PT in HD patient care is merited in larger patient cohorts. PT goals are patient-specific and include maintenance as well as improvement of function, with implications for the trajectory of frailty.

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TH-PO672

Physical Activity and Fatigue as Measures of Day-to-Day Resilience in Older Hemodialysis Patients

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Background: Hemodialysis (HD) is a physiological stressor requiring day-to-day resilience, or an innate ability to recover after a HD session. Our objective was to assess whether physical activity (PA) and self-reported fatigue are representative measures of day-to-day resilience.

Methods: We recruited ambulatory adults aged ≥55 years receiving HD who did not have advanced dementia, hospice care, or long-term care residence. Participants completed PA monitoring via wrist actigraphy for 14 days with concurrent fatigue assessment: "On a scale from 0-10, rate your fatigue, with 10 being fatigue as bad as you can imagine". Fatigue was assessed within 4 hours after HD and in the morning and afternoon on non-HD days. Prior to a HD session, we assessed physical function via the short physical performance battery (SPPB) (range, 0-12) and grip strength. We measured correlation between PA (steps) and concurrent fatigue in 4-hour intervals. PA variability, a measure of PA change when not at HD, was calculated from the standard deviation of the difference (absolute value) in steps of each 4-hour interval. We measured correlation between PA variability and physical function.

Results: Among 29 participants, mean±SD age was 70.6±4.8 years, 55.2% (n=16) male, 72.4% (n=21) black race, and mean years of dialysis was 3.9±3.6. Mean SPPB, gait speed (from SPPB), and grip strength were 6.3±3.2 (<10 indicates functional impairment), 0.72±0.3 m/s, and 57.8±16.7 kg, respectively. Mean PA monitoring time was 12.9±5.7 days. Mean daily steps was lower on HD days than non-HD days (967.1±557.0 vs. 1158.6±816.4) (p=0.004). Mean fatigue scores on HD days and non-HD days were similar (4.1±2.7 vs. 3.5±2.5) (p=0.06). The correlation between 4-hour post-dialysis PA and fatigue was -0.19 (n=102, p=0.06). The correlation between PA and fatigue at all other 4-hour intervals was -0.17 (n=210, p=0.01). Mean PA variability was 140.0±67.3 steps and its correlation with SPPB, gait speed, and grip strength was 0.47 (n=28, p=0.01), 0.52 (n=27, p=0.01), and 0.71 (n=27, p<0.0001), respectively.

Conclusions: In this sample of older HD patients, higher PA and greater PA variability were associated with lower fatigue and better physical function, respectively. PA monitoring and interval fatigue may be useful measures for interventions targeting resilience.

Funding: Other NIH Support - National Institute on Aging; National Center for Advancing Translational Sciences, Private Foundation Support

TH-PO673

Peripheral Artery Disease Exacerbates the Prognosis of Frailty in Patients with Hemodialysis

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Background: The clinical condition of frailty is the most problematic expression of the patients with hemodialysis (HD). The development of frailty is tightly associated with peripheral artery disease (PAD). However, the prognosis of the HD patients with frailty complicated with PAD remains unexplored. The purpose of this study is to identify the influence of PAD on the prognosis of HD patients with frailty.

Methods: We conducted a prospective and multicenter clinical study at 6 institutions. To evaluate the frailty status, we used the modified Fried's frailty phenotype model. PAD was defined according to the definition of TASC II (Trans-Atlantic Inter-Society Consensus II). Our primary endpoint of this study was the patients' survival and hospitalization.

Results: Of the 542 patients, 388 HD patients including 82 patients with frailty (21.4%), 204 with pre-frailty (52.6%) and 101 without frailty (26.0%), were enrolled in this study. At baseline, the participants were 67.2 ± 11.9 years of age with more male gender (62.4 %) than female. With an average follow-up period of 24.2 months, a total of 68 patients died; 26.5% of patients with frailty, 17.6% with pre-frailty and 9.9% without frailty. Cox proportional hazards model analyses indicated that frailty was associated with risk of death (hazard ratio [HR] 2.42, 95% confidence interval [CI] 1.12–5.23, adjusted for age and gender) and independently associated with the combined outcome of death or hospitalization (HR 2.85, 95% CI 1.74–4.69, adjusted for age, gender and all comorbidities), despite that PAD had no independent association with death and lower risk of the combined outcome. Furthermore, frailty complicated with PAD was independently associated with higher risk of death (HR 4.72, 95% CI 1.37–16.26, adjusted for age, gender and all comorbidities) and the combined outcome (HR 5.89, 95% CI 2.94–11.77, adjusted for age, gender and all comorbidities), compared with frailty only or PAD only.

Conclusions: Frailty itself significantly worsens the prognosis of patients with hemodialysis, and the presence of PAD further exacerbates the prognosis of frail patients with HD.

TH-PO674

Blood Pressure Lowering for the Prevention of Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis

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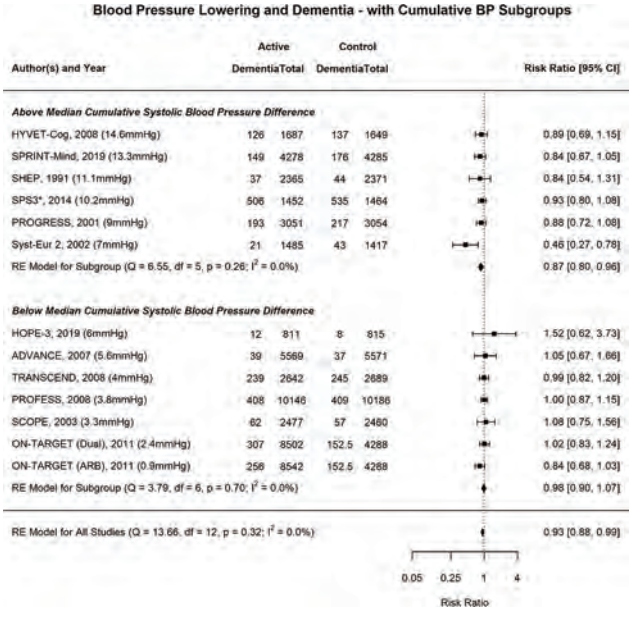
Background: The benefit of blood pressure lowering for the prevention of cognitive impairment and dementia is unclear.

Methods: We performed a meta-analysis of large randomized controlled trials of antihypertensive therapy versus control that reported cognitive decline, cognitive impairment or dementia as an outcome measure. We determined whether antihypertensive therapy reduced the risk of cognitive impairment and/or dementia and explored whether its effect varied by baseline blood pressure, blood pressure difference between treatment groups and/or length of follow-up.

Results: Fourteen randomized controlled trials were eligible for inclusion. Antihypertensive therapy was associated with a statistically significant reduced risk of cognitive impairment (n=9) (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.87-0.98) and dementia (n=12) (OR, 0.93; 95% CI, 0.88 to 0.99). Subgroup analysis of trials with a cumulative blood pressure difference above the median (6.5 mmHg) reduced the risk of dementia further (OR, 0.87; 95% CI, 0.80-0.96) (Figure 1). Antihypertensive therapy was not associated with a statistically significant reduction in the Mini Mental State Examination (MMSE) cognitive impairment score (n=5) (Mean change in MMSE, 0.44, 95% CI, -0.22–1.10) or a combination of the MMSE and the Trail Making Test (TMT) (n=7) (Standardised mean change, 0.10, 95% CI, -0.02–0.22). Meta-regression of baseline blood pressure, blood pressure difference or years of follow-up did not explain significant heterogeneity between studies for cognitive impairment or dementia risk.

Conclusions: Antihypertensive therapy reduces the risk of cognitive impairment and dementia.



TH-PO675

Blood Pressure Lowering and Cognition: A Systematic Review and Meta-Analysis

Aditi Gupta,[1] Sophy Perdomo,[1] Srinivasan Beddhu,[3] Sandra Billinger,[2] Jeffrey M. Burns,[4] Gary Gronseth.[1] *[1]University of Kansas Medical Center, Kansas City, KS; [2]KU Medical Center, Kansas City, KS; [3]University of Utah School of Medicine, Salt Lake City, UT; [4]University of Kansas School of Medicine, Kansas City, KS.*

Background: Hypertension is a known risk factor for developing cognitive impairment and dementia, both vascular dementia and Alzheimer's disease. Here we present the results of our systematic review of the effect of lowering of blood pressure on cognition.

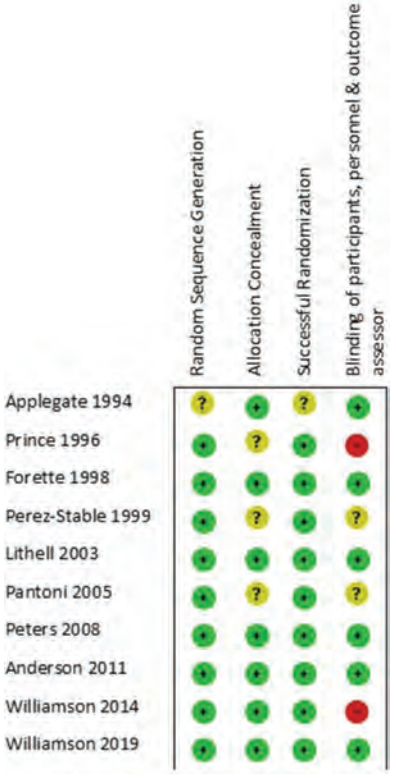
Methods: We conducted a systematic review and meta-analysis of randomized placebo-controlled trials with a pre-specified objective outcome of cognition, and with pharmacological interventions to lower blood pressure for at least 12 months in adults > 60 years. We searched MEDLINE, CENTRAL and The Cochrane Library (inception to May 2019). Two independent reviewers assessed trial quality and extracted data. Since the analyzed outcomes were different in the selected studies, we standardized these outcomes by calculating Cohen's D (SMD).

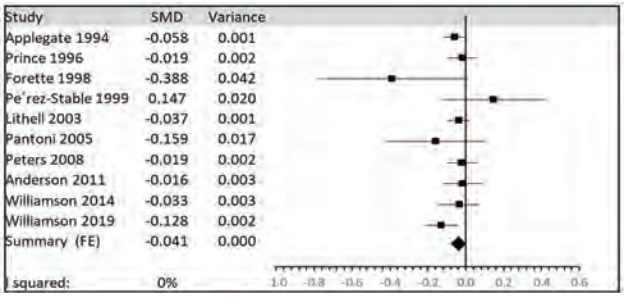
Results: Our initial search identified 2022 records. 1846 abstract were reviewed after removing duplicate records and out of these, 28 full-text articles pulled which met above inclusion criteria. Ten trials including 31,357 participants were included in the final analysis. The duration of the studies ranged from 1 year to median of 5.11 years.

Fig 1 shows internal validity of the included studies. Fig 2 shows the forest plot with the effect on cognition (standardized mean difference with 95% confidence interval). The net standardized mean difference for change in cognition was -0.041 (CI -0.076, -0.005) indicating a positive effect on cognition with lowering of blood pressure. I squared was 0% indicating minimal heterogeneity.

Conclusions: Although the overall effect is small, current data indicates that pharmacological lowering of blood pressure in older adults without prior cerebrovascular events slows cognitive decline.

Funding: Other NIH Support - NIA K23





TH-PO676

Baseline Diastolic Blood Pressure Does Not Influence the Effect of Systolic Blood Pressure Lowering on Cognition in Type 2 Diabetes Mellitus

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Background: In patients with low baseline diastolic blood pressure (DBP), lowering of systolic blood pressure (SBP) would lead to further lowering of mean arterial blood pressure. This can theoretically decrease cerebral perfusion and cognition. We examined the influence of baseline DBP on the effect of SBP on cognition.

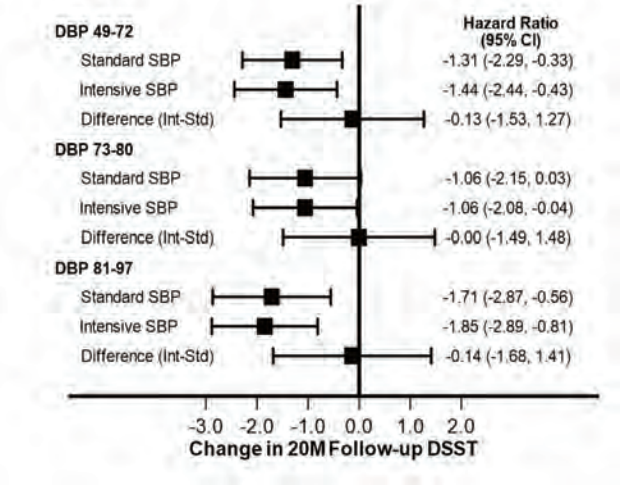
Methods: We analyzed data from the Memory in Diabetes (MIND) sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD). We grouped the subjects by tertiles of baseline DBP and compared the effects of intensive (target <120 mm Hg) and standard (target <140 mm Hg) SBP control on cognition. Cognition was measured by Digit Symbol Substitution test (DSST), Rey Auditory Verbal Learning Test (RAVLT), Stroop test and the Mini Mental State exam (MMSE).

Results: Table 1 summarizes the baseline demographics of the 1,610 ACCORD-MIND participants divided by tertiles of DBP. Participates with lower DBP were older, and had a longer duration of diabetes. Figure 1 shows the DSST scores in the standard and intensive BP groups by baseline DBP tertiles. There was no difference in the change in DSST scores in the three groups.

Conclusions: Intensive SBP reduction in type 2 diabetes mellitus does not adversely affect cognition, even in those with low baseline DBP.

Funding: NIDDK Support, Other NIH Support - NIA

	Tertile 1 DBP 49-72 n=519	Tertile 2 DBP 73-80 n=448	Tertile 3 DBP 81-97 n=463	p-value
Age (yrs)	64.5 ± 6.2	62.5 ± 5.7	61.5 ± 5.2	<0.001
Female gender %	54	57	53	0.49
White race %	69	67	63	0.16
Hemoglobin A1c	8.2 ± 0.9	8.3 ± 1.0	8.3 ± 1.1	0.18
Duration of diabetes (yrs)	13 ± 8	11 ± 8	9 ± 6	<0.001
DSST score	52 ± 16	52 ± 16	53 ± 16	0.19
MMSE score	28 (26, 29)	28 (26, 29)	28 (26, 29)	0.18
RAVLT score	7.3 ± 2.5	7.6 ± 2.5	7.7 ± 2.5	0.03
Stroop interference score	30 (23, 40)	29 (22, 40)	28 (20, 38)	0.012



TH-PO677

Association of Ambulatory Blood Pressure Pattern with Cognitive Function: The SPRINT Ambulatory Blood Pressure Study

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Background: In prior work with healthy older adults, abnormal night-to-day SBP ratio and lower 24 hour diastolic BP on ABPM were associated with worse cognitive function, findings not identified using clinic blood pressures. We examined whether these ABPM parameters were associated with cognitive function in participants in SPRINT, a randomized controlled trial of two different blood pressure targets in hypertensive adults.

Methods: Within SPRINT, 897 participants had 24 hour blood pressure measures collected at the 27 month visit. These readings were within 3 months of a comprehensive cognitive assessment. We examined whether ABPM parameters were associated with scores on the Montreal Assessment of Cognitive Function, logical memory delayed recall, and digit symbol coding test scores, after evaluating for interaction with random treatment assignment. We calculated odds ratios based on a beta-binomial model, with higher odds indicating better cognitive performance.

Results: Mean age was 71.5 ± 9.5, 67% were Caucasian. The intensive BP group had lower SBP and used more BP medication than the standard BP group. On the 3 cognitive tests studied, there was no difference in score between those in the intensive and standard groups, so these were combined. There was no association between night-to-day ratio and cognitive function test scores. After multivariate adjustment there was a modest association between higher diastolic BP (both in clinic and 24-hour) and better cognitive test scores on digit-symbol coding (figure).

Conclusions: Night-to-day blood pressure ratio was not associated with cognition in SPRINT. There was a modest association with diastolic blood pressure both in clinic and over 24 hours. This suggests that in this setting, non-dipping did not strongly associate with scores on cognitive function tests.

Funding: NIDDK Support

	MoCA		LM Delayed Recall		Digit Symbol Coding	
Continuous Analyses	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
24-mo. clinic SBP, per 10 mm Hg	0.98 (0.96, 1.01)	0.158	0.98 (0.94, 1.02)	0.282	1.01 (1.00, 1.03)	0.128
24-mo. clinic DBP, per 10 mm Hg	0.98 (0.95, 1.02)	0.401	1.00 (0.95, 1.05)	0.921	**1.04 (1.01, 1.07)**	**0.003**
Night SBP, per 10 mm Hg	1.02 (0.99, 1.05)	0.131	1.02 (0.98, 1.06)	0.258	1.01 (0.99, 1.03)	0.165
Night DBP, per 10 mm Hg	1.04 (0.99, 1.08)	0.089	1.05 (0.99, 1.11)	0.111	**1.04 (1.01, 1.06)**	**0.011**
Day SBP, per 10 mm Hg	1.02 (0.99, 1.05)	0.232	1.01 (0.97, 1.05)	0.645	1.01 (0.99, 1.03)	0.514
Day DBP, per 10 mm Hg	1.03 (0.99, 1.08)	0.116	1.04 (0.98, 1.10)	0.180	1.03 (1.01, 1.06)	0.020
Night to Day SBP Ratio, per 1 SD	1.01 (0.97, 1.05)	0.601	1.03 (0.97, 1.09)	0.391	1.02 (0.99, 1.04)	0.281
Night to Day DBP Ratio, per 1 SD	1.01 (0.97, 1.05)	0.705	1.02 (0.96, 1.08)	0.579	1.01 (0.98, 1.04)	0.557
24 hour SBP, per 10 mm Hg	1.02 (0.99, 1.05)	0.147	1.02 (0.97, 1.06)	0.433	1.01 (0.99, 1.03)	0.220
24 hour DBP, per 10 mm Hg	1.04 (1.00, 1.09)	0.071	1.06 (0.99, 1.12)	0.094	**1.04 (1.01, 1.08)**	**0.006**

TH-PO678

Dietary Sodium Intake and Cognitive Impairment in the Chronic Renal Insufficiency Cohort (CRIC)

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[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Denver VA Medical Center, Denver, CO.

Background: Cognitive dysfunction is a well-documented occurrence in individuals with chronic kidney disease (CKD), affecting multiple domains of cognitive function. Dietary sodium may influence cognitive function via effects on cerebrovascular function and cerebral blood flow. We hypothesized that high dietary sodium intake, as measured by 24-hr urine sodium excretion, is as associated with a decline in cognitive function over time in adults with CKD.

Methods: 1,724 participants in the observational cohort study, CRIC, with measurement of 24-hr urine sodium excretion, and modified mini mental state exam (3MS) score at baseline and year 4, who were free from baseline cognitive dysfunction were included. Multivariable logistic regression was used to examine the association between baseline 24-hr urine sodium excretion and odds of incident cognitive impairment, defined as a decline 3MS score ≥1.0 SD below the mean change in completion score (mean±SD for change in 3MS score was -0.26±5.08). High baseline sodium intake was defined as excretion >150 mmol/d.

Results: Participants were 59±11 years, baseline estimated glomerular filtration rate (eGFR) was 45±13 ml/min/1.73m², and baseline 24-hr sodium excretion was 164±76 mmol/d. During follow-up of 4.1±0.2 years, 185 CRIC participants (11%) had a clinically significant decline in 3MS score (i.e. incident cognitive impairment). After adjustment for demographics, clinic site, smoking, body-mass index, eGFR, cardiovascular risk factors, physical activity, systolic blood pressure, and 24-hr urine protein, potassium, and creatinine, high baseline dietary sodium intake was associated with increased odds of incident cognitive impairment (OR: 1.56, 95% CI: 1.08-2.27 vs low sodium intake).

Conclusions: In adults with CKD who participated in CRIC, higher sodium intake was independently associated with increased odds of incident cognitive impairment.

TH-PO679

MRI Markers of Cerebral Small Vessel Disease in CKD Patients with TIA and Minor Stroke

Dearbhla Kelly, Peter M. Rothwell. on behalf of the Oxford Vascular Study *Centre for the Prevention of Stroke and Dementia, University of Oxford, Oxford, United Kingdom.*

Background: It has been hypothesized that cerebral small vessel disease (SVD) and CKD may be part of a multi-system vasculopathy, but their association may simply be as a result of shared risk factors (eg, hypertension).

Methods: In a population-based study of transient ischemic attack and ischemic stroke (OXVASC), we evaluated the MRI markers of cerebral SVD, including lacunes, white matter hyperintensities, cerebral microbleeds, and enlarged perivascular space. We studied the age-specific associations of CKD and total SVD burden (total SVD score) adjusting for age, sex, vascular risk factors, and premorbid blood pressure (mean blood pressure during 20 years pre-event).

Results: 1718 patients had complete magnetic resonance imaging protocol and creatinine measured at baseline. CKD was associated with total SVD score (odds ratio [OR], 2.83; 95% confidence interval [CI], 2.28–3.53; P<0.001), but mainly at age <60 years (<60 years: OR, 8.43; 95% CI, 3.12-22.78; P<0.001; 60–79 years: OR, 1.38; 95% CI, 1.02–1.87; P=0.038; ≥80 years: OR, 1.09; 95% CI, 0.74–1.6; P=0.676). The overall association of renal impairment and total SVD score was also attenuated after adjustment for age, sex, history of hypertension, and diabetes mellitus (adjusted OR, 1.05; 95% CI, 0.83–1.34; P=0.67), but the independent association of renal impairment and total SVD score at age <60 years was maintained (adjusted OR, 6.07; 95% CI, 2.22–16.59; P=<0.001). Associations of renal impairment and SVD were consistent for each SVD marker at age <60 years but were strongest for cerebral microbleeds (OR, 9.04; 95% CI, 2.76–29.61; P<0.001) and moderate–severe periventricular white matter hyperintensities (OR, 6.67; 95% CI, 1.95–22.86; P=0.003).

Conclusions: The association of CKD and cerebral SVD was attenuated with adjustment for shared risk factors at older ages, but remained at younger ages, consistent with a shared susceptibility, likely at a genetic level, to premature disease.

TH-PO680

Association Between Geriatric Nutritional Risk Index (GRNI) and the Increased Risk for Stroke in Patients Receiving Hemodialysis: Ten-Year Outcome of the Q-Cohort Study

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Background: Geriatric nutritional risk index (GRNI), a useful tool for the evaluation of nutritional status, is associated with increased risk for cardiovascular events in hemodialysis patients. Few studies have examined the association between GNRI level and the incidence of stroke in patients receiving hemodialysis.

Methods: A total of 3047 patients registered to the Q-Cohort Study, a multicenter, prospective observational cohort of hemodialysis patients, were examined. The main outcomes were the development of brain hemorrhage and infarction. The main exposure was GNRI, calculated by serum albumin level and body mass index. Patients were divided into quartiles based on the baseline GNRI level; Q4 : >99.8, Q3 : 95.6-99.8, Q2 : 90.7-95.5, Q1 : <90.7. The risks for either brain infarction or hemorrhage were estimated by multivariable-adjusted Cox proportional hazard risk models.

Results: During the follow-up period of 10 years, 149 patients developed brain hemorrhage and 326 patients developed brain infarction. Cox proportional hazard risk models showed that the risks for brain hemorrhage and infarction in Q1 were significantly higher than that in Q4 group: hazard ratio [95% confidence interval], 1.69 [1.19-2.42] and 1.85 [1.08-3.16], respectively. Furthermore, restricted cubic spline curves showed that a lower GNRI was incrementally associated with an increased risk for both brain hemorrhage and infarction.

Conclusions: Our results suggest that lower GNRI is a risk factor for brain hemorrhage and infarction in maintenance hemodialysis patients.

TH-PO681

Does CKD Predict Stroke Risk Independent of Blood Pressure? A Systematic Review and Meta-Regression

Dearbhla Kelly, Peter M. Rothwell. *Centre for the Prevention of Stroke and Dementia, University of Oxford, Oxford, United Kingdom.*

Background: Chronic kidney disease (CKD) appears to be an independent risk factor for stroke, with various purported mechanisms proposed. Low glomerular filtration rate (eGFR) is a risk factor for stroke independent of cardiovascular risk factors in epidemiological studies, but there has been no systematic assessment of the impact of more complete adjustment for blood pressure (BP) on the association.

Methods: We did a systematic review to February 2018 (MEDLINE/EMBASE) for cohort studies or randomized controlled trials that reported stroke incidence in adults according to baseline eGFR. Study and participant characteristics and relative risks (RR) were extracted. Estimates were combined using a random effects model. Heterogeneity was assessed by x^2 statistics and I^2, and by subgroup strata and meta-regression.

Results: We identified 168 studies reporting data on 5,611,939 participants with 115,770 stroke outcomes. 85 studies (3,417,098 participants; 72,996 strokes) provided adequate data for meta-analysis of eGFR and stroke risk. Incident stroke risk was increased among participants with eGFR <60 ml/min/1.73m2 (RR=1.73, 95% CI 1.57-1.90; p<0.001), but there was substantial heterogeneity between studies (p<0.0001; I2 - 78.5%). Moreover, the association was reduced after adjustment for cardiovascular risk factors, with progressive attenuation on more thorough adjustment for hypertension: single baseline BP measure (RR=1.63, 1.34-1.99; p<0.001); history or treated hypertension (RR=1.35, 1.24-1.46, p<0.001); multiple BP measurements over months to years (RR=1.10, 1.02-1.18; p=0.01).

Conclusions: The apparently independent relationship between CKD and stroke may be confounded by their shared association with long-term prior blood pressure, rendering other proposed mechanisms and related treatments unnecessary.

TH-PO682

Proteinuria as an Independent Predictor of Stroke: Systematic Review and Meta-Analysis

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Background: Proteinuria has emerged as an important vascular risk factor for adverse cardiovascular events including stroke. Hypertension has been proposed as the principal confounder of this relationship but its role has not been systematically examined. We aimed to determine if proteinuria remains an independent predictor of stroke after more complete adjustment for blood pressure (BP).

Methods: We performed a systematic review, searching MEDLINE and EMBASE (to February 2018) for cohort studies or randomized controlled trials that reported stroke incidence in adults according to baseline proteinuria +/- glomerular filtration rate (eGFR). Study and participant characteristics and relative risks (RR) were extracted. Estimates were combined using a random effects model. Heterogeneity was assessed by x^2 statistics and I^2, and by subgroup strata and meta-regression, with a particular focus on the impact of more complete adjustment for blood pressure (BP) on the association. The quality of cohort studies and posthoc analyses was assessed using the Newcastle–Ottawa Scale.

Results: We identified 38 studies comprising 1,735,390 participants with 26,405 stroke events. Overall, the presence of any level of proteinuria was associated with greater stroke risk (18 studies; Pooled crude RR 2.00, 95%CI 1.63-2.46; p<0.001) even after adjustment for established cardiovascular risk factors (33 studies; Pooled adjusted RR 1.72, 1.51-1.95; p<0.001), albeit with considerable heterogeneity between studies (p< 0.001; I2=77.3%). Moreover, the association did not substantially attenuate with more thorough adjustment for hypertension: single baseline BP measure (10 studies; Pooled adjusted RR=1.92, 1.39-2.66; p<0.001); history or treated hypertension (4 studies; Pooled adjusted RR=1.76, 1.13-2.75, p=0.013); multiple BP measurements over months to years (4 studies; RR=1.68, 1.33-2.14; p<0.001).

Conclusions: Even after extensive adjustment, proteinuria is strongly and independently associated with incident stroke risk, possibly indicating a shared renal and cerebral susceptibility to vascular injury that is not fully explained by traditional vascular risk factors.

TH-PO683

Relationship of Serum Trimethylamine N-Oxide and Betaine Levels with Risk of First Incident Stroke in Chinese Hypertensive Patients

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Background: Trimethylamine N-oxide (TMAO), a gut derived metabolite, has been shown to be atherogenic. Whether TMAO or its dietary precursors is associated with a risk of stroke remains unknown. We aimed to determine the relationship of serum TMAO and its dietary precursors including choline, L-carnitine and betaine levels with first stroke in hypertensive patients, and examine any possible effect modifiers.

Methods: We conducted a nested case-control study, including 622 patients with first stroke (including 502 ischemic stroke, 118 hemorrhagic stroke and 2 uncertain type of stroke) and 622 matched controls from the China Stroke Primary Prevention Trial (CSPPT). The primary outcome was a first stroke.

Results: Overall, the risk of first stroke increased with each increment of TMAO level [per natural log (TMAO) increment: OR, 1.22; 95%CI: 1.02-1.46). Compared with participants in the lowest tertile (<1.79 μmol/L) of TMAO levels, a significantly higher risk of first stroke was found in those in higher TMAO tertiles (≥1.79 μmol/L) (OR, 1.34; 95% CI: 1.00-1.81) or in TMAO tertile 3 (≥3.19 μmol/L) (OR, 1.43; 95% CI: 1.02-2.01). However, a U-shaped association between serum betaine and the risk of first ischemic stroke was observed. The risk of first ischemic stroke decreased with the increment of betaine (per 10 μmol/L increase: OR, 0.87; 95%CI: 0.77-0.99) in patients with betaine <77.7 μmol/L, and increased with the betaine increment (per 10 μmol/L increase: OR, 1.17; 95%CI: 1.01-1.36) in participants with betaine ≥77.7 μmol/L. Serum betaine had no obvious effect on the risk of first hemorrhagic stroke (per 10 μmol/L increase: OR, 0.98; 95%CI: 0.82, 1.17). Moreover, no significant association between either choline (OR, 1.05; 95%CI: 0.68- 1.64) or L-carnitine (OR, 1.05; 95%CI: 0.60-1.85) with the risk of first stroke was found.

Conclusions: Among Chinese hypertensive patients, higher TMAO levels were associated with increased risk of first stroke while the association between betaine levels and the risk of first ischemic stroke was a U-shaped, with a turning point at about 77.7 μmol/L.

TH-PO684

The Impact of Change of Blood Pressure Stage According to the 2017 ACC/AHA Guideline on Cardiovascular Events Among Untreated Low-Risk Populations: A Nationwide Population-Based Cohort Study

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Background: The 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension (HTN) guideline defined new HTN thresholds. However, the evidence was largely based on studies conducted with a single baseline blood pressure (BP) measurement. Therefore, we investigated the impact of the change of BP stage according to 2017 ACC/AHA guideline on cardiovascular events (CVEs), with baseline and mean BP measurements during the follow-up of untreated, low-risk populations.

Methods: This retrospective, longitudinal study was conducted with 322,562 subjects aged ≥ 40 years without diabetes mellitus, chronic kidney disease, or previous CVE, enrolled in the Korean National Health Service-National Health Screening Cohort between 2002 and 2003, who had not taken antihypertensive medication during follow-up period. Subjects were categorized according to the 2017 ACC/AHA HTN guideline based on their baseline and mean BP during follow-up. The primary outcome of the study was newly developed CVEs (cardiovascular disease and mortality).

Results: During the median follow-up of 10 years, 2.51 events per 1,000 person-years occurred. Compared to normal (BP<120/80 mmHg) individuals, significantly increased risk of CVE was observed in individuals with stage 1 HTN (systolic BP 130-139/diastolic BP 80-89 mmHg), with both baseline and mean BP examinations. However, the hazard ratios for the CVEs using mean BP were higher those in using baseline BP. When subjects were categorized into 16 groups according to BP stages (and baseline versus mean BP measurements), the risk of CVD incidence was significantly lower when BP stage calculated using the mean BP decreased compared to the reference (the BP stage remained same between the baseline BP and mean BP) in the population with stage 1 and 2 HTN.

Conclusions: Stage 1 and 2 HTN, defined by the 2017 ACC/AHA guideline, were significantly associated with an increase of CVEs in the analysis with baseline and mean BP measurements among untreated, low-risk individuals. However, the mean BP was superior to the baseline BP for predicting CVEs. Moreover, the study suggests that physicians need to lower BP stage to prevent the occurrence of CVD when their patients, even those at low risk for CVEs, are in the stage 1 or 2 HTN groups at baseline.

TH-PO685

The Prevalence of Nonadherence in Patients with Resistant Hypertension: A Systematic Review

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Background: Resistant hypertension (RH) is common and is a risk factor for higher cardiovascular outcomes. These patients also undergo more screening intensity for secondary hypertension. Not all patients with apparent resistant hypertension have true RH. Reports of the prevalence of non-adherence vary widely from 3 to 86%. However intentional and non-intentional non-adherence are not differentiated in this data. Non-intentional non-adherence refers to occasional forgetfulness and can be diagnosed with pill counts or pharmacy refill data. Intentional non-adherence requires more intensive measures (such as therapeutic drug monitoring or directly observed therapy) to diagnose. The objective of this systematic review is to establish the overall prevalence of non-adherence in the RH population and differentiate the contribution of non-intentional and intentional non-adherence subtypes.

Methods: The databases MEDLINE, EMBASE, and the Cochrane library were searched for observational studies and randomized controlled trials reporting the prevalence of non-adherence in RH. The primary outcome studied is the pooled prevalence of non-adherence in RH. The secondary outcome examined will be the pooled prevalence of non-adherence based on indirect and direct measures of non-adherence. Weighted summary prevalence for the outcomes was estimated using the random effects model.

Results: The literature search retrieved 1415 non-duplicate citations. After applying eligibility criteria, 197 full text citations were retrieved, and 27 studies were included in the review. Most studies were retrospective database studies or cross-sectional in nature and (63%) used indirect measures of assessment such as medication possession ratio or the Morisky scale with 80% adherence being the most common cutoff used for diagnosis of non-adherence. The pooled prevalence of non-adherence was 31%, with high statistical heterogeneity (I-squared 99). The pooled prevalence was higher with direct measures (45%) than indirect measures (19%).

Conclusions: The prevalence of non-adherence varies based on the severity of hypertension, but also based on the method of measurement of adherence. Indirect measures underestimate the extent of true non-adherence. Incorporation of direct measures such as drug assays or direct observed therapy should be considered for more widespread adoption.

TH-PO686

Apparent Treatment-Resistant Hypertension (ATRH) Stratified by Ambulatory Blood Pressure Monitoring (ABPM) in CKD: A Report from the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: ATRH defined using office blood pressure (BP) measurements, is common in patients with chronic kidney disease. Whether measurement of 24 hour ABPM is of value in risk stratification in patients with ATRH is unclear.

Methods: We analyzed data from the CRIC study, a prospective study of participants with chronic kidney disease. Office BP was measured by trained staff; 24 hour ABPM was measured using Spacelabs monitors. ATRH was defined as mean office systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg on ≥ 3 antihypertensive medications, average ABPM daytime systolic BP ≥ 135 mm Hg or diastolic BP ≥ 85 mm Hg on ≥ 3 antihypertensive medications, or the use of > 3 antihypertensive medications. Outcomes were composite cardiovascular disease (CVD)(myocardial infarction, stroke, peripheral arterial disease, heart failure), renal outcomes (end stage renal disease or 50% decline in GFR), and groups were compared using Cox regression analyses.

Results: Of 475 participants with ATRH based on office BP, 40 participants (8%) had controlled ABPM consistent with white coat hypertension. ATRH based on office and ABPM criteria (ABPM-ATRH) was seen in 162 (34%), and 273 (54%) of participants had ATRH based on the use of > three antihypertensive medications. The control group was participants with BP controlled by office and ABPM criteria (n=711). While unadjusted event rates of composite CVD (8.19 vs 2.77 per 100 patient years) renal outcomes (12.75 vs 2.97 per 100 patient years), and mortality (4.93 vs 2.18 per 100 patient years) were higher, in adjusted analyses, the risk of composite CVD (Hazard ratio (HR) 1.27, 95% confidence intervals (CI) 0.59, 2.7), renal outcomes (HR 1.68 95% CI 0.88, 3.21), and mortality (HR 1.27 95% CI 0.5, 3.25) was not statistically significantly higher in participants with ABPM-ATRH group compared to the participants with controlled BP.

Conclusions: In our study population with chronic kidney disease, most patients with ATRH defined based on office BP have ATRH confirmed by ABPM. While ABPM defined ATRH was not an independent risk factor for outcomes, the presence of ABPM-TRH identified participants at high risk for clinical outcomes

Funding: NIDDK Support

TH-PO687

Can Central Blood Pressure Be Accurately Estimated in Individuals with and Without Systolic Blood Pressure Amplification?

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Background: Systolic blood pressure (SBP) does not always amplify from central to peripheral arteries. Individuals without SBP amplification (SBPamp) have higher aortic blood pressure (BP) despite similar brachial cuff SBP. To circumvent this discrepancy, the aim of this study was to determine if aortic SBP can be accurately estimated non-invasively in patients with and without SBPamp.

Methods: Patients undergoing non-urgent percutaneous coronary angiogram were recruited. Individuals with atrial fibrillation, ≥10 mmHg between-arm SBP difference or severe aortic stenosis were excluded. After the procedure, aortic and brachial intra-arterial BP were measured via radial artery approach using a fluid-filled catheter. Simultaneously, brachial and central cuff BP were measured in triplicate using a Mobil-o-Graph (IEM, Germany). This device estimates central BP via brachial pulse wave analysis by type I (SBP and diastolic BP) and type II (mean and diastolic BP) calibrations. Aortic-to-brachial SBPamp was defined as ≥5 mmHg increase between intra-arterial aortic and brachial SBP.

Results: Of the 151 patients recruited, only 85 had SBPamp. SBPamp+ and SBPamp- patients had similar characteristics, apart from higher augmentation in SBPamp- (Table 1). Central BP estimated with Type I or Type II calibration could not accurately determine aortic SBPs in both phenotypes (Table 2). Using the mean of both estimates only provided a slightly better accuracy.

Conclusions: Central BP measurements cannot identify the different aortic BP of the SBPamp phenotypes. A new central BP calibration may be needed to circumvent this problem.

Baseline characteristics	SBPamp+ (n=85)	SBPamp- (n=66)	p-value
Male sex	74%	74%	1.0
Age	66 ± 11	65 ± 9	0.6
Height (cm)	171 ± 10	170 ± 10	0.6
BMI (kg/m^2)	29 ± 6	30 ± 10	0.3
Active smoking	28%	27%	0.9
Diabetes	19%	17%	0.7
Hypertension	59%	55%	0.6
Dyslipidemia	55%	55%	0.9
Prior cardiovascular disease	39%	52%	0.1
eGFR (mL/min/1.73m^2)	80 ± 18	81 ± 18	0.7
Brachial cuff SBP	126 ± 15	126 ±16	0.8
Brachial cuff diastolic blood pressure	78 ± 9	78 ± 12	0.9
Heart rate (bpm)	67 ± 11	65 ± 11	0.3
Augmentation index @ 75 bmp	18 ± 10	22 ± 11	0.03
Pulse wave velocity (m/s)	10 ± 2	9 ± 2	0.09

SBPamp+ and SBPamp- denotes individuals with and without SBP amplification, defined as ≥5 mmHg increase between intra-arterial aortic and brachial SBP. Values are expressed as mean ± standard deviation. All blood pressure measures are expressed in mmHg. P-values are calculated using Pearson's chi-square and Student t-tests. SBP, systolic blood pressure.

Table 1

BP measurements	SBPamp+ (n=85)	SBPamp- (n=66)	p-value
Aortic SBP (intra-arterial)	126 ± 18	133 ± 22	0.05
Brachial SBP (intra-arterial)	140 ± 18	131 ±23	0.01
Central cuff SBP			
Type I calibration	117 ± 15	116 ± 14	0.6
Type II calibration	136 ± 18	135 ± 18	0.7
Mean of Types I and II	126 ± 16	127 ± 15	0.6
Aortic SBP mean difference			
Intra-arterial vs Type I	9 ± 11	16 ± 13	<0.001
Intra-arterial vs Type II	10 ± 15	2 ± 12	0.04
Intra-arterial vs Mean of Type I and II	1 ± 12	7 ± 11	0.2
Brachial cuff mean difference (vs intra-arterial)	14 ± 11	6 ± 13	<0.001

See Table 1. As per ARTERY guidelines, accurate BP estimation are defined as an absolute mean difference ≤5 ± 8 mmHg compared with the reference method.

Table 2

TH-PO688

Life's Simple 7 and Risk of Cardiovascular Disease in the Chronic Renal Insufficiency Cohort

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Background: The American Heart Association (AHA) has identified seven modifiable factors, "Life's Simple 7", that contribute to heart health. The association between these ideal health behaviors and cardiovascular (CV) disease has not been examined among individuals with chronic kidney disease (CKD).

Methods: We studied 2,979 participants from the Chronic Renal Insufficiency Cohort (CRIC) Study. The AHA definitions for non-ideal health were used for body mass index (BMI≥25kg/m^2), total cholesterol (≥200 mg/dL), blood pressure (≥120 systolic and ≥80 diastolic), fasting plasma glucose (≥100 mg/dL), and physical activity (<75 min/week of vigorous physical activity or <150min/week of moderate/vigorous). Due to design constraints, modified definitions were used for smoking (current) and consuming an unhealthy diet (below median fruit and vegetables, fish, and whole grain intake, and above median urine sodium and sweetened beverage intake). The outcome was time to first adjudicated CV event, defined as heart failure, myocardial infarction, ischemic stroke, or death. Population attributable risk percent (PAR%) was estimated from Cox regression models including each Simple 7 factor, age, sex, race, income, education, family history of coronary artery disease, and estimated glomerular filtration rate.

Results: During a median follow-up of 7 years, 1,345 participants had an incident CV event (5.8/100 person-years). High fasting glucose contributed the most to CV burden, with a PAR of 20.1% (95% CI: 15.0-24.8). Physical underactivity, smoking, and high blood pressure accounted for a modest proportion of the population risk, while poor diet, BMI, and high cholesterol had nonsignificant PARs. In race-stratified analyses, high glucose remained the strongest contributor, but among white participants, physical underactivity also contributed significantly to risk (PAR: 17.6%; 95% CI: 9.2-25.2), while high blood pressure contributed significantly among blacks (PAR: 5.1%; 95% CI: 0.04-9.9).

Conclusions: Among individuals with CKD, high fasting glucose contributed the most to CV burden. Understanding the contributions of each modifiable risk factor may help target efforts to reduce CV incidence in this population.

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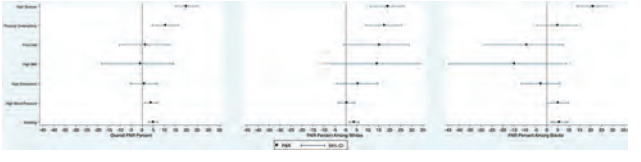

TH-PO689

Hypertension Is Associated with Adverse Cardiovascular Outcomes Only When Both Brachial and Central Blood Pressures Are Elevated

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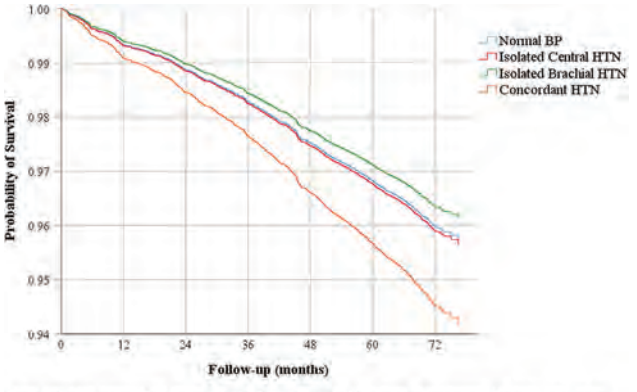
Background: The range of central blood pressure (BP) found in individuals with high-normal brachial BP overlaps the one found in hypertension (HTN) and normotension. As central BP is possibly a better predictor of cardiovascular (CV) disease, the aim of this study was to determine the risk associated with different central/brachial BP patterns.

Methods: 13,759 participants from a populational cohort with central BP and prospective data from governmental databases who were not treated for HTN were selected. Major adverse CV events (MACE) comprised myocardial infarction, stroke, heart failure and CV death. Thresholds for brachial and central HTN were identified as 135 and 125 mmHg respectively. Individuals were separated into 4 BP patterns: normal BP; isolated brachial HTN; isolated central HTN; concordant brachial and central HTN. CVE risk for each pattern was compared to normal BP with a Cox proportional hazard model.

Results: 688 MACE occurred over a median follow-up of 70.0 months. Characteristics of individuals in each BP phenotype are presented in Table 1. Only the concordant brachial and central HTN pattenr had higher risk of MACE [HR 1.37 95%CI (1.15-1.64), p=0.001] compared to normal BP (Figure 1). Sensitivity analyses with different definitions of central HTN and after stratification for sex yielded similar results.

Conclusions: In untreated individuals, both central and brachial BP need to be elevated to increase CV risk. These findings provide support for the utility of routine central BP measurements in clinical practice.

Demographic characteristics	Normal BP (n=10,611)	Isolated brachial HTN (n=394)	Isolated central HTN (n=496)	Concordant HTN (n=2,258)
n	10,611	394	496	2,258
Age	51 (46-57)	53 (47-60)	54 (49-62)	56 (51-63)
Male sex	43%	88%	38%	58%
Caucasian race	89%	88%	91%	89%
Cardiovascular disease	2%	2%	4%	2%
Diabetes	4%	8%	3%	6%
Active smoking	19%	22%	16%	21%
BMI (kg/m^2)	26 ± 5	28 ± 3	28 ± 5	28 ± 5
eGFR (ml/min/1.73m^2)	90 ± 14	87 ± 15	89 ± 14	88 ± 14
10-year Framingham risk score (%)	8 ± 7	17 ± 10	11 ± 7	18 ±12
LDL-c (mmol/L)	3.1 ± 0.8	3.1 ± 0.9	3.3 ± 0.9	3.3 ± 0.9
Heart rate (bpm)	70 ± 10	77 ± 11	65 ± 9	71 ± 11
Aspirin	6%	8%	11%	9%
Statin	10%	16%	16%	13%



Survival plot using Cox proportional hazard modelling with adjustment for age, sex, race, body mass index, active smoking, diabetes, CV disease, CKD, LDL-c, heart rate, aspirin and statin use.

TH-PO690

Abnormal Left Ventricular Metrics and Subsequent Cardiovascular Events in Japanese and US Patients with CKD: Findings from the CRIC and CKD-JAC Studies

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Background: Left ventricular (LV) hypertrophy (LVH) is a risk factor for cardiovascular (CVD) events in patients with chronic kidney disease (CKD). The prevalence of LVH and the associated risk of subsequent CVD events in US and Japanese patients with CKD has not been clearly elucidated.

Methods: 3125 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study and 1097 in the CKD Japan Cohort (CKD-JAC) Study underwent echocardiography. LV mass index (LVMI), LVH (defined as LVMI >50 g/m$^{2.7}$ in males and >47 g/m$^{2.7}$ in females), and LV geometry (concentric hypertrophy, eccentric hypertrophy, and concentric remodeling) were assessed. Cox proportional hazards survival analysis was implemented for the composite outcome of CVD, defined as any of the following events: hospitalization for congestive heart failure, myocardial infarction, stroke, interventions for peripheral artery disease, and any lethal cardiovascular events.

Results: The mean values of LVMI and the proportion of LVH in CRIC and CKD-JAC participants were 55.7 g/m$^{2.7}$ and 46.6 g/m$^{2.7}$, and 59.2% and 36.1%, respectively. CRIC participants had higher proportion of concentric LVH (51.6% and 23.1%, respectively). Incidence rates of the first CVD events in the CRIC and the CKD-JAC were 35.5 and 23.5 per 1000 person-years, respectively. LVH was significantly associated with the subsequent CVD events; HRs were 1.86 (95% confidence interval, 1.53–2.26) in the pooled cohort, 1.85 (1.50–2.29) in the CRIC, and 1.91 (1.15–3.16) in the CKD-JAC (P-interaction = 0.96). Adjusted HRs of LVMI (per 10 g/m2.7) were 1.23 (1.18–1.27) in the pooled cohort. Adjusted HRs stratified by race/ethnicity were 1.23 (1.14–1.31) in non-Hispanic Whites, 1.23 (1.16–1.29) in non-Hispanic Blacks, 1.19 (1.03–1.38) in Hispanics and 1.24 (1.07–1.43) in Japanese Asians (P-interaction = 0.94).

Conclusions: US patients with CKD had a higher prevalence of LVH and higher LVMI than Japanese patients with CKD. Despite the differences in LV metrics, the association between LVMI and subsequent CVD events was similar across ethnic groups. These findings also reinforce that LVMI may be a common therapeutic target across these diverse populations.

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TH-PO691

Changes in QT Interval in Long-Term Hemodialysis Patients

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Background: A prolonged QT interval on the electrocardiogram (ECG) is a risk factor for sudden cardiac death (SCD) in hemodialysis (HD) patients. This study investigated whether the heart rate-corrected QT (QTc) interval becomes prolonged in relation to the number of years undergoing dialysis treatment.

Methods: A total of 102 patients treated with HD for more than 7 years were studied. All patients had ECG data at 1, 4, and 7 years after HD initiation and 75 of the patients also had ECG data at 10 years after HD initiation. The control group comprised 68 age-matched individuals who had normal renal function and two available ECG reports at an interval of more than 4 years. Patients with ECGs showing heart rates <57 or >103 bpm, extrasystoles, or any rhythm other than sinus were excluded. QTc was measured according to the Bazett formula. The association between QTc interval and dialysis vintage was analyzed. Additionally, clinically relevant variables related to QTc duration at 1 year after HD initiation were assessed.

Results: The average QTc interval in the control group was 425 ms in the first year and 426 ms after an average of 6 years, indicating no significant difference. However, the QTc interval at 1 year after HD initiation in 75 HD patients was 436 ms, which was much higher than that in the control group (P<0.001). In addition, the QTc interval at 4, 7, and 10 years after HD initiation was 441, 439, and 449 ms, respectively, increasing with dialysis vintage (p=0.20, 0.42, and <0.001, for 1 year after HD initiation by Dunnett's multiple comparison). Multivariate regression analysis of baseline variables in 102 HD patients revealed that corrected calcium levels (p=0.041) and diabetes (p = 0.043) were independently associated with the longer QTc interval.

Conclusions: The QTc interval at 1 year after HD initiation was longer in HD patients than in the control subjects and was further prolonged over several years of HD treatment. Providing clinical management with a focus on QTc interval may be helpful for reducing the incidence of SCD in HD patients.

TH-PO692

Impact of Pulse Pressure and Mean Arterial Pressure on All-Cause and Cardiovascular Mortality in Subjects with Diabetes in a Nationwide Cohort from a General Japanese Population

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Background: In the general population, blood pressure (BP) and physiological factors that influence arterial stiffness, such as pulse pressure (PP, difference between systolic BP [SBP] and diastolic BP [DBP]) and mean arterial pressure (MAP, 2/3 DBP + 1/3 SBP), are associated with mortality and cardiovascular (CV) outcomes; however, the impact of these markers in diabetic patients remains unclear.

Methods: Study design: Cohort study. Setting, Participants: Data from a nationwide database from the annual "Specific Health Check and Guidance in Japan", including 20,748 people with diabetes, eGFR≥30, aged 40 to 75 years, and 42.4% female. Predictor: SBP, DBP, PP, and MAP at baseline Outcomes: All-cause and CV mortality during a median follow-up of 5.3 years. Measurements: Hazard ratios (HRs) were estimated using Cox's model for the relationships between predictors and outcomes, and adjusted for potential confounders.

Results: During the follow-up, the incidence of death was 448 (4.1 per 1000 person-years), including 101 CV deaths (0.9 per 1000 person-years). HRs for all-cause mortality for each 1-SD elevation in SBP, DBP, PP, and MAP did not significantly increase. On the other hand, HRs for the CV mortality of MAP significantly increased, whereas those of other BP parameters did not, as shown in Table 1. Furthermore, when patients were divided into two groups based on the presence and absence of proteinuria, HRs for CV mortality for each 1-SD elevation in PP and MAP significantly increased in subjects without proteinuria. However, no parameters correlated with cardiovascular mortality in subjects with proteinuria.

Conclusions: In diabetes patients without proteinuria, markers of arterial stiffness, such as PP and MAP, may be suitable for predicting CV outcomes.

Multivariate analysis of blood pressure parameters and cardiovascular death.

Patient group (number)	SBP, 1-SD elevation HR (95% CI)	PP, 1-SD elevation HR (95% CI)	MAP, 1-SD elevation HR (95% CI)
DM* (n=20,748)	1.17 (0.91-1.49)	1.11 (0.88-1.41)	1.30 (1.02-1.64)
DM* with proteinuria (n=5,012)	1.01 (0.68-1.51)	0.86 (0.59-1.24)	1.15 (0.78-1.70)
DM* without proteinuria (n=15,736)	1.28 (0.94-1.75)	1.35 (1.00-1.81)	1.40 (1.04-1.91)

* Diabetes mellitus patients whose eGFR was more than 30 ml/min/1.73m2.

TH-PO693

Association of Metabolic Acidosis with Adverse Cardiovascular Outcomes in Patients with CKD

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Background: Metabolic acidosis is a known risk factor for chronic kidney disease (CKD) progression. Less is known about its association with cardiovascular disease in patients with advanced CKD. Here we assess the association of metabolic acidosis with adverse cardiovascular outcomes and its role as an independent predictor of cardiovascular outcomes in patients with pre-dialysis CKD.

Methods: De-identified electronic medical records (Optum® EMR), 2007–2017 were queried to identify patients with CKD Stages 3-5 with ≥2 consistent serum bicarbonate values 28–365 days apart, ≥3 eGFR values >10 and <60 mL/min/1.73m^2 and ≥2 years of post-index data or until death. Patients were followed for up to 10 years for evidence of new onset heart failure, stroke or acute myocardial infarction (MI), defined using ICD-9 and ICD-10 diagnosis codes. Metabolic acidosis and normal serum bicarbonate groups were defined by two serum bicarbonate values between 12 and <22 mEq/L and 22-29 mEq/L, respectively. Cox proportional hazards models were used to examine potential confounders: age, sex, race, eGFR, diabetes, hypertension, heart failure, coronary artery disease, peripheral vascular disease, and hemoglobin and serum albumin.

Results: 51,558 patients qualified for this longitudinal observational study. The incidence of adverse cardiovascular events at 2 years was significantly higher in patients with metabolic acidosis compared to patients with normal serum bicarbonate, [heart failure: 29.8 % vs. 22.8%, p<0.0001; stroke: 19.5% vs. 17.2%, p<0.0001; MI: 17.2% vs. 12.3%, p<0.0001, respectively]. During the up to 10-years of follow-up, serum bicarbonate was independently associated with adverse cardiovascular outcomes; hazard ratios per 1 mEq/L change: new onset heart failure, 0.976, CI: 0.971-0.981, stroke, 0.979, CI: 0.973-0.985; and MI, 0.964, CI: 0.958-0.970, respectively.

Conclusions: In this longitudinal analysis of > 51,000 non-dialysis CKD patients followed for up to ten years, serum bicarbonate levels below 22 mEq/L were associated with increased incidence of major adverse cardiovascular events independent of age, comorbid conditions and kidney function. Studies evaluating the mechanisms of these associations are needed.

Funding: Commercial Support - Tricida, Inc.

TH-PO694

Plasma Xanthine Oxidoreductase Activity Is Associated with CKD in a General Japanese Population: The Iwate Tohoku Medical Megabank Project

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Background: Xanthine oxidoreductase (XOR, pmol/h/mL plasma) catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to uric acid. An increase in XOR activity could cause intravascular damage through the oxidative stress. XOR activity could contribute to the pathogenesis of cardiovascular disease (CVD). Chronic kidney disease (CKD) and CVD are closely related. However, the association with XOR activity and CKD in a general Japanese population are not known. The purpose of this study is to investigate the association between XOR activity and CKD in a general Japanese population.

Methods: The Iwate Tohoku Medical Megabank Organization pooled individual participant data from a general population-based cohort study in Iwate prefecture (n = 1,675, male / female = 529 / 1,146, age = 66.2 ± 10.1 years). We classified as CKD stage (stage I ~ stage IV) using the estimate glomerular filtration rate of creatinine (eGFR, mL/min/1.73m2; eGFR < 60) and the urinary albumin to creatinine ratio (uacr, mg/gCr; uacr ≥ 30). Suita Score used to estimate the risk of the CVD. XOR activity was expressed as the log-transformed values (log10) for skewed variables.

Results: In males, XOR activity was significantly lower in stage IV of CKD compared to stage II (F = 4.66, p = 0.003; stage II vs. IV, 1.74 ± 0.38 vs. 1.27 ± 0.52, p = 0.009), and was related to CKD (OR = 1.87, 95% confidence interval (CI) = 1.16 – 3.01, p = 0.011). XOR activity was no significant difference among CKD stages in females (F = 1.73, p = 0.159), and was no related to CKD (OR = 1.19, p = 0.375). XOR activity was related to the high risk for CVD (Suita Score ≥ 41, males: OR = 4.24, 95% CI = 1.75 – 10.35, p = 0.001; females: OR = 2.88, 95% CI = 2.01 – 4.13, p < 0.001). The area under the curve (AUC) for XOR activity combined with Suita score was 0.61 (95% CI = 0.50 – 0.72, p = 0.051).

Conclusions: In conclusion, XOR activity is associated with CKD and the high risk for CVD in a general Japanese population. An increase in XOR activity may be related to decreased renal function and the CVD risk.

Funding: Government Support - Non-U.S.

TH-PO695

Individuals Born Preterm Have an Increased Rate of Hypertension from Adolescence to Adulthood

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Background: Preterm birth increases the lifetime risk of hypertension (HTN), but the prevalence of HTN in adolescents and adults and the change in blood pressure (BP) and incidence of HTN from adolescence into adulthood are undescribed. We hypothesized that subjects born preterm have an increased prevalence of high BP and HTN, a greater increase in BP/yr, and an increased incidence of high BP and HTN from adolescence to adulthood compared to term.

Methods: In a longitudinal cohort we measured BP at 3 visits in 220 adolescents born preterm with very low birth weight and 52 born term (mean age 14.4 yr). 148 preterm and 35 term subjects returned as adults (mean age 19.7 yr) and had BP measured at 2 visits. We defined high BP ≥120/80 and HTN ≥130/80 mmHg. We compared high BP and HTN prevalence in preterm vs. term in adolescents and adults with Fisher's exact test and calculated risk ratios with log-binomial regression. We calculated the change in BP/yr in preterm vs. term with linear mixed models. We calculated incident rate ratios comparing number of high BP or HTN measurements per person-yr from adolescence to adulthood in preterm vs. term with Poisson regression. All models were adjusted for race, HTN pregnancy, and birth weight z-score.

Results: Mean follow up was 5.5 yr (range 3.6-9.1). Preterm subjects had significantly higher systolic BP as adolescents and adults vs. term (mean difference 2.5 and 4.6 mmHg, respectively). In adolescents, the preterm vs. term high BP prevalence was 2% vs. 0%

(ns); no participants had HTN. In adults, the preterm vs. term prevalence of high BP was 13% vs. 3% (p=0.14) and HTN 9% vs 3% (ns). Preterm subjects had 4.4x increased risk of high BP as adults vs. term (0.6-31.6); this was attenuated after adjustment. The preterm-term difference in change in systolic BP was 0.3 mmHg/yr (95% CI -0.2 to 0.8); this was attenuated after adjustment. Preterm subjects had a 3.1x increased adjusted rate of high BP per person-yr (1.3-7.0) and a 2.7x increased adjusted rate of HTN per person-yr (0.9-7.5) from adolescence to adulthood vs. term.

Conclusions: Individuals born preterm had increased BP as adolescents and adults and increased rates of high BP and HTN from adolescence to adulthood compared to term-born peers. Early detection and treatment is important in this at-risk population.

Funding: Other NIH Support - Eunice Kennedy Shriver National Institute of Child Health and Human Development (P01 HD047584; HD084227); the Clinical Research Unit of Wake Forest Baptist Medical Center (MCRR/NIH M01-RR07122); the Wake Forest Clinical and Translational Science Award (NIH UL1 TR001420), Private Foundation Support, Clinical Revenue Support

TH-PO696

Obesity and Older Age Are Associated with Uncontrolled Hypertension in Children with Kidney Transplant in the Improving Renal Outcomes Collaborative (IROC)

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Background: Hypertension (HTN) is common in children following kidney transplant (KT) and uncontrolled blood pressure (BP) is associated with long-term outcomes. This study determined risk factors for HTN diagnosis and BP control using registry data from the Improving Renal Outcomes Collaborative (IROC), after standardizing appropriate BP measurement

Methods: We examined the latest clinic visit for each patient >90 days post-KT in the IROC registry that had documented appropriate BP measurement and complete medication data. Appropriate BP measurement was defined as either normal oscillometric measurement (2004 NHBPEP 4th Report), or combined documentation of 5 minutes of rest, use of upper extremity, and appropriate cuff size on a manual measurement. Appropriate BP measurements were next classified using the staging definitions in the 4th Report, which were still in use by IROC for determining BP control in clinic. HTN diagnosis was defined by either active HTN medication or BP ≥ Stage 1. BP control was defined as normal BP stage (BP <90th percentile and <120/80 mmHg) for those with HTN. Overweight was defined as BMI ≥85 %tile or 35 kg/m^2. Clinicodemographic factors associated with HTN diagnosis and BP control were assessed with Chi-square tests, odds ratios (OR), and 95% confidence intervals.

Results: A total of 773 patients from 17 centers were included in the study. Of these, 469 (61%) met criteria for HTN diagnosis. HTN diagnosis was more frequent in patients that were overweight (73% vs 27%, p=0.003), ≥18 years old (72% vs 56%, p<.001), of African American descent (69% vs 59%, p=0.02), or on calcineurin inhibitors (p=0.002). Of those with HTN, 240 (51%) were well-controlled and 32% had BP ≥ Stage 1. Overweight patients (OR 1.71, CI 1.18-2.50) and those ≥18yo (OR 1.79, CI 1.21-2.64) were more likely to have uncontrolled BP. Overweight individuals also had more severe uncontrolled HTN (39% ≥ Stage 1) than normal weight individuals (27%, p=0.01).

Conclusions: Uncontrolled HTN is common in children with KT. Obesity was identified as a significant modifiable risk factor for both HTN diagnosis and BP control. Additional research is needed to identify factors contributing to higher rates of uncontrolled BP in pediatric kidney transplant recipients in early adulthood.

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TH-PO697

Pediatric Hypertension Screening and Recognition in Primary Care Clinics in Canada

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Background: Pediatric hypertension is becoming increasingly prevalent. Comprehensive guidelines have been developed to guide the diagnosis, evaluation and treatment of hypertension in children. Adherence to these guidelines is unknown in Canada.

Methods: Electronic medical record (EMR) data from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) was used to determine rates of hypertension screening, follow-up and recognition across Canada for the 2011-2017 period. Data for children aged 3-17 with at least one clinical encounter were extracted. The 2004 guideline by the National Heart, Lung, and Blood Institute was used to define elevated blood pressure (bp=90-95th%ile), hypertension (bp>95th%ile), and screening frequency, as they were pertinent for the study period. Screening rates and follow-ups were evaluated by year. Bivariate analysis was used to compare clinical characteristics of the screened vs non-screened population.

Results: Of the available 378002 children, 22% had at least 1 blood pressure documented. Rates of hypertension screening increased from 18% (n=43387) of all visits in 2011 to 26% (n= 97835) in 2017. Follow-up visits occurred within 6 months for 25% (SD=0.02) of individuals with a normal blood pressure and 26% (SD=0.02) of individuals with elevated blood pressure. For those with hypertension, 57% (SD=0.07) had a follow-up visit within 6 months and 7% (SD=0.01) had a follow-up visit within 1 month. Blood pressure was measured in 76% (SD=0.03) of well child visits (n=42063). The screened cohort included more females (51.6% vs 50.3%, p<0.0001), had higher rates of pediatric diabetes (0.6% vs 0.3%, p<0.0001), and higher BMI (19.9 ± 5.2 vs. 17.9 ± 4.4kg/m2, p< 0.0001). Overall prevalence of hypertension was 2% (n= 715) based on having 2 documented blood pressures above the hypertension threshold, of those, 5.6% (n=40) had a diagnosis of hypertension or presence of an anti-hypertensive in the EMR.

Conclusions: Across Canada, rates of hypertension screening are low, with higher rates at well child visits. Patients that were screened had more cardiovascular risk factors including higher BMI and rates of diabetes. Recognition of hypertension is also poor suggesting pediatric hypertension should be a priority for knowledge translation interventions.

TH-PO698

Younger Age, Asian Ethnicity, and Better Self-Rated Health Are Associated with Unawareness of Hypertension in Community Population

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Background: Hypertension (HTN) is a major risk factor for chronic kidney disease and its related cardiovascular (CV) complications. It is projected to affect 1.56 billion individuals worldwide by 2025. However, the awareness of HTN remains low; nearly 16% of U.S. adults are unaware of their HTN status. This study aims to explore factors associated with unawareness of HTN in community level.

Methods: Kidney Disease Screening and Awareness Program (KDSAP) provides free screenings and education targeting underserved communities across U.S. and Canada, aiming to early detect and raise awareness of kidney disease. From October 2011 to May 2018, a total of 1,040 KDSAP participants with HTN were enrolled in this study. HTN was defined by self-report being diagnosed with or treated for the disease or high blood pressure during screening with systolic ≥ 140 or diastolic ≥ 90 mmHg. Awareness was defined by self-report.

Results: More than one third (n=374, 36%) of participants were unaware of having HTN; they were younger (57 vs. 66 years old, p<0.001) and higher in proportion of men (51.3% vs. 41.1%, p=0.002). The awareness is positively correlated with increasing age, < 40 (36.9%), 40~59 (56.1%) and ≥ 60 years old (73.0%) (p<0.001), with adjusted odds ratio (OR) 1.02 for every 1-year age increment (p<0.001). While no difference in awareness rates among ethnicities: Asian 64.1%, African American 64.2%, White 60.7% and Hispanic 66.3%; Asians were found to be associated with lower awareness compared with African Americans (OR 1.58, p<0.05) and Hispanic (OR 1.89, p<0.05) after adjusted for age, gender, ethnicity, education level, and self-reported diabetes, hyperlipidemia and CV disease. Interestingly, individuals who rated their health as "very good" or "excellent" were 70% less likely to be aware of having HTN compared to those who self-rated with "poor" or "fair" health (age- and gender-adjusted OR 0.30, p<0.001).

Conclusions: Our results showed a high unawareness of HTN among the KDSAP participants. Younger age and Asian ethnicity were associated with higher unawareness. In addition, self-rated health was inversely correlated with HTN awareness. Our results provide insights in developing effective venues to raise HTN awareness at the community level.

Funding: Private Foundation Support

TH-PO699

The Relationship of Change in Ankle Brachial Index with Mortality Among Individuals with CKD: The CRIC Study

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Background: Patients with chronic kidney disease (CKD) have an increased risk of peripheral arterial disease (PAD). Ankle-brachial index (ABI), a non-invasive measure of PAD, is a predictor of adverse events among individuals with CKD. In general populations, changes in ABI have been associated with mortality, but this association is not well understood among patients with CKD.

Methods: Prospective study of 2987 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study without clinical PAD at baseline, and with at least one follow-up ABI measurement (taken at annual study visits). ABI was obtained by standard protocol. The association of change in ABI and mortality was studied using Cox proportional hazards regression.

Results: We found U-shaped associations of average annual change in ABI and cumulative average ABI with all-cause mortality (p for non-linearity ≤0.0001). Compared to participants with average annual change in ABI of 0 to <0.02, individuals with average annual change in ABI <-0.02, -0.02 to <0, or ≥0.02 had multivariable-adjusted hazard

ratios (95% CI) of 2.04 (1.57, 2.66), 1.25 (0.98, 1.58), and 1.68 (1.37, 2.05) for all-cause mortality, respectively. Compared to participants with cumulative average ABI between 1.0 and <1.4, multivariable-adjusted hazard ratios (95% CI) for those with cumulative average ABI of <0.9, 0.9 to <1.0, and ≥1.4 were 1.64 (1.33, 2.01), 1.22 (0.95, 1.55), and 1.29 (0.95, 1.75), respectively.

Conclusions: Findings from this study indicate that both larger decreases and increases in average annual changes in ABI (>0.02) were associated with higher risk of mortality. Monitoring changes in ABI over time may facilitate risk stratification for all-cause mortality among individuals with CKD.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of General Medical Sciences, National Center for Advancing Translational Sciences

TH-PO700

Natural History of Peripheral Artery Disease in Patients with CKD

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Background: The prevalence and risk of peripheral artery disease (PAD) are higher in patients with chronic kidney disease (CKD) compared to those without. The natural history of PAD in CKD has not been well studied.

Methods: We studied the natural history of PAD among 4571 participants without PAD procedures at baseline in the Chronic Renal Insufficiency Cohort (CRIC) Study. The mean follow-up duration is 7.6 years. Mixed effects models were used to assess the slope of change in ankle-brachial index (ABI). Cox proportional hazards models were used to examine the multivariable association of ABI slopes with PAD events, adjusting for time-updated confounding factors.

Results: The slopes of average annual ABI changes were characterized as rapidly (ABI change < - 0.03) or slowly (-0.3 to -0.001) decreasing, stable (<-0.001 to <0.001), rapidly (>0.05) or slowly (0.001 to 0.05) increasing. Compared to those with stable slope, multivariable-adjusted hazard ratios (95% CI) for incident PAD events were 2.80 (2.49, 3.17), 1.67 (1.55, 1.81), 1.42 (1.32, 1.54), and 1.92 (1.65, 2.23) for those with rapidly decreasing, slowing decreasing, slowly increasing, and rapidly increasing, respectively. The average time to develop the first PAD event was 7.38, 8.48, 8.46, 7.73, 7.50, or 6.59 years for those with baseline ABI of ≤0.9, >0.9-1.0, >1.0-1.2, >1.2-1.3, >1.3-1.4, or >1.4, respectively. Annual event rates per person year were 2.95%, 1.58%, 1.58%, 1.77%, 1.64%, or 2.64 % for CVD and 3.57%, 2.17%, 1.61%, 1.80%, 1.96%, or 2.03% for mortality by baseline ABI categories. Amputation and mortality rates were 17.86% and 8.74%, respectively, in year 1 and 22.02% and 13.69%, respectively, in year 5 after PAD-related revascularization.

Conclusions: This study indicates that either increase or decrease in ABI with time is associated with increased incident PAD events. Latent time of PAD is short for those with normal ABI. Complication rates are high among those with subclinical PAD. Prognosis is poor after revascularization. Our study suggests screening for PAD using ABI along with monitoring ABI changes may facilitate early detection of PAD progression and prevention. Further study is warranted to investigate the effect of intervention for significant change of ABI on improving clinical outcomes.

Funding: NIDDK Support

TH-PO701

Predictive Value of Cardio Ankle Vascular Index on the Risk of ESRD

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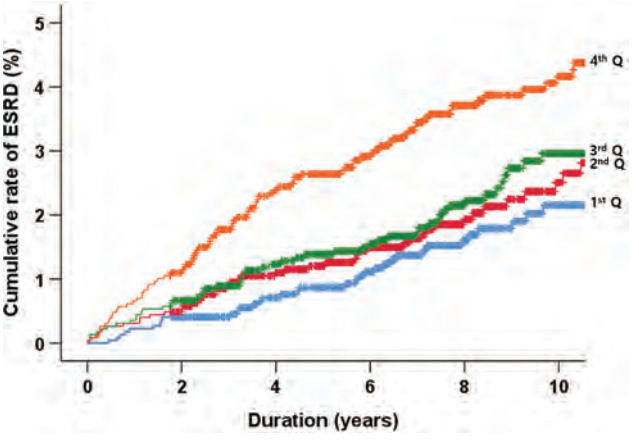
Background: Arterial stiffness is a great concern in relation to high mortality and cardiovascular event. However, the predictive value of pulse wave velocity, one of assessment tools for arterial stiffness, on the risk of end-stage renal disease (ESRD) remains unresolved.

Methods: A total of 9,005 patients who measured cardio-ankle vascular index (CAVI) were included in the study. Patients were divided according to the value (9.0) of CAVI or the quartiles of CAVI. The hazard ratios (HRs) of ESRD and all-cause mortality were calculated using the multivariable-adjusted Cox model. We also analyzed the competing risk regression to adjust the death.

Results: During the median follow-up period of 7 years (maximum 12 years), the events of ESRD and mortality occurred in 215 and 1,079 patients, respectively. The median value of CAVI was 8.5. The high CAVI group (> 9.0) had a higher risk of ESRD than the low CAVI group (HR, 1.65 [1.27–2.16]; $P < 0.001$). The risk of all-cause mortality was also higher in the high CAVI group than in the low CAVI group (HR 2.84 [2.51–3.21]; $P < 0.001$). Although the analysis was performed based on the quartiles, the 4th quartile group had a higher risk of ESRD (HR, 2.20 [1.48–3.27]; $P < 0.001$) than the 1st quartile group. The risk of all-cause mortality was also higher in the 4th quartile than in the 1st quartile (HR, 4.21 [3.46–5.12]; $P < 0.001$). The death-adjusted risk analysis also showed that the 4th quartile group had a high risk of ESRD than the 1st quartile (HR, 2.21 [1.49–3.28]; $P < 0.001$).

Conclusions: The measurement of CAVI by the pulse wave velocity may be needed to predict the risk of ESRD.



TH-PO702

CKD, Atherosclerotic Plaque Characteristics on Carotid Magnetic Resonance Imaging, and Cardiovascular Outcomes

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Background: CKD is associated with high risk of cardiovascular (CV) events but it is unclear whether greater baseline prevalence and faster progression of atherosclerosis accounts for this phenomenon.

Methods: In a subgroup (N = 465) of Systolic Blood Pressure Intervention Trial (SPRINT) participants, we used carotid MRI to measure plaque presence and morphology at baseline and after 30-months. CKD was defined as baseline eGFR <60 ml/min/1.73m^2. Plaque was defined as max wall thickness> 1.5 mm or presence of lipid rich necrotic-core (NC+) or calcified (Ca+) plaques. As only NC+ plaque predicted primary SPRINT CV composite and not any plaque or Ca+ plaque, the current analysis used NC+ plaques. We related CKD status with NC+ plaque and the CV outcome.

Results: Overall, 196 (42%) patients had CKD and 137 (30%) had NC+ plaques. Baseline presence of NC+ plaque was unrelated to CKD status (OR 1.02, 95% CI 0.67 to 1.57). CKD was associated with a lower odds of NC+ plaque progression (OR 0.42, 95% CI 0.18 to 0.98) among participants with NC+ plaque at baseline and non-missing follow-up MRI (N = 96). There were 28 CV events over 1764 participant-years of follow-up. In a multivariable Cox model, both CKD (HR 3.47, 95% CI 1.42 to 8.47) and NC+ plaque (HR 2.58, 95% CI 1.07 to 6.18) were associated with an increased hazard of CV event. The interaction p-value for CKD status and NC+ plaque was non-significant (p = 0.55). However, patients with both had a significantly higher cumulative rate of CV events compared to patients with neither (Fig. 1).

Conclusions: We found no association between CKD status and the presence or progression of NC+ plaques, although both were independently associated with CV events. Thus, CKD may contribute to CV disease principally via mechanisms other than atherosclerosis. Moreover, a combination of carotid MRI and GFR estimation could be used to identify patients with hypertension at exceptionally high CV risk.

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

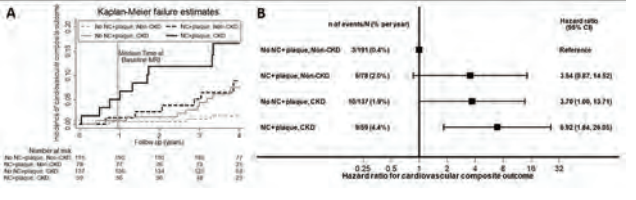

Figure 1: CV Risk Comparison By NC+ plaque and CKD Status.

TH-PO703

A Novel Magnetic Resonance Sequence That Accurately Detects Aortic Calcification

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Background: Vascular calcification is a surrogate marker of cardiovascular disease in patients with renal disease. Computed tomography (CT) is the current gold standard for detecting vascular calcification. StarVIBE (Siemens Healthineers) is a free-breathing, non-contrast magnetic resonance imaging (MRI) sequence that can detect vascular calcification with advantages over CT: it is radiation-free and can be conducted alongside functional cardiac MRI. We compared MRI-StarVIBE with CT for detection of thoracic aortic calcification in patients with renal disease.

Methods: Paired thoracic CT and MRI scans (<24 hours apart) were obtained from patients with renal disease participating in two prospective cohort studies. Two investigators separately reviewed sagittal views on MRI-StarVIBE (JSL) and CT (AJR) of a 10 cm segment of thoracic aorta from the lower level of the descending aortic arch. Aortic calcification was quantified by manually tracing regions of interest on all image slices. We calculated percentage agreement for presence or absence of calcium on CT and MRI-StarVIBE. Linear regression analysis was used to compare calcium content on MRI-StarVIBE and CT. We randomly reassessed 10% of MRI and CT scans, blinded to the original scores, for inter-observer consistency of agreement using the intra-class correlation coefficient (ICC).

Results: Ninety patients (78 renal transplant; 12 haemodialysis) had paired MRI-StarVIBE and CT scans. Calcium was detected on 50.0% of CT scans and 55.8% of MRI-StarVIBE sequences; agreement was 92.2%. There was a strong, linear association between CT and MRI-StarVIBE calcium score (r2 = 0.89). Inter-observer consistency of agreement for calcium quantification was excellent for both CT (ICC 0.966, 95% CI 0.878-0.991, p<0.001) and MRI-StarVIBE (ICC 0.996, 95% CI 0.986-0.999, p<0.001).

Conclusions: MRI-StarVIBE is comparable to CT for evaluating aortic calcification without the need for exposure to potentially hazardous ionizing radiation in patients with established renal disease.

Funding: Private Foundation Support

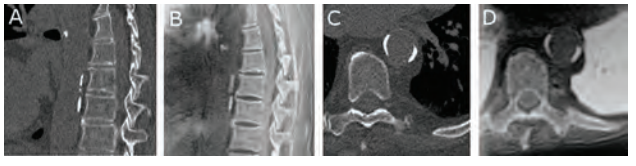

Figure: Representative images of calcification (white areas along aortic wall) on CT (A, C) and MRI-StarVIBE (B, D). Images A and B are sagittal slices; images C and D are illustrative coronal slices.

TH-PO704

Distribution of Myocardial Fibrosis by Native T1 Times Using Cardiac Magnetic Resonance Measurements in CKD

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Background: Previous evidence suggests that native myocardial T1 relaxation times assessed by cardiac magnetic resonance imaging (MRI) are relevant biomarkers of the extension and severity of myocardial fibrosis in patients with chronic kidney disease (CKD). However, detailed classification and cutoffs of the T1 values in correlation with the severity of kidney disease have not been described

Methods: A cohort of 51 patients with eGFR>20 ml/min/1.73m^2 and without congestive heart failure underwent concomitant assessment of kidney function and noncontrast cardiac MRI using T1 mapping sequence technique in a 3T scanner. CKD was defined as eGFR<60 ml/min/1.73m2. T1 times were measured in all myocardial segments using the American Heart Association 16-segment method and utilizing an advanced post processing software. Student t tests and multivariate linear regression analyses were performed to test the association of CKD with segmental T1 times.

Results: 51 patients were enrolled in the study. Global T1 values in individuals with (eGFR<60) and without (GFR≥60) CKD were 1045.91 ±42.74ms and 1019.75±47.16ms (,p=0.02), respectively. T1 values for anteroseptal, anterior, and inferoseptal segments were 1083.33± 38.53ms and 1049.03±49.81ms(p=0.001), 1052.29±51.81ms and 1021.41±47.52ms (p= 0.01), 1061±40.61ms and 1016.4±60.06ms (p<0.001), in CKD and non CKD patients respectively. Basal T1 values were 1062.93±34.55ms and 1030.56±45.41ms (p<0.001) respectively. In models adjusted for demographics, co-morbidities, medications and eGFR, age was the only variable significantly associatiated with global T1 times.

Conclusions: Cardiac MRI T1 relaxation times can be surogate markers to risk stratify patients with CKD. The cardiac fibrosis in CKD is more prevalent in the basal, anterior and septal myocardial segments.

Funding: Other NIH Support - NHLBI

TH-PO705

Association of Noninvasive Measures of Subclinical Atherosclerosis and Arterial Stiffness Cardiovascular Risk with Mortality and Cardiovascular Events in CKD: A Meta-Analysis

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Background: Non-invasive Cardiovascular disease (CVD) risk prediction, in subclinical stages, aiming to stratify patients and tailor interventions remains an unmet need in CKD. We summarize the association of carotid intima-media thickness (cIMT), coronary artery calcium score (CACS) and pusle-wave velocity with all-cause mortality, CVD mortality and CVD events in non-dialysis CKD and patients on dialysis.

Methods: Systematic review and metanalysis of prospective cohort studies.

Results: 24 out of 27984 studies were eligible for quantitative synthesis (5 for cIMT, 11 for CACs and 8 for PWV) involving 708, 3706 and 4393 patients respectively. In dialysis patients, cIMT was associated with all-cause mortality (relative risk (RR) per unit increase 1.08, 95% confidence interval (CI) 1.00-1.17, I^2:68%) and CVD mortality (RR: 1.29, 95% CI 1.14-1.47, I^2:0%). High Vs low CACS was associated with all-cause mortality (RR: 2.51, 95% CI: 1.66-3.79, I^2: 5.7%) and CVD events (RR: 3.77 95% CI: 2.16-6.58, I^2: 20.2%). High Vs low PWV was associated with all-cause (RR: 5.34, 95% CI 3.01-9.47, I^2: 0%) and CVD mortality (RR: 8.55, 95%CI: 4.37 to 16.73, I^2: 0%). The combined estimated for all-cause mortality per 1 m/s increment unit in PWV, was 1.25 (95%CI: 1.17-1.34, I^2: 0%) and for CVD mortality was 1.24 (95%CI: 1.16-1.34, I^2: 15.5%). In non-dialysis patients, CACs was associated with CVD events (RR: 4.02, 95%CI: 1.57-10.29, I^2: 63.4%). High Vs low PWV was associated with all-cause mortality (RR: 2.52, 95% CI 1.40-4.55, I^2: 62.6%).

Conclusions: cIMT, CACS and PWV are associated with all-cause, CVD mortality and events among patients with all stages of CKD. These markers could be considered for the evaluation of cardiovascular morbidity and mortality risks.

Table: Meta-analysis results for all three outcomes, shown separately for HD and non-HD patients.

	All-cause Mortality		CVD Mortality		CVD Events	
	HD patients	Non-HD patients	HD patients	Non-HD patients	HD patients	Non-HD patients
cIMT*	1.08 (1.00-1.17) (I^2: 68%)	n/a	1.29 (1.14-1.47) (I^2: 0%)	n/a	n/a	n/a
CAC†	2.51 (1.66 – 3.79) (I^2: 5.7%)	n/a	n/a	n/a	3.77 (2.16-6.58) (I^2: 20.2%)	4.02 (1.57-10.29) (I^2: 63.4%)
PWV†	5.34 (3.01 – 9.47) (I^2: 0%)	2.52 (1.40 to 4.55) (I^2: 62.6%)	8.55 (4.37-94.39) (I^2: 0%)	n/a	n/a	n/a
PWV*	1.25 (1.17 – 1.34) (I^2: 0%)	n/a	1.24 (1.16-1.34) (I^2: 15.5%)	n/a	n/a	n/a

*Per unit increase analysis
†Cut-off analysis
n/a: Not enough data available to perform meta-analysis

TH-PO706

Change and Clinical Significance of Serum IL-22 Concentration in Hypertensive Renal Damage Patients

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Background: CD4$^+$T cells and their secreted cytokines contribute to the development of hypertensive renal damage. Our previous study showed that Th22 cells and its effect factor interleukin-22 (IL-22) increased significantly in Ang II-induced hypertensive renal damage mice, might play a promoting effects. However, the effects of Th22 and IL-22 in hypertensive patients remain unclear. This study is to explore change of serum IL-22 concentration and its correlation with other clinical indexes in patients with essential hypertension and hypertensive renal damage.

Methods: 97 essential hypertension (EH) patients and 40 healthy control were enrolled in our study. The EH patients were divided into simple hypertension (SH) group (n=45) and hypertensive renal damage (HRD) group (n=52) according to 24h urinary protein (24h-UPRO) level. Basic clinical data were collected; serum IL-22, TNF-α and IL-6 levels were detected by ELISA; the proportion of Th22 cells in peripheral blood was evaluated by flow cytometry; IL-22 and IL-22 receptor (IL-22) expression in kidneys were determined by immunohistochemistry; serum high sensitivity C-reactive protein (hs-CRP) concentration was measured by immune turbidimetry. Correlation analysis was applied between serum IL-22 and other indexes.

Results: Serum IL-22 level and Th22 cells frequency in patients with hypertension were significantly higher than control participants. Compared with SH group, serum IL-22 level was elevated obviously in HRD group), and Th22 cells proportion was also higher in HRD group. Expression of IL-22 and IL-22R in kidneys were increased in hypertensive renal damage patients compared to control. Bivariate linear correlation analysis revealed that serum IL-22 level was positively correlated with systolic blood pressure (SBP), diastolic blood pressure (DBP), TNF-α,IL-6 and hsCRP; there was also a positive correlation between serum IL-22 concentration and Th22 cells proportion in hypertensive patients. Serum IL-22 level was positively correlated with 24h-UPRO level in HRD group.

Conclusions: Serum IL-22 and peripheral blood Th22 cells infiltration were significant increased in HRD group compared with SH group, serum IL-22 was closely

correlated with extent of hypertensive renal damage, indicating that serum IL-22 may involved in the pathogenesis of hypertensive renal damage.

Funding: Government Support - Non-U.S.

TH-PO707

Soluble Neprilysin, NT-ProBNP, and Growth Differentiation Factor 15 as Biomarkers for Heart Failure in Dialysis Patients (SONGBIRD)

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Background: Dialysis patients are at increased risk of congestive heart failure (HF). However, diagnostic utility of NT-proBNP as a biomarker is decreased in patients on hemodialysis or peritoneal dialysis. Growth differentiation factor-15 (GDF15) and neprilysin (NEP) are biomarkers of distinct mechanisms that may contribute to HF pathophysiology in such cohorts.

Methods: We compared circulating concentrations of NT-proBNP, GDF15, and NEP along with NEP activity, individually or in combination, in patients on chronic dialysis without (n=80) and with HF (n=73; composite of HF with reduced [n=40] and preserved ejection fraction [n=33]), as diagnosed by clinical parameters and post-dialysis echocardiography. We used correlation, linear and logistic regression as well as receiver operating characteristic (ROC) analyses.

Results: Compared to controls, patients with HF had higher medians of NT-proBNP (16216 [interquartile range, IQR=27739] vs. 2883 [5866] pg/mL, p<0.001), GDF15 (7512 [7084] vs. 6005 [4892] pg/mL, p=0.014), but not NEP (315 [107] vs. 318 [124] pg/mL, p=0.818). Median NEP activity was significantly lower in HF vs. controls (0.189 [0.223] vs. 0.257 [0.166] nmol/mL/min, p<0.001). In ROC analyses, a base model combining clinical covariates (age, dyspnea score, systolic blood pressure, Charlson comorbidity index, history of HF or severe valve disease, extracellular to total body water ratio) and NT-proBNP distinguished HF from controls with an area under the curve (AUC) of 0.785 (95% confidence interval [CI] 0.714-0.856). NEP activity and GDF15 provided incremental utility over the base model. A multi-marker model combining clinical covariates, NT-proBNP, GDF15 and NEP activity demonstrated best discrimination of HF from controls (AUC=0.902, 95% CI 0.857-0.947, p<0.001 vs. base model).

Conclusions: We present novel comparative data on physiologically distinct circulating biomarkers for HF in patients on dialysis. NEP activity but not concentration and GDF15 provided incremental predictive information over clinical covariates and NT-proBNP and may aid in diagnosing HF in dialysis patients.

Funding: Private Foundation Support

TH-PO708

Urinary N-Terminal Pro-Brain Natriuretic Peptide Is a Useful Biomarker for Cardiovascular Events in a General Japanese population: The Hisayama Study

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Background: Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels have been well accepted as an index for estimating cardiovascular risk in general practices. On the other hands, there is a possibility that urinary NT-proBNP is a non-invasive biomarker without requiring blood sampling, because NT-proBNP is excreted in urine. Therefore, the present study investigated the association between urinary NT-proBNP levels and the risk of cardiovascular disease (CVD) in a general Japanese population.

Methods: A total of 3,060 community-dwelling Japanese subjects aged ≥40 years without history of CVD were followed up for 8 years (2007-2015). Urinary NT-proBNP levels were divided into four categories using cutoff values of 23, 30, and 42 pg/mL, which were corresponding to guideline-based cutoff values of serum NT-proBNP, being 55, 125, and 300 pg/mL, based on the linear regression analysis of serum and urinary NT-proBNP concentrations (Pearson's correlation coefficient=0.75). The associations of urinary NT-proBNP levels with the risk of CVD and its subtypes were estimated by the Cox proportional hazards model.

Results: The median value of urinary NT-proBNP concentrations was 20 pg/mL (interquartile range 18-25 pg/mL). During the follow-up period, a total of 170 CVD events developed. The age- and sex-adjusted risk of CVD increased significantly with higher urinary NT-proBNP levels (p for trend <0.001). This association remained significant even after adjustment for conventional cardiovascular risk factors (hazard ratio [95% confidence interval]: 1.00 [reference] for ≤22 pg/mL, 1.13 [0.74–1.71] for 23–29 pg/mL, 1.59 [0.97–2.61] for 30–41 pg/mL, 1.78 [1.11–2.87] for ≥42 pg/mL; p for trend =0.01). A similar association was observed for total stroke (p for trend =0.01), but not for coronary heart disease (p for trend =0.36).

Conclusions: The present finding suggests that elevated urinary NT-proBNP level is a useful biomarker for the development of CVD, especially stroke, independent of conventional risk factors in a general Japanese population.

TH-PO709

APOL1 Risk Variants, Subclinical Cardiovascular Disease, and Mortality in African Americans Initiating Hemodialysis

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Background: The role of *APOL1* risk variants in cardiovascular disease (CVD) remains unclear, especially among ESRD patients. We evaluated associations of *APOL1* with subclinical CVD and mortality in a cohort of African Americans (AA) initiating hemodialysis (HD) in the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study.

Methods: *APOL1* risk variants and ancestry markers were genotyped using custom Taqman assays and Infinium QC array kits. We defined *APOL1* risk status by a recessive genetic model (high=2 risk alleles; low=0-1 risk allele). We studied associations of *APOL1* high-risk status with baseline subclinical CVD (left ventricular [LV] hypertrophy, LV mass, ejection fraction, coronary artery calcification [CAC], pulse wave velocity) using logistic/linear regression and time to all-cause or CVD mortality using Cox hazards models, adjusting for age, sex and ancestry. In sensitivity analyses, we further adjusted for systolic blood pressure (SBP) and Charlson Comorbidity Index (CCI).

Results: Of 267 AA participants successfully genotyped, 27% were *APOL1* high-risk. At baseline, mean age was 53 years, 41% were female, 56% had diabetes, and mean SBP was 138 mmHg. In cross-sectional analyses, *APOL1* high- vs. low-risk status was independently associated with lower odds of LV hypertrophy and CAC, and lower LV mass. These associations remained robust upon further adjustment for CCI, but were attenuated when adjusted for SBP (Table). Over a mean follow-up of 2.5 years, *APOL1* risk status was not associated with all-cause or CVD mortality.

Conclusions: Among AA incident HD patients, *APOL1* high-risk status was associated with better subclinical measures of CVD, but these did not translate to improved survival. Future studies are needed to clarify the clinical implications of *APOL1* risk variants in AA with ESRD.

Funding: NIDDK Support, Commercial Support - Extramural Grant Program from Satellite Healthcare, a not-for-profit renal care provider

Table: Associations of *APOL1* risk status with subclinical CVD at baseline in PACE.[a]

	Model 1: adjusted for age, sex and ancestry	Model 2: Model 1 + CCI	Model 3: Model 1 + SBP
	Odds Ratio (95% CI)		
LV hypertrophy	0.50 (0.26, 0.94)	0.51 (0.27, 0.96)	0.54 (0.28, 1.03)
CAC>0	0.47 (0.22, 0.98)	0.47 (0.22, 0.98)	0.51 (0.24, 1.07)
	β (95% CI)		
Ejection Fraction	-1.47 (-4.93, 1.99)	-1.69 (-5.13, 1.75)	-1.67 (-5.20, 1.86)
	% Difference (95% CI)		
CAC[b]	68.40 (-36.52, 346.76)	81.88 (-30.93, 378.95)	61.59 (-38.80, 326.61)
LV mass	-10.69 (-18.99, -1.54)	-10.56 (-18.90, -1.36)	-9.00 (-17.40, 0.26)
Pulse wave velocity	-7.86 (-16.08, 1.16)	-7.72 (-15.92, 1.29)	-4.99 (-12.91, 3.64)

[a]Comparing *APOL1* high- vs. low-risk status
[b]Among individuals with CAC>0 (n=109).

TH-PO710

The Combined Prognostic Significance of Vascular Calcification and Alkaline Phosphatase in Patients with ESRD

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Background: Vascular calcification (VC) is a well-known prognostic marker in patients with end-stage renal disease (ESRD), while there are conflicting results on the role of serum alkaline phosphatase (ALP) on cardiovascular event (CVE) and mortality. This study investigated whether there was a combined effect of VC and ALP on prognosis in patients with ESRD starting dialysis.

Methods: This was a retrospective cohort study including 587 incident ESRD patients from a single center. The aortic calcification index (ACI), an estimated of abdominal aortic calcification, was calculated by abdominal computed tomography as a measure of VC.

Patients were stratified into four groups according to the median ACI and serum ALP value. CVE and death were assessed as study outcomes. The association of VC and ALP on composite of end-point was analyzed. The modification effect between VC and ALP on composite of end-point was determined using an interaction product term.

Results: During a median follow-up duration of 3.1 (0.02 – 12.3) years, 140 patients (23.8%) developed CVE and 130 deaths (22.1%) occurred. In the stratified analysis, patients with higher ACI and lower ALP had a greater risk of composite of end-point compared to patients with combined lower ACI and ALP group (adjusted hazard ratio, 2.04; 95% confidence interval, 1.23 – 3.38; $P = 0.006$), and patients with combined higher ACI and ALP had the greatest risk (adjusted hazard ratio, 2.26; 95% confidence interval, 1.05 – 3.62; $P = 0.001$). The interaction between ACI and ALP on CVE and mortality was statistically significant ($P < 0.05$).

Conclusions: In conclusion, the combined effect of VC and higher ALP was associated with greater risk of CVE and deaths in ESRD patients starting dialysis. Serum ALP amplifies the risk of CVE and deaths associated with VC in ESRD patients.

TH-PO711

Adductome of HDL from Non-Diabetic Hemodialysis Patients

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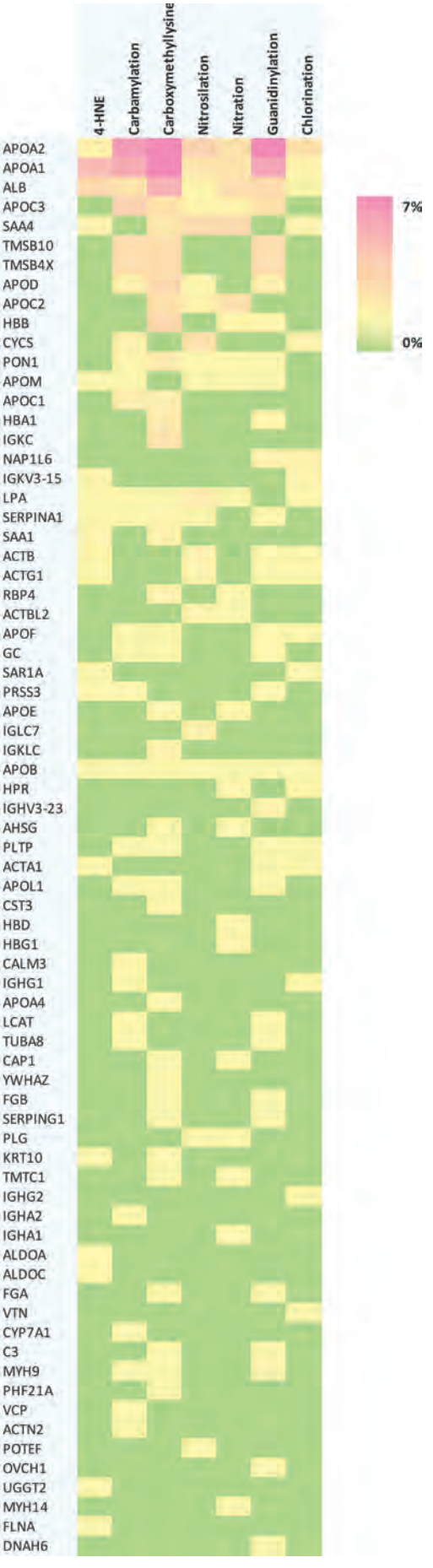
Background: HDL dysfunction could participe in the increased cardiovascular mortality in CKD. have been pointed out in this burden. Post-translational modifications (PTM) of HDL were highlighted as potential mediators of HDL dysfunction. We aimed to describe PTM of HDL proteins from non-diabetic hemodialysis (HD) patients.

Methods: HDL were sampled from the plasma of 9 non-diabetic HD and 9 potential kidney-donors patients with a sequential ultracentrifugation. Samples were analyzed using an nano-RSLC coupled on line with a Q-Orbitrap. Data were processed with Proteome Discoverer 2.2 software and quantified with a label free quantitation approach. Oxidation, acetylation, carbonylation (with 4-HNE), carbamylation, guanidinylation, chlorination, nitration and nitrosylation were set as variable modifications. Protein quantitation was based on pairwise ratios and ANOVA hypothesis test.

Results: 522 proteins were identified in HDL from HD patients and controls among which 73 (i.e. 14%) presented adduction sites. The main PTM were glycation (26%), guanidynilation (17%), carbamylation (15%), nitration (14%), carbonylation by the 4-HNE (11%), nitrosilation (9%) and chlorination (8%). Those proteins were involved in lipid metabolism, acute phase response, hemostasis, wound healing and muscular metabolism. Apolipoprotein A2 and 1 were the proteins the more prone to adduction (28 and 27% respectively) followed by serum albumin (15%), apolipoprotein C3 (9%) and serum amyloid A4 (8%, **Figure 1**). Most of the key-proteins of HDL metabolism were found to be adductable.

Conclusions: HDL from HD patients presented several post-translational modifications of their proteins. Those proteins are involved in most of the biological functions of HDL and their modifications could contribute the dysfunction of HDL in CKD.



TH-PO712

Outcome and Prognostic Factors in ESRD Patients with Acute Coronary Syndrome (ACS) Undergoing Percutaneous Coronary Interventions

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Background: Several risk factors have been recognized for acute coronary syndrome (ACS) undergoing percutaneous coronary interventions (PCI) in the general population. Risk factors for poor outcome in end stage renal disease (ESRD) patients differ from those who do not receive chronic dialysis. Although ESRD patients have been shown to be susceptible to cardiovascular diseases, the overall outcome and factors associated with prognosis is not well elucidated. Therefore, the characteristics and progress of ESRD patients who underwent PCI for ACS have been examined.

Methods: Retrospective analyses were conducted in ESRD patients who underwent PCI due to ACS from 1 January 2005 to 31 December 2018 at Yonsei University Health System, Seoul, South Korea. The patients were followed-up until 30th May, 2019. Demographic characteristics, laboratory parameter, echocardiographic findings, and dialysis related parameters at the time of PCI were collected.

Results: A total of 228 patients were included in the final analysis. The mean age was 66.9 ± 10.6 years, 146 (64.0 %) were male, and 82 (36.0 %) were being treated for diabetes. During a mean follow-up duration of 109.9 ± 94.8 months, 78 (34.2 %) cases of mortality were reported. When the patients were grouped into survivors and non-survivors, peripheral artery occlusive disease (PAOD) and left main coronary disease were more common among non-survivors. Echocardiographic ejection fraction (EF) and serum albumin levels were lower, while serum troponin T and CK-MB levels at the time of ACS were significantly higher among non-survivors. Multivariate logistic regression analysis revealed that concomitant PAOD (OR, 3.95; CI, 1.17-13.1), left main coronary disease (OR, 4.31; CI, 1.13-16.42), EF lower than 50% (OR, 8.30; CI, 1.84-37.41), lower serum albumin (OR, 4.29; CI, 1.44-12.79), and higher CK-MB (OR, 3.51; CI, 1.25-9.85) and troponin T levels (OR, 1.68; CI, 1.08-2.63) were significant factors related with in hospital mortality.

Conclusions: Outcome after PCI in ESRD patients with ACS was grave. Concomitant PAOD, echocardiographic findings, and cardiac enzyme levels could be practical factors predicting mortality in these patients.

TH-PO713

Dialysis Modality-Related Disparities in Sudden Cardiac Death: Hemodialysis vs. Peritoneal Dialysis

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Background: Patients require risk stratification and preventive strategies for sudden cardiac death (SCD) according to dialysis modality, as the process of dialysis itself is a risk factor for SCD. This study aimed to compare the risk of SCD in patients receiving hemodialysis (HD) or peritoneal dialysis (PD).

Methods: Patients on HD or PD were included from the end-stage renal disease registry of the Korean Society of Nephrology between 1985 and 2017. The incidence and associated factors of SCD were analyzed according to dialysis modality.

Results: Among 132,083 patients, 34,632 (35.5%) patients died during 94.8 ± 73.6 months of follow-up. In patients on HD and PD ($P < 0.001$), 22.2 and 19.6% of total death were SCDs. HD was independently associated with SCD even after adjusting age and significant comorbidities (adjusted odds ratio [OR] 1.14, 95% confidence interval [CI] 1.07–1.22, $P < 0.001$). The presence of hypertension (adjusted OR 1.14, CI 1.08–1.22, $P<0.001$) and congestive heart failure (adjusted OR 1.26, CI 1.15–1.39, $P<0.001$) and age<65 (adjusted OR 1.06, CI 1.00–1.13, $P = 0.041$) were independent risk factors for SCD in patients on HD but not in those on PD. Diabetes was significantly associated with SCD regardless of dialysis modality.

Conclusions: Korean patients on HD compared to PD faced a higher risk of SCD attributable to cardiac comorbidities.

TH-PO714

Geographic Variations in Congestive Heart Failure and Ischemic Heart Disease in Dialysis Patients and Associations with Neighborhood Walkability

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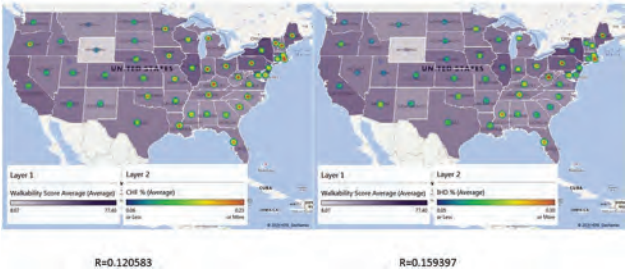
Background: Higher neighborhood walkability associates with better cardiovascular health in the general population (Gaglioti et al., 2018) and positively associates to objective physical activity levels in hemodialysis (HD) patients (Han M et al. 2018). We assessed if neighborhood walkability is related with the prevalence of congestive heart failure (CHF) and ischemic heart disease (IHD) in HD patients throughout the United States (US).

Methods: We used data from HD patients treated at a large dialysis organization in 2018. We calculated the average percent of HD patients with CHF and IHD per state within the US. We obtained data on the Walk Score (www.walkscore.com) in the US. The Walk Score measures neighborhood walkability on a scale of 0 (poorest walkability) to 100 (greatest walkability) based on access to key destinations (e.g. grocery stores, restaurants, retail stores). We calculated the correlation coefficients between the average walkability score for each state versus CHF and IHD prevalence.

Results: Data from 254,322 HD patients was analyzed on a state level in the US. Overall, we found small positive relationships between higher Walk Score and a higher CHF (correlation coefficient (R)=0.12) and higher IHD (R=0.16) prevalence in the US. However, this was not a consistent finding in many geographies and individual states. There appears to be distinct dichotomy between Western States and Eastern States, as well as less significant differences between the Northeast and the Southeast regions of the US (Figure 1).

Conclusions: Findings suggest HD patients tend to have a higher prevalence of CHF and IHD in areas with higher walkability. Despite this, this observation is not universally observed at state level, and county level analysis is needed. Further analyses are needed to understand the relationships between walkability and heart diseases.

Funding: Commercial Support - Fresenius Medical Care North America



TH-PO715

Is It Worth Measuring Home Blood Pressure in Maintenance Hemodialysis Patients?

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Background: The proper control of blood pressure(BP) is an important issue in hemodialysis patients and accurate BP measurement is mandatory. Although various methods of measurement of BP have been proposed, there is no standard method. The aims of this study are that office BP and home BP were compared based on ambulatory blood pressure monitoring (ABPM) in hemodialysis patients and propose the usefulness of home BP.

Methods: A total of 40 patients undergoing maintenance hemodialysis were enrolled for analysis of BP measurement from July 2018 to March 2019. Home BP was defined as the average of BP measured in a relaxed posture 5 minutes after the morning awaking and before sleeping. Office BP was predialysis BP and ABPM was undertaken 24 hours on non-dialysis days using *Mobil-O-Graph® (NG, I.E.M. GmbH, Stolberg, Germany).*

Results: The average BPs according to methods were as follows: home BP, 135.80 ± 17.29/ 73.99 ± 7.92 mmHg; office BP, 145.85 ± 17.44/ 73.70 ± 10.61mmHg; awake ABPM, 130.1 ± 20.78/ 76.48 ± 9.05mmHg. When compared to office BP with ABPM, 35% of the patients had sustained normotension, 42.5% of the patients had sustained hypertension, 22.5% of the patients had white-coat hypertension and masked hypertension cannot be observed. Based on ABPM, type of all patients was non-dipper, of which reverse-dippers were 32.5%. We analyzed the difference in systolic BP(SBP) in the home, office, and ABPM awake BP. SBP was the highest in office BP followed by home BP and ABPM in sequence. BP differences were as follows; ABPM-home SBP (-5.70 ± 14.51mmHg, $P = 0.017$), home-office SBP (-10.05 ± 12.19mmHg, $P = 0.00$), ABPM-office SBP (-15.75 ± 14.51mmHg, $P = 0.00$). 45% of patients had a 10% or more difference and 62.5% had a 5% or more difference in SBP between home and office. Interestingly, patients who had frequent intradialytic hypotension(IDH) tended to have a large difference in home-office SBP.

Conclusions: This study showed that the difference between home BP and ABPM was found to be approximately one third of the difference between office BP and ABPM. Because of the discomfort of ABPM measurements in patients with hemodialysis, home BP is necessary for proper BP management to prevent IDH. Conclusively, we propose that home BP could be a therapeutic target instead of ABPM in hemodialysis patients.

TH-PO716

Appraisal of Kidney-Related Parameters in Predictive Models of Heart Failure

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Background: The clinical course of patients with heart failure (HF) is known to be variable. Insights into factors that relate to subsequent adverse outcomes may help identify those patients in need of more intense monitoring and therapy. Several models have been developed for HF that simultaneously take into account multiple factors to

refine their predictive ability. The clinical relevance of kidney-related parameters has long been recognized in this setting. However, no study so far has explored how consistent they have appeared in various models. We sought to appraise kidney-related parameters (KRP) in contemporary models of HF.

Methods: Articles cited in PubMed database using keywords "heart failure", "prediction", and "model" were searched. Available data from clinical trials performed between January 1995 and December 2018 were included. The studies were selected if they prognosticated outcomes in HF population through a predictive model that consisted of at least 2 factors. Pertinent data on KRP (e.g. serum creatinine, blood urea nitrogen [BUN], and serum sodium level) were extracted and reviewed.

Results: A total of 15 studies with 82,706 participants were included, of which 5 were validated in a HF cohort different from the model derivation cohort. They consisted of a variety of HF populations (e.g. acute, chronic, carrying mechanical circulatory device) and the median number of included parameters was 7. There was substantial variation across models in the reporting of the KRP as well as the studied outcomes. While no study included estimated glomerular filtration rate, serum creatinine and BUN were included in only 6 and 4 studies respectively. Similarly, 4 and 7 models contained data on serum sodium level and blood pressure respectively. Serum uric acid and history of kidney disease were each included in only 1 study.

Conclusions: We found that available models for prediction of HF outcomes do not consistently include KRP while generally portending high prognostic ability. Development of these models is based on multivariate regression methods to define the proportional significance and coefficients of the prognostic variables. Therefore, this finding supports the notion that, contrary to conventional thinking, the impact of KRP on the outcomes of patients with HF may be confounded or modulated by other covariates (e.g. congestion) as the emerging data have implied.

TH-PO717

Sex Disparities and Risk of CKD: A Nationwide Cohort Study of 10.8 Million Adults in Korea

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Background: There are substantial differences in public health issues between men and women. However, longitudinal studies of the relationship between sex disparities and incident chronic kidney disease (CKD) are scarce. In this study, we aimed to evaluate the association between sex disparities and incident CKD in healthy adults with normal baseline kidney function.

Methods: We analyzed a total of 10.8 million adults who underwent National Health Insurance Service health examinations between 2009–2015. The outcome of interest was incident CKD, defined as *de novo* development of eGFR <60 mL/min per 1.73m^2 (definition 1) or ≥25% decline in eGFR from the baseline values accompanied by eGFR <60 mL/min/1.73m^2 (definition 2).

Results: In this large national cohort comprised of 10.8 million healthy Korean adults who had eGFR ≥60 ml/min per 1.73 m^2, there were a total of 178,966 (1.66%) and 81,737 (0.76%) incident CKD events according to each CKD definitions, respectively, during a median follow-up of 4.8 years. Multivariable-adjusted Cox model showed that women were associated with significantly lower risk of incident CKD compared with men: adjusted hazard ratios (95% confidence intervals) for women (*versus* men) were 0.85 (0.84-0.86) and 0.86 (0.85-0.88) in models using CKD definition 1 and 2, respectively. These associations were robust irrespective of comorbid conditions, residential area, health behaviors, and use of antihypertensive drugs or statins. However, in elderly people aged ≥60 years, the risk of CKD was comparable between men and women.

Conclusions: In this large nationwide cohort, women had lower risk of CKD than men among healthy Korean adults.

TH-PO718

Gender Disparities in the Epidemiology and Outcome of Advanced CKD in Ageing Type 2 Diabetes Mellitus: A Multicenter Nationwide Analysis from a Primary Care Cohort of Thailand

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Background: Chronic kidney disease (CKD) is a significant burden in elderly patients with type 2 diabetes mellitus (T2DM). The body of knowledge on the approach to elderly patients with CKD is still evolving. The status of senior women with advanced CKD has not been fully explored in our population.

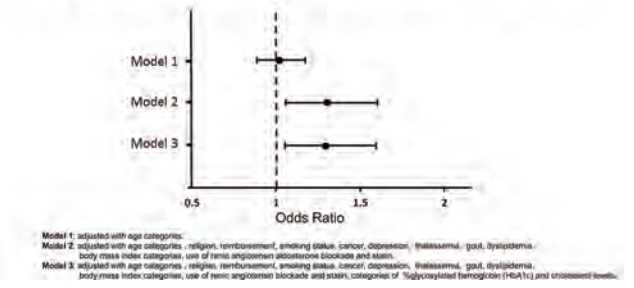
Methods: This study evaluated patients ≥65 years old with T2DM from the largest National Health Security System (NHS) of Thailand from 2011 to 2014. We aimed to determine female gender with respect to the risk of advanced CKD (stages G4 and G5).

Results: Out of the 13,135 patients, 60% were female, 4.8% had CKD stage G4, and 1.4% had CKD stage G5. The mean age was 74±6 years old. The mean body mass index (BMI) was 23.4±4.2 kg/m^2. The prevalence of having advanced CKD by gender was 6.2% and 6.1% in females and males, respectively. The multivariate analysis identified the odds ratio (OR) of the female gender (adjusted OR; 95% confidence interval [CI]; *P*-value) as an independent risk factor for advanced CKD. **Model 1**without adjustment (1.02; 0.88–1.18; 0.76). **Model 2**with adjustments by religion, reimbursements, smoking, body mass index and comorbidity covariates included a history of cancer, depression, thalassemia, gout, dyslipidemia, and use of renin-angiotensin-aldosterone system (RAAS) blockage and statin drugs (1.29; 1.03–1.60; 0.024). **Model 3**was adjusted based on **Model 2**and yielded laboratory categories of cholesterol, and %glycosylated hemoglobin (HbA1c) (1.29; 1.03–1.59; 0.029).

Conclusions: Women have unique risks for developing kidney diseases. Epidemiological studies suggest that pre-dialysis CKD is more prevalent in women than in men. The present study found that elderly T2DM women had increased risks associated with advanced CKD. We hope this focus issue will increase awareness and challenge of the renal health of women.

Funding: Government Support - Non-U.S.

Figure A: Female as a independent risk factor of advanced CKD in elderly T2DM



TH-PO719

The Incidence of CKD and ESRD Is Higher in Hypertensive Men Than Women: A Systematic Review and Meta-Analysis

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Background: Hypertension, defined as systolic blood pressure (SBP) ≥140 mmHg, is an established risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD). Whether sex differences in CKD and ESRD incidence exist among hypertensive individuals remains unclear. This systematic review and meta-analysis was conducted to evaluate the relative effect of hypertension on CKD and ESRD risk in women compared with men.

Methods: Cohort studies were systematically searched in Embase and PubMed until April 2017. Studies were selected if they reported a sex-specific relationship between SBP and CKD and/or ESRD. Random effects meta-analyses with inverse variance weighting were used to obtain sex-specific relative risks (RRs) and the RR ratio (RRR) (women to men) for incident CKD and ESRD.

Results: Data from six cohorts, including 2,382,712 individuals and 6,856 incident CKD events and 833 ESRD events, were identified. The RR for incident CKD or ESRD associated with hypertension versus ideal blood pressure (SBP <120 mmHg) was 1.58 (95% CI, 1.30-1.92) in women and 2.03 (95% CI, 1.65-2.49) in men. The RR for incident CKD or ESRD was 18% lower in women than in men (RRR 0.82 [95% CI, 0.71-0.94]) with no significant heterogeneity between studies (I^2=0%) (Figure 1).

Conclusions: Hypertension confers an 18% lower excess risk of incident CKD or ESRD in women compared with men. Sex differences in onset, duration, and severity of some risk factors, such as albuminuria, diabetes, cardiovascular disease, obesity, and socioeconomic status may explain part of the excess risk in men. Another explanation could be that women might be less likely to initiate dialysis or may be at increased risk of mortality than men. Future studies are warranted to more clearly elucidate the mechanisms responsible for the observed substantial sex differences.

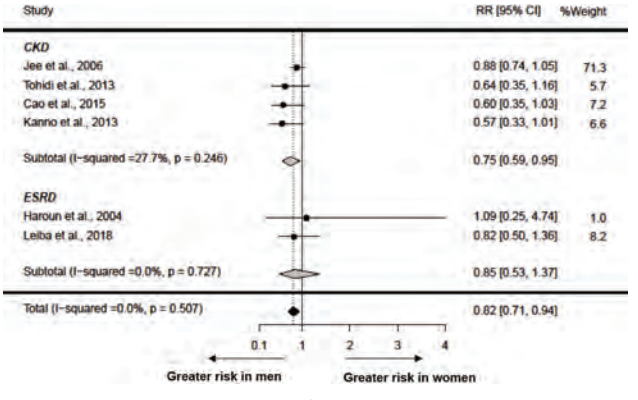

Figure 1. Women-to-men relative risk ratio for CKD and ESRD, comparing individuals in hypertension versus ideal BP

TH-PO720

Survival Advantage of Renal Transplantation over Dialysis Is Blunted in Women

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Background: The effect of gender on long term outcome in end stage renal disease is not well defined. Decreased LFα, a baroreflex index, and increased sdSV (stroke volume variability, a measure of myocardial responsiveness) were shown to predict poor prognosis in hemodialysis (HD) patients.

Methods: To assess factors associated with long term survival, clinical data and death events were monitored in 126 men (M) and 70 women (F) on HD and after renal transplantation (TX) during a follow up of 60 months. Continuous interbeat interval (IBI) and systolic blood pressure (SBP) and their variabilities were recorded using Finometer. LFα and sdSV were calculated from SBP and IBI spontaneous variations.

Results: Kaplan-Meier analysis showed a similar (76%) 5 yr survival in HD M and F. A significantly increased survival was noted in TX M compared with HD M (91%, p=0.031) while no such difference was noted in TX F (Figure1). Main death risk factors, LF α and sdSV are shown in Table 1. Age range, the prevalence of diabetes mellitus, hyperlipidemia and HD vintage were similar in M and F.TX was associated with improved blood pressure in all patients. Renal function was similar in TX M and F.

Conclusions: Our data show that despite higher comorbidity prevalence, TX significantly improved survival in M. The enhanced survival in TX M was associated with increased LFα and decreased sdSV, suggesting improved autonomic function. In F no significant changes in these measures were found and the survival benefit of TX was less prominent. The causes of the reduced effect of TX in F remain to be determined.

Table 1.

n	HD M (75)	HD F (44)	p	TX M (51)	TX F (26)	p
Hypertension [n(%)]	71 (95)	36 (82)	0.025	46 (92)	21 (81)	0.151
Ischemic heart disease [n(%)]	44 (59)	22 (50)	0.358	19 (38)	3 (12)	0.016
Smoking [n(%)]	38 (51)	7 (16)	0.001	19 (38)	0 (0)	0.001
LF α (ms/mmHg)* #	3.44 (2.80)	3.44 (2.80)	0.573	3.87 (4.00)^	4.15 (4.10)	0.249
sdSV (ml)#	6.65 (2.80)	5.40 (2.30)	0.016	4.92 (2.50)^^	4.78 (2.30)	0.914

* Square root of average IBI and SBP powers in the low frequency (LF) range. # Median and interquartile ranges.

p vs. HD M:^0.003;^^0.001:

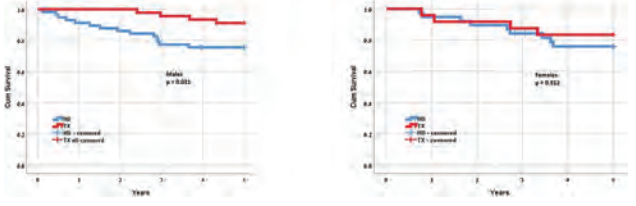

Figure 1.

TH-PO721

Real World, Hard Outcomes, and Sex Differences in AKI

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Background: Several studies focus on sexual dimorphism when suffering AKI, some of them report that women could be a protected against adverse events. We compared hard clinical outcomes between females and males in a real world cohort with AKI.

Methods: Retrospective cohorts study of hospitalized patients with diagnosis of AKI. We used KDIGO-2012 criteria for stratifying AKI severity, analyzed epidemiological and clinical variables and compared clinical outcomes: length of hospital stay, need for dialysis, dialysis dependence, and renal recovery.

Results: We included 1269 cases, 70% male, DM 42%, and CKD 61%. Table 1A shows clinical variables and Table1B results between groups. We found that mean Charlson's was higher in male individuals and women are hospitalized more frequently in medical wards. We found no statistically significant differences in hard clinical outcomes except for dialysis dependence at discharge (more in male individuals). We studied the effect of sex on death was using Cox regression analysis, univariate analysis revealed that sex was not a significant risk factor for death during AKI [HR (sex): 1.01, 95%CI: 0.78-1.30, p=0.95]; multivariate analysis including sex and AKI severity yielded similar results [HR (sex): 0.99, 95%CI: 0.77-1.29, p=0.98].

Conclusions: Experimental studies observe clear differences in clinical outcomes between genders when suffering AKI, some even concluding that female sexual hormones could be not only protective but also a possible treatment. In this real world study we observed a higher incidence of AKI in men than in women, consistent with previous larger epidemiological studies, and we only found that males are more frequently dialysis dependent at discharge. So we observed that women that suffer an AKI episode are not protected against it's deleterious effects.

	Female (385)	Male (883)	P value
A. Feature			
Age - ys	73 ± 14	72 ± 12	0.11*
HT	340 (88)	785 (89)	0.68§
DM	152 (39)	384 (44)	0.17§
CKD	234 (61)	544 (59)	0.79§
Medical Service	268 (69)	540 (61)	0.005§
Charlson's Index	3.9 ± 2.3	4.8 ± 2.4	<0.001*
ICU	39 (17)	76 (16)	0.36§
Community Acquired	272 (71)	598 (68)	0.33§
Etiology			
Prerenal	196 (51)	366 (41)	0.02§
Intrinsic	56 (15)	130 (15)	0.99§
Obstructive	16 (4)	64 (7)	0.04§
Mixed	118 (31)	323 (37)	0.04§
KDIGO Stage			
1	148 (38)	347 (39)	0.78§
2	63 (16)	104 (12)	0.03§
3	175 (45)	432 (49)	0.25§
B. Results			
Hospital Stay	16 ± 14	18 ± 15	0.07*
Need for HD	49 (13)	118 (13)	0.79§
HD Dependence	8 (2)	39 (4)	0.03§
In-hospital Mortality	184 (22)	195 (22)	0.94§
Renal Recovery	204 (62)	486 (67)	0.12§

Table 1 A and B. Features and Results.

TH-PO722

A Sex-Specific Relationship Between Vascular Calcification and Incident Fracture in Patients with ESRD

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Background: Vascular calcification (VC) is a major component of mineral bone disorders in patients with end-stage renal disease (ESRD). The presence of VC is associated with low bone volume in ESRD patients. Bone metabolism is affected by various factors including sex hormones. However little is known about the sex-specific relationship between VC and incident fractures in ESRD patients. This study investigated whether there was a sex-specific relationship between the degree of VC and incident fracture in ESRD patients starting dialysis.

Methods: This was a retrospective cohort study including 593 incident dialysis patients from a single center. The aortic calcification index (ACI), an estimated of abdominal aortic calcification, was calculated by abdominal computed tomography as a measure of VC. Patients with ACI in the upper tertile range were considered to have high ACI (>25.75). The occurrence of fracture was assessed as study outcome. The association between high ACI and incident fracture was analyzed according to sex.

Results: During a median follow-up duration of 34.7 (0.03 – 147.5) months, 74 patients (12.4%) developed fracture. In the male group (n = 328), the fracture-free survival rate was not different between patients with high ACI and those with low ACI (P = 0.075). In the female group (n = 265), the fracture-free survival rate was significantly lower in patients with high ACI compared to those with low ACI (P = 0.002). In the male group, the high ACI was not associated with incident fracture (unadjusted hazard ratio, 1.96; 95% confidence interval, 0.92 – 4.15; P = 0.080). In the female group, the high ACI was independently associated with incident fracture after adjustments for confounding variables (adjusted hazard ratio, 2.53; 95% confidence interval, 1.29 – 4.98; P = 0.007).

Conclusions: In conclusion, VC is associated with incident fracture in female ESRD patients starting dialysis, while there was no association between VC and fracture in male ESRD patients. There may be a sex-specific relationship between VC and fracture in ESRD patients

TH-PO723

Sex and Racial Disparities in Antidepressant Use and Hospitalization Rates Among Patients on Hemodialysis

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Background: Women are more affected by depression than men in the general population (Kimmel et al., 2007). We characterized if there were differences by sex and race in depressive affect (DA), antidepressant use, and hospitalization rates in hemodialysis (HD) patients.

Methods: We analyzed data of patients on HD treated during 2016 to 2017. We studied patients who completed DA screening via the patient health questionnaire-2 (PHQ2) and the Center for Epidemiologic Studies Depression Scale (CES-D-10). Those with PHQ2≥3 were further screened using the CES-D-10. Patients scoring ≥10 on the CES-D-10 or those with a prior diagnosis of depression or bipolar disorder were classified DA positive; screened patients with PHQ2<3 were classified DA negative. Analyses were stratified by DA status, antidepressant use, sex and race. We compared hospitalization rates between groups.

Results: In a population of 267,955 HD patients, A higher percent of women screened positive for DA when compared to men (6.5% vs 4.4%, respectively). Black women had less DA than white women (5.4% vs 7.5%). Antidepressants use by DA positive white women was 5.4% vs 3% for DA positive black women; DA negative white women had a higher use of antidepressants when compared to DA-negative black women (3% vs 2.3%, respectively). Similar findings were observed for men. Twenty-eight percent of patients were using an antidepressant; of those, 51.5% were women. White women had higher antidepressant use (36.7%), followed by white men (25.8%), black women (23.4%), and black men (15.9%). Hospitalization rates were higher for women than for men irrespective of depressive symptoms, antidepressant use or race ($p<0.0001$), and antidepressant use was associated with higher hospitalization rates when compared to non-users (women: 2.3 vs 1.6 per patient year (ppy, $p<0.0001$); men: 2.2 vs 1.4 ppy ($p<0.0001$)). Black women on antidepressants had higher hospitalization rates than white women (2.51 vs 2.27 ppy, $p<0.0001$).

Conclusions: We identified that women, particularly of black race taking antidepressants, have higher hospitalization rates when compared to those not taking any medication, irrespective of their current DA status. Future studies can elucidate reasons for these disparities in outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO724

Gender Differences in Calcium Nephrolithiasis

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Background: Nephrolithiasis continues to develop as a serious problem in the United States and around the world. As yet, the influence of gender on stone formation is unclear. We hypothesized that females are better adapted to higher urine pH than males. This difference could due to higher levels atrial natriuretic peptide (ANP) in pre-menopausal women compared to corresponding men. Interestingly, ANP levels are similar between older women and men. We have previously implicated transient receptor potential canonical 3 (TRPC3), Ca^{2+} channel, in the proximal tubule (PT), in the regulation of calcium stone formation, and have observed that $TRPC3^{-/-}$ mice show higher Ca^{2+} secretion and scattered urine crystals compared to wildtype (WT) mice. In the present study, we aimed to examine the gender-based role of pH by alkalization in $TRPC3^{-/-}$ mice predisposed with elevated [Ca^{2+}].

Methods: Male and female WT and $TRPC3^{-/-}$ mice were orally administered with either acetazolamide (ACZ), a diuretic for alkalization therapy, and/or calcium gluconate (CaG), a calcium supplement, for 4 weeks. Urine samples were collected weekly and assessed for pH, electrolytes, gene expression and crystals. Serum electrolytes and metabolites were also measured. Kidney tissue was collected for PT cell isolation, Ca^{2+} imaging and assessed for degree of calcification by birefringence and histopathology.

Results: Urine analysis showed more calcium crystals, higher [Ca^{2+}] and higher pH in female (WT and $TRPC3^{-/-}$) mice compared to males indicating. Similarly, calcification, fibrotic and inflammatory markers were elevated in female compared to male mice; and in $TRPC3^{-/-}$ compared to WT indicating stone-forming phenotype. PT cells isolated from treated female mice showed a substantial increase in Ca^{2+} entry when compared to corresponding males suggesting aberrant intracellular Ca^{2+} regulation.

Conclusions: Higher [Ca^{2+}] and higher pH are related to elevated calcium crystal formation. We have identified gender-based influences on stone-forming phenotypes following alkalization and/or elevated [Ca^{2+}], and our findings suggest that female mice are more susceptible to stone formation under these conditions. Our work contributes to understanding the complex combination of gender, age and lifestyle on the evolving epidemiology of nephrolithiasis. Crucially, we have unraveled a role for gender-specific therapies for kidney stone interventions.

Funding: NIDDK Support

TH-PO725

Gender Differences in Presentation and Outcomes Among Patients with Atypical Hemolytic Uremic Syndrome (aHUS)

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Background: Gender differences among patients with aHUS are not well established.

Methods: We describe and compare demographic, clinical and genetic data from female and male patients with a history of aHUS enrolled in the Vienna thrombotic microangiopathy (TMA) cohort.

Results: In this single center study, we identified 51 patients with a first manifestation of aHUS between 1981 and 2019. The median age at diagnosis was 28 years and 63% were female. Kidney biopsies were available from 32 patients (63%) and all but 1 showed features of TMA. At time of presentation 31 patients were dialysis dependent (no data for 3 patients). 23 received plasma and 7 eculizumab therapy. 7 recovered kidney function with therapy (3 eculizumab, 3 plasma exchange, 1 supportive). At last follow-up, 9 were deceased, 3 on dialysis, and 17 had a renal graft. Among the remaining 22 patients, 13 had an eGFR ≥ 60 ml/min per 1.73m^2. Gender specific results are indicated in Table 1.

Conclusions: The majority of aHUS patients enrolled in the Vienna TMA cohort were female. Women presented at younger age, more often harbored disease-causing genetic variants or a *CFH*- or *CD46*-risk haplotype, and had better kidney function at last follow-up as compared to males.

Table 1.

	Female	Male	P
Patients, n (%)	32 (63)	19 (37)	0.09
Age at diagnosis, years (median)	27.5	29.0	0.96
Treatment at presentation			0.63
-Plasma-exchange, n (%)	15 (46.9)	8 (31.6)	
-Eculizumab, n (%)	5 (15.6)	2 (10.5)	
-Supportive, n (%)	11 (34.4)	6 (42.1)	
Age at last follow-up/death, years (median)	35.5	34.0	0.87
Kidney function at last follow-up			0.05
-eGFR ≥ 60ml/min, n (%)	10 (31)	3 (16)	
-eGFR <60ml/min, n (%)	6 (19)	3 (16)	
-Dialysis, n (%)	2 (6)	1 (5)	
-Kidney transplant, n (%)	10 (31)	7 (37)	
-Deceased, n (%)	4 (13)	5 (26)	
Maintenance treatment at last follow-up, n (%)	9 (28)	3 (16)	0.16
-Plasma, n (%)	2 (6)	2 (11)	
-Eculizumab, n (%)	7 (22)	1 (5)	
Disease-causing variants*, n (%)	17 (53)	7 (37)	0.33
Variants of unknown significance, n (%)	2 (6)	1 (5)	
CFH-H3 / CD46ggaac, n (%)	31 (97)	13 (68)	0.01

*no data available in 1, 5 showed no genetic variants

TH-PO726

Women on Dialysis and Health-Related Quality-of-Life Measures

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Background: Dialysis patients have poor health-related quality of life (HRQOL). Gender differences in HRQOL are poorly studied in dialysis patients. We performed a cross sectional study to evaluate HRQOL measures in women on dialysis in the State of Qatar.

Methods: A cross-sectional study in dialysis patients. Demographic and clinical characteristics data were obtained from electronic medical records. We performed 3 questionnaires to assess HRQOL measures.1- The Center for Epidemiologic Studies Depression Scale (CESD-R) with depression diagnosed with score ≥18, 2- Brief Pain Inventory (BPI) to evaluate the severity of patients' pain (0-3 scale) and its impact on daily function. 3- The Pittsburgh Sleep Quality Index (PSQI) (poor sleep with PSQI >5).

Results: We studied 253 diaysis patients (female 137, 96 on peritoneal dialysis (PD), age 56+/-14, BMI 29+/-7). Most patients reported mild or no chronic pain (75.6%). More women had moderate to severe chronic pain than men (30% vs.16% p 0.01). 76.5% of diaysis patients reported poor sleep (81% of women vs. 70% of men p=0.069) and 39% had depression (52% women vs. 25% men $p<0.001$). We identified 3 factors associated with both depression and poor sleep. First, diabetic women on dialysis had more depression and poor sleep than non-diabetics (59% vs. 40% p0.03 and 92% vs. 79% p 0.02 respectively). Second, Women on hemodialysis (HD) had more depression and poor sleep than PD (54% vs. 46% $p>0.05$ and 88% vs. 65% p 0.001 respectively). Third, Older women ≥60 years had more depression (59% vs.42% p0.05) and poor sleep (92% vs. 76% p0.0008) vs. younger women. There was a strong correlation of PSQI score and CES-D score in women only ($R=0.67$ $p<0.0001$). There was no correlation between our studied HRQOL measures in women and calcium, phosphorus, PTH, Kt/V, LDL or vitamin D levels.

Conclusions: We found that women on dialysis had higher prevalence of depression, poor sleep and moderate to severe chronic pain than men. DM, HD and old age were

associated with a higher rate of depression and poor sleep. Understanding gender differences in dialysis patient can help guide treatment for high risk groups.

TH-PO727

The Effect and Safety of Postmenopausal Hormone Therapy and Selective Estrogen Receptor Modulators on Kidney Outcomes in Women: A Systematic Review

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Background: The number of postmenopausal women with or at risk of chronic kidney disease (CKD) is increasing exponentially. The benefits and risks of postmenopausal hormone therapy (PHT) and selective estrogen receptor modulators (SERMs) on kidney health outcomes in these women are poorly understood. This systematic review aimed to: 1) determine the effects of PHT and SERMs on kidney function and albuminuria in women, and, 2) characterize the risk of adverse outcomes of PHT and SERMs in the CKD population, who are already at an increased risk of venous thromboembolism and malignancy.

Methods: An electronic literature search was completed using a peer reviewed search strategy in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. We searched published studies (1950- December 2018) examining the effect of PHT and SERMs on kidney function and albuminuria, and adverse outcomes in women with CKD. Two independent investigators screened identified citations examining the effect of PHT and SERMs on kidney outcomes in the general population of women, as well as adverse outcomes in the CKD population. Data was independently extracted from each eligible study, and the risk of bias was assessed. Results were synthesized in a descriptive manner.

Results: A total of 3,078 references were screened, and 18 studies met eligibility criteria. Compared with no treatment, use of PHT was associated with improved kidney function and unchanged or reduced proteinuria in more than 60% of studies that addressed this question. No studies were identified that reported on the safety of PHT in women with CKD. Studies addressing the effects of SERMs on kidney function were conflicting, with 2 studies reporting increased kidney function and reduced proteinuria, and another reporting decreased kidney function. Based on results from 2 small studies, SERMs did not have any increased risk of venous thromboembolism in women with CKD compared to placebo.

Conclusions: Existing studies suggest that PHT and SERMs are associated with improved kidney function, with no increase in albuminuria. Safety data in the CKD population is lacking. Available studies had significant limitations and heterogeneity, highlighting the need for rigorous prospective studies examining the effect of PHT and SERMs on kidney function, and their safety in CKD.

TH-PO728

Screening for Osteoporosis Represents a Missed Opportunity in Women with ESRD

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Background: Women with end-stage renal disease (ESRD) treated with hemodialysis (HD) have increased morbidity and mortality, and shorter life expectancy. In fact, the survival advantage that women have over men in the general population is markedly decreased in the HD population. The purpose of this study was to explore age-appropriate preventive care for women with ESRD on maintenance HD.

Methods: We performed a cross-sectional survey of adult patients with ESRD undergoing HD in two outpatient dialysis centers at the University of Florida. Interviews were conducted using a survey instrument that contained questions on demographic information, types of health care providers, and a number of preventive measures. We used United States Preventive Services Task Force (USPSTF) guidelines to determine eligibility and completion of screening for breast and cervical cancers as well as osteoporosis.

Results: Of the 132 patients who participated in this study, 66 (50%) were female. The average age of women was 60 (range = 22-84). The majority (95.5%, n=63) reported having a primary care provider (PCP). Out of the eligible patients, 81.4% (35/43) reported being up-to-date on breast cancer screening, 75% (33/44) on cervical cancer screening, and 16.7% (4/24) on osteoporosis screening. Having a PCP was associated with a trend towards higher adherence with preventive care measures.

Conclusions: Our study identifies "osteoporosis screening" as an opportunity to improve preventive care of women with ESRD treated with maintenance HD. The rates of osteoporosis screening were found to be even lower than the general population (i.e. 25%) in this cohort. Interestingly, women reported higher rates of screening for malignancies of breast and cervix compared to the general population. While there has been a shifting paradigm in diagnosis and management of osteoporosis in patients with ESRD, future studies are needed to identify patient and provider characteristics associated with higher likelihood of adherence to age-appropriate preventive care for female patients with ESRD.

TH-PO729

Cardiac Mortality in People with ESKD in Australia and New Zealand: A Cohort Study from 1980 to 2013

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Background: The presence of cardiac disease is an important predictor of mortality in people with ESKD. Therapies for reducing cardiac risk and treatment of cardiac events may be less effective in people with ESKD compared to the general population. We aim to review the standardised mortality ratios from cardiovascular disease (CVD) for people with ESKD in the Australian and New Zealand general population.

Methods: Cohort study of incident people with ESKD in Australia and New Zealand, 1980-2013. ANZDATA was linked with death registries to obtain cause of death. Summary data for cause specific death in the general population were obtained. We calculated mortality rates for CVD as defined by ICD10 codes and standardised mortality ratios (SMRs with 95% confidence intervals [CI]), compared with the general population, using indirect standardisation, by age, sex and calendar year.

Results: There were 60,823 participants contributing 381,874 years of observation time. In total there were 6847 cardiac deaths of which 5947 (86.9%) were ischaemic heart disease deaths. The rate of cardiac mortality compared to the general population was higher in women (women: SMR 8.3 95%CI 8.0-8.6, men: SMR 5.695%CI 5.5-5.8). Young women were particularly affected having over double the increased rate of cardiac mortality relative to the general population (ages 30-49: women: SMR 59.7 95%CI 51.8-69.0, men 17.7 95%CI 15.9-19.7). Relative cardiac mortality rates have improved over time for women but have been stable in men (Figure 1).

Conclusions: The mortality rates in the Australian and New Zealand ESKD population are higher than the general population. Young women with ESKD have an excessive relative risk of dying from cardiac disease, compared to young females in the general population. The relative risk of women dying from cardiac disease has reduced over time.

Funding: Government Support - Non-U.S.

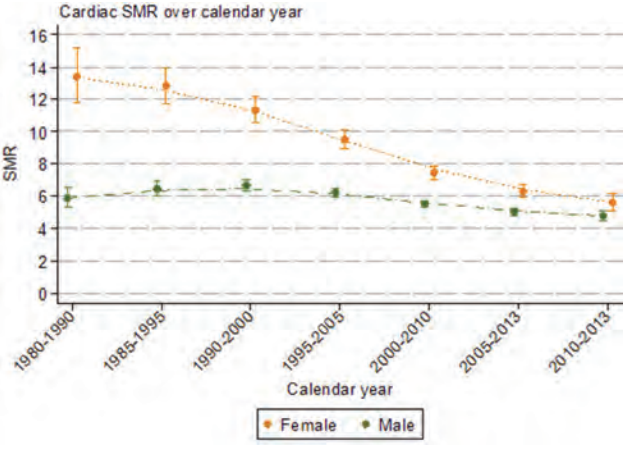

FIgure 1. Standardised mortality ratios for cardiac death over time

TH-PO730

Bisphosphonate Utilization Across the eGFR Spectrum

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Background: KDIGO currently recommends bisphosphonate (BSP) use for osteoporosis patients with CKD G3a-G3b who have normal PTH and high risk of fractures. This study evaluated the frequency and factors associated with BSP use among osteoporosis patients from two healthcare organizations: Geisinger (2006-2017), Pennsylvania, United States; and Stockholm region (2006-2012), Sweden.

Methods: Incident osteoporosis was defined as the first ICD code for osteoporosis, and BSP use was defined as the prescription (Geisinger) or dispensation (Stockholm) of any BSP 6 months prior or up to 3 years following the diagnosis of osteoporosis. BSP use was compared across eGFR categories, accounting for the competing risk of death using multinomial logistic regression.

Results: There were 15887 women and 3200 men in Stockholm and 23645 women and 7026 men in Geisinger with incident osteoporosis. Overall, BSP use was 55% in Stockholm and 36% in Geisinger, with lower rates in the groups with eGFR <45 ml/min/1.73m^2. After adjustment for age and identified confounders, the odds of BSP prescription dropped progressively with lower eGFR, particularly in those with eGFR<60ml/min/1.73m^2 (Figure 1). In Geisinger, BSP use declined significantly over time.

Conclusions: Our results suggest that BSP use is not high in incident osteoporosis, with infrequent use in lower eGFR. Although we lacked data on PTH and fracture risk

score, this study raises concern about osteoporosis under-treatment in patients with eGFR 30-60ml/min/1.73m^2.

Funding: Other NIH Support - R01 DK115534 01A1;

Figure 1.

TH-PO731

Contraceptive Use and Elective Terminations in Women with Glomerular Disease

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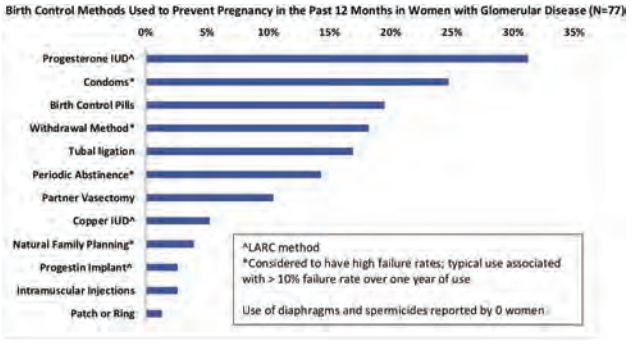
Background: As pregnancy with glomerular disease is considered high-risk, proactive planning is desired. Contraceptive preferences, including use of long-acting reversible contraception (LARC) that avoids estrogen associated hypertension (HTN) and venous thromboembolism (VTE), as well as elective termination rates in this population are largely unknown.

Methods: A women's health survey was distributed by email, mail and in-person to women ages 18-65 in the Glomerular Disease Collaborative Network, a prospective registry in the southeastern United States (US). This analysis was restricted to reproductive age women (< 50 years). Fisher's exact test assessed the association of elective terminations with race and disease type.

Results: Of 106 included (response rate 14.2%), the mean age was 36.7, BMI was 30.8 kg/m^^2, and 17.9% were African-American (AA). The most common diseases were IgA nephropathy (27.4%), Lupus nephritis (22.6%), FSGS (17.0%) and ANCA vasculitis (13.2%). Half (54.7%) had HTN, 23.6% were past or current smokers and 12.3% reported prior VTE. Over one-third (38%) were either unsure or did not believe that kidney disease increases risk for pregnancy complications. A total of 72.6% utilized a birth control method in the past 12 months to prevent pregnancy; one-third of which endorsed ≥ 2 methods in that period. The most common methods included progesterone intrauterine device, condoms, pills, and withdrawal (see figure). At least one elective termination was reported by 16.0% and was higher in AA vs non-AA women (31.6% vs 12.6%, p= 0.08) though not statistically significant.

Conclusions: LARC use within the past 12 months was remarkably high, yet 61.1% endorsed methods associated with high failure rates. This data precludes distinguishing between concurrent use of multiple methods vs single successive methods. Elective termination rates were not significantly different among subgroups and overall rates appeared lower than the general US population (24% by age 45) but this may be due to underreporting.



TH-PO732

Contraceptive Use Among Women with ESKD on Dialysis in the United States

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Background: Pregnancy in women with end-stage kidney disease (ESKD) is challenging. Nephrologists do not routinely counsel dialysis patients about contraception and little is known about contraceptive use in women with ESKD.

Methods: Using the United States Renal Data System from 1/1/2005 to 12/31/2014, we evaluated for each calendar year women aged 15-44 years who were on dialysis and had Medicare as the primary payer for the entire year. We studied trends in the use of contraceptive methods and used multivariable logistic regression with covariates and year, with subject as a repeated effect, to determine factors associated with contraceptive use.

Results: The study cohort included 36,450 women with 122,982 person-years. Mean maternal age was 34±6 year. Rate of any form of contraceptive use during the study period was 7.3 per 100 person-years (PHPY). Contraceptive use increased significantly from 2005 to 2014 (9.2 PHPY vs. 5.4 PHPY). From 2005 to 2014, the rate of intrauterine device insertions increased from 0.8 PHPY to 2.6 PHPY, tubal ligation rate increased from 0.4 PHPY to 0.2 PHPY, implant insertion rate increased from 0.1 to 0.4 PHPY, and hysterectomy rate increased from 1.6 PHPY to 3.7 PHPY. All races except Asians had a consistent increase in contraceptive use from 2005-2014. Compared to women aged 20–24 years, the contraception use was lower in women aged 25-29 years (OR, 0.81; CI, 0.74-0.89) and 30–34 years (OR, 0.65; CI, 0.41-0.77). As compared to white women, Asian women had lower contraceptive use (OR, 0.81; CI, 0.69-0.96) and Native American women had higher contraceptive use (OR, 1.34; CI, 1.09-1.64). As compared to women residing in southern areas, contraceptive use was lower in women residing in northeastern areas (OR, 0.85; CI, 0.77-0.93). Women with ESKD due to glomerulonephritis had higher contraceptive use than women with ESKD due to diabetes (OR, 1.20; CI, 1.10-1.31).

Conclusions: There has been a statistically significant increase in contraceptive use in women with ESKD on dialysis in the last decade. Younger age, Native American race, and ESKD due to glomerulonephritis were associated with higher likelihood of contraceptive use in ESKD patients.

TH-PO733

Racial Disparities and Factors Associated with Pregnancy in ESKD Patients on Dialysis in the United States

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Background: Pregnancy in women with end-stage kidney disease (ESKD) undergoing dialysis is not common due to impaired fertility. Literature concerning pregnancy in the dialysis population is scarce.

Methods: We evaluated a retrospective cohort of 47,667 women who were aged 15-44 years and were on dialysis between January 1, 2005 and December 31, 2013 from the United States Renal Data System, with primary Medicare claims data, and who carried Medicare as the primary payer throughout 40 weeks of follow-up. We calculated pregnancy rates, and using multivariable proportional intensity recurrent event survival analysis, we identified factors associated with pregnancy including race.

Results: Overall, 2354 pregnancies were identified in 47,667 women on dialysis. The pregnancy rate was 17.7 per thousand person-years (PTPY) (95% confidence interval (CI), 17.0-18.5), and was roughly stable over the nine calendar years. Native American, Hispanic, and black women had higher rates of pregnancy than did Asian or white women (23.2, 22.2, 19.2, 15.6 and 12.8 PTPY, respectively). Women on hemodialysis had a higher rate of pregnancy than did women on peritoneal dialysis (19.3 vs. 9.3 PTPY). In the adjusted survival analysis, a higher likelihood of pregnancy was seen in Hispanic women (HR, 1.65; CI, 1.42-1.91), Black women (HR, 1.47; CI, 1.29-1.66), and Native American women (HR, 1.94; CI, 1.43-2.64) than in white women; in women with ESKD due to malignancy (HR, 1.59; CI, 1.22-2.07), miscellaneous causes (HR, 1.50; CI, 1.25-1.80), glomerulonephritis (HR, 1.47; CI, 1.26-1.70), hypertension (HR, 1.41; CI, 1.22-1.64), and secondary glomerulonephritis/vasculitis (HR, 1.25; CI, 1.06-1.48) than with ESKD due to diabetes; and in women residing in the northeast (HR, 1.29; CI, 1.14-1.47) and midwest (HR, 1.20; CI, 1.06-1.35) than in the south. A lower likelihood of pregnancy was seen among women on peritoneal dialysis than on hemodialysis (HR, 0.45; CI, 0.39-0.53).

Conclusions: Factors associated with a higher likelihood of pregnancy includes race (Hispanic, black, and Native American), ESKD cause (glomerulonephritis, vasculitis, neoplasm, and hypertension), geographical region (northeast and midwest), and hemodialysis modality. This study improves our understanding of pregnancy in patients with ESKD.

TH-PO734

Urinary Extracellular Vesicles miR-143-3p: A Novel Candidate Biomarker for Preeclampsia

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Background: Preeclampsia (PE) is a complex pregnancy-associated disorder which is characterized by new-onset hypertension and proteinuria (>300mg) after 20 weeks of gestation. Recent study from our group showed that number of podocytes-derived urinary

extracellular vesicles (EVs) were increased in pregnant women with PE but their content of bioactive molecules are not known. Aim of this study was to assess differential expression of miRNAs in urinary EVs from pregnant women with and without PE.

Methods: Bio-banked cell-free urines from pregnant women with (n=5) and without (normotensive; n=5) PE were used for miRNA expression in urinary EVs. The expressions of miRNAs within urinary EVs were identified by XRNA Exosome RNA-Seq Library Kit. Validation of significantly changed candidate miRNAs between groups was performed by qPCR in the independent cohort of patients with (n=15) and without (n=15) PE. Sn-U6 and cel-miR-39 were used as reference and spike-in control respectively for data validation.

Results: A total of 184 miRNAs were identified in urinary EVs by RNA sequencing analysis whereas twenty eight miRNAs were significantly ($P<0.05$) changed in pregnant women with PE compared to women without PE. Selected candidates of 12miRNAs involved in renal pathophysiological processes were validated by qPCR. Among 12, only miR-143-3p remained significantly increased ($P<0.018$) in PE patients (both early (PE diagnosed <34 weeks) and late (>34 weeks) PE) compared to normotensive controls. The miR-95-3p was significantly decreased ($P<0.048$) only in patients with early PE. There was no correlation between changed miRNAs and urinary protein concentration. ROC analysis for miR-143-3p yielded an AUC of 0.776 and for miR-95-3p AUC=0.659.

Conclusions: Differential expression of miR-143-3p and miR-95-3p in urinary EVs from pregnant women with PE compared to normotensive pregnant women could be a new candidate biomarker for preeclampsia.

TH-PO735

Characterizing Fetal Outcomes in Women with Biopsy-Proven Primary Glomerular Disease

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Background: It is well known that women with chronic kidney disease are at higher risk for worse maternal and fetal outcomes. However, the extent of these risks in women with biopsy proven primary glomerular disease has not been well described. This study aims to further characterize pregnancy outcomes in this population.

Methods: A database of women seen in a Pregnancy and Kidney Disease clinic at a tertiary care centre in Toronto, Canada was searched from January 2003 until July 2018 to identify women with biopsy-proven primary glomerular disease who had at least one pregnancy managed in this clinic. The primary study outcome was the live birth rate. Secondary study outcomes included birthweight, premature birth, spontaneous abortions and perinatal death (defined as stillbirth >20 weeks or neonatal death).

Results: 218 pregnancies in 148 women (IgA nephropathy *n*=79, FSGS *n*=69, membranous nephropathy *n*=23, hereditary nephritis *n*=21, membranoproliferative glomerulonephritis *n*=15, minimal change disease *n*=11), were identified. Of these, 84.6% resulted in a live birth. 35.6% were born under 37 weeks gestational age (GA), with 29.7% of these at less than 32 weeks GA. 57 babies were born under the tenth percentile for their GA, 26.3% of these babies were less than the third percentile. There were 23 spontaneous abortions (SA) at less than 10weeks GA and 5 SA at 10-20weeks GA. In this cohort, 3.9% of pregnancies resulted in perinatal death.

Conclusions: Women with biopsy-proven glomerular disease are at high risk of adverse fetal outcomes. Further work needs to be done to characterize fetal outcomes by sub-category of glomerular disease, as well as to examine maternal outcomes.

TH-PO736

FGFR4 Is Not Required for the Development of Cardiac and Renal Hypertrophy in Pregnancy

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Background: Pregnant women develop cardiac and renal hypertrophy as an adaption to increased blood volume, which is reversible without causing organ injury. Fibroblast growth factor (FGF) 23 is a bone-derived hormone that increases phosphate excretion by targeting the kidney via FGF receptor (FGFR) 1 and klotho. In chronic kidney disease, high FGF23 levels are associated with cardiovascular injury and can directly induce cardiac hypertrophy. FGF23 binds to FGFR4 on cardiac myocytes in a klotho-independent manner, thereby activating pro-hypertrophic signaling. In injured kidneys, FGF23/FGFR4 signaling promotes fibrosis. Here, we investigated whether FGF23/FGFR4 signaling contributes to cardiac and renal hypertrophy during pregnancy.

Methods: Virgin female C57BL/6J wildtype (WT), FGFR4 knockout (KO), and FGFR4-385R/R knockin (KI) mice were mated with proven male breeders. After 24 hours, males were removed, and females were sacrificed after 18 days in late pregnancy (LP). Age-matched, non-pregnant (NP) females served as controls. Heart and kidney mass and serum levels of FGF23, phosphate and calcium were determined. Heart and kidney tissue were further analyzed by qPCR.

Results: WT and KO mice develop cardiac and renal hypertrophy in LP, indicated by increased heart weight/tibia length and kidney weight/tibia length ratios when compared to respective NP controls. This effect is not observed in pregnant KI mice. Serum FGF23 increases in LP in all three genotypes. In WT-LP mice, serum calcium levels increase, while serum phosphate is unchanged when compared to WT-NP controls. Furthermore, cardiac *Fgfr1* mRNA levels are reduced, and *Fgf23* and *Fgfr4* increased. In the kidney, *Fgf23, Fgfr1, Fgfr4* and *NaPi2c* mRNA levels are unchanged, while *NaPi2a* is decreased, and *klotho* and *Pit2* are elevated.

Conclusions: In LP, mice develop cardiac and renal hypertrophy and have elevated serum FGF23 levels. However, in this context FGFR4 does not seem to be required for the development of organ hypertrophy. Surprisingly, we found that activation of FGFR4 inhibits organ hypertrophy suggesting anti-hypertrophic actions of FGF23/FGFR4 signaling in pregnancy, which requires further mechanistic studies.

Funding: Other NIH Support - NHLBI, Government Support - Non-U.S.

TH-PO737

VEGF-Based Apheresis: A Targeted Therapy for Preeclampsia

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Background: Preeclampsia is a pregnancy specific complication, occurring in 6 – 8 % of pregnancy cases and is the leading cause of 76,000 maternal and 500,000 prenatal deaths per year worldwide. Due to the current lack of effective treatment options and its high prevalence, developing an effective therapy for preeclampsia is of great importance. Based on the insight that elevated sFlt-1 plasma levels, by decoying VEGF and PlGF leads to preeclampsia, in the current study we set out to develop a highly specific sFlt-1 adsorption strategy to treat preterm preeclampsia.

Methods: According to *in silico* modeling a number of novel sFlt-1 ligand variants were generated and characterized by determination of equilibrium dissociation constant of the receptor binding affinity. The most affine candidates were chosen for immobilization on an optimized apheresis column. Binding efficiency, unspecifically bound proteins as well as release of VEGF and PlGF were analyzed in *ex vivo* experiments employing serum samples of patients with preeclampsia.

Results: We were able to successfully engineer an array of VEGF-variants with varying affinity to sFlt-1. One of them with a higher affinity to sFlt-1 than all its known isoforms. This VEGF molecule variant not only effectively captures sFlt-1, but additionally competes with and liberates both endogenous VEGF and PlGF. In experiments employing serum samples from 10 patients with preeclampsia this system yields 80% reduction of sFlt-1, while releasing around 85% PlGF and VEGF.

Conclusions: In this study we demonstrate a novel apheresis set up which enables adsorption of up to 80% of circulating sFlt1 with highest specificity, while further restoring angiogenic balance by liberating PlGF and VEGF. Our system is directly applicable for further testing in large animal models of preeclampsia, which is crucial to evaluate the effect of VEGF release on the pregnancy. In the future, our variants may allow for personalized and targeted therapy of preeclampsia at different stages of the disease.

TH-PO738

Infertility and Pregnancy Loss in Hispanic/Latino Women with CKD: Results from the Hispanic Community Health Study/ Study of Latinos (HCHS/SOL)

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Background: Hispanic/Latino individuals are less likely to be screened or receive optimal CKD treatment. This may be particularly detrimental for reproductive age women as CKD has been associated with infertility, menstrual irregularities, and pregnancy loss.

Methods: Using data from the HCHS/SOL baseline (2008-2011) and second study visits (2014-2017), we assessed CKD and self-reported infertility, cessation of menses, and nonviable pregnancy loss (<24 weeks gestation) in women age 18-45 years old. CKD was defined as one of the following at both study visits: albuminuria (urine albumin:creatinine [UACR] >30 mg/g) or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2. To capture mild CKD and variation in visit measurements, we also included those with UACR >300 mg/g at any visit, eGFR <60 mL/min/1.73m^2 at one visit and <70 mL/min/1.73m^2 at the other, or if baseline UACR >30 mg/g while on RAAS-blockade. Survey-specific analyses were used to account for the two-stage probability sampling design. Multivariable survey logistic regression derived prevalence odds ratios (OR) with 95% confidence intervals for our outcomes of interest. Using a 10% change-in-estimate approach, covariates considered were age, body mass index (BMI), hypertension (HTN) and diabetes (DM).

Results: Of 2,589 included, 4.6% had CKD. Women with CKD were older (41 vs 38), had a higher BMI (34 kg/m^2 vs 30 kg/m^2), and more DM (32% vs 11%) and HTN (42% vs 12%). In adjusted analysis, those with CKD did not have a significantly increased odds of infertility, cessation of menses, or nonviable loss (see table). Among 635 women with pregnancies occurring specifically between baseline and second visit, the OR of nonviable loss with CKD was 1.7 (95% CI 0.5-5.8) but not statistically significant.

Conclusions: In this Hispanic/Latino cohort, CKD was uncommon and not associated with our outcomes of interest but our sample size limited statistical power. Considering the temporality of CKD diagnosis and pregnancy in a larger sample warrants further study.

		Infertility		Cessation of Menses		History of Nonviable Loss (total N= 2277, no CKD N= 2167, CKD N= 112)	
Characteristic	N	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Unadjusted OR (95% CI)	Adjusted^ OR (95% CI)	Unadjusted OR (95% CI)	Adjusted^ OR (95% CI)
No CKD	2469	Reference	Reference	Reference	Reference	Reference	Reference
CKD	120	1.20 (0.49-2.95)	1.08 (0.42-2.75)	2.15 (1.15-4.00)	1.30 (0.52-3.27)	0.82 (0.50-1.33)	0.78 (0.47-1.29)

*Adjusted for presence of DM

^Adjusted for age

TH-PO739

Intrapartum Sildenafil Therapy Does Not Impair Renal Function in Young Adult Offspring of Preeclamptic Dahl S Rats

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Background: Up to 10% of pregnancies are complicated by preeclampsia, and up to 15 million Americans are offspring of preeclamptic pregnancies. The Developmental Origins of Health and Disease hypothesis proposes that an adverse intrauterine environment programs the fetus to increased susceptibility to hypertension and renal function loss. We have shown that sildenafil citrate, a phosphodiesterase-5 (PDE-5) inhibitor, improves the maternal syndrome of preeclampsia in the Dahl S rat and reduces blood pressure of their offspring up to 21 weeks of age; however, long term kidney function in these offspring has not been examined. We hypothesized that PDE-5 inhibition during preeclamptic pregnancy improves long-term BP without significant reduction in renal function.

Methods: Female Dahl S rats on a 0.3% salt diet were mated and treated orally with sildenafil (50 mg/kg/day) or vehicle from gestational day 10 to delivery. Lactating dams and offspring were on normal chow for the duration of the study, and measurements were made at 12 weeks of age. Urine was collected (n=18-27/group) for measurement of urinary protein (Bradford assay) and creatinine (Jaffe reaction). Plasma was also collected at euthanasia (n=13-17/group) for measurement of blood urea nitrogen (BUN, enzymatic method) and creatinine, and creatinine clearance was calculated.

Results: Systolic BP (n=5-9/group, tail cuff) was greater in Dahl S rats of untreated mothers compared to offspring of sildenafil treated dams (VEH: 177±4 mmHg; SLD: 158±2 mmHg; p=0.0001). BP data were pooled due to lack of significant sex differences between treated groups. No significant differences in proteinuria were observed (VEH male: 102±8; SLD male: 101±8; VEH female: 55±5; SLD female: 75±6 mg/day). No significant differences in BUN were found between either sex or treatment group (VEH: 20.3±0.8; SLD: 18.16±0.7 mg/dL). While expected sex differences in creatinine clearance were maintained, there was no significant difference between the treatment groups (VEH male: 0.75±0.05; SLD male: 0.70±0.05; VEH female: 0.56±0.07; SLD female: 0.64±0.06 mL/min/g renal mass).

Conclusions: These data support the hypothesis that the use of a PDE-5 inhibitor during preeclamptic pregnancy improves the long-term BP without reduction of renal function in the offspring at 12 weeks of age.

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TH-PO740

Obstetric Complications in Pregnant Dialysis Patients

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Background: Obstetric complications, including spontaneous abortion (SAB) and pre-term labor (PTL), are more common in dialysis patients than the general population. Information, however, is limited by small numbers of patients studied. To examine these complications and the risk factors for their development in a national cohort, we queried the United States Renal Data System (USRDS).

Methods: Women ages 14 to 50 years starting dialysis between 2004-2011 were included. ICD-9 codes from hospital, physician, or detailed claims identified pregnant patients with SAB or PTL. CMS Form 2728 was used to identify demographics and etiology of ESRD. Generalized linear models were used to estimate the adjusted relative risk (aRR) of each outcome.

Results: There were 1393 pregnancies, with mean maternal age 34±9, 40% white race, and 91% on hemodialysis. ESRD etiologies were: 43% diabetes, 7% hypertension (HTN), 29% SLE, 18% glomerulonephritis (GN), and 3% polycystic kidney disease. The incidence of SAB and PTL was 7% and 10%, respectively. For SAB, there were no differences between ESRD causes. For PTL, the incidence was higher in those with renal failure from HTN, SLE, and GN. The aRR of SAB was higher in non-white, non-black race [2.30] and decreased with increasing maternal age [0.96]. For PTL the aRR increased with pre-eclampsia [1.66], eclampsia [2.00] and intrauterine growth retardation [3.56]. Risk of PTL decreased with increasing maternal age [0.91] and a diagnosis of septicemia [0.58].

Conclusions: SAB and PTL are common obstetric complications in pregnant ESRD patients and greatest in those with ESRD from HTN, SLE, and GN. It is unclear from this work why the risk of complications was decreased in older patients; however we would speculate that younger patients have higher prevalence of SLE, and thus more extensive systemic disease. Similarly, we would suggest that septic patients received more intensive medical therapy and pre-term care, decreasing the risk of complications. Understanding the high-risk groups for complications may improve pre-term care and outcomes.

TH-PO741

Successful Pregnancies In Kidney Transplant Recipients with Complement-Mediated Thrombotic Microangiopathy

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Background: Pregnancies in patients with complement gene variant mediated thrombotic microangiopathy (cTMA) are challenging, and pregnancies in such patients after kidney transplantation (KTX) even more so.

Methods: We identified pregnancies of patients enrolled in the Vienna TMA cohort and report maternal demographics and pregnancy as well as delivery outcomes of eight pregnancies after KTX in three genetically high-risk cTMA patients (Case 1: CFH, CFI, CFHR1, CFHR3, and CD46 variants. Case 2 & 3: CFH and CD46 variants).

Results: The three women were 21±2 years of age at cTMA manifestation, 25±1 years of age at KTX, and 32±2 years of age at their latest deliveries. Preventive plasma therapy was used in three pregnancies, and one patient had ongoing eculizumab (ECU) therapy during two pregnancies. Six out of eight pregnancies (75%) resulted in the delivery of healthy children, all of them appropriate for gestational age (delivery at gestational week 38±1.5; one preterm, case 1/pregnancy 4; two caesarean sections; four vaginal deliveries). The mean birth weight was 3305±317g, the mean birth length was 50±1cm, and the mean head circumference was 34±1cm. In addition, one pregnancy is still ongoing at gestational week 28+5 (case 3/pregnancy 5). The other two included one early abortion (case 3/pregnancy 1 at gestational week 12 during ongoing ECU therapy) and one late fetal death (case 1/pregnancy 3 at gestational week 33+3), most likely not related to complement dysregulation. Kidney transplant function after delivery remained stable in all but one pregnancy (case 2/pregnancy 3). In this latter case, a severe cTMA flare occurred after delivery despite use of preventive plasma infusions. Kidney graft function could be rescued in this patient by terminal complement blockade.

Conclusions: Successful pregnancies can be accomplished in kidney transplant recipients with a history of cTMA. We used preemptive plasma therapy or ongoing ECU treatment in selected cases. Thus, becoming pregnant can be encouraged in kidney transplant recipients with native kidney cTMA. Extensive preconception counseling, however, is mandatory in such cases.

TH-PO742

Feto-Maternal Cross-Talk via Extracellular Vesicles and Sterile Inflammation During Preeclampsia Reprograms the Offspring for Increased Risk of Anti-GBM Disease

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Background: Gestational vascular diseases such as preeclampsia (PE) are associated with maternal and fetal morbidity and mortality. PE is often associated with intra-uterine growth restriction (IUGR) predisposing for diseases later in life. We have shown that maternal extracellular vesicles (EVs) and platelets promote PE and placental sterile inflammation. We now aim to evaluate whether fetal re-programming due to EV induced pregnancy complications may predispose the offspring to an increased risk of renal diseases later in life.

Methods: EVs were injected in pregnant C57Bl/6 mice and pregnancy outcome (fetal death, IUGR, renal pathology) was studied. Proteinuria, renal histology, blood pressure and sFlt-1 was measured in the mother to establish PE-like symptoms. Embryonic and neonatal kidneys were evaluated for in-utero reprogramming. Offsprings from control and EV injected mothers were subjected to glomerulonephritis using anti-GBM serum and kidneys were studied for signs of renal disease.

Results: EV injections resulted in PE in the mother and IUGR in embryos and low birth weight. Whole embryos and neonatal kidneys from EV injected PE-mothers showed enhanced basal inflammasome activation (elevated NLRP3, cleaved IL-1β expression) indicating in-utero reprogramming. Anti-GBM serum injections into offsprings (age 8 weeks) from EV injected PE-mothers showed elevated albuminuria, impaired glomerular pathology (PAS staining), enhanced inflammasome activation, KIM-1 expression and reduced nephrin expression in kidneys compared to control offsprings (no PE) exposed to anti-GBM serum. Mechanistically, maternal EVs were taken up by trophoblast cells and reached the embryonic circulation. Maternal EVs contained bioactive cargos such as RNA and IL-1β. Importantly, exposure of EVs to RNase prior to injection or inhibition of IL-1R-signaling using anakinra abolished the inflammatory effects of maternal EVs on the embryo.

Conclusions: These results show that increased maternal EVs affect the embryo proper in addition to acute pregnancy complications. These effects on embryos persist during pregnancy and increase the risk for renal diseases in later life. Further studies are required to evaluate the mechanisms by which EVs can possibly cross the placenta predisposing the offspring to deleterious health effects.

TH-PO743

Maintaining Low Mean Blood Pressure Reduces Severe Adverse Events in Pregnant Women with IgA Nephropathy: A Single-Center Retrospective Study

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Background: A number of young female patients with IgA nephropathy experience pregnancy because the disease population peaks at adolescent age. The clinical course of IgA nephropathy varies; therefore, not all cases receive treatment and follow-ups. However, the risk of pregnancy outcomes among the females with different disease severity and past treatment is not well-known.

Methods: Patients with IgA nephropathy who underwent perinatal care at our institution for 8 consecutive years were recruited for this study. We collected the clinical data by reviewing medical records of patients. Further, we analyzed the correlation between pregnancy outcomes and baseline characteristics, including age, BMI, eGFR, urinary protein (UP), mean blood pressure (MBP), anti-hypertensive drugs use, and past treatment for IgA nephropathy at the time of referral. We set the occurrence of severe adverse events (SAE) as primary outcome and preterm delivery (PreD), small for gestational age (SGA) infants, and low infant birth weight (LBW) as secondary outcomes. We performed logistic regression analysis for each outcome. According to CKD stages, eGFR and UP were categorized into 5 stages and 3 stages, respectively.

Results: We observed 33 pregnancies of 27 patients. Median age was 31 years, median eGFR was 95.5 ml/min/1.73 m^2, and median UP was 0.11 g/gCr. SAE occurred in 9 pregnancies. Age (OR = 1.26, p = 0.021), UP stage (OR = 2.92, p = 0.029), MBP (OR = 1.24, p = 0.01), and past methylprednisolone pulse therapy combined with tonsillectomy (OR = 0.14, p = 0.033) were the candidate predictor according to the univariate analysis. Consequently, MBP (OR = 1.33, p = 0.049) was the only predictor for SAE according to the multivariate analysis. Among PreD, SGA, and LBW, univariate analysis showed statistical significance in baseline characteristics as candidate predictors for SAE. However, multivariate analysis showed no statistical significance among those candidates.

Conclusions: Univariate analysis showed that less proteinuria, lower MBP, and treatment with combined therapy reduce risk of SAE, whereas multivariate analysis showed that MBP is the only predictor for SAE. Our study implies that patients with IgA nephropathy should receive treatments until their blood pressure normalizes before initiating pregnancy.

TH-PO744

Animal Models of Preeclampsia: A Renal Perspective

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Background: Preeclampsia is a heterogeneous syndrome with different pathophysiological subtypes. Many animal models have been proposed, each based on different pathophysiology. The preeclampsia phenotype may differ depending on the model, the lab or personnel, or the animal supplier. Whereas some models reproduce the glomerular endotheliosis observed in preeclamptic women, others cause hypertensive renal injury. This systematic review examines the types of measurements performed to assess renal damage in papers that use animal models of preeclampsia.

Methods: PubMed and EMBASE were searched to identify articles using animal models of preeclampsia, published between January 2000 and September 2016. The search strategy included terms for hypertensive pregnancy disorders and term lists for identifying animal studies. Two independent reviewers followed standardized screening and abstraction protocols. Detailed information was abstracted from papers that included a common (>20 publications) model.

Results: 364 papers included a common model (NOS inhibition: n=112 (22%), reduced uterine perfusion pressure or subrenal aortic coarctation: 101 (19.8%), sFlt-1: 35 (6.9%), low dose endotoxin: 33 (6.5%), NaCl administration: 28 (5.5%), transgenic human angiotensinogen renin: 25 (4.9%), agonistic autoantibodies against the angiotensin II type 1 receptor: 23 (4.5%), or NaCl and corticosteroids: 20 (3.9%). 80.5% of studies reported maternal blood pressure. 44.2% measured proteinuria. Renal histopathology was rarely examined (12.4%). The proportion of papers that measured each characteristic was highly variable among models (blood pressure: 43% to 100% (range), proteinuria: 21% to 95%, renal histopathology: 5% to 40%). The proportion of papers reporting proteinuria and renal histopathology did not differ between papers with vs. without a preclinical agent. 40 (11%) studies acknowledged that the model may not apply to all preeclamptic women.

Conclusions: Renal histopathology is rarely reported, suggesting a need for better characterization of renal changes caused by preeclampsia models and preclinical agents. This is particularly important given that hypertensive renal injury observed in some models differs from the glomerular endotheliosis observed in preeclamptic women.

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TH-PO745

Mechanisms of Vascular Dysfunction in the Interleukin-10-Deficient Murine Model of Preeclampsia

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Background: Preeclampsia (PE) is characterized by new-onset hypertension, proteinuria, endothelial dysfunction, and both macrovascular and microvascular injury in the second half of pregnancy. Based on observations that PE is associated with derangements in IL-10 signaling, we sought to test the hypothesis that endothelium-dependent vascular dysfunction is exacerbated in a murine model of PE based on the administration of human PE sera to interleukin (IL)-$10^{-/-}$ mice.

Methods: Pregnant wild type (WT) and IL-$10^{-/-}$ mice were injected with either normotensive (NT) or severe preeclamptic (sPE) patient sera on the 10th day of gestation. Blood pressure was measured at the beginning of pregnancy and before sacrifice on the 17th day of gestation. Vasomotor function of isolated aortas, albuminuria, and aortic gene expression were assessed.

Results: Pregnant IL-$10^{-/-}$ mice injected with sPE sera exhibited higher blood pressure (P = 0.002) and albuminuria (P = 0.0066) compared to controls. Contractions of the isolated aortas to phenylephrine were significantly augmented in the IL-$10^{-/-}$ mice injected with sPE sera compared to the pregnant controls (P < 0.001). This group also demonstrated impaired endothelium-dependent relaxation to acetylcholine compared to controls (P = 0.002). Treatment of isolated aortas with indomethacin normalized vascular reactivity of aortas derived from pregnant IL-$10^{-/-}$ mice injected with sPE sera (contraction: P = 0.009; relaxation to acetylcholine: P < 0.001).

Conclusions: In aggregate, this murine IL-$10^{-/-}$ PE model exhibits significant pregnancy-specific macrovascular dysfunction caused by enhanced contraction to phenylephrine and impaired endothelium-dependent relaxation. Observed alterations in vasomotor function are predominantly caused by enhanced activation of the cyclooxygenase pathway.

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TH-PO746

Maternal and Fetal Outcomes in Women with CKD Diagnosed During Pregnancy

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Background: Diagnosis of Chronic Kidney Disease (CKD) during pregnancy, has increased in recent years. It is associated with worst outcomes for the mother and the baby. Mexico has one of the highest incidence of CKD, but, little is known about the impact of CKD in our population. The purpose of this work is to present the outcomes in a cohort of Mexican women with CKD diagnosed during pregnancy.

Methods: A prospective observational study, 32 pregnant women with CKD were included with quarterly follow-up until three months after delivery and were compared with 117 age matched pregnant woman without CKD for hypertensive disorders of pregnancy, gestational age, low birth weight, preterm delivery and relevant clinical kidney events.

Results: No differences were found in baseline characteristics except for the serum creatinine. Hypertension was associated with CKD (P=0.001). Women with CKD had a greater number of caesarean sections (P=0.001), and their babies had lower birth weight, gestational age, and preterm delivery (P=0.006, 0.001 and 0.007 respectively). During pregnancy three patients required renal replacement therapy (RRT), which started at 8.6±4.1 gestational weeks. Two of them continued in RRT after the delivery. Only 19 (59.4%) of CKD patients went to the follow-up, eight (66.7%) of 13 patients with a hypertensive disorder of pregnancy were classified as chronic hypertension, and nine (90%) of 10 patient had persistent proteinuria. No deaths were reported during the follow-up.

Conclusions: CKD is associated with worse maternal and fetal outcomes. In our country, it is necessary to implement strategies to allow diagnosis of CKD during or ideally before pregnancy, a close follow-up by nephrologist and evaluate the impact of its intervention in maternal and fetal outcomes.

Table 1. Maternal and fetal outcomes

	CKD n= 32	Without CKD n= 117	*P*
Hypertension	16 (50%)	24 (20%)	**0.001**
Hypertensive disorders of pregnancy			
Before 20 GW	4 (25.0)	5 (20.8)	
After 20 GW	2 (12.5)	4 (16.7)	0.267
Preeclampsia	7 (43.8)	4 (16.7)	
Chronic hypertension	3 (18.8)	9 (37.5)	
Delivery			
Vaginal	6 (20)	47 (45.6)	**0.001**
Cesarean section	21 (70)	56 (54.4)	
Abortion	3 (10)	0 (0.0)	
New born characteristics			
Weight (g)	2832.74±470.29	3137.83±507.94	**0.006**
Height (cm)	47.98±2.83	48.98±3.48	0.170
Gestational age	35.507±7.47	38.31±3.8	**0.001**
Pre term (<37 GW)	8 (29.6)	8 (7.9)	
Term (37-42 GW)	19 (70.4)	89 (88.1)	**0.007**
Post term (<42 GW)	0 (0.0)	4 (4)	
Low birth weight[a]	5 (18.5)	9 (8.7)	0.114
Small for gestacional age[b]	12 (44.4)	35 (34.0)	0.314

Data are presented as the mean ± S.D. and frequency (%).
[a] Weight < 2,500 g
[b] Bellow 10th percentil for gestational age
Abbreviations: CKD: chronic kidney disease; GW: gestational week.

TH-PO747

Preeclamptic Women Have Decreased Circulating IL-10 Levels at the Time of Active Disease: Systematic Review and Meta-Analysis

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Background: Preeclampsia (PE) is a pregnancy specific disorder characterized by hypertension and proteinuria after 20 weeks of gestation. One hallmark of PE is an abnormal maternal immune response. As a key immunomodulatory cytokine, Interleukin-10 (IL-10) has been shown to be dysregulated in PE. However, studies have reported inconsistent findings about circulating IL-10 levels in PE and normotensive (NT) patients. The aim of the present systematic review and meta-analysis is to assess circulating IL-10 levels in PE and NT patients at two time points: before PE diagnosis and at the time of active disease.

Methods: PubMED, EMBASE, and Web of Science databases were searched to include all published studies examining circulating IL-10 levels in PE and NT patients. Differences in circulating IL-10 levels between PE and NT women were evaluated by standardized mean differences.

Results: Out of the 876 abstracts screened, 56 studies were included in the meta-analysis. At the time of active disease, women with PE (n = 1496) had significantly lower circulating IL-10 levels compared to NT women (n =1897) (SMD: -0.68, 95% CI: -1.08, -0.28; *P* = 0.0008). Circulating IL-10 levels were lower in both early/severe and late/mild forms of PE. Subgroup analysis revealed that the methodology used to measure circulating IL-10 levels (ELISA or multiplex bead array) and the sample type (plasma or sera) significantly influences the observed differences in circulating IL-10 levels between PE and NT women. Circulating IL-10 levels were not different before the time of active disease (SMD: –0.01, 95% confidence interval [CI]: –0.11, 0.08; *P* = 0.76).

Conclusions: These findings provide further evidence about the significance of decreased IL-10 levels in the pathophysiology of PE. Further studies are needed to elucidate the clinical implications of these findings and the treatment potential of IL-10 in PE.

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TH-PO748

Autoimmunity and Altered Renal Function Precede the Development of Hypertension in Female Mice with Lupus

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Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by circulating autoantibodies, hypertension, and renal injury. Kidney involvement is common in SLE and renal dysfunction is evident in patients with active renal disease, yet little is known about early changes in renal function that may contribute to the pathogenesis of hypertension. We hypothesize that the loss of immunological tolerance and subsequent production of autoantibodies in SLE leads to impaired renal hemodynamic function that precedes the development hypertension.

Methods: Female NZBWF1 mice, an established experimental model of SLE, and female NZW (control) mice were instrumented with carotid artery and jugular vein catheters to determine mean arterial pressure (MAP) and glomerular filtration rate (GFR) respectively at ages 15, 20, 24, 28, 31, and 34 weeks. MAP was measured in conscious, freely-moving mice. GFR was measured by the clearance of fluorescein isothiocyanate-inulin (FITC-inulin) after achieving steady state through continuous infusion for five hours.

Results: Circulating autoantibodies are signifcantly increased by 28 weeks of age in mice with SLE (P = 0.0135), whereas autoantibodies are unchanged in control mice (Figure 1). GFR increases at 28 weeks of age followed by a significant decline by 34 weeks of age (P = 0.0127, P = <0.0001) compared to 34 and 15 weeks of age respectively, in SLE mice. GFR is increased in control mice by 28 weeks of age (P = 0.002) and remains unchanged at other time points (Figure 2).

Conclusions: These data suggest that changes in renal hemodynamic function occur in female SLE mice prior to changes in MAP suggesting a mechanistic role for autoimmunity to directly impair renal hemodynamic function and promote the development of hypertension.

Funding: Veterans Affairs Support

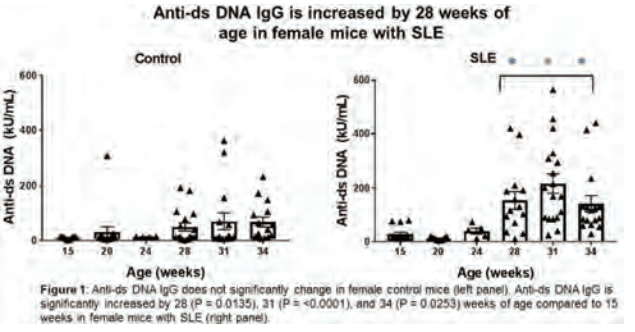

Figure 1: Anti-ds DNA IgG does not significantly change in female control mice (left panel). Anti-ds DNA IgG is significantly increased by 28 (P = 0.0135), 31 (P = <0.0001), and 34 (P = 0.0253) weeks of age compared to 15 weeks in female mice with SLE (right panel).

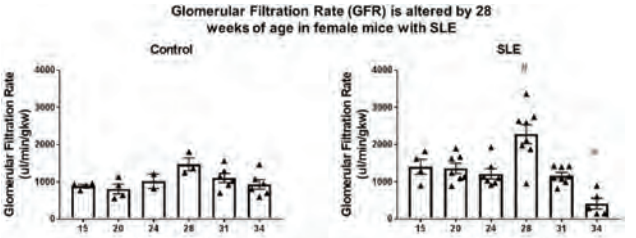

Figure 2: GFR does not change in female control mice (left panel). GFR is significantly increased by 28 weeks (# P = <0.0001) compared to 34 weeks of age and significantly decreased by 34 weeks (* P = 0.0127) compared to 15 weeks of age in female mice with SLE (right panel).

TH-PO749

Sex Differences in Bioimpedance in Humans with Obstructive Sleep Apnea with Normal Kidney Function Before and After Continuous Positive Airway Pressure Therapy

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Background: Sex differences exist in obstructive sleep apnea (OSA) and chronic kidney disease (CKD), both of which are strongly associated and predispose patients to expanded total body water (TBW) and aberrant volume redistribution, resulting in significant morbidity. Continuous positive airway pressure (CPAP) therapy is an effective treatment for OSA which may alleviate this predisposition. While there are established sex differences in the pathophysiology of OSA and CKD, whether sex differences exist in TBW and other bioimpedance parameters in OSA subjects with normal kidney function and the impact of CPAP therapy remains unknown.

Methods: Twenty-nine (10 women, 19 men; age 49±2y) incident, otherwise healthy, and sodium replete OSA subjects (oxygen desaturation index [ODI] >15h^{-1}) with and nocturnal hypoxemia (SaO_2<90% for >12%/night) were studied pre- and post-CPAP therapy (>4h/night x 4 weeks) using bioimpedance technology. Total body water (TBW), extracellular and intracellular fluid volumes (ECF and ICF), ECF:TBW, ECF:ICF, fat free mass (FFM), body mass index (BMI) and other bioimpedance and anthropometric parameters were measured and evaluated for sex differences before and after CPAP therapy.

Results: Pre-CPAP, TBW (74.6±0.4 vs 74.3±0.2% of FFM, p=0.14; all values women vs men) and BMI (36±3 vs 35±1 kg/m^2, p=0.9) were similar between sexes, though FFM (56.3±1.7 vs 71.7±1.5% of weight, p<0.001) and absolute TBW (42.4±3.0 vs 57.1±1.6L, p<0.001) were lower in women. The proportion of ECF:TBW (0.50±0.006 vs 0.44±0.009, p<0.001) and ECF:ICF (1.00±0.002 vs 0.80±0.004, p<0.001) was increased in women despite overall reduced absolute ECF (21.3±1.7 vs 25.2±0.8L, p=0.006) and ICF (21.1±1.2 vs 31.9±1.0L, p<0.001) compared to men. Though CPAP corrected both OSA (ODI: 47.4±4.4 vs 3.3±0.4h^{-1}, p<0.001) and nocturnal hypoxemia (46.2±5.7 vs 8.3±2.7%, p<0.001), there were no within sex differences in bioimpedance or arthropometric parameters in response to CPAP therapy.

Conclusions: Women with OSA had expanded ECF compared to men. Differences in TBW distribution may contribute to sex differences in the pathophysiology of OSA in humans with normal kidney function. CPAP therapy for 1 month did not mitigate these differences.

TH-PO750

Characterizing Nonlinear GFR Decline in Children with Kidney Diseases

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Background: GFR decline in kidney disease is frequently treated as linear in clinical research. The Chronic Kidney Disease in Children (CKiD) cohort provided long-term follow-up to characterize and describe GFR decline using non-linear models and accounted for risk stage using the newly developed pediatric classification.

Methods: CKiD participants contributed up to 13 follow-up years and provided annual estimated GFR data. To account for diagnosis, separate models were fit by non-glomerular and glomerular diseases. Linear mixed effects models were fit with log GFR as the outcome and a quadratic effect of time, with random effects for intercept, time and time^2. Baseline proteinuria categories (<0.5, 0.5 to 2, >2mg/mgCr) modified each parameter. Empirical Bayes estimates quantified individual-specific entry GFR, and changes within 5 years and between 5 and 10 years and were stratified by baseline CKD risk stage (initial GFR entry and observed proteinuria). Stable GFR was defined as no decline.

Results: A total of 757 and 275 children with non-glomerular and glomerular CKD, contributed 3926 and 1213 observations with 45% and 30% contributing at least 5 years. Most participants entered at Stage A or B (lowest severity) risk: for the non-glomerular and glomerular groups, 48% and 39% were in Stage A; 32% and 31% were in Stage B, respectively. The quadratic term for time offered significantly better fit than a linear effect only, for both groups (both $p<0.001$), and proteinuria significantly modified GFR trajectory. Nearly all children (95%) with non-glomerular diseases and 74% of those with glomerular diseases experienced faster percent decline in the second 5 years compared to the first 5 years, regardless of initial CKD stage. About 1/3 had stable GFR in the first 5 years in both non-glomerular and glomerular groups (27% and 31%), and Stages A and B comprised the vast majority of these first 5 year stable groups (86% and 69%). However, only 5% and 14% had a stable GFR in the second 5 years, respectively.

Conclusions: In general, in children with kidney diseases, GFR decline was not constant, but accelerated over time, and there was substantially more variability in glomerular disease. Mixed effects models provided individual non-linear trajectories and the challenge of heterogeneous disease duration at study entry was overcome by stratification by baseline CKD risk stage.

Funding: NIDDK Support

TH-PO751

Validation of Different Serum Creatinine-Based Estimating Equations in Pediatric Kidney Transplant Recipients in Comparison with Measured Glomerular Filtration Rate

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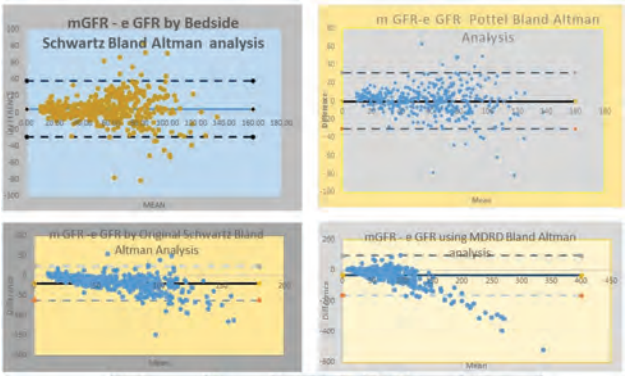
Background: The evaluation of allograft function is vital in the management of pediatric kidney transplant (pKTx) recipients. Serum creatinine (Scr) is the easiest everyday estimator of glomerular filtration rate (GFR) but both the absolute Scr value and the corresponding estimating equations (eGFR) are prone to considerable error. Measured GFR (mGFR) using plasma clearance of exogenous markers, while very accurate, is laborious as well as expensive, not suitable for everyday use. Prior studies have shown conflicting results regarding which eGFR equations are most accurate in comparison to mGFR. At our center, we have been performing measured GFR at 1 year post-pKTx; repeated every 2 years if mGFR > 40 ml/min/1.73m2, or yearly if mGFR ≤ 40. The aim of this study was to validate the different Scr-based eGFR equations in comparison to mGFR.

Methods: This retrospective study was conducted at St. Louis Children's Hospital from January 2000 to March 2019. We compared 415 mGFR values to 4 different Scr-based pediatric eGFR formulae (original Schwartz formula, modified Schwartz formula, Pottel formula and Modification of Diet in Renal Disease (MDRD) formula) from 125 pKTx recipients. Scr and children's height was measured on the same day as mGFR. We used Bland-Altman analysis to evaluate the bias between eGFR and mGFR. Higher precision was defined as lower width between the 95% limits of agreement (LOA). Accuracy was defined as percentage of eGFR that are within 30% of mGFR.

Results: The Pottel and modified Schwartz formulae had a high accuracy of 80% each and a low bias of < 5 ml/min/1.73 m2 (Figure). In contrast, the original Schwartz and MDRD formulae displayed a high bias and low precision and accuracy.

Conclusions: Of the Scr-based formulae, height independent Pottel and height dependent modified Schwartz formulae had low bias and high accuracy and either can be used to assess GFR in pKTx recipients. The original Schwartz and MDRD equations should not be used in this population.



Equation	Bias	Standard Deviation	95%LOA	Accuracy
Original Schwartz Formula	-19.62	21.9	-62.7 to 23.4	47%
Bedside Schwartz Formula	4.45	17.21	-29.98 to 38.18	80%
MDRD Formula	-35.42	65	-162 to 91.97	39%
Pottel Formula	-0.25	15.61	-30.84 to 30.35	80%

TH-PO752

Novel Nuclear Magnetic Resonance-Based Method for Prediction of Glomerular Filtration Rate Performs Well in Children

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Background: Estimation of glomerular filtration rate ($eGFR_{creat}$) in children requires different equations than in adults. This led to the development of different pediatric equations; however, these equations still show suboptimal performances in the upper and lower GFR range. Recently, a novel serum-based method for accurate prediction of GFR using a nuclear magnetic resonance (GFR_{NMR}) spectroscopy-based biomarker constellation (creatinine, myo-inositol, valine, and dimethyl sulfone) was developed. This method outperformed the conventional $eGFR_{creat}$ equations when validated in three separate cohorts of predominantly adult patients.

Methods: The value of the NMR-based biomarker constellation for GFR prediction specifically in children was investigated by testing its performance in a cohort of 39 children (20 girls, 19 boys) aged between 2 and 17 years. The NMR-based method was compared to $eGFR_{creat}$ obtained by the bedside Schwartz equation using measured GFR (mGFR) as reference standard. Pearson correlation coefficient (r) with 95 % confidence interval, root mean square error (RMSE), and the percentage of eGFR values within 30% of measured GFR (P30) were calculated to assess the accuracy of the methods.

Results: In a cohort comprising pediatric patients with various degrees of kidney impairment covering the whole GFR range, the NMR-based method showed a higher correlation with mGFR compared to $eGFR_{creat}$ (r=0.85 vs. r=0.80). Moreover, the RMSE was reduced from 35.5 for $eGFR_{creat}$ to 21.6 for GFR_{NMR}. The NMR biomarker constellation also showed a higher accuracy in mGFR prediction with a P30 of 79.5 % compared to 71.8 % for $eGFR_{creat}$.

Conclusions: Our results demonstrate that the NMR-based biomarker constellation accurately predicts GFR not only in adults but also in pediatric patients. In fact, the novel method outperformed the established bedside Schwartz equation. Thus, GFR_{NMR} allows reliable and continuous monitoring of kidney function at the transition from pediatric to adult renal care without the need to switch the estimation equation.

Funding: Commercial Support - numares AG

TH-PO753

Serum Cystatin C Levels at Birth in Very-Low-Birth-Weight Infants

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Background: Serum Cystatin C (CysC) is commonly used as a marker of glomerular filtration rates in children and adults. Although the reference intervals (RIs) of serum CysC has been well investigated, few reports demonstrated serum CysC levels in premature infants. The aim of this study was to investigate the RIs of serum CysC levels at birth in premature infants.

Methods: Eighty very low birth weight (VLBW, birth weight less than 1,500 g) infants admitted to our NICU between January 2018 and May 2019 were included, except for neonates with congenital anomalies of the kidney and urinary tract. Clinical data and serum CysC at birth were retrospectively collected from their medical records. All serum CysC concentrations were analyzed using a latex immunoturbidimetric assay. The RIs was defined as the set of CysC values 95% of these population.

Results: Data of 69 VLBW infants were available for this study. The CysC levels of 66 cases were distributed within 95% of these population. The gestational age was 29.2±3.1 weeks, and the birth weight was 1,061±290 g. It was included 27 (40.9%) male infants. The RIs of serum CysC levels at birth was 1.58±0.21 mg/L. Serum CysC levels in male infants were significantly higher than that in female infants (1.59 vs. 1.53 mg/L,

p< 0.05). Serum CysC levels at birth did not related to gestational age, birth weight, and APGAR score. There was no difference between serum CysC levels in small-for-gestational age (SGA) and that in non-SGA infants.

Conclusions: The RIs of serum CysC levels at birth is higher than that in later life. Unlike serum creatinine, serum CysC concentrations are not affected by their mothers' kidney function, therefore serum CysC levels might be a useful marker to evaluate the kidney function of neonates at birth.

TH-PO754

Serum Creatinine, Cystatin C, and a Comparison of Estimated Glomerular Filtration Rates in Very Low Birth Weight Children at 6 Years Old

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Background: According to the developmental organs of health and disease (DOHaD) theory, low birth weight is a risk factor for chronic kidney disease (CKD) in adulthood. However, there has been insufficient research into the renal function in school-aged children. In our research, we aimed to investigate the renal function of very low birth weight (VLBW), defined as less than 1,500g, children at six-year old and reveal risk factors of CKD.

Methods: We investigated 380 six-year old children who underwent a preschool physical examination, and had been among 504 VLBW infants discharged from the NICU in 1999-2011. The serum creatinine (Cr) and cystatin C (CysC) were measured, and for the >95 percentile group, a logistic regression analysis was used to study the relationships between the factors of gender, gestational age (GA), weight, height and head circumference at birth, and weight, height and BMI at the time of the physical examination. Additionally, the estimated glomerular filtration rate (eGFR) at the examination was calculated with the equation of Japanese child (JPN), Schwartz and chronic kidney disease epidemiology collaboration (CKD-EPI) and compared.

Results: Data for 337 subjects was recorded (age: 5.4±0.5 years, male:female ration = 167:170, GA: 28.3±2.7weeks, birth weight: 995±301g). Serum Cr was 0.34±0.07mg/dL and CysC was 0.77±0.13mg/L. In the >97.5 percentile group for Cr there were 7 subjects (2.1%), while for CysC, it was 13 subjects (6.4%). In the logistic regression analysis, the independent risk factors for high Cr values were GA (OR:2.25, 95%CI:1.06-4.80) and birth weight (OR:0.41, 95%CI:0.22-0.77). In the eGFR comparisons, the values were as follows: JPN (Cr:113.0±18.8 ml/min/1.73m^2, CysC:130.6±19.9 ml/min/1.73m^2), Schwartz(Cr:137.6±23.4 ml/min/1.73m^2, CysC:92.1±12.4 ml/min/1.73m^2), and CKD-EPI(Cr:191.1±19.5 ml/min/1.73m^2, CysC:125.6±15.1 ml/min/1.73m^2).

Conclusions: In this study of VLBW, there was a high frequency of high CysC values, and GA and birth height were identified as perinatal factors related to high Cr values. When CKD-EPI (Cr) was used in Japanese child, the values were higher than with other predictive equations.

TH-PO755

Is the Prognosis of a Single Functioning Kidney Benign? A Population-Based Study

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Background: Solitary functioning kidney (SFK) is an important condition in the spectrum of congenital anomalies of kidney and urinary tract (CAKUT). The long term outcome of congenital SFK is underactive research. We conducted a large scale population based study to investigate an early renal injury in adolescents with SFK.

Methods: We accessed data from the compulsory medical evaluation of 17 years old in Israel, prior to their enlistment for military service during 2006-2018. The incidence of SFK and the incidence of renal injury defined as proteinuria, hypertension or decreased eGFR were documented.

Results: of 978997 candidates, 354 had diagnosis of SFK. The peak incidence was 1:1500 in 2012. Male to female ratio 2.7:1. 28.1% of the cohort were overweight (BMI>25) Proteinuria was reported in 17% of the cohort. Systolic blood pressure above 120mmHg/ 130mmHg was documented in 53.8% and 28.1% respectively. Diastolic blood pressure above 80mmHg/ 85mmHg was documented in 12.8 and 9.1% respectively. eGFR below 90ml/min/1.73m2 was reported in 12.1%. Concomitant genital malformations were documented in 5.5%.

Conclusions: this large population based study documents a significant risk for renal injury among adolescent with SFK at the age of 17 years old.

TH-PO756

Pubertal Delay and Impact on Short Stature Among Girls with CKD

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Background: Children with chronic kidney disease (CKD) have delays in normal growth and pubertal development. We aimed to describe factors associated with delayed puberty including short stature among children with CKD.

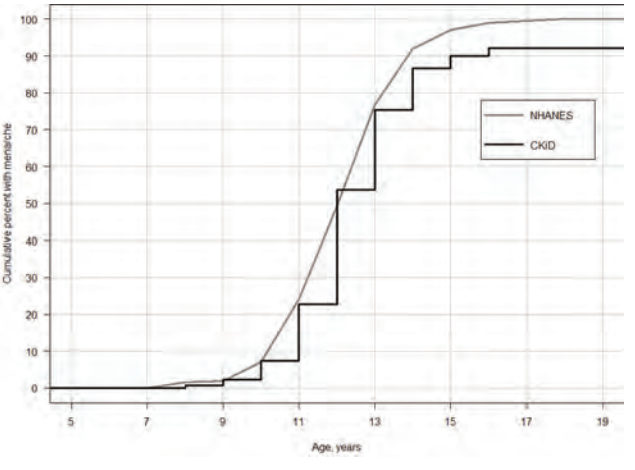
Methods: A prospective cohort study was conducted using the Chronic Kidney Disease in Children (CKiD) study. Delayed puberty was defined as menarche at age 15 years or older. Short stature was defined as last available height 2 standard deviations below projected mid-parental height. Chi-squared and Wilcoxon rank-sum tests were used to assess factors associated with delayed menarche.

Results: Median age at menarche was 12 years (IQR, 12 to 14 years, Figure). 10% had delayed menarche. African American race, lower eGFR, and longer CKD duration at time of menarche were associated with delay in menarche ($p < 0.05$), and girls with delayed menarche had lower height and weight percentiles ($p<0.05$, Table). 61% of girls with delayed menarche had short stature compared to only 35% of girls without delayed menarche ($p=0.03$).

Conclusions: Median age at menarche is similar among girls with CKD and healthy girls. However, 10% of girls with CKD have delayed menarche, which may negatively impact final adult height.

Funding: NIDDK Support

	Normal Menarche n = 124	Delayed Menarche n = 21	P-value
Sociodemographic			
Age at Menarche (yrs), median (IQR)	12 (12,13)	15.7 (15,17.4)	<0.001
African American Race	15 (12.1%)	6 (28.6%)	0.047
Abnormal Birth History	45 (36.3%)	9 (42.9%)	0.621
Kidney Disease Characteristics			
Age Onset (yrs), median (IQR)	0 (0,3)	0 (0,9.5)	0.672
Duration of CKD at Menarche (yrs), median (IQR)	12 (8.5,13.0)	15 (7.9,16.3)	<0.001
Glomerular Disease	35 (28.2%)	7 (33.3%)	0.633
eGFR at Menarche (ml/min/1.73m2), median (IQR)	47.8 (32.6,64.0)	30.6 (25.3,37.1)	0.007
Growth			
Weight Percentile at Menarche, median (IQR)	52.4 (24.3,81.6)	14.1 (2.8,74.1)	0.007
Height Percentile at Menarche, median (IQR)	32.8 (8.4,65.8)	10.4 (2.5,26.3)	0.003



Menarche in NHANES versus CKiD

TH-PO757

Autotaxin Early Predicts Progressive Renal Fibrosis in CKD

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Background: Single-kidney FUBI (Failure of Ureteric Bud Invasion) mice in susceptible animals causes glomerular sclerosis and interstitial fibrosis in the remnant kidney. To identify potential biomarker, we applied cDNA microarray.

Methods: We examined serial changes with aging and investigated the single-kidney-FUBI mice for 15 months. Using microarray, gene expression and validation workflow, we identified potential biomarkers and validation using plasma samples from 146 patients with chronic kidney disease (CKD) of diverse etiologies.

Results: We identified autotaxin that were shared by FUBI mice and CKD patients. Autotaxin (ATX) protein expression expressed dramatically after age of 12 months in the single-kidney compared with double-kidney-FUBI mice. During the progression of human CKD, a gradual increase of plasma autotaxin level became significant in stage 3 CKD with the amplification of CKD severity. ATX was absent in normal human renal tissue but detected immunohistologically in the human specimen of renal dysplasia. ATX

also contributed a drastic increase in the expression of fibrotic components including: fibronection, α-smooth muscle actin, collagen I and TGF-β in aging. Also fibrotic proteins upregulated in cultured human podocytes treated by ATX in a dose dependent manner.

Conclusions: Our results indicated that ATX might serve as a novel tool for monitoring the progression of CKD. ATX might also be as a possible therapeutic target to slow progression of CKD.

TH-PO758

Predicting Pediatric CKD Progression with Urinary Metabolomics

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Background: Predicting progression in children with chronic kidney disease (CKD) may improve care and planning for renal replacement therapy. Adding urinary metabolome changes to existing clinical models may improve prognostication.

Methods: Urine samples from patients in the CKiD Study had targeted urinary profiling (138 metabolites/creatinine ratio). Time to event (TTE) was measured, with event defined as 50% decline in eGFR, eGFR <15 or start of renal replacement (composite). A TTE predictor was trained using partial least squares discriminant analysis (PLS-DA), reported as discriminant score (dscore). Log-logistic accelerated failure time (AFT) models were fitted to predict survival based on clinical features without/with dscore, and compared the mean bias for accuracy (t test) and precision (F test).

Results: 703 patients (61% male, aged 12.1±4.4 years, iGFR 51.7±23.9) were divided into 2/3 training, 1/3 test sets, and 222 had an event (cases). The dscore was trained on cases (2 PLS components) and validated in the test set. The dscore was significantly correlated with TTE (r=0.61, p<0.001). The model performed similarly using only the top 10 metabolites (r=0.60, p<0.001). No improvement was noted when training separate glomerular vs. non-glomerular strata. An AFT survival model fit to training data (N =469 with 148 cases) included GFR, proteinuria, and glomerular disease as predictors. The model including dscore & clinical features (AIC=756) had improved fit compared to clinical features alone (AIC=793, likelihood ratio test p<0.001). Using test cases (N=74), the mean bias (years) was 1.8±3.1 vs. 2.4±4.3, demonstrating superior accuracy (mean difference 0.6, p=0.04) and precision (F ratio=0.53, p=0.007). Empiric and predicted AFT survival curves were compared using test data (N=234, 74 cases) stratified by baseline GFR <60. The predicted survival curves ± dscore are shown for both strata (Figure).

Conclusions: The addition of a urinary metabolite classifier improves both predictive accuracy and precision of a CKD progression model, compared with clinical features alone.

Funding: NIDDK Support

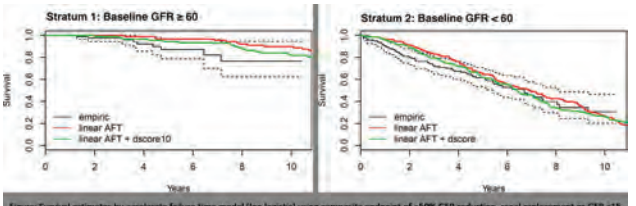

Figure: Survival estimates by accelerate failure time model (log-logistic) using composite endpoint of >50% GFR reduction, renal replacement or GFR <15 ml/min/1.73m², stratified by baseline iohexol GFR <60 ml/min/1.73m². In the test sample set (n=234), reported empiric survival is compared to the model with clinical features only (glomerular diagnosis, proteinuria, GFR) and to clinical features and the metabolite discriminant score (linear AFT + dscore).

TH-PO759

Plasma Kidney Injury Molecule 1 Is Associated with Left Ventricular Hypertrophy in Children with CKD

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Background: Left ventricular hypertrophy (LVH) is common in children with CKD and is associated with an increased risk of cardiovascular disease and mortality. Novel plasma biomarkers may help identify children at increased risk of developing LVH. We investigated whether the circulating plasma biomarkers of tubular injury (KIM-1) and inflammation (TNFR-1, TNFR-2, suPAR) are associated with LVH in children.

Methods: In the CKiD Cohort Study, children aged 6 months to 16 years old with an eGFR of 30-90 ml/min/1.73m² were enrolled at 54 centers in the US and Canada. We measured plasma KIM-1, TNFR-1, TNFR-2, and suPAR in stored plasma collected 5 months after study enrollment. Echocardiograms were performed one year after study enrollment. We assessed the cross-sectional association between the $\log_2$ biomarker levels and LVH (left ventricular mass index ≥95th percentile) using a Poisson regression model, adjusted for demographics (i.e., age, sex, race), body mass index, hypertension, glomerular diagnosis, proteinuria, as well as estimated glomerular filtration rate at study entry.

Results: Of the 544 children included, median age was 11 years [IQR: 8, 15], 335 (62%) were male, 162 (30%) had a glomerular cause of CKD, 92 (17%) had hypertension, median baseline eGFR was 54 [IQR: 40, 68] ml/min/1.73m², and median urine protein to creatinine ratio was 0.32 [IQR: 0.11, 0.94] mg/g. The overall LVH prevalence was 12% (N=65 events). All median biomarker levels were higher in children with LVH compared to those without LVH (p<0.05). In unadjusted models, two-fold greater plasma KIM-1, TNFR-1, TNFR-2, and suPAR concentrations were associated with LVH (KIM-1 relative risk [RR] per doubling: 1.39; TNFR-1 RR: 1.29; TNFR-2 RR: 1.54 and suPAR RR: 1.77) (**Table**). After adjusting for demographic and clinical characteristics, only higher plasma KIM-1 concentrations were associated with an increased risk of LVH (RR per doubling: 1.31, 95% CI: 1.04-1.64).

Conclusions: Elevated plasma KIM-1 is independently associated with LVH in children with CKD.

Funding: NIDDK Support

Table. Baseline Biomarker Concentrations and Risk of LVH

Biomarker, per doubling	Biomarker alone			Adjusted Model (age, sex, race)			Adjusted Model (plus BMI, hypertension, glomerular diagnosis)			Full Adjusted Model (plus eGFR, Pr/Cr)		
	RR	95% CI	P-value	RR	95% CI	P-value	RR	95% CI	P-value	RR	95% CI	P-value
Plasma KIM-1	1.39	[1.18, 1.64]	<0.001	1.40	[1.18, 1.67]	0.001	1.45	[1.19, 1.77]	0.001	1.31	[1.04, 1.64]	0.02
Plasma TNFR-1	1.29	[1.00, 1.65]	0.05	1.42	[1.10, 1.83]	0.007	1.41	[1.09, 1.83]	0.009	0.98	[0.66, 1.45]	0.92
Plasma TNFR-2	1.54	[1.05, 2.27]	0.026	1.65	[1.13, 2.42]	0.01	1.56	[1.08, 2.31]	0.02	1.02	[0.64, 1.64]	0.93
Plasma suPAR	1.77	[1.20, 2.61]	0.004	1.75	[1.18, 2.58]	0.005	1.59	[1.08, 2.34]	0.02	1.07	[0.67, 1.73]	0.77

Left ventricular hypertrophy (LVH) is defined as (LVM ≥95th percentile for healthy children and adolescents. Left ventricular mass index (LVMI) is an index of left ventricular mass to height (mass [g]/height [m]$^{2.7}$) to account for body size. Full model is adjusted for age, gender, race, glomerular diagnosis, body mass index, hypertension, protein to creatinine ratio (Pr/Cr), and baseline eGFR. KIM-1: kidney injury molecule-1. TNFR: tumor necrosis factor receptor. suPAR: soluble urokinase-type plasminogen activator receptor. *: Per doubling. RRs are for a continuous log2 change in biomarker levels.

TH-PO760

Primary Hyperoxaluria Type 2: New Insight into Clinical Outcomes

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Background: Primary hyperoxaluria type 2 (PH2) is a rare inherited disorder of glyoxylate metabolism causing nephrocalcinosis, renal stone formation and ultimately renal failure. PH2 had previously been considered to have a more favorable prognosis than PH1, but earlier reports are limited by low patient numbers and short follow up periods.

Methods: This study is based on gathered data from the European Hyperoxaluria Consortium (OxalEurope), encompassing the largest known PH2 cohort worldwide, providing a unique cohort enabling the description of longer-term outcomes in this rare disease.

Results: The dataset contained 101 patients from eleven countries. Median follow up was 12.4 years. Median ages at first symptom and diagnosis for index cases were 3.2 years and 8.0 years, respectively. Urolithiasis was the most common presenting feature (82.8%). Genetic analysis revealed 18 novel mutations in the *GRHPR* gene. Of 238 spot-urine analyses, 23 (9.7%) were within normal range as compared to less than 4% of 24-hour urine collections. Median intra-individual variation of 24-hour oxalate excretion was substantial (34.1%). At time of review 12 patients were lost to follow-up; 45 of 89 (50.6%) experienced chronic kidney disease (CKD) stage ≥2 and 22 patients (24.7%) had reached CKD5. Median renal survival was 43.3 years. 15 transplantations in 11 patients are described. Renal outcome did not correlate with genotype, biochemical parameters nor with the presence of nephrocalcinosis at presentation.

Conclusions: PH2 is not a benign disease and accurate diagnosis by 24-hour urine analysis and careful follow-up is required, in order to attempt to ameliorate its poor outcome. The role of liver transplantation remains unclear although it is evident that renal transplantation alone does not cure the disease.

TH-PO761

Phase 1, Single-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Etelcalcetide in Pediatric Subjects with Secondary Hyperparathyroidism Receiving Hemodialysis

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Background: The calcimimetic etelcalcetide is approved for treatment of sHPT in adult patients receiving hemodialysis. However, there are limited data on etelcalcetide safety and efficacy in pediatric patients.

Methods: This Phase 1 study (NCT02833857) evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of etelcalcetide after single-dose administration (0.035 mg/kg IV, corresponding to the approved lowest dose of 2.5 mg) in pediatric hemodialysis subjects in 2 cohorts (cohort 1: aged 12–<18 y; cohort 2: aged 2–<12 y). Treatment-emergent adverse events (AEs) were assessed. Etelcalcetide PK/PD was assessed post-dose on D1 at 10 min and 4 h, on multiple days until D10, and at the end of study (D30).

Results: Etelcalcetide administered to 11 subjects (mean [SD] age=10.3 [4.3] y; cohort 1, n=6; cohort 2, n=5) was well tolerated and reported AEs were consistent with the known etelcalcetide safety profile. One subject each in both cohorts reported treatment-related AEs (cohort 1: hypocalcemia; cohort 2: headache, paresthesia, and vomiting) and no serious AEs or deaths were observed. Mean serum corrected Ca (cCa) for all subjects was maintained >2.25 mmol/L. After dosing, PK exposures declined over time in both cohorts (Table). Median percent change in serum intact parathyroid hormone (iPTH) from baseline (cohort 1: 51.2 pmol/L; cohort 2: 84.0 pmol/L) reached the nadir on D1 at 4 h (cohort 1: –33.4%; cohort 2: –64.2%). In both cohorts, mean total Ca and cCa reached nadirs on D3 at 2.4 mmol/L, and mean ionized Ca on D1 at 4 h (1.1 mmol/L). Serum iPTH and cCa levels returned to baseline as etelcalcetide concentrations declined prior to the end of study in all subjects.

Conclusions: A single dose of 0.035 mg/kg was well tolerated, with no new safety concerns and PK/PD response was as expected. Given the high inter-subject variability, overlap in etelcalcetide concentrations, and small sample size, the differences in etelcalcetide exposures between the age groups were not likely to be clinically meaningful.

Funding: Commercial Support - Amgen Inc.

Pharmacokinetic parameter	Cohort 1 (age 12 – <18 y) N=6		Cohort 2 (age 2 – <12 y) N=5	
	Mean (SD)	Coefficient of variation (%)	Mean (SD)	Coefficient of variation (%)
Cmax (ng/mL)	67.0 (24.0)	35.9	31.4 (23.8)	75.8
AUClast (h*ng/mL)	1790.0 (1360.0)	76.1	839.0 (397.0)	47.3
t1/2 (d)	5.7 (2.8)	49.7	5.9 (3.0)	50.9

TH-PO762

Growth in Children with Non-Glomerular Kidney Disease

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Background: Growth retardation is one of common complications of chronic kidney disease (CKD) in children. Children with CKD from non-glomerular disease have been reported to have a higher risk of severe growth retardation than children with glomerular CKD. The objective of this study was to systematically compare growth parameters in children with non-glomerular CKD to those with glomerular CKD.

Methods: Baseline data from 437 children participating in the KoreaN cohort study for Outcomes in patients With Pediatric CKD (KNOW-Ped CKD) were analyzed. Growth was quantified by age-sex-specific height and weight standard deviation scores (SDS). We compared the height and weight SDS in children with non-glomerular CKD (*n*=325) to those with glomerular CKD (*n*=112).

Results: Median height and weight SDS in children with non-glomerular CKD was -0.82 [interquartile range (IQR) -7.67 to 2.75] and -0.81[IQR -10.54 to 3.05] while those of glomerular CKD were -0.41[IQR -5.58 to 2.91] and -0.35[IQR -6.72 to 3.44]. 24.9% of the non-glomerular CKD had height SDS below -1.88 (16% in glomerular CKD) and 32.3% had weight SDS below -1.65 (16% in glomerular CKD). 9.5% were using growth hormone (1.8% in glomerular CKD). Non-glomerular CKD patients were significantly shorter and lighter than glomerular CKD, and proportion of short stature and proportion of underweight were larger in non-glomerular CKD than glomerular CKD. When further grouped according to age, children younger than 2 years-old with non-glomerular CKD were the shortest and the most underweighted (median height SDS -2.04; IQR -6.86 to 1.95, median weight SDS -2.32; IQR -6.76 to 1.83). Significance of non-glomerular CKD was also found in analysis of risk factors for growth impairment; In multivariable analysis, the most significant risk factor of underweight was non-glomerular CKD, followed by anemia and proteinuria. In turn, underweight itself was the most important risk factor for height impairment in children with CKD.

Conclusions: In concordance with the previous report, children with non-glomerular CKD have a high prevalence of growth abnormalities in the KNOW-Ped CKD cohort. In this population, more intensive and early intervention through growth hormone treatment and nutritional supplementation is necessary, especially in young children with non-glomerular CKD.

Funding: Government Support - Non-U.S.

TH-PO763

Catch-Up Growth but Not Growth Hormone Itself Is Associated with Renal Injury in Subjects Born Small for Gestational Age

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Background: Subjects born with low birth weight including those born small for gestational age (SGA) are at a risk for developing hypertension and chronic kidney disease due to reduced nephron number. Growth hormone (GH), given to SGA children without catch-up growth, can induce hyperfiltration leading to glomerulosclerosis. Catch-up growth may also be a risk factor of kidney disease. We investigated the effects of GH and catch-up growth in the development of renal injury in subjects born SGA.

Methods: Twenty-eight subjects (12 males and 16 females, age 4 to 27 years) born SGA were retrospectively investigated. Twenty-three were preterm-SGA, and 4 out of 5 term-SGA were syndromic. Fourteen subjects were treated with GH. Estimated GFR (eGFR) was determined by quintic equation for Japanese children (<19 years) or formulas for Japanese adults (≥19 years) by age and gender. Renal injury was defined as reduced eGFR <90 ml/min/1.73 m^2, elevated urine microalbumin/creatinine ratio (malb/Cr) ≥30 mg/g, or the presence of hypertension. Catch-up growth was defined as change in SD score in height or weight from birth to the time when the final height was achieved or to the time of study for those who have not reached final height.

Results: There was no difference in current age, gestational age, birth weight, eGFR, malb/Cr, renal injury, height catch-up, or weight catch-up between subjects treated with GH and those not treated with GH (Table). Of all subjects, there was no cut-off SD score of height catch-up that separates those with and without renal injury. On the other hand, 12 out of 16 subjects (75%) with weight catch-up ≥1.6 SD had renal injury, whereas only 2 out of 11 (18%) with weight catch-up <1.6 SD had renal injury (P<0.05). On ROC analysis, a cut-off value of 1.595 SD in weight catch-up best predicted renal injury with 86% sensitivity and 62% specificity.

Conclusions: There was no difference in the prevalence of renal injury between SGA subjects treated with GH and those not treated with GH probably because the latter had spontaneous catch-up growth. Weight catch-up ≥1.6 SD appears to be a risk factor for renal injury.

Funding: Government Support - Non-U.S.

GH	Age (yr)	Gestational age (wk)	Birth weight (g)	eGFR (ml/min/ 1.73 m^2)	malb/Cr (mg/g)	Renal injury	Height catch-up	Weight catch-up
+	11.3 (5.5)	30.5 (6.6)	1060 (759)	98.3 (24.6)	6.6 (3.0)	8/14	0.97 (0.94)	1.62 (0.72)
-	13.1 (4.4)	28.1 (2.9)	700 (199)	92.6 (13.4)	40.4 (78.6)	7/14	1.48 (1.48)	2.05 (0.86)

+, treated: -, not treated. Mean (SD).

TH-PO764

Patiromer Treatment of Hyperkalemia in Adolescent Children with CKD: Initial Results from EMERALD

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Background: Patiromer (PAT) is a sodium-free potassium (K^+) binder approved for treatment of hyperkalemia (HK) in adults (8.4 g once daily starting dose); it is not currently approved for use in children.

Methods: EMERALD (NCT03087058), an open-label, multiple-dose study, evaluates the pharmacodynamics (PD) and safety of PAT in children (2-<18 yr) with HK and CKD. It consists of a 14-d dose finding PD phase and a 5.5-mo long-term treatment (LT) phase. Patients (pts) must have eGFR <60 mL/min/1.73m^2, HK (serum K [sK] 5.1-<6.5 mEq/L) and not be on hemodialysis (HD). RAASi doses must be stable for ≥28 days before screening. Up to 54 pts will be enrolled into 3 sequential cohorts based on age. Cohort specific PAT starting doses with titration to obtain a target local K level of 3.8-5.0 mEq/L are being evaluated. Up to 3 starting doses per cohort may be assessed. The primary endpoint is the change in central lab sK from baseline to Day 14. Secondary endpoints include the proportion of pts with target sK (3.8-5.0 mEq/L, central lab) at Day 14 and through Week 26.

Results: Cohort 1 (age 12 to <18 yr, now completed) pts (N=14, mean age 14.5 yr) had a mean (SD) baseline sK of 5.54 (0.32) mEq/L and eGFR of 28.7 (13.7) mL/min/1.73m^2. The most common etiology of CKD was CAKUT (64%) and 57% of pts were on RAASi. All pts completed the PD phase of the study; 2 pts withdrew consent in the LT phase and 1 began HD after which sK data were censored. The starting dose for all patients was 4.2 g/d; 8.4 g/d was the most common final prescribed dose at study end (33.3%). sK decreased by -0.50 (0.54) mEq/L at Day 14 (N=14) and by -1.08 (0.74) mEq/L at Week 26 (N=11); 50% and 82% of pts achieved the target sK by Day 14 and Week 26, respectively. Adverse events (AE) were observed in 71% of pts and were mostly mild or moderate in severity (one severe, none serious). The most common class of AEs was gastrointestinal disorders (43%; diarrhea [21%], flatulence [14%], nausea [14%]). There was one AE of hypokalemia. Three pts experienced AEs considered related to study drug (none severe); no AEs led to study drug discontinuation.

Conclusions: Preliminary results from EMERALD suggest a 4.2 g/d PAT starting dose with titration resulted in clinically meaningful sK reduction in adolescents with CKD and HK and was generally well tolerated.

Funding: Commercial Support - Funded by Relypsa, Inc., a Vifor Pharma Group Company

TH-PO765

Rates of Prevalent Fracture Differ by Race and Ethnicity in Children with CKD

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Background: Studies of healthy children demonstrate higher rates of fracture in Caucasian as compared to minority children. Although studies in adults with CKD have demonstrated greater risk of fracture in Caucasian adults as well, there is limited data on fracture rate differentials by racial-ethnic group in the pediatric CKD population.

Methods: In a sample of 742 children between the ages of 1.5 years and 18 years, with CKD stages 1-4 from the CKD in children (CKiD) cohort, we determined the relationship between racial-ethnic group and the reported history of fracture upon entry to the study. Using logistic regression, we sequentially controlled models for the potential confounders in Table 1 which were chosen based upon prior literature and bivariate p-values <0.1. Multiple imputation was used for missing values in the final model.

Results: The cohort characteristics and laboratory values are displayed in Table 1. Vitamin D levels were lowest in African-American children. 142 subjects reported ever having experienced a broken bone. In the fully adjusted and multiply imputed model, African-American and Hispanic children had 74% (OR [CI] 0.26 [0.14, 0.49] p=0.001) and 66% (OR [CI] 0.34 [0.17, 0.65], P<0.0001) lower odds of any fracture than Caucasian children at study entry, respectively (Figure 1).

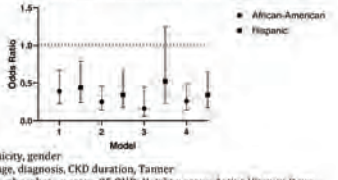
Conclusions: Despite lower vitamin D levels, African-American children with CKD reported lower fracture frequency than Caucasian children. These findings in children with CKD are similar to those in healthy children. Additional studies to understand the pathophysiologic mechanisms behind these differentials are warranted.

Funding: NIDDK Support, Other NIH Support - NIH-NIMHD Loan Repayment Program

Table 1: Cohort characteristics at baseline

Variable	Black	White	Hispanic	p
N	163	462	117	
Age, yrs median (IQR)	12.5 (8.7, 15.4)	11.5 (8.2, 14.9)	11.5 (7, 15.1)	0.5
Gender, n (%)				0.09
Male	107 (65.6)	285 (61.7)	62 (53)	
CKD stage, n (%)				0.001
1	12 (7.4)	22 (4.8)	1 (0.9)	
2	65 (39.9)	122 (26.4)	30 (25.6)	
3	75 (46)	272 (58.9)	71 (60.7)	
4	6 (3.7)	42 (9.1)	13 (11.1)	
Unknown	5 (3.1)	4 (0.9)	2 (1.7)	
Diagnosis				<0.0001
Glomerular, n (%)	72 (44.2)	110 (23.8)	39 (33.3)	
Non-glomerular, n (%)	91 (55.8)	352 (76.2)	78 (66.7)	
CKD duration, yrs, median (IQR)	6.1 (2.7, 11.2)	9 (4.7, 13.4)	7.5 (4, 11.3)	0.001
Tanner, n (%)				0.05
1	78 (49.1)	260 (59.1)	60 (52.2)	
2	11 (6.9)	43 (9.8)	10 (8.7)	
3	15 (9.4)	39 (8.9)	9 (7.8)	
4	28 (17.6)	65 (14.8)	21 (18.3)	
5	27 (17)	33 (7.5)	15 (13)	
Unknown	4 (2.5)	22 (4.8)	2 (1.7)	
Calcium, mg/dL, median (IQR)	9.4 (9.1, 9.7)	9.2 (9, 9.5)	9.3 (9, 9.5)	0.002
Phosphate, mg/dL, median (IQR)	4.4 (3.9, 5)	4.4 (4, 4.9)	4.5 (4, 4.9)	0.9
Phosphate z, median (IQR)	0.2 (-0.7, 1.4)	0.03 (-0.9, 1)	0.1 (-0.7, 1.1)	0.2
iPTH, pg/mL, median (IQR)	50.2 (28.7, 74)	44.9 (28, 73.8)	47.5 (30, 69.1)	0.6
25 OHD, ng/mL median (IQR)	20.2 (12.8, 27.6)	31 (24, 38)	25.2 (18.2, 33.3)	<0.0001

Figure 1: Odds of prevalent fracture relative to Caucasian children



Model 1: race-ethnicity, gender
Model 2: + CKD stage, diagnosis, CKD duration, Tanner
Model 3: + calcium, phosphate-z score, 25 OHD, Height z score, Active Vitamin D use
Model 4: Multiple imputation of model 3

TH-PO766

A 24-Month Interim Analysis of a Phase 2 Trial Evaluating the Long-Term Efficacy and Safety of Oxabact OC5 in Dialysis Patients with Primary Hyperoxaluria Type 1 (PH1)

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Background: In PH1, endogenous overproduction of oxalate in the liver results in significantly elevated plasma oxalate (Pox), high urinary oxalate excretion, recurrent urolithiasis and/or progressive nephrocalcinosis. This can lead to end-stage renal disease (ESRD) with patients requiring dialysis and combined liver and kidney transplantation. Dialysis is insufficient to remove oxalate and cannot match the endogenous production, resulting in high Pox and thus systemic oxalate deposition. Oxabact (OC5), is a formulation of *Oxalobacter formigenes*,an oxalate-metabolizing bacterium, that induces active secretion of oxalate from plasma to the intestinal lumen. This Phase II, open-label single-arm study investigated efficacy in reducing Pox and safety of OC5 in PH1 patients on a stable dialysis regimen.

Methods: Patients received OC5 (≥10^9 CFU lyophilized *O. formigenes*per dose, twice a day) until transplantation or until they reached a maximum of 36 months treatment duration. Pox was evaluated monthly. Cardiac function (echocardiography) was evaluated every 6 months. Safety was assessed continuously. This 24-months interim analysis represents the longest treatment intervention observed in patients with PH1 on dialysis to date.

Results: Eight subjects with a mean (SD) age of 33 (13) years were enrolled into the long-term treatment study. Three patients discontinued before reaching 24 months of treatment; two due to non-compliance to treatment and one due to a liver transplantation. The drop-outs did not have an impact on results. Total Pox was 158.3 (43.9) µmol/L at baseline (n=8), 119.8 (11.3) µmol/L at Week 52 (n=6), and was further reduced to 94.6 (31.9) µmol/L at Week 104 (n=5). Mean Left ventricular ejection fraction improved from 51.6 % at baseline (n=8) to 59.8% at Week 52 (n=6) and 59.4% at Week 104 (n=5). Seven subjects reported any Adverse Event (AE), most frequent AEs were infections and infestations and gastrointestinal disorders. Four subjects experienced 5 serious AEs, unrelated to treatment

Conclusions: Two years treatment with OC5 reduced mean Pox by approximately 40% in PH1 patients with ESRD without intensifying their dialysis regimen. This was also associated with an improved and stabilized cardiac function. OC5 was safe and well-tolerated.

Funding: Commercial Support - OxThera

TH-PO767

DNA Methylation Program in Human Kidney Development

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Background: Epidemiologic studies indicate that in utero nutritional alterations increase the risk of hypertension, and kidney disease in adults. Changes in the epigenome have been proposed to mediate the metabolic programming effect, as epigenome editing enzymes are regulated by substrates of the intermediate metabolism and changes in the epigenome can be maintained after cell division. DNA methylation is one of the most studied epigenetic factor that plays a key role in gene expression regulation and cell type specification. The methylation dynamics of human kidney development (pre and post-natal) remains unknown, therefore we analyzed genome-wide methylation changes of human kidney development and maturation.

Methods: Here we performed base resolution methylome analysis by whole genome bisulfite sequencing of human fetal kidneys, from 11.4 to 19.0 weeks of gestation and postnatal kidney tubules from 27 to 61 years of age (n=12). The SMART genome segmentation method was used to identify differentially methylated regions (DMRs). RNA-sequencing was performed to detect gene expression changes.

Results: Whole genome methylation analysis identified dynamic methylation changes during kidney development and maturation including, 5,280 regions gaining methylation (hyper-DMRs) and 4,316 regions losing methylation (hypo-DMRs) in adult kidney tubules. Methylation changes were enriched on gene regulatory regions. Hyper-DMR regions lost histone enhancer marks (H3K4me1 and H3K27ac) while hypo-DMRs gained enhancer marks. Function enrichment analysis indicated that developmental genes are gaining methylation while proximal tubule specific genes undergo demethylation. Consistently hyper-DMRs were enriched for kidney developmental transcription factors binding sites such as HOXC9 and SIX2, while hypo-DMRs were enriched for the proximal tubule-specific transcription factors (HNF family). Methylation showed correlation with gene expression such as the increase in expression of proximal tubule specific genes in adult and loss of expression of fetal genes in adult. Methylation and gene expression dynamics were conserved in mice.

Conclusions: Cytosine methylation, specifically enhancer regions, show dynamic changes in fetal development and postnatal maturation, the most prominent of them is the decrease in enhancer methylation and increase of expression of proximal tubule genes.

TH-PO768

Paradigm Shift: The Impact of Early Rapid Genomic Sequencing in the Diagnosis of Kidney Disease

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Background: Rapid genomic sequencing with results available in clinically meaningful timeframes is becoming feasible. Its role in the diagnosis and management of patients with kidney disease is unclear.

Methods: Patients were recruited prospectively for rapid whole exome sequencing (WES) with analysis of a pre-determined phenotype specific list of genes of interest and results available in less than 2 weeks. This followed review by a nephrologist, clinical geneticist and genetic counsellor who considered inclusion if a result was likely to significantly impact clinical management, particularly avoiding kidney biopsies in younger children. Full author list online at KidGen.org.au

Results: Ten patients (7 pediatric, 5 female) were recruited ranging in age from 1 month to 55 years. Indications for rapid testing were to avoid a renal biopsy (8) and to facilitate transplant planning (2). Five patients received a definitive diagnosis (ADPKD, Dent disease, primary hyperoxaluria, Alport syndrome and ciliopathy), 1 received a diagnosis which was likely unrelated to their kidney disease (MIRAGE syndrome). One patient's negative result facilitated sibling donor workup. The most significant result in this cohort was an unexpected diagnosis of primary hyperoxaluria in a 6-month old presenting in renal failure. WES results were available within 5 days informing conversion from peritoneal dialysis to hemodialysis and planning for a sequential liver-kidney transplant. This avoided the significant morbidity of oxalate deposition in extra-renal tissues leading to fractures, visual impairment and heart failure and recurrence of the disease if an isolated renal transplant had been performed.

Conclusions: Rapid genomic sequencing has high diagnostic utility in selected patients with renal disease and can inform clinical management within meaningful timeframes. It has the potential to transform the diagnostic pathway for young children, particularly where invasive renal biopsies can be avoided.

Funding: Government Support - Non-U.S.

TH-PO769

Longitudinal Associations Between Vitamin D and Blood Pressure in the CKD in the Children (CKiD) Cohort

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Background: Preclinical studies suggest that 25 hydroxy vitamin D (25OHD) modulates the renin-angiotensin-aldosterone system, vascular smooth muscle cells and the endothelium. Analysis of data from the "Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of CKD in Pediatric Patients" study showed that subjects with 25OHD levels <20 ng/ml had a higher diastolic BP than those with levels ≥20 ng/ml (p=0.004). Children with 25OHD levels < 20 ng/ml in the CKiD cohort had SBP 0.29 standard deviations higher (95%CI: 0.07, 0.51, p=0.009) at baseline.

Methods: Longitudinal associations between hypertension (SBP or DBP ≥95th percentile) and baseline 25OHD (deficiency < 20 ng/ml) and 1,25$(OH)_2$D (per 10 pg/ml) levels), adjusted for baseline covariates, were examined using mixed-effects logistic regression that included a random subject effect to account for repeated measurements of the outcome within each subject. Covariates included were age, gender, race, years from visit 2, CKD etiology, BMI, GFR, proteinuria and medications used (antihypertensive, steroids, active and inactive vitamin D supplements). Study population included 536 subjects contributing 2741 visits (subset of n=365 with available ABPM measurements at visit 2 contributing 803 visits).

Results: Participants with 25OHD deficiency had greater odds of having systolic (OR 1.80, 95%CI: 1.22, 2.65; p=0.003) as well as casual hypertension (OR: 1.48, 95% CI: 1.04, 2.11, p=0.03). Male gender decreased the odds of hypertension. Higher BMI, nephrotic range proteinuria and active vitamin D use were associated with higher odds of systolic hypertension (Table 1). 1,25$(OH)_2$D was significantly associated with hypertension (OR= 0.81, 95%CI: 0.70, 0.95) in univariate analysis only. Neither vitamin D measures were associated with ABPM hypertension.

Conclusions: 25OHD deficiency is associated with higher odds of persistent casual hypertension. It may be beneficial to maintain 25OHD levels >20 ng/ml to optimize BP control in children with CKD.

Funding: NIDDK Support

Table 1. Multivariate Associations of baseline 25 hydroxyvitamin D with hypertension

	Systolic Hypertension [a] (n=536, 2741 kid-visits)		Diastolic Hypertension [a] (n=536, 2741 kid-visits)		Casual Hypertension [b] (n=536, 2741 kid-visits)	
Characteristics	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*
25OHD <20 ng/ml	**1.80 (1.22, 2.65)**	**0.003**	1.23 (0.82, 1.85)	0.311	**1.48 (1.04, 2.11)**	**0.031**
Years from Visit 2	1.04 (0.98, 1.10)	0.181	1.06 (1.00, 1.13)	0.069	1.04 (0.99, 1.09)	0.115
Male gender	**0.67 (0.46, 0.98)**	**0.041**	**0.49 (0.34, 0.72)**	**<.001**	**0.68 (0.49, 0.95)**	**0.024**
Caucasian	0.76 (0.51, 1.13)	0.174	0.73 (0.49, 1.09)	0.123	0.73 (0.52, 1.04)	0.078
Glomerular diagnosis	0.82 (0.53, 1.27)	0.368	1.27 (0.85, 1.88)	0.242	0.89 (0.60, 1.32)	0.554
BMI z-score, per 1 SD	**1.26 (1.06, 1.50)**	**0.009**	NI		1.14 (0.99, 1.32)	0.077
Proteinuria ≥2 mg/mg	**1.87 (1.12, 3.15)**	**0.018**	**2.84 (1.68, 4.78)**	**<.001**	**2.02 (1.24, 3.31)**	**0.005**
Inactive vitamin D use	NI		0.54 (0.28, 1.01)	0.055	NI	
Active vitamin D use	**1.63 (1.09, 2.44)**	**0.018**	1.44 (0.94, 2.20)	0.096	**1.56 (1.09, 2.22)**	**0.015**
Antihypertensive use	1.51 (0.96, 2.38)	0.076	NI		1.25 (0.85, 1.85)	0.249
Corticosteroid use	NI		NI		NI	

Abbreviations: BMI= body mass index, GFR= glomerular filtration rate, NI = Not included in multivariable models due to lack of association of univariable models with casual BP hypertension (p>0.15)
[a] Hypertension defined as BP ≥95th percentile for systolic and diastolic, respectively
[b] Casual Hypertension defined as SBP ≥95th percentile or DBP ≥95th percentile

TH-PO770

Mental Health Diagnoses and Substance Use in Children with CKD in the CKD in Children (CKiD) Study

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Background: Mental health disorders are more common in children with chronic illness than in healthy counterparts. While a high prevalence of depression has been noted in children with chronic kidney disease (CKD), other mental health diagnoses and substance use have not been well described.

Methods: We evaluated the prevalence of mental health diagnoses utilizing parent-reported child mental health diagnoses and self-reported substance use among participants age 1-16 years at enrollment in the CKiD study. Descriptive statistics were used to characterize the distribution of mental health diagnoses and age of onset. Chi-squared, t-test, and log binomial regression were used to compare demographic factors including sex, race, and maternal education, and CKD characteristics including glomerular versus nonglomerular disease, disease progression, and height between those with and without a reported mental health diagnosis.

Results: Among CKiD participants (n=891) prevalence of any mental health diagnosis or substance use was 55% with mean onset reported at 13 years. The most common conditions were learning disorders (22%), alcohol use (22%), attention deficit and hyperactivity disorders (19%), depression (15%), anxiety (13%), and cannabis use (10%), with 30% reporting multiple diagnoses. Those with mental health diagnoses were more likely to have a mother with some college education (PR 1.2, 95%CI 1.1-1.4) than those without a diagnosis. Reported mental health diagnoses were less common among those who identified as Latino. (PR 0.5 95%CI 0.2-0.8). There were no other significant differences in the assessed demographic or CKD characteristics between those with and without mental health diagnoses.

Conclusions: A broad spectrum of mental health diagnoses are common in children with CKD. Despite limitations inherent in using self-reported retrospective survey data, this study provides impetus for more in-depth assessment of mental health in children with CKD, advocacy for greater mental health resources, and the development of targeted therapies for children with CKD and their families.

Funding: Other NIH Support - T32 DK007662-27

TH-PO771

A Young Adult Nephrology Transition Clinic: A Successful Model

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Background: Survival of pediatric patients with chronic disease has increased leading to a greater number of patients transitioning from pediatric to adult care. A formal pediatric to adult transition process is important in improving medical adherence in these young adults. Despite this, few adult nephrology centers have transition protocols in place. To address this, we implemented a combined nephrology transition of care program at Lurie Children's Hospital (LCH) and Northwestern Medicine (NM). Here we present our 5 year data.

Methods: The pediatric team identified transfer patients and communicated with the adult team, a nephrologist, PA and social worker, about patient history and potential obstacles to successful transition. The initial appointment occurred at LCH with subsequent visits at NM. During all visits, patients had one on one time with each of the providers. Monthly reviews were conducted to determine if proper follow up had occurred and if not, procedures of enhanced follow up including phone calls and email were implemented.

Results: A total of 84 patients were seen with the results outlined in Table 1. Successful transition was defined as at least one follow up visit in the adult clinic. 40% of patients required enhanced follow up. 21% of patients either unsuccessfully transitioned or had delayed drop out, defined as lost to follow up after a successful transition.

Conclusions: Based on our five year experience, transition of care from pediatric to adult nephrology providers can be successfully facilitated with a protocol driven model that includes engagement of adult and pediatric teams. This patient group, however, is still at high risk of being lost to follow up.

Table 1: Patient outcomes.

Outcome	Transition Program Particpants (n=84)
Successful Transition One visit Two visits Three + visits	65 (78%) 13 (15%) 15 (18%) 37 (44%)
Unsuccessful Transition	6 (7%)
Delayed Drop Out	12 (14%)
Pending Follow Up	7 (8%)
Un enrolled	6 (7%)

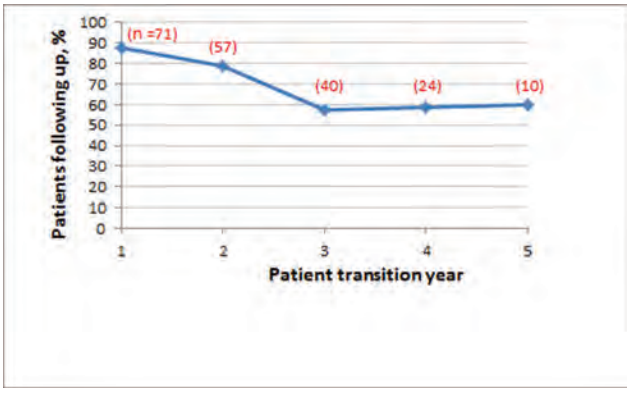

Figure 1: Follow up as a function of transition year.

TH-PO772

Current Practice and Resources for Medication Adherence Assessment Among Pediatric Kidney Transplant Programs

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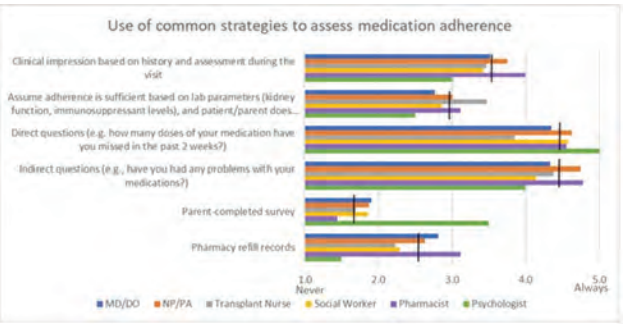
Background: Adolescent/young adult kidney transplant recipients have 3 times the risk of allograft failure compared to other age groups. This is multifactorial, but barriers to medication adherence are a major contributor, present in up to 40%. To inform future adherence interventions, we assessed current practice patterns and resources available to address barriers to medication adherence among US pediatric kidney transplant programs.

Methods: Kidney transplant team members, including physicians (MD/DO), nurse practitioners (NP), physician assistants (PA), social workers (SW), and pharmacists, from 22 kidney transplant programs in the Improving Renal Outcomes Collaborative were surveyed about institutional characteristics, resources and current practice assessing medication adherence. 64 unique surveys were included, with representation from 22/26 (85%) of IROC-affiliated institutions.

Results: All teams indicated they have at least one MD/DO, nutritionist, and SW, which form the core team. Additional roles of NP, PA, transplant nurse, pharmacist, psychologist, and child life specialist were available in only some institutions. Each of 10 common barriers to medication adherence was reported to be assessed by at least one provider type during routine clinic visits. The majority reported assessing barriers to adherence at every clinic visit. However, subjective assessment methods were most commonly used, including forming a clinical impression based on history/exam and indirect and direct questions (Figure).

Conclusions: Provider assessment of medication adherence for pediatric kidney transplant patients varies among practices. While centers report that it is frequently assessed, subjective measures, which may overestimate adherence, are used most commonly. There is opportunity to standardize adherence barriers assessment with standard surveys/tools and to use objective measures, such as pharmacy refill records, to more accurately assess adherence. Future studies are needed to improve assessment of adherence.

Funding: Private Foundation Support



TH-PO773

A Single-Center Experience of Bortezomib in Pediatric Kidney Transplants With Long-Term Graft Outcome

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Background: Acute antibody mediated rejection (aAMR) remains a challenge with poor renal allograft longterm outcome and unclear therapeutic efficacy of current therapies. We report the use of Bortezomib for treatment of persistent aAMR after failure of conventional therapy and long term graft and patient outcomes,.

Methods: Review of 118 kidney transplants (txp) from 2004-2019, noted - 4 had primary graft failure, 3 patients were deceased (2 with functioning grafts) and 3 were lost to follow up. 32 rejections- 12 with TCR and 20 with aAMR (biopsy proven by Banff criteria); All 20 aAMR received MP pulse, IVIG (1-2 g/Kg),10 PP treatments (1.5 to 2 plasma vol exchange/ rx) and Thymoglobulin (if ACR). On follow up 9/20 received Bortezomib 1.3mg/m2/dose IV x4 for persistent graft dysfunction with postivie DSA. Mean DSA titers (pre and post rx), eGFR, graft outcome, adverse effects infections were tracked in Bortezomib group. Graft outcome was also followed in patients with no rejection and + rejection aAMR/TCR.

Results: 9 received 10 doses of Bortezomib; Ethnicity: AA/Wh/ His/ Asian=33%(3)/33%(3)/22% (2)/ 11%(1), male 8 (89%), Age at txp :median 16.8 (3-20yrs), 7 (78%)received DDT, all received Induction (4 thymo for pre txp PRA >25%). Time to rejection: median 2.5 yrs (8 days- 8 yrs), 2 neg C4D and DSA; 1 de novo anti GBM GN and 1 had AT1R abs+. Infections: 1 oral Herpes+ oral candidiasis+ pneumonia, 1 herpes + atypical mycobacteria+ candida, 3 gastroenteritis and 1 C. difficle colitis, 1 prolonged EBV viremia and 1 cellulitis.(1.4 infections/pt) Follow up time: after txp 1-12 yr (median =3.8), postbortezomib = 0.5-9 yrs (median 1.5). Post bortezomib: eGFR improved from 58 to 79 ml/min/1.73M^2 (21%) and reduction in DSA = 36%. Other therapies: 1 Rituximab; 1 Cytoxan (anti GBM GN); 4 Thymoglobulin for TCR. Graft survival with Bortezomib: 100% at 1 and 3 yrs. 2 progressed to ESRD at 9 and 12 yrs (22% graft loss). Graft survival with no rejection (86): 92 % Graft loss overall: 24% (28/115): 4 primary non function, 2 expired with functioning grafts; Patient survival: 97.4%

Conclusions: Bortezomib was well tolerated well with few adverse effects; 36% reduction in DSA, 21% improvement in eGFR and graft loss 22%. Graft loss in children with no rejection was 8% compared to 47% with rejection (aAMR and TCR). Overall, graft loss was 24% and patient survival 97.4% as of last follow up.

TH-PO774

Fibroblast Growth Factor 23 and Anemia in Pediatric Renal Transplant Recipients

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Background: Pre-clinical studies have shown that anemia-related factors, specifically iron deficiency and increased erythropoietin (EPO), can induce FGF23 production. Studies of adult renal transplant recipients (RTR) have demonstrated independent associations between both lower iron levels and higher EPO concentrations and increased FGF23. In the present study, we evaluated cross-sectional and longitudinal associations between hematologic and FGF23 parameters in pediatric RTR.

Methods: Demographic, clinical, and standard biochemical data were collected from a cross-section of 59 pediatric RTR during routine clinic visits. Iron, EPO, C-terminal (total) FGF23 (cFGF23), and intact FGF23 (iFGF23) concentrations were measured in additional blood samples. Follow-up biochemical data and blood samples were collected from a subset of 29 patients six months later.

Results: Demographic, clinical, and baseline serum parameters are shown in **Table 1**. Neither cFGF23 nor iFGF23 was significantly associated with iron or EPO (**Table 2**). cFGF23 correlated inversely with hemoglobin (r=-0.38, p=0.003), while iFGF23 correlated positively with hemoglobin (r=0.28, p=0.03). The cFGF23-hemoglobin association remained significant after adjusting for eGFR, iron, and EPO. Change in cFGF23 over time tended to inversely correlate with change in hemoglobin (r=-0.34, p=0.07).

Conclusions: In pediatric RTR, differential associations between hemoglobin and cFGF23 vs. iFGF23 are observed, suggesting complex relationships among anemia, FGF23 production, and FGF23 metabolism that warrant further study.

Funding: Other NIH Support - T32 NIH Training Grant 5T32DK104687-04, Private Foundation Support

Table 1: Baseline demographic, clinical, and serum parameters (n=59)

Variable	N (%) / Median (IQR)
Age (years)	16 (13, 18)
Sex, Male	36 (61%)
Race	
White	41 (69%)
Asian	4 (7%)
Black	4 (7%)
Other	10 (17%)
Etiology of ESRD	
CAKUT	25 (42%)
Glomerulonephritis	15 (26%)
Other or Unknown	19 (32%)
Deceased Donor	36 (61%)
eGFR (ml/min/1.73 m^2)	66 (53, 87)
Hemoglobin (g/dL)	12.5 (11.2, 13.4)
C-terminal (total) FGF23 (RU/mL)	64 (52, 92)
Intact FGF23 (pg/mL)	115 (47, 216)
Iron (µg/dL)	81 (62, 104)
Erythropoietin (mIU/mL)	8.7 (5.8, 12.9)

Table 2: Cross-sectional Spearman rank order correlation coefficients (n=59)

C-terminal (Total) FGF23 (RU/mL)	Spearman's rho	P-value
Intact FGF23 (pg/mL)	0.09	0.52
eGFR (ml/min/1.73m^2)	-0.37	0.003
Hemoglobin (g/dL)	-0.38	0.003
Erythropoietin (mIU/mL)	0.22	0.09
Iron (µg/dL)	-0.09	0.47
Intact FGF23 (pg/mL)	**Spearman's rho**	**P-value**
eGFR (ml/min/1.73m^2)	-0.06	0.65
Hemoglobin (g/dL)	0.28	0.03
Erythropoietin (mIU/mL)	-0.24	0.08
Iron (µg/dL)	-0.01	0.94

TH-PO775

Risk Factors for Early Readmission Post-Pediatric Kidney Transplantation: A Multicenter Study

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Background: Early hospital readmissions are associated with morbidity, mortality, significant health care costs and poor outcomes. To date, no published studies have evaluated risk factors for early readmission following pediatric kidney transplantation.

Methods: Retrospective chart review was performed for all pediatric kidney transplant recipients from 2012 – 2017 at the UCSF, UCD, UCLA and UT at San Antonio. Early hospital readmissions were defined as any unplanned admission within 30 days of being discharged from the hospital following a kidney transplant; admissions for elective procedures were excluded. Baseline characteristics evaluated included age, insurance type, race, prior dialysis, donor type, ischemia times, placement of transplant, induction agent, length of hospital stay, weekend discharge, hypertensive medications at discharge, tacrolimus levels, hemoglobin, albumin, and creatinine at discharge. Data regarding readmissions was collected, and analyzed using Student t-test for continuous variables and the chi square test for categorical variables.

Results: There were 308 pediatric kidney transplant recipients. The rate of early readmission was 31%. The leading causes for readmission were: elevated creatinine (30%), vomiting/diarrhea with dehydration (13%) and tacrolimus toxicity (8%). Discharge on weekend ($p<0.05$) and acute change in tacrolimus trough on day of discharge from 24-hours prior to discharge ($p=0.05$) significantly predicted readmissions. Other predictors that did not meet our criteria for significance for readmission included: elevated tacrolimus level on day of discharge($p=0.08$), more than 2 anti-hypertensives at discharge ($p=0.07$) and presence of ureteral stent at discharge ($p=0.07$). No difference was seen in readmission rates based on age, donor type, ischemia times, induction agent or length of initial hospitalization.

Conclusions: The rate of early readmissions for our pediatric population was similar to that reported in adult patients. Weekend discharge and change in tacrolimus significantly predicted readmission. Hospital course and discharge level factors were more predictive than patient related factors providing modifiable clinical factors for targeted interventions to reduce rate of readmissions in pediatric patients.

TH-PO776

Tandem Plasmapheresis on Continuous Renal Replacement Therapy in Pediatrics

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Background: Plasmapheresis (TPE) has been used successfully to reduce concentration of pathogenic antibodies, immune complexes, cryoglobulins and lipoproteins Continuous renal replacement therapy (CRRT) is the treatment modality for acute kidney injury, fluid overload and electrolyte and metabolic imbalance for unstable patients. Reported experience about simultaneous use of TPE and CRRT (referred to as tandem TPE) in pediatric (ped) patients (pts) is scarce.

Methods: We describe tandem TPE experience from our institution. Retrospectively reviewed ped pts receiving tandem TPE from 2013 to 2016. Centrifugal based TPE was performed, all CRRT patients received hemodiafiltration at minimum starting dose of 2000 ml/1.73m2/hour with regional citrate anticoagulation. For tandem TPE apheresis lines were "Y"ed in the circuit in parallel without using additional anticoagulation.

Results: 63 pts received tandem TPE, for a total 378 of TPE procedures on 1676 days of CRRT. Age ranged from newborn to 19 years old, weights ranged from 2.31 to 112.3 kg (17 pts were <10 kg and < 1 year old). Most common indications were coagulopathy and hepatic encephalopathy caused by acute liver failure (20 pts), thrombocytopenia associated multi-organ failure (TAMOF) (19 pts) and thrombotic microangiopathy (5pts). Median number of TPE session per pt was 5 (IQR:3;7). Median number of CRRT days was 12 (6; 37). All treatments were completed successfully. 57 (90%) patients had hypocalcemia and 59 (94%) patients had hypercalcemia at least one time during the treatments. 27 (43%) patients had citrate accumulation (defined by plasma total calcium/ionized calcium >2.5 mmol) during the treatments. All episodes were asymptomatic. Case mortality rate was 40%. Time to CRRT and TPE initiation was longer in non-survivors (NoS) vs survivors (3 d (1,9) vs 1 (1,2) & 4 d (2,13) vs. 2 (1,3) TPE) ($p=0.02$). PRISM score at ICU admission of NoS is significantly higher ($p=0.031$).

Conclusions: Tandem TPE treatment during CRRT can be effectively used in pediatric pts over a broad age and weight range. Complications including hypocalcemia are common though pts remained asymptomatic. Complex treatments need to be planned carefully with interdisciplinary team to address indications, technicalities and complications.

TH-PO777

Renal Replacement Therapy of Hyperammonaemia in Pediatric Patients

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Background: Hyperammonemia is the accumulation of ammonia in the blood that may result in an acute life-threatening event in pediatric populations. Management of hyperammonemia proves to be difficult in pediatric populations given the non-specific clinical symptoms, the age-specific etiologies, and the lack of consensus in the treatment plan. In our review, we sought to systematically search the published literature to comprise guidelines for non-renal replacement therapy (RRT) and renal replacement therapy in pediatric patients.

Methods: A database search using PubMed/Medline, Embase and Cochrane was performed to include publications about hyperammonemia and renal replacement therapy in the pediatric population. An expert panel of pediatric nephrologists made up the workgroup and they were responsible to review and propose recommendations for renal replacement therapy guidelines for hyperammonemia children.

Results: The initial search returned a total of 477 citations of which only 25 studies met our inclusion criteria. A total of 132 patients were included in the study. Hemodialysis indications included hyperammonemia refractory to medical management and hyperammonemia coma. The most common of hyperammonemia was inborn errors of metabolism (IEM). Among the type of RRT used, CRRT had a 60% success rate and peritoneal dialysis (PD) had a 65% success rate

Conclusions: We recommend initiating renal replacement therapy when blood ammonia levels >150µmol/L with coma or cerebral edema and when blood ammonia level > 400µmol/L refractory to non-RRT measures. Intermittent hemodialysis is more effective than PD or CRRT as it clears ammonia faster but associated with rebound hyperammonemia and can cause hypotension and rapid osmotic shifts. PD is a quick alternative to immediate hyperammonemia management if CRRT is not available. Treating with high dose-CRRT allows for rapid clearance of ammonia done on a single dialysis run. A hybrid method of CRRT with ECMO support can increase the patient's blood volumes, allows for use of a larger cannula, avoids hemodynamic instability.

TH-PO778

A Case Series of Iodine-Induced Hypothyroidism in Children on Peritoneal Dialysis

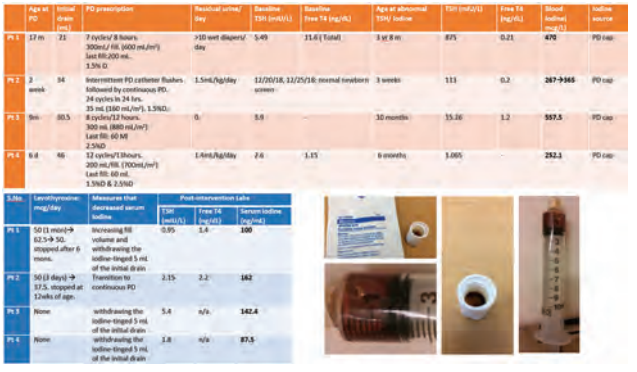
Sai Sudha Mannemuddhu,[1] Heather Morgans,[3] Naile Tufan pekkucuksen,[4] Bradley A. Warady,[2] Lawrence R. Shoemaker.[4] *[1]University of Florida. College of Medicine., Gainesville, FL; [2]Children's Mercy Kansas City, Kansas City, MO; [3]Children's Mercy Hospital, Kansas City, MO; [4]University of Florida, Gainesville, FL.*

Background: Young patients with end-stage renal disease who receive chronic peritoneal dialysis (CPD) are at increased risk for thyroid dysfunction. An extremely rare cause of thyroid dysfunction in these patients is iodine exposure. We report four patients who received CPD and developed Iodine overload and secondary hypothyroidism.

Methods: case series

Results: The 4 children, 3 weeks to 3.5 years of age, were cared for in two academic institutions in 2017-2019. Three patients were on automated cycler PD and one received manual flushes over a week and was on continuous PD. PD fill volumes ranged from 160 to 880 mL/m^2 BSA. They had normal baseline thyroid stimulating hormone (TSH) levels or normal newborn screens. They were on PD for periods of 1 week to 27 months, with median age of 6 months at presentation. 3 out of 4 patients had high TSH values ranging from 15-875 mIU/L, 2 of the 4 had a low free T4 from 0.2- 0.21 ng/dL, and all 4 had high serum iodine levels: 222-557.5 mcg/L (normal: <100 mcg/L). In every case, a transfer set with betadine gauge was utilized as part of their PD procedure. One patient developed overt hypothyroidism and heart failure and one experienced growth failure, while the other two were asymptomatic. Two patients required temporary treatment with levothyroxine (2.5 months – 6 months). Iodine levels decreased in all patients after switching them to continuous manual PD or by withdrawing the first 5 mL of iodine tinged fluid from the transfer set before connecting them to the PD cycler. Despite extensive investigation, no alternative sources of iodine exposure were detected.

Conclusions: Excessive iodine exposure and the potential for thyroid dysfunction, especially during infancy, is a poorly recognized complication of CPD. Increased awareness among nephrologists is needed so that prevention strategies and regular monitoring for this complication can be instituted.



Patient summary table. syringe and PD cap with iodine tinged fluid.

TH-PO779

Physician Practices Regarding Physical Activity Restriction in Pediatric Hemodialysis Patients: A Qualitative Study

Raja Dandamudi,[1] Katherine Twombley,[2] Joseph T. Flynn,[3] Aadil K. Kakajiwala,[4] Deepa H. Chand.[5] *[1]Washington University in St. Louis School of Medicine, Glencoe, MO; [2]Medical University of South Carolina, Charleston, SC; [3]Seattle Children's Hospital, Seattle, WA; [4]Washington University in St Louis, St. Louis, MO; [5]Abbvie, Chicago, IL.*

Background: Children with chronic kidney disease (CKD) due to multiple hospitalizations and interventions have less physical activity. This sedentary lifestyle in CKD is associated with a higher cardiovascular mortality risk. In those patients receiving hemodialysis (HD) time spent on dialysis and restrictions on physical activity due to access also contribute. No consensus exists regarding physical activity restrictions based on vascular access type. The aim of the study is to assess pediatric nephrologists' practices regarding physical activity restrictions in children receiving HD.

Methods: The study was conducted through the Midwest Pediatric Nephrology Consortium using an anonymous, self-administered survey of pediatric nephrologists to evaluate the activity restrictions placed on HD patients with arteriovenous fistulae (AVF) and central venous catheters (CVC). The survey consisted of 19 items, 6 questions detailed physician characteristics with the subsequent 13 addressing physical activity restrictions.

Results: 35 responses (35% response rate) were received Average years in practice after fellowship: 11.5 years (range: 1-35). Dialysis units had 1– 12 stations (mean 6) Physical activity restrictions by physicians are summarized in tables. None of the participants reported accesses damage or loss that was attributed to physical activity and sport participation. Physicians practice is based on their personal experience, standard practice at their hemodialysis center and the clinical practices they were taught.

Conclusions: There is no consensus amongst pediatric nephrologists about physical activity that can be allowed in children receiving HD. Due to the lack of objective data, individual physician beliefs have been utilized to restrict activities in the absence of any deleterious effects to accesses. This survey clearly demonstrates the need for more prospective and detailed studies and guidelines regarding the physical activity and dialysis access care in order to optimize quality of care in these children.

Table I

Age groups(in Years) with number of patients in each group				
<2	2-5	6-10	10-18	>18
17	17	30	78	21

Table II

Type of Physical Activity	% physicians restricting	Comments
Push-up exercise	27	
Chin-up Exercise	34	
Weight Lifting	25	Those allowing weight use light weights of 5-10 lbs.
Organized sports	24	Among the organized sports wrestling and martial arts were universally restricted. Football, field hockey, ice hockey was also restricted by most of the physicians. 2 physicians restricted using Rifle/Shotgun.

Table III

Water exposure restrictions in patients with CVC	% physicians restricting activity
Showering	34
Bathing	66
Swimming in chlorinated pools	95
Swimming in Oceans	97.5
Swimming in fresh water	0

TH-PO780

Colostomy in Children on Chronic Peritoneal Dialysis

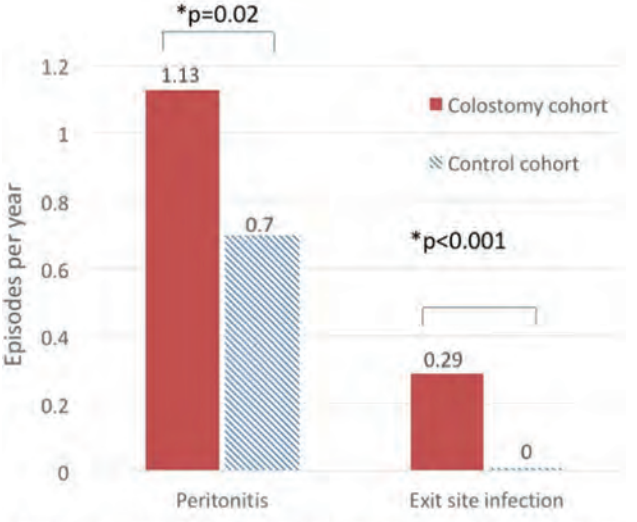
Yu hin E. Chan,[1] Dagmara Borzych-duzalka,[4] Franz S. Schaefer,[3] Bradley A. Warady.[2] International Pediatric Peritoneal Dialysis Network *[1]Paediatric Nephrology, Hong Kong Children's Hospital, Hong Kong, Hong Kong; [2]Children's Mercy Kansas City, Kansas City, MO; [3]University of Heidelberg, Heidelberg, Germany; [4]Medical University of Gdansk, Gdansk, Poland.*

Background: The aim of this study was to evaluate the outcome of children on chronic peritoneal dialysis (PD) with a concurrent colostomy.

Methods: Patients were identified through the International Pediatric Peritoneal Dialysis Network (IPPN) registry. Age-matched controls were randomly selected from the registry. Data were collected through the IPPN database and a survey disseminated to all participating sites.

Results: 15 centers reported 20 children who received chronic PD with a co-existing colostomy. The commonest cause of end-stage kidney disease was congenital anomalies of kidney and urinary tract (n=16, 80%). The main reason for placement of a colostomy was anorectal malformation (n=13, 65%). The median age at colostomy creation and PD catheter (PDC) insertion were 0.1 [IQR, 0-2.2] and 2.8 [IQR 0-2.2] months, respectively. The colostomies and PDCs were present together for a median 18 [IQR, 4.9-35.8] months. The median age at PDC placement in 46 controls was 4.2 [IQR, 3.6-10.8] months. 14 patients (70%) developed 39 episodes of peritonitis. The annualized peritonitis rate was significantly higher in the colostomy group (1.13 vs 0.70 episodes per patient year; p=0.02). Predominant causative microorganisms were staphylococcus aureus (15%) and pseudomonas aeruginosa (13%). There were 10 exit site infections (ESI) episodes reported exclusively in colostomy patients. Seven children (35%) died during their course of PD, in two cases due to peritonitis.

Conclusions: Although chronic PD is feasible in children with a colostomy, it is associated with an increased risk of peritonitis, ESI, and mortality. Continued efforts to reduce the infection risk for this complex patient population are essential.



Catheter-associated infection rates in the colostomy and control cohorts

TH-PO781

Mortality in Children with ESRD: A Guatemalan Retrospective Cohort Study

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Background: Mortality rates and long-term survival data in ESRD children are sparse although different modalities of RRT have been used during decades We evaluate the mortality overtime in a tertiary hospital in Guatemala

Methods: After ethics approval, we performed a single center retrospective cohort study of all patients with ESRD younger than 18 years, between Jan2015 and Dec2017 Mortality rate was expressed as number of deaths/1000patients Mortality incidence rate, expressed as number of deaths/100patient-years was determined by, sex, RRT and age Long-term survival rates were calculated by Kaplan Meier test and significant confirm by Log Rank and Breslow tests

Results: A total of 370 charts were reviewed. Of those, 115 were from PD, 221 from HD and 34 from transplant. During the study period 25 patients died. Of those, 52%(13/25) were female, the mean age was 12.7yr(SD 3.4), 72%(18/25) were from HD and the rest from PD(7/25). No deaths from transplanted patients were reported during the study. The mortality rate in 2015, 2016 and 2017 were 50, 50 and 32/1000patients. The mortality incidence rate was 8.20/100patient-years. No difference in mortality incidence rate was found by sex (fem 8/100patient-years, masc 8.4/100patient-years). The highest incidence of mortality rate was found in the HD and in the 5-9 age group (17.35/100patient-years, 20/100patient-years). When analyzing long-term survival rates using Kaplan Meier, the overall mortality rate at 3 years was 20%; no significant difference was identified by sex (p, 0.509) nevertheless; a significant difference was found between HD(38%) and PD(16%), p, 0.001. Regarding age, no significant difference in mortality rate between the 5-9, 10-14 and 15-18 age groups was identified at 2 years (25%,15%,10%), (p, 0.174)

Conclusions: In our study, the overall mortality incidence rate was higher than reported in literature Mortality rate, incidence mortality rate and long-term survival were similar between the sexes. Among age, the 5-9 years group demonstrated the highest mortality rates Regarding RRT, the incidence mortality rates in PD is comparable with literature; however, our HD mortality rates are 4 times higher than what has patient-years Increasing the proportion of children treated with renal transplantation and PD rather than HD can improve survival further and costs in our centre

TH-PO782

The Effect of Socioeconomic Status and Distance to Specialist Hospital on Access to Paediatric Nephrology Care in England

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Background: For children with end-stage kidney disease (ESKD), transplantation is the preferred treatment of choice, offering improved survival and quality of life. Pre-emptive transplantation (PET) is advocated as best practice. Access however is limited by late presentation of kidney disease, defined as starting renal replacement therapy (RRT) within 90 days of first presentation to a nephrologist. In this study we aim to explore whether socio-economic status (SES) or geographical remoteness from centre are associated with 1) timing of presentation to nephrology services and 2) access to PET.

Methods: A cohort study using UK Renal Registry and NHS Blood & Transplant data from 01/01/1996-31/12/2016 was performed. Children in England aged up to 16 years receiving chronic RRT were included. Exposures of interest were distance from home to paediatric nephrology unit (per 10km) and SES, as measured by the UK Index of Multiple Deprivation (IMD) quintiles. Study outcomes were 1) late presentation and 2) PET (transplant recorded as first RRT modality). Late presenters were excluded from the PET analysis. Multivariable logistic regression analyses were performed, covariates were determined *a priori* and included age, gender, ethnicity, renal disease and time-period.

Results: During the study-period, 1856 children received RRT (776 females, 41.8%), with a median age of 3.8 years at presentation. Of these, 426 were late presenters (24.4%); 37.4% of non-late presenters (n=1271 without missing data) underwent PET. No association was seen between distance or SES with late presentation, on crude or adjusted analyses. As SES increased, odds of PET increased by 12% per quintile (OR 1.12, 95% CI 1.02, 1.23, p=0.02). Similar findings were seen among White patients only to exclude any effect of ethnic minorities. Increasing distance from centre was strongly associated with PET in crude analyses, however this effect was markedly attenuated (p=0.16) in the fully adjusted model.

Conclusions: SES or distance from centre are not associated with late presentation of childhood kidney disease. Access to PET increases with SES. Clinicians should be aware of this finding and ensure timely support is provided to disadvantaged families in the pre-dialysis phase to ensure optimum access to early transplantation.

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TH-PO783

Differential Metabolomic Profile Within Primary Hyperoxaluria Patients

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Background: The three types of primary hyperoxaluria (PH) are liver specific enzyme defects inducing endogenous oxalate overproduction, thus hyperoxaluria, urolithiasis and/or nephrocalcinosis, as well as intrarenal deposition of calcium oxalate crystals, leading to chronic kidney disease and renal failure (PH1&2). Severe infantile cases (PH1) directly present systemic crystal deposition (oxalosis), but otherwise the clinical progression of PH subtypes profoundly differs, for unknown reasons. PH patients bear pathogenic mutations in either *AGXT* (PH1), *GRHPR* (PH2) or *HOGA1* (PH3) genes, causing a misbalanced hepatic glyoxylate metabolism that overproduces oxalate. Here, we aimed to unveil other misbalanced metabolites in PH1, PH2 and PH3 both in mouse models and patients to understand the heterogenous pathogenesis of PH, to reveal new biomarkers for differential diagnosis and to find modulators of their immune response.

Methods: All patients signed an informed consent. Serum from 19 PH1, 5 PH2, 7 PH3 and 9 control patients as well as plasma from 4 PH1, 4 PH3, 4 PH1/PH3 and 4 wildtype mice were obtained. Samples were analyzed by the global metabolomics technology of Metabolon®, and stool samples (18 PH1, 6 PH3 patients; 4 PH1 and 4 wt mice) by the Institute of Microecology (Germany). Data followed log transformation and Welch's two-sample t-test for statistical analysis.

Results: PH3 mice metabolome showed stronger differences to wt than PH1, mostly in aminoacid, carbohydrate and xenobiotic related metabolism. Both PH1 and PH3 mice shared a strong misbalanced lipid metabolism. Xenobiotic metabolism correlated with differential microbiota in PH1 compared to wt mice. Ongoing human metabolome and microbiota analysis is aimed at translating our findings into the human situation.

Conclusions: Our preliminary findings suggest: i) increased levels of diverse metabolites may reflect impaired kidney function accumulating these compounds in the blood; ii) general reduction on lipid levels may reflect a weakened oxidative metabolism for energy production and impaired intracellular cascades, some of them related to inflammatory signaling; iii) microbiota may influence PH pathogenesis. Further exploration of candidate metabolites *in vitro* and *in vivo* may help elucidating their role in mechanisms of disease and their use as biomarkers for diagnosis and treatment.

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TH-PO784

Impact of Dialysis Adequacy on Morbidity in Children on Chronic Hemodialysis: A North American Pediatric Renal Trials and Collaborative Studies Report

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Background: Reliance on small solute clearance as a measure of dialysis adequacy fails to fully quantify the intended clinical effects of dialysis therapy. We aimed to study the relationship between dialysis adequacy, as measured by single-pool Kt/V (spKt/V) and urea reduction ratio (URR), and patient morbidity as measured by growth, nutrition and anemia control.

Methods: We included 391 patients (median age of 14.3 years [range: 1.0 - 18.9]) in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) database receiving chronic hemodialysis three times a week. Using goal sp Kt/V of 1.2-1.5 and URR of 65-75% we compared weight, height, albumin, hemoglobin (Hb) and erythropoiesis stimulating agent (ESA) dose at 12 months from initiation of HD (initiated between Jan '03 to Dec '18). Kruskal-Wallis test was used to compare these measures in patients at, above, and below goal values of dialysis adequacy.

Results: Results of the univariate analysis are summarized (Table 1A & B). For patients with URR and spKT/V above goal, the median weight z-scores was 0.6 and 0.7 points lower when compared to those with values within goal levels. Similarly, for patients with URR and spKT/V above goal, the height z-scores was 1.0 and 0.8 lower than the within goal levels. Patients with URR < 65% had 0.7 g/dL higher median Hb compared to within goal levels of URR. We noted no significant relationship between dialysis adequacy and serum albumin, ESA doses

Conclusions: Preliminary results show significantly lower weight and height in patients with dialysis adequacy above goal values. This may reflect low volumes of distribution (V). Further analysis of the database at multiple time points from initiation of HD with help describe associations between dialysis adequacy and patient morbidity.

Univariate analysis between URR (1A) and Kt/V (1B) and measures of patient morbidity at 12 months after initiation of dialysis

Table 1A

	URR < 65%	URR 65-75%	URR > 75%	p-value
		Median (Min, Max)		
Age at initiation in years	15.4 (9.6 , 18.8)	14.4 (1.0 ,18.9)	13.8 (1.6 ,18.8)	0.03
Weight z-score	0.5 (-5.7, 2.7)	-0.7 (-8.8, 2.8)	-1.3 (-10.0, 4.8)	< 0.01
Height z-score	0.3 (-5.4, 2.3)	-1.2 (-7.4, 5.3)	-2.0 (-7.2, 8.6)	< 0.01
Albumin (g/dL)	3.9 (2.2 , 4.8)	3.9 (2.1, 4.8)	3.9 (1.6, 9.9)	0.97
Hemoglobin (g/dL)	12.2 (10.4, 14.3)	11.5 (6.5, 15.8)	11.3 (7.1, 14.9)	< 0.01
Erythropoietin dose (units/kg/week) [n = 269]	121.8 (34.5, 750.0)	160.4 (0.2, 1822.1)	200.0 (20.6, 2142.9)	0.08
Darbepoetin dose (mcg/kg/week) [n = 62]	0.61 (0.12, 1.09)	0.46 (0.02, 1.22)	0.75 (0.01, 3.29)	0.04

Table 1B

	Sp Kt/V < 1.2	Sp Kt/V 1.2 to 1.5	Sp Kt/V > 1.5	p-value
		Median (Min, Max)		
Age at initiation in years	14.4 (1.0 ,18.4)	14.9 (1.4 ,18.8)	13.8 (1.6 ,18.9)	0.07
Weight z-score	-0.5 (-5.7, 2.4)	-0.4 (-10.0, 2.7)	-1.1 (-8.8, 4.8)	< 0.01
Height z-score	-1.7 (-5.4, 2.0)	-1.0 (-7.2, 5.3)	-1.8 (-7.4, 8.6)	< 0.01
Albumin (g/dL)	3.9 (1.6 , 4.9)	3.9 (2.3 , 4.8)	3.9 (2.0, 9.9)	0.85
Hemoglobin (g/dL)	11.5 (10.2, 14.0)	11.7 (6.5, 15.8)	11.3 (7.1, 14.9)	0.06
Erythropoietin dose (units/kg/week) [n = 269]	203.9 (52.2, 750.0)	156.3 (4.1, 874.6)	184.6 (0.2, 2142.9)	0.11
Darbepoetin dose (mcg/kg/week) [n = 62]	0.93 (0.61, 1.09)	0.50 (0.04, 2.26)	0.53 (0.01, 3.29)	0.26

TH-PO785

Metabolomic Profiling for Discovery of Biomarkers of Neurocognitive Impairment in Children with CKD

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Background: Mechanisms underlying neurocognitive impairment in CKD remain unknown. We sought to perform the first large-scale discovery of novel blood metabolite biomarkers of neurocognitive impairment in children with CKD.

Methods: Untargeted GC/MS2 and LC/MS2-based metabolomics quantification (Metabolon) was performed on baseline plasma samples from 498 Chronic Kidney Disease in Children (CKiD) participants. We applied linear regression models to examine the cross-sectional association between standardized, log transformed metabolites (n=825) and intellectual functioning (IQ score), adjusted for demographics, CKD-related clinical characteristics, and socioeconomic status (SES). Statistical significance was determined using a threshold to keep the false discovery rate (FDR) <0.05.

Results: Cohort characteristics were: 312 (63%) male; median age 12 years (IQR 8,15); median eGFR 52 mL/min/1.73m^2 (IQR 38, 64); 377 (76%) non-glomerular diagnosis. Median IQ score was 99 (IQR 87, 108). In unadjusted analyses, 13 metabolites were associated with IQ score. (Figure) Two metabolites, 2-hydroxyarachidate (a fatty acid) and xanthurenate (a product of tryptophan metabolism), were positively associated with IQ independent of age, sex, race, BMI z-score, hypertension, low birthweight/prematurity, glomerular vs. non-glomerular diagnosis, duration of CKD, proteinuria and estimated glomerular filtration rate (eGFR). With additional adjustment for SES, no metabolite associations with IQ were statistically significant.

Conclusions: Untargeted metabolomic profiling identified two metabolites associated with IQ in children with CKD that were independent of most demographic and CKD-related clinical factors, although the inclusion of SES eliminated the statistical significance of these relationships. Further studies are needed to extend these analyses to other neurocognitive domains and delineate mechanisms.

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		Unadjusted		FDR	Adjusted (age, sex, race, BMI, hypertension, G vs. NG diagnosis)		FDR	Adjusted (plus eGFR, CKD duration, proteinuria, low birthweight/prematurity)		FDR
		β (95% CI)	p-value	p-value	β (95% CI)	p-value	p-value	β (95% CI)	p-value	p-value
Overall Cohort										
2-hydroxyarachidate*	Fatty Acid Monohydroxy	6.07 (3.59, 8.55)	0.000002	0.002	5.61 (3.10, 8.11)	0.000013	0.011	5.40 (2.83, 7.97)	0.000044	0.027
xanthurenate	Tryptophan	2.81 (1.24, 4.39)	0.000496	0.040	-	-	-	3.54 (1.81, 5.26)	0.000061	0.027
isovalerylcarnitine (C5)	Leucine, Isoleucine and Valine	-4.41 (-6.95, -1.88)	0.000460	0.040	-	-	-	-	-	-
1-myristoylglycerol (14:0)	Monoacylglycerol	5.92 (1.78, 5.27)	0.000085	0.027	-	-	-	-	-	-
5alpha-pregnan-3beta,20alpha-diol disulfate	Progestin Steroids	-2.28 (-3.57, -0.99)	0.000580	0.040	-	-	-	-	-	-
4-oxo-retinoic acid	Vitamin A	4.24 (2.00, 6.48)	0.000225	0.037	-	-	-	-	-	-
sphingomyelin (d18:2/24:1, d18:1/24:2)*	Sphingomyelins	-13.21 (-19.82, -6.61)	0.000097	0.027	-	-	-	-	-	-
tryptophan	Tryptophan	9.70 (4.43, 14.97)	0.000320	0.040	-	-	-	-	-	-
sphingomyelin (d18:2/24:2)*	Sphingomyelins	-7.05 (-11.10, -3.00)	0.000681	0.045	-	-	-	-	-	-
dihomo-linoleoylcarnitine (C20:2)*	Fatty Acid Acyl Carnitine	-4.27 (-6.48, -2.05)	0.000176	0.036	-	-	-	-	-	-
adrenoylcarnitine (C22:4)*	Fatty Acid Acyl Carnitine	-3.51 (-5.45, -1.58)	0.000403	0.040	-	-	-	-	-	-
octadecanedioate (C18:1-DC)*	Fatty Acid Dicarboxylate	3.97 (1.77, 6.17)	0.000422	0.040	-	-	-	-	-	-
N6-methyllysine	Lysine	2.88 (1.23, 4.52)	0.000555	0.040	-	-	-	-	-	-

TH-PO786

Outcomes of Maintenance Dialysis in Children Younger Than 24 Months: A NAPRTCS Report

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Background: Peritoneal dialysis (PD) is the preferred mode of renal replacement therapy (RRT) in infants and young children with end-stage renal disease (ESRD). Hemodialysis (HD) is less used due to technical challenges and risk of complications in smaller patients. There are limited data on the impact of different dialysis modalities on clinical outcomes in this group

Methods: Data were extracted from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry. Demographic, clinical, and laboratory data on patients < 24 months age between January 1992 and December 2018 were analyzed. We compared patient survival and access to kidney transplantation using log rank test between children treated with PD or HD

Results: 1014 infants initiated dialysis therapy on PD; 114 on HD. Mean(SD) age at PD onset was 6.9 (6.8) months and at HD onset was 12.0 (7.2) months. Infants treated with PD more often had congenital anomalies of the kidney and urinary tract/obstructive uropathy (55% vs 40%, p<0.05). At 1, 6 and 12 months post dialysis onset, PD patients had significantly lower serum albumin (Figure 1). Hemoglobin was lower in HD patients at 1 and 6 months, but similar at 12 months between the groups. Time to transplant was lower for HD patients, but patient survival on dialysis was similar (Figure 2)

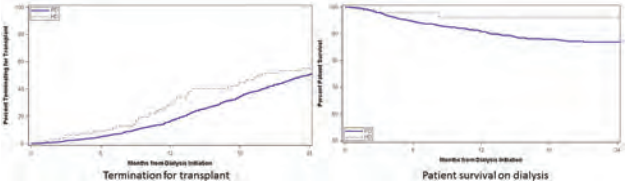
Conclusions: Although HD is not first line modality for RRT in younger children, 10% of children < 2years age start maintenance dialysis on HD therapy. Patients starting HD are more likely to be older and non-white. Patient survival on dialysis is similar irrespective of dialysis modality

Table 1: Characteristics of young children on peritoneal and hemodialysis

	Peritoneal Dialysis	Hemodialysis
N	1011	114
Age (months)	6.9 (6.8)	12.0 (7.2)*
Female	335 (33.1%)	41 (36.0%)
Non-White	388 (38.4%)	58 (50.9%)*
Primary disease		
Congenital anomalies of kidneys and urinary tract/Obstructive uropathy	568 (56.2%)	45 (39.5%)*
Other	443 (43.8%)	69 (60.5%)
Hematocrit (%)		
At 1 month	32.1 (5.9)	28.8 (6.4)*
6 month	32.9 (5.6)	30.1 (7.0)*
12 month	32.7 (5.6)	32.1 (5.6)
Albumin g/dL		
At 1 month	3.2 (0.8)	3.7 (0.7)*
6 month	3.4 (0.6)	4.0 (0.6)*
12 month	3.5 (0.6)	4.2 (0.6)*

*p<0.05

Patient Characteristics



Time to transplant and survival on dialysis

TH-PO787

Cerebral Oxygenation Changes in Pediatric Chronic Hemodialysis

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Background: Intradialytic circulatory stress has been well described in adults as tissue ischemia to diverse organs (heart, gut and brain) during hemodialysis (HD). We aimed to determine if pediatric patients had intradialytic changes in cerebral oximetry (CEOx) by using near infrared spectroscopy (NIRS), a continuous, non-invasive method that uses infrared light to penetrate the skull and provides real time regional oxygen saturation (rSO2) from the frontal cortex. NIRS correlates well with more invasive measures of cerebral perfusion, doppler ultrasound and MRIs.

Methods: Prospective study in 14 patients <21 years old with more than 90 days on HD, on room air, without congenital heart disease. We used continuous NIRS and pulse oximetry (SpO2) monitoring, and obtained co-oximetry measured central venous oxygen saturation (SvO2) at the start, middle, and end of HD treatment. CEOx data was extracted at the exact times SvO2 was measured. Data collected over 2 HD treatments for each patient.

Results: Continuous monitor of spO2 showed no hypoxia during recorded HD treatments. Svo2 decreased from HD start 73(SD=7.7) to end of treatment 64.8(SD=9.1), mean difference 8.17(CI 2.3 to 14) p=0.01; CEOx also decreased from 74(SD=6.3) to 70(SD=5.7) mean difference 3.8(CI 1.5 to 6.2) p=0.002. For every 1 unit drop of SvO2 the CEOx decreased by 0.5 at the end of HD (β-1.0 (CI -2.6 to -0.4)).

Conclusions: Intradialytic CEOx and SvO2 falls significantly during HD in the absence of declining SpO2. These data suggest HD leads to cerebral dysoxia, though it is unclear whether the mechanism is related to decrease oxygen delivery, increased extraction or a combination of both at the tissue level. Future studies are needed to explore these physiological changes as well as the impact the cognitive functioning of children receiving chronic HD.

TH-PO788

Guidelines on Prescribing Prolonged Intermittent Renal Replacement Therapy (PIRRT) in a Child in an ICU Setting

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Background: Renal replacement therapies (RRT) are a cornerstone in the management of critically ill children who are often hemodynamically compromised. By virtue of their small size and large volume required in the extracorporeal circuit it often becomes difficult to perform conventional hemodialysis to provide RRT support in these children. Continuous renal replacement therapy (CRRT) is the accepted alternative but is associated with the high cost and limited availability. Thus, in resource-poor settings, peritoneal dialysis becomes the mainstay of management but has the disadvantages of increased risk of infections, inability to control the ultrafiltration and interfering with the ventilatory parameters. Prolonged intermittent renal replacement therapy (PIRRT) which is RRT given intermittently over a prolonged session is a modality that provides the advantages of a CRRT in a cost-effective way. PIRRT has been widely accepted in adults but data on PIRRT in children is sparse.

Methods: We searched the PubMed/Medline, Embase and Cochrane Database for all the publications on PIRRT and two experts from the Pediatric Continuous Renal Replacement Therapy (PCRRT) Workgroup assessed titles, abstracts, and full-text articles for extraction of data. The data from the literature search was shared with the PCRRT workgroup and expert panel recommendations were developed.

Results: We recommend that sustained low-efficiency dialysis (SLED) be initiated for all critically ill children requiring RRT along with inotropic support if necessary. SLED should also be initiated for acute kidney injury (AKI) with multi-organ dysfunction and poor Pediatric Risk of Mortality (PRISM) scores. The rates of blood flow and dialysate flow are decided based on hemodynamic stability and are usually similar to CRRT. Duration of therapy may be anywhere between 6-18 hours and may be performed 3 times a week or more. Any machine that is used for IHD may be used for delivering PIRRT provided it has the provision of lowering the blood flow and dialysate flow rates and can prolong the duration of therapy to 6-8 hours.

Conclusions: We recommend that sustained low-efficiency dialysis (SLED) be initiated for all critically ill children requiring RRT along with inotropic support if necessary.

TH-PO789

Identifying Factors Associated with Mortality in Pediatric Hemodialysis Patients Using a Machine Learning Approach

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Background: Mortality in pediatric end-stage renal disease patients is ≥30 times higher than in healthy children, and higher on chronic dialysis than after kidney transplantation. We aimed to explore factors associated with mortality on chronic hemodialysis (HD) in patients having started HD at pediatric age.

Methods: Data used originate from a cohort of patients <30 years on chronic HD since childhood, having received thrice-weekly HD between 2004 and 2016 in outpatient DaVita dialysis centres. Patients with 5-year follow-up since initiation of HD, or death within 5 years, were included. 106 variables ("features") relating to demographics, HD treatment and laboratory measurements were considered as predictors for 5-year mortality using a machine learning approach (random forest). Among correlated features (ρ>0.7) only the variable with higher clinical significance was retained. Accuracy was evaluated by 30 bootstraps.

Results: 363 patients were included in the analysis (n=84 <12 years and n=279 of 12-19 years at initiation of HD). Albumin and lactate-dehydrogenase were retained as the two most important features of 5-year mortality, other features retained in the final model included: lymphocyte count, red blood cell distribution width, red blood cell count, hemoglobin, z-score weight for age, post-HD systolic blood pressure, albumin/globulin ratio, ultra-filtration rate, creatinine and total spKt/V. Mortality was predicted with an accuracy of 81% (standard deviation: ±5%).

Conclusions: Mortality in paediatric patients on chronic HD is associated with multifactorial unspecific markers of nutrition, inflammation, anemia, cardio-vascular risk and dialysis dose. This highlights importance of multimodal intervention strategies besides adequate HD treatment. The association with lactate-dehydrogenase was not expected, but may indicate relevance of blood-membrane interactions, organ-malperfusion or metabolic changes during chronic HD treatment.

TH-PO790

CG200745, a Novel Histone Deacetylase Inhibitor, Attenuates Kidney Fibrosis in a Murine Model of Alport Syndrome

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Background: Histone modification has been a target of therapy for progressive renal fibrosis. Here we report the protective effect of CG200745, a novel histone deacetylase inhibitor, on tubulointerstitial fibrosis in a murine model of Alport syndrome.

Methods: Col4a3$^{-/-}$ mice were used as a murine model of experimental AS. To examine the effects of CG200745 on the kidney of Col4a3$^{-/-}$ mice, CG200745 was orally administered in drinking water. To investigate the cellular mechanisms, HK-2 cells, a human proximal tubular epithelial cell line, were treated with CG200745 and/or angiotensin II (Ang II).

Results: Expression of fibrosis markers, such as αSMA, fibronectin and collagen I, significantly increased in Col4a3$^{-/-}$ mice at the age of 7 weeks, which was counter-regulated by CG200745 treatment, indicating attenuation of kidney fibrosis. CG200745 prevented the activation of transforming growth factor β (TGFβ) and its downstream Smad signaling in the kidney of Col4a3$^{-/-}$ mice. As critical upstream regulators of TGFβ signaling, Ang II, angiotensin converting enzyme (ACE), and TNFα-converting enzyme were upregulated and ACE2 and Mas receptor were downregulated, respectively, in the kidney of Col4a3$^{-/-}$ mice, suggesting activation of intra-renal renin-angiotensin system, with concurrent activation of inflammation and apoptosis, which were effectively suppressed by CG200745. Mechanistically, we found the positive feedback loop between RAS and TGFβ in HK-2 cells. CG200745 alleviated upregulation of TGFβ and activation of its downstream in Ang II-stimulated HK-2 cells by histone modification, preserving the protein expression of ACE2 and Mas receptor.

Conclusions: CG200745 targets TGFβ to preserve ACE2-Ang-(1-7)-Mas receptor axis and attenuates tubulointerstitial fibrosis in the kidney of Col4a3$^{-/-}$ mice.

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TH-PO791

SMPDL3b Regulates Proteinuria in Experimental Alport Syndrome

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Background: Sphingosine-1-phosphate lyase insufficiency causes accumulation of sphingosine-1-phosphate (S1P) and is associated with focal segmental glomerulosclerosis (FSGS), that is often characterized by the recurrence of proteinuria after kidney transplantation. We previously reported that podocyte injury in recurrent FSGS is associated with downregulation of sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b), an enzyme localized in lipid raft domains that regulates lipid composition and plasma membrane fluidity. Alport syndrome (AS) is an inherited glomerular disease with FSGS-like lesions. In this study we tested the hypothesis that dysregulation of renal SMPDL3b expression affects the generation of bioactive sphingolipids thus contributing the renal disease in AS.

Methods: Mice with experimental AS (Col4a3-/- mice) were used in this study. To investigate the contribution of SMPDL3b to the renal phenotype in AS mice, AS mice were crossed to mice with podocyte-specific *Smpdl3b* deficiency to generate Smpdl3b deficient AS mice (DKO). Animals were sacrificed at 20 weeks of age for in-depth phenotypical analysis of kidneys. All animal studies were performed in accordance with the NIH IACUC Guide. For statistical analysis One-Way ANOVA followed by Bonferroni's posttest was used.

Results: Mice with experimental AS develop proteinuria at 4 weeks of age and die of renal failure at 25 weeks of age. We demonstrated that SMPDL3b expression is 7-fold increased in kidneys of AS mice compared to wildtype littermates. We found decreased albumin-creatinine ratio (6,091±4,098μg/mg) in DKO mice compared to AS mice (27,395±17,387μg/mg). Improved proteinuria was not associated with improved body weight, serum creatinine levels, glomerular filtration rate (130.5±51.5μl/min/100gBW in controls and 153.7±34.4μl/min/100gBW in double knockout) or renal histology. DKO mice also demonstrated significantly lower levels of S1P (0.07±0.01pmol/mg) in kidney cortexes compared to AS mice (0.17±0.04pmol/mg).

Conclusions: Our data indicate that SMPDL3b expression may affect availability of S1P and regulate proteinuria levels in experimental AS. Thus, targeting SMPDL3b expression levels in the kidney may represent a novel approach to improve renal outcome in patients with AS.

Funding: NIDDK Support

TH-PO792

The E3-Ubiquitin Ligase HUWE1 Is a Central Regulator in Podocyte Homeostasis

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Background: As terminally differentiated cells, podocytes depend on precise regulation of protein turnover and response to cellular stress in order to preserve homeostasis. Disruption of these processes can lead to podocyte damage and loss and subsequently to glomerular scarring and kidney disease. Ubiquitination is a posttranslational modification that targets proteins not only to proteasomal degradation, but also to different cellular pathways such as DNA repair, cell cycle regulation, and apoptosis. The HECT type E3-ubiquitin ligase Huwe1 has been shown to be a regulator of various intracellular signaling cascades in different cell types. To characterize the effects of Huwe-mediated ubiquitination in podocyte homeostasis *in vivo* and *in vitro*, we generated a podocyte-specific *Huwe1*-knockout mouse and HUWE1-deficient human podocyte cell lines.

Methods: To phenotype podocyte-specific *Huwe1*-knockout mice, we analyzed the urinary albumin/creatinine ratio and performed immunohistochemistry and electron microscopy. To elucidate the molecular effects of HUWE1 knockout on podocyte signaling, we generated a CRISPR/Cas9-mediated HUWE1-deficient human podocyte cell line and analyzed protein expression by mass spectrometry and RNA sequencing. To investigate HUWE1 specific alterations of ubiquitination, mass spectrometry after enrichment of ubiquitination sites was performed.

Results: Podocyte-specific loss of Huwe1 in mice caused kidney disease beginning at 5 weeks of age. Affected mice developed massive proteinuria and died prematurely of uremic complications. At the ultrastructural level, we saw extensive foot process effacement, podocyte vacuolization, and cell loss. Proteome and transcriptome analysis of HUWE1-knockout cells revealed significant differential regulation in a number of relevant pathways such as cell division, mitochondrial metabolism and autophagy. Analysis of the ubiquitome is ongoing.

Conclusions: The E3-ubiquitin ligase Huwe1 is pivotal for podocyte function and overall survival in mice. We identified HUWE1 as a central regulator of a multitude of cellular pathways to preserve human podocyte signaling and homeostasis. To address the complexity of affected cellular systems within the podocyte, a systems biology approach is required in order to develop new diagnostic and therapeutic strategies.

Funding: Private Foundation Support

TH-PO793

Targeting of Endoplasmic Reticulum Stress Signaling Pathways for the Amelioration of $ANLN_{R431C}$-Induced Podocyte Apoptosis

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Background: We previously reported that mutations in anillin (ANLN) cause familial FSGS and that the $ANLN_{R431C}$ mutation induces aberrant activation of the PI3K/AKT/mTOR pathway and ER-stress-induced apoptosis in podocytes. To identify potential therapeutic targets for $ANLN_{R431C}$-induced podocyte apoptosis, we sought to further delineate the ER-stress signaling pathways downstream of the PI-3K/AKT/mTOR signaling pathway.

Methods: We quantified apoptosis in our established tGFP-, $ANLN_{WT}$- and $ANLN_{R431C}$-overexpressing podocyte lines using the BioTek® Lionheart FX automated live cell imaging system. Biochemical pathway analyses were performed in immunoblot assays.

Results: ER-stress signaling was activated in $ANLN_{R431C}$-overexpressing podocytes at 24 hours and knockdown (KD) of *CCAAT-enhancer-binding protein homologous protein* (*CHOP*), significantly reduced $ANLN_{R431C}$-induced podocyte apoptosis ($p<0.0001$). $ANLN_{R431C}$-overexpressing podocytes showed significantly increased apoptosis relative to $ANLN_{WT}$ and tGFP-overexpressing podocytes at 56 hours ($p<0.0001$). Pharmacologic inhibiton of mTOR and p70S6K significantly reduced $ANLN_{R431C}$-induced podocyte apoptosis at 72 hours ($p<0.0001$). Similarly, inhibition of calcineurin phosphatase and GSK3β, two upstream regulators of *CHOP* expression, significantly reduced apoptosis in $ANLN_{R431C}$-overexpressing podocytes relative to $ANLN_{WT}$ and tGFP-overexpressing podocytes ($p<0.0001$). *GSK3*β (KD) also significantly inhibited podocyte apoptosis at 72 hours ($p<0.0001$). These results confirmed our prior findings. Pharmacologic inhibition of the PERK and c-Jun N-terminal Kinase (JNK) significantly reduced $ANLN_{R431C}$-mediated apoptosis in podocytes ($p<0.0001$) highlighting the pathologic contributions of two additional signaling pathways to $ANLN_{R431C}$-induced podocyte apoptosis.

Conclusions: These findings broaden our understanding of the pathologic role of ER-stress signaling in $ANLN_{R431C}$-induced podocyte apoptosis and expand the repertoire of potential therapeutic targets for familial FSGS caused by ANLN mutations. *In vivo* modeling of the effects of the $ANLN_{R431C}$ mutation are needed to confirm the pathologic contribution of ER-stress signaling to podocyte apoptosis and to evaluate the efficacy of therapies targeting ER-stress pathways for the amelioration of $ANLN_{R431C}$-induced podocyte loss.

Funding: NIDDK Support, Private Foundation Support

TH-PO794

TBC1D8B Mutations Implicate RAB11-Dependent Vesicular Trafficking in the Pathogenesis of Nephrotic Syndrome

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Background: Steroid-resistant nephrotic syndrome (NS) frequently underlies CKD. Mutations in about 50 genes were identified as monogenic causes of NS and these genes rendered significant insight into podocyte biology. We previously reported mutations in *TBC1D8B* in two families with NS. TBC1D8B harbors a TBC domain, that commonly confers a functional role as a GTPase-activating protein (GAP) for specific Rab-GTPases. GAPs promote the inactive state of their Rab protein. However, the function of TBC1D8B and its pathogenetic role remained unclear.

Methods: To identify additional mutations of *TBC1D8B*, we performed whole-exome sequencing (WES). We analyzed the functional role of TBC1D8B and its mutations *in vitro* and conducted studies in podocyte-like *Drosophila* nephrocytes.

Results: We identified one hemizygous missense mutation (c.1316T>G, p.Phe439Cys) and two hemizygous nonsense mutations (c.1030C>T, p.Arg344* and c.1383G>A, p.Trp461*) in patients with NS. To explore the function of TBC1D8B and its target Rab proteins, we performed co-immunoprecipitation assays (coIP). We observed strongest interaction between RAB11 and TBC1D8B and specificity for the active form. Overexpressed murine *Tbc1d8b* bearing patient-derived mutations exhibited lower affinity for endogenous RAB11 than wild type protein. Silencing *TBC1D8B* in HEK293T cells increased basal autophagy and exocyst activity, two cellular functions that are independently regulated by RAB11. This suggests disinhibition of endogenous RAB11 and thus a regulatory role of TBC1D8B. CoIP assays further indicated interaction between TBC1D8B and the slit diaphragm protein nephrin. Both proteins co-localized in cultured podocytes. Knockdown of *Tbc1d8b* in *Drosophila* impaired function of the podocyte-like nephrocytes, and caused mistrafficking of the *Drosophila* ortholog of nephrin. Expression of *Rab11*-RNAi in nephrocytes entailed defective delivery of slit diaphragm protein to the membrane while *RAB11* overexpression revealed a phenotypic overlap to *Tbc1d8b* loss-of-function.

Conclusions: Novel mutations in *TBC1D8B* are monogenic causes of NS and our data indicate that TBC1D8B serves as a GAP protein for RAB11. TBC1D8B interacts with nephrin, being required for its trafficking. This connects RAB11-dependent vesicular trafficking to the pathogenesis of human NS.

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TH-PO795

Disruption of Crb2 in Podocytes After Birth Leads to Proteinuria

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Background: Crumbs 2, Crb2 is one of the components of the Crumbs cell polarity complex and known to be expressed in the podocytes. There have been reports that CRB2 mutations were associated with steroid-resistant nephrotic syndrome in human. However, its precise mechanism is still unclear.

Methods: Crb2 floxed mice that had loxP sites flanking exon 7 and 8 were bred with NPHS2-Cre ERT2 mice to generate NPHS2-Cre ERT2 positive Crb2 floxed mice. Podocyte-specific Crb2 knockout mice after birth were made by injecting tamoxifen or negative control intraperitoneally for three days at two months of age. Urine, blood, and kidneys were analyzed in the two mouse groups at four months of age.

Results: NPHS2-Cre ERT2 positive Crb2 floxed mice that were injected tamoxifen showed massive proteinuria at four months of age compared to those that were injected negative control. Blood urea nitrogen or serum creatinine at four months of age was comparable between the two groups. Glomerular indices or fibrotic indices at four months of age were similar between the two groups.

Conclusions: Disruption of Crb2 in the podocytes after birth is related to inducing proteinuria.

Funding: Private Foundation Support

TH-PO796

CRISPR/Cas9 Zebrafish Models Do Not Recapitulate 4 Human Monogenic Causes of Nephrotic Syndrome

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Background: Steroid-resistant nephrotic syndrome (SRNS) is characterized by proteinuria due to disruption of the glomerular filtration barrier and is a frequent cause of chronic kidney disease. Currently, more than 60 monogenic causes of human SRNS are known. Historically, zebrafish have been a commonly used animal model for human monogenic SRNS, using morpholino oligonucleotides. Recently, generation of zebrafish shifted to CRISPR-mediated knockout (KO), which often showed lack of recapitulation of the human disease phenotype in zebrafish (*Dev Cell* 32:97, 2015). We recapitulated the human SRNS phenotype due to Magi2 mutation (*Nat Commun* 9:1980, 2018) in a CRISPR model of magi2a (*Kidney Int* 95:1079, 2019). Recently, we discovered recessive mutations as novel causes of human SRNS in the following genes: *advillin* (*AVIL*) (*J Clin Invest* 127:4257, 2017), *PR/SET domain 15* (*PRDM15*), *deleted in liver cancer 1* (*DLC1*) and *Intersectin1* (*ITSN1*) (*Nat Commun* 9:1980, 2018).

Methods: To recapitulate monogenic causes of human SRNS and to study developmental phenotypes by CRISPR/Cas9 KO of the zebrafish orthologues *avil*, *dlc1*, *itsn1* and *prdm15*, we performed microinjections of multiple guide RNAs for each of the genes and generated stable KO zebrafish lines for these genes. Survival curves as well as phenotye assessments were generated for acute knockdown (KD) and stable KO zebrafish by monitoring larvae for 21 days.

Results: To assess larval-onset phenotype, we generated acute KD animals, which did not show a significant difference in survival or phenotype compared to animals injected with a non-binding control guide RNA and wildtype animals. We subsequently generated stable KO lines with 4 different KO-alleles for *AVIL*, 3 for *DLC1*, 4 for *ITSN1* and 6 for *PRDM15* respectively. None of these alleles showed a significant phenotypical difference in homozygous fish compared to heterozygous and wildtype controls.

Conclusions: Failure to recapitulate disease phenotypes in CRISPR models is currently predominantly attributed to upregulation of paralogues, triggered by mRNA degradation (*Nature* 568:197, 2019). In line with these results, CRISPR/Cas9 zebrafish models of the human SRNS genes *AVIL*, *DLC1*, *PRDM15* and *ITSN1* do not recapitulate the human phenotype of nephrotic syndrome and do not impede zebrafish larval survival.

Funding: NIDDK Support

TH-PO797

Biallelic ANKS6 and NPHP1 Mutations Alter Ciliary LKB1 Assembly in Late-Onset Ciliopathies

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Background: Nephronophthisis is a frequent cause of renal failure in children, presenting with progressive renal fibrosis and commonly include extrarenal organ involvement. The use of technological advances in DNA sequencing has led to a better understanding of molecular causes in rare kidney diseases. However, for most of these the cellular pathways involved still need to be identified. ANKS6 is a known member of the Inversin compartment and interacts with ANKS3. The Liver kinase B1 (LKB1) was recently shown to form a regulatory module in primary cilia with proteins linked to NPHP.

Methods: Genetic testing was performed in affected individuals with CKD of unknown origin. DNA was extracted from whole blood, enriched, and sequenced on a HiSeq2500. Patient-derived fibroblasts were harvested and cultured from skin biopsies of affected individuals, healthy parent and controls. From these patient derived cells functional studies on protein and RNA level using immunoblotting, immunofluorescence and qRT-PCR were performed.

Results: We identified biallelic mutations in the genes *NPHP1* and *ANKS6* in affected individuals with CKD of unknown origin. These segregated with the affected status and were absent from healthy controls. Functional studies in patient derived fibroblasts demonstrate that the identified mutations alter the ciliary assembly of LKB1 as well as of downstream signaling pathways, compared to healthy controls and heterozygous parental cells. Moreover, the detected mutations in *ANKS6* disrupt the Inversin-complex as the mutations lead to a loss of ANKS6, NPHP3, Inversin and NEK8 in primary cilia.

Conclusions: We identified the underlying molecular cause in affected individuals with CKD of unknown origin and observed an alteration of the ciliary assembly of LKB1 as well as of downstream signaling in patient derived cells. These findings support the presence of a ciliary LKB1-NPHP functional interaction. Moreover the results indicate that an alteration of ciliary LKB1 signaling could be a relevant mechanism for human ciliopathy and may play a wider role in renal disease. Functional studies on patient derived cells with rare inherited kidney diseases may lead to a better understanding of disease mechanisms. This could help to develop novel therapeutic strategies for treatment of such rare disorders.

TH-PO798

Accumulation of Globotriaosylceramide (GL3) in Podocytes (PC) in Fabry Nephropathy (FN) Is Associated with Progressive PC Loss

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Background: Males with classic Fabry disease (FD) have a high incidence of end stage renal disease (ESRD). Processes leading to ESRD are poorly understood. α-galactosidase A gene defects lead to GL3 accumulation in the glomerulus, but this is progressive with age only in PC. PC are relatively resistant to enzyme replacement therapy and replicate poorly when lost. We aimed to examine if PC GL3 accumulation in FD is associated with PC loss.

Methods: Unbiased morphometric electron microscopic renal biopsy studies were performed in 58 males ages 27±13 years with classic FD genotype and/or phenotype.

Results: With increasing age there was an increasing fraction of PC cytoplasm occupied by GL3 inclusions [Vv(Inc/PC)], but this plateaued at age ~30. However mean PC volume (VPC) and total volume of GL3 inclusions/PC [V(Inc/PC)] continued to increase. V(Inc/PC) correlated with PC injury and loss evidenced by increased foot process width (FPW) and decreased PC number density per volume of glomerulus [Nv(PC/glom)]. The relationship between Nv(PC/glom) *vs.* V(Inc/PC) was best depicted by a power regression [$V(Inc/PC)=0.189\times Nv(PC/glom)^{-0.954}$] or 2 linear regression lines with an initial steep and a later milder slope. Piecewise linear regression analysis explained 81% of the variance of Nv(PC/glom) by V(Inc/PC), providing a breakpoint of V(Inc/PC) = 2009 μm^3. Patients with V(Inc/PC) > breakpoint showed an inverse correlation between age and Nv(PC/glom) (r=-0.70, p=0.008) and direct correlations between age and V(Inc/PC) (r=0.57, p=0.04) and VPC (r=0.67, p=0.01). Also, urinary protein excretion rate (UPER), a strong predictor of adverse renal outcomes in FD, correlated inversely with Nv(PC/glom) (r=-0.64, p=0.03) and directly with VPC (r=0.79, p=0.002), and FPW correlated inversely with Nv(PC/glom) (r=-0.74, p=0.04) in patients with V(Inc/PC) > breakpoint. However, in subjects with V(Inc/PC) ≤ the breakpoint there was no statistically significant relationship between age or UPER and PC parameters.

Conclusions: Given the known association between PC loss and irreversible focal and global glomerulosclerosis, this study supports an important role for PC loss, which beyond a certain point, is associated with the clinical progression of FN and argues for therapeutic intervention before critical PC loss has occurred.

Funding: Other NIH Support - NCATS, Commercial Support - Sanofi

TH-PO799

Epigenetic Downregulation of Klotho via H3K27me3 Associated with Suppression of SGK-1 Survival Signaling in Aged Mouse Kidney

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Background: Klotho deficiency is an important mechanistic driver of cell aging. However, the underlying mechanisms by which how Klotho is downregulated by epigenetics in aging cell have not been clearly elucidated.

Methods: In this study, we examined the role of H3K27me3 in the regulation of Klotho gene expression and pathways that influence the cell aging in the kidney of 30-months-old wild type (aged WT) C57BL/6 mice, and Klotho mutant mice compared to 6-months-old WT (young) mice, respectively.

Results: We demonstrated that the level of H3K27me3 was increased in the kidney of aged WT and Klotho mutant mice compared to young WT mice. Elevation of H3K27me3 was largely due to the downregulation of the histone 3 lysine 27 specific demethylase UTX and/or JMJD3 in the aging kidneys. Inhibition of Polycomb Repressive Complex C 2 (PRC2) using EED226 and GSK343 decreased the expression of H3K27me3 leading to increase in the expression of Klotho in primary cultured renal tubule cells determined by Western blot and Klotho promoter assay. Inhibition of PRC2 reduced level of H3K27me3 associated with Klotho promoter, suggesting that epigenetic downregulation of Klotho gene expression was due, at least in part, to histone 3 modification in the Klotho promoter region. ChIP qPCR revealed that H3K27me3 was enriched in the Klotho promoter region in the kidney of aged WT and Klotho mutant mice compared to young WT mice. Furthermore, our results showed that aging impaired SGK-1/FOXO3a signaling leading to upregulation of p53 and p16 in the kidney of aged WT and Klotho mutant mice.

Conclusions: We have first shown that epigenetic modification of histone mark H3K27me3 directly downregulates Klotho in the kidney of aged wild type mice. Aging exerts renal effects through hyperphosphorylation of mTOR which is independent of Klotho status. The normal aging and Klotho-deficient mediated aging share a common pathway through impaired SGK1 survival signaling leading to upregulation of FOXO3a, p53 and p16 in the kidney of aged WT and Klotho mutant mice. Thus, hormonal action of Klotho may be an alternative approach to activating SGK1 survival signaling for treating aging-mediated kidney disorders.

Funding: Other NIH Support - NIA

TH-PO800

Efficacy and Safety of the Long-Acting C5-Inhibitor Ravulizumab in Adult Patients with Atypical Hemolytic Uremic Syndrome (aHUS)

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Background: Ravulizumab was engineered to achieve extended complement C5 inhibition, given every 8 weeks, while retaining the proven efficacy and safety of eculizumab. Here we evaluate the efficacy and safety of ravulizumab in adults with aHUS.

Methods: This was a phase 3, single arm study (NCT02949128). Complement inhibitor-naïve patients (pts) aged ≥18 years who fulfilled diagnostic criteria for aHUS (exclusion of ADAMTS13 <5% activity and Shiga toxin-producing *Escherichia Coli*) and active thrombotic microangiopathy (TMA) received ravulizumab at 8-week intervals during the maintenance phase. The primary endpoint was complete TMA response during the initial 183-day evaluation period. Secondary endpoints included time to complete TMA response, components of complete TMA response over time, CKD stage, dialysis-free status over time and time to dialysis-free status.

Results: Fifty-six eligible pts were analyzed. Median age at baseline was 40 (range, 20–77) years and 36 (66%) were female. Complete TMA response was achieved in 30 pts (54%). 17/29 (59%) pts stopped dialysis (at a median time of 30 days). Primary endpoint and TMA parameter response over time is shown in the figure. Improvement in CKD stage from baseline was observed in 32/47 (68%) pts at Day 183. The most frequent serious adverse events were hypertension and pneumonia, each reported in 3 (5%) pts; 4 deaths not attributed to treatment occurred. No meningococcal infections were reported.

Conclusions: 8-weekly ravulizumab dosing produced immediate, sustained and complete complement inhibition resulting in rapid hematologic and renal response with no unexpected safety concerns.

Funding: Commercial Support - Alexion Pharmaceuticals, Inc.

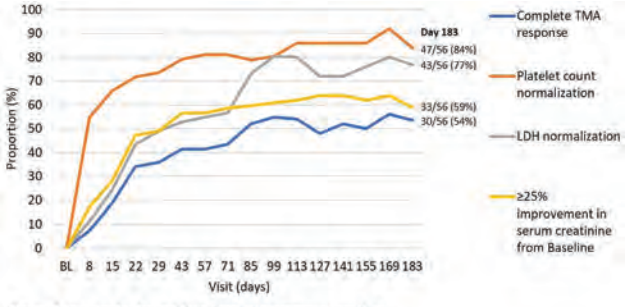

Figure. Primary endpoint and TMA parameter response over time

Complete TMA response is defined as normalization of platelet count, normalization of LDH, and ≥25% improvement in serum creatinine from baseline at 2 separate assessments obtained ≥28 days apart.

Platelet count normalization is defined as ≥150 x 10^9/L.

LDH normalization is defined as ≤246 U/L.

TH-PO801

Identifying Thrombotic Microangiopathy Mimics

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Background: Thrombocytopenia is one of the key diagnostic criteria for the clinical diagnosis of thrombotic microangiopathy (TMA). When thrombocytopenia presents with other hemolytic processes, distinguishing the correct diagnosis can be difficult. In an era of terminal complement blockade, the correct diagnosis is critical to determining the optimal treatment approach. Here we describe a cohort of patients clinically diagnosed with TMA but then incidentally identified to have a pathogenic variant in the glucose-6-phosphate dehydrogenase (*G6PD*) gene.

Methods: Targeted genomic enrichment with massive parallel sequencing (TGE+MPS) of genes implicated in TMA was used to screen 329 patients. Multiplex ligation-dependent probe amplification (MLPA) for copy-number variations (CNVs) in the *CFH-CFHR5* region was also performed.

Results: Of 329 patients screened, 7 patients were positive for well-described, pathogenic *G6PD* variants including 3 with the Union variant, 3 with the Sassari variant and 1 with the Chatham variant. All variants identified have been described as class II variants (1-10% G6PD residual activity). Of the 7 patients, 5 carry at least one complement gene variant, including 3 variants of unknown significance (1 *CFH* and 2 *CFI*), 1 pathogenic variant (*DGKE*), and 1 likely pathogenic variant (*CFHR5*). MLPA detected a heterozygous deletion of *CFHR1-CFHR4* in one patient while the remaining were unremarkable. Our findings indicate that approximately 2% of TMA diagnoses may be accounted for by G6PD deficiency.

Conclusions: G6PD deficiency should be included on the differential for someone diagnosed with a hemolytic anemia associated with thrombocytopenia. It remains unclear if G6PD deficiency plays a primary or a modifier role in the TMA-like presentation. Similarly, if G6PD deficiency is the primary etiologic agent, what role does enzyme deficiency play in the individual features of the underlying pathology of the TMA-like presentation (including thrombocytopenia and renal insufficiency) is unknown. Despite this gap in our understanding, considering G6PD deficiency on the differential has clear diagnostic and treatment implications. We conclude that *G6PD* gene testing is recommended in the workup of a clinical TMA, and G6PD enzyme testing is warranted when the acute process has resolved.

Funding: NIDDK Support

TH-PO802

Risk for TMA Recurrence and Renal Outcomes After Eculizumab Discontinuation in aHUS: Results from the Global aHUS Registry

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Background: Eculizumab (Ecu) modifies the course of disease in patients (pts) with atypical hemolytic uraemic syndrome (aHUS), but there are limited data to describe thrombotic microangiopathy (TMA) recurrence rates and long-term outcomes after Ecu discontinuation (d/c).

Methods: Pts in the Global aHUS Registry (NCT01522183) who received ≥1 month (mo) of Ecu with evidence of hematologic or renal response prior to d/c and with ≥6 mo of follow-up (f/u) were included. Those on chronic dialysis (≥3 mo) at the time of Ecu d/c were excluded. Classification as pediatric (<18 years) or adult was made at time of Ecu d/c.

Results: 151 pts (62% female) were included in the analysis: 34% were pediatric and 66% were adults (median [range] age at enrolment, 6.0 [0.6–17.1] and 35.7 [18.4–81.2], respectively), 11% had a family history of aHUS and 41% had a pathogenic variant or anti-CFH antibody. Median (range) duration of Ecu prior to d/c was 1.0 (0.1–5.1) and f/u was 2.3 (0.1–7.1) years. 24% experienced TMA recurrence after Ecu d/c. More pts required antihypertensives at f/u vs at d/c (71% vs 54%). Pts with a family history of aHUS, pathogenic variants, lower eGFR and extrarenal manifestations appeared to be at a higher risk of TMA recurrence (Table).

Conclusions: Discontinuation of Ecu is not without risk and may lead to TMA recurrence in some patients with aHUS. A careful assessment of risk factors prior to the decision to d/c Ecu is warranted.

Patient characteristics by TMA recurrence status			
Variable	All N=148*	TMA recurrence n=35	No TMA recurrence n=113
Median (range) duration of Ecu before discontinuation, years	1.0 (0.1– 5.1)	1.0 (0.1– 5.1)	1.0 (0.1– 4.5)
Median (range) eGFR prior to Ecu discontinuation, mL/min/ 1.73 m^2	57.1 (4.9–183.1)	50.5 (13.0–183.1)	65.8 (4.9–176)
Median (range) time to TMA recurrence after Ecu discontinuation, months	N/A	All: 5.3 (0.1–49.9) Pediatric: 5.1 (1.4–49.9) Adult: 10.2 (0.1–49.6)	N/A
Extra-renal manifestation at baseline, n (%)	CV 31 (21) Pulm 19 (13) CNS 36 (24) GI 55 (37)	CV 10 (29) Pulm 9 (26) CNS 10 (29) GI 14 (40)	CV 21 (19) Pulm 10 (9) CNS 26 (23) GI 41 (36)
Pathogenic variant, n (%)	49 (33)	16 (46)	33 (29)
Anti-CFH antibody tested and positive, n (%)	19 (13)	2 (6)	17 (15)
Family history, n (%)	16 (11)	9 (26)	7 (6)
eGFR by age category, mL/min/1.73 m^2, median (range)			
Time point	All N=148	Pediatric n=51	Adult n=97
Baseline	20.7 (3.5–183.1)	33.8 (3.9–183.1)	18.1 (3.5–156.8)
Discontinuation	74.7 (3.6–144.0)	93.4 (6.6–144.0)	56.0 (3.6–132.3)
Last available follow-up	70.2 (3.8–176.0)	83.0 (6.1–176.0)	61.4 (3.8–131.0)

*TMA recurrence status missing for n=3. Baseline was defined as period prior to first dose of Ecu. CV, cardiovascular; pulm, pulmonary; CNS, central nervous system; GI, gastrointestinal

TH-PO803

Familial Pregnancy-Associated aHUS and Acute Heart Failure Successfully Treated with Eculizumab

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Introduction: Atypical HUS is a rare thrombotic microangiopathy (TMA) characterized by anemia, thrombocytopenia (TP) and AKI. Mutations in genes encoding complement proteins have been identified in ~60% of patients. We report 3 sisters who developed aHUS after pregnancy. ADAMTS13 was normal in all.

Case Description: Sister 1: 25-yr-old Hispanic female (HF) presented 10 days postpartum (pp) in 2015 with anemia, TP, and AKI. Kidney biopsy showed a TMA which was treated with plasma exchange (PE) and steroids. Later she developed heart failure (HF) from mitral valve perforation requiring intubation, valve replacement & hemodialysis (HD). Eculizumab was initiated. Creatinine improved in 2 wk and HD was discontinued. Sister 2: 24-yr-old HF developed anemia, TP, and AKI 7 days pp in 2014, treated with PE. Creatinine deteriorated and HD was initiated. One year later, after the diagnosis in sister #1, aHUS was considered and eculizumab initiated. Creatinine improved and HD was discontinued after 2 years. Sister 3: 18-yr-old HF presented 7 days pp in 2006 with anemia, TP, and AKI. Kidney biopsy revealed a TMA which was nonresponsive to PE and HD was initiated. Course was complicated by HF due to severe mitral and tricuspid regurgitation. She was not treated with eculizumab since aHUS was not considered until after it was diagnosed in her two sisters (8 years later). Genetic testing for all 3: 1) Splice-site variant (c.287-2A>G) in membrane cofactor protein (MCP) known to be aHUS-associated; 2) A novel variant (G918E) in Factor H (FH) of uncertain significance; 3) A heterozygous variant (K441R) in Factor I, likely benign; 4) A heterozygous variant (N1050Y) in FH, likely benign. Our functional analysis for these variants reveals that the G918E is not secreted and leads to low FH levels. The N1050Y is normally secreted and has normal C3b and heparin binding properties. The K441R has normal secretion and activity. The splice-variant in MCP is expected to cause decreased expression of MCP leading to low levels.

Discussion: The sisters carry pathogenic mutations in both MCP and FH. It is unusual for patients with aHUS to carry multiple rare variants. Pregnancy was the trigger in this family (patients' paternal grandmother lost 10 of 12 pregnancies). Acute heart failure due to valvular disease is novel. Possible mechanism is thrombus formation followed by endocarditis.

TH-PO804

Complement Activation Causes Major Metabolic and Energetic Changes on Endothelial Cells

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Background: Complement dysregulation and formation of the membrane attack complex (MAC, C5b-9) on vascular endothelial cells (ECs) cause EC injury and can lead to thrombotic microangiopathy (TMA). Effects of chronic complement exposure on cellular level are not well established. Here, we especially focused on metabolic and energetic changes as previous data indicated that C5b-9 formation on the surfaces of ECs did not result in cellular necrosis or apoptosis.

Methods: Human blood outgrowth endothelial cells (BOECs) derived from healthy donors were sensitized with an anti-CD59 antibody. Complement activation was initiated by adding normal human serum. Microscopy, luminescence, flow cytometry and western blot were used to measure intracellular calcium, ATP, mitochondrial membrane potential as well as autophagy pathways, respectively.

Results: BOECs exposed to complement showed cell surface C5b-9 deposition followed by an abrupt rise in intracellular Ca^{2+} that was sustained over 6 hours. Under complement stress, cell motility was impaired, which resulted in defective wound healing. We suggested a defect in endothelial cell energy homeostasis as likely cause for the observed functional defects. Indeed, complement activation caused a sustained drop in intracellular ATP levels and mitochondrial membrane potential. These effects were reversible following discontinuation of complement stress (i.e., removal of serum or blockage of complement activation via C5-depleted or heat inactivated serum), indicating that ECs were still viable. Thus we hypothesized that ECs are able to switch on a survival machinery. In keeping with this we found upregulation of autophagy, as indicated by the degradation of the markers LC3 and p62.

Conclusions: In summary, chronic complement activation leads to an EC energy deficit. BOECs activate a survival machinery to sustain complement attack, including the re-sealing of the plasma membrane and the activation of autophagy. All cellular effects were reversible, implying a window of opportunity for treatment initiation and recovery of endothelial cell function.

TH-PO805

Epithelial Membrane Protein 2 (EMP2) Is Predominantly Expressed in Vascular Smooth Muscle Cells of the Kidney

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Background: Mutations in human gene Epithelial Membrane Protein 2 (EMP2) have been linked to childhood-onset nephrotic syndrome. However, we have previously reported that loss of Emp2 in mice does not cause nephrotic syndrome and that Emp2 lacks notable expression in podocytes or the glomerulus. Instead, we find that Emp2 has a distinctive vascular pattern of expression in multiple tissues including the kidney. As Emp2 is currently being investigated as a novel target for treatment of pathologic neovascularization and vasculo-proliferative diseases such as diabetes, we studied in detail the vascular expression of Emp2 across different organs as well as the kidneys.

Methods: We created a conditional floxed *Emp2* allele carrying a lacZ cassette that allows whole-mount β-galactosidase (β-gal) histochemical analysis of Emp2 expression. Tissues were evaluated as whole mount and additionally embedded in OCT and cryosectioned for immunohistochemical analysis. We created endothelial-specific knockout mice by breeding floxed Emp2 animals with a Cdh5-Cre/ERT2 driver strain. Emp2 mRNA was profiled in various tissues using qRT-PCR analysis.

Results: Expression of Emp2 by β-gal histochemistry was seen in the arterial vasculature of multiple tissues including the kidney. Within the kidney, β-gal activity is localized to renal arterial vessels where it is expressed in $Tagln^+$ ($SM22a^+$) vascular smooth muscle cells and is absent in $Podxl^+$ arterial endothelial cells, $Emcn^+$ renal veins and glomerular endothelial cells. *Emp2* expression within the kidney is unchanged upon endothelial specific knockout of the *Emp2* gene consistent with the lack of β-gal activity in the endothelial cells of $Emp2^{lacZ}$ reporter mice.

Conclusions: Our analysis reveals that Emp2 expression is largely confined to vascular smooth muscle cells of the arterial vasculature in the kidneys as well as multiple other organs. These findings provide important insights into the specific site of action of therapeutics designed to target Emp2.

Funding: NIDDK Support

TH-PO806

Analysis of Mutant Human MUC1 Transgenic Mice with Mapped Transgene Suggests Systemic Manifestation of ADTKD-MUC1

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Background: Autosomal dominant tubulointerstitial kidney disease caused by mucin-1 gene mutations (ADTKD-*MUC1*) is an important cause of end-stage renal disease, the reported manifestations of which have been limited to within the kidneys. However, no reports about ADTKD-*MUC1* transgenic model animals have been published. Almost all *MUC1* mutations were previously identified in variable-number tandem repeats (VNTRs), within which sequencing is difficult. However, we previously discovered a novel *MUC1* mutation before these VNTRs.

Methods: We thus developed mu*MUC1* tg mice using this mutated cDNA driven by mouse *Muc1* promoter and examined their phenotypes. We identified the transgene integration site by targeted locus amplification.

Results: We identified the transgene integration site by targeted locus amplification, revealing that transgene integration did not disrupt any endogenous genes. Surprisingly, mice with high mutant MUC1 protein expression showed growth retardation with massive inflammation in skin, gut, lungs, and kidneys, due to ER stress. Because of malnutrition due to gastrointestinal tracts with inflammation, almost all growth-retarded mutant animals died after weaning. Interestingly, most animals with high mutant protein were male. Our patient re-examination in response to these tg mouse data revealed that patients had interstitial pneumonia, gastrointestinal inflammation, and dermatitis with sebaceous gland inflammation with mutant protein accumulation and ER stress.

Conclusions: These findings show that ADTKD-*MUC1* can exhibit systemic inflammatory manifestations.

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TH-PO807

A Uromodulin Mutation Resulting in Innate Immune System Activation

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Background: Uromodulin (Tamm-Horsfall) is secreted by the thick ascending limb into urine but also crosses basolateral membranes into the interstitium and blood. Uromodulin may function as part of kidney's innate immune system with pro and anti-inflammatory effects. Mutations in the UMOD gene are a cause of autosomal dominant tubulointerstitial kidney disease (ADTKD) due to tubular injury and endoplasmic reticulum (ER) stress. We identified a family with a novel UMOD mutation (C106F). Biopsies from affected members showed glomerular and interstitial inflammation atypical for ADTKD.

Methods: To determine if this mutation causes the observed phenotype through changes in membrane targeting and activation of the innate immune system, we examined a kidney epithelial cell line with stable transfection of mutant protein and developed a transgenic (tg) mouse with an orthologous cysteine to phenylalanine mutation (C105F) in the UMOD gene using CRISPR-Cas9 gene editing.

Results: LLC-PK1 cells expressing wt and mutant protein had increased basolateral secretion of protein compared with cells expressing wt or mutant protein alone. EM examination of mutant medium showed protein aggregates in contrast to filaments in wt medium. Immunoprecipitation of plasma uromodulin from tg/tg mice demonstrated dimer formation not seen in tg/+ or wt mice. Tg/+ and tg/tg mice displayed increased inflammasome activity at baseline with increased NLRP3 receptor, phospho NF-kB p65 and cleaved caspase 11 levels but no expression of ER stress markers. NLRP3 expression was located in macrophages and podocytes. Tg/+ mice developed glomerular and interstitial matrix deposition, myofibroblast proliferation and increased creatinine with aging. Following ischemia-reperfusion injury, tg/+ mice had no increase in inflammasome activation over baseline in contrast to wt littermates and displayed improved tubular repair and renal function at 7 days.

Conclusions: In summary, the C106F mutation results in glomerular and interstitial inflammatory kidney disease. A mouse model demonstrates that mutant protein enters the interstitium and blood and activates the innate immune system resulting in fibrosis with aging but improved repair following acute injury.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO808

Kidney Disease-Associated Variants of Apolipoprotein L1 Show Gain-of-Function in Cation Channel Activity

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Background: Variants in Apolipoprotein L1 (ApoL1) are responsible for increased risk of some progressive kidney diseases among people of African ancestry. ApoL1 is known to function as an amphitropic protein that can insert into phospholipid membranes and confer pH-regulated Cl- or K-selective permeability. Cl permeability is optimal when protein and vesicles are both mixed and assayed at pH 5.0. K permeability is optimal when protein and vesicles are mixed at pH 6.0 and assayed at pH 7.5. Whether these activities differ among the variants or contribute to disease pathogenesis is unknown.

Methods: Recombinant WT (G0) or each variant (G1, G2) were purified from E. Coli. We used a vesicle-based assay of voltage-driven ion flux. In brief, KCl-loaded vesicles were mixed with protein, extravesicular KCl removed, and voltage-driven efflux intiated by addition of either a K- or Cl-selective ionophore to assess Cl or K permeability, respectively. To assess membrane association, protein was mixed with vesicles under conditions that support K permeability, stripped with alkali, the membranes isolated by flotation through a sucrose cushion, and associated protein determined by quantitative western blotting.

Results: In each of 5 sets of purified protein, the K selective permease of G1 and G2 isoforms was significantly increased compared to G0. Combining all sets, initial efflux rates were 0.361 ± 0.028 for G0, 0.738 ± 0.081 for G1, and 0.688 ± 0.069 for G2 (%/sec, mean ± SEM; P<0.0025 for comparison of G0 with either G1 or G2). In contrast, we find no difference in the Cl selective permease activity among the isoforms. Compared to the WT, the two disease-associated variants show increased stable membrane association under conditions that support the K permease activity (amount bound: 56.2 ± 3.4 for G0, 76.6 ± 5.1 for G1, and 100.2 ± 11.8 for G2 (ng, mean ± SEM, n=8 for each; P<0.006 for G0 vs either G1 or G2; G1 vs G2 NS)).

Conclusions: Kidney disease-associated variants of ApoL1 show gain of function in the K permease activity, and show increased capacity to stably associate with membrane vesicles, suggesting that the increased activity may be due to more efficient membrane association and/or insertion. These data support a model in which enhanced potassium permeability may contribute to the progressive kidney diseases associated with high-risk ApoL1 alleles.

Funding: NIDDK Support

TH-PO809

Bifunctional VDR-miR193a Axis Modulates APOL1 Expression in Human Podocytes

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Background: APOL1 plays an important role in the maintenance of podocyte molecular phenotype. We have recently demonstrated that a vitamin D receptor (VDR) agonist (VDA) enhances the expression of APOL1 in human podocytes through down-regulation of miR193a. miR193a plays a vital role in the development of focal segmental glomerulosclerosis (FSGS) both in experimental animal models and humans. miR193a induces oxidative stress and negatively regulate the expression of Wilms Tumor Type (WT) 1 expression in podocytes. We hypothesize that VDR and mir193a inversely regulate each other.

Methods: Differentiated immortalized human podocytes (DPDs) and human embryonic kidney cells (HEKs) were treated with different concentrations of a VDR agonist (VDA, EB1089, 0, 5, 10, 50, 100 nM) for 48 hours (n=6); HEKs were transduced with either control or VDR plasmid (n=4); DPDs were transfected with either control of miR193a plasmids (n=4); DPDs were treated with either an empty vector or a specific miR193a inhibitor for 48 hours (n=4). RNAs and proteins were extracted. Protein blots were probed for VDR, APOL1, WT1, and GAPDH. RNAs were assayed for miR193a. cDNAs were amplified for VDR, APOL1, and WT1. To validate the putative binding of mi193a-5p to VDR 3'UTR, Luciferase assay was carried out. To examine the binding of VDR at miR193a promoter, ChiP assay was carried out. To evaluate the role of WT1, HEKs were transfected with control, VDR, or WT1 plasmids and protein blots were probed for VDR, WT1, APOL1, and GAPDH; RNAs were assayed for miR193a.

Results: Both VDA-treated DPDs and HEKs displayed upregulation of APOL1, VDR, and WT1 in a dose-dependent manner. VDR-transfected HEKs as well as DPD-treated with a miR193a inhibitor also showed an increase in APOL1 and WT1 but attenuated miR193a expressions. DPDs overexpressing miR193a showed diminished APOL1, WT1, and VDR expressions (both protein and mRNA). Interestingly, WT1 transfected HEKs showed downregulation of VDR, and VDR-transfected HEKs displayed increased expression of WT1. Luciferase assay showed putative binding sited of miR193a on VDR gene. ChiP assay also showed binding of VDR on miR193a gene. These binding sites suggest that both VDR and miR193a regulate each other.

Conclusions: Bifunctional VDR-miR193a axis regulates APOL1 regulate APOL1 directly as well as through modulation of WT1.

Funding: NIDDK Support

TH-PO810

APOL1: A "Novel" Genetic Variant Associated with Podocytopathy in Chile

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Background: The APOL1 G1 risk allele (rs73885319) is associated with kidney disease in African Americans. According to ExAC data, the G1 allele has an uneven distribution, reaching a high frequency (23%) in Africans, but is very rare (0.6%) in the Latino population. In 2016-2017, three patients in Southern Chile affected by kidney disease were identified as homo- or heterozygous G1 carriers. Here, we describe a study as a first effort to determine the prevalence and association of the G1 allele with podocytopathy in Chileans.

Methods: 50 FFPE-DNA samples of adult patients with a biopsy-proven podocytopathy and 1666 DNA samples of ChileGenomico DNA repository recruited along the whole country were analyzed to determine prevalence of the APOL1 G1 risk allele. Genetic analysis was performed by PCR combined with (NGS+Sanger) sequencing technology. Genetic association between the G1 allele and podocytopathy was analyzed by a 2x2 contingency table to estimate OR.

Results: Among the 50 cases with a biopsy-proven podocytopathy, 4 subjects carried one risk allele (G1/G0), while 8 out of the 1666 ChileGenomico subjects carried this genotype, resulting a positive genetic association between the allele and the podocytopathy (G1 allele frequency 4% vs. 0.24%; p<0.001). One of the 4 G1/G0 cases was HIV-positive; the second hit remains unknown in the other 3 cases. Odds ratio for the effect of the APOL1 G1 risk allele resulted 19.8 (95% CI 5.7-67.7).

Conclusions: Chilean population has a 1-5% African genetic ancestry that decreases from North to South. To our knowledge, this is the first study in Chile that explores the prevalence of the APOL1 G1 risk allele and its association with a podocytopathy. We confirmed a very low frequency of the APOL1 G1 risk allele dispersed in the Chilean population, but a significant prevalence among patients with podocytopathy. The clinical value of APOL1 risk alleles is still uncertain in our population and second hits in some patients remain unknown. More evidence is needed before considering the APOL1 genotype as an input to define clinical management and ethical issues have to been considered, particularly for the Afrodescendant migrants that have arrived in Chile the last years. Grants FONDECYT 11140242 and 1160465.

Funding: Government Support - Non-U.S.

TH-PO811

APOL1, Bone Lead, and Kidney Disease: A Pilot Study Using Recall by Genotype

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Background: The *APOL1* high-risk genotype is frequent (14%) in African Americans (AAs) and is associated with increased risk of chronic kidney disease (CKD). However, only a fraction of individuals with the genotype have CKD indicating the presence of modifiers of disease risk ('second hits'). Nephrotoxic metals, including lead (Pb) are associated with kidney disease risk. We sought to assess whether *APOL1* genetic risk and bone lead concentration interact for CKD.

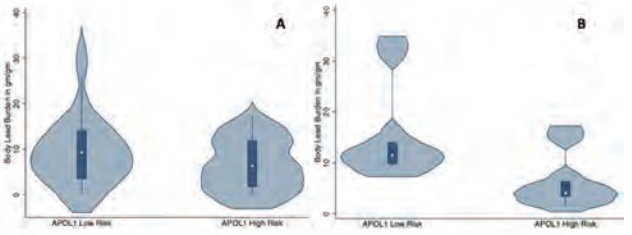
Methods: We recalled AA participants with *APOL1* high risk and low risk genotype from the Bio*Me* Biobank and matched them on age, sex, most estimated glomerular filtration rate (eGFR) and socio-demographics. We then measured tibia Pb indicating body lead burden (BLB) using X ray fluoroscopy. We then estimated the difference in BLB by APOL1 risk for a given eGFR using non-parametric tests.

Results: We recalled 30 AA participants (15 with *APOL1* high risk and 15 with *APOL1* low risk). The median age was 56, 66% were female and median eGFR was 59 ml/min. The median Pb was 9.2 gm/gm of bone (IQR 2.7-12) and was correlated with lower eGFR (R^2=-0.19). There was a trend towards lower Pb in individuals with *APOL1* high risk vs. low risk (median 6.9 vs. 10.6 gm/gm; p=0.10). This was more evident in individuals (n=10) with eGFR≤45 ml/min (median 3 vs. 11.5 gm/gm; p=0.07). (**Figure 1**)

Conclusions: Conditional on low eGFR, Individuals with *APOL1* high risk have lower BLB compared to those with *APOL1* low risk. Although larger studies are needed, this may suggest that CKD risk is potentiated by BLB at lower exposure levels in persons with *APOL1* high risk. Finally, this also serves as a proof-of-concept study using 'recall by genotype' for deep phenotyping of environmental exposures.

Funding: NIDDK Support

Figure 1. Distribution of Body Lead Burden in APOL1 high and low risk individuals



This figure shows the distribution and density of body lead burden in 30 APOL1 low (n=15) and high risk (n=15)individuals matched by age, sex, socio-demographics and recent kidney function. Figure 1 A shows distribution in all individuals and Figure 1B shows 10 individuals with a recent eGFR of <45 ml/min

TH-PO812

APOL1 Genetic Variants Are Associated with Increased Risk of Coronary Artery Disease and Sudden Cardiac Death: An Autopsy Study in Sudden Death Registry

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Background: Two genetic risk variants (G1 and G2) in APOL1, which encodes apolipoprotein L1, have been associated with kidney disease in African Americans, but whether these variants are associated with coronary artery disease or sudden cardiac death is conflicting.

Methods: Here we determined the APOL1 genotype (G0, G1, or G2) for 687 African Americans from the Sudden Death Registry of CVPath Institute. The cause of death was determined through cardiac autopsy and histopathology analyses, and categorized as sudden coronary death with or without coronary thrombosis (n=269), cardiac (non-coronary) death (n=174), and other causes (n=244). Genotyping revealed risk variants of APOL1 in 396 patients with 306 patients carrying 1 risk allele (182 G0/G1, 124 G0/G2), and 90 patients harboring 2 risk alleles (28 G1/G1, 46 G1/G2, 16 G2/G2). The APOL1 reference allele (G0/G0) was observed in 291 patients.

Results: Carriers of APOL1 risk alleles had a significantly increased risk of coronary thrombosis (relative risk 1.2006, ; 95% confidence interval, 1.0003 to 1.4409), particularly of coronary plaque rupture (relative risk, 1.2425; 95% confidence interval, 1.0136 to 1.5230). Individuals with only one risk allele (G0/G1 or G0/G2) still had significantly increased risk of coronary plaque rupture (relative risk, 1.2980; 95% confidence interval, 1.0083 to 1.6708). Further analyses suggested risk allele and hypertension are two independent factors contributing to plaque rupture. Moreover, carriers of G2 risk allele had a higher risk of cardiac causes of death (relative risk, 1.5040; 95% confidence interval, 1.0430 to 2.1705). Histopathologic analysis of the kidneys in selected age and gender matched 50 G0/G0 carriers and 50 carriers of two risk alleles showed borderline significant increases of glomerular density (p=0.08) and microcystic tubular dilation (p=0.07). A significantly higher global glomerulosclerosis was seen in carriers of two risk alleles (p=0.049), and the glomerulosclerosis is correlated with the coronary artery plaque burden (p=0.035).

Conclusions: The APOL1 high risk status is associated with higher risk of plaque rupture in coronary artery disease and sudden cardiac death.

Funding: Veterans Affairs Support, Commercial Support - This study was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

TH-PO813

Cystinosis Nonsense Mutation Read-Through Mediated by ELX-02 Restores Protein Function Using In Vitro and In Vivo Models

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Background: Cystinosis is a rare disorder caused by mutations of the cysinosin (*CTNS*) gene. Approximately 15% of cystinosis patients worldwide carry one or more nonsense mutations which halt translation of the CTNS protein through introduction of a premature stop codon. ELX-02 is an investigational synthetic eukaryotic ribosomal selective glycoside that induces read-through of nonsense mutations through interaction with the ribosome resulting in full-length functional proteins. ELX-02 is being developed as a therapy for genetic diseases caused by nonsense mutations such as nephropathic cystinosis and polycystic kidney disease.

Methods: This study evaluated the effects of ELX-02 on fibroblasts from patients with cystinosis homozygous for *W138X* mutation, as well as ELX-02 effects on mouse models of cystinosis with a *Y226X* mutation.

Results: In cystinosis patients' fibroblasts homozygous for the nonsense *W138X* mutation incubation of ELX-02 at escalating dose for 72 hours resulted in reduced half-cystine levels (at ≥100 μg/mL) up to normal levels, and significantly increased *CTNS* mRNA levels (at ≥200 μg/mL) by 2.5- to 3.5-fold. Treatment of compound heterozygous cystinosis patient human fibroblasts, $CTNS^{W138X/57kbDel}$ and $CTNS^{W138X/Frameshift}$ mutations, with ELX-02 resulted in increased *CTNS* mRNA levels and a trend in reduction of half-cystine levels. In a mouse model of cystinosis bearing a *Y226X* mutation, the PK of ELX-02 in plasma and kidneys and the renal half-cystine levels were evaluated following single and repeated bi-weekly subcutaneous administration of ELX-02 at 9 mg/kg for up to 21 days. Cystine levels decreased by 30% compared to control animals.

Conclusions: The pharmacodynamic effect of ELX-02 treatment on cystine levels suggests that ELX-02 induced functional read-through of cystinosin and demonstrated that the expressed protein reduced the accumulated lysosomal cystine by one third in the time frame of the experiment at the given dose. These results support the continued development of ELX-02 for the potential treatment of nephropathic cystinosis and other nonsense mutation mediated diseases of the kidney.

Funding: Commercial Support - Eloxx Pharmaceuticals, Inc

TH-PO814

Studying the Link Between Nephropathic Cystinosis and Tubular Acidosis

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Background: Recently, a 23-month old girl presented with rickets, metabolic acidosis, signs of renal Fanconi syndrome and increased granulocyte cystine levels. The suspected diagnosis was cystinosis, a disease caused by mutations in the *CTNS* gene (cystine transporter), leading to the lysosomal accumulation of cystine, causing organ damage, particularly the kidneys. However, genetic testing revealed no mutation in *CTNS*, but compound heterozygous pathogenic mutations in the *ATP6V1B1* gene. *ATP6V1B1* encodes the B1 subunit of the lysosomal V1 ATPase, which is deficient in distal renal tubular acidosis type 1B, but with an unknown link to cystinosis. The present study aimed to determine the link between renal tubular acidosis and nephropathic cystinosis.

Methods: CRISPR/Cas9 technology was used to knock-out the *ATP6V1B1* gene in conditionally immortalized proximal tubular epithelial cells (ciPTEC) and cell characteristics were compared to isogenic *CTNS*-/- cells. An untargeted metabolomics approach based on UHPLC-MS/MS was applied for the intracellular quantification of metabolites differentially expressed in knock-out and control cells. Fluorescence-based imaging assays were applied to monitor the lysosomal-autophagy dynamics (TFEB, LC3, and DQ-BSA) in ciPTEC.

Results: The *ATP6V1B1*-/- isogenic ciPTEC showed a significant increase in cystine accumulation compared to healthy control cells (0.26 vs. 0.13 nmol/mg protein; p<0.05). But this was significantly lower as compared to cystine accumulation in *CTNS*-/- cells (6.32 vs. 0.26 nmol/mg protein; p<0.05). Like the *CTNS*-/- cells, *ATP6V1B1*-/- cells demonstrated an abnormally increased autophagy as shown by the increased TFEB nuclear translocation (2-fold; p<0.05), increased accumulation of LC3 (2.3-fold; p<0.05), and increased lysosomal degradation of DQ-BSA (2-fold; p<0.05). Moreover, using metabolomics, we identified several metabolites and pathways that were altered (p<0.05) in both renal acidosis and cystinotic cells.

Conclusions: We successfully developed a new genetically engineered renal tubular acidosis cell model with isogenic controls. These cells provide a novel versatile tool to study the pathology of renal tubular acidosis. Metabolomics allowed us to bridge the gap between cystinosis and renal acidosis, with the future aim of finding druggable targets.

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TH-PO815

Impact of Enzymatic Degradation of Plasma Cysteine in a Mouse Model of Cystinuria Under Dehydration Challenge

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Background: Cystinuria is a genetic disease resulting from mutations in the *SLC3A1* and/or *SLC7A9* dibasic amino acid transporter genes. Disruption of transporter function leads to increased urine cystine concentrations that exceed the limit of solubility with cystine precipitation and stone formation. In addition to severe episodic symptoms including abdominal pain, affected patients require multiple procedural interventions with an increased risk of hypertension and chronic kidney disease. Although high fluid intake remains a cornerstone of therapy, these regimes are problematic and can lead to nocturia and increased day time frequency. Maintaining an adequate urine output is particularly challenging when oral hydration is compromised or during periods of increased fluid loss including occupational commitments such as troop deployments (PMID:16001591). We previously reported that enzymatic degradation of cystine reduces the propensity for kidney and bladder stone formation in a mouse model of cystinuria. Herein, we investigated the therapeutic potential of cystine enzymatic degradation as a therapeutic approach to prevent cystine stone formation in dehydration prone environments.

Methods: We used a murine model of cystinuria (*SLC3A1*-/-) that develops stones between 4 & 7 weeks of age (PMID:28165480) and rationed water to 65% to model

dehydration conditions. During water rationing, mice were administered either vehicle or a cystine degrading enzyme, and urine cystine concentration was monitored at specific timepoints prior to and after treatment.

Results: Pharmacodynamic analysis of urinary cystine demonstrated that enzymatic degradation of plasma cystine results in reduction of total cystine levels in urine despite temporary dehydration.

Conclusions: This study demonstrates that enzymatic degradation of cystine is effective at reducing the levels of cystine in urine in a mouse model of cystinuria in temporary dehydration conditions. Given that the incidence of urolithiasis is higher in conditions causing dehydration (e.g. warmer climates) (PMID:12709088), enzymatic degradation of cystine warrants further investigation as a new potential approach for disease management of cystinuric patients.

Funding: Commercial Support - Aeglea BioTherapeutics, Inc.

TH-PO816

Whole-Exome Sequencing Reveals ATP6V1C2 as a Novel Candidate Gene for Recessive Distal Renal Tubular Acidosis

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Background: Distal renal tubular acidosis (dRTA) is a rare renal tubular disorder characterized by hyperchloremic metabolic acidosis and impaired urinary acidification. Mutations in 3 genes (*ATP6V0A4, ATP6V1B1* and *SLC4A1)* constitute a monogenic causation in 58-70% of familial childhood-onset dRTA cases. *ATP6V0A4* and *ATP6V1B1* both encode for subunits of the vacuolar V-ATPase. Just recently, mutations in *FOXI1* have been identified as an additional cause. Therefore, we hypothesized that additional monogenic causes of dRTA remain to be discovered.

Methods: We performed panel sequencing and whole exome sequencing (WES) in a cohort of 17 families with 19 affected individuals with pediatric onset dRTA. Yeast growth assays and immunoblot analysis of vacuolar V-ATPase subunits were performed for *ATP6V1C2*. Transmembranous transport experiments were performed for *SLC4A2* after expression in *Xenopus* oocytes.

Results: We identified a causative mutation in 1 of the 3 "classical" known dRTA genes in 10/17 families (58%). Genomic DNA of the 7 unsolved families was then subjected to WES analysis. We identified mutations in 3 genes: *ATP6V1C2*, which encodes another kidney- specific subunit of the V-type proton ATPase (1 family); *WDR72* (2 families) which is an established disease gene for amelogenesis imperfecta, but was also previously implicated in V-ATPase trafficking in cells; and *SLC4A2* (1 family), a paralog of known dRTA gene *SLC4A1*. We then assessed 2 of these mutations for deleteriousness through functional studies. Yeast growth assays and immunoblot analysis of vacuolar V-ATPase subunits for *ATP6V1C2* revealed loss-of-function for the patient mutation with impairment of V-ATPase stability, strongly supporting *ATP6V1C2* as a novel dRTA gene. In contrast, *Xenopus* oocyte experiments did not reveal a functional impact of the *SLC4A2* mutation in the transmembranous transport experiments.

Conclusions: We provided a molecular diagnosis in a known dRTA gene in 10/17 families with dRTA (58%), identified a mutation in *ATP6V1C2* as a novel human dRTA candidate gene, and provided further evidence for phenotypic expansion in *WDR72* mutations from amelogenesis imperfecta to dRTA.

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TH-PO817

Proteomic Analysis of Urinary Exosomes in Patients with Gitelman Syndrome

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Background: Gitelman syndrome (GS) are hereditary salt-losing tubulopathies resulting from defects of sodium-chloride cotransporter (NCC). Urinary exosome analysis of NCC by western blotting has been evaluated. However, the urine exosomal protein alterations in patients with GS remains unclear. Our purpose to examine urine exosomal protein alterations in patients with GS.

Methods: Urinary exosomes were further isolated by ultracentrifugation method. We applied isotopic demethylation labeling coupled with liquid chromatography-tandem mass spectrometry (LC–MS/MS) with CID to discover urinary exosomal target proteins in patients with GS (n=10) compared to health controls (n=10).

Results: We identified a total of 253 nonredundant proteins that were based on at least two distinct tryptic peptides. Of these, 241 proteins were quantified. Specifically, 90 proteins showed an altered pattern ($Log2|GS/Control| \geq 1$) in patients with GS including 50 upregulated proteins and 40 down-regulated protein. Renin-angiotensin system was the shared KEGG pathway/biological process in the upregulated differentially genes that compatible with the clinical presentation in GS patients with salt-losing tubulopathy and volume depletion. NCC has been identified in urinary exosome from health control but not from patients with GS that was consistent with the finding of NCC mutation in GS. Of interest, there is no significant change in specific exosome markers in CD9, CD81, phosphoglycerate kinase 1 (PGK1), L-lactate dehydrogenase A chain (LDHA), and Alpha-enolase (ENOA) that could be used as an internal control.

Conclusions: The identified proteins constitute potential targets for understanding the signal pathway or pathogenesis in in patients with GS. Further target protein needs to be validated in the future.

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TH-PO818

Investigating the Pathophysiology and a Potential Therapeutic Approach for Cystinosis

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Background: Nephropathic cystinosis is a severe genetic disorder caused by mutations in *CTNS* gene (cystine transporter), leading to the lysosomal accumulation of cystine and progressive organ damage. To date, no appropriate *in vitro* isogenic cystinotic cell models exist, a pre-requisite to study the link between the *CTNS* gene and the disease, and to investigate potential therapeutic strategies. Hence, our aim was to generate a cystinosis phenotype in human kidney cells using CRISPR/Cas9 and study cystinosis pathology.

Methods: We selectively knocked-out the *CTNS* gene in conditionally immortalized proximal tubular epithelial cells (ciPTEC). An untargeted metabolomics approach based on UHPLC-MS/MS was applied for the intra- and extracellular quantification of cystine and other metabolites differentially expressed in knock-out and control cells. Various assays were applied to monitor the lysosomal-autophagy dynamics (TFEB, LC3-II and DQ-BSA) in ciPTEC.

Results: The *CTNS-/-* isogenic cell line of ciPTEC showed a significant increase in cystine accumulation compared to healthy control cells (6.32 *vs.* 0.05 nmol/mg protein; $p<0.001$). Upon treatment with cystine depleting drug cysteamine, *CTNS-/-* cells showed a significant reduction in cystine levels (0.74 nmol/mg protein; $p<0.01$). Using metabolomics, we identified that not only cystine but also >25 metabolites and 9 metabolic pathways were affected ($p<0.05$) in cystinotic cells. *CTNS-/-* cells demonstrated an abnormally increased autophagy, confirmed by the increased TFEB nuclear translocation (2-fold; $p<0.05$), increased accumulation of LC3-II (2.3-fold; $p<0.05$) and increased lysosomal degradation of DQ-BSA (2-fold; $p<0.05$). Of note, cysteamine had no effect on the restoration of autophagy, which might explain its limited effect on treating renal Fanconi syndrome. However, a promising registered drug molecule was found to be effective either alone or in combination with cysteamine in resolving cystinotic manifestations.

Conclusions: We developed a genetically engineered cystinotic cell model with isogenic controls. These cells provide a novel versatile tool to study the pathology of cystinosis and develop screens for drugs with the potential to reverse the symptoms. Metabolomics allowed an unbiased analysis of potential new targets for treatment of cystinosis.

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TH-PO819

Clinical and Genetic Characteristics in Dent Disease 2 and Lowe Syndrome

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Background: Dent disease is associated with low molecular weight proteinuria and hypercalciuria and caused by mutations in either two genes of *CLCN5* (Dent disease 1) or *OCRL* (Dent disease 2). On the other hand, Lowe syndrome is characterized by congenital cataract, developmental delay and Fanconi syndrome. Lowe syndrome is also caused by *OCRL* gene mutations, but the clinical severity differs between these two diseases. The reason for this difference remains unclear, but previous reports have shown that patients with any type of mutations before exon 7 were diagnosed with Dent disease, and those with truncating mutations after exon 8 were diagnosed with Lowe syndrome. The purpose of this study is to investigate the difference in clinical and genetic characters between Dent disease 2 and Lowe syndrome in the Japanese population.

Methods: We conducted gene test for clinically suspected cases of Dent disease or Lowe syndrome. In total, 22 male cases in 20 families were detected the mutations in *OCRL* gene. We retrospectively studied these patients to investigate the genotype-phenotype correlation in *OCRL* disorders.

Results: Eleven patients were clinically diagnosed with Lowe syndrome and 11 patients in 9 families with Dent disease 2. Seven novel mutations were identified. Four cases had mutations before exon 7, all of which were Dent disease 2. All patients who had truncating mutations or large deletions after exon 8 were diagnosed with Lowe syndrome, whereas missense mutations after exon 8 were associated with both Lowe syndrome and Dent disease 2. In other words, all cases of Dent disease 2 with mutations after exon 8 had missense mutations. Four of the patients diagnosed with Lowe syndrome were able to walk independently. Of these four cases, two had missense mutations and the other two had splice-site mutations.

Conclusions: As in previous reports, all patients with any type of mutations before *OCRL* exon 7 were Dent disease 2, and truncating mutation after exon 8 were Lowe syndrome. However, missense and splice-site mutations after exon 8 showed a spectrum ranging from Dent disease 2 to relatively mild Lowe syndrome.

TH-PO820

Inflammasome Activation in Primary Hyperoxaluria

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Background: In the primary hyperoxalurias (type I - III), increased production of oxalate in the liver consecutively leads to hyperoxaluria, urolithiasis and/or nephrocalcinosis. Hyperoxaluria causes deposition and internalization of calcium oxalate (CaOx) crystals in the epithelial cells of the proximal tubule. As a result, it activates the inflammasome pathway, which is a protein complex in the cytosol of macrophages. In a mouse model of CaOx induced inflammasome activation, the progression of renal damage was delayed by administration of a specific NLRP3 inflammasome pathway inhibitor. The aim of our present study was to investigate inflammasome activation in PH patients.

Methods: Serum samples from 50 PH patients (39 PH I, 6 PH II, 5 PHII) were collected. Thirtyfive patients had preserved renal function, 14 PH I an d1 PH II patient were on maintenance hemodialysis (HD). In addition, samples from 8 healthy controls and from 9 non PH HD patients were collected. So far, results from 9/6 PH patients with good renal function/HD and from 4 controls are available. Samples were examined for inflammation and organ damage markers by use of a proximity extension assay (PEA) (n=184). In PEA antibody pairs bind to the desired target structure and, if in close proximity to another, form a new PCR target sequence, which can be quantified using real-time PCR.

Results: The preliminary findings have shown no differences in inflammatory/organ damage markes among the three types of PH patients with preserved kidney function. However, there were signficiant reactions in dialysis dependent PH I patients. So far it is not yet clear whether these differences are caused by the advanced kidney disease or the dialysis therapy per se.

Conclusions: Our current results might allow the following conclusions: 1) the activation of the inflammasome described in the mouse model is only detectable late, e.g. in ESRD, 2) there is no inflammatory reaction to oxalate at all, 3) the response is below the detection limit, or 4) all three forms have a comparable inflammation and therefore no difference can be seen. The latter might suggest protective factors in type III or predisposing factors in types I and II.

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TH-PO821

Understanding the Increased Burden of Advanced Primary Hyperoxaluria Type 1 (PH1): A Survey of Physician Experiences

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Background: PH1 is a genetic disorder characterized by persistent hepatic overproduction of oxalate. Oxalate crystalizes with calcium to ultimately cause renal insufficiency and multi-organ damage. As PH1 progresses, patients may require intensive dialysis, and dual liver/kidney transplant is the only option to resolve the underlying metabolic defect and replace damaged kidneys. Here we describe the disease burden of PH1 in patients who have progressed to advanced kidney disease using insights from physician interviews conducted to better understand PH1.

Methods: Select participation criteria included: physicians in practice 2+ years; active role in diagnosing, treating, or managing 1+ PH1 patient(s) within last 5 years; spend ≥50% of time in direct patient care; able to review PH1 patient records. Patient history served as basis for further probing in 60-minute interviews involving open-ended questions from a semi-structured interview guide.

Results: 37 physicians reported on 54 PH1 patients. By time of diagnosis, 54% (N=29) of patients had progressed to advanced disease. Among patients with preserved renal function at diagnosis (N=25), 20% progressed to dialysis, with many others showing evidence of renal decline since diagnosis. Of all patients, 48% (N=26) required hemodialysis; of these, 47% required dialysis ≥4x/week, and 35% (N=9) required 6x/week. Patients were on dialysis for a mean of 2 (range: 0.25–6.5) years. 34% (N=19) of patients ultimately underwent transplant, typically dual liver/kidney transplant.

Conclusions: As PH1 progresses, the disease burden increases substantially, necessitating intensive dialysis and transplant. Often, patients progressed to advanced kidney disease before diagnosis, limiting opportunity to modify disease course. While intensive dialysis is intended to be a bridge to transplant, as it cannot keep pace with the oxalate overproduction and systemic deposition of oxalate that occurs at this stage, many patients spent an extended time on dialysis, which is associated with poorer outcomes. Patients require earlier diagnosis and effective therapies to prevent disease progression and the associated burden.

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TH-PO822

Whole-Exome Sequencing Identifies Nephrolithiasis (NL) Candidate Genes in Large Consanguineous Pakistani Families

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Background: Nephrolithiasis (NL) affects 1 in 11 individuals worldwide and causes high patient morbidity, frequent hospitalizations and surgical interventions. We previously detected a monogenic cause in established NL disease genes in 15% of 268 American and European NL families (Halbritter *JASN* 26:543, 2015) and 7% of 235 Pakistani NL families (Amar *Hum Genet* 138:211, 2018). We, then, performed whole exome sequencing (WES) in 17 unsolved Pakistani NL families with multiple affected members and prominent consanguinity to discover novel candidate NL genes.

Methods: We performed WES variant analysis by applying multiple recessive and dominant genetic models based on pedigree structure. Candidate disease genes were evaluated further by kidney single-cell mRNA expression (Park *Science* 360:758, 2018), because known NL genes predominantly exhibit nephron tubular segment expression. Dominant candidate genes were additionally assessed for population variant intolerance, as known dominant NL genes associated with severe phenotypes show high genomic constraint.

Results: We detected deleterious mutations in 24 candidate genes in 12/17 total families. In 10 families with significant homozygosity (>100 Mb in at least 1 affected family member), we detected deleterious recessive mutations in 10 genes. Of these, we identified 2 novel recessive candidate genes (*INPP5B, GGTLC1*) based on nephron tubular expression. In 8 families with >3 affected members, we evaluated for dominantly inherited variants and detected deleterious mutations in 14 genes. Of these, we identified 1 dominant candidate gene (*HIPK3*) based on nephron tubular expression and high population variant intolerance.

Conclusions: By WES of 17 Pakistani NL families, we identified 2 novel recessive and 1 novel dominant candidate NL disease genes.

TH-PO823

Hypophosphatemia Linked to Chromosome X (XLH): Impact on the Quality of Life

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Background: XLH is a rare disease, with dominant inheritance and where the genetic basis is the mutation of the PHEX gene, located in the short arm of chromosome 22. This gene codes for an endendendopeptidase, homologous named, which causes the overproduction of FGF- 23, a counterregulatory hormone of phosphate reabsorption by the sodium/phosphate cotransporters in the renal tubule, as well as increasing catabolism and decreasing the synthesis of the active form of vitamin D. The disease has a wide phenotypic variability and different studies have shown a significant impact on the quality of life (QoL) of these patients with reduced mobility and functional disability. A human anti-FGF-23 monoclonal antibody, burosumab, approved in the USA and Europe for the treatment of XLH, corrects the underlying pathophysiology of the disease. It has shown impressive efficacy in children and its study in symptomatic adults with this disease is under study. The objective of this study is to know the impact on the quality of life of a series of patients affected by XLH.

Methods: Longitudinal study with retrospective data collection of a series of patients affected by XLH who were in follow-up in the Department of Nephrology of the Hospital Universitari i Politècnic La Fe (Valencia). Data on the impact of the disease has been collected through a QoL test (EQ-5D-5L), and clinical and radiological variables were collected from the time of diagnosis until 2019.

Results: Data were collected from 18 patients, 38% males of 21.64 ± 11.61 years, of which all had osteomalacia or rickets of some degree, 94.4% short stature, 44% some type of affectation joint 16.6%, enthesopathies, 5.5% stenosis of the medullary canal and none craniosynostosis. Regarding the QoL, 75% referred problems for walking, 50% reported problems to perform their daily activities, 25% even for their own self-care, 50% referred anxiety or depression and 75%, pain. Their average score with respect to their state of health was 63.75 ± 22.86 out of 100.

Conclusions: XLH is a disease with different musculoskeletal manifestations that condition an important impact on the quality of life of patients in both physical and psychological aspects. That is why the appearance of burosumab as a new therapeutic strategy that blocks the physiopathological mechanism of the disease will change this paradigm.

TH-PO824

The Value of Genotypic and Imaging Information to Predict Outcomes in a Large Longitudinal ADPKD Mayo Cohort

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Background: Variability in severity of ADPKD is influenced by genic and allelic factors at the causative locus, plus other genetic and environmental factors. In a mutation characterized ADPKD cohort, we analyzed the predictive ability of the germline mutation and Mayo Imaging Class (MIC) to predict renal functional and structural outcomes.

Methods: Mayo Clinic patients >15 years having a *PKD1* or *PKD2* pathogenic variant were included (n=1072). Longitudinal eGFR (n=870) and htTKV (n=600) data were collected until ESRD. PKD1 patients were divided into truncating (Mutation Strength Group 1; MSG1), and strongly and weakly predicted non-truncating mutations (MSG2 & 3). The associations between MSG group or MIC and time to 50% loss of eGFR or ESRD or 50% increase in TKV were evaluated using Cox regression with age as the timescale.

Results: Median time from baseline to 50% eGFR loss/ESRD was 8.1, 8.8, 15.5 and 15.6 years for *PKD1* MSG1, 2, 3, and PKD2, and 6.7, 8.2, 10.7 and 17.2 years for MIC classes 1E, 1D, 1C & 1B, respectively (MIC class 1A survival was >50% throughout follow-up). This equates to *PKD1* MSG2, 3, and PKD2 being associated with a lower risk of 50% eGFR loss/ESRD compared to MSG1 [HR (95% CI): 0.69 (0.51-0.93), 0.35 (0.25-0.49), and 0.28 (0.20-0.40), respectively; P<0.001]; MIC classes 1A-1D were also associated with a lower risk of ESRD compared to class 1E [HR (95% CI): 0.039 (0.018-0.087), 0.10 (0.065-0.16), 0.19 (0.13-0.28), and 0.44 (0.30-0.63), respectively; P<0.001]. A multivariable model including both MSG and MIC had strong discriminatory ability (C-statistic of 0.802). Median time to 50% increase in htTKV was 8.3, 11.1, 12.9, 13.3 & not reached, respectively, for MIC 1E, 1D, 1C, 1B & 1A; hence the other imaging classes had a lower risk of reaching this endpoint than MIC group 1E (P<0.001). However, genotypic class was not found to be associated with a 50% increase in htTKV (p=0.56).

Conclusions: Genotype (MSG) and MIC are strong predictors of functional renal outcome in ADPKD; however, genotype was not associated with htTKV increase of 50%. Utilizing both genotype and imaging class is helpful for identifying patients with severe disease, thereby aiding selection of patients for clinical trials and treatment.

Funding: NIDDK Support

TH-PO825

ADPKD Calculator: A New Tool to Help in the Detection of Patients with Rapid Progression

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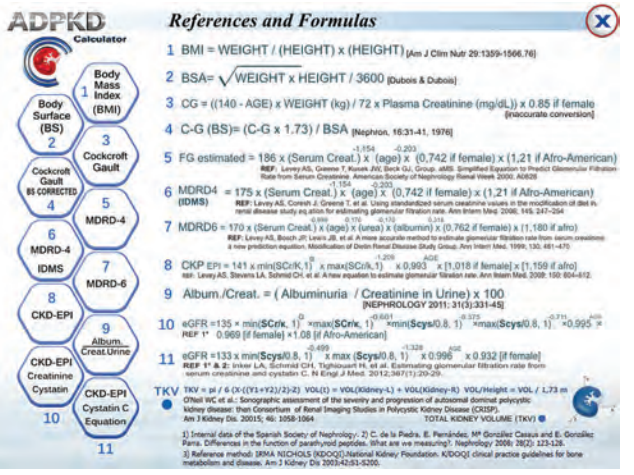
Background: Autosomal dominant polycystic kidney disease (ADPKD), a frequent hereditary renal disorder, is the etiology of 10% of t dialysis or renal transplant patients and approximately 70% will progress to end-stage renal disease in the fifth decade of life. In 2016 the ERA-EDTA published the Recommendations for the use of Tolvaptan, that included an Algorithm for the recognition of patients with rapid progression, to assess indications for initiation of treatment in ADPKD patients. Starting from this point, we have developed a new App for free use (Scientifically Endorsed by the SCALN), to facilitate detection of rapid progressions. The aim of this App is calculate variables of Renal Function, Total Renal Volume and by means of an Algorithms and Prediction Models, identify ADPKD patients with Rapid Progression.

Methods: Once the conditions of use have been accepted, the patient's data can be entered in various ways. The methods are described in the App itself in "References and Formulas" button as you can see in attached image.

Results: Body Mass Index. Body Surface. Renal Function (Cockroft Gault BMS corrected; MDRD-4; MDRD-4 IDMS; MDRD-6; CKD-EPI; Urine Albumin/Creatinine Ratio; CKD-EPI Cystatin; CKD-EPI Cystatin C Equation). CKD Stage KDIGO 2012 (wiht graphic representation). KIDNEY TOTAL VOLUME with link to Mayo Clinic Website (The user must be previously accepting Mayo Clinic Terms of Use). Identification of Rapid Progressing patients through the use of: 1) the Digitalized Algorithm of the ERA-EDTA Workings Groups cited; and 2) PRO-PKD Prediction Model.

Conclusions: ADPKD Calculator, allows the nephrologist to quickly and easily identify patients as Rapid Progressives, in order to proceed to implement those measures that may slow the progression to ESRD. Finally, the free access to this App from www.scaln.es, its availability in multiplatform and English/Spanish languages, facilitates the use of it.



TH-PO826

Expanded Imaging Classification of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Mayo imaging classification of ADPKD is a widely accepted tool that uses height-adjusted total kidney volume (htTKV) and age to identify patients at highest risk for disease progression. The current Mayo classification, however, is applicable only to patients who have typical disease with diffuse cystic involvement (Class 1) by excluding 5-10% of patients (Class 2) with atypical kidney morphology whose htTKV do not appear to predict eGFR decline. Thus, for Class 2 patients, predicting the risk for progression remains uncertain.

Methods: Twenty-one patients of Class 2 with predominant exophytic cyst distribution were identified from the HALT-A study (558 ADPKD adults), and their htTKV were remeasured by excluding exophytic cysts to estimate revised htTKV (rev-htTKV). For the analysis, the odds ratio of reaching CKD stage 3 (CKD3) per 100 ml/m increment in htTKV were compared in both unadjusted and adjusted (covariates: baseline age, eGFR, BMI, sex and race) logistic models for (1) only Class 1 participants, (2) all participants with original htTKV and (3) all participants with rev-htTKV.

Results: All 6 logistic models showed significant association (p<0.001) between baseline htTKV and reaching CKD3. Estimated odds ratios of reaching CKD3 for all participants increased from use of htTKV to rev-htTKV for both unadjusted (from 1.26 to 1.31) and adjusted (from 1.18 to 1.26) models. Because rev-htTKV was always less than htTKV, the probability of reaching CKD3 decreased for all Class 2 participants. Furthermore, with rev-htTKV, the probability of outcome for Class 2 participants who did not reach CKD3 decreased more than those who reached CKD3.

Conclusions: For Class 2 with predominant exophytic cyst distribution, the association between baseline htTKV and CKD3 outcome became stronger with the use of htTKV remeasured after excluding exophytic cysts, compared to the use of original htTKV.

Funding: NIDDK Support

Comparison of odd ratios of reaching CKD3 with and without including class 2 in two different models

Outcome: CKD3, eGFR<60		Unadjusted model			Adjusted model		
Models	N	OR	95% CI	P	OR	95% CI	P
Excluding Class 2	433	1.29	1.21-1.38	<0.001	1.23	1.14-1.33	<0.001
Including Class 2, original htTKV	451	1.26	1.18-1.34	<0.001	1.18	1.10-1.27	<0.001
Including Class 2, rev-htTKV	451	1.31	1.22-1.40	<0.001	1.26	1.16-1.36	<0.001

TH-PO827

A Computable Phenotype for ADPKD

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Background: Autosomal Dominant Polycystic kidney disease (ADPKD) is the most common inherited disease causing of end-stage kidney disease (ESKD). A computable phenotype is an algorithm used to identify a certain set of patients within an electronic

medical record system. Developing a computable phenotype that can identify patients with ADPKD will assist researchers in designing studies and clinical trial recruitment within this population.

Methods: We reviewed a random sample of 1000 medical charts from the University of Kansas Medical Center database. The sample was divided into four groups (A, B, C, and D) of 250 patients each. Group A included patients followed in nephrology clinics who had ICD (International Classification of Diseases) 9 or 10 codes for ADPKD, Group B included those with no ICD codes of ADPKD, but with ICD codes of renal cysts. Group C and D had patients who did not attend the nephrology clinic, with and without ICD 9/10 codes for ADPKD respectively. We used the ICD 9 codes 753.12-13, and the ICD 10 codes Q61.2-3 for ADPKD. We used the ICD 9 code 593.2 and the ICD 10 code N28.1 for renal cysts. For all medical records, we extracted family history of PKD, hypertension, glomerular filtration rate, proteinuria, kidney size, number of kidney cysts. Then, we compared the data to internationally accepted diagnostic criteria for ADPKD to determine the diagnosis of ADPKD (reference standard). We calculated test accuracy results for the proposed computable phenotype for ADPKD.

Results: The computable phenotype to identify patients with ADPKD who attended the nephrology clinic has a sensitivity of 98.7% (95% CI 96.4-99.7), a specificity of 84.1% (95% CI 79.5-88.1), a positive predictive value (PPV) of 83.4 % (95% CI 79.43 - 86.72%), and a negative predictive value (NPV) of 98.8% (95% CI 96.4-99.6). For those who did not attend the nephrology clinic the computable phenotype has a sensitivity of 97.1% (95% CI 93.3-99.0), a specificity of 82.0% (95% CI 77.4-86.1), a PPV of 74.0% (95% CI 69.2-78.3), and a NPV of 98.2[RM1] % (95% CI 95.7-99.2).

Conclusions: A computable phenotype using the ICD9 and 10 codes can correctly identify most patients with ADPKD, and can be used by researchers to categorize ADPKD patients' cohorts with limited inaccuracy.

TH-PO828

A Convolutional Neural Network for Large-Scale Segmentation of Kidneys in Autosomal Polycystic Kidney Disease

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Background: Total kidney volume (TKV), along with age and Glomerular Filtration Rate (eGFR), is an early prognostic marker of progression in autosomal dominant polycystic kidney disease (ADPKD). Current manual or semi-automated methods for estimation of TKV from imaging data are laborious, time-consuming approximations subject to human perception and experience; this has hampered a widespread adoption of TKV as a biomarker in ADPKD. We report the development and performance of a fully automated method for kidney segmentation and TKV estimation from magnetic imaging (MR) data in patients with ADPKD on a large patient cohort using a deep learning approach. In addition, we describe how such an estimate can be employed for predicting disease progression and monitoring progression, with the aim of supporting clinical management.

Methods: We employ a fully-convolutional neural network based on the volumetric U-net architecture, trained on an extensive dataset of 1620 T2-weighted magnetic resonance imaging scans extracted from the multicenter TEMPO3:4 trial (NCT00428948); expert outlines were available as ground truth. The method is validated on 490 scans, not included in the training dataset, extracted from 179 individual subjects. Based on the data from the same trial, we develop a similarity model for the prediction of the expected TKV growth over time.

Results: We obtained a 90th percentile estimation error of TKV and its change over time of 13% and 11% of the baseline volume, respectively. We predict 3-year TKV based on baseline characteristics with R2 of 0.954 on the TEMPO3:4 placebo data.

Conclusions: The present work represents the first, large-scale example of fully automated TKV estimation in ADPKD that has been trained and validated on a large-scale, multi-centric dataset. When coupled with clinical data from the same trial, we demonstrate the ability of a machine learning algorithm to predict likely TKV progression with high accuracy. This prognostic information combined with other clinical findings may support clinical care.

TH-PO829

Expert-Level Segmentation Using Deep Learning for the Volumetry of Polycystic Kidney and Liver

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, with serious impacts on patients. In polycystic kidney and liver diseases (PKLD), including ADPKD, volumetry is used to assess disease progression and drug efficiency. However, since no rapid and accurate method has been developed, volumetry has not been established in clinical practice, hindering the development of therapies for this disease. This study presents an AI-based PKLD volumetry method that showed powerful performance.

Methods: As a first experiment, the performance of AI was evaluated compared to ground-truth (GT). We trained a V-net based convolutional neural network on 175 ADPKD computed tomography (CT) segmentations (GT) produced by 3 experts using images from 214 patients. The Dice similarity coefficient (DSC), inter-observer correlation coefficient (ICC), and Bland-Altman plots of 39 GT and AI segmentations in the validation set were compared. Next, the performance of AI on the segmentation of 50 random CT images was compared to that of 11 PKLD specialists based on the resulting DSC and ICC.

Results: The DSC and ICC of the AI were 0.961 and 0.999729, respectively. The error rate was within 3% for approximately 95% of CT scans (error <1%, 46.2%, 1% ≤ error <3%, 48.9%). Compared to the specialists, AI showed moderate performance. Furthermore, an outlier in our results confirmed that even PKLD specialists can make mistakes in volumetry.

Conclusions: PKLD volumetry using AI was fast and accurate. AI showed comparable performance to that of human specialists, suggesting its practical use in clinical settings.

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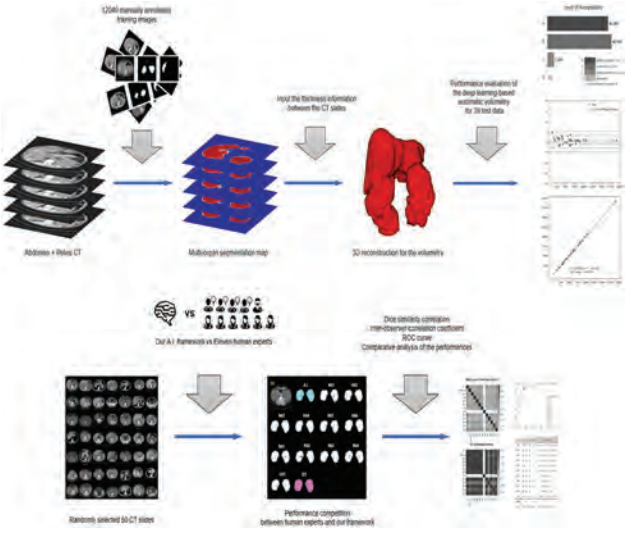

TH-PO830

Total Kidney Volume (TKV) Measurements in Autosomal Dominant Polycystic Kidney Disease (ADPKD) by 3D Ultrasound (3D-US) vs. Ultrasound Ellipsoid (US-EL)

Pedram Akbari,[3] Fatemeh Nasri,[3] Crystal F. Quist,[3] Elsa Guiard,[3] Ioan-Andrei Iliuta,[1] Syed E. Ahmed,[3] Luca Calvaruso,[2,4] Mostafa Atri,[1] Korosh Khalili,[1] York P. Pei.[1] *[1]University Health Network and University of Toronto, Toronto, ON, Canada; [2]University Health Network, Toronto, ON, Canada; [3]Toronto General Hospital UHN, Toronto, ON, Canada; [4]Università Cattolica del Sacro Cuore, Roma, Roma, Italy.*

Background: Total kidney volume (TKV) is a validated prognostic biomarker for risk assessment in ADPKD. TKV by magentic resonance imaging and manual segmentation (MRI-MS) is the "gold standard", but is relatively expensive, time-consuming, and not readily accessible. 3D-US is a new technology which may provide greater precision and accuracy for measuring TKV than US-EL. Here, we report a comparative study of these two US techniques for TKV measurements against MRI-MS.

Methods: We conducted a prospective study of 123 patients recruited at a PKD specialty center who underwent a standardized 3D-US and MRI. Kidney volumes (i.e. single kidney and TKV) by 3D-US and US-EL measured by 5 different experienced ultrasound technicians were compared to those by MRI-MS derived from an experienced radiologist blinded to patient clinical results. Bland-Altman plots were used to assess the agreement of TKV measurements by US vs. MRI.

Results: Table 1 shows the study patient characteristics. We found the accuracy of TKV measurements by US was operator-dependent and varied between different technicians. Compared to MRI-MS, Bland-Altman plots of TKVs by 3D-US and US-EL revealed a similar bias (-9.0% vs. -10.2%), range of diagreement (-42.25 to 24.31% vs. -41.25 to 20.85%), and difference of greater than 20% (27.2% & 24.3%), respectively. Converting height and age-adjusted TKV's to the Mayo Class Imaging Class (MCIC) we found a misclassifcation rate of 22.8% and 23.5% by 3D-US and US-EL, respectively.

Conclusions: TKV measurements by 3D-US and US-EL are less accurate than MRI-MS. Both US tecniques displayed similar bias, accuracy, and are operator-dependent; however, TKV by US-EL is simpler to use and more readily available. These factors need to be considered when US-dervied TKV is used for risk assessment in ADPKD as misclassification of MCIC (esp. 1B to 1C) can have important clinical consequence.

Funding: Government Support - Non-U.S.

Table 1. Patient characteristics

	N=123
Age (years) mean ± SD	45 ± 15
Gender, M:F	1 : 1.2
s-Cr (mg/dL) mean ± SD	1.14 ± 0.48
Height (meters) mean ± SD	1.69 ± 0.9
TKV (mL) mean ± SD	1116 ± 822

TH-PO831

Simplification of Total Kidney Volume Measurement Procedures for ADPKD

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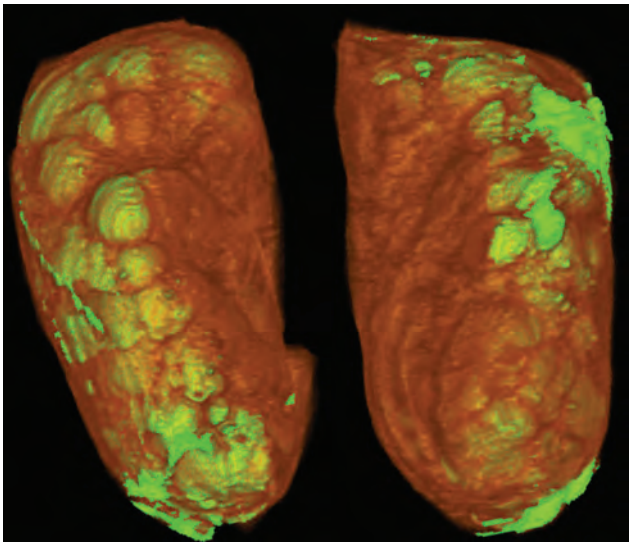
Background: Total kidney volume (TKV) is an important measure of risk of disease progression in autosomal dominant polycystic kidney disease (ADPKD). Methods to measure TKV are labor-intensive and time-consuming, and not all centers have ability to measure TKV. We developed a technique to provide timely and reliable quantification of TKV using any sequence of abdominal magnetic resonance imaging (MRI).

Methods: Abdominal MRI scans of 74 consecutive patients from the UCSF Polycystic Kidney Disease Center of Excellence were selected. The technique was developed using functionality readily available in an FDA-approved commercial medical imaging analysis software (Ziosoft). Scans for the subjects were acquired from different scanner types (GE, Phillips) and field strengths (1.5 T, 3 T). On each scan the volumes of left and right kidneys were assessed. Measurements were done on coronal T2-weighted DICOM images (single shot fast spin echo/half-Fourier, slice thickness between 3 and 9 mm). The outer kidney contour was defined manually by tracing on each slice. The contour from each 2D slice was merged to create a true 3D volume of the kidney. The process is calibrated using parameters available in DICOM images. For some cases the cystic volume was measured for each kidney as well via a binary intensity value thresholding. The non-cystic volume was determined by digital subtraction of cystic volume from total kidney volume.

Results: Average time to implement these measures on standard non-contrast MRI sequence was 30 minutes. Comparing the TKV to measurements obtained by alternative methodology (reported by prior institutions on the same scans) revealed a concordance of > 90%.

Conclusions: Our technique is readily applicable to routine MRI images obtained for clinical purposes in ADPKD patients. Use of this technique may improve risk stratification availability for ADPKD patients.



3D volume rendering; cysts green.

TH-PO832

Performance of Ultrasound-Derived Average Kidney Length (aKL) for Risk Prediction in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Pedram Akbari,[3] Fatemeh Nasri,[3] Crystal F. Quist,[3] Elsa Guiard,[3] Ioan-Andrei Iliuta,[1] Syed E. Ahmed,[3] Luca Calvaruso,[2,4] Mostafa Atri,[1] Korosh Khalili,[1] York P. Pei.[1] *[1]University Health Network and University of Toronto, Toronto, ON, Canada; [2]University Health Network, Toronto, ON, Canada; [3]Toronto General Hospital UHN, Toronto, ON, Canada; [4]Università Cattolica del Sacro Cuore, Roma, Roma, Italy.*

Background: Total kidney volume (TKV) is a validated prognostic biomarker for risk assessment in ADPKD. However, accurate TKV measurements require magnetic resonance imaging (MRI), which is relatively expensive, time-consuming, and not readily accessible. To circumvent these issues, an ultrasound-derived aKL >16.5 cm (Kidney Int 88: 146-151, 2015) has been proposed as a diagnostic thresohld to identify patients with ADPKD at high-risk for progression. However, this approach has not been tested in a real world patient cohort.

Methods: We conducted a prospective study of 123 patients recruited from a PKD specialty center who underwent a standardized 3D-US and MRI. KLs from 3D-US were measured by 5 different experienced technicians; KLs and TKVs from MRI were derived by an experienced radiologist blinded to patient clinical results. Bland-Altman plots were used to assess the agreement of KLs by US vs. MRI. TKV adjusted for age and height was used to derive the Mayo Clinic Imaging Class (MCIC) and used as a "gold standard" for classifiying patients into low-risk (1A-1B) vs. high-risk (1C-1E) grouping.

Results: Table 1 shows the study patient characteristics. Good agreement was observed between US- and MRI-derived aKL with 98% of cases within 20% difference. Using aKL >16.5 cm as a diagnostic threshold yielded a sensitivity of 0.53, specificity of 0.92, false positive rate (FPR) of 0.14, false negative rate (FNR) of 0.31, and accuaracy of 0.74 for predicting high-risk MCIC (1C-1E).

Conclusions: US-derived aKL >16.5 cm provides a simple approach for risk stratification in ADPKD, but is associated with a FPR of 0.14 (i.e. 14% of low-risk patients misclassified as high-risk) and FNR of 0.31 (i.e. 31% of high-risk patients misclassified as low-risk). When a therapeutic decision (i.e. use of Tolvaptan) is based on accurate risk stratefication these errors have clinical consequence.

Funding: Government Support - Non-U.S.

Table 1. Characteristics of Patient Cohort

	Total (n=123)
Age (years) mean ± SD	45 ± 15
Gender, M:F	1 : 1.2
s-Cr (mg/dL) mean ± SD	1.14 ± 0.48
Height (meters) mean ± SD	1.69 ± 0.9
TKV (mL) mean ± SD	1116 ± 822

TH-PO833

How Well Do Risk Assessment Guidelines Perform for Autosomal Dominant Polycystic Kidney Disease (ADPKD)?

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Background: The approval of Tolvaptan for treatment of ADPKD heralds a new era when mechanism-based therapy is now possible. However, Tolvaptan is an expensive drug that is associated with potentially serious side-effects. Thus, it is currently reserved for patients who are at high-risk for progression. Two sets of risk assessment guidelines for ADPKD are now available based on the consensus of two panels of nephrologists from Canada and Europe. However, how well do these guidelines perform in risk assessment has not been formally assessed.

Methods: We conducted a prospective study in 474 patients with typical imaging pattern of ADPKD by MRI who also had detailed clinical and laboratory data including total kidney volume (TKV). We used age- and height-adjusted TKV to derive Mayo Clinic Imaging Class as a "gold-standard" for risk assessment (i.e. low-risk: 1A-1B; high-risk: 1C-1E). We then applied the revised Canadian guidelines (Can J Kidney Health Dis. 2018; 5:2054358118801589) and European guidelines (NDT 2016; 31: 337-348) to our patient cohort to assess their performance.

Results: Applying the updated Canadian risk assessment algorithm resulted in exclusion of 52% (245/474) of patients in whom 65% were deemed to be low-risk (i.e. MCIC 1A-1B) and 35%, high-risk (MCIC 1C-1E). The resultant cohort (221/503) was enriched with 88% high-risk patients but also included 12% of low-risk patients. The European guidelines provide a 5-step hierarchal algorithm. Applying the first step based on age and CKD stages resulted in exclusion of 74% (351/474) of patients in whom 69% were deemed to be high-risk and 31%, low-risk. The resultant cohort (123/474) was enriched with 72% high-risk patients but also included 28% of low-risk patients. Applying the second step based on rate of eGFR decline resulted in a total exclusion of 93% (440/474) of patients in whom 59% were deemed to be high-risk and 41%, low-risk. The resultant cohort (34/474) was enriched with 82% high-risk patients but also included 18% of low-risk patients.

Conclusions: Risk assessment in ADKPD is an evolving process to be refined by new clinical data and test technologies. Guidelines that enrich "high-risk", while minimizing "low-risk", patients, have most clinical utility.

Funding: Government Support - Non-U.S.

TH-PO834

Long-Term Safety and Tolerability of Tolvaptan (TLV) in Later-Stage ADPKD

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Background: A hepatic safety signal for TLV emerged in the TEMPO clinical ADPKD program with the 1st 18 months (m) of treatment the time of greatest susceptibility. This phase 3b, open-label extension study (NCT02251275) evaluated long-term TLV safety in ADPKD pts; liver enzyme monitoring frequency was q1m for the first 18 m of treatment and q3m thereafter.

Methods: Pts entered from REPRISE, TEMPO 4:4, or prior trials (9 pts). TLV exposure before entry was ≤5 yrs for TEMPO 4:4 pts and ~1 yr for REPRISE TLV pts. Hepatic safety was monitored q1m in pts with <18m TLV treatment, then q3m thereafter. Starting TLV dose depended on prior trial; maintenance regimens in this study were daily split doses 45/15mg, 60/30mg, and 90/30mg, with down-titration allowed for tolerability.

Results: Of 1803 pts enrolled, 1800 received ≥1 TLV dose. Range of duration TLV exposure in this study was 1-1435 days (d); median exposure 651d (mean 697; SD 334, IQR: 538-924). Percentages of treatment-emergent AEs (TEAEs) were similar across the 3 subgroups but REPRISE PBO pts reported more TEAEs (3678) vs TLV (2965) and TEMPO 4:4 (3297). Most common TEAEs overall: thirst (23%), renal pain (20%), polyuria (20%), hypertension (17%), nasopharyngitis (15%), nocturia (15%). Aquaretic AEs (AAEs) were most frequent in REPRISE PBO (thirst 32%, polyuria 32%, nocturia 22%). No Hy's Law cases. TEAE ALT increased 2.8%; AST increased 0.6%. Median 245d to ALT increased, 251d to AST increased.

Conclusions: AAEs and discontinuations due to AEs were less frequent in pts with longer TLV exposure. No new Hy's Law cases with monthly monitoring during the first 18m of treatment, nor in previously TLV treated pts, nor in the 570 pts who started TLV in the present study. (Funding: Otsuka.)

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

Prior trial participation	REPRISE		TEMPO 4:4
	PBO	TLV	
Number of pts (% of total)	570 (31.6%)	506 (28.1%)	718 (39.8%)
Pts with eGFR ≤45 mL/min/1.73 m2, %	67.4%	65.0%	30.5
Pts with TEAEs, n (%)	531 (93.3%)	473 (93.7%)	643 (89.7%)
Pts with serious TEAEs, n (%)	96 (16.9%)	87 (17.2%)	103 (14.4%)
Pts discontinued due to AEs, n (%)	65 (11.4%)	33 (6.5%)	38 (5.3%)
Deaths,* n	5	1	3

*None considered TV-related; causes: cardiac arrest; CKD/septic shock; acute respiratory distress syndrome; cerebral aneurysm; aortic dissection; subarachnoid hemorrhage; sudden death; meningeal metastases; tuberculosis.

TH-PO835

Quality of Life and Tolerability of Tolvaptan in Swiss ADPKD Patients

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Background: Previous HRQoL assessments in ADPKD patients yielded conflicting results. In addition, the impact of Tolvaptan treatment on HRQoL outcomes in ADPKD patients is currently unknown.

Methods: The Bern ADPKD registry is an observational cohort study initiated in 2015. Inclusion criteria are age ≥ 18y, clinical diagnosis of ADPKD, informed consent. The main exclusion criterion is need for renal replacement therapy. We assessed HRQoL of ADPKD patients with the standardized Short Form-36 (SF-36) as part of the KDQOL-SF™ 1.3 questionnaire in yearly intervals. The SF-36 consists of 8 multi-item subscales (physical functioning, role-physical, bodily pain, general health, energy/vitality, social functioning, role-emotional, mental health), and two summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS). We transformed raw scores into T-scores (mean=50, SD=10, range 0-100) using contemporaneous Swiss general population norms. Higher scores indicate better HRQoL.

Results: Between October 2015 and May 2019, 121 ADPKD patients were recruited and Tolvaptan treatment has been initiated in 38 patients. In six patients (16%) treatment had to be discontinued within the first three months of treatment due to aquaretic side effects (n=4, 11%) or due to elevated liver enzymes (n=2; 5%), and in eight patients (21%) a dose reduction was necessary. We included 93 patients (28 with and 65 without Tolvaptan treatment) for which baseline and 1-year follow-up data were available. Thirty-nine patients were male (42%), median age was 45.7 y, median eGFR 70.4 ml/min and median total kidney volume 1197 ml. HRQoL at baseline was similar to the general population with a PCS of 48.6 (95% CI 46.2 – 51.0) and a MCS of 49.6 (95% CI 47.5 – 51.7). Patients with future Tolvaptan treatment had higher PCS scores than patients without future Tolvaptan treatment (52.8 versus 46.8; p<0.05). Individual subscales were not different. At 1 year follow-up HRQoL subscales, MCS and PCS scores were similar to baseline scores in both patients who received Tolvaptan and those who did not.

Conclusions: HRQoL in Swiss ADPDK patients is comparable to HRQoL in the general Swiss population. Furthermore, our data reveal that, beyond an initial adaptation to increased aquaresis, long-term treatment with Tolvaptan does not negatively affect HRQoL of ADPKD patients.

Funding: Commercial Support - Otsuka Pharmaceuticals

TH-PO836

Using Tolvaptan for ADPKD: Feasibility and Patient-Reported Outcome in the Real-Life Setting

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Background: Considering the polyuria induced by V2R-antagonists, there is concern regarding tolerability of tolvaptan in the real-life setting. How do patients cope with the increased urine volume? Is adherence sufficient to reach the desired effect and how is the quality of life (QoL) affected?

Methods: In the AD(H)PKD study, we collect data of ADPKD patients presenting with the question whether they should take tolvaptan on a yearly basis. As one aspect, we use self-developed questionnaires to raise patient-reported outcomes, aiming e.g. at complications and adherence. In addition, QoL and pain are recorded using the SF-12 Health Survey and a translated version of the HALT-PKD pain questionnaire.

Results: Since the start of the study in late 2015 we enrolled more than 560 patients. Urine volume increases to 5-7.5 liters in the majority of patients on tolvaptan. The largest increase occurs when starting the first dose step, whereas any further uptitration only leads to a minor change. Adherence to longterm-therapy is about 80%; most patients that discontinue tolvaptan report polyuria-associated events. The majority of patients do not consider the therapy a major problem. However, around two-thirds report that a minor adaptation of everyday life is necessary. The increased urine volume presents a burden *rarely* for ~65% and *often or always* for ~23%. Nonetheless, over 90% would recommend the therapy to other patients. Patients rarely skip a dose (1-2X p.m.) and do so equally spread for leasure-time, professional and medical reasons. QoL does neither differ between patients with or without tolvaptan in the whole cohort nor longitudinally in individual patients before and after starting.

Conclusions: Our data indicates that taking tolvaptan – despite the increase in urine volume – is well feasible for most patients without major adaptations to everyday life. Around 20% consider the polyuria a significant burden and about the same percentage discontinues the therapy in the long term. QoL is not affected by polyuria and nearly all participants would tell other patients to try the therapy if recommended by their nephrologist. Taken together, our data will help to increase confidence of nephrologists in using tolvaptan for ADPKD and to guide patient counselling when starting the treatment.

Funding: Commercial Support - Otsuka Pharma GmbH

TH-PO837

Relationship of Tolvaptan Dose with the Rate of Decline in Kidney Function in ADPKD Patients

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Background: Vasopressin receptor 2 antagonist, tolvaptan (TLV), has been shown to suppress the decline in kidney function and increase in total kidney volume in patients with autosomal dominant polycystic kidney disease (ADPKD). TEMPO 3:4 trial and REPRISE trial demonstrated that TLV suppressed the decline in kidney function. However, the dose of TLV and its relationships to kidney function decline have not been clarified. Therefore, we analyzed the TLV doses in ADPKD patients at our hospital, who were introduced to TLV, and the rate of eGFR decline after starting TLV.

Methods: The subjects were 57 patients who were administered TLV for at least 6 months at Tokyo Women's Medical University Hospital from September 2014 to December 2017. For patients who stopped the drug due to liver dysfunction, the observation period was until they discontinued the drug. TLV dose was calculated by dividing the accumulated dose that was actually prescribed by the number of administration days during the follow-up period. The primary outcome was Δ%eGFR during the follow-up period. The median value was calculated and logistic regression analysis was performed on the decreased kidney function group whose Δ%eGFR were less than the median value.

Results: There were 34 men and 23 women. The follow-up period was 2.1 years, age at start of administration was 41, TKV was 2,023.54 mL, and eGFR was 42.3 mL/min/1.73 m^2 (all median values). For CKD stage, there were 3 patients of G1, 11 patients of G2, 29 patients of G3, and 14 patients of G4. For the Mayo classification, there were 3 patients of class 1B, 21 patients of 1C, 20 patients of 1D, and 13 patients of 1E. The accumulated dose was 63.5 mg/day, and ΔeGFR was -4.3 mL/min/1.73 m^2 /year, Δ%eGFR was -11.0%.(all median values). The multivariate logistic analyses included age, sex, eGFR, hemoglobin, urinary osmolality the day after administration, accumulated dose of TLV, hypertension, hyperuricemia, determined that age (P <0.05), and accumulated dose of TLV (P <0.05) were independently associated with a decreased kidney function.

Conclusions: Increasing the TLV dose appears to suppress the decline in kidney function in ADPKD patients.

TH-PO838

Could Glomerular Filtration Rate be an Exclusion Criteria to Initiate Tolvaptan Therapy in Those Patients with ADPKD with Risk of Rapid Progression and Predict Renal Outcomes?

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent inherited renal disease and located among the four main causes of end stage renal disease (ESRD) in adult population.

Methods: To analyze the role of tolvaptan (TOLV) along time according with the initial estimated glomerular filtration rate (CKD-EPI) in those patients with CKD 1-4 with risk of rapid progression to ESRD (clinical, analytical and imaging scoring). **PATIENTS AND METHODS**: This is an observational and transversal study of our first cohort of 15 pts which initiates in TOLV at a 45/15 mg/d dose and escalating every two weeks until 120 mg/d (13 pts) or maximal tolerated dose (90 mg/d (2 pts)). Controls were made initially every two weeks and every 3 months at 18 months of TOLV.

Results: At the time of inclusion all patients 45.4 +/- 6.5 years old and 83.0 +/- 14.2 kg. 65% were men and the plasma creatinine were 0.98 to 2.58 mg/dl with a CKD-EPI of 53.3 +/- 23 ml/min (25.6 to 102.3). Total kidney volume adjusted for age and height ranged from 997 to 2634 cc. After being log-transformed GFR was normally distributed and parametric comparison was made. All treated patients showed a reduction in their GFR in correlation with the used doses (p=0.002). Since in the previous comparison de-escalation patients were included, patients were distributed in quartiles of GFR excluding filtering values corresponding to de-escalated doses as follows: (< 30 ml/min: 2 pts; 30-44 ml/min: 5 pts; 45-60 ml/min: 4 pts and >60 ml/min: 4 pts). In this analysis we do not show any correlation between GFR and TOLV treatment, even after one year of therapy. These data are in agreement with the REPRISE study (Torres V et al, NEJM 2017) results. In any of the quartile established we cannot find any significant relation between TOLV treatment, dose of TOLV and reduction of GFR.

Conclusions: The use of TOLV seems to be safe and effective even in those patients older than 50 years and with CKD stage 3b-4. Those patients with a GFR less than 30 ml/min must be on a one-to-one basis evaluated.

Funding: Private Foundation Support

TH-PO839

Differential Effects of Tolvaptan on Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease Patients with PKD1 and PKD2 Mutations

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common renal disease with a genetic origin. The renal prognosis of patients with polycystin 1 (*PKD1*) mutations was reported to be worse than those with *PKD2* mutations. At our hospital, 17 patients with ADPKD with known gene mutation profiles have been treated with the vasopressin antagonist tolvaptan since 2015. However, the relationship between specific gene mutations and the protective effect of tolvaptan on kidney volume and renal function remains unclear. Therefore, we assessed outcomes of patients with different gene mutations after one-year tolvaptan treatment.

Methods: All patients provided consent for genetic analyses. Genetic analysis by Sanger sequencing with a 3730 DNA analyzer was performed in 17 ADPKD patients, including 8 males and 9 females (mean age; 51 ± 11 years), who were treated with tolvaptan for one year. Total kidney volume (TKV) was evaluated with computer tomography using Ziostation 2, an auto-analysis system for TKV measurement.

Results: Mean values for TKV, eGFR, Δ%TKV/year, and ΔeGFR were 1569 ± 575 ml, 56.0 ± 22.5 ml/min/1.73 m^2, 14.1 ± 6.1%, and –5.9 ± 7.5 ml/min/1.73 m^2, respectively. *PKD1* and *PKD2* mutations were found in 4 and 3 patients, respectively, whereas no mutations in either gene were found in the remaining ten patients. The baseline total TKV, renal function, and changes in TKV did not differ among the patients with *PKD1* and *PKD2* mutations and those with unknown status (TKV, 1199 ± 212, 1449 ± 277, and 1770 ± 667 ml; eGFR, 58.6 ± 22.7, 60.7 ± 11.7, and 53.6 ± 24.4 ml/min/1.73 m^2; Δ%TKV/year, 10.8 ± 2.7%, 12.3 ± 4.3%, and 15.9 ± 6.7%, respectively). Tolvaptan treatment significantly improved the Δ%TKV/year in patients with *PKD1* mutations (–8.3 ± 10.2%, p = 0.03) and those with unknown status (–6.8 ± 8.6%, p < 0.001), but not in those with *PKD2* mutations (–1.7 ± 8.8%, p = 0.20). ΔeGFR did not change in any of the groups studied.

Conclusions: One-year tolvaptan treatment reduced Δ%TKV/year in patients with ADPKD with *PKD1* mutations and those with unknown mutation status but not in those with *PKD2* mutations.

Funding: Private Foundation Support

TH-PO840

Clinical Pattern of Tolvaptan (TLV)-Associated Liver Injury in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Patients: Analysis of Pivotal Clinical Trials

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Background: In the TEMPO clinical program, an imbalance in the proportion of pts with elevated aminotransferases >3X upper limit of normal (ULN) was seen vs placebo (PBO). As 3 pts (2 from TEMPO 3:4 [NCT00428948], and 1 from the open-label extension, TEMPO 4:4 (NCT01214421]) met Hy's Law criteria, increased monitoring frequency was recommended. In the REPRISE clinical program, monitoring was q1m during the first 18m of TLV exposure and q3m thereafter.

Methods: An independent, blinded Hepatic Adjudication Committee examined data from REPRISE (NCT02160145) and its open-label extension (NCT02251275) in pts with aminotransferases >3X ULN using the 5-point U.S. DILI Network classification.

Results: In REPRISE 1370 pts were randomized to TLV (AM/PM split doses of 60/30mg or 90/30mg) or PBO. 1362 pts had postbaseline assessments of serum aminotransferases. 72 pts with ALT elevations >3X ULN were reviewed, and 14 were judged to have liver injury at least probably related to the study drug, but without liver failure or persistent liver injury. Elevations began ~2-3 m after study drug initiation and were seen to develop over the course of 12 m. No association with dose or systemic exposure was found, and no pts on TLV (n=681) or PBO (n=685) met the definition of Hy's Law. In the open-label extension, 1803 pts were enrolled (REPRISE: 60%; TEMPO 4:4: 40%); 1800 received ≥1 TLV dose and were analyzed. 1488 pts (83%) completed the study. The duration of TLV exposure ranged from short (≤1 m) to extended (>42 m), with a median exposure of 651 days. 1267/1800 (70.4%) pts had >18m TLV exposure. 53 cases were adjudicated, and 2 judged as probably related to TLV, but no Hy's Law cases were identified. The safety profile of TLV in these studies did not differ from that in TEMPO 3:4 except for the absence of Hy's Law cases, despite more advanced ADPKD pts being included in REPRISE.

Conclusions: In the REPRISE clinical program all cases of probable liver injury were reversible, consistent with earlier experience in TEMPO. No pts met Hy's Law criteria for more serious liver injury, possibly due to more frequent monitoring and earlier interruption of therapy. (Funding: Otsuka)

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

TH-PO841

Two Years of Follow-Up Experience with Tolvaptan Treatment in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycistic kidney disease (ADPKD) is the most common inherited kidney disease, it accounts for 10% of end renal disease cases. The aproval of tolvaptan in 2014 as the first targeted therapy of ADPKD was a significant progress. Since this year there are only a few data reported of the real experience with patients ADPKD. The objective of our study was to describe the effectiveness and safety profile of patients during the two first years of treatment.

Methods: Retrospective observacional study. We ncluded ADPKD patients with chronic kidney disease stage 1-3 and treated with Tolvaptan We collect data baseline data from 15 centres from Madrid (Spain). These data inludes lab values and kidney volumen.

Results: We included 143 patients. The mean follow up period was 8,7± 5,1 months. 51 % women, aged 42,7± 10,55 years with eGFR of 63,86±22,75 mL/min/1.73m2 and urine osmolality 445,89 ± 172,25 mOsm/kg. Baseline CKD: stage 1 (19,6%), 2 (34,3%), 3a (27,3%), 3b (16,8%) and 4 (2,1%). The total kidney volumen (TKV) was 1696,47± 1399 and class of Mayo Clinic classification :1B (0,7%), 1C (23,8%), 1D (31,5%), 1E (24,5%). The medium dose achieved was 100,69 ± 6,54 mg in 4,9 ± 3,8 weeks. The rate of adverse events was 74,1%. 68,56%)were those related to increase aquaresis (thrist, polyuria, nocturia and polidipsia). A total of 14 cases (9,8 %) experienced an elevation of liver-enzyme levels, but no cases of sever liver injury was reported. 31 patients (21,6 %) discontinued treatment after a period of 10,9± 5,4 months. The main reasons to dicontinuate were: aquretic effects (86% %), elevations of liver-enzyme levels 7% and 3,5% other efects. 9 patients (29%) reinitaed the treatment after a medium period of 7,02 ± 4,11 months. Adherence to the teraphy was 84,6 %. Renal function (Efgr) at 1, 6, 12, 18, 21 and 24 months was respectively:59, 83± 21,71 ml/min, 56,58 ± 20,22 ml/min, 58,38±19,5 m/min, 60,21 ±21,85 and 62,87 ± 21,83.

Conclusions: In our experience Tolvaptan could be considered as a safety drug in patients with ADPKD. The adherence of the treatment was good, with similar data

obtained in TEMPO 3:4 trial. Due to adverse events its neccesary monitor the enzyme liver levels, but no cases of fatal liver damage was reported. The renal function remains stable after two year of treatment.

TH-PO842

Tolvaptan Slows the Decline of Renal Function in Autosomal Dominant Polycystic Kidney Disease Independent of the Response to Total Kidney Volume: Analysis of the TEMPO 3:4 Japanese Cohort

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Background: In TEMPO 3:4 (NCT00428948), TLV slowed the increase in TKV and renal function decline over a 3-year period in patients with ADPKD. We conducted a post-hoc analysis of TEMPO 3:4 in the Japanese cohort to determine if there was an association between change in TKV and renal function in patients treated with tolvaptan.

Methods: The TLV-treated group of the Japanese cohort of TEMPO 3:4 was subdivided into responders (R; net TKV decrease) and non-responders (NR; net TKV increase) at Year 3. An analysis of potential correlations between TLV treatment and the effects on TKV and eGFR were performed.

Results: 147 patients (placebo (PBO): 55; TLV : 92 [R: 37; NR: 55]) were analyzed. At Year 3, the mean changes in TKV for PBO, TLV R, and TLV NR were 16.99%, -8.33% and 13.95%; mean changes in eGFR were -12.61, -8.47 and -8.58 mL/min/1.73 m^2. Female gender was a significant predictive factor for TLV inhibition of TKV growth. Compared with PBO, eGFR decline was significantly reduced in both R and NR groups (P<0.05), however, no difference was seen between R and NR. No difference in urine osmolality at Year 1, 2, and 3 was observed between R and NR.

Conclusions: TLV slowed the decline in renal function over a 3-year period in the Japanese cohort of patients irrespective to the effect of TLV on TKV. TLV treatment should not be terminated by the short-time growth of TKV.

Funding: Commercial Support - Otsuka Pharmaceuticals and Otsuka Pharmaceutical Development and Commercialization

TH-PO843

Glucocorticoid Metabolism in ADPKD Patients and the Effect of Treatment with a Vasopressin V2 Receptor Antagonist

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Background: Vasopressin concentration is increased in Autosomal Dominant Polycystic Kidney Disease (ADPKD), and increases even further when a vasopressin V2 receptor antagonist (V2RA) is used as renoprotective treatment. We investigated the stimulatory function of these elevated vasopressin levels on the hypothalamic-pituitary-adrenal axis.

Methods: 24-hour urinary excretion of total cortisol, cortisone, THE, THF and aTHF were measured in 27 ADPKD patients using a validated high-performance LC-MS/MS assay. Results were compared to those in healthy controls (HC, n=81) and in IgA nephropathy patients (IgAN, n=27) that were matched for sex, age and kidney function. Next, in the ADPKD patients the effect of the V2RA tolvaptan (3 weeks of 90/30 mg split dose) was investigated on both urine and plasma glucocorticoid levels.

Results: In comparison to HC, ADPKD patients demonstrated lower 24 hour urinary excretion of total cortisol (p=0.001), cortisone (p<0.001) and cortisone break-down product THE (p<0.02), whereas in comparison to IgAN patients no differences were found (Table). Treatment with the V2RA increased urinary cortisone (p<0.001) and decreased aTHF excretion (p<0.001), without changing the urinary excretion of other glucocorticoid compounds or plasma levels.

Conclusions: ADPKD patients demonstrated a decreased urinary excretion of glucocorticoids compared to HC, both of biologically active and inactive compounds. This is not disease specific, but likely caused by their impaired kidney function. The V2RA increased excretion of glucocorticoids in the form of the inactive glucocorticoid cortisone, but without increasing active cortisol, neither in urine nor in plasma. Overall, renal function appears to have a stronger effect on glucocorticoid metabolism than vasopressin.

	Healthy controls	ADPKD baseline	ADPKD + VR2A	IgA Nephropathy
Number	81	27	-	27
eGFR (ml/min/1.73m2)	96 ± 14	57 ± 33*	-	54 ± 20
Cortisol (µmol/24hr)	0.34 [0.26 -0.45]	0.23* [0.19 – 0.30]	0.24* [0.17 – 0.35]	0.26* [0.20 – 0.33]
Cortisone (µmol/24hr)	0.52 [0.42 – 0.67]	0.29* [0.22 – 0.42]	0.44# [0.35 – 0.61]	0.34* [0.26 – 0.43]
THE (µmol/24hr)	12.5 [8.0 – 16.6]	9.27* [6.14 – 14.6]	9.24* [4.54 – 12.5]	10.2* [7.42 – 15.0]
THF (µmol/24hr)	6.95 [5.13 – 9.10]	5.91 [4.07 – 7.88]	5.54* [4.07 – 8.00]	5.81 [4.07 – 8.91]
aTHF (µmol/24hr)	3.87 [2.33 – 7.12]	4.16 [1.94 – 6.31]	3.54# [0.76 – 5.16]	5.29 [3.34 – 8.35]
Total glucocorticoid (µmol/24hr)	25.1 [17.1 – 34.0]	21.7 [14.2 – 28.4]	18.3* [13.8 – 24.8]	22.7 [16.9 – 31.6]

mean ± SD or median [IQR], * p<0.05 vs healthy controls, # p<0.05 vs ADPKD baseline

TH-PO844

Effect of Lixivaptan on Pharmacokinetic (PK) and Pharmacodynamic (PD) End Points in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) in the ELiSA Study (PA-102)

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Background: Blockade of the vasopressin V2 receptor has beneficial effects in non-clinical and clinical studies of patients with ADPKD. Lixivaptan is a novel, potent antagonist of the V2 receptor in Phase 3 development for treatment of ADPKD. We report the PK and PD results of the ELiSA study, the first clinical study with lixivaptan in ADPKD patients.

Methods: 32 subjects, Chronic Kidney Disease (CKD) Stages 1, 2, and 3, were enrolled at 14 sites in the US. Subjects received lixivaptan for 7 days at 1 of 2 BID dose levels to assess PK and PD endpoints after 1 and 7 days of treatment. AM and PM doses were separated by 10 hours. Full 24 hour PK profiles were obtained on Days 1 and 7 of dosing. PD endpoints were urine osmolality (Uosm), total kidney volume measured by MRI, eGFR, serum sodium, and plasma copeptin. Adverse events were assessed. Aquaretic tolerability was assessed through a specially designed questionnaire.

Results: At the high dose, lixivaptan caused profound declines in Uosm below the iso-osmolar level (300 mOsm/kg), indicating effective V2 receptor inhibition over extended time periods. Mean Uosm declined 80% to a minimum value of 84 mOsm/kg 2 hours after the first dose of lixivaptan. Importantly, 100% of subjects in CKD Stages 2 and 3 maintained Uosm below 300 mOsm/kg over 24 hours. The high dose of lixivaptan showed a strong, reversible effect on other PD variables, including serum sodium (mean increase of 1.9% from baseline) and serum copeptin (2.5 fold increase from baseline). The effect of lixivaptan on all PD endpoints tested compares favorably with historical data for tolvaptan. Conversely, the low dose of lixivaptan tested in this study acutely reduced Uosm but did not provide continued suppression below iso-osmolar levels over an extended period of time.

Conclusions: These Phase 2 data confirm that the high dose of lixivaptan tested is a fully pharmacologically effective dose of lixivaptan for ADPKD, whereas the low dose is emerging as the starting dose of lixivaptan. These results inform the appropriate titration dose range in the upcoming pivotal Phase 3 study with lixivaptan in ADPKD patients.

Funding: Commercial Support - Palladio Biosciences, Inc.

TH-PO845

Safety and Efficacy Results from the SILK (Safety in Larger Kidneys) Cohort of KD019-101: A Phase 1b/2a Trial of the Tyrosine Kinase Inhibitor Tesevatinib for Patients with ADPKD

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Background: The KD019-101 trial has evaluated safety and efficacy of tesevatinib in ADPKD patients. Tesevatinib is a tyrosine kinase inhibitor targeting the EGF receptor pathway previously implicated in the pathogenesis of ADPKD. Tesevatinib has been demonstrated to inhibit the growth of kidneys and preserve kidney function in PKD animal models.

Methods: The SILK cohort enrolled patients with eGFR ≥ 35 but ≤ 80 mL/min/1.73m^2 and htTKV ≥ 1000mL. Subjects were treated with 50 mg tesevatinib QD for up to 24 months. Subjects had MRIs to determine TKV at baseline and 6, 12, 18, and 24 months. Future eGFR prediction was performed using the Mayo Foundation and Medical Education and Research online tool.

Results: Thirteen patients (6M/7F) were enrolled. Ten of 13 subjects received at least 12 months of tesevatinib and are included in efficacy analysis. All subjects are included in safety analysis. Over 24 months the increase in htTKV was 8.7% per year. The mean slope of the best-fit line through eGFR measurements was -0.03 ml/min/1.73m^2. Modelled data using matching subject baseline criteria produced a line with a mean slope of -0.33. Similarly, while modelled data for a matched population predicts a 13.8% loss in eGFR, the mean decrease in eGFR over the treatment period was 6.6%. Commonly reported AEs were HTN, UTI, CPK increase, muscle spasm, and sinusitis. Grade 3 AEs were reported in 3 patients (CHF, HTN, and Herpes zoster) and were considered unlikely or unrelated to study drug. The CHF and Herpes zoster were considered SAEs. Four subjects discontinued treatment before 24 months, 2 due to AEs (increased amylase, fatigue), 1 to withdrawal of consent, and 1 lost to follow-up.

Conclusions: Tesevatinib 50 mg QD is well tolerated by ADPKD patients. Tesevatinib treatment results in preservation of kidney function as measured by eGFR when compared to predictive modelling data. An ongoing randomized placebo controlled trial is actively recruiting.

Funding: Commercial Support - Kadmon Corporation LLC

TH-PO846

High Salt Intake but Not High Protein Intake Leads to Increased Disease Progression in ADPKD

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Background: In chronic kidney disease salt restriction is advocated as renoprotective treatment, especially in proteinuric diseases. Whether protein restriction is beneficial remains controversial. It has been suggested that in autosomal dominant polycystic kidney disease (ADPKD), a mostly non-proteinuric disease, moderate salt restriction may also be beneficial. We investigated the association of sodium and protein intake with rate of disease progression in ADPKD, and what mediating factors could be.

Methods: We performed a post-hoc analysis of the DIPAK-1 trial, in which 305 ADPKD patients were randomized to 2.5 years treatment with lanreotide or standard care. Blood was collected every 3 months for eGFR assessment and 3 MRI-scans were performed to analyze total kidney volume (TKV). Blood pressure and plasma copeptin (a surrogate for vasopressin) were measured at baseline. Salt and protein intake were estimated from 24h urines, which were collected 6 times and calculated per kg ideal body weight. The effect of salt and protein intake on eGFR decline and TKV growth was analyzed with mixed models. We performed mediation analyses to elucidate potential mechanisms.

Results: Of the participants 53% was female, with an age of 48±7 yr, eGFR 51±11 mL/min/1.73m^2, TKV 2.4±1.6 L, salt intake 9.5±3.9 g/day and protein intake of 87±25 g/day. Salt intake was associated with annual eGFR decline during follow-up (-0.18 mL/min/1.73m^2 per gram of salt, p=0.02), whereas protein intake was not (p=0.3). Results were similar per kg ideal body weight (p=0.02 and p=0.3, respectively). The association between salt intake and annual change in TKV did not reach statistical significance (0.30% per gram of salt, p=0.07). There was also no association between total protein intake and TKV growth (p=0.1). The effect of salt intake on eGFR slope was not mediated by systolic blood pressure (3.5% mediation, p=0.3), but was significantly mediated by plasma copeptin (53% mediation, p<0.001).

Conclusions: Higher salt intake, but not higher protein intake may be detrimental in ADPKD. A five grams lower salt intake was associated with a 0.9 ml/min/1.73m2 lower rate of annual eGFR decline. The substantial mediation by plasma copeptin suggests that this effect is primarily a consequence of a sodium-induced rise in vasopressin.

TH-PO847

Self-Monitoring of Urine Specific Gravity Using Study Smartphone Applications Promotes Adherence to High Water Therapy and Facilitates Remote Data Capture in the DRINK Randomised Trial

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Background: High water (HW) intake inhibits vasopressin, a key promoter of disease progression in Autosomal Dominant Polycystic Kidney Disease (ADPKD). Maintaining HW intake requires patient motivation and commitment to self-management. We evaluated the role of a smartphone application to facilitate adherence in 'DRINK', a randomised feasibility trial of HW versus ad libitum water intake in ADPKD (NCT02933268).

Methods: We developed a cross-platform smartphone application for home monitoring and remote submission of twice weekly urine specific gravity (uSG) results by participants enrolled in 'DRINK'. Participants targeted uSG ≤1.010 (HW) or >1.010 (AW). Fluid intake instructions were embedded in the app. Submitted data were transferred in real time to a central administration portal.

Results: 81% (34/42) of trial participants (HW n=16, AW n=18) used the app. Over the 8 week follow-up period, HW patients used the app to submit uSG data 92% (165/179) of the time compared to 91% (199/219) in the AW group, p=0.38. Baseline characteristics were similar between treatment arms amongst app users (female 53% vs 56% p=0.75, White British 81% vs 83% p=0.82, mean age 47±11 vs 43±11 years p=0.38, in the HW and AW groups respectively). Plasma osmolality was 290±9 (HW) vs 289±7 (AW) mOsm/kg (p=0.68) with a corresponding median uSG 1.010 IQR 1.010-1.015 (HW) and 1.010 IQR 1.010-1.015 (AW), p=0.52. Target uSG was achieved 79% of the time in the AW group and 80% in the HW group, p=0.75 (Figure).

Conclusions: Smartphone technology resulted in high levels of adherence to the study intervention, reliable remote data collection and attainment of target USG with separation between treatment arms. Incorporation of this methodology into future trials is feasible and enhances research efficiency.

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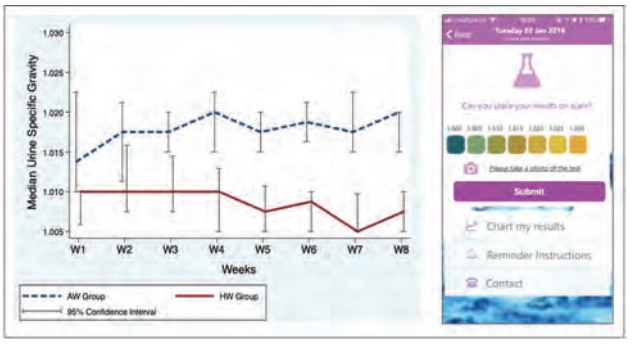

Figure: Separation in urine specific gravity (left), smartphone app (right)

TH-PO848

Sotradecol Foam Sclerotherapy for Treatment of Symptomatic Cysts in ADPKD and Autosomal Dominant Polycystic Liver Disease

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Background: Patients frequently describe mass symptoms & reduced quality of life (QoL) that correlate with visible large liver/kidney cysts in ADPKD/ ADPLD. Since 1/18/2017 we have used cyst drainage followed by sotradecol foam sclerotherapy (SFS) to treat symptomatic, large (≥5 cm in diameter) cysts. Small volumes (20cc max) of sotradecol sclerosant admixed with air are injected under fluoroscopy to ablate the epithelial cyst lining. We studied its safety & impact on QoL & organ volumes.

Methods: In this single-center, single-arm, prospective observational study, ADPKD and ADPLD patients with compressive symptoms due to dominant (liver or kidney) cysts are referred for SFS with 3% sotradecol performed under local anesthesia. QoL using linear analog scale assessment tool (LASA), SF-12, the polycystic liver disease QoL tool (PLD-Q), equivalent opioid dose (mg/24hr), & organ volumes (planimetry using CT/MR) are recorded at baseline & 6 months post-SFS. Changes over time were tested using Wilcoxon tests and confirmed using repeated measures mixed models. Improvements >0.5 SD were considered clinically meaningful.

Results: 45 patients (mean age 55yr, 84% female) are enrolled: 12 (27%) with ADPKD, 31 (69%) with ADPLD, & 2 (4%) with cystic disease NOS. 31 (69%) & 14 (31%) underwent first SFS for symptomatic liver & kidney cysts, respectively. 56 SFS procedures (mean 1.24 per patient) have been performed to treat 68 cysts (mean 1.51 per patient). Total PLD-Q, overall QoL, physical well-being, bodily pain, & vitality improved at month 6 (**Table**). Non-significant reductions in organ volumes seen at 6 months is likely due to small numbers. Longer term follow-up to 12 months is ongoing.

Conclusions: SFS directed at symptomatic large cysts was well tolerated, improved QoL at 6 months, & decreased early satiety, SOB, pain & fullness. Smaller volume instillations of SFS have replaced alcohol sclerotherapy in our practice and are a safe option for directed therapy of symptomatic large cysts in ADPKD and ADPLD.

Funding: Private Foundation Support

Endpoint	Baseline Mean (SD)	Change from Baseline to Month 6	p-value (Wilcoxon)
Liver Volume (mL) (n=9)	4587.8 (2136.3)	-866.2 (1713.9)	0.1679
Kidney Volume (mL) (n=7)	2198.9 (3937.3)	-663.6 (951.1)	0.1144
PLD-Q (n=20)	60.1 (18.3)	-15.5 (19.7)	0.0023
LASA Overall QoL (n=28)	6.3 (2.3)	1.1 (2.4)	0.0258
LASA Physical Wellbeing (n=28)	5.3 (2.1)	1.3 (2.2)	0.0053
SF-12 Vitality (n=29)	44.2 (31.7)	12.9 (31.8)	0.0369
SF-12 Bodily Pain (n=27)	53.0 (31.2)	16.7 (27.7)	0.0044
SF-12 General Health (n=29)	48.6 (26.5)	10.5 (30.6)	0.0750
Equivalent Opioid Dose (mg/24h) (n=26)	4.5 (12.1)	-1.5 (6.1)	0.2196

TH-PO849

KITGAG: A New Method for Urine and Liquid Biopsy Diagnostics: From Proteoglycan Urinary Fingerprint to Extracellular Like Vesicles (EVLs) Isolation

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Background: Glycosaminoglycans (GAG) are large polysaccharides formed by repeated sequences of disaccharides. These molecules are secreted and interact through glycosidic bonds with other molecules, such as proteins and lipids, forming the cellular matrix. GAGs are also part of the structures that cells use for endocrine or paracrine communication, like extracellular vesicles or exosomes; or interact with different secreted proteins. Glycosylation status of secreted glycoproteins/lipids can be altered in different

pathologies, as cancer or kidney diseases. Current techniques are not able to predict the evolution of kidney diseases. So there is a need of a new methodology that can be used as an indicator of early phases of the disease or prognosis of their evolution. A new method (KITGAG) has been developed for the separation of free GAGs and the fraction bound to them: based on "Dimethylmethylene blue" (DMB) dye property of specifically binding and precipitating sulfated GAGs in any type of biological sample (urine, serum, tissues...). After the obtaining of this fraction, proteins or lipids profiles can be analyzed by quantitatively or qualitatively methods (proteomics, lipidomics, image techniques...).

Methods: Urine samples have been collected from patients with polycystic kidney disease type I and type II in different stages of disease. Using KITGAG, GAG fraction has been isolated and characterized by different techniques; like Western Blot, mass spectrometry, and electron microscopy.

Results: We have identified markers in the urine from renal patients that appear to be altered in comparison to the healthy population. Likewise, several complexes formed by extracellular vesicles (ELVs), glycoproteins (uromodulin, albumin, IgA or IgG) and GAGs have also been discovered in urine samples, their function may be modulating the dialogue between different nephron segments and it can be altered in renal patients.

Conclusions: Analysis of GAGs fraction in urine samples lead to identification of new prognostic/diagnostic biomarkers of kidney diseases and other different pathologies; or for discovering and monitoring the effect of a therapy. Beside, we have discovered its potential as an isolation method for EVLs for its use in the study of new cellular communication pathways.

TH-PO850

AD(H)PKD-Copeptin as Biomarker in Patients with Autosomal-Dominant Polycystic Kidney Disease (ADPKD)

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Background: Prediction of disease progression in ADPKD is a challenging task. While there are established biomarkers such as total kidney volume (TKV), the identification of new and easily obtainable biomarkers is required to facilitate both prognostic assessment and patient selection regarding targeted therapy. Moreover, new biomarkers would ideally allow the prediction of long-term treatment responses. Post-hoc analyses of the TEMPO 3:4 study showed that copeptin could be one of those biomarkers. We investigated copeptin as a possible new biomarker in participants of the AD(H)PKD study.

Methods: Copeptin was tested in serum samples from patients of the AD(H)PKD study. These were collected and analyzed at first presentation as well as at follow-up visits. In total, we collected copeptin values from 369 patients, 54 of these during treatment with Tolvaptan. Copeptin values were analysed for both, their distribution in different patient groups (e.g. age, Mayo Class) as well as their response to Tolvaptan treatment.

Results: Copeptin values from 315 patients without tolvaptan treatment were significantly lower than copeptin values from patients receiving tolvaptan (8.65 pmol/l vs. 19.74 pmol/l; $p < 0.0001$). A consistent trend towards higher copeptin values with increasing stages of chronic kidney disease (CKD) was observed in both groups. This trend also applied for increasing TKV. Patients receiving tolvaptan showed higher copeptin values than patients without Tolvaptan treatment in all stages of CKD as well as all Mayo classes. In 8 patients longitudinal copeptin measurements prior to tolvaptan administration and on a dose of 90/30mg were available and revealed a significant increase after start of tolvaptan treatment (copeptin before tolvaptan: 5,6 pmol/l, copeptin while receiving tolvaptan 21,25 pmol/l; p=0.0007).

Conclusions: Our findings in the real-life setting are in line with the results from the post-hoc analysis of the TEMPO 3:4 study. Copeptin may serve as a new biomarker in ADPKD regarding both disease progression and response to tolvaptan treatment. Future analyses regarding disease outcome in correlation to copeptin will help to support the use of copeptin as an easily obtainable biomarker in daily clinical routine.

TH-PO851

Association Between Baseline Renal Blood Flow and CKD Progression in Autosomal Dominant Polycystic Kidney Disease

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Background: Previous Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) studies have shown height-adjusted total kidney volume (htTKV) and renal blood flow (RBF) were independent predictors of renal disease progression. Here we describe an extended study to identify and evaluate the prognostic value of baseline RBF in ADPKD.

Methods: Linear mixed models were utilized to model the effect of baseline RBF on changes in GFR over time adjusting for baseline variables (age, htTKV, gender, mean arterial pressure, hypertension status, genotype, serum HDL cholesterol, serum LDL cholesterol, filtration fraction and protein intake) and (1) either urine albumin, sodium or phosphorus excretions and (2) either BSA or BMI. Logistic regression models were applied to predict CKD using baseline RBF adjusting for baseline age and htTKV. Likelihood ratio tests were conducted to assess the significance of the variables. Area under ROC curve (AUROC) were calculated to assess the models' prognosis ability for reaching CKD outcomes (stage 3A, 3B or 4).

Results: Higher baseline RBF is significantly ($p<0.001$) associated with higher GFR in ADPKD patients over time when adjusting for the baseline variables: (1) either urine albumin, sodium or phosphorus excretions and (2) either BSA or BMI. Baseline RBF is a strong independent predictor of CKD outcomes in both an unadjusted logistic model ($p<0.001$; AUROCs, from 0.75 to 0.78), or after adjustment for baseline age ($p<0.01$; AUROCs, 0.82 to 0.85), with similar results across CKD stages 3A, 3B or 4. The combination of baseline RBF and htTKV showed strong prognosis value for CKD outcomes after adjustment for baseline age (AUROCs, from 0.90 to 0.91).

Conclusions: Baseline RBF is a strong independent prognostic marker for renal disease progression in ADPKD. Renal blood flow could be used as a prognostic and potentially monitoring biomarker in this disease.

Funding: NIDDK Support

TH-PO852

Peak Renal Blood Flow Rate Correlates with Renal Function in Adults with ADPKD

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Background: Changes in renal blood flow (RBF) occur early in the course of autosomal dominant polycystic kidney disease (ADPKD) and precede the decline in glomerular filtration rate (GFR). The specific hemodynamic factors responsible for the decline in RBF and GFR in ADPKD are poorly defined. The objective of this study was to determine the relationships between flow hemodynamic parameters and GFR in adults with ADPKD.

Methods: All participants provided informed consent and studies were performed in accordance with the Helsinki guidelines. Renal flow indices were obtained by phase-contrast MRI situated in the mid-section of renal arteries. Images were acquired as previously described by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). GFR was measured by 125I-iothalamate clearance.

Results: Forty-five participants (18 male and 27 female) with a confirmed diagnosis of ADPKD were included in the study. The participant characteristics are shown in Table 1. Both Max Q (ml/s) (peak renal RBF)($r = 0.52$, $p= 0.05$) and Min Q (ml/s) (minimum RBF)($r = 0.52$, $p = 0.04$) were significantly positively correlated with measured absolute GFR ml/min. This relationship was independent of age, sex, systolic blood pressure and body mass index. However, neither total blood flow volume (ml) or maximum flow velocity (cm/s) correlated with measured GFR.

Conclusions: In this cohort of people with ADPKD with preserved kidney function both peak and minimum RBF rates significantly correlated with measured GFR. These data suggest that early hemodynamic alterations may be useful biomarkers of kidney function in early disease.

Funding: Other U.S. Government Support

Demographic characteristics of the study population

Parameter	Mean (N = 45)	Standard deviation
Sex M/F	18/27	
Age (years)	41	9
Body Mass Index	27.0	6.3
Iothalamate GFR (ml/min)	101	28
Estimated GFR (ml/min/1.73m^2)	92	17
Systolic Blood Pressure (mmHg)	124	11

TH-PO853

Effect of Clinical, Radiological, and Genetic Factors on Progression to ESKD in Autosomal Dominant Polycystic Kidney Disease

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Background: Cystic expansion damaging the renal parenchyma is thought to lead to end-stage kidney disease (ESKD) in autosomal dominant polycystic kidney disease (ADPKD). Here we examined (1) whether factors independent of cystic growth contribute to disease progression and (2) their role in *PKD1* compared to *PKD2* associated disease.

Methods: We designed a cross-sectional study of ADPKD patients with ESKD seen at the Mayo Clinic between 1992 and 2018 with available abdominal imaging at or near ESKD (n=294). Clinical, laboratory, genetic, and radiological data at the time of ESKD were obtained from electronic medical records. Kidney volumes were measured and adjusted to height (HtTKV).

Results: Compared to females (n=154, 52%), males had similar mean age of ESKD (54.6 vs 54.9 years), larger HtTKV (2440 vs 1594 ml/m, $p<0.01$) and higher incidence of macrovascular disease (27% vs 17%, $p=0.03$). In the univariate analysis, age ($p<0.01$) and HDL cholesterol ($p=0.02$) were negatively associated whereas male sex ($p<0.01$) and ischemic heart disease ($p=0.03$) were positively associated with HtTKV at ESKD. In the multivariate analysis, only age, sex and ischemic heart disease were significantly

associated with HtTKV at ESKD. ADPKD genotype was known in 182 patients (110 *PKD1* T, 55 *PKD1* NT, 17 *PKD2*). Age at ESKD was 49.8±9.4 years in patients with *PKD1* T, 57.4±10.4 in those with *PKD1* NT, and 65.2±10.3 in those with *PKD2* mutations (p<0.01). HtTKV was 2129±1141, 1835±1331 and 2019±1162 ml/m in patients with *PKD1T*, *PKD1NT* and *PKD2*, respectively (p<0.02). A negative correlation between age and HtTKV at ESKD was observed in the *PKD1* T group (r= -0.32, p<0.01) but not in the smaller and older *PKD1* NT and *PKD2* groups.

Conclusions: ADPKD patients who reach ESKD at an older age have smaller kidney volumes. This suggests that cyst burden is the main cause of GFR decline in patients reaching ESKD at younger age, whereas additional factors associated with aging (e.g. vascular remodeling) may contribute significantly to ESKD in older patients.

TH-PO854

Serum Bicarbonate but Not Urine Ammonium Predicts Renal Outcomes in Polycystic Kidney Disease

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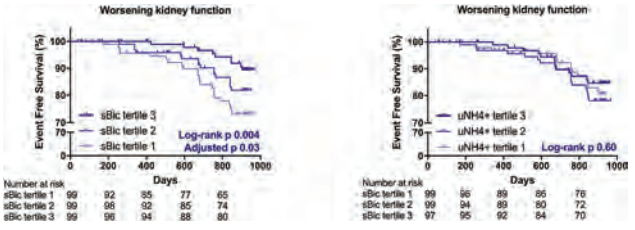
Background: Recently, urine ammonium ($uNH4^+$) was shown to better predict renal outcomes in CKD than serum bicarbonate (sBic). Urinary acidification is impaired in patients with autosomal dominant polycystic kidney disease (ADPKD). Our aim was to analyze whether sBic or uNH4+ predicts renal outcomes in ADPKD.

Methods: We studied the predictive value of baseline sBic and $uNH4^+$ for worsening kidney function (30% decrease in eGFR or ESRD) in 305 ADPKD patients from the DIPAK-1 trial (lanreotide vs. placebo). Secondary outcomes were eGFR slope and change in height-adjusted total kidney volume (hTKV). Patients were followed for 2.5 years with monitoring of eGFR and 24-hour urine every 3 months. uNH4+ was measured using a phenol-hypochlorite reaction in 24-hour urine. Logistic regression was used for analysis. The fully adjusted model included age, sex, eGFR, albuminuria, serum potassium, hTKV, PKD mutation, treatment group, hospital, BMI, cardiovascular disease, hypertension, net endogenous acid production (NEAP) and sBic or $uNH4^+$.

Results: A lower sBic at baseline was associated with worse renal outcomes (adjusted hazard ratio lowest vs. highest sBic tertile 2.68, 95% CI 1.11 to 6.46, Figure). A lower sBic at baseline was also associated with steeper eGFR slope (p=0.01), and greater increase in hTKV (p=0.05). As expected, $uNH4^+$ correlated with dietary protein intake and NEAP (r 0.45 and 0.26, P<0.0001). However, $uNH4^+$ was not associated with the primary and secondary outcomes in both the unadjusted and adjusted models (Figure).

Conclusions: sBic but not $uNH4^+$ predicts renal outcomes in ADPKD. These findings support the notion that mechanisms of disease progression in ADPKD differ from other causes of CKD.

Funding: Private Foundation Support



TH-PO855

Biomarker Identification Using Serum Proteomics in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: The variable course of autosomal dominant polycystic kidney disease (ADPKD) makes it important to identify biomarkers that predict disease progression to allow optimal counseling and selection of patients for targeted therapies. Currently, MRI-based volumetric analysis is used as a standard diagnostic tool. In order to identify easily measurable biomarkers of ADPKD progression, we used mass spectrometric quantification of the serum proteome.

Methods: Hence, serum proteome analysis was performed by MALDI-TOF MS using label-free quantification. We compared ADPKD patients (n = 292) with healthy control subjects (n = 58) and IgA nephritis patients (n = 30) as an independent CKD control. Randomization of the samples was achieved using random sampling. For data evaluation normalized $\log_2$ transformed intensities were used and proteins were examined for their distribution in different patient groups (e.g. age, CKD stage, Mayo class). Clinical data of all patients were available from the AD(H)PKD registry.

Results: Mass spectrometric analysis of the serum proteome in ADPKD patients revealed differential expression of 19 proteins compared to healthy control subjects (q<0.05), 8 of these proteins also differed from IgA nephritis patients suggesting specificity for ADPKD. The identified proteins could be assigned to the regulatory pathways of IGF activity and hemostasis.

Conclusions: These results provide valuable insights into the alterations of the serum proteome in ADPKD and indicate that selected serum proteome markers may contribute to the improvement of ADPKD management and disease severity assessment in the future. The newly identified markers will now be investigated for their predictive potential and their role in the pathogenesis of ADPKD.

TH-PO856

Urinary Adenosine and Adenosine/Xanthine Ratio Associate with the Rate of eGFR Decline in a Cohort of Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: The variable course of autosomal dominant polycystic kidney disease (ADPKD), and the advent of renoprotective treatment make it important to discover novel biomarkers for predicting renal disease progression. Based on in vivo data, we hypothesised that urinary ATP excretion is increased in ADPKD, which might contribute to disease progression. We applied urinary metabolomics to explore differences in purine metabolism compounds, as an indirect readout of ATP, and the association with estimated glomerular filtration rate (eGFR; CKD-EPI equation), and progressive loss of eGFR.

Methods: Targeted metabolic profiling using Liquid Chromatography-Mass Spectrometry was performed on single, spot urine samples of 187 ADPKD patients (mean age 48±10 years, 53% female, mean eGFR 53±20 ml/min/1.73m^2), and 139 other chronic, renal disease patients (mean age 56±17 years, 48% female, mean eGFR 54±33 ml/min/1.73m^2). Multiple regression analysis was used to describe the association between a pre-selected set of the metabolites and actual eGFR, and annual change in eGFR.

Results: Abundancies of adenosine, inosine, hypoxanthine, xanthine, and uric acid were determined and normalized. For all metabolites, no differences were found between ADPKD and non-ADPKD patients. Adenosine was most strongly associated with eGFR in the total cohort (F=92.35, P<2.2e-16, r^2=0.222) as well as in patients with ADPKD. In ADPKD, we additionally evaluated the association with rate of eGFR progression over time. For 131 patients (mean age 49±7 years, 50% female, mean eGFR 49±11 ml/min/1.73m^2, mean eGFR decline -3.4±-2.7 ml/min/1.73m^2 per year), sequential eGFR data were available. Linear regression analysis showed that the combination of adenosine and the adenosine/xanthine ratio had the strongest association with annual change in eGFR (F=6.70, P=0.002, r^2=0.095). Moreover, this model had additional value beyond that of baseline eGFR, age and/or total kidney volume.

Conclusions: In this pilot study, urinary adenosine and adenosine/xanthine ratio were associated with the rate of eGFR decline in patients with ADPKD. Validation of these findings is needed in a larger cohort with a varied distribution in rate of renal function decline.

Funding: Other NIH Support - Duth Kidney Foundation and Health-Holland (DIPAK Consortium)

TH-PO857

Systemic Endothelial Function Is Associated with Renal Disease Severity in Early Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: *In vitro* studies have shown impaired endothelium-dependent relaxation of small resistance vessels in patients with ADPKD. Peripheral-arterial tonometry (PAT) provides, with high reproducibility and no operator dependency, non-invasive measures of nitric oxide-mediated endothelial response. However, no study has evaluated endothelial function by PAT in patients with ADPKD. This pilot study tested the hypothesis that systemic endothelial dysfunction, as determined by PAT, would be detectable prior to development of hypertension and would correlate with renal disease severity determined by height adjusted total kidney volume (htTKV) in patients with ADPKD.

Methods: Twelve young (18-40 years), early stage (eGFR>90 mL/min/1.73 m^2), normotensive (without blood pressure medication) patients with ADPKD and age/sex matched controls (2:1), underwent medical questionnaire, blood and urine collection, abdominal MRI for TKV and renal blood flow (RBF), and PAT for reactive hyperemia index (RHI, normal value ≥2) determination.

Results: Main clinical and laboratory characteristics are shown in table 1. ADPKD patients presented with abnormal RHI levels, which correlated inversely with htTKV (R^2=0.394, p=0.039), and directly with RBF (R^2=0.485, p=0.017). There was no correlation between RHI, htTKV, or RBF and eGFR or other parameters listed in table 1.

Conclusions: Systemic endothelial dysfunction as determined by PAT may be an early marker of vascular changes in patients with ADPKD, and is associated with renal disease severity. These observations may suggest systemic endothelial function as a diagnostic and therapeutic target in patients with ADPKD.

Funding: NIDDK Support, Other NIH Support - Kansas PKD Center P30 DK106912, MTPC P30 DK090728

Table 1. Clinical and laboratory characteristics of study participants

	ADPKD patients	Healthy volunteers	P-value
Gender (F/M)	11/1	5/1	N/A
Age (years)	28 ± 8	28 ± 6	0.759
BSA (m^2)	1.8 ± 0.2	1.8 ± 0.2	0.700
Smokers	None	None	N/A
GFR (ml/min/BSA)	107 ± 14	120 ± 4	0.081
SBP (24hrs) (mmHg)	117 ± 6	107 ± 6	0.155
DBP (24hrs) (mmHg)	79 ± 6	70 ± 7	0.131
HtTKV (ml/m)	319 (228-691)	175 ± 17	0.002
Class B (N)	6	---	
Class C (N)	6	---	
Class D (N)	0	---	
RBF (cc/min/BSA)	892 ± 134	941 ± 163	0.498
PAT index	1.88 ± 0.5	2.14 ± 0.6	0.548
Serum Creatinine (mg/dL)	0.9 ± 0.1	0.8 ± 0.1	0.680
Uric Acid (mg/dL)	4.4 ± 1.0	4.3 ± 1.1	0.929
Cholesterol Total (mg/dL)	169 ± 27	177 ± 13.5	0.457
HDL Cholesterol (mg/dL)	60 ± 9	69 ± 11	0.112
LDL (mg/dL)	94 ± 23	98 ± 13	0.662
Triglycerides (mg/dL)	77 ± 28	55 ± 24	0.180
hs-C-Reactive Protein (mg/L)	1.5 ± 0.5	0.6 ± 0.3	0.246
Lipoprotein, S (mg/dL)	7.7 ± 3.3	6.9 ± 3.6	0.847

TH-PO858

Risk of Hospital Encounters for Kidney Stones in Autosomal Dominant Polycystic Kidney Disease: A Cohort Study

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Background: Patients with autosomal dominant polycystic kidney disease (ADPKD) are may be more likely to develop kidney stones than the general population. However, empirical evidence to this effect is lacking in the current literature. We studied the incidence of (i) a *de novo* hospital encounter with kidney stones, and (ii) stone interventions among patients with ADPKD compared to patients without ADPKD who were similar in their baseline health indicators.

Methods: Using large healthcare databases from Ontario, Canada, patients with and without ADPKD were identified using hospital encounters between April 1st, 2002 and March 31st, 2016. We used inverse probability of treatment weighting (IPTW) based on propensity score to ensure characteristics of baseline health indicators between the two groups were similar. We followed patients from cohort entry until the first recorded hospital encounter with a *de novo* stone, death, emigration from Ontario, or March 31st, 2017. We used a weighted Cox proportional hazards model to compare stone rates between the two groups. Death was treated as a censoring event in the primary analysis, and as a competing event in secondary analyses. We also performed analyses for time to first recorded stone intervention and abdominal imaging across all settings. Patients were followed for a mean (maximum) of 7.5 (15.6) years.

Results: ADPKD compared to no ADPKD was not associated with a higher risk of a hospital encounter with stones (92 patients of 2094 with ADPKD [4.3%] vs 80 patients of 2096 without ADPKD [3.8%]; 7.4 vs 6.2 events per 1000 person-years; hazard ratio 1.2 [95% CI, 0.9 to 1.6]. Similarly, ADPKD compared to no ADPKD was not associated with a higher risk of stone intervention (52 of 2094 [2.5%] vs 62 of 2096 [3.0%]; 4.1 vs 4.7 events per 1000 person-years; hazard ratio 0.9 [95% CI 0.6 to 1.2]). The results were similar when treating death as a competing event. ADPKD compared to no ADPKD was associated with a significantly higher rate of abdominal imaging (hazard ratio 1.2 [95% CI 1.1 to 1.3]).

Conclusions: ADPKD was not a significant risk factor for a hospital encounter with kidney stones. The perception that patients with ADPKD are more likely to develop stones may be due to increased surveillance.

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TH-PO859

Outcome of Kidney Transplantation in Patients with Polycystic Kidney Disease: A Single-Center Study

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Background: Renal transplant (RTx) is the best choice of life-quality of renal replacement therapy for patients with end-stage renal disease (ESRD). Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder and common cause of ESRD. Different from other causes of ESRD, ADPKD patients need more delicate pre-RTx evaluation for intracranial aneurisms, cardiac manifestation, and complications of liver and renal cysts. The outcome of RTx with ADPKD is still unknown in Taiwan.

Methods: We retrieved our 1327 RTx recipients with 1382 times (two recipients with 3 times, 48 recipients with 2 times) of RTx in the past 35 years. There were 41 recipients with ADPKD. This study evaluated the demographics, outcomes, and complications of RTx in patients with ADPKD compared with other nephropathies.

Results: The mean recipient age at first RTx was 42.9 ± 12.6 years, however, the ADPKD group (52.5 ± 10.1 yrs) was elder than other group (42.7 ± 12.7 yrs, P = 0.001). The gender of RTx recipients was female 586 (44.2%) and male 741 (55.8%), though, ADPKD group had higher male gender (28, 68.3%) than other group (713, 55.4%) without statistically significance (P = 0.245). Interestingly, the new onset diabetes after transplant (NODAT) was higher in ADPKD group (21, 51.2%) than other group (326, 25.3%; P = 0.005), and more malignancy (18; 43.9% vs. 360; 28.0%; P = 0.041). The patient survival was inferior in ADPKD group (38.9% vs. 70.3%; P = 0.018).

Conclusions: Further studies with multiple centers and greater numbers of patients are needed to compare more precisely the complications and results of transplant between patients with ADPKD and other recipients in Taiwan.

TH-PO860

Post-Kidney Transplant Intracranial Aneurysm and Hemorrhagic Stroke in Polycystic Kidney Disease

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Background: Polycystic Kidney Disease (PKD) is associated with 6-9 times higher prevalence of intracranial aneurysm (ICA) and consequently, of hemorrhagic stroke than the general population. An appropriate screening strategy for ICAs in PKD post-kidney transplantation is not known.

Methods: The Wisconsin Allograft Recipient Database was queried to identify adult patients who received a primary kidney transplant at University of Wisconsin between 1/1/2000-12/31/2015. Cause of ESRD among kidney transplant recipients (KTRs) was categorized as PKD or non-PKD. History of ICA and hemorrhagic stroke at the time of transplant and incidence post-transplant were compared between PKD vs non-PKD using logistic regression and survival analysis.

Results: PKD recipients (N=520) were, in comparison to non-PKD (N=3494), older (52.8 vs 49.4 years), more often female (45% vs 38.8%) and white (93.5% vs 80.2%; p<0.01 for all). Pre-transplant dialysis was less common in PKD KTRs (56% vs 77%; p< 0.01). No significant difference was observed in pre-transplant hypertension (97.5% in PKD vs 96.2% in non-PKD KTRs; p=0.15). A history of ICA and prior hemorrhagic stroke was significantly higher in PKD recipients compared to non-PKD KTRs (2.7% and 1.92% vs 0.3% and 0.63%;p<0.01) even after adjusting for demographics and pre-transplant hypertension. Over a median post-transplant follow up 5.6 years (2.4-9.1) in PKD and 5 years (2.1-8.1) in non-PKD recipients, the incidence of ICA was higher in PKD (1.6 vs 0.3 per 1000 person years in non-PKD; p=0.02). The incidence of hemorrhagic stroke was similar between PKD and non-PKD recipients (0.3 vs 0.8 per 1000 person years; p=0.36). No strokes occurred at time of transplant.

Conclusions: Our findings show that incidence of hemorrhagic stroke in PKD KTRs was low. Regular interval screening for new ICA may not be necessary in PKD patients following kidney transplantation. The factors contributing to change in frequency of hemorrhagic stroke in PKD and non-PKD group in the post-transplant setting need further investigation.

Table 1

	PKD (N=520)	Non-PKD (N=3494)	Odds/Hazard Ratio	P-value
Pre-transplant ICA [N (%)]	14.7 (2.7)	12 (0.3)	8.6 (3.8,19.4)	p<0.01
Pre-transplant Hemorrhagic Stroke [N (%)]	10 (1.92)	22 (0.63)	2.9 (1.4, 6.3)	p>0.01
Post-transplant ICA [N (%)]	5 (0.99)	6 (0.17)	4.6 (1.3,15.9)	p=0.02
Post-transplant hemorrhagic Stroke [N (%)]	1 (0.2)	16 (0.46)	0.39 (0.05,2.94)	p=0.36

TH-PO861

Engaging Patients and Defining Outcomes: A Minority Engagement Effort

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Background: Polycystic kidney disease (PKD) is an irreversible inherited disease that causes permanent worsening of kidney function. Despite being rare, PKD is the most common genetic cause of chronic kidney disease. The Establishing Meaningful Patient-centered Outcomes With Relevance for patients with Polycystic Kidney Disease (EMPOWER PKD) initiative aims to engage PKD stakeholders and patients to learn about health priorities, insurance issues, and patient engagement.

Methods: We utilized semi-structured focus groups. We developed and pre-piloted a guide that allowed for both conversational flow and consistency in questions among groups. We audio-recorded each group and transcribed the conversations verbatim. We performed an inductive thematic analysis. Two investigators completed all data coding independently and in duplicate. We compare the results of an ethnically diverse focus group to the other 7 that mainly included Caucasian participants.

Results: 14 individuals participated in this part of the study. Of these, (64.2%) reported having PKD, and (14.2%) being caregivers. The mean age of participants was 48.8 (range 29-75) years. The group included 85.75% African American and 7.1% reported more than one race. It was challenging to recruit this group and it required establishing relation with community nephrologists and faith-based organizations leads. Multiple participants stated that they would not have participated in the group was not exclusively ethnically diverse as they fear that their opinion may be outnumbered by a Caucasian majority. Some discussed believing that PKD was a "white" disease. Many discussed hiding their diagnosis which affected their activation and engagement and came with unanticipated psychological impacts. Several other themes emerged including fear of others finding out, isolation,

lack of support, helplessness, the need to lie about their condition, and victimization. Participants unanimously described lack of trust-worthy easy to understand educational resources for minorities as a main barrier to engagement.

Conclusions: With a treatment now approved for use in the US, it is important to be aware of patients' values and barriers to engagement which have pivotal effects on care. Additionally, it is essential to utilize resources to help activate patients of all racial and ethnic groups to be prepared for future treatments.

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TH-PO862

Frequency of Polycystic Kidney Disease in Patients with Intracranial Aneurysm

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Background: Polycystic kidney disease (PKD) is characterized by the multiple cystic formation in the bilateral kidneys. It is also famous for the highly accompanying extra-renal manifestations such as intracranial aneurysm, valvular heart disease, liver cysts, pancreatic cysts, or intestinal diverticulum. The underlying and unifying mechanism of PKD is the abnormality of cilia. The frequency of intracranial aneurysm in patients with PKD is reported to be approximately 4 to 12%. However, the rate of PKD in patients with intracranial aneurysm is not known. Here, we aimed to investigate the frequency of PKD in patients with intracranial aneurysm.

Methods: Seventy-two patients with intracranial aneurysm who visited department of neurosurgery in our hospital, also visited department of nephrology between Nov 2017 and May 2019 for PKD screening. The screening modality was basically kidney ultrasound. If abdominal CT or MRI was already performed, we utilized them to diagnose whether or not the patients have PKD. In cases where PKD is highly suspected by questionnaire to the patients, we performed abdominal MRI or CT. We also investigated the family history of kidney disease, dialysis, intracranial hemorrhage, intracranial aneurysm, sudden death, or liver cysts. Thus we retrospectively investigated the PKD rate in cases with intracranial aneurysm. The ethics committee in our hospital approved this retrospective study.

Results: The patients' characteristics were as follows; age median 69 IQR (53-76) y.o., sex F/M 60/12, eGFR 69 (61-81) mL/min/1.73m^2. Out of the 72 cases, 43 patients had single intracranial aneurysm and 29 patients had plural intracranial aneurysm. Out of 72 patients, typical PKD was detected in one patient, and atypical PKD in another patient. Family history taking showed that 9 patients had relatives with kidney diseases, 4 had those with dialysis, 7 had those with intracranial aneurysm, 14 had those with intracranial hemorrhage, 14 had those with sudden deaths, and 2 had those with liver cysts.

Conclusions: PKD screening indicated that approximately 1-3% of patents with intracranial aneurysm had PKD.

TH-PO863

Clinical Characteristics of Patients with Early-Onset ESKD in Autosomal Dominant Polycystic Kidney Disease: A Case Series

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) has high phenotypic variability. Mutations in *PKD2* versus *PKD1* lead to milder disease, with average ages at End-Stage Kidney Disease (ESKD) of 79.7 and 58.1yrs, respectively. Some patients reach ESKD in early adulthood, but factors leading to such poor prognosis are unclear.

Methods: This is a cross-sectional study of patients with ADPKD presenting between 1992 and 2018 to Mayo Clinic who reached ESKD by age ≤ 35 and had detailed clinical information pre-ESKD. Among 4307 patients with ADPKD, 1079 reached ESKD with 18 by age 35. Clinical, genetic and radiological data prior to ESKD onset were collected. Kidney volumes were measured and adjusted by height (HtTKV).

Results: Ten patients (55%) were male and 16 (89%) were Caucasian. The average age at ESKD was 30.3 (± 4.3) yrs. Average body mass index was 27.3(±5.6) Kg/m^2. Among the 13 patients with genetic screening, 8 (61%) had *PKD1* truncating and 5 (38%) had *PKD1* non-truncating mutations, and one had a possible in *trans PKD1* modifying allele. Seventeen patients were hypertensive (94%) with average age of onset of 23 (±6.5) yrs. Among 16 patients with abdominal imaging, 13 (81%) were classified as Mayo Class 1E and 3 (19%) as 1D. Mean HtTKV was 2148 (±1169) ml/m. Mean PROPKD score was 7.4 (± 1.5). The majority of patients had cyst hemorrhage (89%) and more than half had ≥ 2 episodes (55%). The average age of the cyst hemorrhage occurrence was 22 ± 8.5 yrs. Four (22%) patients had cyst infections, and 13 (72%) had at least a history of one episode of acute kidney injury. Seven patients (38%) had bilateral nephrectomies at time of ESKD due to recurrent cyst hemorrhage, three of whom were done concomitantly with their kidney transplantation.

Conclusions: We describe a series of patients with ADPKD who reached ESKD before age 35. All patients had *PKD1* mutations and large kidney volumes (Mayo Class 1E and 1D). The majority of the patients had one or more episode of cyst hemorrhage. Prospective studies would be helpful in ascertaining the role of cyst hemorrhage in accelerating the decline of kidney function in patients with ADPKD.

TH-PO864

Multiple Urinary Tract Infections Are Associated with Genotype and Phenotype in Adult Polycystic Kidney Disease

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Background: The association between UTI among genotypic and phonotypic properties of ADPKD patients is still obscure. Thus, we investigated the relationship between UTI and polycstin gene mutation with total kidney volume.

Methods: Ambulatory blood pressure monitoring was performed in all participants. Magnetic resonance imaging (MRI) was performed with a 1.5-T system, and total kidney volumes were calculated using mid-slice technique. To determine PKD1 and PKD2 genotype, we performed molecular and genetic tests involving the following steps: DNA isolation, next-generation sequencing (NGS) and data analysis.

Results: ADPKD patients with UTI had lower eGFR values than those without UTI [64.9(32.2-100.8) vs 89.5(59.0-110.0), (p:0.041)]. In addition, patients with UTI had significantly increased height adjusted total kidney volume than patients without UTI [950(290-1350) vs 345(243-780.0), (p:0.005)] (Figure-1). Multiple logistic regression analysis showed that the PKD1 truncating mutation and hTKV independently predicted UTI. The sensitivity and specificity of hTKV were 65% and 77% (cut-off >727cm^3) with an area of under the ROC curve of 0.70 (95% CI: 0.56-0.85, p:005) (Figure-2).

Conclusions: ADPKD patients with larger kidneys and PKD1 mutation are susceptible to increased risk of multiple UTI. Additionally, renal function decreased in ADPKD patients with multiple UTI history.

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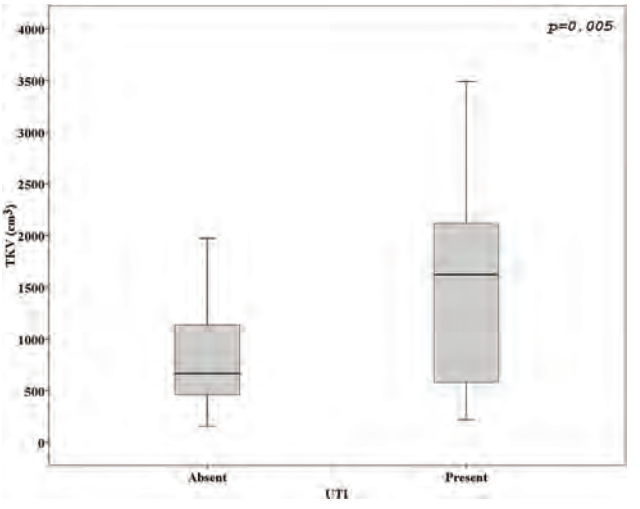

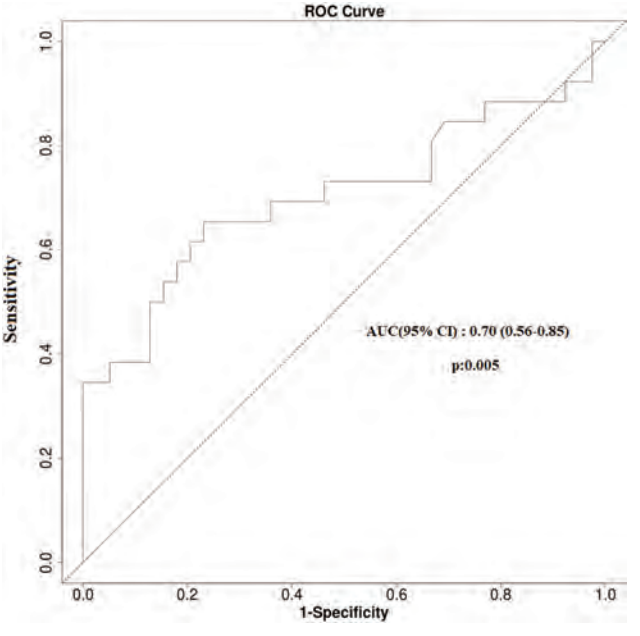

TH-PO865

RAPID-ADPKD, the Retrospective Epidemiologic Study of Asian-Pacific Patients with Rapid Disease Progression of Autosomal Dominant Polycystic Kidney Disease: Design and Methods

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Background: For effective treatment and early intervention in Autosomal dominant polycystic kidney disease (ADPKD) patients, identifying subgroups with rapid renal progression are important in ADPKD. This study was designed to identify the clinical characteristics of rapidly progressing ADPKD patients in Asia-Pacific area.

Methods: The RAPID-ADPKD is a multinational retrospective observational cohort study of ADPKD patients in the Asia-pacific area.

Results: Six hospitals from six regions (Australia, China, Hong Kong, South Korea, Taipei and Turkey) are participating in this study. Adult ADPKD patients, diagnosed by the unified criteria and with eGFR ≥45 mL/min/1.73m^2 at baseline will be included. Patients with other comorbidities that can affect renal function will be excluded. Demographic information, clinical characteristics, premorbid comorbidities, medications, eGFR, radiologic findings that can calculate height adjusted total kidney volume (htTKV), PKD-related complications and the PRO-PKD score will be collected. Rapid progression will defined as when any of following criteria are met: (i)an annual eGFR decline ≥5 mL/min/1.73m^2 in 1-year and/or ≥2.5mL/min/1.73m^2 per year over a period of 5-years; (ii)an increase in htTKV ≥ 5% per year from ≥3 radiologic images; (iii)Mayo classification 1C, 1D, or 1E or kidney length from ultrasonography of >16.5 cm (iv)*PKD1* truncated mutation with early symptoms (PRO-PKD score >6). All other patients without any of the criteria are classified as slow progression. The clinical characteristics of rapid progression group will be compared to slow progression group. In addition, the incidence rate, age of diagnosis, treatment complications between rapid and slow progression will be analyzed. The planned sample size of the cohort is 1,000 patients, and as Feb 28th 2018, data from 400 patients have been collected.

Conclusions: RAPID-ADPKD is the first large-scale multinational retrospective observational study of ADPKD in Asia-Pacific region and will identify the clinical characteristics, risk factors for disease progression and patterns of complications in Asian populations with ADPKD.

Funding: Commercial Support - Korea OIAA

TH-PO866

Neurological Complications After Very Early Bilateral Nephrectomies in Patients with Autosomal Recessive Polycystic Kidney Disease (ARPKD)

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Background: Autosomal recessive polycystic kidney disease (ARPKD) is a pediatric disorder with pronounced phenotypic variability. Severely affected patients may undergo bilateral nephrectomies in the first months of life. The neurological outcome of these patients has not been studied in defined cohorts.

Methods: Within the international registry study ARegPKD 18 patients with very early (≤3 months of age at second nephrectomy, VEBNE) and 9 with early (3-15 months, EBNE) bilateral nephrectomies as well as 13 patients with very early dialysis onset (≤3 months, VED) not receiving bilateral nephrectomies were identified. Eleven patients with total kidney volumes (TKV) comparable to the TKV of VEBNE patients but without bilateral nephrectomies served as an additional control group. Descriptive statistics, multivariate and Kaplan-Meier analyses evaluated the neurological outcome and potential risk factors of the cohorts.

Results: Mean (SD) follow-up time ranged from 1.6(2.6) years for VED patients to 7.8(5.9) years for EBNE patients. VEBNE patients suffered more frequently from seizures (67%) and severe neurological complications (61%) in comparison to EBNE patients (seizures 11%, severe neurological complications 11%), VED patients (seizures 31%, severe neurological complications 15%) and patients of the TKV control group (seizures 27%, severe neurological complications 0%). In total, 5/51 (10%) patients suffered from severe hypotensive episodes. Multivariate Cox regression analysis revealed the report of a severe hypotensive episode as well as very early bilateral nephrectomies to be independent risk factors for severe neurological complications. Mortality, including mortality after palliative care, was highest among patients with very early onset of dialysis without bilateral nephrectomies.

Conclusions: Bilateral nephrectomies within the first three months of life may be associated with severe neurological sequelae. The indication for very early bilateral nephrectomies must be carefully considered.

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TH-PO867

Genetic and Functional Investigation of Nephron Number on Diabetic Kidney Disease

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Background: Low nephron number has been linked with susceptibility to hypertension and CKD, but a clear connection between nephron number and hyperglycemic renal injury is lacking. Our current work seeks to investigate the association between nephron deficiency and the development of diabetic CKD using a unique model of nephron deficiency, the HSRA rat. HSRA are born with a single kidney 50-75% of the time while the remaining pups are born with two. The model provides a unique advantage for direct comparison of congenital one-kidney, nephron-deficient animals (HSRA-S, ~20,400 nephrons), nephrectomized two-kidney animals (HSRA-UNX, ~25,100 nephrons) and two-kidney littermates (HSRA-C, ~50,000 nephrons). Previous work demonstrated that HSRA-S develops increased renal dysfunction with age compared to HSRA-UNX and HSRA-C, which is greatly exacerbated in the presence of DOCA hypertension. This suggests that even slight nephron differences (-S vs –UNX) are important driver of elevated blood pressure, kidney injury and accelerate decline in kidney function.

Methods: To investigate the impact of hyperglycemia on renal injury in the HSRA rat, streptozotocin (STZ) was administered at 9 weeks of age in all three groups; animals were followed for 15 weeks.

Results: Despite overt hyperglycemia (350-450 mg/dl), the diabetic groups did not develop increased proteinuria compared to their non-diabetic counterparts, contrary to the impact of second insult of hypertension.

Conclusions: Current studies are investigating the impact of hyperglycemia after overt injury ("late insult") in HSRA-S (week >24) is observed. Additionally, studies to revisit the "early insult" of hyperglycemia with the addition of modest hypertension (130 mmHg) via DOCA have begun. To better understand the underlying genetic cause of renal agenesis, altered nephrogenesis in the solitary kidney, and perhaps the differential response of injury to hypertension and hyperglycemia, genetic linkage analysis has been initiated in the HSRA model to map the quantitative trait loci/modifier genes. This work, along with completed whole genome sequencing and annotation of HSRA genome will hopefully identify new genes/pathways relevant to nephrogenesis and provide insight into differences in the interaction between nephron number and secondary insults of hypertension and hyperglycemia.

Funding: Other NIH Support - NIGMS

TH-PO868

Genetic Susceptibility of Diabetic Kidney Disease in Mice Is Linked to a Promoter Variant of XOR

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Background: Diabetic kidney disease (DKD) is the leading single cause of ESRD in the United States. Approximately 10-30% of diabetic patients develop DKD with comparable blood glucose levels, indicating a significant genetic contribution for disease susceptibility. Differential susceptibilities are also observed in well-defined inbred mice strains. The glomerulus is the primary site of injury with hypertrophy and podocyte depletion being the hallmarks for progressive DKD. We have demonstrated that ROS and mitochondrial oxidative damage accumulation in glomerular endothelial cells (GECs), leads to podocyte loss via endothelial-to-podocyte crosstalk in experimental DKD. However, the underlying mechanisms that contribute to differential susceptibility to DKD are poorly understood.

Methods: Inbred DBA/2J (D2) mice are susceptible, while C57BL/6J (B6) mice resistant to diabetes-induced podocyte depletion. We used the 39 strains of BXD (B6XD2) recombinant inbred and parental strains to map genetic loci associated with podocyte numbers after long-term diabetes (6mth). We identified a *cis*-acting regulatory (promoter) of the *Xdh* gene encoding xanthine dehydrogenase XDH/XO (xanthine oxidoreductase (*XOR*)). XORs catalyze the oxidation of purine substrates, xanthine and hypoxanthine, producing uric acid, and are a major enzymatic source of ROS.

Results: XOR expression in the kidney and XOR circulating activity were significantly increased in diabetic D2 but not B6 mice. XOR inhibition in diabetic D2 mice significantly reduced albuminuria, oxidative damage in glomeruli and prevented podocyte loss. The two nucleotide variant was shown to influence XOR activity *in vitro*. To determine whether the variant in *XOR* promoter underlie the differential responses to diabetes, we used CRISPR/Cas9 to knock-in the *XOR* variant of D2 into B6 mice. Indeed, the mutant B6-*Xor* mice had significantly higher XOR activity. These mice developed endothelial injury, with increased ROS and mitochondrial oxidative stress in GECs, podocyte foot process effacement and depletion, basement membrane thickening, albuminuria, glomerular sclerotic lesions and tubular injury, furthermore DKD in B6-*Xor* mice was prevented with XOR specific inhibition.

Conclusions: These data suggest that the identified promoter variant regulates XOR activity, and may be causal for DKD susceptibility.

Funding: NIDDK Support

TH-PO869

Genes Involved in Diabetic Nephropathy in a Greek Population of Diabetic Type 2 Patients

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Background: The incidence and prevalence of diabetic nephropathy (DN), the major cause of end stage renal disease in diabetic type 2 patients (DM2), are continuously rising. Important role in the pathogenesis of DN play metabolic factors, the oxidative stress (OS) pathway and the patient's genetic substrate. Nevertheless, genome-wide association studies regarding the genetic causes of DN are few and inconclusive. The aim of our study was to find a possible genetic association between the single-nucleotide polymorphisms on the athway of OS studied and DN development.

Methods: Data from a genome-wide association study were utilized to perform a study between 102 DM2-DN (cases) and 230 DM2-non-DN (controls) diabetic type 2 patients of greek origin.

Results: The polymorphisms that exhibited a significant correlation with DN development were 44 and the corresponding genes were 20. Some polymorphisms are probably potentially protective and others could be implicated in DN development. The genes with an odds ratio below 1, possibly exhibiting a protective role, were: SPP1 (p=0.001), CCS (p=0.019), ALOX12 (p=0.04), OXR1 (p=0.042), PRNP (p=0.049). The genes with an OR>1, possibly contributing to DN development, were: TPO (p=0.002), TTN (p=0.002), AOX1 (p=0.005), NOS3 (p=0.005), PDLIM1 (p=0.005), EPHX2 (p=0.013), GPX4 (p=0.019), TXNRD2 (p=0.019), MTL5 (p=0.033), EPX (p=0.035), GPX3 (p=0.036), IPCEF1 (p=0.041), GSTA7P (p=0.041), GPX6&5 (p=0.044), VKORC1 (p=0.047).

Conclusions: In our study 44 polymorphisms with their 20 genes on the oxidative stress pathway were found to be potentially associated with DN in greek DM2 patients.

CHROMOSOME	SNP-GENE	MINOR ALLELE	% PATIENT GROUP	%CONTROL GROUP	MAJOR ALLELE	χ^2	p-VALUE	ODDS RATIO (CONFIDENCE INTERVAL)	STANDARD ERROR (SE)
4	rs7685225-SPP1	C	25,21	37,27	T	10,28	0,001	0,567 (0,4-0,81)	0,1779
2	rs6588678-TPO	A	51,24	38,86	G	9,743	0,002	1,653 (1,2-2,27)	0,1616
2	rs56307213-TTN	G	4,959	1,136	C	9,385	0,002	4,539 (1,58-13,04)	0,5385
2	rs72648987-TTN	A	4,959	1,142	G	9,318	0,002	4,518 (1,573-12,98)	0,5385
2	rs9678469-TPO	G	17,36	9,545	A	8,818	0,002	1,99 (1,256-3,153)	0,2348
2	rs72650006-TTN	A	6,25	2,074	T	7,849	0,005	3,148 (1,356-7,307)	0,4296
2	rs17532665-SGO2	G	18,6	10,91	A	7,832	0,005	1,865 (1,2-2,9)	0,2251
7	rs7830-NOS3	A	40,91	30,23	C	7,937	0,005	1,598 (1,152-2,217)	0,1669
10	rs4458497-PDLIM1	C	4,545	1,142	T	7,861	0,005	4,124 (1,416-12,01)	0,5455
2	rs17448235-SGO2	G	18,6	11,47	A	6,561	0,01	1,763 (1,138-2,732)	0,2234
8	rs11780592-CLU	G	25	17,05	A	6,176	0,013	1,622 (1,105-2,381)	0,1957
2	rs1567919-TPO	T	0	2,273	G	5,582	0,018	0	infinity
2	rs13431646-TPO	T	0	2,273	C	5,582	0,018	0	infinity
2	rs72677233-TTN	T	1,24	0	C	5,479	0,019	not computable	not computable
2	rs72646855-TTN	C	1,24	0	T	5,454	0,019	not computable	not computable
11	rs486584-CCS	G	43,39	52,73	A	5,447	0,019	0,6871 (0,5011-0,9422)	0,1611
19	rs201633492-GPX4	A	1,24	0	G	5,479	0,019	not computable	not computable
22	rs201971987-TXNRD2	G	1,24	0	A	5,479	0,019	not computable	not computable
22	rs737866-TXNRD2	G	38,02	29,32	A	5,393	0,02	1,479 (1,062-2,059)	0,1688
4	rs2725236-SPP1	T	38,02	46,82	C	4,916	0,026	0,6967 (0,5059-0,9595)	0,1633
2	rs6732480-TPO	T	51,24	42,5	C	4,807	0,028	1,422 (1,038-1,948)	0,1607
8	rs2741335-EPHX2	G	38,84	30,68	T	4,663	0,031	1,435 (1,033-1,993)	0,1676
11	rs3019593-MTL5	G	11,57	6,818	A	4,531	0,033	1,788 (1,041-3,071)	0,276
2	rs2048727-TPO	A	42,5	34,32	G	4,45	0,035	1,415 (1,024-1,954)	0,1647
17	rs9904720-EPX	A	37,19	29,32	C	4,438	0,035	1,427 (1,024-1,989)	0,1693
5	rs2230303-GPX3	G	1,653	0,2273	T	4,36	0,036	7,378 (0,82-66,39)	1,121
4	rs6833161-SPP1	T	33,88	42,01	C	4,321	0,037	0,7075 (0,5102-0,981)	0,1668
5	rs8177413-GPX3	C	1,653	0,2294	G	4,308	0,037	7,311 (0,8125-65,78)	1,121
8	rs7824574-CLU	A	5,785	10,45	C	4,243	0,039	0,5259 (0,2829-0,9778)	0,3164
22	rs12106549-TXNRD2	T	25,62	18,86	G	4,257	0,039	1,482 (1,019-2,155)	0,1911
17	rs14309-ALOX12	A	7,438	12,5	G	4,186	0,04	0,5625 (0,3222-0,9819)	0,2843
6	rs1293928-IPCEF1	G	30,58	38,41	A	4,174	0,041	0,7063 (0,5057-0,9866)	0,1705
6	rs6905523-GSTA7P	G	26,03	19,32	A	4,143	0,041	1,47 (1,013-2,133)	0,1898
8	rs10087808-OXR1	G	22,31	29,55	A	4,144	0,042	0,6849 (0,4753-0,9871)	0,1864
6	rs35062161-GPX6	T	3,719	1,364	A	4,027	0,044	2,794 (0,9824-7,946)	0,5333
8	rs10109171-OXR1	A	38,43	30,82	G	4,048	0,044	1,401 (1,008-1,947)	0,1678
2	rs2465661-AOX1	T	38,02	45,91	C	3,966	0,046	0,7226 (0,5246-0,9954)	0,1634
16	rs75586809-VKORC1	T	3,306	1,136	C	3,93	0,047	2,974 (0,9622-9,195)	0,5758
7	rs6947821-NOS3	C	29,75	37,27	T	3,902	0,048	0,7128 (0,5091-0,998)	0,1717
8	rs10108813-OXR1	C	22,73	29,77	T	3,907	0,048	0,6938 (0,4823-0,9979)	0,1855
6	rs72944451-GSTA4	T	2,479	68,18	G	3,874	0,049	3,703 (0,9179-14,94)	0,7117
8	rs1503573-OXR1	G	42,15	50	A	3,862	0,049	0,7286 (0,531-0,9996)	0,1614
17	rs11652709-EPX	C	37,6	30,23	G	3,851	0,049	1,391 (1-1,935)	0,1685
20	rs6052780-PRNP	A	1,65	4,545	G	3,848	0,049	0,3529 (0,1192-1,045)	0,5537

TH-PO870

Enhancer of Zeste Homolog-2 (EZH2), a Histone H3 Methyltransferase, Launches Deptor Downregulation for Mesangial Cell (MC) Hypertrophy and Matrix Expansion in Diabetic Nephropathy (DN)

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Background: mTOR has emerged as a centerpiece in pathogenesis of DN. Deptor is an inhibitory component of both mTOR complexes (C1 and C2). We investigated epigenetic control of deptor expression and its relevance to mesangial cell hypertrophy and matrix protein expansion during the progression of DN.

Methods: Human MCs and OVE26 mice were used. Activation-specific antibodies, real time qRT-PCR, immunoblotting, plasmid-derived expression vector and shRNA transfection were employed.

Results: In MCs, 25 mM glucose (HG) decreased expression of deptor mRNA and protein in a time-dependent manner, resulting in increased activation of mTORC1 and C2 as judged by phosphorylation of S6 kinase (T-389) and Akt (S-473), respectively. To determine the mechanism of deptor downregulation, we considered the epigenetic mechanism involving the polycomb repressor complex-2 in which EZH2 promotes the trimethylation (Me3) of histone H3 at K27. HG increased the expression of EZH2 concomitant with increased H3K27 Me3. Deazaneplanocin (DZNep), an inhibitor of EZH2, blocked H3 Me3 and deptor downregulation induced by HG. Also, DZNep inhibited HG-stimulated mTORC1 and C2 activities. Similarly, shRNA against EZH2 inhibited H3K27 Me3, reversed HG-induced deptor inhibition and suppressed mTORC1 and mTORC2 activities. In contrast, expression of EZH2 increased H3 K27 Me3, decreased deptor expression and enhanced mTORC1 and C2 activities, similar to HG treatment. Furthermore, DZNep and shEZH2 significantly inhibited HG-induced MC hypertrophy and expression of fibronectin and plasminogen activator inhibitor-1 (PAI-1). On the other hand, EZH2 increased fibronectin and PAI-1 expression similar to HG. To address the *in vivo* relevance of our observations, we used OVE26 diabetic mouse. In the renal cortex of these mice, expression of EZH2 was significantly increased concomitant with increased H3K27 Me3, mTORC1 and C2 activities, and fibronectin and PAI-1 expression.

Conclusions: Our results for the first time uncover a precisely tuned balance between deptor suppression by EZH2 and activation of mTORC1 and C2 for HG-induced MC hypertrophy and matrix accumulation. The data lend support for testing EZH2 inhibitors in preclinical model for attenuation of complications of DN.

Funding: Veterans Affairs Support

TH-PO871

Urinary Kidney-Specific DNA Methylation Signature Correlates with Renal Function Decline in Diabetes

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Background: Renal tubular injury contributes to the silent decline in kidney function in patients with diabetes. Cell type-specific DNA methylation patterns have been used to calculate proportions of particular cell types. In this study, we developed a method to detect renal tubular injury in diabetic patients based on tubule-specific DNA methylation patterns in urine sediment.

Methods: To identify gene loci exhibiting proximal tubule-specific DNA methylation in the human urinary system, we used two approaches: genome-wide DNA methylation analysis using the Infinium MethylationEPIC BeadChip Kit and extrapolation from mouse CpG data obtained in our previous study. We next determined the methylation levels of proximal tubule-specific loci in urine sediment of diabetic patients and analyzed correlation with clinical variables.

Results: Genomic loci in gene A and G6PC were selectively unmethylated in proximal tubular cells compared to other parts of micro-dissected tissues obtained from normal kidney and bladder epithelium. The methylation levels of gene A and G6PC in urine sediment, deemed to reflect the proportion of exfoliated proximal tubular cells, correlated well with each other. Multivariate analysis with classic tubular injury markers and known risk factors of renal insufficiency in diabetic patients revealed that lower eGFR and lower methylation levels of gene A were independently associated with larger annual decline in estimated glomerular filtration rate (eGFR). Moreover, addition of urinary gene A methylation to a model containing eGFR and urinary albumin/Cr improved discrimination of diabetic patients with faster eGFR decline, which were defined as those losing eGFR at a rate of more than the 25th percentile of annual eGFR decline, with c-statistics from 0.698 to 0.756 and a significant improvement in reclassification with category-free net reclassification improvement.

Conclusions: This study demonstrates that diabetic patients with continual loss in kidney function may be stratified by a specific DNA methylation signature and provides the approach for using kidney cells in the urine for the non-invasive diagnosis of kidney diseases through epigenetic urinalysis.

Funding: Government Support - Non-U.S.

TH-PO872

Analysis of DNA Repair Factor KAT5 and DNA Methylation Modulators in Urinary Shedding Cells of Patients with Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of ESRD worldwide. Therefore, early diagnosis is needed. We have recently discovered that DNA repair factor KAT5 is decreased in DKD podocytes, which may lead to impaired DNA repair with aberrant DNA methylation (Cell Rep 2019). Here we investigated the expression profiles of KAT5 and DNA methylation modulators in urinary shedding cells of patients with DKD as a potential diagnostic marker.

Methods: 60 outpatients who visited the nephrology department at Keio University Hospital were enrolled (Gender [Male 39, Female 21], Age 63±2, patients with diabetes 17 [eGFR 59.4±5.4], patients without diabetes 43 [eGFR 63.9±3.4]). 50ml of urine samples were collected and centrifuged, and mRNA was extracted to analyze the expression of phenotypical markers (nephrin; podocytes, AQP1; proximal tubular cells, AQP2; collecting duct cells) and epigenetic modulators in urine-derived cells by quantitative RT-PCR method as previously described. The association of the marker expression levels with

clinical data including presence of diabetes (DM) or hypertension (HT) was investigated using multivariate regression analysis.

Results: Urine KAT5/nephrin was decreased in diabetic patients (p=0.04) consistent with our previous basic study. On the other hand, KAT5/nephrin was increased in HT patients without DM (p=0.08), whereas it decreased in HT patients with DM (p=0.02). In addition, DNA methyltransferase DNMT1, 3A, 3B and DNA demethylation enzyme TET1, 3 expression adjusted with AQP1 or AQP2 respectively, increased in patients with HT. These expression tendencies correlated with the severity of HT especially in AQP1 adjustment. Moreover, DNMT1/AQP1 and DNMT3A/AQP1 had positive correlation with 1-year eGFR reduction rate. Multivariate regression analysis adjusted for proteinuria, age, eGFR and presence of DM also showed that DNMT1/AQP1 was associated with 1-year eGFR decline as the same extent with the presence of DM.

Conclusions: Urine KAT5/nephrin may be a potential diagnostic marker of DKD. Urine DNMT1, 3A/AQP1 is increased in HT patients and associated with 1-year eGFR reduction rate suggesting its possible role as a predictor of renal prognosis.

TH-PO873

Epigenetic Regulation of Gremlin-1, a Key Player in Diabetic Nephropathy Development

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Background: Gremlin-1 (Grem1) is a protein highly expressed in the kidney of both diabetic nephropathy (DN) patients and experimental models. However, the molecular mechanism underlying the induction of Grem1 in DN is not fully understood. Emerging evidence supports a role for epigenetic regulation in the pathogenesis of diabetic nephropathy, but the epigenetic regulation of Grem1 has not been explored. This work aimed to study the role of epigenetic mechanisms in the control of renal expression of Grem1 and its association with diabetic nephropathy.

Methods: We first evaluated the renal expression of Grem1 in 4, 8, 12, and 16-week-old mice from a diabetic nephropathy model (BTBR ob/ob) and in 8-week-old mice from an epigenetic disruption model (Mecp2-null) by RT-qPCR. Additionally, we determined renal expression levels of Mecp2 in 16-week-old BTBR ob/ob mice by Western Blot. Next, the DNA sequence of Grem1 was analyzed with bioinformatics tools to identify potential methylable CpG islands (CGI). Chromatin immunoprecipitation using anti-Mecp2 antibody followed by PCR was performed to assess the binding of Mecp2 to the Grem1 CGI previously identified. Methylated DNA enrichment by MBD-capture was performed to evaluate the methylation level of the Grem1 CGI.

Results: We observed that Grem1 renal expression is increasing in BTBR ob/ob mice starting from 8 weeks of age and according to the progression of the phenotype associated with DN. Renal expression of Mecp2 in 16-week-old BTBR ob/ob mice was also increased. Additionally, Grem1 renal expression was increased in Mecp2-null mice compared to wild-type. Next, we identified a ~2 kb CGI in Grem1 sequence, that includes its transcription start site. We found that in the kidney of wild-type mice, there is a ~4% of basal methylation in two zones of Grem1 CGI and Mecp2 binds to several regions of the Grem1 CGI.

Conclusions: Our results strongly suggest that Mecp2 epigenetically represses Grem1 expression by binding to a methylated CpG island in Grem1 promoter and coding gene. These results allow us to propose that an epigenetic mechanism underlies the induction of Grem1 gene expression in diabetic nephropathy development. Funding acknowledgement: PFB CECs 01/2007, FONDECYT 1160465, FONDECYT 1181574, CONICYT-PFCHA 21160495.

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TH-PO874

Comparison of Kidney Transcriptomic Profiles Between Patients with Early and Advanced Diabetic Nephropathy Reveals Potential New Mechanisms for Disease Progression

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Background: Genome-wide gene expression profiling can be useful in providing a global picture of the disease pathogenesis and to identify potential new biomarkers and drug targets for DN.

Methods: We performed RNA sequencing of the whole kidney biopsy samples from 28 patients with early DN (n=6), advanced DN (n=22) and normal kidney tissues (n=9) from nephrectomy samples. Correlation of differentially expressed genes (DEGs) with renal function (eGFR) and histological parameters in the DN patients was analyzed. We took advantage of the recently published scRNA-seq data to perform a computational deconvolution analysis of the gene expression data from whole kidney to estimate the number of cells in the normal and diseased kidneys. Finally, we validated some of these findings by immunostaining of the kidney tissues from these patients.

Results: We found that a group of genes were upregulated at early DN but down-regulated in late DN, many of which were shown to be renoprotective, including those in the retinoic acid and glucagon-like peptide-1 receptor (GLP1R) pathways. Another group of genes that were downregulated at early DN, but highly upregulated in advanced DN, consisted mostly of genes known to be involved in progression of DN, such as those related to immune response and fibrosis. We found that the DEGs in the pathways of iron transport and cell differentiation were positively associated with eGFR, while those in the immune response and fibrosis pathways were negatively associated. We also found that individual renal pathology features were associated with the DEGs belonging to the unique GO terms and pathways. We performed deconvolution analysis of the RNA sequencing data to deduce the number of different cell types in DN by using recently published single-cell transcriptome datasets, which showed a significant increase in monocytes/macrophage, fibroblasts, and myofibroblasts in the kidneys from patients with advanced DN. Finally, we validated the expression of RBP4 and GLP1R and the markers of immune cells in the kidney tissues of these patients by immunostaining.

Conclusions: Our study provides potential molecular mechanisms for DN progression as well as the associations of DEGs with the functional and structural changes observed in patients with both early and advanced DN.

Funding: Government Support - Non-U.S.

TH-PO875

Bioinformatic Analysis of Kidney Transcriptome Sequencing from Patients with Diabetic Nephropathy Based on Different Sequencing Platforms

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Background: Diabetic Nephropathy (DN) is one of serious complications of diabetes mellitus. The changes in kidney gene expression profile in patients with DN remain unclear. The field has seen studies of kidney transcriptome sequencing data from patients with DN using different sequencing platforms with varied results. Our aim is to combine those sequencing data and find the differentially expressed genes(DEGs) profile in the kidneys of DN patients by means of bioinformatic analysis.

Methods: The microarray data of human diabetic glomeruli and tubules were screened in GEO database. The selection criteria were as follows: 1. The samples include both DN kidney tissue and normal ones; 2. The samples must be detected after the glomeruli or tubules were separated. 3. DN tissue is not subject to other experimental biological factors. In total, 82 cases of glomeruli and 77 cases of kidney tubule tissues, coming from GPL11670,GPL14663,GPL30122 platforms, were included to identify the DEGs. The contrast model is constructed on the DN and CTL data from the three platforms respectively, using limma function package in R software. We performed Bayesian Test according to contrast Model (Log FC > 1 and P < 0.05 were defined as DEGs). The results of gene intersection between different sequencing platforms were analyzed with STRING and DAVID on-line tools. Cytoscape was used to screen proteins with stable differential expression trend.

Results: There were 134 common DEGs with multiple sequencing platforms in the glomerular of DN patients which were enriched in the exosome process and Rap1 signaling pathway. Among them, 7 genes (WT1,FGF9,IGF1,ALB,TJP1,EGF,BMP7) exhibited the most stable protein interaction. 20 genes show a consistent trend of differential expression in kidney tubule. Exosome process is the most enriched biological process in functional analysis. Moreover, 3 genes (LUM,THBS2,VCAN) exhibited the most stable interaction. We confirmed the expression of these genes in the human protein library(HPA) and verified the different expressions in the kidneys of DN patients by RT-qPCR.

Conclusions: DEGs of microarray data in glomeruli and tubules of DN patients are not the same. DEGs from different sequencing platforms are inconsistent. The function of common DEGs in different platforms may be more closely related to the pathogenesis of DN.

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

TH-PO876

Whole-Kidney 3D Imaging and Transcriptome Assessment in the UNx db/db Mouse Model of Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is associated with increased cardiovascular risk and shortened survival. The DN therapeutic landscape has remained almost completely unchanged for decades, largely due to the lack of translatable preclinical models. In this study, we assessed renal changes in uninephrectomized (UNx) *db/db* mice using light sheet microscopy (LSM) and RNA sequencing to better define the structural and functional changes associated with early progression of DN.

Methods: UNx was performed in 7-8 week old male and female *db/db* mice. Sham-operated *db/+* mice served as controls. Kidneys were preserved for histology, stereology, and RNA sequencing. In a separate study, UNx was performed in 18 week old male *db/db* mice. Mice were injected with lectin-594 immediately prior to termination to visualize glomerular morphology and to assess glomerular permeability via LSM. All mice were terminated at 24 weeks.

Results: Male and female UNx *db/db* mice showed similar progression of type 2 diabetes and urine albumin to creatinine ratio (UACR). Glomerular volume was increased in both genders relative to non-diabetic controls. Tubulointerstitial collagen III was increased in female UNx *db/db* vs. control mice, whereas glomerulosclerosis, as assessed by collagen IV/podocin colocalization, was significantly increased in male UNx *db/db* mice. Kidney RNAseq revealed increased expression of the glomerular marker *Nphs1* and the tubule markers *Lcn2*, *Spp1*, *Havcr1*, confirming glomerular hypertrophy and kidney injury. Glomerular number was determined by LSM and subsequent stereological assessment on the same kidneys, allowing direct comparison of the two methodologies. UNx and control mice demonstrated similar glomerular numbers (~16,000), whereas UNx

mice had increased glomerular volume (81,000 mm^3 vs 145,000 mm^3). Moreover, LSM revealed a marked increase in cortical lectin-594 staining, indicating glomerular leakage and emerging glomerular dysfunction in UNx *db/db* mice.

Conclusions: The use of whole-kidney 3D imaging in tandem with RNAseq offers a novel means of assessing individual glomerular structure and function during DN progression and represents a powerful technique to profile the preclinical efficacy of forthcoming DN therapeutics.

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TH-PO877

Early Changes in Kidney Transcriptomics and Proteomics in Streptozotocin-Induced Diabetes Model

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Background: Diabetic kidney disease (DKD) is a progressive and feared microvascular damage in diabetes patients. It is the leading cause of end-stage kidney disease (ESKD) globally. There is strong evidence that cellular insulin resistance is a major driver of DKD progression. However, early pathways involved in the development of DKD are still poorly understood. Here we explored transcriptomics and proteomics of kidney tissue in streptozotocin (STZ) induced diabetic rat kidneys in order to confirm known and establish new early molecular changes associated with DKD.

Methods: To induce diabetes, one dose of STZ (50mg/kg) was administered in the intraperitoneal cavity to animals fasted overnight. Urine and kidneys were collected at days 1, 7 and 15 post injection. Sections cut of kidney cortex were used to isolate RNA and proteins. RNA was isolated using RNeasy Fibrous Tissue and subjected to small and long RNA sequencing. For protein analysis, tissue was homogenized in 7M urea, 2M thiourea, 4% CHAPS using Percellys® 24 homogenizer and subjected to LC-HDMS.

Results: 1 day after injection of STZ, an increase of in serum glucose levels and urine volumes was detected in STZ treated groups as expected. Distinct differences between diabetic and control groups in regard to miRNA, mRNA and proteins, respectively, were observed as early as day seven and also at day 15 post injection. At day 15, the gene enrichment analysis (GO: Biological process) of proteins reflected many known pathways involved in diabetes type II. These included pathways modulated at the onset of diabetes and those associated e.g. with glycolysis/gluconeogenesis and others. An exclusive transcriptional expression pattern was seen at each timepoint which should be very valuable to establish new molecular targets now available for verification in human DKD.

Conclusions: Our approach describes early molecular changes of DKD at transcriptomics and proteomics level. These results are valuable to define previously unidentified pathways involved and novel molecular targets in DKD.

TH-PO878

Urinary Proteomics Identifies Signature of Early Type 1 Diabetes Linked to Keratan Sulfate Degradation and Lysosomal Enzymes

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Background: Maladaptive changes have been described in the diabetic kidney long before the onset of microalbuminuria, in the form of renal hyperfiltration and hypertrophy. Our aim is to examine the urinary proteome of youths with early, uncomplicated type 1 diabetes and to examine the biological processes and pathways underlying early changes in the diabetic kidney.

Methods: We performed urinary proteomics on samples from 15 otherwise healthy youths with type 1 diabetes and 15 non-diabetic peers. All youths were < 19 years of age, free of comorbidity including microalbuminuria, and not using anti-hypertensive drugs. Urine volumes normalized to creatinine were subjected to 10-kDa ultrafiltration to isolate proteins. Proteins (200 micrograms) were digested with trypsin, fractionated using strong cation exchange chromatography, and analyzed on Q-Exactive mass spectrometer. MaxQuant software was used for peptide/protein identification and label-free quantification. The PathDIP database was searched to identify the top pathways associated with differentially excreted proteins. Proteins were validated in a second cohort of 30 youths with and without diabetes using enzyme-linked immunosorbent assays.

Results: Of the 2313 proteins quantified, 576 were detected across all thirty urine samples. Of these, 34 were differentially excreted between groups (Benjamini-Hochberg FDR, $Q < 0.05$). More than half of these differentially excreted proteins were lysosomal enzymes, and the dominant terms associated with these lysosomal enzymes include “hydrolase activity”, “glycosaminoglycan degradation”, and “keratan sulfate proteoglycan”. Increased urinary excretion rates of lumican and hexosaminidase A were validated in a second cohort, representing a core protein and an enzyme that degrades glycosidic bonds in keratan sulfate.

Conclusions: Lysosomal enzymes associated with keratan sulfate degradation were overrepresented in urines from youths with diabetes, suggesting that extracellular matrix remodeling may be an early response of the kidney to hyperglycemia.

TH-PO879

The Feasibility and Utility of Urinary Single-Cell Sequencing

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Background: At present, histological assessment of renal biopsies remains the only approach to firmly diagnose renal diseases. However, it requires an invasive procedure which is associated with a small but existent risk for the patient. As kidney cells are continuously shed into the urine, we sought to investigate whether urinary single cell sequencing(SCS) can be used to predict changes occurring in renal biopsy samples. Here we report on the feasibility and utility of urinary SCS in the TRIDENT (Transformative research in diabetic nephropathy) cohort.

Methods: Patients with diabetes undergoing clinically indicated kidney biopsy were enrolled into the TRIDENT study, and were consented to participate in this ancillary study. Urine samples, spot and 24-hour collections, were obtained twice at one-month interval from 5 subjects for a total of 20 specimen. Urine scRNA-Seq was performed using 10xGenomics Chromium system. Results were correlated with kidney tissue pathology and compartment specific RNA sequencing.

Results: High-quality data was generated for 4 patients. Total number of cells detected in urine varied between 185-7260 across individuals but was not different between spot and 24-hour specimen and samples collected over a month. Cell identity was matched using mouse single cell gene expression markers. 20 different kidney cell types were identified in addition to the identity of several cell types are still being matched. Neutrophils and an unknown cell type (possibly bladder cells) were the predominant cell type in the urine. Endothelial and collecting duct intercalated cells were only detected in the spot urine sample, but all other cells were present in both collection. Urinary podocyte number correlated with proteinuria and eGFR. Urinary fibroblasts correlated with the degree of fibrosis measured histologically in renal biopsies obtained from the same patients. Urinary cell proportions correlated with renal bulk mRNA cell proportions.

Conclusions: Urine scRNA-Seq is feasible. This method can provide an insight into renal molecular, cellular, and histological changes. Urinary cell number and proportions seem stable and correlated with kidney specific changes. Overall, urinary scRNA-Seq may provide a non-invasive approach to diagnosing renal diseases.

TH-PO880

MicroRNA-155 Upregulation Induces Podocyte Insulin Resistance: A New Therapeutic Target in Diabetic Nephropathy?

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Background: Loss of podocyte-specific insulin-sensitivity results in histological features of diabetic nephropathy (DN) in mice, implicating this pathway in disease development. MicroRNAs (miRNAs) regulate expression of most mammalian protein coding genes at the post-transcriptional level, and are critical regulators of insulin responses in “traditionally” insulin-sensitive tissues, liver, fat and muscle. The role of miRNAs in podocyte insulin-signalling is unknown. We hypothesise that miRNA-driven loss of podocyte insulin responses triggers DN development.

Methods: Podocytes were rendered insulin-resistant by culture in diabetogenic media containing high dose insulin, glucose and inflammatory cytokines. Microarray analysis was performed to compare miRNA expression profiles of wild type and insulin-resistant podocytes, and differential expression of selected miRNAs was validated by RT-qPCR. *In vitro* manipulation of differentially expressed miRNAs was achieved using miRvana mimics and inhibitors, and insulin responses assessed by Western Blot and tritiated glucose uptake assay.

Results: Differential expression of 103 miRNAs was detected. Five miRNAs were selected for further study based on expression fold change, a statistical significance threshold of $p<0.0002$ and bioinformatic evidence of targets in insulin-signalling pathways. MiR-155,-146a,-222 and -204 were validated by RT-qPCR. MiR-155 overexpression in podocytes repressed expression of target mRNA PI3KR1, reducing subsequent Akt phosphorylation. Furthermore, Insulin-stimulated glucose uptake was reduced in miR-155 over-expressing podocytes.

Conclusions: MicroRNA-155 is upregulated in podocyte insulin-resistance *in vitro*. Insulin-resistance may be effected via PI3KR1 repression, leading to reduced insulin-signalling via the PI3K/Akt pathway and impaired downstream glucose uptake. Thus miR-155 may be therapeutically manipulated as a novel podocyte insulin-sensitiser to halt the progression of DN.

TH-PO881

The Role of LncRNA Meg3 in the Mitochondrial Dysfunction Induced by High Glucose in Podocytes

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Background: Podocytes have plenty of mitochondrial density to keep up with their high energy need. Mitochondrial dysfunction plays a key role in diabetic nephropathy(DN), which has been assumed related with Maternally expressed gene 3 (Meg3),a long

noncoding RNA expressing in normal human tissues. While the exact mechanism of Meg3 on this pathophysiological process is poorly understood.

Methods: FISH+IF was used to detect the expression of Meg3 in podocytes of patients with DN. Podocytes were exposed or not to 30mM high glucose in vitro to study the effect of high glucose on Meg3 expression. In addition, the expression of Meg3 was regulated by CRISPR-Cas9 system and lentiviral vector to explore its function in mitochondrial dysfunction.

Results: Meg3 expression in podocytes of diabetic kidney tissue was higher than that in normal kidney tissue. In cultured human podocytes, the expression of Meg3 increased with the prolongation of high glucose exposure time. The results of PCR detection were consistent with those of Arraystar, suggesting that high glucose can up-regulate the expression of Meg3. Knocked out Meg3 can improve podocyte injury and mitochondrial dysfunction induced by high glucose. By contrast, the podocytes over-expression of Meg3 aggravated injury, expressing less Nephrin and Synaptopodin. Abnormal expression of proteins associated with mitochondrial fusion and fission caused dynamic imbalance of mitochondria, more fragmentation, lower mitochondrial membrane potential levels.

Conclusions: Our study demonstrates for the first time that Meg3 can be upregulated by high glucose, inducing a dynamic imbalance of mitochondria, leading to damage to podocytes. This finding will provide a potential treatment strategy to alleviate the development of DN.

TH-PO882

Extracellular Vesicle Cargo Derived from Kidney Cell Lines Is Affected in Insulin-Resistant and Highly Insulin-Sensitive Conditions

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Background: Kidney disease (DKD) is common, costly and the most feared complication of long standing diabetes. It is now clear that cellular insulin resistance is a major driver of this disease. Here we explored the extracellular vesicle (EV) secretion pattern by key DKD target cellsin the glomerulus (podocytes, endothelial and mesangial cells) and proximal tubular cells by harvesting the entire secreted EV repertoire in insulin sensitive and insulin resistant cells using Hydrostatic Filtration Dialysis (HFD).

Methods: EVs were isolated from 50ml of cell culture mediafrom conditionally immortalized human cells. Cells were rendered hyperinsulin-sensitive by stable insulin receptor expression, and insulin resistant by culturing in a diabetic environment as recently published. Quality of the EV yield was verified with negative staining Electron Microscopy (EM) and Western blotting (WB). Vesicle concentration and size was determined by Nanoparticle Tracking Analysis (NTA). EV RNAs were profiled with Bioanalyzer Pico kit and subjected to miRNAseq, and mRNAseq. EV proteins were analyzed using tandem mass tag labeling.

Results: The isolated EVs appeared typical at EM and were positive for the EV-marker TSG101 in WB. RNA quantity and quality proved appropriate for miRNA analysis. 96 EV miRNAs and 109 mRNAs could characteristically discriminate between the cell types. Some EV miRNAs, mRNA and proteins showed treatment effects. KEGG and Gene Ontology gene enrichment analysis showed pathways associated with DKD.

Conclusions: EV analysis provides a novel approach to reveal valuable new details of the kidney secretome in the setting of insulin-resistant diabetic conditions. It is noteworthy that the characteristic changes can be found from culture medium of DKD target cell. Changes in the EV miRNAs, mRNA and proteomics may thus give valuable insight into mechanisms and targets to insulin resistance in DKD.

TH-PO883

Exosome-Mediated Tubulointerstitial Communication Promotes Renal Fibrosis in Diabetic Kidney Disease

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Background: Renal tubular injury initiates fibroblast activation and drives overproduction of extracellular matrix, leading to renal fibrosis which is a final common pathway in progressive kidney diseases including diabetic kidney disease(DKD). However, it is unclear how injured tubular epithelial cells relay signals to neighboring fibroblasts and trigger the differentiation of fibroblasts to myofibroblasts. Recently, exosomes have been recognized as crucial mediators of intercellular communication. We hypothesized that exosomes might be involved in the communication between injured tubular cells and fibroblasts during the progress of DKD.

Methods: Exosomes were isolated from kidney tissues and mouse proximal tubular cells by differential centrifugation. In *in vivo*, renal cortex of Akita mice and STZ-induced C57/b6 mice were examined. In *in vitro*, BUMPT cells were cultured with normal glucose(NG) or high glucose(HG) for 8 days to collect exosomes in the conditioned medium(CM). Exosomes were characterized by TEM, NTA and western blot. The content of exosomes was analyzed by proteomics. To study the effect of tubular cell exosomes on fibroblasts, the tubular CM-derived exosomes were added to NRK-49 fibroblasts for 48 hrs, followed by the evaluation of cell proliferation and fibrosis.

Results: Exosome secretion decreased in renal cortex of DKD mice as compared to non-diabetic mice. Consistently, HG-incubated BUMPT cells had lower exosomes than NG cells. Notably, the exosomes from HG-incubated BUMPT cells stimulated higher levels of proliferation, morphologic change, and production of fibronectin, a-SMA, and collagen I in fibroblasts. 15 proteins showed differential expression in the exosomes from HG BUMPT-cells versus those from NG cells. Cytoscape analysis suggested two correlation networks of the differentially expressed genes. The higher expression of Eno1 and close relationship with clinical manifestation in DKD were further proved using Nephroseq v5 online platform.

Conclusions: DKD is associated with a decreased ability of exosome production and/or secretion in renal tubular cells. The exosomes from HG-incubated tubular cells are more effective in stimulating the proliferation and activation of fibroblasts. Thus, exosomes may provide a mechanism of tubulointerstitial communication in renal fibrosis and disease progression in DKD.

TH-PO884

Mass Spectrometry Imaging Reveals Alerted Metabolic Profiles of Small Molecules in Kidney Tissue Sections of Diabetic Mice

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Background: It was reported that 1,5-naphthlenediamine (1,5-DAN) hydrochloride assisted laser desorption ionization (LDI) mass spectrometry imaging (MSI) of kidneys, liver, and brain tissues allowed to visualize the spatial distribution and alteration of a broad range of small molecule metabolites including metal ions, amino acids, carboxylic acids, nucleotide derivatives, peptides, and lipids simultaneously. MSI has potential applications in small molecule *in situ* analysis (Huihui Liu et al., 2014).

Methods: In the current study, we employed a high resolution MALDI-MSI approach using 1,5-DAN hydrochloride as matrix to characterize small molecules in Akita (n = 3) and non-Akita (n = 3) mice kidney tissue sections at 20 μm spatial resolution. The data output was coupled to METASPACE for the annotation. SCiLS Lab and MetaboAnalyst were used for data processing and statistical analysis.

Results: In total, 107 metabolites were annotated by METASPACE in mice kidney tissue sections. MALDI MSI of kidney sections of F_1 Akita mice clearly exhibited profound alterations of intermediates in the tricarboxylic acid cycle (TCA) cycle, glutamate-glutamine cycle, malate-aspartate shuttle, and phospholipid metabolism, simultaneously. Various metabolites underwent relatively remarkable changes in diabetic kidney tissues compared with the non-diabetic ones. Particularly, diabetic kidneys had higher relative abundance of glucose, xanthine and hypoxanthine, while lower relative levels of citric acid, glutamine, linoleic acid and arachidonic acid were observed.

Conclusions: In summary, MALDI-MSI is potentially effective and widespread application in small molecule *in situ* analysis of mice kidney tissues. MALDI-MSI technology coupled with METASPACE shed new light on our understanding of pathobiology of diabetic kidney disease.

Funding: NIDDK Support

TH-PO885

The Effect of Kidney Cell Sex and Sex Hormone Stimulation on Kidney Metabolism: Implications for Diabetic Kidney Disease

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Background: Male sex predisposes to diabetic kidney disease (DKD). We uncovered androgen-induced proteome perturbations in renal metabolism that may drive faster DKD progression in men. Our goal is to study cell sex- and sex hormone-specific metabolic alterations in human primary proximal tubule epithelial cells (PTEC).

Methods: PTEC from 3 male and 3 female donors were stimulated with control, dihydrotestosterone (DHT), or estradiol (EST) for 16h/24h. Chronic hyperglycemia was simulated by exposing sex hormone-treated PTEC to high glucose (25mM) for 96h. We assessed glycolysis (extracellular acidification rate, ECAR) and oxygen consumption rate (OCR) in a Seahorse analyzer. We measured extracellular glucose, intracellular ATP, oxidative stress (O_2^-), and apoptosis (phosphatidilserine). IL-6 and MCP1 were quantified by a Multiplex Assay.

Results: Male PTEC showed significantly higher ECAR and OCR, ATP-linked respiration, maximal glycolitic and respiratory capacity, superoxide levels and apoptosis compared to female PTEC ($p<0.05$). In male PTEC, ECAR was increased by DHT stimulation, whereas OCR was increased by DHT and EST. In male PTEC, media glucose levels were reduced by DHT. DHT-induced increase in glycolysis, OCR, oxidative stress and glucose consumption was prevented by androgen receptor (AR) inhibitors. ATP, O_2^-, apoptosis and secretion of IL-6 and MCP1 were increased by DHT, especially in male PTEC. Under hyperglycemia, DHT increased O_2^- and ATP. Promoter analysis revealed that 46/60 of our DHT-upregulated proteins may be regulated by MYC and/or SRY transcription factors (involved in glucose/glutamine metabolism and in male sex determination). Male sex and DHT were associated with increased AR and SRY gene levels ($p<0.05$). MYC was upregulated by DHT in male PTEC and by EST in female PTEC ($p<0.05$).

Conclusions: The metabolic function of PTEC and their response to sex hormones are influenced by cell sex. Male PTEC show higher glycolysis, oxygen consumption, and respiratory capacity than female PTEC. These differences are related to increased oxidative stress and apoptosis, and to enhanced AR and SRY expression. In male PTEC, DHT-induced protein changes are linked to a more glycolytic and oxidative phenotype, higher glucose consumption, oxidative stress, apoptosis, and IL-6/MCP1 secretion.

TH-PO886

Alteration of Tryptophan-Kynurenine Metabolites in the Serum and Kidney in Diabetic Nephropathy

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Background: It has recently been suggested that several metabolic pathways associated with diabetes interact to influence systemic metabolism, humoral response, and chronic inflammation, contributing to complications of diabetes. Tryptophan-kynurenine (TRP-KYN) metabolites play a vital role in several physiological and pathological conditions including diabetes. However, the contribution of TRP-KYN metabolites to the pathogenesis of diabetic nephropathy has not been established. Metabolomic data analysis was used to detect pathways of systemic interaction associated with the pathogenesis of diabetic nephropathy. We identified that TRP-KYN metabolism was one such pathway that contributed to the progression of diabetic nephropathy.

Methods: To identify TRP-KYN metabolites associated with diabetic nephropathy, we analyzed serum, urine, and tissue levels of TRP-KYN metabolites in an animal model of diabetic nephropathy using uni-nephrectomized spontaneously diabetic Torii fatty rats on 0.3% salt supplementation. Distributions of TRP-KYN metabolites in the kidney were analyzed using matrix-assisted laser desorption/ionization imaging mass spectrometry. Finally, we identified serum TRP-KYN metabolites in patients with diabetic nephropathy proved by renal biopsy.

Results: Profiling of TRP-KYN metabolites in an animal model of diabetic nephropathy revealed activation of the KYN pathway and accumulation of metabolites in kidney tissues. Changes in levels of TRP-KYN metabolites were also observed in patients with diabetic nephropathy. Additionally, the concentration of some metabolites was related to the severity of proteinuria, percentage of glomerular sclerosis, and grade of interstitial cellular infiltration.

Conclusions: Changes in the profile of TRP-KYN metabolites were observed both in animal models and humans with diabetic nephropathy. The concentrations of TRP-KYN metabolites may be associated with the progression of diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-PO887

Impact of Angiotensin Receptor Blockade on Metabolic Profiles in a Mouse Model of Diabetic Nephropathy

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Background: Changes in energy metabolism have been associated with susceptibility to diabetic nephropathy (DN). Blockade of the renin-angiotensin system (RAS) is renoprotective in DN, but effects of RAS inhibition on metabolic profiles in DN have not been clearly defined. To investigate this issue, we carried out metabolomics profiling in a mouse model of DN and tested the effects of RAS blockade on kidney metabolism.

Methods: We generated a mouse model of DN with underlying activation of the RAS by a renin transgene (ReninTg) driven by the albumin promoter on the *Akita* background of type I diabetes. We have shown that on a 129 strain background, *Akita-ReninTg* mice exhibit cardinal characteristics of human DN including high-grade albuminuria and glomerulosclerosis. 12-week old 129 *Akita-ReninTg* mice were treated with vehicle or the angiotensin receptor blocker (ARB) losartan for 12 weeks. Following treatment, kidneys were collected and metabolic profiles were determined by liquid chromatography-mass spectrometry.

Results: Before treatment, the 129 *Akita-ReninTg* mice had significant albuminuria (833±112 μg/day). Over the next 12 weeks, there was a progressive increase of albuminuria in the vehicle group that was prevented by ARB (1480±562 vs 193±42 μg/day; p=0.045). When compared to age-matched 129/SvEv parental controls, metabolomics profiles of kidneys from vehicle-treated 129 *Akita-ReninTg* mice showed significant reductions in levels of most amino acids, except for the branched-chain amino acids, while C3 and C5 acyl-carnitine levels were increased. ARB had no effect on these profiles. By contrast, most even-chain acyl-carnitine levels were substantially reduced in 129 *Akita-ReninTg* mice compared to parental controls and C2 acyl-carnitine level was increased toward normal with ARB.

Conclusions: There is a range of metabolic alterations in this DN model, suggesting multiple disruptions of metabolic pathways in the kidney. Reduced levels of even-chain acyl-carnitines in mice with DN suggest altered renal fuel metabolism and may reflect impaired fatty acid oxidation. The impact of RAS blockade on renal metabolic profiles was discrete, confined to a partial restoration of kidney C2 acyl-carnitine level, reflecting normalisation of renal fuel metabolism. These metabolic actions may contribute to the renoprotective effects of ARB.

Funding: Government Support - Non-U.S.

TH-PO888

Enarodustat, Hypoxia-Inducible Factor Stabilizer, Counteracts the Diabetic Renal Energy Metabolism Alterations Occurring in the Early Stages of Diabetic Kidney Disease

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Background: Hypoxia-inducible factor stabilizers (HIF stabilizers) increase endogenous erythropoietin production and serve as novel therapeutic agents against anemia in chronic kidney disease. Although HIF induces the expression of various genes related to energy metabolism, the effects of HIF stabilizers on energy metabolism in renal tissue, especially in pathological conditions, remain obscure. Here, we analyzed the effects of enarodustat (JTZ-951; HIF stabilizer) on renal energy metabolism in streptozotocin (STZ)-induced diabetic rat model.

Methods: We divided the rats into three groups; group A (Sham), B (DKD) and C (DKD+enarodustat). First, vehicle (n = 5; group A) or 65 mg/kg of STZ (n = 19) were intravenously administered into rats 7 days before grouping. We selected the rats for group B and C (n = 7, for each group) by matching blood glucose and body weight of STZ-induced diabetic rats. Group A and B were given normal feed, while group C was given the feed mixed with 0.01% (w/w) of enarodustat. Kidney samples were collected 14 days after grouping. We conducted the transcriptome and metabolome analysis of these rats' renal cortical tissue.

Results: Transcriptome analysis of renal cortex revealed that fatty acid and amino acid metabolism were upregulated by diabetes and downregulated by enarodustat, while glucose metabolism was upregulated by enarodustat, showing that enarodustat reversed the renal metabolic alterations induced by diabetes. Metabolome data indicated accumulation of glucose and tricarboxylic acid (TCA) cycle metabolites and a reduction of amino acid concentration in diabetic renal cortex, while these metabolic alterations were mitigated by enarodustat. Moreover, enarodustat alleviated the accumulation of glutathione disulfide (GSSG) observed in diabetic kidney, indicating that enarodustat relieves the oxidative stress in diabetic kidney.

Conclusions: Enarodustat, HIF stabilizer, counteracts the diabetic renal energy metabolism alterations occurring in the early stages of diabetic kidney disease. Our study suggests that HIF stabilization may serve as a potential intervention targeting dysregulated energy metabolism of diabetic kidneys.

Funding: Government Support - Non-U.S.

TH-PO889

Selection of Suitable Housekeeping Genes for Mesangial Cell Studies with High Glucose and Angiotensin II Receptor Blocker

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Background: Real-time PCR (qPCR) is currently the gold standard method to gene expression studies. Identification of the best reference gene is a key point to perform high quality qPCR, being able to provide strong support for results, as well as acting as a source of bias when inappropriately chosen. Mesangial cells (MC), as an essential cell line in diabetic kidney disease (DKD) physiopathology, demand accurate analysis of the most excellent housekeeping (HK) gene to enhance validity of gene expression studies, especially regarding high glucose (HG) and DKD treatments, being angiotensin II receptor blockers (ex. Losartan) the most commonly used. Our objective was to evaluate the suitability and define the most stable reference gene for MC studies of an *in vitro* DKD model of disease and its treatment.

Methods: Five software packages (RefFinder, NormFinder, GeNorm, Bestkeeper, and DataAssist) and the comparative ΔCt method were adopted to analyze six different candidate genes: *HPRT, ACTB, PGAM-1, GAPDH, PP1A,* and *B2M*. RNA was extracted and cDNA was synthesized from immortalized mouse MC cultured in 4 groups: control (n=5; 5mM glucose), mannitol (n=5; 30mM, as osmotic control), HG (n=5; 30mM glucose), and HG+losartan (n=5; 30mM glucose and 10-4 mM of losartan). qPCR was performed according to MIQE guidelines in QuantStudio 7Flex (Applied Biosystems).

Results: *HPRT* presented higher stability values in RefFinder, ΔCt method, and NormFinder softwares (Table 1), while frequently used HK such as *GAPDH* and *ACTB* (Biederman et al. 2004) showed lower scores compared to *HPRT*.

Conclusions: This analysis provides support to the use of *HPRT* as a HK gene in mouse mesangial cell studies of gene expression via qPCR technique.

Funding: Government Support - Non-U.S.

Ranking of the candidate reference genes by each method used. Lower values indicate higher stability in gene expression.

RefFinder	Geomean	ΔCt method	Mean SD	NormFinder*	Stability value	GeNorm	M value	BestKeeper	CV	SD	DataAssist	Score
HPRT	1.00	HPRT	0.67	HPRT	0.118	ACTB	0.031	ACTB	2.96	0.87	PGAM-1	5.324
ACTB	2.21	ACTB	0.75	ACTB	0.158	GAPDH	0.031	HPRT	2.99	0.70	PP1A	5.514
PP1A	3.41	PGAM-1	0.77	GAPDH	0.179	PGAM-1	0.0341	B2M	3.03	0.57	HPRT	5.525
PGAM-1	3.94	PP1A	0.77	PGAM-1	0.181	HPRT	0.0380	PP1A	3.41	0.63	ACTB	5.624
GAPDH	4.47	GAPDH	0.86	PP1A	0.226	PP1A	0.0390	GAPDH	3.51	0.79	GAPDH	5.907
B2M	4.56	B2M	0.92	B2M	0.244	B2M	0.0422	PGAM-1	3.65	0.80	B2M	6.835

SD, standard deviation; CV, coefficient of variation.

*Best reference genes analyzed by NormFinder considering the intra- and intergroup variations.

TH-PO890

A Comprehensive Bioinformatics Analysis Reveals the Pivotal Role of Tubulopathy in Diabetic Nephropathy

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Background: Diabetic nephropathy(DN) is one of the main causes of ESKD worldwide. However, there is still a lack of a comprehensive understanding of the unique molecular mechanism of DN.

Methods: Over 250 Affymetrix microarray datasets of human glomerular and tubulointerstitial tissues were collected (Table 1). Next, a linear model was constructed, and the empirical Bayes method was used to select the unique differentially expressed genes (DEGs) of DN. The DEGs were further analyzed using the enrichment analysis. Finally, the protein-protein interaction networks(PINs) with established physical interaction were constructed, and based on the networks, hub genes were selected.

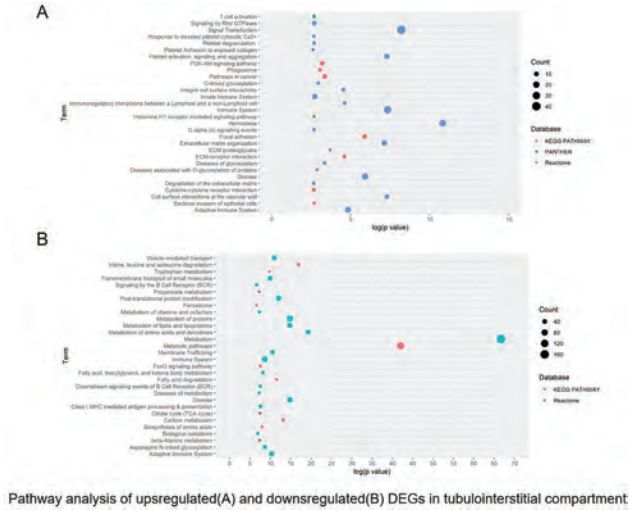
Results: A total of 980 unique DEGs were identified. Enrichment analysis revealed that a wide arrange of pathways are dysregulated in the pathogenesis of DN. Notably, the upregulated DEGs of tubulointerstitial compartment are mainly enriched in pathways related to glycosylation and immune responses, while the downregulated DEGs are strongly related to metabolism disorders(Figure 1). Moreover, a complex interaction network were found among the DEGs of tubulointerstitial compartment. Lastly, a list of genes, including EGFR, SUZ12 and TERF1, were identified as hub genes.

Conclusions: This bioinformatic analysis suggests that tubulopathy might play a pivotal role in the pathogenesis of DN.

Funding: Government Support - Non-U.S.

Table 1

	Number of cases	Number of controls	Resources	Platforms
DN Glomeruli	7	18	GSE37463, GSE47185	Affymetrix U133 Plus 2.0
DN Tubules	11	22	GSE35489, GSE47185	Affymetrix U133 A
HN Glomeruli	15	22	GSE47185, GSE37463	Affymetrix U133 A
HN Tubules	21	22	GSE47185, GSE37463	Affymetrix U133 A
IgAN Glomeruli	43	22	GSE37463,GSE21785, GSE20602	Affymetrix U133 A
IgAN Tubules	25	22	GSE35489, GSE47185	Affymetrix U133 A
MN Glomeruli	18	22	GSE47185, GSE37463,GSE21785, GSE20602	Affymetrix U133 A
MN Tubules	18	22	GSE35489, GSE47185	Affymetrix U133 A
FSGS Glomeruli	23	40	GSE37463, GSE47185, GSE20602, GSE21785	Affymetrix U133 A Affymetrix U133 Plus 2.0
FSGS Tubules	12	22	GSE35489, GSE47185	Affymetrix U133 A



Pathway analysis of upsregulated(A) and downsregulated(B) DEGs in tubulointerstitial compartment

TH-PO891

Small RNA Sequencing Identifies Circulating sncRNAs That Are Differentially Expressed in Type 1 Diabetic Patients at Risk of Progressive Renal Decline

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Background: Progressive renal decline is the fundamental disease process that underlies the development of end-stage renal disease (ESRD) in Type 1 diabetes (T1D). Work by our group and others has demonstrated that microRNA (miRNA) expression profiles are altered in T1D patients with diabetic nephropathy. In the present study, we used small RNA sequencing (sRNA-Seq) to identify circulating small non-coding RNAs (sncRNAs), non-coding regulatory RNAs typically 18-200 nucleotides in length, that are associated with progressive renal decline in T1D patients with normal renal function (eGFR>60 ml/min per 1.73m^2) from the Joslin Kidney Study (JKS).

Methods: sRNA-Seq was used to determine circulating sncRNA expression profiles in baseline plasma specimens obtained from two sub-groups of patients who were followed for 5-10 years from entry to the JKS: 76 rapid progressors, who experienced significant loss of renal function over the course of their follow-up (eGFR slope=-12.61 ml/min/1.73m^2/year), and 70 non-progressors, who experienced minimal decline in eGFR during their follow-up (eGFR slope=-1.43 ml/min/1.73m^2/year).

Results: Differential expression analysis identified more than 50 sncRNAs, including miRNAs, small nucleolar RNAs (snoRNAs), and small nuclear RNAs (snRNAs), that were significantly differentially expressed among rapid progressors and non-progressors, including miR-3168 (P = 8.7x10^{-7}), SNORD36C (P = 1.1x10^{-6}), and SNORD30 (P = 3.7x10^{-6}). Interestingly, we also found miR-3168 to be differentially expressed in an independent cohort of non-progressors and rapid progressors with impaired renal function from the JKS (P-value = 0.0006).

Conclusions: These data suggest that sncRNAs, including miR-3168, SNORD36C, and SNORD30, may be able to distinguish diabetic individuals who are at the greatest risk of losing renal function from those who are protected against these complications. The differentially expressed sncRNAs identified in this study represent novel therapeutic targets that may prove useful in inhibiting renal function decline in T1D.

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TH-PO892

A Novel Deep Learning Model Outperforms Cox Regression Model to Predict Renal and Cardiovascular Risk in Patients with Diabetic Kidney Disease

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Background: Predicting long-term risk in patients with type 2 diabetes and chronic kidney disease is important in clinical practice. We hypothesize that by using short-term dynamic changes in clinical characteristics, deep learning algorithm can accurately predict long-term renal and cardiovascular risk.

Methods: In total 3228 patients with type 2 diabetes and chronic kidney disease from two randomized controlled trials were used in this study: RENAAL (= 1513), IDNT (= 1715). We used a 2D convolutional neural network (CNN) to predict renal (doubling of serum creatinine and/or end-stage renal disease) and cardiovascular (CV; myocardial infarction, stroke and cardiovascular death) outcomes. We compared the prediction performance with a traditional Cox proportional hazard regression (Cox) model. Eighteen clinical characteristics from baseline until 6 months follow-up were used as predictors to train the model on RENAAL data. The model was then externally validated on the IDNT trial. The area under the receiver operator curve (AUC) was used to assess the performance of the CNN and Cox model in the IDNT trial.

Results: A total of 462 (27%) and 518 (30%) of patients in IDNT experienced a renal or CV outcome respectively during a median follow-up of 2.6 years. The AUC of the CNN model, including UACR, HbA1c, SBP, albumin and uric acid as important predictors, was significantly higher compared to the Cox regression model (figure) and obtained the state-of-the-art performance to predict the long-term renal and CV outcomes.

Conclusions: Using 6-month short-term dynamic changes in clinical characteristics, a deep learning algorithm identifies patterns to accurately predict long-term renal and CV risk. The proposed method offers the potential to create accurate and automated risk predictions models to identify high-risk patients who could benefit from intensified therapy.

	Combined		Treatment		Placebo	
Outcome	Renal	CV	Renal	CV	Renal	CV
CNN	0.87 (±0.06)	0.70 (±0.04)	0.86 (±0.08)	0.69 (±0.05)	0.87 (±0.07)	0.70 (±0.03)
Cox	0.73 (±0.02)	0.62 (±0.02)	0.73 (±0.03)	0.62 (±0.02)	0.74 (±0.01)	0.63 (±0.01)
p-value	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

The performance comparison (mean AUC ± standard deviation) of CNN and Cox model for the prediction of renal and cardiovascular risks.

TH-PO893

The p21-Mediated and Senescence-Associated Hyperglycemic Memory in Diabetic Nephropathy Is Therapeutically Amendable

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Background: Diabetic nephropathy (DN) is a major cause of end-stage renal disease. A major challenge in DN is the failure of renal recovery upon improved blood glucose levels. The mechanisms underlying this phenomenon, known as the metabolic memory, remain unknown. We aimed to identify mechanisms contributing to the metabolic memory in DN.

Methods: Two mouse models with established DN (16 weeks after STZ-induced persistent hyperglycemia or 16 weeks old db/db mice) were used. Blood glucose was normalized for 6 weeks using an SGLT2-inhibitor. An unbiased approach (mRNA-seq) was used to evaluate pathways involved in metabolic memory. Candidate genes were studied in human diabetic patients and mice after lowering blood glucose. In vitro and in vivo studies were conducted to determine mechanistic and translational relevance.

Results: Despite a marked reduction of blood glucose levels, albuminuria and glucose induced changes in renal gene expression persisted, enabling to study mechanisms contributing to metabolic memory. PI3-kinase-Akt signaling, cellular proliferation and senescence, and complement-coagulation cascades were linked with metabolic memory. Sustained tubular expression of p21 – a senescence-associated cyclin-dependent kinase inhibitor –was confirmed in humans (histology, urinary p21) and mice (histology, RNA, protein) despite blood glucose lowering. Sustained p21 expression was linked with promoter demethylation and reduced DNMT activity and DNMT1 expression. In silico and in vitro analyses identified miR-148a as a potential regulator of DNMT1. The nephroprotective zymogen protein C was among the genes persistently repressed in DN. Increased tubular senescence, interstitial fibrosis, and albuminuria was confirmed in diabetic mice with a superimposed genetic deficiency of protein C activation. Substituting the protease activated protein C (aPC), mimicking biased aPC-signaling (parmodulin-2), or reducing miR-148a in addition to normalizing blood glucose reversed sustained tubular p21 expression, senescence, and renal damage in DN.

Conclusions: Epigenetically sustained p21-expression and associated senescence contribute to the metabolic memory in DN. This pathogenic mechanism can be targeted by inhibiting miR-148a or by mimicking cytoprotective aPC-signaling.

Funding: Government Support - Non-U.S.

TH-PO894

Inhibition of Yap/Taz Ameliorates Renal Fibrosis in Type 2 Diabetic Mice

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Background: Yap/Taz are central mediators of the Hippo pathway, which have been found to be involved in the pathogenesis of chronic kidney disease including diabetic nephropathy. The expression of Yap increases in both the kidney of diabetic mice and the renal proximal tubule epithelial cells in response to high glucose. However, the underlying mechanism of Yap/Taz in renal fibrosis remains largely unknown.

Methods: The HK2 cell line (human proximal renal tubular epithelial cells) were challenged by advanced glycation end-products (AGEs) for 48 hours. Cells were harvested for RT-PCR. Diabetic mice (*db/db*) and their control counterparts (*db/+*) were gavaged with atorvastatin (10 mg/kg/day for 2 months). Urine was collected by metabolic cages. At sacrifice, kidneys were harvested for Periodic Acid-Schiff staining, Masson's trichrome staining, and immunostaining. Expression of target proteins and genes were analyzed by Western blot and RT-PCR.

Results: In the present study, we found that the elevated expression of Yap/Taz target genes (CTGF and CYR61), COL1A1 and FN in HK2 cells after exposure to AGEs for 48 hours. Besides, the expression of Yap increased in the kidney of *db/db* mice. By contrast, oral treatment of *db/db* mice with atorvastatin (10 mg/kg/daily), a lipid-lowering drug with newly identified YAP inhibitory property, ameliorated albuminuria, glomerular hypertrophy, and renal fibrosis in diabetes. Atorvastatin suppressed the activity of YAP and TAZ as well as the expression of collagen 1, fibronectin, α-SMA and vimentin in the kidney of *db/db* mice.

Conclusions: In summary, atorvastatin is effective in ameliorating renal fibrosis probably in part through suppressing the activity of Yap in type 2 diabetic mice.

Funding: Government Support - Non-U.S.

TH-PO895

The GPR120 Agonist TUG-891 Ameliorates Fibrosis in Diabetic Nephropathy

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Background: GPR120/FFAR4 is a member of the G protein-coupled receptors that is activated by Omega-3 fatty acids. Recent studies demonstrate that GPR120 inhibits inflammation, regulates lipid and glucose metabolism, which mediates potent insulin sensitizing and anti-diabetic effects. TUG-891 is an a potent and selective agonist for GPR120. In this study, we examined the protective effects of GPR120 agonist TUG-891 in diabetic nephropathy (DN) and investigated the possible mechanisms.

Methods: The expression of GPR120 was detected in human renal biopsy tissue obtained from 18 patients with early or advanced DN and in normal renal tissues from patients with renal-cell carcinoma. Effects of TUG-891 on development of DN was investigated in male C57BLKS/J db/db mice and podocytes. TUG891 was administered by oral gavage at 35 mg/kg body weight once every 24 h in db/db mice for 4 weeks. Murine podocytes (MPC5) were cultured in high glucose (30mmol/L) and with TUG-891 (10umol/L). Collagen type 4, fibronectin, αSMA and TGF-β/smad2/3 were examined in vivo and in vitro. Furthermore, GPR120/β-arrestin2/TAK1 binding protein-1 pathway was measured.

Results: Decrease levels of GPR120 were detected in renal tissues from patients with DN. The intensity of GPR120 staining was negatively correlated with the progression of the disease. In db/db mice, administration of GPR120 agonist, TUG-891, attenuated urinary albumin excretion and delay the extent of glomerulosclerosis and tubulointerstitial fibrosis. Renal fibronectin, collagen type 4 and TGF-β/smad2/3 expressions were reduced by TUG-891. Nevertheless, GPR120 and β-arrestin2 expression were increased after TUG-891 treatment. The coexpression of GPR120 and nephrin were detected in kidney. In high-glucose-treated murine podocytes (MPC5), TUG-891 decreased the subsequent expression of collagen type 4, fibronectin, αSMA and TGF-β/smad2/3. It upregulated expression of GPR120 and β-arrestin2, suppressed the downstream TAK1/IKK/JNK/NF-κB signaling pathway of TAK1 binding protein-1, thus restored podocytes dysfunction.

Conclusions: Our results show that TUG-891 ameliorates kidney fibrosis and podocyte injury by activating the intracellular GPR120/β-arrestin2/TAK1 binding protein-1 pathway, which suggests its efficacy for treating type 2 diabetes associated DN.

Funding: Government Support - Non-U.S.

TH-PO896

Angptl4 Is a Critical Mesenchymal Inducer That Contributes to Renal Fibrosis

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Background: Kidney fibrosis is characterized by excess deposition of extracellular matrix leading to renal function deterioration and kidney injury. Several angiopoietin-like proteins (ANGPTLs) regulate lipid metabolism in the kidneys. However, the role of angiopoietin-like 4 (ANGPTL4) protein has not been explored yet. We hypothesized that loss of ANGPTL4 would be protective against renal fibrosis.

Methods: Two mouse models were used to recapitulate renal fibrosis. In one model, a single dose of streptozotocin (STZ) was used to induce diabetes and diabetic nephropathy in global Angptl4 knockout mice (ANGPTL4 KO) and wild-type littermates; mice were monitored for 4 months post-STZ. In the second model, the surgical procedure of unilateral ureteral obstruction (UUO) was used to induce renal fibrosis in 10-week old global ANGPTL4 KO mice and wild-type littermates. Interstitial fibrosis was analyzed by histological analysis of Trichrome, Sirius red and Periodic-Acid–Schiff staining in the kidneys. Immunofluorescent staining of kidney tissue for mesenchymal markers was also performed. Blood glucose, kidney weight, and severity of proteinuria as measured by albumin-to-creatinine ratios were measured in animals subjected to both models. One way Anova with Tukey's post-test was performed for the analysis of statistical significance.

Results: At the time of sacrifice, diabetic global ANGPTL4 KO mice did not shown any significant difference in blood glucose compared to controls. However, kidney weight (-14.5%), collagen deposition (-55.4%), and albumin-to-creatinine ratios (-59.2%) were significantly lower in global ANGPTL4 KO mice when compared to wild-type controls (n=6/gentoype; $p<0.05$). Similarly, in the UUO model, we observed that the UUO-operated kidneys of global ANGPTL4 KO mice showed less collagen deposition (-48.9%) and interstitial fibrosis (-45.2%) when compared to those of the controls (n=7/genotype, $p<0.05$). Immunofluorescence analysis of kidney tissue from both genotypes revealed suppression of fibronectin and collagen-1 deposition in global ANGPTL4 KO mice compared to controls, in both models, suggesting suppression of mesenchymal activation.

Conclusions: We conclude that ANGPTL4-associated mesenchymal activation is critical for disruption of kidney homeostasis and contributes to renal fibrosis.

TH-PO897

Proteasomal Activation and the p38 and ERK Pathways Promote Loss of NF-E2 Expression and Induction of Pro-Fibrotic Signaling in TGF-b Treated Tubule Cells

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Background: TGF-β is a critical mediator of diabetes-induced renal fibrosis. Preliminary studies found TGF-β (10 ng/ml; 24 h) treatment of human renal proximal tubule (HK-11) cells decreased Nuclear Factor-Erythroid derived 2 (NF-E2) protein

expression and increased pro-fibrotic signaling in the kidney. Current studies identified signaling mechanisms by which TGF-β/diabetes regulates NF-E2 expression and renal fibrosis which may lead to generation of new therapies.

Methods: HK-11 cells were treated with 10 ng/ml of TGF-b for 24 h or pre-treated with p38 and MEK/ERK MAPK inhibitors namely, (0.3 μM) SB203580 and (25 μM) PD98059, or proteasome inhibitor MG132 (0.125 μM, 0.25 μM, 0.5 μM and 1 μM), for an hour prior to treatment with TGF-b. Cell lysates were immunoblotted with appropriate antibodies. HK-11 cells were transfected with pUSe vector/pUse-NF-E2 or with control siRNA or NF-E2 siRNA for 24 h followed by treatment with vehicle/TGF-b for additional 24 h. Cell lysates were immunoblotted with appropriate antibodies. Kidney homogenates from STZ-type 1 diabetic mice, OVE26 type 1 diabetic mice treated with vehicle/MG132, and db/db type 2 diabetic mice, were immunoblotted with appropriate antibodies.

Results: NF-E2 expression was decreased in kidney homogenates from STZ, OVE26, and db/db mice. Moreover, TGF-β (10 ng/ml; 24 h) treatment of human renal proximal tubule (HK-11) cells decreased NF-E2 expression and increased p38 and ERK activation and expression of pro-fibrotic proteins including, CTGF, FN and PAI-1. Over-expression of NF-E2 inhibited CTGF, FN, and PAI-1 expression in TGF-b treated HK-11 cells. Silencing NF-E2 expression induced CTGF expression. TGF-β treatment did not have any effect on NF-E2 transcription or on miRNA-361-5p in HK-11 cells. However, blockade of proteasome, in HK-11 cells and OVE26 mice preserved NF-E2 expression and inhibited pro-fibrotic signaling. Moreover, dual blockade of p38 and MEK/ERK prevented NF-E2 degradation and pro-fibrotic signaling.

Conclusions: Blocakade of p38 and MEK/ERK pathways and proteasomal activation during diabetes and TGF-b treatment of HK-11 cells prevents NF-E2 degradation and attenuates pro-fibrotic signaling in kidney cells.

TH-PO898

Activated Alpha 2-Macroglobulin (α2M*) Mediates High Glucose-Induced Cell Surface GRP78 Activation and Profibrotic Responses in Mesangial Cells

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Background: Diabetic nephropathy is the leading cause of kidney failure in developed countries, characterized by glomerular accumulation of extracellular matrix proteins. High glucose (HG) induction of glomerular mesangial cell (MC) profibrotic responses plays a central role in its pathogenesis. We recently showed that the endoplasmic reticulum resident protein GRP78 translocates to the cell surface in response to HG to mediate Akt activation and profibrotic responses in MC. We also identified mesangial cell surface GRP78 (csGRP78) *in vivo* in diabetic mice. How csGRP78 is activated by HG, however, is unknown. The general protease inhibitor α2M, upon binding and activation by a protease, is known to interact with csGRP78 in cancer cells to elicit prosurvival signaling. Importantly, α2M was shown to be increased in diabetic patients' serum and saliva. We thus investigated its role in HG profibrotic responses in MC.

Methods: Primary rat and mouse MC were treated with HG (30mM) or the osmotic control mannitol and responses assessed using standard molecular biology techniques. Kidneys from type 1 diabetic Akita mice were stained for α2M and the activated α2M*.

Results: HG, but not mannitol, increased α2M mRNA and protein expression as well as media secretion by 24h. Significantly more α2M* was also seen in media after HG treatment. By immunohistochemistry, both native α2M and activated α2M* were increased in glomeruli and tubules of type 1 diabetic Akita kidneys, with expression increasing to 40 weeks of age. By immunofluorescence, glomerular α2M* was localized to the mesangium, identified by α8 integrin positivity. Knockdown of α2M prevented HG-induced Akt activation and upregulation of the matrix proteins collagen IV and fibronectin. Neutralization of α2M* using an antibody specific for the activated form prevented HG-induced matrix protein upregulation.

Conclusions: Production and activation of α2M is increased by HG in MC and in diabetic kidneys, and mediates HG-induced matrix upregulation. Future studies will determine whether inhibiting α2M* interaction with csGRP78 is an effective therapeutic target for the treatment of diabetic nephropathy.

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TH-PO899

Ketogenic Diet as a Protective Tool Against Progression to Diabetic Nephropathy in db/db Mice

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Background: The prevalence of diabetic nephropathy (DN) is increasing rapidly worldwide. A recent research reported that a ketogenic diet (KD) may reverse pathological processes, but the mechanism is uncertain. The purpose of this study was to investigate the efficacy and mechanism of KD against progression of DN in db/db mice.

Methods: *In vivo* experiment, 5-week-old C57 BLKS/J lar-Lepr^{db}/Lepr^{db} mice (n=27) were divided into the three groups as follows: normal chow diet group (n=7), high fat diet group (n=9), and KD group (n=11). We measured the random glucose until ≥ 250 mg/dL until 7 weeks, and fasting glucose and body weight weekly after that. At 12 weeks, we analyzed urine albumin to creatinine ratio after collecting urine during 24 hours. At 16 weeks, we measured energy expenditure of mice using metabolic cage. We sacrificed mice at 18 weeks, and checked histological change, reactive oxygen species (ROS), and autophagy analysis. *In vitro* experiment, we evaluated ROS production in HK-2 cells, which are renal proximal tubule cells, with low and high glucose media with 3-beta hydroxybutyrate at 24 hours. We also analyzed autophagic flux activation in HK-2 cells for the evaluation of mechanism.

Results: Body weights were significantly lower in the KD group compared with other groups, but there was no significant difference in the fasting blood glucose level among three groups. Urinary albumin/creatinine ratio was significantly lower in the KD group compared with other groups. Serum BUN and creatinine were significantly lower in the KD group compared with other groups. Histology and quantitative analysis showed KD delayed the progression in view of less thickened glomerular basement membrane and smaller mesangial area. KD showed an antioxidant effect in DCF-DA+DAPI staining and ROS level, and increased autophagy via the change of p62, Nrf2, and LC3 expressions *in vivo* study. *In vitro* mechanistic study showed 3-beta hydroxybutyrate inhibited oxidative stress by decreased ROS level, and stimulated autophagy by increasing LC3 and Nrf2 in HK-2 cells. Finally, we validated the effect of KD by *in vivo* and *in vitro* studies.

Conclusions: This study showed that ketogenic diet might delay the progression of diabetic nephropathy by augmentation of autophagy and inhibition of oxidative stress and inflammation through *in vivo* and *in vitro* studies.

TH-PO900

QiDiTangShen Granules Activated Renal Autophagy by Regulating Nutrient-Sensing Signal Pathways in db/db Mice

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Background: Proteinuria is an independent risk factor for diabetic nephropathy (DN). QiDiTangShen granules(QDTS) have been proven to reduce the proteinuria in patients with DN effectively. The present study was aimed at investigating the renoprotective mechanism of QDTS granules.

Methods: Firstly, main components of QDTS were identified by ultra-high liquid chromatography-tandem mass spectrometry and pharmacological databases, among which active components were screened by oral bioavailability and drug-likeness. The role on autophagy-related nutrient-sensing signal molecules was retrieved and analyzed through the Pubmed database. Secondly, C57BL/6J mice as normal control, db/db mice were randomly divided into three groups (model control, Valsartan and QDTS), and given intragastric administration for 12 weeks. Effectiveness and safety indicators, such as fasting and random blood glucose, urinary albumin excretion (UAE) and injury markers of liver and kidney were tested by glucose oxidase and radioimmunoassay, enzyme-linked immunosorbent assay and biochemical methods, respectively. Renal histological changes were evaluated by H&E, methenamine silver and Masson's trichrome staining. The quality and quantity of mitochondria and autophagic vesicles was observed by transmission electron microscope. Expressions of proteins related to nutrient-sensing signals and autophagy were assessed by western blot and immunofluorescence.

Results: 13 active components were screened from 78 components identified. Over half the components had already been reported to improve nutrient–sensing signals (AMPK, SIRT1 and mTOR). Compared with the model group, QDTS reduced UAE independent of blood glucose control, ameliorated renal mesangial hyperplasia and deposition of collagen fiber, improved the quality of mitochondria and the quantity of autophagic vesicles of renal tubular cells in db/db mice. The expression of Atg14, Beclin1and LC3-II were up-regulated, autophagic substrate transporter p62 was down-regulated in QDTS group. The expression of SIRT1, the proportion of both p-AMPK (thr172) / AMPK (total) and p-mTOR (ser2448) / mTOR (total) were also regulated by QDTS.

Conclusions: QDTS granules may regulate the nutrient-sensing signaling pathways to improve the renal autophagic activity and exert renoprotective effect.

Funding: Government Support - Non-U.S.

TH-PO901

Comparison Study of Calorie-Matched High-Fat and High-Sugar Diets on Renal Injury with Lysosomal Dysfunction in Pre-Diabetic Mice

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Background: High fat and high sugar intakes are risk factors for diabetic nephropathy. However, no comparison study with calorie matched high fat and high sugar diets has been performed. In the present study, a high fat low carbohydrate (HFLC) diet and a normal fat high sugar (NFHS) diet, calorie/weight matched to the AIN93M standard rodent diet, were given to low dose streptozotocin (STZ) injected mice. Equal amounts of feed were given to determine whether HFLC or NFHS induce renal injury in the pre-diabetic stage.

Methods: CD1 male mice were randomly allocated to three pair-feeding groups from 7 to 20 weeks of age. The energy of all diets was 380 kilocalorie/100g. CONT: AIN93M diet with 10% (wt/wt) sucrose, 46.6% cornstarch, 15.5% alpha-cornstarch, 4% soybean oil; HFLC: diet with 31.1% alpha-cornstarch, 22% lard; NFHS: diet with 40.9% sucrose,

15.6% cornstarch, 15.5% alpha-cornstarch, 4% soybean oil. All other dietary ingredients were the same between diets. STZ (100mg/kg body wt) was injected at 17 and 18 weeks of age. Fasting blood glucose (FBG) was measured before and after STZ injection. After termination, kidneys were obtained for histology.

Results: Terminal body weight, total intake of food and energy, and serum creatinine level were not different between all groups. FBG was higher in HFLC but not in NFHS compared with CONT mice both before (at 17 weeks of age) and after STZ injection (at 20weeks of age). In kidney, the number of LAMP1 (lysosome-associated membrane protein 1)-positive vacuoles was significantly higher in HFLC compared with CONT and NFHS mice.

Conclusions: The present results suggest that the high fat diet, but not the high sugar diet, induces renal injury with impaired lysosome-mediated autophagic degradation, when total energy intake is identical in pre-diabetic mice.

Funding: Government Support - Non-U.S.

TH-PO902

Targeting the Gut-Kidney Axis Through Dietary Modification in Diabetic Nephropathy

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Background: Dietary fibre has been associated with decreased inflammation and mortality in CKD, with short-chain fatty acids (SCFA) derived from gut microbial fermentation of fibre proposed to mediate this effect. Here we explored the impact of dietary fibre content on the development of experimental diabetic nephropathy (DN).

Methods: Diabetes was induced using streptozotocin (STZ) in wild-type (WT) B6 and GPR43-/- mice. Diabetic mice were randomized to 4 diets; resistant starch (RS), high fibre (HF), zero fibre (ZF), control diet (NF), or supplemented with oral SCFAs (acetate 150mM, proprionate 100mM, butyrate 50mM). Gut microbiota composition was assessed by 16S rRNA sequencing of faecal DNA.

Results: All STZ treated mice developed diabetes and remained similarly hyperglycaemic. HF and RS fed mice were protected from DN, with reduced albuminuria ($p<0.01$), glomerular hypertrophy ($p<0.0001$), interstitial fibrosis ($p<0.0001$) and podocyte injury ($p<0.05$) at 12 weeks compared to those on NF and ZF. Diet markedly altered gut microbial composition by weighted UniFrac, with cluster separation of diabetic mice according to diet (ANOSIM p=0.0001, R=0.93). HF and RS feeding increased relative abundance of phylum *Bacteroidetes* at the expense of *Firmicutes* and expanded the SCFA producing *Prevotella* ($p<0.001$) and *Bifidobacterium* ($p<0.001$) genera compared to controls. This change in microbial ecology correlated with a significant increase in faecal SCFAs and serum acetate. Supplementation with SCFAs in diabetic mice achieved similar degrees of protection from albuminuria and histological injury. Acetate reduced expression of pro-inflammatory cytokine (IL6, IFNγ), chemokine (CCL2, CXCL10) and fibrosis (fibronectin, TGFβ1) genes in diabetic kidneys compared to controls ($p<0.05$). Diabetic mice deficient in GPR43, a receptor for SCFAs, were unresponsive to acetate supplements with no reduction in albuminuria compared to WT diabetic mice at 12 weeks.

Conclusions: Dietary fibre protects against DN through modulation of the gut microbiota, enrichment of SCFA producing bacteria and increased SCFA production. Similar protection achieved by SCFA supplement and absence of protection in GPR43-/- mice identify SCFAs as likely mediators of this effect. Dietary interventions targeting the gut microbiota warrant further investigation as a novel reno-protective therapy in DN.

TH-PO903

Effects of Esculin Treatment on $P2X_7$ Receptor and Klotho in Experimental Diabetic Nephropathy

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Background: $P2X_7$ is a purinergic receptor which is activated under high concentrations of extracellular ATP, a common situation seen in *diabetes mellitus*, induced by the hyperglycemia. This receptor promotes calcium influx, which in large quantities activates biochemical processes culminating in programmed cell death. Constant activation of $P2X_7$ induces inflammatory responses and oxidative stress. A previous study in our Laboratory showed a correlation between $P2X_7$ and Klotho, since the latter can control phosphate metabolism. Coumarin derivates, as esculin, reduces oxidative damage seen in intestinal inflammation, arthritis and cognitive impairment related to diabetes. However, their pharmacodynamics are not yet fully understood. Thus, we aimed to evaluate the effects of esculin treatment on $P2X_7$ receptor expression and Klotho in the kidneys of diabetic rats.

Methods: Male Wistar rats, 7 weeks old, received a single dose of streptozotocin (60 mg/kg; i.v.) for diabetes induction; control received only the drug vehicle. Diabetes was considered at blood glucose levels greater than 200 mg/dL. The animals received daily doses of esculin (50 mg/kg, p.o.), during 8 weeks, forming CTL+ESC and DM+ESC groups. 24-hours urine and a small aliquot of blood were collected for biochemical analysis and the rats were euthanized at the end of the protocol. The kidneys were collected for Western blotting. Statistical analysis was performed in GraphPad Prism 6 and the results are described as mean ± SEM; significance for $p<0.05$.

Results: The diabetic rats presented 50% increase in $P2X_7$ protein content when compared to CTL. DM group treated with ESC had a 46% decrease in $P2X_7$. Klotho levels increased after ESC. We previously showed that Klotho, depleting phosphate, reduced $P2X_7$ and protected the rats against diabetic nephropathy. Furthermore, DM treated with ESC also presented lower proteinuria (38.72±4.82 vs 45.42±3.0) and urinary TBARS (indicative of lipoperoxidation) (232.3±28.83 vs 282.0±7.2) when compared with untreated ones.

Conclusions: Our data suggest that decreased $P2X_7$ perhaps via increasing Klotho, could be one of possible pathways for esculin to promote beneficial effects on the kidneys of diabetic animals.

Funding: Government Support - Non-U.S.

TH-PO904

The Effect of A1AR on Diabetic Megalin Loss-Associated Albuminuria by Inhibiting Caspase-1/IL18 Signaling

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Background: The mechanism of exacerbation of albuminuria observed in A1 adenosine receptor knock-out ($A1AR^{-/-}$)mice with diabetic nephropathy (DN) is unclear. Here, we investigated the relationship of megalin loss and albuminuria, to identify the effect of A1AR in the pyroptosis signaling caspase-1/IL-18 of DN.

Methods: Successfully collected diabetic nephropathy patients' samples and built streptozotocin-induced diabetes mice model. Megalin, cubilin, and A1AR expression were detected in kidney tissue samples from DN patients and mice through immunohistochemical and immunofluorescent staining. A1AR, caspase-1, Interleukin -18 (IL-18) expression were analyzed using western blotting in wild-type and $A1AR^{-/-}$ mice. Human renal proximal tubular epithelial cells (PTC) were cultured with high glucose to observe the effect of A1AR agonist and antagonist on caspase-1/IL-18 and megalin injury.

Results: The loss of megalin, co-localized with A1AR at PTC, was associated with the level of albuminuria in diabetic patients and mice. The injury of megalin-cubilin was accompanied by the A1AR upregulation and the caspase-1/IL-18 signaling activation in mice with DN. More severe pathological injury, albuminuria, and megalin-cubilin loss were observed in $A1AR^{-/-}$ DN mice with more pronounced caspase-1 and IL-18 secretion. High glucose could stimulate the secretion of caspase-1 and IL-18, which was completely abolished by A1AR agonist and further aggravated by A1AR antagonist.

Conclusions: A1AR played an important role in protecting megalin loss associated albuminuria by inhibiting the pyroptosis signaling caspase-1/IL-18 in DN.

Funding: Government Support - Non-U.S.

TH-PO905

Urinary L-FABP Reflects the Degree of Sarcopenia in a Diabetic Kidney Disease Model

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Background: Diabetic kidney disease (DKD) is a high-risk factor for onset of sarcopenia which leads to increase in all-cause mortality in patients with type 2 diabetes. Although the sarcopenia in DKD should be focused just before a super-aging society, there had not been a useful biomarker for monitoring the sarcopenia. The aim of this study is to reveal the correlation between urinary L-type fatty acids binding protein (L-FABP) known as a tubular marker and sarcopenia using novel model of DKD with sarcopenia.

Methods: Male spontaneously diabetic torii (SDT) fatty rats (n =5) were used as an animal model of type 2 diabetes with sarcopenia. Age- and sex-matched Sprague–Dawley rats (SD) (n = 7) were used as controls. Urine samples were obtained from the rats at 8, 12, 16, 20, and 24 weeks of age and muscle strength was evaluated by forelimb grip test at 12, 16, 20, and 24 weeks of age. Their kidney, and soleus and extensor digitorum longus (EDL) muscles were obtained at 24 weeks of age.

Results: Urinary L-FABP increased and muscle strength decreased along with age in the SDT rats. Renal tissue damage and accumulation of renal oxidative protein were observed at 24 weeks of age of the SDT fatty rats. Muscle weight, and cross-sectional areas of both type I and type IIb muscle fibers were significantly decreased in the SDT fatty rats compared to the SD rats. The muscle atrophy in the SDT fatty rats was induced due to decreased phosphorylation of S6K1 and increased expression of E3 ubiquitin ligases, atrogin-1 and murf-1. The levels of urinary L-FABP and the degree of renal tissue damage were significantly correlated with muscle weigh, diameter of muscle fibers and muscle strength.

Conclusions: Urinary L-FABP increased along with the progression of sarcopenia and reflected the degree of sarcopenia in DKD. In clinical practice, urinary L-FABP may be useful for monitoring the sarcopenia as well as DKD in the type 2 diabetic patients.

TH-PO906

Insulin Resistance Impacts the Host Defense Transcriptome in Kidney Intercalated Cells

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Background: Urinary tract infection (UTI) is a common problem in women. Select populations have increased UTI risk, including those with insulin resistance and diabetes. The kidney's intercalated cells (IC) play a key role in preventing UTI by regulating urine pH, releasing cytokines, secreting antimicrobial peptides (AMPS), and creating a barrier with apposing principal cells to prevent bacterial invasion. Our data show that insulin receptor (IR) deletion in murine ICs inhibits IC-insulin signaling and increases UTI risk *in vivo* while having no impact on glucose homeostasis or urine acidification. Here, we profile the transcriptome of ICs isolated from IR knockout (IRKO) mice and controls (IRflox) to identify insulin-mediated host defense mechanisms.

Methods: To delete the IR gene *Insr* in murine ICs, V-ATPase-Cre transgenic mice were bred with IR floxed mice. A tdT reporter was added to aid fluorescence-assisted cell sorting (FACS) of ICs and visualize IC-specific Cre-recombination. Limited cell RNAseq was performed on FACS-isolated ICs and read count data were analyzed for differentially expressed genes (DEG) using the R package edgeR. DEGs with fold-change >1.5 and a false discovery rate adjusted p-value < 0.05 were defined as differentially expressed. Pathway and gene ontology term enrichment analyses of DEGs were performed using the Enrichr tool and DAVID.

Results: FACS-enriched IC cells expressed IC-specific genes, like *Aqp6* and *Atp6v0d2*. Differential expression analysis revealed downregulation of 138 genes and upregulation of 232 genes in IRKO IC vs IRflox IC. A decrease in *Insr* as well as other downstream IR-regulated genes was confirmed in IRKO ICs. Functional annotation analysis identified enriched KEGG pathways including adherens junction, insulin resistance, and adipocytokine signaling. Gene ontology terms involved in innate immunity and intracellular trafficking were enriched. AMPs, including members of the defensin and ribonuclease A families, were downregulated.

Conclusions: These data suggest that IR-signaling impacts the IC host defense transcriptome and identifies IR-sensitive transcripts that may aid in pathogen defense by maintaining paracellular boundaries, regulating intracellular trafficking, and expressing AMPs. These studies may uncover new immune targets to prevent/treat diabetes-associated infections.

Funding: NIDDK Support

TH-PO907

Alk/bmp9 Signalization as a New Target of Therapy in Diabetic Nephropathy

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Background: Diabetic kidney disease one of the most frequent microvascular long-term complications in diabetic patients and is a major cause for the need of dialysis. Currently therapies in diabetic nephropathy are focusing on glycemia control and adequate arterial pressure levels in order to maintain an adequant glomerular filtration rate. However, a few of them are targeting the endothelial damage or podocyte-endothelial crosstalk, which play a critical role in diabetic kidney disease progression. We have previously shown that Alk1, along with its ligand BMP9, plays an important function to maintain vascular integrity in diabetic animals. Loss of Alk1 signaling in diabetic animals led to dissociation of vascular junctions and increased vascular leakage. Given its role in the maintenance of endothelial quiescence and integrity, we evaluated the effects of Alk1 suppression on kidney integrity and renal function in diabetic mice.

Methods: We used mice with conditional deletion of Alk1 in the endothelium (Alk1ΔEC) to evaluate the role of Alk1 in glomerular filtration in STZ-induced diabetic mice. Mice were euthanized four months after the onset of diabetes and urine and serological analyzes were performed, along with immunohistochemical studies. Healthy patients biopsies were compared with patients already diagnosed with diabetic nephropaty

Results: We demonstrated that Alk1 haploinsufficiency worsens microalbuminuria and induces podocyte loss. Alk1 haploinsufficiency also increases extracellular matrix expression at the gromerular basement membrane. Furthermore, a significant increase in glomerular apoptosis was observed in Alk1ΔEC mice. Analysis of homozygous Alk1ΔEC mice also revealed a significant loss of glomerular endothelial cells. Alk1 expression in the glomeruali was observed in patients diagnosed with diabetic nephropay compared to the healthy patients.

Conclusions: 1. Partial loss of Alk1 in type I diabetic mice leads an increase in microalbuminuria compared to WT mice. 2. Heterozygous diabetic mice have an increase in apoptosis associated with podocyte loss. 3. Partial Loss of Alk1 in Diabetic mice Induces an increase in extracellular matrix synthesis. 4. The alk1 / bmp9 signaling could be a potential target of theraphy because it plays a critical role in the maintenance of glomerular endothelial cells and has an important functions to maintain glomerular integrity through a crosstalk podocyte-endothelial mechanism.

Funding: Clinical Revenue Support

TH-PO908

Deletion or Inhibition of ARF6 Improves Albuminuria in Type 2 Diabetic Mice

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Background: Podocytes are key glomerular cells that determine the progression of diabetic kidney disease (DKD), the leading cause of renal failure in the U.S. Small GTPase proteins regulate quintessential roles that govern cellular health – too much or too little GTPase activity can render podocytes susceptible to kidney injury. ADP-ribosylation factor 6 (ARF6), is a small GTPase protein that we previously showed is present in human and mouse podocytes and involved in podocyte response to *in vivo* glomerular injury models. Since ARF6 is involved in diverse cellular events (e.g. actin remodeling or endocytic trafficking) we hypothesized that hyperglycemia might result in alterations in ARF6 activity and contribute to the progression of DKD.

Methods: To investigate the *in vivo* role of ARF6 in diabetes, we generated an inducible podocyte-specific ARF6 knockout diabetic animal model. We also explored whether pharmacological intervention of ARF6 using an ARF6 inhibitor, Nav2729 (R&D Systems), might recapitulate the observations from our aforementioned transgenic animal model.

Results: High glucose cultured podocytes expressed significantly higher Arf6 mRNA and protein levels compared to normal glucose cultured podocytes. Isolated podocytes from diabetic ($Lepr^{db/db}$) mice had increased ARF6 expression compared to control ($Lepr^{db/+}$) mice. Furthermore, podocyte-specific ARF6KO mice had decreased urine albumin to creatinine ratio (UACR). To determine whether ARF6 might serve as a molecular target for pharmacological inhibition in DKD, diabetic mice were treated with an ARF6 inhibitor (NAV2729) or vehicle (DMSO) at 8 weeks of age. NAV2729-treated diabetic mice demonstrated significant improvement in the UACR compared to diabetic mice treated with vehicle suggesting a renal-protective effect of ARF6 inhibition.

Conclusions: These results suggest that ARF6 is an important protein involved in podocyte health and DKD. Inhibition of ARF6 might serve as a molecular target to prevent podocyte injury, albuminuria, and progressive renal functional decline.

Funding: NIDDK Support, Private Foundation Support

TH-PO909

Activation of Notch Signaling in Podocytes by Growth Hormone

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Background: Growth hormone (GH) plays a significant role in normal renal function and overactive GH signaling has been implicated in nephropathy particularly in diabetes and acromegaly. Previous results have shown that podocytes, which play an essential role in kidney filtration, express the GH receptor (GHR), suggesting the direct action of GH on these cells. Activation of Notch signaling, which is crucial in early podocyte development, contributes to the glomerular disease upon maturation. In this study, we investigated whether GH activates Notch1 signaling in podocytes in γ-secretase dependent manner.

Methods: Swiss Webster male mice were infused with GH i.p (1.5mg/kg/day) for 4 weeks. Another group of mice was administered GH and DAPT (10 mg/kg/day) while control mice received PBS. Renal functional and histological studies were performed at the end of the experimental period. Simultaneously, human podocytes (HPC) were treated with GH (500ng/ml) in the absence or presence of DAPT (5μg/ml) and assessed the expression of Notch signaling and its downstream targets.

Results: Employing HPC *in vitro* and GH-injected mice model *in vivo*, we demonstrate that GH activates Notch1 signaling in a γ-secretase-dependent manner in podocytes. Pharmacological inhibition of Notch1 by a γ-secretase inhibitor (DAPT) abrogated GH-induced epithelial to mesenchymal transition (EMT) and associated podocyte injury. Importantly, our results show that DAPT treatment blocked the GH-induced cytokine release and attenuated glomerulosclerosis. Further, DAPT prevented glomerular basement membrane thickening as well as proteinuria induced by GH. Kidney biopsy sections from diabetic nephropathy patients reveal activation of Notch signaling in podocytes.

Conclusions: GH induces Notch1 signaling in podocytes, which may contribute to proteinuria through podocyte EMT as well as renal fibrosis. Blocking Notch activation with γ-secretase inhibitors ameliorates glomerular injury and proteinuria in conditions of GH-associated nephropathy.

Funding: Government Support - Non-U.S.

TH-PO910

Empagliflozin as an Add-On to Linagliptin Ameliorates Renal Interstitial Fibrosis in Spontaneously Diabetic Torii Fatty Rats

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Background: Recent clinical trials have shown that SGLT2 inhibitor significantly attenuates the rapid decline in eGFR and enhances blood pressure control. Further, DPP4-inhibitor has become the first-line therapy of blood glucose control in patients with diabetic kidney disease (DKD). However, whether dual therapy could prevent the development and progression of DKD are yet to be elucidated. Therefore, we investigated the effects of

empagliflozin as an add-on to linagliptin or vice versa on diabetes-induced renal injury in SDT fatty rats, a type 2 diabetic model of DKD.

Methods: Eight-week-old SDT fatty rats were divided into 5 groups, 1) SDT fatty rats untreated (SDT), 2) SDT fatty rats given 30 mg/kg of empagliflozin for 12 weeks (EMPA), 3) SDT fatty rats given 3 mg/kg of linagliptin for 12 weeks (LINA), 4) SDT fatty rats given empagliflozin for 6 weeks in addition with linagliptin for 6 weeks (EMPA–EMPA+LINA), and 5) SDT fatty rats given linagliptin for 6 weeks in addition with empagliflozin for 6 weeks (LINA–LINA+EMPA). All experimental groups were given water supplemented with 0.5% salt. All animals (20 weeks of age) were euthanized and parameters such as urine and blood chemistry, blood pressure (BP), renal pathology, and GFR were measured.

Results: At 14 weeks of age, SDT exhibited hypertension, which was not ameliorated in EMPA and LINA groups. However, at 20 weeks of age, BP decreased in all treated groups. Treatment with empagliflozin showed glycosuria and increased urinary sodium excretion. SDT showed albuminuria and glomerulosclerosis, which were not ameliorated in all the treated groups. Compared with SD, GFR was significantly higher in SDT, suggesting hyperfiltration, and it further increased in LINA. SDT manifested dramatically increased urinary L-type fatty acid binding protein levels, which were attenuated in LINA–LINA+EMPA (p=0.069 vs SDT). Besides, renal interstitial fibrosis was ameliorated in EMPA, EMPA–EMPA+LINA, and further reduced in LINA–LINA+EMPA, as evidenced by the Masson trichrome staining. Diabetes-associated interstitial TGF-b expression was inhibited only in LINA–LINA+EMPA (p<0.05 vs SDT).

Conclusions: Empagliflozin as an add-on to linagliptin might be a better therapy for diabetes-induced renal fibrosis than linagliptin as an add-on to empagliflozin and each drug.

TH-PO911

Stakeholder Perspectives on Implementing Precision Medicine in Diabetic Kidney Disease

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Background: One of the important aims of the Innovative Medicine Initiative BEAt-DKD consortium is to promote implementation of Precision Medicine (PM) in treating diabetic kidney disease (DKD). Engaging stakeholders is crucial in this process. We held a consensus workshop and conducted a survey of diabetes stakeholders to identify benefits and obstacles of PM, and to strategize solutions.

Methods: Sevently-one participants from 26 countries met in Amsterdam, the Netherlands over 2 days to develop a strategy to move PM forward in DKD. Represented stakeholder groups included patients with diabetes and advocates (n=11), academia (n=18), drug regulators (n=7), health technology assessors (HTAs)(n=6), industry (n=11), and health care providers (HCPs)(n=18). A survey was developed and pilot tested prior to implementation. Respondents were asked about their opinions on needs, benefits, and obstacles for introducing PM in DKD. A consensus discussion was held to strategize solutions.

Results: Stakeholders were mostly positive for PM in DKD (Figure). HTAs least agreed, while HCPs most agreed. Obstacles and concerns for PM included data safety, time contraints, and increased burden for assessments. Keys to successful implementation of PM would be increased engagement with patients, specific training for HCPs in PM, and early collaboration between stakeholders. All stakeholders responded that quality of life outcomes would be important to assess the impact of PM.

Conclusions: Diabetes stakeholders view PM in DKD positively. Implementing PM is complex as different stakeholders have different priorities. The consensus of all stakeholders was that early engagement and aligning stakeholders goals are critical to implement PM in DKD.

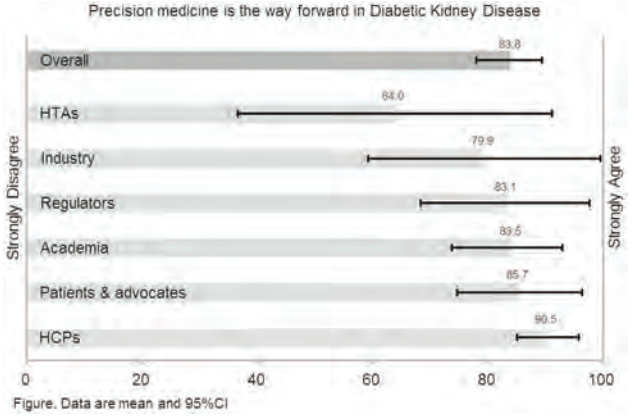

Figure. Data are mean and 95%CI

TH-PO912

Urinary Complement-Enriched Inflammatory Proteome of an Overt Progressive Diabetic Kidney Disease

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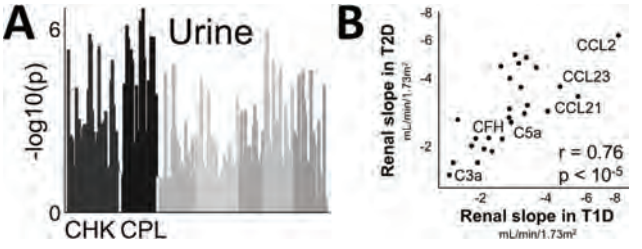
Background: We aimed to advance our knowledge of the role of the local kidney inflammation in the progressive diabetic kidney disease (DKD) reflected by the urinary profiles of the inflammatory proteome.

Methods: We conducted a nested case-control study comprising a discovery panel of Joslin subjects with T1D and a validation panel of Joslin subjects with T2D (total n=112). All study subjects had an overt DKD at baseline (CKD stage 3-4 and albuminuria (median GFR: 46 mL/min/1.73m^2; median ACR: 653). Subjects experiencing renal function loss of eGFR > 40% within 5 years were defined as progressive DKD cases. 194 inflammatory proteins were measured in baseline urine samples using aptamer proteomics (SOMAscan).

Results: In the multivariate screen we identified a urinary proteomic profile consistently associated with progressive DKD in T1D and T2D. Complement proteins (CPL) accounted for almost half of our profile (twelve out of 26 (46%); enrichment: p<0.001). Chemokines (CHK) comprised the second-most abundant group of our profile (enrichment: p=ns; Fig. A - needle plot). In the adjusted mediation model (ACR - intermediate phenotype), all 26 proteins were associated with the renal slope. The protein effects were mainly independent from albuminuria (median proportion mediated (PM): 25%). One unit change in these proteins resulted in renal function loss between 1.5-7.3 mL/min/1.73m^2/yr. These proten effects markedly correlated between the T1D and T2D panels (p <10^{-5}; Fig. B - β estimates).

Conclusions: We have identified a significant urinary profile of the inflammatory proteome strongly associated with progressive DKD in subjects with an overt disease in both types of diabetes. Our data suggest that the complement system and chemokines seem to be important players of the disease process. Larger studies including subjects with early DKD are needed to evaluate the dynamic of these processes across DKD stages.

Funding: Private Foundation Support



TH-PO913

Proteomic Study of Circulating Proteins to Identify Novel Surrogate Markers for Progressive Renal Decline

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Background: Clinical trials of renoprotection in diabetic nephropathy have been limited to high-risk patients with impaired renal function due to low incidence of clinical and traditional surrogate end-points. End-points based on serum creatinine may be affected by its high variation, especially in patients with normal renal function. No efficient trial design exists to test early interventions in moderate-risk patients with eGFR > 60 ml/min.

Methods: We followed 196 patients (44% female) with type 1 diabetes from Joslin Proteinuria Cohort (median albumin/creatinine ratio 852 mg/g) with normal baseline renal function (median eGFR 100 ml/min). During median 10 years of follow-up there were 110 cases of end-stage renal disease (ESRD) and 15 deaths. We quantified 455 proteins in baseline plasma samples using OLINK (Uppsala, Sweden) Proximity Extension Assay. In 110 patients we measured these proteins in a second sample collected after median 4 years of follow-up. Annualized proteins' increments (DELTAs) were tested as surrogate of ESRD using Cox regression models.

Results: In regression models adjusted for the change in eGFR the DELTAs of 13 proteins were significantly (Bonferroni-corrected) associated with time to ESRD. Also, their baseline concentrations were associated with time to ESRD independently from baseline eGFR (see Table). Prediction of time to ESRD was much more accurate with DELTAs of these proteins than with the change in eGFR (for example C-statistic for LAYN was 0.85 versus 0.78 for eGFR).

Conclusions: Serial measurements of circulating protein markers during a short follow-up are more accurate in ESRD prediction than measurements of creatinine-based eGFR. Surrogate outcomes derived from these candidate proteins may help designing efficient clinical trials. Replication of the findings in independent cohorts is under way.

Funding: NIDDK Support, Private Foundation Support

Protein	Function	Association of DELTAs with ESRD Hazard ratio	P	Association of baseline with ESRD Hazard ratio	P
FSTL3	fibrosis	1.90	3.05×10^{-6}	1.92	3.52×10^{-2}
EPHB6	axon guidance pathway	1.86	5.42×10^{-6}	1.76	3.74×10^{-2}
TNFRSF12A	TNF receptor superfamily	2.12	7.06×10^{-6}	1.70	7.00×10^{-3}
IGF1R	growth factor	2.08	1.29×10^{-5}	1.53	2.34×10^{-2}
LAYN	inflammation	2.12	3.36×10^{-5}	1.69	4.47×10^{-4}
DKK4	Wnt pathway	1.38	3.36×10^{-5}	1.39	1.62×10^{-2}
TNFRSF19	TNF receptor superfamily	2.93	4.62×10^{-5}	1.41	1.73×10^{-2}
PRSS8	serine protease	2.88	5.49×10^{-5}	1.96	7.48×10^{-4}
TNFRSF7	TNF receptor superfamily	2.87	6.06×10^{-5}	1.75	2.70×10^{-4}
VEGFA	growth factor	2.23	6.52×10^{-5}	1.70	1.34×10^{-4}
TNFRSF10A	TNF receptor superfamily	2.70	8.08×10^{-5}	1.66	5.17×10^{-3}
ACAN	fibrosis	2.14	9.12×10^{-5}	2.08	4.36×10^{-3}
TNFRSF11A	TNF receptor superfamily	1.68	9.50×10^{-5}	1.5	3.96×10^{-2}

Candidate surrogate outcome proteins, adjusted for baseline eGFR and DELTA of eGFR

TH-PO914

Multi-Omics Data Integration Identifies Molecular Pathways Associated with Renal Response to Atrasentan

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Background: The endothelin-1 receptor antagonist atrasentan lowers urinary albumin:creatinine ratio (UACR) and reduces renal risk in patients with type 2 diabetes and chronic kidney disease (CKD). This effect markedly varies among patients. Aim of this study was to identify molecular pathways and biomarkers predicting the renoprotective effect of atrasentan.

Methods: In vivo and in vitro transcriptomics profiling was performed in kidney tissue from atrasentan treated BTBR ob/ob mice and human mesangial cell cultures respectively. A transcriptomic dataset from human diabetic kidney biopsies was used for cross-validation. Critically, microRNA, proteomics, and metabolomics profiles were generated in plasma and urine samples of a phase 2 trial (RADAR) in patients with type 2 diabetes and CKD treated for 12 weeks with atrasentan. Logistic regression analysis was performed to identify features associated with atrasentan response (UACR reduction ≥30%, n=42) versus non-response (UACR reduction <10%, n=8). Omics features were subjected to pathway analysis to identify patterns of UACR response to atrasentan across model systems and human disease.

Results: Clinical characteristics between responders and non-responders were similar. More than 1000 genes that were dysregulated in DKD mouse tissue were significantly reversed after atrasentan treatment and 513 genes in mesangial cells significantly changed after atrasentan treatment. Four miRNAs, 68 metabolites, and 210 proteins measured before atrasentan exposure in human samples predicted UACR response to atrasentan ($p<0.1$). Multi-omics integration revealed Sirtuin and ephrin signaling, NRF2-mediated oxidative stress response among the top ranked pathways associated with atrasentan response. A biomarker panel of 5 urinary proteins (including SOD1, CXCL10, PDGF) reflecting the identified pathways predicted UACR response to atrasentan with an area under the ROC curve of 0.82

Conclusions: We implemented a multi-omics data integration approach to derive molecular pathways associated with UACR response to atrasentan. The marker panel predicting atrasentan response in humans reflects a non-invasive surrogate of molecular pathways activated in human DKD and CKD, linking individual atrasentan response to known and novel CKD progression pathways.

Funding: Commercial Support - Abbvie, Bayer, Sanofi, Government Support - Non-U.S.

TH-PO915

Magnetic Resonance Imaging Biomarkers Independently Predict GFR and Urine Albumin Creatinine Ratio

Lars Johansson,[1] Paul Hockings,[1] Kianoush Makvandi,[2] Gert Jensen,[2] Tim Unnerstall,[2] Henrik Leonhardt,[2] Lisa Jarl,[1] Camilla Englund,[1] Fredrik Erlandsson,[3] Anna K. Sundgren,[3] Johannes Hulthe,[1] Seema Baid-Agrawal.[2] *[1]Antaros Medical AB, Molndal, Sweden; [2]Sahlgrenska University Hospital, Göteborg, Sweden; [3]AstraZeneca, Gaithersburg, MD.*

Background: Estimated GFR (eGFR) and urine albumin/creatinine ratio (UACR) are the standard methods for assessing glomerular damage and renal function changes in clinical practice, Within-person variations are large in people with diabetes due to the complex nature of diabetic kidney disease (DKD). New non-invasive markers are needed to increase understanding of disease pathogenesis. We recently showed that magnetic resonance imaging (MRI) markers correlated strongly to both measured GFR (mGFR) and UACR. Here we seek to determine which MRI markers are independent predictors of mGFR and UACR.

Methods: ***Subjects*:** The study included 2 CKD2, 16 CKD3, and 20 CKD4 subjects with DKD, 18-79 years old, and 20 age- and gender-matched healthy controls. GFR was measured using iohexol clearance. UACR was assessed in the first morning sample. ***MRI techniques*:** - Renal hemodynamics with mean arterial flow (ml/s) - Renal microstructure, such as fibrosis and cellular infiltration, by measurement of Apparent Diffusion Coefficient (ADC) (mm^2s^{-1} x 10^{-3}) and R_1 (s^{-1}) - Renal oxygenation by measurement of BOLD R_2* (s^{-1}) - Renal macrostructure by kidney volume assessment (ml) ***Statistics*:** We performed multiple regression analyses in the control group and the CKD group separately: 1) with UACR, mean arterial flow, R_1 cortex, R_2* cortex, ADC cortex, and kidney volume as independent variables, and mGFR as the dependant variable; and 2) with mGFR, mean arterial flow, R_1 cortex, R_2* cortex, ADC cortex, and kidney volume as independent variables, and UACR as the dependent variable.

Results: The only independent predictors of mGFR in the CKD group were mean arterial flow ($p < 0.0001$) and kidney volume ($p = 0.03$), with none in the control group. The only independent predictors of UACR were cortical R_1 in the CKD group ($p = 0.005$) and kidney volume in the control group ($p = 0.01$).

Conclusions: It is well known that GFR is strongly linked to renal blood flow and therefore not surprising to see mean arterial flow emerge as an independent predictor of mGFR. The strong link between cortical R_1 and UACR indicates that cortical R_1, a measure of cellular infiltration in the cortex where the filtration barrier exists, may be a novel biomarker of kidney damage and warrants further investigation.

Funding: Commercial Support - Antaros Medical; AstraZeneca

TH-PO916

Assessment of MRI Filtration Fraction in Healthy Subjects and Patients with Diabetic Kidney Disease

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Background: Filtration fraction (FF) is the ratio of the glomerular filtration rate (GFR) to renal plasma flow (RPF) and therefore an important marker of glomerular health. FF is not normally measured, as estimation of RPF requires constant infusion of para-aminohippurate over 8 h (1). Therefore, quicker, simpler assays of FF are needed. We assessed a novel magnetic resonance imaging (MRI) technique to measure FF in patients with diabetic kidney disease (DKD). MRI was previously used to measure FF in kidney donors (2,3).

Methods: The study included 2 CKD2, 16 CKD3, and 20 CKD4 patients with DKD, 18-79 years old, eGFR between 15-60 ml/min/1.73 m^2 and 20 age-, gender-matched healthy controls. GFR was measured using iohexol clearance (mGFR). Renal blood flow (RBF) (ml/min) was measured by phase contrast MRI. The phase contrast MRI scan is a 5 minutes add-on to an MRI examination. MRI FF = (mGFR x BSA)/(RBF x 1.73) RBF was corrected for Body Surface Area (BSA) to use the same units as GFR. EVF (hematocrit) was not available and therefore RPF was not calculated.

Results: MRI FF % (Mean (SD)) was 8.28 (1.00)% for Healthy Controls; 6.57 (2.62) % for CKD2; 6.30 (0.93)% for CKD3; and 5.15 (1.36)% for CKD4. We tested for significant differences between groups (p 0.05) using Bonferroni/Dunn multiple testing correction. p-values less than 0.008 were significant. Differences in FF in controls vs both CKD3 and CKD4 ($p < 0.0001$), and CKD3 vs CKD4 (p 0.005) were significant.

Conclusions: Standard deviations in the CKD 2 group were relatively large as there were only 2 subjects in this group. All MRI FF comparisons between control subjects, CKD3 subjects and CKD4 subjects were statistically significant. This MRI FF measurement can be further improved by correcting RBF for extracellular volume in order to calculate RPF. **References** 1) Costanzo L (2007) Physiology. Lippincott Williams and Wilkins, Philadelphia; 2) Eikefjord, et al AJR (2016) 207, 1022-1030; 3) Cutajar, et al. Eur Radiol (2015) 25: 2390.

Funding: Commercial Support - Antaros Medical; AstraZeneca

TH-PO917

Prediction of Rapid Kidney Function Decline in Type 2 Diabetes Using Machine Learning Combining Blood Biomarkers and Electronic Health Record Data

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Background: Individuals with type 2 diabetes (T2DM) are at increased risk of rapid kidney function decline (RKFD). The application of machine learning to integrate biomarkers with EHR data may lead to improved prediction of RKFD.

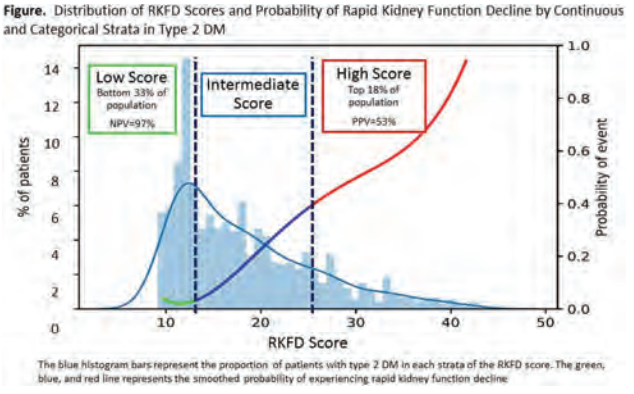
Methods: We selected individuals with T2DM with a baseline eGFR ≥45 and <90 ml/min/1.73 m^2 from the Mount Sinai Bio*Me* Biobank (n=871). We measured plasma levels of tumor necrosis factor (TNFR)1 & 2, and kidney injury molecule(KIM)-1 and employed

random forest (RF) models to combine the biomarkers with longitudinal clinical features extracted from the electronic health record (EHR) to predict RKFD (eGFR decline of ≥5 ml/min/1.73 m^2/year).

Results: In 871 participants, baseline eGFR was 74 ml/min/1.73 m^2, and median UACR was 13 mg/g. Overall, 164 (19%) of individuals experienced RKFD over a median follow-up of 4.7 years from the baseline specimen collection. In the training and test sets respectively, the combined RF model (clinical features plus biomarkers) had an AUC of 0.82 (95% CI, 0.81-0.83) and 0.80 (95% CI, 0.78-0.82), which outperformed a standard clinical model via logistic regression (AUC 0.64, 95% CI 0.63-0.65), a biomarker model alone (AUC 0.76, 95% CI 0.72-0.79), and RF model using clinical features alone (AUC 0.74, 95% CI 0.73-0.76). The RKFD score stratified 18%, 49%, and 33% of patients in the entire cohort to high, intermediate, and low-probability strata, respectively, with a PPV of 53% in the high-probability group and an NPV of 97% in the low-probability group (**Figure**).

Conclusions: In patients with type 2 DM, a RF model combining plasma biomarkers and longitudinal EHR data significantly improved prediction of RFKD over standard clinical or biomarker-only models. Further validation of such approaches is needed.

Funding: NIDDK Support, Commercial Support - RenalytixAI



Distribution of RKFD Scores and Probability of Rapid Kidney Function Decline by Continuous and Categorical Strata

TH-PO918

Determinants of Urinary C-Megalin Among a Large Diabetes Cohort: Albuminuria, Reduced Kidney Function, and Demographic Factors

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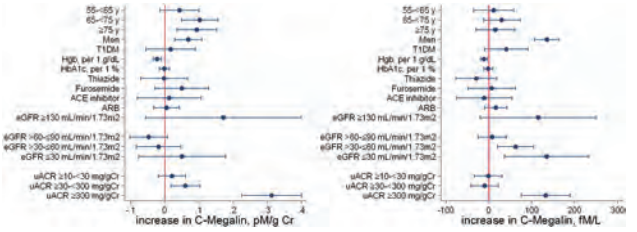
Background: Urinary c-megalin is a multi-ligand receptor shed from proximal tubule cells. It is expected as a biomarker for early kidney injury associated with diabetic kidney disease (DKD) among diabetes. The aim of this study was to examine the determinants of urinary c-megalin values.

Methods: This single-center cross-sectional study included 1491 Japanese patients with diabetes (including 104 type 1 and 1387 type 2 diabetes). The outcome was urinary c-megalin measured by enzyme-linked immunosorbent assay and expressed as both urinary creatinine (Cr)-corrected value (unit: pM/gCr) and non-corrected value (unit: fM/L). The candidate predictors were: age, type 1 diabetes, hemoglobin, hemoglobin A1c, antihypertensives, estimated glomerular filtration rate (eGFR: ≥130, >90-<130 [ref.], >60-≤90, >30-≤60, ≤30 mL/min/1.73m^2), and urine albumin Cr ratio (uACR: <10 [ref.], ≥10-<30, ≥30-<300 [i.e., microalbuminuria], ≥300 mg/gCr [i.e., macroalbuminuria]). The two-part model was fit to estimate the marginal effects of the predictors as urinary c-megalin values of both units have zero-inflated heavily skewed distributions.

Results: Cr-corrected c-megalin showed higher values associated with both microalbuminuria and macroalbuminuria (difference: 0.06 and 0.31 pM/gCr), whereas aging (≥65-<75 yr and ≥75 yr compared to <55 yr) was also associated with higher c-megalin values (Figure1). Uncorrected c-megalin showed higher values associated with macroalbuminuria (difference: 132 fM/L), eGFR >30-≤60, and ≤30 mL/min/1.73m^2 (difference: 62 and 134 fM/L). For both units, higher c-megalin values were associated with male sex and lower hemoglobin values.

Conclusions: Uncorrected c-megalin was independently associated with reduced kidney function and macroalbuminuria, both of which were included in a current concept of DKD. However, for both units, careful interpretation would be required as anemia and sex affect both units and especially, aging affects Cr-corrected values.



Marginal effects of predictors on urinary c-megalin values expressed as Cr-corrected (left panel) and uncorrected values (right panel). Error bars indicate 95% confidence intervals.

TH-PO919

Urinary Glycolic Acid Predicts Kidney Function Decline in Type 1 Diabetic Subjects

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Background: Diabetes is the common cause of chronic kidney disease (CKD) and end-stage renal failure. Albuminuria and eGFR are widely approved biomarkers to identify disease progression. However, due to considerable heterogeneity not all subjects progress at the same rate. Here we evaluated a set of urine metabolites toward prediction of rapid progression of CKD in patients with type 1 diabetes.

Methods: We used a nested case-control study in four diverse cohorts (CACTI, EDC, FinnDiane, and Steno) with long-standing type 1 diabetes and normal kidney function. Subjects were classified into slow decliners/controls with eGFR decline ≤1ml/min/1.73m^2/yr or rapid progressors/cases with eGFR decline of ≥3ml/min/1.73m^2/yr. In training phase 34 urine metabolites were measured from 595 subjects. The most prognostic biomarkers were validated on additional 200 subjects from the same 4 cohorts. Logistic regression model was used to predict rapid eGFR decline. Area under the curve (AUC) were used to assess model performance.

Results: Baseline mean eGFR and median ACR in training phase controls (n=340) and cases (n=212) were 91.97 (sd 18.68) and 9.44 (IQR 30), and 98.37 (sd 25.44) and 33.49 (IQR 283.01), respectively. Analysis with clinical variables revealed age, baseline ACR, and baseline eGFR to be significant predictors of rapid decline. Three metabolites 3-methylcrotonylglycine, glycolic acid and citric acid had a univariate association to rapid progression (FDR ≤ 0.05). When these 3 metabolites were added to the model with the clinical variables, 3-methylcrotonylglycine and glycolic acid remained significant ($p < 0.005$) but the predictive performance of the model did not improve. In a stratified analysis of eGFR≥60 ml/min/1.73m^2 and micro- or macroalbuminuria (MA+) group, 3 methylcrotonylglycine and glycolic acid significantly improved the AUC from 0.69 (0.45-0.84) to 0.76 (0.61-0.89). The metabolites were further validated in 95 controls and 95 cases with eGFR≥60 ml/min/1.73m^2 and micro- or macroalbuminuria (MA+). Glycolic acid was univariately associated with rapid decline (P<0.01) and remained significant when added to clinical model (P:0.04).

Conclusions: In subjects with albuminuria and normal eGFR (≥60 3ml/min/1.73m^2) urine glycolic acid may be useful as a prognostic biomarker along with clinical variables for loss of renal function.

Funding: NIDDK Support

TH-PO920

Metabolomics Analysis of Urinary Biomarkers That Correlate with Kidney Injury in Diabetic African American Men

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Background: African Americans (AA) are disproportionately burdened by diabetes and diabetic kidney disease (DKD). However, little is known about the cellular and molecular mechanisms underlying the onset and progression of DKD in this population. This is due, in part, to the fact that AAs are often underrepresented in biomedical research. We recently reported undiagnosed kidney injury in a significant proportion of diabetic AA men served by a community clinic in Greensboro, NC. The goal of the current study was to determine the association between specific metabolites and kidney injury in this population.

Methods: We used Biocrates Absolute IDQ p400 kits together with high-resolution liquid chromatography-mass spectrometry to analyze fasting urine samples from three groups of AA men; 1) diabetics with DKD (n=10), 2) diabetics but no diagnosed DKD (DM; n=55), and 3) age-matched non-diabetic controls (ND; n=15). Patients in the DM group were further stratified based on their urinary albumin-to-creatinine ratios (UACR) into normo- (UACR<30 mg/g; n=28), micro- (30 mg/g<UACR < 300 mg/g; n=20); and macroalbuminuria (UACR>300 mg/g; n=7). The concentrations of metabolites were normalized to the urinary creatinine levels, and compared through linear mixed models.

Results: The differentiating metabolites included glycerides, cholesterol esters, sphingolipids, glycerophospholipids, biogenic amines and amino acids. The levels of several metabolites correlated with UACR. These include the Pro and the Arg derivative, citrulline, and three biogenic amines (kynurenine, 4-hydroxyproline, and a-aminoadipic acid). 87 urine metabolites exhibited levels above the limit of detection of the assay.

Conclusions: The current data suggest that key metabolic pathways are altered in diabetes and DKD for this population. For instance, proline is a precursor during the biosynthesis of both 4-hydroxyproline and citrulline. Likewise, citrulline is also involved in nitric oxide production, consistent with our previous observation that inflammation markers correlated with severity of DKD in this population. Together, the metabolic biomarkers offer insights into the cellular and metabolic pathways that are dysregulated during the development of DKD in this population.

Funding: NIDDK Support, Other NIH Support - NIMHD, NIGMS

TH-PO921

LC-MS/MS-Based Proteomics Analysis Reveals Correlations Between Kidney Injury and Mediators of Vascular Pathology, Inflammation, and Oxidative Stress in Diabetic African American Men

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Background: The prevalence of diabetic nephropathy (DN) is disproportionately high among minority ethnic groups in the US. African American (AA) men are especially underrepresented in research to identify biomarkers of DN which are then used for the development of diagnostic tools and therapeutics targets. The goal of the current study was to identify biomarkers present in the serum of diabetic AA men which correlate with kidney injury and thus gain insights on the cellular and molecular mechanisms underlying the progression of DN in this population.

Methods: Fasting blood and urine samples were obtained from AA men aged 18-65 years; (i) non-diabetic controls (n=22), (ii) diabetics (n=65), and (iii) diabetics with diagnosed kidney disease (n=13). Assays for urinary albumin, creatinine, kidney injury molecule 1 (KIM-1) and neutrophil gelatinase associated lipocalin (NGAL) were used for evaluation of kidney function. The serum samples were depleted of abundant proteins then subjected to global LC-MS/MS-based analysis. The data were searched using Proteome Discoverer 2.2 utilizing Sequest HT search algorithm. Linear regression modeling was conducted for screening changes in association with urinary albumin and creatinine ratio (UACR), and odds and fold changes calculated across groups.

Results: 29 of the identified proteins correlated with UACR. Among these are proteins involved in vascular pathology (vasorin, fibulin-1, neuropilin), inflammation (protein disulfide-isomerase, tenascin-X, vascular cell adhesion protein 1), oxidative stress (sulfhydryl oxidase 1), and ECM/ fibrosis (tenascin-X, fibulin-1).

Conclusions: The data suggest that the progression of kidney injury in AA men is associated with vascular pathology, inflammation, and oxidative stress. Vasorin has distinct glomerular localization and is down-regulated during vessel repair. Reversal of vasorin down-regulation inhibits TGF-β signaling diminishing injury-induced vascular lesions. AGEs, which are linked to DN, suppress the expression of neuropilin-1 in podocytes. Tenascin X, localizes in the mesangium of kidney glomeruli, activates latent TGF-β, and induces TFG-β/Smad signaling. Increased levels of fibulin-1 also associate with impaired kidney function.

Funding: NIDDK Support, Other NIH Support - NIGMS, NIMHD

TH-PO922

Prediction and Validation of Exenatide Risk Marker Effects on Progression of Renal Disease: Insights from EXSCEL

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RA) may slow progression of renal disease in patients with type 2 diabetes (T2D). We previously developed the PRE score that translates multiple short-term drug effects into a predicted effect on long-term outcomes. We assessed the short-term effects of the GLP-1 RA exenatide on multiple cardio-renal risk markers, and aimed to determine whether the PRE score could predict the renal effects of exenatide observed in the EXSCEL cardiovascular outcomes trial.

Methods: Changes from baseline to six months in multiple risk markers were evaluated for glycated hemoglobin (HbA_{1c}), systolic blood pressure (SBP), urine albumin:creatinine ratio (UACR), body mass index (BMI), hemoglobin and total cholesterol. The renal outcome was defined as a composite of a sustained 30% decline in estimated glomerular filtration rate (eGFR) or end-stage renal disease. The effect of exenatide on the composite of 40% eGFR decline or ESRD was also assessed. Relationships between multiple risk markers and long-term renal outcomes were determined in patients with T2D from the ALTITUDE study using multivariable Cox regression analysis. These relationships were applied to short-term changes in risk markers observed in EXSCEL to predict the likely drug induced impact on renal outcomes.

Results: Compared with placebo, mean HbA_{1c}, BMI, SBP, and total cholesterol were lower at six months with exenatide, as was the incidence of micro- or macroalbuminuria. The PRE score predicted a relative risk reduction for the 30% eGFR decline / ESRD endpoint of 11.3% (HR 0.89; 95%CI 0.83 to 0.94), compared with 12.7% (HR 0.87; 95%CI 0.77 to 0.99) observed risk reduction. For the 40% eGFR / ESRD endpoint, the predicted and observed risk reductions were 11.0% (HR 0.89; 95%CI 0.82 to 0.97) and 13.7% (HR 0.86, 95%CI 0.72 to 1.04), respectively.

Conclusions: The PRE score, integrating multiple short-term risk marker changes, predicted the observed renal risk reduction with exenatide treatment as observed in the EXSCEL trial. The results of the present study support further clinical trials to prospectively assess the renal efficacy of exenatide.

Funding: Commercial Support - AstraZeneca

TH-PO923

Myostatin Promotes Tubular Inflammation in Diabetic Nephropathy

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Background: Inflammation contributes to the tubulointerstitial lesions of diabetic nephropathy. Myostatin (MSTN), a member of the Transforming growth factor-β family, has been identified as a mediator of inflammation and insulin resistance in type 2 diabetes. MSTN has also been identified in the tubulointerstitium of porcine kidney, but its role in the human kidney is not known. The aims of the current study were (1) to investigate MSTN expression in the normal kidney and in kidney biopsies with documented diabetic nephropathy (DN); (2) to the functional role of MSTN in tubular inflammation and fibrosis, using an established PTEC culture system.

Methods: MSTN mRNA was analyzed in microdissected tubuli and glomeruli from normal kidneys (N=19), DN (n=23, proteinuria 3.8±1.0 g/d, eGFR= 33±7 ml/min) and IgA biopsies (n= 12, proteinuria 2.7 g/d, eGFR= 39±5 ml/min) and protein was studied by immunohistochemistry. In vitro, HK-2 (human PTEC line) was exposed to MSTN (500 ng/ml) for 48 hours. We evaluated mRNAs by rt PCR, proteins by western blot, cell proliferation by CFSE incorporation, oxidative stress by CellROX staining.

Results: Laser capture microdissection showed an overexpression of MSTN mRNA (~8- to 10-fold increase) in the tubulointerstitium compartment in DN. Immunoreactive MSTN was overexpressed in the tubulointerstitium from DN patients (~4-8 fold increase) but not in nondiabetic control subjects and co-localized with interstitial infiltrating CD45+ cells. The intensity of tubulointerstitial MSTN expression correlated directly with tubular atrophy (R= 0.64; p<0.001). When proximal tubule HK-2 cells were treated with MSTN, they showed a decrease in proliferation, together with NF-kB activation and upregulation of downward inflammatory chemokines, SMAD 2/3 and fibronectin mRNA and protein. In addition, MSTN induced intracellular ROS release and upregulated NADPH oxidase, an effect which was mediated by ERK activation.

Conclusions: In conclusion, our data show that MSTN is upregulated in the tubulointerstitium of DN and associates with tubulointerstitial fibrosis. Its proinflammatory and profibrotic effects in human tubular cells suggests that MSTN plays a role in the progression of DN.

Funding: Government Support - Non-U.S.

TH-PO924

Gut Microbiome-Derived Phenyl Sulfate Contributes to Albuminuria in Diabetic Kidney Disease (Part 2)

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Background: Diabetic kidney disease (DKD) represents a major cause of ESRD. However, since it is difficult to identify patients who are at risk of progression, specific biomarker is needed.

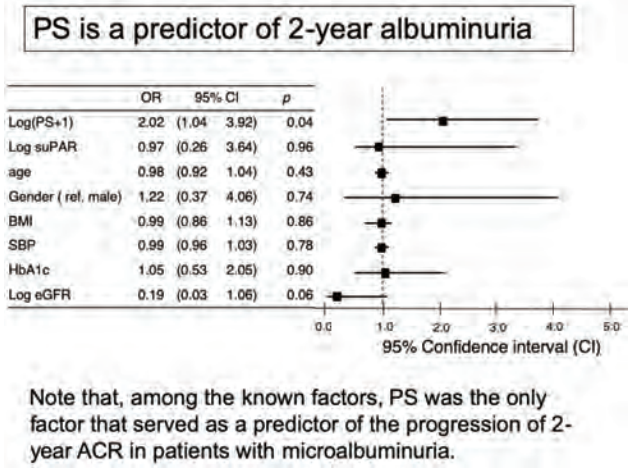
Methods: 362 patients in a multi-center clinical study in diabetic nephropathy (U-CARE) with full data were selected. The plasma PS level was measured by LC–MS/MS. The correlation between the PS level and various factors was calculated using Spearman Rank-Order Correlation. Multiple regression analysis and logistic regression analysis were used to identify the factors independently associated with PS or the development of 2-year ACR deterioration, respectively.

Results: Participants had a mean age of 63.3 years and 56.9% were male. The blood glucose was 154.2 ± 56.4 mg/dl and the HbA1c was 7.2 ± 1.1 %. The eGFR was 73.8 (17.1 – 115.4) ml/min/1.73 m^2 and the albumin to creatinine ratio (ACR) was 11.0 (1.0 – 6407.4) mg/gCr. The serum PS level was 3.3 μM (0 – 68.1 μM) and suPAR was 460.8 (142.0. – 2740.2) pg/ml. The basal plasma PS level significantly correlated with ACR, eGFR, age, duration, HbA1c and uric acid, but not with suPAR. Multiple regression analysis revealed that ACR was the only factor that significantly correlated with PS. By stratified logistic regression analysis, in the microalbuminuria group, PS was the only factor related to the amount of change in the 2-year ACR in all models, with an odds ratio of 2.02 (CI: 1.04-3.92). ROC curve analysis further showed that a combination of suPAR

with known factors increased the c-statistics value and the value were further increased with the PS combination.

Conclusions: PS is related to ACR and could predict the 2-year ACR deterioration in DKD patients, especially with microalbuminuria (Nature Commun. 10: 1835, 2019).

Funding: Government Support - Non-U.S.



TH-PO925

The Acute Effect of Selonsertib on eGFR Is a Result of Creatinine Transport Inhibition, Not Alteration of Renal Function

Elijah J. Weber, Cara H. Nelson, Brian J. Kirby, Winnie Weng, Fang Chen, Uptal D. Patel, Anita Mathias. *Gilead Sciences, Inc., Foster City, CA.*

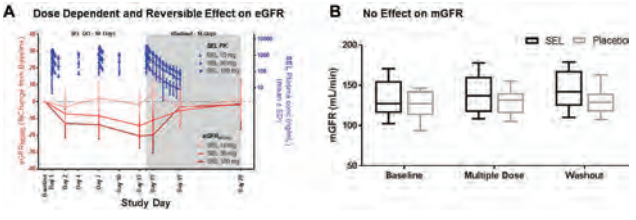
Background: Selonsertib (SEL) is a first-in-class small molecule inhibitor of apoptosis signal-regulating kinase 1 (ASK1) in clinical development for the treatment of diabetic kidney disease (DKD). As small, dose-dependent, and reversible increases in serum creatinine were observed across clinical studies, an analysis of in vitro and clinical data was conducted to identify and confirm the mechanism by which SEL decreases estimated GFR (eGFR) without changing measured GFR (mGFR).

Methods: In vitro studies assessed the potential for SEL and its inactive metabolite, GS-607509, to inhibit renal transporters (OCT2, MATE1, and MATE2K) and determined their IC_{50} values. Clinical studies in healthy subjects included a multiple ascending dose (MAD) study (SEL 1 to 100 mg or placebo, QD) to assess the effects of SEL on eGFR. Additionally, a mechanistic study (SEL 18 mg or placebo, QD) evaluated the effect of SEL on renal function using iohexol to measure GFR before, during, and after treatment for 2 weeks. Meta-analyses of clinical studies were conducted to quantify the magnitude and consistency of the acute effect across patient populations.

Results: Based on the 2017 FDA drug interaction guidance, SEL and GS-607509 demonstrate low potential for inhibition of OCT2 ($C_{max,u}/IC_{50} > 0.1$). SEL, but not GS-607509, is a potential inhibitor of MATE1 and MATE2K ($C_{max,u}/IC_{50}$ of > 0.02). In the MAD study, a dose-dependent reduction in eGFR was observed and was reversible upon washout of SEL (A). Results from the mechanistic study showed no change in mGFR for subjects taking SEL or placebo (B). Regardless of baseline eGFR, meta-analyses showed at the 18 mg dose, a consistent acute percent decrease (median 7.3%) in eGFR across patient populations.

Conclusions: The totality of data from in vitro and clinical studies indicate that the acute effect of SEL on eGFR is dose-dependent, reversible, and a result of inhibition of renal creatinine transporters without altering mGFR. Clinical trials evaluating the efficacy of SEL on slowing the loss of kidney function will need to account for these acute effects.

Funding: Commercial Support - Gilead Sciences, Inc.



TH-PO926

Genome-Wide Expression Quantitative Trait Loci Analysis for Circulating miR-1287-5p and miR-339-5p and ESRD in Type 1 Diabetes

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Background: microRNAs are short endogenous non-coding RNA molecules that are involved in gene regulation and play important roles in the pathogenesis of various kidney diseases. Previously, we identified risk and protective miRNAs (miR-1287-5p and miR-339-5p) strongly associated with progression to end stage renal disease (ESRD) in diabetes. To identify expression quantitative trait loci (eQTL) that influence plasma levels of these miRNAs and onset of ESRD in Type 1 diabetes (T1D), we performed a genome-wide miR-eQTL analysis.

Methods: Plasma levels of the two miRNAs were measured using HTG Molecular Diagnostics' EdgeSeq platform and genotyping of 325,735 single nucleotide polymorphisms (SNPs) was performed using Illumina's HumanCoreExome BeadArray in 240 T1D patients. Association analyses between plasma levels of miR-1287-5p and miR-339-5p were used to identify eQTL using linear regression implemented in PLINK. To assess the relationship between the candidate eQTLs and the development of ESRD, we applied logistic regression using an additive model in 437 T1D patients.

Results: Trans miR-eQTL analysis revealed that 13 SNPs that affect plasma levels of miR-1287-5p or miR-339-5p (P<5e-5). Among them, in logistic models, we identified 2 SNPs associated with onset of ESRD: rs4624519 in the LINC02033 (OR: 0.64 (95%CI=0.48-0.85); p=0.0024) and rs10963040 in the CNTLN gene (OR: 1.43 (95%CI= 1.04- 1.96); p=0.028).

Conclusions: We identified SNPs that have regulatory effects on circulating miRNAs and play roles in progression to ESRD in T1D.

Funding: NIDDK Support, Private Foundation Support

TH-PO927

The Circulating Exosomal MicroRNAs Related to Albuminuria in Patients with Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is associated with high risk of cardiovascular disease and mortality. Exosomal microRNAs (miRNAs) regulate gene expression in a variety of tissues and play important roles in the pathology of various diseases. We hypothesized that the exosomal miRNA profile would differ between DN patients and patients without nephropathy.

Methods: We prospectively enrolled 74 participants, including healthy volunteers (HVs), diabetic patients without nephropathy, and those with DN. The serum exosomal miRNA profiles of participants were examined using RNA sequencing.

Results: The expression levels of 107 miRNAs differed between HVs and patients without DN, whereas the expression levels of 95 miRNAs differed between HVs and patients with DN. Among these miRNAs, we found 7 miRNAs (miR-1246, miR-642a-3p, let-7c-5p, miR-1255b-5p, let-7i-3p, miR-5010-5p, miR-150-3p) that were uniquely up-regulated in DN patients compared to HVs, and miR-4449 that was highly expressed in DN patients compared to patients without DN. A pathway analysis revealed that these eight miRNAs are likely involved in MAPK signaling, integrin function in angiogenesis, and regulation of the AP-1 transcription factor. Moreover, they were all significantly correlated with the degree of albuminuria (figure 1).

Conclusions: Patients with DN have a different serum exosomal miRNA profile compared to HVs and these miRNAs may be promising candidates for the diagnosis and treatment of DN and cardiovascular disease.

Correlation between miRNAs and albuminuria

Mature miRNAs	albuminuria (r/p-value)
miR-1246	0.373/0.001
miR-642a-3p	0.362/0.002
let-7c-5p	0.428<0.001
miR-1255b-5p	0.240<0.039
let-7i-3p	0.300/0.009
miR-5010-5p	0.254/0.029
miR-150-3p	0.347/0.002
miR-4449	0.497/<0.001

TH-PO928

Hypoxia in Individuals with Type 1 Diabetes and Macroalbuminuria Is Associated with Autonomic Dysfunction

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Background: Blood oxygen saturation (SpO2) in the supine position is lower in individuals with type 1 diabetes (T1D) compared to healthy controls (CON). This has been suggested to be linked with cardiovascular autonomic dysfunction (CAD). Presence of CAD in individuals with T1D and diabetic nephropathy is associated with cardiovascular mortality. Our aims were to investigate SpO2 levels in individuals with T1D and different albuminuria-stages compared to CON and to explore associations between SpO2 and baroreflex sensitivity (BRS), a sensitive measure of CAD.

Methods: One-hundred-and-five individuals with T1D and normoalbuminuria (NORMO) and 24 individuals with T1D and macroalbuminuria (MACRO) were compared to 55 CON. SpO2 was measured with pulse oximetry first for one minute in the supine position and then for five minutes in the standing position. A linear mixed-effects model was fitted with SpO2 as outcome and albuminuria-status as exposure, adjusted for sex, age and smoking, with a random person effect. Association between SpO2 and BRS was tested with linear regression analysis and adjusted for albuminuria-status, sex, age and smoking.

Results: In CON, NORMO and MACRO respectively, mean (SD) age was 42.7 (12.6), 43.9 (11.1) and 58.6 (11.0) years; HbA1c was 33.2 (2.4), 63.9 (12.0) and 63.1 (11.7) mmol/mol; BRS was 15.2 (9.5), 13.8 (10.6) and 4.9 (3.2) ms/mmHg; plasma/serum creatinine was 78.3 (12.6), 67.6 (11.5) and 117.1 (53.1) µmol/L; and baseline SpO2 was 97.5 (1.4), 97.0 (1.4) and 96.2 (1.9) %. From supine to standing position, SpO2 increased in CON and NORMO, but not in MACRO. Overall, in mixed effects model mean difference in SpO2 between NORMO and CON was -0.7% (p=0.03) and mean difference in SpO2 between MACRO and CON was -1.4% (p<0.001). In all participants together, SpO2 was positively correlated with BRS (p=0.03).

Conclusions: Individuals with T1D and normoalbuminuria had lower SpO2 than healthy controls and the macroalbuminuria-group had even lower SpO2. SpO2 was positively correlated with BRS. Microvascular damage in lungs of individuals with macroalbuminuria may lead to hypoxia contributing to autonomic dysfunction. It remains to be investigated if low SpO2 contributes to excess cardiovascular mortality in individuals with T1D and diabetic nephropathy.

Funding: Private Foundation Support

TH-PO929

Biomarker Identification for Diabetic Kidney Disease at the Early Stage

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Background: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease. As the most common microvascular complication of diabetes, DKD is a knotty clinical problem in terms of its diagnosis and management. Currently, renal biopsy remains the most reliable approach to distinguishing a true DKD, non-DKD, or mixed form. Our present study focuses on early biomarker identification to monitor the onset of DKD in type2 diabetes (T2D) patients. We expect the identified biomarker could eventually be translated into the solid backup resources to avoid invasive biopsy in patients.

Methods: Based on our previous findings, combine with the data refinery in public repository centers, we identified 3 proteins which play critical roles in the development of DKD, including Serum Amyloid A-1 (SSA1), matrix metalloproteinase-7 (MMP-7), and Tenascin C (TNC). We designed a standard cohort study by dividing the trial into 3 phases: training, testing, and validation phase. In the training phase, we enrolled 202 candidates including DKD or T2D or healthy adults from a single medical center. In the testing phase, we enrolled 680 patients at different stages of DKD or healthy adults from the same medical center. Serum SAA1, MMP-7, and TNC, urinary MMP-7 and TNC were measured. Two machine learning models, linear discriminant analysis (LDA) and support-vector machines (SVM), were applied in this study. The external validation is now pending.

Results: Compared with the healthy adults, serum and urinary SAA1, MMP-7, and TNC were significantly increased at each stage of DKD in patients. However, if directly compared with the T2D patients without kidney disease, none of the above markers could individually serve as an early warning marker to alert the onset of kidney disease in the T2D patients. The diagnostic outcomes analyzed by SVM were shown via the receiver operating characteristic (ROC) for the direct comparison between the T2D and the DKD patients at early stage. In SVM model, combined serum SAA1, MMP-7, and TNC provided area under curve at 0.95 between the T2D and the DKD early stage patients. In addition, a combination of serum SAA1 and MMP-7 is able to more precisely distinguish the boundary between the early and advance stages of DKD.

Conclusions: Analysis using SVM model by combining SAA1, MMP-7, and TNC in serum is promising to predict the onset of kidney complication in T2D patients.

TH-PO930

Association of Low Serum Adiponectin Levels with Aortic Stiffness in Patients with Diabetic Kidney Disease

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Background: Adiponectin plays an important role in cardiovascular disease through its anti-inflammatory and anti-atherogenic properties. The purpose of the present study was to examine the clinical variables and the relationship between serum adiponectin levels and aortic arterial stiffness in diabetic kidney disease (DKD).

Methods: Fasting blood samples were obtained from 80 patients with DKD. DKD is identified clinically by persistently high urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g and/or sustained reduction in estimated glomerular filtration rate (eGFR) below 60 ml/min per 1.73 m^2. Carotid-femoral pulse wave velocity (cfPWV) was measured by using pressure applanation tonometry. cfPWV values of > 10 m/s represented the high aortic arterial stiffness group, while values ≤ 10 m/s defined the control group, according to the ESH-ESC 2013. Serum adiponectin level was measured using an enzyme immunoassay.

Results: In total, 41 patients with DKD (51.3%) were defined as high aortic stiffness group. Compared to the control group, high aortic stiffness group had high prevalence of male gender (P = 0.043), older age (P = 0.011), higher systolic blood pressure (P = 0.002) and UACR (P = 0.007), whereas serum adiponectin level (P = 0.001) were lower. After adjusting for confounders, serum adiponectin level (odds ratio (OR): 0.930, 95% confidence interval (CI): 0.884–0.978, P = 0.005), age (OR: 1.089, 95% CI: 1.028–1.154, P = 0.004), and systolic blood pressure (OR: 1.040, 95% CI: 1.013–1.068, P = 0.004) were independent predictors of aortic stiffness. Multivariable analysis showed that the serum adiponectin level (β = -0.309, adjusted R^2 change = 0.087, P = 0.002) was negatively associated with cfPWV values in DKD patients. The area under the receiver-operating characteristic (ROC) curve predicting aortic stiffness by serum adiponectin level in DKD patients was 0.728 (95% CI: 0.617-0.822, P = 0.0001).

Conclusions: Among DKD patients, serum adiponectin level was inversely associated with cfPWV values and was independent predictor of aortic stiffness.

TH-PO931

Plasma Biomarkers and Diabetic Kidney Disease (DKD) Progression: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: DKD is the leading cause of end-stage kidney disease (ESKD) in the US. There is an unmet need for biomarkers to identify patients at high risk for DKD progression.

Methods: CRIC participants with diabetes, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2, and plasma collected at baseline (N=1315) were eligible for this case-cohort study. Eligible participants were randomly selected for the subcohort (N=597); cases were all participants who developed DKD progression, defined as ESKD or 40% eGFR decline (N=538, 240 in the subcohort). Plasma biomarkers (KIM-1, TNFR-1, TNFR-2, MCP-1, suPAR, & YLK-40) were measured using a novel multiplex platform. Spearman correlations estimated relationships between markers, eGFR, and proteinuria. Weighted Cox regression models adjusted for age, sex, race, education, blood pressure, hsCRP, body mass index, smoking, eGFR, and proteinuria estimated the relation of markers with DKD progression. Mixed effects models estimated the relationship of markers with change in yearly eGFR.

Results: The median follow-up was 8.7 (6.4-9.3) years. The mean change in eGFR was -0.6 and -4.1 ml/min/1.73m^2 among non-cases and cases, respectively. TNFR-1 and TNFR-2 were the most correlated markers (ρ=0.85). All markers inversely correlated with eGFR. Higher marker levels associated with greater risk of DKD progression **(Table)**. Four markers associated with eGFR decline.

Conclusions: Higher plasma levels of KIM-1, TNFR-1, TNFR-2, MCP-1, suPAR, and YKL-40 were independently associated with increased risk of DKD progression. These biomarkers may yield prognostic and mechanistic value for future DKD research.

Funding: NIDDK Support

Adjusted associations of Plasma Biomarkers with DKD progression.

	ESRD or 40% decline in eGFR (HR, 95% CI)	Change in yearly eGFR ml/min/1.73m2 (β, 95% CI)
KIM-1	1.5 (1.2, 1.9)	-0.5 (-0.8, -0.2)
TNFR-1	2.1 (1.6, 2.8)	-0.4 (-0.7, -0.1)
TNFR-2	2.1 (1.5, 2.7)	-0.5 (-0.8, -0.2)
MCP-1	1.4 (1.2, 1.7)	-0.01 (-0.2, 0.2)
suPAR	1.7 (1.3, 2.2)	-0.3 (-0.6, 0.0)
YKL-40	1.4 (1.2, 1.6)	-0.4 (-0.6, -0.2)

HR = hazard ratio associated with SD in (natural log) biomarker

TH-PO932

Urine Myo-Inositol, the Novel Prognostic Biomarker for Diabetic Kidney Disease: A Targeted Metabolomics Study Using Nuclear Magnetic Resonance

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Background: Estimated GFR (eGFR) and urine proteinuria are currently the strongest predictive biomarker of CKD regardless of the cause. For more precise prediction according to the cause of CKD and to identify treatment options, metabolomics has been increasingly applied to identifying new biomarkers of diseased specific CKD. We investigated the association between urine metabolites and ESRD progression in diabetic kidney disease (DKD) cohort.

Methods: Based on previous our animal study, targeted metabolomics (n=26) was performed using nuclear magnetic resonance. Prospectively stored urine samples consecutive patients with DKD stage 1 to 5 (n=208) and their healthy controls (n=26) were analyzed. Cross-sectional association between measured metabolites and eGFR were compared. Multivariate cox models were conducted for the risk of ESRD and mortality.

Results: ESRD occurred in 103 (44.0%) patients and the number of death was 65 (27.8%). The median fold change of metabolites compared with control groups, 7 metabolites (glucose, mannose, myoinositol, lactate, succinate, fumarate and choline) revealed a trend according to CKD stages. Linear regression identified myo-inositol is best-associated metabolite with eGFR. The relationship between competitive metabolites and outcomes was investigated by multivariate Cox models after adjusting for the baseline covariates (Table1). Of which, 4 metabolites (myoinositol, glycerol, fumarate, oxoisocaproate) had predictive value for ESRD and only myo-inositol retained predictive significance in mortality (aHR 1.004, 95% CI 1.002–1.006, p-value <0.001).

Conclusions: Our results suggest the myoinositol, previously defined as vitamin B8, can be a predictive biomarker to predict the risk of ESRD progression in DKD. Myoinositol, as a secondary messenger of insulin and confirmed safe compound, further mechanism study is needed.

Table 1. Risk of end-stage renal disease according to the urinary metabolites

Metabolites/Cr	Unadjusted			Model 1			Model 2		
	HR	CI	P	HR	CI	P	HR	CI	P
Myo-inositol	1.005	1.000-1.010	<0.001	1.003	1.001 - 1.005	0.001	1.003	1.001 - 1.005	0.011
Glycerol	1.004	1.000-1.010	0.009	1.004	1.001 - 1.008	0.007	1.005	1.001 - 1.009	0.022
Fumarate	1.076	0.840-1.380	0.022	1.093	1.007 - 1.187	0.033	1.105	1.014 - 1.204	0.023
Oxoisocaproate	1.374	0.750-2.520	0.034	2.147	1.557 - 2.959	<0.001	1.670	1.146 - 2.434	0.008

only 4 significant metabolites were described; Model 1: adjusted for age, sex, HTN, eGFR; Model 2: adjusted for model 1 plus laboratory findings

TH-PO933

Angiotensin II Receptor Blocker (ARB) Alters the MicroRNA Profile of Extracellular Vesicles in Diabetic Nephropathy

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Background: The renin-angiotensin system (RAS) is a major target of diabetes nephraphy therapy. Angiotensin II receptor blockers (ARBs) decrease proteinuria and mortality associated with diabetes nephropathy. Extracellular vesicles (EVs) contain miRNAs that play a role in cell-to-cell communication and are biomarkers of disease. Whether ARBs modulate miRNAs in EVs is not known.

Methods: We prospectively enrolled 6 ARB naïve patients (male=4, female=2) with diabetic nephropathy and hypertension along with age-sex matched healthy volunteers (HVs). After collecting baseline samples, an ARB (losartan 50 mg) was added to the patients' drug regimens. Serum EV microRNAs were profiled using RNA sequencing at baseline and 3 months after initiation of ARB therapy.

Results: RNA sequencing identified 130 miRNAs in the EVs from HVs and patients. ARB therapy decreased the expression of 5 miRNAs (miR-328-3p, miR-199a-5p, hsa-miR-16-5p, miR-1277-3p and miR-4284) in the EVs from patients. Expression of 3 miRNAs (miR-660-5p, miR-20b-5p and miR-143-3p) was increased after ARB therapy. Biological analysis identified the predicted involved pathways of the decreased miRNAs after ARB treatment (table 1).

Conclusions: Our study demonstrates that ARBs affect the expression of miRNAs in EVs from hypertensive patients. The change in expression of miRNAs in EVs due to ARB therapy is a novel aspect of the RAS. Further study is needed to identify the role of these miRNAs in diabetes.

The predicitve pathway of angiotensin receptor blocker responsive miRNAs

Pathway	Number of genes	p-value
Pathway in cancer	66	0.000162
Ribosome biogenesis in eukaryotes	20	0.000849
Prostate cancer	25	0.00037
Cell cycle	31	0.000414
Chronic myeloid leukemia	22	0.000414
Small cell lung cancer	23	0.000419
RNA transport	31	0.000419
HTLV-1 infection	42	0.000703
Pancreatic cancer	20	0.000951
Focal adhesion	40	0.0031

TH-PO934

Polyols and Branched Chained Amino Acids Are Associated with Present and Future Renal Impairment in Type 1 Diabetes

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Background: Improved understanding of the pathophysiology causing diabetic nephropathy is imperative. The aim of this study was to uncover associations between serum metabolites and renal outcomes in persons with type 1 diabetes.

Methods: In total, 637 persons with type 1 diabetes were included. Non-targeted serum metabolomics analyses were performed using two-dimensional gas chromatography coupled to time-of-flight mass-spectrometry. Longitudinal data at follow-up on development of renal events were obtained from national Danish health registries over a median of 5.5 years. A composite renal endpoint (n=123) consisted of estimated glomerular filtration rate (eGFR) decline from baseline (≥30%), development of end-stage renal disease (eGFR < 15 ml/min/1.73m^2, dialysis or renal transplantation) and all-cause mortality. Metabolites with significant associations (p<0.05) in cross-sectional analyses were analysed with Cox proportional hazards models for either specific or composite endpoint. Adjustments included traditional cardiovascular risk factors and correction for multiple testing.

Results: A data-driven partial correlation analysis revealed a dense fabric of co-regulated metabolites and clinical variables dominated by eGFR. After statistical analyses, ribonic acid and myo-inositol were inversely associated with eGFR and positively associated with macroalbuminuria (urinary albumin excretion rate (UAER) ≥ 300 mg/24h) (p<0.02). Longitudinally, ribonic acid was associated with the combined renal endpoint (HR 1.8, CI [1.3-2.3], p=0.001). Further, ribonic acid (HR 2.2, CI [1.6-3.0], p<0.001) and myo-inositol (HR 2.7, CI [1.6-4.3], p=0.001) were both associated with higher risk of eGFR decline ≥30%. The hydroxy butyrate 3,4-dihydroxybutanoic acid was cross-sectionally associated with micro- (UAER 30-299 mg/24h) and macroalbuminuria, UAER and inversely associated with eGFR (p<0.04), while branched chain amino acids were associated with eGFR and lower risk of the combined renal endpoint (p<0.02).

Conclusions: Alterations in serum metabolites, particularly polyols and amino acids, were associated with renal endpoints in type 1 diabetes highlighting molecular pathways associated with development of kidney disease.

Funding: Private Foundation Support

TH-PO935

Circulating Long Noncoding RNAs Are Associated with Diabetic Nephropathy and Normalize After Simultaneous Pancreas-Kidney Transplantation

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Background: Diabetes mellitus can lead to end-stage renal disease and cardiovascular injury. Simultaneous pancreas kidney transplantation (SPKT) replaces kidney function and restores endogenous insulin secretion. Circulating long noncoding RNAs (lncRNAs) are promising biomarkers in (cardiovascular) disease and can provide insight into pathogenesis. However little is known about these markers in vascular injury in the context of diabetic nephropathy (DN) and after SPKT.

Methods: We performed a pilot study of 40.173 lncRNAs in plasma of healthy controls and patients with diabetic nephropathy. Based on these results, as well as a dedicated literature search, we assessed 14 candidate lncRNAs of which 9 were detectable in plasma samples in DN (n=14), SPKT (n=35) and healthy controls (n=15). All DN patients were studied longitudinally before and 1, 6 and 12 months after SPKT. LncRNAs that were detected in less than 95% of the samples were excluded from the study. Angiopoietin-2 and soluble thrombomodulin (sTM) were measured using ELISA as a markers for vascular injury.

Results: MALAT1 was significantly higher (p=0.002) in patients with DN (median 13.8, IQR 2.9-16.3) compared with healthy controls (median 0.16, IQR 0.1-1.3). The first month after SPKT MALAT1 normalized from 13.8 to 0.3 (p=0.012). EPHA6, LIPCAR

and G003293 showed a similar pattern with significant decline after SPKT (resp. p=0.01, p=0.01 and p=0.04). Interestingly we observed a strong correlation between MALAT1, EPHA6 and LIPCAR with blood pressure and vascular injury marker sTM.

Conclusions: Circulating lncRNAs associate with DN and vascular injury and normalize after SPKT. As such, lncRNAs are potentially interesting biomarkers for disease progression in diabetic nephropathy and may provide insight into the underlying pathophysiology.

TH-PO936

Systemic Inflammation Precedes New-Onset Microalbuminuria in Diabetes Mellitus Type II: A Post Hoc Analysis of the ROADMAP Study

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Background: The aim of the case-control study was to investigate if serum biomarkers indicative of vascular inflammation and endothelial dysfunction can predict the development of microalbuminuria in patients with diabetes mellitus type II.

Methods: Amongst participants enrolled in the **ROADMAP** (Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention) and observational follow-up (**OFU**) studies, a panel of 15 serum biomarkers was quantified from samples obtained at initiation of the study and tested for associations with the development of new-onset microalbuminuria (defined as a urinary albumin to creatinine ratio (UACR) of more than 35 mg/g in women or more than 25 mg/g in men) during follow-up. A case-control study was conducted with inclusion of 172 patients with microalbuminuria and 188 matched controls. Non-parametric inferential, nonlinear regression, mediation and bootstrapping statistical methods were used for the analysis

Results: The median follow-up time was 37 months. At baseline, mean concentrations of CXCL-16, TGF-β1 and angiopoietin-2 were higher in patients with subsequent microalbuminuria. In the multivariate analysis, after adjustment for age, sex, BMI, HbA1c, duration of diabetes, LDL, smoking status, blood pressure, baseline UACR, eGFR, time of follow-up and cardiovascular disease, CXCL-16 (OR 2.60, 95% CI 1.71-3.96), angiopoietin-2 (OR 1.50, 95% CI 1.14-1.98) and TGF-β1 (OR 1.03, 95% CI 1.01-1.04) remained significant predictors of new-onset microalbuminuria (p<0.001). Inclusion of these biomarkers in conventional clinical risk models for prediction of microalbuminuria increased the AUC from 0.638 to 0.760 (p <0.001).

Conclusions: In type II diabetes patients elevated plasma levels of CXCL-16, angiopoietin-2 and TGF-β1 are independently predictive of microalbuminuria. Thus, these serum markers improve renal risk models beyond established clinical risk factors.

TH-PO937

Soluble Urokinase Receptor Level as Biomarker in Biopsy-Confirmed Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease worldwide associated with significant cardiovascular morbidity and mortality. The serum levels of soluble form of podocyte membrane urokinase activator receptor (suPAR) were found to be significantly elevated in patients with DN, making it a potential biomarker for assessing the severity of disease in these patients. The aim of this study was to explore the association between suPAR levels and renal pathological findings in patients with biopsy-confirmed DN.

Methods: We performed a cross-sectional study on 33 patients with biopsy-confirmed DN admitted in our department. The following clinical variables and laboratory parameters were assessed at the time of kidney biopsy: age, gender, time since DM diagnosis, BMI, arterial blood pressure (BP) values, treatment, serum creatinine, estimated glomerular filtration rate (eGFR, calculated by CKD-EPI equation), 24-hour proteinuria and suPAR levels. Histological scoring was made according to that of Tervaert et al (JASN, 2010, 21 (4) 556).

Results: 33 patients were included (8 F, 25 M), with mean age 56.6±11.5 y, BMI 28,1±4,3 kg/m2, DM1 (n=4) and DM2 (n=29), months since DM diagnosis (140.7±87.9 mo), hypertensive (n=30), SBP(151.5±24.3mmHg), DBP (83.7±11,1 mmHg), eGFR (34.4± 24.8 ml/min), serum creatinine (2.74± 1.78mg/dl), 24-hour proteinuria (2.64±2.9g/l), ACEI or ARB use (20/33). Serum suPAR levels were 7.41±3ng/ml. SuPAR levels were positively correlated with age of diabetes (r=0.363, p=0.038), serum creatinine (r=0.493, p=0.004), degree of glomerulosclerosis (r=0.405, p=0.024), degree of tubular atrophy/interstitial fibrosis (r=0.740, p<0.001), degree of arteriosclerosis (r =0.694, p<0.001), and negatively correlated with eGFR (r = -0.675, p<0.001).

Conclusions: Our study confirmed the presence of high serum levels of suPAR in patients with DN and we suggested that these are associated with age of DM, renal function, degree of glomerulosclerosis, tubular atrophy/interstitial fibrosis and arteriosclerosis. Serum suPAR might be a useful biomarker for assessing severity of renal impairment in DN, but requires future validation on larger series of patients

TH-PO938

Association of Angiogenesis Markers with Kidney Outcomes in Patients with Type 2 Diabetes

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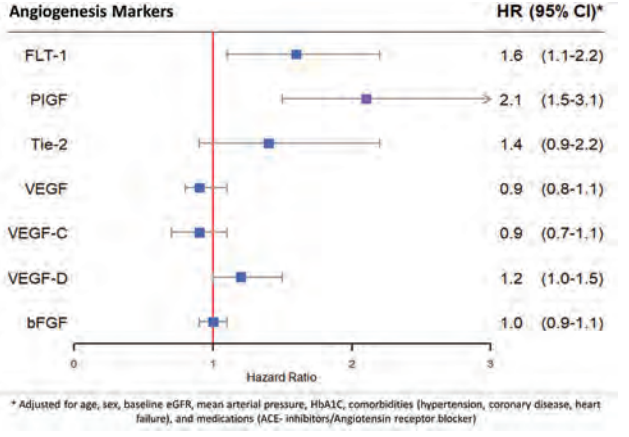
Background: Deregulated angiogenesis may play a key role in kidney disease in type 2 diabetes (T2D). We assessed the associations of 7 angiogenesis biomarkers with kidney outcomes in a contemporary clinical cohort.

Methods: We used banked plasma specimens from a cohort of patients with T2D from the EMR and USRDS-linked Mount Sinai Bio*Me* Biobank (n=870). We measured the angiogenesis biomarkers (FLT-1, PIGF, TIE-2, VEGF, VEGF-C, VEGF-D, and bFGF) in plasma specimens banked from the time of enrollment in Bio*Me* using the Mesoscale multiplex platform. Using multivariable Cox Regression, we evaluated the association of biomarkers with a composite kidney outcome of sustained 40% decline in eGFR or ESRD. We also examined the association between biomarker ratios (FLT-1/PIGF and combination of VEGF, VEGF-C, VEGF-D) with kidney outcomes.

Results: Median follow-up time for the population was 4.5 (IQR, 3.3-6.1) years, baseline eGFR was 68 (IQR, 55-80) ml/min/1.73 m^2, and UACR was 13 (IQR, 4-66) mg/g. After adjusting for demographics, comorbidities, medications, and baseline eGFR, PIGF (adjusted HR 2.1 per doubling; 95% CI 1.5-3.1) and FLT-1 (adjusted HR 1.6 per doubling; 95% CI 1.1-2.2) were independently associated with the kidney outcomes (Figure). However, when adjusted for TNFR1, TNFR2, and KIM-1, the independent associations between biomarkers and the kidney outcomes were attenuated to null. There were no associations between the biomarker ratios and kidney outcomes.

Conclusions: Higher baseline plasma PIGF and FLT-1 are associated with kidney outcomes during follow-up in patients with T2D. Since models including TNFR1, TNFR2, and KIM-1 nullified the association of FLT-1 and PIGF with kidney outcomes, this indicates the possibilities of shared pathways between these biomarkers. More studies are needed to find a definite association between these biomarkers and kidney outcomes in T2D population.

Funding: NIDDK Support



TH-PO939

Characteristics of 24-Hour Ambulatory Blood Pressure in Non-Dialysis Patients with Diabetic Kidney Disease

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Background: Data about characteristics of 24-hour ambulatory blood pressure in non-dialysis patients with diabetic kidney disease was limited.

Methods: We monitored 24-hour ambulatory blood pressure in non-dialysis patients with diabetic kidney disease from the nephrology division, the fifth affiliated hospital of Sun Yat-Sen University from August 2000 to October 2018, and compared with primary chronic glomerulonephritis patients matching in age(±5 years old), sex and CKD stages. The target organ damages were measured by carotid intima-media thickness, left ventricular hypertrophy, diastolic dysfunction, eGFR<60ml/min and massive proteinuria. Blood pressure loads, circadian rhythm and target organ damages in two groups were evaluated and compared. Multivariate logistic analyses were used to evaluated the relationship between blood pressure loads and target organ damage parameters.

Results: 202 patients with diabetic kidney disease were enrolled in this study. The mean age of the patients was 57±9 years and 66.3%(134/203)were men. Compared with control patients, patients with diabetic kidney disease had a higher level of systolic blood pressure in clinic, daytime, nighttime or 24-hour ambulatory measurement. They also had a higher proportion in reversed dippers(34.2% vs. 24.8%,*P*=0.038) and target organ damage evaluations, like the carotid intima-media thickness(69.3% vs. 26.2%,*P*<0.001), left ventricular hypertrophy(63.4% vs. 50.0%,*P*=0.009), diastolic dysfunction(74.3% vs. 46.0%,*P*<0.001) and massive proteinuria(51.0% vs. 25.7%,*P*<0.001). Multivariate logistic analyses, which included both clinic and ambulatory blood pressure, showed that only 24-hour systolic blood pressure independently predicted significantly the target organ damage.

Conclusions: Patients with diabetic kidney disease had a higher systolic blood pressure loads, a higher percentage of reversed dippers and a more severe target organ damage. 24-hour systolic blood pressure was independently associated with target organ damage.

TH-PO940

The Triple Whammy: An Unexpected Case of Leukocyte Chemotactic Factor 2 Amyloidosis (ALECT2) with Diabetic and Hypertensive Nephropathy

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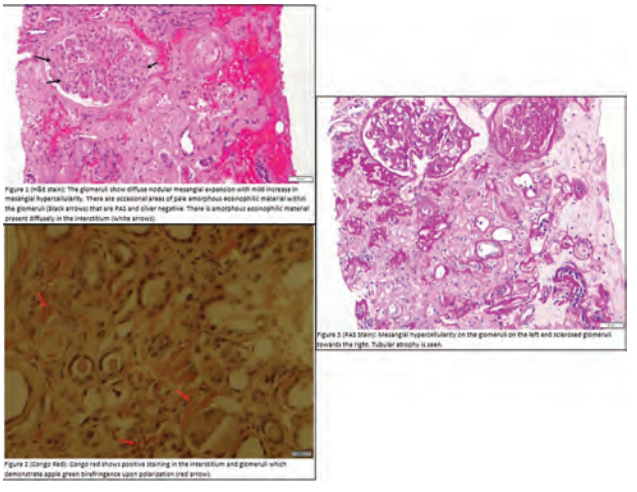
Introduction: Amyloidosis is a disorder resulting from abnormal deposition of misfolded beta-sheet fibrils. ALECT2 is a recently identified entity with high incidence in certain ethnic populations.

Case Description: A 56 year old Hispanic female with history of Diabetes Mellitus (not on therapy for a few years), presented with lower extremity edema and elevated blood pressure. Patient was noted to have nephrotic range proteinuria of >4 gm/day, and elevated Creatinine of 3.6 mg/dl. Serological work up for glomerulonephritis was negative. We proceeded with kidney biopsy given lack of proper explanation for her presentation. Biopsy showed evidence of amyloid deposition, but in the context of negative immunofluorescence study, and patient's ethnicity, LECT2 type amyloid deposition was suspected, which was further identified by Liquid Chromatography (LC) with tandem Mass Spectrometry (MS). Renal biopsy also showed changes consistent with diabetic and hypertensive nephropathy.

Discussion: ALECT2 mostly involves the liver and kidneys. Renal involvement usually presents with slow, progressive renal failure, bland urine sediment, and variable proteinuria. Prognosis of ALECT2 is better than other forms of Amyloidosis, with 1/3rd of patients progressing to ESRD. Renal transplant is an option, but the disease can recur in the transplanted kidney. Our case report demonstrates the need to maintain a high degree of suspicion for ALECT2 in patients of certain ethnicities such as Hispanics, presenting with renal impairment, bland urine, and variable proteinuria. In addition, it is very important to accurately identify the amyloid deposits by LC/MS on the renal biopsy to prevent misdiagnosing ALECT2 as AL amyloidosis, and avoid potentially harmful investigations/therapy.



TH-PO941

A Case of Fibrillary Glomerulonephritis with a High Level of Myeloperoxidase-ANCA

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Introduction: Gross hematuria with renal dysfunction suggests the possibility of rapidly progressive glomerulonephritis (RPGN) and requires urgent attention. Anti-neutrophil cytoplasmic antibody (ANCA)- associated vasculitis (AAV) represents RPGN and is characterized by elevated serum ANCA levels and pauci-immune crescentic glomerulonephritis. But it is well known that the presence of a high titer of ANCA does not imply the presence of disease.

Case Description: A 71 year-old woman was admitted with the chief complaint of gross hematuria. Her laboratory values indicated a Cr 1.52 mg/dl and advanced proteinuria of 7.5 g/g·Cr. There was no fever, and her white blood cells were within the normal range. Further examination revealed a high myeloperoxidase (MPO) -ANCA level (96.6 U/ml, normal < 3.5), no monoclonal proteins, and normal complement levels. Thus, a renal biopsy was performed; it showed mesangial proliferation in all 13 glomeruli and crescents formation in 5 glomeruli. Immunofluorescent staining was positive for IgG, C3, and C1q. The deposition of fibrils was recognized in the glomerulus by electron microscopy. In addition, immunohistochemical staining for DNA-J heat shock protein family member B9 (DNAJB9) was strongly positive in the glomerulus. These results indicated the presence of fibrillary glomerulonephritis (FGN). Hence, we performed induction therapy with prednisolone and intravenous cyclophosphamide, and subsequently the patient's renal function improved.

Discussion: From the histological findings, it was considered that the patient's renal dysfunction was caused by either FGN alone or from concomitant AAV and FGN. FGN is a rare disease found in 1% of renal biopsies. Although renal damage of FGN is caused by immune complexes, only approximately 17% of the cases are positive for M-protein, and 2% have hypocomplementemia. As the diagnosis required electron microscopy examination, some cases may have been overlooked. DNAJB9, a recently discovered histological marker of FGN, is expected to improve diagnosic accuracy and therefore increase the number of reported cases.

TH-PO942

A Rare Case of Dual Glomerulopathy: Fibrillary Glomerulonephritis (FGN) and Membranous Nephropathy (MN) in a Patient with Chronic Inflammatory Demyelinating Polyneuropathy

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Introduction: FGN is a rare glomerular disease characterized by random fibrillary deposits. Usually idiopathic, it can be associated with malignancy, monoclonal gammopathy, or autoimmune disease. Its association with MN with CIDP is rare.

Case Description: A 68-year-old Burmese female presented with lower extremity edema and paraparesis of a 3-month duration. Her history was significant for latent tuberculosis, HTN and uncontrolled DM2 (last A1c of 14.5%). On exam, hypertension, renal anasarca and paraparesis were noted. Labs were significant for hypoalbuminemia (1.8) and nephrotic range proteinuria (6.8g/24hr). Serum Cr was at baseline (0.6). ANA (320), C3, C4, and Kappa/Lambda ratio (1.86) were mildly elevated. HIV, hepatitis panel, RPR, anti-dsDNA Abs, SPEP, UPEP, antiphospholipid Abs, cryoglobulins were negative. CT scan showed left renal vein thrombus. Electromyography showed mixed axonal polyneuropathy and she was diagnosed with CIDP. Renal biopsy revealed diffuse mild mesangial expansion, Congo red negative. No Kimmelstiel-Wilson nodules were seen. Immunofluorescence (IF) demonstrated diffuse granular capillary and mesangial staining for IgG (3+), C3 (2+), IgA (1+), C1q (trace), kappa (4+) and lambda (4+). IF staining for M-type PLA2R showed 3+ diffuse, granular staining predominantly in subepithelial distribution. EM showed segmental mild BM thickening and subepithelial granular deposits with diffuse effacement of foot processes (>90%). In addition, there were regions of mesangial and para-mesangial intramembranous non-branching fibrillary deposits, 12-28nm in diameter. The renal disease was treated with furosemide, lisinopril, prednisone, and tacrolimus with improvement in proteinuria and lower extremity edema. CIDP was treated with IVIG. The patient is currently in clinical remission with stable CKD4.

Discussion: While FGN may have granular subepithelial deposits that mimic MN, positivity for anti-PLA2R is unique, suggesting dual glomerulopathy with coincidental Primary MN. FGN associated with MN in the setting of CIDP is very rare. More studies are needed to help understand these complex associations.

TH-PO943

IgA Nephropathy Associated with Intravesical Bacillus Calmette-Guerin: A Case Report

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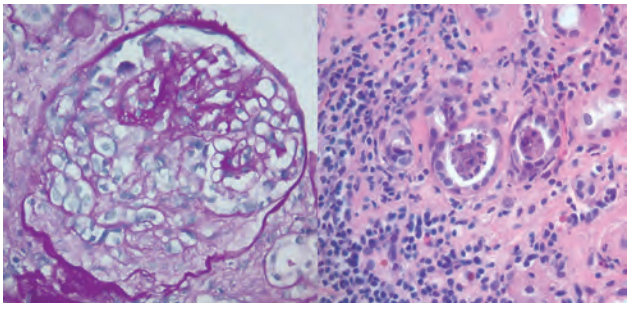
Introduction: BCG immunotherapy has remained crucial in the treatment of non-muscle invasive bladder cancer. Serious systemic complications can occur including granulomatous inflammation in various organs (BCGosis), reactive arthritis, and disseminated BCG. We present a unique case of BCGosis associated with new onset IgA nephropathy (IgAN).

Case Description: A 79 year-old man with type 2 diabetes, chronic kidney disease stage 3A received intravesical BCG therapy two months prior to presentation and developed caseating granulomas of the liver thought secondary to *Mycobacterium bovis* abdominal infection. He subsequently presented with altered mental status, dyspnea, abdominal pain, and acute kidney injury two weeks after starting antitubercular therapy. RIPE therapy was discontinued, however his creatinine continued to rise. He developed uremic symptoms with a creatinine peaking at 4.0 mg/dL, nephrotic-range proteinuria and an active urine sediment with many dysmorphic RBCs and mixed cellular cell casts. Prednisone 50 mg daily was started, and a kidney biopsy was arranged. Serologic evaluation was unremarkable and complement levels were normal. Renal biopsy showed focally crescentic IgAN with acute tubular injury and focal necrosis (Figure). He was continued on a prolonged steroid taper and lisinopril was started. After several months his creatinine had improved to 2.70 mg/dL.

Discussion: This is the first reported case of IgAN associated with intravesical BCG therapy. Treatment is challenging given the need to balance immune suppression with antitubercular treatment. BCGosis is a rare but serious complication of BCG therapy and has been associated with other renal pathology including granulomatous interstitial nephritis, Henoch Schönlein purpura and membranous nephropathy.



TH-PO944

A Rare Case Report of Systemic Lupus Erythematosus (SLE) with Acute Nephritis, Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis, and Thrombotic Thrombocytopenic Purpura (TTP)

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Introduction: Thrombotic thrombocytopenic purpura (TTP) is a potentially fatal disorder that requires urgent identification and treatment. The association of TTP with systemic lupus erythematosus (SLE) and vasculitis has been reported, however, never simultaneously.

Case Description: A 33-year-old woman with history of SLE presented with acute abdominal pain, fever, arthralgias, and skin rash. She had acute severe hypertension, diffuse abdominal tenderness, and petechial rash. Diagnostic work-up revealed active urine sediment with proteinuria and hematuria, elevated creatinine, anemia, and thrombocytopenia. She was diagnosed with acute lupus nephritis and early microangiopathic hemolytic anemia in the setting of hypertensive urgency and started on intravenous methylprednisolone 500 mg once a day. Within 48 hours she developed shock with multiorgan dysfunction and succumbed to her illness. Laboratory tests later showed ADAMTS13 activity less than 10% consistent with TTP and p-antineutrophil cytoplasmic antibody (ANCA) positivity. Autopsy revealed small vessel vasculitis of the visceral organs. Kidney biopsy demonstrated diffuse proliferative glomerulonephritis.

Discussion: This case illustrates the occurrence of SLE nephritis, p-ANCA vasculitis, and severe TTP with rapidly fatal course, and the importance of having a low threshold for initiating plasma exchange therapy. Based on our literature search, this is the first case to report on these three afflictions occurring at the same time. The nonspecific signs and symptoms of TTP may hamper a physician's ability to suspect it on clinical grounds alone, especially in patients with underlying autoimmune conditions. Therefore, when patients with SLE present with thrombocytopenia and features of MAHA, the possibility of TTP should be considered with prompt initiation of empiric plasmapheresis while awaiting test results for confirmation.

TH-PO945

Leukocyte Chemotactic Factor 2 Amyloidosis (ALECT 2) in a Young Female

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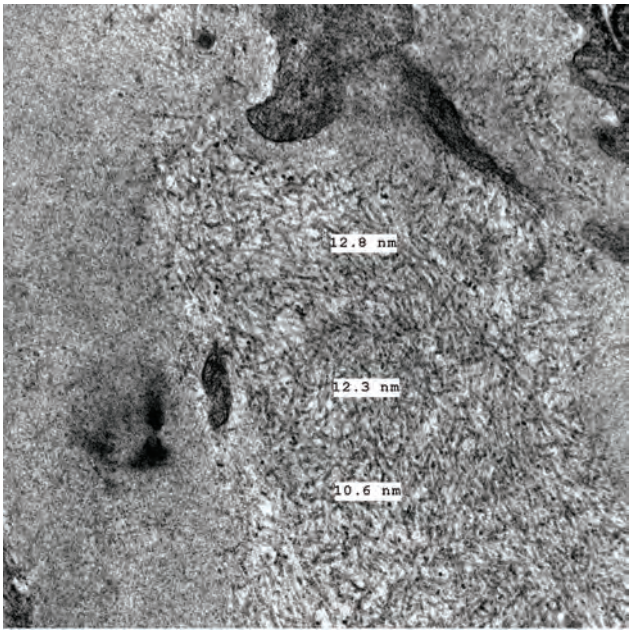
Introduction: ALECT2, initially described in 2008 is now the third most common cause of renal amyloidosis. Patients typically present in the seventh decade of life. We describe a unique case of ALECT2 presenting in a young female after a previous biopsy diagnosis of IgA Nephropathy.

Case Description: A 46-year-old Hispanic female with CKD 3 due to IgA nephropathy was evaluated for rising creatinine from 1.7 to 2.7 mg/dL and proteinuria (Urine protein/creatinine 3.5 g/g). She was on losartan, triamterene-hydrochlorothiazide. Repeat kidney biopsy showed moderate to severe interstitial fibrosis and tubular atrophy with 70% globally sclerotic glomeruli on light microscopy. Immunohistochemistry was positive for Ig A and equivalent lambda and kappa stains. Electron microscopy revealed abundant fibrillary deposits and a Congo red stain for amyloid was strongly positive. Liquid chromatography mass spectrometry analysis was consistent with ALECT2 amyloidosis. She was referred to an Oncologist and placed on doxycycline based on evidence of amyloid resorption from studies of other amyloid subtypes. Her creatinine improved (1.7-2mg/dl) although with persistently elevated proteinuria at 3.7g/day.

Discussion: Most cases of ALECT2 described are in older population and it is unclear if age at diagnosis affects prognosis. There is yet no specific treatment for ALECT2. For patients who progress to ESRD, renal transplantation has been shown to be a good therapeutic option. So far, very few studies have described patients with IgA nephropathy and ALECT2. We describe an uncommon case in a young patient, and it highlights the need for thorough re-evaluation of patients with acutely worsening renal function or proteinuria, in the setting of known renal disease. A repeat biopsy is often required in such cases as a different pathology is a possibility.



TH-PO946

IgA Nephropathy in Patients with Psoriatic Arthritis: A Case Series and Systematic Review of the Literature

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Introduction: There are cases in the literature of patients with IgAN and PsA, leading to the hypothesis that they may be biologically associated. Here, we present 2 cases and a systematic review of the literature of IgAN coexisting with PsA.

Case Description: Case 1: A 26 year-old man with a history of psoriasis in childhood was diagnosed with PsA at age 20 after developing back pain and bilateral dactylitis. NSAIDs and leflunomide were ineffective, but arthralgias improved on oral methotrexate and adalimumab. SCr was 1.1-1.3 mg/dL (eGFR 52 mL/min) and UA showed 2+ blood, trace protein, 10-20 RBCs/hpf and no WBCs. UPCR ranged from 100-300 mg/g. Microhematuria persisted and Cr increased to 1.6. A kidney biopsy showed IgAN (Oxford M1, E1, S0, T0, C1). He continued on methotrexate and adalimumab; 3 years later, SCr is 1.1, he has normal proteinuria and no hematuria. Case 2: A 56 year-old woman had severe psoriasis since childhood and a 10-year history of PsA (axial and non-axial joints) controlled with infliximab until she stopped treatment due to atypical mycobacterial pneumonia. She then presented with AKI requiring hemodialysis. Kidney biopsy showed IgAN (M1, E1, S1, T0) and AIN, attributed to rifampin or ethambutol. She was treated with prednisone and recovered kidney function after 20 days. One year later, she presented with shortness of breath, edema, eGFR 9 mL/min, UPCR 3.64, and microhematuria. Repeat kidney biopsy showed IgAN (M1, E1, S1, T1). She was treated with steroids and cyclophosphamide, with improvement to eGFR 22 mL/min. Four months later, she expired with unknown cause of death.

Discussion: Literature Review Our systematic review of the literature identified 16 additional cases of coexisting IgAN and PsA dating back to 1982. Including our two, the cases comprise 14 male and 4 female patients from the USA, Europe, and Japan. Median age of diagnosis of PsA and IgAN were 42 and 47, respectively, with only 1 pediatric case. PsA predated IgAN in 10 patients (median time from PsA to IgAN diagnosis in these patients 5 years). Serum IgA levels were elevated in 7/8 patients for whom this was described. There is heterogeneity in these patients' presentations, treatments, and outcomes. Conclusion Further study is warranted to determine whether there is a pathophysiological link between IgAN and PsA.

TH-PO947

The Cryo Menace

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Introduction: Membranoproliferative glomerulonephritis (MPGN) and cryoglobulinemia is a well-recognized complication of HCV infection. We present an interesting case of persistent cryoglobulinemia and MPGN despite sustained remission of hepatitis C treated with Harvoni (direct-acting antiviral).

Case Description: 56 year old man with a history of Hepatitis C cirrhosis, previously treated with Harvoni, was referred for proteinuria and hematuria. Besides mildly elevated transaminases and indirect Bilirubin, his metabolic profile was unremarkable. Protein creatinine ratio was 2gm/gm. Hepatitis C PCR was undetectable. Serology showed low complement levels and normal values of HbA1c, ANA, Anti ds-DNA, ANCA,

Anti-PLA2R abs, and hepatitis B and C antibody. Serum and urine, protein electrophoresis with immunofixation, failed to reveal any monoclonal proteins. Interestingly, cryoglobulins were detected in the serum and a renal biopsy demonstrated membranoproliferative glomerulonephritis with abundant, non-organized, predominantly subendothelial deposits (Fig A)

Discussion: MPGN is a pattern of glomerular injury that is characterized by mesangial hypercellularity, endocapillary proliferation, and double-contour formation along the glomerular capillary walls associated with cryoglobulinemia and Hepatitis C infection. Treatment with direct-acting antivirals (DAA) has curative sustained viral response (SVR), which has been shown to demonstrate cryoglobulinemic quiescence. Our case is unique given the persistence of circulating cryoglobulins and continued glomerular injury, despite SVR. Case of vasculitis and DAH in a patient with Hepatitis C treated with Harvoni was previously reported. This probably suggests that these antibodies propagate disease activity independent of HCV RNA load. Treatment with immunosuppression may be warranted, if there is nephrotic range proteinuria, a reduced estimated glomerular filtration, and/or severe histologic changes such as crescents on renal biopsy.

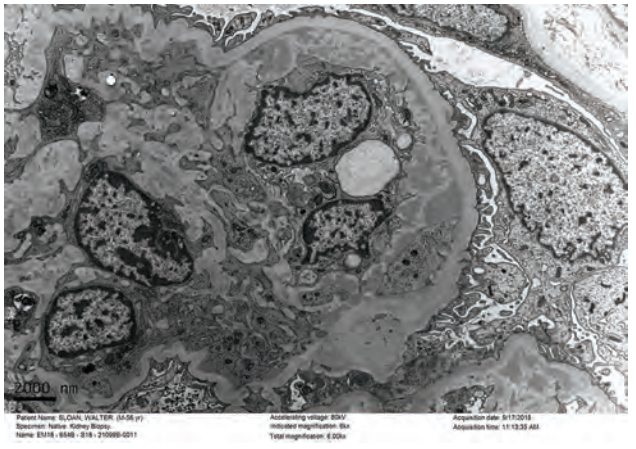

Fig A

TH-PO948

Acute Lupus Hemophagocytic Syndrome as Initial Presentation of Membranous Lupus Nephritis: Case Report with Successful Treatment

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Introduction: Acute Lupus Hemophagocytic Syndrome(ALHS) is a rare entity. It is highly unusual to diagnose lupus nephritis in an adult presenting as ALHS. Both ALHS and SLE responded well to therapy with MMF with steroids, which has rarely been described in literature

Case Description: 40-year-old Hispanic lady with fibromyalgia, hypothyroidism and hypertension, presented with fever, weakness, myalgia and photosensitivity. Physical examination was significant for alopecia and 3/5 muscle strength in lower extremities. No evidence of synovitis or organomegaly. Investigation: creatinine 0.4, albumin 2.4, AST 168, ALT 52, LDH 387, ALP 108, triglycerides 674, ferritin 3211, hemoglobin 7.1, WBC 0.9, platelets 127, ANA+ (>1:160), +dsDNA, +smithAb, low C3 and C4. UA was positive for RBC and protein. Urine protein/creatinine ratio was 1.2g/day. Bone marrow biopsy was done, showing erythrophagocytosis. Soluble IL-2 receptor (CD25) level and CD8 immune competence panel were normal. She fulfilled SLICC criteria for SLE. Renal biopsy showed membranous lupus nephritis class V She was started on prednisone 60 mg daily and MMF 500 mg twice a day and later increased to 1000 mg twice a day and gradually, prednisone was tapered down to 5 mg daily. Significant improvement in symptoms noted and labs including ferritin, triglycerides and blood counts bacame normal and protenuria resolved.

Discussion: HLH (Hemophagocytic lymphohistiocytosis) is a life-threatening disorder associated with high mortality Secondary HLH results from underlying infectious, malignant and autoimmune conditions. When HLH is attributed to SLE, it is called Acute Lupus Hemophagocytic Syndrome(ALHS). Incidence of HLH in SLE is estimated to be around 0.9% to 4.6% with a mortality rate varying from 5% to 35%. Clinical manifestations include high-grade fever, hepatosplenomegaly, lymphadenopathy and coagulopathy. Abnormal laboratory findings include cytopenias, hyperferritinemia and hypertriglyceridemia. There are no randomized trials to guide therapy. Treatment in ALHS is aimed at managing the underlying condition. If unresponsive Etoposide is used. This case highlights the importance of early recognition of ALHS, to prevent high morbidity and mortality. MMF and prednisolone induction and maintenance therapy is a viable option in patients with ALHS

TH-PO949

Minimally Proliferative Glomerulonephritis with Mesangial Deposition of Monoclonal IgM Lambda in a Patient with Marginal Zone Lymphoma and Acute Hepatitis C

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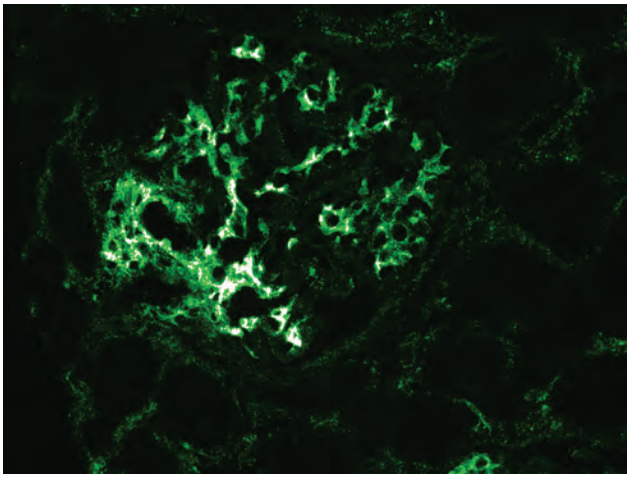
Introduction: We present an unusual renal manifestation of splenic marginal cell lymphoma and hepatitis C virus infection.

Case Description: A 57 year-old man presented with recurrent angio-edema. Abdominal CT showed splenomegaly and enlarged lymph nodes. Bone marrow biopsy showed splenic marginal cell lymphoma (MCL) with monoclonal lambda restriction. Three weeks later he developed acute hepatitis C, viral load > 30 x 106 / IU/ml. One month later he developed nephrotic syndrome and RBC casts. Urine protein increased from 14 mg/dl to 7.8 g/day, serum albumin 3.2 g/dl. Serum cryoglobulins were negative and creatinine was 1.0 ml/dl. ANA, ANCA, C3, C4 were normal. Renal biopsy showed mild focal mesangial hypercellularity and no endocapillary proliferation, necrotizing lesions, crescents, or microthrombi. Congo red negative. There was granular mesangial deposition of IgM lambda. IgG, C3, IgA, Kappa, and C1q were negative. EM showed diffuse foot process effacement and no fibrillary or microtubular forms.

Discussion: MCL is rare, 5-10% of NHL. There is an association of MCL with HCV seropositivity, mechanism unknown. Case reports describe 3 patients with MCL and MPGN with monoclonal IgM deposits, either IgM kappa or IgM lambda predominant. Our patient had acute HCV with negative cryoglobulins; previous cases had both chronic HCV infection and cryoglobulinemia or cryoglobulinuria. Electron microscopy in our patient did not show cryoglobulinemic immune deposits. The hepatitis C virus may be causally involved in MPGN with monoclonal IgM associated with MCL by a mechanism independent of the production of cryoglobulins. References 1 Chelioti E, Efthimiou E et al Nephrourol Mon 2014 (Jul; 6 (4) e18391 2 Yamada M, Deitzer, D et al Am J KidneyDisease2016; 67 (5) A1-A118 3 Bracci, P, Benavente, Y et al J Natl Cancer Inst monographs 2014 48, 52-66;



IgM Lambda in Mesangium

TH-PO950

Congophillic Fibrillary Glomerulonephritis: A Diagnostic Challenge

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Introduction: Fibrillary glomerulonephritis is characterised by the presence of randomly orientated nonbranching fibrils larger than those found in amyloid and lack the histochemical staining of amyloid. The absence of Congo Red reactivity has traditionally been a defining feature to differentiate it from amyloid glomerulopathy. We examined two cases showing the existence of Congophillic fibrillary glomerulopathy.

Case Description: Case 1: A 67 year old man presented with peripheral oedema and subnephrotic proteinuria on a background of poorly controlled hypertension. Initial renal biopsy suggested a focal segmental glomerulosclerosis with 13.9 nm fibrils on electron microscopy in the previous year. Despite treatment with rituximab, cyclosporin and cyclophosphamide, there was ongoing proteinuria with repeat renal biopsy showing Congo Red positive staining with 15.9 nm fibrils present. A monoclonal gammopathy of uncertain significance with IgM lambda was found. Case 2: A 51 year old man presented with newly diagnosed diabetes and was found to have subnephrotic proteinuria and microscopic haematuria. He underwent a renal biopsy finding Congo Red positive deposits with ultrastructural findings of 20 nm fibrils. Subsequent screening for malignancy and lymphoproliferative disease were negative. Despite immunosuppression with rituximab, cyclophosphamide and prednisone, the patient continues to have ongoing proteinuria.

Discussion: These two cases highlight the importance of recognising cases of Congophillic fibrillary glomerulonephritis which represents both a diagnostic and management challenge. Differentiating the renally-limited from the systemic immunoglobulin related amyloidosis is crucial to prevent misdiagnosis and inappropriate treatments such as the chemotherapy used to treat amyloid or immunotactoid glomerulopathy. Careful analysis of the ultrastructural characteristics combined with mass spectrometry and the use of novel biomarkers such as DnaJ homolog subfamily B member 9 (DNAJB9) could help discern such cases of Congophillic fibrillary glomerulonephritis.

TH-PO951

Double Trouble: Pulmonary-Renal Syndrome due to IgG4-RD and Myeloperoxidase-ANCA Vasculitis

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Introduction: IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition that could be similar or overlap with ANCA-associated vasculitis (AAV).

Case Description: 38- year old female with a history of inflammatory arthritis and high ANA titer, but no definite diagnosis of lupus, on hydroxychloroquine presented with chest pain, dyspnea and hemoptysis for one month. She also reported recurrent sinusitis, arthralgia, and Raynaud's symptoms. Urinalysis revealed hemoproteinuria and cellular casts. Urine protein/creatinine was 2.8 grams. Serum creatinine rose from 0.7 to 1.08 mg/dl. CT Chest showed right upper lobe consolidation with cavitation. Anti MPO antibody was positive for >100 U/ml (0.0-9.0 U/mL). Serum complements were normal and anti-double strand DNA was negative. Initially, the patient was diagnosed with microscopic polyangiitis (MPA). However, lung biopsy noted a fibro-inflammatory lesion with elevated IgG4 positive plasma cells (20-30 per HPF) typical of IgG4-RD. Serum IgG4 level was elevated. Kidney biopsy showed membranous glomerulonephritis with cellular crescents and numerous subepithelial and intramembranous deposits that were negative for PLA2R immunofluorescence. Acute tubulointerstitial fibrosis was noted. Lack of C1q deposition and absence of tubuloreticular inclusions argued against lupus membranous disease. Patient was ultimately treated with pulse dose steroid and Rituximab, which induced remission of both IgG4-RD and MPA manifestations.

Discussion: In the literature, two entities have been described: IgG4-RD with ANCA positivity and AAV associated with increased IgG4-positive plasma cells. Our patient presetned with crescentic membranous GN and a very high anti MPO antibody. The histological features of lung biopsy however showed characteristics of IgG4-RD. Although membranous GN is reported both with AAV and IgG4- RD, it is not a typical renal biopsy finding of either of those diseases. Corticosteroids are the first line therapy in IgG4-RD without any adjuant immunosuppressive therapy. However, because of ANCA positivity and the presence of crescentic GN, our patient was treated with rituximab as well in addition to the steroids. We need to consider the possibility of IgG4-RD in patients with AAV and vice versa for appropriate treatment plan and prognosis assessment.

TH-PO952

IgG-4 Positive Linear Deposition Anti-Glomerular Basement Membrane Nephritis with Negative Glomerular Basement Membrane Antibody (GBM Ab)

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Introduction: Anti-glomerular basement membrane (anti-GBM) nephritis is an antibody mediated small vessel vasculitis usually caused by IgG antibodies with predominance of IgG1 and IgG3 directed against basement membrane antigens.

Case Description: 22 years old morbidly obese male with history of asthma, recurrent ear infections requiring Eustachian tubes, smoking and exposure to polyvinyl chloride, presented with 3 months of fatigue and was found to have proteinuria on urinalysis. He denied fever, chills, chest pain, cough or hemoptysis, abdominal pain, melena, arthralgias, edema, dysuria, hematuria or tea-colored urine. On physical exam, he was afebrile with stable vital signs and absence of sinus tenderness, lymphadenopathy, synovitis, rash and edema. Chest, cardiovascular and abdominal exam were unremarkable. 24-hour urine protein was 3.8g and albumin was 2.4g. Urinary sediment showed red cell casts. Labs showed a serum creatinine: 1-1.2mg/dl, serum albumin 3.7g/dl, HbA1c 5.2% and negative anti-DNA, ANA, cANCA, pANCA, PR3, MPO, anti-GBM, RF, Jo-1, cryoglobulins, HIV, HBV, HCV, SPEP and UPEP. Serum complement levels and free light chains ratio were normal. Renal ultrasound showed normal size kidneys. Chest CT showed scattered pulmonary nodules < 5 mm. Renal biopsy showed proliferative glomerulonephritis with 2/17 glomeruli with crescents and positive linear reaction for IgG4 along the GBM in immunofluorescence and foot process effacement in electron microscopy. He was started on prednisone 80mg and cyclophosphamide 2.5mg/kg/d; plasmapheresis was not done due to negative anti-GBM titers. Few months later he was started on lisinopril 40mg. After 19 months of treatment, 24-hour urine protein decreased to 0.14g.

Discussion: Usually anti-GMB nephritis presents as rapidly progressive GN rather than with nephrotic range proteinuria. Patients with deposition of IgG on the GBM on immunofluorescence and negative for circulating antibodies by conventional assays, may be positive when tested by highly sensitive biosensor assays. In anti-GBM disease, IgG1 and IgG3 subclasses are the usual antibodies but rarely IgG4 as these antibodies may not be detected on routine assays. Patients with diabetic nephropathy may present with linear IgG but should not have crescents or cellular casts as noted in our patient.

TH-PO953

A Case of Familial Fibrillary Glomerulonephritis in Living Related Kidney Transplantation (LRKT)

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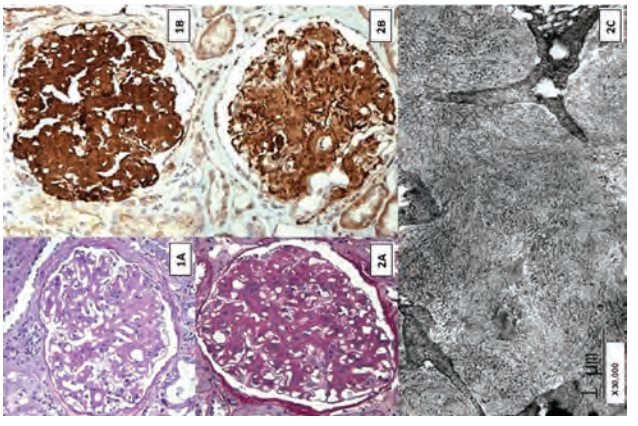
Introduction: Fibrillary glomerulonephritis(FGN) is a rare form of kidney disease found in ~1.0% of adult native kidney biopsies with only 4 reported cases of familial FGN. The discovery of protein DNAJ heat shock protein family (Hsp40) member B9 (DNAJB9) has aided diagnosis of FGN.

Case Description: A 49-year-old African-American man was found to have proteinuria on routine exam with UPCR 6 g/g and serum creatinine(Cr) 1.0 mg/dL. Renal biopsy later revealed FGN. Light microscopy(LM) showed diffuse mesangial matrix expansion with thickened glomerular capillary walls(GCW) (Fig 1A) with negative Congo red stain. Immunofluorescence(IF) showed 3+ staining for IgG, C3 and lambda(L), 2+ staining for kappa(K). Electron microscopy(EM) showed linear, randomly arranged fibrils with average diameter of 16 nm. DNAJB9 stain done later was strongly positive (Fig 1B). Further workup did not reveal monoclonal gammopathy and he had no known family history of kidney disease. He was treated with steroids as immunosuppressive therapy(IST). He presented to Columbia 5 years later with CKD Stage 5, thus further IST was held. At age 55, he underwent LRKT from his son. Prior to organ donation, his son had SCr of 0.88mg/dL, UA with negative blood and trace protein, UPCR 95mg/g. Post revascularization kidney biopsy showed FGN. LM showed mild mesangial proliferation with scattered double contours (Fig 2A) and negative Congo red stain. IF showed mesangial and segmental GCW staining for IgG(2+), C3(1-2+), C1(1+), K(2+) and L(2+). DNAJB9 stain was positive (Fig 2B). EM showed randomly oriented fibrils with mean diameter of 18 nm (Fig 2C). These findings are consistent with donor-derived FGN, indicating a familial form of FGN.

Discussion: We describe a form of familial FGN confirmed by DNAJB9 staining on biopsy. Presence of well-formed fibrils and glomerular changes in the donor kidney despite minimal clinical findings suggest in-depth evaluation of related donors may be important in FGN.



TH-PO954

A Case of Poststreptococcal Glomerulonephritis with Concurrent ANCA-Associated Vasculitis and Aortitis: Challenges in Diagnosis and Treatment

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Introduction: Aortitis is an uncommon condition with either infectious or rheumatologic etiology. Common rheumatologic causes of aortitis include the large vessel vasculitides, Takayasu's arteritis and giant cell arteritis; however, other rheumatologic causes exist, such as ANCA-associated vasculitides (AAV). A few previous cases of aortitis associated with perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and anti-myeloperoxidase (MPO) antibody have been reported, however, in medical literature, AAV is infrequently discussed in association with large vessel involvement. It is rare to find cases of post-streptococcal glomerulonephritis (PSGN) in which there is concurrent AAV affecting large vessels.

Case Description: We report a case of a 36-year old Hispanic woman with an initial presentation of right leg cellulitis with positive antistreptolysin-O titers. Her past medical history was significant for previous right leg skin lesion and right groin lymph node abscesses. She developed hematuria during her admission and severe epistaxis. Due to worsening kidney function and persistent hyperkalemia, hemodialysis was initiated. Kidney biopsy results supported PSGN. P-ANCA, MPO, and proteinase-3 (PR3) antibody assays were positive. Magnetic resonance angiography results supported aortitis. Due to treatment for active infection, immunotherapy was postponed. Repeat P-ANCA, PR3, and MPO were persistently positive. Subsequently, she developed a cough and hemoptysis, after bronchoscopy she was determined to have diffuse alveolar hemorrhage. Methylprednisolone and plasmapheresis were initiated, followed by induction of rituximab.

Discussion: This case highlights a diagnostic dilemma in vasculitis classification: determining whether the aortitis was due to ANCA-associated vasculitis, large vessel arteritis, or an infectious process. Renal biopsy and clinical picture supported an infectious etiology of glomerulonephritis, thus the positive p-ANCA and MPO antibody assay were initially thought to be induced by infection, however, our patient had persistently positive ANCA results and developed DAH. This case also highlights the challenge in starting immunosuppressive treatments during infection, and, finally, the response to Rituximab and plasmapheresis therapies.

TH-PO955

Collapsing Glomerulopathy in an APOL1 Compound Heterozygous Patient with CMV Infection: The Double Hit Theory

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Introduction: Collapsing glomerulopathy (CG) is a rare and aggressive variant of focal segmental glomerulosclerosis (FSGS). Commonly associated with human immune deficiency virus (HIV). We present a case of CG in an HIV-negative African American (AA) patient with Cytomegalovirus (CMV) infection. The patient is compound heterozygous for APOL1 risk variants. We propose that CMV can act as a "second hit" in the pathogenesis of CG in the genetically predisposed individuals.

Case Description: A 31-year-old AA female with sickle cell disease was admitted with 2 weeks of fever, malaise, nausea, vomiting, cough and chest wall tenderness. On admission her serum creatinine was 2.39 mg/dl and peaked at 7.19mg/dl. Urine investigations revealed nephrotic range proteinuria. CMV DNA PCR was positive in plasma and urine. Renal biopsy showed features of collapsing glomerulopathy, characterized by collapse of the capillary loops, prominence of the overlying epithelial cells and extensive effacement of foot processes. Genetic testing showed compound heterozygous mutations in the APOL1 gene. The patient was treated with high dose steroids and anti-viral therapy with ganciclovir. With resolution of CMV infection, she made full renal recovery.

Discussion: CG as well as other nephropathies have well established racial disparity, predominantly affecting AA patients. The discovery of apolipoprotein L1 gene (APOL1) helped improve our understanding of genetic predisposition to renal disease. Increased risk can be attributed to the presence of two specific variants in the APOL1 gene (G1 and G2). These variants are present in about 30% of APOL1 alleles in the AA population. Individuals with one or two risk alleles are at greater risk for developing FSGS, hypertension-attributed ESRD, sickle cell-associated kidney disease, HIV-associated nephropathy, and shortened graft survival of kidney transplants. CG was initially described in HIV patients but also associated with viral infections (e.g. parvovirus B19 and CMV), lymphoproliferative disorders, autoimmune diseases and sickle cell disease. CMV infection could be a second hit in the genetically susceptible patient. Identification of CMV infection in patients with CG is important as they usually improve with treatment of the viral infection.

TH-PO956

Favorable Effect of Bortezomib in Patients with Noninfectious Mixed Cryoglobulinemia Complicated with B Cell Lymphoma: Experience of Two Cases

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Introduction: Non-infectious mixed cryoglobulinemia (MC) is rare disorder associated with autoimmune or hematological diseases, eventually causing systemic vasculitis with organ damage. Due to the low frequency of this disease, the therapeutic strategy for non-infectious MC has not been established. Here we report that two cases with non-infectious MC complicated with B cell lymphoma who had good response to a combination of corticosteroid and bortezomib (BTZ), a proteasome inhibitor used for the treatment of multiple myeloma and B cell Lymphoma.

Case Description: Case1. A 61-year-old man with a medical history of mucosa-associated lymphoid tissue (MALT) lymphoma presented with nephrotic syndrome, purpura, and congestive heart failure. Laboratory tests revealed monoclonal IgM-κ and presence of cryoglobulins (CG). A renal biopsy showed glomerulonephritis with the deposits of IgM-κ. A diagnosis of non-infectious cryoglobulinemic glomerulonephritis was made and treatment was initiated with corticosteroid, rituximab and plasma exchange with no improvement of clinical manifestations. After the informed concent, the patient received BTZ in combination with corticosteroid, leading to amelioration of his clinical manifestations. Case2. A 69-year-old man presented with dyspnea due to severe nephrosis. Serum monoclonal IgM-κ and CG were detected. A bone marrow biopsy revealed low-grade B-cell lymphoma. He was diagnosed with cryoglobulinemic glomerulonephritis due to non-infectious MC complicated with B cell lymphoma. He was treated with a combination therapy of BTZ with corticosteroid, and achieved clinical remission of nephrotic syndrome.

Discussion: We presented two case of non-infectious MC complicated with lymphoma in whom BTZ was added in the treatment protocol to ameliorate renal manifestations. The improvement of renal function was associated with the disappearance of serum CG and decrease of serum levels of monoclonal IgM-κ. These findings suggest that BTZ suppresses the IgM-κ producing plasma cells and the deposition of CG in glomeruli, leading to the improvement of nephrosis. BTZ had anti-inflammatory effects as well, presumably involved in the protection of renal injury. This is a first report to show that treatment protocol including BTZ lead favourable outcome in patients with non-infectious MC with B cell lymphoma.

TH-PO957

Recurrent C3 Glomerulonephritis

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Introduction: C3 Glomerulopathy encompasses dense deposit disease and C3 glomerulonephritis. On electron microscopy it is defined as C3 deposits more than 2 orders of other immunoglubulins. Pathogenesis involves activation of alternative complement pathway due to genetic or acquired mutations. Post infectious glomerulonephritis with persistent hematuria or proteinuria is termed as atypical. We present a case of C3 glomerulonephritis presenting as post infectious glomerulonephritis then crescenteric C3 treated with immunosuppression.

Case Description: A 54 year old female with history of glomerulonephritis (2008, 2017) presented with hemtaturia. Labs significant for creatinine 3mg/dl (baseline1.7), protein excretion 2g/day, C3 9mg/dl and C4 20mg/dl. Urine analysis with 4000 red blood cells. Workup for acquired factors showed normal factor H, serum C5b-9, negative C3 nephritic factor and CH50 less than 10mg/dl. Urine and blood cultures, antibodies to Proteinase-3, myeloperoxidase and genetic testing was negative. Intravenous steriods were given twice daily for 4 days, transitioned to prednisone. Due to increased creatinine hemodialysis was initiated. Biopsy showed crescenteric C3 dominant proliferative glomerulonephritis. Immunofluorescence 3+C3, 2+kappa and 1+lambda. Electron microscopy showed scattered subepithelial hump-like intermembranous and mesangial deposits. After 6 doses of cyclophosphamide 750mg, in 3 months renal function stabilized with creatinine 1.34mg/dl, urine protein excretion 0.8g and C3 153mg/dl. In 2008, kidney biopsy showed post-infectious glomerulonephritis, low C3 and CH50 responsive to steroids. In 2016 she presented with pyelonephritis, creatinine 2.8mg/dl, protein excretion 2 g/day, urinalysis 3+ red blood cells, low C3 and normal C4. Biopsy showed membranoproliferative glomerulonephritis with crescents. Immunofloresence positive for IgG 2+, C3 2+, kappa 1+ and lambda 2+. Creatinine and C3 levels normalized post steriod therapy.

Discussion: Atypical Post infectious glomerulonephritis and C3 glomerulopathy are two sides of the same coin involving alternative complement pathway activation as shown by our patient's biopsy findings. Due to repetitive steriod and immunosuppression responsiveness we conclude that recurrent cases of atypical post infectious glomerulonephritis be investigated for alternate pathway mutations. Novel anticomplement medications such as eculizumab may also be used.

TH-PO958

Anti-GBM Disease: A Case Report of an Atypical Presentation

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Introduction: Anti GMB disease is a rarely encountered, but well known entity. It can present with nephritic syndrome, alveolar hemorrhage, or both. It is typically associated with positive circulating anti GBM antibodies. We are repotting a case of seronegative anti GBM antibody disease presenting with RPGN picture.

Case Description: A 59 year old female with a history of hemochromatosis presented with complaints of night sweats and fevers. She was sent to the hospital by her PCP with abnormal labs and hypertension. Her physical exam was unremarkable. Her labs were remarkable for creatinine of 3.05 mg/dl, BUN of 32 mg/dl, eGFR of 23 ml/min/1.73 m and CRP of 113. Dipstick urinalysis was positive for blood and protein. Urine sediment exam showed dysmorphic RBCs. Measured urine microalbuminuria was 299 mg/g of creatinine. Extensive serological workup, including testing for anti GBM antibodies, was negative. Light microscopy exam of a kidney biopsy showed focal granulomatous and crescentic glomerulonephritis as well as focal interstitial granulomatous inflammation with giant cells. The immunofluorescence studies revealed findings consistent with IgG type anti-glomerular basement membrane disease. After pulse methylprednisolone was started, the creatinime started to trend down. The patient was eventually treated with prednisone tapper and rituximab with continuous improvement in her GFR.

Discussion: Anti GBM disease is frequently associated circulating IgG antibodies that commonly target cryptic, conformational epitopes within the NC1 domain of the alpha 3 chain of Type IV Collagen. These antibodies are usually detected in sera using different conventional serological methods. Seronegativity in anti GBM disease is extremely rare. We identified less than 10 cases describing this atypical presentation in the literature. In one case, anti GBM detection was variable with each relapse. Sero negative anti GMB disease has also been described to recur in renal allografts. Anti GBM antibodies are known to be heterogeneous with respect to collagen type IV domain reactivity in the sera of patients with anti-GBM antibody disease. This could explain the seronegativity of anti GBM disease when conventional serological methods are used. Cases with sero negative anti-GBM disease present challenges not only for diagnosis but also management, since anti GBM titers cannot be used to monitor these patients.

TH-PO959

Hydralazine-Induced Crescentic Pauci-Immune Glomerulonephritis Associated with Multi-Antigenicity

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Introduction: Hydralazine use is common for treatment of hypertension, and heart failure with the ability to induce lupus as a rare complication. Though mechanisms are not understood, it may also be a causal factor in antinuclear cytoplasmic antibody (ANCA) vasculitis (AAV). This emerging syndrome is characterized by crescentic pauci-immune

glomerulonephritis and classically positive antibodies, including anti myeloperoxidase (MPO) and anti-histone. We report a case notable for the wide array of auto antibodies, the combination of which has not been previously reported.

Case Description: A 71 year old male presented to the hospital with a two month history of fatigue. His past medical history included hypertension for which he was taking Hydralazine, and an ischemic cardiomyopathy. His lab results showed an elevation in serum creatinine of 3.2 mg/dL from a baseline of 1.2 – 1.3 mg/dL. Urinalysis revealed proteinuria and hematuria with accompanying red blood cells. Serologies returned positive not only anti-histone antibodies, but also for both MPO and anti-proteinase 3 (PR3) antibodies. In addition, was a high titer ANA, double stranded DNA, low C3, presence of lupus anticoagulant, and anti-cardiolipin IgG. Kidney biopsy revealed focal segmental necrotizing and crescentic glomerulonephritis, pauci-immune type, acute and subacute. CT chest was negative for pulmonary hemorrhage. Taken together, these findings seemed consistent with a drug induced AAV. Deemed to be the culprit, Hydralazine was discontinued and treatment rendered with pulse dose steroids, transitioning to tapering Prednisone and two doses of Rituximab. This led to a marked clinical and serologic improvement, which was not only rapid, but also proved durable.

Discussion: Drug induced AAV has been linked to certain agents, including Hydralazine. The presentation may be severe, and often associated antibody positivity such as MPO and anti-histone may hold the key to the diagnosis. Our case illustrates a vaster splay of antibodies, the combination of which has not been previously described. The mechanism by which these are induced and the implication to disease response and progression need be investigated further. Thorough medication history to identify those at risk, rapid discontinuation of the drug and prompt treatment may all lead to improved clinical outcomes.

TH-PO960

Dupilumab and Primary Membranous Nephropathy

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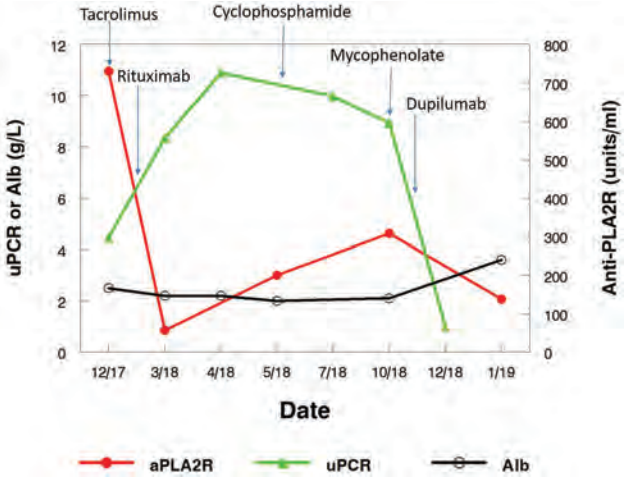
Introduction: Primary membranous nephropathy (MN) is an immune complex-mediated disease. In most cases patients develop autoantibodies to the phospholipase A2 receptor (PLA2R), often of IgG4 subclass. Effective immunosuppressive treatment of MN results in a decline in anti-PLA2R that precedes clinical resolution of the disease. We recently saw a patient who had PLA2R-positive MN that did not have a durable response to multiple therapies. She had severe atopic dermatitis that was treated with dupilumab, an interleukin-4 (IL-4) receptor antagonist. After dupilumab was started the nephrotic syndrome resolved.

Case Description: A 21 year-old female with a history of asthma and severe atopic dermatitis since childhood presented with nephrotic syndrome. A kidney biopsy showed PLA2R-positive MN. The Figure shows treatments, immunologic responses, and clinical responses over time. Despite significant immunosuppression her eczema persisted and worsened so dupilumab was started. Within 2 months of initiating dupilumab the anti-PLA2R levels decreased, albumin normalized, and the nephrotic syndrome resolved.

Discussion: MN, an autoimmune disease that involves activation of T-follicular helper cells and B cells. Several pro-inflammatory cytokines are increased in the urine and serum of patients with MN, including IL-4. IL-4 promotes B cell isotype switching to IgG4, differentiation of naïve T-helper cells to Th2 cells, and inhibits the differentiation of Th1 cells. Th2 cells then release IL-4 leading to a positive feedback loop. MN is characterized histologically by IgG4-dominant subepithelial immune complexes. Dupilumab is a human monoclonal antibody that blocks the IL-4 alpha receptor, inhibiting the effects of IL-4 and IL-13. IL-4 blockade in MN may help attenuate anti-PLA2R IgG4 antibody production, and combined with traditional immunosuppression treat refractory MN. Further prospective studies are warranted to define the role of IL-4 antagonism in the management of MN.



TH-PO961

Is Liposorber an Option for Lipoprotein Glomerulopathy in Pediatric African American Males?

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Introduction: Lipoprotein glomerulopathy is a rare inherited renal disease that is characterized by the accumulation of lipoproteins leading to the formation of lipoprotein thrombi with markedly dilated glomerular capillaries. The disorder is associated with an ApoE mutation leading to massive proteinuria and dyslipidemia with high chance of progression to chronic kidney disease. The first publication of a case was reported in 1989 by Saito, and has since been commonly reported in adult individuals of Japanese and Chinese descent.

Case Description: Interestingly, our report looks into the presentation of lipoprotein glomerulopathy in a 7 year old African American male who has been followed since birth for hypertension, hypercholesterolemia, nephrotic range proteinuria, and multiple past episodes of prerenal AKI. A renal biopsy was performed and diagnosis of lipoprotein glomerulopathy was confirmed by histological diagnosis from Vanderbilt. Genetic testing revealed a heterogeneous *mutation of ApoE2*. The patient also presents with hemihyperplasia of the right lower extremity, increasing our suspicion for a possible accompanying *WT1 gene mutation*. Treatment has been focused on controlling hypertension and symptoms of chronic kidney disease. Patient has been taking a beta blocker, angiotensin converting enzyme inhibitor, and calcium channel blockers for hypertension. These medications have been effective in reducing the blood pressure from 140-150/100 to 120-130/80. To treat for hypercholesterolemia that imposes continued damage on the kidneys of patients with this disorder, he has been taking fibrates and statins, but his cholesterol levels continue to be elevated, while triglyceride levels are well controlled. Further treatment evaluation is being focused on the possibility of beginning patient on Liposorber once per month to remove the high levels of LDL. Kidney transplant consideration is low due to recurrence being reported in all past transplanted kidneys.

Discussion: This case illustrates the possible expansion of a rare renal disease outside of commonly targeted population. Recognition of lipoprotein glomerulopathy and its clinical features will become critical in future evaluation of nephrotic syndromes in the pediatric population.

TH-PO962

Minimal Change Disease in an 82-Year-Old Man with Type 2 Diabetes Without Histologic Evidence of Diabetic Glomerulosclerosis on Renal Biopsy

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Introduction: Minimal change disease (MCD) in older adults with type 2 diabetes mellitus (T2DM) is a rare occurrence. Finding MCD in this population *without* diabetic glomerulosclerosis (DGS) is even more uncommon. We found only 16 reported cases of MCD in the setting of adult type 2 diabetes. Only 4 of those were confirmed to have MCD in the absence of DGS. We report a case of MCD in an 82 year old man with type 2 diabetes whose kidney biopsy showed no histologic evidence of diabetic glomerulosclerosis.

Case Description: An 82 year old man with a 10-year history of T2DM on insulin for 1 year presented with a one week history of lower extremity edema and shortness of breath. On presentation his serum creatinine was 1.4 mg/dl and his serum albumin 2.4 gm/dl. Protein in 24-hour urine was 14 grams. Serology and serum protein electrophoresis were negative. Kidney biopsy was performed. Light microscopy showed normal glomeruli with no evidence of glomerulosclerosis. Electron microscopy revealed diffuse effacement of foot processes diagnostic of minimal change disease. Patient was started on prednisone and achieved complete remission in 5 weeks. At his six-month follow up he was doing well. His creatinine was down to 1.0 and urine protein/creatinine was 0.07 g/g.

Discussion: This case illustrates the value of kidney biopsy in the diagnosis of severe nephrotic syndrome in adults with T2DM. Nephrotic syndrome occurring in a patient with diabetes is often presumed to be due to diabetic glomerulosclerosis and renal biopsy is usually not performed. However, in this patient there were a number of pivot points that suggested further exploration was necessary, including the degree of proteinuria and abruptness of the onset. This case is of clinical significance because MCD in an older diabetic can be easily missed, but if diagnosed, is almost always curable as it was in this patient. Our patient adds to the literature of MCD presenting in older adults with T2DM and provides a new upper age of reported occurrence. It is uncertain as to whether this is a truly rare occurrence or the result of under-reporting because kidney biopsy is infrequently performed in older adults with similar presentation. It is possible that the true incidence of MCD in older adults with T2DM may be less rare than the literature suggests.

TH-PO963

Unusual Presentation of Cryoglobulin-Positive Fibrillary Glomerulonephritis

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Introduction: Fibrillary glomerulonephritis encompasses approximately 1% of adult native kidney biopsies. Although considered a predominantly idiopathic disease, up to 1/3 reveal a secondary cause such as monoclonal gammopathy, autoimmune disease or malignancy. In the two largest case series published to date, only 2 of 126 had positive serum cryoglobulins; it is unclear if these patients had concurrent HCV infection. A

disease already associated with poor outcomes, little is known about those with Fibrillary GN and positive serum cryoglobulins.

Case Description: A 66 year-old female with history of longstanding diabetes mellitus, hypertension and stage III chronic kidney disease with serum creatinine 1.6mg/dL six months prior was admitted with abnormal labs including serum creatinine of 7mg/dL on routine testing. She denied localizing symptoms to explain worsening renal function. She was afebrile and initial blood pressure was 170/90mmHg. On physical exam, lungs were clear and there was no rash or edema. Repeat labs revealed serum creatinine 7.49mg/dL, BUN 57mg/dL, serum albumin 3.3g/dL and 7 grams of protein on 24hr collection. Urine sediment showed hematuria with dysmorphic RBCs and numerous WBCs. Further tests for HBV, HCV, HIV, ANA, ANCA, and anti-GBM were negative. Hypocomplementemia with undetectable C4 and normal C3 was present, along with elevated rheumatoid factor at 152 IU/mL; serum cryoglobulins were positive. SPEP was weakly positive for IgG lambda. Renal biopsy exhibited global glomerular sclerosis, and diffuse deposition of haphazardly arranged 15nm filaments within glomerular capillary walls and mesangial matrix on electron microscopy. Staining for DNAJB9 was positive. Despite treatment with Rituximab for 4 weeks, her disease progressed and required renal replacement therapy. Serum cryoglobulins remained positive after treatment.

Discussion: Fibrillary GN is a rare disease associated with poor renal outcomes and progression to ESRD. Only two previous cases of Fibrillary GN had positive serum cryoglobulins. There is little evidence to guide therapy in this disease, and even less is known about those with positive serum cryoglobulins. Efforts to identify secondary causes in such patients should include viral illness, malignancy and autoimmune disease. Further investigations to evaluate more effective therapeutic options are needed.

TH-PO964

Remission of Refractory THSD7A-Associated Membranous Nephropathy Using Rituximab: A Case Report

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Introduction: Rituximab (RTX) is reported to induce clinical remission in 60-80% of primary membranous nephropathy (MN) patients. Due to the rarity, only four thrombospondin type-1 domain-containing 7A (THSD7A) associated cases were included in clinical trials of RTX treating MN, without detailed description of clinical information or treatment outcome. Here, we reported the successful RTX treatment of a THSD7A-associated MN patient non-responsive to tacrolimus and glucocorticoids.

Case Description: A 72-year-old male was admitted to Xinhua Hospital because of persistent nephrotic-range proteinuria and non-responsive to tacrolimus and glucocorticoids. Laboratory results included 24hr proteinuria 6.2g, serum albumin 2.15g/dL and serum creatinine 1.39mg/dL. Renal biopsy results suggested MN with negative glomerular staining of phospholipase A2 receptor and IgG4 but positive THSD7A by immunohistochemistry. Serum THSD7A-antibody titer was 1:100 by indirect immunofluorescence. The patient had radical rectectomy 7 years ago without metastasis. Rectal cancer tissue was reviewed and weakly positive THSD7A staining was found, which can be seen in 43% of rectal tumors. Intensive screening ruled out cancer recurrence or metastasis and RTX was given at weekly dose of 375mg/m2 for four weeks. At month 6, the patient achieved partial proteinuria remission and THSD7A-antibody titer decreased to 1:10.

Discussion: In this refractory case, the treatment of RTX achieved partial remission of proteinuria and circulating THSD7A antibody depletion at month 6, supporting its good efficacy on THSD7A-associated MN. We also emphasize that screening for malignancy is warranted in THSD7A-associated MN before immunosuppressive therapy.

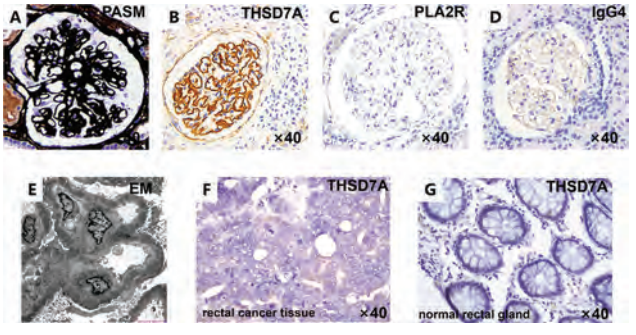

Fig.2 Histological findings.

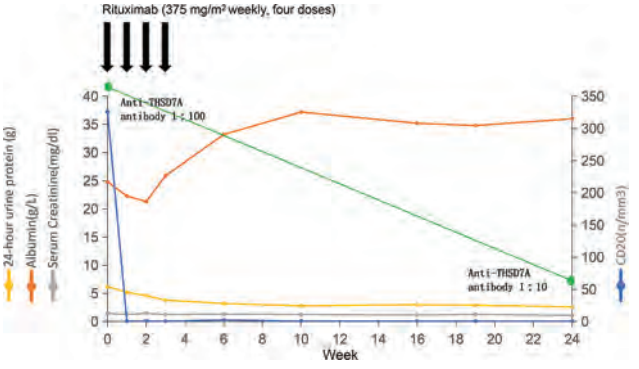

Fig.2 A summary of the clinical course.

TH-PO965

Tubular Basement Membrane Deposits in Lupus Nephritis

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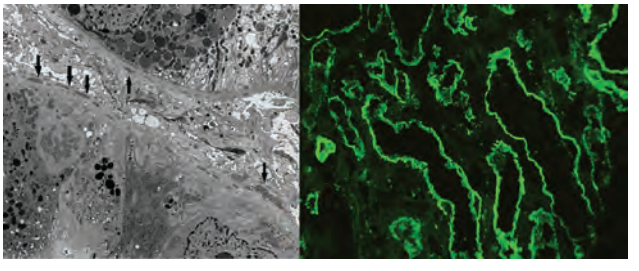
Introduction: Glomerular lesions are the main renal finding in lupus nephritis (LN). Extraglomerular deposits can be observed in more than half of LN biopsies but are typically observed in conjunction with glomerular findings. We present a unique case of LN with tubulointerstitial inflammation secondary to prominent TBM immune deposits without glomerular activity.

Case Description: 27 year old African American male with systemic lupus erythematosus (SLE) for 5 years, with biopsy proven LN class V, was admitted from nephrology clinic for work up of acute kidney injury. He was initially treated with hydroxychloroquine (HCQ) and prednisone at the time of his SLE diagnosis. On diagnosis of LN, 4 years later, mycophenolate mofetil (MMF) was added, which he was intolerant to and discontinued. He had 2 episodes of SLE flares for which rituximab was given. Azathioprine was added to his regimen of prednisone and HCQ after the second SLE flare. Prior to current presentation, the patient had started to taper his prednisone and was on 10mg daily. In this setting, his serum creatinine (SCr) rose to 4.32mg/dl from a baseline of 1.4-1.6mg/dl; C3 was low at 77; C4 was normal; dsDNA antibody was negative. He had an active urinary sediment. He was started on 125mg of methylprednisolone intravenously for 3 days. Renal biopsy was pursued to re-stage his LN and further determine the immunosuppression needed. Pathology showed active tubulointerstitial inflammation secondary to prominent TBM immune deposits without glomerular activity. He also had changes consistent with class V LN. He was discharged on oral prednisone 60mg daily, with a weekly 10mg taper, MMF 250mg daily, which he agreed to retry and HCQ 400 daily.

Discussion: Only 11 cases have shown predominant TBM LN in the literature. Studies have shown a correlation with TBM immune deposits and a twofold higher risk of end-stage renal disease or doubling of SCr after controlling for other factors. Thus, this finding is of prognostic significance. Treatment of predominant tubulointerstitial LN is not established. Most reported patients did not require cytotoxic immunosuppressive treatment and responded well to steroids alone.



TH-PO966

Renal Manifestations Associated with Bartonella Infection

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Introduction: Culture negative endocarditis constitutes about 8% of all cases. Bartonella henselae is a common causative organism. Here we discuss 3 cases of GN associated with B.henselae infections masquerading as vasculitis, IgA and focal necrotizing C3 GN.

Case Description: Case 1: A 56 y/o man with LVAD presented with SOB and AKI with rapid rise in SCr from 1 to 3.45mg/dL over 3 weeks. Lab showed positive ANA, ANCA (+PR3) and normal complements (Table). Renal pathology was highly suggestive of infection-associated GN. Additional w/u revealed B.henselae Ab IgG > 1:1024 and TEE revealed possible vegetation in RV pacemaker lead. He was treated with Doxycycline and rifampin, plus oral prednisone. F/U SCr in 1 year was 1.1mg/dL. **Case 2:** A 42 y/o man with bioprosthetic AV valve presented with a vasculitis rash and AKI

(SCr increased from 1.8 to 4 mg/dL). Labs showed hypocomplementemia and +ANA. Renal pathology revealed focal endocapillary proliferation with crescents. Infectious w/u revealed B.henselae and quintana IgG >1:1024, IgM >1:20. TEE revealed AV vegetation and was taken emergently for AV replacement. AV valve PCR was positive for Bartonella. Despite aggressive care post AVR, pt died on post-op day 9. **Case 3: A** 64 y/o man with prosthetic MV mitral valve, was admitted for evaluation of rapidly rising SCr (1.1 mg/dL to 6 mg/dL) over 2 wks. ANA/ANCA were neg. Renal pathology showed focal necrotizing crescentic GN with which stained for IgM, C3 and C1q. TEE showed MV vegetation and infectious w/u revealed B henselae and B quintana IgG >1:1024. He was started on HD, steroids, abx and underwent MV replacement. Pt was dialysis independent 3 mo after discharge.

Discussion: These cases demonstrate the need for high index for clinical suspicion for infectious etiology for GN in the presence of prosthetic valves or mechanical devices. Our 3 cases had very low clinical suspicion for infection at the time of initial evaluation. Serological tests and renal pathology prompted infection work up. Although all the patients had the same disease and had similar treatment, renal outcomes were very different. Awareness of Bartonella infection and early detection could have favorable patient outcomes.

Case	Age/Sex	Creatinine (baseline/ @Biopsy)	ANA	ANCA	C3/C4	Organism	Location of vegetation	Renal biopsy: Light	Renal biopsy: IF	Renal biopsy: EM	Outcome
1	56/M	1/3.5	1:160	Positive/ PR3	110/19.6	B.henselae IgG >1:1024	RV lead of LVAD	Focal proliferative glomerulonephritis, Cellular crescents	C3, C1q	Rare mesangial electron dense deposits, mild podocyte effacement	F/U Cr at 1 yr - 1.1
2	42/M	1.8/4	1:160	Positive (-MPO/-PR3)	21/4.2	B.henselae/B.quintana IgG >1:1024, IgM >1:20	Prosthetic AV	Focal segmental endocapillary proliferation, Crescents	IgA, C3, C1q	Severe podocyte effacement	Death
3	64/M	1/6	Negative	Negative	70/21.8	B.henselae/B.quintana IgG:1:1024	Prosthetic MV	Focal necrosis and crescents	IgM, C3 and C1q	Scattered mesangial electron dense deposits	Off dialysis after 3 months F/U Cr - 2.8

TH-PO967

Lupus-Like Membranous Nephropathy in the Setting of Well-Controlled HIV Infection

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Introduction: Immune complex glomerulonephritis associated with HIV infection encompasses a heterogeneous spectrum of glomerular diseases associated with immune deposits including membranous nephropathy. Membranous nephropathy with atypical features such as full house immune staining resembling lupus has been rarely described in HIV infection. We report a case of lupus like membranous nephropathy in the setting of well-controlled HIV infection successfully treated with rituximab.

Case Description: 56-year-old Hispanic female with schizophrenia, type 2 diabetes mellitus, hypertension, HIV infection, and serum creatinine 0.7mg/dL presented with 5.3 grams of proteinuria. Her HIV infection was well-controlled with viral suppression on antiretroviral therapy and diabetes was controlled with no microvascular complications. Serologic workup included a positive ANA with a negative double stranded DNA antibody, normal C3 and C4 levels, negative SPEP, negative syphilis antibody, positive hepatitis C antibody and positive hepatitis B core antibody with viral suppression. Renal biopsy demonstrated immune complex glomerulonephritis with a membranous pattern. Full house staining was IgG predominant and numerous subepithelial, paramesangial deposits and tubuloreticular inclusions were seen. PLA2R stain was positive but serum anti-PLA2R antibody was negative. Although she had a positive ANA, she had no other clinical signs or symptoms of lupus. In the absence of another etiology, we concluded she had lupus like membranous nephropathy possibly associated with HIV infection. Despite conservative treatment for 6 months, proteinuria worsened to 7.1 grams. She was subsequently treated with rituximab. Within 2 months, her proteinuria improved to 3.1 grams consistent with partial remission.

Discussion: Lupus like glomerulonephritis with a membranous pattern has been rarely described in HIV infection. Our patient had a positive ANA but no other serological or clinical features of lupus. Although full house immune staining was seen, IgG predominated with mostly subepithelial deposits and her PLA2R stain was positive, suggesting this may be primary membranous nephropathy with atypical features. There are a variety of glomerular diseases observed in HIV positive individuals and this case highlights the importance of the renal biopsy for appropriate diagnosis and treatment

TH-PO968

Laser Microdissection and Tandem Mass Spectrometry, a Valuable Method to Identify Components of Glomerular Deposition Diseases: A Case Report

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Introduction: The diagnosis of glomerular deposition diseases (GDDs), including proliferative glomerulonephritis with monoclonal IgG deposition (PGNMID), requires evidence of pathogenic deposits in the glomerulus. Laser microdissection (LMD) and Tandem mass (MS/MS) spectrometry, which can identify the deposit's structure, might be valuable for this purpose in theory. Here, we report a case of PGNMID suggesting the applicability of MS/MS spectrometry in the diagnosis of GDDs.

Case Description: A 38-year-old woman was admitted to our department with a 7-month history of moderate proteinuria and without a history of hematological disease. A 24 hour urinary test showed proteinuria excretion of 1.2 g/day with no microscopic hematuria. A blood test showed 0.63 mg/dL of creatinine, 5.98 g/dL of total protein and 3.54 g/dL of albumin. Cryoglobulinemia was not detected. A renal biopsy showed membranous nephropathy by light microscopy together with granular deposits in subendothelial, subepithelial, and intra-glomerular basement membranes by electron microscopy. An immunofluorescence (IF) study showed restricted IgG1-Kappa deposition, which was validated by MS/MS spectrometry using several glomerulus dissected by LMD from a paraffin-embedded specimen, which showed an IgG1-heavy chain and Kappa-chain variable lesion. Therefore, we were able to diagnose the patient with PGNMID, and initiate treatment with an angiotensin converting enzyme inhibitor. The patient's renal function has been stable up until the time of writing this report.

Discussion: In the current case, we found that the pathogenic deposit shown by immunostaining was consistent with the result of MS/MS spectrometry. Based on the observations of this case, we validated MS/MS spectrometry's ability to detect deposits. The evidence of pathogenic deposits is critical in the diagnosis of GDDs. Although IF is commonly used, this process can only test for a limited number of deposit antigens. In theory, LMD and MS/MS spectrometry could detect a broader spectrum of deposit and might enable a better understanding of GDDs. <Acknowledgment> LMD and MS/MS analysis was performed by Drs. Yoshinaga, Yazaki, Sekijima (Shinshu University)

TH-PO969

Mercury in Natural Health Products as a Cause of Membranous Nephropathy

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Introduction: Membranous nephropathy (MN) is characterized by subepithelial deposits along the glomerular basement membrane and it is the most common cause of nephrotic syndrome in white adults (1, 2). 80% of cases are primary with antibodies to specific podocyte antigens, Phospholipase A2 Receptor (PLA2R) or thrombospondin type-1 domain-containing 7A (THSD7A). The remainder are secondary to a variety of causes including malignancy and drugs (2). Mercury is a cause of MN with exposures from skin-lightening creams and traditional medicines (1,3). An emerging concern is use of natural health products (NHPs) including vitamins, supplements, and herbal remedies. The composition of these products is not tightly regulated and some have been shown to contain mercury (4). We present a case of MN due to mercury intoxication related to use of NHPs.

Case Description: 39-year-old white male with past medical history of depression presented with worsening bilateral lower extremity edema and abdominal distention over the past month. He was taking multiple herbal supplements daily for 6 months. He denied changes in urine output, use of non-steroidal anti-inflammatory drugs, illicit drugs, or alcohol. He reported eating fish 1 meal per month. On evaluation, He demonstrated anasarca. No other abnormalities noted on physical examination. Lab work demonstrated normal renal function, nephrotic range proteinura, hypoalbuminemia, and hyperlipidemia. Urine protein-to-creatinine ratio was elevated at 14.3 (ref 0.00 - 0.19). ANA, hepatitis B and C, C3, and C4 were normal. Heavy metal serum screen returned mercury of 22.1 ug/L (0.0 to 10.0 ug/L) and 24- hour urine mercury was >80 ug/L (0.0 - 5.0 ug/L). Renal biopsy was consistent with membranous nephropathy. PLA2R and THSD7A were negative. The offending agents were discontinued. He started on Cyclosporine A, Atorvastatin, and Apixaban. Cyclosporine A was weaned off quickly following final diagnosis. He continued on Atorvastatin and Apixaban for 12 weeks. By 12 weeks, all lab parameters returned to normal.

Discussion: Mercury-induced membranous nephropathy is a known, but rare entity that has been associated with skin-lightening creams, Chinese herbal medicines, and now NHPs. Our case highlights the necessity of through medication review to identify causes of nephrotic syndrome that may respond to simple measures such as discontinuation of offending drugs.

TH-PO970

A Horse in the Land of Zebras: A Case of Minimal Change Disease After Celecoxib Exposure

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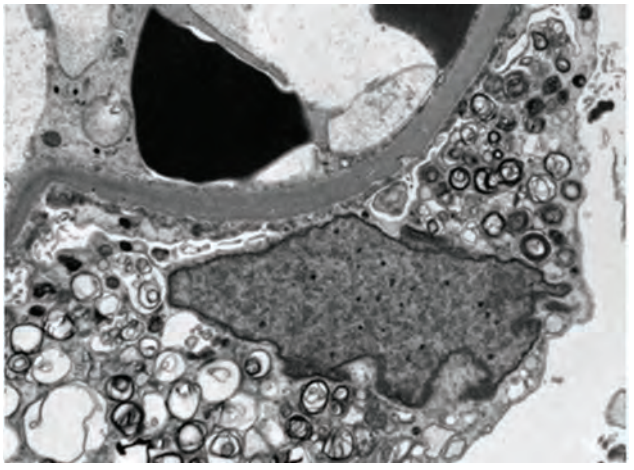
Introduction: Non-selective NSAIDs are the most common cause of secondary minimal change disease (MCD). This association has not been established for selective COX-2 inhibitors, such as celecoxib. We present a case of celecoxib-associated MCD with unique diagnostic and therapeutic features.

Case Description: 71 y/o F presented with abrupt nephrotic syndrome after a 2-week course of celecoxib. She has depression treated with sertraline and HTN controlled with diuretics. On presentation, her serum Cr was 0.8 mg/dl and her proteinuria (PU) measured 8 g. It did not improve with celecoxib discontinuation and lisinopril addition. Kidney biopsy revealed MCD without tubular or parenchymal pathology, however, foot process effacement was accompanied by lamellated "zebra" bodies in some podocytes (Figure) and minimal mesangial IgA deposits. Testing for genetic abnormalities and enzymatic activity of α-galactosidase ruled out Fabry disease. Her PU resolved after a 2-month prednisone course, but she relapsed soon after steroids discontinuation. Retreatment with a longer prednisone taper led to a prompt resolution of PU followed by another relapse accompanied by AKI. The second kidney biopsy showed MCD, new moderate interstitial fibrosis (IF) and tubular atrophy (TA), but no phospholipidosis. Her kidney function

returned to baseline after 2 months, during which she was supported by dialysis, but PU persisted despite steroids. Subsequent addition of mycophenolic acid led to partial PU remission.

Discussion: Unlike prior sparse case reports documenting celecoxib-associated MCD, our patient did not initially have any IF or TA, nor did her PU remit spontaneously after celecoxib discontinuation. Although MCD responded well to prednisone, it eventually became steroid-resistant. While IgA deposits were deemed incidental and benign, sertraline-induced phospholipidosis could weaken the podocyte ability to maintain its structural integrity possibly exacerbating PU.



Zebra bodies

TH-PO971

Fulminant Nephrotic Syndrome with Minimal Glomerular Findings Associated with a Pancreatic Neuroendocrine Tumor

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Introduction: Neuroendocrine tumors (NETs) are a rare, heterogenous group of tumors that can present as benign or malignant lesions. Rare reports have associated NETs with membranous nephropathy. We report a patient with nephrotic syndrome and minimal glomerular findings who experienced clinical remission upon tumor resection.

Case Description: A 53 year old female with history of hypothyroidism presented with anasarca, 24-hour urine protein 4.2 g, hypoalbuminemia 2.1 g/dL, and acute kidney injury (serum creatinine 0.8 mg/dL increasing to 1.8 mg/dL). Kidney biopsy demonstrated normal glomeruli by light microscopy, mild tubular atrophy, and mild interstitial fibrosis. Immunofluorescence was unremarkable and electron microscopy revealed minimal foot process effacement with no electron dense deposits. Congo red staining was negative for amyloid. The acute kidney injury resolved. Eight months later, a pulmonary artery embolism was diagnosed, and she was noted to have 26 g on 24-hour urine protein collection. Serological evaluation for HIV, hepatitis C, hepatitis B, C3/C4, ANA, ANCA, SPEP, UPEP, serum free light chains, and PLA2R antibody were all normal/negative. UPCR decreased to 8 g/g on an ACEi. Six months later, UPCR again increased to 18 g/g, and repeat kidney biopsy demonstrated diffuse and moderate tubular injury, mild interstitial inflammation with clusters of eosinophils, and 25-30 % foot process effacement with no evidence of immune complex deposition. Abdominal MRI revealed an enhancing lesion in the tail of the pancreas that on resection was a well-differentiated, nonfunctional pT1N0 neuroendocrine tumor positive for chromogranin and synaptophysin with KI67 index <1%. One month after resection, urine dipstick protein was negative with albumin 3.5 g/dL, and 6 months later UPCR was 0.08 g/g, albumin 4.0 g/dL, and creatinine 0.9 g/dL.

Discussion: This case expands the association of NETs and nephrotic syndrome to include histologic lesions with minimal glomerular findings. The spontaneous remission with tumor resection supports the role of a circulating tumor-associated factor in the pathogenesis.

TH-PO972

TNF-Alpha Inhibitors and ANCA-Associated Vasculitis: The Culprit or an Innocent Bystander

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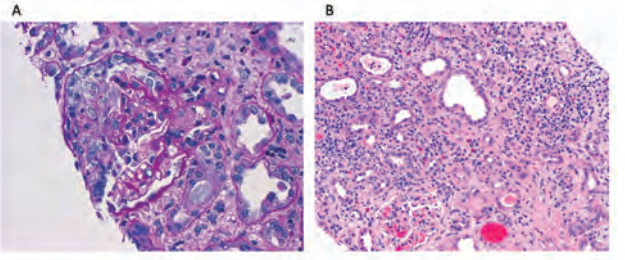
Introduction: Anti-tumor necrosis factor-alpha agents (TNF-α) have become integral in the management of autoimmune diseases such as rheumatoid arthritis (RA). Although these agents are generally well tolerated from a renal perspective, they have been associated with paradoxical development of both systemic and organ-limited vasculitis, including glomerulonephritis. Also, few case reports describe acute interstitial nephritis (AIN) caused by anti-TNF-α agents. We describe a case of simultaneous ANCA-associated vasculitis (AAV) and AIN in a patient with RA maintained on etanercept.

Case Description: A 69-year-old East Indian woman with well-controlled RA on etanercept developed gross hematuria and acute renal injury with serum creatinine peak at 8.4 mg/dl, without any other symptoms such as arthritis, stiffness or rash. Urine microscopy showed numerous isomorphic and few dysmorphic red blood cells, no cellular casts. Serologic studies were notable for positive myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA). Renal biopsy demonstrated ANCA-associated vasculitis (AAV) with rare cellular crescents and acute tubulointerstitial nephritis. Etanercept was discontinued due to concern for drug-induced vasculitis. The patient was treated with high-dose steroids and rituximab with subsequent improvement in renal function.

Discussion: Anti-TNF-α agents have been associated with different renal pathologies including AIN, as well as glomerular processes such as pauci-immune crescentic GN. Determining causality is a challenge because RA is independently linked to AAV as an overlap syndrome. In our patient, lack of clinically evident RA flare and concomitant presence of AIN on biopsy more strongly supported etanercept as the underlying etiology. A high index of suspicion for drug-related vasculitis is required in patients with primary rheumatic disorders treated with biologic agents. Discontinuation of anti-TNF-α therapy and prompt initiation of immunosuppression for treatment of vasculitis are the cornerstone of management.



A: Cellular crescent, B: Acute interstitial nephritis

TH-PO973

Not So Stellar: IgA Nephropathy Secondary to Immunotherapy Treatment for Psoriasis

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Introduction: The increasing use of immunotherapy to treat inflammatory diseases and malignancy has resulted in an increase in glomerular injury reports. IgA deposition in the kidney has been associated with systemic conditions which include ulcerative colitis, seronegative spondyloarthropathies, dermatitis herpetiformis, CLD, and malignancies. These patients may show IgA deposits in the kidney mesangium, but IgA nephropathy is rarely diagnosed as patients do not always develop proteinuria or renal insufficiency. The discovery of IgA deposits in these patients is usually an incidental finding in autopsy. The incidence of glomerular disease in psoriasis is rare. We present this case of a patient with psoriatic arthritis that developed nephrotic syndrome with a kidney biopsy with IgA nephropathy after starting treatment with Ustekinumab.

Case Description: A 40 y/o Caucassian man with past medical history of psoriatic arthritis. He was treated with adalimumab, but became ineffective and it was changed to Ustekinumab. He had been receiving for 2 years at a dose of 45 mg every 2 weeks. After starting Ustekinumab, he developed nephrotic syndrome with proteinuria 6g/24h and worsening kidney function with a creatinine 1.6mg/dL (baseline creatinine 1.0 mg/dL). Physical examination remarkable for hypertension with BP 145/102 mmHg and bilateral leg edema+2. Serologic work up including ANA, ANCA, dsDNA, C3, C4, Hepatitis panel and cryoglobulinemia resulted negative. Kidney biopsy showed IgA nephropathy with mesangial hypercellularity. Ustekinumab was discontinued, and he was started on prednisone 60 mg PO daily and losartan 50 mg po daily. Kidney function has remained stable after 2 months of follow up with significant improvement in the proteinuria.

Discussion: Psoriasis has not typically been associated to glomerular disease. Immunotherapy agents have been mostly described to cause renal injury in the form of TMA, FSGS, ATN, AIN. Few cases have been reported of glomerular disease, particularly IgAN, in patients receiving Ustekinumab. In this case, the patient presented nephrotic syndrome only after receiving treatment with Ustekinumab. Nephrologists should be suspicious of the relationship of this agent and IgAN. It is important to diagnose early to ensure adequate treatment to minimize long term kidney complications.

TH-PO974

A Case of Anti-Glomerular Basement Membrane Disease Recognized a Month After the Diagnosis of Membranous Nephropathy

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Introduction: Most of the patients with anti-glomerular basement membrane (GBM) disease present with rapidly progressive glomerulonephritis. However, in rare cases, this disorder develops following membranous nephropathy (MN). Here, we report a case of anti-GBM disease which developed shortly after the diagnosis of MN.

Case Description: A 76-year-old Japanese woman with hypertension and dyslipidemia was found to have nephrotic-range proteinuria and microscopic hematuria without increase in serum creatinine level. Although a renin-angiotensin system inhibitor was

initiated, massive proteinuria persisted and hypoalbuminemia had deteriorated over the following ten months, resulting in nephrotic syndrome. Kidney biopsy demonstrated thickening of GBM with a diffuse granular pattern of IgG and C3 staining along GBM on immunofluorescence microscopy. Electron microscopy revealed subepithelial and intramembranous electron-dense deposits, which led to the diagnosis of MN (stage II-III). At this diagnosis of MN, anti-GBM antibody was not detected in her serum. One month later, she was admitted with persistent fever and oliguria. She got anuric soon after the admission and hemodialysis (HD) therapy was initiated. Laboratory test revealed a high titer of anti-GBM antibody (276 IU/mL), and plasmapheresis therapy combined with corticosteroids was also initiated. The second biopsy showed severe necrotizing glomerulonephritis throughout all glomeruli with cellular crescents. Immunofluorescence microscopy demonstrated deposition of IgG along GBM in both linear and granular patterns. Her renal function did not recover in spite of decrease in titer of anti-GBM antibody, and she has been eventually on maintenance HD.

Discussion: The conformational change of GBM by MN may unmask hidden epitope in the non-collagenous domain 1 of typeIVcollagen, which could induce autoimmune response. Further studies are needed to determine whether MN could cause such autoimmunity.

TH-PO975

IgA Dominant Infection-Related Glomerulonephritis in the Setting of Acute Ehrlichiosis

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Introduction: IgA-Dominant staining on immunofluorescence (IF) with diffuse endocapillary proliferative glomerulonephritis (GN) on light microscopy (LM) has a differential diagnosis that includes primary IgA nephropathy, Henoch-Schönlein purpura (HSP), and IgA-dominant infection related GN. We report a case of acute ehrlichiosis infection with concomitant GN. To date, there have been no reported cases of ehrlichiosis associated GN.

Case Description: A 70-year-old male with a petechial rash, 13 pound weight gain, bilateral lower extremity edema, and serum creatinine 1.6 mg/dl (12 months prior to presentation was 1.0 mg/dl). Urinalysis revealed 3+ protein, 2+ blood; protein:creatinine ratio of 5.3 g/g (urinalysis 12 months previously was negative for blood and protein). Serum albumin was 3.8 g/dL. Glomerular serologies, including complement levels and antineutrophil cytoplasmic antibodies, were either normal or negative. An IgM titer for *Ehrlichiosis chaffeensis* was strongly positive at 3.7 (normal < 1.0). Renal biopsy findings revealed diffuse endocapillary proliferation, widespread mesangial and global endocapillary hypercellularity, endothelial swelling, and mild activity. Of note, there was significant intracapillary leukocyte accumulation including neutrophils. There was minimal patchy tubular atrophy and interstitial fibrosis, comprising 10% of the cortex. IF was significant for 2+ IgA and 1+ C3. Electron microscopy revealed electron dense deposits in the mesangium and subendothelial locations, along with 40% foot process effacement. No subepithelial humps were identified. Given the patient's clinical timing of acute ehrlichiosis infection and GN, these findings support the diagnosis of an IgA-dominant infection related GN. The presence of neutrophils on LM and 1+ C3 staining on IF, albeit less than the IgA staining of 2+, also support the diagnosis.

Discussion: The LM pattern of proliferative GN with IgA dominance requires clinical correlation. Specific laboratory and biopsy findings including degree of IgA and C3 staining and presence of neutrophils can help distinguish this entity from HSP and IgA nephropathy, as well as timing of renal dysfunction with relationship to onset of infection.

TH-PO976

Case Report of Membranous Glomerulonephritis Secondary to Papillary Thyroid Carcinoma

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Introduction: Secondary Membranous glomerulonephritis(GN) is most commonly seen in the setting of autoimmune disease, infection, neoplasia, and with certain therapeutic agents. Malignancies associated with secondary membranous GN are solid tumors such as carcinomas of the prostate, lung, breast, bladder, or gastrointestinal tract, and less frequently hematologic malignancies, such as chronic lymphocytic leukemia. We report a rare case of secondary membranous GN secondary to papillary thyroid carcinoma(PTC). We are not aware of any previous reports of a similar association.

Case Description: A 35-year-old female without significant past medical history, presented with nephrotic range proteinuria (10.6 g of proteinuria in 24 hours) and other features of nephrotic syndrome. Kidney biopsy diagnosis was consistent with secondary MGN with mesangial deposits and variegated deposits in terms of size and distribution. Anti PLA2R antibody serology and immunohistochemical staining were negative. Further work up for secondary MGN, including ANA and viral hepatitis, was negative. Patient underwent age-appropriate cancer screening and was eventually found to have a thyroid nodule with biopsy-proven diagnosis of PTC. The patient underwent thyroidectomy. One month post surgery, her proteinuria significantly improved (down to 4.5 g of proteinuria in 24 hours) with subsequent improvment of her volume status.

Discussion: Secondary Membranous nephropathy is associated with malignant conditions such as solid tumors and less commonly hematological malignancy. We present a unique case of MGN, secondary to PTC, with dramatic improvement of proteinuria post thyroidectomy. This case emphasizes the importance of clinical workup after a diagnosis of secondary MGN, which in our patient, led to the discovery of an unexpected PTC and its successful treatment.

TH-PO977

Doxycycline-Associated Minimal Change Disease

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Introduction: Minimal Change Disease (MCD) is a disease that usually affects adolescents, however 10-25% of nephrotic syndrome in adults is also caused by MCD. Major causes that precipitate MCD in adults include infection, neoplasm, allergy, and drugs. We describe a rare case of MCD associated with doxycycline use.

Case Description: A 24-year-old Caucasian female with history of IBD presented to emergency department (ED) with worsening swelling of lower extremities. 4 weeks prior she was diagnosed with Influenza A, treated with Oseltamivir, and the week before presentation had mild fever when was diagnosed with acute sinusitis and initiated on doxycycline therapy. After taking doxycycline for 4 days, she started having "dizzy spells" followed by appearance of severe swelling over lower extremities with palpebral and perioral edema. Her systolic BP was 150s which was unusual for her. UA performed at Urgent Care center revealed RBCs in the urine and protein of 300 mg. She was transferred to ED, where was noted to have persistently elevated BP, with repeat UA also showing RBCs and protein. Spot urine protein/Creatinine was elevated at 10.3, with a serum creatinine of 0.62 mg/dL and albumin of 2.1 g/dL. Patient underwent kidney biopsy which showed "extensive effacement of visceral epithelial cell foot processes, suggestive of minimal change disease, and thin glomerular basement membranes, suggesting an inherited abnormality of basement membrane collagens." She was started on high-dose prednisone, to which she responded well. Her lower extremity swelling and proteinuria completely resolved within 2 weeks of corticosteroid therapy, and prednisone was subsequently tapered.

Discussion: Doxycycline is a widely available antibiotic that is readily used in the treatment of multiple pathogens. It is not typically associated with MCD however it has been shown to cause MCD in mice due to causing overexpression of VEGF-A in the kidneys which results in albuminuria and minimal change disease. To our knowledge, there has been only one reported case of doxycycline related MCD in humans. Physicians including internists, infectious disease specialists and nephrologists need to be aware of this potential adverse effect of doxycycline.

TH-PO978

Collapsing Focal Segmental Glomerulosclerosis and Diffuse Infiltrative Lymphocytosis Syndrome with Renal Involvement in Acute HIV Infection

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Introduction: Human Immunodeficiency Virus (HIV) infects and damages podocytes leading to HIVAN, a collapsing form of focal and segmental glomerulosclerosis. HIV also causes dysregulation of the immune system, which rarely can cause CD8+ T-cells to infiltrate and attack various organs, leading to Diffuse Infiltrative Lymphocytosis Syndrome (DILS). We present the first case of simultaneous HIVAN and DILS with renal involvement, occurring only 6-8 weeks after infection during the initial phase of acute HIV seroconversion.

Case Description: A 20 year old Hispanic male was diagnosed with acute HIV based on known exposure, negative serology, and positive p24 antigen. Three weeks later, he was admitted with fever, chills, myalgias, severe dry mouth, neuropathic pain of both legs, and declining urine output. Compared to labwork three weeks prior, new labs showed seroconversion of HIV, a 10-fold increase in CD8+ T-cells, new hyponatremia (123 mEq/L), and renal failure (creatinine 5.24 mg/dL, prior 0.98). Urinalysis showed 300+ protein (while oliguric). Sonogram showed bilaterally enlarged and echogenic kidneys suggestive of interstitial nephritis. He denied using any medications including herbals. Biopsy showed collapsing FSGS with severe interstitial inflammation, and staining demonstrated these were CD8+ T-cells. He started steroids, losartan and anti-retrovirals. His symptoms of xerostomia and neuropathy improved daily, along with an increase in urine output.

Discussion: This report is the first to describe both HIVAN and DILS simultaneously, and of additional significance, both conditions arose early at the time of HIV seroconversion. HIVAN typically occurs in advanced HIV as an AIDS defining illness but was reported twice in early HIV. DILS is a multi-organ disorder of increased, dysregulated CD8+ T-cells that infiltrate one or more organs, most often the salivary glands and lungs. When kidneys are affected, DILS shows similarities to allergic interstitial nephritis (enlarged and echogenic kidneys, tubular proteinuria, interstitial infiltrate on biopsy), but with DILS the cells are CD8+ T-cells. Renal and extra-renal symptoms of DILS can respond to HAART and prolonged steroids.

TH-PO979

Clinical Course of a Patient Treated for Dense Deposit Disease (Monoclonal Protein Associated)

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Introduction: Dense deposit disease (DDD), a subcategory of C3 glomerulopathy is a rare entity characterized by uncontrolled activation of the alternative pathway (AP) of the complement cascade. When diagnosed in the older population, there is often an

accompanying monoclonal gammopathy of undetermined significance (MGUS). As the monoclonal protein may perturb AP regulation, treating with chemotherapy need be considered. We report a case of DDD (MGUS associated) first treated with bortezomib, later switched bortezomib plus cyclophosphamide and dexamethasone (CyBorD). As there was no histologic or serologic improvement, daratumumab was introduced with stability of kidney function.

Case Description: A 62 year old male was evaluated for a serum creatinine (Cr) of 1.3 mg/dL with urine protein of 3 g/g. There were low C3 and C4 levels. Urinalysis showed 3+ blood with 86 red blood cells. Serum immunofixation detected an IgG kappa monoclonal protein. Plasma cell count on bone marrow biopsy was 8%. Renal biopsy showed diffuse mesangial and segmental endocapillary proliferative glomerulonephritis with membranoproliferative features. Immunofluorescence had intense deposition of C3. Global, marked electron dense deposits were seen. As findings were consistent with DDD, bortezomib was initiated. After 3 months, this was held for observation. Cr then was 2.5 mg/dL with urine protein/creatinine of 4.5 g/g. Six months later, bortezomib was resumed but not effective. CyBorD followed, but Cr rose to 3.5 mg/dL. Second kidney biopsy revealed severe tubular atrophy and interstitial fibrosis. At this point, weekly daratumumab with bortezomib was started. After several months, renal function has not declined further and proteinuria reached nadir of 2.9 g/g.

Discussion: Monoclonal gammopathy has emerged as a potential driver of the complement dysregulation, known to characterize DDD. Although there have been several strategies reported, there is no standard approach to guide therapy. While chemotherapy is not used to treat MGUS, it is appropriate in cases whereby the monoclonal protein manifests as a form of C3 glomerulopathy (DDD). This case demonstrates various options which may be utilized to curtail renal morbidity. While bortezomib alone and CyBorD were not effective, our patient has achieved ongoing clinical and laboratory stability with daratumumab.

TH-PO980

Chronic Inflammatory Demyelinating Polyneuropathy and Concurrent Membranous Nephropathy Associated with Anti-Contactin-1 Autoantibodies

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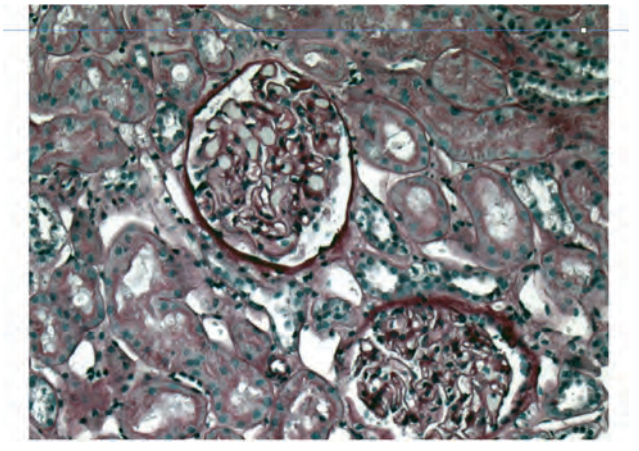
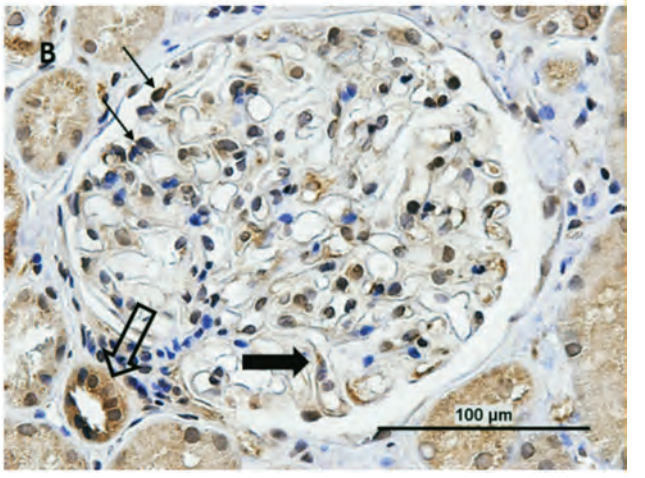
Introduction: MN is a common cause of nephrotic syndrome in nondiabetic adults. CIDP is an acquired disorder of peripheral nerves. Antibodies directed against the paranodal axonal cellular adhesion molecule contactin-1 and its binding partner neurofascin have been identified in some severe cases of CIDP. Case reports of patients with co-existing MN and CIDP have been published, but an underlying disease mechanism has not been described in these patients

Case Description: A 45-year old male was diagnosed with CIDP in March 2015. He was treated with prednisone, IVIG and azathioprine with good response. In September 2016, he presented with nephrotic syndrome with 22 g/day of protein. He underwent a renal biopsy which showed stage 2 MN. Renal function was normal and anti-phospholipase 2 antibody was negative. Malignancy, infectious, and routine autoimmune investigations were negative. Additional serology was positive for IgG4 anti-contactin-1 antibody. Neurofascin antibody was negative. We examined renal tissue for the presence of contactin-1 antigen. The patient's biopsy was strongly positive for this antigen, while 2 control were negative. Cyclosporine was added to the patient's regimen with good resolution of proteinuria.

Discussion: Anti-contactin-1 antibodies have been identified as a cause of CIDP. This is the first report of these antibodies being identified in a case of secondary membranous nephropathy. Anti-contactin 1 antibody may be a novel diagnostic test in this condition.





TH-PO981

A Case of Pediatric Dense Deposit Disease (DDD) in Remission for 7 Years on Eculizumab

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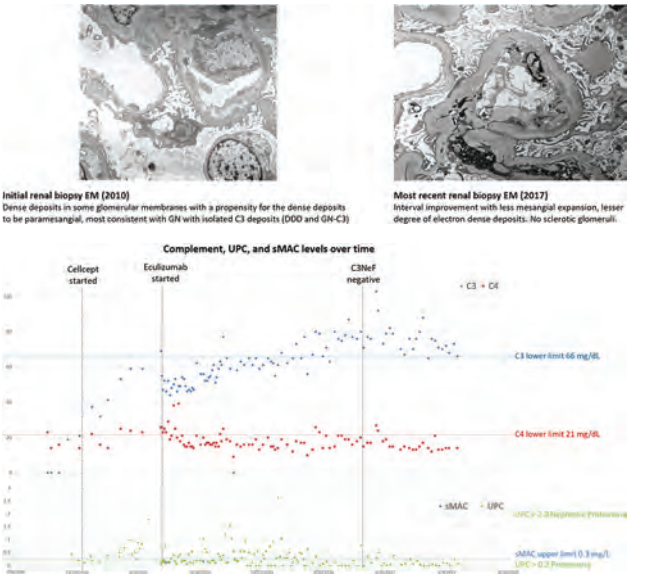
Introduction: DDD affects only 2-3 people per million. Slowing the disease course is critical because 50% of affected children progress to ESRD within 10 years, ultimately requiring dialysis or renal transplant. Recurrence post-transplant leads to at least 50% of graft loss. Current guidelines suggest Eculizumab as a potential treatment for refractory cases defined by persistent proteinuria, hematuria, alternative complement pathway activation or elevated C3 nephritic factor (C3NEF).

Case Description: A 5 year old previously healthy male presented with at least 2 months of asymptomatic microscopic hematuria without associated illness or relevant family history. He had normal BP, a normal exam, mild proteinuria (UPr/UCr 0.43), hematuria (URBCs >25), hypocomplementemia (C3 <20 mg/dL, C4 23 mg/dL), normal renal function and albumin. Renal biopsy had membranoproliferative glomerulonephritis with isolated intramembranous deposits. Complement genetic analysis was negative. Functional studies showed alternative pathway complement activation and the presence of C3NEF.

Discussion: He received steroids and Cellcept 700 mg/m2/d but continued to have complement activation (based on functional studies), microhematuria and worsening proteinuria (UPC peak 1.8). He was weaned off steroids and Cellcept (after 7 months) then received Eculizumab without significant adverse effects or complications. A follow-up renal biopsy improved and his proteinuria, hematuria. Functional studies suggest ongoing complement activation and lapses in therapy increase proteinuria. Thus, eculizumab has been continued for 7 years. To date, he may have one of the longest DDD remissions on Eculizumab monotherapy. Further studies including a randomized controlled trial of Eculizumab monotherapy could define parameters for starting and discontinuing treatment.



TH-PO982

Urinary angiotensinogen predicts renal disease activity in lupus nephritis

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Background: A non-invasive indicator of renal histological lesions and disease activity in lupus nephritis (LN) is needed for timely and targeted treatment before overt renal injury. Here, we tested the utility of urinary angiotensinogen (UAGT) to predict renal disease activity in LN.

Methods: A prospective, three-stage study was performed in patients with LN. In stage I, UAGT was measured in 140 newly-diagnosed LN patients. In stage II, UAGT was monitored in 61 subjects from stage I for up to 12 months. In stage III, UAGT was monitored in 12 LN patients before, during and after the onset of renal flares.

Results: In stage I, UAGT significantly increased in LN patients, correlating well with kidney AGT expression and histological activity. Patients with LN Class IV exhibited the highest UAGT compared with other histopathological classes of LN. For identifying LN class IV, a particularly aggressive type of LN, UAGT outperformed the conventional clinical measures and improved their performances. In stage II, UAGT decreased after immunotherapy and remained low in patients with LN remission during follow-up. In stage III, an elevation in UAGT predicted recurrence of LN, and a decline in UAGT after a renal flare heralded the remission of disease before conventional clinical measures.

Conclusions: UAGT in LN is a promising indicator for dynamical surveillance of renal disease activity and prediction of renal flares.

Funding: Government Support - Non-U.S.

TH-PO983

Association Between Kidney Tissue Estrogen Gene Signature and Nephrotic Syndrome Remission

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Background: Kidney disease severity and rate of progression are reported to be higher in males than females, which may in part be mediated by glomerular sex hormone receptor expression. We developed a kidney tissue estrogen gene signature to examine associations between estrogen signaling and remission from nephrotic syndrome.

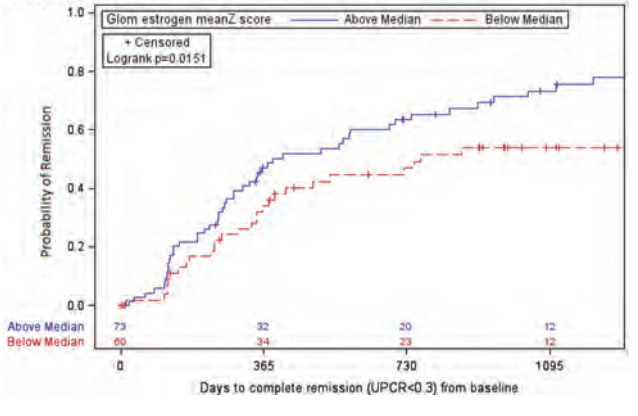
Methods: Patients with active FSGS, MCD, MN, or other nephrotic syndrome at enrollment in NEPTUNE, a multi-center observational cohort study were studied. Our outcome of interest was complete remission, defined as a uPCR ≤0.3 g/g. Our exposure of interest was a novel estrogen z-score. First, genes affected by estrogen signaling were defined as any gene related to ESR1 and 2 in both the HumanBase (Flatiron Institute) and MSigDB (Broad Institute) databases. Genes were limited to only those with estrogen response elements in the promoter region and 21 genes of interest were identified. Genome wide RNA expression data from the glomerular compartment of kidney tissue were used to calculate a z-score (X-mean/SD) for each gene. Each patient's overall z-score was generated from the average of the individual gene z-scores.

Results: Among the 177 patients, 67% were male, mean age was 34 years, mean eGFR was 86 ml/min/1.73m2, and mean uPCR was 2.8 g/g. A cox proportional hazards model controlling for age, sex, eGFR, and uPCR demonstrated a significant association between overall Z score and time to complete remission (HR 4.59; 95% Cl 1.4-15.1; p=0.012). Figure 1 shows unadjusted association of z-score median split with time to remission.

Conclusions: Higher estrogen score was associated with a higher hazard for complete remission. This estrogen gene signature could be used in both research and clinical practice to more carefully risk stratify patients. These findings also identify the estrogen receptor as a potential therapeutic target in glomerular disease.

Funding: NIDDK Support

Figure: Hormone signature median split plotted against time to complete remission (UPCR<0.3) of nephrotic syndrome



TH-PO984

Proximal tubular cell isolation during human acute kidney injury

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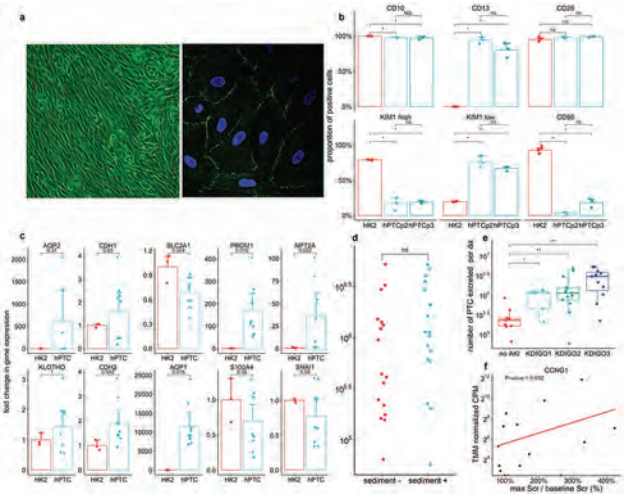
Background: There is an urgent need to discover and validate the pathophysiological pathways involved in human acute kidney injury (AKI). Proximal tubular cells (PTCs) are the cells primarily injured during AKI and their maladaptive repair contribute to AKI to chronic kidney disease (CKD) transition. It is very important to develop non-invasive tools that will help to improve our understanding of the signaling pathways contributing to the maladaptive repair.

Methods: We collected urine from patients hospitalized in the ICU of University Hospital of Geneva, presenting or not AKI. We here propose a novel method to isolate specifically PTCs from human urine using a combination of Magnetic-Activated Cell **Sorting (MACS)** sorting and Fluorescent-Activated Cell **Sorting** (FACS). We have characterized the sorted cells, and show how these cells can be used to determine pathophysiological pathways in human AKI.

Results: Isolated PTCs are viable, can be cultured for at least three passages (a) and retain the expression of several proximal tubule specific markers at the level protein (b) and of mRNA (c). We report that our technique is more sensitive than routine microscopic approach used to identify the presence of tubular cells in the urine during clinical AKI (d). There is a clear correlation between isolated PTC cell numbers and the severity of AKI as defined by KDIGO staging guidelines (e). RNA sequencing and pathway analysis confirmed alterations in PTCs cell cycle in AKI patients, which correlated to the severity of AKI (f).

Conclusions: We show that isolation of PT cells from urine is possible during human AKI episode. These cells can be used to study the pathways involved in AKI and we could confirm alterations of the cell cycle in PTCs collected from AKI patients. Thus, we believe that PTCs isolated from human urine will allow the identification and characterization of novel pathways in AKI and the AKI to CKD transition.

Funding: Private Foundation Support



TH-PO985

Racial/Ethnic Disparities in Protocol Adherence for the Cure Glomerulonephropathy Network (CureGN)

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Background: Racial/ethnic disparities exist among glomerular disease patients with respect to access to care and patient outcomes. However, few data exist on how race/ethnicity influences protocol adherence and data completeness in clinical research studies. Identification of such disparities will improve trial design and enhance generalizability of research findings.

Methods: CureGN is a 70-center prospective cohort study of patients with MCD, FSGS, MN, IgA nephropathy, or IgA vasculitis. We compared metrics on retention, visit completion, data [clinical, patient-reported outcomes (PRO), laboratory, pathology] and biosample collection [urine, blood, including RNA and DNA] across racial/ethnic groups using repeated measures logistic regression with generalized estimating equations and Cox proportional-hazards models.

Results: Overall protocol adherence was high (80-97%) for all races and ethnicities. Among 2243 adults and children enrolled at time of data analysis, significant differences in visit completion and sample collection were observed, with lower scores for Blacks and Hispanics on many metrics (Table).

Conclusions: Significant racial/ethnic differences in protocol adherence exist among enrollees with glomerular disease in CureGN. Rates were significantly lower in blacks and Hispanics. The diversity of research staff and site investigators may influence these disparities. Creation of a diverse Patient Advisory Council might reduce disparities.

Funding: NIDDK Support

Protocol Adherence Metric	Non-Hispanic white	Hispanic white	Black	Asian	*P*-value
# of Participants prematurely exited from CureGN (%)[a,b]	129/1413 (9%)	27/180 (15%)	58/390 (15%)	12/193 (9%)	0.14
Expected in-person visits that were missed (%)[b]	226/4101 (5%)	21/513 (4%)	46/994 (5%)	19/583 (3%)	0.09
Expected in-person or remote visits that were missed (%)[b]	1023/9467 (11%)	164/1203 (14%)	373/2343 (16%)	134/1374 (10%)	0.0001
Expected PROs that were completed (%)[b,c]	5242/5432 (97%)	716/748 (96%)	1269/1334 (95%)	746/762 (98%)	0.04
# of in-person visits with any blood or urine collected (%)[b,d,e]	4961/5118 (97%)	698/718 (97%)	1193/1261 (95%)	716/744 (96%)	0.06
# of participants with annual blood RNA collected (%)[f]	2619/2773 (95%)	331/354 (94%)	629/680 (93%)	394/416 (95%)	0.54
# of participants with annual DNA collected (%)[f,g]	2483/2658 (93%)	308/343 (90%)	577/650 (89%)	366/393 (93%)	0.01
# of participants with DNA sample collected ever (%)[g,h]	1218/1265 (96%)	159/169 (94%)	325/347 (94%)	167/170 (98%)	0.02

[a] numbers of study participants who died, withdrew consent, lost to follow-up, or transferred care
[b] expected visits includes those for participants while active in the study
[c] PRO (patient reported outcomes, including patient and proxy) completed without any non-missing data
[d] protocol varies on what tube(s) of blood are collected at each in-person visit, and this metric is met when at least one sample type was collected at an in-person visit
[e] urine could have been collected as either spot (casual or first AM void) or timed
[f] per # of patient years where at least one in-person visit that occurred
[g] for participants who consented to DNA collection, which was optional
[h] cox proportional-hazards model, accounting for individual patient follow up time and within site variability
[i] repeated measures logistic regression with generalized estimating equations

TH-PO986

Rapid Genome Sequencing to Guide Clinical Decision Making in FSGS

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Background: About 30% of children with focal segmental glomerulosclerosis (FSGS) have a genetic cause. While genetic forms are usually resistant to immunosuppressants, steroids are still the first-line treatment regardless of individual genetic make-up. We hypothesized that rapid whole genome sequencing (WGS) at diagnosis will help guide clinical management by a) improving diagnosis, b) sparing immunosuppressive treatment in cases with Mendelian mutations, c) identifying cases responsive to targeted therapy, d) improving counseling for both renal and extrarenal disease, and e) improving transplant evaluation and outcome.

Methods: We conducted CLIA-certified rapid WGS to guide decision-making in 10 children and young adults affected by biopsy-proven FSGS where a genetic diagnosis could affect therapeutic decision. Return of results (ROR) included therapeutic, familial and pre-transplant counseling.

Results: Turn-around time from consent to ROR averaged 20 days (15-42). WGS identified a diagnostic genotype in 5/10 patients and prompted biopsy revision in 2 cases leading to management change in virtually all cases, including holding/stopping immunosuppression in 6/10 cases, new treatment in 5/10 cases and improved transplant evaluation in 2 cases (Fig. 1). Genetic diagnosis also prompted early screening for subclinical neurological disease in a patient.

Conclusions: Rapid WGS in FSGS can improve medical management and possibly outcome by sparing ineffective and toxic treatment, identifying forms amenable to etiologic treatment, and inform familial counseling and pre-transplant evaluation thus optimizing organ allocation.

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Figure 1. Summary of the 10 cases.

Pt	Age	Sex	Ethnicity and race	Fhx	Current therapy	Mutation	Diagnosis change	Stopped/held IS	New therapy	Follow-up
1	13	M	White Non-Hispanic/Latino	No	No	Neg	No	No	Rituximab	Partial remission
2	12	F	Unknown Hispanic/Latino	No	Yes	Neg	Yes (biopsy revision)	Yes	No	Stable
3	15	F	White Non-Hispanic/Latino	Yes	No	Neg	No	No	CTX	Tx evaluation
4	8	M	White Hispanic/Latino	No	Yes	*INF2*	Yes	Yes	ACEi	Neurological evaluation, worsening renal function, started tacrolimus
5	26	M	White Hispanic/Latino	Yes	Yes	*NPHS2*	Yes	Yes	Sparsentan trial	Stable, starting sparsentan
6	22	M	White Hispanic/Latino	No	Yes	*APOL1* (*PAX2*)	Yes	Yes	IVIG	Tx evaluation, LURT scheduled
7	5	M	White Hispanic/Latino	No	Yes	Neg	No	No	Tacrolimus tapering	Remission on low-dose tacrolimus
8	2	F	White Hispanic/Latino	No	Yes	Neg	No	No	No	Remission on tacrolimus
9	30	F	Asian Non-Hispanic/Latino	No	No	*COL4A4*	Yes	Yes	No	Worsening renal function
10	29	F	White Non-Hispanic/Latino	Yes	No	*COL4A5*	Yes (biopsy revision)	Yes	No	No indication to repeated biopsy

FHx=family history; IS=immunosuppressive therapy; CTX=Cyclophosphamide; Tx=transplant; ACEi=angiotensin-converting enzyme inhibitor; IVIG=intravenous Immunoglobulin; LURT=living unrelated renal transplant

TH-PO987

The Soluble VEGF Receptor sFlt-1 Contributes to Endothelial Dysfunction in IgA Nephropathy

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Background: Endothelial injury is a common manifestation in IgA nephropathy (IgAN). After the previous identification of the upregulated soluble fms-like tyrosine kinase-1 (sFlt-1) correlates with endothelial injury in IgAN, in the present study, we further explored the role of sFlt-1 in endothelial injury in IgAN.

Methods: We enrolled 72 patients with IgAN and detected the sFlt-1 levels. The polymeric IgA1 (pIgA1) complexes were isolated from the pooled plasma samples of another 10 patients with IgAN. Apoptosis proteins were detected in cultured human umbilical vein endothelial cells (HUVECs) with recombinant sFlt-1 or the caspase-9 inhibitor, Z-LEHD-FMK stimulation.

Results: We identified there were positive correlations between sFlt-1 and IgA-IgG complex as well as vWF levels in patients with IgAN. The sFlt-1 levels in HUVECs were

significantly upregulated by pIgA1 complex derived from IgAN patients in a concentration-dependent manner. The proliferation ability of HUVECs was damaged when stimulated by sFlt-1 protein in a time- and dose- dependent manner. And the apoptosis rate was up-regulated significantly as the stimulation concentration of sFlt-1 increased. We found sFlt-1 challenge could significantly increase the expression of vWF and ET-1. In addition, sFlt-1 could increase the levels of caspase-9, caspase-3, Bax and mitochondrial membrane potential; facilitate the release of cytochrome C from mitochondria to cytoplasma. In contrast, Z-LEHD-FMK attenuated high sFlt-1-induced HUVECs apoptosis.

Conclusions: Our study demonstrated that sFlt-1 expression was up-regulated by challenged by pIgA1 complex derived from patients with IgAN, which then facilitated human umbilical vein endothelial cells apoptosis through the mitochondrial-dependent pathway.

Funding: Clinical Revenue Support

TH-PO988

The Levels of Plasma suPAR May Not Discriminate the Patients with Poor Therapeutic Reactivity Among Adult Japanese Focal Segmental Glomerulosclerosis and Minimal Change Disease

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Background: Soluble urokinase-type plasminogen activator receptor (suPAR) was originally reported as a specific biomarker for focal segmental glomerulosclerosis (FSGS). Recently, several studies negatively showed the importance of suPAR on the diagnosis of FSGS. However, there are few reports investigating the utility of suPAR as a marker for predicting therapeutic reactivity among adult minimal change disease (MCD) and FSGS.

Methods: Multicenter retrospective cohort study. Among the biopsy-proven MCD/FSGS patients during 2005-2015 at Nagoya university and 14 affiliated hospitals, the patients who collected their plasma at biopsy according their consent were included. Age>20, relapsed cases, non-nephrotic cases or cases who had already received any immunosuppressive treatment at biopsy were excluded. Plasma suPAR level were measured by ELISA (R&D Systems). The patients were divided into 2 groups whether they could attain complete remission within 4 weeks or not (responders or non-responders). We compared suPAR level between MCD/FSGS or responders/non-responders and evaluated the correlation suPAR level and other clinical variables.

Results: Ninety-nine cases (MCD/FSGS: 65/34, responders/non-responders: 67/32) were included to the analyses. The patients with FSGS or non-responders demonstrated more impaired kidney function at baseline. The median value of plasma suPAR was MCD/FSGS: 2253.8 vs. 3290.9 pg/mL(p<0.001) and responder/non-responder: 2334.1 vs. 3080.7 pg/mL(P=0.020). There was moderate negative correlation between plasma suPAR levels and eGFR (Speaman's rho: -0.42). When analyzing the patients with eGFR>=60, the median value of plasma suPAR was MCD/FSGS: 2253.8 vs. 3290.9 pg/mL(p<0.001) and responder/non-responder: 2334.1 vs. 3080.7 pg/mL (P=0.55).

Conclusions: Plasma suPAR level was observed significantly higher among FSGS and non-responders. However, we cannot ignore the affection from the patients' kidney function. Among patients with preserved renal function, plasma suPAR levels were still higher in those diagnosed with FSGS, whereas the levels were not different between non-responders and responders. We plan to present additional results including urine specimen of same patients.

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TH-PO989

Association Between Histologic Variants of Focal Segmental Glomerulosclerosis and Outcomes: Results from the Japan Renal Biopsy Registry

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Background: Focal Segmental Glomerulosclerosis (FSGS) is a leading cause of end stage kidney disease (ESKD). The previous studies suggested that FSGS histologic variants of the Columbia classification were associated with clinical outcomes, but the impact of FSGS variants on outcomes has not comprehensively been investigated in Japan.

Methods: Data on patients with primary FSGS of Japan Renal Biopsy Registry from 2010 to 2013 were analyzed. The outcome measures were 30% decline in estimated glomerular filtration rate (GFR30), progression to ESKD, and the first clinical remission (CR: proteinuria<0.3g/day) during 60 months after the biopsy. Multivariable Cox models were used to compare the outcomes among variants, adjusted for age, sex, baseline eGFR, nephrotic proteinuria (NP), and immunosuppressive treatment (IS).

Results: 311 patients were enrolled [median age: 52 (IQR 33, 66) years, male: 63%; baseline eGFR: 58 (IQR 40, 80) ml/min/1.73m^2, NP: 54%, IS: 54%]. The distribution of variants was 47% (n=147) FSGS not otherwise specified (NOS), 19% (n=59) tip (TIP), 16% (n=50) perihilar (PERI), 13% (n=40) cellular (CEL), and 5% (n=15) collapsing (COL). During the follow-up, 87 patients (28%) developed GFR30, 25 (8%) ESKD, and 118 (38%) reached CR. No significant differences in GFR30 and ESKD were found among variants, but TIP was significantly associated with CR compared with PERI [adjusted HR (95% CI), 2.2 (1.0, 4.8) (Figure).

Conclusions: Based on the Japanese national registry in the modern era, FSGS variants did not have a significant impact on GFR30 or ESKD during 60 months, while the variant types were associated with CR. Larger sample size, especially for COL, and longer follow-up may be needed to detect a statistically significant difference in the outcomes among FSGS variants.

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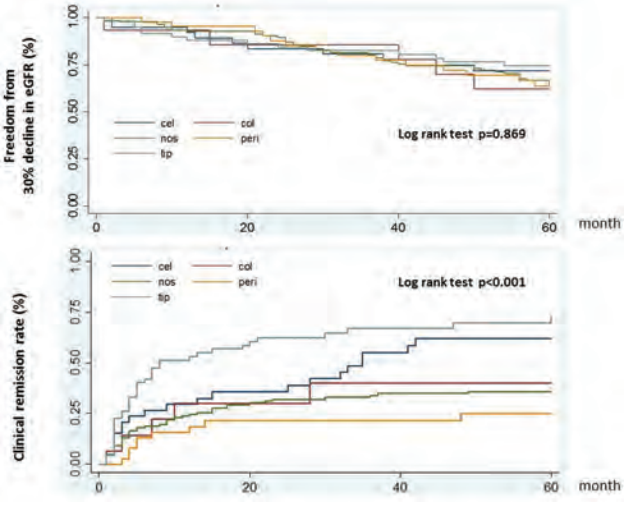

TH-PO990

Clinical Outcome and Molecular Profile of Perihilar FSGS Are Similar to Other FSGS Subtypes

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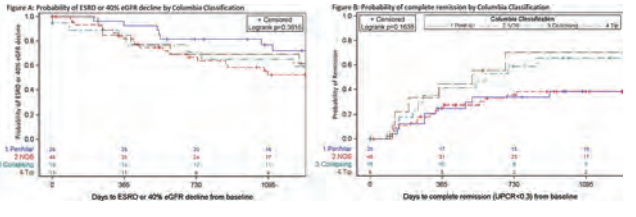
Background: Perihilar (PH) FSGS is hypothesized to be a result of podocyte loss from secondary causes including obesity, hypertension and low nephron mass. It is assumed to have a more favorable outcome than the immune mediated subtypes of FSGS, including FSGS NOS, but prior studies have included a referral population more likely to have a severe phenotype.

Methods: NEPTUNE is a multi-site observational cohort study of children and adults with nephrotic syndrome, enrolled at the time of clinically indicated renal biopsy. Cox models for time to either remission [defined as urine protein to creatinine ratio (UPCR <0.3mg/mg)] or ESRD/40% eGFR decline were adjusted for age, GFR, uPCR, race, and sex. Genomewide mRNA expression data from kidney biopsy tissue was generated using Affymetrx 2.1 ST platform. Differentially expressed genes (FDR <1%) for perihilar FSGS compared to all other subtypes was determined using Significance Analysis of Microarrays (SAM).

Results: Among 111 patients with FSGS, 28 were PH, 19 Collapsing, 13 Tip, and 51 NOS. Gene expression was available from the glomerulus compartment for 39 patients and from tubulointerstitial compartment for 56. Comparing PH to NOS subtype, there were no differences in obesity (71% vs 78%), edema (32% vs. 36%), or hypertension (25% vs. 38%). 52% of patiehts with a PH lesion had >50% foot process effacement. Adjusted survival models showed no difference in time to complete remission or loss of eGFR between PH and NOS subtypes (p-value 0.88 and 0.22, respectively) [Fig 1]. Only 3 glomerular (of 25,583) and 6 tubular genes (of 23,397) were differentially expressed between PH vs other subtypes.

Conclusions: Patients with PH lesions as defined by the Columbia classification criteria had similar clinical presentations, rate of remission and loss of GFR as compared to the NOS subtype. The tissue molecular profile was also similar for PH patients as compared to other subtypes, raising the possibility that the mechanism of underlying tissue damage may be shared across the subtypes despite heterogeneous initial insults and varied pathologic categories.

Funding: NIDDK Support, Other NIH Support - NCATS



TH-PO991

FSGS Outcome Comparison: Idiopathic Collapsing Glomerulopathy vs. Not Otherwise Specified Variant

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Background: Focal segmental glomerulosclerosis (FSGS) is a morphologic pattern of glomerular injury that frequently progresses to end-stage renal disease. Histologic variants express variable rates of progression. Collapsing Glomerulopathy (CG) has usually been associated with poor renal outcomes, while the not otherwise specified (NOS) variant has better outcomes. The goal of this study was to compare the two histologic forms and identify clinical features of progression.

Methods: A retrospective analysis was performed on all CG and NOS cases diagnosed by kidney biopsy between 1996 and 2016 at the University of Sao Paulo. Clinical and laboratory data were collected at baseline and at the end of follow up. We excluded cases chronic viral infection, drugs, any suspected immune-mediated disease and diabetes. We analyzed histological, clinical and follow-up data and compared among variants. Outcome was defined as ESRD or doubling of baseline creatinine.

Results: Clinical features of the groups CG and NOS are summarized in Table 1. There was no significant difference in age, gender, albumine, hemoglobin, hematuria, proteinuria, among the two groups. The immunofluorescence of the renal biopsies showed a greater predominance of IgM and C3 in the CG compared to the NOS variant. The NOS form was significantly associated with a better renal outcome.

Conclusions: The collapsing and NOS variants had similar baseline CKD-EPI, however the collapsing form had a worse renal outcome. Moreover, Further studies are necessary to explore the different immunofluorescence patterns among the forms.

Table 1 -Clinical features of the groups NOS and CG

n	NOS(n=32)	CG(n=57)	p value
Age(Y)	33.2±18.4	32.0±16.3	0.79
Male (n, %)	14(43)	32(56)	0.26
Creatinine (mg/dL)	1.34±1.0	1.84±0.7	0.02
CKD-EPI baseline	74.85±37.7	62.85±39.1	0.16
Proteinuria (g/day)	10.04±4.5	8.08±6.3	0.22
Hematuria	8(25)	28(49)	0.55
Albumin (g/dL)	1.89±0.8	2.15±0.9	0.30
Hemoglobin (g/dL)	13.0±2,1	12.6±2.2	0.51
Creatinine at the end	2.41	7.33	
IgM positive (%)	6 (33)	26(60)	0.05
C3 positive (%)	7 (38)	29(70)	0.02
Creatinine duplication or ESRD (%)	8(25)	32(65)	0.00

Data showed as mean(+/-SD).

TH-PO992

Study on Association of Initial Prednisolone Dose with Remission, Relapse, and Infectious Complication in Adult-Onset Minimal Change Disease

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Background: Majority of patients with minimal change disease (MCD) are steroid sensitive with good renal prognosis. However, about half of the cases relapses during prednisolone (PSL) tapering after remission of nephrotic syndrome. The initial dose of PSL varies by reports from 0.5 to 1 mg/kg/day. But little is known about the optimal PSL dose for initial treatment of MCD.

Methods: This is a retrospective multicenter cohort study on treatment-naïve adult patients with MCD diagnosed by renal biopsy from 1981 to 2015. The exposure of interest was initial dose of PSL <0.683 mg/kg/day (median) (Group L) compared to ≥0.683 mg/kg/day (Group H). Cumulative remission and relapse after remission were compared using Cox regression adjusted with for baseline characteristics. Median time to remission, 4-week remission rate, and incidence of infection that requires hospitalization during the 6 months following steroid therapy were also compared using Mann-Whitney U test and Chi-square test.

Results: Among 70 patients who met the criterion, 38 (54.3%) were male and the average age was 46.8 ± 20.1 years. During a median follow-up of 3.2 years, 67 (95.7%) achieved complete remission and 35 (52.2%) relapsed after remission. The median initial dose of PSL was 0.63 and 0.73 mg/kg/day in Group L and H, respectively. There was no significant difference in remission rate between Group L and H at 4 weeks (74.3 vs 71.4%; p=0.79). The median time to remission in Group L was comparable to that in Group H (15 vs 14 days; p=0.66). Multivariable Cox hazard model revealed that initial dose of PSL was not a significant predictor for remission (HR 1.23, 95%CI 0.67 to 2.26, p=0.51), but Group L had a trend toward higher relapse rate (HR 2.18, 95%CI 0.94 to 5.25, p=0.07). There was no significant difference in 6-month incidence of infectious complication between the groups (Group L, 5.7% and Group H, 2.9%, p=0.56).

Conclusions: The initial dose of PSL was not associated with time to remission and remission rate, but lower initial dose of PSL had a trend toward higher relapse rate. The results in this study suggest that the dose of PSL would be tapered carefully after remission, when initiating treatment with lower dose of PSL.

TH-PO993

A Pilot Study of a Gluten-Free Dairy-Free Dietary Intervention in Children with Steroid-Resistant Nephrotic Syndrome

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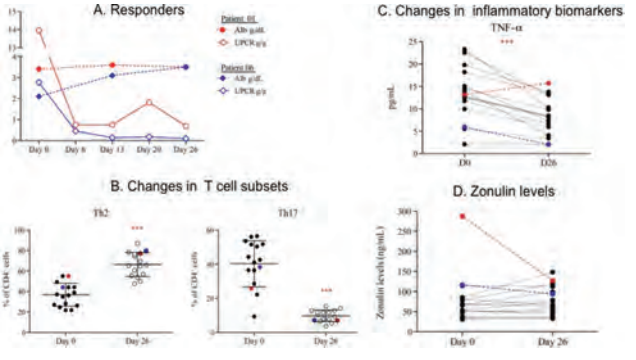
Background: Steroid-resistant nephrotic syndrome (SRNS) in children often fails immunosuppression and progresses to kidney failure. Case reports have suggested potential beneficial effects of dietary changes on SRNS, especially gluten-dairy restrictions. Zonulin is a circulating protein upregulated in gluten sensitivity, which regulates intestinal barrier. We hypothesize that zonulin might also alter permeability of podocyte tight junctions and contribute to SRNS activity.

Methods: Prospective non-randomized pilot study to investigate the effect of a gluten and dairy-free (GF/DF) diet in children with SRNS. The study was organized as a four-week summer camp with prospective collection of blood, urine and stool.

Results: 16 patients (mean age 7 years, range 2-21) met the eligibility criteria. Ten patients had FSGS, while six minimal change disease. Whole exome sequencing did not reveal any SRNS-associated variants. Complete remission following implementation of GF/DF diet occurred in two patients (13%, Fig A –marked in blue and red). Furthermore, GF/DF diet showed anti-inflammatory effects on the immune system in all participants, reducing circulating Th17 cells by 78% (Fig B) and decreasing levels of pro-inflammatory cytokines (Fig C). Microbiota analysis revealed a higher fraction of *Faecalibacterium prausnitzii* upon dietary intervention. Circulating zonulin levels over 106 ng/mL differentiated responders from non-responders (Fig D).

Conclusions: GF/DF may be an effective coadjuvant treatment in a subset of children with SRNS, in particular those with high zonulin levels. Diet intervention can also have anti-inflammatory benefits. A summer camp is a feasible way to implement dietary interventions in children and assess its short-term effect.

Funding: Private Foundation Support



TH-PO994

Rituximab as a Rescue Treatment of Primary Podocytopathies in a Brazilian University Center

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Background: Focal and segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) are two primary glomerulopathies which usually present with nephrotic syndrome and classified together as podocitopathies. The first one is common in adults and the second one in children. The currently available treatments for both diseases have important side effects. High rates of steroid and cyclosporine resistance and dependence are indicative

that new therapeutic options are mandatory. The main objective of our study is to describe the profile of patients with podocytopathy who used rituximab in a brazilina university center.

Methods: This is a retrospective cohort including 18-year-old or older patients with kidney biopsy showing MCD or FSGS who have used at least 1 dose of rituximab between 2012 and 2018, with a minimum of 6 months of follow up after infusion. Epidemiological, clinical and histological variables were analyzed. Were considered responders patients with at least a 35% reduction in proterinuria and an increment of 0.5 g/dL of serum albumin.

Results: Twenty-eight patients fulfilled the inclusion criteria, 57% female, median creatinine and age at the time of the infusion was 1.1 mg/dL and 33 years-old, respectively. The main indications were lack of response to traditional immunosuppressors and frequent relapse during or after corticosteroid withdrawal, with previous use of cyclosporine in 76% and prednisone in 96%. Median 24-h urinary protein at infusion were 8.40 g (5.30 - 12.64, IQR) in non-responders and 7.65 g (1.34 - 17.63, IQR). After 3 months they resulted 7.06 g (5.62 - 9.97, IQR) and 0.25 g (10 - 5.51, IQR), respectively. The complete remission rate in 3 was 24% and in 6 months was 10%. Partial remission was present after 3 months in 33% of the cases. Evaluating non steroid resistant patients, 58% of them had partial remission at 3 months while no steroid resistant individual had any type of remission. In relation to side effects, 18% had an infection episode up to 6 months after infusion and 2 patients presented rash, with no severe drug reaction.

Conclusions: Rituximab is a possible option to use in FSGS and MCD especially in individuals considered steroid-sensitive and dependent and with an acceptable safety profile.

TH-PO995

Rituximab Treatment of Minimal Change Disease (MCD) and Focal Segmental Glomerulosclerosis (FSGS) in Adults

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Background: Previous smaller retrospective and prospective studies have suggested that rituximab may be an effective therapy for adult patients with MCD and FSGS who have steroid dependent nephrotic syndrome.

Methods: We reviewed the charts of 82 adults seen at Columbia University Medical Center between 2014 to 2019 who received rituximab for treatment of MCD or FSGS. We analyzed clinical, biopsy, and laboratory data pre-infusion and at follow up (F/U). We categorized patients as frequently relapsing/steroid dependent (FRSD), infrequently relapsing (IR), steroid resistant (SR), and multi-drug resistant (MDR, failed 2 or more prior immunosuppressive medications(IS)) based on their clinical course.

Results: Of 80 patients biopsied, 41 patients had MCD, 34 had FSGS, 5 had podocytopathy associated with another diagnosis, 2 patients had nephrotic syndrome without previous biopsy. Median age was 40 years and 60% were male. 48 patients were Caucasian, 11 African-American, 17 Hispanic and 6 Asian. Disease categories included 41 FRSD, 7 IR, 9 SR and 25 MDR. The median duration of F/U was 30 months (range 1-156 months). 51/82 (62%) patients achieved complete remission (CR, UPCR <0.5 g/g) and 11/82(13%) achieved partial remission (PR, UPCR 0.5-3.5 g/g) at F/U. All CR/PR occurred by 7 months after infusion of rituximab. 20/82 (24%) did not achieve CR/PR. Of the 61 patients in CR/PR, 48 (79%) patients were off all other IS at F/U. 36/41(88%) FRSD patients achieved CR/PR, and while 11/25(44%) MDR patients achieved PR, none achieved CR. 13/82(16%) patients progressed to ESRD, 8/13(62%) of these patients were MDR. 25/82(30%) patients relapsed, median time to relapse was 22 months from last rituximab infusion. 18 patients were retreated with rituximab, and 13/18(72%) achieved CR.

Conclusions: This large study confirms the benefit of rituximab in achieving remission of proteinuria and reduction of immunosuppression in adults with MCD or FSGS. Patients with MDR disease were less likely to respond to rituximab.

TH-PO996

Study of Long-Term Recurrence and Adverse Effects of Rituximab Treatment in Adults with Steroid-Dependent Minimal-Change Nephrotic Syndrome

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Background: The effect of rituximab treatment on the minimal-change nephrotic syndrome came to be known widely. However, there are few reports about the long term clinical course after rituximab treatment. Therefore, we studied a 60-month recurrence and the adverse effects from start of the rituximab treatment.

Methods: We performed a retrospective study of the clinical course of 52 MCNS patients who had rituximab treatment at interval of 6 months. We compared the clinical findings between the 60-month period before and 60-month period after the first rituximab infusion.

Results: Significant reduction in the average number of relapses was observed during the 60-month period after the first rituximab infusion as compared with the findings during the 60-month period before the first rituximab infusion (8.9 vs 0.7, p<0.001). Oral administration of immunosuppressant containing prednisolone at 60-month was significantly decrease from the start of rituximab. There were no severe adverse effects during the 60 month period after the first rituximab. However, mild infusion reactions occurred 60 times (14.4%). Also, two patients had leukopenia (3.8%), another one had myocarditis (1.9%), another one had buttocks abscess (1.9%), and another two patients had hypogammagolbulinemia (3.8%).

Conclusions: Our results revealed that rituximab therapy was associated with reduction in the number of relapses and in the total dose of immunosuppressant needed. And the results also revealed that rituximab was safe for MCNS patients. However a few patients had some adverse events, so it is important to observe all patients after rituximab treatment regularly.

TH-PO997

The Incidence and Timing of Infectious Complications Relating to Immunosuppressive Treatment Among Adult Japanese Minimal Change Disease and Focal Segmental Glomerulosclerosis: A Retrospective Study

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Background: Among adult minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), some patients require high-intensity or long-term immunosuppressive therapy because of poor treatment response or relapses. However, there are few reports investigating the incidence of infectious complications and its timing during immunosuppressive therapies.

Methods: Multicenter retrospective cohort study. MCD/FSGS diagnosed by kidney biopsy from 2005 to 2015 at Nagoya university and 15 affiliated hospitals were included. Age<20, non-nephrotic cases, secondary cases, patients who did not receive any immunosuppressive treatment or patients who dropped-out within 4 weeks were excluded from the analyses. The incidence and its timing of infections that were treated under hospitalization were evaluated using Kaplan-Meier method.

Results: Among 298 cases (MCD/FSGS: 243/55 cases), 270 (89.9%, MCD/FSGS: 95.1/67.3%) attained complete remission (CR). The median values of duration for CR were 14 days in MCD and 38 days in FSGS (p=0.05). Thirty-nine (13.1%) patients suffered from infections at least once during entire observation and pneumonia was the most common (11 cases). Twenty-two out of 39 (56.4%) cases had infections within 6 months from the initiation of immunosuppressive treatment. In Kaplan-Meier analysis, the risk for infections were higher in FSGS patients (p=0.034 vs. MCD) or elderly patients (age≥65, p<0.001 vs. age<64). When patients were categorized into 4 subgroups according to the duration for CR (patients who attained CR within 4 weeks, 4-8 weeks, 8-16 weeks and over 16 weeks), poor-responders (CR over 16 weeks) demonstrated the highest risk and early-responders (CR within 4 weeks) showed the lowest risk for infections (p>0.001 in log-rank test). Multivariate Cox proportional hazard model showed that elderly patients (adjusted HR: 3.35, 95% CI: 1.61-6.97, p<0.001), baseline eGFR (adjusted HR: 0.83 for every 10 mL/min/1.73m2, 95% CI: 0.63-0.99, p=0.038) and poor-responders (adjusted HR: 4.80, 95% CI: 1.86-12.35, p=0.001) were associated to infections.

Conclusions: Among patients with adult MCD/FSGS, infections relating to immunosuppressive therapies should be taken in mind especially in poor-responders as well as elderly.

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TH-PO998

Incremental Reduction of Proteinuria and Kidney Survival in FSGS

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Background: Proteinuria remission has been shown to predict disease progression in focal segmental glomerulosclerosis (FSGS). This study examines if incremental reductions in proteinuria are associated with improved kidney survival even if a complete or partial remission is not reached.

Methods: Data are from the NIH/NIDDK FSGS clinical trial of 138 steroid resistant patients randomized to cyclosporine or mycophenolate mofetil (no difference in trial endpoint of proteinuria remission). Linear-mixed effects models tested if week 26 proteinuria was associated with subsequent slope of estimated glomerular filtration rate (eGFR). Stratified Cox-proportional hazards models tested if time-varying proteinuria was associated with time to kidney failure. Model interaction terms and sensitivity analyses tested for an incremental impact of proteinuria on outcome for those with urine protein: creatinine ratio >1.5g/g. Analyses were adjusted for age, race, baseline proteinuria and eGFR, and treatment arm.

Results: A 1-log increase in proteinuria was associated with a -5.1 ml/year difference in change in eGFR per year (95% CI=-8.3 to -2.0 p<0.001). There was an analogous relationship between time-varying proteinuria and time to kidney failure: HR per log-proteinuria=3.94 (95% CI=1.79 to 8.68 p<0.001). Findings remained the same when limited to those with proteinuria >1.5g/g at week 26.

Conclusions: These findings agree with previous reports of an important proteinuria threshold at approximately 1.5g/g associated with a large clinical benefit, but also support that a reduction in proteinuria—even if not to below 1.5g/g—is still associated with improved survival. Clinical trials should consider reductions in proteinuria as a marker of future preservation of kidney function.

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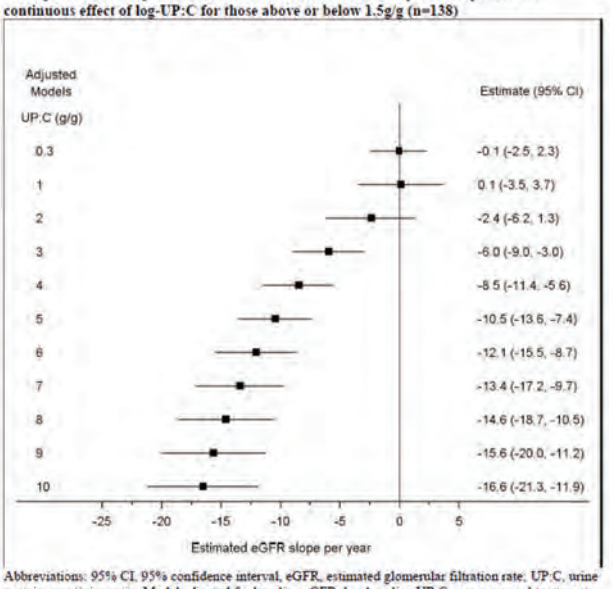
Figure. Results of linear mixed effects model of the impact of week 26 proteinuria on subsequent eGFR slope. Third-order interaction used to fit separate slopes for the continuous effect of log-UP:C for those above or below 1.5g/g (n=138)



Abbreviations: 95% CI, 95% confidence interval, eGFR, estimated glomerular filtration rate; UP:C, urine protein: creatinine ratio. Model adjusted for baseline eGFR, log-baseline UP:C, age, race, and treatment arm.

TH-PO999

Impact of Sparsentan on Quality of Life (QoL) in Focal Segmental Glomerulosclerosis (FSGS) Patients in DUET: An Interim Analysis

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Background: FSGS has been shown to impair patients' (pts) QoL. DUET, a phase 2, randomized, active-control study, examined QoL in pts with FSGS.

Methods: In the 8-week randomized double-blind treatment period (DB), pts received sparsentan (SPAR) or irbesartan (IRB), after which all randomized pts who continued in an open-label extension received SPAR (SPAR:SPAR or IRB:SPAR, respectively). The SF-36 questionnaire was administered to adults at baseline (BL), Week 8, Week 48 and Week 144. Norm-based scoring was used for the physical (PCS) and mental (MCS) component scores (mean±SD).

Results: Seventy-three patients were randomized to SPAR and 36 to IRB with a mean baseline UP/C of 3.61 and 3.12 g/g, respectively, and median eGFR of 73.4 and 65.1 mL/min/1.73 m^2, respectively. There were no clinically meaningful differences between the SPAR and IRB groups in the cross-sectional PCS or MCS at BL and Week 8. The mean change from BL to Week 8 between the SPAR and IRB groups for PCS (p=0.5103) and MCS (p=0.8725) did not differ. Importantly, there were no meaningful changes over time during the open-label extension in PCS or MCS from BL to Week 48, or Week 144 both in SPAR:SPAR and IRB:SPAR (Table).

Conclusions: Using the SF-36, the physical and mental QoL component scores in DUET were similar in SPAR- and IRB-treated patients during the DB. QoL parameters remained stable over time (2 years) in participants electing to remain on long-term open-label treatment with SPAR regardless of original randomization to SPAR or IRB and were not adversely affected by dual blockade of the AT_1 and ET_A receptors.

Funding: Commercial Support - Retrophin, Inc., San Diego, CA

Table. Cross-Sectional Mean±SD for PCS and MCS

SF-36 Dimension	SPAR:SPAR				IRB:SPAR			
	Week 0 n=53	Week 8 n=56	Week 48 n=49	Week 144 n=32	Week 0 n=25	Week 8 n=28	Week 48 n=48	Week 144 n=19
PCS, mean±SD	49±8	49±9	49±9	49±9	50±7	50±7	53±5	53±6
MCS, mean±SD	50±10	50±9	52±10	52±9	50±11	50±10	52±6	50±7

TH-PO1000

FSGS Minimal Change Disease Patient-Reported Outcome (PRO) Measure Development

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Background: Assessment of how patients feel and function are needed for clinical care and research for focal segmental glomerulosclerosis (FSGS) and treatment-resistant minimal change disease (MCD). The objective of this study was to develop a PRO appropriate for use in children and adults with FSGS and MCD.

Methods: Participants (PTS) were recruited from nephrology practices, Kidney Research Network registry and NephCure Kidney International social media. Eligibilty criteria: proteinuria (UPC ≥ 1) within the prior 12 months, eGFR > 30 ml/min and no other severe health condition. Interviews for concept elicitation were conducted in-person for children < 14 yrs and in-person or by phone for ≥ 14 yrs. Interviews were transcribed and reviewed by 2 investigators who developed a hierarchical taxonomy or "codebook" through an ongoing, iterative, deductive and inductive analytical process. Concepts were pooled with those elicited from 30 adults with FSGS participating in the initial FSGS PRO development initiative.

Results: 43 interviews with FSGS children (n=11) and adults (n=11), and MCD children (n=8) and adults (n=13) were completed. MCD interviews are ongoing. Latent content analysis suggests FSGS and MCD impact physical, social and mental HRQOL regardless of age or diagnosis. Physical complaints of swelling, fatigue and pain were endorsed by the majority of PTS. PTS described their experiences with medication and associated side effects, as well as lifestyle changes made to manage disease (i.e., diet and medical visits). Interviews often detailed a profound impact on physical abilities and life participation. PTS described the negative impact these symptoms had on their mood and sense of self with a majority of PTS endorsing feelings of anxiety. Depression was common in MCD and about half of expressed feelings of frustration. Finally, PTS with MCD also talked about the toll that frequent and unpredictable relapse had on leisure and work/school activities.

Conclusions: FSGS and MCD can have a profound impact on HRQOL in children and adults. While there is an existing PRO for adults with FSGS, our results suggest that there are commonalities to the FSGS-MCD patient experience that will enable the generation of a disease specific FSGS- MCD PRO for use in children and adults. Measure validation initiatives will be required prior to broad spectrum use.

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TH-PO1001

Alport Syndrome: Phenotype-Genotype Correlation in Lithuanian Families

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Background: Alport syndrome (AS) is a rare inherited collagen IV nephropathy, caused by mutation in COL4 genes leading to progressive kidney injury with extrarenal manifestations including ocular and hearing abnormalities. Exact incidence of AS is not well known due to clinical and genetic heterogeneity of the disease. The diagnosis of AS is confirmed by a pathogenic mutation in the COL4A5 gene, associated with X-linked AS or pathogenic mutations in COL4A3 or COL4A4 genes inherited in autosomal pattern.

Methods: Data analysis of the clinical, histological and genetic records of the patients with suspected AS was made. Inclusion criteria were associated with a high grade suspicion for AS such as positive family history, hematuria as an early sign of the disease, progressive chronic kidney disease (CKD), sensorineural hearing loss and several ocular abnormalities.

Results: 87 patients with suspected Alport syndrome (23 children and 64 adults), 51 females and 36 males were included. 33 patients were suggested to have Alport syndrome due to specific renal biopsy findings. Other patients had positive family history. Diagnosis of AS was genetically confirmed in 74 % patients, with COL4A3, COL4A4 and COL4A5 genes 82 %, 8%, 10% respectively. In total 20 different familial mutations were found. All patients had hematuria. Progressing chronic kidney disease was seen in 39 % of the patients with an average age at diagnosis 15,4 years (14 – 40 y), whereas 36 % patients with CKD had end-stage renal disease and underwent on dialysis. CKD was significantly more frequent and more numerous in *COL4A5* comparing with *COL4A3* and *COL4A4* genes mutations. Disease progression correlated with the age ($p<0.05$). Hearing abnormalities were presented in 22,4 % of all AS cases. Ocular abnormalities and vision alterations were seen in 18,4 % patients and were strongly associated with COL4A5 gene mutations.

Conclusions: COL4A5 mutations cause more severe phenotypic manifestation in male patients, specially related with a more severe renal phenotype while mutations in COL4A3 or COL4A4 are related with autosomal AS with milder clinical alterations. Further epidemiological studies are needed for better understanding of AS manifestations.

TH-PO1002

Description of Alport Disease in Female Children and Adolescents

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Background: Alport disease (AD) is a multi-system disease historically thought to be presymptomatic in young females given inheritance is most commonly X-linked. Prior descriptive studies and outcome data have focused mainly on males and adult women. The aim of this study was to describe the clinical presentation and course of the females with AD in a large pediatric medical center.

Methods: A single center retrospective review of pediatric females with AD seen at Children's Hospital of Philadelphia between 1987 - 2018. All females with ICD 9/10 codes for Alport, familial hematuria and hereditary nephritis were identified. GFR was calculated using the bedside CKiD equation. Hypertension was defined as systolic or diastolic blood pressure ≥95th percentile for age, gender and height. Proteinuria was defined as ≥ 30 mg/dL of protein.

Results: 217 subjects were identified, 164 of them excluded for an incorrect diagnosis. 16 charts were missing. 37 female patients were confirmed to have AD and included in the analysis. Mean age of presentation was 5.4 ± 3 yrs with mean follow-up of 6.3 ± 4 yrs. 14 patients had genetic testing, with 80% demonstrating heterozygous mutations in the COL4A5 gene. Biopsies were performed in 11 patients. The remaining patients were diagnosed based on clinical manifestation and family history. At the end of follow up at least one episode of gross hematuria was observed in 15 patients, proteinuria in 21 patients, and GFR <90 ml/min/1.73 m2 in 3 patients. Seven patients had an abnormal audiogram. See Table 1 for pertinent clinical findings. One patient required dialysis and received a deceased donor transplant.

Conclusions: Most females diagnosed with AD in childhood have persistent microscopic hematuria and normal renal function. Gross hematuria, proteinuria, and subclinical hearing involvement were common findings suggesting that AD should not be overlooked in girls with nephritis.

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Clinical Characteristics of Females with AD

	Presentation (n=37)	End of Follow Up (n=37)
Family History	29 (78.4%)	29 (78.4%)
Hematuria (microscopic)	33 (89.2%)	35 (94.6 %)
Hematuria (gross)	13 (35.1%)	15(40.5%)
Proteinuria	12 (32.4%)	21(56.8%)
Mean GFR (ml/min/1.73m2)	116 ± 23	119 ± 36
Patients with GFR <90 ml/min/1.73 m2	3/27* (11.1%)	3/26* (11.5%)
Hypertension (SBP or DBP ≥ 95th %)	2(5.4%)	3(8.1%)
Abnormal audiogram	7/23 tested (30.4%)	

*Serum creatinine available for this number of subjects

TH-PO1003

Genetic Polymorphism in C3 Is Associated with CKD Progression in IgA Nephropathy

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Background: A single nucleotide polymorphism (SNP) in complement factors can harmfully affect their activity. The commonest SNP in C3 is R102G, causing two allotypic variants: C3 fast (C3F) and C3 slow (C3S). C3F has been shown to be prevalent in CKD, especialy IgA nephropathy but no study has explored its role in CKD progression.

Methods: Delta (Δ) eGFR (±ml/min/1.73m^2/yr) for 2038 patients in the Salford Kidney Study (SKS) was calculated by linear regression, with ≤-3ml/min/1.73m^2/yr defined as rapid progressors (RP) and those between -0.5 and +1ml/min/1.73m^2/yr labelled stable progressors (SP). All patients had ≥2-years follow-up and eGFR-time graphs were analysed to ensure no AKI episodes contributed to CKD progression. We also studied all biopsy-proven GN patients in SKS regardeless of their ΔeGFR. R102G was analyzed by real-time PCR. The association between C3F and progression (ESRD or ≥40% decline in eGFR) was analysed using Cox regression.

Results: There were 255 SP and 259 RP with median delta eGFR (0.07 vs. -4.7 ml/min/1.73m^2/yr). There was no significant difference in C3 allele frequency between the two groups as a whole: C3F 27% in RP vs. 24.3% in SP p = 0.32. In the subgroups analysis there were 37 patients with IgA nephropathy (21 RP and 16 SP), in this group there was a significantly higher frequency of C3F in RP (38.6% vs. 9.4% in SP; p<0.001). In the GN group there were 269 patients, containing 114 IgA nephropathy patients. Cox regression showed strong and independent association between C3F and progression only in the IgA nephropathy with HR =1.9 (95% CI 1.1 – 3.1; p 0.018) for C3FS, increasing further for C3FF to HR =2.8 (95% CI 1.2 – 6.2; p 0.014).

Conclusions: C3 SNP; R102G; is associated with CKD progression in patients with IgA nephropathy but not in other causes of CKD.

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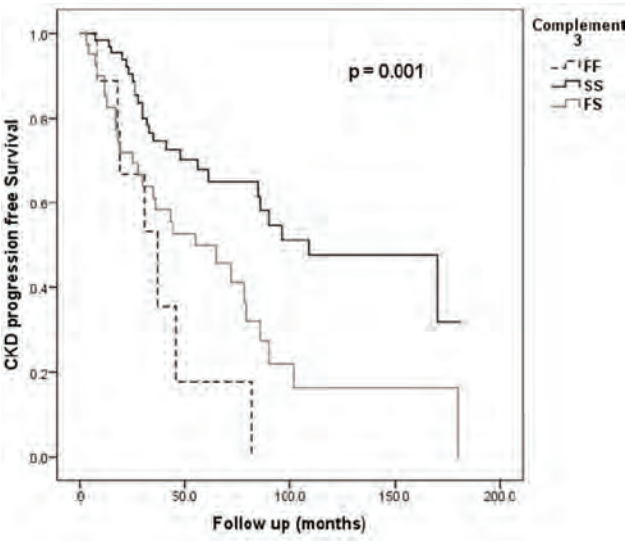

TH-PO1004

The Study of the FUT2 Gene Carrying a Nonsense Mutation in IgA Nephropathy

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Background: The pathogenesis of IgA nephropathy is related to the dysbacteriosis, but FUT2 gene carrying nonsense mutation plays a role in the intestinal flora disorder.

Methods: To verify that FUT2 gene with nonsense mutation is associated with IgA nephropathy. We collected 104 cases of physical examination and 56 cases of IgA nephropathy diagnosed by renal biopsy from June 2017 to December 2018. We extracted genomic DNA to detect FUT2 gene, test serum biochemical markers, intestinal barrier function indicators (diamine oxidase DAO and D-lactic acid DL), and collected the blood pressure(BP), 24 hour urinary protein and renal pathology.

Results: 1. We found that 5 patients (8.9%) of IgA nephropathy carry a nonsense mutation on FUT2 gene and there is no nonsense mutation in 104 healthy people. 2. The levels of the BP 146±11.43mmHg, serum creatinine(Cr)138.34±23.54μmol/L, serum uric acid(UA)424.39±116.45μmol/L, 24 hour urinary protein2.69±1.8g, DAO18.75±4.96U/L and DL 40.14±10.25mg/L are significantly higher in patients carrying a nonsense mutation than those without mutation group which is respectively 111±12.43mmHg, 72.56±25.72μmol/L, 375.96±102.01μmol/L, 1.50±0.73g, 4.25±5.59U/L and 15.78±5.67 mg/L(P<0.01). 3. The number of eGFR 75.71±11.18ml/min/1.73m^2 in the mutation group is obviously decreased than that in the non-mutation group 98.72±12.91 (P<0.01). 4. The melanocyte proliferation, glomerular sclerosis, and interstitial fibrosis were significantly observed in the mutation group, the score was 3.6±0.54. In the non-mutation group, the score was 1.6±0.65 (P<0.05).

Conclusions: 8.9% of patients with IgA nephropathy have nonsense mutations on FUT2 gene. Compared with the non-mutation group, the BP, serum Cr, UA, 24 hour urinary protein, DAO and DL are significantly higher in the mutation group, but eGFR is obviously decreased. Renal pathology suggests that the score of mesangial cell proliferation, glomerular sclerosis and interstitial fibrosis are increased in the mutation group. Studies of IgA nephropathy have shown that higher serum Cr, 24 hour urinary protein, BP and lower eGFR are positively correlated with disease progression and that the higher score of the renal pathology suggest a poor prognosis. Finally we infer that nonsense mutations on FUT2 gene can affect the intestinal barrier function and accelerate the progression of IgA nephropathy, and its mechanism still needs further study.

TH-PO1005

Significant Intestinal Flora Disturbance Is Discovered in IgA Nephropathy Patients

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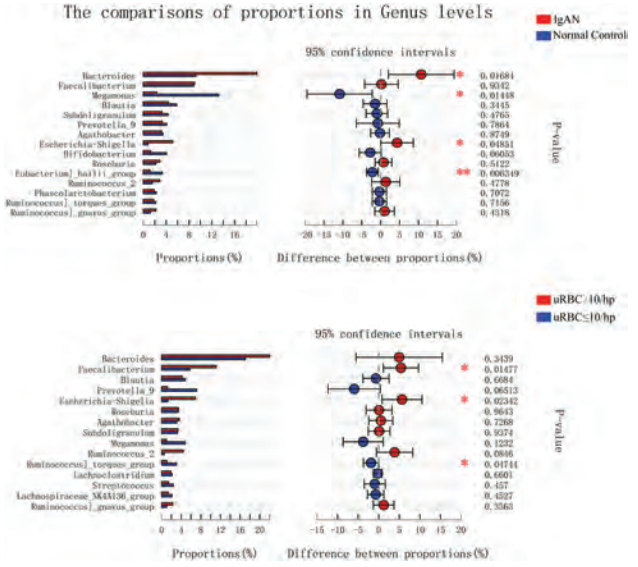
Background: IgA nephropathy (IgAN) is an autoimmune glomerular disease, manifested by hematuria with or without proteinuria. The pathogenesis has not been clarified yet. This study investigated the relationship between IgAN and gut microbiota composition to understand gut-kidney axis.

Methods: 44 patients with biopsy-proven IgAN and 15 healthy controls were enrolled. The patients were divided into two groups based on levels of urine red blood cells (uRBC). Compositions of intestinal flora were assessed by 16sRNA microbial profiling approach.

Results: The proportions of Escherichia-Shigella (5.16%±8.25% vs 0.83%±1.12%, P=0.04) and Bacteroides (19.9%±16.34% vs 9.20%±6.21%, P=0.02) increased significantly in IgAN patients, compared with normal control. Conversely, Bifidobacterium (1.29%±3.51% vs 4.07%±7.62%, P=0.06), Eubacterium hallii (1.16%±2.07% vs 3.36%±3.78%, P=0.01) and Megamonas (2.36%±7.67% vs 13.2%±25.7%, P=0.01) was markedly decreased.

Subgroup analysis indicated patients with higher level of uRBC tended to have higher rates of Escherichia-Shigella (6.93%±9.48% vs 1.27%±1.67%, P=0.02) and Faecalibacterium (11.16%±7.73% vs 5.77%±4.42%, P=0.02), compared with lower uRBC group. Moreover, the levels of Bifidobacterium were not detected in 72.9% IgAN patients. Interestingly, the patients lack of Bifidobacterium were more likely to have lower level of eGFR (87.49±34.50 vs 104.64±13.67, P=0.03) and higher level of uric acid (398.93±135.26 vs 300.56±93.19, P=0.05), suggesting that Bifidobacterium might have potential renoprotective effects and its loss might contribute to the progression of IgAN.

Conclusions: IgAN are featured by increase in pathogenic bacteria and reduction of beneficial bacterium. Potential intestinal flora disturbance might be related to the occurrence of IgAN, which could become a new therapeutic target.



TH-PO1006

BAFF-Dependent IgA Production Does Not Play a Pivotal Role in the Pathogenesis of Murine IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Although our understanding of this disease have improved by remarkable progress, its pathogenesis has not yet clearly understood. Recent studies suggested B cell activating factor belonging to the TNF family (BAFF), which participates in the activation of B cells and class switch of IgA, as a potential disease marker of IgAN. However, the role of BAFF in the development and progression of IgAN remains unclear. In this study, we investigated the pathological role of BAFF in IgAN using a grouped ddY mice which is the spontaneous murine model of IgAN.

Methods: Mice with IgAN designated grouped ddY were treated with PBS or anti-BAFF monoclonal antibody (anti-BAFF Ab) by intraperitoneal injection every three days for four weeks. We measured the levels of urinary albumin, serum immunoglobulins (IgA, IgG, and IgM), and serum IgA-IgG immune complex at the beginning and end of the treatment. The levels of serum aberrantly glycosylated IgA were also measured using biotinylated Ricinus communis agglutinin-I (RCA-I) and Sambucus nigra bark lectin (SNA). We further assessed glomerular depositions of IgA and C3 by immunofluorescence staining, and analyzed changes of B cell population in spleen and bone marrow using flow cytometric analysis.

Results: Anti-BAFF Ab treatment significantly decreased serum levels of IgA, IgG, and IgM as compared with PBS treatment in the murine IgAN model ($p < 0.001$, $p = 0.003$, and $p = 0.002$, respectively). However, it did not affect urinary albumin excretion, serum levels of IgA-IgG immune complex, and serum levels of aberrantly glycosylated IgA. Glomerular depositions of IgA and C3 as well as B cell population in spleen and bone marrow were also not affected by anti-BAFF Ab treatment.

Conclusions: Anti-BAFF Ab treatment was effective to inhibit the production of immunoglobulins, but not nephritogenic IgA in murine IgAN model. Our results suggest that BAFF-dependent IgA production may not play a pivotal role in the pathogenesis of IgAN.

TH-PO1007

High Serum IgA/C3 Ratio Better Predicts a Diagnosis of IgA Nephropathy Among Primary Glomerular Nephropathy with Proteinuria ≤1 g/d: An Observational Cross-Sectional Study

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Background: Serum immunoglobulin A (IgA)/C3 ratio is considered to be an effective predictor of IgA nephropathy (IgAN). This study aims to explore the diagnostic value of serum IgA/C3 ratio in IgAN among primary glomerular nephropathy in China.

Methods: We recruited 1095 biopsy-diagnosed primary glomerular nephropathy patients including 757 IgAN patients and 338 Non-IgAN patients. Social demography, serum immunological indexes and other clinical examinations were measured. IgAN cases were propensity scored matched (PSM) to Non-IgAN cases on the logit of the propensity score using nearest neighbor matching in a 1:1 fashion with a caliper of 0.02 with no replacements, according to age, gender, BMI, proteinuria and eGFR.

Results: We found that, both in the full cohort and PSM cohort, serum IgA/C3 ratio in IgAN group was significantly higher than those in Non-IgAN group. The same results were also obtained at different levels of proteinuria and renal function stratification. In the PSM cohort, there was no difference in IgA/C3 ratio in patients with IgAN between different proteinuria groups and different CKD groups. The area under the ROC curve (AUROC) for IgA/C3 ratio in distinguishing IgAN among primary glomerular disease was 0.767 in the full cohort and 0.734 in the PSM cohort. The highest AUROC of IgA/C3 ratio was in the proteinuria≤1 g/d group (0.801 in the full cohort, and 0.803 in the PSM cohort); however, there was no difference between all the CKD groups. Meanwhile, the diagnose accordance rate of diagnostic of IgAN among all those patients with IgA/C3 ratio > 3.5304 was as high as 92.02% in the full cohort. Multivariate logistic regression analysis showed, IgAN was independently correlated with age, albumin, CKD 2 stage and CKD 3-5 stage (versus CKD 1 stage) and IgA/C3 ratio.

Conclusions: The present study provided clear evidence that IgA/C3 ratio is an effective predictor of IgA diagnosis, especially in patients with proteinuria ≤ 1g/d. In order to study the effectiveness of this biomarker and to determine a standardized cut-off value, large-scale studies are necessary.

TH-PO1008

Single Nephron Parameters in Patients with IgA Nephropathy

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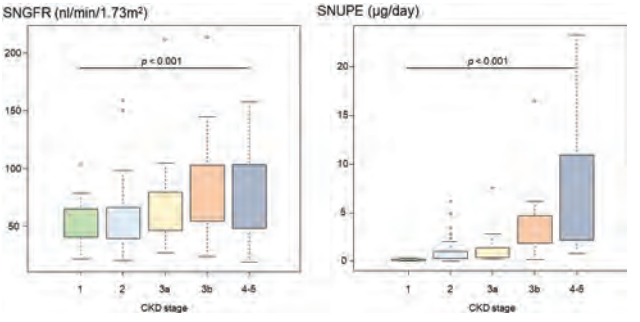
Background: The progression of IgA nephropathy (IgAN) may be characterized by progressive loss of functional nephrons and subsequent alterations in single nephron function in remnant nephrons. In this study, we estimated total nephron number and examined the related single nephron parameters in patients with IgAN at different renal function stages of the disease.

Methods: The total nephron number was calculated using a simplified method based on the combined use of unenhanced computed tomography and stereology-based estimation of non-sclerotic glomerular density on renal biopsy (Sasaki T et al. 2018, ASN). Single-nephron glomerular filtration rate (SNGFR) and single-nephron urinary protein excretion (SNUPE) were calculated by dividing the estimated glomerular filtration rate (eGFR) and urinary protein excretion by total nephron number, respectively. The glomerular volume (GV) was estimated from the measured mean glomerular area.

Results: A total of 107 Japanese IgAN patients (age 43, male 54%, eGFR 61.5 ± 24.2 ml/min/1.73m^2, urinary protein excretion 1.4 ± 1.6 g/day) were included. The total nephron number ranged from 78,000 to 1,989,000 per kidney (602,000 ± 378,000 on average per kidney). SNGFR showed a positive correlation with the GV ($r = -0.37$, $p < 0.001$). Advanced renal impairment of CKD stage 3b or more was characterized by increased SNGFR and markedly elevated SNUPE levels (**Figure**).

Conclusions: These results suggest a close association between loss of functional nephrons and changes in single nephron parameters in remnant nephrons, in parallel with progression of IgAN.



TH-PO1009

Urinary Cytokines as Non-Invasive Biomarkers of IgA Nephropathy

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Background: Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Although renal biopsy is the gold standard of diagnosis, accessibility in clinical practice is poor. Therefore, need for development of non-invasive diagnostic tools such as biomarker has emerged. In this study, we investigated the clinical relevance of 16 urinary cytokines in patients with IgAN.

Methods: The levels of 16 urinary cytokines from 110 biopsy-proven IgAN patients, 15 non-IgAN glomerulonephritis, and 15 normal controls were measured using multiplex assays. Samples were collected from the first spot urine of the morning on the day of renal biopsy. To account for variations in urine concentration, urinary cytokine levels were normalized to urine creatinine. We analyzed the correlations of urinary cytokines with clinical and pathological parameters in IgAN patients. The predictive value of urinary cytokines for adverse renal outcome, which defined as chronic kidney disease (CKD) stage 3 or above at the last follow-up, was also investigated using receiver operating characteristic (ROC) curve analysis

Results: As compared with patients in non-IgAN glomerulonephritis group and normal controls group, patients in the IgAN group showed significant higher urinary cytokine levels of interferon-inducible protein 10 (CXCL10), endocan, growth differentiation factor 15 (GDF15), interferon gamma (IFN-r), interleukin 6 (IL-6), mannan-binding lectin (MBL), nephrin, and transferrin R (TfR) ($p < 0.05$). The urinary levels of endocan, GDF-15, IL-6, and TfR showed significant correlation with estimated glomerular filtration rate (eGFR) (r=-0.240, p=0.005; r=-0.240, p=0.006; r=-0.254, p=0.003; and r=-0.386, p=0.001, respectively). Urinary protein excretion was significantly correlated with CXCL10, IL-6, and TfR (r=0.205, p=0.002; r=0.210, p=0.017; r=0.165, p=0.040, respectively). ROC curve analyses showed that urinary protein to creatinine ratio, GDF-15, and IL-6 had a moderately predictive value for adverse renal outcome (area under the curve > 0.7).

Conclusions: Urinary cytokines have potential as disease specific biomarkers of IgAN. Further large and prospective studies of extended duration are needed.

TH-PO1010

Plasma CXCL16: A Biomarker Predicts Renal Inflammation and Progression of IgA Nephropathy

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Background: Noninvasive biomarkers associated with IGAN prognosis are urgently needed for clinical practice. This study was to investigate whether CXCL16 was associated with pathology and renal outcome in IGAN.

Methods: 230 patients with IGAN diagnosed by renal biopsy between 2012 and 2014 at Huazhong University of Science and Technology Tongji hospital, were included in the study. Follow-up time was up to 42.5 months. The renal outcome was defined as composite endpoints, including ESRD and doubling of plasma creatinine. Plasma CXCL16 level was measured by ELISA. Inflammatory cells including CD4+, CD8+, CD20+ and CD68+ cells in renal biopsy tissues and renal CXCL16 expression were detected by immunohistochemistry.

Results: Plasma CXCL16 levels correlated with serum creatinine ($p< 0.0001$, r=0.362), estimated glomerular filtration rate ($p< 0.0001$, r=-0.411), albumin ($p=0.0019$, r=-0.2068). In renal biopsy specimens, the density of CD8+, CD4+, and CD20+ cells were significantly associated with plasma CXCL16 levels. Mesangial hypercellularity and tubular atrophy/interstitial fibrosis according to the Oxford classification were associated with the plasma levels of CXCL16. ROC curve showed that plasma CXCL16 levels had a predictive value for composite endpoints (cut-off CXCL16=2.968ng/ml, AUC=0.593, sensitivity=0.611, specificity=0.618). Higher plasma CXCL16 levels predicted worse renal outcome during follow-up (Log-rank, $p=0.006$) by Kaplan-Meier analysis. In multivariate Cox proportional hazard analysis, plasma CXCL16 levels at the time of renal biopsy were found to be an independent predictor of composite endpoints after adjustment for age, gender, mean arterial blood pressure and serum albumin ($p= 0.012$). Immunofluorescence results showed that the receptor CXCR6 was expressed in renal CD8+ T cells, not in CD4+ T cells. plasma CXCL16 levels were positively associated with renal CXCL16 expression in tissues (r = 0.316, $p=0.018$). In vitro, IFN-γ promoted CXCL16 expression in HK2 cells through NF-κB pathway. CXCL16 had a chemotactic effect on Jurkat T cells and directly acted on NRK-49F cells to promote fibrosis.

Conclusions: Plasma CXCL16 levels correlate with IGAN pathology and prognosis. CXCL16 may be a risk factor for progression of IGAN.

TH-PO1011

Impact of Histological Findings of Thrombotic Microangiopathy on the Prognosis of Patients with IgA Nephropathy

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Background: IgA Nephropathy (IgAN) is the most common primary glomerulopathy in the world. The Oxford classification considers glomerular and tubulo-interstitial changes as prognostic markers of the disease, however, vascular alterations such as Thrombotic Microangiopathy (TMA) were not included in this classification. The aim of this study is to evaluate the impact of TMA on the prognosis of IgAN patients.

Methods: This is a retrospective cohort study of histological findings of native kidney biopsies between 1999 and 2018 in an academic center. The primary outcome was the TMA impact on loss of renal function and progression to ESRD.

Results: The cohort included 118 patients, 54% women, 73% caucasian, mean age of 33 years (25; 43), followed-up of 65 months (27; 115), with similiar treatment regimens. At the moment of diagnosis, 68% patientes presented with hypertension, 90% hematuria, 12.5% Complement consumption, mean SCr 1.45mg/dL (0.99; 2.6), eGFR 48.8 mL/min/1.73m^2 (27.5; 78), Albumin: 3.4 g/dL (2.9, 3.8), 24h proteinuria 2.01g (1.1, 3.7). Distribution according to Oxford classification: 76% M1, 36% E1, 70% S1, 38% T1 or T2, 29% C1 or C2. Patients with TMA had more hypertension (100 vs 61%, p <0.0001), hematuria (100 vs 87.6%, p = 0.0001), higher SCr (3.8 vs 1.38 mg/dL, p = 0.0001), lower eGFR (18 vs 60 mL/min/1.73m^2, p = 0.0001), Complement consumption (28.5 vs 10.4%, p = 0.003), lower Hemoglobin (10.6 vs 12.7g / dL, p <0.001) and Platelets (207 vs 267 x10^3, p = 0.001) when compared to non-TMA patientes. Comparing the two groups, the only difference at the Oxford classification found was more patients with E1 at TMA group (68 vs 32%, p = 0.002). In the primary outcome analysis, patients with TMA presented faster loss of renal function (ΔeGFR / year: -6.8 vs -1.65 mL/min/1.73m^2, p=0.01), more frequent and faster evolution to ESRD (71.4 vs 21.6%, p <0.0001; 3 vs 16 months, p = 0.003 respectively).

Conclusions: Histological findings of TMA at IgAN implies on worse outcomes. Our findings suggest that vessel assessment may have an impact on prognosis of patients with IgAN and the presence of vascular lesions should be contemplated in the Oxford Classification.

TH-PO1012

Primary IgA and Membranous Nephropathies with Collapsing Glomerular Pattern: A Case Series

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Background: The presence of collapsing pattern is often associated with severe clinical manifestations and renal impairment. These findings and its outcomes in primary Membranous (MN) and IgA (IgAN) Glomerulopathies is poorly studied. The aim of this study is to analyse the impact of collapse lesions on renal survival.

Methods: Clinical data was obtained through the analysis of medical records of patients with IgAN and MN confirmed by kidney biopsies between 2009 and 2018 at a tertiary academic center. Patients presenting collapsing glomerular pattern were investigated for APOL1 risk alleles by direct gene test (sequencing by SANGER). Increase in SCr and progression to ESRD were assessed as primary outcomes.

Results: IgAN and MN were diagnosed in 280 patients and collapsing lesions were identified in 13 samples (9 IgAN and 4 MN). The cohort included 12 patients (one patient was excluded for presenting IgAN associated with HIV infection), 9 men, mean age of 35.5 ± 11 years, 92% caucasian, 50% hypertensive, 42% required dialysis at the time of biopsy. Laboratory findings included: mean SCr 5.3 ± 4.2 mg/dL, eGFR 29.7 ± 32.6 mL/min/1.73 m^2, Serum Albumin 3.1 ± 1 mg/dL, 24h proteinuria 5.2 ± 3.2 g, 83% presence of hematuria, hemoglobin 10.3 ± 2.3 g/dL and platelets 214 ± 80 x 10^3/mm^3. The direct gene test for allele APOL1 was performed in 9 patients resulting only 1 variant of risk (APOL1 G2/G2) in a patient with IgAN. During 1 year of follow-up the mean SCr increased to 5.7 ± 4.1 mg/dL and 50% progressed to ESRD. These findings are greater than our previous IgAN cohort with 111 patients, in which a decline of eGFR of 2.3 mL/min/1,73m^2/year was found.

Conclusions: We observed the presence of collapse lesions in 4.3% of the biopsies with Primary IgAN and MN and it was associated with worse renal outcomes. Although the APOL1 variant is a known factor for Collapsing Glomerulopathy, only 1 patient was found with variant of risk. Unknown predisposing factors may be involved in the collapsing pathogenesis.

TH-PO1013

Influence of Tubular and Interstitial Lesion on Proteinuria Remission and Long-Term Renal Prognosis in IgA Nephropathy with Crescent Lesion Treated with Immunosuppressive Therapy

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Background: Currently, the Oxford classification added crescent (C) score to the conventional mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S), and interstitial fibrosis and tubular atrophy (T) score in IgA nephropathy (IgAN). Although C lesions may be improved with immunosuppressive therapy, renal prognosis with C lesions combined with T lesions remains unclear. We studied proteinuria remission and renal prognosis after steriod therapy in IgAN patients with C lesions in relation to the presence or absence of T lesions.

Methods: This single-center retrospective cohort study included 135 patients with C lesions among 694 patients diagnosed with IgAN and could be followed for ≥1 year or started renal replacement therapy (RRT) within 1 year. Proteinuria remission and renal prognosis (50% decrease in eGFR or initiation of RRT) after steroid therapy were evaluated in relation to the presence of C lesions with and without T lesions (C1T1 and C1T0, respectively). A similar analysis was conducted in a propensity-matched cohort.

Results: There were 101 patients with C1T0 and 34 with C1T1, and 52 patients in C1T0 and 18 in C1T1 were treated with steroid therapy. The mean observation period was 9.2±7.4 years. Age, mean blood pressure, and daily urinary protein excretion were higher and eGFR was lower in C1T1. Compared to supportive care, steroid therapy caused significant proteinuria remission and renal prognosis improvement in C1T0 (log-rank p<0.01). However, in C1T1, steroid therapy achieved significant proteinuria remission (p<0.01), but no renal prognosis improvement effect was seen (p=0.25). In the propensity-matched cohort, significant proteinuria remission (p<0.01) and renal prognosis improvement (p<0.01) were achieved by steroid therapy in C1T0. In C1T1, although proteinuria remission rate at 2 years was higher in those given steroid therapy than those not given (57% vs 29%, p=0.27), there was no significant difference in renal prognosis between the two groups (p=0.46).

Conclusions: In IgAN patients with C lesions, proteinuria remission is achieved by steroid therapy. However, when there are concomitant T lesions, the effect of steroid therapy in improving renal prognosis is limited.

TH-PO1014

Examination of the Factor Related to the Prognosis in IgA Nephropathy Patients with Mild Proteinuria at Diagnosis

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Background: The prognosis for patients with IgA nephropathy (IgAN) with urinary protein <0.5 g / day has been considered good, but there are few reports on factors that affect their renal prognosis.

Methods: A total of 1171 adult patients who was diagnosed with IgAN by the first renal biopsy between 2002 and 2004 were registered in the Nationwide Retrospective Cohort Study in IgAN from 42 institutes all over Japan. In 394 patients with a baseline urinary protein (U-Prot) <0.5 g/day having sufficient data and observation period, a long-term renal outcome was analyzed. The primary outcome was an increase of more than 50 % in serum creatinine levels from the baseline.

Results: Primary outcome was observed in 12 patients (3.0 %). Of 394 patients, 330 had eGFR ≧60 ml/min and U-Prot <0.5 g/day [Clinical Grade (CG) Ia] and 64 had eGFR <60 ml/min and U-Prot <0.5 g/day (CG Ib). There was a significant difference in the incidence of renal outcome between the two groups (log-rank test p<0.001 between CG Ia and CG Ib). Hazard ratio (HR) in CG Ib vs. CG Ia was 9.67 (95 % CI: 2.90–32.23). On univariate analysis using Cox proportional hazards analysis, high uric acid, male, and no remission up to 2 years after renal biopsy were the significant risk factors, whereas tonsillectomy or corticosteroid therapy did not improve the renal outcome. In multivariate analysis using those significant factors, only eGFR <60 ml/min was selected as a significant independent factor (HR in CG Ib vs. CG Ia was 37.1 (95 % CI: 3.11–444.0).

Conclusions: In the present study, we confirmed that eGFR <60 ml/min was an independent risk factor in IgA nephropathy patients with mild proteinuria (<0.5 g/day). It is necessary to verify these results in the ongoing prospective study with a large cohort in the future.

TH-PO1015

Sex-Related Disparities in IgA Nephropathy Progression

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Background: Sex related disparities in prognosis of CKD has been reported. We investigated the influence of gender on prognosis in immunoglobulin A nephropathy(IgA) nephropathy.

Methods: This was a multi-center retrospective study. Patients were divided into two groups according to gender. The clinical features at renal biopsy and renal outcomes during the follow-up were collected and analyzed. Renal outcomes were defined as 30% estimated glomerular filtration rate (eGFR) decline from base line. The prognostic effects of gender were evaluated by Cox regression models

Results: Total of 238 eligible patients with IgA nephropathy were enrolled (male: 124, female: 114). Male patients had higher body mass index and HDL cholesterol levels than female patients. There was no statistical difference on other features including age, blood pressure, eGFR and proteinuria. Median follow-up period was 88 (43 - 133) months. In survival analysis, male showed higher hazard ratio (HR) of 30% eGFR decline than female (HR 1.8, 95% confidence interval(CI): 1.1-3.4, p=0.03). Multivariable Cox regression analyses matched BMI and HDL cholesterol revealed that gender was also detected as a prognostic factor (HR 1.4, 95% CI 1.1-2.2, p=0.02). In gender-based survival analysis, eGFR and proteinuria are common risk factors of 30% eGFR decline. In particular, hypertension in men and lower HDL cholesterol in women was gender specific risk factor of 30% eGFR decline.

Conclusions: Sex related disparities in progression of IgA nephropathy was suggested.

TH-PO1016

Diagnosis, Treatment, and Outcome of IgA Nephropathy with vs. Without Comorbid Diabetes Mellitus

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Background: The U.S. pandemic of diabetes mellitus (DM) has greatly complicated the diagnosis and clinical care of patients with glomerular diseases, such as IgA nephropathy (IgAN), the most common glomerular disease in the world. Our aim was to study the influence of DM on the diagnosis, treatment and clinical outcome of patients with IgAN.

Methods: We conducted a retrospective chart review of patients from the Glomerular Disease Collaborative Network (GDCN) inception cohort of adults with a pathologic diagnosis of IgAN on native biopsies performed between 1/1/1999 - 6/30/2018. GFR was estimated based using the CKD-EPI$_{SCR}$ equation obtained at the time of kidney biopsy. Urine protein:creatinine ratio was measured from a random urine collection.

Results: There was only one patient with type 1 DM and only two patients had histologic diabetic glomerulosclerosis. Indications for kidney biopsy and baseline blood pressure was similar for the two groups. Detailed baseline characteristics, immunosuppressive treatments and clinical outcomes are displayed in Table 1.

Conclusions: Patients with IgAN with versus without diabetes do not differ in the severity of proteinuria or eGFR at the time of diagnosis. Despite a reduced usage of steroids among patients with IgAN and diabetes, follow-up proteinuria and rate of eGFR decline do not differ from those with IgAN without comorbid diabetes. Larger, long term studies are required to fully understand the relationship between DM and IgAN.

Funding: Clinical Revenue Support

Sociodemographic and clinical characteristics of Ig A nephropathy patients with versus without comorbid diabetes.

Characteristics	IgAN without DM N=53 Median (IQR)	IgAN with DM N=25 Medican (IQR)	p-value
Age, years	40 (31, 51)	55 (46, 59)	0.0007
Female, N (%)	20 (37.7)	8 (32.0)	0.8
NonHispanic white race, N (%)	40 (78.4)	20.0 (83.3)	0.8
Baseline eGFR, mL/min/1.73m2	47 (32, 79)	47 (24, 64)	0.4
Baseline urine protein:creatinine, g/g	2 (1.0, 4.0)	2 (1.4, 6.0)	0.1
Baseline body mass index, kg/m2	28 (22, 32)	43 (29, 49)	0.003
Duration of follow-up, months from biopsy	39 (16, 81)	37 (20, 58)	0.5
Immunosuppressives, N (%) Steroids Cyclophosphamide Mycophenolate Mofetil	37 (69.8) 18 (33.9) 9 (16.9)	11 (44.0) 4 (16.0) 2 (8.0)	0.04 0.1 0.4
Rate of eGFR decline, mL/min/1.73m2 per year	-0.5 (-5.8, 5.2)	0.0 (-7.2, 5.6)	0.8
Last available urine protein:creatinine, g/g	0.7 (0.2, 2.0)	0.4 (0.1, 0.8)	0.4
End-stage kidney disease, N (%)	9 (17.0)	6 (24.0)	0.5
Death, N (%)	5 (9.4)	6 (24)	1.0

*p-values calculated by Fisher's exact test for continuous and Wilcoxon two sample test for categorical variables.

TH-PO1017

Characteristics of IgA Nephropathy in the Elderly: Results from a Multicenter, Large-Scale, Long-Term Observational Cohort Study

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Background: Aging of population is a worldwide matter. Especially in Japan, more than 10 years passed after super-aged society had come. Due to increasing number of kidney biopsy underwent for elderly people, the number of aged people who diagnosed IgA nephropathy is also growing. However, little is known about characteristics of IgA nephropathy in the elderly. The indication of corticosteroids or renin-angiotensin system inhibitors is unclear.

Methods: We defined "elderly patients" as patients aged 65 or over at the diagnosis, and "younger patients" as 15-64 years old. Using our multicenter, large-scale, long-term retrospective cohort of IgA nephropathy diagnosed by kidney biopsy during 1981-2013, we extracted elderly patients and investigated their cross-sectional clinical characteristics, pathological features, and renal survival compared to younger patients. Survival analysis was performed by Kaplan-Meier method.

Results: The age at kidney biopsy was dramatically increasing during 30 years of registration period. Among 1,924 patients, 151 (7.8%) patients were aged 65 or older. Their median follow-up period was 46 [18-95] month, and their estimated glomerular filtration rate (eGFR, mL/min/1.73m^2) was 42.7 [27.1-53.4]. The proportion of CKD stage G1-2 in elderly patients was only 16%, while 60% in younger patients. Amount of urine protein was 1.0 [0.42-2.2] g/gCr. Twenty-five percent of elderly patients had diabetes, while only 5% of younger patients had. The percentage of totally sclerosed glomeruli in elderly patients was higher than that of younger patients. In survival analysis, elderly patients with proteinuria ≥1g/gCr, those having diabetes, and those with global sclerosis in more than half of glomeruli, were significantly associated with poor renal prognosis. Similar to younger patients, corticosteroids were used for 37.7% of elderly patients. However, use of corticosteroids or renin-angiotensin system inhibitors for the elderly patients were not associated with better long-term renal outcome.

Conclusions: Population of IgA nephropathy rapidly aged in Japan. IgA nephropathy in the elderly was characterized by progressed CKD with decreased eGFR and global sclerosis of glomeruli. We need to establish a strategy for treatment for IgA nephropathy in the elderly.

Funding: Government Support - Non-U.S.

TH-PO1018

Analysis of Japanese Histological IgA Classification Using Probabilistic Analysis Associated with the Bayesian Theorem

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Background: Regarding the pathological diagnosis of IgA glomerulonephritis (IgAGN), the Oxford classification is widely used globally, although in Japan, the Japanese Society of Nephrology (JSN) published its original pathological classification. For appropriate classification, the Oxford classification requires more than 8 glomeruli, whereas the Japanese classification requires more than 10 glomeruli. However, no study has yet investigated the relationship between the total number of glomeruli and pathological classification by probabilistic analysis. The present study aimed to report how the total number of glomeruli affects the "lumped system" of the Japanese histological IgA classification using probabilistic analysis associated with the Bayesian theorem.

Methods: Ninety-nine patients from 2000 to 2009 diagnosed IgAGN by renal biopsy at Oita University Hospital were included. Certified pathologist diagnosed IgAGN using light microscopy and fluorescence microscopy. We used the third edition of IgAGN classification of JSN. We used Bayesian theorem for Probabilistic analysis. We used three models of the prior distribution. First is actual distribution; Second is a similarity of actual distribution by using the beta function, third is no information for the prior distribution by using the beta function. The ethical committee of Oita University approved this survey.

Results: The median total number of collected glomeruli was 12 [Quartile 7,19]. When the cut-off level was set to less than 60% of the posterior probability, 21 cases (33%) were excluded (7 cases had more than 10 glomeruli, 14 cases had less than 9 glomeruli). When cases with less than 9 glomeruli were excluded before the Bayesian probability test, only 8 cases (12%) showed less than 60% of the posterior probability. However, 19 cases with less than 9 glomeruli showed more than 60% of the posterior probability. Thus, these 19 cases were considered as exclusion cases for classification. The results were the same using the three models of the prior distribution.

Conclusions: It may be better when using the IgA pathological classification of JSN to adopt the probabilistic analysis associated with the Bayesian theorem instead of considering only the total number of obtained glomeruli.

TH-PO1019

Factors Associated with ESRD in an IgA Nephropathy Cohort

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Background: In IgA nephropathy patients, >1 g/day of proteinuria, presence of mesangial hypercellularity, segmental glomerulosclerosis, interstitial fibrosis and tubular atrophy (IFTA) and crescents on kidney biopsy are associated with progression to ESRD. We describe the factors associated with ESRD in an IgA nephropathy cohort with a substantial number of Native Americans and Hispanics.

Methods: We created a cohort of biopsy-proven IgA nephropathy from the UNM kidney biopsy registry which includes biopsies performed between 2002-2016. The demographic and clinical data were abstracted from the electronic medical record. The incidence of ESRD was obtained by chart review until 2016. We used age and sex adjusted Cox proportional hazards models to study the association of the predictor variables (mesangial and endocapillary hypercellularity, segmental glomerulosclerosis, IFTA, crescents, and proteinuria) with the incidence of ESRD. Patients were censored upon death or the last follow-up date for the ESRD outcome. We reported hazard ratios for ESRD with 95% confidence intervals (CI).

Results: Of the 66 patients identified with IgA nephropathy, there were 40.9% females, 36.4% Caucasians, 22.7% Hispanics, and 21.2% Native Americans. Mean biopsy age was 35.2 years (SD 16.9). Median creatinine (Cr) and CKD-EPI Cr equation eGFR were 3.1 mg/dl (IQR 2.8), and 23.2 ml/min/1.73m^2 (IQR 27), respectively. Mean proteinuria was 1.9 g/g (SD 2.7). A total of 45% of patients developed ESRD with a mean follow-up of 4 years. Patients with IFTA involving ≥50% of the cortical area and those with >50% glomeruli exhibiting global glomerulosclerosis were 4.86 and 2.86 times more likely to develop ESRD than the comparison group, respectively. (Fig 1)

Conclusions: This study demonstrates that significant glomerulosclerosis and IFTA are associated with the development of ESRD in an IgA nephropathy cohort comprising of many Native Americans and Hispanics.

Funding: Private Foundation Support

Category	Score	Comparison	HR 95 % CI
Mesangial Hypercellularity	M0: <50% of glomeruli showing mesangial hypercellularity M1: >50% of glomeruli showing mesangial hypercellularity	M1 vs. M0	0.56 (0.25 - 1.23)
Endocapillary Hypercellularity	E0: no endocapillary hypercellularity E1: any glomeruli showing endocapillary hypercellularity	E1 vs. E0	0.82 (0.38 – 1.76)
Segmental Sclerosis	S0: absent S1: present in any glomeruli	S1 vs. S0	2.96 (0.38 – 22.04)
Tubular Atrophy/ Interstitial Fibrosis	T0: 0–25% of cortical area T1: 26–50% of cortical area T2: >50% of cortical area	T1 vs. T0	1.46 (0.48 - 4.53)
		T2 vs. T0	**4.86 (1.50 – 15.43)**
Crescents	C0: absent C1: 0–25% of glomeruli C2: ≥25% of glomeruli	C1 vs. C0	1.06 (0.47 – 2.38)
		C2 vs. C0	3.42 (0.72 – 16.07)
Percent Global Glomerulosclerosis (GS)	<50%: Glomeruli with Global Glomerulosclerosis >50%: Glomeruli with Global Glomerulosclerosis	**GS >50% vs. GS < 50%**	**2.86 (1.18 – 6.91)**
Proteinuria (g/g)		≥1 vs. <1	1.36 (0.51 – 3.62)

Figure 1: Factors associated with ESKD in an IgA nephropathy cohort. The model is adjusted for age and sex. Highlighted rows show statistically significant associations.

TH-PO1020

The Association of Hematuria with MEST-C Score and Renal Outcomes in IgA Nephropathy

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Background: Hematuria is common in IgA Nephropathy. However, current prognostication is largely based on the degree of proteinuria and MEST-C scores found on renal biopsy. We asked: 1) Are MEST-C score components associated with the presence of hematuria at the time of biopsy? 2) Is hematuria an independent risk factor for change in GFR after adjusting for follow-up time, proteinuria, MEST-C score and treatment?

Methods: We identified 125 patients with IgA Nephropathy and MEST-C scoring who were not on immunosuppression at biopsy. We compared clinical and laboratory parameters by hematuria at baseline using equal variance t-test for continuous measures and Chi-square test for categorical measures. Generalized estimating equations were used to evaluate the association between the degree of hematuria and eGFR throughout follow-up, where degree of hematuria was considered as ordinal (<3, 3-10, 11-20, 21-30, 31-40, 41-50, 51-100, >100 RBC/hpf).

Results: Ninety seven of 125 patients had hematuria at baseline (>3 RBCs/hpf), and were more likely to have M1, E1 and C ≥1 lesions (P<0.05 for all) compared to patients without hematuria. Seventy two of the 125 patients had follow up data available (median [IQR] 3.7 years [2.1, 7.0]; of these, 60 (83%) had hematuria at baseline. Nine of the 72 patients progressed to ESKD, with 6 of these 9 having >1 gram proteinuria and hematuria at baseline. An increase in degree of hematuria was significantly associated with an eGFR decline of -0.81 mL/min/1.73 m^2, (95% CI -1.44 to -0.18, P=0.01). Results were similar after adjusting for follow-up time, proteinuria, MEST-C and treatment during follow-up (P<0.05 for all) and after restricting analysis to patients with hematuria and proteinuria >1

gram/d at baseline. T was the only score found to be significantly associated with a decline in eGFR (P<0.001 with and without adjustment).

Conclusions: Hematuria at follow up is an independent predictor of eGFR decline after adjusting for follow-up time, proteinuria, MEST-C score and treatment. This suggests that monitoring the degree of hematuria as well as proteinuria is important for guiding treatment; however, RCTs using a decline in hematuria as a primary surrogate outcome measure are needed.

Funding: Private Foundation Support

TH-PO1021

Application of International Tool for Risk Prediction in IgA Nephropathy in Mexican Patients

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Background: IgA nephropathy is one of the main causes for chronic kidney disease with a progressive deterioration of kidney function with a 10-year risk for end stage kidney disease ranging from 5-60%. Risk stratification is important for immunosuppressive therapy selection so a risk score was developed called international score tool for risk prediction in IgA nephropathy. The aim is determine the strength of association between the international score tool for risk prediction in IgA nephropathy and the lowering of the glomerular filtration rate at 6 months in Mexican patients with IgA nephropathy.

Methods: The study is a retrospective cohort with descriptive statistics, the international score for risk prediction in IgA nephropathy at the Hospital General de Mexico; a Pearson's correlation test was performed with a significative p value <0.05 and IC95%.

Results: Twenty patients were included, mean age 35.2± 14.06 years, 65% (13) were male, glomerular filtration rate(GFR) at biopsy was 72.93± 40.67 ml/min/1.73 m2 CKD-EPI, GFR at 6 months post-biopsy 71.42 ± 36.05 ml/min/1.73m2 CKD-EPI. The correlation between the risk for lowering GFR by 50% at 6 months presented a strong correlation with a statistical significance (Figure 1).

Conclusions: The international score for risk prediction in IgA nephropathy can be used in Mexican patients.

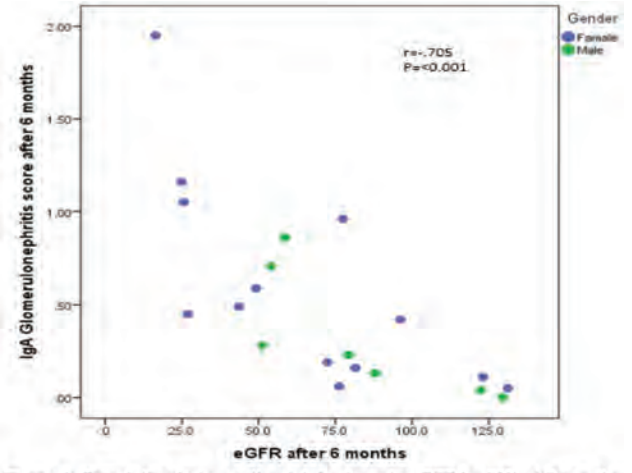

Figure 1: Correlation between the risk for lowering GFR by 50% at 6 months

TH-PO1022

Decision Tree Prediction Models for the Development of ESRD in Immunoglobulin A Nephropathy

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Background: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide and up to 40% will develop end-stage renal disease (ESRD) within 20 years.

Methods: The aim of this study was to develop a predictive model to predict the risk of progressing to ESRD by using decision tree algorithm. Data were evaluated from biopsy-proven IgAN patients in West China hospital, Sichuan University in China between 2009 to 2017. 2 final models were selected by Gini index and the area under receiver-operating characteristic (ROC) curve.

Results: Clinical model was developed by only clinical factors, as pathological model was conducted by both clinical and pathological factors. In clinical model (Figure 1), recursive partitioning indicated that the best single predictor of renal deterioration was proteinuria, followed by severe urine acid for patients with severe proteinuria (> 0.98 g/d). Systolic blood pressure (SBP) and estimated glomerular filtration rate (eGFR) were placed in the third tier of the decision tree model. T and S score were put at high levels in pathological model (Figure 2) and followed with eGFR at third level. Proteinuria and SBP were placed at forth level. Nephrotic syndrome was presented at last. The accuracy of clinical and pathological model were 0.85 and 0.86, respectively. The ROC of clinical model was 0.83, compared with pathological model with 0.85.

Conclusions: Decision model can practically predict the risk of incidence of ESRD in IgAN patients. Model with pathological factors can be more accurate.

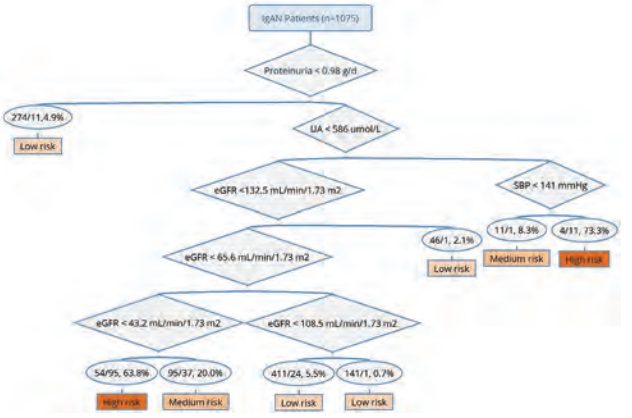

Figure 1. Clinical model of incidence of ESRD in IgAN (Line to left: yes; right: no)

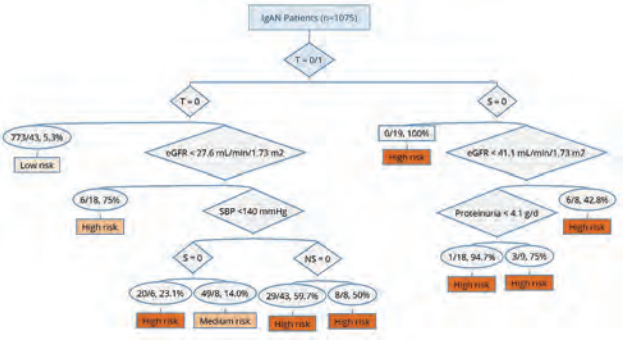

Figure 2. Pathological model of incidence of ESRD in IgAN (Line to left: yes; right: no)

TH-PO1023

Risk Prediction Model Including Therapeutic Options in IgA Nephropathy

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Background: Recently derived prediction model for kidney outcome of IgA nephropathy (IgAN) based on clinical and pathological predictor variables from multi-ethic cohorts (Barbour SJ, JAMA Intern Med. 2019) is a potentially valuable tool in terms of its application to daily clinical practice as well as for clinical trial design. However, since timing of intervention including immunosuppressive therapy is highly variable and is dependent on patient characteristics, pathology, physician preference, country bias etc. The prediction equation currently does not include therapeutic factors after renal biopsy. Therefore, we derived and validated model used at 6 months after renal biopsy with therapeutic factors in Japanese dataset from original multi-ethic cohorts.

Methods: The outcome was defined as the composite outcome of 50% decline in eGFR or ESKD. We derived the renal prediction model including treatment within 6 months after the biopsy by Cox regression modeling with variable selection using the derivation dataset. The performances of the Cox models and the prognostic scores were evaluated based on Akaike information criteria (AIC) and the discrimination ability measured by Chambless and Diao's C-statistics. The derived score was externally validated using the validation dataset by C-statistics, calibration slope.

Results: Japanese patients from the multi-ethnic cohorts were divided to 564 derivation and 582 validation datasets. Over a median 3.31 and 4.63 years of follow-up, 10.1% and 17.2% reached the outcome, respectively. Among the variables at biopsy and treatments, eGFR, blood pressure, proteinuria at biopsy, T and C score, immunosuppression (IS) use, tonsillectomy and interactions between IS and C score, eGFR and tonsillectomy were selected for the prediction model. The derived prediction model achieved better performance compared to the model including only the variables at biopsy (AIC: 599.1 vs 562.6, C: 0.83 95%CI 0.75 – 0.89, ΔC: 0.05, 95%CI 0.00-0.12). The performance of the score remained fine in the validation dataset (C: 0.92, 95% CI 0.86-0.96, calibration slope: 0.97, 95%CI 0.82-1.11).

Conclusions: We derived and validated the risk prediction model at 6 months after renal biopsy including therapeutic options. This model may be useful guide for appropriate treatment in Japan.

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TH-PO1024

Spontaneous Remission in Asian Patients with IgA Nephropathy Treated with Conservative Therapy

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Background: There are few studies describing IgA nephropathy (IgAN) patients with persistent microscopic hematuria with or without minimal proteinuria. However, spontaneous remissions of hematuria and proteinuria were uncommon.

Methods: 62 adult patients with IgAN who received conservative treatment at least 5years were investigated. We investigated remission rate of hematuria and proteinuria and assessed the period and the decline of renal function. Remission of proteinuria and hematuria were defined as consecutive three times of proteinuria <0.3 g/gCr and urine red blood cells <5 /HPF throughout an observation period of at least 6 months respectively.

Results: 38 (61.3%) patients had remission of hematuria, 24 (38.7%) patients had remission of proteinuria, and 19 (30.6%) patients had both remissions. The group with proteinuria <1.0 g/gCr group, the remission rate was 64.2%. The group with proteinuria <0.5 g/gCr group had a higher remission rate than the group with proteinuria ≧0.5 g/gCr group at the time of renal biopsy. The median time to remission of hematuria was 2.8 years (IQR 1.6-4.2), and that of proteinuria was 2.6 years (IQR 1.7-3.4). Patients who showed renal function decline (30% decline of eGFR from baseline) were significantly older, had significantly lower eGFR and higher proteinuria at the time of renal biopsy. Only two patients with normal renal function and normal range of proteinuria at diagnosis showed 30% eGFR decline. The two patients had persistently proteinuria >0.5 g/gCr after five years.

Conclusions: Relatively high rate of spontaneous remission were shown. In the proteinuria <0.5 g/gCr group, there is high rate of remission of hematuria and proteinuria and renal function was preserved. In the case of proteinuria <1.0 g/gCr, it may be possible to observe over three years with conservative therapy.

TH-PO1025

Analysis of Appropriate Treatment for IgA Nephropathy with Mild Proteinuria

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Background: The 2012 KDIGO clinical practice guidelines recommended the renin angiotensin system inhibitors (RASIs) for the IgA nephropathy (IgAN) patients with mild proteinuria (0.5 to 1 g/day) as treatment. However, in Japan, tonsillectomy and steroid pulse therapy (TSP) was frequently employed in a lot of institutions, even though corticosteroid therapy was recommended only for the patients with persistent proteinuria over 1 g/day, despite of 3-6 months of supportive care, and tonsillectomy was not recommended. Then, we analyzed the appropriate treatment for the IgAN patients with mild proteinuria.

Methods: In this retrospective cohort analysis, 127 patients diagnosed as IgAN by renal biopsy from 1980 to 2015 in our institution, and had mild proteinuria (0.5 – 1.0 g/day) and eGFR ≧60 ml/min/1.73m2 were analyzed. We divided them into three groups: patients treated with TSP (TSP, n=34), with oral prednisolone (oPSL, n=33), and with conservative therapy (CON, n=50). We analyzed the clinical and histological backgrounds at renal biopsy, remission rates of proteinuria (U-P) which met < 0.3 g/g creatinine(Cr), urinary red blood cell (U-RBC) < 5/high power field (HPF), and both of them (clinical remission: CR) for 5 years, and 10- years renal survival rate among three groups.

Results: The clinical and histological backgrounds were similar among three groups (median U-P was around 0.70 g/gCr (p=0.28), median eGFR was around 80.0 ml/min/1.73m2 (p=0.14) and median U-RBC were around 20/HPF in each group (p=0.48)). The remission rate of U-RBC was significantly higher in TSP (94.2%) than oPSL (60.4%, p=0.03) and CON (40.5%, p<0.0001), and also higher in oPSL than CON (p=0.02). The remission rate of U-P was significantly higher in TSP (83.1%) than in CON (30.6%, p<0.0001), and higher in oPSL (66.4%) than CON (p=0.0007), but similar between TSP and oPSL (p=0.36). The results of CR were similar with the results of U-P (TSP=oPSL>CON). There was no patient progressed to end-stage renal disease in each group. In multivariate Cox regression analysis, TSP and oPSL were independent factors for the remission of urinary findings, but TSP was not superior to oPSL.

Conclusions: In the treatment for IgAN with mild proteinuria, TSP was superior to oPSL in remission of U-RBC, and TSP and oPSL were superior to CON in the remission of urinary findings, but not for the 10-years renal prognosis.

TH-PO1026

Corticosteroids Improves Renal Survival in Chinese Patients with Early-Stage IgA Nephropathy

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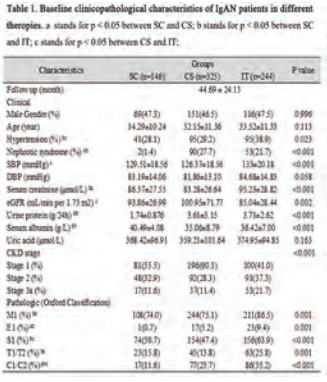
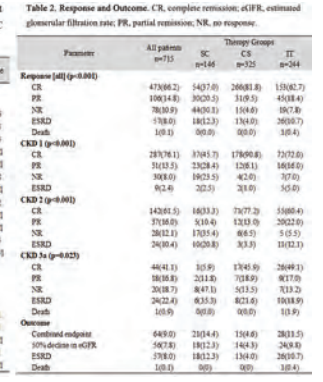
Background: The therapy for immunoglobulin A nephropathy(IgAN) patients remains controversial. This study aims to evaluate the effects of corticosteroids and immunosuppressive therapy in Chinese early stage IgAN patients with estimated glomerular filtration rate(eGFR) ≥45mL/min/1.73 m^2 and mean proteinuria≥1g/24h.

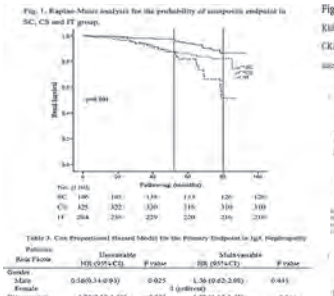
Methods: Patients with biopsy proven IgAN were retrospectively enrolled from 2007 to 2016. Patients were categorized into supportive care (SC), steroids alone(CS), and steroids plus immunosuppressant(IT) groups. Responses to therapy included complete remission(CR), partial remission(PR), no response(NR)and end stage renal disease(ESRD). The renal outcome was defined as a 50% decline in eGFR and/or ESRD.

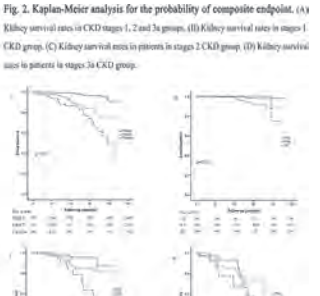
Results: 715 patients(Male 47% and Female 53%)were recruited and followed for a mean of 44.69±24.13 months. The rate of CR was 81.8%, 62.7%, 37% in CS, IT, SC group, respectively. Renal outcomes were remarkably better in CS group(4.6%)compared with SC(14.4%)and IT(11.5%)group(p<0.001). Moreover, 36-month and 80-month renal survival was significantly better in CS group (98.3% and 86.4 %)than in the IT(94.2% and 82.4%)and SC(94.0% and 51.6%)group. Early CKD stage disease presented with better kidney survival(p<0.001). Further analysis for CKD stage 1 patients suggested no difference among 3 groups. In CKD stage 2 patients, CS alone or with IT could improve renal survival rate when compared with SC alone(p<0.001and 0.007). But, no statistical significant difference could be found between CS and IT groups(p=0.219). For CKD stage 3a patients, renal survival rate in 3 groups were poor(p=0.398). Multivariate model showed that hypertension(HR 1.99, 95% CI 1.16-3.42;p=0.012); serum creatinine (HR 1.02, 95%CI 1.00-1.05;p=0.024); E1 lesion(HR 3.10, 95% CI 1.14-8.42;P=0.027) and T1/T2 lesion (HR 3.34, 95% CI 1.98-6.33;P<0.001)remained as independent predictors of renal survival.

Conclusions: The use of corticosteroids in addition to ACEI/ARB significantly improve the short-term renal outcome in early-stage IgAN patients.









TH-PO1027

Effect of Corticosteroid Therapy for Patients of IgA Nephropathy with Crescents

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Background: Patients with IgA nephropathy (IgAN) presented proteinuria≥1g/d and eGFR≥50ml/min/1.73m^2 after supportive treatment had been advised 6-month course of corticosteroids therapy. Update of Oxford classification of IgAN had recommended

crescents be added to the MEST score for they were predictive of outcome. Whether we should take some more positive therapy for crescents?

Methods: We conducted a single-center, retrospective cohort study enrolling 46 patients from 2017.01 to 2018.06, diagnosed with IgAN by renal biopsy. Eligible patients had proteinuria of 0.5~3.5g/d, eGFR≥30ml/min/1.73m^2 and crescent proportion<50%. Patients were divided into two groups, one for classical steroid treatment (intravenous methylprednisolone 0.25g/d for 3 days at the beginning of months 1, 3 and 5, plus oral prednisone 0.5 mg/kg/d for 6 months, called 1-3-5 Group) and the other assigned an optimized steroid therapy (intravenous methylprednisolone 0.25g/d for 3 days at the beginning of months 1, 2 and 3, plus oral prednisone as above, called 1-2-3 Group). The primary endpoint was remission of proteinuria, secondary endpoint was deterioration in renal function.

Results: There were 23 patients in each group and no significant differences in age, gentle, baseline proteinuria and eGFR between the two groups, except for the proportion of crescents (for Oxford C1 and C2: 52.5% and 13% in 1-3-5 Group vs. 95.7% and 4.3% in 1-2-3 Group respectively, p=0.001). After 6 months therapy, proteinuria in 1-3-5 Group was 0.5(0.2,0.8)g/d (vs. 1.2(0.8,2.6)g/d at baseline, p<0.001) and that in 1-2-3 Group was 0.3(0.2,0.6)g/d (vs. 1.5(0.7,2.6)g/d at baseline, p<0.001). 78.3% of patients in 1-3-5 Group had got remission of proteinuria,while 95.7% in 1-2-3 Group (p=0.187). The 6th month eGFR in 1-3-5 Group was 80.7(59.8,116.2)ml/min/1.73m^2 (vs. 77.5(54.8,104.6) ml/min/1.73m^2 at baseline, p=0.212), while that in 1-2-3 Group was 97.8(68.6,130.9)ml/ min/1.73m^2 (vs. 79.5(52.9,108.7)ml/min/1.73m^2 at baseline, p=0.002). The slope of eGFR in 1-3-5 Group was 0.7(-1.7,3.3)ml/min/1.73m2/month, while that in 1-2-3 Group was 3(1.2,5.4)ml/min/1.73m2/month, p=0.027. None of the patients had met side effects.

Conclusions: Our preliminary results had indicated that optimized steroid therapy had equal effect on reducing proteinuria but more significant advantage to protect against renal function deterioration in IgAN with crescents.

TH-PO1028

Clinical Response to Budesonide in Biopsy-Proven IgA Nephropathy

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Background: Primary IgA nephropathy is the most prevalent chronic glomerular disease worldwide. STOP-IgAN trial has questioned the benefit of systemic immunosuppression And significant (24%) mean UPCR reduction from baseline has been concluded from NEFIGAN study. So in this study we aimed at studying the effect of oral controlled release budesonide in biopsy proven IgA nephropathy patients.

Methods: This is a interim analysis of on going study conducted in department of Nephrology, Institute of Nephro-Urology, Bangalore, India from May 2017. A total of 40 patients with biopsy proven IgA nephropathy were included in study. All patients were optimised on RAS inhibitors, Omega 3 fatty acids and budesonide. A decision to start all drugs together was considered as isolated RAS inhibitors will not prevent immunological damage by ongoing IgA deposition. Based on histology (MEST SCORE) patients were started with 9mg and 12mg budesonide. Patients with crescents were treated with oral and IV cyclophosphamide and prednisone followed by budesonide. All patients were regularly followed up every 4 weeks to monitor vitals, Renal function test and Urine PCR. Our primary outcome was mean change from baseline in 24 hr urine protein at the end of 3rd and 6th Month. Clinical response was defined as complete (CR), partial (PR) or non-responders (NR) according to recent definitions.

Results: 22(55%) were males and 18 (45%) were females. Mean age was 48.27 yrs. Mean creatinine at presentation was 3.02 gm Mean proteinuria at presentation was 3.83 gm / 24 hours 11(40) had eGFR > 45ml/min/1.7m2 And 29(40) had eGFR < 45ml/min/1.7m2 All patients were optimised with RAS inhibitors and omega 3 fatty acids 3(7.5%) were treated with cyclophosphamide, prednisone and budesonide 3(7.5%) were treated with prednisone and budesonide. 34 (85%) were treated with budesonide. RESPONSE: CR-7(40)19% PR-18(40)49% NR-12(40) 32% Lost follow up - 3(40) CR and PR was higher in eGFR >45ml/min/1.7m2 (20% vs 18.5% and 50%vs 44%). NR was higher in eGFR < 45ml/min/1.7m2. (37% vs 39%) Percentage change in mean 24 HUP from baseline: 29.02%. Mean change in Serum Creatinine from baseline: 0.9 mg/dl

Conclusions: Budesonide, together with optimised RAS blockade, reduced proteinuria in patients with IgA nephropathy. Our patients probably had the advantage of blocking the intestinal access of IgA dysregulation right from presentation, hence reflecting a slightly better outcome than NEFIGAN trial.

Funding: Government Support - Non-U.S.

TH-PO1029

Systemic GCS Exposure from Nefecon Administration, Estimated from Suppression of Endogenous Cortisol Production

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Background: Nefecon is a unique two-step release oral formulation for the treatment of IgAN by a targeted delivery of budesonide to the Peyer's patches in the lower small intestine, aiming at local immunosuppression of B-cells responsible for the production of secretory galactose-deficient IgA antibodies. In a phase 2b study once daily oral treatment with Nefecon for 9 months reduced proteinuria and stabilised eGFR. Budesonide has a high first-pass metabolism of 90% resulting in limited systemic GCS exposure. The potency of steroids can be assessed by the HPA-axis derived suppression of endogenous cortisol production.

Methods: A study in 24 healthy subjects compared the change in serum cortisol levels over 24 hours after single doses of 8 mg NEFECON, 16 mg NEFECON, and 9 mg ENTOCORT in a randomised cross-over design. Urine cortisol excretion over 24 hours and plasma budesonide pharmacokinetic pqqarameters were also compared.

Results: A 9 mg dose of ENTOCORT corresponded to 11.7 mg of NEFECON for serum cortisol suppression. NEFECON 16 mg and ENTOCORT 9 mg caused similar decreases in urine cortisol excretion. Budesonide $AUC_{(0-24)}$ was comparable for NEFECON and ENTOCORT per mg dose but with approximately double C_{max} values for NEFECON.

Conclusions: The higher ratio Cmax / AUC for Nefecon compared to Entocort demonstrate a shorter duration of release with a longer period of low budesonide plasma concentrations during the 24 hour period. The net effect is a lower cortisol suppression per mg dose. A published study has shown that 29 mg of Entocort is equivalent to 20 mg of prednisolone for plasma cortisol suppression. The combined studies indicate that 16 mg of Nefecon is equivalent to 8 mg of prednisolone for plasma/serum cortisol suppression.

		Baseline	NEFECON 8 mg	NEFECON 16 mg	ENTOCORT 9 mg
Serum Cortisol $AUC_{(0-24)}$ (nmol*h/L)					
	Mean (sd)	5372 (1126)	3479 (1128)	2971 (1153)	3034 (706)
Change	Mean (sd)		-1901 (710)	-2401 (895)	-2215 (778)
Urine Cortisol Amount Excreted (0-24 h) (nmol/day)					
	Mean (sd)	110 (48.0)	65.2 (34.8)	56.1 (32.8)	55.1 (31.9)
Change	Mean (sd)		-44.3 (40.5)	-53.7 (34.6)	-54.8 (35.8)
Plasma budesonide PK parameters					
$AUC_{(0-24)}$ (pg*h/mL)	Mean (sd)	13.076 (7901)	29.493 (21498)	12.220 (8944)	
C_{max} (pg/mL)	Mean (sd)	3154 (2463)	6507 (5920)	1763 (1173)	

Results

TH-PO1030

Effects of Tonsillectomy Monotherapy of Advanced-Stage IgA Nephropathy: A Case Series Study

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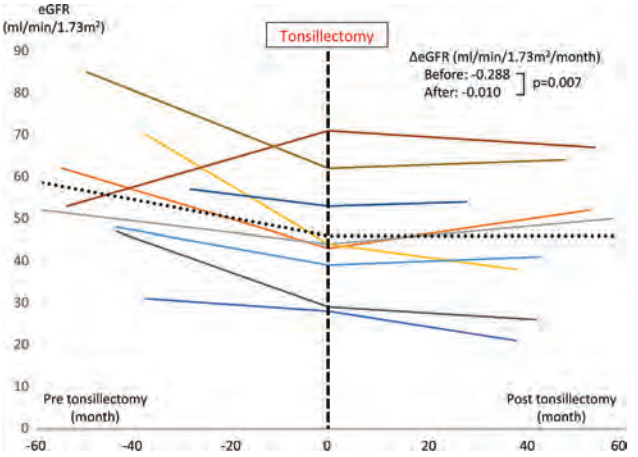
Background: Previous studies on Japanese patients with IgA nephropathy (IgAN) suggest the superiority of combination tonsillectomy and corticosteroid pulse therapy compared to corticosteroid pulse therapy alone; however, the efficacy of tonsillectomy monotherapy remains poorly understood.

Methods: Inclusion criteria consisted of patients with biopsy-proven IgAN with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 after 2 or more years of conventional therapeutic interventions, or those with an average urinary protein excretion > 500 mg/day for at least 6 months. Clinical characteristics, including renal function decline, were compared during the same observation periods before and after tonsillectomy.

Results: The patient cohort consisted of 5 males and 4 females, with an average age of 43 years. All patients had been treated with RAS inhibitors. Mean serum levels of creatinine were 1.32 mg/dL, with patients waiting an average of 161 months from initial diagnosis to tonsillectomy. Microscopic hematuria (1.10 vs. 0.20 grade, p = 0.003) and total urinary protein excretion (646 vs. 389 mg/day, p = 0.03) decreased significantly after tonsillectomy, relative to those before tonsillectomy. The slope of eGFR significantly improved after tonsillectomy versus before tonsillectomy (**Figure**; a mean value is shown as dashed line).

Conclusions: Tonsillectomy is an effective treatment option for advanced IgAN patients with persistent hematuria and proteinuria, independent of conventional therapeutic interventions.



TH-PO1031

Treatment of Henoch-Schönlein Purpura Nephritis with Hydroxychloroquine: A Retrospective Cohort Study

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Background: Hydroxychloroquine (HCQ) is a mild immunosuppressive agent. It has been used clinically as an effective drug in the treatment of rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). We aimed to study

the clinical efficacy of hydroxychloroquine in the treatment of Henoch-Schönlein purpura nephritis (HSPN), as well as the occurrence of adverse reactions.

Methods: This was a retrospective cohort study involving 76 HSPN patients. Twenty-two patients who had been treated with hydroxychloroquine were included in the exposure group, while 54 patients in the non-exposure group were treated with ACEI/ARB and/or other immunosuppressive agents instead of hydroxychloroquine. The patients were followed up for 6-34 months (median 14 months). Death, end-stage renal disease or transferring to renal replacement therapy (dialysis or renal transplant),eGFR decreasing by more than 30% over baseline within 2 years, serum creatinine doubling from baseline level were considered end events.

Results: There was no significant difference in the remission rate of proteinuria between the exposed group and the non-exposed group. The remission rate of proteinuria in patients treated with hydroxychloroquine alone was 88.89%. At the end of the follow-up period, no death or dialysis occurred. The eGFR of 3 patients in the non-exposed group decreased by more than 30% compared with the baseline (30%, 34% and 41% respectively), while only one person in the exposed group (54%). No significant adverse events were recorded during HCQ treatment.

Conclusions: Hydroxychloroquine can mildly and safely reduce proteinuria in patients with HSPN.

TH-PO1032

Long-Term Renal Outcomes In Patients with IgA Vasculitis: A Single-Centre Retrospective Cohort Study

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Background: IgA vasculitis (IgAV; Henoch Schönlein purpura) is a small vessel vasculitis that most commonly affects children but also occurs in adults. The long term outcome from IgAV in adult patients with renal involvement is not well described, and treatment protocols are variable.

Methods: We conducted a retrospective study of renal outcomes in patients with IgAV with histologically confirmed renal involvement seen previously within our adult renal service. We searched our local renal and pathology databases for those diagnosed between 1990-2018. Demographic data including age, sex, ethnicity and date of presentation were recorded. Clinical data included serum creatinine and albumin, proteinuria (urine protein:creatinine ratio; UPCR) at presentation and follow up, as well as biopsy findings and treatment.

Results: We identified 59 patients seen within this time period, with median follow up of 64.5 months (interquartile range (IQR) 20.5-114.8). Mean age at diagnosis was 34.5 (±SD 18.4) years. 37 (63%) were male, 45 (88.2%) were Caucasian. 20 (33.9%) had documentation of a prior skin rash (the remainder presented concurrently), occurring a median of 6 months before, with 11 (18.6%) undergoing a skin biopsy. Median eGFR at diagnosis was 84 (42.3-90) ml/min/1.73m^2. Median UPCR at presentation was 120 (21.7-481.7) mg/mmol, with 19 (32.2%) having nephrotic-range proteinuria (UPCR > 350 mg/mmol), and 8 (13.6%) with nephrotic syndrome (as previous, plus serum albumin ≤ 30 g/L). 24 (40.7%) patients had evidence of crescents on renal biopsy. 16 (28.1%) were treated with prednisolone alone, and 15 (26.3%) combined with another agent, most commonly mycophenolate mofetil. At last follow up, 38 (64.4%) had an eGFR >60 ml/min, and 21 (35.6%) below. 8 reached ESRD, at a median of 25 months (2-68.8) months. All had nephrotic range proteinuria (UPCR >350 mg/mmol) at presentation. When compared to those with similar UPCR at presentation, the patients who reached ESRD were younger, had lower eGFR at presentation and had a higher failure rate in achieving remission from their proteinuria.

Conclusions: Overall, in this cohort, patients with IgAV who achieved proteinuria <1g/d had a good outcome. Those who presented with nephrotic range proteinuria with failure to achieve any remission from their proteinuria had a poor outcome in terms of renal survival.

Funding: Government Support - Non-U.S.

TH-PO1033

Incidence of Biopsy-Proven Kidney Disease Among Kaiser Permanente Northern California Patients in 2018

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Background: Accurate population-level estimates of the incidence of glomerular (G) and primary tubulointerstitial diseases (TI) are lacking. Obtaining such estimates is challenging as accurate diagnosis typically requires a kidney biopsy and lack relevant population-level denominators. Here we provide population-level estimates of biopsy-proven G & TI diseases in a cohort of ~4.3 million at Kaiser Permanente Northern California (KPNC) in 2018.

Methods: We reviewed all KPNC 2018 renal biopsy reports, and categorized patients into known G & TI disease groups. Incidence rates and associated standard deviations were calculated per 100,000 persons, stratified by age and sex.

Results: 673 native kidney biopsies were performed in 2018, corresponding to 15.8 biopsies/100,000 persons. The incidence of common biopsy-confirmed G & TI diseases are provided in the Table. IgA nephropathy is the most common diagnosis (incidence 2.3/100,000 persons), followed by focal and segmental glomerulosclerosis (1.6/100,000), lupus nephritis (1.4/100,000), pauci-immune GN (1.3/100,000), and membranous nephropathy (1.3/100,000). 19.5% patients undergoing kidney biopsy in this cohort had evidence of diabetic nephropathy (n=131), 21.4% of whom had an additional G or TI diagnosis (n=28).

Conclusions: Here we provide incidence estimates of biopsy-confirmed G & TI diseases in a large, racially and ethnically diverse population. Comparison with population-level estimates in other cohorts will help determine the true incidence of these diseases.

Biopsy-proven kidney disease, KPNC, 2018. *Incidence rates/100,000 persons

	Total (rate*; SE)	Males (rate*; SE)	Females (rate*; SE)
All biopsies	673 (15.8; 0.6)	339 (15.4; 0.8)	334 (16.3; 0.9)
IgA nephropathy	96 (2.3; 0.2)	50 (2.3; 0.3)	46 (2.2; 0.3)
Focal and segmental glomerulosclerosis	70 (1.6; 0.2)	45 (2.0; 0.3)	25 (1.2; 0.2)
Lupus nephritis	58 (1.4; 0.2)	7 (0.3; 0.1)	51 (2.5; 0.3)
Pauci-immune glomerulonephritis	55 (1.3; 0.2)	20 (0.9; 0.2)	35 (1.7; 0.3)
Membranous nephropathy	55 (1.3; 0.2)	33 (1.5; 0.3)	22 (1.1; 0.2)
Light chain cast nephropathy and monoclonal gammopathies of renal significance	22 (0.5; 0.1)	11 (0.5; 0.2)	11 (0.5; 0.2)
Acute tubular injury	21 (0.5; 0.1)	11 (0.5; 0.2)	10 (0.5; 0.2)
Minimal change disease	19 (0.5; 0.1)	10 (0.5; 0.1)	9 (0.4; 0.2)
Thrombotic microangiopathy	19 (0.5; 0.1)	9 (0.4; 0.1)	10 (0.5; 0.2)
Acute interstitial nephritis	17 (0.4; 0.1)	7 (0.3; 0.1)	10 (0.5; 0.2)
Infection-associated glomerulonephritis	15 (0.2; 0.1)	12 (0.5; 0.2)	3 (0.2; 0.1)
Amyloidosis	14 (0.3; 0.1)	5 (0.2; 0.1)	9 (0.4; 0.2)

TH-PO1034

One Year of the State Registry of CKD in Aguascalientes Mexico: Have We Found a New Hotspot of CKD?

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Background: According to the Institute for Health Metrics and Evaluation, in Mexico the global burden attributed to chronic kidney disease (CKD) is one of the highest worldwide. Unfortunately the country don't have any official registry. Since June 2018, the Health Council from Aguascalientes brought together the main health institutions that provide renal replacement therapy to start the state registry of CKD

Methods: Describe the results of the first year of data collection of the Aguascalientes CKD registry

Results: Until May 2019, 2,574 patients have been registered, of whom 93 have died and 321 are transplanted. The estimated prevalence is 1,526 pmp (n= 2,160). The most common causes are CKD are: of unknown origin (n= 981, 45.4%), Diabetes Mellitus (n=681, 31.5%), Systemic Arterial Hypertension (n= 326, 15%). The most prevalent modality of renal substitution was hemodialysis (n= 1,365, 63.1%). 59% are men (n= 1,274). The average age of the patients included was 46.5 years, with a bimodal distribution. The first group between 20 and 39 yo (n= 1,107, 51.2%) and the second between 50 and 69 yo (n= 843, 39%). Since January 2012, 389 kidney biopsies have been performed in the state. The main diagnosis was focal and segmental glomerulosclerosis(FSGS) (n= 128, 32.9%), followed by lupus neph (n= 55, 14.1%), IgA neph (n= 48, 12.3%), minimal changes dis (n= 45, 11.5) and membranous neph (n= 22, 5.6%)

Conclusions: In Aguascalientes Mexico, we have a high prevalence of CKD. The main cause is of unknown origin. The main affected group are young adults between 20 and 40 y and the most frequent glomeulopathy in this group was FSGS. At this moment a study of screening of CKD in adolescents in the state is being developed which is expected to contribute to the study of the causes of CKD in our population

Characteristics by age groups

Variable	Group 1 (20 to 39 yo) n= 1,107	Group 2 (50 – 69 a) n= 843	p value
Male sex, n(%)	726 (65.5)	486 (57.6)	<0.01
CKDuknown origin, n (%)	574 (51.8)	225 (26.6)	<0.01
Diabetes, n(%)	83 (7.5)	352 (41.7)	<0.01
HTN, n(%)	109 (9.8)	136 (16.1)	<0.01
Renal Biopsies	N= 136	N=44	p value
FSGS, n(%)	60 (44.1)	12 (27.2)	0.04
Lupus N, n(%)	19 (13.9)	8 (18)	0.45
IgA N, n(%)	17 (12.5)	8 (18)	0.40

FSGS: Focal segmental glomerulosclerosis, HTN: Systemic Hypertension, N: Nephritis

TH-PO1035

Biopsy Proven Diagnosis of CKD in Sub-Saharan Africa: An H3 Africa Cohort Study

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Background: Chronic kidney disease is increasingly prevalent in **Sub-Saharan Africa** (SSA) and a major factor leading to increased morbidity and mortality. Treatment of CKD, specifically glomerulonephritis (GN) is paramount to reducing CKD progression, morbidity and mortality, however, little is known about the types and incidence of primary glomerulonephritis (GN) nor is pathological diagnosis feasible throughout SSA.

Methods: Among 500 native kidney biopsies performed so far at 10 centers across Africa, we assessed patterns and types of glomerular disease in participants with eGFR greater than 15mls/minute enrolled in the H3 Africa Kidney Disease network cohort study from 2017-2019. Biopsies were performed with real time ultrasound guidance and samples were shipped for processing and evaluation of light, immunofluorescence and electron microscopy by 2 US pathologists. We present preliminary results on demographic, clinical and biopsy data obtained.

Results: Demographics and baseline characteristics: The mean age was 30.68 ± 13.12 years, there were 231 males(50.4%), 357 (77.95%) patients were Nigerians, 99 (21.62%) and were Ghanaians. The mean eGFR was 66.27 ± 37.20. 10 (9.17%) had high blood pressure, 11 (2.43%) had diabetes, 6 (1.32%) were hepatitis B positive and 1 (0.22%) was positive to hepatitis C.

Conclusions: FSGS, membranous nephropathy and minimal change disease were the most frequent primary glomerulonephritis among adults in our region. Lupus Nephritis is a common secondary GN in Sub Saharan Africa.

Funding: NIDDK Support

Type	Biopsy diagnosis - (n=500)
Membranous GN	108
FSGS	152
Minimal Change Disease (MCD)	79
MPGN	3
IgA nephropathy	3
Amyloidosis	3
Cresenteric GN	3
Immune complex GN (unclear etiology)	4
FGGS & IFTA, unclear etiology	11
Lupus nephritis	134

Types and patterns of biopsy-proven Glomerulonephritis

TH-PO1036

The Spectrum of the Biopsy-Proven Glomerular Disease in Taiwan: A Single-Center Experience

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Background: Glomerular diseases are still leading causes of end-stage renal disease. The diagnosis of these disease relies on the interpretation of the renal biopsy. The sonography-guided biopsy is still the major tool to acquire an accurate pathologic diagnosis. The spectrums of the glomerular disease are varied in different regions. Grossly, IgA nephropathy is the leading cause of primary glomerular disease in Asia. To date, there are few articles which report the disease spectrum in Taiwan. This study conducts a retrospective investigation of 19-years cohorts in a single medical center. The trend of disease spectrum was evaluated and analyzed.

Methods: This investigation was performed in a tertiary hospital. From 2000-2018 period, totally 2,391 patients first received renal biopsy. After excluding 71 cases of tubulointerstitial disease, 270 cases of end-stage renal disease, advanced chronic kidney disease, inadequate sampling, and failed interpretation, there are still 2,050 cases with a clear diagnosis.

Results: Membranous glomerulopathy is the leading category in 2,050 cases (404, 19.7%), followed by IgA nephropathy (306 cases, 14.9%), minimal change nephropathy (283, 13.8%), focal segmental glomerulosclerosis (180, 8.8%). In the secondary disease, lupus nephritis account for 18.4% of the 2050 cases (378), followed by diabetic nephropathy (200, 9.6%), and paraproteinemic renal disease (60, 2.9%). Notably, the incidence of the membranous glomerulopathy is decreasing by year. In contrast, the ratios of IgA nephropathy is increasing gradually.

Conclusions: Membranous glomerulopathy is the major category in 19-years cohort of a single medical center, although the incidence is decreasing by year. Further investigation of change of disease spectrum is necessary.

TH-PO1037

Positive Family History for CKD in Patients with Primary Glomerular Diseases: Disease Onset and Comorbidities in the CureGN Cohort

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Background: A positive family history (pFHx) has been associated with worse outcomes for some glomerulonephritides (GNs), but this has not been rigorously examined in a prospective cohort. A pFHx for chronic kidney disease (CKD) can be indicative of Mendelian hereditary diseases, or may reflect a polygenic risk or unmeasured environmental risk factors.

Methods: We studied the association of a self-reported pFHx of CKD with renal function, age at the time of diagnosis and comorbidity burden, in the Cure Glomerulopathy Network (CureGN), a prospective multi-center observational study of GN patients (N=2281) with Focal Segmental Glomerulosclerosis (FSGS), Minimal Change Disease (MCD), Membranous Nephropathy (MN), IgA Nephropathy (IgAN), or IgA Vasculitis (IgAV). Comparisons between patients with and without pFHx were analyzed via Chi-square/Fisher and ANOVA/Wilcoxon test.

Results: A CKD pFHx was present in 352 (15%) patients: 28% of FSGS, 21% of MN, 15% of IgAN, 13% of MCD, and 9% of IgAV cases. CKD pFHx was associated with lower eGFR at GNs onset in entire cohort ($p=1.0x10^{-11}$), IgAV (p= 0.0002), FSGS (p= 0.0004), IgAN (p= 0.001), and MN (p=0.02) but not MCD patients. CKD pFHx was associated with older age at the GNs onset with adults IgAN (p= 0.006) patients. CKD pFHx was significantly associated with a higher prevalence of several comorbidities, even after adjusting for age, sex, ethnicity, race, body mass index, and smoking habit (Table 1).

Conclusions: Patients with a CKD pFHx have lower eGFR at presentation and have higher prevalence of certain comorbidities than patients without such family history. The association with allergies, asthma and COPD point to shared biology and environmental factors. Identifying this association may help to elucidate common genetic or environmental causes, shed light on disease pathogenesis, improve GNs management, and ultimately may help develop preventive measures.

Funding: NIDDK Support

Table 1: Comorbidities significantly associated with patients with a pFHx for CKD.

Whole Cohort (n=2281)	*Asthma (p= 0.0009)*	*Hypertension (p= 0.003)*	*Chronic Obstructive Pulmonary Disease (p= 0.04)*	*Sleep Apnea (p= 0.049)*
IgAV Patients (n=167)	Medication allergies (p= 0.01)	Hypertension (p= 0.02)	Asthma (p= 0.03)	Arrhythmia (p= 0.03)
MN Patients (n=477)	Chronic Obstructive Pulmonary Disease (p= 0.002)			
FSGS Patients (n=588)	Hypertension (p= 0.01)			

TH-PO1038

Racial/Ethnic Differences in Socioeconomic Status (SES) and Health-Related Quality of Life (HRQL) Among Children with Glomerular Disease in Cure Glomerulonephropathy (CureGN)

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Background: Race/ethnicity, disease severity/duration, and lower SES have been associated with poorer HRQL in children with glomerular disease; however, the relative importance of these factors has not adequately been explored.

Methods: CureGN is a 70-center cohort study of patients with MCD, FSGS, MN, or IgAN/IgAV. We compared pediatric patient characteristics (demographics, disease duration/severity, medications, SES) at enrolment across racial/ethnic groups. Multivariable logistic and linear regression models, created using best subsets and backwards selection, were used to examine associations between race/ethnicity and HRQL, as measured by missed school days due to kidney disease and baseline PROMIS questionnaire items.

Results: Among 515 White, 146 Black and 74 Hispanic children, Blacks were most likely to have FSGS/MCD and had the lowest eGFR, highest urine protein, lowest serum albumin, and most severe edema. Compared to Whites, Blacks or Hispanics were less likely to have private insurance (59, 35, and 32%, p<0.001), and their parents/guardians were less likely to have completed college (18, 7, and 10% of mothers, and 30, 12, and 12% of fathers, p<0.001). Racial/ethnic differences in HRQL were small (below the Minimally Important Difference of 3) and generally not statistically significant (table). No differences in missed school days due to kidney disease were observed.

Conclusions: Among pediatric CureGN patients, SES varied by minority status such that Black or Hispanic (vs. White) children were less likely to have private insurance and their parents received less formal education. After adjusting for SES and other factors, minority status was not associated with HRQL as measured within this study.

Funding: NIDDK Support

Health-related quality of life across racial/ethnic groups in pediatric CureGN participants				
	Unadjusted (ref=white)		Adjusted (ref=white)	
	Black	Hispanic	Black	Hispanic
Any missed school due to kidney disease, odds ratio (95% CI)[1]	1.27 (0.84, 1.92)	1.08 (0.63, 1.85)	1.32 (0.82, 2.14)	1.29 (0.69, 2.41)
PROMIS Global Health, beta (95% CI) [2,3]	-1.5 (-3.3, 0.3)	-1.8 (-4.1, 0.6)	1.1 (-1.0, 3.3)	-0.9 (-3.6, 1.7)
PROMIS Anxiety, beta (95% CI)[2,4]	-0.4 (-1.9, 1.0)	-1.5 (-3.6, 0.5)	-0.9 (-2.4, 0.6)	-1.5 (-3.6, 0.6)
PROMIS Fatigue, beta (95% CI)[2,5]	1.8 (-0.5, 4.0)	2.0 (-1.0, 4.9)	-0.9 (-3.2, 1.5)	2.0 (-1.0, -4.9)
PROMIS Mobility, beta (95% CI)[2,6]	-1.7* (-3.3, -0.1)	-1.3 (-3.3, 0.8)	1.2 (-0.5, 3.0)	-0.3 (-2.5, 1.9)

[1] Within the last 4 months, modeled using logistic regression and restricting to children who self-reported to be in school full-time (n=614). [2] Based on symptoms in the last 7 days, modeled using linear regression and including the entire cohort (n=735). [3] Higher score (beta) indicates better global health. [4] Higher score (beta) indicates worse anxiety. [5] Higher score (beta) indicates worse fatigue. [6] Higher score (beta) indicates better mobility.
* p<0.05. PROMIS = Patient-Reported Outcomes Measurement Information System.

TH-PO1039

Racial/Ethnic Differences in Socioeconomic Status (SES) and Health-Related Quality of Life (HRQL) Among Adults with Glomerular Disease in Cure Glomerulonephropathy (CureGN)

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Background: Adults with glomerular disease have poor HRQL. However, the effect of race/ethnicity and SES on HRQL in this population remains largely unknown.

Methods: CureGN is a 70-center cohort study of patients with MCD, FSGS, MN, or IgAN/IgAV. We compared adult patient characteristics (demographics, disease duration/severity, medications, SES) across racial/ethnic groups. Multivariable logistic and linear regression models, created using best subsets and backwards selection, were used to examine associations between race/ethnicity and HRQL, as measured by missed school due to kidney disease and baseline PROMIS questionnaire items.

Results: Among 854 White, 220 Black, and 120 Hispanic adults, Blacks were most likely to have FSGS and had the highest urine protein, lowest serum albumin, and most severe edema. Hispanics were most likely to have IgAN/IgAV and had the lowest eGFR. Compared to Whites, Blacks or Hispanics were less likely to have completed college (48, 27, and 29%, p<0.001) or to have private insurance (76, 65, and 50%, p<0.001), and were more likely to be on medical/disability leave or unemployed (11, 23, and 24%, p<0.001). No racial/ethnic differences in missed work/school were observed. Blacks (but not Hispanics) had significantly worse global physical health, global mental health, and fatigue (table). However, after adjusting for SES and other factors, these differences in HRQL largely disappeared.

Conclusions: Among CureGN participants, Black or Hispanic (vs. White) participants were less likely to have completed college, to have private insurance, or to be employed. However, minority race/ethnicity was not independently associated with HRQL as measured in this study.

Funding: NIDDK Support

Differences in health-related quality of life across racial/ethnic groups in adult CureGN participants				
	Unadjusted (ref=white)		Adjusted (ref=white)	
	Black	Hispanic	Black	Hispanic
Any missed school/work due to kidney disease, odds ratio (95% CI) [1]	1.39 (0.92, 2.11)	0.67 (0.36, 1.26)	1.11 (0.64, 1.92)	0.54 (0.26, 1.12)
PROMIS Global Physical Health, beta (95% CI) [2,3]	-3.5 (-4.9, -2.0)**	-0.8 (-2.7, 1.1)	-0.3 (-1.8, 1.2)	0.6 (-1.4, 2.6)
PROMIS Global Mental Health, beta (95% CI) [2,4]	-2.1 (-3.5, -0.7)**	-0.7 (-2.5, 1.0)	-0.2 (-1.6, 1.2)	0.2 (-1.5, 1.9)
PROMIS Anxiety, beta (95% CI) [2,5]	0.5 (-0.7, 1.7)	1.5 (-0.1, 3.0)	-0.4 (-1.7, 1.0)	1.0 (-0.6-2.7)
PROMIS Fatigue, beta (95% CI) [2,6]	2.5 (1.0, 4.0)**	-1.0 (-2.9, 0.9)	0.2 (-1.4, 1.8)	-2.1 (-4.1, -0.2)*
PROMIS Sleep Disturbance, beta (95% CI) [2,7]	1.1 (-0.2, 2.3)	0.3 (-1.3, 2.0)	-0.4 (-1.7, 0.9)	-0.5 (-2.1, 1.1)

[1] Within the last 4 months, modeled using logistic regression and restricting to patients in full or part-time education or employment (n=832). [2] Based on symptoms in the last 7 days, modeled using linear regression and including the entire cohort (n=1194). [3] Higher score (beta) indicates better physical health. [4] Higher score (beta) indicates better mental health. [5] Higher score (beta) indicates worse anxiety. [6] Higher score (beta) indicates worse fatigue. [7] Higher score (beta) indicates worse sleep.
*p<0.005 **p<0.05. PROMIS = Patient-Reported Outcomes Measurement Information System. A minimally important difference (MID) for adolescent or parent responders is considered to be 3 points.

TH-PO1040

A Novel Approach in Differential Diagnosis of Primary Glomerulonephritis Using the Decision Tree Algorithm Model Based on Biomarkers Panel

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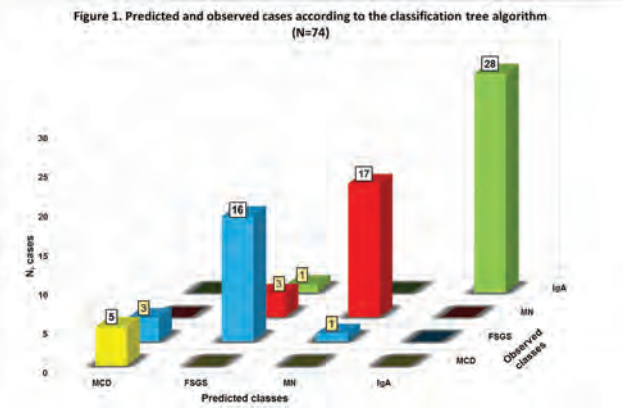
Background: Recent studies showed that measurement of various biomarkers (BM) can be useful in differential diagnosis of some primary glomerulonephritis (GN) forms. Our aim was to develop an algorithm for differential diagnosis of primary GN based on BM panel using decision tree learning approach.

Methods: 74 patients [39 male, age Me (min 18; max 83) – 37,5 (25; 54) years] with biopsy proven primary GN and without AKI, infectious diseases, severe heart failure, respiratory insufficiency, cancer, abnormal thyroid status, treatment with prednisolone more than 10 mg/per day were included in the study. Based on the results of kidney biopsy (KB) in 7% of cases minimal change disease (MCD) was diagnosed, in 27% – FSGS, in 27% – membranous nephropathy (MN), in 39% – IgA-nephropathy. BM were measured in the morning on the day of KB: serum creatinine(sCr), albumin(sAlb), CysC(sCysC), 24-hour total protein(24hTP), urinary (24-hour collection) cystatin C(uCysC), transferrin(uTr), IgG(uIgG), α1-microglobulin(uα1-mg), β2-microglobulin(uβ2-mg), serum/urine magnesium. The Classification and Regression Trees (CART) learning algorithm with FACT-style direct stopping as pruning criteria was used to create a model for differential diagnosis. Complete machine learning, statistical analysis were performed with Statistica v.12.

Results: A decision tree algorithm was developed including ten predictor variables: age, sAlb, uTrans, t24hTP, sCysC, uIgG, uβ2-mg, sCr, uα1-mg, EFMg. This algorithm accurately classified patients with MCD in 100% cases (5 out of 5 cases), FSGS - 80% (16/20 cases), MN - 85% (17/20 cases), IgA-nephropathy - 96,6% (28/29 cases) (Figure 1).

Conclusions: A "decision tree" algorithm based on age and few urinary, serum BM can be a powerful diagnostic tool in differential diagnosis of primary GN. Application of this algorithm allows to evaluate patients with high risk progression of CKD, identify treatment targets before or instead of KB.

Funding: Government Support - Non-U.S.



TH-PO1041

APOL1 Risk Alleles in Glomerular Diseases

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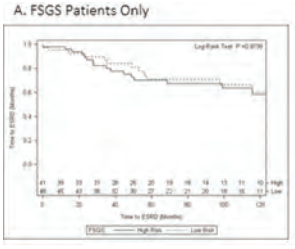
Background: Impact of *APOL1* variants in glomerular diseases is not well described. In published studies, 0 or 1 risk variant in *APOL1* do not influence progression to end stage renal disease (ESRD), but two risk variants increase risk. We examined *APOL1* variant association with developing ESRD in patients with glomerular disease.

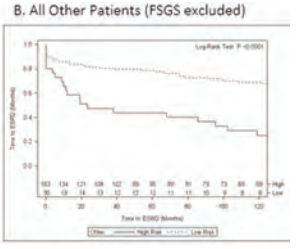
Methods: The Glomerular Disease Collaborative Network (GDCN) is a large registry in southeastern US of patients with glomerular diseases including ANCA vasculitis, membranous glomerulopathy (MN), focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), and lupus. African-American patients with DNA samples from the GDCN were evaluated. Fisher's exact, Wilcoxon rank, and Kaplan-Meier curves with log rank tests were used to evaluate differences between high risk (2 variants) and low risk (0/1 variant). Proportional hazards models adjusted for age were used to evaluate time to ESRD by high vs. low risk variant with hazards ratios and 95% confidence intervals reported (HR, 95% CI).

Results: Two APOL1 variants were observed in 27% of 252 patients across all diseases except MCD, and most frequently in FSGS (50/93=54%), Table. Those with high risk variant were 1.9 times more likely to progress to ESRD (95% CI 1.2-3.0). In FSGS, high and low risk variants progressed similarly to ESRD (HR 1.0, 95% CI 0.5-1.7), but in other glomerular diseases those with the high risk variant were 2.5 times more likely to progress to ESRD (95% CI 1.2-5.1), Figure.

Conclusions: High-risk variants were present in most glomerular diseases studied, and common in FSGS. However, impact on progression to ESRD was not evident in FSGS, but influential in other glomerular diseases.

Characteristic, n (%) unless otherwise noted	Low Risk n=183	High Risk n=69	p-value
Disease Type:			
Focal segmental glomerulosclerosis (FSGS)	43 (23%)	50 (72%)	
ANCA vasculitis	57 (31%)	8 (12%)	
Lupus nephritis	52 (28%)	6 (9%)	
Minimal change disease	9 (5%)	0 (0%)	
Membranous nephropathy	22 (12%)	5 (7%)	
Age at disease onset(yrs), Median(IQR)	31 (17, 53)	28 (17, 40)	0.12
Male	38%	38%	0.99
Progressed to ESRD	27%	45%	0.01





TH-PO1042

Functional Subclasses of Nephrotic Syndrome Identified Using Consensus Non-Negative Matrix Factorization Clustering of Kidney Tubulointerstitial Tissue Transcriptome

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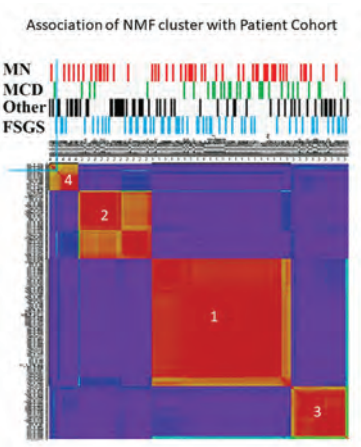
Background: Interstitial fibrosis and tubular atrophy are common patterns of injury in glomerular diseases, but it is unknown whether multiple mechanisms can result in this pattern of injury and if mechanisms change as disease progresses. Consensus non-negative matrix factorization (NMF) is a clustering approach used with tumor specimen transcriptomics to identify functionally relevant subtypes.

Methods: NMF clustering was applied to tubular mRNA expression from kidney biopsies from the NEPTUNE cohort, a prospective cohort of children and adults with nephrotic syndrome enrolled at the time of clinically indicated kidney biopsy. Individual gene expression levels from the tubular compartment were normalized to mean expression to maximize individual patient differences. Cox proportional hazards models were fit for complete proteinuria remission (CR, UPCR <0.3 mg/mg) and ESRD/40% eGFR decline. Significance analysis of microarray identified cluster specific differentially expressed genes that were used in pathway enrichment analysis to determine functional relevance.

Results: NMF separated 188 patients into 4 clusters which did not differ age (p 0.46), sex (p 0.77) or UPCR (p 0.46). The clusters did not segregate by disease etiology (Fig). Cluster 2 had lower mean eGFR (56 mL/min vs 83, 66 and 66; p <0.01) and greater UPCR (5.1 vs 2.8, 2.1,4.0; p <0.01), black race (39.5% vs 25%, 12%, 6%, p <0.01). In unadjusted models, cluster 2 had less CR (HR 0.65, p-value 0.14) and greatest loss of eGFR (HR 2.8, p-value <0.01). Pathway enrichment of cluster-specific genes demonstrated unique processes (Fig).

Conclusions: NMF identified functional subclasses in the tubular kidney tissue mRNA of patients with nephrotic syndrome which crossed traditional diagnostic classifications of FSGS, MCD and MN. Functional analysis revealed both shared and specific pathways associated with the clusters which could help to identify therapeutic targets.

Funding: NIDDK Support, Other NIH Support - NCATS



TH-PO1043

Elevated Plasma Free Sialic Acid Levels in Individuals with Reduced Glomerular Filtration Rates

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Background: Sialic acid (SA) is a negatively charged, terminal monosaccharide present on glycoconjugates. They are important contributors to the polyanionic component of the glomerular filtration barrier, which regulates permeability selectivity. Free SA is filtered but not reabsorbed by the human kidney, in contrast to other sugars known to be reabsorbed by tubular cells. We determined plasma free SA levels of subjects with proteinuric diseases and diverse levels of estimated glomerular filtration rate (eGFR) to assess a correlation and emphasize this understudied feature of SA.

Methods: Free SA (Neu5Ac) was determined in plasma samples from 16 proteinuric subjects and 22 individuals with normal renal function with a validated LC-MSMS assay.

Results: There was a strong inverse relationship between eGFR and plasma SA levels (R^2 =0.70, p <0.0001). Plasma SA levels ranged between 114-206 ng/mL in subjects with normal eGFR (>90mL/min/1.73 m^2). While in subjects with decreased eGFR (<30 mL/min/1.73 m^2), plasma SA levels were at least three-fold higher (431-1260 ng/mL range).

Conclusions: It is important to emphasize the often-overlooked feature of renal handling of free SA. If increased plasma SA levels are encountered in subjects, compromised renal function/decreased eGFR should be considered. Of note is that pathologic hyposialylation of glomerular glycoconjugates, associated with podocyte effacement, has recently been implicated in human glomerulopathies. The relation between plasma free SA levels and glomerular hyposialylation remains to be investigated.

Funding: NIDDK Support, Other NIH Support - NHGRI

TH-PO1044

Urinary Podocalyxin Protein Excretion Is an Early Biomarker in Age-Associated Kidney Disease

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Background: Aging is the strongest known risk factor for end-stage kidney disease. Many factors including aging can cause podocyte injury. If the initiating injury causes a critical level of podocyte depletion, it can lead to glomerulosclerosis and progression. Age-associated reduction in podocyte density (increased glomerular volume per podocyte) is associated with podocyte hypertrophic stress and failure that leads to glomerulosclerosis in model systems and humans. Urinary podocyte excretion can be used to monitor glomerular disease activity and progression. This study investigated whether urinary podocyte protein excretion can be used for monitoring age-associated kidney diseases.

Methods: From June 2018 to March 2019, spot urine samples were collected from 261 healthy volunteers without diabetes, hypertension and albuminuria during medical checkups by age groups (20–29 years: n=48; 30–39 years: n=53; 40–49 years: n=59; 50–59 years: n=52; ≥60 years: n=49) We investigated the urinary supernatant (U-PCX) and sediment (Sed-PCX) podocalyxin protein levels by ELISA to reflect podocyte injury and podocyte detachment, respectively, and urinary albumin/creatinine ratio (U-ACR).

Results: There were no significantly differences in systolic blood pressure, fasting blood glucose, and body mass index among the groups. However, estimated glomerular filtration rate significantly decreased with age (20–29 years: 94±14.5 ml/min/1.73 m^2 vs ≥60 years: 74.5±14.1 ml/min/1.73 m^2, p<0.01)). U-PCX was significantly increased in the ≥60 years group (20–29 years: 94.4±57 vs. ≥60 years: 124.1±63.1 μg/g Cre, p<0.01). U-ACR was also significantly increased in the ≥60 years group (20–29 years: 5.2±4.2 vs. ≥60 years: 8.0±5.6 mg/gCre, p<0.01), but the levels were far lower than the microalbuminuria level. Meanwhile, Sed-PCX did not differ among the groups.

Conclusions: U-PCX, but not sed-PCX, was significantly increased the ≥60 years group without hypertension, diabetes, and microalbuminuria compared with other groups. These results suggest that age *per se* is a risk factor for podocyte injury and that U-PCX can be used for as an early (prior to overt albuminuria and podocyte detachment) biomarker in age-associated kidney disease.

Funding: Government Support - Non-U.S.

TH-PO1045

Exosomal Micro RNA as a Diagnostic Tool in Kidney Biopsy Cohort

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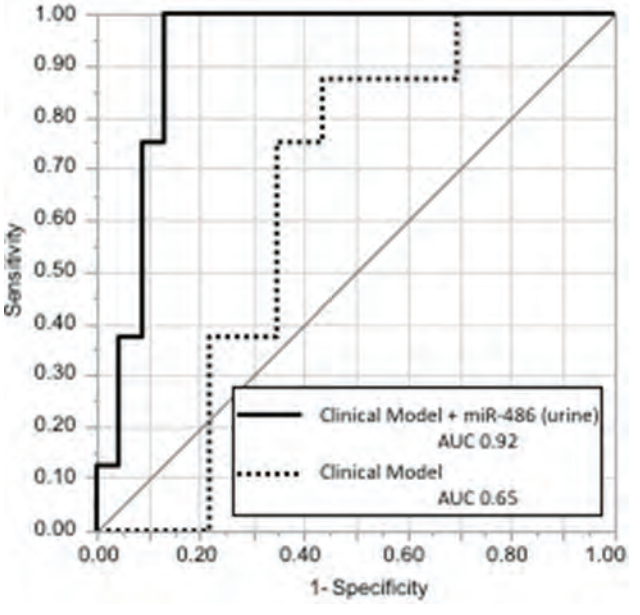
Background: Despite recent advances, clinical renal diagnosis requires pathological examination of a kidney biopsy. Micro RNAs (miRNAs) in exosomes are promising biomarkers for kidney disease diagnosis and management. We sought to identify diagnostic miRNAs in exosomes from blood and urine obtained from subjects with diabetic nephropathy.

Methods: We performed a prospective single-center cohort study, enrolling patients who underwent kidney biopsy at the University of Tokyo Hospital. Blood and urine samples and clinical parameters were obtained at the time of the kidney biopsy. Exosomes were isolated from blood and urine by ultracentrifugation and RNA was extracted. We selected candidate miRNAs by TaqMan array card and measured expression by quantitative PCR. The outcome variable was standardized pathological diagnosis. We confirmed the principal findings by experiments in streptozotocin (STZ)-induced diabetic mice.

Results: The study population consisted of 102 patients who underwent kidney biopsy, including 8 with diabetic nephropathy and 23 with diabetes who had other kidney diseases. For the diagnosis of diabetic nephropathy, a clinical model (diabetic history, retinopathy and hematuria) had moderate accuracy, with AUC [95% CI] 0.65 [0.44-0.81]. Urinary exosomal miR-486 added significant accuracy when combined with the clinical model, showing AUC 0.92 [0.76-0.98] (p=0.003). In STZ diabetic mice, miR-486 expression was reduced by 94% in urinary exosomes (p=0.003) and by 40% in laser capture micro-dissected glomeruli (p=0.02) compared with non-diabetic mice.

Conclusions: Levels of miRNAs in urinary exosomes correlated with the histological diagnosis of diabetic nephropathy and may be a promising non-invasive diagnostic tool.

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



Receiver operating characteristic (ROC) curves for diagnosis of human diabetic nephropathy

TH-PO1046

Differences in Disease Activity by Sex and Pubertal/Menopausal Status in Primary Glomerulonephropathies

Andrea L. Oliverio,[1] Sarah Mansfield,[2] Salem Almaani,[5] Isabelle Ayoub,[5] Kira Clark,[3] Hilda E. Fernandez,[10] Pascale Khairallah,[11] Michelle M. O'Shaughnessy,[6] Monica L. Reynolds,[4] Katherine Twombley,[7] Shikha Wadhwani,[8] Tetyana L. Vasylyeva,[12] Jarcy Zee,[2] Michelle A. Hladunewich,[9] Laura H. Mariani.[1] *[1]University of Michigan, Ann Arbor, MI; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Oregon Health and Science University, Portland, OR; [4]University of North Carolina at Chapel Hill, Cary, NC; [5]The Ohio State University Wexner Medical Center, Columbus, OH; [6]Stanford University, Palo Alto, CA; [7]Medical University of South Carolina, Charleston, SC; [8]Northwestern University Feinberg School of Medicine, Chicago, IL; [9]University of Toronto, Toronto, ON, Canada; [10]NYP-CUMC, New York, NY; [11]Columbia University Medical Center, New York, NY; [12]Texas Tech University Health Sciences Center, Lubbock, TX.*

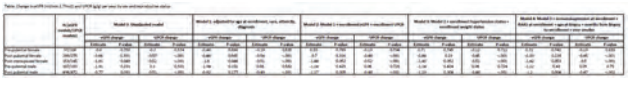
Background: CKD has been observed to progress more slowly in women than men. However, large studies examining associations between sex, reproductive stage, and disease activity and progression in primary glomerulonephropathies are lacking.

Methods: CureGN is a 70-site prospective cohort study of patients with MCD, FSGS, IgAN/IgAV, or MN. Patients with available eGFR, UPCR, and reproductive stage at enrollment were studied. Reproductive stage was categorized as pre-pubertal (Tanner stage I-III), post-pubertal (Tanner stage IV-V, or menarche for females), or post-menopausal (females only). Multivariable mixed linear models adjusted for baseline data at time of enrollment (Table) were fit to examine change in eGFR and UPCR over time.

Results: Median follow-up from enrollment was 2.1 (IQR 1.0-3.1) yrs. Among 1202 patients with available enrollment eGFR, adjusted (Model 3) eGFR slopes amongst females were +0.71, -0.84, and -1.43 ml/min/1.73m2 per year for pre-pubertal, post-pubertal, and post-menopausal women, respectively (Table). For pre-pubertal and post-pubertal males, eGFR slopes were -1.14 and -1.19 ml/min/1.73m2 per year, respectively. Adjusted UPCR slopes by sex and reproductive stage are also shown in the Table.

Conclusions: The protective effect of female sex on eGFR decline was most notable prior to puberty. Of all groups, post-menopausal women had the fastest eGFR decline. Unlike post-pubertal males and females, pre-pubertal participants experienced no significant decrease in UPCR over time, and menopausal status did not seem to impact the rate of UPCR decline seen in post-pubertal females.

Funding: NIDDK Support



TH-PO1047

Development of a Clinician-Reported Outcome Measure for Edema Assessment

Noelle E. Carlozzi,[1] Howard Trachtman,[2] Liron Walsh,[3] Chris Lynam,[3] Debbie S. Gipson.[4] *[1]University of Michigan, Ann Arbor, MI; [2]NYU Langone Health, New York, NY; [3]Goldfinch Bio, Boston, MA; [4]University of Michigan Mott Children's Hospital, Ann Arbor, MI.*

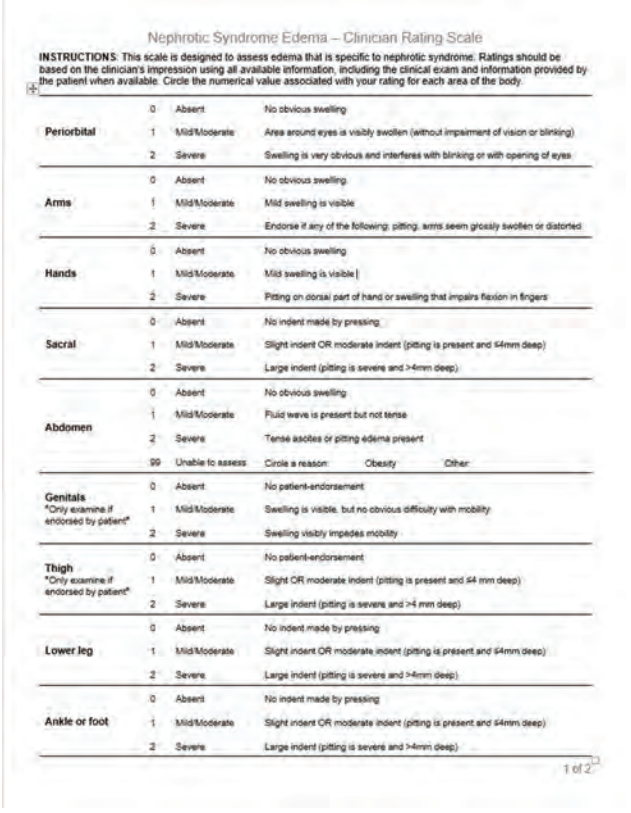
Background: Patients report edema is a high impact manifestation of proteinuric kidney disease. However, evaluation of edema is not standardized and can manifest as localized or generalized swelling. Accurate and valid assessment of edema is important for patient care and clinical trials of patients with proteinuric kidney disease. The objective of this study was to develop a clinician reported outcome measure (ClinRO) for edema assessment for use with patients with glomerular disease.

Methods: Semi-structured interviews were conducted with pediatric and internal medicine nephrology clinicians (physicians and advanced practice providers) to elicit physical exam findings of edema manifestations, documentation, and importance. Concepts were derived from these interviews, confirmed with clinicians and then used to create the Edema ClinRo.

Results: 14 clinicians participated in the study, including 7 pediatric and 7 internal medicine experts. Concepts identified included assessment of body regions (periorbital, extremities, trunk and if patient endorsed genitals) and severity rating. The ClinRO was generated (**Figure**) in an iterative fashion with input from clinician stakeholders. Online training and certification modules were developed for use and a user acceptance testing step was implemented

Conclusions: The Edema ClinRO was developed based upon pediatric and internal medicine clinician input using best practice methods to support implementation of standardized edema assessment in clinical and research contexts. User acceptance testing of the ClinRO has been completed and for the training module is underway. With web-based Edema ClinRo dissemination and data collection, the utility of this measure will be assessed as a future step.

Funding: Commercial Support - Goldfinch Bio



Nephrotic Syndrome Edema – Clinician Rating Scale

INSTRUCTIONS: This scale is designed to assess edema that is specific to nephrotic syndrome. Ratings should be based on the clinician's impression using all available information, including the clinical exam and information provided by the patient when available. Circle the numerical value associated with your rating for each area of the body.

Periorbital	0	Absent	No obvious swelling
	1	Mild/Moderate	Area around eyes is visibly swollen (without impairment of vision or blinking)
	2	Severe	Swelling is very obvious and interferes with blinking or with opening of eyes
Arms	0	Absent	No obvious swelling
	1	Mild/Moderate	Mild swelling is visible
	2	Severe	Endorse if any of the following: pitting, arms seem grossly swollen or distorted
Hands	0	Absent	No obvious swelling
	1	Mild/Moderate	Mild swelling is visible
	2	Severe	Pitting on dorsal part of hand or swelling that impairs flexion in fingers
Sacral	0	Absent	No indent made by pressing
	1	Mild/Moderate	Slight indent OR moderate indent (pitting is present and ≤4mm deep)
	2	Severe	Large indent (pitting is severe and >4mm deep)
Abdomen	0	Absent	No obvious swelling
	1	Mild/Moderate	Fluid wave is present but not tense
	2	Severe	Tense ascites or pitting edema present
	99	Unable to assess	Circle a reason: Obesity Other:
Genitals *"Only examine if endorsed by patient"	0	Absent	No patient-endorsement
	1	Mild/Moderate	Swelling is visible, but no obvious difficulty with mobility
	2	Severe	Swelling visibly impedes mobility
Thigh *"Only examine if endorsed by patient"	0	Absent	No patient-endorsement
	1	Mild/Moderate	Slight OR moderate indent (pitting is present and ≤4 mm deep)
	2	Severe	Large indent (pitting is severe and >4 mm deep)
Lower leg	0	Absent	No indent made by pressing
	1	Mild/Moderate	Slight indent OR moderate indent (pitting is present and ≤4mm deep)
	2	Severe	Large indent (pitting is severe and >4mm deep)
Ankle or foot	0	Absent	No indent made by pressing
	1	Mild/Moderate	Slight indent OR moderate indent (pitting is present and ≤4mm deep)
	2	Severe	Large indent (pitting is severe and >4mm deep)

1 of 2

Figure. Edema Clinician Reported Outcome Measure

TH-PO1048

Can Estimated Glomerular Filtration Rate (eGFR) Slope Be a Good Outcome Measure for Glomerular Disease?

Brenda W. Gillespie,[1] Abigail R. Smith,[2] Jarcy Zee,[2] Debbie S. Gipson,[3] Sarah Mansfield,[2] Laura H. Mariani,[1] Margaret Helmuth,[2] Bruce M. Robinson.[2]
[1]University of Michigan, Ann Arbor, MI; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]University of Michigan Mott Children's Hospital, Ann Arbor, MI.

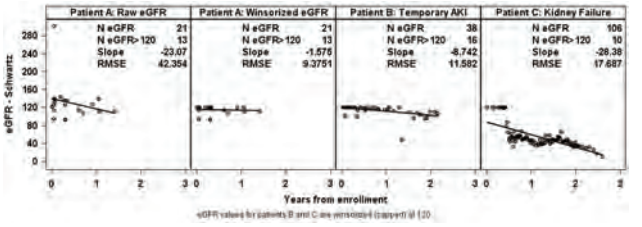
Background: Unlike chronic kidney disease (CKD), where trajectories of eGFR over time are commonly linear, trajectories in glomerulonephropathy (GN) are often variable, with excursions into high eGFR (hyperfiltration), acute kidney injury (AKI) and sudden drops to kidney failure. This makes the use of eGFR slope, a statistically powerful progression outcome, challenging in this population. Our objective was to assess the prevalence of nonlinear features and propose adjustments to facilitate use of eGFR slope as an outcome measure.

Methods: Using data from CureGN, patients with at least one year of follow-up, at least 5 eGFR measurements, and a diagnosis of Minimal Change Disease (MCD) were included. Analysis was restricted to MCD due to high prevalence of high eGFR (>120 mL/min/1.73 m²). Linear regression models were fitted to each participant's data with and without winsorizing (capping) eGFR values at 120 mL/min/1.73m² with the rationale that values above 120 represented high filtration rates but not clinically improved eGFR. Trajectories were deemed linear if root mean squared error (RMSE) was ≤20; we examined individual nonlinear trajectories to assess deviation from linearity.

Results: 74 adult (mean±SD age = 43.2±19.1, range 18-82) and 116 pediatric (mean±SD age = 7.7±3.6, range 2-16) participants were included. At least one eGFR>120 was present in 22% of adults and 83% of children. Linear fits were improved after winsorizing: 76% (95% adult, 64% pediatric) had good fits prior to, and 96% (96% adult, 96% pediatric) had good fits after winsorizing. Based on visual assessment of trajectories, most cases with nonlinear fits had apparent AKI, and a few had sudden kidney failure. In AKI, allowing the fit to include outlying point(s) provided a reasonable overall slope estimate. In kidney failure, the linear fits did not follow each curve but often captured the overall trend very well (Figure).

Conclusions: Linear models of eGFR have previously been used in analyses of CKD data; the added features of winsorizing and data examination will enhance their use for GN patients with MCD.

Funding: NIDDK Support



TH-PO1049

Time-Updated Systolic Blood Pressure and Progression of CKD in Patients with Glomerulonephritis

Hyung Woo Kim,[1] Seonghun Kim,[2] Boyoung Nam,[2] Jimin Park,[2] Jung Tak Park,[1] Seung Hyeok Han,[1] Shin-Wook Kang,[1,2] Tae-Hyun Yoo.[1]
[1]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea.

Background: Many guidelines on optimal target of blood pressure in chronic kidney disease are largely based on studies in diabetic and hypertensive patients. However, there is lack of evidence that this blood pressure goal can also be applied to patients with glomerular diseases. The aim of this study was to clarify the longitudinal association between blood pressure and CKD progression in patients with glomerulonephritis.

Methods: We studied 1,016 biopsy-proven patients who were diagnosed with primary glomerular diseases such as IgA nephropathy (n=756 [74.4%]), membranous glomerulonephritis (n=144 [14.2%]), and focal segmental glomerulosclerosis (n=116 [11.4%]) from 2005 to 2017. The main exposure of interest was baseline and time-updated systolic blood pressure (SBP). The primary outcome was a composite of a ≥50% decrease in eGFR from baseline or end-stage kidney disease. We used time-varying cox model and marginal structural model for time-updated SBP.

Results: During 1,607 person-years follow up, the primary outcome occurred in 658 (64.8%) patients. The mean age was 43.6±14.7 years and baseline eGFR was 90.4±28.0 ml/min/1.73 m². 665 (65.5%) patients had the history of previous hypertension. Using time-varying cox model, compared with SBP of 120 to 129 mmHg, the hazard ratios for the primary outcome were 1.01 (95% CI, 0.84 to 1.22), 1.11 (95% CI, 0.88 to 1.40), 1.36 (95% CI, 1.04 to 1.78), respectively. The marginal structural model also showed consistent results. The corresponding HRs for the noted SBP categories were 1.04 (95% CI, 0.87 to 1.24; *p*=0.68), 1.14 (95% CI, 0.92 to 1.41; *p*=0.24), 1.43 (95% CI, 1.08 to 1.89 *p*=0.01), respectively. This association was consistent regardless of subgroups by age (<60 vs. ≥60), gender, previous hypertension, baseline eGFR (≥45 vs. <45), and proteinuria (<1g vs. ≥1g).

Conclusions: Among patients with glomerular diseases, SBP >140 mmHg was significantly associated with higher risk of CKD progression.

TH-PO1050

Identifying Outcomes Important to Patients with Glomerular Disease and Their Caregivers: A Multinational Nominal Group Technique Study

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Background: Outcomes that are important to patients with glomerular disease remain uncertain and therefore shared-decision making can be challenging. We aimed to identify and prioritize outcomes important to patients and their caregivers, and the reasons for their choices.

Methods: We purposively sampled patients aged ≥18 years with glomerular disease and their caregivers from Australia, Hong Kong, United Kingdom and United States. Participants identified, ranked and discussed outcomes. Each outcome was ranked using a relative importance score between 0 and 1. Qualitative data were analyzed thematically.

Results: Across 16 focus groups, 132 participants (100 patients, 32 caregivers) identified 58 outcomes. Patients were aged 19 to 85 years (mean 51 years), 47 (47%) were female and 29 (29%) were on dialysis or had received a kidney transplant. Thirty eight (38%) had kidney-limited glomerular disease, 31 (31%) had glomerular disease with systemic features, and 31 (31%) had other or unknown subtypes. The ten highest ranked outcomes were: kidney function (importance score 0.42), mortality (0.29), need for dialysis or transplant (0.22), life participation (0.18), fatigue (0.17), anxiety (0.13), impact on family (0.12), infection and immunity (0.12), ability to work (0.11) and blood pressure (0.11; Figure 1). The top five outcomes were identical for patients and caregivers. The top three outcomes were the same across disease subtypes. Three themes explained the reasons for these rankings: constraining day-to-day experience, impaired agency and control over health, and threats to future health and family.

Conclusions: Patients with glomerular disease and their caregivers highly prioritize kidney health and survival, as well as life participation, fatigue, anxiety and the impact on family. Consistent reporting of these outcomes in trials may improve shared decision-making.

Funding: Government Support - Non-U.S.

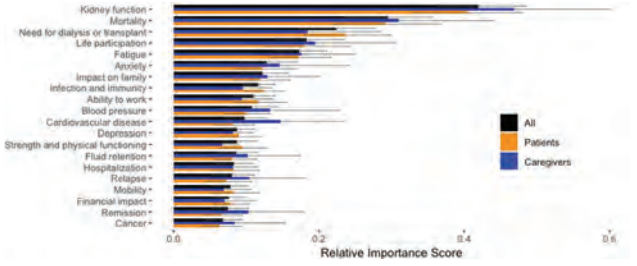

Figure 1. Relative rankings of outcomes by patients and caregivers

TH-PO1051

Mood, Anxiety, and Hyperactivity Disorders in Patients with Glomerular Disease

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Background: Patients with chronic health conditions are at heightened risk for psychiatric disorders; yet in glomerular disease (GD) little is known about the prevalence of mood, anxiety, and hyperactivity disorders or associations with patient and disease characteristics.

Methods: This study included patients with GD enrolled in the Kidney Research Network multisite patient registry. Encounter, diagnosis, medication, lab, and vital sign data are extracted monthly from participants' electronic health records. ICD9/10 diagnosis codes were used to identify psychiatric disorders, including anxiety and depressive disorders and attention deficit disorder (ADD). Longitudinal GEE models were used to analyze the odds of being diagnosed with a psychiatric disorder. Potential covariates in the models included age at kidney disease onset, sex, race, ethnicity, and time-varying treatment, eGFR and urine protein:creatinine ratio (UP:C). Continuous variables are presented as median (IQR).

Results: Data were available for 938 patients with a 51 (IQR: 25-92) month follow up and kidney disease onset age of 19 (IQR: 5-41) yrs. 202 (21.5%) were diagnosed with a psychiatric disorder at a rate of 4.3 per 100 pt-yrs, with 78 of those having two or more disorders. The most common disorders were anxiety (n=145, 3.1 per 100 pt-yrs), depression (n=101, 2.1 per 100 pt-yrs), and ADD (n=29, 0.6 per 100 pt-yrs). Adolescents vs adults (OR: 2.4, 95% CI: 1.5-4.0), white vs Asian race (OR: 2.7, 95% CI: 1.3-5.6), steroid treatment (OR: 2.5, 95% CI: 1.4-3.8) and higher UP:C (OR per log: 1.2, 95% CI: 1.0-1.3) were significantly associated with psychiatric disorder diagnosis.

Conclusions: Select psychiatric disorders were documented in approximately one quarter of patients with GD and were associated with adolescence (vs adulthood), steroid therapy, higher proteinuria, and white (vs Asian) race. This may be an underrepresentation as data is based on what was documented in participants' electronic health record. A difference in prevalence by race may suggest a difference in assessment and diagnosis rather than true difference in prevalence. These findings suggest mental health screening may be warranted in patients with GD.

Funding: Private Foundation Support

TH-PO1052

Nephrotic Syndrome Acquired Hypercoagulopathy Is Strongly Associated with Proteinuria and Hyperlipidemia

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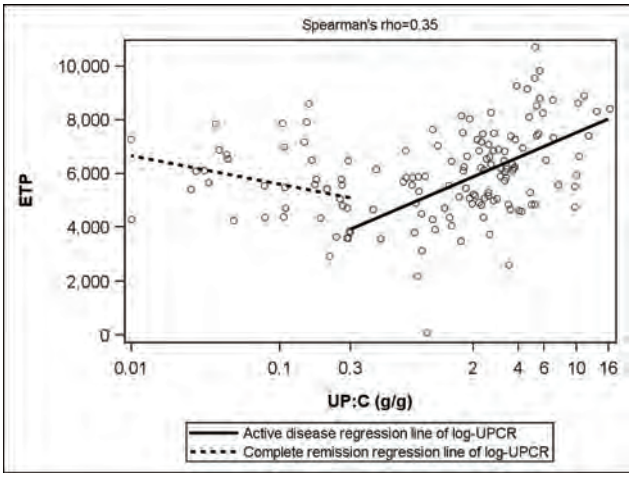
Background: Nephrotic syndrome (NS) is complicated by hypercoagulopathy and predilection for venous thromboembolism (VTE). Routine anticoagulant prophylaxis is controversial. Thrombin generation assay (TGA), a measure of hypercoagulopathy, has known predictive value for VTE in non-NS patients. We have shown that TGA is directly proportional to NS severity in animal NS. We sought to determine if TGA is correlated with human NS severity.

Methods: NEPTUNE biorepository plasma aliquots (*N*=150) were obtained (excluding patients on anticoagulants or with prior VTE) along with phenotypic data. TGA was performed and endogenous thrombin potential (ETP) calculated as the area under the thrombin activity curve. Plasma albumin levels were also determined.

Results: TGA was undetectable in 3 (2%) of the NEPTUNE samples (excluded). Univariate linear regression on the remaining 147 samples revealed significant relationships with: Age (*B*=-16), Proteinuria (log-UP:C; *B*=265), Plasma Albumin (*B*=-657), Total Cholesterol (*B*=2,129), eGFR (*B*=10), and Steroid (*B*=853) or RAAS-blockade (*B*=-573) treatment. Histologic NS classification was not significantly associated with ETP. Multivariable modeling revealed an interaction between remission status and proteinuria, such that UP:C was independently predictive of ETP in patients with active disease (*B*=828; *P*<0.0001; Figure). Age (*B*=-15; *P*=0.005) and Total Cholesterol (*B*=1,448; *P*=0.0001) were also independently predictive. The final multivariable model was highly correlated with ETP (R^2=0.35). Similar NS-severity univariate relationships were demonstrated in our local cohort.

Conclusions: Proteinuria and hyperlipidemia were associated with ETP. These data suggest that analysis of these NS severity markers and ETP in relation to thrombotic events in patients with NS may inform their utility as a future guide to anticoagulant prophylaxis.

Funding: NIDDK Support



TH-PO1053

Anticoagulation and Anti-Platelet Prescribing in Glomerular Disease: An Observational Study

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Background: Nephrotic syndrome confers thromboembolism (TE) risk. We report frequencies of TE and anticoagulation (AC) and antiplatelet (AP) prescribing in patients with/without nephrotic-range proteinuria enrolled in Nephcure Kidney Research Network (KRN) Registry.

Methods: Patients with glomerular disease (GD) from all KRN sites were included. Encounter, diagnosis, meds, lab, and vital sign data were extracted monthly from patients' EMRs. Patients were grouped into those with at least one UPCR ≥3.5 g/g (Nephrotic) vs those with UPCR always <3.5 g/g (Non-nephrotic). TE and AC/AP prescription (Rx) frequencies were determined. Follow-up was censored at ESRD.

Results: Nephrotic (n=568) and Non-nephrotic (n=404) groups were similar in age/sex. Mean eGFR (93 vs. 70 ml/min/1.73m2, p<.001) and UPCR (4.9 vs. 0.7 g/g, p<.001) were higher, and serum albumin lower (3.1 vs. 3.9 g/dL, p<.001) in Nephrotics vs. Non-nephrotics. Nephrotics and Non-nephrotics had: FSGS/C1Q (59% vs 41%); Minimal change/IgM/MesPGN (77% vs 23%); Membranous (79% vs 21%), IgA (28% vs 7%), or other GD (54% vs 46%). 90 Nephrotics and 52 Non-nephrotics had no biopsy (mostly children). Median follow-up for Nephrotics (57 mos) was longer than Non-nephrotics (49) (p<.001). There were 70 TE: 9.2% of Nephrotics (n=52) vs 4.5% of Non-nephrotics (n=18) (p<.005). AC/AP Rxs were more frequent in Nephrotics (203 of 568, 36%) than Non-nephrotics (67 of 404, 17%)(p<.0001). The 203 Nephrotics had AC/AP Rx as follows: heparin, enoxaparin, fondaparinux (64%); aspirin (58%); warfarin (11%); alteplase, urokinase (9%); Factor Xa inhibitors (Xai, 5%); and/or clopidogrel, ticagrelor (4%). Non-nephrotics (n=67) had heparin, enoxaparin, fondaparinux (46%, p<.0001 vs Nephrotics); aspirin (61%); warfarin (12%); alteplase, urokinase (9%); Xai (6%); and/or clopdiogrel, prasugrel, dipyriadamole (9%).

Conclusions: In KRN, TE and AC/AP prescriptions were twice as frequent in Nephrotics than Non-nephrotics. Heparin/congeners were prescribed 6 times more often than warfarin in Nephrotics; 3 times more often in Non-nephrotics. Aspirin was prescribed frequently and Xai infrequently in both groups. These variable practices suggest a need for further exploration of AC/AP indications/efficacy/ safety in GD patients.

Funding: Private Foundation Support

TH-PO1054

Patterns and Trends of Infection Among Hospitalized Patients with Different Types of Chronic Glomerulonephritis: A Retrospective Study Spanning 18 Years from a Single Tertiary Hospital

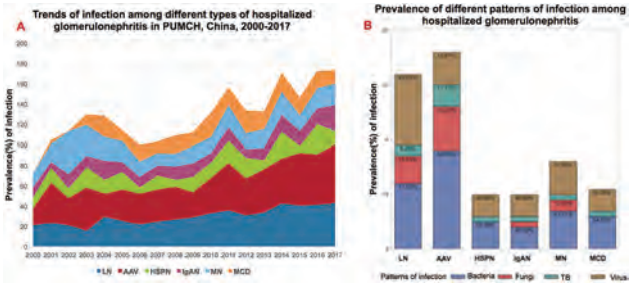
Xiaohong Fan, Hang Li, Xuemei Li, Xuewang Li, Jianfang Cai. *Division of Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China*.

Background: It remains unclear whether the patterns and trends of infection are differentials among different types of glomerulonephritis.

Methods: We conducted a retrospective analysis using the database of hospitalization with chronic glomerulonephritis in Peking Union Medical College Hospital (PUMCH), China from 2000 through 2017. The tenth revision from the International Classification of Diseases (ICD-10) codes of discharge diagnosis was used to identify infectious diseases and 6 kinds of glomerulonephritis including lupus nephritis (LN), systemic vasculitis (AAV), Henoch-Schönlein purpura nephritis (HSPN), IgA nephritis (IgAN), idiopathic membrane nephropathy(MN), and minimal change disease(MCD). Cochran-Armitage trend test and Logistic regression were used for analysis.

Results: Between 2000 and 2017, there were 15,714 hospitalizations with aforementioned chronic glomerulonephritis. Their mean age was 51.7±19.8 years and 39.4% were males. The annual prevalence of overall infection increased steadily from 14.7% in 2000 to 33.0% in 2017 among all (p for trend <0.001). We found significant increasing trends of overall infection in LN, AAV, HSPN, IgAN, and MCD, but not in MN **[**Figure A]. Hospitalized patients with LN, AAV, and MN were more likely to have **the** infection as compared with those with IgAN (OR: 3.53, 95%CI 3.14-3.95, 3.92, 95%CI 3.30-4.64, and 1.36, 95%CI 1.17-1.57, respectively) after adjustment for age, gender, hypertension, and diabetes. The bacteria and virus infections were the top two infectious diseases, patients with LN, AAV, and MN also had **a** higher proportion of fungi infection **[**Figure B].

Conclusions: There had been an increasing trend of infection in hospitalized patients with chronic glomerulonephritis except for those with idiopathic membrane nephropathy. Prevalence of infection and infection patterns varied among hospitalized patients with different glomerulonephritis.



TH-PO1055

Trends of Infection Among Hospitalized Patients with Chronic Glomerulonephritis: A Retrospective Study Spanning 18 Years from a Single Tertiary Hospital

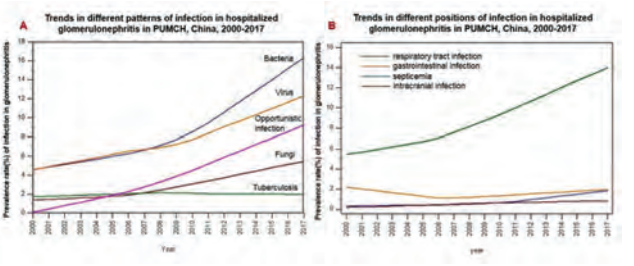
Xiaohong Fan, Hang Li, Xuemei Li, Xuewang Li, Jianfang Cai. *Division of Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China*.

Background: Infection is one of the most important complications in patients with chronic glomerulonephritis. It confers an additional risk of death. However, its trends over the years in patients with chronic glomerulonephritis have seldom been demonstrated.

Methods: We conducted a retrospective analysis using the database of hospitalization to estimate current trends in different infectious diseases among hospitalized patients with chronic glomerulonephritis in Peking Union Medical College Hospital, China from 2000 through 2017. The tenth revision from the International Classification of Diseases (ICD-10) codes of discharge diagnosis was used to identify infectious diseases and different kinds of glomerulonephritis. The diagnosis of glomerulonephritis was further validated by data from our renal pathology reporting system. Cochran-Armitage trend test was used for analysis.

Results: Between 2000 and 2017, there were 18,307 hospitalizations with glomerulonephritis. Their mean age at admission was 51.7±19.8 years and 52.8% were males. The overall prevalence of infection among patients with chronic glomerulonephritis was 21.2%. The annual prevalence of overall infection increased from 14.9% in 2000 to 32.0% in 2017 (p for trend <0.001). The annual prevalence of bacteria, virus, and fungi infection, and opportunistic infection increased from 2000 to 2017, however, that of tuberculosis remained stable [figure A]. Over the years, the prevalence of respiratory tract infection, septicemia, and intracranial infection increased steadily(p for trend <0.001),in contrast, that of gastrointestinal infection stayed unchanged(p=0.49) [figure B].

Conclusions: There had been an increasing prevalence of infection was increasing in patients with chronic glomerulonephritis over the years fro 2000 to 2017, except that of tuberculosis and gastrointestinal infection.



TH-PO1056

Cancer Development and Mortality Differences in Patients with Glomerulonephritis After Renal Biopsy

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Background: This retrospective cohort study was conducted to evaluate the cancer incidence in renal biopsy proven glomerulonephritis (GN) patients during the follow ups and to find out the mortality differences according to cancer occurrence.

Methods: This is a retrospective cohort study conducted in a single center. Among 1,600 patients who have underwent renal biopsy between 2003 and 2017, in Seoul National Bundang Hospital, after excluding 611 patients who are inappropriate for the analysis, a total 929 adult patients were analyzed. (Figure) Baseline clinical characteristics, renal biopsy result and types and dose of immunosuppressant usages during the follow-up were collected. Incidence of cancer was censored when the 1st cancer was diagnosed and the mortality was detected during the follow ups.

Results: During the mean 52.4 months (range 1.0-166.7 months) of follow-up, total 49 cases were newly diagnosed as cancer. When we compared the clinical characteristics between the patients who developed cancer and the others, cancer patient were older and had higher prevalence of coronary heart disease and diabetes, lower level of hemoglobin and higher immunosuppressant usage. When the multivariate Cox regression analysis were conducted to find out the risk factors for the cancer development, membranous nephropathy (MN) pathologic diagnosis showed hazard ratio of 2.6 (95% CI 1.32-5.30) after adjusting age, gender, clinical parameters and usage of immunosuppressant. In the subgroup analyais among MN patients, age was the only significant risk factor for the cancer development afte adjusting other confouders. During the follow up, total 86 patients died. In the MN patients, the patients who developed cancer had higher mortality with hazard ratio of 5.95 (95% CI 1.36-26.09, p=0.018) compared to MN patients without cancer, when the multivariate Cox's proportional hazard model were conducted.

Conclusions: Among the GN population without concurrent cancer, patients with MN should be aware of cancer developments during the follow up, since they have significant higher risk of cancer devolvement and which results in higher mortality rate.

TH-PO1057

CCR2 Inhibition Improves Glomerular Ultrastructure In Vivo in Models of Focal Segmental Glomerulosclerosis (FSGS)

Zhenhua Miao, Linda Ertl, Dale Newland, Xiaoping Zang, Bin N. Zhao, Yu Wang, Simon K. Yau, Shirley Liu, Ton H. Dang, Penglie Zhang, James J. Campbell, Israel Charo, Rajinder Singh, Thomas J. Schall. *ChemoCentryx, Inc., Mountain View, CA*.

Background: FSGS is a histologic diagnosis resulting from glomerular injury primarily affecting podocytes, and characterized by the presence of focal and segmental scarring in the glomeruli. Treatment failure is common with current standard of care, and FSGS is causal in at least 4% of patients with ESRD. Several lines of evidence support roles for CCR2 in the pathogenesis of CKD, including FSGS. We have recently shown that a CCR2 antagonist improved renal structure and reduced proteinuria in the murine models of FSGS. To further understand the mechanism by which CCR2 antagonism affords protection in FSGS, we have used EM to examine the effects of CCR2 antagonist on podocyte integrity.

Methods: The 5/6 nephrectomy model of murine FSGS was used to investigate the efficacy of CCR2 antagonist. Kidney injury was assessed by urinary albumin excretion rate (UAER), urine albumin creatinine ratio (UACR), histopathology and EM. Both transmission EM (TEM) and scanning EM (SEM) were performed on kidney samples.

Results: In 5/6 nephrectomized mice, UACR was rapidly and significantly reduced after treatment with CCR2 antagonist (42% and 77% reduction comparing to vehicle treated by week 1 and 2; p=0.04 and 0.025, respectively). The number of glomeruli with sclerosis was reduced by 54% based on analysis of 50-75 glomeruli per kidney. Podocyte integrity was also improved with CCR2 inhibition. Specifically, analysis by both SEM and TEM revealed that podocyte foot process (FP) effacement and slit diaphragm (SD) disruption were improved by CCR2 antagonism, as were the characteristically thickened and denuded GBM. After two weeks of treatment with CCR2 antagonist, FP number was significantly increased with respect to vehicle treated mice (2.10/um GBM vs 1.53/um GBM, p < 0.0001).

Conclusions: Treatment with CCR2 antagonist provides rapid renal protection in the murine model of FSGS, as measured by improved proteinuria and renal structure. Furthermore, CCR2 blockade protected podocyte integrity, as measured by both SEM and TEM. These results provide further evidence that specific inhibition of CCR2 has therapeutic potential in the treatment of FSGS. CCR2 antagonism thus represents a novel and mechanistically distinct approach for the treatment of FSGS.

TH-PO1058

Non-Canonical Expression of CCR2 on Renal Progenitor Cells and Activated Parietal Epithelial Cells: Key to Therapeutic Effect of CCR2 Inhibition in CKD?

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Background: Rapid benefits to proteinuria and renal structure are seen with inhibition of CCR2 in models of diabetic nephropathy (DN) and focal segmental glomerulosclerosis (FSGS), and in a human DN trial. However, the mechanism of CCR2 inhibition in renal protection is unclear. Known expression of CCR2 on monocytes does not adequately explain the rapid pharmacologic benefits observed. We used a variety of methods to characterize CCR2 expression on renal progenitor cells (RPCs, $CD133^+CD24^+$) in Bowman's capsule, and on activated parietal epithelial cells (PECs, $CD133^+CD24^+CD44^+$), which play a role in glomerulosclerosis.

Methods: One copy of CCR2 was replaced by red fluorescent protein (RFP) under the control of the mouse CCR2 promoter. CCR2-RFP mouse glomeruli were obtained by a non-enzymatic disruption of kidneys, sieving and low speed centrifugation and analyzed by flow cytometry for CCR2 expression. CCR2 in FSGS was modeled by Adriamycin (ADR) induced kidney injury.

Results: CCR2-RFP positive cells were detected in CD45 positive and CD45 negative renal cell populations. The majority of renal $CD45^-$ RFP^+ cells were CD133 positive but CD24 negative, and are yet largely uncharacterized. However $CD133^+CD24^+$ RPC's, while unchanged in absolute number before and after ADR challenge, showed a dramatic increase (20-40 fold) in the proportion that were CCR2-RFP+ after ADR injury. Furthermore, after ADR challenge, the expression of CD44 (a marker for activated PECs) was increased in the $CD133^+CD24^+$ population. Immunofluorescence confirmed an RFP signal in the glomeruli and Bowman's capsule.

Conclusions: This is the first report of the presence of CCR2 on non-hematopoietic renal parenchymal cells. The non-canonical CCR2+ cells are positive for CD133, CD24, and CD44 consistent with their being renal progenitor cells and activated PECs. These populations are markedly upregulated during kidney injury. These cells may be the targets of the CCR2 inhibitors that have been shown to be efficacious in murine models of CKD, as well as in human DN patients. CCR2 antagonism represents a novel approach for the treatment of CKD, including FSGS, and these studies are an important step in understanding the mechanism of their therapeutic benefit.

TH-PO1059

Altered Podocyte-Endothelial Cross-Talk and Increased Oxidative Stress in Patients with FSGS

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Background: The podocyte is thought to be the mainly affected cell type in focal segmental glomerulosclerosis (FSGS). However, recent studies have also indicated a role for glomerular endothelial cells and for changes in crosstalk between these cells and podocytes in the development of FSGS. In an animal model for FSGS, it has been shown that endothelin-1 (ET-1) production by podocytes induces oxidative stress in endothelial cells, which subsequently induces podocyte loss. In this study, we investigated ET-1 signalling and associated oxidative stress and podocyte loss in patients with FSGS.

Methods: We selected 42 biopsies of patients with FSGS and 8 healthy controls and stained them for the endothelin receptor A (ET_AR) and nephrin. The number of glomeruli with ET_AR-positive endothelium and of glomeruli with nephrin loss were scored. In addition, FSGS patients and 10 protocol transplantation biopsies without specific pathology were stained for 8-OXO-G to indicate oxidative stress. Glomerular 8-OXO-G positivity was measured using ImageJ.

Results: In patients with FSGS, the mean percentage of glomeruli with ET_AR-positive endothelial cells was higher compared to healthy controls (52% vs. 7%; $p<0.001$). Also nephrin loss was observed in glomeruli of patients with FSGS. The percentage of glomeruli with ET_AR-positive endothelium correlated with the percentage of glomeruli with nephrin loss (rho=0.49; $p<0.01$). Moreover, the odds of having nephrin loss was higher for glomeruli with ET_AR-positive endothelium compared to ET_AR-negative glomeruli (OR: 2.0; $p<0.0001$). The median percentage of glomerular 8-OXO-G positivity was not significantly different between the two groups (0.90 vs 0.61; $p=0.29$). However, in patients with FSGS 8-OXO-G accumulation (median positivity ≥ 1.5) appeared to be more frequent compared to controls (40% vs 10%; $p=0.07$). Moreover, glomeruli with ET_AR-positive endothelium showed more 8-OXO-G positive staining (1.8 vs 2.3; $p=0.038$).

Conclusions: Patients with FSGS have increased positivity of ET_AR in glomerular endothelial cells and endothelial ET_AR positivity correlates with the degree of podocyte damage. In addition, glomerular oxidative stress, as indicated by the presence of 8-OXO-G, is increased in a subset of patients with FSGS and 8-OXO-G levels are higher in glomeruli with ET_AR-positive endothelial cells.

TH-PO1060

Knockdown of Podocyte Nephronectin by Glomerular Endothelial Cell-Derived MicroRNA-192 Leads to Alterations in GBM

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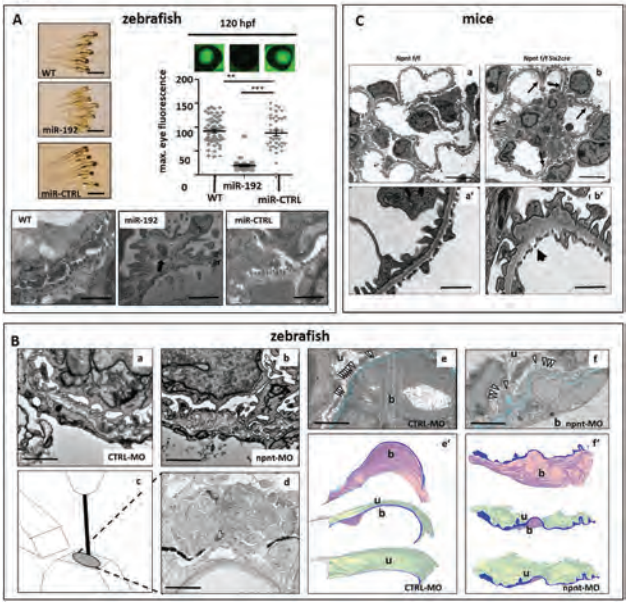
Background: Nephronectin (NPNT) is an extracellular matrix protein downregulated by either TGF-β or miR-378a in podocytes. Knockdown of npnt leads to proteinuria, podocyte effacement and splitting of the glomerular basement membrane (GBM) in zebrafish larvae. Here we investigated the regulation von NPNT by TGF-β and miRs as well as GBM phenotype after knockdown of NPNT more in detail by using cell culture, zebrafish and mice models.

Methods: By using mouse SMAD2/3 knockout podocytes as well as selective inhibitors of the TGF-β pathway we analyzed the TGF-β-NPNT axis more in detail. We overexpressed this miR in zebrafish larvae and analyzed the glomerular phenotype. Finally podocyte specific knockdown of Npnt was investigated in Npnt -/-;Six2-cre mice.

Results: TGF-β regulation of NPNT is mediated by the canonical TGF-β pathway in a SMAD-dependent manner. We identified glomerular endothelial cell-derived miR-192 as a regulator of NPNT in podocytes. Transfection of cultured podocytes with a miR-192 mimic down regulated NPNT expression. Overexpression of miR-192 in zebrafish larvae induced edema, proteinuria and GBM thickening similar to the phenotype after morpholino induced npnt knockdown (Fig. 1A). We characterized the phenotype of npnt knockdown in more detail by using SBF-SEM that allowed a three dimensional on the zebrafish glomerular filtration barrier in zebrafish (Fig. 1B). The unique GBM pathology was further confirmed in a mouse model with specific knockout of Npnt in podocyte progenitor cells (Npnt -/-;Six2-cre mice) (Fig. 1C).

Conclusions: The results confirm the role of podocytic npnt for proper GBM function and suggests its regulation by podocyte- and glomerular endothelial cell-derived miRs.

Figure 2



TH-PO1061

β1 Integrin Activation and Signaling in Endothelium-Initiated Podocyte Injury

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Background: Integrins are heterodimeric transmembrane proteins that anchor cells to the extracellular matrix but also play a key role as bi-directional (outside-in and inside-out) signaling mediators. Our aim is to determine the activation state and role of podocyte β1 integrins in a transient model of podocyte injury.

Methods: 8-10 week-old mice were injected intraperitoneally with LPS (10 μg/g) or PBS (control) and urine collected prior to and after injection. In another set of experiments, mice were injected with a β1 integrin "blocking" antibody (HMβ, 2.5 μg/g) 20 hours prior to LPS. Albuminuria was measured by ELISA. Mouse kidney tissue was processed for immunohistochemistry. Glomerular isolation was performed for western blotting and RT-PCR.

Results: LPS injected mice had significantly higher albuminuria than controls. In podocytes, β1 integrin activation, FAK and nephrin phosphorylation occurred 18 to 32 hours after LPS injection. Pre-treatment with HMβ1 antibody significantly reduced albuminuria 24 h following LPS, suggesting that activation of podocyte β1 integrin plays

a role in albuminuria. Immunofluorescence confirmed binding of HMβ1 to glomerular endothelial cells and podocytes, suggesting a possible crosstalk between these cells. Since β1 integrin activation can occur due to outside-in and inside-out signaling, we investigated the chronology of events involving endothelial, glomerular basement membrane (GBM) and podocytes. By immunohistochemistry, western blotting and RT-PCR, we found that endothelial and GBM injury preceded β1 integrin activation, nephrin phosphorylation and foot process effacement, suggesting an outside-in β1 integrin activation.

Conclusions: LPS activates β1 integrin on podocytes and leads to FAK and nephrin phosphorylation in vivo. Targeting endothelia/podocyte β1 integrin reduces albuminuria. Changes in glomerular endothelial cells and GBM precede podocyte injury, suggesting that activation of podocyte β1 integrin may be triggered by an outside rather than inside signal in this model of podocyte injury.

TH-PO1062

Podocyte Protective Effects of TRPC5 Inhibitor AC1903 in Human iPSC-Derived Podocytes and Kidney Organoids

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Background: The TRPC5-Rac1 pathway has been shown to induce podocyte injury and loss in two pre-clinical rat models: a transgenic rat FSGS model and a spontaneous hypertensive rat model. The TRPC5 blocker AC1903 protects podocytes in both models. However, less is known about the effect of this compound in rat models that are more easily amenable to drug development programs, such as the puromycin aminonucleoside (PAN)-induced nephrosis model. Furthermore, the effect of AC1903 in human podocytes remains elusive. Here, we aim to investigate the effect of AC1903 in the puromycin aminonucleoside(PAN)-induced nephrosis in rat, as well as in PAN-treated human iPSC-derived podocytes and kidney organoids.

Methods: A single i.p. injection of PAN (50mg/kg) was given to wild-type Sprague-Dawley rats (Male, 4-5 weeks, Charles River). AC1903 was administered twice a day for 7 days after PAN injection. 24-hour urine albumin levels were measured on day 7. Human iPS cells were used to generate podocytes and kidney organoids (according to Subramanian A. et al. 2019 http://dx.doi.org/10.1101/516807). PAN treatment was used to induce human podocyte injury in these in vitro model systems, and the effects of AC1903 were assayed by Western Blotting, immunofluorescence staining and confocal microscopy.

Results: We found that a single i.p. injection of PAN-induced podocyte injury and foot process effacement (FPE) as well as a significant increase in urine albumin levels 7 days after injection. Treatment of proteinuric PAN rats with AC1903 significantly reduced foot process effacement and proteinuria. PAN treatment of human iPSC-derived podocytes and kidney organoids triggered the TRPC5-Rac1 injury pathway leading to ROS production and cytoskeletal dysregulation. These effects were reversed by AC1903, showing for the first time that TRPC5 inhibition benefits human podocytes and kidney organoids.

Conclusions: Taken together, our results confirmed the relevance of the TRPC5-Rac1 pathway in human kidney tissue thus highlighting the potential of this therapeutic strategy for patients.

Funding: NIDDK Support

TH-PO1063

GFB-887, a Small Molecule Inhibitor of TRPC5, Attenuates Proteinuria in Animal Models of FSGS, Minimal Change Disease, and Diabetic Nephropathy

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Background: Focal segmental glomerulosclerosis (FSGS) is a podocytopathy with proteinuria and a high likelihood of progression to end stage renal disease (ESRD). Minimal change disease (MCD) is a podocytopathy resulting in nephrotic syndrome and is frequently refractory to current therapies. Diabetic nephropathy (DN), the most common cause of ESRD worldwide, is also characterized by proteinuria and podocyte loss. The Ca^{2+}-permeable transient receptor potential canonical 5 (TRPC5) channel is a critical mediator of proteinuria. Activation of the TRPC5 pathway in podocytes culminates in activation of Rac1, which is the primary driver of proteinuria in many forms of proteinuric kidney disease. Inhibition of TRPC5 channel activity with tool compounds has been shown to protect against proteinuria and podocyte loss in AT1R transgenic and Dahl salt-sensitive rats.

Methods: We evaluated GFB-887, a potent, subtype-selective TRPC5 inhibitor, in two models of FSGS, the unilaterally nephrectomized (UNx) deoxycorticosterone acetate (DOCA)-salt rat model and the AT1R transgenic rat model with the phenotype accelerated by UNx and continuous administration of angiotensin II at a sub-pressor dose. GFB-887 efficacy was also assessed in the low-dose puromycin aminonucleoside nephrosis (PAN) rat model of MCD and the ZDSD rat model of DN.

Results: Inhibition of TRPC5 by GFB-887 attenuated albuminuria in hypertension-induced FSGS in DOCA-salt rat model without altering blood pressure, and also in the non-hypertensive AT1R rats. In both FSGS models, GFB-887 demonstrated efficacy in a therapeutic context by reducing established albuminuria. GFB-887 also reduced albuminuria in the PAN model of MCD and in the ZDSD model of DN.

Conclusions: GFB-887, a subtype-selective small molecule inhibitor of TRPC5, demonstrated efficacy in reducing proteinuria in animal models of FSGS, MCD and DN.

Funding: Commercial Support - Goldfinch Bio., Inc.

TH-PO1064

Aged TRPC6 KO Mice Have a Novel Renal Phenotype

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Background: Focal segmental glomerulosclerosis is a form of nephrotic syndrome which leads to end stage renal failure. The disease can be genetic or idiopathic and mutations in transient receptor potential cation channel 6 (TRPC6) can cause nephrotic syndrome. Patients with TRPC6 mutations tend not to develop symptoms until later life. TRPC6 KO mice have previously reported no detrimental kidney phenotype, with blood pressure, glomerular morphology and albumin excretion like WT animals. However, these have been studied early in life and to date there has been no study on the effect of TRPC6 KO with ageing. We therefore aged TRPC6 KO mice and looked at their phenotype at 10-16 months.

Methods: An ex vivo glomerular albumin permeability assay developed by our group was used to determine glomerular permeability (Desideri *et al*, 2018). Mouse kidneys were harvested and imaged using an electron microscope to measure the dimensions of the glomerular filtration barrier. Mouse urine was collected by spot collection and the urinary albumin-to-creatinine ratio was quantified.

Results: Aged TRPC6 KO mice were not proteinuric and had normal albumin creatinine ratios. However, we also used a highly sensitive, ex vivo glomerular permeability assay, developed by our group, to look for differences in permeability between aged TRPC6 KO and control mice. Glomerular permeability was significantly ($P< 0.0001$) increased in older KO mice (6.615e-007±4.002e-008 cm/s) compared to age-matched wild type controls (2.643e-007±5.332e-009 cm/s), suggesting a pathological effect of TRPC6 KO. An increased width of both ordinary ($P=0.0054$) and anchoring ($P=0.022$) podocyte foot processes was observed in the aged TRPC6 KO mice (ordinary (0.35±0.01 vs 0.27±0.01 μm) and anchoring (0.51±0.05 vs 0.29±0.03 μm)) compared to control mice (ordinary 0.27±0.01 μm) and anchoring (0.29 ± 0.03 μm)). There were also significantly fewer foot processes in the TRPC6 KO mouse $P=0.046$). The GBM thickness was increased ($P=0.018$) from 0.29±0.02 μm in control to 0.36±0.005 in KO animals, demonstrating that old TRPC6–/– mice have morphological changes on the structure of the GFB.

Conclusions: We have demonstrated that in a mouse model, knockout of TRPC6 results in increased glomerular permeability and alterations to the structure of the glomerular filtration barrier in aged mice. This phenotype correlates with disease progression in human patients.

TH-PO1065

Pharmacologically Stimulating Nitric Oxide-Soluble Guanylate Cyclase Signalling to Prevent Podocyte Injury

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Background: The effects of nitric oxide (NO) on podocytes are not known. We hypothesize that NO production by glomerular endothelial cells (GEnC) acts on podocytes as a protective paracrine factor in the glomerulus, thereby preventing podocyte injury. We propose a mechanism in which NO-mediated soluble guanylyl cyclase (sGC) activation results in enhanced cGMP synthesis and reduced expression/activity of the Ca^{2+}-permeable Transient Receptor Potential Channel 6 (TRPC6), thereby inhibiting deleterious podocyte signalling processes. Several market approved drugs for non-renal disorders act on sGC. We aim to investigate glomerular NO-sGC signalling and the potential of repurposing sGC activators to prevent podocyte injury.

Methods: *In vitro* experiments were performed using conditionally immortalized GEnC and podocytes. NO production was visualized using the NO sensitive dye DAF-FM diacetate. Podocyte injury was induced with 0.25μg/mL adriamycin for 24hrs, with or without co-exposure of NO-donor SNAP (200μM) or sGC activators Cinaciguat (2μM) and Riociguat (20μM).

Results: Two forms of nitric oxide synthases (NOS; i.e. iNOS and eNOS) were expressed by GEnC and podocytes, whereas both cell types produced NO. GEnC particularly produced NO under (physiological) flow conditions. Interestingly, neuronal NOS (nNOS) was solely expressed by podocytes when injury was induced. All sGC subunits were expressed by podocytes. Stimulation of sGC via either SNAP or Riociguat elevated cGMP production in podocytes. Importantly, SNAP, Cinaciguat and Riociguat all reduced adriamycin-induced TRPC6 overexpression in human podocytes. No additional reduction of adriamycin-induced TRPC6 overexpression was observed when SNAP was co-administered with either Riociguat or Cinaciguat.

Conclusions: Our data supports the hypothesis of a paracrine NOS-NO-sGC axis between GEnC and podocytes. Moreover, sGC stimulation via SNAP or through repurposing drugs that activate sGC exert a protective effect on podocytes. Glomerular NO production might therefore play an important role in preserving the integrity of the glomerular filtration barrier. When experimental animal models for glomerular disease will confirm our *in vitro* findings, we will design clinical studies to evaluate the therapeutic effect of sGC activators to treat glomerular diseases.

Funding: Government Support - Non-U.S.

TH-PO1066

Evaluation of the Human FSGS-Inducing ANLN R431C Variant in CRISPR-Cas9 Mice

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Background: We previously reported that the *ANLN R431C* variant causes focal segmental glomerulosclerosis (FSGS) and induces endoplasmic reticulum (ER) stress induced apoptosis in cultured human podocyte cells. To further understand the molecular mechanisms underlying disease, we examined the phenotypic effects of this variant *in vivo* using a CRISPR-Cas9 generated mouse model.

Methods: We generated an orthologous *ANLN R431C* knock-in point mutation in mice (*R426C*) using CRISPR-Cas9 technology. $ANLN^{+/+}$, $ANLN^{R426C/+}$, $ANLN^{R426C/R246C}$ mice were challenged with a sub-therapeutic dose of nephrotoxic antibodies at 22 weeks and evaluated for 5 weeks post injection. Kidney sections were evaluated by two independent pathologists, blinded to genotype, through PAS staining and electron microscopy.

Results: When challenged with nephrotoxic antibodies in a kidney disease resistant genetic background, $ANLN^{R426C/R246C}$ mice displayed increased proteinuria compared to $ANLN^{R426C/+}$ (p=0.049) and $ANLN^{+/+}$ (p=0.0064) mice. Light microscopy evaluation of $ANLN^{R426C/R246C}$ kidney sections revealed increased protein casts (p<0.0001), as well as larger (p=0.018) and more sclerotic (p=0.0005) glomeruli when compared to wildtype littermates. Semi-quantitative analysis using electon microscopy revealed increased podocyte effacement and ER stress including evidence of dilated cisternae, damaged mitochondria, and abnormal autophagy in the $ANLN^{R426C/R246C}$ mice. Additionally, cultured primary $ANLN^{R426C/R246C}$ podocytes displayed increased apoptosis compared to $ANLN^{+/+}$ podocytes (p=0.049).

Conclusions: $ANLN^{R426C/R246C}$ mice display increased susceptibility to glomerular injury when compared to $ANLN^{+/+}$ littermates. Additionally, $ANLN^{R426C/R246C}$ mouse podocytes displayed similar ER stress and apoptotic phenotypes to cultured $ANLN_{R431C}$ human podocytes, lending further credibility to these results. Further evaluation of this mouse line in a genetic background that is more kidney susceptible to kidney disease should provide a necessary model to evaluate potential therapeutic compounds that have successfully rescued apoptotic phenotypes in cultured $ANLN_{R431C}$ human podocytes.

Funding: NIDDK Support

TH-PO1067

The Drosophila Nephrocyte Model of Podocyte Slit Diaphragms Reveals a Role for the Basal Polarity Complex in Slit Diaphragm Formation

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Background: The podocyte slit diaphragm (SD) plays a key role in glomerular filtration. Mutations in the apical polarity protein Crb2 are present in some cases of steroid-resistant nephrotic syndrome. Animal models indicate an important role for apical polarity proteins in podocyte polarity and SD formation, suggesting cell polarity is a central aspect of podocyte development and function. Surprisingly however, mutations in basal polarity proteins do not cause significant defects in mouse podocytes, even though they express basal polarity proteins. Thus, it is difficult to interpret the relationships between the polarity complexes in podocyte development and SD formation.

Methods: To explore the potential role of the basal polarity proteins in SD formation, I performed a genetic analysis of the basal polarity proteins in SD formation and SD protein localization using the Drosophila nephrocyte, a popular model for podocyte SDs.

Results: I found that all of the canonical basal polarity proteins (Dlg, Scrib, Lgl, and Par-1) play important roles in the localization of nephrocyte SD proteins (Nephrin, Neph1, ZO-1). Loss of Dlg was also associated with dramatically reduced nephrocyte SD number and SD mislocalization; I am currently examining the role of the other basal proteins on SD formation. Loss of Dlg also appears to perturb Crb localization, suggesting the basal and apical polarity complexes function together in nephrocyte SD formation. Importantly, genetic interaction studies suggest the basal proteins work in concert to direct the formation of the nephrocyte SD. Genetic interaction studies also identified an important relationship between the basal polarity proteins and the SD-associated polarity protein Par-3, as well as the SD adaptor protein ZO-1.

Conclusions: Genetic analysis of the Drosophila nephrocyte has revealed a key role of the basal polarity proteins in SD formation. The genetic interaction studies are consistent with these proteins working as a conserved module, determining the localization of core SD components, likely through their interactions with proteins such as Par-3 and ZO-1. We are continuing to define the mechanism by which the basal polarity complex contributes to SD formation, their relationship with apical polarity proteins like Crb, and extending our analysis of the basal polarity proteins to a vertebrate podocyte model.

TH-PO1068

Functional Analysis of a Novel FSGS-Associated ACTN4 Mutation in Podocytes and Drosophila Melanogaster

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Background: The actin cytoskeleton is a central element of podocyte morphology and homeostasis during health and disease. Alpha-actinin4 (ACTN4) has been shown to play an important role in podocyte architecture and function and mutations in the *ACTN4* gene are associated with focal segmental glomerulosclerosis (FSGS). Here, in a pediatric patient presenting with steroid resistant nephrotic syndrome (SRNS) and FSGS, gene panel sequencing of genes associated with rare kidney diseases identified an undescribed *de novo*, potentially disease-causing variant of *ACTN4* that was not found in available genome or exome databases. Aim of this study was to characterize this variant and elucidate its pathogenic potential for podocyte homeostasis.

Methods: We analyzed patient-derived primary urinary cells (PUCs) as well as cultured human podocytes that express the novel ACTN4 mutant. Results were obtained using quantitative proteomic analysis as well as cell biology studies *in vitro*. In order to perform *in vivo* studies, we exploited *Drosophila melanogaster* genetics and characterized Actinin loss in nephrocytes, podocyte-like cells of the fruit fly. Here, rescue experiments with human *ACTN4* wildtype, other previously described, pathogenic *ACTN4* mutations as well as the novel variant will give further insight into its pathogenicity.

Results: Mapping the PUC proteome, we quantified more than 3000 proteins as compared to healthy controls. PUCs of the index patient showed high abundance of DNA-damage response associated proteins, and depletion of the known ACTN4 interactor ZNF385. Cultured human podocytes overexpressing the ACTN4 mutant present with disturbed appearance and localization of the actin cytoskeleton and first experiments suggest the ACTN4 mutant to impact cell viability. Knockdown of *Drosophila* Actinin in nephrocytes leads to a severe functional phenotype, as cells no longer perform proper filtration. Morphologically, we could show that localization of the nephrocyte diaphragm is perturbed, suggesting false architecture of the nephrocyte.

Conclusions: Our results indicate that the identified novel *ACTN4* mutation leads to a strong phenotype *in vitro*, likely making it a disease-causing mutation. The *in vivo* data underline the importance of actinin in nephrocyte architecture and function.

TH-PO1069

Using Drosophila Nephrocytes to Identify Specific States of Podocyte Disease Correlated with a Dysregulation of Insulin-Dependent Signals

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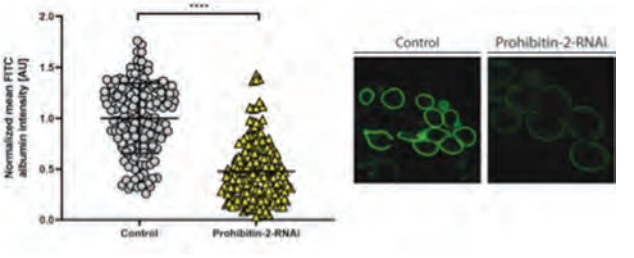
Background: Insulin signaling with its relation to metabolic cascades, including the regulation of anabolic and catabolic processes via mTOR and the FoxO transcription factor, is one of the most complex signaling networks, playing a key role in podocyte health and disease. This study aims to test whether Drosophila nephrocytes can be used to efficiently screen for dysregulated insulin signaling pathways in different forms of steroid resistant nephrotic syndrome (SRNS).

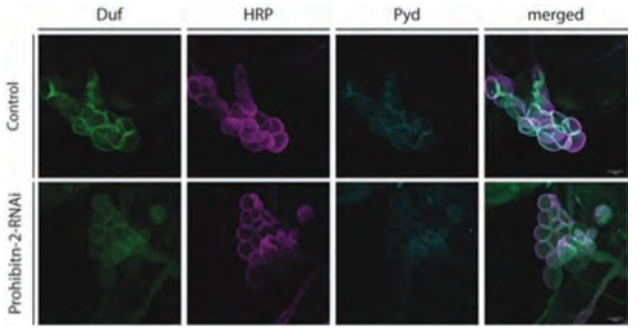
Methods: Several mutations that are known to cause SRNS have been characterized in Drosophila and can be modeled using the GAL4-UAS-system. These mutations lead to a dysfunction in different cellular compartments, e.g. the mitochondria. Here, we use the Drosophila nephrocytes to screen for dysregulated insulin signaling in specific states of podocyte disease. The phenotypic characterization is based on Tracer-Uptake-Assays, IF-staining and electron microscopy, while a dysregulated insulin signaling can be observed via qPCR, Western Blot and a FoxO-mCherry-reporter line.

Results: The correlation between mitochondrial dysfunction and hyperactive insulin signaling, based on a cell-specific Prohibitin-2-knockdown, could be confirmed in *Drosophila* nephrocytes. While the Prohibitin-knockdown lead to a functional phenotype with a reduced uptake of FITC-albumin, there were no obvious morphological changes. This phenotype could be rescued by an inhibition of the mTOR kinase via rapamycin.

Conclusions: Drosophila nephrocytes show a clear correlation between mitochondrial dysfunction, initiated by a Prohibitin-knockdown, and hyperactive insulin signaling. Consequently, the nephrocytes can be used as an efficient *in vivo* model to characterize insulin-dependent signaling pathways in podocytes.

Funding: Government Support - Non-U.S.





TH-PO1070

Linking Polarity Signaling and Mechanotransduction in Drosophila Nephrocytes

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Background: Polarity signaling through the aPKC-Par polarity complex is essential for the development and maintenance of the podocyte architecture and the filtration function of the kidney. Despite its well-established role in aPKC-mediated signaling, neither loss of Par3A nor Par3B causes a glomerular disease phenotype. However, genetic depletion of both, Par3A and Par3B resulted in severe proteinuria and renal failure.

Methods: We utilized *Drosophila* nephrocytes to study the functional role of Par3 proteins in greater detail. Nephrocytes are the homolog cells of mammalian podocytes and express the Par3A/B homolog Bazooka at the nephrocyte diaphragm.

Results: Nephrocyte-specific depletion of Bazooka resulted in disturbed nephrocyte diaphragm morphology and severe filtration defects, indicating the conservation of this important pathway throughout species. To study the underlying mechanisms, we performed proteomic analysis of Bazooka-depleted nephrocytes and identified an upregulation of focal and cell adhesion proteins, actin-associated proteins and mechanosensors such as Cher (Filamin) and Rhea (Talin). The putative mechanosensor protein Filamin was identified to be upregulated upon injury in podocytes as well. As podocytes face constant mechanical stress due to blood pressure and filtration, we further investigated the functional role of the mechanosensor protein Cher in nephrocytes. Interestingly, loss of Cher did not cause morphological changes, but resulted in a significantly increased filtration function. Proteom data from Cher depleted nephrocytes revealed an upregulation of ECM associated proteins such as Viking (Col4A) and Mucin and a downregulation of proteins involved in cell adhesion processes and actin-binding.

Conclusions: Our study thereby provides the first data linking polarity signaling and mechanotransduction in nephrocytes.

TH-PO1071

Rab11-Dependent Recycling Maintains Nephrin at the Slit Diaphragm

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Background: A role of endocytosis for podocyte biology has previously been proposed. In humans, until recently no direct endosomal regulator had previously been implicated in nephrotic syndrome. Whole exome sequencing identified mutations in Rab5 and Rab11 regulatory proteins resulting in congenital nephrotic syndrome and FSGS. Rab5 and Rab11 are expressed ubiquitously, suggesting perturbation of trafficking of podocyte-specific proteins as one potential mechanism for podocyte-restricted phenotype. We reported deletion of nephrin in an adult mature glomerulus, a small fraction (10-15%) of nephrin remains at the membrane and is sufficient to maintain the slit diaphragm for 4-6 week. In vitro studies have suggested that membrane bound nephrin undergoes endocytic recycling. We hypothesized that in our model recycling is responsible for maintenance of nephrin at the membrane following nephrin deletion.

Methods: Standard biochemical and cell biology techniques were used to analyze kidneys from knockout mice. Cre-loxP system was used to generate podocyte specific deletion of nephrin, VPS34 and Rab11.

Results: Combined deletion of nephrin and VPS34 results in an earlier phenotype compared to deletion of nephrin or vps34 alone. Immunogold EM analysis reveals accumulation of Nephrin in vesicles suggesting involvement of Vps34-dependent endocytic pathway in nephrin's maintenance at the slit diaphragm. As VPS34-generated PI3P affects trafficking to early endosome as well as recycling endosomes we generated a mouse model where rab11a and rab11b are deleted in a podocyte-specific manner in an adult mice. Deletion of rab11b alone does not result in a phenotype, whereas combined deletion of rab11a and rab11b results in development of proteinuria at 4-6 week following deletion. Simultaneous deletion of nephrin/rab11a/rab11b results in an earlier phenotype where mice develop proteinuria at 1 week following deletion along with foot process spreading. Analysis of nephrin at the membrane indicates a faster decline following deletion of rab11a/b.

Conclusions: Simultaneous deletion of Rab11 and nephrin results in an earlier phenotype and shortens nephrin's half life at the membrane. Our model provides us with mechanistic insights into human mutations where perturbation of endosomal regulatory proteins result in proteinuric kidney disease.

Funding: NIDDK Support

TH-PO1072

Targeting Defective Trafficking of Slit Diaphragm Protein in INF2-Related Podocytopathy and FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) caused by mutations in INF2 is characterized by mistrafficked nephrin, which comprises the slit diaphragm (SD) of podocytes by its extracellular domain, suggesting INF2 plays an important role in maintaining the surface transport of INF2. This hypothesis is supported by a zebrafish model in which INF2 knockout led to glomerular dysplasia with mistrafficked nephrin, and INF2 R218Q knockin mice which showed defective recycling of nephrin and recovery of the SD following protamine perfusion. This study is to delineate this newly recognized role of INF2 in regulating the trafficking of nephrin, and how it is disrupted by FSGS-causing mutations.

Methods: By performing a yeast 2 hybridization screen, I found the interaction of INF2 with signaling molecules involved in vesicle trafficking pathways. Their interactions with wildtype or FSGS-causing mutants of INF2 were analyzed using yeast mating and co-IP. Podocytes with INF2 knockout or R218Q knockin were treated with antagonists for these pathways, and the trafficking of nephrin was studied by surface biotinylation and fluorescent based trafficking assays, live cell imaging with analysis using KymographClear, KymographDirect and TrackMate software.

Results: Yeast mating and Co-IP demonstrated the interaction of INF2 with mDia (a Rho effector), Dynein light chain 1 (Dynll1), Nipsnap3a (a SNARE protein), molecules involved in cytoskeleton regulation and lipid raft dependent vesicle trafficking. The interactions were disrupted by FSGS-causing mutations of INF2, suggesting the dysregulated pathways by INF2 mutants contributed to the pathogenesis of FSGS. Podocytes with INF2 knockout or R218Q knockin showed impaired nephrin recycling, which was rescued by targeting these pathways using Rho inhibitor (C3 transferase), Dynein inhibitor (Ciliobrevin) or lipid raft sequestrator (Nystatin).

Conclusions: INF2 plays a key role in maintaining the functional trafficking of nephrin by modulating 1) Rho/mDia signaling that halts vesicle movement; 2) Dynein mediated retrograde transport; 3) Lipid raft dependent vesicle trafficking. This role of INF2 can be disrupted by FSGS-causing mutations, leading to mistrafficked nephrin and disintegrity of SD. The dissection of the dysregulated pathways underlying the mistrafficked nephrin will provide new therapeutic targets for INF2 related podocytopathy and FSGS.

Funding: NIDDK Support

TH-PO1073

Inhibition of Kynurenine 3-Monooxigenase (KMO) Alters NAD Balance and Mitochondrial Function in Murine and Human Glomerular Cells and Contributes to Proteinuria in Zebrafish

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Background: KMO is an enzyme of the kynurenine pathway (KP) and as such it is key for tryptophan (trp) catabolism. KMO uses kynurenine (kyn) as a substrate and participates in the production of important bioactive metabolites. Systemic KP dysregulation has been linked to a variety of pathologies, including CKD. Since the enzymes of the KP are expressed in the kidney, we aim to describe the effects of their dysregulation on glomerular cells.

Methods: KMO inhibition was performed in a transgenic zebrafish line that facilitates the detection of proteinuria. Embryos were treated with a KMO inhibitor or kyn starting at 48hpf. At 96hpf the phenotype was recorded and samples were collected for metabolite analysis by mass spectrometry. Since KMO is located in the mitochondria and participates in the production of NAD, mouse parietal epithelial cells (PEC), as well as human and murine podocytes (POD) were incubated with a KMO inhibitor; the levels of NAD^+, NADH and mitochondrial membrane polarization were determined. Alterations in the bioenergetics parameters were also assessed by measuring the oxygen consumption rate after KMO inhibition.

Results: Our results show that inhibition of KMO leads to the accumulation of upstream kynurenine metabolites in the treated larvae. Additionally, proteinuria and edema were observed after KMO inhibition, in line with our previous results from morpholino mediated knockdowns. Treating the larvae with exogenous kyn also leads to mild proteinuria. In vitro data show that KMO inhibition reduces the NAD^+/NADH ratio in POD, and leads to mitochondrial depolarization in POD and PEC. A reduction in spare respiration, coupling efficiency and an increase in proton leak accompanied the mitochondrial phenotype in POD. We also show that glomerular cells are capable of taking up kyn from the media, suggesting that kyn is not only relevant as a biomarker, but may directly contribute to disease etiology.

Conclusions: Taken together our results highlight the importance of trp catabolism via the KP within the context of renal cell biology, where a reduction in KMO activity alters the energy metabolism of POD and leads to kyn metabolite imbalances that ultimately may impact the glomerular filtration barrier.

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TH-PO1074

Sulfatases, in Particular SULF1, Are Important for the Integrity of the Glomerular Filtration Barrier in Zebrafish

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Background: 6-O-endosulfatases (sulfs) are important enzymatic components involved in the regulation of heparan sulfate by altering the sulfatation pattern. Specifically in the kidney, sulfs have been implicated in the glomerular podocyte-endothelial cell crosstalk and in the preservation of the glomerular filtration barrier (GFB) in different mouse models. Since it has been shown that in zebrafish larvae, Sulf1, Sulf2a, and Sulf2b are expressed in the pronephric kidney we set out to establish if a reduction in sulf expression leads to GFB dysfunction.

Methods: To evaluate the integrity of the GFB, we measured a GFP-tagged vitamin D binding protein derived from *Tg(l-fabp:eGFP-DBP)* zebrafish in the retinal vessel plexus of the zebrafish larvae at 96 hpf. Sulf-deficiency was induced using different morpholinos. The integrity of the GFB was evaluated by electron microscopy. Paraffin sections of sulf-deficient larvae were analyzed using immunofluorescence microscopy. Dextran microinjections and *in vivo* confocal imaging of the vasculature using *Tg(flk:mcherry)* larvae were carried out.

Results: Here, we show that a reduced sulf expression following MO-knockdown in zebrafish larvae promotes damage to the GFB leading to renal plasma protein loss from the circulation. Moreover, a combined knockdown of Sulf1, Sulf2a and Sulf2b is associated with severe morphologic changes including narrowing of the fenestration between glomerular endothelial cells as well as thickening of the glomerular basement membrane, and podocyte foot process effacement; suggesting that glomerular damage is an underlying cause of the circulatory protein loss observed after MO injection. Additionally, we show that a decrease in sulf expression reduces the bioavailability of VegfA in the glomerulus of the pronephros, which may contribute to the structural changes observed in the glomeruli of morphant fish. Furthermore, consistent with previous results, knockdown of the sulfs is associated with arteriovenous malformations in particular in the tail region of the larvae.

Conclusions: Overall, taken together our results suggest that 6-O-endosulfatases are important in the preservation of GFB integrity and a reduction in their expression levels induces phenotypic changes that are indicative of renal protein loss.

TH-PO1075

Implementation of an Artificial Neural Network for Automated Podometrics in Human Kidney Specimens

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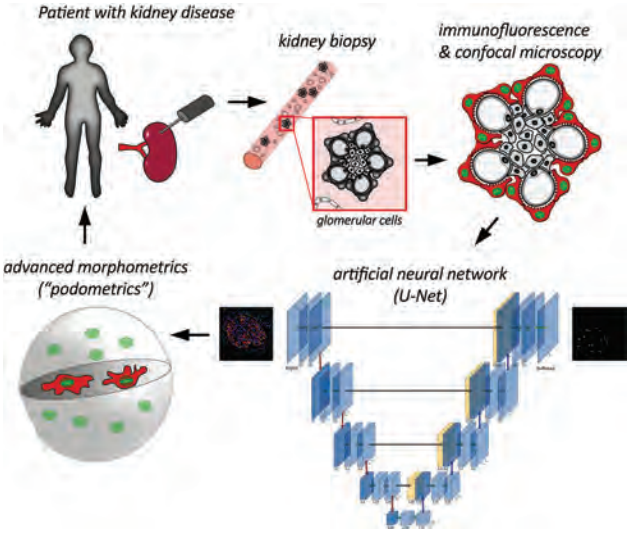
Background: Advanced morphometrics to study podocytes (podometrics) may provide robust readouts for diagnosis, prognosis and management of patients with glomerular diseases. However, their clinical implementation is limited by their time-consuming nature. Thus, artificial neural networks emerge as interesting tools to bring podometrics closer to the bedside.

Methods: Ground truth data was determined in 318 images (144 training, and 174 testing), acquired using immunofluorescence and confocal microscopy. An artificial neural network (U-Net) was implemented, optimised via a systematic grid search and compared to an automatic ImageJ-based segmentation tool. Dice scores (pixel-based), F1 scores (object-based), and spearman correlations were calculated to validate each method against the ground truth. Model-based stereology podometrics were determined using segmented data.

Results: In nephrectomy samples, U-Net provided higher Dice and F1 scores than those obtained with ImageJ ($P<0.0001$), with stronger correlation indices for U-Net ($R=0.94-0.95$, $P<0.0001$) compared to ImageJ ($R=0.61-0.66$, $P<0.01$). In ANCA-associated glomerulonephritis, Dice and F1 scores were also higher in U-Net ($P<0.0001$) compared to ImageJ with stronger correlation indices in U-Net ($R=0.91-0.94$, $P<0.0001$) compared to ImageJ ($R=0.59-0.79$, $P<0.01$).

Conclusions: Our optimised artificial neural network (U-Net) provides readouts that are comparable to manual segmentation and superior to conventional segmentation tools, even in the context of glomerular disease. These findings bring us one step closer to the use of automatic podometrics as a clinical instrument.



We have implemented an artificial neural network to automatically extract the data required for the estimation of podometrics in clinical samples.

TH-PO1076

Single-Cell Transcriptome Profiling of the Mouse and Human Glomerulus

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Background: Though the mouse is widely used to model human glomerular diseases, systematic transcriptome comparison of principal cell types forming the glomerular filtration barrier between two species is lacking. To address this question, we generated single cell RNA sequencing (scRNA-seq) libraries from mouse and human glomerular cells.

Methods: Mouse glomeruli were isolated from 8 wt adult C57BL/6J mice via magnetic bead perfusion. Human healthy glomeruli were purified from 8 donor kidney biopsies via a sieving procedure. Viable single cells of enriched glomeruli were unbiasedly sorted to 384-well plates and scRNA-seq was performed using the Smart-seq2 protocol. For data comparison between 2 species, we focused on podocytes, glomerular endothelial cells (GEC) and mesangial cells (MC).

Results: In total, 2416 mouse cells and 788 human cells passed quality control. Unsupervised clustering of these cells identified Nphs1$^+$ podocytes, Kdr$^+$ GECs, Pdgfrb$^+$ MCs and other cell types such as tubular cells and immune cells. Interestingly, Cldn1$^+$ mouse parietal epithelial cells were captured. Overall comparison showed more genes detected in podocytes than other two cell types. In podocytes, about 70 genes were identified as human-specific, of which half of them showed restricted expression in podocytes. Most human-specific genes have not been implicated in the podocyte function. However, important exceptions were detected, such as PLA2R1 encoding a major autoantigen of human membranous nephropathy, which was absent in mouse podocytes. On the other hand, only 5 genes were identified as mouse-specific. In GEC and MC, < 20 genes showed apparent human-specificity and only 3 genes mouse-specificity. Differential species-specific cell expression patterns for selected genes were validated by analyzing bulk RNA-seq data, qPCR and immunostaining.

Conclusions: Our results highlight differences between mouse and human glomerular molecular signatures that are essential to design and interpret translational studies.

Funding: Commercial Support - AstraZeneca, Government Support - Non-U.S.

TH-PO1077

The Critical Role of Rho Associated Coiled-Coil Containing Protein Kinase 2 for the Enhancement of Actomyosin Contractility in Podocytes

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Background: The highly differentiated podocytes elaborate interdigitated foot processes (FP) to cover the glomerular capillaries and form slit diaphragm (SD) for blood filtration. Therefore, podocytes adhere tightly to glomerular basement membrane (GBM) and generate RhoA/ROCK-mediated contraction force to tolerate the filtration pressure. Two ROCK isoforms, ROCK1 and ROCK2, were identified in mammal. In this study, we characterized that ROCK2 is critical for the enhancement of contractility in cultured podocytes.

Methods: The conditionally immortalized mouse podocytes were used in this study. By Western blotting and immunostaining, the ROCK signaling and cell architecture were detected. ROCK kinase activity was inhibited by the treatment of cells with Y27632 and ROCK2 gene was knockout by CRISPR/Cas9 method.

Results: After temperature switch, the expression of podocyte differentiation marker synaptopodin was increased. The formation of focal adhesions (FA), stress fibers and the

SD-like protrusions labelled by ZO-1 staining were also observed. We found that ROCK2, but not ROCK1, was significantly activated in differentiated cells. The phosphorylation status of MLC and ERM, two ROCK downstream substrates, were also increased. treatment of cells with Y27632 diminished both the phosphorylation of MLC and ERM and the formation of FA and stress fibers. We then generated ROCK2 knockout podocytes by CRISPR/Cas9 and found that loss of ROCK2 decreased MLC phosphorylation, while ERM phosphorylation was not affected. In addition, ROCK2-dificiency also diminished the formation and stress fibers and cellular protrusions.

Conclusions: Our results suggest that ROCK2 is critical for the enhancement of actomyosin contractility in podocytes. The regulation of ROCK2 activation shall plays an important role in the maintenance of cell adhesion and cytoskeletal architecture for podocyte function.

Funding: Government Support - Non-U.S.

TH-PO1078

Vasohibin 1 Is Essential for the Post-Transcriptional Modification of α-Tubulin on Microtubules in Podocytes

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Background: Microtubules in podocytes are important for maintaining the characteristic cell shape as well as normal intracellular transport and dynamic morphologic alterations. The microtubule functions are affected by various post-transcriptional modifications on tubulin proteins. Recent studies have shown that vasohibin-1 (VASH1), an endothelium-derived angiogenesis inhibitor, has an enzymatic activity that catalyzes the detyrosination of α-tubulin in neurons and cancer cells. In the present study, we examined the roles of VASH1 in the modification of α-tubulin and microtubules in podocytes.

Methods: We used B6 wild-type and *Vash1*$^{+/-}$ mice to confirm the localization of detyrosinated (detyr) α-tubulin in the kidney. In addition, 8-week-old female BALB/c wild-type mice received single intravenous injection of 15mg/kg of adriamycin (ADM) or saline to induce podocyte injury and proteinuria. Finally, we cultured immortalized human podocytes, and VASH1 knockdown was performed by siRNA transfection.

Results: In wild-type mice, detyr-α-tubulin was shown to be restricted in podocytes by double immunofluorescence with podocalixyn. The detyr-α-tubulin staining was markedly attenuated in *Vash1*$^{+/-}$ mice. ADM-induced podocyte injury in BALB/c mice led to massive albuminuria and decreased detyr-α-tubulin staining in glomeruli compared to the control group, suggesting the detyrosination of α-tubulin could be altered by morphological changes of podocytes. *In vitro* experiments, immunoblot analysis demonstrated that detyr-α-tubulin remarkably increased in differentiated podocytes compared to undifferentiated cells. In addition, VASH1 knockdown by transfection of siRNA in differentiated podocytes significantly inhibited the detyrosination of α-tubulin.

Conclusions: These results indicate that VASH1 expression is necessary for the detyrosination of α-tubulin in podocytes, and may be involved in the regulation of their microtubule function.

Funding: Government Support - Non-U.S.

TH-PO1079

Transcriptional Reprogramming by Wilms Tumor 1 and FoxC2 Mediates a Repair Response During Podocyte Injury: Studies in Mice and Human Kidney Organoids

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Background: We previously reported that WT1 is a master regulator of gene expression in podocytes, binding nearly all genes known to be crucial for maintenance of the glomerular filtration barrier. We have now performed ChIP-Seq for FoxC2 transcription factor that also binds nearly all the same target genes as WT1, suggesting that WT1 and FoxC2 act as a cell lineage-specific transcriptional activating complex in podocytes.

Methods: We used Adriamycin (ADR)-induced podocyte injury as a model for human Focal Segmental Glomerulosclerosis. WT1 and FoxC2 binding to enhancers and the transcriptional start sites of the *Nphs2* and *Synpo* genes was determined by direct ChIP-qPCR at multiple time points after ADR-induced injury, using both Balb/C and mTmG Nphs2-Cre mice. We also integrated RNA-seq and WT1/FoxC2 ChIP-seq data sets to determine how transcriptional reprogramming occurs during the course of podocyte injury.

Results: WT1 and FoxC2 transiently increase after injury, before decreasing to low levels. *Synpo* and *Nphs2* mRNA levels also transiently increase in response to increases in WT1 and FoxC2 binding. Interestingly, distinct patterns of WT1 and FoxC2 binding were observed dependent on the enhancer or transcriptional start site being interrogated. The transient increased expression after injury was also observed in human kidney organoids, allowing us to identify a window of opportunity for treating glomerular disease in humans. ChIP-seq studies identified sets of WT1 binding sites only bound after treatment with ADR suggesting that WT1 may acquire new target genes during the response to injury. Since transcription factors DNA binding is modulated by chromatin accessibility, we used immortalized podocytes as an *in vitro* model to study epigenetic reprogramming after treatment with ADR or knockdown of *Wt1*. Both treatments result in conversion from activating to repressive histone marks at WT1/FoxC2 bound-enhancers.

Conclusions: Our results demonstrate that WT1 and FoxC2 mediate transcriptional reprogramming during the course of podocyte injury, and specifically that decreased levels of WT1 result in epigenetic silencing of gene expression during the course of podocyte injury.

Funding: NIDDK Support

TH-PO1080

The Ephrin Signaling Pathway Is a Novel Target of Wt1-Induced Gene-Regulatory Reprogramming in FSGS Progression

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Background: While mutations in podocyte transcription factors (TF) can cause FSGS, gene-regulatory processes governed by TFs in glomeruli are unclear. Here, we investigate gene-regulatory reprogramming due to Wt1 depletion in an early and progressed stage of murine FSGS using an epigenomic and transcriptomic approach.

Methods: The Wt1 heterozygous null mouse model (Wt1-hetdel) and littermate controls were used for RNAseq of glomeruli in early proteinuric and progressed sclerotic stages of disease, as well as ChIPseq for Wt1 at an early disease stage. Proteomics and STED microscopy were used to investigate glomerular protein abundance and ultrastructure.

Results: Wt1-hetdel mice show a consistent FSGS phenotype with proteinuria starting at age 4 wks progressing to sclerosis at age 12 wks. Transcriptomic profiling of glomeruli by RNAseq discriminated 4wk from 12wk FSGS. Signaling pathway impact analysis of RNAseq data identified pathways predominantly dysregulated in early vs late FSGS disease phases. The ephrin signaling pathway was exclusively dysregulated in the sclerotic stage of FSGS. Integrative analysis of Wt1 ChIPseq data from healthy and diseased mice and RNAseq data confirmed differential binding of Wt1 at differentially expressed genes relevant to ephrin signaling indicative of Wt1-mediated gene-regulatory reprogramming of ephrin pathway genes. Exclusively in progressed FSGS, targeted proteomics showed reduced protein abundance of EphrinB1, an interactor of nephrin and key molecule to podocyte ephrin signaling. Ultrastructural investigation of EphrinB1 using STED microscopy confirmed co-localization of EphrinB1 with podocin, with clustering of EphrinB1 in presumed signaling hubs. EphrinB1 signals were specifically reduced in sclerotic and preserved in non-sclerotic glomerular areas, respectively.

Conclusions: Transcriptomic profiling differentiated signaling pathways predominantly dysregulated in the proteinuric vs. sclerotic stage of FSGS. Integration of transcriptomics with glomerular Wt1-ChIPseq provided unbiased insight into contribution of Wt1 to FSGS disease progression. The ephrin signaling pathway and specifically EphrinB1 were identified as a differentially expressed in progressed FSGS, affected by Wt1-mediated reprogramming, and reduced specifically in sclerotic glomeruli on the protein level

Funding: Government Support - Non-U.S.

TH-PO1081

The JAK-STAT Pathway in Podocytes Is Activated and Modulated by Monomeric Cardiotrophin-Like Cytokine Factor 1 (CLCF1)

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Background: We detected CLCF1 in recurrent FSGS plasma and showed that it increased glomerular permeability (P_{alb}). Cytokine Receptor-Like Factor 1 (CRLF1) was not detected although it may be secreted and circulate as a heterodimer with CLCF1. CLCF1-CRLF1 or JAK2/STAT3 inhibitors blocked the increase in P_{alb} induced by FSGS serum or by monomeric CLCF1 (Sharma et al, Trans Res 2015;166:384-398). A role for JAK-STAT signaling is supported by its activation in PBMC and kidney tissue of FSGS patients (Tao et al, 2018 Kid Int 94:795-808). The current studies aimed to determine the podocyte effects of CLCF1, CLCF1-CRLF1 and JAK inhibitors on the JAK-STAT system.

Methods: Immortalized murine podocytes were treated with CLCF1, CLCF1-CRLF1 or JAK inhibitors Tofacitinib (Tofa), Baricitinib (Bari) and Ruxolitinib (Rux). Total and phosphorylated (p) STATs and JAKs and expression of SOC and PIAS were analyzed using SDS-PAGE and Western blotting with β-actin as the loading control. Expression of CLCF1 receptor sub-units was determined using RT-qPCR and immunofluorescence.

Results: Podocytes express the components of the CLCF1 receptor complex, CNTFRα, gp130 and LIFRβ, and express (in order of protein expression) JAK2>JAk3>JAK1, and STAT3>STAT1>STAT6 >STAT5, as well as SOCS isoforms (3>2>1) and PIAS (3>4>1). CLCF1 (10-1000ng/mL) upregulated pJAK2 (max at 100ng/mL CLCF1) and pJAK3 (max at 1000ng/mL CLCF1) (each P<0.001). Tyr1007 was the major site of phosphorylation on JAK2. CLCF1 (10-1000ng/mL) upregulated pSTAT3 ^{Tyr705} in a time-dependent manner (max at 100ng/mL CLCF1, 15 min, P<0.001). Heterodimer CLCF1-CRLF1 attenuated CLCF1-induced phosphorylation of JAK2^{Tyr1007} and STAT3^{Tyr705} in a dose-dependent manner (max at 1:2 mol, P<0.001). JAK inhibitors Tofa, Bari, and Rux also attenuated CLCF1-induced pSTAT3^{Tyr705}. SOCS were upregulated by CLCF1 (100ng/mL) in the order SOCS3>SOC2 (P<0.001). CLCF1 (100ng/mL, 15 min) upregulated only PIAS3.

Conclusions: Monomeric CLCF1 influences FSGS-associated podocyte pathophysiology through JAK-STATs and their modulators. CRLF1 may inhibit these effects while clinically available JAK inhibitors may provide effective therapy.

Podocyte-specific expression of JAK, STAT, SOCS and PIAS isoforms provides opportunity for developing additional targets for treating FSGS.

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TH-PO1082

Genetic or Pharmacologic Activation of Nrf2 Worsens Glomerular Injury and Proteinuria

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Background: Proteinuric chronic kidney disease (CKD) is a major cause of progressive renal failure. Nrf2 (nuclear factor 2 erythroid 2) is a transcription factor and master regulator of a multitude of target genes with roles in antioxidant protection, electrophile detoxification, and overall cytoprotection. Nrf2-activating compounds such as CDDO-Me (bardoxolone methyl) and CDDO-Im have been and continue to be explored as treatments for proteinuric CKD in both clinical trials and experimental animal models. The results of some of these studies have suggested that Nrf2 may paradoxically increase proteinuria. To examine this, we tested the effects of genetic or pharmacologic Nrf2 activation on proteinuria in mice.

Methods: Wild type mice and mice with genetic Nrf2 activation (via reduction in the Nrf2 inhibitor Keap1) were compared. Proteinuria was induced experimentally via exposure to 1) adriamycin, 2) angiotensin II, or 3) albumin overload. Injury was assessed with urine albumin excretion, immunohistochemistry, podocyte foot process effacement, and expression of injury genes. Systemic blood pressures were measured with radiotelemetry. We also examined the effect of pharmacologic Nrf2 activation by CDDO-Im in wild type mice during proteinuric injury.

Results: There were no differences in proteinuria at baseline in the wild type and mutant mice. However, genetic Nrf2 activation led to increases in proteinuria in all three proteinuria models, and this was associated with worsened glomerular injury, podocyte foot process effacement, and renal fibrosis. Blood pressures were slightly higher in the mutant mice, due to a lack of dipping during the sleep cycle. In wild type mice, the addition of CDDO-Im to angiotensin-induced injury led to a dramatic increase in proteinuria which could be reversed upon CDDO-Im withdrawal.

Conclusions: Both genetic and pharmacologic Nrf2 activation led to increased proteinuria after injury. This appears to have deleterious effects on the kidney chronically. Increased blood pressures may contribute to this effect. Our results suggest that Nrf2 activation should be used cautiously in proteinuric CKD.

Funding: NIDDK Support, Private Foundation Support

TH-PO1083

Role of Renal PCSK9 in the Rrm2b Mouse Model of Nephrotic Syndrome

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Background: 85% of US chronic disease patient presenting nephrotic syndrome (NS) have high levels of low density lipoprotein cholesterol (LDL-c), compared to 31.5% in the general population. Proprotein convertase subtilisin/kexin type 9 (PCSK9) was shown to play an important role in the regulation of LDL-c levels in the liver. PCSK9 is expressed in the collecting duct (CD) where it plays a role of chaperon protein for the epithelial sodium channel (ENaC). We studied the expression of PCSK9 in NS in the Rrm2b$^{-/-}$ mouse, a model of collapsing glomerulopathy.

Methods: (1) Rrm2b Control (+/+) and knock-out (-/-) mice were followed weekly between the age 5 and 12 weeks. Albuminuria, PCSK9 and cholesterol serum levels were assessed. PCSK9 gene and protein expression in liver, kidney, intestine and serum were studied by RealTime PCR, Western blot, and confocal microscopy. (2) 8 week-old mice were treated or not with amiloride, a specific inhibitor of ENaC located in the renal CD.

Results: Rrm2b$^{+/+}$ mice do not develop albuminuria, hypercholesterolemia, or high levels of serum PCSK9. Rrm2b$^{-/-}$ develop albuminuria from the age of 7 weeks (425±239 μg/18h, P<0.001) and serum PCSK9 and total cholesterol levels significantly increase from the age of 8 weeks (19.75±5.21 ng/ml, P<0.05, and 124.16±10.27 mg/dl, P<0.05, respectively). PCSK9 protein expression was shown by Western blot to increase in the renal cortex from the age of 9 weeks, and decrease in the liver from the age of 7 weeks. By confocal microscopy, PCSK9 was shown to co-localize with Aquaporin-2, indicating expression in the CD where its expression is increased from the age of 7 weeks. When treated with amiloride, Rrm2b$^{-/-}$ mice show elevated levels of blood PCSK9 and cholesterol compared to mice without treatment. Amiloride blocks ENaC, the CD cells then increase the number of active ENaC present in the plasma membrane and the secretion of PCSK9, initiating hypercholesterolemia.

Conclusions: As Rrm2b$^{-/-}$ mice age and develop NS, PCSK9 protein levels increase in the kidney and serum, and decrease in the liver. Amiloride treatment showed that PCSK9 secreted by CD cells into the circulation induces earlier and higher hypercholesterolemia. CD expressed PCSK9 may play an important role in hypercholesterolemia in NS in the Rrm2b mouse model, as a link between the kidney and the liver.

Funding: NIDDK Support

TH-PO1084

Automated High Content Imaging to Identify New Therapeutics for Podocytopathies

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Background: Damage and eventual loss of podocytes is a hallmark of CKD. A key hurdle in the investigation of podocyte loss/damage is the lack of automated relevant cell-based screens. Existing techniques are time consuming and low throughput and cannot be used effectively in drug discovery. Here we describe a novel automated high throughput assay to evaluate and quantify podocytes in animal models of kidney disease.

Methods: Sprague Dawley rat glomeruli were isolated by differential sieving without enzymatic digestion, and plated in 384 well plates. Podocyte quantification was performed using a triple immunofluorescence detection of WT1, Nephrin and DAPI using confocal microscopy Opera QEHS. 3D glomeruli images created by 60X acquisition of 42 planes with 2 μm spacing were quantified using a customised algorithm using Columbus Analysis System that was developed to exclude artefacts, allow normalisation and ensure unbiased analysis. Tailored readouts include glomeruli number and morphology, podocyte number and nephrin expression.

Results: Podocyte identification was based on co-localization of WT1 and nephrin in a specific pattern in a 3D tilt glomerular reconstruction. Capsule cell positive for WT1 were excluded. Analysis was normalized for glomerular area by DAPI staining. We validated the assay using various doses of adriamycin (ADR) to induce podocyte loss. At low dose (50 nM), ADR decreases nephrin expression and changed its localisation, consistent with podocyte damage. At high ADR doses 500nM and 1μM, podocyte loss was evident (31.5-50%), with extensive glomerular damage at 1 μM. We then studied the effect of Ang II on podocyte damage using the same technique: preliminary data indicates that Ang II (100pM-1μM) caused significant podocyte damage (nephrin membrane reorganization) but no podocyte loss.

Conclusions: We have successfully developed a tool to allow high throughput automated assessment of podocyte health in isolated glomeruli. This automated 3D-High Content Imaging platform enables candidate target validation and drug identification.

Funding: Commercial Support - AstraZeneca PLC

TH-PO1085

Rapid Progression of Glomerulosclerosis due to Concurrent Diabetes and Hypertension Correlates with Podocyte Damage Shown by Expansion Microscopy

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Background: Glomerulosclerosis is a hallmark of diabetes (D) and hypertension (HT) induced kidney failure. Here we studied the combined effect of D-HT on the kidney using expansion microscopy for nanoscale imaging of podocyte foot processes (FP).

Methods: In 6-week-old male double transgenic rats (dTGRNeph-hAT1R;Cyp1a1mRen2dF1=dTGR) and TGRCyp1a1mRen2d (TGR) we induced for 8 weeks D by streptozotocin (60mg/kg i.p.) and HT by indol-3-carbinol (0.0125% in chow), alone or in combination (D-HT). After perfusion with 2%PFA, kidneys were ~4.5 times expanded using acrylamide/sodium-acrylate gel embedding, SDS/75°C+90°C denaturation, podocin immunohistochemistry and imaging by confocal microscopy after expansion in H2O. We measured FP width as the distance between two podocin signals and normalized for the expansion factor.

Results: D-HT-WT rats developed massive albuminuria (D-HT 240mg vs HT 20mg, controls 1.5 mg per 24hr) and a drop in GFR (D-HT: 4-fold, HT: 1.6 fold vs. controls), which correlated with histological alterations in glomeruli, including mesangial expansion, podocyte loss and adhesion of the glomerular tuft to the Bowman's capsule. HT rats showed very mild histological injury. D rats did not differ from controls. AT1R overexpression in podocyte aggravated the glomerular damage, drop in renal function in HT and D-HT but did not affect controls. Glomerular size increased similarly in both HT and D-HT and did not differ between dTGR and TGR. In dTGR- and TGR-controls, podocyte FP architecture was regular with long thin processes (200±20 nm width). In HT, FP were homogenously shortened and widened. In D-HT, FP structure within one glomerulus varied from regular with shortened and widened FP to irregular structures to regions with total loss of FP (average FP width 400±20 nm).

Conclusions: In contrast to D and HT, combined HT+D induced rapid progression of glomerulosclerosis and podocyte damage. Podocyte's AT1Rs aggravate damage index. ExM enabled visualization of nanoscale alterations in FPs in 3-D by using traditional immunohistochemistry and confocal microscopy. *Acknowledgements: This study was funded by DFG, CRC 1118 to SH*

TH-PO1086

New Animal Model of Non-HIV Collapsing Glomerulopathy

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Background: Collapsing glomerulopathy, usually classified as a form of focal and segmental glomerulosclerosis (FSGS), is the most severe and progressive form of glomerular disease. Most patients end up developing end stage kidney disease that requires dialysis or transplantation. There is presently no specific treatment for non-HIV collapsing glomerulopathy. Absence of animal models of non-HIV form of this disease was a problem in the past.

Methods: Transcriptional factor Zhx2 was overexpressed in rat podocytes under the control of the native human NPHS2 promoter. Two transgenic (TG) rat lines were generated: 142 and 144 which show increased expression of glomerular Zhx2 mRNA by 50.7% and 309.8% respectively. These 2 lines do not have any phenotype at baseline. We induced Adriamycin nephrosis, a model of FSGS, in wild type and heterozygous transgenic rats (7.5 mg of Adriamycin per kg/BW) and assessed for proteinuria and light microscopy at day 3 and 7 after injection. Different doses of Adriamycin (6.5 and 5.0 mg per kg/BW) were also injected in 144 transgenic rats, and studied at day 2, 5 and 9.

Results: TG 144 and TG 142 rats had significantly higher proteinuria than wild type rats following induction of Adriamycin nephrosis (7.5 mg per kg/BW). Renal histology in TG 144 rats on Day 7 revealed extensive glomerular collapse whereas no collapsing phenotype was noted in TG 142. Injection of 6.5 and 5.0 mg of Adriamycin per kg/BW in TG 144 rats, induced significant proteinuria starting at day 5 and that still continue to rise at day 9. Light microscopy images show classic feature of collapsing glomerulopathy (Collapsed glomeruli, retraction, prominent VEC…) only in TG 144 rats injected with 6.5 mg. 144 TG rats injected with 5.0 mg dose show classic feature of FSGS.

Conclusions: ZHX2 transgenic rats injected with Adriamycin represent a new animal model of non-HIV collapsing glomerulopathy. Longitudinal glomerular gene expression analysis will be performed to study molecular mechanisms of development of the disease in wild type and ZHX2 144 TG rats at 6.5 mg per kg/BW dose.

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TH-PO1087

Common Cold-Induced Cytokines Storm Induces Glomerular Disease Relapse in the ZHX2-Deficient State

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Background: Relapse or worsening of glomerular diseases like MCD and FSGS is commonly found after a common cold. Different cytokines and soluble receptors increase in circulation by or in response of the infection agent. We developed and tested a 'cytokine cocktail' composed of 7 of these cytokines and we assessed it in different animal models of Zhx2 deficiency or FSGS.

Methods: A common cold cytokine cocktail (dose X) containing IL-2, IL-4R, IL-6, IL-10, INF-γ, TNF-α and ICAM-1 was injected into control (BALB/c, n=-5) and Zhx2 deficient mice (BALB/cJ, n=5). Different doses of the cocktail and the effect of individual cytokines was assessed. Podocyte specific Zhx2 deficient ($Zhx2^{flox/flox}$ $cre^{+/+}$, n=3) and floxed control mice ($Zhx2^{flox/flox}$, n=3) (dose X/15); mice deficient in Ephrin B1 or both Zhx2 and Apa were also injected with the cytokine cocktail (dose X/5). Buffalo Mna (B. Mna) rats were injected with the cytokine cocktail (X/50) to study relapse in FSGS (n=7).

Results: Common cold cytokines induced acute albuminuria in BALB/cJ mice (65.3±24.3 μg per 18h), but not in BALB/c (10.8±1.5 μg per 18h), compared with baseline (BALB/cJ 5.1±1.1 μg per 18h; BALB/c 6.5±1.1 μg per 18h) ($p<0.05$), having higher nuclear expression of Zhx1 but not Zhx3. Individually, none of these cytokines caused albuminuria in either strain. Reducing 50% the dose X still induced significant albuminuria in BALB/cJ mice (15.3±0.6 μg per 18h) compared with baseline (2.8±0.9 μg per 18h) ($p<0.05$). Eliminating individually from the cocktail 3 different cytokines against which antibodies are in clinical use (IL-4R, IL6, TNF-α) also eliminated albuminuria in BALB/cJ mice. Cytokine induced albuminuria was also noted in $Zhx2^{flox/flox}/cre^{++}$, but not in control $Zhx2^{flox/flox}$ mice. Mice deficient in APA also developed albuminuria, and it is higher when mice are deficient in both Zhx2 and APA. Mice lacking Ephrin B1 in podocytes did not develop albuminuria. B. Mna rats had a significant increase in proteinuria (61.5±4.2) from baseline (47±4.1), using a much lower dose (X/50) of the rat "cytokine cocktail".

Conclusions: These findings suggest that an altered Zhx2 expression and its transmembrane partners predispose to MCD and FSGS relapse following a common cold.

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TH-PO1088

Identification of Podocyte Secreted Proteins That Drive Parietal Epithelial Cell Proliferation in a Murine Model of Proliferative Glomerulopathy

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Background: Podocyte injury contributing to parietal epithelial cell (PEC) proliferation is a dominant histologic feature in both rapidly progressive glomerulonephritis and subtypes of focal segmental glomerulosclerosis (FSGS), however factors mediating this cross-talk remain unclear. We recently showed that podocyte-specific loss of Krüppel-like factor 4 (*Klf4*), a zinc-finger transcription factor, activates STAT3 signaling leading to mitotic catastrophe in podocytes and eventual FSGS, while triggering PEC proliferation in mice. We utilized this model to identify novel factors secreted by the injured podocyte that drive PEC proliferation.

Methods: Initially, RNA-seq was conducted on glomeruli isolated from mice with podocyte-specific deletion of *Klf4* ($Klf4^{\Delta POD}$) and controls ($Klf4^{fl/fl}$). Since our previously reported data demonstrate that conditioned media (CM) isolated from cultured human podocytes with *KLF4* knockdown (*KLF4-shRNA*) triggers PEC proliferation, we performed quantitative mass spectrometry (iTRAQ) on CM from *KLF4-shRNA* and EV-*shRNA* cultured human podocytes from day 1 to 3 of differentiation. Subsequent differential expression and ChIP-enrichment analysis was performed to identify STAT3-dependent and independent secreted factors by the podocyte that drive PEC proliferation.

Results: Pathway analysis revealed that 421 genes were upregulated in $Klf4^{\Delta POD}$ glomeruli and were related to ECM organization and focal adhesion, whereas 179 identified downregulated genes were enriched for genes critical to podocyte protein-protein interactions, actin cytoskeleton, and cell differentiation. Proteins upregulated in *KLF4-shRNA* as compared to EV-*shRNA* CM were involved in similar pathways. These differentially expressed transcripts from RNA-seq were cross-matched with upregulated proteins from iTRAQ to identify factors that drive PEC proliferation. Published ChIP-seq datasets were used to identify top candidates containing STAT3 binding sites (PAI-1 and CYR61) and those without (PRSS23 and S100A6). These transcripts were then validated by qPCR in $Klf4^{\Delta POD}$ treated with STAT3 inhibitor, S3I-201.

Conclusions: Using a model of proliferative glomerulopathy (podocyte-specific Klf4 knockdown), we identified novel signaling molecules secreted by the injured podocyte that might drive aberrant PEC proliferation.

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TH-PO1089

Reciprocal Regulation Between ANLN and AKT Modulates Podocyte Proliferation

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Background: We previously reported that mutations in anillin (ANLN) cause familial FSGS; however, the physiologic functions of ANLN in podocytes remain unknown. ANLN is widely recognized as a driver of cell survival signaling and proliferation through its CD2AP-mediated interactions with the PI-3K/p85/AKT signaling module. We previously showed that ANLN expression is upregulated in proliferating podocytes and described a dynamic modulation of AKT activation with alterations in ANLN expression. Here, we evaluated the reciprocal influence of AKT on ANLN activity and expression in podocytes.

Methods: We established stably expressing $ANLN_{WT}$-, $ANLN_{S659E}$-, $ANLN_{S659A}$, *ANLN siRNA, AKT1 siRNA, STAT3 siRNA,* β-*Catenin siRNA* and scrambled siRNA podocyte lines. We evaluated the lines in proliferation and apoptosis assays and in complimentary biochemical pathway analyses.

Results: *ANLN Expression* - ANLN expression was markedly reduced with AKT inhibitors and in *AKT1* knockdown (KD) podocytes. We screened the ANLN promoter to search for transcription factors regulated by AKT and identified multiple candidate binding sequences for β-Catenin and STAT3. ANLN expression was significantly reduced in β-*Catenin* and *STAT3* KD podocyte lines and phosphorylation/activation of β-Catenin was downregulated in *AKT1* KD podocytes. Conversely, STAT3 phosphorylation was upregulated in *AKT1* KD podocytes suggesting a compensatory function of STAT3 activation in *AKT1* KD podocytes. *ANLN Phosphorylation* - We identified a highly conserved AKT phosphorylation motif (i.e. R-X-X-S_{658}) in the ANLN F-actin binding domain. We generated a phospho-specific $ANLN_{S658}$ antibody and observed that phosphorylation of ANLN at Ser658 was abrogated in $ANLN_{S658A}$-expressing podocytes demonstrating the specificity of the antibody. Podocytes expressing $ANLN_{S658E}$ exhibited significantly enhanced proliferation relative to $ANLN_{WT}$- and $ANLN_{S658A}$-expressing podocytes suggesting that AKT may enhance the activity/stability of ANLN via direct phosphorylation of Ser658.

Conclusions: ANLN and AKT dynamically regulate one another to modulate podocyte proliferation. This study delineates the mechanisms of this reciprocal regulation and highlights potential therapeutic targets for the treatment of ANLN-induced podocyte dysfunction.

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TH-PO1090

Deletion of p38 MAPK in Podocytes Aggravates Glomerular Injury by Aldosterone in Podocyte-Specific GC-A Knockout Mice

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Background: Previously, we demonstrated that uninephrectomized aldosterone-infused, high salt-fed podocyte-specific guanylyl cyclase-A (natriuretic peptide receptor 1) conditional KO (pod-GC-A cKO) mice exhibited glomerular injury and that pharmacological inhibition of p38 MAPK ameliorates podocyte damage. However, the effects of genetic deletion of p38 MAPK in podocytes of pod-GC-A cKO mice have been unknown.

Methods: We generated p38 MAPK(fl/fl);Nephrin-Cre (pod-p38 MAPK cKO) mice and p38 MAPK(fl/fl);GC-A(fl/fl);Nephrin-Cre (pod-p38MAPK/GC-A DKO) mice. For induction of glomerular injury, we treated them with aldosterone and high salt at 2 months of age for 3 weeks without nephrectomy (B-ALDO). *In vitro*, we examined the effect of p38 MAPK inhibitor in cultured human podocytes transfected with GC-A siRNA.

Results: B-ALDO-treated pod-p38 MAPK/GC-A DKO mice resulted in significant elevation of serum Cr (0.29 ± 0.04 mg/dl), massive albuminuria (42,660 ± 20,200 mg/mgCr) and severe foot process effacement in addition to intracapillary fibrin thrombi which indicated endothelial damage. Vehicle-treated DKO mice, B-ALDO-treated pod-GC-A cKO mice, and B-ALDO-treated pod-p38 MAPK cKO showed normal serum Cr levels (0.14 ± 0.01, 0.18 ± 0.02, 0.20 ± 0.01 mg/dl, respectively), mild increase of albuminuria (223 ± 6.5, 1496 ± 592, 649 ± 303 mg/mgCr, respectively) and only segmental foot process effacement. Blood pressure was not elevated in either mutant mice compared with that of B-ALDO control mice. Furthermore, glomerular mRNA expressions of MCP-1, PAI-1, and FN were upregulated and that of VEGF-A was downregulated in DKO mice. Consistent with this, suppression of GC-A mRNA expression by siRNA in combination with p38 MAPK inhibitor downregulated VEGF mRNA in human cultured podocytes.

Conclusions: Genetic p38 MAPK deletion in GC-A-nul podocytes exacerbated aldosterone-induced glomerular endothelial cell injury as well as podocytes, and resulted in renal dysfunction, probably through VEGF downregulation. These results suggest p38 MAPK in podocytes is necessary to protect endothelial and epithelial cells from aldosterone-induced injury.

TH-PO1091

ARHGEF7 (β-PIX) Protects Podocytes from Cell Apoptosis via Cdc42 Activation

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Background: Rho-family small GTPases (Rho GTPases), including Rac1 and Cdc42, are important for podocyte functions. β-PIX, encoded by ARHGEF7, is a guanine nucleotide exchange factors (GEF) that activates Rac1 and Cdc42. Recently, we established that podocyte-specific β-PIX deficient (KO) mice develop progressive proteinuria starting at ~8 weeks of age, and glomerulosclerosis and podocyte loss by 13 weeks of age. Here, we investigated the mechanism of podocyte loss induced by β-PIX deficiency, with a particular focus on the pro-survival transcriptional co-activator, Yes-associated protein (Yap), which is known to be activated by Cdc42.

Methods: Cultured mouse podocytes (MP) with β-PIX knockdown (KD) and their controls were established using shRNAs. Rac1/Cdc42 activity was assessed by pull-down assay. Rho/Rac/Cdc42 Activator I (Cytoskeleton, CN04) and Adriamycin (ADR) were used as a general Rho GTPase activator and a podocyte toxin, respectively. Apoptosis was studied by TUNEL staining and immunoblotting for cleaved caspase 3 (CC3). Nuclear translocation and activity of Yap were assessed by immunostaining and the TEA domain (TEAD)-luciferase assay. Data are provided as the mean ± SE.

Results: Cdc42, but not Rac1 activity, was significantly decreased by 34% in isolated glomeruli from 5-week-old β-PIX KO mice, compared with controls (n=7-10, $p<0.05$). Similarly, Cdc42, but not Rac1, activation in β-PIX KD MP was significantly blunted by 46%, compared with control MP (n=4, $p<0.01$). At 6 hrs after ADR treatment, KD MP showed 9.4±2.5 % TUNEL-positive cells, as compared with 3.8±0.7 % in control MP (n=3, $p<0.05$). CC3 was also increased in KD MP. Correspondingly, there were less adherent KD MP at 8 hrs of ADR treatment, compared with control MP. Control MP showed predominant nuclear localization of Yap, while KD MP exhibited partial cytoplasmic retention (Nuclear/Total Yap ratio; Control: 0.90±0.02; KD: 0.80±0.04, n=10, $p<0.05$). The TEAD-luciferase activity was significant lower in KD MP than in control MP (Control: 10.3±1.3; KD: 6.9±0.76 a.u., n=9, $p<0.05$). mRNA expression of the Yap target genes by RNA-seq were significantly reduced in the glomeruli of KO mice.

Conclusions: Loss of β-PIX in podocytes resulted in increased apoptosis and detachment from matrix. This may be mediated by the cytoplasmic retention and decreased transcriptional activity of Yap via decreased Cdc42 activity.

TH-PO1092

Role of Pyruvate Kinase M2-Mediated Metabolic Reprogramming During Podocyte Differentiation

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Background: Podocyte, a type of highly specialized epithelial cells with sophisticated foot processes and unique slit diaphragm, requires substantial levels of energy to maintain its integrity and function, but little is known on the regulation of podocyte's energetics. Lack of metabolic analysis during podocyte development led us to explore the role of cellular metabolism and mitochondrial biology during *in vitro* differentiation.

Methods: To study the metabolic alterations caused by differentiation, nuclear magnetic resonance (NMR) spectroscopy was performed to analyze the metabolomic profiling of differentiated and un-differentiated cultured mouse podocytes. Cell metabolism was measured by seahorse XF analyzer. Mitotracker Red CMXRos and MitoProbe JC-1 Assay Kit were used to identify mitochondrial morphology, mass and membrane potential. *Pkm2*-RNAi-Lentivirus was used to explore the regulating role of PKM2 during podocyte differentiation.

Results: In this study, we observed a huge increase in mitochondrial biogenesis. Changes in mitochondrial mass, morphology and function were correlated with the upregulation of the master regulators of mitochondrial biogenesis, TFAM and PGC-1α. Unexpectedly, concomitant with mitochondrial biogenesis, we observed an increase in glycolysis during podocyte differentiation, which was linked to the overexpression of glycolic enzymes. Among them, PKM2 was of particular interest. The real-time quantitative PCR and PK activity assay kit showed both pyruvate kinase M2 (PKM2) expression and activity were upregulated. Knockdown of *Pkm2* showed dramatic reduction of glycolysis and mitochondrial function, resulting in the defects of podocyte differentiation.

Conclusions: Usually, differentiated cells have repressed glycolysis, as they mostly rely on OXPHOS for energy demand. Our findings here first demonstrate that differentiated podocytes boost both glycolysis and mitochondrial metabolism to meet their augmented energy demand. We identified PKM2 as a critical regulator of energy metabolism in podocytes. Selective inhibition of PKM2 indicate existence of metabolic checkpoint that need to be satisfied in order to allow podocyte differentiation.

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TH-PO1093

Human Podocyte Modifies Energy Metabolism During Differentiation

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Background: Previous studies have shown increased oxidative phosphorylation (OXPHOS) with podocyte differentiation and decreased OXPHOS with hyperglycemia. Little is known about the rate of synthesis of mitochondrial proteins or how other components of metabolism, such as the TCA cycle and fatty acid oxidation, change with podocyte differentiation. The goal of this project is to identify metabolic pathways that are required for podocyte differentiation.

Methods: MTS, ATP abundance, and ATP/ADP ratios were done to ensure human podocyte viability and confirm changes in metabolism during differentiation. Oxygen consumption rate (OCR) and Extracellular Acidification Rate (ECAR) were done by SeaHorse at 3, 7, 10, and 14 days of differentiation and compared to undifferentiated cells. Immunostaining for TOMM20 was performed and quantified. SILAC was done in 12 hour pulses with heavy arginine and lysine and subsequent mitochondrial isolation was performed to determine mitochondrial protein synthesis in differentiating podocytes (with pathway enrichment analysis).

Results: We observed a stepwise increase in OXPHOS during differentiation characterized by an increase in mitochondrial biogenesis (TFAM protein quantification), network (TOMM20 staining), and increased mtDNA copy number. With differentiation, we observed an increase in total ATP but a decrease in ATP/ADP ratio. MTS assay showed no significant changes with cell differentiation. Unlabeled proteomics abundance showed the greatest increase in OXPHOS (specifically in complex 1 and 5) followed by TCA cycle. We also observed a significant decrease in mitochondrial fission proteins and an increase in mitochondrial fusion with differentiation. The most dynamic proteins with high abundance and high heavy to light (H:L) ratios during differentiation were ATP5B, NDUFS6, and OXA1l, reinforcing the importance of OXPHOS with differentiation. The most stable proteins with high abundance and low H:L ratios were involved in TCA cycle, fatty acid degradation, arginine and proline metabolism and valine, leucine and isoleucine degradation pathways (KEGG 2019 Human).

Conclusions: These data suggest that podocyte differentiation is dependent on an increase in mitochondrial biogenesis and network with a switch in metabolic programming to oxidative phosphorylation.

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TH-PO1094

Using CRISPR/Cas9 to Generate Second-Generation Cell Lines Used for Detecting Recurrent Focal Segmental Glomerulosclerosis (rFSGS) Patients

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Background: The gold standard for diagnosing glomerular diseases including FSGS requires invasive procedures such as renal biopsy, which may not be safe or feasible to perform in all patients. Recently, we published a cell-based assay for diagnosing rFSGS

patients, which involved constructing cell lines using the rFSGS responsive genes BMF, IL-1β and IGFBP3. While the assay specifically diagnosed rFSGS pateints, the overall assay response was low (~1.5 fold increase over control). To boost the assay response and increase its specificity, a CRISPR/Cas9-based precise genome editing approach was employed, where highly specific and responsive second generation cell lines were created.

Methods: The Genome-CRISPR/Cas9 human AAVS1 Safe Harbor *knock in* kit-Puro (Cat# SH012) from GeneCopoeia, Inc. was used to individually *knock in* BMF, IL1-β or IGFBP3 gene promoter-Luciferase ORF' cassette at the AAVS1 locus in HEK293 cells. PCR analyses were used to determine correct insertion of donor cassette at the AAVS1/ safe harbor site. The response of constructed cell lines towards patient plasma from rFSGS and control patients was tested using a luciferase-based reporter assay.

Results: Remarkably, these cell lines showed significantly increased response to rFSGS patient plasma when compared to plasma from either control or non-rFSGS patients. An increase from ~1.5 fold (originally reported) to more than 10 fold was observed. Moreover, the response was consistent and showed more than 90% specificity in detecting rFSGS patients.

Conclusions: We present here the development and validation of a second-generation cell lines used for diagnosing rFSGS patients that are superior to conventional stably transfected cell lines. Unlike the first-generation cell lines, the second-generation cell lines have defined integration at the "safe harbor locus". These cell lines are highly responsive and demonstrate low variability. Overall, our assay is noninvasive, highly sensitive and specific, and studies are being planned for conducting clinical trials to utilize its full diagnostic potential.

Funding: NIDDK Support

TH-PO1095

Lanosterol Synthase Genetic Variant rs2254524 V642L and Its Role in the Pathogenesis of Kidney Disease

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Background: A single nucleotide polymorphism in the Lanosterol Synthase (LSS) gene, rs2254524, has been recently associated with an increased susceptibility to renal damage and increased Endogenous Ouabain (EO) content in human kidney. Our hypothesis is that the presence of the genetic variant rs2254524 causes increased susceptibility to EO-mediated glomerular damage and impairs cholesterol metabolism leading to podocyte injury.

Methods: Two immortalized human podocyte cell lines, one homozygous (LSS AA) the other heterozygous (LSS AC) for the LSS mutant variant, were used in this study. LSS expression in podocytes was verified by RT-PCR, Western blot and immunofluorescence. Apoptosis and cytotoxicity were assessed 5 days post-treatment with EO using the ApoTox-Glo Triplex Assay. The number of lipid droplets (LDs) per cell was assessed by Nile Red staining after 24h of treatment with EO 10^{-9} M, puromycin 100 μg/ml and TNFα 100 ng/ml, alone and in combination with $CoCl_2$ 100 μM.

Results: We demonstrate for the first time that LSS is expressed in human podocytes. Dose-dependent cytotoxicity of EO was observed only in LSS AA podocytes while dose-dependent apoptosis occurred in both, LSS AA and AC podocyte cell lines. Using *in vitro* models of podocyte injury (e.g. exposure to puromycin or inflammatory cytokine TNFα alone and in combination with $CoCl_2$), we demonstrated that LSS AA podocytes are more susceptible to LDs accumulation when compared to LSS AC podocytes. However, there was no increase in LDs when cells were exposed to EO.

Conclusions: Our data indicate that individuals that carry two LSS mutant variants (rs2254524) are more susceptible to EO-mediated podocyte cytotoxicity. Moreover, the mutation might render podocytes susceptibleto accumulate LDs under certain stress conditions which may contribute to podocyte injury.

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TH-PO1096

Bag3 as Potential Mechanoprotector in Renal Podocytes

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Background: Loss of podocytes in the course of glomerular diseases leads to glomerulosclerosis and progressive kidney disease. Due to their exposed location on the outside of the glomerular basement membrane podocytes are subjected to extensive mechanical strain by perfusion and filtration. These forces are even higher in disease states such as diabetic nephropathy. Overtaxing adaptive mechanisms causes podocyte detachment which in turn increases the mechanical stress for remaining podocytes. The precise mechanisms involved in this vicious circle are yet insufficiently defined. Bag3 is an important mechanoprotector protein in mechanically strained tissues. It replaces mechanically unfolded proteins by chaperone-assisted-autophagy (CASA) and regulates proteins like Filamin A and Synaptopodin, that play a central role in podocyte biology. Above all Bag3 is an important player in diabetic nephropathy in a mouse model. All this brings Bag3 in a prime position as a candidate mediator of mechanical stress protection in podocytes.

Methods: We examined podocytes by immunofluorescence, super-resolution-microscopy and mass-spectrometry for Bag3 expression and characterized the Bag3 interactome using immunoprecipitation. Mechanical stress was induced by stiff matrices and cyclic stretch. The role of Bag3 *in vivo* is being evaluated in two different mouse lines (Bag3.P209L mutation and a conditional knockout).

Results: Bag3 expression can be shown inside the glomerulus with podocytes displaying a Bag3 enrichment in mass-spectrometry data. Furthermore Bag3 expression is regulated by mechanical clues in podocyte cell lines and first interactome results point towards a function at the liquid stress-granula interface. Preliminary analyses of the myopathy causing mutation Bag3.P209L revealed a mild albuminuria starting at an age of 8-12 weeks in a whole-body overexpression mouse line.

Conclusions: Our findings point towards an important role of Bag3 and chaperone-assisted-selective-autophagy in podocytes and their mechanical stress protection. Bag3 localization at the slit diaphragm in STED-imaging further corroborates this hypothesis. Further studies based on two podocyte specific mouse lines (Bag3 mutation and conditional knockout) are currently ongoing to understand the role of podocyte-Bag3 *in vivo* under healthy conditions and in glomerular disease.

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TH-PO1097

PAR-CLIP Identification of Cell Type and Context-Specific miRNA/mRNA Interactions

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Background: miRNA have been implicated as mediators of acute and chronic kidney diseases and as intervention targets. miRNA:mRNA interactions are highly complex and are poorly explored in kidney cells. We applied *in vitro* and *in silico* methods to identify miRNA:mRNA interactions in two cultured kidney epithelial cells and in response to TGFB1, a common damage-associated cytokine.

Methods: Immortalized human podocytes and proximal tubular (HK2) cells were treated with TGFB1 (20 ng/mL) or vehicle for 24 hours (approx. 1 mio cells per sample; n=2). Photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) was used to identify miRNA:mRNA interactions. Target genes identified by PAR-CLIP were compared with miRNA targets identified by computational prediction algorithms. RNA-seq and small-RNA-seq were performed in parallel.

Results: PAR-CLIP identified 3,645 genes targeted by miRNAs in both cell types, while 117 and 24 genes were targeted only in podocytes or HK-2 cells, respectively. 3,744 genes were targeted in TGFB1 and vehicle-treated samples, while 39 and 3 genes were targeted only in cells exposed to TGFB1 or vehicle, respectively. Integration of cell type and treatment revealed that podocyte specific genes targeted by miRNAs after TGFB1 treatment, but not vehicle, were detected as targets in vehicle-, but not TGFB1-, treated HK2 cells, and vice versa. miR-21-5p had one cell type specific target in each podocytes and HK-2 cells, while miR-21-3p had only one gene specific target in HK2 cells. miRDB predicted 10-11%, Target Scan predicted 18-42% and RNA22 predicted 30-19% of PAR-CLIP identified genes per 5p and 3p arms, with limited overlap between different algorithms. RNA-seq identified 3,001 and 3,235 expressed genes in podocytes and HK2 cells, with 3,510 and 2,712 genes differentially expressed after TGFB1. 172 and 135 miRNAs were detected in podocytes and HK2 cells, with expression of 45 and 94 altered by TGFB1.

Conclusions: Together, we identified cell type and context specific targets for miRNAs, with the vast majority of miRNA targets detected in both epithelial cell types. However, miRNA target gene profiles may differ more in non-epithelial cells. Importantly, miRNA targets identified by PAR-CLIP are largely not predicted using computational algorithms.

Funding: NIDDK Support

TH-PO1098

Functional APOL1-miR193a Axis (AMA) Prevents Podocyte Injury

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Background: APOL1-miR193a axis plays a vital role in the maintenance of podocyte molecular phenotype. It is bifunctional in podocytes expressing APOL1G0 (wild-type). APOL1 inversely regulates miR193a expression and vice versa in podocytes. Both Puromycin aminonucleoside (PAN) or Adriamycin (ADR) are known to induce apoptosis in human podocytes. However, the role of APOL1-miR193a axis remain to be elucidated. We asked whether modulation of this axis carries a potential to prevent PAN- and ADR-induced podocyte injury.

Methods: Human podocytes (immortalized) stably expressing either vector (V-podocytes) or APOL1G0 (G0-podocytes) were differentiated (incubating in special media for ten days, V-D or G0-D). V-Dpodocytes and G0-Dpodocytes were incubated in media containing different concentrations of Adriamycin (5, 15, 30, and 35 nM) or PAN (0, 5, 10, 25, 50, and 100 nM) for 48 hours (n=6); in other sets, VD-podocytes and G0-Dpodocytes were treated with Adriamycin (30 mM) or PAN (50 nM), with/without miR193a inhibitor (25 nM) for 48 hours (n=6). Cells were evaluated for reactive oxygen

species (ROS) generation (DCF detection assay), caspase-3 cleavage, and apoptosis (TUNEL assay). Proteins and RNAs were extracted from cells treated under similar conditions (n=6). Protein blots were probed for APOL1 and caspase-3; RNAs were assayed for mIR193a. Differentiated podocytes (DPDs) were transduced with either empty vector or miR193a plasmid and evaluated for APOL1 and caspase-3 expression.

Results: G0-Dpodocytes showed a two-fold increase in expression of APOL1, but a 2.8-fold decrease in miR193a levels when compared to V-Dpodocytes. V-Dpodocytes showed increased (P<0.01) ROS generation and a higher (P<0.01) percentage of TUNEL +ve cells when compared to G0D-podocytes in Adriamycin and PAN milieus. Both Adriamycin and PAN displayed an upregulation in miR193a and caspase-3 expression in both V-D and G0-Dpodocytes from their baseline. MicroRNA193a inhibitor decreased miR193a levels, increased APOL1 expression, and attenuated number of TUNEL +ve cells in both Adriamycin and PAN milieus. DPDs overexpressing miR193a displayed reduced expression of APOL1 and enhanced cleavage of caspase-3.

Conclusions: Functional AMA prevents podocyte injury in adverse milieus through down-regulation of miR193.

Funding: NIDDK Support

TH-PO1099

P2X7 Expressed in Injured Podocytes May Spread the Kidney Injury Through Caspase 3

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Background: We previously generated a mosaic mouse model in which a fraction of podocytes express hCD25 and can be injured by a hCD25-directed immunotoxin, LMB2. After injection with LMB2, not only hCD25(+) but also hCD25(-) podocytes were injured along with dramatic induction of P2X7 mRNA in both types of podocytes. P2X7 is a receptor of extracellular ATP and is known to activate inflammation and induce cell death in immune cells. In the present study, we aim to analyze P2X7 protein expression in the mosaic mouse model and investigate the role of P2X7 in podocyte injury.

Methods: Kidneys were harvested from mosaic mice before or 2 weeks after injection with LMB2 (25ng/gBW). Immunofluorescence staining was performed with primary antibodies against P2X7 and cleaved-caspase 3. For functional study, primary cultured mouse podocytes were transiently transfected by electroporation with P2X7-expression or mock plasmid together with EGFP or tdTomato expression plasmid. Before or 1-2 hours after administration of ATP (0 or 2 mM), the same visual fields were photographed.

Results: No P2X7 staining was observed in the kidney without LMB2. In the kidneys injured by LMB2, which developed FSGS, 69.2±9.2% of glomeruli were positive for P2X7 staining. Some P2X7 staining was observed in GFP-labeled hCD25(-) podocytes, which indicated that indirect injury activated P2X7 expression. Cleaved-caspase 3 staining was also positive in 12.4±3.1% of glomeruli of LMB2-damaged kidneys, but not in those without LMB2. In *in vitro* studies, administration of ATP caused leakage of co-introduced EGFP in 51.7±1.4% of P2X7-transfected cells, incorporation of propidium iodide in 18.1±0.9%, and activation of caspase 3 in 17.9±2.8%. However, increase in LDH activity in the medium remained minimum, corresponding to only 3.0±1.7% of cell death. These phenomena were not observed in mock-transfected cells treated with ATP or P2X7-transfected cells without ATP administration. Caspase-3 inhibitor significantly attenuated the leakage of EGFP induced by ATP (26.4±2.6 vs 37.9±3.3%), whereas Caspase-1 inhibitor did not (37.0±3.0%).

Conclusions: These results indicate that injured podocytes express P2X7, which may further augment injury by inducing caspase-3 dependent apoptosis.

TH-PO1100

Expression Profile of the cGAS-STING Pathway in Podocytes: Implications for Glomerular Diseases

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Background: Recent studies suggest that podocytes express elements of the innate immune system which may be involved in the local immune response and contribute to glomerular damage. As part of the innate immune system, the cGAS-STING pathway is activated in response to cytosolic DNA and is involved in disease pathogenesis for systemic lupus erythematosus. Whether or not podocytes express genes in the pathway remains unknown. This study aims to investigate if genes in the cGAS-STING pathway are expressed in murine and human podocytes and if activation of this pathway by cyclic dinucleotides (CDNs) contributes to podocyte injury in glomerular diseases.

Methods: Immortalized human and murine podocytes were cultured. For treatments, podocytes were differentiated for 14 days and serum starved for 24h starting day 12. STING knockdown human podocytes were established by lentiviral infection with siRNA. c-diAMP treatment was performed in RPMI medium at concentration 10 uM for 24h starting day 13. Plasma membranes were separated by ultracentrifugation (100,000xg, 1h). Several mouse models of glomerular disease of metabolic (db/db, ob/ob) and non-metabolic origin (Alport, NFAT) were used. mRNA was extracted using Qiagen RNAeasy kit according to the manufacturer's protocol. Proteins were separated in 4-20% SDS-PAGE gels (BioRad) and transferred to nitrocellulose membranes for Western blot analysis. All monoclonal antibodies were obtained from Cell Signaling.

Results: Both murine and human podocytes showed expression of cGAS-STING pathway genes under physiological conditions. Treatment with c-diAMP increased expression of cGAS and phosphorylation of STING, IRF3 and TBK1. Notably, inactive STING was localized in the endoplasmic reticulum, while activate STING is translocated to the cytosol. STING knockdown podocytes did not respond to pathway activation after c-diAMP treatment. Among the mouse models of glomerular disease used in this study, only db/db and Alport mice showed increased cGAS-STING activity.

Conclusions: Genes of the cGAS-STING pathway are expressed in murine and human podocytes and the pathway can be activated by CDNs. Activation of the cGAS-STING pathway in mouse models of glomerular disease suggests a possible contribution of this pathway to podocyte injury.

Funding: Other NIH Support - R01DK117599, Private Foundation Support

TH-PO1101

Loss of Ubiquitin-Specific Protease 40 in Podocyte Enhances Kidney Injury

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Background: Although an indispensable role of ubiquitin specific protease-40 (USP40) in podocyte development of zebrafish was revealed, downstream of USP40 function is still unknown. Since there is a close relationship between ubiquitin system and endoplasmic reticulum function, we aimed to explore the protein function of USP40 in the podocyte injury and to determine the interacting partner by focusing on ER resident chaperone.

Methods: USP40-knockout (USP40KO) mice were generated and showed no apparent kidney abnormality. To explore the role of USP40 in podocyte injury, we crossed USP40KO with NEP25 mice, in which selective podocyte injury can be induced by injection with an immunotoxin, LMB2. Urinary protein was analyzed until day 9 after LMB2 injection, and then kidney tissues were subjected to light microscopy, immunohistochemistry of p57 and immunofluorescence microscopy of the ER stress marker BIP and calreticulin (CRT). The glomeruli were isolated and subjected to immunoblot analysis of BIP and CRT. The effect of USP40 knockdown on BIP and CRT expression was studied in cultured mouse podocytes. Finally, the protein binding of BIP and CRT with USP40 was determined by immunoprecipitation using cultured mouse podocytes.

Results: NEP-USP40KO mice developed higher levels of proteinuria compared with NEP mice. Light microscopy and immunohistochemistry showed higher levels of kidney injury in NEP-USP40KO mice compared with NEP mice in terms of hyalinosis (p<0.01), crescent formation (p<0.01), and cell proliferation (p<0.01) in the glomeruli, podocyte loss (p<0.05), and tubulointerstitial injury (p<0.01). Immunoblot analysis and immunofluorescence revealed increased expression of CRT, but not of BIP, in podocytes of NEP-USP40KO mice compared with NEP mice. Gene knockdown of USP40 in cultured podocytes increased the protein expression of CRT, but not of BIP. Finally, apparent protein binding of USP40 with CRT, but not with BIP, was observed.

Conclusions: USP40 may be involved in a self-defense mechanism in podocyte injury probably through interacting with CRT.

TH-PO1102

A Urinary Metabolite Constellation to Detect Acute Rejection in Kidney Allografts

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Background: Post-transplant surveillance for acute rejection is mainly based on regular monitoring of serum creatinine levels and transplant biopsies upon functional renal impairment. Recently, we developed a novel method to detect kidney allograft rejection via a characteristic constellation of the urine metabolites alanine, citrate, lactate, and urea investigated by nuclear magnetic resonance (NMR) spectroscopy (Banas M et al., Metabolomics 2018).

Methods: Within the prospective, observational UMBRELLA study 986 urine specimens were collected from 109 consecutively enrolled renal transplant recipients and metabolite constellations were analyzed by NMR spectroscopy. A metabolite rejection score was calculated and compared to histopathological results of corresponding allograft biopsies (n=206).

Results: The metabolite constellation was found to be a useful biomarker to non-invasively detect acute allograft rejection (AUC = 0.75; 95% confidence interval (CI) 0.68 to 0.83; based on 46 cases with biopsy-proven rejection and 520 controls). A combination of the metabolite rejection score and the estimated glomerular filtration rate (eGFR) at the time of urine sampling further improved the overall test performance significantly (AUC = 0.84; 95% CI 0.76 to 0.91; based on 42 cases and 468 controls). In a subgroup of patients without rejection episodes the test results remained well below a diagnostic threshold associated with high risk of acute rejection. In other cases a marked increase above this threshold indicated an acute allograft rejection already 6-10 days before diagnostic renal biopsies were performed.

Conclusions: In conclusion, a combination of an NMR-based urine metabolite analysis and glomerular filtration rate is promising as a non-invasive test for post-transplant surveillance and to support decision making whether renal allografts need histopathological evaluation.

Funding: Commercial Support - numares AG, Regensburg

TH-PO1103

Plasma Neutrophil Gelatinase Associated Lipocalin (NGAL) Predicts Long-Term Graft Survival in Stable Kidney Transplant Recipients

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Background: Neutrophil gelatinase-associated lipocalin (NGAL) has been evaluated as a biomarker of acute tubular injury in the kidney. The utility of NGAL to predict long-term outcomes in stable kidney transplant recipients (KTR) is unknown.

Methods: We conducted a monocentric, prospective observational study enrolling 709 stable KTR more than two months after renal transplantation. Baseline characteristics, standard laboratory values, and plasma NGAL (pNGAL) levels were determined at the time of inclusion. Patients were followed up for death-censored graft loss, defined by a continued requirement for renal replacement therapy. The utility of pNGAL levels to predict graft loss was evaluated by Receiver Operating Characteristics (ROC) analyses, Cox regression as well as competing risk analyses and Kaplan-Meier estimates.

Results: During a median follow-up of 58 months, death-censored graft loss occurred in 49 patients. The median pNGAL within the entire cohort was 189 [IQR 130-257] ng/ml. Patients who later experienced graft loss had a pNGAL of 304 [IQR 234.5-358] ng/ml (p<0.001). Time-dependent ROC analyses indicated an Area-Under-the-Curve value for pNGAL of 0.795 to predict graft loss within 5 years. pNGAL >230ng/ml had a sensitivity of 0.82 and a specificity of 0.71. Multivariate Cox regression analyses as well as competing risk analyses showed that pNGAL was an independent predictor of graft loss after adjustment for clinical parameters and kidney function. Patients with serum creatinine (sCrea) values ≥ 1.75mg/dl and pNGAL ≥ 230ng/ml had an approximately 9-fold higher risk of graft loss compared with patients with sCrea ≥ 1.75mg/dl and pNGAL < 230ng/ml. (p<0.001).

Conclusions: pNGAL levels in stable KTR may help to predict long-term graft survival.

TH-PO1104

Urinary Biomarkers TIMP-2 and IGFBP7 Are Predictive for Recovery from Ischemia-Reperfusion Injury After Kidney Transplantation

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Background: Conventional clinical markers often fail to predict recovery from ischemia-reperfusion injury in the early phase after kidney transplantation (KTx). Urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor 7 (IGFBP7), markers for G1 cell cycle arrest, have been identified and validated for the early detection of renal injury in critical ill patients. We evaluated whether post-transplant urinary [TIMP-2]*[IGFBP7] can predict renal recovery early after KTx.

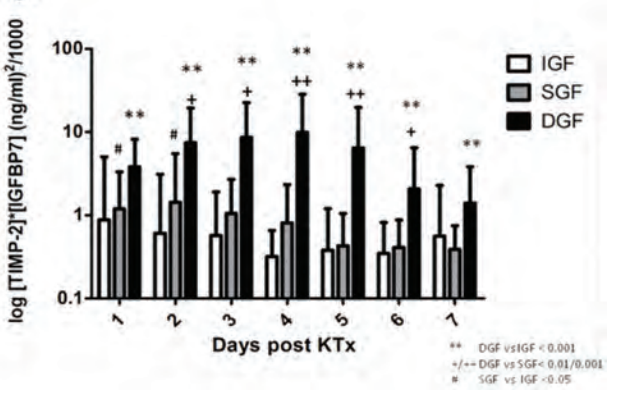
Methods: In a prospective observational multicenter cohort study of renal transplant recipients, urinary [TIMP-2]*[IGFBP7] (NephroCheck®; Astute Medical, San Diego, CA, USA) was evaluated daily from day 1-7 after KTx. Different stages of graft function were defined: immediate graft function (IGF) (decrease ≥ 10% s-crea within 24 h post KTx); slow graft function (SGF) (decrease <10% s-crea within 24 h post KTx) and delayed-graft function (DGF)(any dialysis during first week after KTx). Clinical and laboratory parameter were documented.

Results: A total of 186 KTx patients were analyzed, 138 (74%) with a deceased donor, 48 (26%) with a living donor KTx. IGF was observed in 58.6%, SGF in 23.1% and DGF in 18.3% of the cohort. [TIMP-2]*[IGFBP7] was significantly elevated in patients with DGF compared to other groups during the first week of transplant (Fig. 1). Renal function parameters were not able to differentiate between DGF and SGF early after Ktx. ROC-Analysis of [TIMP-2]*[IGFBP7] at day1 posttransplant for event "Non-DGF" revealed a cut-off value of 0,9 $(ng/ml)^2/1000$ (sensitivity 87%; specificity 71%). Positive predictive value for non-DGF was 93%.

Conclusions: Early [TIMP-2]*[IGFBP7] measurement can predict recovery from ischemia-reperfusion-injury post Ktx. [TIMP-2]*[IGFBP7] is a promising biomarker for clinical decision-making after KTx.

Funding: Commercial Support - Astute (only limited support on test material, no financial support), Clinical Revenue Support

Fig.1



TH-PO1105

Predicting Transplant Rejection by a Composite Urinary Injury Score

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Background: While sequencing or PCR have been used for quantifying donor-derived cell-free DNA in plasma to detect allograft rejection, they remain expensive and inconvenient for patients and physicians. We assessed the performance of a novel urinary assay measuring nucleic acid, protein, and metabolic markers to provide a quantitative composite risk score without sequencing or PCR to detect kidney transplant (KT) rejection.

Methods: 206 urine samples from 95 KT patients were collected and categorized as stable (n = 157) or acute rejection (AR, n = 49). Samples were processed for quantification of urinary cfDNA and 5 additional protein markers using a custom microwell-based assay, to develop a translant rejection score. The score from longitudinally collected samples (n = 47) from 8 KT patients who were stable and had no evidence of subclinical rejection was correlated with days post-transplant to generate a 95% prediction curve which was used to generate a normalized rejection score for all samples.

Results: The urinary rejection score is significantly increased immediately post-transplant and decreases to a steady baseline by 3 months post-transplant (**Figure 1A**). The median level of 95% prediction interval-normalized rejection score was significantly higher in AR as compared with stable samples (0.64 vs. -0.71, P < 0.0001) (**Figure 1B**). The urinary rejection score showed high performance in discriminating the stable and AR samples, with an AUC of 0.9649 (P < 0.0001). At a threshold set at a normalized value of 0, the sensitivity and specificity of the assay was 93.88% and 94.90% respectively (**Figure 1C**), suggesting that the assay could be used to screen patients at risk of rejection to avoid unnecessary biopsies in the clinical setting.

Conclusions: This novel urinary rejection score enables rapid and accurate discrimination of AR from stable patients without the costs associated with sequencing. As collection of urine requires no training and can be performed as often as needed, this assay can provide inexpensive, accurate, and longitudinal assessment of AR in KT patients.

Funding: NIDDK Support

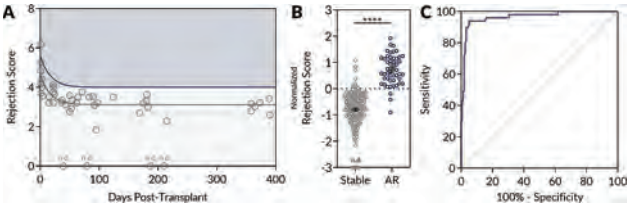

Figure 1. Determination of rejection score kinetics post-transplantation and discrimination of AR.

TH-PO1106

Utility of a Novel dd-cfDNA Test to Detect Injury in Renal Post-Transplant Patients

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Background: Serum creatinine (SC) and biopsy are the standard of care for detecting renal allograft injury and rejection. SC has poor specificity and sensitivity, and biopsies are costly, invasive, and have attendant complications. We report on the clinical utility of a novel method that measures donor-derived cell-free DNA (dd-cfDNA) using a single SNP-based NGS methodologyto diagnose allograft injury/rejection.

Methods: We conducted a randomized controlled trial sampling 154 fellowship-trained nephrologists with two to 40 years of post-residency practice and an active panel

of at least five renal allograft patients. Over two rounds, providers cared for six online, virtual patients—Clinical Performance and Value (CPV) vignettes—a validated tool that accurately measures clinical utility and clinical practice. CPV patients were aged 30-75, were 3-24 months post-transplant, and presented in one of three ways: (1) active rejection with moderate SC increase and proteinuria; (2) subclinical rejection with no change in SC; and (3) elevated SC from another nephrotoxic insult but not rejection. Doctors randomized into the intervention arm were given educational materials on the dd-cfDNA test between rounds and dd-cfDNA results before they cared for patients in round 2. The primary outcome determined whether using dd-cfDNA demonstrated clinical utility and improved patient care as manifested by the workup, diagnostic accuracy, and medical management of these patients.

Results: At baseline, providers correctly determined primary diagnosis in only 50% of cases (p=0.853). In round 2, intervention providers improved 32.9 percentage points (p<0.001); control providers did not improve (p=0.257). Providers in both groups made a correct biopsy or referral decision in 58% of cases at baseline. Intervention improved 30.0 percentage points (p<0.001) while control did not improve in round 2 (p=0.501). Similarly, intervention providers' medical management improved significantly (+14.3 percentage points, p<0.001) in round 2, while controls' did not (p=0.483).

Conclusions: Nephrologists shown dd-cfDNA levels were significantly more likely to accurately diagnose, and make better biopsy, referral and medically management decisions for renal transplant patients.

TH-PO1107

Serial AlloSure Testing with Donor-Specific Antibodies in Renal Transplant Recipients Can Avoid Kidney Biopsy

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Background: Donor derived Cell free DNA testing with targeted next gen sequencing assay (Allosure) has been shown to predict renal allograft rejection at a threshold of 1% having a PPV/NPV of 44%/96% for antibody mediated rejection (AMR). The utility of positive Allosure in the diagnostic algorithm is not well defined and we believe looking at clinical patterns in this subset may shed light on optimal strategy of use.

Methods: A total of 155 patients (pts) transplanted between 2016 - 2019 had 289 Allosure tests. 40 were tested at predetermined intervals (KOAR registry) and remaining 115 had for-cause testing. Pts with Allosure levels >1% were assessed for DSA, indication for biopsy, serum creatinine (Cr), rejection, alternate etiology and therapy change.

Results: Allosure results ranged from detection threshold <0.15% to 13%. 24/155 pts had Allosure >1%. 4/24 were in KOAR registry of which 2 had ACR 1B, 1 had AMR, and 1 had AKI 2/2 obstruction. 19/24 underwent allograft biopsy. 10/24 had AMR, 3/24 had ACR 1B and 1/24 had mixed rejection. 5/24 had no rejection on biopsy 3/10 with AMR and 3/5 with other causes had rise of Cr >0.3mg from baseline at the time of positive result. 5/24 who did not have biopsy had stable Cr with negative/improved DSA. 15/24 had change in therapy, 2 with positive biopsy/Allosure had stable DSA/Cr with no change in therapy. 2 pts were started on Losartan for AT1 R antibody & AMR. 1/24 pt with initial Cr> 12 mg/dl did not recover and declared ESRD. All 15 pts with therapy change stabilized/improved renal function. 2/3 wtih ACR 1B who had >1 value showed a clear trend correlating with renal function. Median peak Allosure was 3 and mean peak was 3.09. The lowest positive result was 1.1 and highest was 13, both in pts with ACR 1B.

Conclusions: Allosure performs well as a test to "rule out " rejection. Serial Allosure combined with DSA and serum Cr trend can safely avoid kidney biopsy. It allows detection of AMR before rise of Cr in the majority of pts. No correlation was found with level of Allosure and Cr. The mean value was higher than the threshold of a positive result. DSA was stable/negative in all patients with positive renal outcome supporting safety of such an approach. Our study adds to a growing repository of Allosure use in kidney transplant. Study limited by small sample, mixed cohort and non adherence to testing protocol.

TH-PO1108

The Serum CTRP9 Concentration Correlates with Cardiovascular Risk in Renal Allograft Recipients

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Background: Cardiovascular disease (CVD) due to atherosclerosis is a major cause of death in renal allograft recipients. Recently, C1q/TNF-α related protein-9 (CTRP9), which is a paralog of adiponectin (ADPN), has been suggested to be related to the suppression of atherosclerosis and the occurrence of CVD, but this relationship has not been confirmed in renal allograft recipients. We evaluated the relationships among the serum CTRP9 concentration, serum ADPN concentration, and vascular calcification were investigated in 50 Japanese kidney allograft recipients.

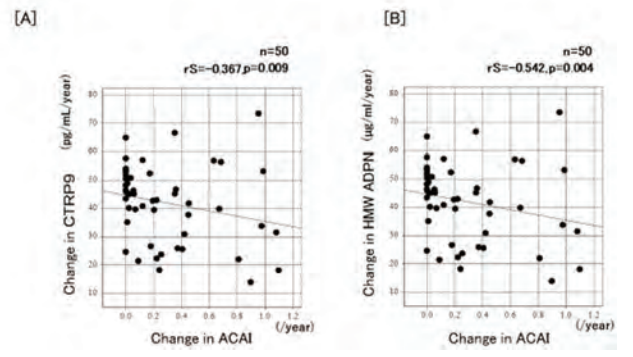
Methods: Calcification of the abdominal aorta was evaluated according to the aortic calcification area index (ACAI) calculated from CT images. Changes in the serum CTRP9 and ADPN fractions and ACAI were examined for 8 years. In addition, the expression of CTRP9 and ADPN and their respective receptors AdipoR1 and R2 in small arteries of the transplanted kidney was examined by immunofluorescence.

Results: In renal allograft recipients, the serum CTRP9 concentration at the start of the observation was not significant correlated with eGFR or serum high-molecular-weight (HMW)-ADPN concentration (rS=-0.009, p=0.950; rS=-0.226, p=0.114, respectively). However, the change in the serum CTRP9 concentration was positively correlated with the change in the serum HMW-ADPN concentration (rS=0.315, p=0.026) and negatively correlated with the change in ACAI (rS=-0.367, p=0.009). Multiple regression analysis revealed that the serum HMW-ADPN concentration was a significant positive factor for the change in the serum CTRP9 concentration. Moreover, for ACAI, an increase in the serum CTRP9 concentration was an improving factor, but aging was an exacerbating factor. Furthermore, colocalization of CTRP9 and AdipoR1 was noted in intrarenal arterial endothelial cells.

Conclusions: In renal allograft recipients, CTRP9 and HMW-ADPN were suggested to produce vascular protective effects mediated by AdipoR1 to suppress the progression of aortic calcification.

Funding: Government Support - Non-U.S.

Figure.



TH-PO1109

Circular RNA in Urine-Liquid Biopsy Biomarker of Acute Rejection in Kidney Transplantation

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Background: Circular RNAs (circRNAs) are long non-coding RNA transcripts with strong gene regulatory function. Their circular structure guarantees stable detection in blood. We hypothesized that circRNAs are detectable in urine as well and serve as biomarker of acute T cell-mediated kidney allograft rejection.

Methods: A global urinary circRNA expression analysis was performed in patients with acute rejection compared to patients without rejection. Differentially concentrated circRNAs were validated in patients with acute rejection (n=62), in stable transplant patients (control, n=18) and rejection dependent concentrations were additionally analyzed after successful anti-rejection therapy (n=10). Biomarker specificity was verified in stable transplant patients with urinary tract infection (disease control, n=13).

Results: A distinct urinary circRNA transcriptome signature identified patients with acute rejection. CircRNAs *hsa_circ_0001334* and *hsa_circ_0071475* were strongly altered and thus validated in the whole cohort. Increased *hsa_circ_0001334* concentrations were specifically confirmed in patients with acute rejection and returned to base level after anti-rejection therapy. *Hsa_circ_0001334* showed promising biomarker value and prognostic potential in predicting higher decline of creatine clearance after one year of transplantation.

Conclusions: In conclusion, patients with acute rejection were identified by a specific urinary circRNA transcriptome signature and circRNA *hsa_circ_0001334* was discovered as novel non-invasive diagnostic and prognostic biomarker of acute T cell-mediated kidney allograft rejection. Measuring concentrations of circRNAs in urine might thus serve as novel liquid biopsy in kidney transplant patients.

TH-PO1110

Longitudinal and Cross-Sectional Analysis of Kidney Transplant Urine mRNAs Reveals Glomerular Disease as an Important Driver of Long-Term Graft Loss

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Background: Biopsies from failing allografts (El-Zoghby) and longitudinal protocol biopsies in two studies (Nankivell; Stegal) suggest that glomerular disease (GD) is associated with late graft loss. In a10yr study Stegal reported GD to be more prevalent than IFTA. To understand why kidney transplants fail over time, we utilized nephron segment specific urine pellet mRNA markers to enable non-invasive analysis of injury patterns

Methods: Longitudinal and cross sectional urine samples covering 20years post-TP for all comers were collected. Two podocyte markers (podocin, nephrin), a distal tubular/collecting duct marker (aquaporin2) and marker of innate immune/profibrotic activity (TGFBeta1) were measured in spot urine samples and normalized to creatinine. Baseline 2kidney (2K) values for 4 markers were obtained from 98 healthy controls and used to derive 1K normal values.

Results: 380 recipients provided 1997 urine pellets. All markers increased immediately after TP but downtrended towards expected ranges. Over 20yrs there was a steady increase in both podocyte markers (UPod:CR,UNeph:CR) compatible with increasing podocyte detachment rate. The ratio of podocin to nephrin (UPod:Neph) a marker of podocyte hypertrophic stress increased markedly after TP, and remained elevated above 2K control. Downstream tubular injury marker (Aqp:CR) remained elevated in the short-intermediate term compatible with tubule-interstitial injury but by 3years decreased to 2K level. The ratio of the glomerular to tubular marker (UPod:Aqp2) continued to increase after TP reflecting increasingly glomerular vs. tubular injury. Urine pellet TGFbeta1CR remained elevated above 2K level suggesting ongoing TP injury.

Conclusions: Urine pellet mRNA data are compatible with long-term protocol biopsy data suggesting that GD is an important driver of long-term kidney allograft failure.

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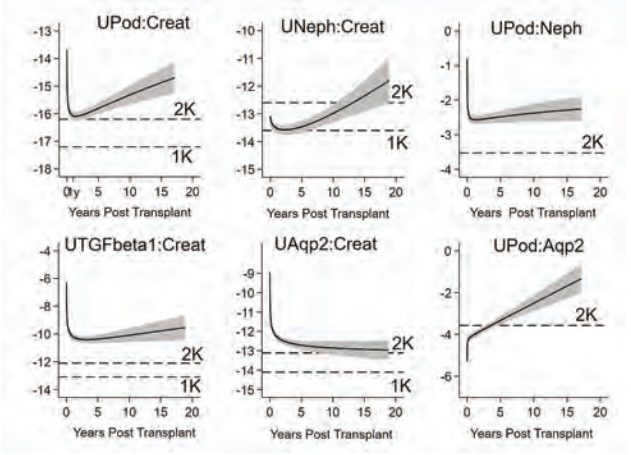

TH-PO1111

Urinary CXCL9 Levels Correlate with Quantitative Tubulitis in Kidney Allograft Biopsies

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Background: Acute and chronic cell mediated rejection (CMR) are histologically characterized by the presence of interstitial inflammation (i) and tubulitis (t), with or without endarteritis, as defined by Banff Classification system [Haas M, et al. AJT, 2018]. The Banff tubulitis score (t) is semi-quantitative, based on the most inflamed tubular profile. These values are then used to establish the grade of CMR. Tubulitis can be difficult to assess using standard staining, and its interobserver reproducibility is poor. Urinary CXCL9 has been shown to correlate with the diagnosis of CMR, and their levels decrease after successful therapeutic interventions [Gandolfini I, et al. KI Rep, 2017]. We used immunohistochemical CD3 stain with a PAS counterstain to elicit a continuous quantitative tubulitis score in kidney allograft biopsies and correlated the findings with urinary CXCL9 levels (Figure 1).

Methods: On digitized whole slide images of CD3+PAS slides (n=12; CMR = 5 biopsies, borderline lesions= 1 and no rejection=6) mean CD3+ cells per tubule (mCD3/t), percentage of tubules showing at least 1 CD3+ cells (tubulitis ratio, tr) and number of CD3+ cells in the most inflamed tubule (maxt) were manually assessed using ViewPoint software (PreciPoint). Urinary CXCL9 levels at the time of diagnosis were measured using ELISA kit (R&D, Quantikine ELISA). Prism GraphPad 5 was used for statistical analysis.

Results: We found significant correlation between urinary CXCL9 levels and mCD3/t (r2 0.75, p=0.0003), tr (r2 0.66, p=0.0012) and maxt (r2 0.70, p=0.0006).

Conclusions: CD3+PAS stain augments current approach's by generating a continuous score quantify tubulitis. This quantification correlates with urinary CXCL9 levels, a biomarker of CMR. Studies on larger cohorts are underway to better establish the clinical significance and utility of quantitative tubulitis evaluation.

TH-PO1112

Donor Nephrectomy Selectively Increases Proximal Tubular Proteins in Urinary Vesicles

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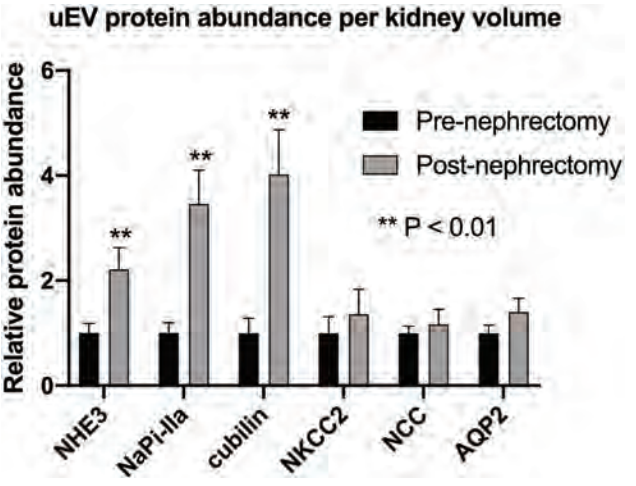
Background: Donor nephrectomy causes hyperfiltration and hypertrophy of the remaining kidney. Uninephrectomy in rats causes a selective increase in proximal tubular proteins. Accordingly, we hypothesize that human donor nephrectomy increases proximal tubular proteins.

Methods: Nineteen kidney donors were included in this study. Kidney volume was calculated from CT scans prior to donation. Urine was collected prior to and three months after donor nephrectomy. Urinary extracellular vesicles (uEVs) were isolated and used as non-invasive read-out for renal tubular protein abundance. uEVs were quantified using nanoparticle tracking analysis. The following proteins were analyzed in uEVs using ultracentrifugation and immunoblotting: NHE3, NaPi-IIa and cubilin (proximal tubule), NKCC2 (thick ascending limb), NCC (distal convoluted tubule), and AQP2 (collecting duct). Relative protein abundance was expressed per remaining kidney volume.

Results: Donor nephrectomy reduced kidney volume by 50±3%, creatinine clearance by 38±10%, and uEV excretion by 20%. The relative abundance of proximal tubular proteins in uEVs increased significantly, whereas no change occurred in distal nephron proteins (Figure).

Conclusions: Donor nephrectomy selectively increases proximal tubular proteins in uEVs. This may be due to hyperfiltration and hypertrophy occurring in this segment. It may also explain why a kidney volume reduction of ~50% is accompanied by a decrease in uEV excretion of only 20%. These results provide insight in the changes after kidney donation and are relevant when analyzing uEVs in kidney donors.

Funding: Private Foundation Support



TH-PO1113

Biomarker Implementation: Evaluation of the Decision-Making Impact of CXCL10 Testing in a Pediatric Cohort

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Background: Children are at high risk for subclinical rejection and invasive kidney biopsy is currently used for active surveillance. Urinary CXCL10 hold the most promise as a biomarker for post-transplant monitoring of rejection. How it will influence clinical decision has never been tested. As such, our objective was to test whether CXCL10 can improve the clinical decision-making to identify organ rejection risk.

Methods: We first assembled a panel of experts to establish a minimum dataset for standard clinical decision-making for an indication biopsy. Clinical vignettes were then built from 15 prevalent pediatric kidney transplant recipients who had surveillance or indication biopsy and biobanked urine sample. Urine samples were tested for CXCL10 and reported as ratio to creatinine. Pediatric nephrologists were recruited review serial clinical vignettes and A) predict rejection risk and B) decide to biopsy; without then with urinary CXCL10 result and rejection diagnosis sensitivity/specificity information for different levels. Biopsy decisions were then correlated with the biopsy results. Inter-rater agreement (IRA) was assessed by Fleiss Kappa (K) for binary choice and interclass correlation (ICC) for probabilities.

Results: Eleven pediatric nephrologists were enrolled. IRA for choice to biopsy was fair both before (K=0.48, p<0.01) and after (K=0.43, p<0.01) incorporating CXCL10 data. ICC of probability assessment for rejection was poor before (0.28, p<0.01) and improved to fair (0.48, p<0.01) with addition of chemokine data (p=0.6 for difference). Clinicians did consider the CXCL10 in their decision making process and CXCL10/Cr correlated with the change in the estimated probability of rejection (r2=0.7756, p<0.0001), with 2.77 as the cutoff for a biopsy-based intervention. The decision-accuracy (majority ordering a biopsy when rejection was found or not ordering one when there was no rejection) improved from 8/15 (53.3%) cases to 11/15 (73.3%) with CXCL10 results. Using the cut-off value for CXCL10/Cr ratio of 2.77 would have been accurate in 12/15 cases (80%).

Conclusions: There is high variability in decision-making on biopsy indication. Urinary CXCL10/Cr improves probability estimates for risk of rejection. However, training may be required to assist nephrologists in using biomarker information for clinical decision-making.

TH-PO1114

Low Soluble Klotho Levels Are Associated with Renal Function Decline in Kidney Transplantation

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Background: Serum soluble klotho levels have been shown to be associated with renal function in pre-dialysis patients with chronic kidney disease. However, there are few reports regarding the association between soluble klotho levels and renal function in kidney transplant (KTx) recipients. Thus, we investigated the association of soluble klotho levels of the pre-KTx with renal function decline in living KTx recipients.

Methods: This is a retrospective, observational study of 41 living KTx recipients who received standard immunosuppressive therapy between 2002 and 2017 in our hospital. The serum soluble klotho levels were divided into 2 groups according to the median value: ≧ 456 pg/ml (High group, n=21), or < 456 pg/ml (Low group, n=20). Renal function decline was defined as a 30% or more decrease in estimate glomerular filtration rate (eGFR) compared with that of baseline within 3 months after KTx. A multivariable time-to-event analysis between the groups was performed.

Results: 4.9% of the recipients received preemptive KTx. 75.6% and 19.5% of the recipients were treated with hemodialysis and peritoneal dialysis before KTx, respectively. Median dialysis vintage was 408 days (interquartile range, IQR :168-1132 days). Median follow-up period was 913 days (IQR: 318-2015 days). KTx recipients in the Low group showed a significant higher incidence of 30% decrease in eGFR than those in the High group (p=0.036). In multivariable Cox models adjusting for patient-age, donor-age, the presence of rejection, and the number of HLA mismatch, the low soluble Klotho levels remained to be associated with a higher risk of 30% decrease in eGFR (HR: 2.78, 95%CI: 1.02-8.26).

Conclusions: These results suggest that lower soluble klotho levels of the pre-KTx are associated with increased risk of renal function decline in KTx recipients. Maintenance of higher serum soluble klotho levels before KTx may be preferable for renal function preservation.

TH-PO1115

Increased Delta Neutrophil Index Is Associated with Poor Prognosis in Cadaveric Donor Kidney Transplantation

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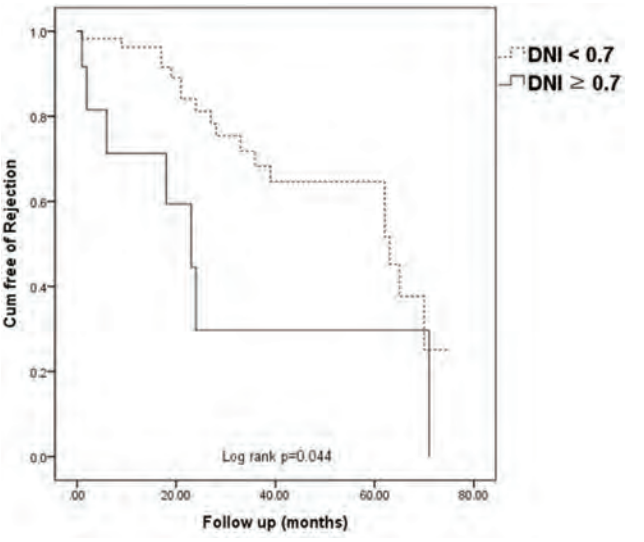
Background: Delta Neutrophil Index (DNI) is the fraction of circulating immature granulocytes. In many studies, DNI has been demonstrated as a useful prognostic marker in critical patients. We hypothesized that increased level of DNI in the recipient is associated with poor prognosis in cadaveric donor renal transplantation (CRT).

Methods: We reviewed medical records of a total of 73 patients undergoing CRT from March 2013 to January 2018 retrospectively. The transplant rejection (TR) was assessed using Banff classification, and subclinical rejection was excluded in the study.

Results: Twenty-five (34.2%) patients were diagnosed with TR. Among them, 11 patients were classified as early TR. The post-operative DNI (po-DNI) was higher in the patients with early TR than that of patients without it (1.21 vs. 0.18, p<0.001). In univariate logistic regression test, cold ischemic time, last creatinine level of the donor before transplantation (last-Cr), po-DNI level, and peri-operative infection predicted early TR. In multivariate-adjusted logistic regression test, only high level of po-DNI predicted early TR (Odds ratio 12.31, 95% CI 1.22-129.82, p=0.034). The c-statistic value of po-DNI in the logistic model was 0.78 (95% CI 0.60-0.95, p=0.004). Multivariate Cox regression analysis showed that last-Cr (Hazard ratio (HR) 2.25, 95% CI 1.26-4.13, p=0.006) and pre-operative DNI (HR 14.02, 95% CI 2.62-75.26, p=0.002) predict renal survival in CRT.

Conclusions: Increased DNI of the recipient in CRT is thought to be a useful marker for predicting early TR and renal survival.



Cumulative early acute rejection free period according to DNI level

TH-PO1116

Predicting Deceased Donor Kidney Transplant Outcomes: Comparing KDRI/KDPI with Machine Learning

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Background: Kidney transplantation is an effective cure for patients suffering from end-stage renal disease. Kidney transplantation is cost-effective, provides a significant survival benefit, and improves the quality of life for patients. One limitation on kidney transplantation is the appropriate assessment of donor quality, for which several indices have been created.

Methods: Machine learning methods (MLM) were compared to kidney donor risk index (KDRI aka KDPI) for the ability to predict graft failure by 12, 24, and 36 months after deceased donor kidney transplantation (DDKT). The MLM model, an ensemble of thousands of randomly generated decision trees, was trained with the same data initially used to develop KDRI.

Results: An MLM trained with the readily available recipient and donor variables performs significantly better than KDRI/KDPI when predicting graft failure by 12, 24, and 36 months after DDKT. When comparing equal prediction failure rates of 10%, MLM successfully predicted 126% more successful DDKTs (an additional 2,148) than KDRI/KDPI from 1995-2005. Over the entire ROC curve, the MLM performed statistically significantly better c-statistic than KDRI/KDPI in all predictions.

Conclusions: Using MLM, many high-KDRI kidney offers resulted in thousands of successful patient outcomes without increasing risk of predicted graft failure. The MLM provided a significant improvement over KDRI for the assessment of kidney offers and give clinical professionals an improved basis for making the critical decisions. This work lays the foundation for future MLM in organ transplantation and describes the steps to measure, analyze, and validate future models.

TH-PO1117

Predicting Health Outcomes for Elderly Renal Transplant Recipients with Machine Learning

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Background: Application of machine learning to nephrology research has been scarce. In this study, we demonstrated the use of classification algorithms in predicting all-cause death at three-year among elderly deceased-donor renal transplant recipients.

Methods: This is a retrospective, population-based, cohort study of all cases of deceased-donor renal transplants performed in Ontario, Canada from March 31, 2002 to April 1, 2013. Recipients aged over 70 years were followed up until death or to April 1, 2016. Bootstrap-aggregating classification tree and K-Nearest Neighbors (KNN) were used to train a predictive model for death at three-year post-transplant. Patient-level attributes at the time of transplantation, including demographic characteristics, lab results, transplant information, comorbidities, and pre-transplant health care utilization, were examined as potential determinants of post-transplant death. A ratio of 3:2 was used to construct training and testing sets. Synthetic Minority Oversampling Technique was applied to generate artificial positive cases (death) and under-sample negative cases (alive) in the training set to reduce bias. Models were trained and tuned using ten-fold cross-validation on the training set and tested on the specificity and sensitivity of prediction using the testing set.

Results: Among 275 elderly transplant recipients, the majority (n=271, 98.5%) were transplanted at 71-80 years and four (1.5%) were older than 80 years. Death occurred in 52 (18.9%) cases at three-year post-transplant. Before sampling, classification tree and KNN had test sensitivity of 0.11 (95% confidence interval [CI], 0.01-0.33) and 0.07 (95% CI, 0-0.18), respectively, while both achieving 0.95 (95% CI, 0.88-0.98) specificity. After sampling, classification tree and KNN achieved test sensitivity of 0.21 (95% CI, 0.06-0.46) and 0.26 (95% CI, 0.03-0.50), respectively, as well as test specificity of 0.89 (95% CI, 0.81-0.95) and 0.84 (95% CI, 0.74-0.90), respectively.

Conclusions: Our findings add to the growing body of knowledge aimed at improving the performance of risk calculators (e.g., iChoose Kidney) that help patients and families to make informed decisions in renal care. Furthermore, our study confirmed the strength of machine learning techniques in population-based nephrology research despite our limited sample size and the rarity of the outcomes assessed.

TH-PO1118

Optimization of Machine Learning Models for Predicting Delayed Graft Function in Renal Allografts

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Background: Delayed graft function (DGF) is associated with worse short- and long-term renal allograft outcomes. Several groups have previously developed models that compute the theoretical risk of DGF for allograft recipients using standard statistical inference methods. In this study, we apply automated computational algorithms to generate tens of thousands of DGF prediction machine learning models based on donor characteristics alone. In this en masse approach, we are able to empirically optimize these machine learning models for the prediction of DGF.

Methods: Deceased donor data available from UNOS for 1,694 renal transplants at our center from 2010-2018 were used in this study, which included various elements of demographics, medical history, and circumstances of death. Cold ischemia time (CIT) and KDPI were included as well. The number of cases was further trimmed randomly to achieve a 50%/50% split in DGF-positive and negative cases, with a final total of 922 cases. These data were used to create 10 runs for each specific parameter combination [each using 90% (n=830) of cases for training phase and 10% (n=92) of cases for each run's validation test] to generate a total of 45,980 unique models within these parameter combinations on 4 distinct machine learning algorithms (logistic regression, k-nearest neighbor, support vector machine, random forest). Models were also produced with fewer donor features, KDPI alone, CIT alone, and KDPI with CIT. The mean accuracy, standard deviation, and area under the curve (AUC) for the best models were calculated.

Results: Of the 45.980 models generated, the best performing models had an accuracy of 74% (5.7) and AUC of 77. A common theme to these optimized models was that they excluded KDPI as a feature but included CIT. KDPI alone performed poorly (accuracy 49-57%; AUC 0.51-0.55). CIT alone was also suboptimal (accuracy 57-63%; AUC 0.56-0.62).

Conclusions: Machine learning algorithms can help to produce improved and optimized prediction models for DGF.

TH-PO1119

Factors Impacting the Disparity in Receipt of Live Donor Kidneys by Women vs. Men

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Background: It was noted in the early 2000's that women received fewer live donor kidneys (LDK) than men. Since that time, more women have entered the workforce, transplantation of highly sensitized individuals has improved and there has been an increase in altruistic donation; factors that might improve the LDK transplant rate in women. We examined the rate of LDK transplants in women compared with men since 1998-00, as well as factors that might affect it.

Methods: All 105,729 primary adult living donor kidney transplants reported to UNOS/OPTN between 1998 and 2018 were analyzed. Only adult recipients were included in the analyses. The time period was divided into 3-year intervals to adjust for yearly fluctuations. Logistic regression models were used to assess the odds to receive a LDK for women adjusted for possible risk factors.

Results: The overall rate of LDK for women was 39%. Odds ratio (OR) for women vs men significantly worsened over time, with a OR of 0.866 (CI 0.845-0.93) for 2004-06, 0.756 (CI 0.719-0.795) in 2010-12 and 0.727 (CI 0.691-0.765) in 2016-18 compared to 1998-00. The OR decreased significantly with increasing age (>70yr, OR 0.192, CI 0.113-0.328). Interestingly, black women were more likely than whites (OR 1.315, CI 1.267-1.365), and women on dialysis were less likely than men (OR 0.791, CI 0.770, 0.813) to receive a LDK transplant. Women were also less likely to receive a non-biological kidney (whether spousal or altruistic) OR 0.806, CI 0.785-0.828, but women with a PRA >20 had a much higher chance of receiving a LDK (OR 3.547 CI 3.389-3.712).

Conclusions: 1. The gender disprity in LDK rate for women has worsened since 1998-00, with a 28% difference in 2016-18. 2. Older women have the least likelihood of receiving a live donor kidney, with women over the age of 70 years 80% less likely. 3. Black women are more likely than whites to receive a LDK. 4. Women on dialysis are 20% less likely to receive a kidney than those who have not yet started. 6. Although biological reaons have been postulated in the past to explain gender disparity, the above findings and the observations that women who are sensitized are 3.5 times more likely to receive a live donor kidney than those who are not and that women are less likely to recieve a non-biologically related kidney suggests that sociocultural and practice patterns may be more important and should be investigated further.

TH-PO1120

Prognostic Value of Standardized Deceased Donor Kidney (DDK) Procurement Biopsies

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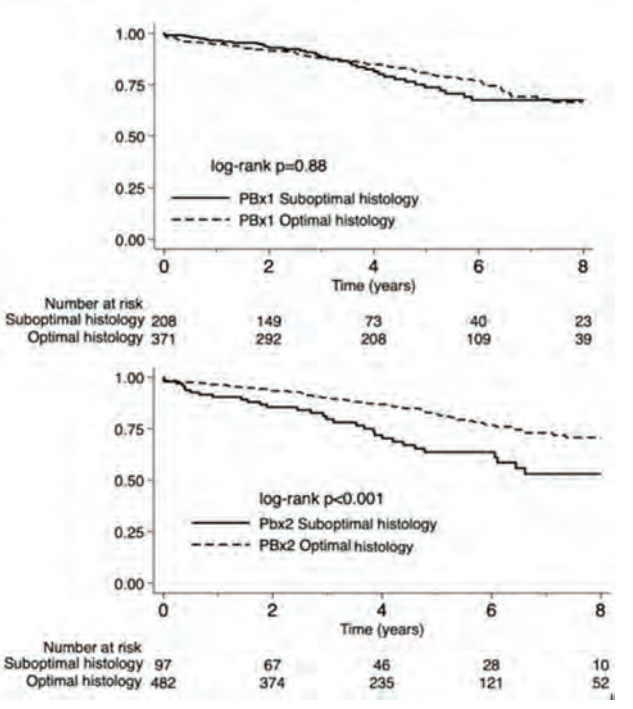
Background: Procurement biopsy (PBx) histology is the most common reason for DDK discard but has been shown to be of limited prognostic value. Occasionally DDK are biopsied twice when transported between OPOs, allowing us to assess the standardized approach to performing and interpreting PBx at our OPO.

Methods: We identified 591 DDKs transplanted at our center from 1/2006-12/2016 (imported from 60 OPOs) with an initial PBx (PBx1) that was repeated by our local OPO (PBx2). "Suboptimal histology" was defined as glomerulosclerosis (GS)>10%, interstitial fibrosis/tubular atrophy (IFTA)>25%, and/or vascular disease (VD) graded as moderate or severe. We calculated kappa coefficients to assess agreement between PBx and used time-to-event analyses to evaluate the association between suboptimal histology on PBx1 and PBx2 with death-censored allograft survival.

Results: 36% PBx1 and 17% PBx2 were classified as having suboptimal histology. 75% of DDK with suboptimal PBx1 had optimal PBx2. Overall histologic concordance (optimal versus suboptimal) between PBx1 and PBx2 was 65% (κ =0.13). Categorical agreement was higher for VD (κ=0.13, 52% concordance) than for IFTA (κ=0.08, 67% concordance) or GS (κ=0.11, 44% concordance). In contrast to PBx1, suboptimal PBx2 histology was associated with death-censored allograft survival in bivariable and multivariable analysis (adjusted hazard ratio 2.17, 95% CI 1.72-3.45, p<0.001).

Conclusions: PBx performed at different OPOs were frequently discordant, likely due to variable PBx technique and interpretation between OPOs. Our results suggest that standardization may improve utility and reliability of PBx for assessing DDK quality.



TH-PO1121

Machine Learning-Guided Measurement of Visceral Fat Area in Computed Tomography and Delayed Graft Function After Kidney Transplantation

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Background: Innovative machine learning can be applied to efficiently provide the information on medical imaging and be useful in the prediction model. Accordingly, the present study measured visceral fat area (VFA) with updated machine learning algorithm in kidney transplant recipients and evaluated its correlation with delayed graft function (DGF).

Methods: A total of 287 adult kidney recipients who examined abdominal computed tomography with full range of torso before transplantation were enrolled. VFA in the

abdominal cavity was measured in cubic meters throughout machine learning algorithm. DGF was defined as the need for dialysis during the first transplantation week.

Results: The mean age was 47.8 ± 11.3 years and male was 66.2%. The mean body mass index was 24.6 ± 3.5 kg/m^2. The VFA was 2.88 ± 1.92 m^3, and the body surface area-adjusted value was 1.59 ± 0.95 m. The adjusted VFA had a linear relationship with the surgery time (β = 0.12; *P* = 0.040). The risk of DGF increased depending on an increase of 1 unit in adjusted VFA with an odds ratio of 1.80 (1.07–3.02). However, body mass index was not associated with DGF (odds ratio, 0.99 (0.83–1.19). The area under receiver operating characteristic curve of adjusted VFA was 0.73, which was greater than 0.50 in body mass index (*P* = 0.032).

Conclusions: Machine learning algorithm may efficiently provide information on VFA of kidney recipients. This issue will improve the predictive capacity of transplant outcomes such as DGF.

TH-PO1122

Construction of a Predictive Model of Delayed Graft Function Using Machine Learning Techniques

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Background: Brazilian studies have been reported incidences of delayed graft function (DGF), 2-3 fold the incidences described by American and European cohorts. The available predictive models of DGF, based on distinct clinical realities, are not validated in our population. The purpose of the study was evaluate the accuracy of the available predictive models and, since none of these models present good accuracy, construct a local prediction model

Methods: Retrospective cohort study including DD KT performed between Jan 2014 and Dec 2017 in two transplant centers (n=443). The predictive DGF models tested were those described by Irish et al., Jeldres et al., Chapal et al., and Zaza et al. For the construction of the new predictive model, machine learning was used

Results: Patients were predominantly men (56.7%), young adults (44.2 ± 14.7 years), mixed race (84.4%), who remained 46.8 ± 45.2 months on dialysis. Donors had a mean age of 31 ± 12.7 years, most of them died from trauma (70.9%), 5.4% were hypertensive (HA), 0.7% were diabetic, and the final creatinine was 1.1 ± 0.6 mg/dL. Only 4.3% were expanded criteria donors. 83.1% of the grafts were perfused with HTK and the mean cold ischemia time (CIT) was 20.9 ± 4 hours. The incidence of DGF in this sample was 53%. The predictive models of DGF available presented regular or poor discriminant power: Irish (AUC 0.686), Chapal (AUC 0.638), Jeldres (AUC 0.613), Zaza (AUC 0.591). The three models with the best performance were decision tree, neural networks and support vector machine. In the final model, the variables considered were: from recipients : age, diabetes and time on dialysis; from donors: age, body mass index, HA, serum sodium, creatinine phosphokinase, final creatinine, cause of death, high dose of vasoactive drugs and diuresis; CIT. The final model showed excellent discriminant power (AUC 0.942)

Conclusions: The incidence of DGF in the sample was high, despite the predominance of standard criteria donors. In addition to variables classically associated with DGF, variables related to donor maintenance were pointed out in non-linear statistical methodologies. The available predictive models had poor accuracy in predicting DGF in our population. The developed model presented excellent performance.

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TH-PO1123

Patient Survival After Kidney Transplantation: Important Role of Graft-Sustaining Factors as Determined by Predictive Modeling Using Random Survival Forest Analysis

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Background: Identification of the relevant factors for death can improve patient's individual risk assessment and decision making. A well-documented patient cohort (n=892) in a renal transplant program with protocol biopsies was used to establish multivariable models for risk assessment at 3 and 12 months posttransplantation by random survival forest analysis.

Methods: Patients transplanted between 2000 and 2007 were observed up to 11 years. Loss to follow-up was negligible (n=15). 2251 protocol biopsies and 1214 biopsies for cause were performed. All rejections and clinical borderline rejections in protocol biopsies were treated.

Results: 10-year patient survival was 78%, with inferior survival of patients with graft loss. Using all pre- and posttransplant variables until 3 and 12 months (n=65), the obtained models showed good performance to predict death (concordance index: 0.77-0.78). Validation with a separate cohort of patients (n=349) showed a concordance index of 0.76 and good discrimination of risks by the models, despite substantial differences in clinical variables. Random survival forest analysis produced robust models over a wide range of parameter settings. Besides well-established risk factors like age, cardiovascular disease, type 2 diabetes, and graft function, posttransplant urinary tract infection and rejection treatment were important factors. Urinary tract infection and rejection treatment were not specifically associated with death due to infection or malignancy but correlated strongly with inferior graft function and graft loss.

Conclusions: The established models indicate the important areas that need special attention in the care of renal transplant patients, particularly modifiable factors like graft rejection and urinary tract infection.

TH-PO1124

External Validation of Predictive Score for Post-Transplantation Outcome in US Deceased Kidney Transplant Recipients

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Background: We previously published a prediction model (www.transplantscore.com (TS)) for allograft and patient survival, which consisted of only predictors available at the time of kidney transplant (KT). Here, we aimed to perform external validation to assess the robustness, reliability, and applicability of our model.

Methods: Five hundred eleven patients who underwent first deceased KT in our Institute between 2010 to 2017 were included. We computed the original prediction score for these patients and compared the results with the observed outcome in terms of the score's calibration (goodness of fit) and discrimination (AUC: Area Under the Curve). We also assessed the predictive performance in terms of re-classification (NRI: Net Reclassification Improvement) when compared with a binary classifier based on the EPTS raw score.

Results: In the entire cohort, the mean age was 51.2±11.8 years old, 83% were African-American, most of the patients were on hemodialysis (81%) before KT and mean time on dialysis was 5.4 years. The TS-predicted mortality probabilities clearly separate patients as demonstrated in the Kaplan-Meier curves using all available follow-up (Figure, panel A). The AUCs based on TS for 1- and 2-year mortality (panel B) were 0.737 and 0.682, respectively. These were higher than those for the classifier based on the EPTS score (AUC of 0.649 and 0.623 for 1 and 2 year mortality, respectively) and the NRI computed to 0.302 and 0.149 for 1 and 2 year classifications in favor of TS. However, the differences in the AUCs were not statistically significant (p = 0.138 and p = 0.149 for 1 and 2 year comparisons). The Hosmer and Lemeshow goodness of fit test of TS indicated some inadequate fitting (p = 0.015 and 0.038, respectively) apparently especially an overestimation for higher-score patients.

Conclusions: TS appears to broadly correctly classify patients with respect to their 1 and 2 year mortality rate.

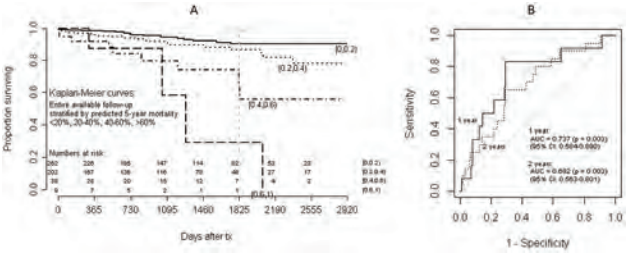

Figure 1

TH-PO1125

Development of Donor Kidney Age: A Simple Score Summarising Deceased Donor Risk

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Background: Although a number of donor factors are known to affect outcome following deceased donor kidney transplantation, many units have no clear criteria for acceptance. Donor quality scoring systems such as KDRI are based on historic data sets, performing less well in the modern comorbid donor pool, and are difficult for patients to understand.

Methods: All deceased-donor kidney offers at a single centre were analysed over a 12 month period in order to develop a patient-friendly scoring system. Donor age is modified according to the presence or absence of a number of risk factors to generate a "donor kidney age" to predict post-transplant outcome.

Results: Out of 388 offers, from 301 donors aged 6 - 84, 109 (28%) were acepted and transplanted. At 3 months post-tranplantation, recipient GFR over 30 was seen in 80%. Organs were declined due to recipient factors in 26% and donor quality concerns in 46%. Donor Kidney Age was derived incorporating 12 risk factors: donor cardiac death, hypertension, diabetes, vascular disease, baseline kidney function, creatinine rise, oliguria, proteinuria, HLA match, cardiac arrest, use of adrenaline, and duration of hospitalisation before donation. Quintiles of donor risk for all offers were identified using DKA cutoffs: 50, 60, 70, and 80. Increasing DKA quintile was associated with poorer post transplant outcome, with low 3 month GFR (below 30ml/min) in 97, 85, 73, 81 and 38% of patients respectively ($p<0.001$). In those with functioning grafts (N=105), GFR at 3 months was strongly correlated with DKA ($R=0.430$, $p<0.001$) and was seen to reduce across increasing DKA quintiles (61, 52, 42, 41, and 29ml/min).

Conclusions: DKA is a simple score based on donor age, adjusted for 12 donor-related risk factors, which strongly predicts post-transplant outcome and is conceptually easy for patients to understand. Prospective evaluation of its influence on deceased donor acceptance decisions will be undertaken.

TH-PO1126

Influence of Donor Characteristics and Delayed Graft Function (DGF) on Renal Function 12 Months After Kidney Transplantation

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Background: The KDPI (Kidney Donor Profile Index) index is a score based on donor characteristics used to predict long-term graft survival. Delayed graft function (DGF), a variable not included in the KDPI score, is associated with reduced graft survival. We hypothesized that increasing KDPI scores and DGF concur to reduce renal function 1 and 12 months after kidney transplantation.

Methods: This single center retrospective study included all consecutive deceased donor kidney transplant recipients (n=1221) between January 2014 to December 2015. Analysis was carried out according to deciles of KPDI. Renal function was evaluated by estimated glomerular filtration rate (eGFR, calculated by the MDRD4 formula).

Results: The mean cold ischemia time was 25±7 hours and it was similar across the deciles of KPDI. The incidence of DGF increased from 39% to 75% ($p = 0.001$) from 0-10% to 91-100% KDPI deciles. The 1 month eGFR showed a negative association with KDPI deciles, 59.5 vs. 39.0 ml/min/1.73m^2 ($p<0.001$) for 0-10% and 91-100% KDPI deciles. This trend persisted in the 12 month analysis (64.6 vs. 46.0 ml/min/1.73m^2; $p<0.001$), respectively. DGF was associated with lower 1 month eGFR across all the KDPI deciles (KDPI [0-10%] 67.9 vs. 46.2 ml/min/1.73m^2, $p=0.029$; KDPI [91-100%] 47.7 vs. 36.2 ml/min/1.73m^2, $p<0.001$), but this trend decreased at 12 months (KDPI [0-10%] 65.5 vs. 63.1 ml/min/1.73m^2, $p=0.84$; KDPI [91-100%] 47.5 vs. 45.4 ml/min/1.73m^2, $p=0.425$).

Conclusions: Renal function 1 and 12 months after kidney transplantation is determined primarily by donor characteristics (KDPI) and the development of DGF.

TH-PO1127

Analysis of Donor Factors for Clinical Prediction of Recipient After Deceased Donor Renal Transplant in a Non-US Transplant System

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Background: There is little data on allograft survival based on deceased donor characteristics outside the United States. Conservative use of deceased donors based on concern for longer term allograft outcomes likely increases the discard rate of deceased donor kidneys despite international deficit of kidney donors. Using South Korea as a model, we analyzed deceased donor characteristics using 1-year creatinine in the recipient as a surrogate marker for longer term outcomes.

Methods: We analyzed 2,858 cases contained within the Korean Organ Transplant Registry data which had conducted renal transplant from 2009 to 2017. Univariate, multivariate linear regression analysis and 5-fold cross validation was performed to make a formula for estimating the serum creatinine of the recipient for 1 year after deceased donor kidney transplant.

Results: Univariate analysis indicated a number of different factors were significant in determining outcome, however only donor age, donor serum creatinine and current smoking status without hypertension were statistically significant in a multivariate model for predicting serum creatinine of the recipient after 1 year of transplant (Table 1). We also found that serum creatinine at 1 year predicted 3 year outcomes in a log rank test.

Conclusions: Currently deceased donor kidney transplant outcomes are extremely good in South Korea (despite a much longer period on dialysis prior to transplant) compared to the US. Given differences in cultural, economic and racial characteristics compared to the US the Korean prediction model obtained from this study relies on checking only 3 donor factors, and thus can be obtained relatively quickly and conveniently and yet provides more information to the recipient candidates before transplant. In particular, we also believe this study indicates that there is underutilization of potential decreased donors in Korea and that a wider pool of deceased donors could be used safely.

A model of expected 1-year post-transplant serum creatinine (mg/dL) of recipient who received deceased donor Renal Transplant in Korea. (Exp: Exponential)

$$\text{Exp}[0.009 \times \text{Donor Age} + 0.015 \times \text{Donor Creatinine} - 0.060 \times \text{If Donor Hx. of Smoking} - 0.276]$$

(Donor's Hx. of Smoking, 0: No Smoking or Former Smoking or Current Smoking with HTN, 1: Current Smoking without HTN), 5 fold cross validated $R2=0.184$, F-statistic: 64.79, p value <0.01

TH-PO1128

Risk Factors, Prediction, and Outcomes of Delayed Graft Function (DGF): An Analysis from a German Cohort of Extended Criteria Donor Kidneys with Post-Explantation Biopsies

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Background: DGF occurs frequently after transplantation and is associated with worse short- and long-term outcomes and associated with higher rejection rates. Risk factors include both donor and recipient characteristics, although their prediction is imprecise. Therefore, we tested known risk factors of DGF and validated the performance of existing risk scores in predicting DGF in recipients of extended criteria donor kidneys with procurement biopsies.

Methods: We retrospectively evaluated the records of 223 consecutive adult cadaver renal transplant recipients with donor evaluation biopsies. 135 patients developed DGF (defined as the need for hemodialysis during the first week after transplantation). Clinical donor and recipient characteristics as well as histological features of the biopsy were compared between the two groups and the following risk scores were evaluated regarding their association with observed DGF: Navarro (2011), Ortiz (2004), Balaz (2013), Lopes (2004), Snoeijs (2008), Remuzzi (1999), Nyberg (2003), Rao (2009), Foucher (2009), Schold (2005), Port (2002), Anglicheau (2008), Leuven (2013) Irish (2010), KDRI/KDPI and EPTS.

Results: Severity of acute kidney injury (similar to AKIN Classification) at ICU stay, last creatinine, proteinuria, macroscopic organ quality, microthrombi by histology, prolonged warm ischemia time, recipient body mass index, and recipient duration of dialysis were significant risk factors for the development of DGF in the recipient in univariable analysis. None of the evaluated scores could accurately predict DGF. In multivariable analysis only severity of acute kidney injury and microthrombi by biopsy remained statistically significant (OR 1.89 95%CI 1.26-2.84, $p=0.002$; OR 3.06, 95%CI 1.00-9.34, $p=0.049$, respectively).

Conclusions: None of the established clinical, histological or combined scores for quality assessment of deceased donor kidneys appeared sufficiently prognostic for DGF in our cohort. We are currently working on a novel combined clinicopathological score better suited for clinical application in the Eurotransplant network.

TH-PO1129

Diffusion MRI Detects an Increase in Interstitial Fibrosis Earlier Than the Decline of Renal Function

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Background: Interstitial fibrosis(IF) is one of the major predicting factors in CKD. Diffusion Weighted Magnetic resonance imaging(DWI-MRI) is a new tool for non–invasive IF assessment, but its value for IF follow up is unknown. We recently adapted a DWI sequence, allowing for the discrimination between the kidney cortex and medulla. The cortico-medullary ADC difference(ΔADC) was better correlated to IF than absolute ADC. We aimed at analyzing the use of DWI-MRI for the follow up of IF in patients having undergone repeated biopsies in comparison to renal function evolution.

Methods: In this prospective study, we included patients having undergone repeated biopsies for clinical purpose and who agreed to undergo repeated DWI-MRI at the time of biopsy.

Results: 19 kidney allografts patients had repeated biopsies for clinical purposes and parallel MRI examinations. The average interval between the two biopsies was 1.7year. There was no significant correlation between eGFR and IF at baseline($r=-0.39$,$p=0.10$), whereas baseline ΔADC correlated negatively with IF($r=-0.76$,$p<0.001$). Between the two visits, IF as estimated from the biopsy, increased significantly from a fibrosis score of 20% to 32.5%($p=0.03$) in individual patients, whereas estimated renal function remained stable(eGFR 54 to 52ml/min/1.73m^2;$p=0.19$). ΔADC decreased significantly from 30 to -23 x10^{-6}mm^2/S(Figure A). Considering the difference between the basal and follow-up values, there was a good correlation between the evolution of IF and ΔADC ($r=-0.51$,$p=0.03$)(Figure B) but not between the evolution of IF and eGFR ($r=0.24$,$p=0.34$).

Conclusions: Thus modifications of ΔADC derived from DWI-MRI outperformed eGFR to follow IF evolution within a given patient. ΔADC may be more reliable than eGFR to allow earlier detection of an increase in IF.

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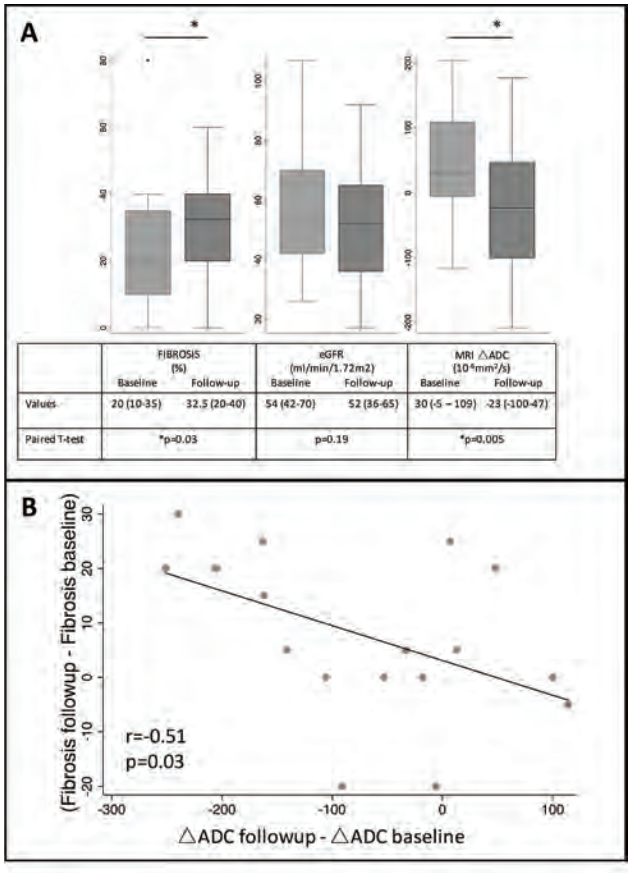

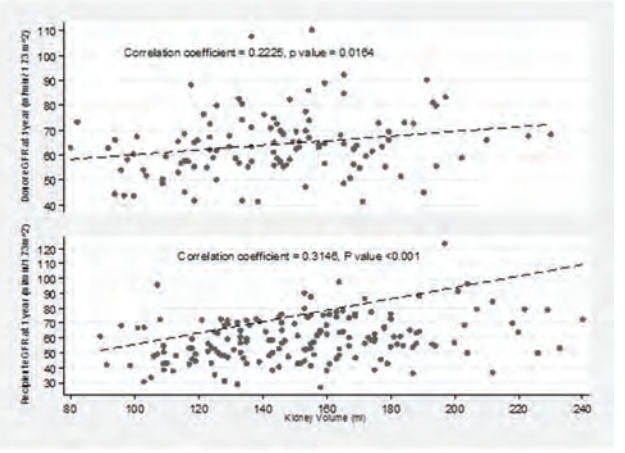

Figure 1: Correlation of renal volume and eGFR in donors and recipients at 1 year

TH-PO1130

Donor Kidney Renal Volume Predicts Recipient and Donor Graft Function at 1 Year

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Background: Renal transplantation is treatment of choice in end stage renal disease of which Living donor kidney transplantation is optimal. The role of renal volume measurement in predicting long-term donor and recipient graft outcome is not clear.

Methods: This retrospective cohort study of living donor kidney transplantaion (2010-2017) from the National Kidney Transplant Service (NKTS) of Ireland. Renal volume was measured bilaterally in living kidney donors using TeraRecon USA. Low eGFR for recipients and donors defined as < 60ml/min 1-year post donation was used in logistic regression modeling with donor volume categorized into tertliles. Donor and recipient characteristics were included in the models as potential confounding variables.

Results: There were 166 living donor kidneys in the study period. Mean donor age was 44.8 years (SD = 10.8). Donor mean BMI was 25.5 (SD = 2.9). Donor kidney volume mean was 152.7 mls (SD = 31.6), divided into tertiles was; 1: 89.2 – 135 mls, 2: 136 – 164 mls, 3:165 – 240 mls. Median donor eGFR at 1 year post transplant was 63.3 (IQR[2]=56.1–70.4).Recipientsoflivingdonorkidneyshadameanageof43.5years(SD=13.3). Median recipient eGFR at 1 year post transplant was 58.3 (IQR = 48.4 – 69.4). Donor kidney volume is slightly correlated with donor eGFR at 1 year post transplant (figure 1) and is marginally non significant in logistic regression for low eGFR using the above tertile categories; Odds Ratio 0.65 [95% conf. int. 0.40 – 1.04, p value = 0.075]. Donor kidney volume is correlated with recipient eGFR at 1-year post transplant (figure 1) and is significant in multivariable logistic regression; Odds Ratio 0.48 [95% conf. int. 0.26 – 0.90, p value = 0.021].

Conclusions: Donor kidney volume predicts recipient graft function 1-year post transplant but is less conclusive for donor kidney function. Cognizance of donor renal volume may help optimise potential kidney donor selection.

TH-PO1131

Interstitial Fibroblasts in Donor Kidney Predict Late Post-Transplant Anemia

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Background: Post-transplant anemia (PTA) is associated with the progression of kidney disease and mortality in kidney transplant recipients. In general, PTA is categorized into early and late types, commonly appearing during the two years following transplantation. Although the main causes of PTA are recipient factors, donor factors have not been fully investigated. In this study, we investigated the association of donor pathological findings with the incidence of PTA in kidney transplant recipients after 3 y (late PTA).

Methods: We conducted a retrospective cohort study at a single university hospital. A total of 50 consecutive adult recipients and donors were enrolled. To assess the structure of interstitial lesions, immunohistochemical staining of interstitial fibrosis and of fibroblasts were assessed in 0-hr biopsies for quantitative analysis.

Results: The incidence of late PTA in this cohort was 30%. Mean hemoglobin (Hb) was 11.6 ± 0.8 g/dL in patients with late PTA, and 14.3 ± 1.5 g/dL in patients without PTA. An inverse association was observed in biopsies between interstitial fibrosis area and interstitial fibroblast area (P<0.01), and each pathological finding was examined for its association with late PTA incidence after multivariate adjustment. For interstitial fibrosis area, the odds ratio (OR) was 1.94, with a 95% confidence interval (CI) of 1.26 to 2.99; P<0.01. For interstitial fibroblast area, OR was 0.01, 95% CI was 0.00 to 0.16, and P<0.01. Receiver operating characteristic curve analysis indicated that interstitial fibroblast area had high predictive power for the incidence of late PTA.

Conclusions: The presence of interstitial fibroblasts in donor kidney may play an important role in predicting the incidence of late PTA.

TH-PO1132

Presence of Renal Dysfunction Even at the Time of Listing Predicts Risk of ESRD in Isolated Heart Transplant Patients

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Background: Presence of chronic kidney disease (CKD) at the time of heart transplant is an independent predictor of post-transplant ESRD (end stage renal disease) and all-cause mortality. We wished to look at the effect of the presence and severity of CKD at the time of listing on post-heart transplant ESRD and mortality.

Methods: We analyzed 2000-2015 UNOS heart transplant data. Adults receiving first isolated heart transplant, who were not on dialysis were included in study. We divided our cohort into four clinically relevant groups based on their listing eGFR (<30 ml/min, 30-44 ml/min, 45-59 ml/min and ≥60 ml/min). Survival analysis was used to generate Kaplan-Meier curves. Results were adjusted for multiple confounding factors.

Results: We had 27,169 patients in our cohort. In the follow up period there were 7595 deaths and 2335 patients reached ESRD (Table 1). Kaplan-Meier curves for ESRD are shown in Figure 1.

Conclusions: Our findings shows that risk of renal replacement therapy post heart transplant increases with worsening eGFR at listing even after adjusting for multiple confounders with the highest risk in the group with eGFR <30 ml/min. This information may help identify patients for combined heart-kidney transplant in a more reasonable time frame.

Risk of post heart transplant ESRD by listing eGFR

eGFR at time of listing	ESRD N (%)	Adj hazard ratio with p value	Mortality N (%	Adj hazard ratio with p value
eGFR <30	157 (21.7)	2.77 (p<0.001)	284 (39.6)	1.10 (p=0.148)
eGFR 30-44	572 (15.7)	2.16 (p<0.001)	1289 (35.5)	1.11 (p<0.001)
eGFR 45-60	617 (10.1)	1.40 (p<0.001)	1961 (32.4)	1.05 (p=0.092)
eGFR > 60	989 (7)	1	4061 (28.9)	1

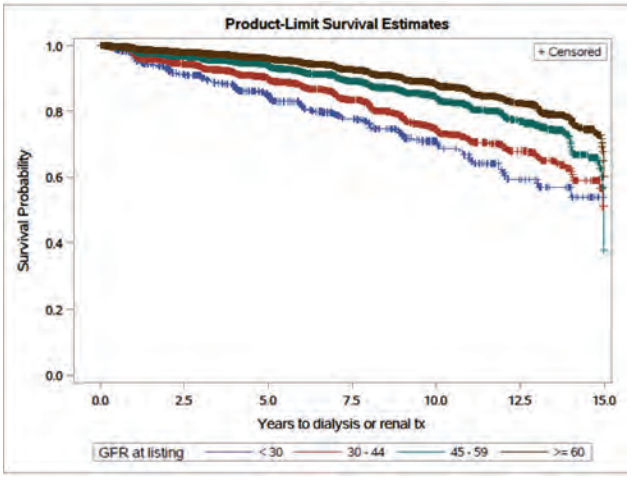
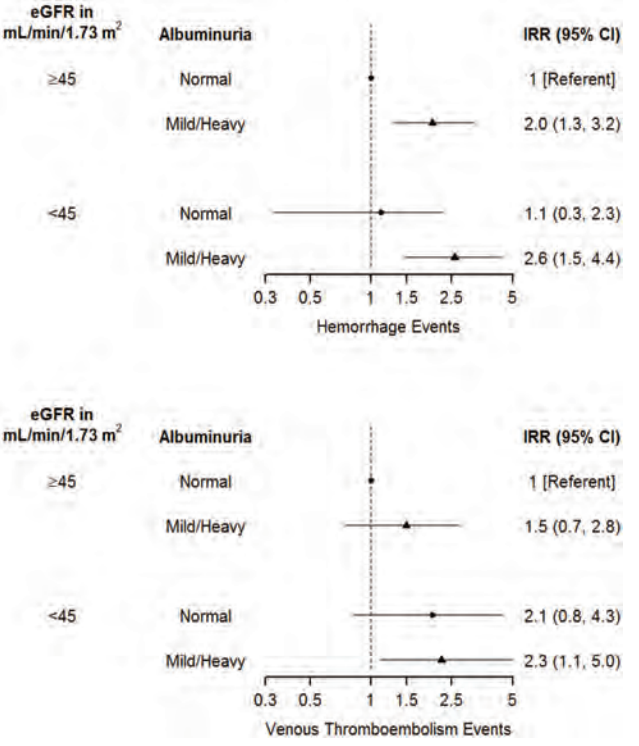


Figure 1: Kaplan-Meier estimate for renal survival



Adjusted Incidence Rate Ratios by Level of eGFR and Albuminuria in Recipients

TH-PO1133

Kidney Function, Albuminuria, and the Risk of Hemorrhage and Thrombosis After Kidney Transplantation

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Background: Compared to the general population, kidney transplant recipients are at increased risk of hemorrhage and thrombosis. Whether this risk is affected by kidney function and albuminuria is unknown.

Methods: We conducted a retrospective cohort study using linked healthcare databases to identify adult kidney transplant recipients from 2002-2015 in Alberta, Canada. Estimated glomerular filtration rate (eGFR) and albuminuria measurements at 1-year posttransplant were used to categorize recipients (eGFR: ≥45 vs. <45 mL/min/1.73 m^2; albuminuria: normal vs. mild-heavy). We determined the association between categories of eGFR and albuminuria and posttransplant hemorrhage and venous thrombosis based on diagnostic and procedural codes.

Results: Of 1,284 kidney transplant recipients at 1-year posttransplant, 21% had an eGFR <45 mL/min/1.73 m^2 and 40% had mild-heavy albuminuria. The mean age of the cohort was 53 years [IQR 41-62]. Previous thrombosis was higher in recipients with lower eGFR, but previous hemorrhage was similar across all groups. Over a median follow-up of 6 years, the age- and sex-adjusted rate of hemorrhage and thrombosis was over 2-fold higher in recipients with lower eGFR and mild-heavy albuminuria compared to recipients with higher eGFR and normal albuminuria (hemorrhage: incidence rate ratio, IRR, 2.6, 95% CI 1.5-4.4, p=0.001; thrombosis: IRR 2.3, 95% CI 1.1-5.0, p=0.046).

Conclusions: Among kidney transplant recipients at 1-year posttransplant, the risk of hemorrhage and venous thrombosis is higher with lower eGFR and mild-heavy albuminuria. Thus, eGFR and degree of albuminuria may help prognosticate kidney transplant recipients long-term.

TH-PO1135

Evaluation of Functional and Nutrition Status in the Older Transplant Candidate

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Background: Measures of functional and nutrition status (NS) at time of kidney transplant (KT) have been shown to be predictive of post-KT outcomes. No gold standard tool to best assess functional status exists. Assessment of physiological reserve is important in the older KT candidate who may have additional risk factors such as malnutrition. Our purpose is to identify the functional and NS measures predictive of ineligibility for KT listing.

Methods: All patients >65 years old evaluated for KT were recruited. Participants completed the short physical performance battery (SPPB) and Fried Frailty assessment (FFA). Nutrition status was assessed using standardized malnutrition criteria. Patient charts were reviewed for KT listing status (ineligible or listed). Differences between SPPB, FFA, NS, and the components of each assessment were tested between groups by ANOVA, Chi-squared and logistic regression analyses.

Results: A total of 105 patients were enrolled and 73 had complete follow-up data at time of analysis. Scores for the SPPB and FFA were not predictive of ineligibility of KT listing [Table 1]. However, slower chair stand time (OR $_{1.05}1.28_{1.55}$, p=0.01) and slower walk time (OR $_{1.11}2.37_{5.10}$, p=0.03) were predictive of KT ineligibility. Those ineligible for KT tended to report lower physical activity levels, have lower handgrip strength and be malnourished compared to those who were listed, but this did not reach significance [Table 1].

Conclusions: Objective measures like walk and chair stand time may be more predictive of KT ineligibility than SPPB and FFA when used at the time of KT candidacy evaluation, but further investigations are needed.

Funding: Private Foundation Support

Table 1

	All N=105	Ineligible N=48	Listed N=25
SPPB score	9.8 (1.6)	9.7 (1.5)	10.3 (1.8)
Balance score	3.6 (0.8)	3.6 (0.7)	3.6 (0.8)
Walk time, sec	4.1 (0.9)	4.1 (0.9)	3.9 (0.7)
Chair stand time*, sec	14.0 (3.5)	14.6 (3.7)	12.0 (2.9)
FFA score	1.1 (1.0)	1.2 (1.0)	0.8 (1.0)
Weight change, lbs	-1.8 (6.9)	-2.6 (7.6)	0.85 (4.7)
Energy scale	6.8 (1.6)	6.6 (1.5)	7.0 (1.8)
Energy expenditure, kcal/week	1257 (1696)	1308 (2035)	1551 (1632)
Hand grip strength, kg	27.4 (10.2)	27.2 (9.6)	30.2 (12.6)
Walk time, sec	4.2 (0.9)	4.4 (1.0)	3.9 (0.7)
Malnutrition	13 (12)	7 (15)	2 (8)

All values reported as mean (SD) except for malnutrition, n (%), *p=0.009

TH-PO1136

Managing High Cardiovascular Risk Patients on Kidney Transplant Waiting List: Costs and Outcome

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Background: High cardiovascular risk patients on the kidney transplant waiting list undergo multiple cardiovascular investigations to ensure fitness for transplant surgery, yet suffering from adverse events. The ideal protocol for managing these patients is unknown. We investigated the benefits of cardiorenal multidisciplinary meetings in managing these patients.

Methods: We analysed data from 126 patients discussed between September 1/10/14 and 30/9/17 in biannual multidisciplinary team (MDT) meetings as per protocol, followed up until 11/05/19. We analysed the results of post-MDT cardiac testing and outcomes, including CV events, mortality, and transplantation status. The cost of post MDT cardiac testing was estimated from NHS best practice tariffs.

Results: Clinical characteristics of 126 patients were: age (median 62 years, Interquartile range [IQR] 57-67), sex (male 60%), Diabetes Mellitus (58%), Smoker (41%), Hypertension (96%), cholesterol (median 3.8 mmol/L, IQR 3.1-4.8), and PTH (median 33 ng/L, IQR 16-67). The patients were followed-up for a median of 970 days (IQR 584-1334). During the follow up, 44 patients were transplanted. 42 patients had adverse outcomes: 13 patients died, 14 suffered ACS, 5 suffered stroke, 1 suffered TIA, 15 underwent PCI, 7 underwent CABG. Diabetic patients were more likely suffer from adverse events (log-rank test p=0.007). Patients with positive stress echocardiogram tended to have more events, but the difference was not statistically significant (log-rank test p = 0.085). There was no difference comparing the group with or without events with respect to age, gender, smoking, hypertension, cholesterol, PTH, phosphate or ferritin levels. The costs of post MDT cardiac tests were as follows: 62 stress echo = £1500, 32 Coronary Angiograms = £88632, 13 PCIs = £52325, and 5 CABG = £38350, and total cost = £193897. The approximate cost per patient is £1538, which is approximately £600 per patient per year.

Conclusions: The biannual cardiorenal MDT maintained 126 high risk patients on the kidney transplant waitlist for 2.7 years with successful transplants in 35%, adverse events in 33%, and mortality in 13%. A cardio-renal MDT approach for high CV risk patients can ensure successful transplantation one-third patients in 2.7 years with acceptable cost of cardiac testing despite adverse outcomes.

TH-PO1137

Prevalence of Pulmonary Hypertension in Patients Listed Active for Kidney Transplantation

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Background: Pulmonary hypertension (PH) is variably defined, with estimated prevalence in CKD and ESRD of 9% and 19%, respectively. PH at the time of kidney transplantation (KTx) can portend a lower graft survival and the prevalence in wait-listed patients is unknown. We sought to ascertain the prevalence of PH in patients listed active for KTx and characterize based on demographics, comorbidities and ECHO characteristics at our center

Methods: A chart review of EPIC EMR was conducted by assessing problem lists, clinic evaluations and ECHO results for patients listed active for KTx at our institution from 2014-2019. We recorded basic demographics, ESRD cause, type of dialysis access, vintage and modality, listing duration, associated comorbidities and comprehensive ECHO measurements. PH was defined as RVSP>35 mm Hg on ECHO

Results: Of 634 patients listed active during this period, 104(17%) patients had ECHO evidence of PH. Demographics and ECHO data are shown in Table 1. Mean age of patients was 57 years, with 61% male, 59% African-American and mean BMI of 29.1. Diabetes was the most prevalent cause of ESRD (38%),75% were on HD and 70% had an AVF as dialysis access. Median dialysis vintage was 36 months and listing duration was 20 months; 25% had a history of obstructive sleep apnea (OSA) and 30% had coronary artery disease. The mean RVSP was 44.7 mm Hg (SD 8.7, range 35-83), 25% of patients with evidence of PH on ECHO were formally reviewed by a cardiologist, only 3 of whom had PH diagnosed and classified as per WHO criteria. Other ECHO findings showed 57% had HFpEF and 22% had valve abnormalities (moderate-severe)

Conclusions: This is the one of the largest studies to elucidate prevalence, clinical and ECHO characteristics in patients with PH listed active for KTx. PH appears to be under-addressed and efforts should be made to ascertain its cause and direct intervention(eg. ultrafiltration, improving lung disease, and pulmonary vasculature vasodilators). Future studies could assess the effect of interventions on post KTx outcomes, particularly in groups stratified by PH severity.

Table 1. Demographics and Echocardiogram Characteristics in Patients with PH Listed Active for KTx

Age, mean (SD) 57.0 (13.3)
Male, n (%) 61 (58.6)
Race
African-American, n (%) 59 (56.7)
Caucasian, n (%) 32 (30.7)
Other, n (%) 13 (12.5)
ESRD cause
Diabetes 38 (36.5)
HTN 28 (26.9)
Other GN 16 (15.3)
Other specified 9 (8.6)
Idiopathic 5 (4.8)
PCKD 4 (3.8)
GN (CTD) 4 (3.8)
BMI, mean (SD) 29.1 (5.3)
Normal (<25), n (%) 26 (25)
Overweight (25-29), n (%) 33 (31.7)
Obese (30-35), n (%) 31 (29.8)
Morbidly obese (>35), n (%) 14 (13.4)
Dialysis type
HD, n (%) 75 (72.1)
PD, n (%) 16 (15.4)
CKD IV/V, n (%) 13 (12.5)
Dialysis access
AVF, n (%) 70 (67.3)
AVF on PD, n (%) 1 (0.9)
AV graft, n (%) 3 (2.8)
Tunneled catheter, n (%) 5 (4.8)
Dialysis vintage, mths, median (IQR) 36 (25-55)
Listing duration, mths, mean (SD) 23.4 (17.2)
Listing duration, mths, median (IQR) 20 (9-35)
COPD, n (%) 9 (8.6)
Asthma, n (%) 4 (3.8)
OSA, n (%) 26 (25.0)
Smoking status
Current smoker 10 (9.6)
Ex-smoker 62 (59.6)
Never smoker 32 (30.7)
History of PE, n (%) 3 (2.8)
History of DVT, n (%) 5 (4.8)
HIV positive, n (%) 2 (1.9)
SLE, n (%) 2 (1.9)
Scleroderma, n (%) 3 (2.8)
HTN, n (%) 100 (96.1)
Hyperlipidemia, n (%) 70 (67.3)
Coronary artery disease, n (%) 30 (28.8)

TH-PO1138

Exercise Stress Electrocardiogram for Pretransplant Cardiac Evaluation: A Costly but Generally Useless Effort

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Background: There is an ongoing debate on the informative values of cardiac evaluation tests in renal transplant candidates. Exercise stress electrocardiogram (ES-ECG) is advocated and widely used as a non-invasive test to rule out significant coronary artery disease before renal transplantation. The precondition of a test sufficient for interpretation is the achievement of an age adjusted maximal work capacity. We were interested in the fundamental question, whether the test yields meaningful results in transplant candidates at all and how achieved exercise capacities compare to healthy individuals.

Methods: Of 1319 dialysis patients transplanted at our institution (between 29/02/2000 and 30/09/2017) 453 (mean age 51,2+/-12,6 yrs) underwent cycle-ergometer ES-ECG testing during their pre-transplant work-up. 137 kidney donors (mean age 50,4+/-9,8 yrs), who were also evaluated by ES-ECG served as control group. We evaluated two endpoints related to the tests meaningfulness and sufficiency: 1) whether study subjects reached maximal work capacity (according to exercise resistance level, measured in Watts or expected heart rate (HR) reached) and 2) whether patients had sufficiently diagnostic test results (i.e. achievement of the maximal work capacity (Watt) or the expected HR or experienced symptoms at lower work intensities. In order to assess test result sufficiency of transplant candidates and kidney donors, absolute and relative frequencies plus 95% CIs for both endpoints were computed and compared by a two-sided two proportion z-Test.

Results: see Table

Conclusions: While maximum exercise capacity (measured in Watt) was achieved by 82 % of healthy kidney donors only a minority of dialysis patients was fit enough to adequately perform during ES-ECG. Consequently meaningful results during ES-ECG were observed in only 37 % of dialysis patients, making Exercise stress electrocardiogram a generally useless, but with regard to time and resources costly effort in the cardiac evaluation of renal transplant candidates.

	Transplant candidates	Kidney donors	P-Value
Maximal work capacity reached	0.32 [0.30;0.34] (144/453)	0.82 [0.79;0.85] (112/137)	<0.0001*
Test sufficiently diagnostic	0.37 [0.35;0.39] (166/453)	0.82 [0.79;0.85] (112/137)	<0.0001*

* P-values are based on the two-sided two proportion z-Test

TH-PO1139

Embolization of Polycystic Kidneys as an Alternative to Nephrectomy Before Kidney Transplant

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is responsible for progressive end-stage renal disease. In case of a massive enlargement of polycystic kidney, renal transplantation surgery may be hindered due to the limited pelvic space. In such cases a radical nephrectomy prior to renal trasplantation is warranted. Recently, transcatheter arterial embolization (TAE) has been described as an alternative to nephrectomy. We prospectively evaluated the safety and efficacy on long-term kidney volume reduction of TAE procedures in a group or patients with ADPKD before renal transplantation.

Methods: Between January 2016 and December 2018, 16 patients with end-stage renal disease associated to massive ADPKD were prospectively recruited. Informed consent was obtained from all participants. All procedures were carried out according to the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration. All TAE were performed under local anesthesia and sedation and using cyanoacrylate as embolic agent. A previous CT scan and further CT at 6 and 12 months after TAE were performed. The variables collected were: age, gender, size, renal volume measured by volumetry before and after TAE and score on the visual analog scale (VAS) for pain and complications. A descriptive statistical analysis was made.

Results: A total of 16 patients (9 men and 7 women) were included. The average age was 52.38 (± 9.19) years. The average hospital stay was 3.71 (± 1.32) days. 11 patients presented with mild complications (Clavien-Dindo I). The average score on the VAS scale was 3.38 (± 2.46) points. Only one patient presented a partial embolization of the renal artery, which was resolved by a new TAE with cyanoacrylate and a coil. Before embolization average kidney volume was 2509.08 ± 946.7 cc. Six months later volume was 1303.71 ± 836.2 cc. and 12 months later 1098.41 ± 684.9 cc. During the first 6 months a reduction of 48.05% in renal volume was observed. Of these patients, 9 (56.25%) have received a kidney transplant without problem of space.

Conclusions: Our results indicate that TAE is a safe and effective alternative to nephrectomy before renal transplantation in patients with ADPKD.

TH-PO1140

Liver Biopsy Does Not Change Transplant Candidacy Decisions for Hepatitis B Virus-Positive Living-Donor Kidney Transplant Recipients

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Background: Hepatitis B virus (HBV) infection in kidney transplantation (KT) recipients is associated with increased overall mortality, graft loss, and progression of liver disease after KT. Liver biopsy is the gold standard for hepatic diagnosis, but it is an invasive and painful procedure. This study evaluated the necessity of liver biopsy in the decision concerning transplant candidacy among HBV-positive living-donor KT recipients.

Methods: This single-center retrospective study reviewed 3,532 patients who underwent KT from February 1997 to March 2015. Outcomes were analyzed for 144 hepatitis B surface antigen (HBsAg)-positive patients with end-stage renal disease who underwent liver biopsy. To compare clinical characteristics, we divided the patients into two groups according to the degree of fibrosis based on METAVIR score. Pathologic findings without fibrosis (F0) were found in 65 (49.6%) cases, and 79 (50.4%) patients were included in the fibrosis group (fibrosis score F1 to F4).

Results: There was no significant difference in age, sex, mode of dialysis before KT, proportion of deceased-donor KT, aspartic acid transaminase levels, total bilirubin, albumin levels, and prothrombin time between non-fibrosis patients and fibrosis patients The Child–Pugh scores were similar between patients with or without fibrosis (p=0.155). There was no liver failure after KT in non-fibrosis patinets, and five (6.3%) fibrosis patients progressed to liver failure (p=0.064). Hepatocellular carcinoma was diagnosed in 2 (3.1%) non-fibrosis patients and 6 (7.6%) fibrosis patients (p=0.294). Biopsy-confirmed acute rejection occurred in 12 (18.5%) non-fibrosis patients and 22 (27.8%) fibrosis patients (p=0.187). The 5-year graft survival rate was 96.9% in non-fibrosis patients and 94.6 % in fibrosis patients. There were no significant differences in graft and patient survival between patients with or without fibrosis (p=0.381 and p=0.113, respectively).

Conclusions: The graft and patient survival were not affected by fibrosis detected by pre-KT liver biopsy. Additionally, fibrosis status did not significantly affect liver-related outcomes among HBsAg-positive recipients. In the new antinucleos(t)ide era, liver biopsy findings might not be helpful for guiding the management of HBsAg-positive KT candidates.

TH-PO1141

Pre-Transplant Cognitive Impairment Is Associated with Increased Rates of Early Post-Transplant Rehospitalization

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Background: Cognitive impairment is common in patients with kidney disease and can affect patients understanding of transplant care and kidney transplant (KT) outcomes.

Methods: We conducted a single-center longitudinal cohort study to evaluate the association of pre-transplant Montreal cognitive assessment (MoCA) scores with length of hospitalization for KT and post-transplant rehospitalization rates. We used multiple regression for duration of hospitalization for KT and logistic regression for rehospitalization within 30 days.

Results: In total, 207 patients underwent MoCA testing before transplant and were included in the analysis. Patients with cognitive impairment were more likely to be older, black, and smokers (Table 1). The duration of hospitalization was independent of MoCA score, but associated with a history of coronary artery disease (β coeff=2.29, p= 0.002) and duration of dialysis before KT (β coeff=0.56, p<0.001). The odds of readmission within 30 days was higher with lower MoCA scores (Table 2).

Conclusions: Pre-KT cognitive impairment does not affect length of hospitalization for KT, but is associated with higher odds of 30-day rehospitalization after KT.

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Table 1.

Patient Characteristics	MoCA <26 (n=92)	MoCA ≥26 (n=115)
Age at KT (years)	48.3 ± 12.4	46.7 ± 15.1
Female gender, n (%)	56 (61)	34 (30)
Race, n (%)		
Caucasian	64 (70)	95 (83)
African American	13 (14)	11 (9)
Other	15 (16)	9 (8)
Education level n (%)		
≥ Bachelor's Degree	26 (28)	37 (32)
Some College	33 (36)	46 (40)
H/o smoking, n (%)	23 (25)	32 (28)
H/o diabetes	23 (25)	18 (16)
Coronary Artery Disease n (%)	10 (11)	8 (7)

Table 1

Table 2.

	30-day readmission	
Covariates	**β Coefficient**	***P* value**
MoCA score	-0.20	0.02*
Age	-0.06	0.02*
Gender (male)	-0.38	0.50
Race/ethnicity (black)	-0.67	0.42
Race/ethnicity (other)	-2.02	0.08
Coronary artery disease	0.99	0.21
Diabetes	-0.11	0.90

Table 2

TH-PO1142

Non-Candidacy for Kidney Transplant: An Experience from Rural Eastern North Carolina

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Background: Kidney transplant is the optimal therapy for the end-stage renal disease patients in order to improve the expectancy and quality of life. Recently there are many studies investigating how to improve the referral process to improve the access to kidney transplantation. However, there is not much data looking into the rate and causes disapproval of these referred patients by the transplant program to be activated in the waiting list. Thus it is important to study the disapproved population so that we can identify the barriers and intervene to improve kidney transplant rates.

Methods: The electronic health records of 309 ESRD patients undergoing dialysis by one major dialysis practice, East Carolina University were accessed manually to obtain information about the referral by the nephrologists for a transplant and the decision of the transplant selection committee. Disapproval rate for transplant was calculated by percent, and any disparities in disapproval was measured based on gender and race of the patients. Statistical analysis was conducted with t-test and a $p<0.05$ was considered significant.

Results: Our preliminary data shows although all ESRD patients were referred for transplant within 1 year of initiation of dialysis, about 63 percent of the referred ESRD patients were initially disapproved for further evaluation for a transplant. 40 percent of these patients were disapproved because of modifiable factors like smoking, alcohol abuse, overweight, not completing age appropriate screening tests. Only 40% of these patients were able to successfully modify the risk factors and were accepted as transplant candidates in following transplant evaluation visits. Interestingly, 83% of the disapproved patients were African-Americans, and 41% were females.

Conclusions: Our reports shows that there are major barriers to transplant in ESRD patients in eastern North Carolina even after patients have been referred early. Majority of the disapproved patients were African-Americans and only less than half of the patients with modifiable risk factors were able to be enlisted for transplant after proper intervention. More quality improvement endeavors are required to reduce the disparity in race and to support ESRD patients to overcome modifiable barriers to improve transplant rates in this population.

TH-PO1143

Longer Distance from Dialysis Facility to Transplant Center Is Associated with Lower Access to Transplantation

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Background: The distance between patients' residence and their kidney transplant center is not associated with access to transplantation. However, distance from the dialysis facility to the transplant center (DFTC distance) may be important for access to transplantation, as dialysis providers closer to the transplant center may maintain better communication with the transplant center and expedite patient work-up. We hypothesized that longer DFTC distance would associate with longer time to transplantation.

Methods: We included adults who started dialysis between 2005-2015 according to the US Renal Data System. The primary predictor was DFTC distance ≥100 miles vs. <100 miles (reference group). Outcome was time from dialysis initiation to kidney transplantation. We used adjusted Cox models and tested for interactions by region of the US, calendar year, and dialysis modality.

Results: 172,995 patients were included; mean age was 51.6 yrs; 30.3% were black. DFTC distance varied by region of the US (table). Overall, DFTC distance ≥100 miles (vs. <100 miles) was associated with lower access to transplantation regardless of dialysis treatment modality, (table), but the association was modified by region of the US and calendar year ($p<0.05$ for interaction). Longer DFTC distance was associated with lower access especially among patients living in the South and West. The association between DFTC distance and access to transplantation has attenuated over time (table).

Conclusions: Longer DFTC distance was associated with lower access to kidney transplantation even after accounting for distance between patients and the transplant center. Our data suggest that system-level factors such as proximity between referring and transplant providers may contribute to access to transplantation, but this association varies across the US.

Funding: Veterans Affairs Support

Table. Adjusted Cox models of the association between dialysis facility-to-transplant center (DFTC) distance and outcome of transplantation.

	DFTC distance in miles, median (IQR)	Access to transplant by DFTC distance ≥100 miles vs. <100 miles (HR*, 95% CI)
All patients (n=172,995)	19.8 (6.8-67)	0.94 (0.92-0.96)
Region of the US*		
West (n=42,033)	23.4 (9.7-80.6)	0.94 (0.90-0.99)
Midwest (n=33,904)	19.3 (6.1-62.9)	1.05 (1.01-1.10)
South (n=63,325)	28.1 (7.9-86.4)	0.90 (0.87-0.93)
Northeast (n=33,693)	11.0 (3.2-28.1)	1.00 (0.92-1.08)
Dialysis modality		
Hemodialysis (n=143,843)	19.6 (7.0-65.9)	0.93 (0.91-0.96)
Peritoneal dialysis (n=29,042)	20.4 (5.3-71.4)	0.95 (0.90-0.996)
Time period*		
2005-2009 (n=88,354)	19.3 (6.4-67.9)	0.93 (0.90-0.95)
2010-2015 (n=84,601)	20.4 (7.1-65.9)	0.97 (0.93-1.00)

*Hazard ratio for a dialysis facility to transplant center distance ≥100 miles compared to <100 miles (reference) using cox model adjusted for age at first dialysis, race/ethnicity, sex, insurance status, median income and distance patient lives from transplant center.
*$p<0.05$ for interaction
IQR = interquartile range

TH-PO1144

Utilizing the Estimated Post-Transplant Survival Score (EPTS) to Assess Dialysis Facility Referral for Pre-Transplant Evaluation

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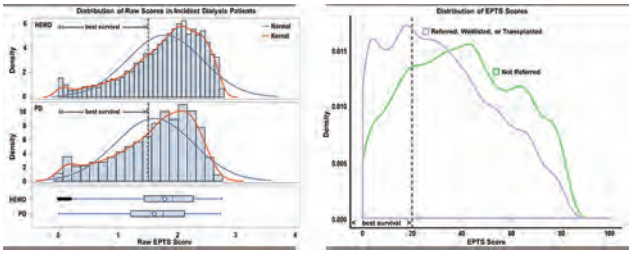
Background: Although transplant (txp) is the optimal treatment for End Stage Kidney Disease (ESKD), only ~ 15% of prevalent patients (pts) are waitlisted annually. It is estimated that approximately half of ESKD pts would have a survival advantage from txp. The 4-factor (age, vintage, diabetes, & prior txp) EPTS in conjunction with the Kidney Donor Profile Index maximizes the use of donor kidneys with the highest predicted survival by allocating them to potential recipients with the highest predicted post txp survival. Lower EPTS is associated with higher projected longevity. With the exception of diabetes, the 4 factor EPTS does not include comorbidities. We calculated EPTS for incident ESKD pts cared for in outpatient dialysis facilities operated by a nonprofit provider, to determine if pts with a favorable prognosis were being appropriately referred for evaluation.

Methods: We studied 14,043 hemodialysis (HD) & 2,739 peritoneal dialysis (PD) pts, 18 -71 years who started dialysis between 2009-2018 & were followed for 1 year unless transplanted. SAS & R statistical packages were utilized for data analysis.

Results: EPTS distributions in HD & PD pts differed (see figure). The median (IQR) scores were 36 (19- 54) & 29 (14- 46) in HD & PD pts, respectively. Overall, 47.9% of HD & 71.0% of PD pts were evaluated in the first year. The % pts in the lowest EPTS quintile was higher among PD (36.7%) vs. HD (27.9%) pts. Among pts with the best predicted longevity by EPTS, 41.3% HD vs. 20.9% PD pts were not evaluated in the first year. Reasons included patient referred but not evaluated, patient refusal of referral, medically unsuitable or unknown reason.

Conclusions: Overall, the present referral practices within this nonprofit dialysis provider demonstrate that pts are being actively referred for pre-txp evaluation. Better referral rates & EPTS scores among PD vs. HD pts likely reflect the overall health of those pts selected for home dialysis. EPTS use in conjunction with an incident comorbidity review will allow dialysis facilities to optimize transplant referral practices.

Funding: Commercial Support - Dialysis Clinic, Inc.



TH-PO1145

Accessibility and Graft Outcome According to Economic Inequality in South Korea: A Widening Gap After Expansion of Insurance Coverage

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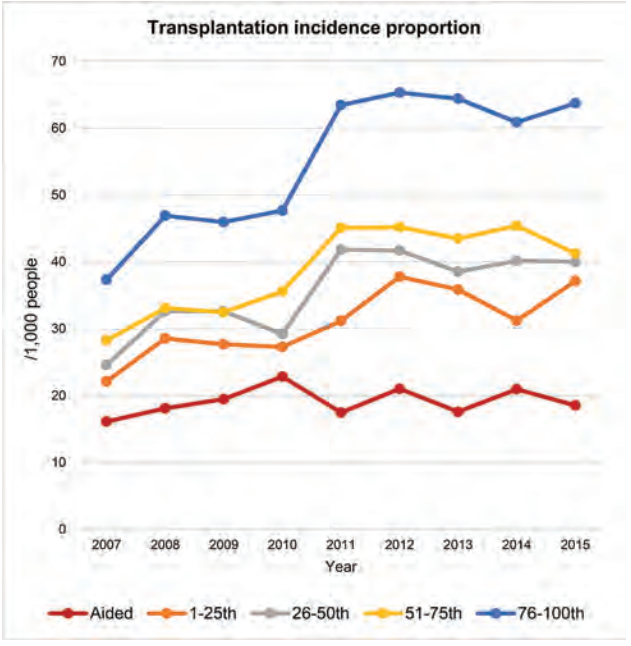
Background: Disparity in accessibility to and prognosis of kidney transplantation according to wealth inequality has been an important issue.

Methods: We performed a nationwide, population-based cohort study using the national claims database of Korea in which nationwide health insurance is provided. End-stage renal disease (ESRD) patients from 2007 to 2015 were included. As their wealth status was identifiable annually, the financial states were collected and stratified into five subgroups in each year. Time-trends of incidence proportion of kidney transplantation among ESRD patients in each year was initially assessed. The risk of graft failure was analyzed as prognostic outcome within the transplant recipients.

Results: Significant disparity in kidney transplantation accessibility was present and it was further widening, particularly from the year 2009 in which the national health insurance service started to cover desensitized kidney transplantation. Desensitized or preemptive transplantation was less common in the poorest group who were more frequently receiving transplantation after 5 years of dialysis in the recent periods. The prognosis of kidney transplantation was significantly worse in the poorer people, and this disparity also worsened during the study periods.

Conclusions: Prominent disparity regarding accessibility to and prognosis of kidney transplantation presented in Korea according to wealth inequality and was further worsening. Worsening pressure of donor shortage was less severe in the richer people who were preferentially benefited from the recent expansion of donor pool.



TH-PO1146

It's Now or Never: A Retrospective Audit of Patients Suspended from the Deceased Donor Transplant List

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Background: The primary purpose was to evaluate the outcomes of patients suspended from the deceased donor renal transplantation list in Northern Ireland. A three year follow-up period was used from October 2015 to December 2018. The primary outcomes measures were to assess the proportion of patients who were alive and had been transplanted by December 2018. Secondary outcomes were to measure the duration patients were suspended, the reasons for this and to examine the relationship between duration and reason for suspension and likelihood of transplantation.

Methods: A list of patients suspended from the deceased donor transplant list on 28thOctober 2015 was obtained from the regional transplant centre in Belfast City Hospital. Regional medical databases were used to extract data on the date of initial listing on the active list, dates of suspensions, reasons for suspensions and outcomes. The end of follow-up period was 10thDecember 2018.

Results: 56 patients were identified on the initial deceased donor renal transplant list. 41 patients (73%) were alive at the end of follow-up, 14 (25%) were deceased and 1 (2%) unknown (moved out of region). 30 patients (53%) had received a renal transplant, 25 patients (45%) had not, with 1 (2%) unknown outcome. The three most common causes for suspension were: the patient was medically unfit to undergo transplant surgery, the patient was awaiting a specialist opinion or investigation and suspension on patient request. Mean time suspended was 645 days and from original listing to transplantation was 807 days. In patients suspended for under one year, 11 of 14 patients were transplanted (79%), however in patients suspended for over one year, only 13 of 34 patients were transplanted (38%). Patients suspended as they were medically unfit had the lowest rate of transplantation (6/20). All patients suspended on patient request, awaiting radiological investigaton or obesity were transplanted (12 patients).

Conclusions: In a three year follow-up period, most patients who had been suspended in October 2015 were alive and had undergone renal transplantation. The fitness of recepients was the most common reason for suspension from the list and is associated with poorer outcomes. Patients suspended for over one year had a significantly lower rate of transplantation. Regular multi-disciplinary review is required to try to minimise the duration of suspensions.

TH-PO1147

Does This Patient Still Want a Kidney Transplant? Changing Treatment Preferences Among African Americans on the Kidney Transplant Waiting List

Tyler M. Barrett,[1] Matthew J. Ellis,[1] Debra Sudan,[1] Tara S. Strigo,[1] Clementina A. Davenport,[1] Xiyuan Zhang,[1] Jennie Riley,[1] Aviel N. Alkon,[1] Patti Ephraim,[2] Ashley N. Cabacungan,[1] Dinushika Mohottige,[1] L. Ebony Boulware.[1] *[1]Duke University, Durham, NC; [2]Johns Hopkins University, Baltimore, MD.*

Background: African Americans spend substantial time on the kidney transplant waiting list. However, it is not known if their desires to receive transplants change while waiting for a kidney.

Methods: We studied self-reported treatment preferences among 300 African Americans on the deceased donor kidney transplant waiting list. Using a standard questionnaire, we listed each treatment option and asked, "As of today, which treatment option for kidney failure do you prefer?" We considered participants preferences as concordant (preference for kidney transplant) or discordant (preference for non-transplant treatment). We also measured participants' decisional conflict using the validated Decisional Conflict Scale (DCS), including subscales assessing the role of information, value clarity, support, uncertainty, and perceived decision effectiveness in decisional conflict. In multivariable analyses adjusting for participant demographics and history of nephrology care, we quantified associations between decisional conflict and discordant treatment preferences.

Results: Participants' mean (SD) age was 52 (11) years, 56% were male, 18% were in or near poverty, 39% had a high school education or less, and their median (IQR) waitlist time was 0.8 (0.2-1.9) years. Most were undergoing dialysis (82%). Fewer than half (44%) had concordant treatment preferences, while 30% preferred in-center hemodialysis, 4% home hemodialysis, 11% peritoneal dialysis, 9% conservative management, and 1% were unsure. Most (63%) had at least some decisional conflict (score >0 on the DCS [range 0-100]). After adjustment, participants with conflict about the clarity of their values (OR [95% CI]: 1.72 [1.0-2.94], $p<0.05$) and about their ability to make an effective decision (OR [95% CI]: 2.06 [1.06-4.01], $p<0.05$) had statistically significant greater odds of discordant treatment preferences.

Conclusions: When provided with a range of potential treatment options, many African Americans on the kidney transplant waiting list stated that a kidney transplant was not their preferred therapy. Screening for decisional conflict among patients on the waiting list may help identify those who need further decision support.

Funding: NIDDK Support

TH-PO1148

Willingness to Consider Increased-Risk Public Health Service Organs Among Waitlisted African Americans

Dinushika Mohottige,[1] Matthew J. Ellis,[2] Debra Sudan,[2] Clementina A. Davenport,[2] Xiyuan Zhang,[1] Tara S. Strigo,[2] Patti Ephraim,[4] Tyler M. Barrett,[3] Ashley N. Cabacungan,[5] L. Ebony Boulware.[3] *[1]Duke University, School of Medicine, Durham, NC; [2]Duke University Medical Center, Durham, NC; [3]Duke University School of Medicine, Durham, NC; [4]Johns Hopkins University, Baltimore, MD; [5]Division of General Internal Medicine, Durham, NC.*

Background: It is unknown if African Americans (AAs), who have historically experienced medical mistrust and health care discrimination, are willing to accept Public Health Service increased risk (PHSIR) kidneys with increased risk of transmitting hepatitis B, C and HIV.

Methods: We conducted a cross-sectional study among AAs listed for a kidney transplant. We assessed participants' willingness to accept PHSIR kidneys using transplant center written consent forms. In logistic regression models, we quantified the independent association of willingness with participants' sociodemographics, attitudes including medical mistrust, concerns about medical experimentation (e.g. 'how likely is it that you or people like you might be used in experiments without your consent'), trust in doctors (e.g. 'I trust doctors to put my needs above all others'), and racial, gender, income, and age-based discrimination experience (e.g., 'Do you believe you have ever received worse medical care than other patients because of your race').

Results: Among 300 AA participants, mean (SD) age was 52 (11), 77% were dialysis dependent for a median of 3 (IQR 1,4) years, 45% were female, and 61% college educated. Most (89%) were willing to accept PHSIR kidneys. Participants' trust in doctors was high (95%), while prior perceived racial or income-based discrimination was lower (20% and 22%). Individuals willing (vs. not) to accept PHSIR kidneys were older (mean 52 vs. 48 years), had lower prevalence of high health literacy (21% vs. 42%), poorer (18% vs. 9%), and reported more racial (16% vs. 10%) or income (19% vs. 12%) discrimination. After adjustment, those with greater than HS literacy (versus less) had lower odds of willingness (OR [95% CI] 0.36 [0.13, 0.99]). Medical mistrust measures were not associated with willingness.

Conclusions: AA potential kidney transplant recipients had high willingness to accept PHSIR kidneys, suggesting utilization of these kidneys could help to increase transplant rates among minorities.

Funding: NIDDK Support

TH-PO1149

Decision Aid to Inform Patients of Transplant Centers That Transplant Patients Like Them

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Background: Patient feedback to the Scientific Registry of Transplant Recipients (SRTR) and Organ Procurement and Transplantation Network (OPTN) indicated interest in tailoring the transplant center search based on patient-specific characteristics such as age, and comorbidities such as body mass index (BMI) (Clin Transplant. 2017; e13125).

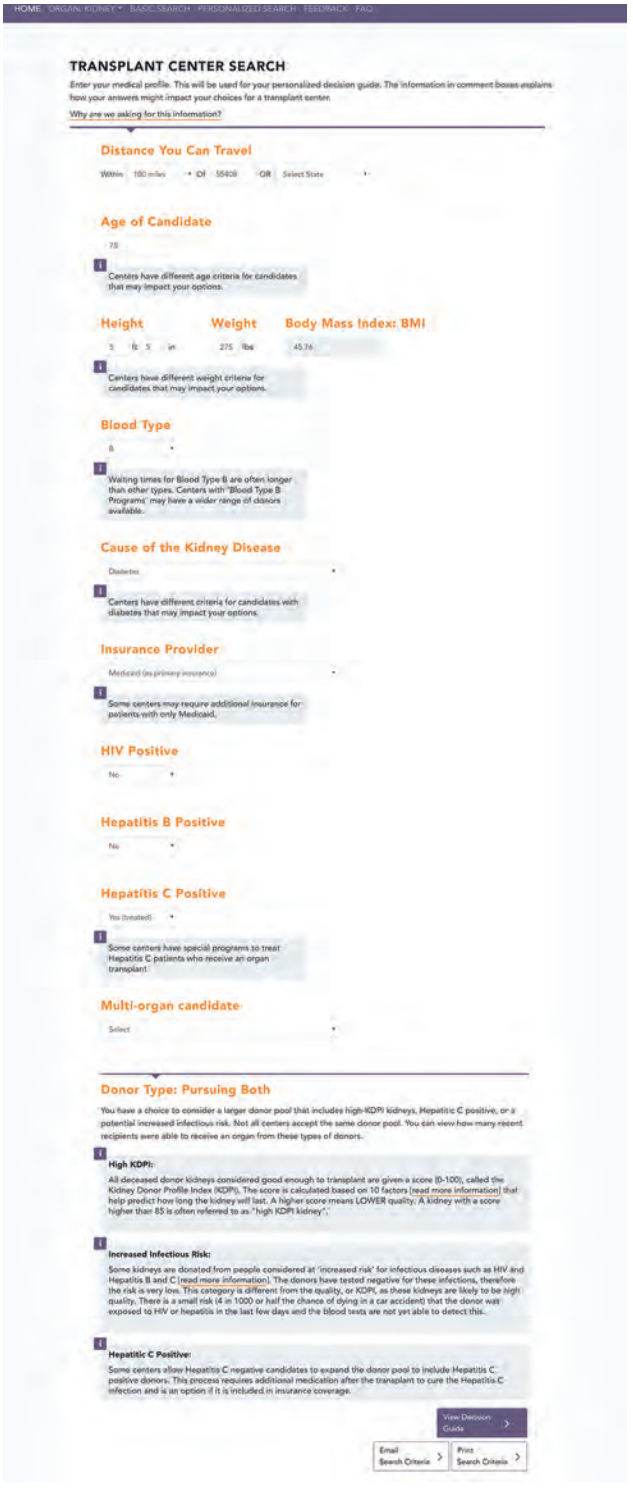
Methods: We conducted 20 interviews and 13 focus groups with local kidney transplant candidates and their family members plus 3 focus groups with recipients of kidney transplants recruited nationally (n=89 in total). Participants were shown prototypes of the patient specific search decision aid to evaluate the efficacy of reporting customized

search results for identifying transplant centers that treat patients like them. We used this feedback to develop a new website.

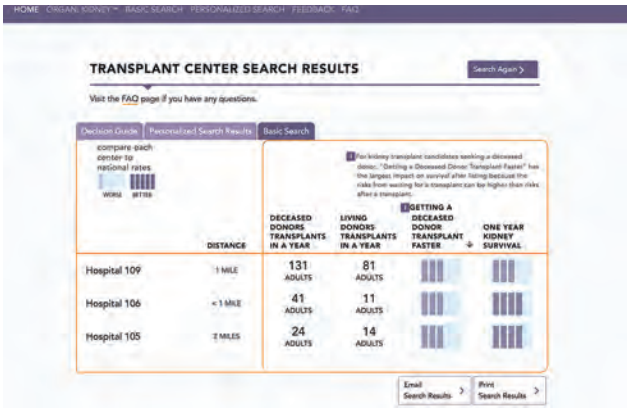
Results: A website based decision aid informed subjects about transplant center's use of high KDPI organs and PHS increased risk organs. It also informed subjects about transplant centers that perform transplants in candidates with age over 70 and other comorbidities such as high BMI. [figure1] [figure2]

Conclusions: Patient-specific information using SRTR data can be provided to patients using an interactive web-based decision tool.

Funding: Other U.S. Government Support



Website Showing Program-Specific Recipient Characteristics with pop-up boxes to better inform patients.



Website Search Results Displaying Overview of Patient-Specific Services

TH-PO1150

Care Practices for Patients with Advanced Kidney Disease Who Were Evaluated for Transplant but Did Not Receive a Kidney

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Background: There is strong public and professional support for increasing access to kidney transplant for patients with advanced kidney disease. However, more liberal referral practices will likely also increase the number of patients who are evaluated for transplant but do not receive a kidney. A deeper understanding of the implications of being referred for transplant evaluation but not receiving a kidney may help to support shared decision-making about transplant referral.

Methods: Qualitative analysis using documentation in the electronic medical record for 148 adults with advanced kidney disease referred to the Veterans Affairs Puget Sound Health Care System's transplant coordinator from 2008-2018 who did not receive a kidney during the follow-up period (among a total of 209 adults evaluated for kidney transplant). Participants were followed through their date of death or January 1, 2018. We performed an inductive content analysis to ascertain dominant emergent themes related to transplant evaluation.

Results: By the end of follow-up, 148 of 209 patients evaluated for transplant (71%) had not received a kidney. Three dominant themes emerged from analysis of the electronic medical record for this subset of patients: 1) Sources of forward momentum in the transplant evaluation process: Patients were often referred for transplant evaluation reflexively and the process tended to move forward until an absolute contraindication was identified or patients passively disengaged. 2) Potential for transplant shapes other medical decisions: Engagement in the transplant evaluation could have far-reaching effects on many other aspects of patients' medical care. 3) Personal responsibility and psychological burden: Patients felt personally responsible for their progress through the transplant evaluation and the process could take a significant emotional toll on both patients and families.

Conclusions: Most patients evaluated for transplant at our center did not receive a kidney. The evaluation process could be burdensome and emotionally taxing for these patients and their families and could intrude on many other aspects of their care. These findings highlight the potential tradeoffs involved in being evaluated for kidney transplant and argue for engaging patients in a deliberate and shared approach to referral decisions.

Funding: NIDDK Support

TH-PO1151

Donation After Cardiac Death for Pediatric Kidney Transplantation

Sarah J. Kizilbash, Scott T. McEwen, Michael D. Evans, Blanche M. Chavers. *University of Minnesota, Minneapolis, MN.*

Background: Donations after cardiac death (DCD) constitute 20% of adult deceased-donor kidney transplants. There is a paucity of data on long-term transplant outcomes associates with the use of DCD donors in children.

Methods: We used the Scientific Registry of Transplant Recipients to identify all pediatric (< 18 years at transplant) deceased donor kidney transplants that were performed in the US using DCD kidneys between 1987 and 2017. We used 4:1 propensity score matching (for age at transplant, gender, race, pretransplant dialysis, and transplant center and year) and exact matching by center to create a comparison group. Patient and graft survival were evaluated using mixed effects Cox proportional hazards modeling and delayed graft function using logistics regression.

Results: Our final analysis cohort included 285 DCD and 1132 non-DCD recipients. The demographic and clinical characteristics of recipients and donors are given in tables 1 and 2. DCD donors were younger (21.8 vs. 23.5 years; p 0.03), and more likely to be white (89.5 vs. 79%; p <0.001). We found no difference in 5-year graft survival (76.1% vs. 72.6%; p 0.55) and 5-year patient survival (95.1% vs. 95.7%; p 0.58) between DCD and non-DCD recipients. The differences in graft survival (aHR: 0.93; 95% CI: 0.72 – 1.3; p 0.45) and patient survival (aHR: 1.02; 95% CI: 0.60 – 1.7; p 0.99) remained insignificant

after multivariate adjustment. DCD recipients demonstrated a higher risk of delayed graft function (adjusted OR: 3.2; 95% CI: 2.1 – 4.7; p <0.001).

Conclusions: Although DCD recipients are at higher risk of delayed graft function, we found no difference in 5-year patient or graft survival between DCD and matched non-DCD recipients.

Demographic and baseline characteristics of donors and recipients

Variables	Donation after cardiac death N = 285	Non-cardiac death donation N = 1132	p value
Recipients age at transplant (years) Mean (SD)	13.4 (4.4)	13.0 (4.6)	0.12
Recipient gender n (%) Male	162 (56.8)	642 (56.7)	0.99
Recipient race n (%) White Black Other	187 (65.6) 74 (26.0) 24 (8.4)	755 (66.7) 297 (26.2) 80 (7.1)	0.78
Pre-emptive transplant n (%)	50 (17.5)	240 (21.2)	0.20
Delayed graft function n (%)	56 (19.6)	91 (8.0)	<0.01
Age at donation (years) Mean (SD)	21.8 (9.0)	23.3 (10.1)	0.025
Donor gender n (%) Male	194 (68.1)	772 (68.2)	0.99
Donor race n (%) White Black Other	255 (89.5) 23 (8.1) 7 (2.5)	894 (79.0) 195 (17.2) 43 (3.8)	0.002
KDPI Mean (SD)	26.7 (18.4)	21.3 (18.3)	< 0.01

TH-PO1152

Use of Expanded Criteria Donors for Pediatric Kidney Transplantation in the United States

Sarah J. Kizilbash, Scott T. McEwen, Michael D. Evans, Blanche M. Chavers. *University of Minnesota, Minneapolis, MN.*

Background: The use of marginal kidneys for transplantation has increased in the recent years to expand the deceased donor pool. Transplant outcomes associated with the use of expanded criteria donors (ECD) in children are unknown.

Methods: We used the Scientific Registry of Transplant Recipients to identify all pediatric (<18 years at transplant) deceased donor kidney transplants that were performed in the US using ECD (donors older than 60 years or older than 50 years with co-morbidities) between 1987-2017.

Results: Our final cohort included 96 ECD and 375 non-ECD recipients. The demographic and baseline characteristics of donors and recipients are presented in table 1. ECD donors were older (58.4 vs. 25.1 years; p<0.001), and less likely to be males (33.3 vs. 62.4%; p<0.001). Compared with non-ECD recipients, ECD recipients were at significantly higher risk of delayed graft function (aOR: 3.2; 95% CI: 1.8 5.6; p< 0.001), graft failure (aHR: 1.6; 95% CI: 1.2 2.1; p 0.001) and mortality (aHR: 1.6; 95% CI: 1.02–2.3; p 0.01). Five-year acute rejection free survival tended to be lower in ECD vs. non-ECD recipients (24.3 vs. 34.4%; p 0.06).

Conclusions: ECD kidney transplants in children are associated with higher risks of delayed graft function, graft failure and mortality compared with matched non-ECD recipients. We recommend that kidneys from ECD donors not be considered for pediatric candidates.

Demographic and baseline characteristics of kidney transplant recipients and donors

Variables	Expanded criteria donor recipients N = 96	Non-expanded criteria donor recipients N = 375	p value
Recipients age at transplant (years) Mean (SD)	13.4 (4.3)	12.7 (4.4)	0.18
Recipient gender n (%) Male	51 (53.1)	212 (56.5)	0.63
Recipient race n (%) White Black Other	57 (59.4) 34 (35.4) 5 (5.2)	235 (62.7) 117 (31.2) 23 (6.1)	0.92
Pre-emptive transplant n (%)	13 (13.5)	62 (16.5)	0.58
Delayed graft function n (%)	35 (36.5)	66 (17.6)	<0.001
Age at donation (years) Mean (SD)	58.4 (5.6)	25.1 (14.4)	<0.001
Donor gender n (%) Male	32 (33.3)	234 (62.4)	<0.001
Donor race n (%) White Black Other	84 (87.5) 9 (9.4) 3 (3.1)	311 (82.9) 54 (14.4) 10 (2.7)	0.06
KDPI Mean (SD)	82.5 (11.4)	31.3 (23.2)	<0.001

TH-PO1153

The Pediatric Renal Transplant Experience: Reflecting Through Photographs

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Background: Poor self-management contributes to reduced renal allograft survival during adolescence and young adulthood. For many pediatric patients and their families, the symptoms, complications, and natural history related to ESRD and its treatments are unfamiliar. These unmet information needs lead to uncertainty, interfere with goal setting and result in ineffective self-management. Providing patients with self-reflection tools to help explore the question "Is my experience normal?" may help mitigate these challenges. We present data from a pilot study exploring how photo-elicitation, a qualitative method where images are used to prompt individuals to talk about their personal experiences and values, engages pediatric transplant recipients and their families to generate insight into their experiences living with kidney disease.

Methods: Pediatric renal transplant recipients from a single center, along with one family member, were invited to participate. All participants were asked to submit 5 photographs telling their transplant story. No restrictions were placed on what photos individuals could submit. During interviews, participants were asked to tell their story utilizing the photos as prompts. Interviews were recorded, transcribed and analyzed using an inductive grounded theory approach to identify common themes.

Results: 13 individuals (7 patients: ages 9 - 19, >1 year post transplant, and 6 parents) completed the study. The photographs generated conversations on four emergent themes: (1) feeling different/isolated from their peers; (2) importance of peer support, including those with and without kidney disease; (3) fear about transitioning to self-care; and (4) the need to create a "normal" child/adolescent experience. Finally, subjects reported significant value in the self-reflection that took place during the photo elicitation process and wanted to share their photos with their clinicians to provide additional insight into their personal experiences.

Conclusions: Photo elicitation generated a rich dataset describing a range of pediatric renal transplant experiences, showing potential as a clinical intervention to support patient and family self-reflection. Finally, the process of self-reflection and sharing visual stories with peers and clinicians can result in greater empathy from caregivers and medical professionals, ultimately improving self-management.

Funding: NIDDK Support

TH-PO1154

Is Age Just a Number? Outcomes of Older Living Donors for Pediatric Kidney Transplant Recipients

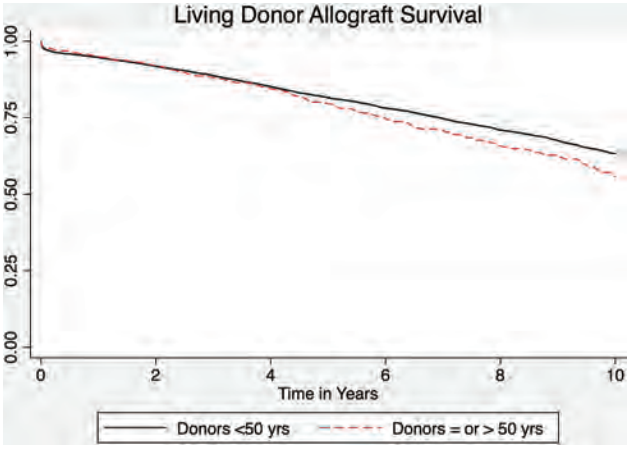
Swee-Ling Levea, Malcolm Macconmara, Christine S. Hwang. *University of Texas Southwestern Medical Center, Dallas, TX.*

Background: Living donor kidney transplantation is encouraged in the pediatric population due to better long term allograft survival compared to deceased donor kidney transplantation. Often, pediatric recipients are listed inactive while awaiting evaluation of their living donors. However, there are limited data addressing the impact of age on allograft survival from living donor. We therefore examined the association of living donor-recipient age combinations with allograft survival in children.

Methods: Using the Scientific Registry of Transplant Recipients (SRTR), we analyzed graft survival among living donor kidney transplant pediatric recipients from older living donors (≥50 years old) compared to younger donors (< 50 years old) between 1993 - 2017. Statistical analysis was performed using STATA and a p value of <0.05 was considered to be significant.

Results: The age of the younger living donors was 35.4 ± 7.6 years while that of the older living donors was 53.4 ± 3.6 years (p< 0.05). The pre-operative creatinine for the younger donors was 0.86 ± 0.34 mg/dL vs. 0.89 ± 0.19 mg/dL for the older donors (p=NS). The average post-operative creatinine for the younger donors was significantly lower at 1.26 ± 0.42 mg/dL while that of the older donors was 1.34 ± 0.30 mg/dL (p<0.05). The BMI, presence or absence of hypertension or diabetes, and cigarette use were not significantly different between the two groups. The HLA mismatch in younger donors was 2.6 ± 1.2 and 2.8 ± 1.3 in the older donors (P<0.05). The allograft survival from younger living donors were superior compared to those from older donors (Figure 1) (p<0.05).

Conclusions: Allograft survival from younger living donors is superior at ten years compared to older living donors. In potential pediatric kidney transplant recipients on the wait-list, deceased donor kidney transplant consideration is beneficial if these individuals have older living donors.



TH-PO1155

Kidneys from African American Donors Are Associated with Accelerated Podocyte Detachment After Kidney Transplantation

Abhijit S. Naik,[1] Jawad Aqeel,[1] Diane M. Cibrik,[2] Milagros D. Samaniego-Picota,[3] Su Q. Wang,[1] Mahboob A. Chowdhury,[1] Roger C. Wiggins.[1] *[1]University of Michigan, Ann Arbor, MI; [2]University of Kansas Hospital, Parkville, MO; [3]Henry Ford Health Services, Detroit, MI.*

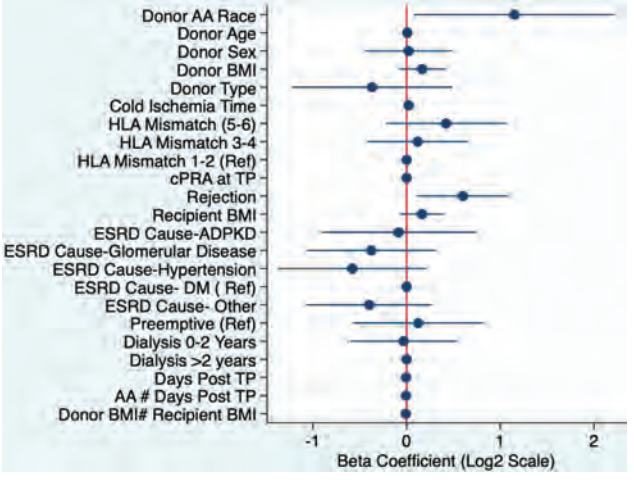
Background: Kidneys from AA donors have reduced survival compared to kidneys from non-AA donors. Longitudinal histological data to better delineate the relationship of donor race, post-transplant histology and outcomes is lacking. We used urine ***nephron segment specific mRNA markers*** to understand whether kidneys from AA donors have different injury patterns than non-AA donors. We tested the hypothesis that high prevalence of glomerular disease in AA donors would be associated with differences in urine podocyte markers

Methods: We used a published cohort (*Naik AS, et al, NDT, 2018*) with linear mixed model with random intercept (pt. level) and slope (time post-transplant) with Urine Podocin mRNA:Urine creatinine ratio (UPodCR) as the dependent variable. The model was adjusted for an ***a priori*** selected group of variables

Results: 534 urine samples from 125 recipients were analyzed. 14 recipients recieved kidneys from AA donors contributing to 59 urine samples. AA donors were younger (34 vs.41,p=0.04). Other characteristics were well balanced. One-year surveillance biopsy revealed no difference in burden of observable glomerular disease between AA and non-AA groups (p=0.21). There was no difference in proteinuria by donor race. Although at time of TP there was no difference in nephrin expression, by 1yr post-TP nephrin expression was significantly down-regulated in AA vs. non-AA groups. Figure 1 demonstrates factors associated with podocyte detachment.

Conclusions: These data are compatible with AA donors developing podocyte injury and loss that is observable prior to development of proteinuria or glomerular disease on surveillance biopsies. Further studies expanding the current cohort and assessing relationships of accelerated podocyte loss with APOL1 genotype are ongoing.

Funding: NIDDK Support, Other NIH Support - MNORC



Donor AA race and rejection in 1st year were associated with accelerated podocyte detachment.

TH-PO1156

Early Post-Donation Hyperfiltration Is Associated with Accelerated Podocyte Detachment

Abhijit S. Naik, Dustin Le, Su Q. Wang, Mahboob A. Chowdhury, Roger C. Wiggins. *University of Michigan, Ann Arbor, MI.*

Background: Living kidney donation is associated with increased long-term risk of CKD/ESRD post-donation. The remaining kidney is rarely biopsied and thus mechanisms behind progression remain unproven. Parallel data from uni-nephrectomized rat models shows podocyte hypertrophic stress, detachment and depletion, progressive proteinuria and FSGS. While proteinuria is common among donors vs. matched non-donors, it is often low grade

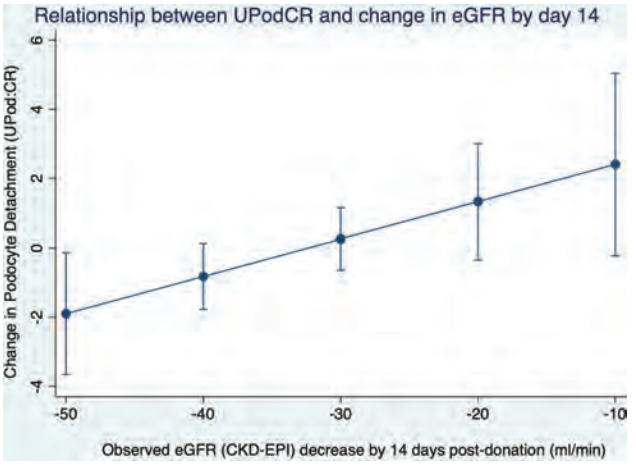
Methods: SpotUrine pellet mRNAs from 87 living donors were used. Data was normalized to creatinine for one podocyte markers (podocin), and urine protein. UPod:CR is a marker of podocyte detachment rate and UProt:CR as marker for proteinuria (both log transformed). We measured differences in UPod:CR, UProt:CR and eGFR before (day 0) and after donation (day 14) to estimate their "delta" values. Multivariable linear regression using either podocyte detachment or proteinuria were used as the dependent variable adjusted for baseline eGFR, donor age, BMI, MAP (Mean Arterial Pressure)at donation and the change in eGFR by 14 days post donation.

Results: In a multivariable linear regression model the change in eGFR by 14 days post donation was significantly associated with podocyte detachment rate but not proteinuria.

Conclusions: Early post donation hyperfiltration is associated with accelerated podocyte detachment even in the absence of proteinuria. Longer term follow up is required to understand relationship of hyperfiltration, podocyte detachment and progressive kidney dysfunction after donation.

Funding: NIDDK Support

UPod:CR	B. Coef	Std. Err.	P value	LCL	UCL
Delta eGFR (ml/min)	0.11	0.05	0.04	0.005	0.21
Donor Age	0.016	0.04	0.68	-0.06	0.1
BMI at Donation (Kg/m2)	-0.01	0.09	0.89	-0.19	0.16
MAP before donation	-0.006	0.05	0.91	-0.10	0.09
Baseline eGFR	0.07	0.04	0.12	-0.02	0.15



TH-PO1157

Living Kidney Donation Is Accompanied by Persistently Increased Urine Pellet Nephrin mRNA in the First Year After Donation

Abhijit S. Naik,[1] Diane M. Cibrik,[2] Milagros D. Samaniego-Picota,[3] Su Q. Wang,[1] Mahboob A. Chowdhury,[1] Roger C. Wiggins.[1] *[1]University of Michigan, Ann Arbor, MI; [2]University of Kansas Hospital, Parkville, MO; [3]Henry Ford Health Services, Detroit, MI.*

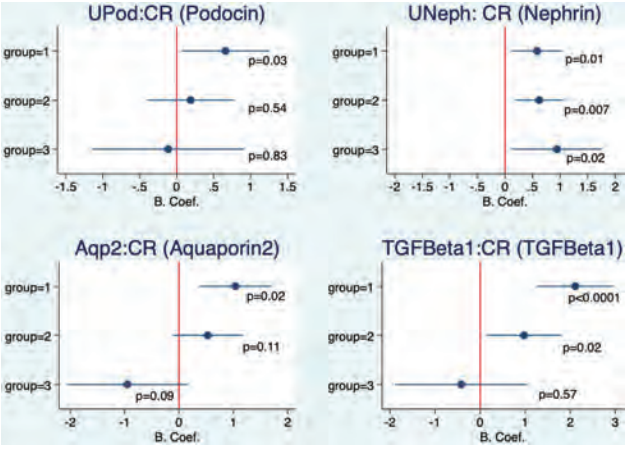
Background: Living kidney donation is associated with increased long-term risk of CKD/ESRD post-donation. Diabetes and hypertension are reported to be associated with ESRD. The remaining kidney is rarely biopsied and thus mechanisms behind progression remain unproven. Parallel data from uni-nephrectomized rat models shows podocyte hypertrophic stress, detachment and depletion, progressive proteinuria and FSGS. While proteinuria is common among donors vs. matched non-donors, it is often low grade

Methods: We used urine pellet nephron segment specific mRNA markers expressed per creatinine to understand biology of the remaining kidney early post-donation. Donor urine samples were divided by time of collection. Group 0, before donation; Group 1, 1-2days post donation; Group 2, 10-14days and Group 3, 6-12months post donation. Linear mixed model clustering for patients was used to assess trends across two podocyte specific markers (podocin, nephrin), a distal collecting duct marker (Aqp2) and a marker of innate immunity/profibrotic activity (TGFbeta1) and proteinuria

Results: 72 donors provided 178 urine samples for the analysis. Figure 1 reveals that proteinuria and podocin, Aqp2 and TGFbeta1 mRNAs were increased immediately post donation (referenced to Group 0) but normalized by 2weeks post-donation. Nephrin remained significantly increased over the first year.

Conclusions: All markers showed evidence for hypertrophic kidney stress immediately post-TP. Sustained increased urinary nephrin mRNA in living donors after TP may represent hypertrophic adaptation to the single kidney state requiring up-regulation of nephrin to maintain increased filtration slit length. Whether higher level nephrin mRNA expression is related to future risk of progressive kidney disease remains to be tested.

Funding: NIDDK Support



Coefficient Plot demonstrating change in 4 markers at Group1, 2 and 3 (relative to time 0)

TH-PO1158

Clinical Significance of AKI and Kidney Donor Profile Index on Clinical Outcomes in Deceased Donor Kidney Transplantation: A Multicenter Cohort Study

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Background: It is important to evaluate the donor quality before allocation in deceased donor kidney transplantation (DDKT). Kidney Donor Profile Index (KDPI) is an effective tool, but the association with acute kidney injury (AKI) is uncertain. The aim of this study was to investigate the clinical significance of AKI and KDPI on clinical outcomes in DDKT.

Methods: Four transplant centers enrolled 657 kidney transplant recipients (KTRs) from 526 deceased donors (DDs). We divided the high KDPI and low KDPI by the median of 65%, and each group was divided into AKI-KT and non-AKI-KT subgroups according to DDs with AKI.

Results: There was no significant difference in the incidence of delayed graft function between high KDPI-KT and low KDPI-KT groups, but AKI-KT subgroup showed significantly higher incidence of delayed graft function compared with non-AKI subgroup in the two groups (P=0.001, P<0.001). There was no significant difference in the incidence of biopsy-proven acute rejection between high KDPI-KT and low KDPI-KT groups regardless of DDs with AKI. Death-censored graft survival rate was significantly lower in the high KDPI-KT group compared with the low KDPI-KT group (P=0.005), but there was no significant difference in the death-censored graft survival rate between AKI-KT and non-AKI-KT subgroups in the each group. Only in the high KDPI-KT group, the KT group from DDs with AKI stage 3 was lower in death-censored graft survival rate compared with that from DDs with non-AKI, AKI stage 1, or 2.

Conclusions: KTs from DDs with AKI showed an adverse effect on the allograft outcome, especially from DDs with AKI stage 3 in the high KDPI-KT group. Therefore, closed observation and prevention of severe AKI will be required, especially for KTs from DDs with high KDPI.

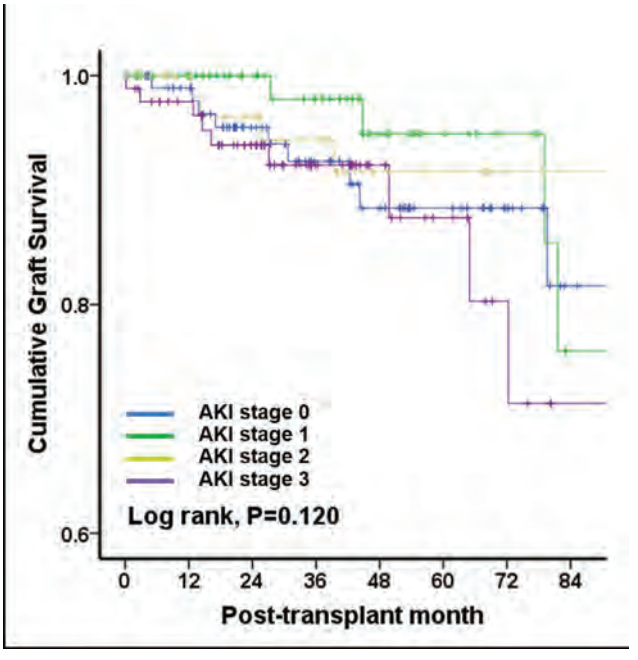

Figure 1. Death-censored graft survival according to AKI stage in high KDPI group

TH-PO1159

Kidney Transplantation from Small Pediatric Donors May Be Feasible to Those Who Developed Chronic Refractory Dialysis Hypotension: A Single-Center Experience

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Background: Chronic refractory dialysis hypotension (CRDH) is a serious issue in dialysis patients waiting for transplants. CRDH leads to fatal clinical outcomes and disqualification from kidney transplantation. Kidney transplantation from small pediatric donors to adult patients with lower blood pressure(BP) may be an option. To our knowledge, there has been no report on the benefit of transplantation from pediatric donors to CRDH recipients.

Methods: Ten single-kidney transplantations from five small pediatric donors after cardiac death in our center between August 2016 and April 2018 were analyzed. Half of the recipients were CRDH (group A) and each of them was matched with no-CRDH patient (control, group B) from same deceased pediatric donor. The operation method of vascular anastomosis and ureterocystoneostomy was the same as that of adult donors. Clinical characteristics, post-operative treatment and outcomes were retrieved. Postoperative BP, graft function and size were compared between the two groups. The follow-up time was up to April 2019.

Results: There were no acute rejection, graft loss or death in CRDH patients after kidney transplantation. The postoperative systolic BP in four recipients in group A was above 100mmHg persistently. Their renal function was recovered despite three transient delayed graft function (2 in group A and 1 in group B). There was no significant difference in serum creatinine or graft size (P=0.84, 0.94) after transplantation between two groups.

Conclusions: In conclusion, kidney transplantation from small pediatric donors may be feasible to CRDH patients and their BP may return to normal after transplantation.

Figure1 The change of Scr after transplantation in two groups

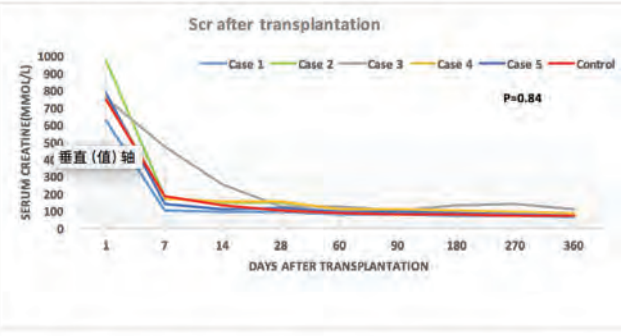

Figure1 shows the changes of serum creatinine (Scr) after transplantation in two groups. The levels of Scr were recorded for all recipients 1,7,14,28,60,90,180 and 360 days after transplantation. The post-operative Scr in group A was listed respectively(case1-5). The post-operative Scr in group B was expressed by the average Scr of four recipients because the other one(control 4) was a five-year-old child whose renal function recovered obviously better than others and Scr was much lower. There was no significant difference in serum creatininebetween two groups (group A vs group B 191.24±211.64 vs 169.94±205.82, P=0.84).

TH-PO1160

Donor Source of Kidney Transplantation in New Zealand by Ethnicity: A Longitudinal Cohort Study

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Background: Marked disparity is present in access to kidney transplantation based on ethnicity. We explored whether donor source for kidney transplantation in New Zealand was associated with recipient ethnicity adjusting for socioeconomic and clinical factors.

Methods: We performed a longitudinal cohort study in patients ≥18 years with ESKD who commenced kidney replacement therapy in New Zealand between 2006-2015, using ANZDATA. Deprivation score and treating centre were obtained by data linkage with the National Health Index. Primary outcomes were time to receiving first transplant (live and deceased donor) and proportion who received a pre-emptive kidney transplant. Poisson regression was performed for pre-emptive and competing risks regression for live and deceased donor transplantation (accounting for competing risks of death and alternate donor source) with 95% confidence intervals. Estimates were adjusted age, sex, smoking, deprivation, BMI, late referral, treating centre, diabetes, and coronary artery disease.

Results: Among the 5106 participants, 822 received a kidney only transplant (479 living and 343 deceased donor). Māori and Pacific patients were younger, more frequently had diabetes and referred late to specialist care, and lived in more socioeconomically deprived areas than Europeans. In European patients, 65% received a live donor kidney transplant, while the proportion was smaller for Asian (44%), Māori (44%), and Pacific (39%) patient groups. Compared to European participants, those who identified as Māori, Pacific and Asian were markedly less likely to receive a pre-emptive and live donor kidney transplant even after adjustment for socioeconomic factors, comorbidity, and referral practices (Table 1). The difference in transplantation rates between participant groups was less marked for deceased donor kidney transplantation and was not evident in Māori and Asian groups after adjustment.

Conclusions: Transplantation rates for pre-emptive and live donor transplantation but not deceased donor transplantation vary with ethnicity, socioeconomic factors and late referral to specialist services within New Zealand after adjustment for comorbidity.

Variable	Pre-emptive Adjusted IRR (95% CI)	Living donor Adjusted SHR (95% CI)	Deceased donor Adjusted SHR (95% CI)
Maori (ref: European)	0.34(0.18-0.64)	0.40(0.28-0.56)	0.72(0.50-1.03)
Pacific (ref: European)	0.09 (0.02-0.36)	0.24 (0.12-0.41)	0.60 (0.38-0.96)
Asian (ref: European)	0.33 (0.16-0.68)	0.50 (0.32-0.78)	1.13 (0.79-1.61)
NZdep13 deciles 9-10 (ref: deciles 1-5)	0.45 (0.28-0.74)	0.56 (0.41-0.78)	0.76 (0.54-1.06)
Current smoker(ref: nonsmoker)	0.30 (0.15-0.59)	0.37 (0.24-0.55)	0.57 (0.39-0.85)
Late referral (ref: not late)	n/a	0.66 (0.49-0.88)	0.76 (0.58-1.02)
Diabetes (ref: no diabetes)	0.26(0.14-0.47)	0.30 (0.22-0.42)	0.28 (0.20-0.38)
Coronary artery disease (ref: none)	0.35(0.19-0.65)	0.41 (0.28-0.62)	0.33 (0.22-0.49)

TH-PO1161

Association of Perceived Information and Knowledge with Pursuit of Live Donor Kidney Transplants (LDKTs) Among African Americans

Ashley N. Cabacungan,[3] Matthew J. Ellis,[3] Debra Sudan,[4] Clementina A. Davenport,[3] Patti Ephraim,[5] Tara S. Strigo,[3] Iris Pounds,[3] Aviel N. Alkon,[3] Dinushika Mohottige,[3] Nicole DePasquale,[1] Sarah B. Peskoe,[3] Jane F. Pendergast,[3] Clarissa J. Diamantidis,[3] Jennifer St. Clair Russell,[2] L. Ebony Boulware.[3] *[1]Duke University School of Medicine, Durham, NC; [2]National Kidney Foundation, Washington, DC; [3]Duke University, Durham, NC; [4]Duke University Medical Center, Durham, NC; [5]Johns Hopkins University, Baltimore, MD.*

Background: It is unknown whether African Americans' (AAs) pursuit of LDKT is related to their perceived information or knowledge about LDKT.

Methods: We conducted a cross-sectional analysis among AA kidney transplant candidates enrolled in the Talking about Living Kidney Donation Support (TALKS) trial. We quantified associations between participants' perceived sufficiency of LDKT information and knowledge with pursuit of LDKT or the occurrence of live donor inquiries. We asked: "How well informed do you feel you are about live donor kidney transplant?" and "How much knowledge do you feel you have now about live donor kidney transplant?" We characterized pursuit of LDKT by self-reported behaviors reflecting low (no family/friends LDKT discussion, no donor), moderate (family/friends LDKT discussion, no donor) or high (family/friends LDKT discussion and potential donor identified) activation toward LDKT. In adjusted logistic regression models, we quantified the association between perceived sufficiency of LDKT information and knowledge with LDKT activation or live donor inquires.

Results: Among 300 AAs, the mean age was 52 (SD 11), 56% were male, 61% had a greater than high school education, and 50% had below 9th grade-level health literacy. The median time on the waitlist was 292 (IQR 81, 697) days. A total of 117 (39%) felt "very" or "extremely" well informed about LDKT and 114 (38%) reported "a great deal of knowledge" about LDKT. Compared to those less informed, participants who reported feeling "very" or "extremely well" informed had statistically significantly greater odds of having moderate or high LDKT (versus low) activation (OR: 2.71, 95% CI 1.02, 7.17), but there was no difference in live donor inquiries. Greater perceived knowledge was not associated with LDKT activation or live donor inquiries.

Conclusions: Fewer than half of African Americans on the deceased donor kidney waiting list felt well informed or very knowledgeable about LDKT. Efforts to increase African American potential recipients' perceived LDKT information and knowledge could enhance their access to LDKT.

Funding: NIDDK Support

TH-PO1162

A Cultural Competence Assessment of the Living Donor Navigator Program Reveals Sex Differences

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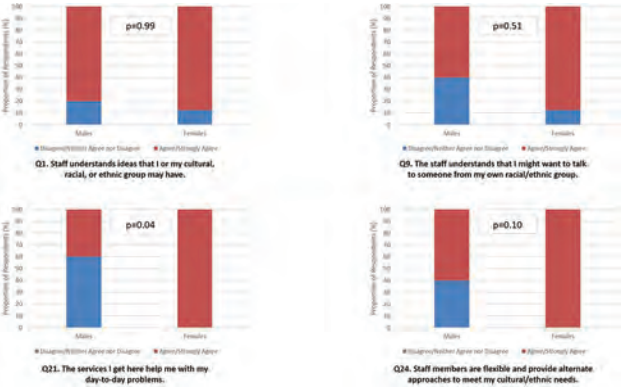
Background: The Living Donor Navigator (LDN) Program aims to separate the patient's burden of asking for a kidney transplant and improve potential living donor comfort with the evaluation process and has been particularly successful among African Americans. Care that is sensitive to the cultural needs of patients can result in improved health outcomes, especially among a high minority patient population. We sought to assess the cultural competence of the LDN program.

Methods: A modified Iowa Cultural Understanding Assessment was mailed to advocates from the LDN program and potential living donors who were screened on behalf of transplant candidates in the program. Response choices were on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). Proportions who agreed/strongly agreed were compared by sex and race using Fisher's exact test.

Results: There were 13 responses from 62 surveys (21% response rate). Twelve (92%) respondents were African American, and 61.5% were female. Overall, satisfaction with cultural competence was high, with > 60% of respondents reporting that they agreed/strongly agreed with 24/25 items. When comparing by sex, all female respondents (vs. 40% of males) agreed that the program helped them deal with problems in their day-to-day life (p=0.04) (Table). All female respondents (vs. 60% of males) agreed that the navigators were flexible and provided alternate approaches to meet their cultural needs (p=0.10). When exploring by race, the single Caucasian respondent agreed strongly with all items.

Conclusions: Though limited by small sample size, these preliminary data suggest that the LDN program reflects cultural sensitivity and meets the needs of participants socially, culturally, and linguistically. However, further qualitative exploration to understand sex differences is warranted.

Funding: Private Foundation Support



TH-PO1163

Knowledge and Receipt of Information About Living Donor Kidney Transplant Among Individuals with Advanced CKD

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Background: Knowledge about live donor kidney transplant (LDKT) is modifiable and is associated with access to LDKT. Yet, little is known about factors associated with LDKT knowledge or receipt of information about LDKT.

Methods: We conducted a cross-sectional study among nephrology clinic patients who were eligible for pre-emptive LDKT and enrolled in a trial on interventions to improve access to LDKT. We assessed participants' LDKT knowledge [10 pt. scale based on correct answers to questions about prognosis, donation, and financial aspects of LDKT; (high knowledge >8)], self-reported receipt of LDKT information from health professionals, and self-reported information sharing with family/friends. Using logistic regression (adjusting for participants age, race, and income), we quantified the association of LDKT knowledge with participants' receipt of LDKT information and their sharing of LDKT information with family/friends.

Results: The 130 participants had mean (SD) age 58.3 (9) years, 60% were female, 47.7% were African American, and 49% had a high school education or less. Participants' had a mean (SD) GFR of 26.6 (9.1) ml/min/1.73m2 and they had seen their nephrologists for 3.4 (4) years. Over half (55.4%) had high LDKT knowledge, and 33.1% reported having received LDKT information. Few (28.5%) had shared LDKT information with family/friends. Participants who reported receipt (vs. not) of LDKT information were more likely to have high knowledge (45.8% vs. 17.2%, p=0.001). Those who shared (vs. did not) information about LDKT with a family/friend were also more likely to have high LDKT knowledge (38.9% vs. 15.5%, p=0.006), as were those who received (vs. did not) LDKT info from health professionals (24.6% vs. 10.3%, p=0.001). After adjustment, those who received (vs. did not) LDKT information from health professionals had 4-fold higher odds of high LDKT knowledge (adjusted OR [95% CI]: 4.01: [1.49, 12.18], while those who shared information with family/friends had 3-fold higher odds of high LDKT knowledge (3.05 [1.24, 8.08]).

Conclusions: Improved provision of LDKT information to patients with advanced CKD and involvement of family members or friends could aid efforts to improve LDKT rates.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO1164

Use of Opioids and Nonsteroidal Anti-Inflammatory Drugs in Living Kidney Donors: Clinical Correlates and Early Outcomes

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Background: Limited data are available on pain medication use in living kidney donors (LKD). While there is growing national concern related to opioids, there is also concern for non-steroidal anti-inflammatory (NSAID) use due to potential nephrotoxicity.

Methods: We examined a novel database wherein national LKD registry identifiers were linked to records from a large U.S. pharmaceutical claims warehouse (2007 to 2017 fills). We selected LKD with 1 year of postdonation pharmaceutical fill records. Associations of baseline demographic and clinical factors with opioid and NSAID use (adjusted odds ratio, 95% $_{LCL}$ aHR 95% $_{UCL}$) were quantified by multivariate logistic regression.

Results: Among 23,564 eligible LKD, opioid use declined postdonation: 36.6%, mos. >0-0.5; 14.7%, mos. 0.6-6; 12.6%, mos. 7-12. NSAID use was uncommon, but increased: 0.5%,

mos. >0-0.5; 2.2%, mos. 0.6-6; 3.3%, mos. 7-12. With adjustment including predonation estimated glomerular filtration rate, hypertension, donor-recipient relationship and nephrectomy type, opioid use in mos. 7-12 was associated (P<0.05) with female sex ($_{1.13}$1.24$_{1.35}$), black race ($_{1.03}$1.17$_{1.32}$), obesity ($_{1.24}$1.38$_{1.53}$), lower education ($_{1.19}$1.31$_{1.43}$), not working ($_{1.02}$1.12$_{1.24}$), smoking ($_{1.33}$1.45$_{1.58}$), and surgical complications ($_{1.11}$1.29$_{1.49}$) (Fig.). NSAID use was more common in women, black and Hispanic LKD, obese LKD, those with lower education, not working, and with surgical complications. Patterns were similar in earlier postdonation periods. Neither opioids nor NSAIDs were associated with eGFR change or proteinuria to 2 years

Conclusions: Opioid and NSAID use in LKD vary with demographic and clinical traits. Work is needed to define safety and optimal choice of pain medications in LKD.

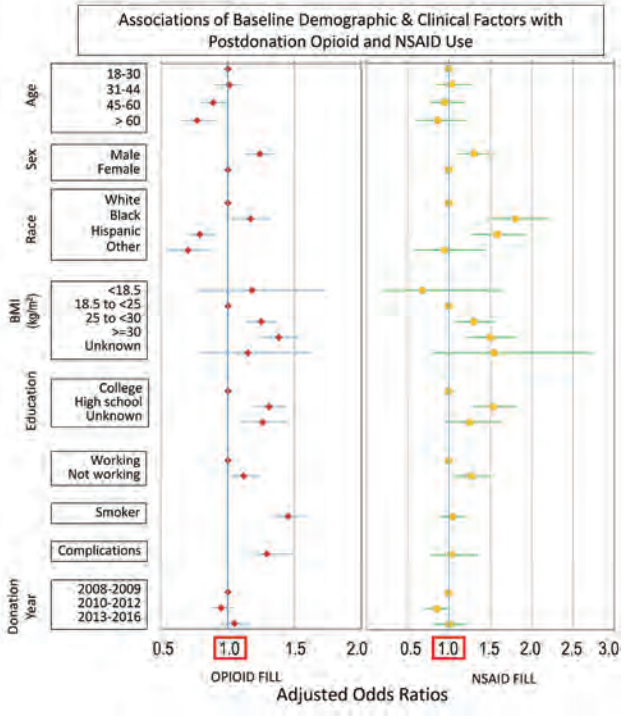

Fig 1. Associations of baseline traits with pain medication use

TH-PO1165

Public Survey of Financial Incentives for Kidney Donation in Bahrain

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Background: With the increasing prevalence of end-stage kidney disease in Bahrain, kidney donation is of vital importance. In this study we want to assess how financial incentives will influence peoples' views and decisions regarding kidney donation. The aim is to establish strategies to increase the number of kidneys for transplantation in Bahrain.

Methods: We adapted a previously established questionnaire on financial incentives for living kidney donations. The questionnaire assessed the public opinion in Bahrain on how kidney donation can be influenced by two different financial incentives, namely 10,000 BHD and life-long health insurance. We collected a convenient sample of 446 participants by distributing an electronic version of the questionnaire. SPSS-23 software was used for data entry and analysis

Results: Of the total participants 39% were male and 61% were female. Eighty-percent of the participants believed that their chances for kidney donation will not increase in turn of receiving a financial compensation, while 20% of them believed that it will increase. Our study found that generally married participants (70%) find it a preferable development for health insurance companies to offer financial compensation for kidney donation, while non-married participants (30%) found it not a preferable but also not an adverse development (P-value 0.038). Furthermore, there is a positive correlation between age and preferable views toward financial incentives to increase kidney donation (P-value <0.001).

Conclusions: Although financial incentives for kidney donation might encourage a minority of the population, the majority will not be influenced by implanting a financial incentives' system for kidney donation.

TH-PO1166

Living Kidney Donors with Metabolic Risk Increased in South Korea

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Background: Living donor kidney transplantation is the best treatment option with regard to patients' prognosis for end-stage renal disease(ESRD) if only donor safety is secured. Hence, it is worthwhile to review of epidemiology of living kidney donors nationwide and living kidney donors with higher risk including metabolic syndrome.

Methods: Living kidney donors in 4 national university hospital of South Korea were enrolled. Demographic and laboratory data were collected. Hyperuricemia was defined as uric acid greater than 7 mg/dL. Underweight, overweight and obesity were defined as body mass index (BMI) <18.5, 25-29.9 and ≥30 kg/m^2, respectively. The era of the transplant was classified into 4 groups with quartiles of the number of donors as follows; 1982-2001, 2002-2009, 2010-2014, and 2015-2019.

Results: A total of 2,002 living kidney donors were enrolled and the number of living kidney transplants increased rapidly from 109 in the 1980s to 987 in the 2010s. Mean age were 42.6±11.5 years and 45.9% were male. The most common donor-recipient relationship was parent-child (39.5%), followed by siblings(30.6%), and husbands-wife(21.1%). Husband-wife relationship was increased over time(4.5% at 1982-2001, 34.7% at 2015-2019). The proportion of old donors(age >60 years) were increased across the era of transplant(3.7% at 1982-2001, 11.2% at 2015-2019). Mean estimated glomerular filtration rate(eGFR) was 90.9±20.5 and 98.8±16.3 mL/min/1.73m^2 by MDRD and CKD-EPI equation, respectively. The baseline eGFR were increased in course of time. Patients with diabetes and impaired glucose tolerance (IGT) were 5(0.25%) and 37(1.85%), respectively. Patients who had history of dyslipidemia accounted for 18% and mean total cholesterol value tended to increase over time. Mean BMI was 23.75±3.39 kg/m^2. Overweight and obese donors were 527(27.05%) and 93(4.77%), respectively. The proportion of donors with IGT, dyslipidemia, and overweight /obesity tended to increase over time.

Conclusions: The factors related to metabolic syndrome generally tended to increase in kidney donor over time, and living kidney transplants between couples increased. Whether the donors' metabolic syndrome affect post-donation morbidity or not should be further evaluated.

Funding: Government Support - Non-U.S.

TH-PO1167

Financial Strain and Pursuit of Live Donor Kidney Transplants Among African Americans on the Kidney Transplant Waiting List

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Background: The extent to which financial strain may influence African American's (AAs) pursuit of LDKT is unclear.

Methods: We studied cross-sectional associations between financial strain and LDKT activation or live donor inquiries to the transplant center among AAs on the kidney transplant waiting list. We measured financial strain using the InCharge Financial Distress/Financial Well-being 8-item Scale (IFDFWS-- responses ranging from 1 (high) to 10 (low/no) distress). We measured LDKT activation as participants' self-reported behaviors reflecting low (no family/friends LDKT discussion, no donor identified), moderate (family/friends LDKT discussion, no donor identified) or high (family/friends LDKT discussion and donor identified) activation. In logistic regression models, we quantified the association between financial strain and LDKT activation or inquiries.

Results: Among 300 participants, the median time on the wait list was 292 (IQR 81, 700) days. The mean age was 52 (SD 11), 56% were male, 50% were retired due to disability, 43% had household income < $40,000 and 25% were near or below poverty. The mean (SD) IFDFWS score was 6.2 (2), indicating moderate financial distress. Subscale mean (SD) scores were: 4.7 (2.8) for current and 4.7 (2.8) general financial stress; 4.5 (2.9) for financial concern, 5.4 (2.7) satisfaction and 5.6 (2.6) comfort, 6 (3.2) for confidence to obtain emergency funds, 5.2 (3.3) for paycheck-to-paycheck living and 3.5 (2.7) for ability to afford recreational activities. Overall financial distress was not associated with LDKT activation (OR: 1.04, 95% CI 0.91, 1.19) or donor inquiries (OR: 1.08, 95% CI 0.95, 1.22). However, participants with greater (versus less) confidence in obtaining emergency funds had statistically significantly greater odds of having a donor inquiry (OR: 1.14, 95% CI 1.04, 1.24).

Conclusions: Financial confidence may be associated with access to LDKT, including the receipt of live donor inquiries. The impact of financial strain on pursuit of LDKT among African American transplant candidates requires further study.

Funding: NIDDK Support

TH-PO1168

Attitudes and Beliefs About Organ Donation in a Cohort of Physicians Attending Medical Grand Rounds

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Background: Lack of referral of appropriate candidates for deceased donor evaluation may result from attitudes or education of the primary physician.

Methods: We evaluated the knowledge, attitudes and beliefs of a cohort of physicians attending Medical Grand Rounds at a University teaching hospital using a validated questionnaire which was returned anonymously to a box. It contains questions related to brain death, willingness to donate and perception of fairness in the system, using yes/no answers and 5-point Likert scales. Between group comparisons were performed with X square and associations by Pearson r or Spearman rho.

Results: 12 Faculty and 28 Resident physicians responded. There were 13 men and 27 women, 3 Black, 17 Asian, 14 Caucasian, and 4 other, with 13 identified as Atheist/unaffiliated, 9 Muslim, 5 Jewish, 9 Christian, 3 Hindu. 17 (43%) had signed an organ donor card (ORGD) and they were more likely to have discussed donation with their family (r=0.5, p=0.001) and to have taken an organ donation course (p=0.025). There was no difference in age group, religion, training level, gender, ethnicity, or marital status. 10 (25%) of respondents did not know the definition of brain death and 17 (43%) believed organs could be harvested before brain death. ORGD were more likely to agree to donate a family member's organs (r=0.4, p=0.01), and believe the system is fair (r=0.32, p=0.047). Religion affected the decision to donate a family member's organs with no Muslim or Hindu agreeing (p=0.011). Faculty were more likely to strongly believe that organ donation should be taught in Med School (p=0.018).

Conclusions: 1. The majority of MDs attending Medical Grand Rounds at a University teaching hospital had not signed an organ donor card or discussed donation with their family. 2. Organ donors were more likely to have taken a course on donation and to donate a family member's organs. 3. 25% did not know the definition of brain death and 43% believed that it was not necessary before organ harvesting. 4. Religious beliefs did not affect signing the card but did affect willingness to donate a family member's organs. 5. Faculty were more likely to agree that organ donation should be taught in Med School. 6. Education programs for graduate MDs should be created as misunderstanding of organ donation and personal beliefs may affect referral of patients under their care.

TH-PO1169

Kidney Transplantation in Females: Impact of Living Donor Relationship on Outcomes

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Background: Female kidney transplant recipients(KTRs) are likely exposed to different HLA types through pregnancy and child birth. This may make them susceptible to memory response when re-challenged with same HLA types through organ transplant from child or spouse may increase the risk for rapid development of donor specific antibodies (DSA); increasing risk of early antibody mediated rejection; thus compromising transplant outcomes. To test this, we assessed long-term outcomes in female living donor KTRs based on their relationship to the organ donor.

Methods: Using OPTN/UNOS database, we identified all adult female living donor KTRs from 2001-2015 who received induction and CNI/MMF maintenance. Group was divided based on relationship to the donor: biologically related (sibling vs. child) and unrelated (spouse vs. all other unrelated). A subgroup of the latter was also identified in order to account for donor gender disparity: (spouse vs. unrelated males). Using a Cox model that adjusted for donor, recipient and transplant variables, we calculated overall and death-censored graft failure risks as well as patient death risk for the female recipients based on donor category: sibling vs. child; spouse vs. all unrelated and spouse vs. unrelated males.

Results: The results shown in table 1. Adjusted overall graft failure risk and patient death risk were significantly lower in sibling compared to child in female KTRs.

Conclusions: Increased patient death risk associated with child to mother transplant when compared to sibling could be related to the immunological risk from child as a consequence of maternal exposure to neonatal HLA during delivery. This can lead to DSA formation from memory response increasing risk of humoral injury, microvascular inflammation, leading to worse allograft function which has a graded association with mortality. Siblings on the other hand could have an immunological advantage by being identical twin or by providing 6 antigen match. Interestingly this phenomenon was not observed in spouse to female transplant despite limiting unrelated donor gender to male in order to minimize the impact of renal volume on outcomes.

Biological category	Living related	Living unrelated	
Donor category	Sibling (n=3560) vs. child (n=2852)	Spouse (n=1405) vs. all unrelated (n=4513)	Spouse (n=1405) vs. male unrelated (n=1453)
Overall graft failure risk [HR (95%CI)]	0.75 (0.59-0.95)*	1.13 (0.97-1.31)	1.08(0.89-1.31)
Death-censored graft failure risk [HR (95%CI)]	0.76 (0.56-1.04)	1.10 (0.92-1.32)	1.03 (0.81-1.30)
Patient death risk [HR (95%CI)]	0.70 (0.53-0.93)**	1.07 (0.88-1.31)	0.93 (0.70-1.22)

p-value; * = 0.017; ** = 0.015

TH-PO1170

Low GFR in Healthy Individuals Is an Important Factor Preventing Kidney Transplantation from Living Kidney Donors in India

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Background: More than 80% kidney transplantation (KT) are from Living Kidney Donors (LKD) in India. There are no validated equation for GFR estimation or CKD risk prediction in Indians, making the use of GFR criteria for accepting LKD problematic. Previous studies using inulin clearance have demonstrated relatively low GFR in healthy LKDs in India. How often LKDs are found unfit to donate based on GFR criteria is unknown.

Methods: A LKD database was created in 2012 & data were collected prospectively using a pre-defined data collection form. Screening evaluation include blood group, history taking with pre-specified data points, measurement of BMI & BP & lab tests (Serum creatinine, fasting & postprandial blood glucose, lipid profile and Urine R/E) & LKD having no abnormalities on screening were enrolled in the database & evaluated further. A minimum GFR (by DTPA renogram - multiple plasma sampling technique) of 70ml/minute/1.73m^2 was necessary for a LKD to be accepted for kidney donation. All LKDs registered for KT from 1st January 2012 to 31st December 2018 were included in the analysis.

Results: A total of 316 LKDs were evaluated during the study period, with mean age of 44.11 (±10.85) years & 253 (80%) were females. 274 (89.5%) of our LKDs were 'Below Poverty Line (BPL)', with family income less than INR 2000 ($28) per month. Only 101 (33%) ESRD - LKD pairs initiated on evaluation eventually underwent KT. On 92 instances factors related to the LKD prevented the KT. Low GFR (n=40, 43.5%) and impaired OGTT (n=12, 13%) were the major LKD factors precluding KT, along with withdrawal of consent (n=18, 19.5%). 40 LKDs found to have GFR <70ml/minute/1.73m^2 were rejected as VKD. None of them had hypertension or any other abnormality on evaluation. In a subset of LKD studied, the average protein intake estimated by urine Urea Nitrogen excretion was 0.6gm/kg/day & Renal Reserve Study done by IV Amino Acid infusion showed an average rise by 34.6% in GFR; with GFR >70ml/minute/1.73m^2 in 75% of LKDs who had baseline GFR <70ml/minute/1.73m^2

Conclusions: Only one third of LKD were eventually able to donate their kidney. Low GFR in otherwise healthy LKDs was an important reason precluding KT. The low baseline GFR may be related to low dietary protein intake, as suggested by significant renal reserve.

Funding: Government Support - Non-U.S.

TH-PO1171

Suboptimal Renal Recovery and Progressive CKD After Living Kidney Donation

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Background: Post-operative renal recovery after nephrectomy is a substantial problem to be addressed in living kidney donors. Herein, we explored factors associated with renal recovery and progression to chronic kidney disease (CKD) in living kidney donors.

Methods: Kidney donors who underwent nephrectomy in 5 different tertiary hospital were retrospectively reviewed. We extracted donors who had estimated glomerular filtration rate (eGFR) at 1 month after kidney donation with follow-up period over one year. Percent change of eGFR from initial to one month after donation was calculated. The sub-optimal renal recovery was defined as percent change of eGFR at 1 month after donation with the lowest quartile range. The development of CKD, latest eGFR < 60 ml/min/m^2 was the clinical end-point. Cox-regression and logistic regression analysis were used to determine the risk factor related with sub-optimal renal recovery and progressive CKD.

Results: In total, 883 donors were included in the study. The mean follow-up period was 59.0 ± 50.3 months. Of which 129 donors progressed to CKD, eGFR <60 ml/min/m^2. A patient with CKD showed older age, male sex, higher body mass index, higher hemoglobin, calcium, uric acid, cholesterol, lower eGFR, higher percent change in eGFR at 1 month after donation. Also, older age (adjusted HR 1.02, 95% CI 1.00-1.04, p=0.048), initial eGFR (adjusted HR 0.95, 95% CI 0.93-0.96, p <0.001) and decreased percent in eGFR at 1 month(Q3 adjusted HR 3.54, 95% CI 1.97-6.36, p <0.001; Q4 adjusted HR 5.71, 95% CI 3.10-10.54, p <0.001)) were the significant risk factors for development of CKD in multivariate Cox-regression analysis.

Conclusions: Percent change of eGFR at 1 month after donation is significant risk factor for development of CKD. Earnest evaluation and management to reduce eGFR decreasing at 1 month after donation could be helpful in improving long-term renal outcomes in living kidney donors.

TH-PO1172

Are We There Yet? Meeting the Goal of Increased Utility Under the New Kidney Allocation System

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Background: The Kidney Allocation System (KAS) was designed to improve limitations of the previous deceased donor kidney transplant (DDKT) allocation algorithm in the United States. A key feature in the KAS is a scoring system that matches longest recipient life expectancy with longest donor graft survival expectancy, trading fairness for utility by prioritizing the best kidneys to the healthiest candidates. This study compared outcomes between patients aged 50 years and younger (<50) versus patients aged 51 and older (>50), the patient groups specifically impacted by the longevity matching scores.

Methods: This study used patient-level data from the Scientific Registry of Transplant Recipients. Relative risk of DDKT and waitlist mortality or removal from the waitlist due to deteriorating health was estimated in the pre- versus post-KAS eras with logistic regression models including fixed effects for organ supply and several patient clinical and demographic characteristics. The post-KAS era was divided into four distinct periods (0-6 months, 6-12 months, 12-24 months, 24-36 months) to assess trends over time. Survival benefit of transplant compared to remaining on the waitlist by KAS era and age group was estimated with a Cox proportional hazard regression model.

Results: This study included 239,265 incident and prevalent adult candidates on the kidney transplant waitlist between December 4, 2011 and December 3, 2017. Relative risk of DDKT for younger candidates versus older candidates was greatest in the first six months post-KAS compared to the pre-KAS era (1.17 95% CI 1.11-1.23). Candidates aged <50 years and >50 years had 1.15 (95% CI 1.00-1.30) and 1.19 (95% CI 1.07-1.30) times the risk of mortality on the waitlist or removal due to deteriorating condition in the third year post-KAS compared to the pre-KAS era, respectively. There was no difference in relative risk of mortality within age group in the first two years post KAS compared to the pre-KAS era. The survival benefit of DDKT compared to remaining on the waitlist was greater in the post-KAS era compared to the pre-KAS era among both age groups.

Conclusions: This study suggests the KAS is at least partly meeting the goal of improved utility in DDKT in the first years of implementation; however, inefficiencies in DDKT still exist. Continued analysis is needed to assess the sustained benefit of the KAS.

Funding: Other U.S. Government Support

TH-PO1173

Contraindications to Transplant and Home Dialysis: Variation in Nephrologist Practices

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Background: There is notable variation in ESRD patients' transplant waitlisting rates and home dialysis use across care providers. This variation persists after controlling for differences in patients' clinical need and community factors. It is unclear how much variation there is in nephrologists' decisions about whether a given patient is eligible for transplant or home dialysis.

Methods: We are administering a new and innovative survey—the Transplant and Home Dialysis Recommendations Survey of Nephrologists, or THRoNe—in a nationally representative sample of n=120 nephrologists (non-pediatric). The THRoNe, which we have pre-tested and validated rigorously using a modified Delphi approach with 12 nephrologists and subject experts, collects data on nephrologists' decision processes and other practice and physician characteristics that may affect treatment choices. Nephrologists are asked to rate 35 clinical and psychosocial patient evaluation criteria (e.g., not hypotensive, adequate social support) individually—as a major or relative contraindication, a minor concern, or not a concern—in the contexts of determining whether to recommend transplant, peritoneal dialysis, or home hemodialysis for a given patient. We will construct indices—overall and by modality—to support classifying nephrologists as highly restrictive (i.e., more often interpreting criteria as major or relative contraindications vs. minor concerns), moderately restrictive, and unrestrictive. We will describe the distributions of nephrologists' restrictiveness overall and by modality, and we will test for differences in these distributions across different nephrologist characteristics—by geographic region, sex, race/ethnicity, and years in practice—using Pearson's χ^2 tests and linear regression models adjusting for other physician and practice characteristics.

Results: Data collection is ongoing. We anticipate obtaining a response rate of ≥70%, in line with response rates achieved in other difficult-to-reach clinician samples using our evidence-based recruitment protocol.

Conclusions: We will determine how meaningfully U.S. nephrologists' judgments differ about whether a given patient should be referred for transplant evaluation or home dialysis training. There are important implications for developing interventions to improve the evidence basis of ESRD treatment.

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TH-PO1174

Kinetic Estimated Glomerular Filtration Rate (KeGFR), a New Tool to Predict Delayed Graft Function (DGF)?

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Background: Delayed graft function (DGF) is a common clinical problem in pediatric patients and in deceased donor kidney transplantation. Early prediction of DGF could be beneficial. It could improve the adjustment of nephrotoxic drugs, such as CNI and antibiotics are routinely used as prophylaxis.

Methods: A retrospective study was carried out, from une 2016 to August 2018, which included 145 kidney transplant patients, either living or deceased kidney donor transplantation, in the immediate postoperative period, in a hospital in Western Mexico. Creatinine was measured at the time of reperfusion (hour 0), and 10 and 18 hours after kidney reperfusion. The Kinetic estimated Glomerular Filtration Rate (KeGFR) was calculated were sCr10h constituted both the basal creatinine and creatinine at first point, and sCr18h was used as creatinine at second point. The primaryoutcome was DGF, defined as need for dialysis (according to the nephrologist consideration) during the first time of transplantation.

Results: 157 patients, between 17 and 69 years old, received a kidney transplant during that period, 113 males (71.9%) and 44 females (28.02%); in most of the patients (146/92.9%) the etiology of CKD was unknown. 108 patients (68.7%) received a kidney from a related living donor, 32 patients (20.3%) from a non-related living donor, and 17 (10.8%) patients from a deceased donor. 20 patients presented DGF (12.7%), with a mean GFR estimated with creatinine kinetics (KeGFR) of 5.09 ml/min, while137 patients (87.2%) didn't present DGF and had a mean KeGFR of 14.9 ml/min, with a statistically significant difference and a p value of 0.000. When establishing a KeGFR threshold value of 7 ml/min, it had a sensibility of 70% and a specificity of 81% to predict DGF, with an area under the curve of 0.759.

Conclusions: An eGFR was determined using unstable creatinine values. Our goal was to evaluate the KeGFR using serum creatinine values at 10 and 18 hours after reperfusion of the kidney, which is the time the blood samples are routinely taken in our center. When establishing a KeGFR threshold value of 7 ml/min, we could predict DGF with a sensibility of 70%, a specificity of 81%, and an AUC of 0.759.

TH-PO1175

Changes in Kidney Function After Live Donor Nephrectomy

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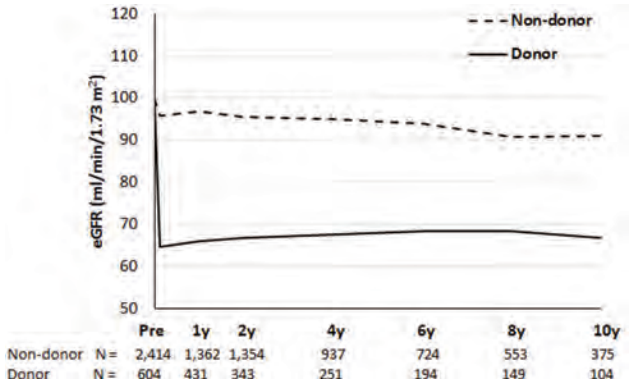
Background: Better understanding the decline in kidney function after live donor nephrectomy and how this differs by donor characteristics can inform counselling, selection, and follow-up care.

Methods: We conducted a retrospective matched cohort study of living kidney donors in Alberta, Canada between 2002 and 2016 using linked healthcare administrative databases. We matched 604 donors to 2,414 healthy non-donors from the general population based on age, sex, year of cohort entry, urban residence, and estimated glomerular filtration rate (eGFR) before cohort entry (nephrectomy date for donors and randomly assigned date for non-donors). The primary outcome was rate of eGFR change over time (median follow-up 7 years, maximum 15 years).

Results: The median age was 43 years, 64% were women, and the baseline (predonation) eGFR was 100 mL/min/1.73 m^2. Overall, from 6 weeks onwards, the eGFR increased by +0.32 mL/min/1.73 m^2 per year (95% CI +0.17 to +0.46) in donors and decreased by -0.88 mL/min/1.73 m^2 per year (95% CI -0.96 to -0.79) in non-donors ($p<0.001$). The change in eGFR between 6 weeks to 2 years, 2 to 5 years, and ≥5 years onwards in donors was +1.05, +0.61, and -0.09 mL/min/1.73 m^2 per year, respectively. The change in eGFR over time in donors varied by sex, percent decline in eGFR within the first 6 weeks, and eGFR category at 1 year, but not by age category at donation, predonation hypertension, or predonation eGFR category.

Conclusions: The function in the remaining kidney of a living donor initially increases by 1 mL/min/1.73 m^2 per year due to hyperfiltration; however, this begins to plateau by 5 years postdonation. In contrast, non-donors experience a steady age-related decline of 1 mL/min/1.73 m^2 per year.



Mean estimated glomerular filtration rate (eGFR) over time in living kidney donors (solid line) and matched, healthy non-donor controls (dotted line).

TH-PO1176

Survival Benefit of HLA-Incompatible Living Donor Kidney Transplantation Compared with Deceased Donor Kidney Transplantation or Dialysis in Korea

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Background: HLA-incompatible(HLAi) living donor(LD) kidney transplantation(KT) is one of efforts to increase KT opportunity for sensitized ESRD patients. Although removing anti-HLA antibodies may be high risk, to find a compatible LD or wait for a deceased donor(DD) may be long. Recently, there are controversies for outcomes of HLAi KT. US data showed better outcomes of HLAi LDKT compared to HLA-compatible(HLAc) DDKT or dialysis, whereas UK data demonstrated that waiting for HLAc DDKT or HLAc LDKT by donor exchange has good outcomes comparable to HLAi LDKT. Therefore, we tried to compare outcomes of HLAi LDKT with those of DDKT or dialysis in Korea.

Methods: One hundred eighty-nine patients underwent HLAi LDKT after desensitization that consisted of rituximab, plasmapheresis, and intravenous immunoglobulin between 2002 and 2018 in Seoul National University Hospital and Severance Hospital. Indications of desensitization were positive cytotoxicity cross-match, positive flow-cytometric cross-match, and positive donor-specific antibodies with negative cross-match. We compared outcomes among HLAi LDKT patients, DDKT patients(HLAc-DDKT group;n=930), wait-listed patients who had continued to undergo dialysis(dialysis-only group;n=930), or patients who underwent either dialysis or DDKT(dialysis-or-DDKT group;n=930) using propensity score matching.

Results: In the HLAi LDKT group, patient survival rates were 98% at 5-year and 96 % at 7-years post-KT. Patient survival rates at 5- and 7-years in the HLAc-DDKT group were 92%, and 91%, respectively, those in the dialysis-only group were 90%, and 85%, respectively, and those in the dialysis-or-DDKT group were 91%, and 88%, respectively. HLAi LDKT group showed significantly better patient survival rate compared to HLAc-DDKT group, dialysis-only group and dialysis-or-DDKT group. And there was no significant difference in the graft survival rates between HLAi LDKT and HLAc-DDKT group. In multivariate analysis, waiting or DDKT was a significant risk factor for mortality(HR,3.93; 95% CI,1.44-10.74) indepently of old age, diabetes and blood type O.

Conclusions: In conclusion, patients undergoing HLAi LDKT has a survival benefit as compared with patients who were still on the waitlist for HLAc DDKT or received HLAc DDKT in Korea that has longer waiting time for DDKT than Western countries.

TH-PO1177

Low Nephron Numbers and Larger Glomerular Size Are the Predictors of Long-Term Kidney Function in Kidney Donors

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Background: Microstructural findings of larger nephron size and nephrosclerosis on kidney biopsy are predictive of kidney function after donation at short-term follow up. Our hypothesis is that kidney structural findings also predict long-term kidney function after donation.

Methods: We contacted living kidney donors who were at least 5 years post-donation to obtain blood pressure and kidney function test results. Microstructural (biopsy) and macrostructural (contrast CT scan) findings of the kidney at the time of donation were assessed as predictors of estimated glomerular filtration rate (eGFR), proteinuria, and hypertension with adjustment for years since donation and baseline clinical characteristics.

Results: Among 1687 donors contacted, 807 (48%) participated a mean 10.5 years after donation. At follow-up, 6.4% had developed an eGFR<45 ml/min/1.73 m^2, the mean residual eGFR ratio (post-/pre-donation eGFR) was 75%, proteinuria (self-reported) occurred in 5.1 %, and new onset hypertension occurred in 19% (119/653). An eGFR <45 ml/min/1.73 m^2 was predicted by larger glomerular volume per SD (OR=1.48, p=0.01) and low nephron number (below age-specific 5th percentile) (OR=3.40, p=0.01). Residual eGFR ratio was predicted by low nephron number (-6.1%, p=0.004) and cortical volume per BSA (1.3%, p=0.03). Proteinuria was predicted by glomerular volume per SD (OR=1.42, p=0.01). Hypertension was not predicted by any structural finding. Nephrosclerosis (glomerulosclerosis, interstitial fibrosis, or arteriosclerosis) did not predict any outcome.

Conclusions: Lower nephron numbers and large glomeruli appear to be the most important structural determinants of long term kidney dysfunction after donation.

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TH-PO1178

Non-Simultaneous Kidney Exchange Cycles in Resource-Restricted Countries Without Nondirected Donation

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Background: Recent reports suggest that bridge donor renege is rare (1.5%) as part of non-simultaneous kidney exchange chains. In developing countries, surgical space and resources limit the number of simultaneous kidney exchange transplant surgeries.

Methods: The aim of this study was to evaluate the bridge donor renege rate during non-simultaneous kidney exchange cycles in a prospective single center cohort study (n=44). We describe the protocol to prepare donor-recipient pairs for non-simultaneous surgeries designed to reduce the renege rate. We propose using standard criteria deceased donor kidneys in the event of a bridge donor renege to protect vulnerable recipients

Results: We report 12 successful non-simultaneous kidney exchange cycles resulting in 44 living donor kidney transplants. These cycles involved 16 bridge donors who were trusted to donate after their incompatible recipient was transplanted, placing 15 recipients at risk (two were at risk from two bridge donors), and no donor reneged. We propose that non-simultaneous kidney exchange cycles could increase living donor kidney transplantation, especially for difficult to match sensitized pairs (17 of 44), in countries with limited transplantation resources

Conclusions: Our study confirms that non-simultaneous kidney exchange cycles can be safely performed with careful patient-donor selection and non-anonymous kidney exchange.

TH-PO1179

Glomerular Filtration Rate Measurement by Iohexol Plasma Clearance in an Ethnically Diverse Living Donor Population

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Background: Iohexol is a good agent for measurement of GFR (mGFR) due to its low extrarenal excretion, tubular secretion or reabsorption, and protein binding affinity. We compared mGFR by plasma clearance of iohexol with serum creatinine (sCr) based GFR estimations in our living kidney donor candidates and investigated the association between GFR and donor demographic characteristics.

Methods: All potential living donors with GFR measurement by iohexol plasma clearance at our center between 10/2016 – 4/2019 were included. Linear regression was performed for comparison of mGFR by ethnicity, sex, age, and BMI. Medical records were reviewed for age, BMI, ethnicity, and sCr to calculate eGFR by CKD-EPI and MDRD.

Results: Of 407 potential living donors evaluated, 35% were men and the mean age was 42. Racial distribution: 47% Caucasian, 29% Hispanic, 28% Asian, 4% Black. Median mGFR was 102 ml/min/1.73m2. Median mGFR was higher for Hispanics (106) and Asians (108) compared to Caucasians (96) [Figure1]. Women > 50yrs had faster mGFR decline than men the same age. Correlation between mGFR and sCr-based eGFR showed that CKD-EPI had a closer correlation (slope=0.42, R = 0.27) than MDRD (slope=0.37, R =0.25) [Figure 2]. Compared with Caucasians, Hispanics had higher mGFR than eGFR by CKD-EPI. Both Hispanics and Asians had higher mGFR compared to eGFR by MDRD.

Conclusions: Hispanic and Asian ethnicities have higher mGFR compared to Caucasians in our potential living donor population, which is an important finding that requires further delineation. CKD-EPI and MDRD eGFR calculations may also underestimate mGFR when used in these ethnicities.

Figure 1

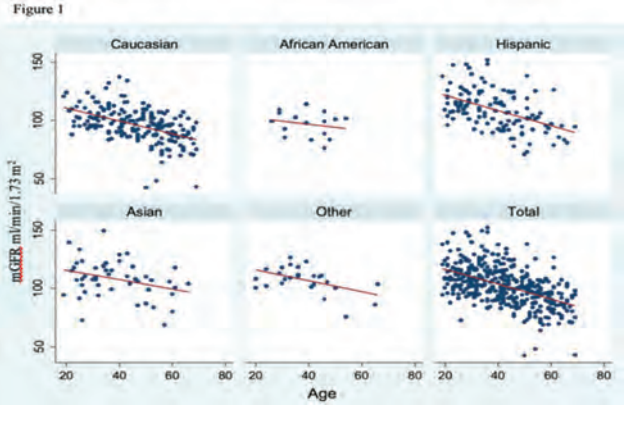
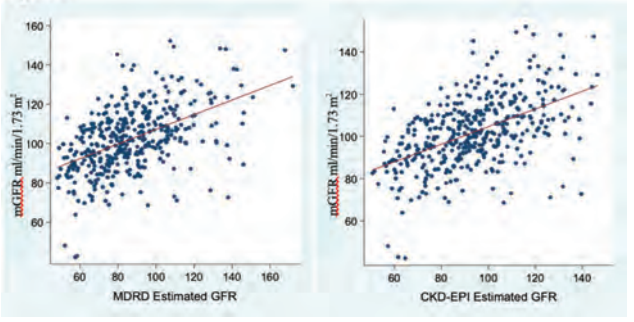


Figure 2



TH-PO1180

Temporal Trends in Transplant Modalities Used for Highly Sensitized Kidney Transplant Candidates and Recipients

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Background: Prioritization of highly sensitized (HS) candidates under the Kidney Allocation System (KAS) and expansion of kidney-paired donation (KPD) have broadened the transplant options available to HS candidates.

Methods: To quantify temporal trends in utilization of these differing transplant modalities, we used national SRTR registry data from 2009-2017 to study 45,759 adult HS (cPRA≥80%) waitlisted candidates and 19,003 HS transplant recipients. We used competing risks regression to quantify temporal trends in likelihood of deceased donor kidney transplantation (DDKT), KPD, and non-KPD living donor kidney transplantation (LDKT) for HS candidates over time (Era 1: 01/01/2009-12/31/2011; Era 2: 01/01/2012 – 12/3/2014; Era 3: 12/4/2014 – 12/31/2017).

Results: Although the likelihood of DDKT and KPD increased over time for all HS candidates (adjusted subhazard ratio [aSHR] for Era 3 vs. 1 for DDKT: $_{1.64}1.72_{1.80}$, p<0.001; aSHR for KPD: $_{1.30}1.57_{1.88}$, p<0.001), the likelihood of LDKT decreased over time (aSHR for Era 3 vs. 1: $_{0.71}0.82_{0.95}$, p=0.007). However, these changes affected HS recipients differently depending on their cPRA. For example, an increased proportion of cPRA 80-89% recipients were transplanted with KPD over time (8.6% of candidates in Era 3 vs. 3.8% in Era 1, p<0.001), whereas DDKT was used for fewer recipients (80.1% in Era 3 vs. 86.2% in Era 1). In contrast, an increased proportion of cPRA 98-99.9% and 99.9%+ recipients were transplanted with DDKT (96.2% in Era 3 vs. 59.1% in Era 1 for cPRA 99.9%+, p<0.001), at the expense of fewer recipients being transplanted with either LDKT (1.9% in Era 3 vs. 30.9% in Era 1 for cPRA 99.9%+) or KPD (2.0% in Era 3 vs 10.0% in Era 1 for cPRA 99.9%+).

Conclusions: HS candidates had an increased likelihood of DDKT and KPD over time, although the effect of this varied across cPRA. In the KAS era, the most HS candidates (cPRA 98%+) have seen significant declines in use of KPD and LDKT.

Funding: NIDDK Support

Table. Changes in the transplant modalities used for HS recipients by cPRA categories by era of transplantation.

cPRA	Era 1	Era 2	Era 3	p-value*
80-89% (%)				
DDKT	86.2	89.7	80.1	
LDKT	10.0	6.2	11.3	<0.001
KPD	3.8	4.1	8.6	
90-97% (%)				
DDKT	85.4	86.8	87.9	
LDKT	10.2	7.2	6.2	<0.001
KPD	4.3	6.1	5.9	
98-99.9% (%)				
DDKT	78.6	80.3	96.2	
LDKT	16.9	9.4	1.9	<0.001
KPD	4.5	10.3	1.9	
99.9%+ (%)				
DDKT	59.1	68.7	96.2	
LDKT	30.9	20.2	1.9	<0.001
KPD	10.0	11.2	2.0	

cPRA, calculated panel reactive antibody; DDKT, deceased donor kidney transplantation; KPD, kidney-paired donation; LDKT, living donor kidney transplantation.

TH-PO1181

Patients with Pretransplant eGFR < 20 mL/min Are at High Risk for ESRD Within 2 Years of an Isolated Heart Transplant

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Background: Preexistent advanced chronic kidney disease can progress to ESRD after heart transplantation. We examined if risk of ESRD and mortality was different in isolated heart transplant patients with a pre-transplant eGFR between 20 and 30 ml/min as compared to an eGFR <20 ml/min. We chose a cutoff between groups of 20 ml/min as, at this level of kidney function, patients qualify for a kidney transplant as per current kidney allocation rules.

Methods: We analyzed UNOS heart transplant data in adults receiving an isolated heart transplant between 2000 and 2015 who had a pretransplant eGFR ≤30 ml/min. Survival analysis was used to generate Kaplan-Meier curves. Results were adjusted for multiple confounding factors.

Results: We had 1093 patients with a pretransplant eGFR of ≤30 ml/min in our cohort. Of these 915 patients had data on a renal event (ESRD and/or kidney transplant) and 1057 had data on mortality. Incidence and hazard ratios for renal events and mortality are shown in Table 1. Kaplan Meier curve for renal event is shown in Figure 1.

Conclusions: Patients with an eGFR <20 ml/min had 61% higher risk of renal event than the group with eGFR between 20-30 ml/min. 50% of the renal events in the cohort with an initial eGFR <20 ml/min, occurred within the first two years post transplant. 76.4% of patients with an eGFR of 20-30 ml/min did not develop ESRD or need a kidney transplant over a 15 year followup period. These observations may help refine criteria for patients who could benefit from a combined heart kidney transplant rather than having to face the need for ESRD care with uncertain access to a kidney transplant within 2 years of their heart transplant.

eGFR at time of Heart Transplant	Renal event N (%)		Adjusted Hazard Ratio	p value with 95% CI	Mortality N (%)		Adjusted Hazard Ratio	p value with 95% CI
	YES	NO			YES	NO		
eGFR <20	64 (36.6 %)	111	1.61	0.003 (1.17-2.22)	148 (64.1%)	83	1.22	0.148 (0.92-1.62)
eGFR 20-30	182 (24.6 %)	558			416 (50.4%)	410		

Table 1. Event rates and hazard ratios

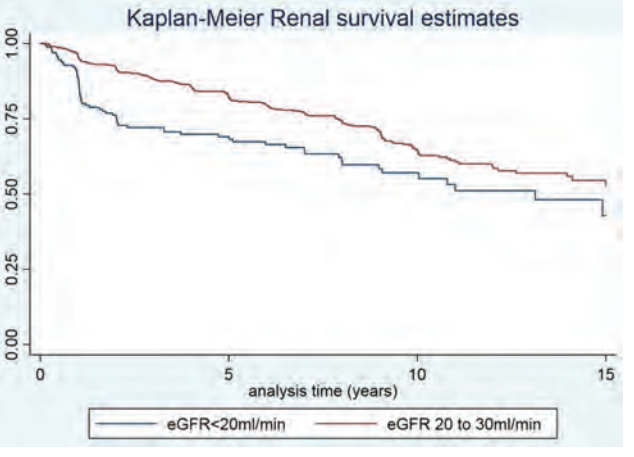

Figure 1. Kaplan Meier Renal Survival

TH-PO1182

Prelisting Cancer Diagnosis and Outcomes in Candidates Waitlisted for Kidney Transplant

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Background: As outcomes for kidney transplant candidates with a previous history of cancer are not well described, transplant centers have difficulty determining whether and when to list such patients.

Methods: We used data from the Transplant Cancer Match Study, which links data on all solid organ transplant candidates and recipients in the US with data from 18 state and regional cancer registries, to describe outcomes for kidney transplant candidates with a pre-listing cancer diagnosis.

Results: Of 7017 kidney transplant candidates with a pre-listing history of cancer starting in 1983 (Table 1), 2600 (37.1%) were female and 4417 (62.9%) were male. Median age at listing was 59.0 years. Kidney (n=1238, 17.6%), prostate (n=1102, 15.7%), breast (n=703, 10.0%), liver (n=565, 8.1%), and colorectal (n=611, 8.7%) cancers were the most common; 5140 (73.2%) cancers were in situ or localized, 1316 (18.7%) were regional or distant stages. Median time from cancer diagnosis to listing was 4.7 years. In total, 5901 patients (84.1%) subsequently underwent transplant; 689 (9.8%) were removed from the list due to death, medical unsuitability, or deteriorating medical condition. Median time to transplant from listing was 1.2 years, with 1-year patient and graft survival 93.6% and 89.0%, respectively.

Conclusions: Many waitlisted kidney transplant candidates have a previous history of cancer, and many underwent transplant. Their data can be used to estimate likely outcomes for similar patients presenting for transplant evaluation, compared with waitlisted patients with no history of cancer.

Funding: Other NIH Support - NCI, Other U.S. Government Support

Characteristic	n (%)
Age at listing	
0-18	94 (1.3)
19-30	154 (2.2)
31-50	1396 (19.9)
51-60	2166 (30.8)
61-70	2527 (36.0)
70+	680 (9.7)
Sex	
Female	2600 (37.1)
Male	4417 (62.9)
Cancer type	
Kidney	1238 (17.6)
Prostate	1102 (15.7)
Breast	703 (10.0)
Liver	565 (8.1)
Colorectal	611 (8.7)
Other*	2985 (42.5)
Cancer Stage	
In situ	887 (12.6)
Localized	4253 (60.6)
Regional	794 (11.3)
Distant	522 (7.4)
Unstaged/not available	561 (8.0)
Waitlisted year	
1983-2000	1415 (20.2)
2001-2010	4269 (60.8)
2011-2018	1333 (19.0)
Transplant	
Yes	1116 (15.9)
No	5901 (84.1)

*Most common: Cervical (n=280), melanoma (n=291), bladder (n=276), testicular (n=113), vulvar (n=86), uterine (n=160), thyroid (n=239), lymphoma (n=290), and myeloma (n=118).

Table 1. Demographics and waitlist outcome of 7017 patients waitlisted for kidney transplant with previous history of cancer

FR-PO001

Significant Numbers of Hospitalized Patients with AKI Are Seen in Primary Care Before Admission, Representing Opportunities for Early Intervention

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Background: Acute kidney injury (AKI) confers increased morbidity and mortality and e-alerts are evenly distributed between hospital and community settings (Holmes et al, CJASN, 2016). Primary care physicians (PCPs) are well-placed to enact sick-day guidance, forming a critical juncture to reduce potential hospital admission, length of stay and emergency intervention. PCPs make decisions with limited time and information, hampering adherence to 'Think Kidneys' guidance (UK Renal Registry, Renal Association). In light of recent advice balancing the opposing risks of ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) cessation during AKI on cardiorenal outcomes, greater support from renal services at the primary/secondary care interface is required to effectively manage these patients (Thomson & Tomlinson, CJASN, 2019 and Clark et al, Heart, 2019). We sought to determine the proportion of patients with AKI, who might benefit from advice in primary care.

Methods: Retrospective data were collected on hospitalized patients (Nov 2018-May 2019) identified by elevated serum creatinine results (as per national AKI reporting guidance). Data sources were patient records and computerized reporting systems.

Results: 150 patients were identified (data available for 148). 38/148 (26%) saw a PCP in the fortnight pre-admission (11/38 subsequently referred) and 27/148 (18%) were referred by a PCP to hospital. 41/148 (28%) were inpatients in the preceding month and 48/148 (32%) were care home residents.

Conclusions: A quarter of patients saw a PCP before admission, representing an opportunity to intervene. Patients were elderly and co-morbid therefore decisions involving medication cessation and cardiovascular review require specific expertise and training, through enhanced physician relationships. Better community support and admission avoidance may represent the best possible medical care for some patients and urgent improvement in links between primary care and secondary renal service is recommended for all.

AKI risk factors by stage

AKI	Stage 1 (n=58)	Stage 2 (n=58)	Stage 3 (n=32)	All AKI (n=148)
Age (median years)	82	83	78	82
History of CKD (%)	30 (52)	22 (38)	12 (38)	64 (43)
Previous AKI (%)	19 (33)	24 (41)	13 (41)	56 (38)
Prescribed ACEi/ARB (%)	18 (31)	22 (38)	11 (34)	51 (34)

FR-PO002

Underreporting of In-Hospital AKI in Taiwan: A Nationwide Study

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Background: Hospital-acquired AKI is associated with high morbidity and mortality. We used ICD-9 CM code and Taiwanese National Health Insurance (NHI) dialysis procedure codes to identify in-hospital acute kidney injury and evaluate their outcomes over a twelve years period in Taiwan.

Methods: In a nationwide retrospective study based on the NHI Database, we identified all adult patients requiring the first in-hospital dialysis, or with ICD-9 code 584 between 2003 and 2014. We excluded patients with previous renal transplantation or chronic dialysis from 2000 to 2002.

Results: A total of 628,120 in-hospital AKI episodes were identified, and 203,064 episodes were dialysis-requiring AKI. Among 203,064 dialysis-requiring AKI episodes, 22,746 patients (11.2%) had advanced chronic kidney disease (CKD); 121,054 patients (59.6%) had history of CKD; 59,271 patients (29.2%) received dialysis during admission without documented CKD. Among patients without pre-existing CKD, 46.7% had sepsis; 6.6% were related to cardiac surgery; 91.2% had been admitted to ICU and 42.5% received CRRT. Patients without pre-existing CKD showed the highest in-hospital mortality (71.1%). Time trend analysis showed that there were decreased trends of in-hospital mortality and increasing trends of long-term dialysis from 2003 to 2014. For those who was discharged without receiving regular dialysis, 25% and 12% of patients died within 1 and 2 years after discharge.

Conclusions: We found in-hospital AKI was severely under-reported and was associated with high mortality. Strategies to increase the accuracy of discharge diagnosis is required to improve patient safety.

Funding: Government Support - Non-U.S.

FR-PO003

Epidemiology of Patients Receiving Continuous Renal Replacement Therapy: The Multicenter CRRTNet Study

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Background: There have been limited studies evaluating key performance metrics of patients undergoing continuous renal replacement therapy (CRRT). Our aim was to assess the case-mix, acuity, diagnosis, clinical course and outcomes of patients undergoing CRRT.

Methods: CRRTnet is an international multicenter data registry of adult patients undergoing CRRT to assess the variations in CRRT prescription and delivery across quality domains and to develop and benchmark CRRT specific key performance indicators. We evaluated the demographic criteria of adult critically ill patients undergoing CRRT for greater than 24 hours. Data was analyzed descriptively.

Results: In total, 1116 patients treated with CRRT were included in the registry. The mean (SD) age 57.9 (14.2) years, 58.5% were male, mean (SD) APACHE II and SOFA score were 28.8 (7.3) and 13.8 (3.9), respectively, 81.2% of patients were mechanically ventilated and 83.0% required vasopressor support. The most common admission diagnosis was respiratory failure (20.1%), followed by sepsis (16.2%), cardiovascular emergency (14.3%) and acute liver failure (6.0%). Mean serum creatinine at ICU admission was 331.9 (256.7) umol/L. The most common triggers for CRRT initiation were volume overload (47.8%), oligo-anuria (27.5%) hyperkalemia (5.7%), metabolic acidosis (3.7%) and uremia (1.9%). 46.9% of patients survived the ICU stay and 43.6% survived to hospital discharge. 34.2% of patients had complete renal recovery, 19.5 % of patients had partial renal recovery while 46.4% had ongoing need for RRT. Mean ICU and hospital lengths of stay were 20.5 (26.2) and 43.2 (44.4) days, respectively.

Conclusions: In this large multi-centre prospective registry of critically ill patients treated with CRRT the most common etiology of AKI requiring CRRT was sepsis and the most common specific indication was volume overload.

Funding: Private Foundation Support

FR-PO004

Dialysis Initiation in AKI: An Evaluation of the Wait and See Approach

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Background: The optimal timing of RRT initiation in critically ill patients has been an area of intense investigation. Recent trials have suggested that dialysis may be avoided in patients with severe AKI by waiting to initiate therapy unless there are life-threatening complications requiring emergent intervention. We evaluated the outcomes of this "wait and see approach" (WS) in comparison to elective intervention based on the severity of AKI and non-emergent indications. We hypothesized that the WS approach would be associated with higher mortality and resource utilization.

Methods: We conducted a retrospective multinational cohort study of critically ill adult patients admitted to four centers in Germany, UK and USA between Jan2014 and Dec2017. We excluded patients with ESRD, kidney transplant and those who stayed <72hrs. in the ICU. Need for dialysis was classified as emergent, defined as AKI Stg2 or higher, in the presence of any one of the criteria 1) arterial blood gas pH<7.15, 2) K>= 6.5 Meq/L, 3) BUN>112 mg/dl or 4) PO2/FIO2<=150 with cumulative fluid balance from admission >= 15%. Urgent initiation was considered if patients had AKI Stg3 and none of the emergency criteria, and elective for the rest of the indications. The primary outcome was ICU and hospital mortality.

Results: Of 20,560 eligible patients, 9712 (47.2) developed AKI (2,156;10.5) received dialysis (D); of whom 438(20) at dialysis initiation were at Stg1, 124(5) Stg2, 380(17) Stg3 and 953(44) no AKI. They were categorized as elective (2156;76), urgent (252;11) and emergent (252;11). Among 18404 non-dialyzed (ND) patients, 253(1.4%) met the urgent and 127(0.7%) the emergent criteria. Dialyzed patients had higher SOFA scores, vasopressor need, mechanical ventilation, and cumulative fluid balance. Hospital mortality in D patients was almost 2 fold higher as compared to urgent and elective groups, and in the ND patients hospital mortality was > 2 fold higher when urgent and 4.5 fold higher when emergent criteria were present. D and ND patients had similar mortality in emergent category.

Conclusions: Reaching emergency criteria was associated with higher ICU and hospital mortality in dialyzed and non-dialyzed patients. Further studies are needed to identify appropriate criteria for initiating dialysis in ICU patients.

Funding: NIDDK Support, Veterans Affairs Support, Other U.S. Government Support

FR-PO005

Outpatient Dialysis for AKI: A Nonprofit Provider Experience

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Background: Medicare approved reimbursement of outpatient hemodialysis (HD) for patients with acute kidney injury (AKI) in 2017. Lack of national data hinders a consensus on optimal management. We describe the experience of a multi-state non-profit dialysis provider.

Methods: We reviewed electronic medical records of all patients treated for AKI between 1/1/17 and 12/31/18 with follow-up until 3/31/19. We describe demographics, dialysis prescriptions/practices, and disposition from 187 outpatient centers with a mean (median) population of 4.4 (3.0) AKI patients treated during the two-year study period.

Results: A total of 815 AKI patents (2017 = 318; 2018 = 497) were admitted across units with a mean age 65.1 (range: 15.7 to 97) years, 56% male, 56% Caucasian and over 98% were treated via HD catheter. Thrice weekly HD was prescribed on admission for 92% (rest <3/week) with median treatment time of 3.5 (Q1-3.0, Q3-4.0) hours and blood/dialysate flow rate of 400/600 (350/600, 400/700) ml/min, and 60% on 3K bath (36% 2K). Lab draws (e.g. creatinine, Cr) averaged weekly (lowest quartile: bi-weekly). Mean duration of AKI therapy was 47 (range: 1 to 327) days, with 45% transitioning to ESRD (averaging 61 days as AKI). Among discharges, 66% had >25% decline in Cr, indicating potential renal recovery rate of 37%. After being deemed ESRD, 22% died and 5% recovered kidney function over the study period.

Conclusions: Since Medicare changed reimbursement, successful treatment of stable AKI occurs in the outpatient setting. By leveraging patient-level treatment data, dialysis providers are uniquely positioned to contribute studies that may help define best practices and to benchmark clinical outcomes.

FR-PO006

Medication Prescribing Patterns in AKI Patients Undergoing Outpatient Dialysis

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Background: Beginning 2017, Medicare patients with acute kidney injury (AKI) could receive outpatient dialysis care. We describe medication prescribing trends as recorded in electronic medical records of a large non-profit dialysis provider.

Methods: A retrospective review of AKI patients treated between 1/1/17 and 12/31/18 with follow-up until 3/31/19 at 187 outpatient dialysis clinics. Medications were classified for home/clinic use and by Medi-Span® categories. Demographics, polypharmacy prevalence (PolyRx; ≥ 10 medications) and medication classes were determined at 1 week and 30 days.

Results: A total of 799 patients were identified, 415 (52%) having continuous AKI treatment at least 30 days. Patients were 65 ±14 years, 52% male, 56% white and 95% had at least 1 medication order. We identified 5,035 medications orders at week 1 and 8,185 medications at 30 days. Number of medications and PolyRx occurrence at end of week 1 and 30 days was 7.8 ± 6.6 (median 5) medications vs. 14.4 ± 8 (median 13) ($p<0.05$) and 32.3% vs. 68% ($p<0.001$), respectively. As expected, over time, larger proportion of patients were undergoing management of bone-mineral dysfunction or anemia. There were 71 (0.9%) potentially contraindicated or nephrotoxic medications: 5 metformin; 8 NSAIDs; 5 digoxin; 3 rivaroxaban; 50 aminoglycoside. Changes in top medication classes are shown in table.

Conclusions: Patients with AKI have complex medication regimens, high PolyRx incidence and significant changes over time. Incorporating medication reconciliation processes can flag potential unsafe or nephrotoxic medication, and improve patient safety and improve prospects for recovery in AKI patients.

Medi-Span® Medication Class	AKI patients @ week 1 (n=415)			AKI patients @ 30 days (n=415)		
	% Patients	Clinic Rx	Home Rx	% Patients	Clinic Rx	Home Rx
HEMATOPOIETIC GROWTH FACTORS	44%	181		86%	355	1
IRON	32%	118	15	86%	355	1
VIRAL VACCINES	27%	111		59%	244	
HEPARINS AND HEPARINOID-LIKE AGENTS	46%	187	4	53%	216	5
INSULIN	22%		91	47%	5	188
PHOSPHATE BINDER AGENTS	18%		73	43%		178
PROTEINS/PROTEIN	26%	106	1	41%	288	5
OIL SOLUBLE VITAMINS	18%	20	53	37%	67	88
HMG COA REDUCTASE INHIBITORS	21%		88	35%		145
CALCIUM CHANNEL BLOCKERS	18%		75	33%	1	136
LOOP DIURETICS	12%		48	33%		135

FR-PO007

Epidemiology of Hospitalization Preceding Initiation of Outpatient Dialysis for AKI Among Medicare Beneficiaries

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Background: Little is known about hospital admissions preceding initiation of outpatient (OP) dialysis for acute kidney injury requiring dialysis (AKI-D), which presumably represent transitions of AKI-D care from inpatient to outpatient settings. We examined Medicare claims to assess hospitalizations preceding the initiation of OP dialysis for AKI-D.

Methods: We analyzed the 100% sample of institutional claims in 2014–2017 Medicare Limited Data Sets. To identify initiation of OP dialysis for AKI-D, we located the first OP dialysis facility claim in 2017 with condition code 84 and Healthcare Common Procedure Coding System code G0491. We excluded any patients with Medicare claims history of OP dialysis indicated for end-stage kidney disease, dating to January 1, 2014. We retained the subset of patients with Medicare coverage during the 6 calendar months preceding the month of initiation of OP dialysis for AKI-D. We then analyzed hospitalization claims, including ICD-10 diagnosis codes.

Results: The cohort comprised 8500 patients. Mean age was 70.5 ± 11.0 years, 77% were white, and 44% were female. During the 6 months preceding the initiation of OP dialysis for AKI-D, 8209 (97%) patients were hospitalized, with cumulative totals of 1.9 admissions and 27 hospitalized days. Regarding the last hospitalization preceding initiation of OP dialysis for AKI-D, mean (median) length of stay was 20 (15) days; 29% were discharged home under self-care, 25% to home health care, 42% to a skilled nursing facility, and 3% to intermediate care settings. The number of days between hospital discharge and initiation of OP dialysis for AKI-D was ≤1 in 34% of patients, 2–3 in 52%, 4–7 in 8%, and >7 in 6%. During the last hospitalization preceding initiation of OP dialysis for AKI-D, chronic kidney disease (CKD) was documented in 86% of admissions, diabetes in 59%, heart failure in 53%, and atrial fibrillation in 34%. Clinical events included acute respiratory failure in 29% of admissions and sepsis in 20%.

Conclusions: In Medicare beneficiaries, hospitalizations preceding initiation of OP dialysis for AKI-D are typically long and often complex, with 1 in 5 experiencing sepsis and 1 in 3 acute respiratory failure. CKD is common in this population, as is concurrent care in a skilled nursing facility at initiation of OP dialysis for AKI-D.

FR-PO008

Predictors of Recovery of Kidney Function and Transition to ESKD in Patients on Outpatient Dialysis for AKI

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Background: Most patients initiating outpatient hemodialysis (OP HD) for acute kidney injury requiring dialysis (AKI-D) recover function or transition to end-stage kidney disease (ESKD) within 3 months. Identifying factors predisposing patients to either outcome may improve clinical care processes. We assessed associations of baseline patient characteristics and biochemistry at initiation of OP HD for AKI-D with competing risks of recovery of kidney function and transition to ESKD.

Methods: We analyzed patients initiating OP HD for AKI-D in a Fresenius Kidney Care (FKC) dialysis facility between May 1, 2017, and December 31, 2018, excluding those discharged from FKC facilities within 7 days of initiation of OP HD or with incomplete biochemical data. We followed patients to the earliest of recovery of kidney function, transition to ESKD, death, or loss to follow-up (typically, transfer to another dialysis provider), with end of follow-up on March 31, 2019. We used Fine-Gray regression to model subdistribution hazards of recovery of function and transition to ESKD, as a function of age, sex, and biochemistry measured within 7 days of initiation of OP HD; death was classified as a competing risk.

Results: The cohort comprised 12,221 patients. During follow-up, 4786 (39%) recovered kidney function, 5606 (46%) transitioned to ESKD, and 1136 (9%) died. Adjusted hazard ratios of recovery of function and transition to ESKD per standard deviation (SD) of each factor are displayed in the table.

Conclusions: Younger age, female sex, lower serum creatinine, lower serum potassium, higher serum phosphorus, and lower serum parathyroid hormone are most strongly associated with recovery of kidney function after initiation of OP HD for AKI-D, whereas higher serum creatinine is most strongly associated with transition to ESKD.

	SD	Recovery of Function		Transition to ESKD	
		AHR	95% CI	AHR	95% CI
Age (years)	14.6	0.78	0.76-0.81	1.05	1.02-1.09
Female sex		1.24	1.17-1.32	0.86	0.82-0.91
Creatinine (mg/dL)	2.3	0.65	0.62-0.68	1.27	1.24-1.31
Potassium (mEq/L)	0.6	0.85	0.82-0.88	1.12	1.09-1.16
Sodium (mEq/L)	3.9	1.10	1.07-1.13	1.02	0.99-1.04
Hemoglobin (g/dL)	1.3	1.08	1.05-1.11	0.93	0.91-0.96
Ferritin (ng/mL)	747	1.11	1.08-1.15	0.83	0.79-0.86
Transferrin saturation (%)	12.7	0.86	0.83-0.89	1.06	1.03-1.08
Phosphorus (mg/dL)	1.5	1.31	1.26-1.35	0.84	0.81-0.87
Intact PTH (pg/mL)	267	0.79	0.76-0.82	1.18	1.15-1.22
Albumin (g/dL)	0.6	1.14	1.10-1.17	0.99	0.96-1.01

FR-PO009

The Relationship Between Intra-Parenchymal Renal Resistive Index Variation and Renal Functional Reserve Under Physiologic and Pathologic Conditions

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Background: The assessment of renal functional reserve(RFR), which is the increase of glomerular filtration rate after a protein load, has been proposed for the risk stratification of patients undergoing potentially nephrotoxic procedures. In a previous study, we described a bedside ultrasound(BUS) test (intra-parenchymal renal resistive index variation, IRRIV test) to identify the presence of RFR. The aim of the present study is to externally validate IRRIV test in a validation cohort of healthy subjects and preliminary explore the correlation between IRRIV and RFR under pathologic conditions.

Methods: We enrolled a group of healthy subjects and a group of patients scheduled for cardiac surgery. Each underwent protein loading test and IRRIV test. It relies on a mechanical abdominal stress consisting of compressing renal vessels through an externally applied weight on the abdomen (fluid-bag 10% of subject's body weight) which reduces blood flow and activates the autoregulation mechanism. This leads to afferent vasodilation which can be measured by a fall in RRI. Pearson and logistic regression analyses were used to assess the correlation between IRRIV and RFR in both groups.

Results: In 47 healthy subjects, Pearson correlation coefficient between RFR and IRRIV is 0.83, CI95%[0.71-0.90], p<0.01. Among these, concordance between RFR and IRRIV is described in 45 subjects (95.7%). IRRIV predicts RFR with a ROC-AUC of 0.86, CI95%[0.68-1]. In 31 cardiac surgery patients, Pearson correlation coefficient between RFR and IRRIV is 0.81, CI95%[0.63-0.90], p<0.01. Among these, concordance between RFR and IRRIV is described in 27 (87.1%) patients. IRRIV predicts RFR with a ROC-AUC of 0.80, CI95%[0.64-0.96].

Conclusions: IRRIV test is a feasible BUS test that significantly predicts the presence of RFR in healthy subjects. Correlation between IRRIV and RFR seems to be also maintained in pathologic conditions.

FR-PO010

Pathological Characteristics and Prognosis of Community-Acquired AKI: Risk Factors of AKI to CKD Transition

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Background: Community-acquired acute kidney injury(CA-AKI) wins more attentions from society. Underlying pathological damages are regraded as major determinants to AKI to CKD transition. In this study, we clarified the pathological characteristics of CA-AKI and evaluated the influence of morphologic changes in the renal biopsy on the rapid loss of renal function and AKI-CKD transition.

Methods: This single-centered cohort study enrolled CA-AKI patients with renal biopsy examination from January 1, 2010 to September 30, 2017 admitted to Shanghai Changzheng Hospital. All patients were followed up for 90 days after diagnosis. The demographic characteristics, pathological lesions and outcomes were recorded and analyzed. Cox proportional hazard models were used to evaluate the risk factors for all-cause mortality and renal replacement therapy requirement after diagnosis. Logistics regression analyses were used to identify the risk factors associated with progression to CKD or maintained dialysis, and renal recovery as well.

Results: A total of 251 eligible CA-AKI patients were recruited into the cohort, of whom 144(57.4%) were male and age ranged from 18 to 85 years old(median 53). Our results showed that pathological lesions played critical role in AKI-CKD progression and renal recovery. With regard to progression on 90th day, segmental glomerulosclerosis(Relative Ratio(RR) 6.44; 95%CI, 2.03 to 20.38, p=0.002), severe vascular lesion(RR 14.92; 95% CI, 2.35 to 94.80, p=0.004), and crescent index (RR 3.50; 95% CI, 2.07 to 5.91, p=0.037) were significantly associated with progression to maintained dialysis. Over 50% area of Interstitial inflammation(RR 8.09; 95%CI 2.54 to 25.77, p<0.001) and crescent index(RR 3.30; 95%CI 1.78 to 6.12, p<0.001) were risk factors for progression to CKD. Moreover, interstitial fibrosis and crescent were risk factors for partial renal recovery. While, renal morphologic changes showed little impact on in-hospital all-cause mortality and RRT requirement by Cox proportional hazard modeling analysis.

Conclusions: Pathological damages played a part in the rapid loss of renal function and AKI-CKD transition of CA-AKI patients in a short term,affected renal recovery as well. Whereas, it did not interfere with severity of AKI: all-cause mortality and RRT requirement.

Funding: Government Support - Non-U.S.

FR-PO011

Association Between Pre-ESRD Outpatient AKI and Post-ESRD Mortality

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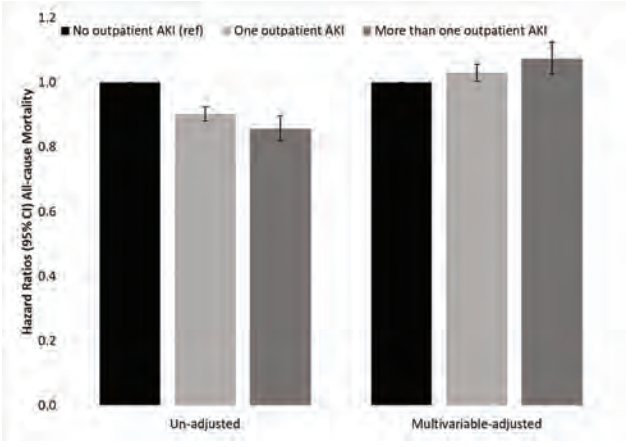
Background: Acute kidney injury (AKI) often occurs in patients with advanced CKD. The incidence of AKI and its impact on outcomes in hospitalized patients has been reported. However, information about the association between pre-ESRD outpatient AKI (oAKI) and post-ESRD outcomes is lacking.

Methods: We examined 54,085 US veterans who transitioned to dialysis during 2007-2014 and had serum creatinine measured in three years preceding the dialysis initiation. oAKI was defined as a 50% increase in creatinine compared to the preceding creatinine value. We compared patients with no oAKI (N=38,348) to patients who had 1 oAKI (N=12,399) and patients who had ≥2 oAKI (N=3,338). The association between pre-ESRD oAKI and post-ESRD all-cause mortality was assessed using Cox proportional hazards model adjusted for demographics, comorbidities, medications, nephrology care, number of outpatient visits, cumulative length of hospitalizations and vascular access type.

Results: The mean (SD) age of the cohort was 70 (11) years; 98% were male; 27% were African American; and 75% were diabetic. Patients with oAKI were younger (age 71 (11) vs. 67 (11) vs. 64 (11) years in patients with no vs. one vs. ≥2 oAKI events). Also, patients with oAKI displayed significantly higher multivariable adjusted mortality than patients without oAKI, with incrementally higher risk observed in patients experiencing ≥2 episodes of oAKI [Figure]. The hazard ratios (95%CI) associated with 1 and ≥2 (vs. no) oAKI were 1.03 (1.00-1.06) and 1.07 (1.03-1.13), respectively.

Conclusions: Prior AKI event in outpatient setting is associated with higher risk of all-cause mortality in advanced CKD patients who transition to maintenance dialysis therapy. Clinical trials are indicated to examine whether preventing AKI can improve CKD outcomes.

Funding: NIDDK Support



FR-PO012

Underreported AKI in Pediatric Intensive Care: Incidence, Risk Factors, and Outcomes

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Background: Acute kidney injury (AKI) is increasingly recognized in critically ill pediatric patients. AKI is frequently underreported leading to the potential for increased morbidity and mortality associated with this disorder. Our study seeks to identify the incidence, risk factors, and outcomes of patients with undocumented AKI in the pediatric critical care population.

Methods: We conducted a retrospective chart review of patients admitted to the PICU at Comer Children's Hospital between January 1, 2017-December 31, 2017. Patients with a rise in serum creatinine (SCr) levels consistent with the KDIGO AKI criteria were considered to have AKI. Patients with a physician note in their electronic medical record (EMR) containing the terms "AKI", Acute Kidney Injury" or "Acute Renal Failure" were labeled as having "Documented AKI". The primary outcome of interest was a comparison between AKI patients with and without EMR documentation of disease. All statistical analyses were performed using STATA software with a p-value of < 0.05 considered statistically significant.

Results: AKI was identified in 8.3% of the total population, with 71% of these patients not having any documentation of AKI in the EMR. There was a significant increase in documentation of AKI in patients with oliguria, nephrotoxic medication and inotropic/vasopressor exposure. Patients with documented AKI had a statistically significant increase in their median length of PICU admission (13.5 days vs 2 days, p=0.00) and median length of mechanical ventilation (12.94 days vs 6.84 days, p=0.034). A nephrology consultation was placed in 2.2% of patients with undocumented AKI.

Conclusions: Our data shows that a substantial number of all AKI diagnosis were not documented in the EMR. Of note, this does not indicate that the provider failed to recognize AKI, but it does represent a deficiency to convey to the medical team the occurrence of this disorder. There were also a significant number of patients with AKI that did not receive a nephrology consultation, an intervention that has been shown to reduce morbidity and mortality of AKI.

Clinical Outcomes

Outcome	Documented AKI (n=38)	Undocumented AKI (n=93)	p-value
Mortality (Within 90 days)	0 (0%)	6 (6.5%)	0.109
Length of PICU Admission, Median [IQR]	13.5 [3, 20]	2 [1, 8]	0.000
Length of Mechanical Ventilation, Mean (+/- SD)	12.94 (+/- 15.44)	6.84 (+/- 6.96)	0.034

FR-PO013

Burden and Outcomes of Drug-Induced AKI

Prakash S. Gudsoorkar,[1] Karthikeyan Meganathan,[1] Amy Sears,[1] Evan P. Singleton,[1] Samantha M. Kramer,[1] Kathleen Harrison,[1] Charuhas V. Thakar.[1,2] *[1]University of Cincinnati, Cincinnati, OH; [2]Renal, Cincinnati VAMC, Cincinnati, OH.*

Background: Acute kidney injury (AKI) affects up to third of all hospitalizations. Although drug induced AKI (DI-AKI) is reported to be frequent, limited data exists in determining its true burden, and description of associated risk factors and outcomes.

Methods: All AKI consults (defined by KDIGO guidelines) across an academic health system were retrospectively recorded in an approved electronic registry. Of the available 500 cases of AKI (January to June 2018), 321 were studied (exclusion: kidney transplants, end stage renal disease, transfers on dialysis). AKI was classified by etiology on the day of consult as either nephrotoxic, biologic, or multifactorial; multifactorial was then scored (1 to 10 scale) based on contribution of the drug class. Drug induced (DI-AKI) was defined as either nephrotoxic or those with a multifactorial score > 5, and others as Biol-AKI. AKI was also classified as community acquired (CA-AKI), < 2 days or 2 or more days after admission (hospital acquired, HA-AKI),. The composite outcome was death, hospice discharge, dialysis dependence at discharge or 1.5 times median length of stay. Chi-square tests, and logistic regression were used for covariate adjustment (demographic, co-morbidities, and admission details).

Results: Of the 321 AKI cases (62% Male, 29% Black, median age 59 years, median baseline creatinine 1.3 mg/dl) DI-AKI occurred in 88 cases (27%). DI-AKI cases were more likely to be Black (40% vs 25%, p=0.01). Compared to Biol-AKI, DI-AKI admissions were mostly Medical (91% vs 78%, p=0.008). The most common drug classes associated with DI-AKI were diuretics 48%, antimicrobials 42%, renin-angiotensin system inhibitors 39%, contrast agents 30%, chemotherapy 7%. Most common source of DI-AKI was community acquired (64%). Need for dialysis was similar across two groups (DI-AKI - 22% vs Biol-AKI 34%). Overall, 50% of cases met the primary composite outcome [(DI-AKI – 38% vs Biol-AKI – 54%, p=0.008); risk-adjusted odds ratio (OR) 0.52 (95% CI, 0.31 – 0.86)].

Conclusions: Almost 1-in-3 AKI consults are drug induced, and attributable to commonly prescribed agents. Although Biol-AKI cases had a greater risk of composite outcome, DI-AKI cases continue to face devastating consequences, including similar risk of dialysis dependence. Strategies to mitigate drug induced AKI could improve clinical outcomes.

FR-PO014

Drug-Induced AKI: Can We Prevent It?

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Background: Acute kidney injury (AKI) can affect 1-in-3 hospitalizations, with an adverse impact on both patients and health systems. AKI is far too commonly drug induced (DI_AKI). Limited data exists in identifying whether DI_AKI can be prevented, and whether patient or provider interventions could improve kidney safety.

Methods: We studied all inpatient nephrology consults with AKI (defined by KDIGO guidelines) at two centers across our academic health system between January and June of 2018. Based on a prior quality improvement program, AKI cases were retrospectively adjudicated to be Biologic (Biol_AKI) or Drug Induced (DI_AKI). We further identified DI_AKI as Preventable (Prv_AKI) when the use of the culprit drug(s) was not considered to be of life-saving value for diagnosis or treatment. Source of AKI was defined as community acquired (CA_AKI = AKI criteria met < 2 days of admission) or hospital acquired (HA_AKI). A composite outcome was hospital death, discharge to hospice or dialysis dependence on discharge. Chi-square tests were used for comparison.

Results: Of the 500 AKI consults, 321 were studied (exclusion: kidney transplants, end stage renal disease, transfers on dialysis). DI_AKI occured in 27% (88/321), and was deemed preventable (Prv_AKI) in 24/88 (27%) of cases. Prv_AKI cases were 63% Men, 54% Black (median age 60.5 years; median baseline creatinine 1.3 mg/dl) Prv_AKI predominantly occurred in Medical settings (96%), and admissions for sepsis or cardiovascular causes comprised 50% of all cases. The top two drug classes associated with Prv_AKI were diuretics (63%) and Renin-Angiotensin System (RAS) blockers (54%). For non-Prv_AKI cases, anti-microbial use (50%) and diuretics (42%) were the top two offending drug classes. Contrast agents were third common class for both groups. Source of AKI in the Prv_AKI group was CA_AKI 54% vs HA_AKI 46% and not significantly different with non-Prv_AKI group (p=0.26). The composite outcome was similar in Prv_AKI (38%) and non-Prv_AKI (38%) groups.

Conclusions: Almost third of drug induced AKI can be preventable, and the majority of these AKI cases manifest within 2 days of admission. Preventable AKI cases faced the same devastating outcome as their counterparts. These findings suggest that patient or provider education about medication safety could improve clinical outcomes in AKI.

Funding: Clinical Revenue Support

FR-PO015

AKI Associated with Fenofibrate

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Background: Fenofibrate was widely used to treat hypertriglyceridemia for many years. It was well known that fenofibrate can trigger acute kidney injury. We studied to investigate the relationship between acute kidney injury and fenofibrate.

Methods: We retrospectively evaluated the medical records of patients to start fenofibrate prescription for hypertriglyceridemia from January 2010 to December 2018 in the tertiary hospital. We reviewed their underlying disease, laboratory findings, dose of fenofibrate, duration of fenofibrate, and concomitant drug use. We did the effort to find factors related to acute kidney injury by fenofibrate.

Results: Total 169 patients were included. The mean age was 63.3 ± 11.5 years old. 40 of 169 patients had acute kidney injury(n=40, 23.6%), and 17 patients had chronic kidney disease(n=17, 10.0%). Patients with diabetes mellitus showed significantly increased risk of acute kidney injury without diabetes mellitus (29.0% vs 15.9%, p=0.04). We found significant correlation between hypertension and acute kidney injury. (30.8% vs 12.3%, p=0.006). Patients with concomitant use of RAS blockers showed significantly decreased

renal function compared with non-user of RAS blockers(31.4% vs 10.9%, p=0.002). In subgroup analysis, patients with chronic kidney disease have statistically significant risk of acute kidney injury by fenofibrate (47.1% vs 21.1%, p=0.017). Mean estimated glomerular filtration rate(eGFR) by MDRD was each 28.4 ± 12.1 mL/min/1.73m2 in chronic kidney disease group and 66.2 ± 20.3 mL/min/1.73m2 in non-chronic kidney disease group.

Conclusions: Diabetes mellitus, hypertension, and concomitant use of RAS blocker have a statistically significant association with acute kidney injury by fenofibrate in our study. And patients with chronic kidney disease have greater risk in acute kidney injury by fenofibrate.

FR-PO016

The Incidence, Risk Factors, and Clinical Outcomes of Rhabdomyolysis Associated with Fenoverine Prescription: A Retrospective Study in South Korea (1999–2014)

Junhyeong Cho,[1] Jeonggu Na,[1] Eunjin Bae,[1] Tae won Lee,[1] Ha nee Jang,[5] Hyun Seop Cho,[5] Se-Ho Chang,[4,3] Dong Jun Park.[2,3] *[1]Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea; [2]Gyeongsang National University Changwon Hospital and Gyeongsang National University College of Medicine, Changwon, Republic of Korea; [3]Institute of Health Science, Gyeongsang National University, Jinju, Republic of Korea; [4]Gyeongsang National University Hospital and Gyeongsang National University College of Medicine, Jinju, Republic of Korea; [5]Gyeongsang National University Hospital, Jinju, Republic of Korea.*

Background: Fenoverine is a spasmolytic drug that has been used to treat abdominal pain. Although sporadic case reports of rhabdomyolysis associated with fenoverine have been published, there are no studies evaluating the correlation of this drug with rhabdomyolysis.

Methods: We retrospectively reviewed the medical records of 22 patients admitted with rhabdomyolysis associated with fenoverine from January 1999 to December 2014, while excluding other well-known risk factors of rhabdomyolysis. This period was subdivided into two periods, January 1999–December 2007 and January 2008–December 2014. We analyzed the clinical and laboratory characteristics, and the prognosis of fenoverine associated with rhabdomyolysis for these times.

Results: The incidence of rhabdomyolysis associated with fenoverine was 0.27% during the total period (22/8257), 0.34% in the first period (18/5298), and 0.14% in the second period (4/2959) ($p < 0.001$). Rhabdomyolysis occurred in 22 liver cirrhosis (LC) patients (2.03%), whereas only 3 cases (0.04%) occurred in non-LC patients ($p < 0.001$). Drug duration, total dose, muscle enzymes, and clinical characteristics were not different between the LC and non-LC groups. Acute renal failure (ARF) occurred in 5 patients in the LC group and 2 patients in the non-LC group ($p = 0.227$). Severity of hepatic derangement according to the Child-Pugh classification was not different between the ARF group and non-ARF group ($p = 0.227$). Four patients died, having complications of oliguric ARF ($p = 0.005$) and underlying severe LC ($p = 0.017$). Higher serum lactate dehydrogenase, blood urea nitrogen, creatinine, and potassium levels but lower serum sodium levels were found in the group that died ($p = 0.001$).

Conclusions: Physicians should not use fenoverine in patients with LC because of a high incidence of rhabdomyolysis and its poor prognosis.

FR-PO017

Postoperative AKI and Intraoperative Mean Arterial Pressure Variability: A Multi-Cohort Observational Study

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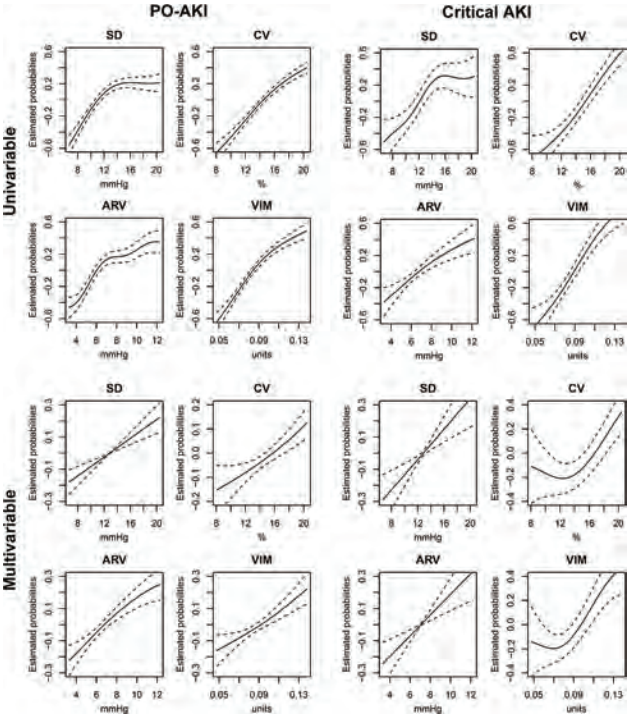
Background: Clinical evidence for the association between intraoperative mean arterial pressure (MAP) variability and the risk of postoperative acute kidney injury (PO-AKI) in non-cardiac surgeries is rare.

Methods: This study included three distinct cohorts in Korea with different time intervals for recording blood pressure during surgery. Non-overlapping first surgery cases were included, excluding those without creatinine measurements or with preexisting renal failure. The main study outcome was PO-AKI, defined by KDIGO serum creatinine criterion cutoffs, and critical AKI, which merged stage 2 KDIGO PO-AKI and post-AKI death or dialysis within 90 days. Standard deviation, coefficient of variation, variation independent of mean, and average real variability were calculated with measured MAP values.

Results: We analyzed 45,575/3,182,502, 29,724/1,354,820, and 7,435/48,923,796 patients/measured MAP values from the three cohorts, respectively. On discovery analysis, the variability parameters were significantly associated with the risk of the studied AKI outcomes, even after adjusted for duration of significant intraoperative hypotension (MAP < 65 mmHg). An increment of 10 mmHg average difference between the measured MAPs, which were measured at a median interval of 2 minutes, was associated with higher risks of PO-AKI [adjusted OR 1.549 (1.307-1.820)] and critical AKI [adjusted OR 1.566 (1.098-2.211)] events. The above results were similar in the other two validation cohorts, and the average real variability was the most significant variability parameter.

Conclusions: High intraoperative MAP variability is an independent risk factor for the risk of PO-AKI and associated patient-oriented outcomes in non-cardiac surgeries.



FR-PO018

Influence of Perioperative Statin Use on Risk of AKI Following Cardiac And Noncardiac Major Surgery: A Nationwide Population-Based Cohort Study

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Background: Postoperative acute kidney injury (AKI) is independently associated with high morbidity and mortality following surgery. The effects of perioperative statin use on the occurrence of AKI are not well understood. The present study investigated the association between perioperative statin use and AKI following cardiac and non-cardiac major surgery in the Korean population.

Methods: All patients aged 30 years and over who underwent cardiac or non-cardiac major surgery between 2013 and 2015 were included in this nationwide population-based cohort study (n = 382,198). The primary outcome was defined as the occurrence of AKI after surgery. Four patterns of statin use were analyzed in this study according to perioperative and/or previous statin use. The generalized logit model was used to evaluate the association between statin use and the risk of AKI. Subgroup analysis was conducted to investigate the differences in the effect sizes of statin use patterns.

Results: Perioperative statin use was associated with an increased risk of AKI after surgery in patients who were naïve to statin prior to both cardiac and non-cardiac surgery (OR 1.35, 95% CI 1.11–1.64; OR 1.20, 95% CI 1.01–1.44, respectively). Non-cardiac patients who underwent perioperative statin therapy and who had previously taken statins had a higher risk of AKI following surgery, whereas withdrawal of statins led to a significant reduction in the occurrence of AKI in these patients (OR 0.82, 95% CI 0.76–0.87).

Conclusions: The results presented here demonstrate the association between perioperative statin use and the increased incidence of AKI following major surgery. Our findings reveal that the risk of AKI of non-cardiac major surgery is reduced when statin treatment is withdrawn at the time of surgery.

FR-PO019

Preoperative Medication Use and Development of Postoperative AKI

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Background: The use of medications such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and proton pump inhibitors (PPI) has been associated with acute kidney injury (AKI), whereas animal data suggest that aldosterone antagonists (AA) may be protective. The aim of this study was to examine the relationship between the preoperative use of these medications and development of postoperative AKI.

Methods: This was a retrospective study of adult patients (excluding those with CKD stage 5) who underwent abdominal, cardiothoracic, vascular or orthopedic surgery at the University Hospital in Reykjavik in 2006-2015. Clinical data and disease diagnoses was retrieved from electronic medical records. AKI was defined based on serum creatinine (SCr) according the the KDIGO criteria. Information on medication use was obtained from the National Prescription Drug Database of the Directorate of Health and patients were considered to be using a medication if they had filled a prescription within six months prior to surgery. A daily defined dose (DDD) was determined for all patients. Risk of AKI was assessed using multivariable logistic regression analysis.

Results: A total of 42,047 abdominal, cardiothoracic, vascular or orthopedic surgeries were performed on 28,418 patients during the study period. Pre- and postoperative SCr was available for 19,279 cases. Postoperative AKI occurred in 1,455 (7.5%) cases. A total of 6,568 (34%) patients filled a prescription for a PPI prior to surgery, 547 (8.3%), of whom developed AKI. Of 6,717 (35%) patients who received ACEi, ARB or AA before surgery, 724 (10.8%) developed AKI. In adjusted analysis, the odds ratio (95% CI) for AKI was 1.00 (0.89-1.13) for PPI, 1.07 (0.93-1.23) for ACEi, 1.30 (1.15-1.48) for ARB and 0.83 (0.62-1.09) for AA. When DDD were examined, there was no evidence of a dose-response relationship between medication use and postoperative AKI.

Conclusions: In this surgical cohort, we found that preoperative use of ARB associated with postoperative AKI. However, no such a risk was evident for PPI and a protective effect of AA was not observed.

Funding: Government Support - Non-U.S.

FR-PO020

AKI After Lung Transplantation: A Meta-Analysis

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Background: Lung transplantation has been increasingly performed worldwide and considered as an effective therapy for patients with various end-stage lung diseases. We performed this meta-analysis to evaluate the incidence and impact of acute kidney injury (AKI) in patients after lung transplantation

Methods: A literature search was conducted utilizing MEDLINE, EMBASE and Cochrane Database from inception through April 2019. We included studies that evaluated the incidence of AKI, severe AKI requiring renal replacement therapy (RRT), and impact of AKI among patients after lung transplantation. Pooled incidence and odds ratios (OR) with 95% confidence interval (CI) were calculated using random effects meta-analysis.

Results: 25 cohort studies with a total of 40,293 patients after lung transplantation were enrolled. Overall, the pooled estimated incidence rates of AKI (by standard AKI definitions) and severe AKI requiring RRT following lung transplantation were 52.1% (95%CI: 45.0%-59.1%) and 9.5% (95%CI: 7.7%-11.8%). Meta-regression analysis showed that year of study did not significantly affect the incidence of AKI (p=0.11) and severe AKI requiring RRT (p=0.54). The pooled OR of hospital mortality among patients after lung transplantation with AKI and severe AKI requiring RRT were 2.75 (95% CI, 1.18-6.41) and 10.89 (95% CI, 5.03-23.58). At 5 year, the pooled OR of mortality among patients after lung transplantation with AKI and severe AKI requiring RRT were 1.47 (95% CI, 1.11-1.94) and 4.79 (95% CI, 3.58-6.40), respectively.

Conclusions: The overall estimated incidence rates of AKI and severe AKI requiring RRT in patients after lung transplantation are 52% and 9.5%, respectively. Despite advance in medicine, incidence of AKI in patients after lung transplantation does not seem to decrease over time. In addition, AKI after lung transplantation is significantly associated with reduced short-term and long-term survival.

FR-PO021

The Association of AKI with Hospital Readmission or Death After Pediatric Cardiac Surgery

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Background: AKI in children undergoing cardiac surgery (CS) is strongly associated with increased hospital morbidity, however post-discharge AKI outcomes are less studied. Hypotheses: In children undergoing CS with cardiopulmonary bypass (CPB), a) AKI is associated with increased risk for readmission or death within 30 days and 1 year of CS discharge, and b) the association of AKI with outcomes is modified by surgical severity and cyanotic heart disease.

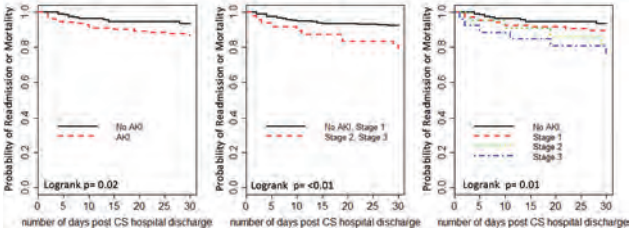
Methods: Prospective 3-centre cohort study of children surviving to hospital discharge after CS with CPB. Main exposure: AKI during index CS admission defined by KDIGO. Composite outcome: readmission to hospital or death at a) 30 days and b) 1 year from CS hospital discharge. Other data: detailed pre/post-op CS patient/treatment variables (including Risk Adjustment for Congenital Heart Surgery-1 [RACHS-1] score; presence of cyanotic heart disease). Association of AKI with time to outcomes was determined using multivariable Cox-proportional hazards analysis (adjusted for age, RACHS-1 score ≥3, CPB time>120 mins). RACHS-1 score≥3 and cyanotic heart disease were evaluated as effect modifiers.

Results: Of the 360 participants included (mean age 4.0±4.6 years, 155 [43%] AKI, 47 [13%] ≥Stage 2 AKI), 4 (1.1%) and 6 (1.7%) died and 30 (8.3%) and 99 (27.5%) were readmitted within 30 days and 1 year post-discharge, respectively. Figure illustrates a graded increase in the risk of the composite outcome with increasing AKI stage. AKI and ≥Stage 2 AKI were associated with time to outcome within 30 days (adjusted HR 2.14 [95%CI 1.04-4.41] and 2.39 [95% CI 1.08-5.27], respectively) but not within 1 year of CS discharge. RACHS-1 and cyanotic heart disease did not modify these relationships (interaction p value>0.1).

Conclusions: Children with AKI post-CS were more likely to be readmitted or die within 30 days of CS discharge, compared to children without AKI. Future research should evaluate measures to reduce short-term morbidity and mortality risk in children who develop AKI after CS.

Funding: NIDDK Support

Figure. Kaplan Meier Curves for Readmission or Mortality within 30 days, by AKI status and by AKI severity



FR-PO022

Correlation Between Incidence and Attributable Mortality Fraction of AKI: A Systematic Review

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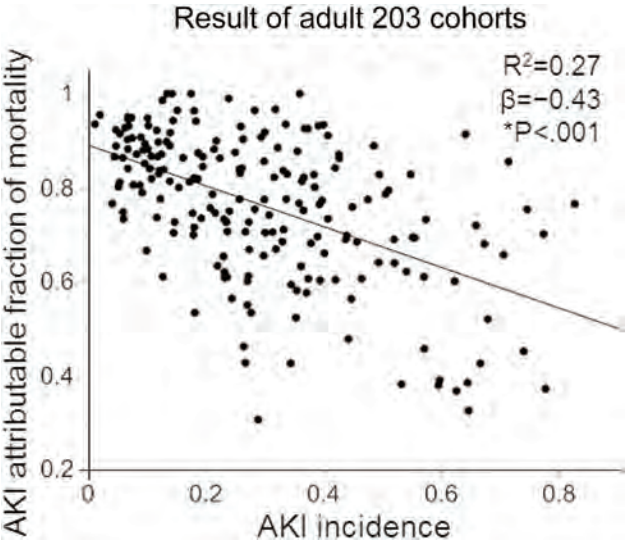
Background: The incidence and mortality of acute kidney injury (AKI) has extremely varied, even after the introduction of RIFLE, AKIN and KDIGO criteria. The quality of AKI diagnosis and management may also be influential. The present study aimed to investigate the association between AKI incidence and mortality of each cohort. We also investigated the effect of publication year and economic index on AKI mortality.

Methods: Our study aggregated the incidence and mortality of AKI through a systematic review of manuscripts on AKI patients diagnosed by Kidney Disease: Improving Global Outcomes (KDIGO)-equivalent criteria from 2004 to May, 2018. The search was conducted in MEDLINE, EMBASE, and Cochrane Library. We investigated the correlation between AKI incidence, mortality, and AKI attributable fraction of mortality. AKI attributable fraction of mortality in each cohort was calculated as follows: {(mortality of AKI patients)-(mortality of patients without AKI)} / (mortality of AKI patients). The impact of publication year and gross domestic product (GDP) on the mortality were also studied.

Results: The systematic review screened total 4149 manuscripts, and finally yielded 287 eligible cohorts (adults: 203 cohorts consisted of 7076459 patients; children: 84 cohorts of 69677 patients). In the adult cohorts, the mortality of AKI patients became higher (R^2=0.023, β=0.12, P=0.033) but the attributable fraction of mortality otherwise decreased (R^2=0.27, β=−0.43, P<0.001), as incidence of AKI augmented. Although the crude mortality of AKI patients decreased in more recent publications and in reports from higher GDP countries, the AKI attributable fraction did not decline in the same settings.

Conclusions: The AKI attributable fraction of mortality in the cohorts with high AKI incidence was relatively low, which possibly indicated the advantage of more experience in AKI diagnosis and management.



FR-PO023

The Value of Plasma Inflammatory Biomarkers in Sepsis-Associated AKI

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Background: Sepsis-associated acute kidney injury (SA-AKI) may be mediated by inflammation. We evaluated the association of plasma inflammatory biomarkers with SA-AKI beyond traditional AKI risk factors and markers of structural damage (uNGAL and UACR).

Methods: We included 453 adults with sepsis (SIRS and adjudicated infection) with collected samples within 24 hours of ICU admission. Admission AKI risk factors were adjudicated into the following categories: hypotension, hypovolemia, nephrotoxins, obstruction and other (e.g. rhabdomyolysis). AKI was defined by ≥ 50% serum creatinine (SCr) rise within 7 days from preadmission SCr or nadir SCr if the former was missing. Plasma and urine biomarkers were $\log_{10}$-transformed. We evaluated the relationship between plasma biomarkers and AKI using univariate and multivariable logistic models with and without backwards stepwise selection ($p<0.05$). Analysis was repeated for severe AKI (KDIGO stage 2-3).

Results: 275 subjects (60%) had AKI, 100 (22%) had severe AKI, 42 (9%) required dialysis and 140 (31%) died in-hospital. A model with demographics and clinical variables (Table 1) had AUC of 0.68 for AKI. The addition of structural damage markers improved the AUC to 0.71, and all plasma biomarkers further increased the AUC to 0.73 ($p\leq0.01$). No plasma biomarkers remained after backwards selection for AKI. Findings were replicated for severe AKI. Inclusion of all plasma biomarkers improved the AUC from 0.75 to 0.79 (p=0.03). Only ICAM remained during backwards selection.

Conclusions: Inflammatory biomarkers only modestly improve SA-AKI prediction. Inflammation and structural damage are likely to have occurred before ICU admission. Efforts targeting systemic inflammation to prevent SA-AKI in the ICU may be limited.

Funding: NIDDK Support

Logistic Regression Models	AKI AUC [95% CI]	Severe AKI AUC [95% CI]
Age + Sex + Race	0.60 [0.55-0.66]	0.50 [0.43-0.57]
+ Diabetes + Liver disease + Baseline SCr + APACHE III	0.68 [0.63-0.73]	0.71 [0.64-0.77]
+ # of AKI Risk Factors (0, 1, 2+)	0.68 [0.63-0.73]	0.71 [0.65-0.78]
+ Structural damage markers [urine neutrophil gelatinase-associated lipocalin (uNGAL) + Urine albumin creatinine ratio (UACR)]	0.71 [0.66-0.76]	0.75 [0.70-0.81]
+ all plasma inflammatory biomarkers* OR	0.75 [0.71-0.80]	0.79 [0.73-0.84]
+ Qualifying plasma markers with backwards selection (AKI: none qualified; Sepsis AKI: only ICAM)	0.71 [0.66-0.76]	0.77 [0.71-0.82]

*Plasma inflammatory biomarkers included: Interleukin 6 (IL6), Interleukin 8 (IL8), C-C Motif Chemokine ligand 8 (CCL8), CXC Motif chemokine ligand 9 (CXCL9), Matric metallopeptidase (MMP)-8, MMP-9, Advanced glycation end products (RAGE), Tumor necrosis factor receptor 1 (TNFR-1), Angiopoietin-2, Protein C, intracellular adhesion molecule (ICAM), vascular endothelial growth factor (VEGF) and Von Willebrand Factor (VWF)

FR-PO024

Renin-Angiotensin System Blockade After AKI and Risk of Recurrent AKI

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Background: How to best medically manage patients who survived hospitalized acute kidney injury (AKI) is unclear. These patients are at higher risk of further loss of renal function so angiotenin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) may be reno-protective. However, recurrent AKI is common and use of ACE-I/ARB in this setting may increase risk of recurrent AKI.

Methods: This is a retrosepctive cohort study of 10,242 members of an integrated healthcare delivery system in Northern California who experienced AKI and survived a hospitalization between January 1, 2006 and December 31, 2013. All study participants did not have prior heart failure or previous use of ACE-I or ARB therapy up to five years prior. New receipt of ACE-I/ARB was identified based on dispensed prescriptions found in outpatient health plan pharmacy databases. The pirmary outcome of interest was subsequent episode of hospitalized AKI after discharge from an initial index hospitalization complicated by AKI. Recurrent AKI episode was defined using acute changes in serum creatinine concentrations. Marginal structural models (MSM) were used to adjust for baseline and potential time-dependent confounders.

Results: During follow-up, we observed 22.0 episodes of recurrent AKI/100 person-years while taking ACE-I/ARB (95% CI: 20.5 to 23.6 episodes per 100 person-years) compared to 14.1 episodes/100 person-years while not receiving ACE-I/ARB (95% CI: 13.7 to 14.5 episodes per 100 person-years). However, in MSM causal inference models that adjusted for baseline and potential time-dependent confounders, exposure to ACE-I or ARB use was not associated with higher incidence of recurrent AKI (adjusted odds ratio 0.71, 95% CI: 0.45 to 1.12).

Conclusions: Our study provided reassuring data about the safety of initiating ACE-I or ARB after an episode of AKI.

Funding: NIDDK Support

FR-PO025

Hospitalized AKI Among Black and White Individuals with CKD: The CRIC Study

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Background: Although black race and *APOL1* high-risk genotypes are risk factors for various forms of kidney disease, few studies have rigorously examined whether an independent association of black race and *APOL1* genotypes exists for occurrence of hospitalized AKI. Prior studies have not accounted for baseline eGFR and proteinuria levels near the time of AKI and have relied only on diagnostic codes to define AKI.

Methods: We studied black and white participants enrolled in the CRIC Study, a multicenter prospective cohort study of CKD, who had an annual in-person study visit between July 2012-June 2013. The primary outcome was hospitalized AKI in the subsequent 2 years (defined as a ≥50% increase from nadir to peak inpatient serum creatinine). We evaluated the association of race, *APOL1* genotype and AKI using multivariable logistic regression.

Results: Among 1,162 eligible CRIC participants, 481 were black with 86 (18%) having a high-risk *APOL1* genotype. The overall mean (SD) eGFR was 47 (16) mL/min/1.73m^2 and neither eGFR or proteinuria significantly differed by *APOL1* risk status (**Table**). The crude risk of AKI was similar between black and white patients (5.2% vs. 5.3%). After adjusting for eGFR and urine protein-to-creatinine ratio, age, sex, educational attainment, blood pressure, prevalent cardiovascular disease, diabetes and receipt of ACE-I/ARB, there was no significant association of race or *APOL1* status with AKI (**Table**).

Conclusions: Among black and white participants with similar baseline eGFR, neither black race nor *APOL1* genotype is significantly associated with subsequent hospitalized AKI.

Funding: NIDDK Support

Baseline characteristics and risk of AKI among CRIC participants by APOL1 status.

Characteristic	White (N=681)	Black/Low-risk APOL1 (0 or 1 allele) (N=395)	Black/High-risk APOL1 (2 alleles) (N=86)
Mean (SD) age, yr	66 (10)	66 (9)	62 (12)*
Women, %	42	55*	56*
High school graduate, %	97	78*	83*
Cardiovascular disease, %	37	46*	39
Diabetes mellitus, %	44	56*	42
Receipt of ACE-I/ARB, %	63	66	70
eGFR, mL/min/1.73m2, mean (SD)	47 (16)	47 (18)	47 (20)
uPCR, g/g, median (IQR)	0.12 (0.06-0.35)	0.16 (0.08-0.71)*	0.16 (0.07-0.47)
SBP, mmHg, mean (SD)	122 (18)	133 (22)	126 (19)
No. of AKI events, n	36	22	3
Unadjusted risk of AKI, % (95% CI)	5.3 (3.7-7.2)	5.6 (3.5-8.3)	3.5 (0.7-9.9)
Adjusted odds ratio of AKI (95% CI)	Ref	0.94 (0.5-1.8)	0.62 (0.18-2.2)

* $p<0.05$ compared to white patients

FR-PO026

Renal Outcomes and Recovery in a Large Cohort of Critically Ill Patients Requiring Venoarterial or Venovenous Extracorporeal Membrane Oxygenation and CRRT

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Background: The development of acute kidney injury in adult patients requiring venoarterial or venovenous ECMO is very common. Many of these patients will require renal replacement therapy. Despite an extremely high mortality in such a patient population, centers are reporting improving outcomes with respect to survival. Little is known about the renal outcomes and renal recovery rate of those who required renal replacement therapy patients who survive to discharge.

Methods: Over the last 6 years, we have performed over 600 cannulations for VA or VV ECMO at our institution. Of these patients, 268 of them required renal replacement therapy for acute kidney injury. We have collected demographic and epidemiologic data as well as outcome data on those that have survived.

Results: Of the survivors, the cohort of patients most likely to recover renal function were patients with no prior known renal dysfunction who were on venovenous ECMO. The patients most likely to require ongoing hemodialysis at the time of discharge were patients with heart failure who were on venoarterial ECMO. Diabetes seemed to be a major risk factor in overall renal recovery, as did preadmission creatinine levels. Patients that recovered renal function after 30 days were typically those with no prior renal disease

Conclusions: Many of the traditional predictive measures for renal recovery after critical illness apply to the ECMO population. Despite having a large cohort of ECMO patients requiring renal replacement therapy, there is no clear pathway to being able to predict renal recovery.

FR-PO027

Initial Lactate Level and Lactate Clearance on Renal Outcomes in Critically Ill Patients with Sepsis

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Background: Lactate level and lactate clearance have been implicated as predictors of mortality in patients with sepsis. However, their roles for renal outcomes remain uncertain. In this study, we investigated the impacts of initial lactate level and lactate clearance on renal outcomes in critically ill patients with sepsis.

Methods: We retrospectively reviewed a total of 151 adult patients with sepsis who met the Sepsis-3 definition. Serum lactate levels were measured at initial and 24 hours from the intensive care unit admission. Among patients with initial lactate level ≥2 mmol/L, the lactate clearance was calculated as (initial lactate–24-hour lactate)/initial lactate × 100, then, they were divided as those with lactate clearance <20% and ≥20%. Acute kidney injury (AKI) was defined using the KDIGO guideline.

Results: AKI occurred in 52 (68.4%) patients with initial lactate level <2 mmol/L and 69 (92.0%) in those with initial lactate level ≥2 mmol/L (P<0.001). In addition, patients with initial lactate level ≥2 mmol/L had higher probabilities of renal replacement therapy than those with its level <2 mmol/L, independent of age, sex and the sequential organ failure assessment (SOFA) score (OR 2.9, 95% CI 1.1–7.3, P=0.025). However, the lactate clearance was not related with AKI occurrence and renal replacement therapy use (P=1.000 and 0.293). The lactate clearance <20% was associated with 28-day mortality, independent of age, sex and the SOFA score (HR 3.8, 95% CI 1.5–9.7, P=0.005), but Initial lactate level was not (P=0.164). Among 116 survivors, estimated glomerular filtration rate (eGFR) at discharge were assessed, and we found that the eGFR did not differ according to initial lactate level and lactate clearance in multivariate linear regression analyses (P=0.954 and 0.203).

Conclusions: In critically ill patients with sepsis, initial lactate level can predict the AKI occurrence and renal replacement therapy need, however, lactate clearance cannot. In addition, renal function recovery may be associated with neither initial lactate level nor lactate clearance.

FR-PO028

Diastolic and Systolic Dysfunction on Renal Outcomes in Critically Ill Patients with Sepsis

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Background: Diastolic and systolic dysfunction have been regarded as predictors of mortality in patients with severe sepsis and septic shock. Myocardial dysfunction may contribute to hemodynamic instability and may result in organ failure, but their impacts on renal outcomes remain uncertain. In this study, we investigated the impacts of diastolic and systolic dysfunction on renal outcomes in critically ill patients with sepsis.

Methods: We retrospectively reviewed a total of 164 adult patients with sepsis who met the Sepsis-3 definition. Left ventricular (LV) function was assessed using echocardiography within 5 days from the intensive care unit admission. Systolic dysfunction was defined as an ejection fraction <50%, and diastolic dysfunction was defined as the septal E/e' ratio >15 among patients with ejection fraction ≥50%. Acute kidney injury (AKI) was defined using the KDIGO guideline.

Results: There were 86 (52.4%) with normal LV function, 37 (22.6%) with diastolic dysfunction and 41 (25.0%) with systolic dysfunction. The incidence rate of AKI was 68.6%, 83.8% and 87.8% in the respective groups (P=0.029). Patients with diastolic and systolic dysfunction had more highly required renal replacement therapy than those with normal LV function, and these results persisted after the adjustment for age, sex and the sequential organ failure assessment (SOFA) score (OR for diastolic dysfunction 3.6, 95% CI 1.0–12.3, P=0.045 and OR for systolic dysfunction 3.1, 95% CI 1.0–9.4, P=0.045). Moreover, diastolic dysfunction predicted 28-day mortality, independent of age, sex and the SOFA score (HR 3.3, 95% CI 1.1–9.9, P=0.033), but systolic dysfunction did not (P=0.094 in multivariate analysis).

Conclusions: Both diastolic and systolic dysfunction could predict the AKI occurrence and renal replacement therapy need in critically ill patients with sepsis. More studies are needed to investigate individualized approaches according to LV function in this disease population.

FR-PO029

Outcomes of Patients on Extracorporeal Membrane Oxygenation with AKI Requiring Dialysis

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Background: Acute kidney injury (AKI) is a common complication among critically ill patients including those receiving Extracorporeal Membrane Oxygenation (ECMO). Despite increasing application of ECMO and improved outcomes for patients receiving it, little is known about outcomes of AKI requiring dialysis (AKI-D) in these patients. We therefore sought to investigate the epidemiology and outcomes of AKI-D among patients receiving ECMO.

Methods: We utilized data from National (Nationwide) Inpatient Sample from 2007-2014. ECMO and with AKI-D were identified using ICD-9-CM codes. We compared proportions of patients meeting various outcomes use the Chi square test. Our primary outcome was inpatient mortality. We also stratified our analysis by time comparing 2007-2010 and 2011-2014. Finally we conducted multivariable logistic regression adjusting for patient/hospital demographics, co-morbidities, acute organ dysfunction, and cardiac surgery during the index hospitalization to assess the impact of AKI-D on mortality.

Results: Of estimated 16,368 (95% CI: 14,185-18,551) hospitalizations receiving ECMO, 2,266 (13.8%) had AKI-D. The proportion of AKI-D was similar between the two time periods (14.3% vs 13.7%, p=0.8) as was the proportion of those started on dialysis on the same day or after ECMO initiation (64.8% vs 73.6%, p=0.1). Compared to patients without AKI-D, those with AKI-D were more male (67.2% vs 61.2%, p=0.03), less often on Medicare/Medicaid (41.4% vs 53.2%, p=0.02) and admitted more often at larger hospitals (91.5% vs 87.2%, p=0.02). Mortality was significantly higher in those with AKI-D (70.9% vs 54.0%, p<0.001) and did not differ by time period. In multivariate analysis AKI-D was an independent predictor of mortality (OR 1.43; 95% CI: 1.09-1.87).

Conclusions: About 14% of patients on ECMO develop AKI-D with majority started on dialysis on the day of or after ECMO initiation. Though there has been a reduction in mortality, it remains significantly high in patients with AKI-D.

FR-PO030

Underrecognition of Neonatal AKI and Lack of Follow-up

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Background: Recent data show an incidence of 30% of acute kidney injury (AKI) in neonatal intensive care units (NICU). AKI is associated with increased mortality and risk of chronic kidney disease (CKD) in children. To assess the follow-up of these patients (pt) and early CKD signs, we retrospectively reviewed long-term outcomes of Cincinnati Children's Hospital Medical Center (CCHMC) cohort of neonates included in the AWAKEN trial (2014).

Methods: 81 CCHMC pt were extracted from AWAKEN data. KDIGO criteria for serum creatinine (SCr) and urine output (UOP) < 1 mL/kg/h, reported per 24h on post-natal days 2-7, were used to define AKI. Charts were reviewed until May 2019 for pt death, inpatient nephrology consult, AKI diagnosis on discharge summary, follow-up anywhere at CCHMC, as well as potential early CKD signs at > 6 months of age and after AKI (defined as any one of an estimated GFR (eGFR) by Schwartz < 90 ml/min/1.73m^2, hyperfiltration, proteinuria, hypertension, or abnormal ultrasound). Pt were considered to have a renal follow-up if they had at least one visit anywhere in that timeframe with at least one of the following: SCr, urinalysis or a blood pressure measurement.

Results: 77 pt had sufficient data to ascertain an AKI diagnosis. 47/77 (61%) were AKI+ by either SCr or UOP criteria (13 stage 3, 14 stage 2 and 20 stage 1). Of those, 4 died during their initial admission (2 AKI- and 2 AKI+, stage 1 and 2) and 5 pt with significant urologic anomalies were removed from the CKD analyses. Taken separately, AKI-UOP alone outnumbered AKI-SCr (respectively 45 AKI+ vs 5 AKI+ for all stages, 10 and 27 pt with insufficient data for AKI ascertainment). 33% of pt had < 2 SCr measured in the NICU. Only 3/47 AKI+ pt had a nephrology consult (all stage 3 by SCr) and 2/47 had AKI reported on their discharge summary. 67% of AKI+ pt had some form of renal follow-up. 10/43 (23%) AKI+ vs 12/25 (48%) AKI- pt had ≥1 marker of early CKD signs measured after 6 months. Only hyperfiltration was positive in 3/7 (43%) AKI+ vs 0/7 (0%) AKI- pt with SCr available (p=0.19). Median eGFR in AKI+ pt was 120 vs 126 ml/min/1.73m^2 for AKI- (p=0.46).

Conclusions: AKI is vastly under-recognized in the NICU, especially if based on SCr alone. This leads to insufficient follow-up to ascertain renal sequelae in this high risk population despite a trend toward more hyperfiltration.

FR-PO031

Adherence to AKI Best Practice Guidelines in Hospitalized Children

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Background: The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines recommends a non-invasive diagnostic workup and cessation of nephrotoxins in all stages of AKI. We evaluated the provider adherence to these consensus guidelines in hospitalized children

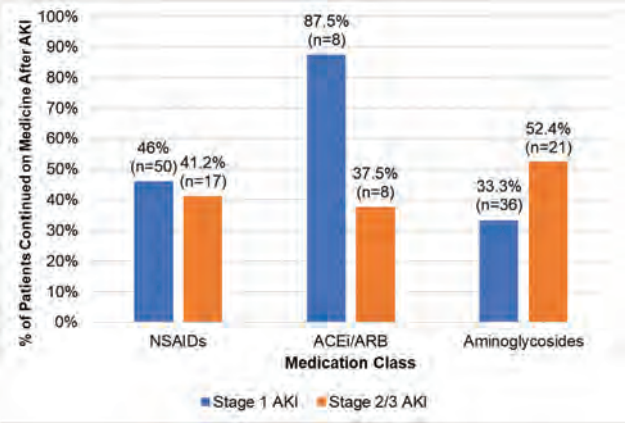
Methods: We reviewed the medical records of children <18 years old, who had at least two creatinine values measured during a hospital admission in a large, tertiary care hospital. We defined AKI based on serum creatinine per the KDIGO guidelines, with a minimum absolute creatinine value of 0.5 mg/dL. We calculated the baseline daily rates of performing non-invasive diagnostic tests such as urinalysis in children with AKI compared to all patients in the cohort. To evaluate adherence to general preventive measures, we calculated the percentage of patients who continued to receive nephrotoxic agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) after the development of AKI

Results: Among the 8634 encounters studied, AKI occurred in 779 (9%) encounters. Median age was 4.5 years [IQR, 0-13.2], 4559 (52.8%) were male, and 48% were admitted to the ICU (PICU or NICU). Development of AKI increased the rate of receiving a repeat creatinine measurement from a baseline 54% to 81% per day in children with AKI, a urinalysis from 6% to 19%, and a renal ultrasound from 1% to 6%. Children with AKI were 5 times more likely to have a nephrology consultation as compared to those without

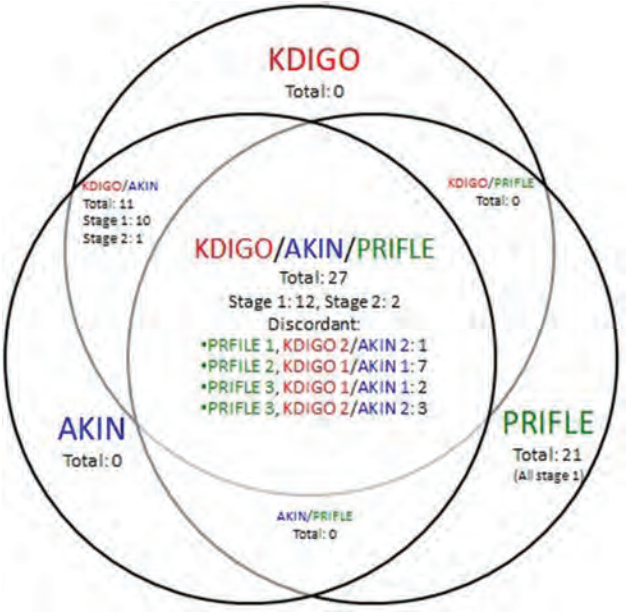
AKI. After developing AKI, 30/67 (44.8%) children receiving NSAIDs and 10/16 (62.5%) children receiving angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers continued receiving them (Figure)

Conclusions: We identified gaps in provider adherence to AKI management guidelines in hospitalized children. We recommend establishing electronic health record-integrated best practice bundles to improve care for children with AKI

Funding: NIDDK Support



Percentage of patients continued on nephrotoxic medications after developing AKI



FR-PO032

Pediatric Kidney Stone-Associated AKI

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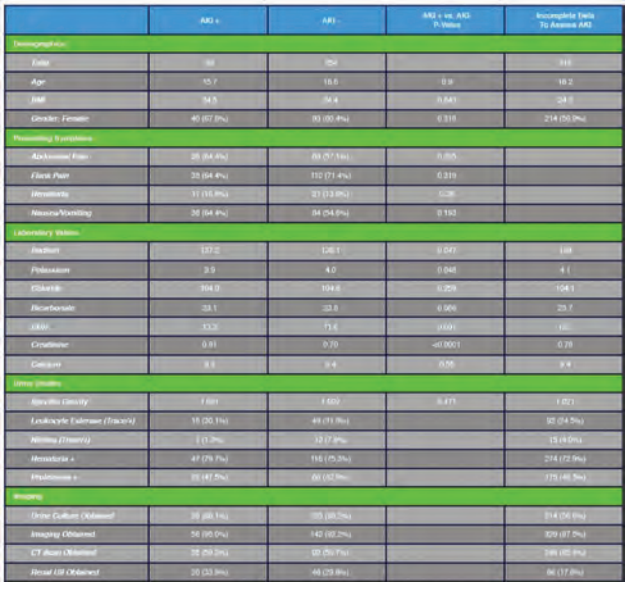
Background: Rates of stone AKI in children may be as high as 30%. Retrospective review examined children for AKI at emergency department (ED) visits for renal colic.

Methods: Retrospective: 1-26 years Akron Childrens Hospital 1/08-1/17. ICD code and radiographic evidence of stones or documentation by nephrologist. ED visits with + imaging for stones or physician documentation. Anthropometric, lab and management data were collected. AKI defined by Kidney Disease: Improving Global Outcomes, Acute Kidney Injury Network and Pediatric Risk Injury Failure End Stage criteria.

Results: 399 patients with 589 visits. 39% unique patients had data to assess AKI, with 33% AKI+. 36% visits had data to assess AKI with 27.7% +AKI. Data was not sufficent to assess for AKI in 65.6% of patients and 63.8% visits. Among AKI patients, 15% had documentation of AKI; 22% with Cr in lab documentation, but no mention of abnormal cr assessment/plan. 55.9% of AKI+ visits, patients were treated with NSAID in the ED; 47% of AKI visits were discharged home with NSAIDs.

Conclusions: Pediatric AKI due to stones is under recognized. 27.7% of ED stone visits AKI+. Only 64% of visits had data to asses for AKI. Only 15% of AKI+ had documentation by physician of AKI, and 55% of AKI patients received NSAIDs. Concerning given known association of stones with chronic kidney disease.



FR-PO033

The Incidence and Frequency of Diagnosing AKI in Non-Critically Ill Pediatric Patients

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Background: Acute kidney injury (AKI) is commonly seen among hospitalized pediatric patients. Most studies have focused on critically ill patients and the incidence in non-critically ill (NCI) patients is less well studied. There has been only one study, McGregor et al (2016), that has looked at the incidence of AKI in this population and no studies evaluating the frequency of AKI diagnosis during NCI admissions. McGregor et al found that the rate of AKI among NCI patients to be 5%. The purpose of our study is to validate the finding of McGregor et al. and to assess the frequency of provider diagnosis of AKI in NCI patients during admission.

Methods: We performed a retrospective cohort study on all patients admitted to the NCI hospitalist service at our tertiary care pediatric hospital between July 1 2017 and June 31 2018. Patients included in the study were between the ages of 2 weeks and 18 years without history of chronic kidney disease or intensive care unit admission at any time of their hospitalization, and who had 2 or more serum creatinine values. We used the KDIGO criteria, defined as serum creatinine increase by ≥0.3mg/dL within 48 hours or increase by ≥1.5 times the baseline within 7 days, to identify patients with AKI. Of those identified with AKI, we reviewed the chart to assess whether providers had identified the AKI during the admission.

Results: Of the 14,495 patients admitted, 1,223 (8%) patients were included in the study. 132 (10.8 %) patients met the KDIGO criteria for AKI. Of these 132 patients, only 51 (37.8%) were identified to have AKI by providers during their admission.

Conclusions: Our study suggests that the incidence of AKI in the NCI setting is higher than previously reported; 10.8% of NCI patients in our institution had AKI, compared to the 5% reported by McGregor et al. Since we were only able to analyze 8% of the total patients admitted, due in part to lack of data, it is possible that the rate of AKI is even higher. This shows the limitations of applying the KDIGO criteria in diagnosing AKI in the clinical setting. We also found the frequency of identifying AKI was low at 37.8%. As prompt identification of AKI is crucial in preserving kidney function, new strategies are needed to help providers identify these patients.

FR-PO034

Use of Tramadol and Reduced Risk of AKI in Hospitalized Children

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Background: Various interventions have been reported to prevent the development of AKI, but only few have been validated in children. This study is aimed to investigate the potential renoprotective effect of tramadol on the risk of pediatric AKI.

Methods: We conducted a multicenter retrospective cohort study in hospitalized children aged 1 month to 18 years from 25 tertiary hospitals across China during 2013-2015. Patient-level data were obtained from the electronic hospitalization information system. The outcome was hospital-acquired (HA-)AKI. AKI was defined and staged by Kidney Disease Improving Global Outcomes criteria. Patients who developed AKI after two days of admission were identified as having HA-AKI. We used a cox proportional hazards model to estimate the risk of HA-AKI, in which exposure to tramadol was modeled as a time-varying variable.

Results: Among 46295 children analyzed, 1779 (3.8%) used tramadol and 3555 (7.68%) had HA-AKI events during hospitalization. Most of tramadol (53.18%) was prescribed for postoperative analgesia. After adjusting for demographics status, prevalent comorbidities and concomitant use of medications, use of tramadol was associated with a significantly reduced risk of HA-AKI compared with non-users (HR 0.20; 95% CI, 0.15-0.27). The results were consistent in subgroups and multiple sensitivity analysis. An increasing cumulative dosage of tramadol use was associated with a graded lower risk of HA-AKI.

Conclusions: Tramadol was associated with a reduced risk of HA-AKI in hospitalized children. Future intervention study should evaluate whether tramadol use could prevent AKI in high risk patients.

Funding: Government Support - Non-U.S.

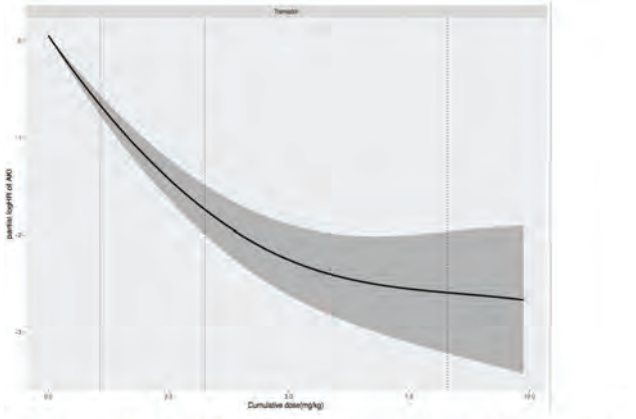

Figure. Dose response curve of the risk of HA-AKI and the cumulative dose of tramadol.

Table. Association Between Tramadol Use and AKI Stratified by Subgroups.(AKI definition:Kdigo)

Subgroup	Tramadol users		Non-users		Adjusted HR* (95% CI)	P for interaction
	Total Patients	No. of Events	Total Patients	No. of Events		
Age						0.71
1-12month	362	11	14189	1653	0.15 (0.10-0.24)	
1-5year	526	10	13197	988	0.35 (0.21-0.58)	
5-18year	891	9	17130	884	0.27 (0.16-0.49)	
Gender						0.50
Male	1020	19	27143	2146	0.23 (0.16-0.32)	
Female	759	11	17373	1379	0.18 (0.11-0.29)	
Diuretic						0.48
Yes	1098	24	14000	1660	0.23 (0.16-0.31)	
No	681	6	30516	1865	0.25 (0.13-0.46)	
ICU						0.44
Yes	1216	26	14340	1496	0.22 (0.16-0.29)	
No	563	4	30176	2029	0.16 (0.07-0.38)	
Operation						0.68
Yes	946	16	14744	1242	0. 33(0.22-0.50)	
No	833	14	29772	2283	0.17 (0.11-0.26)	

*adjusted for age, gender, hospital, division,baseline SCr,comorbidities, clinical procedures, need for intensive care and other nephrotoxic drugs use need for operation;**Abbreviation:** ICU,intensive care unit; HR,hazard ratio; CI, confidence interval.

FR-PO035

Prevalence, Risk Factors, and Prognosis of AKI in Pediatric Nephrotic Syndrome

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Background: Children with nephrotic syndrome (NS) are at an increased risk of severe infection, thrombosis, and acute kidney injury (AKI). In NS patients, AKI is associated with an increased risk of chronic kidney injury, and its incidence is increasing. Despite this, there is limited data regarding the epidemiology and risk factors of AKI in pediatric NS patients. Thus, the aim of this study was to investigate the incidence, clinical profiles, and risk factors of AKI in pediatric NS patients.

Methods: This was a retrospective multicenter study involving 14 pediatric nephrology centers. From 2013 to 2017, a total of 814 patients with idiopathic NS were reviewed, and 487 patients hospitalized for NS were analyzed.

Results: Among 363 children, 574 hospitalizations occurred. AKI occurred in 10.9% (89 patients) of the 814 children with NS and 16.2% of the 363 children who were hospitalized. Among the 588 cases of hospitalization, AKI was found in 93 (16.2%) cases: 30 (33.3%) had stage 1 AKI; 24 (25.8%), stage 2 AKI; and 39 (41.9%), stage 3 AKI. Refractory NS was the major predisposing factor for AKI in 26 (28.0%) cases. Pediatric NS patients with AKI were older; had a longer disease duration, steroid resistance, and a lower serum albumin level; and were administering of calcineurin inhibitors. Logistic regression analysis revealed that longer disease duration, lower albumin level, and steroid resistance were significantly associated with the development of AKI in pediatric NS patients. AKI was associated with a longer length of hospital stay (median duration, 10 days compared to 7 days for hospitalized patients without AKI; P = 0.001). A total of 84 (90.3%) children recovered from AKI, whereas 6 (6.5%) developed chronic kidney injury, and 3 children had neurologic sequelae related to an accompanying infection.

Conclusions: AKI, often leading to chronic kidney injury, is common in children who are hospitalized with NS. Risk factors for AKI include a longer disease duration, steroid-resistance, and infection; these can be potential tools in the recognition and management of AKI in children with NS.

FR-PO036

Rhabdomyolysis in Young Adults

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Background: Rhabdomyolysis is a clinical entity that directly causes AKI and is associated with a subsequent increase in patient mortality. The primary means of diagnosis is made via clinical suspicion from patient history, clinician knowledge of risk factors, and laboratory testing such as the utilization of CK for diagnosis. However, patient risk factors are dependent upon age and if not adequately assessed can lead to a missed diagnosis. Furthermore, other serum markers can potentially be used to aid in prognosis. Our study seeks to describe the risk factors for rhabdomyolysis in adults younger than 50 years. It explores etiology and demographic characteristics in relation to severity of illness, length of stay, and short-term outcomes. Finally, it indicates the accuracy of NLR as a prognostic tool.

Methods: A single-center retrospective cohort study was completed to evaluate patients admitted to hospital for primary diagnosis of rhabdomyolysis. NLR was calculated and compared to CK levels to determine association and assistance with diagnosis.

Results: 331 Rhabdomyolysis patients were included in the study. Data were stratified into 3 groups based on CK level (1500-5000, 5000-50000, >50000 IU/L). 34.83% of cases were due to illicit drugs with 80% attributed to Heroin and/or Cocaine use. Drug use was also the major etiology (28.1%) when CK level was 1500 - 50000 IU/L. The second leading cause of Rhabdomyolysis was exercise-induced (16.47%). Exercise was the major etiology (40%) in subjects with CK levels above 50,000 IU/L. Subjects with exercise-induced rhabdomyolysis had a median serum CK (8,840) more than twice the median for the entire group (4,012), but their median length of stay (2 days) was half the entire group's median (4 days). On the other hand, there was a statistically significant positive correlation between the NLR (4.79, 5.61, and 10.19 respectively) and the length of stay (4.58, 6.59, 7.8 days respectively) (p= <0.001; Spearman correlation 0.22).

Conclusions: Illicit drug use was the major cause of rhabdomyolysis in adults < 50 years old. Exercise was the second leading cause of rhabdomyolysis with a higher median serum CK but lower than the median length of stay indicating that CK is not an accurate prognostic indicator. NLR has a positive correlation to serum CK and the total length of stay suggesting it is an important prognostic biomarker. Larger studies in different patient populations are warranted to validate findings.

FR-PO037

Change in Right Ventricular Systolic Function After CRRT Initiation and Renal Recovery

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Background: Echocardiographic parameters have been associated with outcomes in patients on continuous renal replacement therapy (CRRT). We investigate the impact of CRRT on echocardiographic parameters and the association between improvement of these parameters with renal recovery and mortality.

Methods: This is a retrospective analysis of patients admitted to the intensive care units (ICU) at a tertiary care hospital from December 2006 through November 2015 who underwent CRRT and had an echocardiogram available within ±2 weeks from CRRT initiation. The primary outcome was Major Adverse Kidney Events at day 90(MAKE90). Multivariate logistic regression was performed to identify independent predictors of MAKE90. Secondary outcome included mortality at 30 days.

Results: The cohort included 303 patients with acute kidney injury (AKI). The median age was 62 (IQR 52-71) years with 130 (43%) female and median SOFA on the day of CRRT initiation 12 (IQR 10-14). Overall MAKE90 occurred in180 (60%) patients. The median time of echocardiogram relative to CRRT initiation was 1 day prior to CRRT and 4 days after the CRRT initiation. Among 136 patients, 35 (25%) had improvement in RV systolic function on the repeat echocardiogram. Among 106 patients, 47 (44%) had improvement in their RVSP, and 23 (21%) had at least 20% lower RVSP. Rates of MAKE90 were lower in patients who had improvement in their RV systolic function (43% vs. 67%), or had 20% reduction in RVSP (35% vs 59%), p<0.05 for both. On multivariate logistic regression, the improvement in RV systolic function (adjusted OR 0.33; 95%CI: 0.14-0.76, p=0.008) and decrease in RVSP by >20%(OR 0.36; 95%CI: 0.13-0.98, p=0.047) were associated with lower MAKE90 after adjusting for age, SOFA score, fluid balance before CRRT initiation and baseline serum creatinine. For 30-day mortality, adjusted hazard ratio (HR) for improvement in RV systolic function was 0.48 (95%CI: 0.24-0.93, p=0.031). Patients who had an improvement in their RV systolic function were in negative fluid balance leading to the day of repeat echocardiogram -2.1L vs. + 0.22L p=0.026.

Conclusions: Right ventricular dysfunction has been previously shown to predict mortality in ICU patients. Improvement in RV systolic function after CRRT was associated with decreased mortality and better renal recovery and this might be affected by volume overload.

FR-PO038

Net Ultrafiltration Rate and Its Impact on Mortality in Patients with AKI Receiving CRRT

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Background: Fluid overload, a critical consequence of acute kidney injury (AKI), is associated with worse outcomes. The optimal volume of fluid removed per day during continuous renal replacement therapy (CRRT) is unknown. The purpose of this study is to evaluate the impact of ultrafiltration rate on mortality in critically ill patients with AKI receiving CRRT.

Methods: We retrospectively reviewed 1,398 patients with AKI who received CRRT between December 2006 and November 2015 at Mayo Clinic, Rochester, MN. The net ultrafiltration rate (UF^{NET}) was categorized into low- and high-intensity groups (< 35 and ≥ 35 ml/kg/day, respectively). The impact of different UF^{NET} intensities on 30-day mortality was assessed using logistic regression after adjusting for age, sex, body mass index, fluid balance from ICU admission to CRRT initiation, APACHE III and SOFA scores, baseline serum creatinine, ICU day at CRRT initiation, Charlson comorbidity index, and need for mechanical ventilation.

Results: The mean age was 62±15 years, 827 (59%) were male. There were 696 patients (49.8%) in low- and 702 (50.2%) in high-intensity groups. Thirty-day mortality was 755 (54%). There were 420 (60.4%) deaths in low-, and 335 (48%) in high-intensity group (p<0.001). UF^{NET} ≥ 35 ml/kg/day remained independently associated with lower 30-day mortality (adjusted odds ratio (aOR): 0.49; 95% Cl: 0.39-0.63, p<0.001) compared to < 35 ml/kg/day.

Conclusions: More intensive fluid removal, UF^{NET} ≥ 35 ml/kg/day among AKI patients receiving CRRT is associated with lower mortality. Future prospective studies are required to confirm such a finding.

FR-PO039

CKD and AKI Outcomes After Left Ventricular Assist Device Implantation

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Background: Left ventricular assist devices (LVAD) are used as a bridge to heart transplant or destination therapy for patients with end-stage heart failure. Acute kidney injury (AKI) or need for renal replacement therapy (RRT) post LVAD implant can lead to poor outcomes. Identifying risk factors of AKI post LVAD can help stratify LVAD candidates.

Methods: A retrospective study of all patients who received continuous-flow LVAD at our institution from January 2015 until August 2017. We calculated incidence of AKI and need for RRT post LVAD implant, rate of renal recovery and survival rates at 30 days and 1-year post implant. Presence of Chronic kidney disease (CKD) with staging and proteinuria was assessed and a prior kidney ultrasound (KU) was reviewed for all patients if available. CKD was present if eGFR<60 ml/min per 1.73m^2 for >3 months preceding LVAD implant and/or proteinuria> 20mg/dl on 2 or more urine analysis prior to implant and/or an abnormal KU with increased echogenicity or small size <9 cm. AKI was defined per KDIGO guidelines

Results: A total of 137 patients received LVAD. 112 males and 25 females with mean age of 59.2 years. Race: 64 Caucasians, 38 Africans, 30 Hispanics and 5 Asians. Incidence of AKI and need for RRT during hospitalization post LVAD implant were calculated in all patients and in sub-groups based on the presence of CKD, underlying CKD stage, proteinuria and KU findings. See table. 30 day and 1-year mortality rates post LVAD implant were 4.3% and 21.1% respectively. Out of the 27 patients requiring RRT, 9 (33%) were off RRT at 1 year. Compared to eGFR on day of LVAD implant, eGFR at 30 days post LVAD showed 57% patients with higher and 42% with lower eGFR. At 1 year, eGFR was higher in 32% and lower in 67% patients.

Conclusions: Incidence of AKI and need for RRT post LVAD implant are very high. Of all patients, 2 out of 3 patients had a lower eGFR at 1-year post implant and only 1 out of 3 patients requiring RRT recovered at 1-year post implant. Presence of CKD, advanced CKD stage and abnormal KU are statistically significant (P <0.05) risk factors of AKI post LVAD and/or need for RRT.

Incidence of AKI and need for RRT

	All Patients	No CKD	CKD Present	CKD stage 1-2	CKD stage 3-5	No Proteinuria	Proteinuria Present	Normal Kidney Ultrasound	Abnormal Kidney Ultrasound
Incidence of AKI	88/137=64%	18/42=43%	64/84=76%	15/25=60%	41/47=87%	49/85=58%	33/45=73%	63/103=61%	17/24=71%
		P value=0.028		P value=0.0081		P value=0.0778		P value=0.376	
Need for RRT	27/137=19.7%	4/42=9%	23/84=27%	6/25=24%	11/47=23%	15/85=18%	10/45=22%	16/103=15%	8/24=33%
		P value=0.0153		P value=0.775		P value=0.5288		P value=0.0448	

FR-PO040

The Influence of Left Ventricular Assist Device Implantation on Short-Term and Long-Term Renal Functions in End-Stage Heart Failure Patients

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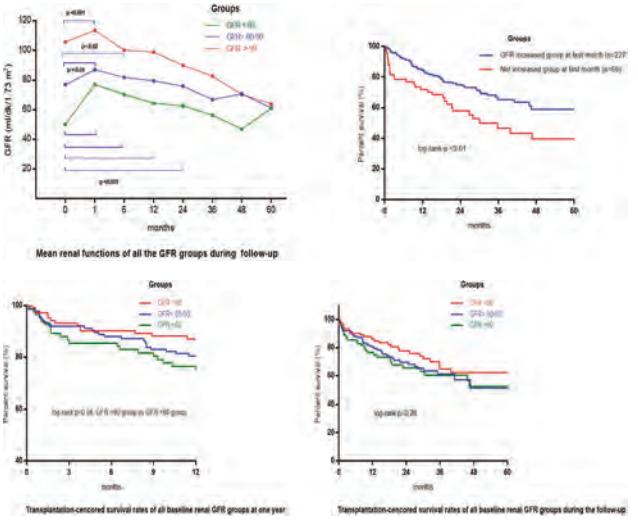
Background: Left Ventricular Assist Devices(LVAD) are used as an interventional treatment method for patients with decompensated heart failure(HF). The aim of this study is to retrospectively evaluate the short and long-term effects of LVAD implantation on renal function and survival in patients with end-stage HF.

Methods: 329 patients with LVAD were investigated. Basal and follow-up GFR(CKD-Epi) values were calculated retrospectively. Patients were divided into three groups according to baseline GFR; group 1(GFR<60,n=85), group 2(GFR 60-90,n=138) and group 3(GFR>90,n=106). SPSS 22.0 software was used for all statistical analyses.

Results: The mean age of the patients was 50.8±13.2, 86% was male, mean basal GFR was 77.6±25.7 ml/min, 29.5% patients had DM, 34.1% had HT. Mean follow-up time was 22.6±17.9(0,2-71,6) months. There was a significant increase in mean GFR values of all patients in the postop first month(p <0.01). In group 1, there was a significant increase in GFR at 1, 12, 24 months after implantation compared to baseline(p<0.001), but this increase was not significant at 36 months(p=0.08). One-year transplantation-censored survival was 81.9%, 70.3% for 2-year, 55.8% for 4 and 5-years. The survival rate at first year was 87.9% in group 3, 81.9% in group 2 and 76.2% in group 1. Patients with postoperation first month GFR increased(n=227); 2-year survival rate was 73%, 4-year was 58% and patients with not increased group(n=69), 2-year survival rate was 56% and 4-year was 38%(p <0.01).

Conclusions: In patients with LVAD, short- and long-term results are quite good in terms of renal function. Even though GFR was low before, we observed that there was a significant improvement in GFR after LVAD implantation and this improvement continued for the first 3 years.



FR-PO041

Safety and Efficacy of In-Series Continuous Renal Replacement Therapy in Patients on Venoarterial and Venovenous Extracorporeal Membrane Oxygenation

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Background: There is no standardization or consensus on performing continuous renal replacement therapy in patients on extracorporeal membrane oxygenation in the adult population. Given the limited access points available for patients on extracorporeal membrane oxygenation, it has been the practice at our institution to run CRRT in line with ECMO and then transition to a tunneled dialysis catheter at the time of ECMO decannulation.

Methods: We have performed over 600 ECMO cannulations, 268 of which have required dialysis for renal failure and metabolic clearance or primarily for ultrafiltration and volume removal. Of these 268, we performed CRRT in series on 265 of them using the Nxstage System One with both the Maquet Rotaflow as well as Cardiohelp ECMO systems. There are two separate connections used on the rotaflow ECMO circuit, and a single connection in the Cardiohelp system detailed in the images attached.

Results: In 265 patients, we successfully performed well over 1000 dialysis days of treatments in series with ECMO with virtually no complications. Efficacy was determined by adequate control of acid/base abnormalities as well as overall clearance of urea. Volume removal was typically determine by the overall hemodynamics of the patient, but there were no machine or circuit imitations regarding ultrafiltration.

Conclusions: We have found and demonstrated safety and efficacy of in series CRRT with ECMO in the adult population in a large cohort of patients.

FR-PO042

Use of Nesiritide in Total Artificial Heart to Rescue From Dialysis Dependence

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Introduction: It is well described in the literature that patients with total artificial heart implantation as a bridge to transplant have low atrial natiuretic peptide levels. Patients post ventriculectomy may lose the ability to produce urine in some cases as a consequence to having low ANP levels

Case Description: We present a 62yo man who underwent total artificial heart implantation. Post operatively, he developed severe shock and was placed on VA ECMO as well as CRRT. He was initially on niseritide post operatively but after a relatively quick decannulation and cessation of niseritide in 48 hours, he became anuric and required ongoing hemodialysis. After 10 days of hemodialysis, it was decided to restart niseritide as a trial to see if we could promote some urine production. On day 1, he made a liter of urine and by day 6 his creatinine had gone from 6 down to 1.3 and he no longer required dialysis. He was discharged home and received a heart transplant a month later. To date, he remains off dialysis with creatinine level of 1.0

Discussion: There are a few case reports detailing such a response to niseritide. This particular case was an extreme example of a patient going from an anuric state on hemodialysis with really no ability to discharge him from the hospital, to making ample urine and recovering renal function.

FR-PO043

The Role of Perioperative Renal Replacement Therapy in Heart Transplantation

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Background: Heart transplantation (HT) is the treatment of choice for patients with end-stage heart failure. Although several studies had reports about association with acute kidney injury (AKI) and HT, little is known about the impact of perioperative renal replacement therapy (RRT) on clinical outcomes of HT. We compared the clinical characteristics and outcome of patients according to RRT at the time of HT.

Methods: A total of 23 patients were underwent heart transplantation from January 1995 to May 2019 at Seoul St. Mary's hospital and Eunpyeong St. Mary's hospital. The most recent patient was excluded because of the short follow-up duration. We reviewed data including the cause of heart failure, cardiac function and renal function based on electronic medical records. The patients were divided as heart transplant recipients (HTRs) who underwent perioperative RRT (RRT group, n=9) and HTRs who did not received RRT (non-RRT group, n=14). Renal function was analyzed at baseline, 1 month, 3 months, 6 months and 12 months after HT.

Results: The most common cause of HT was dilated cardiomyopathy (n=11, 50%), then followed by ischemic cardiomyopathy (n=8, 36%). The LVEF before HT in the RRT group was significantly lower than that of the non-RRT group (LVEF 15.2 % vs 24.8%, P=0.014, respectively). In the RRT group, six patients (27.6%) underwent RRT before HT including with five patients of continuous renal replacement therapy (CRRT) and a patient of peritoneal dialysis. Finally, eight patients (36.4%) received RRT before and after HT, including five patients who initiated RRT prior to transplantation. After 1 month and 6 months post-transplantation, the renal function of RRT group were significantly worse than that of non-RRT patients (eGFR 40.95 vs 63.48 ml/min/1.73m^2, p=0.031, after 1 month; 39.40 vs 71.01 ml/min/1.73m^2, p=0.011, after 6 months). However, after 12 months post-transplantation, there was no significant difference of renal function between RRT group and non-RRT groups (eGFR 54.98 vs 68.30 ml/min/1.73m^2, p=0.294). All the patients in the RRT group were tolerated without dialysis after HT.

Conclusions: RRT at the perioperative period in the heart transplant recipients will be a good bridge therapy for recovery of renal function in the cases with a high risk of cardiorenal AKI with low LVEF.

FR-PO044

Impact of Intermittent Online Hemodiafiltration vs. High-Flux Hemodialysis on Markers of Inflammation and Fluid Status Assessed by Bioimpedance Analysis in Septic AKI Patients: A Randomized Trial

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Background: In sepsis, fluid assessment is a widely accepted challenge. Traditional approaches have limited utility. Bioimpedance (BI) has been used in CKD patients for dry weight assessment and studies have shown cardiovascular benefits when BI was utilised for fluid status assessement. We aimed at comparing impact of two modes of clearance i.e online HDF and high flux HD on fluid status and inflammation markers as assessed by BI analysis.

Methods: This pilot study was conducted in PGIMER, India between Sep 2017 to Sep 2018. Non critically ill septic AKI patients requiring dialysis were included. Patients in ICU and those requiring more than one ionotrope and/or mechanical ventilation were excluded. Alternate day RRT was provided till renal recovery using either HD or online HDF with target effluent rate of 25 ml/Kg/Hour. High flux polysulphone dialyzer was used in both the arms. BI was performed using single frequency bioimpedance analyser at prespecified intervals i.e before commencement of RRT, alternate day for 1st week, weekly till discharge and during 1st and 3rd monthly visits. All patients were followed for a period of 3 months from discharge. Plasma cytokine (IL6 a& TNF alpha) levels were assessed before and after one week of RRT initiation.

Results: 80 patients were randomized in each RRT arm. Baseline characteristics and sepsis parameters (qSOFA) were similar. Phase angle(PA), body cell mass(BCM), fat free mass(FFM) and Total body water(TBW) at baseline were comparable. No significant improvement in BCM and PA were noted at 1st month however significant improvement seen at 3rd month. Mean PA at initiation of RRT and at 1 month after discharge was 6.05 and 10.5 respectively (P= 0.628). Likewise, no difference in plasma cytokine clearance was noted between the arms. At 3 months, change in PA within the arms was significant (p<0.005), with no difference across the arms. BCM and PA correlated with qSOFA score and plasma cytokine levels throughout. Mean eGFR at day 30 was 37.28 ml/min and 30 day mortality was 12.5%.

Conclusions: Phase angle and body cell mass correlated with other traditional markers of sepsis. There was no differential impact of convective and diffusive clearance on PA and BCM when applied intermittently.

Funding: Government Support - Non-U.S.

FR-PO045

Mortality in Patients with Sepsis and Non-Sepsis AKI Requiring CRRT: A Retrospective Single-Center Experience

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Background: Short term and long term renal and survival outcomes of pts who undergo CRRT is highly variable in published literature. We have done a retrospective analysis on patients who have required CRRT at our institution over a 3 year period and have analyzed their survival outcomes based on their reason for initiation of CRRT.

Methods: Single center retrospective analysis on all patients who underwent CRRT between January 2015 and December 2017 were included for the analysis. Patients who expired within 12 hours after initiation of CRRT were excluded. All the patients underwent CRRT (CVVHDF) using the PrismaFlex machine. Patients were grouped under sepsis (sepsis group) vs other etiologies (non-sepsis group) based on the reason for initiation of CRRT. Renal and overall survival outcomes were analyzed between the 2 groups across multiple variables including comorbidities. Comparisons were made using T-test and correlations on primary outcomes based on need for CRRT was done using Pearson's test. Each variable was independently correlated with etiology of CRRT using logistic multiple regression analysis.

Results: Sepsis was the underlying etiology for initiating CRRT in 64% of pts. Cardiogenic shock was the most common cause for the rest. Patient groups were comparable across all variables analyzed. There was 51% mortality in the patients who needed CRRT in the study population. Mortality was 55% in patients in the sepsis group and 48% in non-sepsis group (p=0.4). Mean duration of CRRT in patients with sepsis who were alive at the end of 1 month was 7.1 (5.5) days and 3.2 (2.8) days in pts who were in non-sepsis group (p< 0.001).

Conclusions: Hemodynamically unstable patients who were initiated on CRRT irrespective of sepsis or non-sepsis etiology had a significantly high mortality at the end of 30 days. Patients initiated on CRRT due to sepsis required CRRT 3.9 days more than patients in the non-sepsis group. However randomized clinical trials are needed to compare the need and efficacy of CRRT on renal and survival outcomes in patients requiring continuous slow dialysis.

Mean duration of CRRT

Mean duration of CRRT (days)	Sepsis (n=83)	Non-sepsis (n=46)
Dead	3.4 (3.1)	4(2.9)
Alive	7.1(5.5)	3.2(2.8)

FR-PO046

Outcomes with Implementing CRRT in a Community Hospital

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Background: Acute kidney injury incidence in critically ill patients ranges from 20 to 50% and is associated with a high mortality rate. The CDC reports a 2.29% increase in acute kidney injuries treated with dialysis from 2000 to 2014. Renal replacement therapy is commonly required in patients with severe acute kidney injury. AKI was associated with higher hospitalization costs than myocardial infarction and gastrointestinal bleeding, and costs were comparable to those for stroke, pancreatitis, and pneumonia. In February 2016, continuous renal replacement therapy (CRRT) became available in our community hospital in Chesterfield, Missouri. We analyzed our initial usage of CRRT to evaluate outcomes and costs.

Methods: We conducted a retrospective study of adult patients initiated on CRRT at St. Luke's Hospital in Chesterfield, MO between February 2016 and May 2018. The data was collected via Cerner Powerchart. Data collection included baseline characteristics, hospitalization costs and disposition.

Results: Among 52 qualified patients, the average age was 66.75. 92% were Caucasian with a male predominance (62%). The prevalence of Hypertension was 75%, Anemia 70%, CKD 47%, Multiorgan Failure 79%, Mechanical Ventilation 73% and ECMO 12%. Our mean duration of CRRT days was 3.84 in 2016, 2.53 in 2017, and 2.2 in 2018. The average direct total cost of hospitalization was $82,858. Our mortality rate was 51%. Patient dispositions: home 21%, LTAC 11%, Rehab 9%, SNF 8%, Hospice 6% and Deceased 45%.

Conclusions: Our community hospital implementation of CRRT over a two year period had a mortality rate of 50.9%, which was better than mortality rates found in the literature of ~62%. CRRT in our community setting was associated with similar to better outcomes than reported in literature. We attribute this to a common CRRT EMR order set, limited settings in which CRRT is utilized (medical and surgical ICU) and initiation of CRRT limited to nephrology.

FR-PO047

Continuous Renal Replacement Therapy with AN69ST Membrane Reduces Plasma IL-8 in Sepsis Patients

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Background: Polyethylenimine-coated polyacrylonitrile (AN69ST) membrane has a hydrogel structure, which enables adsorption and thereby exhibits an increased capacity for cytokine removal in continuous renal replacement therapy (CRRT). This capability is expected to improve the outcomes of severe sepsis and septic shock. IL-8 is a chemokine with a molecular weight of 8000 MW and is known as a neutrophil chemotactic factor in sepsis.

Methods: APACHE II scores after ICU admission were evaluated for 23 sepsis patients. Patients with sepsis underwent CRRT using the AN69ST membrane. Plasma IL-8 was measured at the start of CRRT and 24 hours after the start of CRRT. At the start of CRRT, plasma IL-8 was measured pre AN69ST membrane and post. Patients were divided into two groups: survival group and death group.

Results: There were 12 cases in the survival group and 11 cases in the death group. The APACHE II score was 25.0 (20.5-30.0). Plasma IL-8 at the start of CRRT was 87.3 (28.1-182.8) pg/mL and was significantly reduced to 35.9 (19.6-62.0) pg/mL 24 hours after initiation of CRRT ($P < 0.01$). At the start of CRRT, plasma IL-8 was significantly reduced to 31.2 (13.1-65.9) pg/mL downstream of the AN69ST membrane ($P < 0.01$). Logistic analysis for death was associated with age (1.15, 95%CI: 1.02-1.49, $P = 0.02$), and plasma IL-8 reduction rates at 24 hours after CRRT initiation (0.89, 95%CI: 0.74-0.96, $P < 0.01$).

Conclusions: CRRT with the AN69ST membrane reduces plasma IL-8 in sepsis patients. Our results suggest that plasma IL-8 reduction rate 24 hours after initiation of CRRT is an independent contributing factor to death.

FR-PO048

Effects of a Novel CRRT Fluid Protocol on Electrolyte Stability

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Background: Continuous renal replacement therapy (CRRT) is the standard treatment for critically ill patients with acute kidney injury. During CRRT, electrolyte disturbance such as hypokalemia or hypophosphatemia frequently occurs unless dialysate and replacement solutions are adequately adjusted. Samsung Medical Center CRRT team developed a new protocol to prevent electrolyte disturbance by adjusting dialysate and replacement fluids depending on serial changes in serum potassium and phosphorus levels. We evaluated the impact of the new CRRT fluid protocol on electrolyte stability.

Methods: Adult patients who received CRRT for 3 days or more during the previous two years (2013 to 2014; pre-protocol group) and the last two years (2016 to 2017; protocol group) following the development of the fluid protocol were compared. Individual coefficient of variation (CV) and the number of abnormal measurements for electrolytes during CRRT were analyzed. The frequency of potassium, phosphorus, or magnesium replacement therapy was also compared. The Wilcoxon rank sum test was used for analysis.

Results: A total of 1456 patients were included. There were no significant differences in age, gender, and CRRT duration between the two groups. The CV of serum potassium was lower in the protocol group (pre-protocol group vs. protocol group, 0.113 [0.066 - 0.160] vs. 0.092 [0.052 - 0.132], $p<0.0001$). The CV of serum phosphorus was also lower in the protocol group (pre-protocol group vs. protocol group, 0.292 [0.173 - 0.411] vs. 0.248 [0.140 - 0.356], $p<0.0001$). The event rates of abnormal potassium levels (pre-protocol group vs. protocol group, 0.205 [0.199 - 0.211] vs. 0.083 [0.079 - 0.087], $p<0.0001$) and abnormal phosphorus levels (pre-protocol group vs. protocol group, 0.406 [0.398 - 0.415] vs. 0.280 [0.273 - 0.286], $p<0.0001$) were lower in the protocol group. The CV of serum magnesium, sodium, and ionized calcium was also lower in the protocol group. The frequency of potassium, phosphorus, and magnesium replacement was significantly reduced after application of our new CRRT fluid protocol ($p<0.001$).

Conclusions: Our novel CRRT fluid protocol significantly increased electrolyte stability and consequently prevented electrolyte disturbance during CRRT.

FR-PO049

Potential Adverse Hemodynamic Effects of Higher-Intensity Continuous Renal Replacement Therapy

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Background: Higher intensity continuous renal replacement therapy (CRRT) has been studied as a potential therapeutic advance for the treatment of severe acute kidney injury (AKI). We hypothesized that compared to standard intensity CRRT, higher intensity CRRT leads to greater hemodynamic instability due to the increased removal of small solutes.

Methods: Using detailed hemodynamic data recorded during the Acute Renal Failure Trial Network (ATN) trial, we assessed the incidence of hemodynamic instability in those randomized to higher (35 ml/kg/hour) versus lower intensity (20 ml/kg/hour) CRRT treatment. We used Poisson regression to model the count of hypotensive events, defined as a composite outcome including hypotension requiring an increase in vasopressor dose sufficient to increase the Sequential Organ Failure Assessment (SOFA) score, hypotension requiring cessation of RRT and hypotension requiring other interventions.

Results: Of 1124 individuals enrolled in the ATN Trial, 817 were managed with CRRT (N = 399 standard intensity and 418 higher intensity therapy). 204/817 (25%) patients experienced hypotension during the study period, with hypotensive events occurring most frequently on day 1 of treatment (Figure 1). Patients randomized to higher intensity CRRT had a 1.34-fold (95% CI, 1.02-1.76; p = 0.03) higher rate of hypotensive episodes than those randomized to standard intensity CRRT, using a Poisson model adjusted for age, gender and oliguria.

Conclusions: Higher intensity CRRT is associated with a significantly greater risk of hypotensive events compared to standard intensity CRRT.

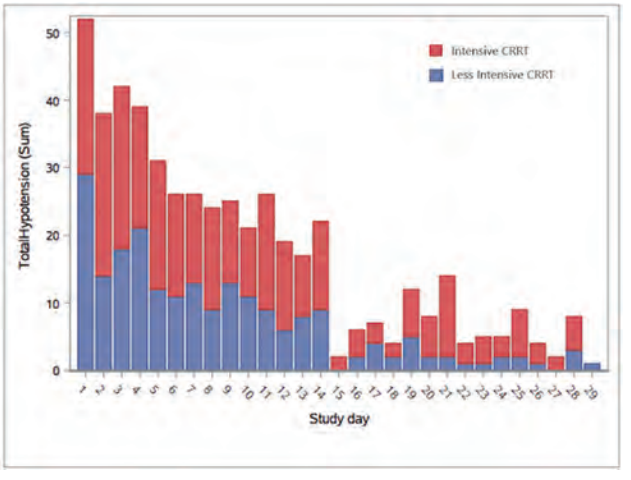

Figure 1: Temporal distribution of hypotensive events between higher intensity and standard intensity CRRT treatment groups in the ATN trial

FR-PO050

The Effect of Therapeutic Hypothermia on Urine Output After Cardio-pulmonary Resuscitation

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Background: Therapeutic temperature management (TTM) was strongly recommended by the 2015 International Lision Committee on Resuscitation as a component of post-resuscitation care. It has been known to be effective in improving the survival rate and neurologic functional outcome of patients after cardiac arrest. While commonly described cold diuresis, renal tubular function is diminished in the induction and maintenance phase of TTM, few studies have characterized cold-induced diuresis or rewarm anti-diuresis during TTM. In this study, we sought to characterize urine output changes during postcardiac arrest therapeutic hypothermia.

Methods: We conducted retrospective cohort study to determine urine output changes during TTM of the postcardiac arrest patients. We analyzed 104 patients who underwent all phase TTM for 3 years from Jan 1, 2012 to Dec 31, 2014. We calculated the hourly IV fluid input and urine output rates for each TTM phase. We fit a generalized linear mixed model with each TTM phase as a categorical variable to compare the urine output at each phase of analysis.

Results: Four-fifths of the patients suffered out-of-hospital arrest. Approximately 70% survived to hospital discharge. Urine output rate was highest at 249.1 ± 255.7 mL/hr in the hypothermia induction phase but lowest at 96.4 ± 65.3 mL/hr during rewarming phase even though total I/O showed the most positive balance during the rewarming phase.

Conclusions: We observed modest increases in urine output during induction phase of TTM. This has important implications for fluid management in patients undergoing therapeutic hypothermia. We will collabrate with the statistics team to analyze changes in continuous urine output and overall I / O data rather than average data of the larger number of patients.

Fluid input and output during therapeutic hypothermia

	Hypothermia induction	Hypothermia maintenance	Hypothermia rewarm	Post-rewarm	P-value
IV fluid input (mean, mlL/hour)	300.5 ± 189.1	206.7 ± 92.3	181.9 ± 77.5	165.0 ± 63.7	<0.001
Urine Output (mean, mL/hour)	249.1 ± 255.7	130.4 ± 97.5	96.4 ± 65.3	119.9 ± 72.7	<0.001
Output except urine output (mean, mL/hour)	15.8 ± 94.2	3.5 ± 8.6	3.5 ± 7.7	4.1 ± 8.5	0.193
Total Output (mean, mL/hour)	264.9 ± 259.9	133.9 ± 98.1	99.9 ± 67.1	124.0 ± 71.7	<0.001
Total I/O balance (mean, mL/hour)	35.7 ± 261.8	72.8 ± 92.2	82.9 ± 81.8	39.6 ± 73.2	0.081
MAP (mmHg)	107.0 ± 26.2	95.6 ± 11.6	89.8 ± 11.8	89.6 ± 12.7	<0.001

FR-PO051

A Study of Severe Tropical AKI Requiring Renal Replacement Therapy in a Tertiary Care Hospital in South India

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Background: The etiology of tropical AKI can be divided into infections, toxins, poisons and miscellaneous causes like heat stroke and obstetric AKI etc. Acute tubular injury occurring secondary to community acquired infections remains the commonest cause of tropical AKI. Through this study we attempt to study the causes and factors associated with morbidity and mortality of severe AKI requiring RRT in south India

Methods: This is a retrospective observational study done in Narayana Medical College, Nellore. Patients admitted in the ICU with AKI within a period of 3 years (2016-2018) were screened. Patients with non-tropical causes of AKI and AKI not requiring RRT were excluded from the study. The baseline eGFR was calculated according to the MDRD 75 formula. All patients eGFR was calculated 3 months after discharge to look for recovery or classify as CKD. Complete recovery was defined as improvement in the eGFR to more than the calculated baseline eGFR, at the end of 3 months after discharge. Descriptive analysis and univariate regression analysis were done to find factors associated with recovery, progression to CKD and death

Results: A total of 130 patients were studied with the mean age of presentation being 42.7 years and 62.3% (n=81) of the patients were males. The mean duration of stay in the hospital was 12.35 days. 8.4 % (n=11) patients received peritoneal dialysis and 91.5 % (n=119) received hemodialysis (HD). The most common etiology of AKI was acute gastroenteritis (40.7%) followed by snake bite (15.3%), hair dye poisoning (11.5%), malaria (9.2%), obstetric AKI (6.9%), dengue (5.3%), leptospirosis (3.8%), scrub typhus (3.0%), rhabdomyolysis (1.5%), paraquat poisoning (0.7%) and petroleum product consumption (0.7%). 96.9% patients presented with KDIGO stage 3 of AKI with average eGFR of 9.72. The average eGFR after 3 months of discharge was 40.93. Out of 130 patients 18.4% recovered completely, 14.6% (n=19) expired and 66.92% progressed to CKD. Snake bite, dengue fever, thrombocytopenia, presence of diabetes mellitus, hypertension and coronary artery disease were independently associated with progression towards to CKD. Paraquat poisoning and petroleum product ingestion were independently associated with death

Conclusions: Severe tropical AKI requiring RRT holds a poor prognosis with majority of patients progressing to CKD

FR-PO052

The Interactive Effects of Input and Output on Managing Fluid Balance in Patients with AKI Requiring Continuous Renal Replacement Therapy

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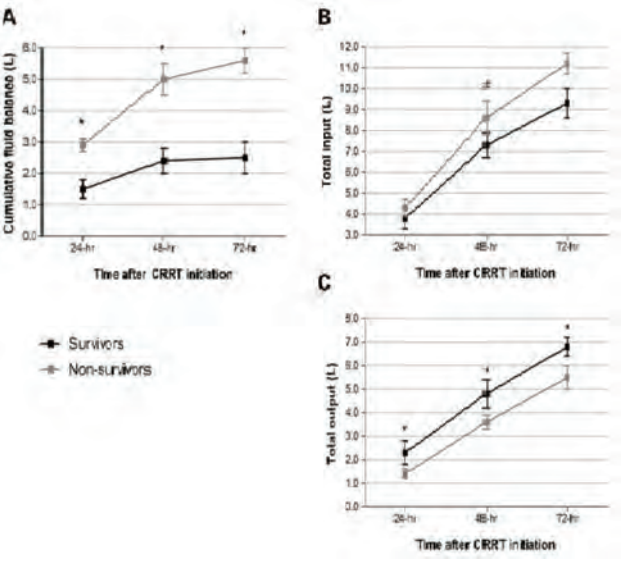
Background: Fluid balance is a key factor for better survival rate in patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT). However, appropriate regulation of input and output to achieve optimal fluid balance is not well elucidated yet. This study aimed to evaluate the effect of fluid components on mortality in patients with AKI requiring CRRT.

Methods: A total of 258 patients who were in the intensive care units of Ewha Womans University Hospital and with AKI required CRRT were enrolled (from 2016 to 2018). The amounts of fluid input and output were assessed by electronical medical charts with 24-hr and 72-hr intervals immediate after initiation of CRRT. The study endpoints were 7-, 14-, and 28-days all-cause mortality.

Results: The mean age of study subjects were 64.7 ± 15.8 years and 165 (64.0%) were male. The 28-day mortality was observed 118 (53.9%) cases during the follow-up. The amounts of cumulative fluid balance and cumulative input were higher and cumulative output was lower in non-survivors compared to survivors during 72-hr after CRRT initiation. A positive value of both 24-hr and 72-hr assessed cumulative fluid balance was associated with increased risk for 7-, 14-, and 28-days mortality. When the subjects were classified according to tertiles of total input or output, the increasing amount of cumulative fluid balance assessed with 24-hr and 72-hr was associated with the increased risk for mortality irrespective of tertiles of total input. However, increasing amount of cumulative fluid balance was not associated with the mortality risk according to tertiles of output.

Conclusions: The impact of CFB on mortality might be more dependent on cumulative output. The physicians need to decrease the CFB of CRRT patients as much as possible and consider increasing patient removal.

Funding: Government Support - Non-U.S.



FR-PO053

Fluid Balance After Continuous Renal Replacement Therapy Initiation Is a Predictor of Mortality

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Background: Higher cumulative fluid balance in critically ill patients was associated with hospital mortality. Inbody, impedance body fat analyzer, can measure body water, and segmental water values. In this study, we examined the fluid balance by time using bioimpedance analysis (inbody), and investigated the association of fluid balance with clinical outcomes in the CRRT patients.

Methods: Among the patients who started CRRT at multi-center from May 2017 to March 2018, Inbody was measured at D0, D1, D2, and D7. Fluid overload was defined when either of the following two conditions is met; total body water (TBW)/height^2 more than 13 L/m^2 or the change of body weight more than 5%. Reaching euvolemia was defined when either of the following two conditions is met; at day 7, TBW/height^2 was less than 13 L/m^2 or the change during 7 days was less than -2.1 L/m^2. The association with 60-days mortality was investigated.

Results: 72% patients showed fluid overload. These patients were younger and had lower urine amount during 2 hours before CRRT, and started CRRT later compared to those without fluid overload. The change of body weight and TBW/height^2 at CRRT initiation were much more than those without fluid overload. There is no statistical significance; however, the patients with fluid overload at CRRT initiation were shown to have a higher risk for mortality. Among the patients with fluid overload, 36 patients reached euvolemia at 7 days after CRRT initiation. Comparing with patients who failed to reach euvolemia, TBW/height^2 at each time point and delta value during 7 days were significantly lower in the patients who reached euvolemia. Failing to reach euvolemia was a risk factor of 60-day mortality. After adjusted for age, gender, BMI, charlson comorbidity index, APACHE II, and SOFA score, failing to reach euvolemia were closely correlated with 60-day mortality, doubling the risk of mortality.

Conclusions: Fluid overload at CRRT initiation, defined based on the change of body weight and TBW/height^2, was associated with the 60-day mortality. Based on the definition using TBW/height^2 measured by InBody®, patients who failed to reach euvolemic status within 7 days after CRRT initiation showed a higher mortality rate, compared to those who reached euvolemic status.

FR-PO054

The Use of Machine Learning to Predict the Renal Replacement Therapy-Free Survival in Patients Who Require Continuous Renal Replacement Therapy

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Background: AKI in critically ill patients is common and continuous renal replacement therapy (CRRT) is the preferential mode of renal replacement therapy patients who are hemodynamically unstable. Prior studies have yielded conflicting results for predictors of CRRT discontinuation and mortality. Therefore, we tested machine learning algorithms for predicting renal replacement therapy-free survival (RRTFS) in patients who required CRRT

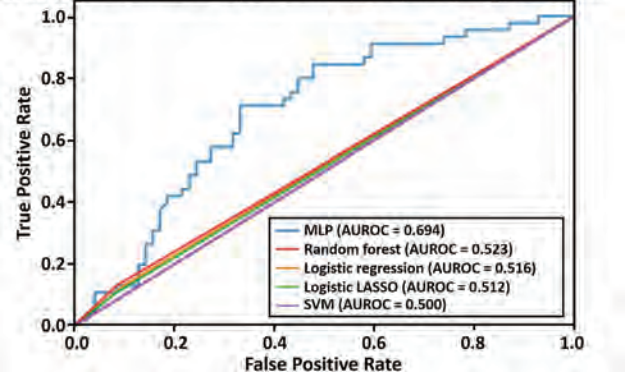
Methods: We used the Medical Information Mart for Intensive Care III database to identify patients ≥18 years old, and who had AKI requiring CRRT for ≥24 hours. ESRD patients were excluded. RRTFS was defined as patients who were discharged alive and did not require RRT 7 days prior to hospital discharge. Five machine learning algorithms: the multi-layer perceptron neural network (MLP), random forest (RF), support-vector machine (SVM), logistic least absolute shrinkage and selection operator (LASSO) and logistic regression were trained. We evaluated model performance using area under the receiver operating characteristic (AUROC). Features included laboratory values and patient features and were selected for inclusion based off of prior published data.

Results: Out of 566 patients, 179 (31.6%) patients had RRTFS. Patients who had RRTFS were younger (60 years vs. 65 years, p =0.006), and more likely to be white (73% vs. 67%, p=0.001). MLP had the highest AUROC, 0.694 (95% CI 0.586-0.791), followed by RF 0.523 (95% CI 0.469 – 0.583), logistic regression 0.516 (95% CI 0.457 – 0.575), logistic LASSO 0.512 (95% CI 0.456 – 0.571), and SVM 0.500 (95% CI0.500-0.500).

Conclusions: Compared to the standard logistic regression model, machine learning models, particularly the MLP method, had better performance at predicting RRTFS in patients started on CRRT using features prior to CRRT initiation.

Funding: NIDDK Support

Figure 1 The receiver operating characteristic curves and the area under the receiver operating characteristic (AUROC) for predicting the RRT-free survival after CRRT using machine learning algorithms the multi-layer perceptron neural network (MLP), random forest, support-vector machine (SVM), logistic least absolute shrinkage and selection operator (LASSO) and logistic regression



FR-PO055

Machine Learning Algorithm to Predict Mortality in Patients Undergoing Continuous Renal Replacement Therapy

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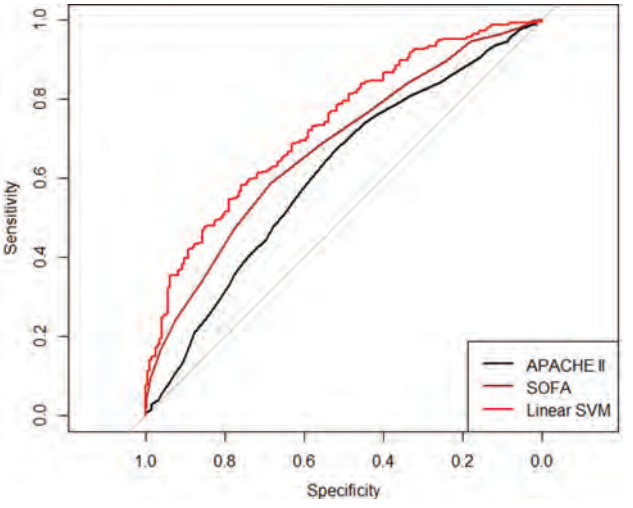
Background: Many scoring systems such as the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) have been used in predicting outcomes in patients admitted to the intensive care unit (ICU), but these original systems show poor predictability in the subset of patients undergoing continuous renal replacement therapy (CRRT). Accordingly, this study developed the machine learning model to improve the predictability in this subset.

Methods: 1,571 adult patients undergoing CRRT were reviewed from 2010 to 2016 years: 70% and 30% of patients were randomly assigned into training and testing set. The primary outcome was mortality in the ICU or hospital admission. To develop the machine learning model, several algorithms were used. (logistic regression, linear discriminant analysis, κ-nearest neighbors, support vector machine, multivariate adaptive regression spline, random forest, extreme gradient boosting and neural networks model) Area under the receiver operating characteristic curves (AUCs) from original scoring systems and the machine learning models were compared using the DeLong test.

Results: Among the machine learning models for ICU mortality, the linear support vector machine showed the highest AUC (0.733), and logistic regression and linear discriminant analysis were the second (0.730 in both). The AUCs of APACHE II and SOFA scores were 0.611 and 0.677, respectively. The support vector machine showed greater predictability than the original systems (*Ps*<0.05). The machine learning models for in-hospital mortality had a similar trend.

Conclusions: Machine learning models show a better performance in predicting mortality of CRRT patients than the original scoring systems. Accordingly, incorporating the machine learning-based mortality-prediction may be needed when starting CRRT.



FR-PO056

Inpatient Kidney Function Recovery Among Septic Shock Patients Who Initiated Hemodialysis in the Hospital

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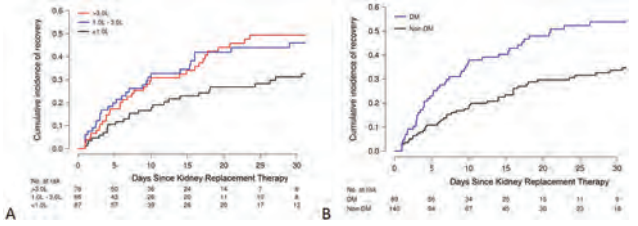
Background: Sepsis and septic shock are life-threatening causes of acute kidney injury (AKI) frequently seen and managed in the intensive care unit. Sepsis-associated AKI independently contributes to the mortality of sepsis. Understanding the potential predictors of recovery may aid in the prevention and management of sepsis-associated AKI. This study aimed to describe the clinical features of septic shock patients who required kidney replacement therapy and to examine the rate of kidney recovery and factors associated with recovery.

Methods: We conducted a retrospective cohort study using data from 229 adult septic shock patients who started in-hospital kidney replacement therapy at Mayo Clinic Rochester medical intensive care unit (MICU) from January 2006 to May 2018. Kidney recovery was defined as sufficient kidney function for stopping kidney replacement therapy prior to hospital discharge. Associations between clinical features and kidney recovery were analyzed with multivariable Fine and Gray regression accounting for death as a competing event.

Results: This cohort consisted of 229 patients with a median (IQR) age of 64 (52-74) years, 55% men, 75% Caucasian, 39% with diabetes, 16% with heart failure, APACHEIII of 105 (84-123) and SOFA of 12 (9-14). Patients received 1,567(524-4,108) mL intravenous fluid in the first 3 hours of resuscitation, 92% required vasopressor support and 83% required mechanical ventilation. The median MICU and hospital stays were 7(4-13) and 19 (10-31) days, respectively. Total kidney replacement duration was

7 (3.5-17.1) days. 41% patients discontinued dialysis prior to discharge and 38% died. Higher volume of fluid resuscitation in the first 3 hours (HR 1.07; CI 1.01-1.14; p = 0.03) and diabetes (HR 1.75; CI 1.17-2.61; p = 0.006) were associated with kidney recovery.

Conclusions: Among septic shock patients who initiated kidney replacement therapy in MICU, 41% recovered kidney function prior to hospital discharge. A higher initial fluid resuscitation volume was associated with recovery, and interestingly, patients with diabetes had a higher chance of recovery.



Kidney recovery stratified by **A** Fluid in 1st 3 hrs; **B** Diabetes

FR-PO057

Clinical Usefulness of Contrast-Enhanced Computed Tomography in Patients with Nonobstructive Acute Pyelonephritis-Associated AKI

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Background: The aim of this study is to investigate the clinical utility of contrast-enhanced computed tomography (CE-CT) in patient with non-obstrcutive acute pyelonephritis (APN).

Methods: From 2007 to 2013, 537 APN patients who underwent a CE-CT scan within 24 hours after hospital admission were enrolled. We divided these patients into greater (50% or greater involvment, n=143) and lesser (less than 50% involvement, n=394) groupsbased on renal parenchymal involvement in CE-CT examination. We compared clinical characteristics between two groups and analyzed the clinical value of CE-CT scan asa reliable marker for predicting clinical severity and disease course in patient with non-obstructive APN.

Results: The mean age of these patients was 55.2±17.9 years and 93.9% were women. The mean estimated glomerular filtration rate was 70.6±25.5 mL/min/1.73m^2. Compared with patients in lesser group, the patients in greater group had lower serum albumin levels (3.5 ± 0.5 vs 3.8± 0.6, p<0.01) and longer hosptal stay (10.1± 4.7 vs 8.8± 4.5, p<0.05). In addition, AKI (23.1% vs 11.4%, p<0.005) and bacteremia (36.4% vs 26.8%, p=0.02) were frequently developed in greater group, respectively. The overall incidence of AKI was 14.8%; of which 9.3%, 4.9% and 0.6% were classified as risk, injury and failure, respectively, according to RIFLE criteria. In a multivariate logistic regression analysis for predciting AKI, age, presence of diabetes mellitusand the presence of renal parenchymal involvement of greater than 50% in CE-CT were significant predictors of AKI.

Conclusions: The CE-CT scancould be useful to predict the clinical severity and course including AKI in non-obstructive APN patients with preserved renal function.

FR-PO058

Early High-Dose Thiamine Supplementation for Dialysis-Requiring Septic AKI: A Nationwide Inpatient Database Study

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Background: Recent studies have reported that high dose thiamine supplementation potentially reduces mortality and progression of acute kidney injury (AKI). However, these studies had small sample size and the impact of thiamine is still controversial. Therefore, we investigated the association of early thiamine supplementation with mortality and short-term non-recovery from renal replacement therapy (RRT), using a propensity-score inverse probability of treatment weighting in a cohort of septic dialysis-requiring acute kidney injury.

Methods: In this retrospective observational study using the Japanese nationwide Diagnosis Procedure Combination inpatient database during a period between April 2010 and March 2017, we identified patients with septic AKI who required continuous renal replacement therapy within 2 days of admission. Patients were divided into those who received high dose (100 mg or more) thiamine supplementation within 2 days of admission (thiamine group) and those who did not (control group). We performed propensity-score inverse probability of treatment weighting to adjust for measured confounders. Primary outcome was 28-day mortality and secondary outcome included in-hospital mortality and major adverse kidney events (MAKE), which was defined as death and RRT-dependence at discharge.

Results: A total of 9,927 patients (2809 in thiamine group and 7118 in control group) were eligible. The 28-day mortality was 31.5% (884/2809) in thiamine group and 30.5% (2168/7118) in control group. After adjustment for confounders (a total of 49 covariates, including comorbidities and co-interventions by inverse probability of treatment weighting, there were no significant differences in 28-day mortality between the two groups (adjusted risk difference, 0.2%; 95% adjusted confidence interval [CI], -2.0% to 2.3%). There were no significant differences in in-hospital mortality (adjusted risk difference, 0%; -2.4% to 2.3%), in MAKE (adjusted risk difference, -0.4%; -2.8% to 2.0%), nor in RRT dependence at discharge (adjusted risk difference, -0.4%; -1.5% to 0.7%).

Conclusions: Early high dose thiamine supplementation was not associated with decrease in mortality or MAKE, in patients with septic dialysis-requiring AKI.

FR-PO059

Short-Term Dietary Restriction for Prevention of Contrast-Induced AKI in Patients at Risk Undergoing Percutaneous Coronary Angiography: A Randomized Controlled Pilot Trial

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Background: Short-term dietary restriction (DR) has been proven effective to prevent acute organ damage from ischemic or toxic insults in animal models but clear evidence for effectiveness in humans is missing. Contrast media-induced acute kidney injury (CI-AKI) represents a leading cause of hospital-acquired acute kidney injury and both, ischemia and cytotoxic effects contribute to its pathophysiology. The objective of this trial was to determine the effectiveness of a 4-day dietary restriction for the prevention of CI-AKI in patients undergoing percutaneous coronary intervention (PCI).

Methods: Patients scheduled for PCI were randomized to receive either a formula diet containing 60% of calculated daily energy requirement (DR group, n=40) or ad-libitum food (control group, n=40) in the 4-day interval before PCI. Primary endpoint was the change of serum creatinine 48h after PCI (Δcreatinine). Further exploratory analyses included various renal function parameters, incidence of CI-AKI, and safety evaluation.

Results: With a median Δcreatinine post PCI of 0.03 (-0.15,0.14) mg/dL in the DR group vs. 0.09 (-0.03,0.22) mg/dL in the control group there was no difference in the primary endpoint (p=0.797). Subgroup analyses revealed a significant beneficial impact of DR in patients that received ≤100ml of contrast agent (DR n=26: Δcreatinine -0.03 (-0.20,0.08) mg/dL vs. control n=24: Δcreatinine 0.10 (-0.08,0.24) mg/dL; p=0.041) and in patients with ≤2 risk factors for CI-AKI (DR: n=27; Δcreatinine -0.01(-0.18,0.07) mg/dL vs. control n=31: Δcreatinine 0.09 (-0.03,0.16) mg/dl; p=0.030). Most patients in the experimental group reported a good physical condition (59.4%) with respect to DR and only 5.6% reported a profound sensation of hunger.

Conclusions: Although the primary endpoint was not met, the results of this trial suggest a beneficial impact of DR in low-to-moderate risk patients. Moreover, in this setting DR appears safe and feasible. Further investigations are needed in order to optimize DR protocols and to exploit its therapeutic potential.

Funding: Government Support - Non-U.S.

FR-PO060

Timing of Initiation of Renal Replacement Therapy in Critically Ill Patients with AKI: A Systematic Review and Meta-Analysis

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Background: Acute Kidney Injury is common in critically ill patients and has been associated with increased morbidity and mortality. The timing of initiation of renal replacement therapy(RRT) has been controversial in Acute Kidney Injury with no guidelines to help physicians make this decision. We aimed to analyze the prospective randomized clinical trials (RCTs) addressing this question and synthesize the evidence to guide clinical decision making for acutely ill patients who suffer from acute renal failure (ARF).

Methods: We performed a literature search using PubMed, Embase, clinicaltrials.gov, National Kidney Foundation and American Society of Nephrology meeting abstracts for 5 years. We identified RCTs involving critically ill patients and initiation strategies for renal replacement therapy. We then performed a meta-analysis, using Review Manager version 5.3. The outcome of interest included mortality, dialysis dependence, length of stay (LOS) in the hospital and in the intensive care unit (ICU).

Results: We identified 13 randomized control trials. The pooled estimates did not show a mortality difference between “early RRT” versus “Late RRT” with a RR of 1.01 (95% CI 0.99-1.10, p=0.88). We did not find a significant difference in the dialysis dependence at 90 days with a RR of 0.77 (95% CI 0.40-1.48, p=0.44). There was a decreased ICU LOS with a mean difference of 1.52 days (95% CI 0.6-2.44, p = 0.001) and hospital LOS with a mean difference of 6.26 days (95% CI 4.97-7.56, p<0.001) in the early RRT versus late RRT. Early RRT was associated with decreased hyperkalemia with RR of 0.57 (95% Cl 0.34-0.97, p=0.04) and respiratory complications with RR of 0.86 (95% CI 0.77 – 0.97, p=0.01).

Conclusions: Early initiation of RRT in ARF in critically ill patients does not seem to alter mortality or the dependence on long term dialysis. However, it does shorten the ICU and hospital LOS, and is associated with decreased hyperkalemia and respiratory complications.

FR-PO061

Incidence and Clinical Outcomes of Outpatient Hemodialysis for AKI in a Large Dialysis Organization

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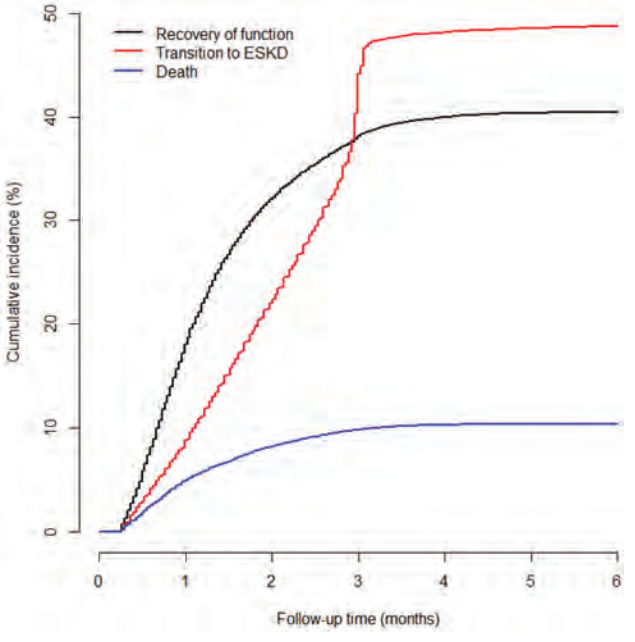
Background: Little is known about patients undergoing outpatient hemodialysis (OP HD) for acute kidney injury requiring dialysis (AKI-D) in the US. We examined the incidence and clinical outcomes of such patients in a large dialysis organization.

Methods: We examined patients initiating OP HD for AKI-D in a Fresenius Kidney Care (FKC) dialysis facility between May 1, 2017, and December 31, 2018; we excluded those discharged from FKC facilities within 7 days of initiation of OP HD. Patients were followed from initiation until the earliest of recovery of kidney function, transition to end-stage kidney disease (ESKD), death, or loss to follow-up (typically, transfer to another dialysis provider), with end of follow-up on March 31, 2019.

Results: The cohort comprised 15,606 patients with AKI-D; monthly counts increased from approximately 650 during mid-2017 to 850 during late 2018. Mean age was 63.6 ± 14.6 years and 41% were female. The vast majority (97%) were prescribed thrice-weekly HD, with mean session duration of 223 ± 26 minutes. During follow-up, 6028 (39%) recovered kidney function, 7104 (46%) transitioned to ESKD, and 1550 (10%) died. Cumulative incidence of these events is displayed. At 1 month after initiation of OP HD for AKI-D, 18% had recovered function, 9% had transitioned to ESKD, and 5% had died; at 3 months, percentages were 38%, 44%, and 10%. In 14,682 patients who reached any endpoint, mean (median) days between first and last OP HD sessions was 50 (45).

Conclusions: During 2017 and 2018, an increasing number of patients underwent OP HD for AKI-D in one large dialysis organization. Within 3 months after initiation of OP HD, approximately 40% of patients recovered enough kidney function to discontinue dialysis and 45% transitioned to ESKD.



FR-PO062

AKI in Renal Trauma Patients

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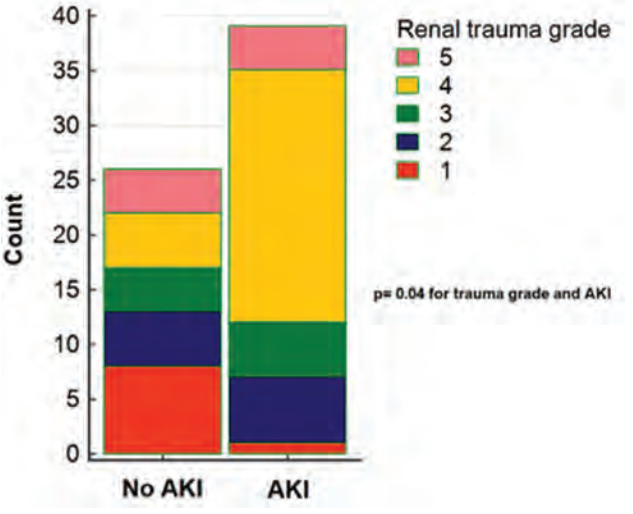
Background: Kidney is the most commonly injured organ of the genitourinary system during trauma; little is known about the relationship that this event has with the incidence of acute kidney injury (AKI). In this cohort we describe the associated risk factors for the development of AKI in patients with renal trauma (RT).

Methods: In a prospective cohort, we analyzed patients with RT during 2015 to 2019 at the Hospital Civil de Guadalajara. We describe their demographic, clinical characteristics and risk factors for development of AKI with univariate and multivariate analysis.

Results: During the study period 65 patients were analyzed, sixty (92.3%) were men, mechanism of trauma was firearm in 26 (40%), transfusion was indicated in 18 (25%), and 46 (70%) required emergent surgery, nephrology was consulted in 12 (18%) cases. AKI was present in 39 (60%) patients. Creatinine and urea at hospital admission was highest in AKI group (1.56 ± 0.91mg/dL vs. 0.85 ± 0.24mg/dL, p = <0.001 and 56 ± 41mmol/L vs 34 ± 20mmol/L, p = 0.005; respectively). Nephrectomy was not different between those with 14 (35.9%) and without AKI 5 (19.2) (p=0.15), left kidney is the most affected (57%), Intestine and liver were the most common organs affected (37, 32%, respectively), there were only 4 deads, all in AKI group. RT was considered high-grade (4-5) in 37 (56.9%), which has a significant association (p = 0.04) with the incidence of AKI in the univariate analysis, but this association was lost in the multivariate analysis. We built a model for prediction of AKI with the most relevant variables: firearm injury, shock, emergent surgery, high grade RT, and liver injury (p= 0.02, AUC 0.74).

Conclusions: RT occurs mainly in young men, 60% of cases are complicated with AKI, the most significant risk factor is high grade RT. It is necessary to confirm this association in other populations and larger sample sizes.



FR-PO063

Unresolving Renal Failure After Treatment of UTI

Sukit Raksasuk, Ratana Chawanasuntorapoj, Boonyarit Cheunsuchon. *Siriraj Hospital, Bangkok, Thailand.*

Introduction: Malakoplakia is a rare granulomatous inflammation. Most of the patients had the history of previous urinary tract infection and around one-third were immunocompromised hosts. The most common pathogen is *Escherichia Coli*. Pathogenesis postulated by inadequate lysosomal enzyme in the bactericidal process of macrophages resulting in the specific histological finding of Michaelis-Gutmann bodies. Due to lack of specific radiological morphology, histological diagnosis is mandatory.

Case Description: A 46-year-old alcoholic woman has presented with prolonged fever without any specific organ symptoms after UTI treatment. Laboratory showed Hb 9.6 g% WBC 11990 cell/uL N 92% Platelet 21,000 cell/uL, Cr 6.44 mg/dL, UA: RBC 100-200/HP, WBC 30-50/HP, few bacteria. Hemoculture was *E.Coli*. After 2 weeks of ATB, she still had septic shock and high creatinine with persistent pyuria. CT scan showed rt.kidney 11x7 cm. and lt.kidney 14x10.6 cm. with heterogeneous density without demarcation of cortex and medulla. Kidney pathology showed 2/3 glomeruli infiltrated with cells described in tubulointerstitial area into Bowman space. The interstitium showed massive infiltration of cells with granular eosinophilic cytoplasm (PAS+, PASD resistant). These cells were marked with CD68, a histiocytic marker. There were a few round basophilic lamellated bodies identified as Michaelis-Gutman bodies. AFB and GMS stains were negative. She was continuing antibiotic and surgical drainage of pus. Due to oliguric AKI with pulmonary edema, she was transiently done hemodialysis. Her clinical was improved and kidney function was recovery with 6 weeks of ATB.

Discussion: Un-resolving renal failure and persistent pyuria after proper antibiotic treatment of UTI in immunocompromised host (alcoholism) with *E.Coli* sepsis and enlarged heterogeneity kidney introduced the differential diagnosis of complication of UTI such as abscess, malakoplakia, and xanthogranulomatous pyelonephritis or otherwise kidney mass. Due to unexplained cause of kidney injury in our patient, kidney biopsy should be considered. Typical Michaelis-Gutmann bodies in cytoplasm of histiocyte were found. Treatment of renal malakoplakia is prolonged ATB and surgical drainage or resection depend on the severity of kidney damage. Therefore, promptly diagnosis and proper treatment are essential to keep the kidney tissues and function in renal malakoplakia.

FR-PO064

Postoperative AKI in Noncardiac Surgery and Long-Term Renal Outcome

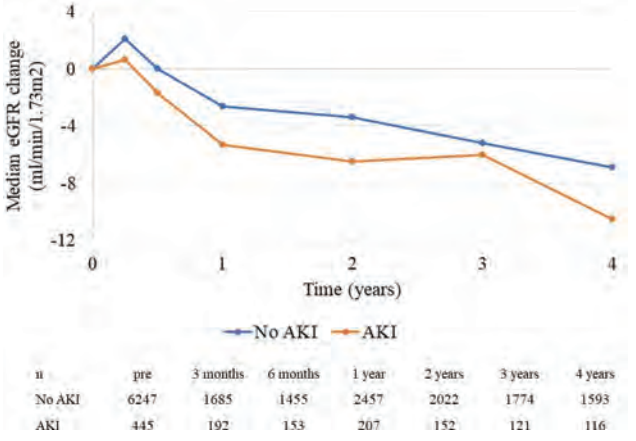
Miho Tagawa,[1] Masatoshi Nishimoto,[1] Maiko Kokubu,[3] Takayuki Hamano,[2] Masaru Matsui,[3] Masahiro Eriguchi,[1] Ken-ichi Samejima,[4] Yasuhiro Akai,[1] Kazuhiko Tsuruya.[1] *[1]Nara Medical University, Nara, Japan; [2]Osaka University Graduate School of Medicine, Suita, Japan; [3]Nara Prefecture General Medical Center, Nara, Japan; [4]First Department of Internal Medicine, Nara Medical University, Kashihara, Japan.*

Background: It is well known that acute kidney injury (AKI) is an independent predictor of long-term renal dysfunction. As a result, the KDIGO guideline recommended evaluation of renal function 3 months after AKI. However, there has been no data to support the recommendation.

Methods: This is a retrospective cohort study on adult patients who underwent non-cardiac surgery under general anesthesia from 2007 to 2011 at Nara Medical University. Exclusion criteria were pre-operative dialysis, urologic, obstetric surgery, or missing creatinine levels pre- and post-operatively. Postoperative AKI (within 1 week from surgery) was determined by the KDIGO criteria. Association between AKI and renal outcome (development of end-stage renal disease or doubling of creatinine) was analyzed using Cox regression and time course of renal function between those with and without AKI was compared by a mixed effects model.

Results: Among 6,692 patients, 445 developed AKI. During a median follow-up of 1.4 years, 493 renal outcomes were observed. Postoperative AKI was an independent predictor of the renal outcome (adjusted HR 3.18 [2.38-4.25]). Decline of estimated glomerular filtration rate (eGFR) was faster among those with AKI (p=0.001). The eGFR decline started at 6 months postoperatively. Even when analysis was limited to those with eGFR≥60 at baseline and 3 months, AKI was significantly associated with development of incident chronic kidney disease (eGFR<60) (HR 1.81 [1.09-3.03]).

Conclusions: AKI after non-cardiac surgery was an independent predictor of renal outcomes. Decline in renal function was more prominent more than 6 months after AKI. Those with preserved renal function at 3 months after AKI have higher risk of progressive renal dysfunction compared with those without AKI. Longer follow-up than KDIGO recommendation is necessary.



ti	pre	3 months	6 months	1 year	2 years	3 years	4 years
No AKI	6247	1685	1455	2457	2022	1774	1593
AKI	445	192	153	207	152	121	116

FR-PO065

Quality of Life and Long-Term Survival After Persistent AKI in Sepsis Patients

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Background: Acute kidney injury (AKI) is one of the most common complications among hospitalized patients. It is important to consider the duration of renal recovery in order to characterize the natural history of this complex condition and its effect on kidney health and long term functional status. We have determined the epidemiology of persistent AKI and its effect on long-term functional status and survival in sepsis patients.

Methods: In the prospective observational study of 245 sepsis patients, AKI types were adjudicated using KDIGO criteria and ADQI recommendations. In contrast to rapidly reversed AKI, persistent AKI is characterized by the persistence of KDIGO creatinine beyond 48 hours of the onset. The Zubrod Scale has been used to measure and compare the performance status of a patient's ambulatory nature and Zubrod score of 0 indicated that patients were fully active. One-year survival was compared using log-rank test and Cox proportional hazards model was fit to examine association between AKI type and long-term mortality.

Results: Two percent (6/245) had preexisting end-stage renal disease (ESRD) and 15% (36/245) had pre-existing chronic kidney disease (CKD). Sixty-two percent of the study population developed AKI. Only one third of AKI episodes rapidly reversed within 48 hours and had sustained renal recovery at discharge while the remaining 68% had persistent AKI. Prevalence of 1 year mortality in patients with persistent AKI (44%) was significantly higher than patients with rapidly reversed AKI (11%) and patients who did not develop AKI (9%). Percentage of those who were fully active and able to carry out activities without restrictions at 1 year of sepsis onset were only 8% among for patients with persistent AKI, whereas it was 29% for both patients who had rapidly reversed AKI and those who did not develop AKI. Hazard rate (HR) was about five-fold for persistent AKI group (HR 5.38, 95% confidence interval 2.74-11.80) compared to patients who did not develop AKI, while there was no evidence of significant difference in hazard ratios of those with rapidly reversed AKI and no AKI.

Conclusions: Among critically ill septic patients, persistent AKI is a significant risk factor for reduced functionality and increased long-term mortality.

Funding: Other NIH Support - NIH NIGMS

FR-PO066

Clinical Outcomes of Patients Admitted to the ICU with AKI in a Jordanian Tertiary Hospital

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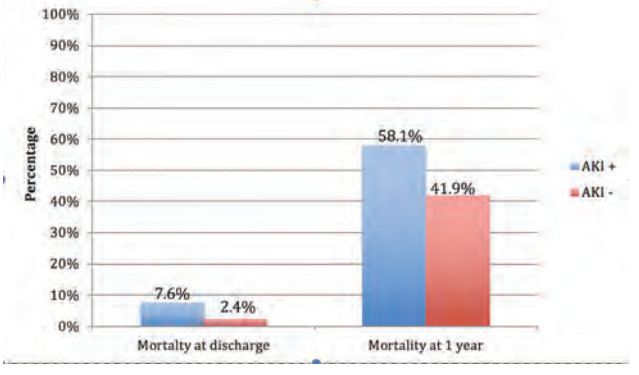
Background: Despite advances in medical technologies, therapeutic options, acute kidney injury (AKI) still a major contriputor of death in intesive care units (ICU) regardless of renal replacment therapy used to treat severe AKI

Methods: We retrospectively reviewed electronic patients records for all patients admitted to our ICU. We used acute kidney injury network (AKIN) classification to define and stage AKI, For continuous variables; mean, standard deviation, minimum and maximum were used, and for differences between normally distributed values we used unpaired t test. Percentages used for categorical variables. Pearson Chi- square test was used to test categorical variables. Univariate and multivariate regression analyses were performed to determine the independent predictors of AKI.

Results: We evaluated 1500 patient electronic records who were admitted to our ICU between 2014 -2015 with at least one year follow up. Using univariate analysis age was predictor of AKI, Serum albumin at admission was a strong predictor of AKI, mean serum albumin for the AKI group 30.1 g/l (SD 9.4), and 33.5 g/l (SD 8.9) for the non AKI group, P=0.001, also admission Hb predicted AKI, mean Hb for the AKI was 10.9 (SD 3.1) vs. 11.4 (SD 2.9), P=0.0004. The incidence of AKI was 35.6%, most of them were with stage1 AKI. Mean serum creatinine was 150.7 mmol/l (SD 147.7) for patients with AKI vs. 118.2 mmol/l (SD 135.3) for the other group, P=0.001. Out of the patients who developed AKI, 52.2% (82 patients) started on dialysis for different reasons (Hyperkalemia 15%, fluid overload 46.6%, combination of both 38.4%). of whom 22 patients continued dialysis as outpatients. Renal recovery (defined as return to baseline creatinine) at discharge was 17.2% (51 patients), Mortality by the time of discharge was 4.3% (62 patients).

Conclusions: AKI incidence in Jordan is comparable to worldwide incidence with significant effect on long term survival after discharge, correctable factors should be addressed to decrease incidence in the future.



FR-PO067

Three-Year Outcomes After AKI in a Prospective Cohort: Effects on CKD, Survival, and Cardiovascular Events

Isma Kazmi,[1] Rebecca A. Packington,[2] John Monaghan,[3] Nicholas M. Selby.[1,2] ARID study investigators *[1]Centre for Kidney Research and Innovation, University of Nottingham, Derby, United Kingdom; [2]Department of Renal Medicine, University Hospitals of Derby and Burton, Derby, United Kingdom; [3]Department of Clinical Biochemistry, University Hospitals of Derby and Burton, Derby, United Kingdom.*

Background: Acute Kidney Injury (AKI) is associated with adverse long-term outcomes. There is a need for prospective studies to identify those at highest risk and to improve understanding of the effect size across different outcomes and patient groups. Here we report three-year outcomes from a large prospective parallel group cohort study.

Methods: In a single UK centre, hospitalised patients who sustained AKI were recruited and matched 1:1 with controls (hospitalised patients without AKI) for age,

baseline eGFR stage and diabetes. Biochemical parameters including renal function and proteinuria were measured at 3 months, 1 year and 3 years following index hospitalisation. CKD progression was defined as ≥25% decline in eGFR with decline in eGFR stage, and a composite renal endpoint as a doubling of serum creatinine, eGFR<15ml/min or initiation of renal replacement therapy.

Results: 1125patients were recruited of whom 866 were successfully matched. There was no difference between AKI and control groups in age (71 yrs (IQR 14) vs. 71 yrs (IQR 13), p=0.7) or baseline eGFR (70.3±20ml/min vs 69.6±20ml/min, p=0.58). Two-thirds of AKI episodes were stage 1 with median duration 3 days (IQR 3). Mean eGFR was lower at all-time points in AKI group. At 3 years, eGFR was 61±20ml/min in AKI group versus 70±20ml/min in controls (p<0.001), and CKD progression occurred in 26.7% of the AKI group, as compared to 6.6% in the control group (p<0.001). The greatest odds of CKD progression rates were seen at three months, with progressive attenuation over time. Proteinuria was also more common and more severe in the AKI group at each time point. The composite renal endpoint occurred in 3% of AKI group versus 0.7% of controls (OR 4.4, 95% CI 1.3-15.7, p=0.012). Mortality rates were also significantly higher in the AKI group (15.7% versus 9.7%, p=0.008), as were heart failure events. Binary logistic regression demonstrated that presence of AKI and non-recovery by 90 days had independent associations with CKD progression.

Conclusions: AKI is associated with long term renal dysfunction, proteinuria, higher rates of ESKD and increased mortality. This is true even in a general hospitalised population in which a majority of patients had AKI stage 1. Non-recovery of renal function by 90 days is an important predictor of subsequent CKD.

Funding: Private Foundation Support

FR-PO068

Comparison of Outcomes of Early vs. Delayed Renal Replacement Therapy in Critically Ill Patients: A Meta-Analysis of Randomized Controlled Trials

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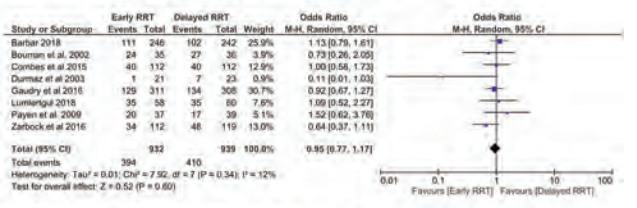
Background: The question of optimal timing of Renal Replacement Therapy (RRT) initiation in Acute Kidney Injury (AKI) remains unanswered. We collected data from available randomized controlled trials (RCTs) comparing the early RRT (ERRT) with delayed RRT (DRRT) and performed a meta-analysis of outcomes.

Methods: A literature search was done using electronic databases from Pubmed, Cochrane and Embase from inception until April 2019 for RCTs comparing early RRT with delayed RRT. The relevant data was extracted and statistical analysis was done using RevMan 5.3.

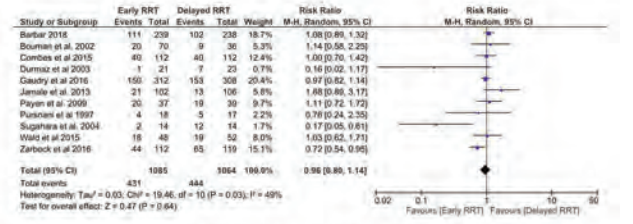
Results: A total of 12 RCTs comparing ERRT vs DRRT in patients older than 18 years were included, yielding 2267 patients of which 1143 were in early RRT group and 1124 were in delayed RRT group. Mortality at 30 days (8 RCT) [OR 0. 95, 95%CI (0. 77, 1. 17), p=0. 60, I^2 =12%] and 90 days (11 RCTs) [OR 0. 96, 95%CI (0. 80, 1. 14), p=0. 64, I^2 =49%] did not show any difference between the 2 groups. There was no significant difference between the 2 groups in dependence on RRT at 90 days (5 RCTs) [OR 0. 80, 95%CI (0. 52, 1. 23), p=0. 31, I^2 =0%] or incidence of arrythmias (5 RCTs) [OR 1. 01, 95%CI (0. 74, 1. 38), p=0. 94, I^2 =29%]. Patients in DRRT group had significantly lower rates of catheter related complications (5 RCTs) [OR 1.80, 95%CI (1.08, 3. 01), p=0. 02, I^2 =0%].

Conclusions: ERRT did not show any benefit in mortality, dependence on RRT or arrythmias. However, ERRT did show increased rates of catheter related complications. This suggests that DRRT may not offer benefits in mortality or renal outcomes, but may lead to less vascular access related complications. More data is needed to better elucidate the cause of less catheter related complications in the DRRT group.

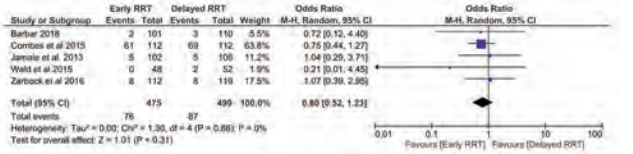
Forest plot comparing Mortality at 30 days in ERRT vs DRRT



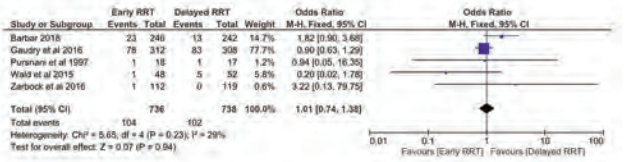
Forest plot comparing Mortality at 90 days in ERRT vs DRRT



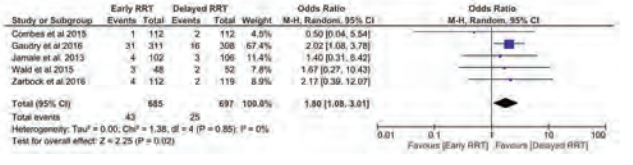
Forest plot comparing RRT dependence at 90 days in ERRT vs DRRT.



Forest plot comparing arrythmia in ERRT vs DRRT



Forest plot comparing incidence of catheter related complications in ERRT vs DRRT



FR-PO069

Myoglobin Clearance in Acute Rhabdomyolysis: Theralite and Theranova

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Background: Rhabdomyolysis is a cause of acute kidney injury (AKI) in a large number of cases where traumatic or non-traumatic causes induce muscle cell disruption. Although the rationale for a quick and effective removal of myoglobin in acute rhabdomyolysis would be strong and logical, the practical results obtained with extracorporeal therapies are modest. Theralite2100 and Theranova400 (Baxter) are new generation membranes designed to increase the removal of larger middle molecules like myoglobin. While Theralite takes advantage of the membrane high cut-off (HCO), the high retention onset (HRO) and internal filtration are the peculiarities of Theranova. We report a critically ill patient case to describe and compare two novel strategies for extracorporeal elimination of myoglobin in rhabdomyolysis-associated AKI with Theranova and Theralite continuous venovenous hemodialysis (CVVHD).

Methods: The treatment included 22 hours of HRO-CVVHD (Qb 200 ml/min, Qd 4000 ml/h, Quf 150 ml/h), followed by 6 hours of HCO-CVVHD (Qb200 ml/min, Qd 4000 ml/h, Quf 0 ml/h). Samples were collected from arterial, venous, and effluent lines in two timepoints: t1 (30 minutes after starting each session) and t2 (before changing hemodialyzer). Plasmatic clearance for myoglobin (K_m) was calculated at t1 and t2 to evaluate the efficiency in myoglobin removal. The intensity (K_m x hours of treatment) was estimated using the mean value of calculated K_m.

Results: During CVVHD the K_m in t1 and t2 were 37.99 and 16.88 ml/min and 66.05 and 46.68 ml/min, using HRO and HCO respectively (Fig 1). The blood volume cleared of myoglobin after the entire treatment was 36.22l and 20.29l for twenty-two hours of HRO-CRRT and six hours of HCO-CRRT, respectively (Fig 2).

Conclusions: Theralite-CVVHD guaranteed quick and efficient removal of myoglobin. Theranova-CVVHD might be considered as efficient for longer treatment and even more when an adjunctive convective mechanism is desirable, customizing the prescription on the basis of the patient clinical status.

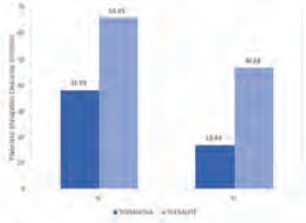

Fig 1 - Theranova (dark blue bars) and Theralite (light blue bars) efficiency in myoglobin removal.

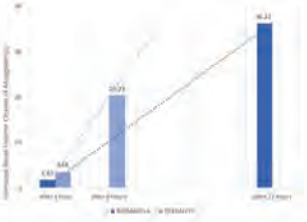

Fig 2 - Theranova (dark blue bars) and Theralite (light blue bars) intensity for myoglobin removal after 1 hour and at the end of each treatment.

FR-PO070

Standardization of a Furosemide Stress Test in the Pediatric Intensive Care Unit

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Background: Early prediction of patients (pt) at risk of severe acute kidney injury (sAKI) and need for renal replacement therapy (CRRT) in pediatric intensive care unit (PICU) is a desired strategy for early intervention. Functional assessment of tubular reserve with diuretic, furosemide stress test (FST), has been validated in acutely ill adults with promising prediction for sAKI and CRRT requirement but has not been evaluated in critically ill children.

Methods: Prospective observational study. All PICU admissions have an automated renal angina index (RAI) calculated 12h after admission. RAI positive pt (≥8, RAI+) are assessed with a urine NGAL to improve risk prediction. RAI+/NGAL+ (>150ng/mL, NGAL+) pt are assessed for the FST. The FST include a standard dose of furosemide (1mg/kg if naïve or 1.5mg/kg if exposed within 24h) and hourly urine output (OUP) monitoring 6 hours prior and after the dose administration. Increase in (iOUP) at 2 and 6h were calculated by subtracting the mean hourly UOP per kilogram using the same time length before and after administration. FST was considered positive (FST-responder) if the iOUP met a certain threshold at either one of the time marks.

Results: From 7/1/2018 to 2/28/2019, 1730 pt were admitted, 15 had a FST done, 3 (20%) of which required CRRT. Incremental hourly iOUP cutoff from 1 to 10ml/kg/h show an excellent AUC of 0.847 for CRRT prediction. 5ml/kg/h iOUP had the best Youden's J index at 0.58 but a 4ml/kg/h cutoff, with second best index, was deemed more clinically relevant due to a better specificity. At this cutoff, 2/4 (50%) FST non-responder vs 1/10 (10%) FST responder required CRRT (p=0.15) (see table).

Conclusions: FST seems applicable in acutely ill children to predict CRRT requirement but with an increase threshold of iUOP. However this prospective cohort will need more FST pt to make any definitive conclusions.

Funding: NIDDK Support

Table - CRRT need prediction with variable iOUP threshold after an FST

iOUP cutoff (ml/kg/h)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Youden
1	33%	100%	100%	86%	0.33
2	33%	92%	50%	85%	0.25
3	33%	83%	33%	83%	0.17
4	67%	83%	50%	91%	0.50
5	100%	58%	38%	100%	0.58
6	100%	50%	33%	100%	0.50
7	100%	50%	33%	100%	0.50

FR-PO071

Effect of CME on Nephrologists' Knowledge and Confidence Related to Management of Hepatorenal Syndrome Type 1

Amy Larkin,[1] Donald Blatherwick,[2] George Boutsalis,[2] Juan Carlos Q. Velez.[3] *[1]Medscape Education, Nicholasville, KY; [2]Medscape, Medford, NJ; [3]Ochsner Clinic Foundation, New Orleans, LA.*

Background: As emerging therapies hold promise to improve management of hepatorenal syndrome type 1 (HRS-1), clinicians are in need of improved understanding of these therapies and the current management of HRS. We sought to determine if online continuing medical education (CME) could improve the clinical knowledge and confidence of nephrologist in HRS.

Methods: The online CME activity consisted of a video-based roundtable discussion with leading faculty in the area of HRS-1. The educational effects were assessed using a repeated pairs pre-assessment/post-assessment study design, where individual participants served as his/her own control. For all questions combined, the chi-squared test assessed whether there was improvement in the proportion of participants who answered questions correctly at post as compared to pre. P values <.05 are statistically significant. Cramer's V was used to calculate the effect size (0.06-0.15 is a noticeable effect, 0.16-0.26 considerable, and >0.26 extensive). The activities launched between December 4, 2018 and data were collected through February 14, 2019.

Results: Improved knowledge and confidence was demonstrated among nephrologists: Overall, the effect of the education was considerable (V=.153, P<.001, N=115) 21% demonstrated improved identification of predictors of death or renal replacement therapy in patients with liver disease and stage 3 acute kidney injury (*P*<.05, V=.139) 21% demonstrated improved related to timing of dosage adjustment of terlipressin (*P*=.0727, V=.118) 36% demonstrated improved recognition of the goal of initial vasopressor therapy in HRS-1 (*P*<.001, V=.330) 38% reported increased confidence in their ability to appropriately diagnosis HRS-1 Persistent knowledge/competence gaps remain: 46% incorrectly identified predictors of death or renal replacement therapy in patients with liver disease and stage 3 acute kidney injury 30% did not understand timing of dosage adjustment of terlipressin 23% failed to recognize of the goal of initial vasopressor therapy in HRS-1

Conclusions: This study demonstrates the success of an online, video-based CME activity on improving knowledge and confidence of nephrologists related to current and emerging treatment for HRS-1. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Developed through an independent educational grant from Mallinckrodt

FR-PO072

Implementation of Clinical Decision Support for AKI: Mixed-Methods Evaluation of Healthcare Providers' Perceptions and Experiences

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Background: Clinical decision support (CDS) initiatives can be effective strategies for enhancing healthcare delivery and improving patient outcomes. However, such interventions for acute kidney injury (AKI) have reported variable effectiveness. Involvement of end-users in the development and implementation may help optimize accessibility and uptake of CDS systems for AKI. Evaluation of healthcare providers' experiences can inform the process.

Methods: We used a multi-phase approach involving healthcare providers, decision-makers, and implementation science experts to deploy an electronic CDS system on surgery units in Calgary, Alberta. The system consisted of: AKI stage alerts, Adverse medication alerts, AKI clinical summary display, and AKI order set. Implementation included usability testing of tools, co-development of tailored strategies for using the tools, education programs for staff, and audit and feedback of AKI quality indicators. The perceptions and experiences of end-users were evaluated using surveys and interviews; the latter were analyzed using a qualitative descriptive approach.

Results: During the initial 12 month post-implementation period, 318 AKI alerts and 48 adverse medication alerts were generated on the units. 104 clinical end-users have completed surveys and 10 have participated in interviews. Overall 88% of physicians and 98% of nursing staff stated it was important to improve AKI care on their hospital units. There was variable uptake of the specific tools with interview responses indicating that the AKI stage alerts and flagged medications were most valuable for the users. Interviews identified themes related to CDS implementation; 1) culture of increased AKI awareness, 2) credibility around communicating about AKI within an interdisciplinary team, 3) system barriers for recognition and timely AKI management.

Conclusions: End-user engagement in the process of developing and implementing CDS tools for AKI can enhance the acceptability and perceived value of tools by care providers outside the discipline of nephrology. Further strategies may be needed to address system-wide barriers to early management for AKI and to evaluate whether this degree of intensive end-user engagement enhances the impact of CDS interventions on processes of care and outcomes of AKI.

FR-PO073

Chloride-Liberal vs. Chloride-Restrictive Intravenous Fluids to Prevent Contrast-Induced AKI

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Background: For decades plasma expansion by intravenous volume application constituted the central cornerstone in the prevention of contrast-induced acute kidney injury (CI-AKI) for patients with preexisting chronic kidney disease (CKD). The recent AMACING study challenged this approach and showed no benefit by isotonic saline solution. Consequently, several institutions have stopped prophylactic fluid application in CKD. Based on considerations regarding the tubuloglomerular feedback there are increasing data from intensive care and emergency room settings showing that chloride restrictive fluids might be superior to isotonic sale in the prevention of AKI.

Methods: Based on the above mentioned data, we changed our standard operating procedure for the management of CKD patients with contrast media enhanced computed tomography scans from periprocedural infusion of chloride-liberal to chloride-restrictive solutions. The present work compares the CI-AKI rates of the first n=100 CKD patients with Ringerlactat (Cl^- concentration 112 mmol/l) or Jonosteril (Cl^- concentration 110 mmol/l) to a historical cohort of 100 subjects with 0.9% saline solution as periprocedural fluid application (1l before and 1l after contrast application in each group). CI-AKI was defined as a ≥ 0.3 mg/dl increase of serum creatinine concentration from baseline to day 2-3 after radio contrast application.

Results: CI-AKI occurred in 14 subjects of the overall cohort (7%). The incidence of CI-AKI was 44% lower in those subjects receiving chloride-restrictive fluids (n=5, incidence 5%) than in those ones with isotonic saline application (n=9, incidence 9%) without reaching statistical significance (chi-squared p=0.27). In multiple logistic regression analysis, use of diuretics turned out to be an important risk factor for a periprocedural decrease of eGFR (B=-7.5). In contrast, the effects of congestive heart failure, diabetes, and use of inhibitors of the renin angiotensin system were below significance level.

Conclusions: The present analysis compares the potency of chloride-liberal vs. chloride-restrictive fluid application in the prevention of CI-AKI for the first time. It reveals a trend to a lower incidence of CI-AKI using chloride-restrictive fluid application and may thereby constitute a rationale for a sufficiently powered randomized prospective trial.

FR-PO074

The Effect of 0.9% NaCl Compared with Plasma-Lyte on Biomarkers of Kidney Damage in Patients Undergoing Primary Uncemented Hip Replacement

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Background: Isotonic saline (0.9% NaCl) induces hyperchloremic acidosis and is suspected to increase risk of acute kidney injury (AKI) and the need for renal-replacement-therapy in critically ill patients. Novel biomarkers such as neutrophil gelatinase associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) may have potential as early indicators of AKI.

Methods: In a double-blinded, placebo-controlled study, 38 patients undergoing primary uncemented hip replacement surgery were randomized to 0,9% NaCl or Plasma-Lyte (PL). Infusion was given during surgery as 15 ml/kg the first hour and 5 ml/kg the following two hours. Urinary spot samples were collected upon admission and the day after surgery. As surgery initiated, urine was collected over the course of 4 hours. Hereafter another urine collection proceeded until the following morning. Urine was analyzed for concentrations of NGAL, KIM-1, Cl, Na, and albumin. Arterial and venous blood samples for measurements of pH and plasma electrolytes were collected as surgery was initiated, at the end of surgery and the following morning.

Results: NaCl induced an increase in P-Cl (111±2 mmol/L after NaCl and 108±3 after PL, p = 0.004) and a drop in pH (7.39±0.02 after NaCl and 7.43±0.03 after PL, p = 0.001). Urinary excretion of NGAL increased significantly in both groups (ΔNGAL: 5.5 [4.1;11.7] µg/mmol creatinine p=0.004 after NaCl vs. 5.5 [2.1;9.4] µg/mmol creatinine after PL, p<0.001). There was no difference in the increase between groups (p=0.839) Similarly, urinary excretion of KIM-1 also increased significantly in both groups (ΔKIM-1: NaCl 115.8 [74.1;156.2] ng/mmol creatinine, p<0.001 vs. PL 152.4 [120.1;307.9] ng/mmol creatinine, p<0.001). There was no difference in the increase between groups (p=0.064) eGFR decreased after surgery for both groups (116±26 ml/min after NaCl vs. 111±21 after PL, p =0.470), but no difference in response was found between groups (p=0.891).

Conclusions: A hyperchloremic acidosis was present in the group receiving isotonic saline. No difference was found between the groups in the excretion of u-NGAL and u-KIM-1 and responses to fluid infusion. However, both NGAL and KIM-1 were dramatically increased in both groups after surgery, despite no changes in eGFR. These results may indicate that surgery induced subclinical kidney damage.

Funding: Private Foundation Support

FR-PO075

Adherence to Best-Practice Guidelines in Severe AKI: A Multicenter Study

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Background: In the absence of a specific therapy for acute kidney injury(AKI), consensus guidelines recommend certain supportive measures to improve patient outcomes. We quantified adherence to those measures in patients with severe AKI.

Methods: We reviewed the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for recommended diagnostic and therapeutic interventions after AKI. We quantified rates of adherence to 22 best practice measures at 3 hospitals within 2 health systems for patients with severe AKI (KDIGO stage 2 or higher).

Results: We identified 13,039 patients with severe AKI. The cohort was 52% women, 34% black and had a mean age of 63 years. Baseline creatinine ranged between 0.9-1.0mg/dl. Of this cohort, 42% were surgical patients and 62% were in the ICU. Among the 22 best practice measures, we found a low rate of discontinuation of nephrotoxic agents. Of patients on ACEi/ARBS 24 hours before AKI, 51% continued to use this drug upto 24hours after AKI. Similarly, 38% of patients were continued on Aminoglycosides and 42% on NSAIDs. We also observed inadequate maintenance of some hemodynamic metrics (61% of patients still had a mean arterial pressure <65mmHg upto 24hours post AKI) in patients with severe AKI (**Figure**).

Conclusions: We noted a low rate of adherence to certain best practice measures, particularly a failure to discontinue nephrotoxic agents in patients with severe AKI. Future research could attempt to improve adherence to best practice guidelines using electronic health record-based alerts.

Funding: NIDDK Support

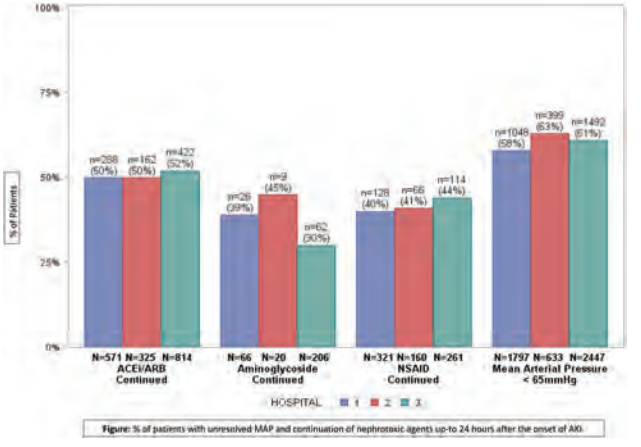

Figure: % of patients with unresolved MAP and continuation of nephrotoxic agents up-to 24 hours after the onset of AKI.

FR-PO076

A Simplified, Weight-Based CVVHDF-RCA Prescribing Algorithm That Works Regardless of Citrate Metabolism Is Verified in Ex Vivo Simulations

Balazs Szamosfalvi, Lenar T. Yessayan. *University of Michigan, Ann Arbor, MI.*

Background: In practice great variations in CRRT-RCA protocols exist with many centers avoiding RCA in severe shock and liver failure patients and most small intensive care units avoiding RCA completely. Complications of hypocalcemia and hypercalcemia, hypo- or hypernatremia, and metabolic- alkalosis or acidosis are reported with most protocols. We present a new, simplified approach to CRRT-RCA prescribing and demonstrate in an ex vivo simulation system devoid of citrate metabolism that all electrolyte complications due to CRRT-RCA can be avoided by careful protocol design.

Methods: We used a recently FDA-approved CRRT system to deliver CVVHDF-RCA in an ex vivo system (Figure 1). IV pumps delivered infusions of urea/creatinine, ACDA and calcium. PRBCs and plasma filled the CRRT circuit and reservoir to target Hct. We tested QB 20, 40, 60 ml/min and Hct 45, 33, 21. Commercial 140Na, 4K, 35HCO3, 1.5Mg, 0Ca, 5.5mMGlu CRRT fluid spiked to phosphate 4.2 mg/dL (1.5 mM) was used. A 136 mM CaCl2 solution was prepared in 0.9% saline. Dosing weight (DW) = round(weight)+10 if patient weight (Kg) <100 otherwise round (weight)+20 (kg). QB (ml/min) = 0.5 * DW. ACDA (ml/h) = 2.5* QB, QDialysate (ml/h) = 30 * QB, QReplacement (ml/h) = 10 * QB and QCa (ml/h) about 0.7 * QB and Qurea (ml/h) = QB. Blood and fluid samples were collected and analyzed by I-stat and in the laboratory.

Results: We had no CRRT alarms. The reservoir iCa was 1-1.3 mM. All circuit iCa was < 0.25 mM. Reservoir Na was 135-140 and other major electrolytes were at physiologic values. Single pass citrate removal was 80-90%. Effluent dose was 25-35 ml/kg/hour.

Conclusions: We showed that a simple approach to CVVHDF-RCA prescribing using commercially available equipment achieved target effluent dose, below 0.25 iCa in the CRRT circuit and normal iCa and systemic electrolytes in the patient without any concern for citrate metabolism.

Funding: Private Foundation Support, Clinical Revenue Support

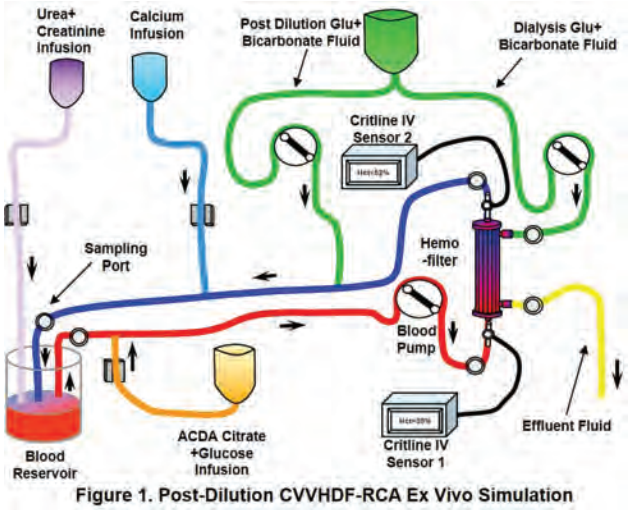

Figure 1. Post-Dilution CVVHDF-RCA Ex Vivo Simulation

FR-PO077

Design of the 1128-CL-0201 Study: A Phase 2 Proof of Concept, Double-Blind, Randomized, Placebo-Controlled Study of ASP1128 in Patients at Risk for AKI After Cardiac Surgery

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Background: AKI occurs in approximately 20-30% of cardiac surgery patients, but can reach 70% in high risk or biomarker-defined populations. No treatments are approved to treat AKI. ASP1128 is a peripherally active selective modulator of PPARd that improves metabolic and mitochondrial function. In AKI animal models, ASP1128 ameliorated renal function, histopathology, and injury biomarkers. It was shown to be safe in healthy human volunteers.

Methods: This is a randomized, double-blind, placebo-controlled, proof-of-concept, phase IIa study, to be conducted in patients at risk for AKI following cardiac surgery. A maximum of 220 patients will be randomized at ~40 sites in North America. The study comprises three parts: 1) pre-surgery screening period, 2) CABG and/or valve surgery, and 3) post-surgery double-blind treatment period with a 90-day follow-up. To evaluate patient outcomes, patients with moderate/severe risk of AKI (based on urinary biomarkers TIMP-2/IGFBP-7) at 2-6 hours post-surgery will be randomized, while the biomarker negative patients will be followed-up as an observational standard-of-care cohort. Randomized patients will receive ASP1128 (n=110) or matching placebo (n=110) IV once daily for 3 days. Primary end point: %patients developing AKI based on KDIGO serum creatinine criteria within 72 hours post-surgery. Secondary endpoints include AKI rate based upon all KDIGO criteria and within 7 days, as well as Major Adverse Kidney Events (defined as all-cause mortality, renal replacement therapy, and/or ≥ 25% sustained reduction in eGFR) within 30 and 90 days. **Ethics**: This study is approved by the relevant institutional review boards/independent ethics committees and conducted in accordance with the Declaration of Helsinki, guidelines of Good Clinical Practice, Code of Federal Regulations and all other applicable regulations. Trial registration: NCT03941483.

Results: Study results are expected in the second half of 2020.

Conclusions: The Aim of this study is to develop a short-term early intervention treatment for AKI to improve patient outcomes following cardiac surgery. The study will provide insight into the role of mitochondrial injury and fatty-acid oxygenation in propagating AKI.

Funding: Commercial Support - Astellas Pharma Inc.

FR-PO078

Clinical Efficacy of Intraoperative Hemodialysis During Open-Heart Surgery with CKD Stage G4 and G5

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Background: Severe acute kidney injury after cardiac surgery frequently requires renal replacement therapy (RRT) and moreover increases mortality rates and a prolonged length of hospital stay. Recently, we performed intraoperative hemodialysis (IHD) during open-heart surgery for the patients with chronic kidney disease (CKD) to prevent postoperative RRT. However, the clinical implication is unclear, therefore we investigated the efficacy of IHD.

Methods: This is a single-center cohort study with patients undergoing non-emergency cardiac surgeries between Jan, 2008 to Dec, 2018 in our hospital. The subjects were 61 patients classified as CKD G4 or G5 without chronic dialysis and post-transplant. Until Aug 2013, patients underwent surgery without IHD. Since Sep, 2013, patients were dialyzed intraoperatively. We evaluated the efficacy of IHD, comparing an IHD group (IHD) with a non IHD group (non-IHD).

Results: Comparing IHD and non-IHD, the patient number was 19 vs. 28 (CKD G4) and 9 vs. 5 (CKD G5). Preoperative eGFR (CKD G4) was 19.1±5.6 vs. 22.0±5.2 mL/min/1.73m^2 (p = 0.039), and 19.1±5.6 vs. 22.0±5.2 (CKD G5). Diabetic mellitus accounted for 35.7% vs. 42.4% (P=0.384), and operative duration 331±99 vs. 295±65 min (p = 0.16). Clinical characteristics and preoperative renal function were similar between two groups. Ninety-day mortality, hospital days, duration of postoperative intubation, renal function at discharge were not significantly different between IHD and non-IHD. Regarding CKD G4, the rate of RRT within 30 days after surgery (30-day RRT) was significant lower in IHD.

Conclusions: IHD had lower incidence of 30-day RRT than non-IHD in patients with CKD G4 prior to surgery.

Clinical features and Outcome between IHD group and non IHD group

patients undergoing cardiac surgery (N = 61)	IHD (N=28)	non IHD (N=33)	P value
Age, years	74.5±7.0	72.9±9.4	0.744
Male, n, %	17(60.7)	16(50.3)	0.339
Preoperative eGFR, G4 ml/min/1.73m2.	22.2±3.7	23.8±3.2	0.123
G5 ml/min/1.73m2	19.1±5.6	22.0±5.2	0.663
CKDG4, n.	19	28	0.116
90-day mortality, %.	7.1	3.0	0.482
30-day RRT G4, n, %	0 (0)	7 (25.0)	0.037
G5, n, %	5 (55.6)	3 (60.0)	0.933

FR-PO079

Glucose, Citrate, Calcium, Na, HCO3-, and Phosphate Mass Balance Studies in Ex Vivo Simulations of a Simplified CVVHDF-RCA Protocol That Works Regardless of Citrate Metabolism

Lenar T. Yessayan, Balazs Szamosfalvi. *University of Michigan, Ann Arbor, MI.*

Background: We developed a new, simplified approach to CRRT-RCA prescribing with commercially available equipment and CRRT fluids. It is important to study the mass balance of glucose (Glu), citrate, Ca, Na, HCO3-, and phosphate in an ex vivo system to demonstrate that a new CRRT protocol will approximate physiologic values of these solutes in the patient even in the absence of citrate metabolism.

Methods: We used a recently FDA-approved CRRT machine to deliver CVVHDF-RCA in an ex vivo system (Figure 1). IV pumps delivered infusions of urea/creatinine, ACDA and calcium. Human PRBCs and plasma filled the CRRT circuit and reservoir to target Hct. Commercial CRRT fluids were spiked to 139 or 140Na, 4K, 35HCO3, 1.5Mg, 0Ca, 1.5mMPhos with 0 or 5.5mMGlu. A 136 mM CaCl2 solution in D50.9% or 0.9% saline was paired with 0 or 5.5mM Glu CRRT fluid, respectively. We tested QB 20, 40, 60 ml/min and Hct 45, 33, 21. ACDA (ml/h) = 2.5* QB, QDialysate (ml/h) = 30 * QB, QReplacement (ml/h) = 10 * QB, QCa (ml/h) about 0.7 * QB and Qurea (ml/h) = QB. Blood and fluid samples were collected and analyzed by I-Stat point-of-care device and in the laboratory.

Results: The reservoir iCa was 1-1.3 mM. All circuit iCa was < 0.25 mM. Reservoir Na was 135-140 and other major electrolytes were around physiologic values. The reservoir glucose remained in the 70-150 mg/dL range with either CRRT fluid/Ca-infusion pair and glucose dialysance was 80-90% of CRRT circuit plasma flow. Single pass citrate removal on the filter was 80-90% and clinically significant citrate accumulation in the reservoir was avoided.

Conclusions: Ex vivo simulation suggests that the new CVVHDF-RCA protocol will approximate normal systemic solute levels without citrate metabolism. I-stat bedside glucose dialysance may be used in a clinical study to indirectly monitor plasma citrate- and Ca-clearance.

Funding: Private Foundation Support, Clinical Revenue Support

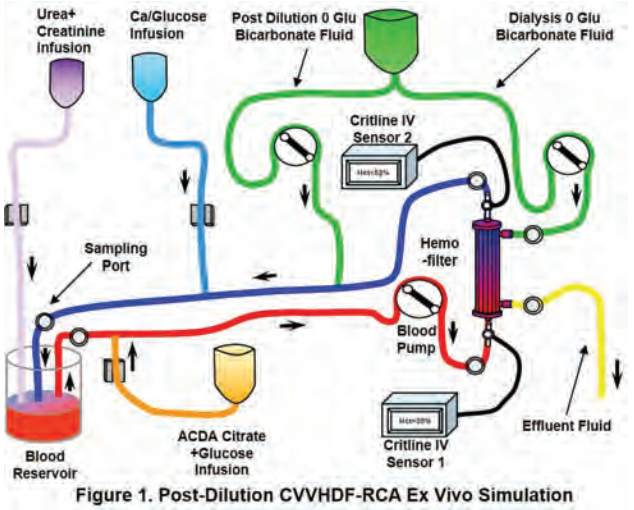

Figure 1. Post-Dilution CVVHDF-RCA Ex Vivo Simulation

FR-PO080

Crossover Study Comparing Bioavailability of Captisol-Enabled (CE) Iohexol Injection with Reference Iohexol Injection in Healthy Subjects

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Background: Iodinated contrast agents may place patients with certain risk factors at an increased risk for acute kidney injury during cardiac imaging procedures.[1] Studies in renally-compromised mice and rats demonstrated that the addition of sulfobutylether β-cyclodextrin (Captisol®) to a clinically administered dose of Iohexol significantly reduced renal pathology scores, and increased survival in rats from 50% to 88%.[2] A Phase 1, single-center, randomized, double-blind, two-period crossover study was conducted to determine relative bioavailability of CE-Iohexol and a reference Iohexol injection (OMNIPAQUE™) after intravenous (IV) administration in healthy adults.

Methods: A total of 24 subjects were enrolled in the study as 2 groups of 12 subjects in 2 treatment periods. Subjects received each of the following treatments as a single IV dose (80 mL infused over 20 seconds): CE-Iohexol -755 mg/mL iohexol (350 mgI/mL)/50 mg CAPTISOL/mL; OMNIPAQUE - 755 mg/mL iohexol (350 mgI/mL). Serial blood samples were collected for Iohexol plasma concentration determination, and safety was assessed during the 48 hours following each dose. Subjects were discharged on day 3.

Results: 22 subjects completed the study; 2 subjects were withdrawn for technical reasons. Bioequivalence was demonstrated by calculation of geometric mean ratios (GMR) between CE-Iohexol and OMNIPAQUE for key pharmacokinetic parameters. GMR of the area under the concentration-time curve for time 0-infinity ($AUC_{0\text{-}inf}$) was 1.00 (90% confidence interval [CI], 0.98-1.02). GMR of the maximum concentration (C_{max}) was 1.00 (90% CI, 0.95-1.06). Other PK parameters, including time to maximum observed concentration (T_{max}), half-life ($t_{½}$) and elimination rate constant (K_{el}) were similar between treatments. All treatment-emergent adverse events during the study were mild to moderate in severity. No subject had a serious adverse event or discontinued from the study due to an adverse event.

Conclusions: The observed PK profile supports clinical development of CE-Iohexol as a next-generation contrast agent with a reduced risk of renal toxicity (NCT03869983).

[1] McCullough PA, et al. *J Am College of Cardiology* 2016;68:1465-73 [2] Rowe ES, et al. *J Neuroimaging.* 2016;26:511-518.

Funding: Commercial Support - Ligand Pharmaceuticals Incorporated

FR-PO081

Membrane Therapeutic Plasma Exchange (mTPE) with Citrate Regional Anticoagulation: A Single-Center Experience

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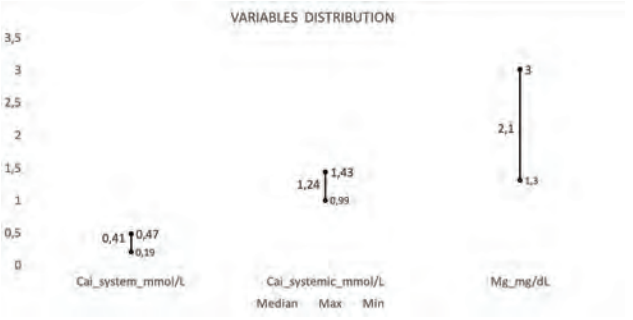
Background: Membrane Therapeutic Plasma Exchange (mTPE) is an extracorporeal blood therapy that uses convection through pressure applied upon a semi permeable membrane to remove from plasma elements such as antibodies, cytokines, lipids and viral particles. Usually, the anti coagulation method utilized is systemic unfractionated heparin (UFH). Coagulation components loss in mTPE in association with UFH enhances bleeding risk. Considering that risk, our center proposed the use of regional citrate anticoagulation as a safe option in patients undergoing mTPE. Below, we describe 12 sequential sessions performed using our citrate protocol.

Methods: mTPe was performed on the PrismaFlex with TPE 2000 membrane. We used 4% Sodium Citrate with a target concentration of 3mmol/L of treated blood. We delivered 10% Calcium gluconate to the patient at 3+-0.1mmol/L of effluent flow. A Solution 5% Albumin plus 10% Magnesium sulfate (1mmol/L) was used as replacement fluid. Within 2 hours of treatment we measured ionized calcium in the extracorporeal circuit, systemic ionized calcium and systemic magnesium.

Results: No changes were observed on serum concentrations of magnesium in all treatments. Median systemic ionized calcium concentration was 1,24mmol/L. No symptoms of hypocalcemia, arrhythmias or bleeding were reported. Median ionized calcium in the extracorporeal circuit was 0,36mmol/L. No sessions were interrupted due to system clotting. The median time of therapies was 170 minutes with similar costs to our center.

Conclusions: mTPE using regional citrate anticoagulation can be used by the nephrologist to provide a safe and cost effective option of plasma exchange. This modality of anticoagulation is an option for patients at risk or with active bleeding.

Funding: Private Foundation Support



Variables of distribution : ionized calcium in the extracorporeal circuit, systemic ionized calcium and systemic magnesium.

FR-PO082

Effect of Remote Ischemic Preconditioning to Prevent AKI in CKD Patients Undergoing Contrast-Enhanced Computed Tomography: A Randomized Controlled Trial

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Background: Chronic kidney disease (CKD) is an important risk factor of contrast-induced acute kidney injury (CI-AKI). Remote ischemic preconditioning (RIPC); transient ischemia followed by reperfusion of the extremity may subsequently protect against ischemia-induced injury in the other organs. Whether RIPC can prevent CI-AKI after contrast-enhanced computed tomography (CT) is not known.

Methods: We conducted a randomized controlled trial in CKD patients, glomerular infiltration rate (GFR) less than 60 mL/min/1.73m^2, whom underwent contrast-enhanced CT during July 2018 to January 2019 at Phramongkutklao Hospital. All patients received standard protocol to prevent CI-AKI. Patients were allocated in 1:1 ratio to receive RIPC or not (control) by using block of 4 randomization. RIPC consistsof 4 cycles of 5 minutes of cuff to induce arm ischemia with 5 minutes of reperfusionbefore undergoing contrast-enhanced CT. All patients were closely monitored for possible complications.

Results: A total of 70 CKD patients (35 in the RIPC group, 35 in the control group) were enrolled. Mean age was 73.6±9.9 years and baseline GFR was 45.3±12.2 mL/min/1.73m^2. Forty-two (60%) patients were male. The incidence of CI-AKI is lower in the RIPCgroup than the control group (8.57% vs 0%), p-value=0.07. Changes of serum creatinine from baseline to 48-hour and from 24-hour to 48-hour were better in the RIPC group than the control group; -0.09 ±0.16 vs -0.02±0.20 mg/dL, p-value=0.13 and 0.00±0.12 vs 0.08±0.17 mg/dL, p-value = 0.03, respectively. Change of GFR from 24-hour to 48-hour was also better in the RIPC group than the control group; -0.0±5.4 vs -2.4±6.3 mL/min/1.73m^2. In the RIPC group, 25 (71.4%) patients had local numbness. Eighteen (51.4%) patients experienced armpain, mean pain score 3.1±1.2 out of 10, which immediately resolved after the procedure. No serious complication was observed.

Conclusions: RIPC may decrease the risk of CI-AKI in CKD patient undergoing contrast-enhanced CT, without any serious side effect.

FR-PO083

Mind the Gap: Achieving Less Than Prescribed Net Ultrafiltration with CRRT Associates with Mortality

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Background: Management of fluid overload (FO) via ultrafiltration (UF) is an important goal of continuous renal replacement therapy (CRRT). Clinicians carefully assess volume status, recommending individualized UF goals. Unfortunately, UF goals are not always met, which may worsen FO. As FO is associated with poor outcomes, we hypothesize that failing to achieve UF goals will also be detrimental.

Methods: Prospective cohort study of 656 ICU adult patients requiring CRRT admitted to the University of Kentucky Hospital from 08/2017 to 04/2019. We excluded

anyone missing UF data or with a mean net UF goal less than 500 mL/day. We calculated the mean percentage of achieved net UF from the prescribed net UF and the net fluid balance throughout the time on CRRT (UF_{net} goal achieved). Using Cox regression models adjusting for relevant confounders, we evaluated the association between UF_{net} goal achieved and hospital mortality.

Results: Mean age (SD) was 63.6 (25.6) years, 60% were male and 91% white. 536 (81.7%) patients required CRRT for AKI with the remainder being ESKD. Median [IQR] Charlson score was 5 [2-7] and SOFA at CRRT initiation was 13 [11-16]. Median time on CRRT was 5 [3-9] days. Hospital mortality rate was 59.5%. Time from ICU admission to CRRT initiation and prescribed net UF were not different between survivors and non-survivors. However, total fluid removal rate (ml/kg/day) was higher in survivors vs non-survivors (median 27 vs 21, p<0.001) while FO% per CRRT day was lower in survivors vs non-survivors (median -0.5% vs 0.6%, p<0.001). UF_{net} goal achieved was higher in survivors vs non-survivors (median, IQR: 44%, -40 to 83 vs 4.3%, -115 to 54, p<0.001). In fully adjusted models, every unit decrease in UF_{net} goal achieved was independently associated with hospital mortality (HR, 95% CI: 1.003, 1.001-1.006, p=0.018).

Conclusions: Our study examined UF_{net} goal achievement, a CRRT deliverable that requires closer attention. We found that UF_{net} goal underachievement was independently associated with higher mortality. Our study reinforces the value of optimizing fluid management with CRRT. Future work should focus on closing this net UF prescribed vs achieved gap by developing better tools for assessing UF goals and monitoring patient response to fluid removal.

FR-PO084

Fluid Overload, AKI, and Mortality in Influenza Patients: Our Two-Year Experience

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Background: Influenza virus, especially A(H1N1) has been associated with high mortality in critically ill patients who develop Acute Distress Respiratory Sydrome (ADRS). ARDS is considered as a septic condition and one of the cornerstones for its treatment is an adequate fluid resuscitation. Fluid overload (FO) is now a recognized as a cause of acute kidney injury (AKI), and its association with mortality in critically ill patients has been well documented. The impact of FO in mortality of ARDS influenza patients has not been well described

Methods: This is a retrospective 2-year study of patients admitted to the ICU with ARDS and suspicion of influenza infection during the Influenza seasons 2016-2017 and 2017-2018. Demographic, laboratory, and clinical data were obtained. We calculated FO as the algebraic sum of the inputs and outputs during the ICU stay divided by the patient's weight at admission and expressed as a %. We divided patients in grouo: A) < 10% FO and B) > 10% FO and compared mortality and AKI incidence among both groups

Results: 40 records met the inclusion criteria. Mean age in our cohort was 43.5yrs, 60% were male. Influenza was confirmed in 55% of the patients; 22.7% with A(H1N1). Mortality among A(H1N1) patients was 100%. AKI was diagnosed in 24 patients (60%) with 12.5%, 7.5% and 40% of KDIGO stages 1-3 respectively. RRT was initiated in 13 (32%) of AKI patients. Among groups A and B AKI was diagnosed in 52% and 73% of patients respectively p=0.182. ICU mortality was 55% among the whole cohort. Median fluid balance (FB) among survivors was +3,813ml (2,131-7,284) and among non-survivors +8,370ml (4,477-16,502) p=0.008. Mortality in group A was 40% and in group B 80% p=0.014. The OR for AKI development in group B was 2.53 (CI 95% 0.634-10.166) p=0.182, and for mortality was 6.0, (CI 95% 1.34-26.8), p= 0.014

Conclusions: In our two-year retrospective study of ARDS patients, FO >10% was significantly associated with increasing incidence of AKI and mortality. Ah1N1 diagnosis involved 100% mortality. With these findings, we can strongly recommend a conservative fluid strategy in the treatment of this kind of patients. And we can advise to implement strategies to maintain the fluid gain in less than 10% of the initial patient's weight. More studies with bigger cohorts are needed to clearly demonstrate these associations

FR-PO085

Laparoscopic Gastrectomy Lowers Postoperative AKI in Stomach Cancer Patients: A Propensity Score Analysis

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Background: Acute kidney injury (AKI) is a common and morbid complication in the surgical patient, but there are insufficient reports on AKI after abdominal surgery. Thus, we compared the renal outcomes, including AKI, of stomach cancer patients who underwent laparoscopic surgery (LS) and open surgery (OS).

Methods: We conducted a retrospective cohort study of 6603 patients who underwent stomach cancer surgery between 2003 and 2017. Postoperative AKI was determined according to the serum creatinine criteria of the Kidney Disease: Improving Global Outcomes classification.

Results: Of the 6603 patients, 5190 patients (78.6%) underwent LS and 1413 patients (21.4%) underwent OS. The incidence of postoperative AKI in LS group was significantly lower than in OS group (2.9% vs. 7.8%, respectively, p < 0.001). After matching propensity scores (1:1), 714 patients were included in each group. Cox proportional hazard models adjusted for age, sex, smoking, BMI, American Society of Anesthesiologists (ASA) score, tumor size, preoperative hemoglobin (Hb), and cancer stage in entire cohort revealed that the LS group had lower incidence of postoperative AKI than the OS group (HR, 0.545; 95% CI, 0.400-0.742; p < 0.001, respectively). The effects were also consistent in matched cohort (HR, 0.527; 95% CI, 0.333-0.834; p=0.006). But, there was no significant difference in the risk of 1 year survival after surgery between groups in matched cohort (HR, 0.836; 95% CI, 0.413-1.697; p=0.618). Its reduction in risk for postoperative AKI in the LS group was also consistent with subgroup analysis including all groups of age, sex and BMI. And, the effect of reducing the incidence of postoperative AKI in the LS group was remarkable in the lower preoperative Hb, ASA score, and cancer stage.

Conclusions: Our findings suggest that postoperative AKI with stomach cancer after gastrectomy has been attenuated in the LS group, especially in the subgroup including low ASA score, low hemoglobin, small tumor size, low grade cancer stage and smoking.

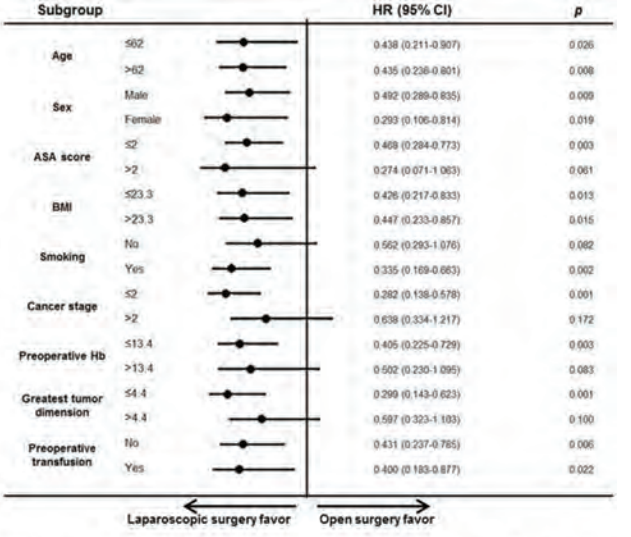

Figure 1. Cox proportional hazards analyses of type of operation and acute kidney injury in the subgroups among propensity matched patients.

FR-PO086

Preceding High-Phosphate Diet Exacerbates AKI in Rats

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Background: Animal studies and epidemiological studies suggest that high phosphate diet accelerates the progression of chronic kidney disease. However, little is known whether high dietary phosphate intake affects the severity of acute kidney injury (AKI).

Methods: Six-week-old male rats were subjected to 35-min bilateral ischemia reperfusion injury (IRI) or sham surgery. For 1 week preceding the surgery, the rats were fed either standard diet (0.9% calcium and 0.8% phosphate) or high phosphate diet (0.9% calcium and 1.2% phosphate). After surgery, all rats were placed on standard diet. We evaluated the time course of changes in renal function and mineral metabolism for 3 days following IRI.

Results: Compared to rats on standard diet, rats fed high phosphate diet for 1 week showed normal renal function, normophosphatemia, non-significant increases in FGF23 and PTH, and markedly increased urinary phosphate excretion. In rats kept on standard diet, IRI led to a 10-fold increase in blood urea nitrogen on day 1, which were accompanied by a 1.7-fold increase in serum phosphorus, a 2.4-fold increase in PTH, an 8-fold increase in FGF23, and a 2-fold decrease in 1,25-dihydroxyvitamin D. Rats fed high phosphate diet for 1 week prior to IRI showed more severe kidney injury and alterations in mineral metabolism. The renal and metabolic changes following IRI stared to regress by day 3 in rats kept on standard diet, but persisted for 3 days in rats fed high phosphate diet prior to surgery.

Conclusions: We show that high phosphate diet exacerbates AKI in rats even if they are switched to standard diet at onset. Our results suggest the need for routine dietary phosphate restriction in individuals who are at high risk for AKI.

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FR-PO087

Role of Macrophages in Human AKI

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Background: Macrophages are an important player in the injury and repair of experimental ischemia/reperfusion injury (IRI). While M1 macrophage contribute to IRI, phenotypic shift from pro-inflammatory M1 to anti-inflammatory M2 macrophages is important in repair process. However, emerging evidence also show persistence of M2 macrophages is associated with fibrosis. The purpose of this study is to examine the role of macrophages in human acute kidney injury (AKI).

Methods: We retrospectively reviewed the medical records of 72 patients with biopsy proven acute tubular necrosis (ATN) without chronic lesions, including 29 cases of native kidneys and 43 cases of deceased donors. M1 and M2 macrophage infiltration was determined by immunohistochemistry of CD68 and CD163 respectively. Healthy kidney sections obtained from nephrectomy was used as control.

Results: CD163+ macrophage outnumbered CD68+ cells in control kidneys and both of these macrophage subtypes increased significantly in ATN. The number of CD68+ M1 macrophage was significantly higher in stage 3 AKI compared to stage 1 or 2. However, there was no difference in the number of CD163+ M2 macrophages according to different stages of AKI. During the mean follow up period of 35.4 ± 30.9 months, 72.2% showed renal functional recovery defined as eGFR≥60ml/min/1.73m2. In contrast to CD68+ M1 macrophage that showed no association with renal recovery, the number of CD163+ M2 macrophage was significantly lower in patients with renal recovery (3.34 ± 2.3 vs 5.23±2.92 cells/HPF, X200, p=0.005). This association was evident especially in native kidney ATN, more advanced stage AKI and also in late biopsy groups. The number of CD168+ M2 macrophage was found to be an independent predictor of no recovery of renal function at 3 months in advanced stage AKI.

Conclusions: This is a first human study demonstrating the possible important role of macrophages with heterogenous phenotypes in injury and repair of AKI.

FR-PO088

Kidney-Resident Macrophages Exist in Unique Subsets and Demonstrate Subset-Specific Responses to AKI

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Background: Myeloid cell-mediated inflammation plays a key role in AKI. Kidney resident macrophages (KRMs) are embryonically derived, self-renewing, and are a distinct lineage from infiltrative macrophages. The means by which these cells differentiate and facilitate these events is unknown. Our objectives were to define KRM subsets using single cell RNA-sequencing (scRNAseq), identify subsets that are responsive to AKI, and determine target genes for intervention.

Methods: C57BL/6J mice were subjected to 20 min bilateral ischemia-reperfusion AKI (n=3) under ketamine/xylazine anesthesia. At 6 d post-injury, KRMs ($F4/80^{Hi}$/$CD11b^{lnt}$) were isolated by FACS and subjected to scRNAseq using the Chromium 10X genomics platform. KRMs from untreated mice were used for controls. 6885 and 4253 cells were sequenced, for AKI and control, respectively.

Results: We used Seurat V3.0 to cluster cells with UMAP (uniform manifold approximation and projection) to reveal four major and two minor subsets. Cluster 0 constituted the majority of cells (57%). After IRI, cluster 0 decreased to 14% and cluster 1 increased from 0.2% to 36%. There were minimal changes to proportions of clusters 2 to 5. Expression of MHCII related transcripts (H2-Aa, H2-Ab1, and Cd74) in cluster 1 were decreased by 2 to 8-fold compared with cluster 0 ($p<10^{-100}$). Transcripts increased in cluster 1 included Ctsd, F13a1, Fabp5, Fos, Cxcl2 ($p<10^{-20}$). Pseudotemporal ordering produced by the Monocle algorithm (V2.3.6), which constructs a "trajectory" of cellular progress through differentiation, predicted that cluster 0 transitions to cluster 1 and that there are 2 potential decision points during that transition. Gene ontology analysis suggests cluster 1 is enriched for transcripts involved in an immune defensive response (e.g. innate immune response $p=2.9x10^{-12}$, leukocyte differentiation $p=1.6x10^{-11}$, inflammatory response $p=2.0x10^{-11}$).

Conclusions: Six transcriptionally unique KRM subsets exist and demonstrate subset-specific responses to AKI. The largest subset (cluster 0) demonstrated injury-responsive changes defined by downregulation of transcripts associated with MHCII that are consistent with a defensive posture involving innate immunity. KRM heterogeneity at the single cell level provides an opportunity to leverage KRM biology for interventions for AKI or the AKI to CKD transition.

Funding: NIDDK Support

FR-PO089

Impact of Aging on Transition of AKI to CKD

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Background: Although acute kidney injury (AKI) in the elderly is thought to contribute to a higher incidence of end-stage renal disease, mechanisms underlying the transition from AKI to chronic kidney disease (CKD) in elderly is poorly understood. Here, we investigated the effects of aging on AKI to CKD transition in animal model of ischemia-reperfusion injury (IRI).

Methods: Aged (48wks) and young (8wks) C57BL/6 mice were subjected to bilateral IRI. Cytokine level as well as functional, histological changes were examined on days 1, 3, 7, and 28 days.

Results: Baseline level of proinflammatory cytokines were slightly but significantly elevated in the kidneys of aged mice than in young mice, suggesting the presence inflammaging. Compared to young mice, kidneys from aged mice showed a persistent M1 dominant inflammation with increased iNOS, TNF-a and IFN-r expression during the recovery phase. Among several factors for macrophage M2 polarization, increase of colony stimulating factor-1 (CSF-1) and interferon regulatory factor-4 (IRF-4) were significantly blunted in aged mice. However, the in vitro macrophage polarization into M2a or M2c by IL-4/IL-13 or IL-10/TGF-b stimulation was not different between young and aged bone marrow derived mononuclear cell, suggesting that macrophage interaction with adjacent cells might be responsible for persistent M1 mediated inflammation in aged mice. Immunohistochemistry and western blot analysis showed that tissue inhibitor of metalloproteinase-2 (TIMP2) expression significantly increased in tubules of aged mice, suggesting that increase of tubule cells that are in the state of cell cycle arrest. In vitro transwell experiment showed that bone marrow derived mononuclear cells cocultured with mouse tubular cells pretreated with inducer of cell cycle arrest showed significantly impaired M2 polarization compared with those without cell cycle inducer, suggesting that prolonged G1 arrest of tubule cells might be partially responsible for persistent M1 mediated inflammation during the recovery phase in aged mice. Finally, M1 predominant renal inflammation in old mice resulted in fibrosis progression on day 28.

Conclusions: Our data show that persistent M1 mediated inflammation driven by adjacent arrested tubule cells is thought to be one of the mechanisms of impaired recovery and progression to CKD in aged mice.

FR-PO090

Deletion of the EGFR Ligand Amphiregullin Attenuates Renal Fibrosis After Severe Ischemic Injury by Inactivating Renal Macrophage Responses

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Background: The activation EGFR signaling pathway is a mediator of recovery from acute kidney injury (AKI) but is also a mediator of renal fibrosis in chronic kidney diseases. EGFR can be activated by a family of ligands including amphiregulin (AREG). Macrophage polarization plays a key role in propagation of AKI and in the development of chronic renal damage. The role of AREG in macrophage polarization and recovery from AKI and subsequent renal fibrosis has not been previously investigated.

Methods: AREG-/- and wild type mice (male, 3 months, C57BL/6) were uninephrectomized, immediately followed by unilateral ischemia-reperfusion for 29 min or 30 min for survival and fibrosis development. An AKI/CKD fibrotic model was also used. Renal macrophages were isolated with a mixture of CD11b and CD11c microbeads. Both a murine macrophage cell line Raw264.7 and a human macrophage cell line THP1 were used.

Results: In both Raw264.7 and THP1 cells, M1 polarization with LPS/IFNγ increased AREG expression. After AKI, AREG was the only EGFR ligand that markedly increased in both kidney and isolated renal macrophages. Surprisingly, renal macrophages of AREG-/- mice exhibited a less activated, M0-like phenotype, being lower in both Th1/M1 (TNF-α, IL-6, IL-1α, IL-1β, CCL-2, IRF5) and Th2/M2 (CD206, IL-4Rα, Arginase 1, YM-1, CD209, CD150) cytokines under normal condition or 2 days after AKI. AREG-/- mice had faster functional recovery after AKI. AREG-/- mice developed less renal fibrosis after severe AKI, as indicated by Sirius red and Masson's trichrome staining, decreases in profibrotic and fibrotic components (TGF-β, collagen I, III, IV, FSP-1, α-SMA, fibronectin, vimentin, CTGF, IL-11), as indicated by qPCR, immunoblotting, and immunohistochemistry, in association with decreases in renal macrophage and neutrophil infiltration, renal proinflammatory cytokines, and renal injury (less renal KIM-1 and NAGAL expression). AREG-/- also developed less fibrosis in AKI/CKD fibrotic model. Finally, AREG-/- had increased survival rate after severe AKI.

Conclusions: Amphiregulin deficiency protects against AKI and renal fibrosis after severe AKI, at least in part due to less renal macrophage activation in response to kidney injury.

Funding: NIDDK Support

FR-PO091

P2X4 Receptor Deficiency Protects Against Ischemic AKI in Mice

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Background: Ischemic acute kidney injury (AKI) is a major clinical problem with high mortality and morbidity. Although P2X4 receptor induces inflammation and cell death in some cell types, the role for P2X4R in ischemic AKI is unknown. Here, we tested the hypothesis that P2X4R activation by ATP released from necrotic renal cells exacerbates ischemic AKI by promoting renal tubular epithelial inflammation and apoptosis.

Methods: Wild type or P2X4R knockout mice were subjected to sham surgery or 30 min kidney ischemia reperfusion (IR) injury. Twenty-four hours later, plasma and kidney were harvested to measure markers of kidney injury (plasma creatinine, blood urea nitrogen, kidney NGAL expression, necrosis scores), inflammation (neutrophil infiltration, pro-inflammatory cytokine/chemokine mRNA induction) and apoptosis (TUNEL staining).

Results: P2X4R knockout mice were protected against renal IR injury with decreased plasma creatinine (1.33 ± 0.17 mg/dL), blood urea nitrogen (91.4 ± 8.6 mg/dL), and NGAL mRNA (395.3 ± 74.4 fold increase over sham) compared to wild type mice (PCr = 2.36 ± 0.1 mg/dL, BUN = 115.1 ± 4.1 mg/dL, and NGAL mRNA = 1194.2 ± 169.2 fold increase over sham, N=4 for all groups). In addition, P2X4R knockout mice had lower necrotic (Jablonski Score reduction of 31 ± 5.6%, N=4) and apoptotic (reduced TUNEL positive cells by 78.2 ± 1.5%, N=4) tubular cells compared to wild type mice. P2X4R knockout mice were also protected against renal inflammation with lower pro-inflammatory cytokine/chemokine mRNA induction after renal IR (monocyte chemoattractant protein-1 [MCP-1] = 2.2 ± 0.7, macrophage inflammatory protein [MIP-2] = 34.1 ± 6, Interleukin 6 [IL-6] = 19.3 ± 0.1, and intercellular adhesion molecule 1 [ICAM-1] = 0.98 ± 0.2 fold increase over sham) compared to wild type mice (MCP-1 = 11.1 ± 1.7, MIP-2 = 206 ± 65.2, IL-6 = 123.5 ± 29.6 and ICAM-1 = 3.7 ± 0.4 fold increase over sham) after renal IR injury. Consistent with this, kidney neutrophil infiltration was reduced by 49.3 ± 5.7% (N=4) in P2X4R knockout mice compared to wild type mice after renal IR injury.

Conclusions: Taken together, our studies suggest that P2X4R activation exacerbates ischemic AKI by promoting renal tubular inflammation and apoptosis after renal IR injury. Our studies provide a novel insight into the pathophysiology of P2X4R in ischemic AKI, suggesting a potential therapy for ischemic AKI.

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FR-PO092

A Novel Noncoding RNA (LRNA9884) Promotes AKI via Maintaining Mincle-Dependent M1 Macrophage Phenotype

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Background: Macrophages are key inflammatory cells and play a critical role in renal inflammation in acute kidney injury (AKI). M1 inflammatory macrophage and M2 anti-inflammatory macrophage act reverse role. Phenotype of macrophages is highly flexible and can be changed over time. However, the underlying mechanism of M1 and M2 macrophage phenotype switching during AKI is still largely unclear. In our previous study, we identified a novel lncRNA (LRNA9884) might contribute to inflammation according to modifying macrophages. The present study was designed to uncover the pathogenic role and the underlying mechanism of LRNA9884 in cisplatin-induced AKI.

Methods: Expression level and pattern of LRNA9884 were examined in cisplatin-induced AKI mice. The regulatory mechanisms of LRNA9884 was investigated in cultured bone marrow–derived macrophages (BMDMs) *in vitro* by silencing or overexpressing of LRNA9884. Flow Cytometer, fluorescence in situ hybridization (FISH) and other multiple molecular biological techniques were applied to figure out the role of LRNA9884 under acute kidney injury.

Results: LRNA9884 was significantly upregulated in the kidney of cisplatin-induced mice and was associated with the progression of the renal inflammation by using RT-PCR and ISH assay. FISH assay with IF co-staining detected that LRNA9884 was largely expressed in the nucleus of macrophage in cisplatin-induced mice kidney compared with the sham group at day 1 after AKI injury. LRNA9884 was remarkedly induced by TNF-α (10ng/ml) in BMDMs as time- and dose- dependent. Western blot and RT-PCR showed that silencing of LRNA9884 effectively inhibited upregulated of macrophage-inducible C-type lectin (Mincle) and iNOS induced by TNF-α. More importantly, we identified that LRNA9884 maintained M1 macrophages phenotype by triggering mincle production at transcriptional level as evidenced by ChIP assay.

Conclusions: LRNA9884 is a mincle-dependent lncRNA that highly-expressed in macrophages under AKI development. Targeting of LRNA9884 effectively blocked the inflammatory response via promoting the transition M1 macrophage to M2 macrophage phenotype. This study will shed new lights on the understanding of pathological role of novel LRNA9884 in AKI.

FR-PO093

Kidney Residency of VISTA-Positive Macrophages Accelerates Repair from Ischemic Injury

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Background: V-domain Ig suppressor of T cell activation (VISTA), expressed primarily in myeloid cells, promotes the progression of cancer via acting as an inhibitory immune-checkpoint molecule. Nevertheless, the VISTA-dependent role of tissue myeloid cells within the normal organ environment remains unresolved.

Methods: VISTA expression was analyzed in homeostatic condition and compared between tissues. To address the role of VISTA, we adopted ischemia-reperfusion injury. Human renal mononuclear phagocytes were used to translate the mouse results to the human condition.

Results: In contrast to lung, liver, and skin, the renal residency of macrophages highly expressed VISTA in ischemic injury as well as homeostasis. When these kidney-resident macrophages were predominantly depleted, the repair from ischemic injury was hindered. VISTA functioned as a scavenger of apoptotic cells and served as a checkpoint to control kidney-infiltrating T cells upon T cell receptor-mediated stimulation. All of these functions eventually improved the repair process after ischemic injury. $CD14^+$ $CD33^+$ mononuclear phagocytes of human kidney also expressed VISTA, which had similar functions to the mouse counterpart.

Conclusions: VISTA is upregulated in kidney macrophages in a tissue-dependent manner, which plays a repair role from ischemic injury.

Figure 1

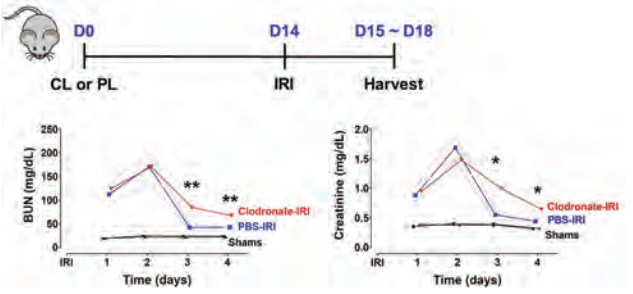
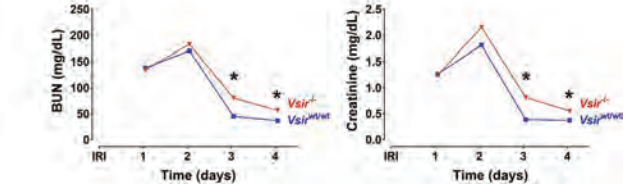


Figure 2



FR-PO094

Single-Cell Deconvolution of Macrophage Heterogeneity in Mouse Ischemia-Reperfusion Kidney Injury

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Background: Acute kidney injury (AKI) is a clinically critical illness without effective treatment. It has been known that macrophage plays important roles in the repair and fibrosis after acute injury, whereas its heterogeneity in subtypes and the related pathophysiological functions during the progression of AKI have not been well established.

Methods: Unilateral ischemia reperfusion (uIRI) acute kidney injury model was set up in C57BL/6J male mice (37°C for 45minutes). Macrophages were collected from the injured kidney on day 1, 3,10,17 post surgery by flowcytometry cell sorting through costainting with F4/80 and Cd11b. Meanwhile, monocytes costaining with Ly6c and Cd11b were sorted from peripheral blood and spleen respectively. Single cell transcriptome sequencing was performed through 10X genomics method.

Results: Altogether eleven clusters of macrophages were discovered in the kidney. There were three subclusters of kidney resident macrophages in normal kidney and they almost disappeared after injury. On day 1 post uIRI surgery, $S100a4^{high}$ and $S100a8^{high}$ macrophage took the majority of macrophage subtypes in the kidney, while $Stmn1^{high}$ macrophage was the major populations on day 3, which had a strong ability of proliferation. $Cxcl2^{high}$ macrophage and $Gdf15^{high}$ macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, $Cxcl2^{high}$ macrophage exhibited inflammatory response and TNF signaling pathway activation, while $Gdf15^{high}$ macrophage had more repair related genes and thus might promote repair after injury. Through single-cell trajectory analysis on integrated datas, MHC-II^- $Gpx3^{high}$ kidney resident macrophage developed into $S100a4^{high}$ macrophage through $Stmn1^{high}$ macrophage and $S100a8^{high}$ macrophage mainly derived from spleen in the acute phase. In the chronic phase, MHC-II^+ $MMP13^{high}$ and MHC-II^- $F13a1^{high}$ kidney resident macrophage developed into $Cxcl2^{high}$ macrophage while $Stmn1^{high}$ macrophage proliferate and different into $Hspa1a^{high}$ macrophage and $Gdf15^{high}$ macrophage.

Conclusions: Macrophages have strong heterogeneity in AKI. $S100a4^{high}$ and $S100a8^{high}$ macrophages might contribute to inflammation during acute injury phase. $Gdf15^{high}$ macrophage was likely to promote repair, while $Cxcl2^{high}$ macrophage could be involved in the chronic inflammation and fibrosis processes. Kidney resident macrophages and monocytes derived from spleen might play important role in AKI.

Funding: Government Support - Non-U.S.

FR-PO095

Increased Expression of the Ca2+ Channel Orai1 and IL-17 in Blood CD4+ Cells in Critically Ill Patients with AKI

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Background: Acute kidney injury (AKI) affects up to 50% of critically ill patients and is associated with high mortality rates approaching 60%. In surviving patients, reduced kidney function is reversible, however AKI increases the risk developing of chronic kidney disease (CKD). IL-17, a pro-inflammatory cytokine secreted by CD4+T cells (Th17 cells), has been linked to the activation of the store-operated calcium channel, Orai1. Th17 cells, have been associated with various autoimmune diseases such as psoriasis and SLE and also in delayed graft function. In rodent models of kidney injury, Th17 cells have been shown to enhance the severity of AKI and AKI-to-CKD transition. However, no direct evaluation of Th17 cells has been conducted in AKI patients.

Methods: Prospective, case-control study of critically ill patients with AKI (KDIGO stage ≥2, n=9) and ICU matched-controls without AKI (n=8). Matching criteria included age, gender and baseline eGFR. Venous blood was collected 12-24 hours post AKI diagnosis and 12-24 h ICU admission and analyzed for expression of CD4+/IL17+ cells and the expression and activity of Orai1.

Results: The percent of CD4+/IL17+ was significantly higher in AKI patients (0.98%±0.11) vs ICU controls (0.15%±0.06, $p<0.05$). In addition, there was a enhancement in the expression of Orai1, from 3.5% in ICU controls vs with 30% in the AKI group. To determine if the increase in Orai1 expression was involved in mediating IL17 activity, we isolated CD4+ cells and stimulated in vitro for ~12 hours with either elevated extracellular sodium (170mM) and/or AngII (10^{-7} M), which was previously shown to enhanced IL17 production in kidney T cells of post-AKI rats. In blood from AKI patients, there was significant increase in IL17 producing CD4+ in response to in vitro stimulation (from 2.3% to 5.2%, $p<0.05$). Furthermore, the increased IL17 response from blood of AKI patients was completely blocked by the inclusion of the Orai1/SOCE inhibitor YM58483 ($p<0.05$ vs. stimulated). Interestingly, there was no IL17 response in CD4+ cells from ICU controls without AKI.

Conclusions: These results suggest that circulating Th17 cells are activated early in critically ill patients with AKI vs ICU controls without AKI. Th17 cells and/or IL17 may represent a target as a potential early biomarker of AKI in the ICU, and Orai1 may represent a therapeutic target.

Funding: NIDDK Support

FR-PO096

Regulatory Innate Lymphoid Cells Suppress Innate Immunity and Reduce Renal Ischemia-Reperfusion Injury

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Background: Innate lymphoid cells (ILCs) are a recently recognized group of immune cells with critical roles in tissue homeostasis and inflammation. Regulatory innate lymphoid cells (ILCregs) are a newly identified subset of ILCs, which play a suppressive role in the innate immune response, favoring the resolution of intestinal inflammation. However, the expression and role of ILCregs in kidney has not been reported.

Methods: ILCregs were assessed by flow cytometry in human and mouse kidney. Mouse ILCregs isolated from IL-10-GFP mice were used for phenotypic and functional analysis. Bilateral renal ischemia was imposed in C57BL/6 or Rag-/- mice. Adoptive transfer of ILCregs into mice with ischemia/reperfusion injury (IRI) was used to assess their *in vivo* functions. IL-2/IL-2Ab complexes (IL-2C) was given by 3 consecutive daily injections prior to IRI operation to inducing expansion of ILCregs in vivo.

Results: Here, we show that ILCregs are present in both human and mouse kidney. Human and mouse renal ILCregs expressed similar surface markers and formed a similar proportion of total kidney ILCs. ILCregs from kidney were expanded *in vitro* with a combination of IL-2, IL-7 and TGF-β. The expanded ILCregs exhibited immunosuppressive effects on innate immune cells, such as ILC1 and macrophages, via secretion of IL-10 and TGF-β. Adoptive transfer of *ex vivo* expanded ILCregs improved renal function and attenuated histologic damage when administered before or after induction of IRI, in association with reduction of neutrophil infiltration and induction of M2 macrophages in kidney. Moreover, treatment with IL-2C promoted expansion of ILCregs *in vivo*, and prevented renal IRI in Rag-/- mice. Depletion of ILCregs with anti-CD25 Ab abolished the beneficial effects of IL-2C in Rag-/- mice.

Conclusions: This study shows that ILCregs protect against renal IRI through suppressing innate renal inflammation. This demonstrates a novel strategy of manipulating ILCregs to treat kidney disease.

Funding: Government Support - Non-U.S.

FR-PO097

Ex Vivo Gene Editing and Pharmacologic Modification of T Cell Keap1/Nrf2 Towards Immunotherapy for Experimental AKI

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Background: Adoptive transfer of Keap1 deficient T cells with enhanced Nrf2 activity has been shown to lead to significant protection from IR-induced AKI in mice (*JASN 2015*), and gene editing of Keap1 in human T cells enhances Nrf2 products (*J Immunol 2018*). Pre-clinical studies in mice with Keap1/Nrf2 gene editing and pharmacologic manipulation in AKI are needed to set the stage for human cell-based therapies.

Methods: Primary mouse CD4+ or pan T cells were isolated from B6 WT spleen by negative selection using Dynabeads. Nrf2 activity was modulated either by treating T cells with different concentrations (10nM, 20nM and 50nM) of the pharmacologic Nrf2 activator CDDO-Im or using CRISPR/Cas9 system to edit Keap1 gene. The efficiency of gene editing was assessed by using ATTO 550-labeled tracrRNA. Various T cell culture conditions were tested and viable cells were enriched using flow-sorting. Viable cells were detected by 4′6-diamidino-2-pheylindole (DAPI). Functional effects of *ex vivo* Nrf2 activation and Keap1 editing were assessed on Nrf2 dependent antioxidant genes NADPH dehydrogenase quinone 1 (NQO1), heme oxygenase 1 (HO-1) and Glutamate-Cysteine Ligase Catalytic Subunit (GCLC) expression using quantitative real-time PCR.

Results: *Ex-vivo* murine CD4+ T cell CDDO-Im treatment resulted in a dose dependent response in Nrf2 target gene expression. The higher dosage of 50nM CDDO-Im had the highest impact on NQO1 (~16.4-fold), HO-1 (~3.6-fold) and GCLC (~2.8-fold) mRNA expression. T cells cultured longer before gene editing using CRISPR/Cas9 technique resulted in significantly higher (32.5%) viable CRISPR edited (ATTO 550 positive) cells compared to cells that underwent CRISPR editing soon after isolation (1%). CRISPR/Cas9 based Keap1 editing resulted in significant increase in NQO1 (~15.5-fold), HO-1 (~3.0-fold) and GCLC (~2.5-fold). Changes in levels of IL-10, IFN-γ and IL-17 were measured.

Conclusions: Pharmacologic and gene editing techniques increased murine T cell Nrf2 target genes *ex vivo* for infusion in studies to prevent AKI and accelerate repair during AKI. These studies set the stage for immunotherapy treatment for AKI and other immune mediated kidney diseases.

Funding: NIDDK Support, Private Foundation Support

FR-PO098

Ischemia-Reperfusion Injury Affects Co-Signaling Molecules TIGIT/CD226 in Kidney T Cells

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Background: T-cells play important roles in AKI pathogenesis and repair processes, but detailed mechanisms are not known. Unbiased cell specific RNAseq is a powerful tool to discover new therapeutic targets, and led to the discovery of AKI stimulated kidney CD4 cell co-inhibitory molecule, T-cell immunoreceptor with Ig and ITIM domain (TIGIT) and its co-stimulatory counterpart CD226

Methods: 8-week-old male C57BL6/J wild type (WT) mice underwent bilateral IR surgeries to induce AKI. CD4 T-cells from post ischemic and control kidney were flow sorted 24 hours after inducing AKI and RNA sequencing (RNA-seq) performed. Flow cytometric analysis was performed to validate RNA-seq findings in T-cells from post ischemic mouse kidney, and "normal" portion of pre and post-clamp human kidney samples of renal cell carcinoma nephrectomies

Results: RNA-seq analysis showed significant increase in TIGIT expression (63.0±12.6 vs 21.8±2.6; p≤0.03) in CD4 T-cells from post IR mouse kidneys compared to control. Alternatively, CD226 mRNA was significantly reduced (13.0±1.8 vs 78.4±4.0; p≤0.0001) in post IR kidney CD4 T-cells. Flow cytometric analysis showed significant TIGIT protein expression in CD4 (11.7±5.0 vs 2.3±1.6; p≤0.008) and CD8 (13.0±6.7 vs 4.3±0.7; p≤0.04) T-cells from post IR kidneys compared to control. CD226 protein expression was not different in CD4 and CD8 T-cell isolated from post IR and control kidneys, however, double negative T-cells (CD3+CD4-CD8-; DN) showed significantly reduced (17.1±6.8 vs 56.3±10.2; p≤0.0002) expression in post IR kidneys. Human kidney assessment showed significant increase in absolute number of TIGIT positive CD8 (74.9±22.7 vs 14.4±5.1; p≤0.04) and DN T-cells (18.1±4.9 vs 1.3±0.9; p≤0.01) as well as CD226 positive DN T-cells (23.8±6.2 vs 2.4±1.4; p≤0.01) in post-clamp "normal" human kidney compared to pre-clamp kidney tissue

Conclusions: These data demonstrate that ischemia reperfusion leads to marked changes in TIGIT and CD226 in mouse and human kidney T-cells. Given the effectiveness as well as renal side effects of traditional anti CTLA4 and anti PD1 therapies, TIGIT/CD226 may be a novel target for developing next generation check point inhibitor therapies for AKI and other kidney diseases

Funding: NIDDK Support

FR-PO099

Multifaceted Role of ST2/IL-33 Axis During Kidney Injury

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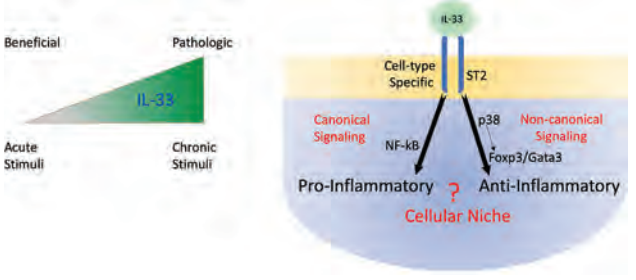
Background: Renal diseases are a major cause of morbidity and mortality. Inflammation elicited by variety of cytokines and chemokines are a major player in initiation and progression of the disease. Interleukin 33 (IL-33) belongs to IL-1 family of cytokines, which was identified for eliciting T helper-2 (Th2) cytokines. IL-33 acts as an 'alarmin' that regulates the immune response during injury. IL-33 acts in an autocrine/paracrine manner on the ST2 membrane receptor IL33R or Il1rl1, triggering innate and adaptive immune response. ST2 is widely expressed in immune cells including regulatory T cells (Tregs). Importance of ST2/IL-33 signaling in Tregs has been demonstrated in multiple inflammatory conditions. However, cell specific contribution of ST2/IL33 signaling is not understood. Here, we investigated the cell specific ST2/IL33 signaling activity using murine renal injury models.

Methods: Murine ischemia-reperfusion injury (IRI) model was used to investigate cell specific ST2/IL-33 signaling using IL1RL1^{tm1a} and cell specific Pepck, Foxd1 and Foxp3 -cre mice to delete ST2 expression in proximal tubular cells (PTC), pericytes and Tregs respectively. The structure and function of the kidney were probed using flow cytometry, histology, immunohistochemistry, qRT-PCR and biochemical analysis.

Results: In vivo experimental data indicated that deletion of ST2 in PTC and pericytes attenuated renal injury suggesting that activation of ST2/IL33 signaling in these cells leads to impaired renal function following IRI, leading to fibrosis. On the contrary, elimination of ST2/IL33 signaling from Tregs resulted in greater renal injury to the indicating that activation of ST2/IL33 signaling in Tregs mediate renal protection during inflammation and injury.

Conclusions: This study addresses the cell specific role of ST2/IL33 signaling in immune-regulation, fibrosis and repair. Our findings try to delineate the multifaceted role of ST2/IL33 axis in renal injury. We conclude modulation of ST2/IL33 siganling as a promising therapeutic option.

Funding: NIDDK Support



IL33/ST2 Signaling is a Double Edge Sword

FR-PO100

CC-Chemokine Receptor 7 Deficient Mice Are Resistant to Renal Ischemia-Reperfusion Injury

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Background: One of the most prominent chemokine receptors in the adaptive immune system is CC-chemokine receptor 7 (CCR7), which has been established as an important component of lymphocyte-driven immune function. CCR7 promotes homing of T cells and antigen presenting cells to areas of lymphoid tissues where T cell priming occurs. Apart from chemotaxis, CCR7 defines a precursor for natural killer T (NKT) cells in the thymus and periphery. Manipulation of the CCR7 axis has either protective or deleterious role in mouse kidney injury models. We sought to clarify the role of CCR7 in the pathogenesis of renal injury after ischemia reperfusion injury (IRI).

Methods: Experiment (Exp.) 1: CCR7 deficient mice (KO) or wild-type mice (WT) underwent IRI. Mice were euthanized at 1, 3 or 7 days after the surgery. Kidney & serum were collected for biochemical analysis & histological evaluation. Exp. 2: KO or WT were injected intravenously with alpha-galactosylceramide: a specific ligand for NKT cells. NKT cells were isolated from spleen 24 hours later, and cytokine profiles were assessed by qPCR. Exp. 3: Prior to IR surgery on Day 0, KO mice were injected intraperitoneally with IFNγ or vehicle on Days -3, -2, -1, and 0. Kidney & serum were harvested on Day 1.

Results: Exp. 1: Blood urea nitrogen & creatinine levels in KO were lower than WT throughout experimental periods. Similarly, KO developed milder tubulointerstitial injuries than WT. Exp. 2: Serum IFNγ concentration & IFNγ mRNA expression in isolated NKT cells were lower in KO than WT. Exp. 3: KO injected with IFNγ showed similar kidney damage to KO injected with vehicle.

Conclusions: CCR7 KO mice are resistant to IRI. KO mice show blunted production of IFNγ. We speculate that less production of IFNγ in KO induces insufficient development of an effector T cell response and reduces kidney damage. However, supplementation of IFNγ alone was not sufficient to increase the susceptibility to IRI in KO mice. Although we need further investigation to resolve the mechanism(s), intervention of CCR7 axis could have therapeutic potential for AKI, especially IRI.

Funding: NIDDK Support

FR-PO101

Superagonistic CD28 Protects Against Renal Ischemia Injury-Induced Fibrosis Through a Regulatory T Cell Expansion Dependent Mechanism

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Background: To investigate the potential protective effect of superagonistic CD28 (CD28sa) on the chronic outcome post acute kidney ischemia injury and related mechanism.

Methods: Male C57BL/6N mice were treated with CD28sa via peritoneal injection 6 days before the induction of ischemia renal injury (IRI), IRI was induced by bilateral clamping of renal pedicles for 35 min followed by reperfusion. 7, 14 and 28 days after the IRI surgery, mice were euthanized and specimens were harvested. The role of regulatory T cells (Tregs) expansion in the renal protection conferred by CD28sa treatment was examined using an anti-CD25 antibody (PC61) to partially deplete Tregs. The chronic pathological outcome of mice renal was identified by Masson staining, Sirius Red staining and renal fibrosis related extracellular matrix immunochemistry (IHC) staining.

Results: CD28sa treatment significantly promoted the percentage of Tregs in the spleen, kidney and peripheral blood 24 h after the IRI. Serum creatinine level was remitted by CD28sa administration in a short term (7 days). Histological analysis indicated that CD28sa attenuated renal tubular damage. CD28sa also attenuated the extracellular matrix deposition in the renal medulla site 28 days after IRI. Immunoblot showed that Collagen IV expression of kidney was lowered by CD28sa administration 28 days after IRI. Immune cells in kidneys from CD28sa pre-treated IRI mice were characterized by an increased percentage of Tregs and MHCII^{+} CD11c^{+} dendritic cells, significantly decreased Th17 cells and also increased secretion of Tregs effector cytokine IL-10. CD28sa pretreatment also resulted in less cells apoptosis and less oxidative stress of renals marked by less TUNEL and 8-OHdg positive stained cells. On the other hand, the renal protection bestowed by CD28sa was abolished by PC61 administration.

Conclusions: CD28sa alleviated renal chronic outcome after the acute ischemic injury, probably associated with the inchoate up-regulation of Treg cells.

Funding: Government Support - Non-U.S.

FR-PO102

Enhancement of Tregs with IL233 Hybrid Cytokine Rescues Kidney Function in Aristolochic Acid-Induced Nephropathy

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Background: Aristolochic acid (AA) is used as a "traditional medicine" to induce labor and for treatment of arthritis and inflammation. The Balkan nephropathy is supposedly caused by chronic dietary consumption of AA and genetic predisposition. However, recent studies showed that consumption of AAleads to tubular epithelial cell (TEC) injury and inflammation, which triggers acute and chronic renal dysfunction. Our goal in this study was to investigate the role of T-regulatory cells (Tregs) and susceptibility of TEC in experimental AA nephropathy.

Methods: We induced renal injury in male C57Bl/6 mice with AA injection (i.p.) and evaluated the progression of acute nephropathy for 4 weeks. Additionally, PC61 (anti-CD25 Ab to deplete Tregs) and IL233 (a novel Treg-enhancing hybrid cytokine bearing the activities of IL-2 and IL-33) were appliedto evaluate the progression of nephropathy. Sera samples were collected and used for plasma creatinine (PCr) and blood urea nitrogen (BUN) assessment with the commercially available kits. Tubular necrosis in the kidneys was assessed on H&E sections. KIM-1 and NGAL were used for kidney injury markers. Flow cytometry was used to evaluate inflammatory cells and cytokine profile in kidneys, spleen and blood. The effect of IL233 in PD1 and IL-33R (ST2) KO mice in AA nephropathy was also studied to understand the underlying mechanisms. All animal procedures and personnel were approved by institutional animal care and care committee.

Results: Mice treated with AA developed severe renal dysfunction, inflammation and tubular necrosis. Immune cells were elevated alongside renal inflammation. Administration of anti-CD25 mAb PC61 worsened renal dysfunction in AA-treated mice, increased the susceptibility of mice to AA-induced nephrotoxicity, suggesting a role of Tregs. Treatment of mice withIL233 (a Treg-enhancing hybrid cytokine containing IL-2 and IL-33), after the onset of injury suppressed inflammation, renal dysfunction and injury, evident by the reduced levels of plasma creatinine, BUN and in these animals, whereas PC61 mAb ameliorated the IL233-mediated protection indicating Tregs as primary immune cells rendering protection.

Conclusions: IL233 protects from AA induced nephrotoxicity in a Treg-dependent manner with a role for ST2 and PD-1, and bears therapeutic potential.

Funding: Other NIH Support - NIH-R01DK104963

FR-PO103

TCR+CD4-CD8- (Double-Negative) T Cells Protect from Cisplatin-Induced Renal Epithelial Cell Apoptosis and AKI

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Background: Acute kidney injury (AKI) due to cisplatin is a significant problem that limits its use as an effective chemotherapeutic agent. TCR+CD4-CD8- (double negative - DN) T cells constitute a major T cell population in human and mouse kidney and protect from ischemic AKI. However the pathophysiologic roles of DN T cells in cisplatin-induced AKI is unknown

Methods: Mice were treated with cisplatin (30mg/kg) or vehicle and effect on kidney DN T cell numbers and function assessed using flow cytometry. *In vitro* studies evaluated effects of kidney DN T cells on cisplatin-induced apoptosis and PD ligand 1 (PD-L1) in renal epithelial cells. *In vivo* adoptive transfer studies assessed role of DN T cells on kidney structure and function during cisplatin-induced AKI

Results: Kidney DN T cell population increased ($p<0.01$) at 24 hours and declined ($p<0.01$) by 72 hours after cisplatin treatment. Cisplatin increased kidney DN T cell proliferation ($p<0.05$), apoptosis, CD69 ($p<0.05$) and IL10 ($p<0.01$) expression whereas CD62L ($p=0.03$), CD44, IL-17A, IFN-γ and TNF-α were ($p<0.05$) downregulated. Cisplatin decreased both kidney DN T cell PD1 ($p<0.05$) and NK1.1 ($p<0.05$) subsets with pronounced effect on PD1 subset. *In vitro* kidney DN T cells co-culture decreased cisplatin-induced apoptosis ($p<0.05$) in kidney proximal tubular epithelial cells (PTECs), increased expression of Bcl-2 ($p<0.05$) decreased cleaved caspase 3 ($p<0.05$), and attenuated PTEC PD-L1 expression ($p<0.05$). Adoptive transfer of DN T cells attenuated kidney dysfunction ($p<0.05$) and structural damage ($p<0.05$) from cisplatin-induced AKI

Conclusions: These results demonstrate that kidney DN T cells respond rapidly and play a protective role during cisplatin-induced AKI. DN T cells may have important translational implications for humans undergoing cisplatin and immune checkpoint inhibitor therapy for cancer

Funding: NIDDK Support

FR-PO104

B Cells Are Associated with Renal Recovery After AKI

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Background: The mechanisms associated with renal recovery after an episode of Acute Kidney Injury (AKI) are still poorly understood but immune factors seem to play a role. We aim to determine the association between the urinary immune profile of AKI patients and renal recovery.

Methods: Adult patients with AKI ≥stage 2 by KDIGO and sterile leukocyturia at admission in 2 Intensive Care Units (ICUs) of a Portuguese tertiary Hospital were prospectively included in a consecutive way. Anuria, CKD > stage 3, dialysis one week previous admission and absence of informed consent were exclusion criteria. Urinary flow cytometry was performed at Day 1 (D1) and 3 (D3). Renal recovery was defined as a decreased of at least one stage of AKI classification by KDIGO at 7days of ICU admission.

Results: From January to September 2018, a total of 552 patients were admitted in both ICUs, 108 with AKI ≥stage 2 by KDIGO at admission. Of these, 18 had sterile leukocyturia and no exclusion criteria. Median age was 75 years, 83.3% male, 88.9% caucasian, 33.3% diabetic and 66.7% hypertensive. Median baseline serum creatinine was 1.14mg/dl. APACHE II score was 30.5, 66.7% medical and 33.3% surgical admissions. Sepsis alone 44.4% or sepsis+hypoperfusion 38.9% were the most common causes of AKI, 33.3% needing Renal Replacement Therapy. Mortality at ICU and hospital discharge was 25.0% and 38.9%, respectively. Half the patients recovered renal function (REC) and half did not (NREC). Serum creatinine and cystatin C at admission did not differ between REC and NREC groups (3.06 SD0.56 vs 3.74 SD1.90 mg/dl, NS; and 3.25 SD1.24 vs 4.08 SD1.21mg/dl, NS, respectively). At D1, REC patients had similar % of T Cells (CD45+CD3+) (0.5 vs 0.6%, NS) and more B Cells (CD45+CD19+) (19.6 vs 4.3%, $p=0.046$), NK Cells (CD45+CD161+) (4.5 vs 1.1%, NS), neutrophils (28.7 vs 16.5%, NS) and dendritics (CD45+CD1c+) (4.9 vs 1.7%, NS). Patients who recovered also had a higher macrophages M1 (CD45+CD11b+CD68+) ratio D1/D3 (3.4 vs 1.3%, NS).

Conclusions: Immune mechanisms seem to play a role in renal regeneration and recovery after an episode of AKI. In our critically ill population, urinary B Cells were statistically significantly associated with renal recovery at 7 days after AKI at ICU admission.

FR-PO105

CpG C Dinucleotide Is a TL9 Agonist That Increases IgM Levels and Attenuates AKI in Mice

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Background: Acute kidney injury (AKI) is a common complication in hospitalized patients with high mortality rates and no FDA approved therapies available except dialysis and kidney transplant. CpG oligodinucleotides (ODNs) are short synthetic single-stranded DNA molecules containing unmethylated CpG dinucleotides in particular sequence contexts (CpG motifs). CpG class B has been approved by FDA in vaccine therapy as it strongly activates B-cells and IL-6 secretion but weakly stimulates interferon (IFN)-alpha secretion. CpG class C equally activates B-cells and IFN-alfa secretion but mild IL-6 secretion. It is known that CpG has protective effect on ischemic brain and heart injury. We hypothesize that CpG can have protective effect on the AKI.

Methods: C57BL/6 mice were anesthetized and subjected kidneys to ischemia-reperfusion (IR: 26 min of ischemia and 24 hrs of reperfusion). 50μg of CpG B or CpG C were administered i.v. 5 days before IR. Serum creatinine and BUN were measured and survival rates were recorded. In *in vitro* assays, freshly isolated murine splenocytes were activated with CpG C and intracytoplasmic IgM levels in B cells were evaluated by flow cytometry on day 5 (Figure 1).

Results: As depicted in Table 1, following IR the increase in plasma creatinine as well as mortality was significantly reduced by CpG C. In vitro studies CpG significantly increased intracytoplasmic IgM (Figure 1).

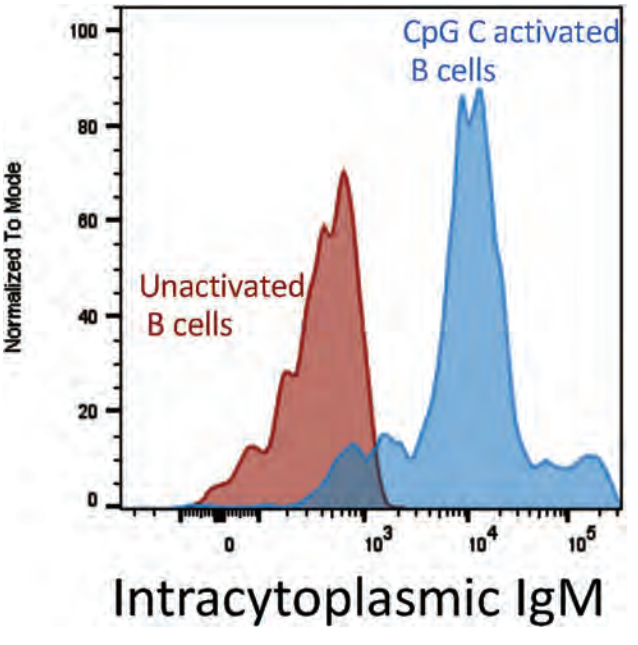
Conclusions: CpG C is more effective in ameliorating ischemia induced AKI than CpG B and also reduces post injury mortality rates. Potential mechanisms include increasing natural IgM levels (see Figure 1) and inducing regulatory activity in B cells and antigen presenting cells (Lobo PI, Frontiers in Immunology, 2017). CpG C has a broad range of applications that could be useful for preventive treatment of patients with AKI.

Funding: NIDDK Support

Table 1

	Day1 (creatinine)	Day3 (creatinine)	Survival
Control	1.8±0.1	1.5±0.3	45% on Day 12
CpG B	1.5±0.2	1.0±0.2	45% on Day 12
CpG C	1.1±0.1#	0.8±0.1#	100% on Day 30*

*p≤0.05, #p≤0.01



FR-PO106

Inhibition of BRD4 Leads to Reduced Activated Neutrophils and Adhesion to Endothelium After Ischemia-Reperfusion Injury

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Background: Following ischemia reperfusion injury (IRI), pro-inflammatory cascades partly dependent on NFkB, lead to neutrophil recruitment to the site of injury. Neutrophil accumulation then contributes to tissue injury through the release of pro-inflammatory cytokines, reactive oxygen species and proteases. We hypothesize that blockade of NFkB with the BRD4 inhibitor, MS417, will reduce neutrophil recruitment to the kidney following IRI.

Methods: Male C57BL/6 mice were treated with 1μM of MS417 for 7 days before unilateral ischemia was performed followed by reperfusion for 24 hours. Kidney tissue, blood and bone marrow was collected for neutrophil analysis using a custom flow cytometry panel. For *in vitro* studies, freshly isolated neutrophils from healthy volunteers were labeled with Calcein AM and incubated with MS417 media for 1 hour. HUVEC were activated by TNFα for 4 hours and then incubated with neutrophils and allowed to adhere for 30 minutes. Non-adherent cells were removed and neutrophil adhesion was quantified using a fluorescent plate reader.

Results: Absolute neutrophil counts increased in the bone marrow ($p<0.0001$ vs sham) and blood ($p<0.04$ vs sham) 24 hours after IRI and there was a trend towards increased neutrophils in the kidney ($p=0.12$ vs sham). Primed neutrophils (upregulated CD66a expression) did not increase in the bone marrow and blood at 24 hours, but increased in the kidney ($p=0.06$ vs sham). BRD4 inhibition reversed IRI induction of neutrophil counts in the bone marrow ($p<0.0001$ vs IRI) and blood ($p<0.03$ vs IRI), and in the kidney (trend). In contrast, BRD4 inhibition did not lead to significant decrease in primed neutrophils in the bone marrow and blood, but did reduce primed neutrophils in the kidney ($p<0.03$ vs IRI), reversing the effects of IRI alone. *In vitro* studies showed that TNFα increased neutrophil adhesion to HUVEC ($p<0.0001$ vs control). Pre-treatment of neutrophils with the BRD4 inhibitor led to a significant decrease in neutrophil adhesion ($p<0.0001$ vs TNFα–activated HUVEC).

Conclusions: BRD4 inhibition blocked neutrophil upregulation of the adhesion receptor, CD66a, neutrophil adhesion to activated endothelial cells, and recruitment of neutrophils to the kidney, following IRI. BRD4 inhibition may represent a therapeutic approach to limiting IRI in the kidney.

FR-PO107

The HMGB1-IL17A Axis Promotes Neutrophil Infiltration in Renal Ischemia-Reperfusion Injury

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Background: Renal ischemia/reperfusion (I/R) injury is the leading cause of acute kidney injury (AKI), which is associated with increased morbidity and mortality. Neutrophils are first to be recruited to the site of inflammation and also play a central role in the inflammatory cascade. We reported previously that inhibition of HMGB1 release ameliorated IR-induced neutrophils infiltration in mice. However, it is poorly understood whether HMGB1 was involved in regulating and activating the IL23/IL17 axis in renal IR injury. In this study, we aim to delineate whether the HMGB1/TLR4 signaling provokes the IL23/IL-17 axis and inducing the renal IR injury in mice.

Methods: C57BL/6 mice ischemia was induced by 60 min clamping of the left renal pedicle and followed by right nephrectomy and up to 24 h of reperfusion. The involvement of HMGB1 and IL17A was assessed in functional assays by neutralizing HMGB1, IL23 or IL17A antibody, and recombinant HMGB1 (rHMGB1), IL23 or IL17A (rIL17A), respectively. Urea nitrogen, creatine kinase and lactate dehydrogenase levels were measured. Renal histopathological changes and neutrophils infiltration were assessed by immunohistochemistry. The expression of HMGB1, TLR4, IL23, IL17A were assessed by western blot analysis and mRNA expression. The levels of MCP-1, IL8 and RANTES were assessed by ELISA.

Results: IL23, IL17A and neutrophils infiltration were increased after renal IR injury in mice. HMGB1 antibody significantly ameliorated IR induced neutrophils infiltration, renal injury and IL23, IL17A levels. TLR4-/- mice following renal IR injury were treated with rHMGB1 significantly reduced the expression of IL23, IL17A and neutrophils infiltration. Furthermore, IL-23 or IL17A antibody significantly inhibited IR induced neutrophils infiltration. Moreover, HMGB1 or IL17A antibody remarkably decreased production of neutrophil chemoattractant MCP-1, IL8 and RANTES, whereas rHMGB1 or rIL17A may promote production of them.

Conclusions: These results suggested that HMGB1 facilitated the injury effect of the IL23/IL17 axis, which contributed to neutrophils infiltration in renal IR injury.

Funding: Government Support - Non-U.S.

FR-PO108

Dexamethasone Pretreatment Prevented Chemotherapy-Induced Acute Renal Failure by Inducing Polymorphonuclear Myeloid-Derived Suppressor Cells

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Background: Chemotherapy for cancer patients leads to renal toxicity which was the main cause for chemotherapy discontinuation. Current preventive measures failed to be successful. Previous studies indicated dexamethasone cured renal diseases. The present study was aimed to reveal the efficacy and mechanism of dexamethasone in preventing chemotherapy induced renal toxicity.

Methods: Cisplatin was utilized to build acute renal failure mice model. Th17, Treg, polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC) and monocytic MDSC (M-MDSC) was tested in injured kidney. Dexamethasone pretreatment was used to relieve renal failure with the immune mechanism investigated.

Results: Cisplatin induced acute liver failure confirmed by increased serum creatinine. Th17 cells were increased in injured kidney, with increased PMN-MDSC and decreased Treg cells. Dexamethasone pretreatment decreased serum creatinine and induced PMN-MDSC and Treg in kidney and increased Th17 cells. Gr-1 antibody was utilized to eliminate PMN-MDSC after dexamethasone pretreatment. PMN-MDSC depletion eliminated the efficacy of dexamethasone in relieving renal failure. Dexamethasone induced PMN-MDSC was transferred to mice before cisplatin administration, which decreased serum creatinine. Dexamethasone induced PMN-MDSC suppressed T cell proliferation through reactive oxygen species (ROS) pathway.

Conclusions: Dexamethasone pretreatment relieved chemotherapy induced renal failure by inducing PMN-MDSC, which suppressed Th17 cells and induced Treg cells.

FR-PO109

Sepsis Alters Renal Tubular Epithelial Phenotype and Disrupts Intercellular Communication

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Background: The success of sepsis therapy requires an understanding of time and cell-specific responses to infection. Such knowledge will allow accurate staging of septic patients and precise spatial and temporal therapy. We recently showed that the renal response to endotoxin (LPS) involves the sequential activation of inflammation, antiviral signaling and translation shutdown leading to organ failure. This propagation of injury was mediated in part by tubular epithelial and macrophage cross-talk. However, the kidney is composed of over twenty cell populations including epithelial, endothelial, immune and stromal cells. We therefore hypothesize that many of these cell types have precise roles in injury propagation along the sepsis timeline. To address this hypothesis, we used single cell RNAseq to dissect each cell subpopulation's contribution to endotoxin injury over time.

Methods: We harvested single cell suspensions from murine kidneys at time points spanning the injury and recovery phases of sepsis. Cells were processed via 10x Chromium RNA sequencing platform and analyzed with Seurat R package.

Results: We identified 26 clusters representative of major renal cell populations defined by known canonical markers. Endothelial cells and macrophages showed early transcriptional changes but opposite metabolic profiles. Interestingly, the pericyte also showed early signaling activation that persisted well into the recovery phase. In contrast, tubular epithelia exhibited a delayed response characterized by loss of expression of traditional markers such as the tubular SGLT2 transporter while simultaneously acquiring novel phenotypes such as the unexpected expression of antigen presenting MHC-II-related genes. This may indicate that under stress, epithelial cells assume the role of defenders rather than transporters. Remarkably, CellPhone Database analysis identified global shutdown of intercellular communication in the absence of cell death.

Conclusions: We propose that, in addition to propagation of injurious signaling, organ shutdown in sepsis also results from failure of cell-cell communication. This time-layered, cell-specific approach to the pathophysiology of sepsis may reveal biomarkers that allow the accurate staging of septic patients and identify temporally and spatially precise therapeutic targets.

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FR-PO110

Photoacoustic Microscopy Reveals Early Decrease in Peritubular Capillary (PC) O_2 Tension Associated with Temporal Changes in Cell Metabolism and Injury Despite Unimpaired PC Flow in Sepsis-Induced AKI

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Background: The ability to monitor dynamic changes in the renal metabolic rate of oxygen (MRO_2) is critical to understanding the time course of changes in local microenvironmental factors that lead to acute kidney injury (AKI). Technical limitations have impeded *in vivo* measurement of three key hemodynamic parameters—total hemoglobin concentration (C_{Hb}), oxygen saturation of hemoglobin (sO_2) and peritubular capillary blood flow (PCBF)—at the microscopic level. To address this, we developed a new technique - intravital multi-parametric photoacoustic microscopy (PAM).

Methods: To validate our system C57BL/6 mice were subjected to 1) hypoxia or 2) LPS-induced sepsis (5 mg/kg LPS, ip). The new intravital PAM platform uses nanosecond-pulsed lasers (532 and 558 nm) for dual-wavelength excitation-based spectroscopic measurement of sO_2. *In vivo* PAM imaging was performed over time on kidneys at depths of up to 200 μm. Plasma and kidneys were collected for measurement of creatinine, Kim1, NGAL, ATP, and various injury markers.

Results: *In vivo* PAM performed in mice challenged with 12 or 100% oxygen showed a strong correlation between sO_2 and inhaled oxygen concentration. After LPS, time-dependent changes in hemodynamic parameters and injury markers were observed. PCBF increased within 10 min but returned to and remained normal from 20-200 min. PC sO_2 began to decline immediately and a 30% decrease persisted from 20-200 min. Kidney ATP decreased by ~80% at 40 min. Abrupt increases in *Kim1* (~20-fold) and *Ngal* (~300-fold) and decreases (~80%) in *Nrf2* mRNA were observed at 12 hr. Creatinine increased at 24 hrs. *Tlr4* and *Myd88* mRNA increased at 12 hr.

Conclusions: *In vivo* PAM enables dynamic monitoring of renal MRO_2 in AKI. The immediate decrease in sO_2 but maintenance of PCBF indicates that blood flow was maintained yet sO_2 was limiting and produced marked temporal changes in biochemical parameters of cell metabolism and injury. This technical innovation lays the foundation for dynamic monitoring of renal oxygen metabolism in AKI, as well as chronic kidney disease, providing a new tool for AKI and CKD studies. [Zheng & Sun are co-first authors and contributed equally]

Funding: NIDDK Support

FR-PO111

BAM15, A New Mitochondrial Uncoupler, Improves Sepsis AKI

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Background: (2-fluorophenyl){6-[(2-fluorophenyl)amino](1,2,5-oxadiazolo[3,4-e] pyrazin-5-yl)}amine (BAM15) is a new mitochondrial uncoupler protects mitochondria with more specificity and less cytotoxicity than other uncouplers. Kenwood et al. (Mol. Metab. 2013) demonstrated that BAM15 treatment improved renal outcomes after renal ischemia/reperfusion injury. We evaluated the therapeutic potential of BAM15 for sepsis AKI.

Methods: Cecal ligation and puncture (CLP) was performed to 10-week-old CD-1 mouse to induce sepsis. BAM15 (5mg/kg, i.p.) was injected 0 hours after CLP. We also evaluated kidney injury and systemic organ damage and inflammation 18 hours after CLP. A survival study was conducted with both early (0hrs) and delayed (6hrs) BAM15 treatmement.

Results: BAM15 treatment at the time of CLP surgery improved both survival (fifteen of twenty of non-treatment group and five of twenty of treatment group were died in 7days: $P<0.05$) and kidney function at 18 hours along with reduced tubular histological damage, tubular hypoxia, systemic inflammation (e.g. IL-6 and IL-10) and splenic apoptosis (a marker of late immunosuppression), but did not improve other organs (e.g. liver and muscle). Furthermore, delayed treatment of BAM15 (6 hours after CLP) also improved survival (seventeen of twenty of non-treatment group and ten of eighteen of treatment group were died in 7days: $P<0.05$) and kidney dysfunction after sepsis.

Conclusions: Sepsis increased mitochondrial damage, tubular hypoxia, renal histological damage and, accelerated splenic apoptosis and systemic inflammation resulting in AKI and death. BAM15 significantly attenuated these processes, improved survival, and selectively improved septic AKI.

Funding: NIDDK Support

FR-PO112

Circulating Peroxiredoxin 1 Is a Novel DAMP and Aggravates Acute Kidney Induced by Lipopolysaccharide via Promoting Inflammation

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Background: Damage-associated molecular patterns (DAMPs) are initiators of sterile inflammation, which is a key contributor to acute kidney injury (AKI). However, the current knowledge on those DAMPs that activate renal inflammation under AKI remains incomplete. Peroxiredoxin-1 (Prdx1) is a small protein in the Peroxiredoxins family, which are ubiquitous expressed enzymes reducing peroxide levels. Interestingly, recent studies indicated that intracellular Prdx1 could be released to extracellular space under certain stimuli and extracellular Prdx1 has been recently identified as a novel DAMP due to its pro-inflammatory property by binding to Toll-like receptor (TLR) 2/4. However, the crucial role of Prdx1 in AKI remains unclear.

Methods: Prdx1-deficient mice and patients with AKI were used to determine its function in AKI, potential mechanisms and human relevance.

Results: Intraperitoneal injection of lipopolysaccharide (LPS) elicited a progressive course of AKI in mice developed from 12 to 24-hour post injection along with renal inflammation evident by macrophage infiltration and upregulation of cytokines (IL-1β, IL-6); these alterations were concurrently occurred with a robust and progressive production of serum Prdx1. Similar observations were also obtained in ischemia-reperfusion-induced AKI mouse model in mice. Removal of the source of serum Prdx1 protected mice deficient in Prdx1 from LPS-induced liver injury, and decreased macrophage infiltration, IL-1β and IL-6 production. As a result, Prdx1-/- mice were strongly protected from LPS-induced death that was likely progressed from AKI. Additionally, intravenous re-introduction of recombinant Prdx1 (rPrdx1) in Prdx1-/- mice reversed or reduced all the above events, demonstrating an important contribution of circulating Prdx1 to AKI. rPrdx1 potently induced in primary macrophages the expression of pro-IL-1β, IL-6, TNF-α, and IL-1β through the NF-κB signaling as well as the NOD2 signaling. Furthermore, a significant elevation of serum Prdx1 was demonstrated in patients (n=31) with AKI; the elevation is associated with serum creatinine.

Conclusions: Our findings reveal a previously unrecognized detrimental role of prdx1 in LPS-induced renal inflammation and tissue damage and thereby identify novel and important therapeutic target for LPS-induced AKI.

FR-PO113

Renal Proteome Changes Reveal a Substantial Renal Acute Phase Response in Sepsis-Induced AKI in Mice

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Background: Sepsis-induced acute kidney injury (AKI) is the most common form of AKI with poor outcomes. Both differential diagnosis and management of septic AKI are unresolved issues. Our aim was to study the temporal profile of the renal proteome changes in bacterial lipopolysaccharide (LPS)-induced AKI.

Methods: Male NMRI mice were injected with LPS or saline (control). AKI was studied at early (EP, 1.5 and 6 h after LPS at 40 mg/kg i.p.) and late phases (LP, 24 and 48 h after LPS at 10 mg/kg i.p.) by HPLC-MS/MS screening. Renal mRNA expression of 13 acute phase proteins (APP) was measured by qPCR.

Results: AKI was indicated by increased renal TNFα, IL-6 and neutrophil gelatinase-associated lipocalin (Lcn-2) mRNA expression from 1.5 h after endotoxin administration. At 24 and at 48 h 53% of the top 30 significantly upregulated proteins were APPs, with complement C3, fibrinogen, haptoglobin and hemopexin demonstrating the greatest increases. LPS upregulated renal ceruloplasmin and haptoglobin mRNA expression from 1.5 h, and fibrinogen-α, -β, -γ, serum amyloid A, hemopexin, ferritin heavy chain and inter alpha-trypsin inhibitor 4 mRNA from 6 h. Complement C3 and transferrin mRNA were upregulated only in LP. Expression of most APP mRNAs peaked at 24 h and some mRNA started to recover by 48 h. Albumin mRNA was downregulated in LP.

Conclusions: Our proteomic analysis demonstrated a marked upregulation of local renal APR that commenced a few hours after treatment and peaked at 24 h in LPS-induced AKI in mice. Many more APPs were involved in the renal APR than previously identified.

Funding: Government Support - Non-U.S.

FR-PO114

Renal Ischemia-Reperfusion Followed by Sepsis Increases Mortality Despite Reducing Multiorgan Damage: Reversal by IL-6

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Background: Sepsis frequently develops after AKI and portends a poor prognosis. We previously showed that sepsis 48 hours after ischemia reperfusion (I/R) AKI worsened kidney function and survival compared to sepsis alone, although there was less liver, muscle, spleen damage, and systemic cytokines. Thus, AKI unexpectedly dissociated renal function from systemic responses to sepsis. We hypothesized that the I/R injured kidney could alter the systemic response to subsequent sepsis. We investigated pathophysiological conditions of sepsis after AKI focusing on IL-6 and its upstream mediator Tumor necrosis factor-inducible gene 6 (TSG-6) which has anti-inflammatory properties.

Methods: We used 12 weeks old male C57/BL6 mice. We performed 40 minutes bilateral I/R for AKI, waited 48 hours, then performed cecal ligation and puncture (CLP) for sepsis. We measured outcomes at 48 hours after I/R and 24 hours after CLP. We also performed a 4 day survival study. In some animals, bilateral nephrectomy was performed at the same time of CLP surgery.

Results: I/R intensified sepsis-induced AKI [sCr; I/R+CLP vs $sham_{I/R}$+CLP, 1.40±0.58 vs 0.82±0.37 mg/dl ($p<0.05$)]. Survival rate in I/R+CLP was significantly worse than $sham_{I/R}$+CLP. In contrast, AST, LDH and CK, systemic inflammatory cytokines (HMGB-1, IL-10 and IL-6) and spleen apoptosis (immunohistochemistry of active caspase 3) were significantly lower in I/R+CLP than $sham_{I/R}$+CLP. Although I/R caused a slight elevation of systemic IL-6 at 48 hours, prior I/R surgery suppressed subsequent CLP stimulated IL-6, that was reversed by bilateral nephrectomy. Surprisingly, continuous administration of IL-6 starting immediately before CLP surgery improved the mortality of sepsis after I/R. In contrast, it worsened mortality in sepsis alone. Systemic and kidney TSG-6 was significantly increased at 48 hours after I/R injury and 24 hours after CLP in I/R+CLP compared to CLP alone.

Conclusions: AKI, followed by sepsis, worsened survival and kidney function, although liver and muscle enzymes, systemic cytokines and spleen apoptosis were improved compared with sepsis alone. Treatment with IL-6 improved survival of sepsis after AKI, counterintuitively. TSG6 derived from I/R injured kidney might contribute to changes in systemic and organ responses to subsequent sepsis.

Funding: NIDDK Support

FR-PO115

Integrated Stress Response Mediates Epithelial Transport Dysfunction During Septic AKI

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Background: Septic acute kidney injury (AKI) is a common cause of in hospital morbidity and mortality. Sepsis induced AKI is known to be associated with significant impairment of urine concentration, which requires establishment and maintenance of epithelial transport. However, the pathogenesis of endotoxemic tubular dysfunction with the failure of epithelial transport is poorly understood. Integrated stress response (ISR) is a common adaptive pathway for restoring cellular homeostasis under stress conditions such as infection and hypoxia. Previous studies have demonstrated that ISR is activated in AKI. Therefore, we investigate that ISR plays key roles in epithelial transport dysfunction during septic AKI.

Methods: Male C57BL/6 mice (6-8 weeks, 20–25g) received a single-dose of LPS (E. coli serotype 0111:B4, Sigma, 5 mg/kg) or sterile saline with tail vein injection and were killed at 1,3,6,12,24 and 48h (n=6 per group). To further explore the relationship between epithelial transport and ISR, C57BL/6 mice were treated with saline or ISRIB (ISR inhibitor, Sigma, 4 mg/kg) intraperitoneally 30 min after LPS injection and sampling at 3 and 24h. Kidney injury, inflammation, the expression of epithelial transport and ISR were measured.

Results: LPS-AKI model have demonstrated an inflammatory state with increased levels of IL-1β and TNF-α,and serious kidney injury indicated by BUN, plasma NGAL and KIM-1. At the same time, we determined that activation of the eukaryotic translation initiation factor 2-α kinase 2/eukaryotic translation initiation factor 2α (Eif2ak2/Eif2α) axis, which is the key mediator of ISR. We divided epithelial transport into 5 categories: Na+/K+-ATPase, tubular ion transport (ENaC, NKCC2, ROMK, NCC, CLCK), acid-base transport(NHE), glucose and urea transport(SGLT1,2,GLUT1,2,UTA,UTB) and water transport(AQP). The mRNA and protein levels of those transport proteins were all downregulated following ISR activation. ISRIB was an inhibitor of ISR. We found that ISRIB could ameliorate inflammatory state and restore renal function and the expression of those epithelial transport proteins after LPS injection.

Conclusions: ISR mediates the dysfunction of renal epithelial transport during septic AKI.

Funding: Government Support - Non-U.S.

FR-PO116

Role of Intestinal Alkaline Phosphatase (IAP) in Lipopolysaccharide (LPS)-Induced Septic AKI

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Background: LPS plays a significant role in septic AKI. IAP is known to dephosphorylate LPS and render it inactive. LPS has also been suggested to play a role in leaky gut associated with septicemia. We hypothesized that overexpressing IAP will be beneficial for septic AKI. To test this hypothesis, we developed IAP transgenic mice (IAPTg). This was compared with IAP knock out (IAPKO) and wild type mice of the same background.

Methods: Septic AKI was induced by IP injection of 10 mg/kg LPS. Mice used were IAPTg which had human chimeric IAP under the control of villin promoter making them intestine and kidney specific. This chimeric human IAP (IAPTg) contains domains from human placental alkaline phosphatase which has a high turnover number and selectivity for LPS. The second group was IAP knockout (IAPKO). Both groups received LPS and compared with LPS-treated wild type (LPS-WT) and saline-treated wild type mice (Control). FITC-Dextran (FD) was given by gavage 2 hours before sacrifice to measure intestinal permeability. Blood and kidneys were harvested for biochemical and immunoblot analysis

Results: The table clearly shows the IAPTg mice have significantly improved renal function compared to LPS-WT and IAPKO mice. Creatinine and BUN of IAPKO mice were not significantly different from LPS-WT; serum FD levels were highest in IAPKO>LPS>IAPTg>Control. The kidney inflammasome markers measured by western blot of IAPKO mice were significantly higher than in the LPS-WT, IAPTg, and control groups. High mobility group box protein (HMGB-1), a late phase mediator of LPS, and gasdermin D, a marker for pyroptosis, were significantly high in IAPKO followed by LPS.

Conclusions: Increased serum FD in IAPKO and LPS-WT group suggests that endotoxemia can breach intestinal barrier function resulting in the leakage of intestinal toxins from the gut and aggravating inflammation. IAP abates leaky gut, inflammation, and cell death (pyroptosis) and improves renal function by inactivating LPS.

Funding: Private Foundation Support

	FD absorption ug/ml	BUN mg/dl	Creatinine mg/dl	NFkB arb units	Caspase1 arb units	IL1-β arb units	HMGB-1 arb Units	Gasdermin arb units
Control	4.3±2 b,c,d	58.2±7 b,c,d	0.47±.2 b,c,d	0.4±.06 b,c,d	0.4±.05 b,c,d	0.13±0.02 b,c,d	0.09±.03 b,c,d	0.1±.02 b,c,d
LPS-WT	12±1 a,c	173±3 a,c	2.2±.2 a,c	1.3±.4 a,c,d	0.9±.2 a,c,d	0.5±.1 a,c,d	0.8±.1 a,c,d	0.5±.1 a,c,d.
IAPTg+LPS	5.8±0.5 a,b,d	101±4 a,b,d	1.1±.3 a,b,d	0.8±.1 a,b,d	0.6±.08 a,b,d	0.3±.04 a,b,d	0.22±.01 a,b,d	0.7±.1 a,b,d
IAPKO+LPS	19.4±3 a,bc	174±1.3a,c	1.8±.5 a,c	2±.6a,b,c	1.3±.2 a,b,c	0.8±.08 a,b,c	1.3±0.14 a,b,c	1±0.3 a,b,c

a<0.05 than control; b<0.05 than LPS; c<0.05 than IAPTg+LPS; d<0.05 than IAPKO+LPS

FR-PO117

The Kidney Protects Other Organs During Sepsis by Producing and Circulating Tamm-Horsfall Protein (Uromodulin)

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Background: Acute kidney injury (AKI) significantly increases the mortality in patient with sepsis. Although retention of uncleared toxins could potentiate this effect, the loss of a protective factor released by the kidney could also play a role. Tamm-Horsfall Protein (THP) is uniquely made in the kidney. The majority of THP is secreted into the urine, but a portion is also released into the circulation. We previously showed that AKI is an acute state of THP deficiency and that circulating THP protects against systemic inflammation. Therefore, we propose that increased systemic release of THP from the kidney protects the organism with sepsis, and that the loss of THP is a major cause of increased mortality during septic AKI.

Methods: We used the cecal ligation and puncture (CLP) model of sepsis in $THP^{+/+}$ and $THP^{-/-}$ mice and measured plasma THP in small patient cohorts admitted to the intensive care unit (ICU) with sepsis.

Results: In THP+/+ mice, the level of serum THP increases within 6 hours after CLP, and remains elevated up to 48 hours in surviving mice. This trend was also observed in ICU patients with sepsis, where increased plasma THP correlated with worsening SOFA scores (a measure of organ failure) within 48 hours of admission. We also detected high levels of THP in the bronchoalveolar lavage fluid of patients who had developed acute respiratory distress syndrome, whereas levels were undetectable in healthy controls, demonstrating that THP localizes to dysfunctional organs during sepsis. To study the effect of THP deficiency on mortality, we compared $THP^{-/-}$ to $THP^{+/+}$ mice, and found that $THP^{-/-}$ mice have decreased survival (10% vs. 60% survival, respectively. $p<0.05$) within 48 hours after CLP. Additionally, treatment of $THP^{-/-}$ mice with purified exogenous THP restores survival to the levels seen in $THP^{+/+}$ mice. Mechanistically, THP increases the phagocytic activity of macrophages, which could partially explain the benefits of THP in the setting of a systemic infection.

Conclusions: Our work strongly supports that THP potentiates a protective cross-talk between the kidney and other organs during sepsis, and underscores the importance of maintaining kidney health in septic patients. This work could lead to the development of a new therapy for sepsis by administering THP or modulating its potential targets.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO118

Increased Gut Permeability in Septic AKI: Role of Na Butyrate (NaB)

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Background: Increased intestinal permeability is associated with multiple organ dysfunction syndromes in sepsis. In septic AKI, TLR 4 receptors located on the basolateral side of the intestine can be targeted by systemic lipopolysaccharide (LPS) and cause leaky gut. Intestinal leakage further exaggerates the kidney inflammation and deteriorates AKI. NaB produced by gut microbiota has been shown to curb inflammation and gut permeability. We hypothesize that NaB will protect against LPS-induced leaky gut and ameliorate inflammation and septic AKI.

Methods: Septic AKI was induced by injecting 10 mg/kg LPS (IP). C57Bl6 mice were divided into 3 groups: Control (Ctl), AKI group received LPS (AKI) and treated (TR) group received 300 mg/kg NaB by gavage 30 mins before LPS. Mice were sacrificed after 10 hours. To measure intestinal permeability FITC-Dextran (FD) was given by gavage 2 hours before sacrifice. Blood, kidneys, and colon were harvested for biochemical and immunoblot analysis.

Results: Serum creatinine and BUN of AKI were 0.74±.05 mg/dl and 169±5 mg/dl which measured 2-fold higher than the Ctl ($p<0.01$). NaB significantly reduced both creatinine and BUN ($p<0.05$). Serum FD (14±1 μg/ml) of AKI was more than 3-fold higher than Ctl($p<0.01$). NaB treatment reduced FD levels by 13% ($p<0.05$). Compared to Ctl, colonic tight junction protein ZO-1 was significantly reduced in the colon of AKI ($p<0.05$), but was restored in TR. Inflammatory markers such as high mobility group box protein (HMGB-1), NFkB and IL-1β in the kidney of AKI were 2 to 3 fold higher than Ctl ($p<0.05$) but NaB treatment decreased them suggesting that NaB can decrease kidney inflammation in LPS induced AKI.

Conclusions: Higher levels of serum FD and loss of intestinal tight junction protein shows that endotoxemia can increase intestinal permeability which may cause leakage of toxic biomolecules from the intestine. LPS can activate inflammatory responses through HMGB-1. NaB activates intestinal alkaline phosphatase which dephosphorylates LPS and renders it inactive. In addition, NaB can act as a HMGB-1 antagonist and a GPR109A agonist, both of which support intestinal barrier integrity. These might be some of the mechanism by which NaB can decrease the inflammatory burden and improve renal function in AKI.

FR-PO119

A Novel Circular RNA-has_circ_0114427 Regulates Inflammation via miR-494 in AKI

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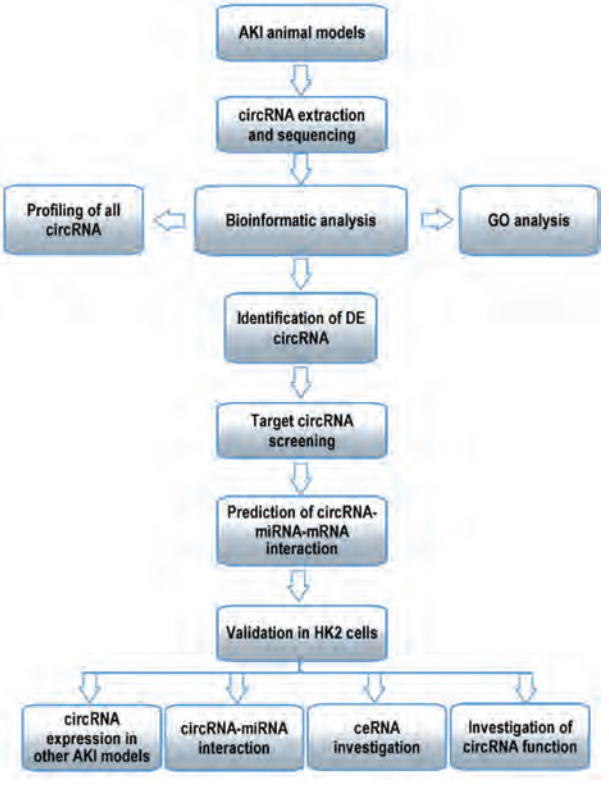
Background: Acute kidney injury (AKI) is a common serious syndrome characterized by a rapid decrease of glomerular filtration rate and the progressive increase of serum creatinine. CircRNAs are novel regulatory RNAs that recently became popular among researchers of various diseases. However, the expression profile and function of circRNAs in AKI remain largely unknown. CircRNAs act as competing endogenous RNAs (ceRNAs) to regulate transcription level by binding with microRNAs (miRNAs), as indicated by recent research.

Methods: In the current study, we established a cisplatin-induced AKI mice model and then extracted circRNAs from isolated renal tubular tissues for next-generation sequencing at different time points during AKI's early stage. By using bioinformatic analysis, we identified out a certain number of significant differentially expressed mmu-circRNAs in AKI. Furthermore, we validated the expression pattern and explored the function of the significant homologous circRNAs in HK2 cells.

Results: We successfully identified differentially expressed circRNAs related to AKI. By finding homologous genes between mouse and human, we identified a new circRNA, circ-0114427, in humans. Circ-0114427 expression was significantly up-regulated in different AKI cell models. Knockdown of circ-0114427 indicated that circ-0114427 bound to miR-494 as a miRNA sponge to regulate ATF3 expression and further affected the expression of downstream cytokine IL-6.

Conclusions: Elevated circ-0114427 may play an important role in anti-inflammation in the early stage of AKI. Our findings provide a novel insight into the regulatory mechanism of circRNAs in AKI and may become a new molecular target resource for early diagnosis and treatment strategies.



The workflow of our experiments

FR-PO120

Genome-Wide Association Study for AKI in the ASSESS-AKI Study

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Background: Identifying genetic risk factors for AKI could provide insights into pathophysiology and help identify novel pathways for therapeutic development.

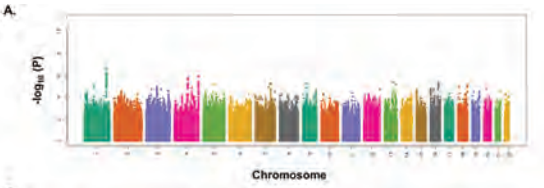
Methods: We conducted a genome-wide association study in a multi-ethnic population of 1,370 prospectively enrolled subjects in the ASSESS-AKI Study. Genotyping was completed using the Illumina MEGA chip and the Haplotype Reference Consortium was used for genome-wide multiple imputation. Genetic association testing for AKI was conditioned on: age, sex, diabetes, center and first three principal components of ancestry. Threshold for significance included single-nucleotide polymorphisms (SNPs) with a $p < 5 \times 10^{-6}$.

Results: Among 637 AKI and 733 non-AKI participants, 5,645,675 SNPs were tested for the association with AKI. Among AKI participants, 72% had Stage 1 AKI and 7% required new dialysis during hospitalization. We found that 56 SNPs in six novel loci were associated with the development of AKI (**Figure 1**). The SNP with the strongest association with AKI was rs17538288>A. The minor allele of rs17538288 was associated with an increased risk for AKI (adjusted odds ratio 1.53, 95% confidence interval 1.30 – 1.79, $p=2.08 \times 10^{-7}$). Utilizing integrated functional epigenomic analyses, we found that top-performing SNPs localized to regulatory DNA elements in primary human glomerular and cortex cell culture. We also investigated 22 SNPs identified in two prior AKI GWAS studies and found that none of the SNPs replicated in ASSESS-AKI ($p<0.05$).

Conclusions: We identified six novel genetic loci that were associated with prevalent AKI. Functional annotation in kidney cells/tissue provides insights into the mechanism of kidney injury. Future work will require replication in well-phenotyped AKI cohorts and mechanistic studies to understand the relationship of genetic variation and AKI development.

Funding: NIDDK Support

A.



B.

SNP	Chr	Position	Gene	Minor Allele	Minor Allele Frequency	OR (95% CI)	P*
rs17538288	1	223192017	*Intergenic*	A	0.439	1.53 (1.30-1.79)	2.08×10^{-7}
rs6533107	4	104706914	*Intergenic*	A	0.352	0.67 (0.56-0.79)	1.63×10^{-6}
rs9998646	4	188592759	*LINC02492*	C	0.441	0.69 (0.59-0.80)	1.29×10^{-6}
rs4414368	13	83974202	*Intergenic*	T	0.177	0.59 (0.47-0.74)	4.20×10^{-6}
rs12926740	16	79485791	*MAF*	C	0.494	1.47 (1.25-1.73)	4.44×10^{-6}
rs4352929	9	28887250	*LINGO2*	G	0.447	0.68 (0.58-0.80)	4.88×10^{-6}

Figure 1. Six novel loci are associated with the development of AKI in the ASSESS-AKI study. (A) Manhattan plot demonstrates 56 total single-nucleotide polymorphisms (SNPs) in six loci with a $p < 5 \times 10^{-6}$ for the development of AKI. (B) List of top performing SNPs at each genomic loci for the development of AKI using an additive genetic model. Odds ratio (OR) and *p*-value after adjusting for patient's age, gender, diabetes, center and the first three principle components of ancestry.

FR-PO121

Mechanisms of Remote Organ Dysfunction in AKI

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Background: While ~1.7 million acute kidney injury (AKI) patients die each year, the very high mortality rate is largely due to failure of extra-renal organs and not typically caused by renal dysfunction. We and others have shown persistent coagulation abnormalities and impaired renal microvascular function in experimental AKI. We hypothesize that the clotting abnormalities are systemic and contribute to multi-organ dysfunction in AKI.

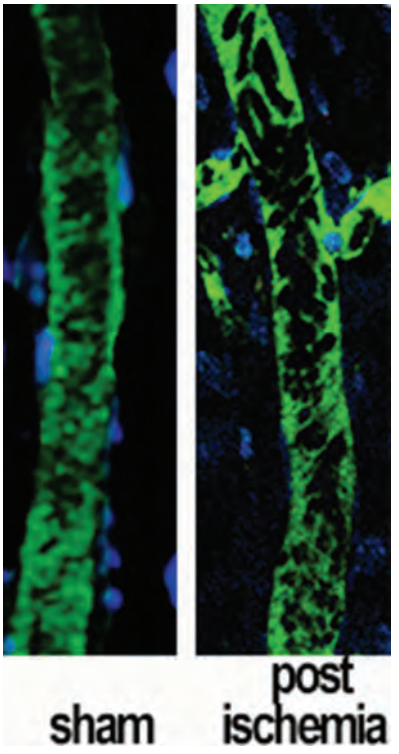
Methods: The role of activated coagulation, microvascular dysfunction and impaired perfusion were assessed in a model of ischemic AKI using multiphoton, intravital imaging. The effects of a fibrinolytic agent were also examined.

Results: In addition to diffuse renal microvascular thrombi, we found heterogeneous clotting in the microvasculature of the brain, intestine, mesentery, liver, spleen and lung

after renal ischemia. Microvascular flow was significantly decreased 48 hours after renal ischemia, to 24-58% of sham levels in different organs. In addition, tissue factor was increased postischemia in the kidney, heart, lung, liver and serum (2.4-4.2 fold, $p<0.04$). In the heart, expression of tissue factor pathway inhibitor was 0.54 +/- 0.1 fold that seen in shams ($p<0.05$). In addition, left ventricular function was impaired. Plasma flow and microvascular thrombi in remote organs improved with fibrinolytic therapy given after renal failure was established.

Conclusions: Our data indicate persistent systemic coagulation abnormalities after ischemic renal injury contributes to sustained, heterogeneous ischemia, leading to inflammation and tissue injury in multiple extra-renal organs. We have previously shown decreased cardiac function in experimental AKI. The systemic abnormalities likely contribute to the morbidity and mortality of AKI, but are amenable to therapeutic intervention.

Funding: Veterans Affairs Support, Private Foundation Support



representative intravital images

FR-PO122

Modulation of Oxidative Stress Prevents Deleterious Lung Kidney Interactions in a Novel Experimental Model of Pulmonary Renal Syndrome

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Background: AKI is the most common organ dysfunction in acute lung injury (ALI) and ARDS. In fact, AKI increases the mortality rate to more than 40%, with the rate rising with AKI severity. Deleterious interactions between kidney and lung play a major role in multiorgan failure in critically ill patients. But, the casual relationships between lung injury and kidney injury is not well understood. Large body of evidence suggests oxidative stress mediates lung-kidney organ crosstalk. However, specific therapies are lacking. Since ALI/AKI, once initiated, is much less susceptible to treatment we need to investigate potential protective treatment which requires developing experimental model to translate drug findings from bench to bedside.

Methods: In a novel model of ALI/AKI induced by a toxic alkaloid (Tox-ALK) injection to evaluate the effects of antioxidant treatment, rats were treated with an Angiotensin II Type 1 (AT1) receptor blocker with antioxidant activity daily starting a week before and continued for 1 wk post-(Tox-ALK) injection. Serial echocardiography was performed weekly to non-invasively monitor evolution of pulmonary hypertension secondary to lung injury. At 4 weeks lungs and kidneys were analyzed for antioxidant enzyme activities including superoxide dismutase, glutathione peroxidase, catalase and oxidative stress. Lungs wet/dry weight ratios were measured to assess edema. After sacrificing the animals, the renal cortex and the lung were removed for histology

Results: At 4 wks post-Tox-ALK, there was acute lung injury, characterized by lung edema, neutrophil infiltration, hypoxemia and acute tubular necrosis in the Kidney. Losartan treatment attenuated Tox-ALK induced oxidative stress in lung and the kidney, ALI, PH and importantly, increased the activities of SOD and GSHPx in the lung and the kidney.

Conclusions: In this experimental model ALI and AKI in rats correlates with a decrease in antioxidant and increase in oxidative stress in the lung & the kidney. Inhibition of the RAS prevent ALI and AKI, improved survival as well as oxidative stress parameter in the kidney. This study suggest the beneficial effects of AT1 receptor blocker as a kidney–lung protective strategy in critically ill patients.

FR-PO123

Metabolomics in the Lung After Ischemic AKI Reveals Increased Oxidative Stress, Altered Energy Production, and Energy Depletion

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Background: Acute kidney injury (AKI) is a systemic disease with deleterious effects on distant organs, including the lung. Lung function is dependent upon redox homeostasis and ATP generation through oxidative phosphorylation. Acute lung injury (ALI) after AKI is characterized by acute inflammation and neutrophil accumulation. Metabolically, ALI shows increased oxidative stress, energy depletion, and altered energy production. We sought to determine the effect of AKI on lung metabolism.

Methods: Normal mice and mice after sham (surgery alone) or surgery for ischemic AKI (22 minutes of bilateral renal pedicle clamping) were studied at 4-hours, 24-hours or 7 days post procedure. Lung metabolomics was performed via ultra high-pressure liquid chromatography coupled to online mass spectrometry (UHPLC-MS). Untargeted UHPLC-MS-based metabolomics analysis provided the measurement of 132 annotated metabolites in the lung. Commercially available reagents (Abcam; ab833355) were used to measure lung ATP.

Results: AKI had a significant effect on the lung metabolome at 4- and 24-hours post-procedure. There was evidence of 1) increased catabolism characterized by decreased amino acids and their metabolites (ie. Leucine/Isoleucine, Phenylalanine, S-Adenosyl-L-Methionine at 4 hours and lysine, D-O-phosphoserine, L-adrenaline, L-carnitine and O-propanoylcarnitine at 24 hours), 2) increased oxidative stress and dysregulated redox system via decreased levels of glutathione, thioredoxin disulfide, nicotinamide and adenosine, and 3) use of alternative energy sources characterized by decreased intermediates in glycolysis (ie. lactate and D-glucose) and the pentose phosphate pathway (ie. D-Ribitol-5-Phosphate and D-Ribose). Lung ATP levels were reduced in the lung after AKI compared to sham and control at 4 hours [control CI 2.5-6.8 ($p<0.0001$), sham CI 2.3-6.0 ($p<0.0001$)] and 24 hours [control CI 0.8-5.6 ($p=0.003$), sham CI 0.5-4.9 ($p=0.007$)].

Conclusions: This is the first study to examine the metabolome and ATP levels post-ischemic AKI in the lung. Our findings show depleted ATP levels and evidence of increased oxidative stress, energy depletion and use of alternative energy production. Further metabolomic profiling in the lung post-AKI is needed to identify pathways for future clinical interventions.

Funding: Other NIH Support - 1R01 HL095363 provided to Sarah Faubel, MD, Veterans Affairs Support

FR-PO124

Elucidation of the Mechanism of Kidney-Gut Cross-Talk via the D-Serine Derived from Gut Microbiota

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Background: While dysbiosis of the gut microbiota has been closely associated with kidney disease, the precise underlying mechanisms remain unclear. Recent advances have shed light on the chirality of amino acids. Free D-amino acids and their L-forms were quantified by 2D HPLC. Accumulating data revealed that D-amino acids were the primary microbial products, which showed physiologic roles in several organs. However, the involvement of D-amino acids in kidney diseases have yet to be revealed. Thus, we explored the pathophysiological role of D-amino acids in association with the gut microbiota in kidney disease.

Methods: Six-week-old male C57BL/6 (B6) mice and germ-free (Gf) B6 mice were subjects to sham or ischemia-reperfusion (I/R) operation, and evaluated 2, 5, 7 and 10 days after surgery. D-serine was administered to mice via drinking water during I/R induced kidney injury. We performed 16S rRNA gene sequencing analysis of the mouse gut microbiota and evaluated D- and L-amino acids in the mouse feces, plasma, kidney and urine using 2D HPLC system. We also obtained blood samples from patients with AKI to evaluate D- and L-amino acids.

Results: Specific gut bacteria were influenced by I/R. Further, I/R induced kidney injury was more severe in Gf B6 mice compared to B6 mice. Interestingly, fecal transplantation from normal mice attenuated the renal pathology in the Gf B6 mice. Next, we performed comprehensive analyses of chiral amino acids in I/R induced kidney injury. While various D-amino acids were detected in the feces, only D-serine was detected in the injured kidney. Furthermore, D-serine was not detected in the feces of Gf B6 mice, suggesting that gut microbiota produced D-serine in response to kidney disease. Further, the oral administration of D-serine attenuated I/R injury in normal mice. In addition, we assessed the association between D-serine and renal function in patients with AKI. The plasma levels of D-serine in patients with AKI was higher than in the plasma of healthy subjects, showing a high correlation with creatinine ($r > 0.9$).

Conclusions: These results demonstrate the renoprotective effects of gut-derived D-serine in AKI, shed light on the novel interactions between the gut microbiota and the kidney, and highlight D-serine as a potential new therapeutic target and biomarker for AKI.

FR-PO125

Sham Surgery Suppresses Autophagy in the Kidney and Heart

Carolyn N. Brown, Sara Holditch, Nataliya Skrypnyk, Chris Altmann, Jelena Klawitter, Sarah Faubel, Charles L. Edelstein. *UC Denver Anschutz Medical Campus, Aurora, CO.*

Background: Renal ischemia/reperfusion (IR) and compensatory hypertrophy induced by unilateral nephrectomy (UNX) activate mTOR, a suppressor of autophagy. Autophagy maintains proteostasis by sequestering proteins into autophagosomes for delivery to the lysosome where cargo is recycled. The aim of the study was to determine the effect of sham surgery (SHAM), UNX, or IR on mTOR and autophagy in the kidney & heart in wildtype mice.

Methods: IR was induced by bilateral renal pedicle clamp; mice were sacrificed 24 or 72hr later. UNX was performed; mice were sacrificed 2hr later. Normal mice without surgical manipulation (NORM), SHAM, IR, and UNX mice were treated with vehicle or bafilomycin (BAF) 2hr before sacrifice. LC3-II and p62 were measured by immunoblot. Increased LC3-II (autophagosome marker) after BAF or decreased p62 (degraded by autophagy) were used as markers of autophagy.

Results: Autophagy was suppressed in the kidney 2hr after UNX and SHAM compared to NORM kidneys, but only 2hr after UNX in the heart. There was suppressed autophagy in the heart at 24hr of both IR & SHAM that normalized by 72hr. Suppressed autophagy in the kidney & heart in SHAM, UNX, & IR was associated with statistically significant increases in mTOR (pS6, p4E-BP1, pAkt). To determine a possible mechanism of suppressed autophagy, metabolomics analysis was performed on 2hr NORM, SHAM, & UNX kidneys. Of 225 metabolites measured, folate, fructose phosphate, & glycine with known roles in autophagy regulation were significantly decreased (P<0.05) in both SHAM and UNX vs. NORM kidneys.

Conclusions: SHAM suppresses autophagy in the kidney & heart. Increased mTOR and suppressed autophagy in the kidney & heart caused by SHAM have important implications for researchers using models requiring surgery. The connection between suppressed autophagy & folate, fructose phosphate, & glycine merits further study.

Funding: Veterans Affairs Support

Table 1. UNX		NORM	NORM+BAF	SHAM	SHAM+BAF	NEPH	NEPH+BAF
KIDNEY	LC3-II	0.5	0.8*	1.0*	1.2	1.4*	1.4
	p62	0.3	0.3	1.0*	1.3	1.7*	1.8
HEART	LC3-II	0.3	1.1*	1.1*	2.3#	1.0	1.0
	p62	0.9	1.0	1.3	1.5	0.8#	0.8

Table 2. IR		NORM	NORM+BAF	24HR SHAM	24HR SHAM+BAF	24HR IR	24HR IR+BAF	72HR SHAM	72HR SHAM+BAF	72HR IR	72HR IR+BAF
KIDNEY	LC3-II	0.2	0.7*	0.6*	1.0#	1.5#	1.8	0.9	2.1^	1.0	1.9&
	p62	1.3#	1.4	0.4	0.5	1.4#	1.9	0.5	0.6	0.6	1.0
HEART	LC3-II	1.0	1.4*	1.0	0.8	1.0	1.2	0.8	1.0	0.7	1.1&
	p62	0.3	1.2*	1.1*	1.3	1.4*	1.4	0.7	0.6	0.6	0.5

Table 1: *P<0.05 vs NORM #P<0.05 vs SHAM

Table 2:*P<0.05 vs NORM, #P<0.05 vs 24HR SHAM, ^P <0.05 vs 72HR SHAM, &P<0.05 vs 72HR IR

FR-PO126

Real-World Use of Calcimimetics in Small and Independent Hemodialysis Facilities

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Background: In 2018, when etelcalcetide [ETE] became commercially available, dialysis organizations became newly responsible for providing calcimimetics to Medicare patients due to a reimbursement change from Part D to Part B. This study describes calcimimetic utilization and control of circulating parathyroid hormone (PTH), calcium (Ca) and phosphorous (P) in adults with a record of calcimimetics during the first 9 months of 2018 in small and independent hemodialysis facilities (SDO/IDOs).

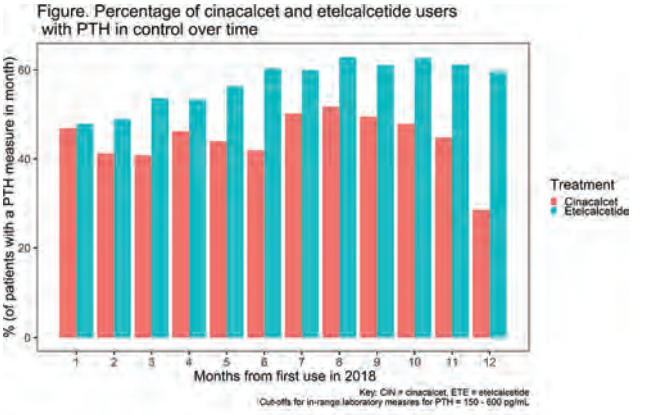
Methods: This is a retrospective study of electronic health records from SDO/IDOs (Visonex) from 10/1/2017 to 12/31/2018. Adults ≥18 years of age were identified as a Cinacalcet (CIN) or ETE user based on their first calcimimetic in 2018. Patients were followed until kidney transplant, death, or end of data collection. Descriptive analyses of patient characteristics and laboratory control at baseline and follow-up were conducted.

Results: In the first 9 months of 2018, 2601 patients received a calcimimetic (CIN (n=1346, mean (SD) age=60.5 (14.0), 43.5% female, 47.1% black) or ETE (n=1255, mean (SD) age=63.4 (14.5), 46.6% female, 38.5% black). Median (IQR) months of follow-up was 5.0 (2-9) for CIN, and 8.0 (4-11) for ETE. Median (IQR) PTH (pg/mL), P (mg/dl) and Ca at baseline were 670 (356-1094), 5.6 (4.7-6.8), and 9.2 (8.7-9.7)) for CIN; and 686 (453-1044), 5.6 (4.7-6.7), and 9.1 (8.7-9.6), respectively for ETE users. Cut-offs for in-range laboratory measures were: PTH=150-600 pg/mL; P=3.5 – 5.5 mg/dL; and Ca=8.4 – 10.2 mg/dL. See figure for proportion of patients in control for PTH by month.

Conclusions: ETE users in SDO/IDOs had improved control during a longer follow-up compared with CIN, with 61% of patients having PTH in control at 9 months.

Funding: Commercial Support - Amgen

Figure. Percentage of cinacalcet and etelcalcetide users with PTH in control over time



Patients with PTH measure

Treatment	1	2	3	4	5	6	7	8	9	10	11	12
Cinacalcet	452	691	789	528	566	539	396	321	289	209	154	21
Etelcalcetide	549	978	903	784	698	674	522	515	414	343	250	109

FR-PO127

Timing of PTH Reduction with Cinacalcet (CIN) or Etelcalcetide (ETL) Treatment and Effect of Previous CIN Dose

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Background: The calcimimetics ETL and CIN reduce serum parathyroid hormone (PTH) in subjects with secondary hyperparathyroidism (sHPT) on hemodialysis (HD) (NCT1896232; Block *JAMA* 2017). This post-hoc analysis investigated the timing of PTH reductions following CIN or ETL treatment and their relation to previous CIN treatment.

Methods: Data were derived from a phase 3, randomized, active control, dose-titration trial comparing the safety and efficacy of CIN and ETL in adults with sHPT receiving HD with PTH ≥500 pg/mL. Subjects received CIN (titrated from 30-180 mg PO QD) and IV placebo (TIW); or ETL (titrated from 5-15 mg IV TIW) and placebo (PO QD) for 26 weeks to target a PTH ≤300 pg/mL. Subjects could not have received CIN during the 3 months prior to screening. Achievement of >30% PTH reduction by 8 or 18 weeks and maintenance of the target PTH reduction during the efficacy assessment phase (weeks 20-27) were analyzed. Stratified by previous CIN dose, PTH levels over time were summarized using descriptive statistics.

Results: At baseline, subjects (N=683 [343 CIN; 340 ETL]) had a median PTH of 930 and 900 pg/mL in the CIN and ETL groups, respectively. By week 8, >70% of subjects had achieved >30% PTH reduction from baseline (Table). Of these, 80% receiving ETL vs 68% receiving CIN maintained >30% PTH reduction in weeks 20-27. By week 18, >85% of subjects had achieved >30% PTH reduction from baseline. Of these, 77% receiving ETL vs 65% receiving CIN maintained >30% PTH reduction in weeks 20-27. In both groups, subjects with a lower previous CIN dose showed mostly consistent declines in PTH over time, with the ETL group achieving a greater magnitude reduction from baseline by week 26.

Conclusions: CIN and ETL can effectively reduce PTH levels within 8 weeks, and ETL may better preserve this reduction over time.

Funding: Commercial Support - Amgen Inc.

Table. Reduction in PTH following treatment with etelcalcetide or cinacalcet and its relation to previous calcimimetic treatment.

	Head-to-Head Trial	
Treatment Group	**Cinacalcet (N = 343)**	**Etelcalcetide (N = 340)**
>30% PTH reduction from baseline by week 8, N1	252	245
Maintained >30% PTH reduction in week 20-27, n (%)[a]	172 (68.3)	195 (79.6)
>30% PTH reduction from baseline by week 18, N1	299	299
Maintained >30% PTH reduction in week 20-27, n (%)[b]	195 (65.2)	230 (76.9)

Previous Cinacalcet Dose	**30-90 mg (n = 51)[c]**	**>90-180 mg (n = 3)**	**30-90 mg (n = 50)[d]**	**>90-180 mg (n = 3)**
PTH, pg/mL – median				
Baseline	1251.2	1186.1	1128.2	1709.5
Week 4	1210.9	1110.7	820.6	1947.2
Week 8	816.4	1232.2	644.2	1849.6
Week 16	768.5	999.8	457.2	2091.8
Week 20	750.1	665.0	321.8	2229.2
Week 26	609.1	1121.5	389.5	932.5

N = number of subjects in full analysis set; N1 = number of subjects with at least 1 PTH record showing >30% PTH reduction from baseline by the week indicated
[a]Percentages are based on N1; subjects with missing data (n=16 for cinacalcet, n=25 for etelcalcetide) are not included
[b]Percentages are based on N1; subjects with missing data (n=17 for cinacalcet, n=27 for etelcalcetide) are not included
[c]At week 26, n = 45; [d]At week 26, n = 41

Reduction in PTH with treatment and effect of previous CIN dose

FR-PO128

PTH Levels Prior to Initiating Hemodialysis: Associations with Prescription of PTH-Lowering Therapies and Risk of Uncontrolled PTH During the First Year of Hemodialysis

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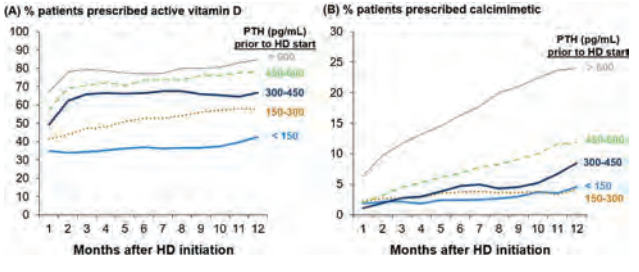
Background: PTH levels during pre-dialysis may influence subsequent management and achieved PTH levels after onset of ESRD.

Methods: We studied 5683 incident HD patients from 21 countries in phases 4-6 (2009-2018) of the Dialysis Outcomes and Practice Patterns Study (DOPPS) with information on PTH measured immediately prior to HD initiation. We stratified by PTH prior to HD start and reported the monthly prescription prevalence of active vitamin D and calcimimetics over the first year of HD, and risk of PTH >600 pg/mL after 9 months on HD.

Results: Median (IQR) PTH prior to HD start was 275 (155, 472) pg/mL and 16% of patients initiated HD with PTH >600 pg/mL. Patients who initiated HD with higher PTH levels were more likely to be prescribed active vitamin D in the early months of HD, and these differences were steady over the first year of HD (Figure A). Patients starting HD with PTH >600 pg/mL were much more likely to initiate calcimimetic treatment during the first year of HD, amplifying differences in calcimimetic use by PTH at HD start over the first year of HD (Figure B). Among a subset of 2728 patients who remained in DOPPS with PTH measured 9-12 months after HD initiation, the prevalence of PTH >600 pg/mL was much greater for patients who initiated HD with PTH >600 (29%) vs. 150-300 (7%) pg/mL.

Conclusions: The findings were consistent with the hypothesis that management of PTH in the pre-ESRD phase influences subsequent PTH management and levels after onset of ESRD. Patients with greater PTH concentrations prior to start of dialysis were more likely to receive active vitamin D and calcimimetic therapy in the first year of HD. However, despite more aggressive management, high PTH prior to initiation of dialysis was associated with high PTH (>600 pg/ml) 9 months after the start of hemodialysis. These findings help inform clinical management and research goals and provide insight into cost drivers for PTH management in HD.

Funding: NIDDK Support, Commercial Support - This analysis was supported by Vifor. The DOPPS Program is supported by Amgen (since 1996, founding sponsor), Kyowa Hakko Kirin (since 1999 for Japan DOPPS), and Baxter Healthcare Corp. Additional support for specific projects and countries is provided by Akebia Therapeutics, AstraZeneca, European Renal Association-European Dialysis & Transplant Association (ERA-EDTA), Fibrogen, Fresenius Medical Care Asia-Pacific Ltd, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGfN), Italian Society of Nephrology (SIN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Otsuka America, Proteon Therapeutics, the Association of German Nephrology Centres, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Belgian Federal Public Service of Public Health in Belgium, Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN) in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN), and Kidney Research UK (KRUK) in the United Kingdom, and the Agency for Healthcare Research and Quality (AHRQ) and National Institutes of Health (NIH) in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health., Private Foundation Support, Government Support - Non-U.S.



FR-PO129

Parathyroidectomy vs. Cinacalcet for Secondary Hyperparathyroidism in Patients Undergoing Hemodialysis

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Background: Parathyroidectomy (PTx) and cinacalcet are both effective in treating secondary hyperparathyroidism in patients undergoing hemodialysis. However, there is a paucity of data comparing the long-term outcomes of these treatments.

Methods: We analyzed data from a nationwide cohort of hemodialysis patients in Japan who had intact parathyroid hormone (PTH) levels >300 pg/ml and no history of prior PTx on December 2007. Patients who underwent PTx or initiated cinacalcet between January 2008 and December 2009 were matched for baseline intact PTH levels and propensity score in a 1:3 ratio. Mortality follow-up started on December 2009 and continued until December 2015. Mortality risk was assessed using Cox proportional hazards models.

Results: A total of 894 patients who underwent PTx and 2,682 patients who initiated cinacalcet had similar propensity scores and were included in the analysis. Median baseline intact PTH levels were 588 pg/ml (interquartile range [IQR], 422-809 pg/ml) and 566 pg/ml (IQR, 427-777 pg/ml) in the PTx and cinacalcet groups, respectively. Following either treatment, the intact PTH levels decreased to 83 pg/ml (IQR, 19-225 pg/ml) in the PTx group and 218 pg/ml (IQR, 138-364 pg/ml) in the cinacalcet group. During the 6-year of follow-up period, 201 patients in the PTx group and 736 patients in the cinacalcet group died. PTx was associated with a significantly lower risk of death compared with cinacalcet (hazard ratio, 0.78; 95% confidence interval, 0.67-0.91). The survival benefit associated with PTx versus cinacalcet was more pronounced in patients with baseline intact PTH levels >500 pg/ml and in patients with baseline serum calcium levels >10.0 mg/dl (both P <0.001 for interaction). The difference in mortality between PTx and cinacalcet was attenuated by adjustments for time-varying intact PTH, calcium, and phosphorus levels.

Conclusions: PTx compared with cinacalcet is associated with a lower risk of death, particularly among patients with severe secondary hyperparathyroidism.

FR-PO130

Thrice Weekly vs. Daily Cinacalcet: Virtual Clinical Trial and Its Subsequent Clinical Validation in a Large US Hemodialysis Population

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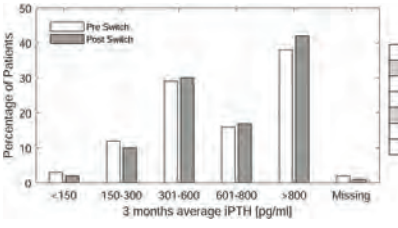
Background: Secondary hyperparathyroidism affects most hemodialysis (HD) patients. Current therapies include cinacalcet. Its label indicates a daily, oral administration with food. However, high pill burden and gastrointestinal side effects limit patient adherence. The aim of this study was to explore in a virtual clinical trial (VCT) whether directly observed 3x weekly in-center (IC) administration is sufficient to control parathyroid hormone (PTH) levels. The VCT findings were compared to observations in a subsequent roll-out of 3x weekly IC cinacalcet in a large U.S. HD population.

Methods: We utilized 2 mathematical models, a cinacalcet pharmacokinetic model (Schappacher-Tilp, Cell Phys Biochem 2019) and a comprehensive model of parathyroid gland biology (Schappacher-Tilp, Phys Rep 2019). We simulated 2 populations, cinacalcet naïve patients and patients on cinacalcet for ≥ 12 weeks. We then compared PTH levels attained with directly observed 3x weekly vs. daily administration; for the latter we considered a real-life adherence rate of 64%, based on pharmacy data. A subsequent clinical roll-out involved 4865 HD patients on daily cinacalcet for ≥ 12 weeks who were subsequently switched to 3x weekly IC cinacalcet for ≥ 12 weeks.

Results: Our VCT showed that patient adherence significantly impacts PTH levels. The PTH lowering effects of prescribed daily cinacalcet administration with limited patient adherence were almost identical to directly observed 3x weekly IC administration. Model predictions were corroborated by subsequent clinical observations (Fig 1).

Conclusions: Directly observed 3x weekly IC administration of cinacalcet is not inferior to daily administration with realistic adherence rates. Our results support the utility of VCTs for exploring alternative therapy regimens.



	Ranges [mg/dl]		
Phosphate	< 3.0	3.0-5.5	> 5.5
pre [%]	1	48	50
post [%]	1	48	51
Calcium	< 8.5	8.5 – 10.0	> 10.0
pre [%]	14	81	5
post [%]	13	83	4

FR-PO131

Efficacy and Safety of Cinacalcet in Chinese Maintenance Hemodialysis Patients with Different Stages of Secondary Hyperparathyroidism: Rationale and Design of ACTIVE Study

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Background: Secondary hyperparathyroidism (SHPT), as a common complication in advanced Chronic kidney disease (CKD) has become a global public health problem. Patients with CKD and uncontrolled SHPT are at high risk of cardiovascular events and associated mortality. Cinacalcet, a calcimimetic agent was reported to effectively and safely reduce PTH levels in CKD patients with SHPT previously. However there has been no large-scale study and stratified analysis of cinacalcet in China and the optimal therapeutic doses of different levels of severity of SHPT still remain unknown.

Methods: A phase IV, open-label, multicenter study was designed and conducted in 23 hospitals in China. The study was performed in two phases. In phase 1, a cohort study for 32 weeks follow-up was designed to explore the efficacy and safety of cinacalcet. In phase 2, a real-world study of 20 additional weeks was designed in which patients completing the cohort study decided on their own whether to continue taking cinacalcet at their own cost or not. Patients with a baseline iPTH ≥300 pg/mL should receive at least 12 weeks of maintenance hemodialysis before enrollment. The primary efficacy endpoint is the proportion of patients achieving iPTH targets (iPTH between 150-300pg/mL) at 20 and 32 weeks after the initiation of cinacalcet treatment (shown in Fig.1)

Results: Up to 2019/05/12, a total of 750 maintenance hemodialysis patients with SHPT were enrolled and stratified into 3 groups according to baseline iPTH level (mild 300~600, moderate 600~900 and severe ≥900 pg/mL respectively). The trial is still in progress and enrollment has been completed. Analysis of the baseline data is ongoing and the corresponding results will be released at ASN meeting this year.

Conclusions: We expect that the results of this study will allow us to draw valuable conclusions related to these objectives and expand the medical knowledge of end stage kidney disease(ESKD) especially for patients with SHPT

Funding: Commercial Support - Kyowa Hakko Kirin (China) Pharmaceutical Co., Ltd.

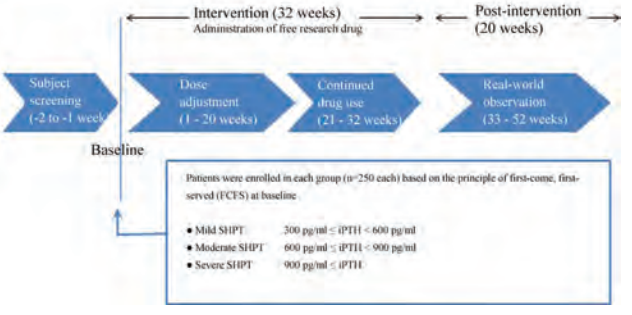

Figure 1. Clinical trial design

FR-PO132

Role of Etelcalcetide in the Management of Secondary Hyperparathyroidism in Hemodialysis Patients After 10 Months of Therapy

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Background: Secondary hyperparathyroidism (sHPT) is common in hemodialysis (HD) patients. The present study aimed to evaluate the efficacy and safety profile of etelcalcetide in an observational study for the treatment of SHPT in CKD patients on hemodialysis.

Methods: 60 HD stable patients with sHPT were received etelcalcetide for 10 months, who were receiving oral or iv VDRA's and/or cinacalcet or were naïve before start of the protocol. Dose of VDRA's remained stable and adjustments to etelcalcetide dose were taken place every month. PTH levels, Ca, Ph, alb were measured before starting etelcalcetide and every month until the end of the protocol. Heart function of patients evaluated at the start and at the end of the study. The primary outcome was estimation of intact-parathyroid hormone (PTH) concentrations. Secondary outcomes were monitoring of calcium, phosphate (ph) albumin. Our study population was divided to sub-groups: a. diabetics and non-diabetics, b. patients over and below 65 years old, c. patients that were naïve regarding CKD-MBD therapy, or were receiving monotherapy or replaced cinacalcet with etelcalcetide and d. according to their previous PTH levels (below 500 pg/ml, between 500-700 pg/ml and over 700 pg/ml|). Adverse events (AEs) were also evaluated.

Results: PTH significantly decreased from the first month of the treatment with etelcalcetide (771.53±438.58 vs 586.55±497.30, p<0.05, approximately 24% reduction from baseline). This trend carried out until the end of the study period (363.08.±373.90.60, p<0.05, approximately 47% reduction from baseline). We also noticed significant reduction of the ph levels even from the second month of treatment (from 4.98.±1.24 to 4.64±1.86 mg/dl, p<0.05). This trend also carried out for 8 months period (4.67±1.22 mg/dl, p<0,05). Heart function remained stable. In all the sub-groups we had significant reduction of PTH and Ph during the whole study period. Remarkable finding was the stable bevaviour of Ca levels from the first week until the end of the study period along with albumin. None of the patients of the protocol dropped out due to adverse events.

Conclusions: Etelcalcetide is safe, well tolerated and effective in reducing iPTH in HD s patients with sHPT. As the only available intravenous calcium-sensing receptor agonist, etelcalcetide is likely to provide a new treatment option for sHPT in HD patients.

FR-PO133

Effect of Switching from Cinacalcet to Etelcalcetide on Secondary Hyperparathyroidism in Patients with Hemodialysis: An ESCORT Trial

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Background: Cinacalcet (Cina) is used in the management of secondary hyperparathyroidism (SHPT) in patients undergoing hemodialysis (HD). Etelcalcetide (Etel) is a novel intravenous calcimimetic for the treatment of SHPT, which could improve drug adherence and reduce adverse gastrointestinal events. Here, we evaluated the efficacy of switching from Cina to Etel in the management of SHPT and constructed the dose conversion factor in this ESCORT trial.

Methods: A total of 138 HD patients on Cina were screened, and 93 patients with serum-intact parathyroid hormone (iPTH) ≥60 pg/mL and serum albumin-corrected calcium (cCa) ≥8.4 mg/dL were enrolled. The patients were divided into three groups (Cina 25 mg, 50 mg, and ≥75 mg). Etel was administered intravenously for 24 weeks. The primary endpoint was the dose distribution of Etel in patients who achieved target iPTH levels (60–240 pg/mL) after 24 weeks. Further, we investigated serum bone alkaline phosphatase (BAP), tartrate-resistant acid phosphatase 5b (TRACP 5b), and fibroblast growth factor 23 (FGF23).

Results: A total of 90 patients completed the study. At the end of the study, mean iPTH levels significantly decreased in the Cina 25 mg group (Cina 25 mg: from 179.8 ± 97.1 to 137.4 ± 62.9 pg/mL, $p = 0.003$; Cina 50 mg: from 177.0 ± 122.5 to 177.2 ± 80.3 pg/mL, $p = 0.996$; Cina ≥75 mg: from 289.4 ± 300.7 to 236.9 ± 211.6 pg/mL, $p = 0.110$). cCa levels significantly decreased ($p < 0.001$). Serum BAP, TRACP5b, and FGF23 levels also decreased following the drug switching ($p = 0.001$, $p < 0.001$, $p = 0.009$, respectively). Sixty patients (66.7%) maintained target iPTH levels before and after the study (pre: 133.5 ± 45.6 pg/ml; post: 148.2 ± 46.9 pg/ml). In these patients, the dose of Cina before the switch was 42.9 mg/day, and the final dose of Etel was 6.17 mg/HD. The dose conversion factor for the switch from Cina to Etel was 4.640 + 0.036*pre-dose (Cina/day). No adverse events, such as hypocalcemia and gastrointestinal symptoms, led to study discontinuation in this trial.

Conclusions: Switching from Cina to Etel effectively improved MBD and ameliorated high iPTH in patients undergoing HD for 24 weeks. No serious adverse events were observed. These results suggest beneficial effects of Etel administration in managing SHPT in patients undergoing HD.

Funding: Commercial Support - ONO Pharmaceutical

FR-PO134

Role of Etelcalcetide in the Management of Secondary Hyperparathyroidism: Clinical Experience

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Background: Etelcalcetide is the first intravenous calcimimetic authorized for the treatment of SHPT in haemodialysis (HD). It has proven to be effective in lowering parathyroid hormone (PTH), with an acceptable and comparable safety profile. There have only been a few reports regarding treatment of SHPT using etelcalcetide in clinical practice.

Methods: The aim of this deriptive study was to evaluate the results of using etelcalcetide in patients on HD with SHPT.

Results: Thirty patients on HD received etelcalcetide were enrolled (figure 1). The minimum observation period was 6 months. Fifteen (50%) were previously with cinacalcet (group 1) and 15 (50%) received etelcalcetide at onset (group 2). In global, serum PTH levels were significantly decreased at the end of follow up compared to baseline levels (PTH pretreatment 784 +/- 707 *(p 0.0077) vs* PTH end of follow- up 671 +/- 680 *(p 0.0077))*. When comparing both groups, we found a significant decrease of Ca, P and PTH in group 2. However, we only found significant decrease of Ca in group 1 (figure 2). The dosage of calcium binders (33.3% pretreatment vs 56.7% at the end of follow-up, p 0.054), non-calcium binders (40% pretreatment vs 63.3% at the end of follow-up, p 0.02) and vitamin D analogues (56,7% pretreatment vs 66,7% at the end of follow-up, p 0,3) were increased when etelcalcetide treatment was started. No changes were made in dialysate calcium concentration. Six patients, presented hypocalcemia (Ca < 7.5 mEq/l)

Conclusions: In our cohort, etelcalcetide has shown to be effective in reducing serum PTH. An increase in the use of vitamin D analogues, calcium binders and non-calcium binders has been observed, probably due to the hypocalcemia.

Funding: Government Support - Non-U.S.

FR-PO135

Etelcalcetide Utilization and CKD-MBD Marker Responses in US Hemodialysis Patients

Douglas S. Fuller,[1] Tzu-Chieh Lin,[2] Nisha Bhatt,[2] Bruce M. Robinson,[1] Ronald L. Pisoni.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Amgen, Thousand Oaks, CA.*

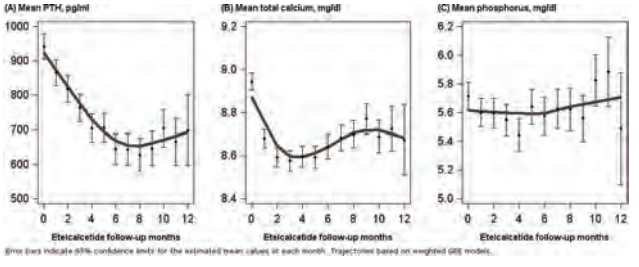
Background: Etelcalcetide is a new intravenous calcimimetic approved in February 2017 for treating secondary hyperparathyroidism in US adult hemodialysis (HD) patients. Real-world etelcalcetide utilization practices are not well understood.

Methods: Monthly cross-sectional data from a national sample of 6041-9113 HD patients/month treated at 113-157 HD units/month in the US Dialysis Outcomes and Practice Patterns Study (February 2017-February 2019) were used to describe: (1) etelcalcetide use (% of patients prescribed ≥1 dose each month) and dose at etelcalcetide initiation, by dialysis organization (DO) size (LDO sample, 10+ units; non-LDO and hospital-based sample, <10 units), and (2) trends in serum parathyroid hormone (PTH), total calcium (Ca), and phosphorus (PO_4) levels up to 12 months after etelcalcetide initiation.

Results: In February 2019, 6.1% of US HD patients were prescribed etelcalcetide, representing 21% of all US calcimimetic use. Etelcalcetide use was markedly higher in non-LDO facilities (25-26% of patients/month) than LDO facilities (2-3%). Mean initial etelcalcetide dose was 13.1 mg/wk (median: 11.5; IQR: 7.2, 13.4). At drug initiation, serum PTH was higher in LDO (median: 976 pg/ml, IQR: 596, 1709; >600: 75%) than non-LDO (median: 735 pg/ml; IQR: 448, 983; >600: 61%) facilities, mean serum total Ca was 9.0 mg/dl (median: 9.0; IQR: 8.5, 9.4), and mean serum PO_4 was 5.7 mg/dl (median:5.4; IQR: 4.4, 6.6). Among patients remaining on treatment: (1) mean and median serum PTH decreased 32% and 46% by month 6, respectively; (2) mean total Ca decreased 0.35 mg/dl by month 2, and hypocalcemia (<7.5 mg/dl) was uncommon (4.8%; range by month: 2.1-7.5%); and (3) mean PO_4 levels were relatively unchanged (range by month: 5.5-5.9 mg/dl).

Conclusions: Rapid uptake of etelcalcetide occurred in the US through February 2019, with substantial differences by DO size. Serum PTH steadily declined while treated with etelcalcetide, while calcium levels remained in the recommended range. Continued monitoring of etelcalcetide utilization will offer insights regarding titration patterns and laboratory target achievement.

Funding: NIDDK Support, Commercial Support - Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details, see https://www.dopps.org/AboutUs/Support.aspx., Private Foundation Support, Government Support - Non-U.S.



Error bars indicate 95% confidence limits for the estimated mean values at each month. Trajectories based on weighted GEE models.

FR-PO136

Effect of Active Vitamin D and Calcium-Sensing Receptor Agonists on the Responsiveness of Bone to the Parathyroid Hormone in Hemodialysis Patients

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Background: Levels of the serum parathyroid hormone (PTH) and serum tartrate-resistant acid phosphatase-5b (TRACP-5b), a bone resorption marker derived from osteoclasts, show a positive correlation. In hemodialysis (HD) patients, however, the responsiveness of bone to the serum PTH level varies widely among individuals, and the serum TRACP-5b level relative to the serum PTH level varies. This study examined factors related to the responsiveness of bone to PTH in HD patients.

Methods: This study of HD patients in Kawasaki Municipal Tama Hospital (Kanagawa, Japan) and Yonaha Medical Clinic (Okinawa, Japan) excluded those with HD for <6 months, a combination of peritoneal dialysis, cancer bone metastases, and myeloma. The TRACP-5b/intact PTH (iPTH) ratio was newly created as an index of responsiveness of bone to PTH, categorized by tertiles of the ratio (low, medium, and high), and a cross-sectional study was conducted. In each analysis, P<0.05 was considered statistically significantly different.

Results: One hundred six patients were analyzed. Age (P=0.010), body mass index (BMI) (P=0.003), use of calcium-sensing receptor (CaSR) agonists (P=0.008), use of active vitamin D (VD) (P=0.012), iPTH level (P=0.0001), $1,25(OH)_2D$ level (P=0.003), and TRACP-5b level (P=0.0001) were statistically significantly different among the three categories. In the simple linear regression analysis, age (P=0.016), corrected serum calcium level (P=0.007), and ln [$1,25(OH)_2D$] (P=0.044) showed a statistically significant positive correlation with ln (TRACP-5b/iPTH), whereas BMI (P=0.026), use of CaSR agonists (P=0.001), use of active VD (P=0.009), and serum phosphorus level (P=0.018) showed a statistically significant negative correlation. When conducting multiple linear regression analysis incorporating significant variables in the simple linear regression analysis, a statistically significant negative correlation was shown between the TRACP-5b/iPTH ratio and use of active VD and CaSR agonists.

Conclusions: The administration of active VD or CaSR agonists may reduce the stimulatory effect of PTH on bone resorption in HD patients.

FR-PO137

Relationship Between Parathyroid Hormone and Renin Angiotensin Aldosterone System in Hyperparathyroidism

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Background: Parathyroid hormone (PTH) is known to be one of the regulators for calcium and phosphate metabolism. On the other hand, it has been reported that PTH has several effects on the cardiovascular system. However, its mechanism remains to be not fully elucidated. As a possible mechanism, PTH is thought to be associated with the renin angiotensin aldosterone system (RAS). Therefore, we investigated their hormonal interaction in patients with primary and secondary hyperparathyroidism (HPT).

Methods: Twenty-seven HPT patients (primary HPT: N=10, secondary HPT: N=17) were included in this study. All the study patients underwent parathyroidectomy (PTx) in our institution. We measured serum intact PTH, plasma renin activity (PRA) and plasma aldosterone levels (ALD) before and after PTx. In addition, we evaluated blood pressure before and after PTx.

Results: Baseline estimated glomerular filtration rate (eGFR) was 44.3±35.4 ml/min/1.73m^2 in the primary HPT group. All patients in the secondary HPT group received maintenance hemodialysis. Pre-operative serum intact PTH levels were positively correlated with pre-operative ALD and PRA in both HPT groups (primary HPT group (ALD: r= 0.685, p< 0.05, PRA: r= 0.661, p< 0.05), secondary HPT group (ALD: r=0.493, p< 0.05, PRA: r=0.446, p= 0.072)). Along with changes of serum intact PTH levels after PTx, both PRA and ALD were also significantly decreased after PTx in both HPT groups. In addition, changes of serum intact PTH levels were positively correlated with changes of PRA and ALD in both groups (primary HPT group (ALD: r= 0.774, p< 0.05, PRA: r=0.815, p<0.05), secondary HPT group (ALD; r= 0.451, p= 0.069, PRA; r= 0.466 p= 0.059)). Although blood pressure was significantly decreased after PTx in the primary HPT group, it did not change in the secondary HPT group.

Conclusions: Our findings suggest that the effects of HPT on the cardiovascular system could be partially mediated by RAS in secondary and primary HPT.

FR-PO138

Parathyroidectomy: Good for the Bones, but a Pathway to Metabolic Syndrome

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Background: Increased levels of parathyroid hormone (PTH) are associated with weight loss, weakness, and muscle atrophy. Recent publications point out that PTH can regulate muscle and adipose tissues metabolism by the activation of thermogenic and atrophy-related genes. The aim of this study is to investigate the effect of parathyroidectomy (PTX) on body composition, biochemical and metabolic parameters in chronic kidney disease (CKD) patients on dialysis.

Methods: We are prospectively evaluating body composition of 30 patients before and after 6 months of PTX by using dual-energy x-ray absorptiometry (DXA), and correlating with CKD-MBD parameters.

Results: In those patients that have already completed the protocol (n=8), we observed a significant drop in PTH and alkaline phosphatase (1,329 ± 332 vs. 155 ± 151 pg/ml and 264 ± 36 vs. 79 ± 30 IU/L, p<0.001). A significant increase in body mass index (24.6±5 vs. 25.2 ± 5 kg/m^2), fat mass (FAT; 17.8 [16-23] vs. 23.2 [19-29] kg; p= 0.02), body fat percentage (%FAT; 27.7 [20-37] vs. 32 [31-42] %; p=0.006] and bone mineral content (BMC; 1.8 [1.4-2.1] vs. 2.1 [1.8-2.7]; p=0.0008] was seen. However, lean body mass (LBM) decreased (42.2 [38-55] vs. 38.9 Kg [37-51]; p=0.001]. We noticed a tendency toward an increase in fast glucose (74 [67-82] vs. 85 [80-90] mg/dl, p=0.058) and in HOMA index (1.6 [0.5-2.7] vs. 2.4 [1.3-7.1]; p = 0.10). There was a significant correlation between the percentage decrease in PTH and in LBM (r = 0.90; p = 0.0046) and a trend toward the percentage decrease in PTH and in BMC (r = -0.62; p = 0.12) and in FAT (r = -0.52; p = 0.19).

Conclusions: We demonstrated that reduction in PTH levels after PTX is associated with FAT increasing, most likely related to energy production regulation, and LBM loss. Future prospective studies should evaluate the crosstalk between muscle and fat mediated by PTH, and its impact in insulin resistance and muscle wasting.

FR-PO139

Relationship of Serum Parathyroid Hormone (PTH) Levels with Objective Measures of Nerve Function in ESRD

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Background: Advanced kidney disease is a risk factor for motor and sensory nerve deficits, independent of diabetes. The pathophysiology for nerve deficits in renal failure remains unclear. We tested the hypothesis that secondary hyperparathyroidism is associated with a distinct nerve function profile in ESRD patients.

Methods: Seventeen patients with ESRD underwent testing after their routine dialysis session. We measured action potentials (amplitude) and nerve conduction velocity (NCV) in motor (ulnar, peroneal) and sensory (ulnar, sural) nerves in the upper and lower extremities. Symptoms were assessed using the neuropathic pain questionnaire (NPQ). Muscle function was measured as handgrip strength and knee extension strength using a dynamometer. Physical performance was measured as gait speed during a 4 meter walk test. Labs drawn closest to date of testing were used for all analyses. Predefined and validated cut-offs were used to define a deficit. Statistical analyses were done using SPSS 24.

Results: Seventeen pts were enrolled: aged 23-66, 9 male, 15 black, 10 diabetic, median dialysis vintage 5.4 yrs. Ten patients had high PTH ie > 500 pg/ml (median 522 pg/ml; range 25-2364). Neuropathic pain was noted in ~60% patients overall. NCV deficits were prevalent but mean motor NCV (ulnar: 46 vs 46, peroneal 39 vs 40 m/s) or sensory NCV (ulnar 26 vs 26, sural 26 vs 28 m/s) measures were not different between high vs low PTH groups. Vibration detection threshold (48 vs 52 microns) was also similar. A deficit in ulnar motor amplitude was seen in 2 patients with high PTH levels (566 and 528) (1/2 diabetic). Both patients had neuropathic pain (function score >0), low grip strength (<20 kg) and low gait speed (<0.8 m/s).

Conclusions: Deficits in NCV, a marker of myelination, were noted in most patients on dialysis and did not differ between groups. Deficits in amplitude, a marker of axonal damage, were noted exclusively in patients with elevated PTH levels. Whether elevated PTH levels predispose to axonal neuropathy will be evaluated by ongoing enrollment of subjects and follow up testing after decreases PTH in this study.

FR-PO140

Etelcalcetide for Managing Secondary Hyperparathyroidism in Hemodialysis Patients

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Background: We retrospectively assessed the efficacy of a new calcimimetic, etelcalcetide, in Japanese chronic hemodialysis patients with secondary hyperparathyroidism (SHPT). The aim of this study was to assess the factors related to the therapeutic effects of etelcalcetide.

Methods: The subjects were 43 patients (average age: 60 years; average dialysis period: 90.7 months) with serum intact parathyroid hormone (iPTH) >240 pg/mL. Intravenous injection of etelcalcetide was started at 15 mg/week for 12 weeks and the dose was adjusted to control the serum levels of iPTH, corrected calcium (cCa), and phosphorus (P).

Results: In total, 81.3% of the patients had a reduction of iPTH of ≥50% at 12 weeks, and 32% achieved the target levels for P, cCa and iPTH. In multivariate analysis, female sex and a history of cinacalcet administration were independent inhibitory factors for iPTH reduction. Compared to patients with a history of cinacalcet administration (n=22), those without this history (n=21) had higher rates of reduction of iPTH of ≥50% (63.6% vs. 95.2%, p=0.007) and of achievement of target levels for P, cCa, and iPTH (22.7% vs. 42.9%, p= 0.15). The side effects in all the subjects during the study period were hypocalcemia (44%), nausea (7%), and muscle spasms (2.3%).

Conclusions: Our results suggest that etelcalcetide can improve management of iPTH together with cCa and P levels in Japanese hemodialysis patients with SHPT. Thus, adherence enhancement and better control of SHPT with etelcalcetide might allow improved management of mineral metabolism, compared to cinacalcet. There was a tendency for iPTH levels to decrease more slowly in patients with a history of cinacalcet administration.

Summary of the MBD markers at the end of observation period

	All patients (n=43)	History of cinacalcet treatment		P-value
		Yes (n=22)	No (n=21)	
≧50% reductions in iPTH, n (%)	34 (79.0)	14 (63.6)	20 (95.2)	0.007
60≦iPTH<240 pg/ml, n (%)	26 (60.5)	12 (54.6)	14 (66.7)	0.41
P, cCa, and iPTH , n (%) ✣	14 (32.6)	5 (22.7)	9 (42.9)	0.16

Abbreviations: iPTH, intact parathyroid hormone; cCa, corrected calcium; P, phosphorus.
✣ Patients who achieved all the target levels for P, cCa, and iPTH.

Summary of MBD markers at the end of the 12-week observation period in patients with ((+), n=22) and without ((-), n=21) a history of cinacalcet treatment before etelcalcetide administration.

FR-PO141

Impact of Parathyroidectomy on Left Ventricular Function in ESRD Patients

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Background: Secondary hyperparathyroidism is a common complication in End Stage Renal disease patients, and parathyroidectomy is an effective treatment of SHPT. The biochemical parameters and clinical symptoms has been proven to be drastically improved after the surgery, but the curative impact of parathyroidectomy on left cardiac function is still controversial. To evaluate the impact of parathyroidectomy on left cardiac function in ESRD patient, we conducted this retrospective study.

Methods: We collected and analyzed the basic data including serum calcium, phosphor, ALB, PTH, alkaline phosphatase(ALP) pre and post-operation, and the ultrasonic cardiogram including EF, FS, LA, AO, LVSd, LVSs, LVDd, LVDs, PWd, PWs, LVM and LVMI before and after 1 year of patients who accepted total parathyroidectomy (PTX) with forearm Autograft.

Results: There were totally 135 patients invovled, all of whose postoperative serum calcium, phosphor, PTH, ALB has been obviously improved compared with preoperative group, but the statistical change of EF and FS which stand for left cardiac function after 1 year didn't exist. We then carried out a further subgroup analysis, picking out patients whose EF were lower than or equal to 60%(n=35) before the surgery. Compared with preoperative group, the EF, FS of postoperative group increased, and LVDs, LVM.LVMI declined($p<0.05$).

Conclusions: PTX+AT is an effective curative method to secondary hyperparathyroidism which can significantly improve the postoperative biochemical parameters. For patients whose EF≤60%,PTX+AT can markedly increase their left cardiac function.

Table 3 ultrasonic cardiogram and dry weight change of ESRD patients whose EF%≤60% before the surgery

	pre-operative	Post-operative 1 year	P value
EF（%）,x±s	55.71±4.78	64.90±7.90	p<0.001
FS（%）,x±s	29.54±2.88	35.48±6.34	p<0.001
LA（mm）,x±s	36.61±8.66	36.70±7.06	p=0.592
AO（mm）,x±s	30.91±5.14	29.89±4.76	p=0.423
IVSd（mm）,M（0.25,0.75）	11.15（9.30,12.0）	10.00（9.40,12.60）	p=0.918
PWd（mm）,M（0.25,0.75）	11.00（9.85,12.93）	10.00（9.00,11.30）	p=0.245
LVDd（mm）,x±s	52.61±6.87	50.79±6.92	p=0.117
LVDs（mm）,x±s	36.99±6.10	33.34±6.48	p=0.001
PWs（mm）,x±s	15.59±2.62	15.84±3.01	p=0.202
IVSs（mm）,x±s	16.19±3.48	15.42±2.97	p=0.486
LVM（g）,M（0.25,0.75）	207.45（176.18,278.46）	193.96（148,87,251.60）	p=0.035
LVMI（g/m²）,M（0.25,0.75）	135.75（110.13,178.11）	117.24（102.15,159.40）	p=0.013
dry weight（kg）,x±s	56.28±11.96	57.44±11.96	p=0.018

FR-PO142

Loss of PTH Circadian Secretion in Peritoneal Dialysis Patients: A Case Series

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Introduction: Chronic Kidney disease (CKD) affects calcium and phosphorus metabolism and in PTH secretion. Under normal conditions, PTH is secreted by parathyroid gland with circadian rhythm and can be influenced by calcium, phosphate and vitamin D levels. These factors find peculiar expression in peritoneal dialysis patients. We report PTH levels, serum calcium and phosphorus in six patients on peritoneal dialysis during the 24-hours period.

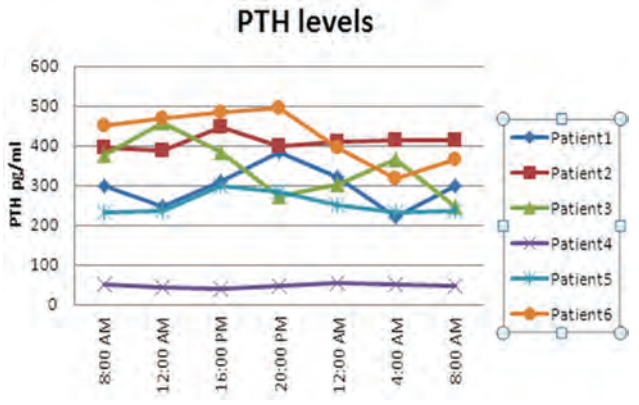
Case Description: In 6 patients, PTH, calcium and phosphorus were evaluated at the following times every 4 hours at 8 am o'clock, 12 am, 4 pm, 8 pm, middle night and 4 am (+ 1day) and 8 am (+ 1day). Some parameters related to peritoneal dialysis (such as type of dialysis, peritoneal solution), hemoglobin, creatinine, sodium, and albumin levels were evaluated for each patient. Moreover, when present we described calcium, and phosphate urine excretion in 24 hours collection. Patients characteristics are described in table 1. In figure 1 are described the levels of PTH for each patient and in figure 2 the levels of calcium and phosphate for each patient.

Discussion: These clinical reports suggest the loss of circadian rhythm in PTH secretion in peritoneal dialysis patients.

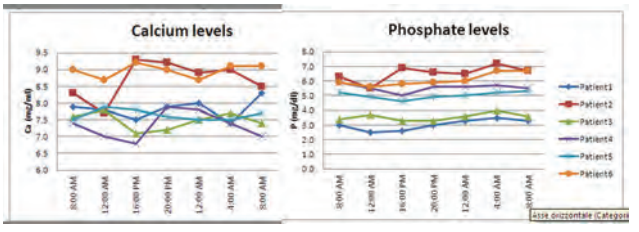
Clinical and dialysis parameters

	Gender	Age (years)	type of dialysis	PERITONEAL SOLUTIONS	Ca bath (mmil/l)	Ultrafiltration/urine output (cc/d)	Hemoglobin (g/dl)	Na (mmol/l)	Albumin (g/dl)	U-Ca (mg/dl)	U-P(mg/dl)	LP-Ca (mg/dl)	LP-P (mg/dl)
Patient1	male	30	CAPD	3 x 1.5% G daytime, Ico7.5% night-time	1.75	1200/ 600	11.6	139	3.9	3.9	3.75	1.9	8.3
Patient2	female	46	APD	Ico 7.5% day-time 2 x 1.36% G+1 X 2.27% G night-time	1.75	1050/400	9.2	139	3.3	4.6	9.5	4.5	6.4
Patient3	male	60	CAPD	3 x 2.27% G day-time Ico 7.5% night-time	1.25 day-time 1.75 night-time	1200/0	10.8	130	3.2	3.45	2.87	0	0
Patient4	male	53	APD	1 x 1.36% G+2 X 2.27% G night-time	1.25	1280/0	9.4	132	2.6	2.35	3.05	0	0
Patient5	female	66	CAPD	2 X 1.36 % G +1 x 2.27% day-time 2.27 % G night-time	1.25	1240/800	10.1	144	3	2.15	1.77	1.9	14.8
Patient6	female	62	CAPD	4 X 1.5% G	1.75	800/0	11	133	3.1	1.7	1.52	0	0

G=glucose; Ico=Icodestrin



PTH levels during 24 hours



Calcium and phosphate levels during 24 hours

FR-PO143

Paricalcitol for Severe Secondary Hyperparathyroidism in Hemodialysis Patients

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Background: Severe secondary hyperparatiroidism (SSHP) is associated with renal osteodystrophy, extraosseous calcifications, fractures, and increased mortality in end-stage kidney disease (ESKD) patients, especially those in hemodialysis (HD). Currently, their treatment consists on control of hyperphosphatasemia with phosphate binders, vitamin D or its analogues, as well as calcimimetics to suppress PTH release and ultimately surgery. Our main objective was to determine the effectiveness of paricalcitol to control PTH levels in HD patients with SSHP

Methods: Phase 2 placebo control double blinded trial that included patients with ESKD on HD for more than six months with SSHP resistant to management with calcitriol. The patients were assigned to receive paricalcitol (at dose dependent on their iPTH levels/80) or placebo and conventional treatment with phosphate binders

Results: During March to April 2019 there were screened 650 patients in our center, after application of selection criteria ten patients were allocated to paricalcitol group and nine to the control group. The median PTH level in the paricalcitol group was 1162 pg/ml, while in the placebo group was 925 pg/ml. After one month of treatment, the paricalcitol group had a mean reduction of 798.5 pg, and the control group had a median increase of 179.2 pg (p=0.013). There were no reported adverse effects in either group

Conclusions: Paricalcitol showed an important reduction in PTH levels in patients with SSHP on HD, without increased risk for hyperphosphatemia or other adverse events

	Total N=19	Paricalcitol group n=10	Control group n=9	P
Age (years)	34 (29-39)	35 (31-53)	32 (29-36)	0.35
Male	12 (63)	5 (50)	7 (77.8)	0.40
Adragao score				
Skeletal pain	19 (100)	10 (100)	9 (100)	NA
Phosphate binder based on calcium	19 (100)	10 (100)	9 (100)	NA
Calcitriol use (previous)	19 (100)	10 (100)	9 (100)	NA
Calcium	7.9 (7.2-8.8)	8.45 (7.6-8.5)	7.4 (7.2-9.5)	0.66
Phosphate	5 (4-6.2)	4.1 (3.7-4.7)	6.2 (5.9-6.9)	<0.001
PTH	1073 (783-1738)	1162 (895-1738)	925 (756-1527)	0.45
Hemoglobin	11.1 (9.1-11.5)	10.6 (8.5-11.5)	11.2 (9.6-11.5)	0.5
Albumin	4.3 (4.1-4.5)	4.2 (4-4.5)	4.3 (4.2-4.3)	0.5
BNP	19823 (5623-25000)	24127 (18997-25000)	5623 (256-25000)	0.07

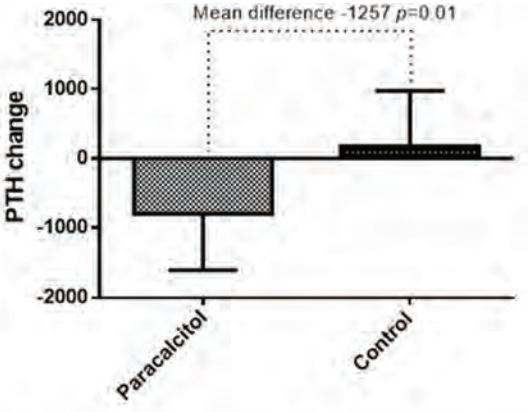

Figure 1. Median difference in PHT changes between paricalcitol and control groups.

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EOS789, a Novel Pan-Inhibitor of NaPi-IIb/PiT-1/PiT-2, Suppressed Intestinal Phosphate Absorption in Healthy Subjects: A Phase 1 Clinical Trial

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Background: Hyperphosphatemia in patients with chronic kidney disease is not well managed by existing treatments. Sodium-dependent phosphate co-transporters NaPi-IIb, PiT-1, and PiT-2 are considered to play a central role in intestinal phosphate (P) absorption, and are recognized as promising targets for a novel therapeutic strategy for hyperphosphatemia. Past clinical trials suggest blocking only NaPi-IIb is not sufficient for suppressing intestinal P absorption. We identified EOS789, a novel pan-inhibitor against NaPi-IIb, PiT-1, and PiT-2. Here we report the safety, tolerability, pharmacokinetics, and pharmacodynamic activity of the novel pan-inhibitor EOS789 in the first-in-human clinical trial in healthy subjects.

Methods: A randomized, double-blind, placebo-controlled, Phase 1 clinical trial in healthy subjects was conducted. It consisted of single (32 Japanese) and multiple (32 Japanese and 8 Caucasian) ascending dose parts. Primary endpoints were safety and tolerability of EOS789; exploratory endpoints included pharmacokinetics and pharmacodynamics, including P excretion in feces and urine.

Results: In the single ascending dose part, EOS789 was tolerated up to 600 mg and the most common adverse events were gastrointestinal (GI) disorders. In the multiple ascending dose part, EOS789 was tolerated up to 200 mg/day. Moderate GI disorders were observed in the 600 mg/day cohorts and dosing was discontinued in these cohorts. EOS789 increased fecal P and decreased urinary P excretion in a dose-dependent manner. Exposure-response analysis showed that thrice-daily dosing of EOS789 has the potential to show good efficacy at about 200 mg/day.

Conclusions: EOS789 was well tolerated up to 200 mg/day at repeated dosing for 14 days. This was the first clinical trial that showed a decrease of intestinal P absorption by inhibiting intestinal P transporters, and it suggests a new strategy for the treatment of hyperphosphatemia by pan-inhibiting NaPi-IIb, PiT-1, and PiT-2. The safety, tolerability, and efficacy of EOS789 in patients with hyperphosphatemia will be further investigated in future clinical trials.

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FR-PO145

Associations of Calciprotein Particle Transformation with Arterial Calcification, Arterial Stiffness, and All-Cause Mortality in Hemodialysis Patients

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Background: Transformation of primary to secondary calciprotein particles (CPP) in the serum may be a marker for arterial calcification as suggested by *in vitro* studies. Using dynamic light scattering, we can measure the size of secondary CPP aggregates (CPP2) and time of transformation (T_{50}). We hypothesized that a higher ratio of CPP2 to T_{50} (CPP2:T_{50}) is associated with greater arterial calcification, arterial stiffness, and mortality among hemodialysis (HD) patients.

Methods: We measured baseline CPP2:T_{50} in 387 incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) cohort. We examined cross-sectional associations of CPP2:T_{50} with serum markers of arterial calcification (fetuin-A, matrix Gla protein and osteoprotegerin), coronary arterial calcification (CAC), thoracic aortic calcification (TAC) and pulse wave velocity (PWV), as well as its longitudinal associations with PWV and all-cause mortality. Models were adjusted for demographics, co-morbidities, smoking history, body mass index, serum calcium and phosphorous.

Results: Mean age was 55 ± 13 years; 41% were female; 71% were black and 58% had diabetes mellitus. Median CPP2 was 295 nm (IQR 208-382); T_{50} was 303 min (IQR 229-387); CPP2:T_{50} was 1.01 nm/min (IQR 0.57-1.66) and follow up length was 3.5 years (IQR 1.7-6.2). Per 0.1 nm/min higher CPP2:T_{50}, fetuin-A level was 9 mg/L lower (95% CI: -10 to -7) and matrix Gla protein level was 1.0% higher (95% CI: 0.1-2.0%). CPP2:T_{50} was not associated with osteoprotegerin, baseline CAC, TAC and PWV, or with changes in PWV. Higher CPP2:T_{50} was associated with greater all-cause mortality [HR 1.02 (95% CI 1.00-1.04) per 0.1 nm/min higher CPP2:T_{50}, p=0.02].

Conclusions: In incident HD patients, higher serum CPP2:T_{50} was associated with lower fetuin-A, higher matrix Gla protein levels, and higher risk of all-cause mortality, but not with arterial calcification or arterial stiffness. These findings support CPP transformation as a marker for calcification inhibitors and mortality, but not for arterial calcification.

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

FR-PO146

Sevelamer Use Is Associated with Decreased Vitamin K Levels in Hemodialysis Patients: Results from the Vitamin K Italian (VIKI) Study

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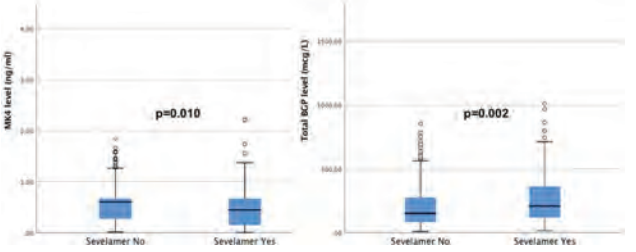
Background: Sevelamer (S) is a phosphate binding drug used to treat hyperphosphatemia in patients with CKD. Our aim was to evaluate the hypothesis that the use of (S) could interfere with Vitamin K absorption in hemodialysis (HD) patients of VIKI study.

Methods: We tested this hypothesis in VIKI, a cross-sectional study of 387 hemodialysis patients, we established the prevalence of vitamin K deficiency and to assessed the relationship between vitamin K status, vertebral fractures, vascular calcification. We determined serum concentrations of vitamin 25(OH)D; alkaline phosphatase (ALP); vitamers K1, MK4, MK5, MK6, MK7; osteocalcin (BGP) and Matrix Gla Protein (MGP). We highlighted that MK4 deficiency was the strongest predictor of aortic calcification (OR, 2.82; 95% CI, 1.14–7.01) while vitamin K1 deficiency was the strongest predictor of vertebral fractures fractures (OR: 2.94; 95% CI, 1.38–6.26).

Results: 163 of 387 patients (42.1%) were treated with S. There were no differences in levels of 25(OH)D, K1, MK5, MK6 and MK7 among patients treated with and without S. Remarkably, the prevalence of MK4 deficiency was higher in S treated patients (13.5% vs 5.4%, **p=0.005**). S treated patients also had higher median levels of ALK (89 UI/L vs 77.5 UI/L, **p=0.001**) and total BGP (210 mcg/L vs 152 mcg/L, **p=0.002**) and lower median levels of total MGP (16.4 nmol/L vs 20.3 nmol/L, **p=0.037**). In multivariable logistic regression, the odds ratio of MK4 deficiency (dependent variable) in patients treated with compared to without S was ~3-fold higher (OR: 2.64, 95% CI: 1.25-5.58, **p=0.011**) after adjustment for confounders of Vitamin K levels, including older age, previous myocardial infarction, type of HD, ALP, PTH, MGP, BGP, cholesterol and albumin.

Conclusions: These data support the hypothesis that S could interfere with MK4 absorption in HD patients. Longitudinal interventional studies are needed to prove the causal nature of these associations.



FR-PO147

Achievement of In-Range Serum Phosphorus (sP) and Decrease in Pill Burden Among Peritoneal Dialysis Patients Prescribed Sucroferric Oxyhydroxide for 12 Months

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Background: Elevated levels of sP are associated with increased risk of cardiovascular and all-cause mortality in dialysis patients (pts). Phosphate binders (PB) are routinely prescribed for management of hyperphosphatemia. A cohort of peritoneal dialysis (PD) pts prescribed the PB sucroferric oxyhydroxide (SFO) as part of routine care was analyzed for changes in sP and PB pill burden over 12 months.

Methods: De-identified clinical data was extracted from electronic health records of a large dialysis organization (LDO; DaVita Inc) and prescription data extracted from the LDO's pharmacy service. Adult PD pts who received 1 year of SFO monotherapy prescriptions between 5/1/2014 and 9/30/2018 were included in this retrospective database analysis. Baseline (BL) and follow-up (Q1-Q4) were divided into 3-month intervals. Mixed effects linear regression and Cochran's Q test were used to test for statistical significance.

Results: Pts (n=82) had a mean BMI of 29 ± 28 kg/m^2 and dialysis vintage of 41 ± 29 months. 55% of pts were male and 51% had diabetes. At BL, 35 pts had no PB prescriptions recorded in the pharmacy and the remaining pts were prescribed sevelamer (68%), calcium acetate (17%), lanthanum (8.5%), or switched between PB (6.4%). The table describes changes in laboratory measurements and PB pill burden. The % of patients achieving sP ≤ 5.5 mg/dl increased from 25.6% at BL to 34.2-41.5% during SFO. This was accomplished with fewer PB pills/day (8.6 at BL vs 4.5-5.5 SFO pills/day). Pts with sP ≤ 5.5 mg/dL during SFO had a mean sP of 4.69 mg/dL.

Conclusions: PD pts from an LDO prescribed SFO as part of routine care, experienced significant reductions in sP along with a >40% reduction in PB pills/day and increase in % of patients with sP ≤5.5 mg/dl.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	BL	Q1	Q2	Q3	Q4	p-value
PB pill burden (pills/day)	8.6	4.5**	4.9**	5.3**	5.5**	<0.001
Serum phosphorus (mg/dL)	6.63	6.21**	6.07**	6.21**	6.23**	<0.001
Patients with sP ≤ 5.5 mg/dL (%)	25.6	34.2	41.5**	35.4*	35.4*	0.027
Patients with sP ≤ 4.5 mg/dL (%)	3.7	13.4*	13.4*	7.3	14.6*	0.019
Serum calcium (mg/dL)	8.94	8.87	8.81*	8.82	8.76*	0.02
Intact PTH (pg/mL)	621	604	587	639	614	0.71

* p<0.05; ** p<0.001

FR-PO148

Serum Phosphorus and Pill Burden Decreases Among In-Center Hemodialysis (ICHD) Patients Switched to Sucroferric Oxyhydroxide for 12 Months

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Background: According to DOPPS data, >75% of ICHD patients (pts) are prescribed phosphate binders (PB) for the control of serum phosphorus (sP); however, >35% of pts have hyperphosphatemia (sP>5.5 mg/dl). The current analysis is a 12-month follow-up on sP and PB pill burden changes in ICHD pts switched from another PB to sucroferric oxyhydroxide (SFO) as part of routine care.

Methods: This retrospective database analysis utilizes de-identified clinical data extracted from electronic health records from a large dialysis organization (LDO; DaVita Inc) and prescription records from the LDO's pharmacy service. Adult ICHD pts who received 1 year of SFO monotherapy between 5/1/2014 and 9/30/2018 were included in the analysis. Baseline (BL) and follow-up (Q1-Q4) were divided into 3-month intervals. Mixed effects linear regression and Cochran's Q test were used to test for statistical significance.

Results: Pts (n=364) had a mean BMI of 29.8 and dialysis vintage of 52.6 months. 53% of pts were male and most (74%) had a fistula for vascular access. Sevelamer was the most frequently prescribed monotherapy BL PB (64%), followed by calcium acetate (18%) and lanthanum carbonate (7%), and the remaining pts either switched between PB or had combination therapy. Comparisons between BL and SFO follow-up on mineral bone disease markers and PB pill burden are shown in Table. There were consistent improvements in pts achieving sP ≤5.5 mg/dL (increased from 18% at BL to 36.8-38.7% during SFO, p<0.001). Pts were prescribed an average of 9.3 pills/day at BL and 4.3 to 4.9 pills/day during Q1-Q4. Pts who achieved quarterly sP ≤ 5.5 mg/dl had a mean pill burden of 4.7 pills/day and mean sP of 4.72 mg/dL.

Conclusions: ICHD pts from an LDO prescribed to switch PB to SFO as part of routine care for 12 months, experienced significant reductions in sP along with a 47% reduction in PB pills/day and increase in the % of pts with sP ≤5.5 mg/dl.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	BL	Q1	Q2	Q3	Q4	p-value
PB pill burden (pills/day)	9.3	4.3**	4.7**	4.8**	4.9**	<0.001
Serum phosphorus (mg/dL)	6.77	6.13**	6.07**	6.08**	6.13**	<0.001
Patients with sP ≤ 5.5 mg/dL (%)	18.4	36.8**	38.7**	38.5**	38.7**	<0.001
Patients with sP ≤ 4.5 mg/dL (%)	3.6	11.5*	11.8*	14.3**	12.4*	<0.001
Serum calcium (mg/dL)	9.0	8.97	9.0	9.0	8.98	0.47
Intact PTH (pg/mL)	622	650	657*	681**	712**	<0.001

* p<0.05; ** p<0.001

FR-PO149

Phosphate Binder Therapy with Sucroferric Oxyhydroxide Reduces Calcification Propensity in Hemodialysis Patients: Results from a Randomized, Controlled, Crossover Trial

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Background: High calcification propensity (i.e. short T50 times in the calciprotein particle formation test) is associated with a higher risk of cardiovascular events and mortality in ESRD patients. So far, no clinical trial has investigated the effect of lowering serum phosphate with oral phosphate binder therapy on calcification propensity in ESRD patients.

Methods: Single-center, open-label, controlled, randomized, cross-over study in chronic hemodialysis patients with hyperphosphatemia. Patients were randomized in a 1:1 ratio to either low-dose (250mg/d) sucroferric oxyhydroxide (PA21) followed by high-dose (2000mg/d) PA21 or vice versa, with wash-out phases (no phosphate binder therapy) in between. The primary endpoint was change in T50 time between wash-out and high dose PA21 treatment in patients with ≥85% adherence to the prescribed PA21 dose (per protocol analysis). There was no carry-over effect as determined by a linear mixed model, and thus a paired t-test was calculated.

Results: Thirty-nine patients were randomized and 28 patients were available for per-protocol analysis. Compared to phosphate binder wash-out, 2000mg/d PA21 treatment resulted in a mean increase in T50 times of 66 min (95% CI 49-84 min, p<0.0001), from 243 (± 63 min) to 309 (± 74 min). Serum phosphate decreased from 2.28 (±0.5) to 1.63 (±0.43) mmol/l. In the secondary intention to treat (ITT) analysis, treatment with 2000 mg/d PA21 resulted in a mean increase in T50 times of 60 min (95% CI 36-83 min, p<0.0001) compared to phosphate-binder wash-out. Serum phosphate decreased from 2.18 +/- 0.5 to 1.64+/- 0.46 mmol/l. In patients achieving a decline in serum phosphate ≥ 0.5 mmol/l between wash-out and the 2000 mg/d treatment phase (N=20, pre-specified subgroup), T50 time increased by 85 min (95% CI 58-112 min, p<0.0001). PA21 at 250 mg/d did not influence T50 times (p=0.4) or serum phosphate values (p= 0.9) compared to phosphate binder wash-out. No major adverse cardiovascular event, case of calciphylaxis or death occurred during the study.

Conclusions: Lowering serum phosphate with PA21 therapy reduces calcification propensity of serum of hemodialysis patients.

Funding: Commercial Support - Vifor Pharma

FR-PO150

Effect of Dietary Phosphate, Binder, and Pill Burden on Phosphate Control in Dialysis Patients

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Background: Management of hyperphosphatemia is a major problem in end-stage renal disease (ESRD) with dietary control and phosphate (Phos) binders being the mainstay of therapy. Most ESRD patients require numerous medications, resulting in a high pill burden which may affect adherence and achievement of serum phosphate (sP) levels ≤ 5.5 mg/dL.

Methods: A prospective comparative study was performed in 31 chronic dialysis patients. Subjects underwent a baseline evaluation in which they continued their routine binder regimen for 4 weeks, with weekly blood draws. This was followed by a 2 week washout in which all binders were stopped and labs obtained weekly. They were then randomized to either sucroferric oxyhydroxide (SO) or sevelamer (SEV) for 6 weeks, with weekly blood draws except during week 4 when they had daily blood draws. Subjects then underwent a second 2 week washout with weekly labs, followed by 6 weeks with the alternative binder and the same blood draws. Subjects maintained a food diary which was reviewed with a dietician to estimate average daily dietary Phos intake. Total pill burden and achievement of target sP was determined.

Results: Complete data was collected for 24 subjects. Subjects were divided in three dietary Phos groups (n=8): low (334-796 mg/day), medium (821-1129 mg/day) and high (>1140 mg/day). Baseline sP with SEV was 6.21±2.55 mg/dL with a decrease to 5.50±2.40 mg/dL (mean 6 pills/day), whereas with SO baseline sP was 6.20 + 2.50 mg/dL with a decrease to 5.30 ± 2.41 mg/dL (mean 4 pills/day). Table demonstrates the pill burden and achievement of target sP while taking SO and SEV stratified by Phos intake.

Conclusions: Comparable number of subjects achieved target sP in both groups. However, SEV resulted in a 50 % higher average pill burden compared to SO. A direct correlation was observed between Phos intake and daily pill burden. Despite increase in binder doses, the percent of subjects that achieved sP ≤ 5.5 was significantly lower in the high Phos diet group compared to the low and medium groups. This suggests that high pill burden may be associated with non-adherence to treatment.

Funding: Commercial Support - Frenova

Phosphate Control and Pill Burden Based on Dietary Phosphate

	SO		SEV	
Phosphate Diet	Avg Pill Burden/Day	Subjects with sP < 5.5	Avg Pill Burden/Day	Subjects with sP < 5.5
Low	3.4	6	4.5	5
Medium	3.0	5	6.0	6
High	6.8	3	8.1	2

FR-PO151

Longitudinal Serum Phosphorus Levels over 2 Years in Incident Dialysis Patients Who Initiate Sucroferric Oxyhydroxide (SO) as a First-Line Phosphate Binder

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Background: Phosphate binder (PB) therapy is usually initiated in the first year of dialysis therapy in chronic hemodialysis (HD) patients (pts). A historical cohort study was conducted to examine longitudinal serum phosphorus (sP) among pts who begin sucroferric oxyhydroxide (SO) as a first-line PB within the first year of HD as part of routine care in real world setting.

Methods: Adult HD pts first prescribed SO between 4/1/14-9/30/17 during their first year of HD were included in this database analysis. Pts were required to have no PB prescription during a 3-month baseline (BL) and continue SO for 2 years. All clinical data was extracted from Fresenius Kidney Care electronic health records, deidentified, and averaged over each quarter (Q1-Q8). Mixed effects linear regression and Cochran's Q test were used for statistical significance testing.

Results: Pts (n=59) had a mean age of 56±13 years and dialysis vintage of 7.3±2.9 months at BL. Changes in mean sP, serum calcium, PTH, and Kt/V are provided [table]. After SO initiation, overall mean sP decreased by 0.7 mg/dl and % of pts achieving sP ≤ 5.5 mg/dl increased from 36.5% at BL to a high of 64.9%. After limiting to pts with BL sP > 5.5 mg/dl, mean sP decreased by 1 mg/dl, from 6.86 to 5.86 mg/dl, with a high of 48.4% of pts achieving sP ≤ 5.5 mg/dl. These pts were prescribed, on average, 4.9-5.9 SO pills/day.

Conclusions: HD pts initiating SO as a first-line PB within the first year of dialysis were able to reduce mean sP levels by 0.7 mg/dl with mean phosphate binder pills/day of 4.4 to 5.2 pills over the 2-year follow-up. The % of patients with ≤ 5.5 mg/dl increased from to 36.5% at baseline to 41.5-64.9% during follow-up. SO is an effective first-line PB therapy with least pill burden.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	BL	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	p-value
PB pills/day	0	4.4	4.8	5	5	5.1	5.1	5.2	5.1	by design
sP (mg/dL)	6.14	5.87	5.77	5.63	5.53	5.48	5.33	5.61	5.49	<0.001
% of pts with sP ≤ 5.5 mg/dL	36.5	41.5	47.2	54.6	64.3	62.5	64.9	53.5	50	<0.001
Serum Calcium (mg/dL)	9.12	9.1	9.17	9.12	9.06	9.04	9	9	9.01	0.15
Intact PTH (pg/ml)	435	475	433	471	529	514	476	502	513	0.39
Single-pool Kt/V	1.6	1.66	1.68	1.68	1.67	1.7	1.66	1.66	1.76	0.27

FR-PO152

Low-Protein Rice Plus Low-Phosphorus Whey Improve Hyperphosphatemia in Hemodialysis Patients

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Background: Hyperphosphatemia is common in end stage renal disease patients. Although adequate dialysis, dietary restriction, and phosphorus binders are prescribed, phosphorus control is still poor in dialysis patients.

Methods: Hemodialysis patients who had average serum phosphorus ≥5.5 mg/dl for consecutive three months were enrolled in this self-controlled trial. First, the patients received low phosphorus diet instruction. Then the patients received low protein rice plus low phosphorus whey for ten weeks. The protein gap between low protein rice and normal rice was replaced by low phosphorus whey. Finally the patients returned to normal rice for eight weeks. The changes of serum phosphorus, calcium, intact parathyroid hormone (iPTH), serum albumin and nutritional evaluation were observed and analyzed.

Results: 29 patients were enrolled. Serum phosphorus at baseline was (6.66±0.87) mg/dl. After four weeks diet instruction, serum phosphorus decreased to (6.27±1.54) mg/dl but with no significance (p>0.05). Serum phosphorus further decreased to (5.43±1.71) mg/dl, (5.36±1.50) mg/dl, (5.79±1.35) mg/dl respectively after changed to low protein rice for 2, 6 and 10 weeks (p<0.05 compared to the baseline). Serum phosphorus increased to(6.05±0.98) mg/dl after returned to normal rice. Dietary analysis showed the phosphorus intake was significantly low for low protein rice compare to normal rice (p<0.05). Besides, serum albumin increased significantly with low protein rice plus low phosphorus whey (p<0.05). There was no change in serum calcium, iPTH levels, dialysis strategy and phosphorus-binding agents throughout the study.

Conclusions: For hemodialysis patients who consume rice as their main source of calories, low protein rice plus low phosphorus whey can reduce serum phosphorus and improve serum albumin.

Funding: Commercial Support - Sinofn (Tianjin) Pharmaceutical Technology Company Limited

Serum phosphorus, calcium, intact parathyroid hormone and albumin changes during food intervention

	baseline	2w	6w	10w	18w
P(mg/dl)	6.66±0.87	5.43±1.71 *	5.36±1.50 *	5.79±1.35 *	6.05±0.98 *
iPTH (pg/ml)	358.78±291.75			350.90±356.94	367.24±309.76
ALB(g/dl)	3.98±0.32			4.23±0.35 *	4.15±0.32 *

Values are expressed as mean ± standard deviation. *, Compared withbaseline, p<0.05

FR-PO153

48-Hour Post-Dialysis Serum Phosphate Rebound in Hemodialysis Patients Consuming a Controlled, Low-Phosphorus Diet

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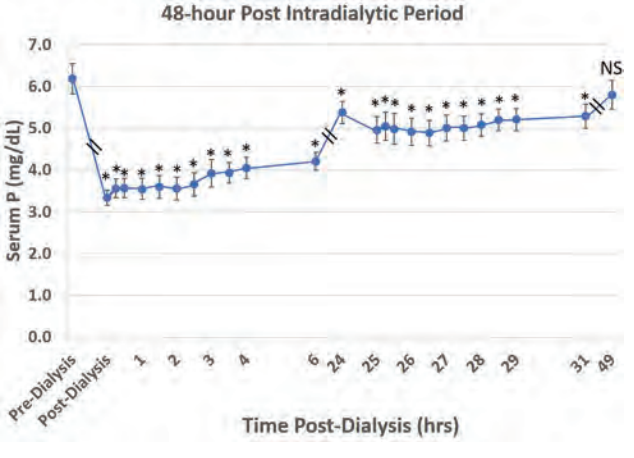
Background: Studies have demonstrated poor phosphorus (P) control with thrice weekly hemodialysis (HD). However, these studies did not control for dietary P intake, nor test blood frequently during the intradialytic interval. We aimed to determine serum P reduction and rebound over 48h in HD patients consuming a controlled low P diet.

Methods: Serum P (mg/dL) was analyzed pre-HD and post-HD for 48h in patients (N=13) consuming a controlled diet of ~900 mg P/day taking part in a placebo arm of a clinical trial. Subjects had been off phosphate binders for 10 days. Linear regression was used to determine relationships between the decline in serum P post-HD (post-HD drop); 48h area under the curve of serum P (48h AUC); and pre-HD serum P (Pre-HD). Repeated Measures ANOVA with Dunnett's post-hoc test was used to determine return to pre-HD serum P levels.

Results: In our controlled diet study, 5 of 13 subjects returned to >90% of their pre-HD serum P within the first 24h post-HD, and 11 of the 13 subjects by 48h after the completion of HD. Pre-HD serum P is positively associated with 48-hr AUC (P<0.001). We found an expected correlation (r= 0.58; P= 0.04) between post-HD drop in serum P and 48h AUC of serum P post-HD. All serum P measures in the 48h post-HD period were statistically different than pre-HD serum P (p<0.0001) until 48h post-HD (p=0.15).

Conclusions: Adhering to a low P diet, even in the absence of P binders, may benefit patients receiving HD by delaying post-HD serum P rebound. Delaying the return of serum P values to pre-HD levels to between 24h and 48h post-HD may lessen overall P exposure and may translate into achieving long-term target serum P values in HD patients.

Funding: NIDDK Support, Other NIH Support - NIH NCATS UL1TR002529 Indiana CTSI, Veterans Affairs Support, Commercial Support - Chugai Pharmaceutical Co., Ltd.



FR-PO154

Association Between Abnormalities of Serum Phosphate and Increased Mortality in Incident Australian and New Zealand Dialysis Patients

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Background: Abnormalities of mineral and bone metabolism in chronic kidney disease (CKD) are associated with increased cardiovascular and all-cause mortality. Serum phosphate is associated with adverse outcomes in a U-shaped relationship, with levels above and below the normal range associated with increased mortality in end stage renal failure. The optimal target for serum phosphate levels in CKD remains unclear. Therefore, the aim of this study was to determine if abnormalities of serum phosphate are associated with cardiovascular death and all-cause mortality in Australian and New Zealand dialysis patients.

Methods: The Australia and New Zealand Dialysis and Transplant (ANZDATA) registry was utilized to identify incident adult dialysis patients between 2005 and 2015 with ≥1 phosphate level. Phosphate levels were stratified into 3 groups; <1.6 mmol/L, 1.6-1.7mmol/L and >1.8 mmol/L. Adjusted risk of all-cause death were calculated for categories of phosphate using multivariate Cox proportional hazards regression models with phosphate levels, comorbidity and dialysis modality as time-varying covariates. Competing risk analysis was also used for cause-specific risk of death.

Results: The cohort consisted of 42,735 patients with a mean age of 58.8 (SD=15.8) years and male predominance (60.8%). Dialysis modality was 73.8% hemodialysis (HD) and 26.2% peritoneal dialysis (PD). 45.6% of patients were diabetic and 43.9% had coronary artery disease. Multivariate regression for all cause-mortality demonstrated a U-shaped relationship with highest mortality in those with phosphate <1.6 mmol/L (HR 1.17, 95%CI 1.11-1.22, p<0.001) and phosphate >1.8mmol/L (HR 1.31, 95%CI 1.24-1.38, p<0.001). Cardiovascular mortality was highest for phosphate levels >1.8mmol/L (SHR 1.25, 95%CI 1.15-1.35, p<0.001).

Conclusions: The lowest mortality was observed in patients with phosphate levels between 1.6-1.7mmol/L. Levels outside this range were associated with increased all-cause and cardiovascular mortality. This has clinical implications for target phosphate levels to reduce mortality the Australian and New Zealand dialysis population.

Funding: Government Support - Non-U.S.

FR-PO155

Mortality Risk with Serum Phosphorous in Twice-Weekly vs. Thrice-Weekly Hemodialysis Patients

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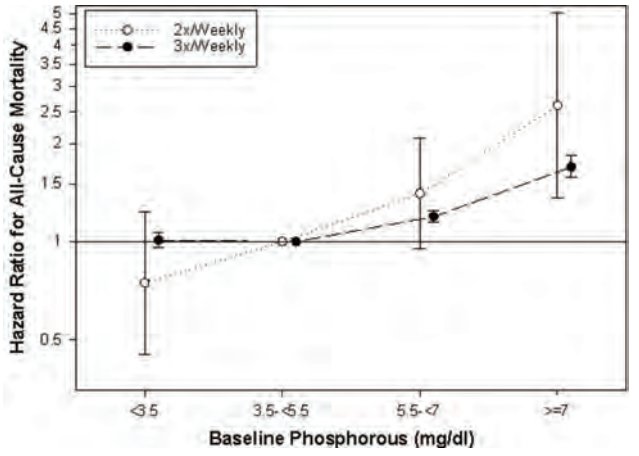
Background: Patients on dialysis commonly have abnormally elevated serum phosphorous levels. Both high and low serum phosphorous have been associated with greater mortality risk in thrice weekly incident hemodialysis (HD) patients. However, less is known about this relationship in patients undergoing twice weekly HD. This study examines the phosphorous-mortality relationship in twice weekly compared to thrice weekly HD patients.

Methods: From a large national dialysis cohort of incident HD patients (2007-2011), we identified 78,849 thrice weekly and 3,989 twice weekly HD patients. For each dialysis type, patients were divided into four groups of phosphorous levels: <3.5, 3.5-<5.5 [ref.], 5.5-<7 and ≥7 mg/dL. We examined the association of phosphorous levels and all-cause mortality using Cox models adjusted for case-mix and markers of malnutrition and inflammation.

Results: In thrice and twice weekly patients respectively, the mean age was 63 ± 15 and 68 ± 14 years, 43% and 47% were female, 31% and 15% were African American. Higher phosphorous was associated with a higher mortality risk in both twice and thrice weekly patients; however, the risk appeared stronger for twice weekly [Figure]. Lower phosphorous was not associated with any difference in mortality risk compared to the reference group, while it appeared to trend toward lower mortality risk in twice weekly HD patients. The p-for-interaction was 0.02 indicative of a significant effect of dialysis type on the phosphorous-mortality relationship.

Conclusions: The relationship of phosphorous and mortality differs in patients receiving twice and thrice weekly HD treatment. Patients with lower phosphorous levels receiving twice weekly HD treatment overall had lower mortality rates compared to thrice weekly HD patients.

Funding: NIDDK Support



FR-PO156

Spurious Hyperphosphatemia in Patients with ESRD on Hemodialysis

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Background: Hyperphosphatemia is common in patients with CKD. In most instances, the high phosphorus is due to a combination of increased intake and reduced urinary excretion. Despite the frequency of this finding, some patients with high phosphorus levels have normal kidney function. This can be associated with hypoparathyroidism, a monoclonal gammopathy or extracellular shifts as can be seen with lactic acidosis or rhabdomyolysis. Here we present three patients on hemodialysis with sudden, transient very high phosphorus levels.

Methods: Three patients with ESRD on hemodialysis were noted to have high phosphorus levels of 29.6 mg/dL, 31.5 mg/dL and 25.0 mg/dL during routine monthly laboratory evaluation. All were compliant with phosphate binders and a low phosphate diet. Blood samples were drawn from the hemodialysis catheter ports which had been locked with tissue plasminogen activator (tPA). In these patients, tPA was used to limit blood clot formation and poor blood flow through the hemodialysis catheters. tPA contains phosphoric acid to balance the pH.

Results: Below are the phosphorus levels in patients before tPA (first column) and with tPA (second column) administration. In these three patients, 5 ml of blood or less was discarded from the dialysis catheters at the time the highest phosphorus levels were resulted (second column). The third column shows improvement in phosphorus levels after we removed at least 10 ml of blood from the dialysis catheters containing tPA before sending for laboratory evaluation for phosphorus levels.

Conclusions: The severe hyperphosphatemia in our three patients appears to be secondary to the blood draw technique employed. If tPA contaminates the blood sample, high phosphorus levels are likely to result. Hence we recommend always discarding the first 10 ml of blood drawn from the hemodialysis catheter with tPA dwelling before sending the required sample for analysis. While these findings are unusual, even small quantities of tPA could lead to inappropriate conclusions of patients' non-compliance with oral phosphate binders. When possible, phosphorus levels should not be drawn if tPA has been administered and is still dwelling in the dialysis catheter.

	No tPA	With tPA (5 ml)	With tPA (10 ml)
Patient 1	5.4 mg/dL	29.6 mg/dL	6.1 mg/dL
Patient 2	3.5 mg/dL	31.5 mg/dL	4.0 mg/dL
Patient 3	8.1 mg/dL	25.0 mg/dL	6.0 mg/dL

FR-PO157

Analysis of the Association Between Serum Phosphorus Concentration and Mortality in Patients with Decreased Renal Function: Results from NHANES 2003-2006

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Background: High serum phosphorus concentration is associated with increased mortality among the different stages of chronic kidney disease (CKD). However, studies are very heterogeneous and most of them lack an appropriate adjustment for relevant confounders. This concern is particularly notable in the pre-dialysis setting. We investigated the association between serum phosphorus concentration and mortality in individuals with decreased renal function using a prospective nationwide cohort of adults from the United States of America.

Methods: We analyzed non-dialysis-dependent adults with an estimated glomerular filtration rate (eGFR) inferior to 90 ml/min/1.73m2, using data from the National Health and Nutrition Examination Survey (NHANES) 2003-2006. Serum phosphorus concentration and several covariates including albuminuria, intact parathyroid hormone (PTH), 25-OH-vitamin D, C-reactive protein (CRP) and ingested phosphorus were evaluated at baseline. All-cause and cardiovascular deaths were recorded through 31 December 2011. We used the terciles of serum phosphorus concentration which were < 3.6 (T1), 3.6-4.1 (T2) and > 4.1 mg/dL (T3). Adjusted Cox proportional hazard models were fitted to estimate hazard ratios (HR) for all-cause and cardiovascular mortality.

Results: We included 3480 individuals (males 56.9%, age 61.1±18.5 years). A total of 735 deaths was recorded over a median follow-up of 80 months. Comparing with the T1, the adjusted HR for all-cause mortality was 0.84 (95% confidence interval (CI) 0.66-1.08) for T2 (p=0.178) and 1.31 (95% CI 1.1-1.6) for T3 (p=0.013). Decreasing eGFR (p<0.001) and 25-OH-vitamin D (p=0.019) and increasing PTH (p=0.038) and CRP (p=0.02) presented a significant independent association with all-cause mortality, however, none of them had a significant interaction with serum phosphorus terciles. For cardiovascular mortality, the adjusted HR was 0.94 (95% CI 0.56-1.57) for T2 (p=0.823) and 1.24 (95% CI 0.88-1.76) for T3 (p=0.201).

Conclusions: We observed a significant independent association between the highest tercile of serum phosphorus and all-cause mortality in patients with decreased eGFR. Despite a numerical trend, it was not found a significant association with cardiovascular mortality.

FR-PO158

Zinc Supplementation for 3 Months Increases Serum Levels of C-Terminal FGF-23 in Zinc-Deficient Children with CKD

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Background: Chronic Kidney Disease (CKD) has been associated with increased fibroblast growth factor 23 (FGF23), decreased Klotho concentrations and subclinical zinc (Zn) deficiency (Fukushima 2019). FGF23 promotes phosphate clearance but is dependent on Klotho expression by tubular cells. In animal models Zn supplementation stimulates Klotho production (Morishita 2001) and reduces vascular calcification, frequently seen in CKD (Voelkl 2018). This study investigated whether 3 months of Zn therapy corrects the deficiency in CKD and leads to changes in circulating FGF23 and Klotho concentrations.

Methods: Children with primary CKD and CKD secondary to declining function of kidney transplant from two tertiary pediatric nephrology centers in Southern Ontario, Canada were screened for Zn deficiency (plasma Zn < 11.5 μmol/L). Deficient children were treated with Zn citrate tablets (10 mg Zn/day for age 4-8 yr and 20 mg/day for age 9-18 yr) for 3 months. Plasma Zn was measured at baseline and 3 months by High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry. Serum c-terminal FGF23 (cFGF23, Biomedica) and human soluble alpha-Klotho (TECO medical) were measured by ELISA, serum 25-hydroxyvitamin D (25-OHD) by LC/MS-MS (Waters). Paired t-tests and Wilcoxon tests were performed for normally and non-normally-distributed data, respectively. Children taking calcitriol were excluded from the final analysis due to its significant impact on FGF23 and Klotho metabolism.

Results: Table 1

Conclusions: In most patients we observed changes toward normal levels of Zn following three months of Zn supplementation in Zn deficient children with CKD (p=0.028). The concentration of cFGF23 also increased (p=0.008) while no change was observed in the level of Klotho. 25-OHD levels remained stable and did not affect the results. Either higher Zn doses or longer treatment may be needed before changes in Klotho might be seen.

Funding: Other NIH Support - Hamilton Health Sciences New Investigator fund, Clinical Revenue Support

Table 1 - Results

Biomarker, mean ± SD or median (25th – 75th percentiles)		No treatment (zinc sufficient) N=14			Zinc citrate treatment N=11	
	Baseline	3 months	p-value	Baseline	3 months	p-value
Zn μmol/L	12.6 (12.3-13.2)	11.9 (11.1-12.6)	0.196	10.3 (9.8-10.9)	11.8 (10.8-13.2)	0.028
cFGF23 (pmol/L)	1.2 (0.8-2.6)	2.1 (1.3-3.0)	0.320	2.2 ± 1.6	3.4 ± 2.7	0.008
Klotho (pg/mL)	1012 (646-1719)	713 (594-1678)	0.542	826 ± 445	812 ± 502	0.370
25-OHD (nmol/L)	73.7 ± 22.7	70.4 ± 18.7	0.522	61.1 (55.9-74.2)	67.5 (63.8-76.1)	0.426

FR-PO159

FGF-23 and Cause-Specific Mortality in Community-Living Individuals (Health ABC Study)

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Background: FGF23 is a protein that was initially identified as a key regulator of phosphorus and vitamin D metabolism. Elevated concentrations of FGF23 are associated with poor clinical outcomes in different patient populations, but cause-specific mortality is under-studied.

Methods: Among 2763 healthy community-living older adults who participated in the Health, Aging, and Body Composition (Health ABC) study, plasma intact FGF23 levels were measured from samples drawn in 2000 and 2001, and participants were followed through 2012. Mortality was adjudicated by a reviewing committee. Associations of FGF23 with total and cause specific mortality were evaluated using Cox proportional hazards models.

Results: At baseline, the mean age was 75 (±3) years old, 40% were black, and 55% were women. Median FGF23 was 47 (IQR 37, 60) pg/ml and was inversely correlated with eGFR (rs= -0.260). During 8.3 years (median) follow-up, there were 821 deaths. In the multivariable Cox PH regression analysis (**Table**), each two-fold higher concentration of plasma FGF23 was associated with all-cause mortality and cardiovascular, gastrointestinal bleed, and kidney failure deaths, but not with cancer, dementia, sepsis or pulmonary related deaths.

Conclusions: Although high FGF23 concentrations are associated with total mortality, the association appears restricted to certain death types. Future studies are needed to evaluate potential mechanisms linking FGF23 concentrations with specific causes of death.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging (NIA) 5R01AG027002 (Drs. Sarnak and Shlipak)

Association of (intact) FGF23 and Cause Specific Mortality

Cause of Mortality	Events	FGF23 (per doubling) Hazard Ratio (95% CI)*
GI bleed	8	2.54 (1.02, 6.32)
Renal Failure	24	1.58 (1.05, 2.38)
Cardiovascular	309	1.35 (1.16, 1.56)
Pulmonary	40	1.34 (0.86, 2.08)
All-Cause	821	1.26 (1.15, 1.39)
Cancer	245	1.01 (0.83, 1.23)
Dementia	56	0.82 (0.54, 1.25)
Sepsis	15	0.70 (0.33, 1.48)

*Adjusted for age, gender, race, site, education, diabetes, systolic blood pressure, hypertension meds, body mass index, smoking, prevalent cardiovascular disease, serum albumin, c-reactive protein, estimated glomerular filtration rate and urine albumin creatinine ratio

FR-PO160

An FGF-23-Independent Association Between Serum Phosphorus and Left Ventricular Hypertrophy: Findings from the KNOW-CKD Study

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Background: Previous studies have shown that serum phosphorus is related to left ventricular hypertrophy (LVH) in chronic kidney disease (CKD). However, those studies were small in size or did not show significant association when fibroblast growth factor-23 (FGF23) was included in the analysis. The aim of this study was to verify the FGF23-independent association between serum phosphorus and LVH in a CKD cohort of Korean adults.

Methods: This cross-sectional study analyzed 1,545 predialysis CKD patients from the KNOW-CKD cohort. Left ventricular mass index (LVMI) and presence of LVH were assessed by echocardiography. Multivariate regression analysis was adjusted for various cardiovascular risk factors including FGF23.

Results: The LVMI was higher among the higher serum phosphorus groups (88.6±20.7, 90.3±22.5, 91.1±22.0, and 96.2±25.4 for the 1st to 4th phosphorus quartiles, respectively, P<0.001). LVH was more prevalent among the higher serum phosphorus groups (15.2%, 15.8%, 23.7%, and 35.9% for the 1st to 4th phosphorus quartiles, respectively, P<0.001). For each 1 mg/dL increase in serum phosphorus, LVMI increased by 3.88 g/m^2. The adjusted odds ratio for LVH in the 4th quartile of serum phosphorus compared to the 1st quartile was 1.79 (95% CI, 1.19-2.70; P=0.005). Results were summarized in the Table 1.

Conclusions: High serum phosphorus was associated with high LVMI and LVH in predialysis CKD patients. This relationship was independent of various cardiovascular risk factors, including FGF23.

Funding: Government Support - Non-U.S.

Table 1. The association between serum phosphorus quartile and left ventricular hypertrophy

Serum phosphorus quartiles	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
1	reference		reference		reference	
2	1.04 (0.72-1.52)	0.823	0.91 (0.61-1.36)	0.650	0.97 (0.65-1.45)	0.893
3	1.73 (1.21-2.48)	0.003	1.17 (0.78-1.74)	0.445	1.27 (0.85-1.89)	0.251
4	3.12 (2.21-4.39)	<0.001	1.68 (1.12-2.52)	0.011	1.79 (1.19-2.70)	0.005

Model 1: unadjusted; Model 2: adjusted for age, sex, BMI, systolic blood pressure, diabetes, eGFR, LDL cholesterol, hsCRP, random urine PCR, hemoglobin, current smoking, taking renin-angiotensin system blockers, serum calcium, 25-OH-vit D and iPTH; Model 3: adjusted for model 3 + FGF23

FR-PO161

Determinants of C-Terminal vs. Intact FGF-23 in CKD: The COMBINE Trial

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Background: C-terminal FGF23 assays measures full-length and c-terminal fragments and intact assays measure full-length only. Iron deficiency and inflammation may enhance FGF23 production and cleavage and CKD may impair FGF23 cleavage. Few studies have measured both FGF23 assays concurrently in CKD. We sought to identify determinants of the FGF23 C terminal / Iintact (C/I) ratio in CKD stage 3b-4.

Methods: 203 patients with eGFR 20-45 ml/min/1.73m^2 participated in a randomized trial evaluating lanthanum and nicotinamide for phosphate and FGF23 lowering. FGF23 was measured using the Immutopics C-terminal and Kainos intact assays at baseline. We calculated the C/I ratio and used linear regression to identify independent determinants.

Results: Mean eGFR was 32±7 ml/min/1.72m^2. Mean C-terminal FGF23 was 271±186 RU/ml and intact FGF23 was 123±92 pg/ml, which were moderately correlated (r=0.40, p<0.001). The mean C/I ratio was 2.62±2.2RU/pg. Female gender and lower calcium were independently associated with higher C/I ratio. We found no associations of eGFR, anemia, iron deficiency, or inflammation with C/I ratio.

Conclusions: Gender and calcium are differently associated with C-terminal vs. intact FGF23; associations that appear stronger than iron deficiency, anemia, inflammation, or CKD severity, in CKD stages 3b-4.

Funding: NIDDK Support

Independent Determinants of C-terminal / Intact FGF23 in Patients with eGFR 20-45 ml/min/1.73m2 who Participated in the COMBINE Trial

Variable	Δ C-terminal / Intact FGF23 Ratio (95% Confidence Interval)
Age (per year)	0.01 (-0.02, 0.03)
Female	1.44 (0.71, 2.16)
Non-white race	-0.61 (-1.30, 0.07)
Diabetes	-0.22 (-0.85, 0.41)
SBP (per mmHg higher)	-0.02 (-0.03, 0.06)
eGFR (per ml/min/1.73m2 higher)	0.02 (-0.03, 0.06)
ACR (per log unit higher)	0.06 (-0.13, 0.24)
Calcium (per mg/dL higher)	-1.05 (-1.71, -0.39)
Phosphate (per mg/dL higher)	-0.16 (-0.72, 0.40)
1,25(OH)2 Vitamin D (per pg/mL higher)	0.02 (-0.01, 0.04)
Ferritin (per 10 ng/mL higher)	-0.00 (-0.02, 0.01)
Transferrin saturation (per % higher)	-0.03 (-0.07, 0.01)
Hemoglobin (per g/dL higher)	0.19 (-0.03, 0.40)
C-reactive protein (per log unit higher)	-0.23 (-0.51, 0.05)

All variables mutually adjusted.

FR-PO162

Improvement in Biomarkers in Pediatric X-Linked Hypophosphatemic Rickets After 1 Year of Treatment with Burosumab

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Background: X-linked hypophosphatemic rickets (XLH) is the most common genetic cause of rickets in children. Burosumab, an FGF-23 monoclonal antibody, was approved in 2018 for the treatment of XLH. Prior therapy consisted of phosphate supplementation and calcitriol, but therapeutic response was often incomplete. Clinical trial results with burosumab have been promising, but real world data regarding effectiveness in clinical practice is lacking.

Methods: 11 patients <= 18 years with XLH and treated with burosumab were identified, all of whom received calcitriol and phosphorus prior to starting burosumab. Retrospective laboratory data obtained during standard of care visits was analyzed. Monthly laboratory testing was performed for 3 months after intiation of burosumab and with dose changes. Serum phosphorus, alkaline phosphatase, PTH, and urinary fractional excretion of phosphorus were measured. Statistical analysis utilized paired T-test with p<0.05 deemed significant.

Results: The mean age of patients was 7 years old (range 2 -18). The mean length of burosumab therapy was 9.7 months (range 6-11 months). The mean pre-treatment and post-treatment lab values are displayed in Table 1. Mean serum phosphorus and alkaline phosphatase over time is displayed in Image 1. Fractional excretion of phosphorus fell below 15% in 82% of our patients following treatment with burosumab.

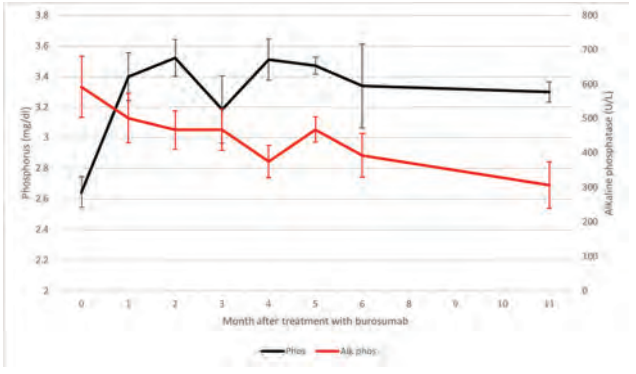
Conclusions: Burosumab, a newly approved FGF-23 monoclonal antibody, is effective in improving the biochemical profile of children with X-linked hypophosphatemic rickets previously treated with phosphorus and calcitriol.

	Pre-burosumab	1 month after burosumab	p-value*	Most recent lab on burosumab#	p-value**
Phosphorus (mg/dL)	2.6	3.4	0.004	3.4	<0.001
Alkaline phosphatase (U/L)	593	502	0.01	366	<0.001
intact PTH (pg/mL)	83.8	55.4	0.01	53.8	0.02
FE phosphorus (%)	33	9	0.04	12	0.01

* One month on burosumab vs pre-burosumab

** Most recent labs vs pre-burosumab

Mean 8.2 months after burosumab initiation



Mean serum values. Month 0 = pre-burosumab

FR-PO163

Postprandial Serum Phosphorus and Calcium Concentrations in Adults and Children with X-Linked Hypophosphatemia (XLH) Are Within Normal Range During Burosumab Treatment

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Background: In patients with XLH, excess FGF23 causes hypophosphatemia leading to musculoskeletal impairments. In Phase 3 trials (NCT02526160, NCT02915705), subcutaneous burosumab, 1 mg/kg every 4 weeks in adults or 0.8 mg/kg every 2 weeks in children, significantly improved *fasting* serum phosphorus (Pi) in subjects with XLH. Burosumab also improved fracture healing, stiffness, and physical function compared to placebo in adults; and rickets severity and growth compared to oral phosphate and active vitamin D in children. We evaluated the effect of burosumab on *postprandial* serum Pi and calcium in a sub-set of trial subjects.

Methods: Postprandial assessments were made in 26 adults and 13 children, 10-14 days after the prior dose of burosumab. Serum samples were obtained in the morning after an overnight fast. Subjects then consumed a typical phosphorus-containing breakfast, and samples were obtained 1 and 2 hours after breakfast. In adults, additional samples were obtained before and 1 and 2 hours after lunch.

Results: Adults (mean [SD] age 43 [12] years, 77% female, 89% white) and children (mean [SD] age 6 [3] years, 77% female, 92% white) had received burosumab for a mean of 24 and 15 months, respectively. At baseline, before any doses of burosumab, mean (SD) fasting serum Pi concentration was below the normal range (Table). After burosumab treatment, mean morning fasting Pi level increased significantly in each group. In adults, Pi levels decreased slightly if not significantly after breakfast, increased slightly before lunch, and remained stable 1 and 2 hours after lunch. In the children, serum Pi levels increased slightly if not significantly 1 and 2 hours after breakfast. Importantly, no subject had post-prandial hyperphosphatemia. There were no changes in serum calcium.

Conclusions: In adults and children with XLH receiving stable doses of burosumab, fasting and postprandial serum Pi and calcium concentrations are maintained within the normal range.

Serum Phosphorus mg/dL

Subjects (Phosphorus Normal Range)	Pre-Burosumab	With Burosumab					
	Before Breakfast	Before Breakfast	1hr Post Breakfast	2hr Post Breakfast	Before Lunch	1hr Post Lunch	2hr Post Lunch
Adults (2.5-4.5 mg/dl)	2.1 (0.4)	3.1 (0.5)	2.9 (0.6)	2.8 (0.6)	3.1 (0.5)	3.2 (0.4)	3.1 (0.5)
Children (3.2-6.1 mg/dl)	2.3 (0.3)	3.3 (0.5)	3.3 (0.6)	3.5 (0.5)	-	-	-

Data are expressed as Mean (SD)

FR-PO164

Intact FGF-23, Intact PTH, and Other CKD-MBD Markers After Successful Living Renal Transplantation: A Longitudinal Study

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Background: Markers of CKD-MBD cause LVH & CV mortality. Compared to general population CV mortality remain high post RT. MBD abnormalities post RT can be due to persistence of CKD induced abnormalities or can develop *de novo* due to immunosuppressive drugs & lower GFR & may contribute to increased CV mortality. Though, few studies have prospectively looked at MBD markers post RT, their course in post RT period remains poorly defined particularly in patients receiving living donor RT (LDRT) where renal function normalizes faster. This prospective, longitudinal study analyses serial changes in these variables pre & post LDRT

Methods: 83 consecutive & consenting adults aged 18-65 years undergoing first LDRT were enrolled. Investigations were done pre-RT & at 1, 6 & 12 months post RT. Patients with diabetes & those having persistent eGFR <40 ml/min post RT were excluded

Results: 74 patients completed study. 91.8% were male, mean age was 35.5±10.6 years & median dialysis vintage was 14 months. Basic disease was presumed CTID in 45.9% & presumed CGN in 39.1%. All were on 3-drug immunosuppression of MMF, steroids & CNIs. Intact FGF 23 was assayed using ELISA method (Kainos Labs Japan). 25-OH Vit D levels & iPTH levels were measured by chemiluminescence method (Abbott Labs, IL USA) Table shows study parameters at baseline & their course post RT. Taking standard cut-off values: 7% patients had hypocalcemia while 3% had hypercalcemia before RT while none in post RT period had hypo or hypercalcemia. Before RT 97% had hyperphosphatemia while 32.3, 4 & 0% had hypophosphatemia at 1,6 & 12 months post RT. 100% patients had hyperparathyoidism pre RT while 64.8, 24.3 &10.7% had hyperparathroidism at 1,6 & 12 months post RT. 100% patients had high iFGF 23 levels pre RT while 36.4, 12. & 0% had increased iFGF23 levels at 1, 6 & 12 months post RT

Conclusions: In younger CKD-5D cohort having shorter dialysis vintage who underwent LDRT we document rapid & significant decline in iPTH & iFGF 23 levels post RT. iFGF23 normalised faster as compared to iPTH

Parameter	Baseline	1 month	6 month	12 month	Friedman test (p)
eGFR ml/min	8.4±4.1	88.1 + 36.5	72.6 + 20.4	74.9 + 21.8	0.001
S. Calcium mg/dl	8.9±1.4	9.1±0.6	9±0.8	9±0.6	0.3
S. Phosphorus mg/dl	5±1.6	2.9±0.8	3.1±0.7	3.3±0.6	0.001
Intact PTH pg/dl	370.4±226.2	110.6±86.4	87.8±65.9	53.7±22.2	0.001
Intact FGF-23 pg/dl	2652.5±910.4	72.2±68.1	48.2±39.3	42.6±16.8	0.001
Serum 25 (OH) Vitamin D ng/dl	10.5±8.2	10.7±7.1	11.3±6.2	11.5±7.2	0.7

FR-PO165

Interaction Between FGF-23 and Soluble Klotho on Cardiovascular Events in Patients Receiving Hemodialysis

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Background: Membrane Klotho binds to FGFR1 and forms a specific receptor for FGF23. Recent investigations have demonstrated that soluble Klotho, a cleavage product of membrane Klotho, also mediates FGF23-dependent bioactivity. Elevated FGF23 may have detrimental effects on several tissues that do not express membrane Klotho. It is not known whether this process is mediated through the binding of soluble Klotho to FGFR1 and FGF23.

Methods: We conducted a 3-year prospective cohort study of 654 maintenance hemodialysis patients. We examined the interaction between FGF23 and soluble Klotho for the composite of all-cause mortality and cardiovascular events using multivariate Cox regression.

Results: During the follow-up period, 103 patients reached the primary composite endpoint. After adjustments for confounding, elevated FGF23 was independently associated with a higher risk of the primary composite end point only in patients with soluble Klotho greater than the median value (HR per doubling, 1.20; 95% CI, 1.04-1.39; P=0.005 for interaction). Likewise, elevated soluble Klotho was associated with a higher risk of the primary composite end point only in patients with FGF23 greater than the median value (HR per 100 pg/ml increase, 1.25; 95% CI, 1.08-1.46; P=0.005 for interaction). When we categorized the patients into 4 groups according to their medians of FGF23 and soluble Klotho, the highest risk for the primary composite endpoint was observed in patients with high FGF23 and high soluble Klotho.

Conclusions: These data suggest that elevated levels of FGF23 and soluble Klotho contribute to cardiovascular disease in a coordinated manner.

Funding: Commercial Support - Roche Diagnostics K.K. (Tokyo, Japan), Government Support - Non-U.S.

FR-PO166

Performance of Soluble Klotho Assays in Clinical Samples of Kidney Disease

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Background: There is considerable interest in investigating soluble Klotho as a biomarker in patients with different types and severity of kidney diseases. Unfortunately, there remains uncertainty regarding the best method to measure soluble Klotho in human serum samples.

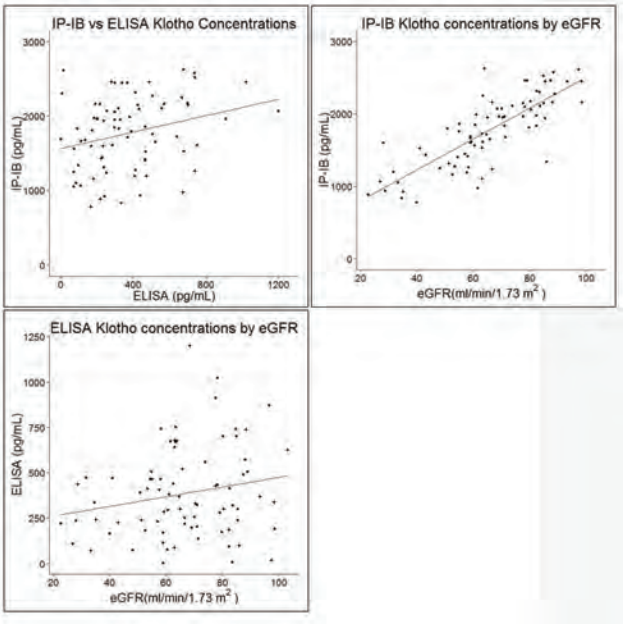
Methods: Using human serum samples obtained from several clinical cohorts with a wide range of kidney function, we measured soluble Klotho using a commercial enzyme linked immunosorbent assay (ELISA - IBL America) as well as with an immunoprecipitation-immunoblot (IP-IB) assay utilizing a synthetic antibody with high affinity and specificity for Klotho. Recovery of spiking with known amounts of exogenous Klotho was tested. A subset of samples was analyzed with and without the addition of a protease inhibitor cocktail at time of collection or after first freeze/thaw cycle.

Results: The IP-IB assay was superior to the ELISA at recovery of exogenous Klotho (81-115% vs. 60-81%) across the spectrum of kidney function. The IP-IB and ELISA assay were modestly correlated (R = 0.28, p = 0.01). Klotho concentrations by IP-IB were highly correlated with eGFR (R=0.80, p<0.001) in comparison to the commercial ELISA, which exhibited minimal correlation with eGFR (R=0.18, p=0.12) [Figure 1]. Use of a protease inhibitor cocktail neither improved nor impaired performance of the IP-IB assay; however, a subsequent freeze-thaw cycle resulted in a significant reduction in Klotho recovery and dissipated the correlation between Klotho levels and eGFR. With the ELISA, use of a protease inhibitor cocktail resulted in an increase of intra-subject variability.

Conclusions: The IP-IB assay is preferable to the commercial ELISA to measure soluble Klotho concentrations in never-thawed serum samples with varying severity of kidney disease.

Funding: NIDDK Support

Figure 1: A) Correlation between IP-IB and ELISA (R = 0.28, p = 0.01); B) Correlation between IP-IB and eGFR (R = 0.8, p < 0.001); C) Correlation between ELISA and eGFR in SPRINT CKD participants (n=77) (R = 0.18, p = 0.12)



FR-PO167

Vitamin K-Dependent Proteins After Kidney Transplantation: Results from a Prospective Study

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Background: Two Vitamin K-dependent proteins (VDKPs) link bone and vasculature in CKD-MBD: Bone Gla Protein (BGP) and Matrix Gla Protein (MGP). In ESKD, Vitamin K deficiency is highly prevalent and leads to increased levels of inactive VKDPs (undercaboxylated(uc) BGP and dephosphorylated(dp)-uc MGP), which are linked to greater risk of fractures and severity of vascular calcification. We hypothesized that kidney transplantation (KT) would improve Vitamin K status and lower levels of inactive VKDPs.

Methods: Between 2014-2017, we conducted a study in 34 patients to assess changes in VKDPs during the 1st year of KT. In a specialized lab we determined VKDPs pre- and 1-year post-KT: total BGP, uc BGP, total MGP, and dp-uc MGP. We determined the prevalence of Vitamin K deficiency based on levels of uc-BGP and dp-uc MGP

Results: Our cohort had a mean+/-SD age of 48+/-14 years, 32% were female and 97% were Caucasian. 1 year post-KT, there was a decrease in the levels of all VKDPs and the prevalence of Vitamin K deficiency(Table). Patients with greatest severity of Vitamin K deficiency pre-KT had the largest decreases of inactive VDKPs post-KT (Figure).

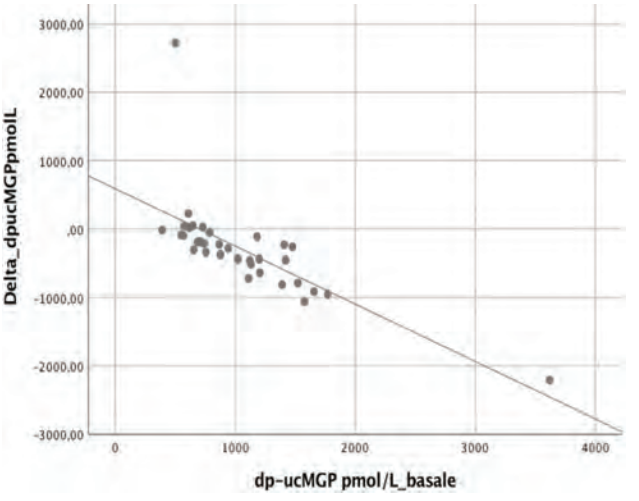
Conclusions: KT was associated with improvement in Vitamin K status as manifested by decreased levels of inactive VKDPs. These are the first prospective data on VKDPs in CKD patients pre- and post-KT. Studies are needed to assess the impact of improvement in VKDP status after KT on CKD-MBD outcomes.

Funding: Private Foundation Support

VKDPs pre- and post-KT

Variable	Pre-KT	Post-KT	P-Value
uc-BGP ng/mL (median; IQR)	8.56 (5.45, 9.55)	3.41 (1.24, 4.80)	< 0.001
Vitamin K deficient by uc-BGP – n (%) (Cut-Off: uc-BGP>=4.5 ng/ml) *	26 (76.5%)	11 (32.4%)	<0.001
BGP ng/mL (median; IQR)	132 (79.85, 279.5)	22.55 (18.85, 30.6)	<0.001
MGP nmol/L (median; IQR)	29.19 (26.67, 32.30)	20.15 (14.68, 23.23)	<0.001
dp-ucMGP pmol/L (median; IQR)	910.5 (653.3, 1396.5)	637 (517, 777.5)	< 0.001
Vitamin K deficient by dp-ucMGP- n (%) (Cut-Off: dp-uc MGP>500 pmol/L)	33 (97.1%)	27 (79.4%)	0.012

*(Kuwabara et al. Osteoporos Int 2009)



Changes in circulating dp-ucMGP levels in relation to baseline values

FR-PO168

Association of Serum Phosphate with Peripheral Artery Disease (PAD) in Hemodialysis Patients: Ten-Year Outcomes of the Q-Cohort Study

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Background: Peripheral artery disease (PAD) is caused by arteriosclerosis and is one of the critical cardiovascular complications in hemodialysis patients. Although serum phosphate is a known risk factor for cardiovascular events, it is unclear whether serum phosphate is associated with PAD. The aim of the present study was to clarify the relationship between serum phosphate level and the risk for PAD in hemodialysis patients.

Methods: A total of 3,506 hemodialysis patients registered to the Q-cohort Study was followed up for 10-years. PAD was defined as intervention for PAD including endovascular therapy, revascularization, and amputation. Patients were divided into quartiles based on baseline serum phosphate level; Q1 (n=886), <4.2 mg/dL; Q2 (n=838), 4.2 to 4.8 mg/dL; Q3 (n=909), 4.9 to 5.6 mg/dL; Q4 (n=873), 5.7≤ mg/dL. Multivariable-adjusted Cox proportional hazards risk model was employed to examine the association between serum phosphate level and the risk for PAD.

Results: During the follow-up period, 257 patients developed PAD. Cox proportional hazards risk model showed a significant association between baseline serum phosphate level and PAD: hazard ratio [HR] (95% confidence interval [CI]) per 1 mg/dL increase in serum phosphate level, 1.23 (1.09 -1.37). The risk for PAD in Q4 was significantly increased compared with that in Q1: HR (95% CI), 1.72 (1.19-2.50). When a multivariable-adjusted restricted cubic spline curve was depicted, the HR for PAD increased nonlinearly as the serum phosphate level increased. Furthermore, the effect of hyperphosphatemia on the risk for PAD was significantly enhanced in patients without diabetes, patients with history of cardiovascular events or patients with high serum C-reactive protein levels.

Conclusions: Elevated serum phosphate level was associated with an increased risk of intervention for PAD in hemodialysis patients.

Funding: Private Foundation Support

FR-PO169

Differential Effects of Phosphate Binders on Vitamin D Metabolism in CKD

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Background: Phosphate binders are commonly used in the treatment of patients with advanced chronic kidney disease (CKD) and end stage renal disease. While phosphate binders are used to lower phosphate, the effects of specific phosphate binder types on vitamin D metabolism is unknown.

Methods: We performed a secondary analysis of the phosphate normalization trial, in which 148 patients with moderate to severe CKD were treated with either sevelamer carbonate, lanthanum carbonate, calcium acetate or placebo. We used linear mixed models to evaluate the relationship between treatment arm and changes in 24,25-dihydroxyvitamin D3 [24,25(OH)2D3], 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], the ratio of 24,25(OH)2D3, to 25-hydroxyvitamin D (the vitamin D metabolite ratio or VMR) and the ratio of 1,25(OH)2D to 25-hydroxyvitamin D.

Results: Compared to placebo, randomization to the calcium acetate arm was associated with a 0.6 ng/ml (95%CI 0.2,1) and 13.5 ng/µg (95%CI 5.5,21.5) increase in $24,25(OH)_2D$ and VMR, respectively, and a 5.2 pg/ml (95% CI 1.1,9.4) reduction in $1,25(OH)_2D$. Randomization to sevelamer carbonate was associated with a 0.5 ng/ml (95% CI -0.9,-0.1) and 11.8 ng/µg (95% CI -20,-3.5) reduction in $24,25(OH)_2D_3$ and VMR respectively. There was no association of sevelamer arm with change in $1,25(OH)_2D_3$, and randomization to lanthanum carbonate was not associated with a change in any of the vitamin D metabolites.

Conclusions: Administration of different phosphate binder classes to patients with moderate-severe CKD results in unique changes in vitamin D metabolism. These findings may have important clinical implications in the management of hyperphosphatemia and vitamin D deficiency.

Funding: NIDDK Support, Commercial Support - Shire, Inc., Fresenius NA, Genzyme, Inc., Denver Nephrologists, PC, Novartis, Inc., and Davita, Inc

Adjusted differences in vitamin D metabolite concentrations, by treatment group

	Difference in time trend (95% CI)			
Treatment group	1,25(OH)D3 (pg/mL)	24,25(OH)D3 (ng/mL)	1,25(OH)D3:25(OH)D3 (pg/ng)	24,25(OH)D3:25(OH)D3 (ng/µg)
Placebo	Ref	Ref	Ref	Ref
Lanthanum	4 (-0.3, 8.2)	-0.3 (-0.7, 0.1)	0.13 (-0.03, 0.3)	-0.3 (-8.5, 7.9)
Sevelamer	0.3 (-3.9, 4.6)	-0.5 (-0.9, -0.1)	0.12 (-0.05, 0.28)	-11.8 (-20, -3.5)
Calcium	-5.2 (-9.4, -1.1)	0.6 (0.2, 1)	-0.21 (-0.37, -0.05)	13.5 (5.5, 21.5)
p-value	0.003	<0.001	<0.001	<0.001

Entries are modeled differences in time trends (between time t ≥ 3 and baseline), comparing treatment group to placebo, adjusted for age, sex, race, and weight.

FR-PO170

Serum Phosphate and Microvascular Function in a Population-Based Cohort: The Maastricht Study

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Background: Higher serum phosphate is associated with cardiovascular events and all-cause mortality. Explanations of this association have focused on large vessel-calcification and stiffness. Studies suggest that higher serum phosphate induces microvascular dysfunction, but relationships in humans with direct measures of microvascular function are lacking.

Methods: We performed a cross-sectional analysis of 3,189 community-living participants that underwent skin capillaroscopy, laser-Doppler flowmetry, or flicker-light induced retinal vessel responses. The primary outcome was capillary recruitment during post-occlusive peak reactive hyperemia by capillaroscopy. Secondary outcomes included capillary recruitment during venous congestion, heat-induced skin hyperemic response, flicker-light induced retinal arteriolar and venular dilation.

Results: The mean age of the cohort was 59 years, 48% were women, 7% had an eGFR< 60ml/min/1.73 m^2, and the mean serum phosphate concentration was 3.2±0.5 mg/dl. A 1 mg/dl higher serum phosphate was independently associated with a 5.0% lower post-occlusive capillary recruitment (95%CI -10.0%,-0.1%). Results were similar for capillary recruitment with venous congestion (**Table**). A 1 mg/dl higher serum phosphate was also independently associated with a 0.23% lower retinal venular dilation in response to flicker-light (95%CI -0.44%,-0.02%). A higher serum phosphate was not associated with change in flicker-light induced retinal arteriolar dilation or heat-induced skin hyperemic response, however a higher serum phosphate was associated with a lower heat-induced skin hyperemic response among men (-149% 95%CI -260,-38, per 1 mg/dl higher serum phosphate).

Conclusions: Higher serum phosphate concentrations are associated with microvascular dysfunction in community-living individuals.

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

Adjusted Association of Phosphate with Microvascular Measurements

Measurement Technique	Per 1 mg/dl higher Phosphate	P
% Capillary Recruitment during Post-Occlusive Reactive Hyperemia	-5.0(-10.0, -0.1)	0.04
% Capillary Recruitment during Venous Congestion	-4.5(-9.8, 0.7)	0.09
% Heat-Induced Skin Hyperemic Response	- 25(-113, 63)	0.57
% Retinal Arteriolar Dilation	-0.12(0.3, 0.15)	0.39
% Retinal Venular Dilation	-0.23(-0.44, -0.02)	0.03

Adjusted for age, sex, smoking, systolic blood pressure, anti-hypertensives, lipid medications, glucose metabolism, eGFR and serum calcium

FR-PO171

Effect of Hypomagnesemia on Vascular Calcification in Peritoneal Dialysis Patients

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Background: Vascular calcification is a non-traditional risk factor for cardiovascular disease in patients with chronic kidney disease (CKD) and main cause of this is disturbance in the mineral and bone metabolism. Magnesium (Mg) was known as a calcification inhibitor and there was a high prevalence of hypomagnesemia in peritoneal dialysis (PD) patients. However, a longitudinal study of the effects of hypomagnesemia on vascular calcification in PD patients was rare.

Methods: 167 patients with PD were included from Seoul National University Hospital. We investigated the relationship between lower serum magnesium and vascular calcification progression. Patients were categorized as hypomagnesemia (n=20), normomagnesemia (n=85), and hypermagnesemia (n=62). Vascular calcification was assessed by abdominal aortic calcification (AAC) score with lateral lumbosacral X-ray. The study end point was vascular calcification progression, defined as the change in AAC score per year >0.

Results: During the median follow-up period of 3.1 years [interquartile range 2.0-4.3 years; maximum 7.6 years], 38 (42.7%) patients developed vascular calcification progression. In a multivariable logistic regression model, the hypomagnesemia group was associated with higher risk of vascular calcification progression (C1, serum Mg ≤ 1.7 mg/dl, OR 27.3 [1.07 – 691.2]; *P*=0.045), as compared with the normal range magnesium group. All-cause mortality was not associated with hypomagnesemia in a multivariable hazard model (C1, serum Mg ≤ 1.7 mg/dl, HR 0.7 [0.07 – 6.89]; *P*=0.755).

Conclusions: Hypomagnesemia is associated with vascular calcification progression in peritoneal dialysis patients.

FR-PO172

Effect of Spironolactone on the Progression of Coronary Calcification in Hemodialysis Patients

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Background: Aldosterone, through its action on the mineralocorticoid receptor, has been recognized as a factor involved in osteoinductive pathways of vascular calcification (VC). Clinical and experimental studies have shown that the use of spironolactone is related to the prevention of VC progression. The aim of this study was to evaluate the effect of spironolactone on the progression of coronary calcification (CC) in hemodialysis patients.

Methods: Patients witha coronary calcium score (CCS) > 30 AU, evaluated by multiple-detector computed tomography (MDCT), were randomized into two groups: treatment group (GT group, n=22) corresponding to patients receiving spironolactone and control group (GC group, n=23), those who did not undergo drug intervention and did not receive placebo. The main outcome was a percentage change in CCS (relative progression), at the end of the follow-up period, which was one year. The patients were evaluated monthly, through consultations and collection of laboratory tests. At the end of the study, a new MDCT was performed in order to evaluate the progression of CC. Patients with a relative progression rate> 15% were considered progressive.

Results: Data from 35 patients who completed the follow-up period were analyzed, being 18 in the GT group and 17 in the CG group. The relative progression of CCS was similar in both groups, being 21.5% and 27% in the GT and GC groups, respectively. The majority of the patients progressed to the CC, 61.1% in the GT group and 70.6% in the CG group. At the end of the follow-up, there was an increase in intact parathyroid hormone (p=0.035) and a decrease in sclerostin (p=0.002) in the GT group. Among the groups, also at the end of the study, total alkaline phosphatase was lower in the GT group when compared to the GC group (p=0.002). Treatment with spironolactone determined an increase in high-density lipoprotein in the GT group (p=0.007). The use of spironolactone did not increase the frequency of side effects.

Conclusions: The use of spironolactone did not attenuate the progression of the CC in patients undergoing hemodialysis. The use of spironolactone was safe in the study population.

FR-PO173

Coronary Calcification in Peritoneal Dialysis Patients: The Contribution of Traditional and Uremia-Related Risk Factors

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Background: Coronary calcification (CC) is commonly observed in dialysis patients and is associated with cardiovascular and all-cause mortality. Its pathogenesis is complex and involves a series of markers that interact in the vascular microenvironment. There are very few studies that assess the presence of CC in peritoneal dialysis (PD). The aim of this study was to evaluate the frequency and the factors associated with CC in PD patients.

Methods: A total of 81patients were enrolled. Coronary calcification was assessed using a multislice coronary tomography. Patients with a coronary calcium score (CCS) ≥ 30 Agatston units were considered as having CC. Demographic data were collected and the serum levels of biochemical and bone-derived biomarkers, including sclerostin and fetuin-A, were measured.

Results: Thirty-eight patients (47%) presented with CC. Calcified patients were older adults (p <0.001), presenting with more comorbidities, such as diabetes mellitus (p=0.043), dyslipidemia (p=0.040), and smoking (p=0.003) Calcified patients presented higher serum levels of sclerostin (p=0.005). There was a tendency for calcified patients to have lower levels of fetuin-A (p = 0.05). In a multivariate logistic regression analysis, age, serum sclerostin level, and smoking were independently associated with CC. For each increase of 100 units in the serum level of sclerostin, there was a 13% increase in the likelihood of CC. CCS was positively correlated with age, time on PD, and serum sclerostin levels

Conclusions: Coronary calcification is highly prevalent in PD patients and is associated with older age, diabetes and smoking. Serum levels of sclerostin were independently associated with CC.

FR-PO174

Effect of Warfarin on Progression of Vascular Calcification

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Background: Advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD), as well as diabetes are potent risk factors for medial arterial calcification, a lesion associated with poor cardiovascular outcomes. Warfarin use may be an additional risk factor, possibly by reducing levels of matrix gla protein, a vitamin K-dependent inhibitor of vascular calcification. To quantify the effect of warfarin on medial arterial calcification and determine if this is augmented in CKD and ESRD or diabetes, we retrospectively measured the progression rate of breast arterial calcification (BAC), a marker of systemic medial arterial calcification in women with or without warfarin use.

Methods: Subjects with and without warfarin use were identified from an electronic medical record search of all digital mammograms at Emory Healthcare. Records were manually reviewed to identify mammograms performed during warfarin use. Subjects without baseline calcification were excluded. Control patients were selected to match the eGFR range in warfarin patients. Lengths of calcified arteries were measured on digital mammograms separated by ≥ 1 year. Progression rates are reported as mm/breast/y and expressed as medians and interquartile ranges. Statistical significance was determined by the Mann-Whitney U and Wilcoxon tests.

Results: Of the 77 sets of mammograms, eGFR was >60 in 36 and <60 in 28, and ESRD was present in 11. Diabetes was present in 44%. In subjects with eGFR >60, warfarin use was associated with faster progression of BAC compared to controls: 10.0 (3.8-17); n=36 vs. 2.6 (0.8-7.0); n=58, *p=0.002*. A similar effect was seen in ESRD but resulted in much higher rates: 46.9 (31-183); n=11 vs. 15.2 (7-52); n=32, *p=0.025*. Warfarin's effect was not augmented in patients with CKD (eGFR 17-58) or in diabetics vs. non-diabetics. Mammograms before or after warfarin use were available in 11 and 13 patients. BAC rate increased after starting warfarin (13.8 [7.8-39] vs. 2.1 [0.3-3.9]; p=0.01) and slowed, but not significantly, after stopping warfarin (1.9 [-7.4-6-8] vs. 8.8 [1.3-10]; p=0.11).

Conclusions: Warfarin accelerates progression of medial arterial calcification. This effect is magnified in ESRD, resulting in marked increases in calcification in this population. These data suggest that warfarin should be used with caution in ESRD, particularly in patients with extensive vascular calcification.

FR-PO175

Associations Between Undercarboxylated Osteocalcin and Peripheral Vascular Calcification in CKD5

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Background: Increasing evidence proposes a link between bone and vasculature in CKD. Osteocalcin (OCN) is the most abundant non-collagenous peptide found in the mineralized bone matrix. In vitamin K deficiency, such as advanced CKD and dialysis, OCN is predominantly in the undercarboxylated form (ucOCN). We hypothesized that ucOCN levels are associated with peripheral VC in patients with advanced CKD.

Methods: We studied 34 patients with CKD5-5D. Radial artery (RA) and Tibial artery (TA) VC were quantified by high-resolution peripheral computed tomography (HRpQCT), a validated tool to assess VC. Using specialized assays, we measured total OCN (LIASON® Osteocalcin Assay 310950 DiaSorin Inc., Stillwater MN, USA) and ucOCN (Glu-OC EIA Kit MK118 Takara Bio Inc., Otsu, Shiga, Japan). Spearman correlation analysis determined relationships between uc- and total circulating OCN and VCs.

Results: Our cohort had a mean+/-SD age of 48+/-14 years, 32% were female and 97% were Caucasian. Higher levels of ucOCN were associated with: (1) the presence of VC at the radius (r=0.4, p=0.03) but not at the tibia (r=0.3, p=0.06); and (2) greater severity of VCs at the TA (r=0.4, p=0.04) but not at the RA (r=0.3, p=0.07). Total OCN was not associated with either the presence of RA or TA VCs (p=0.1 and p=0.2 respectively) or the severity of RA and TA VCs (p=0.1 and p=0.3 respectively).

Conclusions: ucOCN is associated with the presence and severity of peripheral VC in patients with advanced CKD. This association has not been previously described in the literature. Larger studies are needed to confirm and determine mechanisms underlying this association and whether vitamin K supplementation improves peripheral VC severity.

Funding: Private Foundation Support

FR-PO176

Prevalence and Risk Factors of Vascular Calcification Among Chinese Patients with Early CKD

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Background: Extensive evidence suggests that vascular calcification(VC) independently predicts the risk of all-cause and CVD mortality. Here, we retrospectively studied the prevalence and risk factors of VC among Chinese patients with chronic kidney disease(CKD).

Methods: 138 patients diagnosed with CKD in Sun Yat-sen Memorial Hospital were included for analysis. Abdominal aortic calcification (AAC), Coronary artery calcification (CAC) were assessed by plain lateral lumbar radiograph and multi-detector computed tomography (MDCT) respectively. The AAC score will be classified into three levels(0-5, 5-16 and ≥16) and the CAC score will be classified into four levels(0-100, 100-400, 400-1000 and ≥1000). Risk factors were analyzed using logistic regression.

Results: Among the 138 patients, 63 (45.7%) were diagnosed with early CKD(stage 1-3) who had an eGFR of 30 mL/min/1.73 m or greater. Of the 63 patients, 30 (47.6%) were found abdominal aortic calcification who had AAC score greater than 0; Specifically, level 1 accounted for 30.2%; level 2 for 17.5% and level 3 for 1.6%. The high prevalence rate of AAC among patients with CKD stage 1-3 is similar to stage 4-5(49.3%) but the latter is more severe on calcification degree. At the same time, we found that 41.1% patients of early CKD have coronary artery calcification while 52.8% patients of advanced CKD(stage 4-5). Both the prevalence rate and severity of CAC among patients with stage 4-5 are higher than stage 1-3. The multivariate logistic regression identified that older age [OR (95%CI) 1.131 (1.060, 1.206), *P*<0.001], DM [OR (95%CI) 6.523(1.490, 28.544), *P*=0.013] and increased SUA [OR (95%CI) 1.006(1.001, 1.011), *P*=0.028] were the risk factors of VC among Chinese patients with early CKD. However, except for age and DM, it was SBP [OR (95%CI) 1.037(1.005,1.070), *P*=0.022] but not the SUA(*P*=0.533) increased the risk of VC among patients with advanced CKD.

Conclusions: There is limited knowledge about the impact of VC on Chinese patients with CKD, causing poor prognosis and inadequate management. We were surprised to find such a high prevalence of VC in patients with early CKD. Now, we are conducting a multi-center, large sample prospective study (ChiCTR1900020925) for establishing a predictive model for VC in patients with chronic kidney disease(stage 1-3) and hope to help us prevent it more effectively.

Funding: Government Support - Non-U.S.

FR-PO177

Quantitative Systems Pharmacology Model of Metabolic Bone Disorder and Vascular Calcification in CKD

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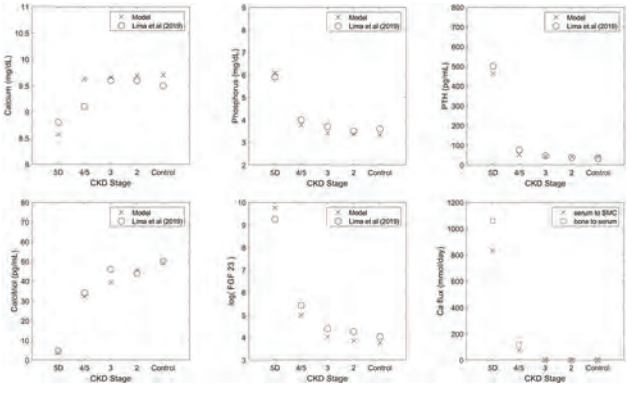
Background: Changes in Calcium (Ca) and Phosphorus (P) metabolism in patients with Chronic Kidney Disease (CKD) and the associated Mineral Bone Disorder (MBD) and Vascular Calcification (VC) pose significant morbidity and mortality risk in this patient population. We propose a Quantitative Systems Pharmacology (QSP) model of CKD-related MBD / VC to enable precision dosing of pharmacologic agents used in treatment of these conditions.

Methods: Based on the published data, we developed a QSP model of Ca / P metabolism. The model represents the movement of Ca and P between serum, gut, bone, kidney, and the soft tissue. The model also includes the FGF23 pathway and the effects of calcimimetic, vitamin D, and P binders. We validated the model against recently published clinical data describing the effect of CKD on the markers of MBD progression. We also investigated the ability of the model to predict different treatment effects in a virtual CKD patient.

Results: The impact of kidney function decline on Ca, P, PTH, Calcitriol, FGF23, and the Ca fluxes between serum, bone, and soft tissue predicted by the model is shown in the six plots below. The model correctly captures the decrease in serum Ca and the increase in P and PTH. In addition, the model correctly identifies the changes in Calcitriol and FGF23. Predicted changes in bone-to-serum and serum-to-soft tissue Ca fluxes are consistent with the pathophysiology of CKD-MBD/VC. The effects of combined P binder, Calcitriol, and a calcimimetic administration are consistent with the expected mechanism of action.

Conclusions: We propose a QSP model of Ca / P homeostasis and their effect on bone and vascular health. Validation against published clinical data proves the feasibility of the model. The model will be used to benchmark personalized treatment options to minimize the impact of MBD/VC in CKD patients.

Funding: Veterans Affairs Support



Predicted levels of Ca, P, PTH, Calcitriol, FGF23, and the Ca fluxes between serum, bone, and soft tissue at different levels of CKD.

FR-PO178

CPP (Calciprotein Particle) Is a More Sensitive Marker That Predicts Vascular Calcification in Patients with CKD

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Background: Vascular calcification in atherosclerotic diseases is an important issue related to the prognosis in patients with chronic kidney disease (CKD). Since vascular calcification occurs in an early stage of CKD, it should be evaluated to improve the prognosis by early intervention. Phosphorus, parathyroid hormone and FGF-23 are identified as markers of CKD-mineral bone disease, but are within normal range in an early stage of CKD. CPP stands for calciprotein particles, which are nanoparticles composed of calcium-phosphate (CaP) crystals and mineral binding proteins such as Fetuin-A. Serum CPP levels could be a useful marker of vascular calcification in an early CKD patients. In this study, we determined whether CPP is a more sensitive marker of vascular calcification of patients with CKD than existing markers.

Methods: In a single-center longitudinal study of 58 patients with CKD stage G1-5, we evaluated clinical parameters (s-Cr, eGFR, CPP, FGF-23, intact-PTH, 1.25 VitD) and arterial calcification score (ACS) of lower extremities by MDCT at the start and one year later to determine the risk factors related to the development of vascular calcification in CKD.

Results: Average age and average s-Cr were 69.0±12.9 years and 1.78±1.26mg/dl, respectively. CPP significantly correlated with serum phosphorus but not with s-Cr or eGFR. The rate of change in s-Cr, eGFR, FGF-23, intact-PHT, and 1.25 VitD did not show significant correlation with the rate of change in ACS of the lower extremities, but the rate of change in CPP showed significantly negative correlation with the rate of change in ACS ($r = -0.292$, $P = 0.0258$), and the rate of change in CPP was also an independent risk factor ($p = 0.0144$) in the progression of vascular calcification in multivariate analysis.

Conclusions: CPP effects protectively for vascular calcification by capturing calcium and phosphorus. CPP is a more sensitive marker of arterial calcification than other CKD-MBD markers such as FGF-23.

FR-PO179

Clarification of the Mechanism of Acute GFR Change by SGLT2 Inhibition with In Vivo Imaging Technique

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Background: SGLT2 inhibition (SGLT2i) exerted the effects to lower the risk of kidney failure in patients with type 2 diabetic kidney disease (DKD). Improvement of glomerular hyperfiltration via tubuloglomerular feedback (TGF) has been considered to be involved in this mechanism. We have successfully developed the novel method to measure single nephron GFR (SNGFR) in mice using multiphoton laser microscopy (MPM). We demonstrated that adenosine/adenosine 1a receptor (A1aR) pathway plays a pivotal role in the TGF mechanism in type 1 diabetic model, Akita mice (Circulation 2019). The purpose of this study is to clarify the acute effects of SGLT2i on glomerular hemodynamic in type 2 diabetic rat.

Methods: Zucker lean (ZL) rats and zucker diabetic fatty (ZDF) rats were used. Both rats were divided to the following groups; luseogliflozin (10mg/kg, gavage) group, luseogliflozin + adenosine A1 receptor (A1aR) antagonist (8-cyclopentyl-1,3-dipropylxanthine, 1mg/kg) group, and insulin group. SNGFR was measured after four weeks of treatment. For the acute phase study, catheter was inserted into the ureter to collect urine. Serial urine-collections of urine were performed every 30 minutes after administration of luseogliflozin. Urinary excretions of glucose, sodium, and adenosine were measured. At the same time points, SNGFR was measured to evaluate the correlation between urinary excretions of these parameters and GFR change.

Results: SNGFR in the untreated ZDF group was significantly higher than in the ZL group. Luseogliflozin treatment increased urinary sodium and glucose excretion and reduced serum glucose level in the ZDF group. SNGFR significantly declined after 30 minutes and became stabilized until 90 minutes after administration, with inverse relationship to urinary sodium. The A1aR-antagonist group showed similar urinary excretion pattern, but initial decline of SNGFR was not observed.

Conclusions: Adenosine/ A1aR pathways play an important role in the regulation of GFR and is involved in the acute decline of GFR by SGLT2i treatment.

FR-PO180

Empagliflozin Attenuates PGE2-Mediated Inhibition of Arginine Vasopressin-Stimulated Water Reabsorption in Type II Diabetic (db/db) Mouse Collecting Duct

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Background: Sodium-glucose cotransporter 2 inhibitors such as empagliflozin (EMPA) are promising therapeutics in diabetic kidney disease (DKD) since they lower blood glucose, induce diuresis, and reduce glomerular hyperfiltration and proteinuria. Prostaglandin E_2 (PGE_2), the main renal product of cyclooxygenase 2 (COX2), inhibits vasopressin (AVP) mediated water reabsorption in the collecting duct via its EP1 and EP3 receptors. We examined whether PGE2 inhibition of AVP-mediated water transport is affected by EMPA.

Methods: Four groups of male mice were studied: control (db/m), db/m+EMPA (10 mg/kg/day in chow for 6 weeks), diabetic (db/db), and db/db+EMPA. Collecting ducts were microdissected for quantitative PCR and water transport studies. Isolated perfused inner medullary collecting ducts were stimulated with 10^{-12} M AVP followed by 10^{-7}M PGE_2.

Results: Collecting ducts from db/db mice expressed elevated mRNA for COX2, EP1 receptors, and vasopressin V2 receptors (n=4-6) compared to db/m mice, but levels were unaffected by EMPA. Urine PGE_2 by ELISA was increased in db/db mice (n=5), but not altered by EMPA. AVP-stimulated water reabsorption was comparable in db/m and db/m+EMPA mice, and equally attenuated by up to 50% by PGE_2. In db/db mice, the AVP response was reduced by 50%, and this reduction was unaffected by EMPA. However, a greater attenuation of AVP-mediated water transport in response to PGE_2 was observed in db/db mice (62%), and this PGE_2 attenuation was significantly reduced in response to EMPA, to 28% (n=3-4).

Conclusions: PGE2 levels and EP1 receptor expression are increased in type II diabetic mice, leading to attenuation of collecting duct AVP-stimulated water reabsorption. This attenuation is reduced in response to EMPA treatment, which may prevent excessive water losses.

Funding: Government Support - Non-U.S.

FR-PO181

SGLT2 Inhibition Attenuates ROS Production by Regulating Cytochromes P450 and Their Metabolites in Diabetic Kidney

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Background: Diabetic kidney disease (DKD) is currently the major common cause of end-stage renal disease worldwide. DKD is a main contributor to the increased risk of cardiovascular death in diabetes consequently increasing the global burden of diabetes-associated morbidity and mortality. Sodium–glucose cotransporter 2 (SGLT2) inhibitors, a new class of oral antihyperglycemic agents, revealed promising cardiac and renal protection in diabetic patients. However, the complete spectrum of pathways that can be affected by SGLT2 inhibition is not yet fully elucidates. Arachidonic acid (AA) is metabolized by several cytochrome 450 (CYP) isoforms to produce 20-hydroxyeicosatetraenoic acid (20-HETE) and epoxyeicosatrienoic acids (EETs). CYPs of the 4A and 4F subfamilies form 20-HETE, the 2B, 2C and 2J subfamilies form EETs. Previous data from our lab show that alteration in CYPS metabolites contribute to renal damage in a diabetic milieu by altering ROS production. Moreover, CYPs have been shown to be significant sources of oxidative stress in kidneys and other organs. In this study we aim to investigate the mechanistic pathway by which SGLT2 inhibition exerts its reno-protective effect.

Methods: Dapagliflozin (SGLT2 inhibitor), HET0016 (20-HETE inhibitor), and AUDA (sEH inhibitor increasing EETs availability) were administered to Type-2 diabetic mice. Functional, histological and biochemical studies were performed.

Results: In our study, we show that diabetes-induced extracellular matrix accumulation, increases glomerular hypertrophy, induces glomerulosclerosis and albuminuria. These observations were accompanied by increased ROS production associated with alteration in CYPs 4A and 2C11 expression concomitant with alteration in 20-HETE and EETs formation. Diabetes-induced glomerular injury was blocked by HET0016, an inhibitor of CYPs 4A or by the use of AUDA, an EET activator. Of interest, SGLT2 treatment restored glomerular integrity and renal function by decreasing 20-HETE production and increasing EETs formation. Concomitantly, SGLT2 inhibition regulated the observed increase in the expression and accumulation of TGF-Beta, known to Play a major role in glomerular injury.

Conclusions: These findings suggest a new mechanistic pathway by which SGLT2 inhibitors exerts their protective effect in DKD

FR-PO182

SGLT2 Inhibition Promotes Restoration of Podocyte Number and Regression of Diabetic Nephropathy in BTBR ob/ob Mice

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Background: The SGLT2 inhibitor empagliflozin (EMPA) lowers blood glucose in diabetic patients via enhanced urinary excretion of glucose and ameliorates complications of type II diabetes, including cardiovascular disease and nephropathy (DN) through additional mechanisms, not fully defined.

Methods: Cohorts of 18 week old BTBR *ob/ob* and BTBR WT littermates (n=12) were fed chow formulated with 300 mg/kg EMPA with and without concurrent losartan (LOS) treatment, normal chow or were given leptin (LEP) for 6 weeks.

Results: Treatment with LEP, EMPA and EMPA+LOS but not LOS alone all resulted in significant reductions of blood glucose and HbA1c. BTBR *ob/ob* mice have elevated albumin creatinine ratio (ACR) (737 ug/mg); treatment with LEP, EMPA, LOS and EMPA+LOS all reduced ACR (88, 224, 162 and 112 ug/mg respectively, $p<0.01$). Morphologic analysis of silver stained tissue sections demonstrated significant reductions in mesangial matrix accumulation as percentage of glomerulus (G) tuft area in all treatment groups except LOS (*ob/ob* 20.8%, LEP 13.3%, EMPA 14%, and EMPA+LOS 12.5%, $p<0.01$; LOS 18.4%, ns). Podocyte density increased with EMPA treatment vs. untreated *ob/ob* (*ob/ob* 89.2, LEP 124, $p<0.05$; EMPA 145.3, $p<0.001$; EMPA+LOS 171.1 podos/$x10^6$ um^3, $p<0.001$). EMPA treatment decreased Mac2+ macrophages within glomeruli (*ob/ob* 1.85, EMPA 0.95 Mac2+ cells/G, $p<0.01$), but EMPA+LOS had numbers of glomerular macrophages similar to the untreated *ob/ob* mice (1.64 Mac2+ cells/G, ns). In contrast, qPCR for 3 inflammatory cytokines, MCP-1, IL-6 and TNFa were unchanged with EMPA, but significantly decreased with LOS and EMPA+LOS ($p<0.05$). In the interstitium, F4/80+ macrophages were decreased only with LEP treatment. Oxidative stress, measured by urinary 8OHdG/Cre and in tissue sections by cellular localization of nonspecific protein oxidation was decreased in all groups.

Conclusions: EMPA and EMPA+LOS treatment is similar to leptin replacement in ameliorating many of the pathologic and clinical manifestations of DN in the leptin deficient BTBR *ob/ob* mouse. Podocyte density was restored, oxidative stress and proteinuria decreased with SGLT2 inhibition. These may all be contributing factors in the improvement seen in human diabetic patients treated with SGLT2 inhibitors.

Funding: Commercial Support - Boehringer Ingelheim

FR-PO183

Identification of a Novel Smad Target in SGLT2-Mediated CTGF/CCN2 Expression

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Background: Drugs inhibiting Sodium Glucose Transporter 2 (SGLT2) activity are providing unexpected and significant benefits by the reduction of a number of conditions including CVD and mortality in diabetic patients. The precise mechanisms underlying the benefits are not fully understood. Proximal tubule cell SGLT2 is believed to be the major site of action for these drugs. We have investigated putative signaling pathways in these cells regulating SGLT2 induced effects, and have now identified a target already known to be involved in cardiovascular disease and fibrosis.

Methods: PTECs (primary proximal tubule epithelial cells) were cultured on collagen IV. They were treated with D glucose 7 mM (control), 25mM (high) or 7 mM + 18 mM L glucose (osmotic control), +/- TGFβ1 at 0.75ng/ml. The cells were also administered Dapagliflozin and MEK Inhibitor U0126 (0.1μ -10μM). Western blotting was used to detect the level of Connective Tissue Growth Factor (CTGF/CCN2), phosphorylated extracellular signal regulated kinase 2 (ERK 2), Smad3, and Smad3 linker region serine 204 (LR) protein.

Results: Our high glucose (HG) +TGFβ1 treated PTECs significantly upregulated CTGF/CCN2 protein ($P^*<0.05$). This rise was significantly attenuated by Dapagliflozin ($P^{**}< 0.01$). Hence, we investigated a potential convergence of the glucose and TGFβ signaling. TGFβ1 phosphorylated ERK 2 (42kDa) from 5 - 60 min after treatment with HG ($P^{**}<0.01$), while HG treatment exclusively phosphorylated ERK 2 from 15 - 45 min ($P^*<0.05$). Smad3 (52kDa) was phosphorylated by TGFβ1 from 5 - 60 min, +/- high glucose ($P^{**}<0.01$). HG+TGFB1 treatment at 30 min caused a significant rise of LR (25kDa) phosphorylation ($P^*<0.05$), which was significantly reduced in the presence of U0126 ($P^*<0.05$).

Conclusions: SGLT2 mediates high glucose induced CTGF/CCN2 in the presence of TGFβ1. We have identified a novel alternative mechanism by the convergence of TGFβ1 and HG treatment; phosphorylation of a serine on the Smad3 LR. Hayashida (2013) showed that glucose mediated ERK activation of LR potentiated Smad regulated transcription in mesangial cells. As MEK inhibition was able to reverse LR phosphorylation in our PTECs, our data indicates an important role for ERK in facilitating the observed glucose mediated pro-fibrotic effect.

FR-PO184

Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Deficiency Attenuates Hyperglycemia, Hypertension, and Nephropathy via Downregulation of Sodium-Glucose Co-Transporter 2 Expression in db/db Mice

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Background: Sodium-glucose co-transporter 2 (Sglt2) expression is up-regulated in renal proximal tubules (RPTs) in the diabetic kidney. The underlying molecular mechanisms, however, remain undefined. We have identified putative nuclear factor erythroid 2-related factor 2 (Nrf2)-responsive elements (REs) in mouse and human Sglt2 gene promoters. We investigated the impact of global Nrf2 knockout (KO) in db/db mice and transgenic (Tg) mice specifically overexpressing Nrf2 in renal proximal tubules (RPTs) on Sglt2 expression and studied the underlying mechanisms of NRF2-regulation of SGLT2 transcription in vitro.

Methods: Male and female db/m, db/m Nrf2 KO, db/db and db/db Nrf2 KO mice were studied up to age 16 weeks. Body weight (BW), blood glucose (BG), systolic blood pressure (SBP) and urinary albumin/creatinine ratio (ACR) were measured at week 16. Nrf2 and Sglt2 expression in isolated RPTs were assessed by RT-qPCR and western blotting. Tg mice specifically overexpressing Nrf2 in their RPTs by employing kidney-specific androgen-regulated promoter were studied. *In vitro*, the effect of oltipraz (Olz, an Nrf2 activator) and overexpression of NRF2 cDNA on SGLT2 expression and SGLT2 promoter activity in human RPTC (HK-2) were assessed.

Results: BW, BG, SBP, kidney weight/tibia length ratio, ACR, Nrf2 and Sglt2 expression in RPTs were significantly increased in db/db mice as compared to db/m mice. Genetic deletion of Nrf2 significantly attenuated these changes except BW in db/db Nrf2 KO mice. Nrf2 and Sglt2 expression were also significantly increased in RPTs of Nrf2-Tg mice compared to non-Tg mice. *In vitro*, Olz or overexpression of NRF2 cDNA significantly increased SGLT2 expression and SGLT2 promoter activity via NRF2-REs in the SGLT2 promoter in HK-2.

Conclusions: Nrf2 deficiency attenuates hyperglycemia, hypertension, kidney injury and RPT Sglt2 expression in db/db mice. Overexpression of Nrf2 increases RPT Sglt2 expression in Nrf2-Tg mice. NRF2 stimulates SGLT2 transcription via NRF2-REs in HK-2. These results identify a novel mechanism by which Nrf2 mediates hyperglycemia-stimulation of Sglt2 expression in diabetes.

Funding: Government Support - Non-U.S.

FR-PO185

Loss of Heterogeneous Nuclear Ribonucleoprotein F in Renal Tubules Attenuates Hyperfiltration and Kidney Injury in Diabetic Mice via Downregulation of SGLT2 Expression

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Background: We previously showed that tubular deficiency of heterogeneous nuclear ribonucleoprotein F (hnRNPF) results in up-regulation of renal angiotensinogen (Agt) and down-regulation of sodium-glucose co-transporter-2 (SGLT2) in mice. Non-diabetic tubule-specific hnRNPF knockout (FKO) mice developed hypertension and renal fibrosis but had similar blood glucose (BG) levels or glomerular filtration rate (GFR) as control mice. Here, we investigated the effects of FKO in diabetic Akita mice, a murine model of type 1 diabetes.

Methods: FKO mice were generated via cross-breeding of Pax8-Cre mice with floxed hnRNPF mice on a C57BL/6 background. Akita-FKO mice were created by cross-breeding of female FKO mice with male heterozygous Akita mice. Both male and female Akita-FKO mice and Akita control littermates were studied (n=8/group). Body weight (BW), BG, and systolic blood pressure (SBP) were monitored up to age 24 weeks. GFR was measured by inulin-FITC clearance in awake mice; kidneys were processed for histology (PAS, Masson's trichrome, electron microscope).

Results: Akita-FKO mice had better glycemic control, lower kidney weight/BW ratio, and lower GFR/BW ratio than Akita control mice. SBP was significantly higher in male but not in female Akita-FKO mice as compared to Akita. Urinary albumin/creatinine ratio did not differ in the two groups. Renal histology in Akita-FKO mice showed an attenuated glomerulomegaly and tubulointerstitial fibrosis with improved GBM thickness and foot process effacement cf. Akita. Real-time qPCR on kidney cortex confirmed down-regulated expression of SGLT2 and fibrosis marker genes (fibronectin 1, α–smooth muscle actin, collagen 1) and up-regulated Agt expression in Akita-FKO mice cf. Akita.

Conclusions: Kidney hypertrophy and glomerular hyperfiltration were attenuated in Akita-FKO mice, likely due to SGLT2 down-regulation activating tubuloglomerular feedback. The renoprotective effect of SGLT2 down-regulation overcomes the renal injurious effect of Agt when these opposing factors coexist. The Akita-FKO mouse is a unique tool for studying the molecular mechanisms of SGLT2 regulation in diabetes.

Funding: Government Support - Non-U.S.

FR-PO186

Empagliflozin Attenuates Diabetic Tubulopathy by Improving Mitochondrial Fragmentation and Autophagy

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Background: We examined the effects of empagliflozin, a selective inhibitor of sodium glucose cotransporter-2 (SGLT-2) on mitochondrial quality control and autophagy in renal tubular cells in a diabetic environment in vivo and in vitro.

Methods: Human renal proximal epithelial cells (hRPTCs) were incubated in high-glucose conditions. Diabetes was induced with streptozotocin in male C57/BL6J mice.

Results: Improvements in mitochondrial biogenesis and balanced fusion/fission protein expression were noted in hRPTCs after treatment with empagliflozin in high-glucose media. Empagliflozin also increased autophagic activities in renal tubular cells under high glucose environment which was accompanied with mTOR inhibition. Moreover, reduced mitochondrial ROS production and decreased apoptotic and fibrotic protein expression were observed in hRPTCs after treatment with empagliflozin, even in hyperglycemic circumstance. Importantly, empagliflozin restored AMPKα phosphorylation and normalized the levels of AMP/ATP ratios in human renal tubular cells subject to a high-glucose environment which suggested the way of empagliflozin to involve in mitochondrial quality control. Empagliflozin effectively suppressed SGLT2 expression and ameliorated renal morphologic changes in the kidneys of STZ-induced diabetic mice. Electron microscopy analysis showed that mitochondrial fragmentation was decreased, and 8-OHdG content was low in the renal tubular cells of the empagliflozin treatment groups compared with those of the diabetic control group.

Conclusions: We suggest one mechanism related to the renoprotective actions of empagliflozin, which reverse mitochondrial dynamics and autophagy.

Funding: Government Support - Non-U.S.

FR-PO187

Effect of Canagliflozin on Glomerular Hyperfiltration Evaluated by Transcutaneous GFR Monitor in Spontaneously Diabetic Torii Fatty Rats

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Background: Sodium glucose cotransporter 2 (SGLT2) inhibitors reduce glomerular hyperfiltration, thereby preventing the progression of diabetic kidney disease. However, since consecutive measurements of total nephron GFR in a same experimental model is not fully established, it is difficult to assess the precise effects of SGLT2 inhibitors on tubuloglomerular feedback (TGF). Transcutaneous GFR monitor (MediBeacon®) allows consecutive measurements by detecting fluorescence of FITC-sinistrin on the same animal, including multiple measurements with no sampling. Therefore, we assessed the effects of canagliflozin (CANA) on glomerular hemodynamic effects using transcutaneous GFR monitor in Spontaneously Diabetic Torii fatty rat (SDT-fatty rat), an obese type 2 diabetic model.

Methods: Eight week-SDT-fatty rats were given 100 mg/kg of CANA. Sprague Dawley (SD) rats were used as control. Fluorescence monitoring device was placed onto back of rats, and FITC-sinistrin was injected intravenously. After 2 hours, device was removed and half-life of sinistrin was measured, and then GFR was calculated. GFR could be measured one day before, 2 hours after, and 1 week after the treatment with CANA in a same rat. Adenosine production in response to increased sodium chloride reabsorption by CANA is evaluated by measuring urinary adenosine levels. SDT-fatty rats are treated with selective A1 adenosine receptor (A1aR) antagonist before administration of CANA.

Results: Serum glucose levels significantly increased in SDT-fatty rats (235.0mg/dL vs 133.8mg/dL). Baseline GFR in SDT-fatty rats was significantly higher than that in SD rats (23.7ml/min/kg, 15.3ml/min/kg, respectively). Treatment with CANA dramatically reduced diabetes-induced increased GFR at 2 hours after administration (17.3ml/min/kg) compared to baseline ($p<0.01$ vs baseline GFR). GFR at 1 week after administration with CANA in a same rat returned to baseline level without glucosuria (22.7ml/min/kg, $p=0.49$ vs baseline GFR). Urinary adenosine levels at 2 hours after administration with CANA and the effects of co-administration with A1aR antagonist on CANA-induced reduction of GFR will be evaluated.

Conclusions: SGLT2 inhibition plays a pivotal role in the regulation of GFR via TGF in SDT-fatty rats, which may contribute to renal protective effects reported in clinical trials.

FR-PO188

Liraglutide Reduces Renal Tubular Ectopic Fat Deposition in Rats with Diabetic Nephropathy by Inhibiting Sterol Regulatory Element Binding Proteins

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Background: Liraglutide, a long-acting GLP-1 receptor agonist, has show significantly improved renal outcomes in patients with T2DM and delayed the development of DN. But we still not know the renal protective mechanism of liraglutide.

Methods: 30 SPF male Sprague-Dawley rats weighing 180-200 g were randomly divided into 3 group (n=10). Normal control group, DN group: diabetes+single nephrectomy group, Liraglutide treatment group: DN + liraglutide intervention group. Intraperitoneal injection of 35 mg/kg STZ and high fat diet to establish a T2DM model. The tail vein random blood glucose over 16.7 mmoL/L was determin to establish a T2DM model. T2DM group underwent unilateral nephrectomy at 1 week after modeling. After 1 week of nephrectomy, the subcutaneous injection of Liraglutide was given at a dose of 0.3 mg/kg/12 h for 12 weeks. Rat body weight was measured every 4 weeks during Liraglutide injection. Automated biochemical analyzer detected serum TG, TC, SCr, BUN, ALB, 24h urine protein at 12th week sacrificed. Sterol regulatory element binding protein (SREBP1) and fat differentiation-related protein (ADRP) were detected by immunohistochemical in 4% paraformaldehyde fixed rat renal.

Results: Liraglutide could decrease body weight of DN rat after 8th week ($P<0.05$). 24-hour urine protein quantitation showed a slight increase in the 10th week in DN group (867.03±17.2 0μg/24 hours), which was significantly higher in control group (289.98±37.85) ($P<0.05$), SCr, Urea and ALB were no significant change in 3 group. TG and TCh level were higher in DN than that in Liraglutide group ($P<0.05$) (Figure2). ADRP and SREBP1 tesed by immunohistochemistry expressed in renal tubules were significantly higher in DN than Liraglutide and control group (Figure1).

Conclusions: Liraglutide can reduce TG levels of DN rats via inhibiting SREBP1 in renal tubular and reduce fat ectopic deposition.

Funding: Government Support - Non-U.S.

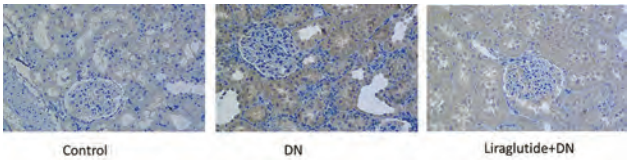

Figure 1. IHC for SREBP1 expression in rat kidney

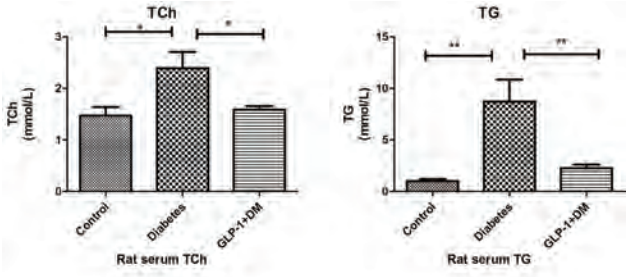

Figure 2. TCh and TG expression in rat serum

FR-PO189

Reno-Protective Effect of GLP-1 Receptor Agonists: Silencing the Cross-Talk Between TRPC6 and NADPH Oxidases

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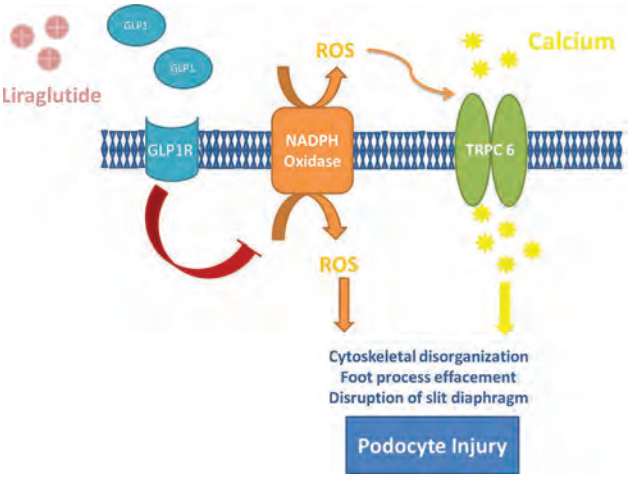
Background: Diabetic kidney disease (DKD) is a life-threatening complication of Diabetes. DKD is characterized by podocyte injury which compromises the glomerular filtration barrier leading to proteinuria. Podocyte injury is thought to be mediated by reactive oxygen species (ROS) production via NADPH oxidases. DUOX 1 & 2 are NADPH oxidases that acquire in their structure a calcium binding site. Calcium signaling through TRPC channels is essential in podocyte function and disruption of its homeostasis leads to cytoskeleton disorganization, foot process effacement and disruption of slit diaphragm. Besides, hypoglycemic treatments such as GLP-1 receptor agonists (GLP-1RA) have been shown to exert a reno-protective effect, yet this mechanism is still not well elucidated. Herein, we aim to investigate the role of TRPC-6 channel and NADPH oxidases in kidney injury and the effect of GLP-1RA on reversing this process.

Methods: Sprague Dawley rats were allocated into five groups: control, STZ induced type I diabetic group, STZ induced type 1 diabetic group treated with Metformin or GLP-1RA or combination for a duration of 8 weeks. Functional, histopathological, biochemical and molecular studies were performed on kidney tissues from all groups.

Results: GLP-1RA treatment ameliorates kidney injury. This was transduced by a reduction in BUN, SCr, proteinuria, collagen deposition and fibrosis. Kidney tissues showed downregulation of collagen IV & fibronectin mRNA expression versus an upregulation of nephrin mRNA expression upon treatment. In addition, we noticed decreased ROS production, NADPH oxidases activity and mRNA expression of DUOXs. Moreover, reduced expression of TRPC6 but not TRPC3 was noticed upon treating with GLP-1RA. GLP-1R and AMPK expression were assessed too.

Conclusions: GLP-1RA seems to retard diabetic nephropathy by modulating the cross-talk between TRPC6 and NADPH oxidases. These clues could pinpoint novel molecular mechanisms in DKD.

Funding: Other U.S. Government Support, Private Foundation Support



FR-PO190

Sitagliptin Ameliorated Mitochondrial Dysfunction in Diabetic Kidney Disease via SDF-1α/CXCR4/STAT3

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Background: Dipeptidyl peptidase-4 (DPP-4) inhibitors, which can hinder degradation of bioactive incretins, have been developed as a new type of glycemic control agent in both clinical and basic studies. Moreover, recent studies indicate that DPP4 inhibitors can improve albuminuria suggesting a favorable effect on kidney,but the exact mechanism remains unclear. We test whether an SDF-1α/CXCR4/STAT3 signaling pathway regulates mitochondrial dysfunction when inhibited DPP4 in DKD.

Methods: *In vivo,* male DBA2/J mice were subjected to streptozotoxin to form diabetic mice models, then sitagliptin was used for gavage to inhibit DPP4. We collected and analyzed kidney samples, urine and serum. *In vitro,* human HK2 cells were exposed to human serum albumin (HSA), then regulated DPP4, CXCR4 and STAT3 with inhibitors, siRNAs and mutant plasmids. Outcome measures included mitochondrial dynamics, expression of SDF-1α, CXCR4 and STAT3, mitochondrial membrane potential and mitochondrial ROS production.

Results: In diabetic mice, Sitagliptin decreased renal DPP4 expression, improved renal function, attenuated tubular damage, and partly attenuated mitochondrial dysfunction, yet sitagliptin cannot significantly control glycemia of these mice. Besides, sitagliptin obviously upregulated SDF-1α/CXCR4 expression and mitochondrial STAT3. *In vitro,* HK2 cells exposed to HSA exhibited increased DPP4 accompanied by mitochondrial fragmentation, altered mitochondrial dynamics and elevated mitochondrial ROS production. Inhibited DPP4 improves SDF-1α/CXCR4 expression, which has a positive effect on diabetic mitochondrial function, whereas upregulated DPP4 aggravated these mitochondrial perturbations. Moreover, partly through SDF-1α/CXCR4 pathway, inhibition of DPP4 regulated mitochondrial STAT3 and phosphorylation of Ser^{727} in STAT3,which is required for STAT3 to import into mitochondria. Our work found that the inhibition of DPP4 ameliorated mitochondrial dysfunction in DKD partly through SDF-1α/CXCR4/STAT3 signaling pathway.

Conclusions: The results suggest a novel mechanism linking DPP4 to impair mitochondrial quality control during tubular injury in the pathogenesis of DKD and suggest SDF-1α/CXCR4/STAT3 pathway may become a potential therapeutic point to ameliorate DKD.

Funding: Government Support - Non-U.S.

FR-PO191

GSK3-α/β Inhibition Attenuates Progression of CKD in Lepr-/- Mice with Type 2 Diabetes (T2D) Beyond Standard-of-Care Therapy (SOC) with Metformin/Ramipril/Empagliflozin

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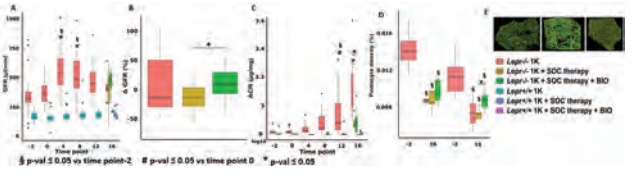
Background: Dual RAS/SGLT2 inhibition significantly reduces cardiovascular, renal morbidity in patients with T2D but further retarding progression of CKD remains a global unmet medical need. GSK3α/β inhibitor BIO (6-bromo-indirubin-3'-oxime) was shown to promote podocyte differentiation in vitro, to limit Adriamycin-induced podocyte loss in vivo, hence we hypothesized that BIO's specific mechanism-of-action would have therapeutic effects beyond SOC therapy on diabetic kidney disease (DKD)

Methods: Male BKS-*Lepr*-/- mice with obesity-related T2D their respective non-diabetic BKS-*Lepr*+/+ controls underwent uninephrectomy (1K) at 6 weeks of age to mimic CKD G2, accelerated progression of DKD. From week 12-16, all 1K mice were put to SOC therapy (1500mg/kg metformin, 6mg/kg ramipril, 480mg/kg empagliflozin) and randomized to either additional BIO (2μmol/kg) or vehicle therapy. *Lepr*-/- mice without proteinuria at week 12 were excluded from the study. N=10-11 per group. GFR, albuminuria, Blood glucose were monitored at regular intervals. Glomerular tuft area, density of WT-1+ podocytes and glomerulosclerosis were quantified in cortical and juxtamedullary glomeruli. Density of tertiary podocyte foot processes was analyzed as a marker of terminal podocyte differentiation by STED microscopy

Results: Primary endpoint: *Lepr*-/- mice, GFR increased after uninephrectomy with a progressive decrease later (A). SOC+BIO significantly attenuated GFR loss during treatment interval compared to SOC therapy alone (B). Secondary endpoints: In *Lepr*-/- mice, albuminuria was significantly attenuated bySOC therapy (C). SOC+BIO therapy significantly increased podocyte densityin juxtamedullary glomeruli (D). BIO showed significantly better preservation of tertiary podocyte foot processes (E)

Conclusions: GSK3-α/β inhibitor BIO has renoprotective effects beyond SOC therapy in a clinically meaningful model of progressive DKD. Optimizing animal models of DKD to better mimic the study population, co-medication, study endpoints used in clinical trials may improve the notoriously poor predictive value of animal models of DKD



FR-PO192

Elevated Podocyte DAAM2 Expression in Diabetic Nephropathy

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Background: Previously, by using proteomic analysis in isolated glomeruli, we identified several novel differentially expressed proteins in human diabetic nephropathy (DN) vs control, including DAAM2. DAAM2, the dishevelled associated activator of

morphogenesis 2 protein, binds the Wnt effector Disheveled, nuclear actin and mediates Wnt-induced cytoskeletal changes. We now aimed to study possible contributions of DAAM2 to DN.

Methods: We assessed DAAM2 by immunostaining in non-cancer regions of human nephrectomy (Nx), DN and normal transplant donor kidney tissues. Nx patients were middle-aged with varying arterionephrosclerosis. ACEI- or glipizide-treated DN mice (db/db/eNOS$^{-/-}$ model) were compared with vehicle-treated DN mice. Primary cultured podocytes were exposed to high glucose or mannitol, and DAAM2 was knocked down by siRNA to study effects on podocyte injury.

Results: In human glomeruli, DAAM2 was expressed only on podocytes. DAAM2 expression was increased in both nephrectomy and DN vs normal donors. DAAM2 gradually decreased with increasing severity of DN, from class II to class III or IV (2.21±0.15 vs 1.58±0.14 vs 1.40±0.14). Glipizide and ACEI reduced DAAM2 podocyte expression in mice DN, accompanied with reduced proteinuria and maintained GFR and more preserved WT1^{+} podocytes. DAAM2 mRNA was increased in cultured podocytes treated with high glucose vs mannitol (0.36±0.01 vs 0.77±0.03). ROCK1, the downstream kinase of Wnt/Rho/ROCK signaling pathway, regulates podocyte process elongation. High glucose induced more ROCK1 expression than mannitol (1.04±0.04 vs 0.79±0.13), which was reversed by DAAM2 knockdown (0.64±0.07).

Conclusions: DAAM2 is up-regulated in podocytes in both nephrectomy and DN, which we postulate could be contributed to both by glomerular hypertrophy, prevalent in both DN and Nx, and high glucose. We hypothesize that DAAM2 may regulate podocyte function through the Rho/ROCK signaling pathway.

Funding: NIDDK Support

FR-PO193

Podocyte and Endothelial-Specific Elimination of BAMBI Identifies Differential TGF-β Pathways Contributing to Diabetic Glomerulopathy

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Background: Transforming growth factor-β (TGF-β) is considered a central mediator of diabetic nephropathy (DN). The effect of TGF-β, mediated by type I TGF-β receptor, ALK5, and subsequent Smad2/3 activation is shown to result in podocyte apoptosis and loss. We previously demonstrated that the genetic deletion of BAMBI (BMP and Activin Membrane-Bound Inhibitor), a negative modulator TGF-β signaling, accelerates DN progression. Interestingly, worsening of DN phenotype in BAMBI-deficient mice was associated with heightened activation of ALK1 type I TGF-β receptor, whose expression is largely restricted to endothelial cells (ECs). ALK1 acts in an opposing manner to ALK5 in ECs via Smad1/5/8 activation, which results in EC activation, proliferation, and neo-angiogenesis.

Methods: Therefore, to evaluate the glomerular cell-specific effects of TGF-β in DN, we examined the effects of the podocyte- or EC-specific loss of *Bambi* in streptozotocin-induced diabetic mice with eNOS deficiency (eNOS$^{-/-}$). Kidneys were examined at 20 weeks post diabetes induction.

Results: Interestingly, while hyperglycemia and body weight loss were similar in all groups of diabetic mice, significant hypertension was present only the diabetic mice with EC loss of BAMBI. Diabetic mice with podocyte- or EC-specific loss of BAMBI (Pod-Bambi$^{-/-}$ or EC-Bambi$^{-/-}$) displayed markedly worsened albuminuria and DN severity in comparison to the control diabetic eNOS$^{-/-}$ mice. However, activation of Smad3 was further heightened in the glomeruli of diabetic Pod-Bambi$^{-/-}$ mice, whereas Smad1/5 activation was observed only in the glomeruli of diabetic EC-Bambi$^{-/-}$ mice. Consistent with the increased ALK1-Smad1/5-mediated angiogenesis in DN, significant EC proliferation was observed only in the glomeruli of diabetic EC-Bambi$^{-/-}$ mice.

Conclusions: These results identify cell type-specific TGF-β signaling in DN and further underscore the endothelial TGF-β signaling as a major contributor of diabetic glomerulopathy progression. Thus, attenuation of ALK1 and ALK5 signaling through BAMBI may be a potential therapeutic approach against DN progression.

Funding: NIDDK Support

FR-PO194

A Novel Role for NPY-NPY2R Signalling in Albuminuric Kidney Disease

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Background: Albuminuria is an independent risk factor for the progression to end-stage kidney failure and premature mortality. It is well-established that podocyte damage is a major cause of albuminuria, yet the pathways involved are incompletely understood. In this study, we analysed the transcriptomes of insulin-sensitive and insulin-resistant podocytes to identify molecules regulated in podocyte damage and novel pathways regulating albuminuria in diabetes. This revealed that *Neuropeptide Y* (*Npy*) was highly downregulated in insulin-resistant podocytes. While NPY is implicated in many conditions including obesity, diabetes and insulin resistance, a role for NPY in albuminuric kidney disease has not been described.

Methods: Gene expression was analysed *in vitro* in conditionally-immortalised podocytes using RNA sequencing and focused qPCR arrays, and *in vivo* in the Pima type-2 diabetic nephropathy cohort and the "nephroseq" database. The effect of reduced *Npy* expression on albuminuria was analysed in streptozotocin (STZ)-induced diabetic nephropathy and Adriamycin-nephropathy models, using wild-type and NPY-deficient (NPY-/-) mice. Conditionally-immortalized human and mouse podocytes were studied *in vitro* to determine the effects of NPY signalling. The effects of pharmacological NPY2R inhibition were investigated *in vitro* and *in vivo*, using BIIE0246.

Results: Transcriptome analysis demonstrated that *Npy* was significantly down-regulated in insulin-resistant vs insulin-sensitive mouse podocytes. Human diabetic nephropathy (DN) patients also had reduced glomerular *NPY* expression in both early- and late-stage DN. However, NPY-/- mice had reduced levels of albuminuria and podocyte injury in both diabetic and non-diabetic kidney disease models. Furthermore, both human and mouse podocytes responded to NPY stimulation, via activation of PI3K and ERK MAPK signalling cascades, as well as the calcium-dependent activation of NFAT; responses which were mediated through NPY2 receptor (NPY2R) activity. The pharmacological inhibition of NPY2R *in vivo* significantly reduced albuminuria in adriamycin-treated mice.

Conclusions: Our findings reveal a novel role for the NPY system in the glomerulus and suggest that manipulating NPY-NPY2R signalling in albuminuric kidney disease may be therapeutically beneficial.

Funding: NIDDK Support

FR-PO195

The Evolving Importance of mTORC2/Rictor in Autophagy Dysregulation and Diabetes-Associated Kidney Disease

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Background: Accumulating evidence suggests that autophagy plays an important role in many critical aspects of normal and disease states of the kidney including diabetic kidney disease (DKD). Podocyte integrity has been described to rely on basal autophagy. However, the exact role of autophagy in podocyte dysfunction and the mechanisms underlying diabetic-induced podocyte injury remain to be elucidated. Several signaling pathways such as mTORC1, NADPH oxidase, and the Liver-X-Receptor (LXR) pathways have been shown to orchestrate podocyte integrity in DKD. Yet, the role of mTORC2 in autophagy and its crosstalk with these key mechanistic pathways remain to be identified. For that, we investigated the role of the Nox4/LXR/mTORC2 axis on autophagy and their possible link to podocyte integrity *in vitro* and in animal models of type 1 and type 2 diabetes.

Methods: A conditionally immortalized human podocyte cell line was used for the *in vitro* studies. In parallel, type 1 diabetes was induced in mice by streptozotocin (STZ) injections and type 2 diabetes was initiated by high-fat diet followed by low-dose STZ injections. Pharmacological means were utilized to alter the expression of Nox4 (GKT), LXR (T0) and the mTORC2 (JR) signaling pathways and functional, pathological and biochemical studies were performed

Results: High glucose (HG)-induced podocyte injury is reflected by alterations in the slit diaphragm proteins and podocyte depletion accompanied by autophagy dysregulation. This was paralleled by activation of the mTORC2 pathway. HG also increased the levels of Nox4 and NADPH oxidase activity. Inhibition of mTORC2, activation of LXR, or inhibition of Nox4 decreased HG-induced ROS generation, restored autophagy homeostasis, regulated podocin levels, and reduced podocyte loss. In isolated glomeruli from the diabetic mice, there was a similar activation of the mTORC2 signaling pathway with an increase in Nox4 and NADPH oxidase activity. Inhibition of mTORC2, activation of LXR or inhibition of Nox4 restored podocin levels, reduced podocyte depletion, attenuated glomerular injury and albuminuria and regulated autophagy levels. More importantly, Chloroquine treatment, an autophagy inhibitor, mimicked the effect of HG/hyperglycemia.

Conclusions: Our data provide evidence for a novel function of mTORC2 in regulating autophagy and its role in DKD.

FR-PO196

Mesenchymal Stem Cells Attenuate Diabetic Kidney Disease by Inhibiting the mTOR Signaling Pathway

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Background: Diabetic kidney disease is one of the most serious complications of diabetes worldwide. The earliest clinical manifestation of DKD is increased albuminuria, which eventually progresses to overt proteinuria. Glomerular injury is characterized by hypertrophy, mesangial matrix expansion, basement membrane thickening, and podocyte loss. Emerging body of evidence has revealed that mesenchymal stem cells treatment induces glomerular repair either through differentiation or by acting in a paracrine manner. However, the mechanistic pathway has not yet been identified. We and others have previously shown that in the glomeruli of diabetic animals, the mTORC1/p70 S6Kinase and Rictor/mTORC2 pathways are activated, promoting podocyte injury. In addition, we demonstrated that mTORC1 and mTORC2 inhibition attenuates HG-induced NADPH oxidase activity and decreases Nox1 and Nox4 expression. The present study aims to assess the reno-protective role of MSCs and to investigate the mechanistic pathway by which MSCs exert this protective role.

Methods: Sprague-Dawley rats were divided into the following groups: a control group and a streptozotocin-induced type 1 diabetic group each treated with medium, MSCs-derived medium, or $1x10^6$ MSCs. After eight weeks of treatment from diabetes onset, functional, histological, biochemical, and molecular parameters of the kidneys were assessed.

Results: MSCs treatment restored normal urinary albumin excretion levels. Protection against DKD imparted by MSCs was denoted by decreased glomerulosclerosis. Moreover, MSCs treatment restored podocyte foot process effacement and glomerular basement membrane thickening and reversed podocyte depletion. More importantly, and for the first time, we show that MSCs treatment restored the mTORC1/mTORC2 complex integrity. This was paralleled by a decrease in NADPH oxidases activity and NOX4 protein expression. All of these observations were mirrored when diabetic rats were treated with MSCs-derived medium.

Conclusions: Our results suggest that MSCs have a potential therapeutic effect in the treatment of DKD by attenuating mTOR signaling pathway. Furthermore, and to our knowledge, this is the first study to report that MSCs-derived medium mimics the beneficial effect of MSCs suggesting that the trophic factors secreted by the MSCs exert the observed reno-protective effect.

Funding: Private Foundation Support

FR-PO197

Honokiol Improves Diabetic Kidney Disease by Activating SIRT3 to Regulate Podocyte Mitochondrial Function

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Background: Diabetic kidney disease(DKD) is the main cause of end-stage renal disease. Current studies have shown that podocyte mitochondrial dysfunction is closely related to the progression of DKD.

Methods: Eight-week-old db/db and db/m mice were injected with honokiol(HKL,5 mg/kg)intraperitoneally for 5 consecutive days. STZ was used to induce diabetes mellitus models in wild type(WT) and SIRT3 knockout (SIRT3 KO) mice and HKL was injected intraperitoneally for 5 days. ACR of mice in each group were detected. The morphological changes of mitochondria were observed under electron microscopes. The activity of podocytes mitochondrial complex I and II were detected by extracting mitochondrial DNA. The expression of mitochondrial metabolism related genes and mitochondrial DNA copys was detected by RT-PCR. In vitro, western blot was used to detect the expression of SIRT3 in podocytes after high glucose stimulation for 48h with or without HKL(5umol/L). Mitotraker, Mitosox and TMRM kits were used to detect the morphology and function of mitochondria. Flow cytometry (V-FITC/PI) was used to detect the apoptosis of podocytes.

Results: The expression of mitochondrial complex I and II in podocytes of db/db mice was lower than that of db/m mice, accompanied by the decrease of mitochondrial DNA Copys. The expressions of SIRT3, PGC1α and TFAM in db/db mice were significantly lower compared with db/m mice. The number of podocytes in db/db mice was decreased by immunohistochemistry. It was found that HKL restore the expression of SIRT3 in podocytes of db/db mice and STZ-induced diabetic mice. Aslo, the mice treated with HKL had lower ACR and improved mitochondrial morphology, but no significant improvement in SIRT3 KO mice. The expression of mitochondrial complex I, II, mitochondrial DNA Copys in podocytes of db/db mice and WT mice were upregulated by HKL. In vitro, it was also found that HKL could upregulate the expression of SIRT3 in podocytes. Compared with high glucose alone, mitochondrial membrane potential decreased in podocytes co-stimulated by high glucose and HKL, and ROS production decreased. Also, flow cytometry (V-FITC/PI) showed that podocyte apoptosis was reduced with HKL incubation.

Conclusions: Honokiol can improve the morphology and function of podocyte mitochondria by upregulating the expression of SIRT3, thus reduce the apoptosis of podocytes.

Funding: Government Support - Non-U.S.

FR-PO198

The Insulin/Insulin-Like Growth Factor Axis Is Critical for Podocyte Function but Partial Inhibition of IGF1 Signalling Is Physiologically Beneficial

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Background: Abnormalities in insulin signalling through the insulin receptor (IR) have previously been found to be critical for podocyte function and this study aims to define the physiological importance of the related insulin-like growth factor 1 receptor (IGF1R) and combined IR/IGF1R in podocytes.

Methods: The Cre-loxP system was used to generate mice with podocyte-specific IGF1R and simultaneous IR/IGF1R gene inactivation. *In vitro* models of receptor knockdown were engineered by applying extrinsic lentiviral Cre recombinase to podocytes derived from IR, IGF1R and IR/IGF1R floxed mice.

Results: We initially generated podocyte IGF1R knockout (podIGF1RKD) mice by crossing IGF1R floxed with mice expressing conventional Cre recombinase under the control of a podocin promotor. Despite 80% knockdown of the IGF1R in this model, podIGF1RKD mice exhibited no changes in renal histology or urinary albumin:creatinine (uACR) at 9 months when compared with littermate controls. However, when these mice were stressed with Adriamycin we, surprisingly, found that podIGF1RKD mice were protected against disease progression with uACR 50% lower than IGF1R sufficient controls. To increase the efficiency of knockout and understand if there was compensation within the IR/IGF1R axis we also generated two additional models using a new podocyte specific Cre driver that is not subject to epigenetic degradation (podIGF1RKO and podIR/IGF1R DKO mice). podIGF1RKO mice were albuminuric at 24 weeks while podIR/IGF1R DKO mice developed a severe kidney phenotype with global sclerosis, renal failure and death between 4 and 24 weeks. >95% loss of IGF1R in cultured podocytes augmented AKT and ERK activation in response to insulin but resulted in ~50% cell death after 7 days. To identify further differentially regulated signalling pathways, IR, IGF1R and IR/IGF1R knockout cells were subjected to TMT phosphoproteomic analysis in the basal state and when acutely stimulated with insulin or IGF1.

Conclusions: Collectively this work reveals the critical importance of podocyte IGF/insulin signalling and that only a fraction of receptor activity is required to maintain function. We also show that partial inactivation of podocyte IGF1R is beneficial in some disease settings.

FR-PO199

Therapeutic Effects of Klotho on Palmitate-Induced Podocyte Damage

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Background: Anti-aging gene klotho has been identified as a multi-functional humoral factor and implicated multiple biological processes. However, the effects of klotho on podocyte injury of diabetic nephropathy (DN) are not known. We therefore investigated the renoprotective effects of exogenous klotho on podocyte injury in DN.

Methods: Lipid accumulation and klotho expression were examined in the kidneys from diabetic patient and animals. Cultured podocytes were stimulated with palmitate to induce diabetic mimic condition with or without recombinant klotho (rKL). Western blot, quantitative real time-PCR, immunofluorescence, and albumin permeability analysis were carried out to evaluate the effects of rKL on palmitate-induced podocyte injury.

Results: Glomeruli from diabetic patients showed an increased lipid accumulation. The klotho expression in kidney from diabetic animals and in palmitate-treated podocytes was decreased. Palmitate-treated podocytes increased apoptosis, intracellular ROS, ER stress, inflammation, and fibrosis, and these were significantly attenuated by rKL stimulation. Palmitate-induced downregulation of an antioxidant molecules was ameliorated by rKL. Furthermore, Palmitate-mediated actin cytoskeleton reorganization and increased albumin permeability were recovered significantly by rKL.

Conclusions: The results suggest that palmitate-mediated functional and morphological podocyte injury were recovered by exogenous klotho, and this may implicate klotho as a potential therapeutic target for treatment of podocyte injury of DN.

Funding: Government Support - Non-U.S.

FR-PO200

Podocyte Nox5 Expression Increases Microparticle Formation and Oxidative Stress in Mice

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Background: Urinary microparticles (MPs) released from podocytes are predictive of injury associated with diabetic kidney disease (DKD) prior to albuminuria. Oxidative stress due to reactive oxygen species (ROS) overproduction is one factor that contributes to MP formation. Podocyte NADPH oxidase 5 (Nox5) produces superoxide and is upregulated in human DKD. Transgenic mice expressing podocyte-specific Nox5 ($Nox5^{Pod+}$) show increased blood pressure, glomerular basement membrane thickening and albuminuria. However, whether podocytes expressing Nox5 produce more MPs under conditions of stress associated with diabetes and hypertension, and whether these microparticles contain Nox5 and are capable of producing reactive oxygen species remains unknown.

Methods: For *in vitro* studies, Nox5 was activated in conditionally immortalized human podocytes through exposure to ionomycin for 24 hours. MPs released into the media were isolated and quantified by nanoparticle tracking analysis. Nox5 content and ROS production from isolated MPs were assessed by immunoblotting and DHE/HPLC, respectively. For mouse studies, $Nox5^{Pod+}$ mice and nontransgenic littermate controls were either implanted with angiotensin II-containing miniosmotic pumps (400mg/kg/day) or sham operated. Systolic blood pressures were determined by tail cuff plethysmography. Urinary MPs were quantified once per week for 5 weeks using 24 hour urine collections.

Results: MP formation was increased two-fold in cultured human podocytes when stimulated with Ionomycin compared to unstimulated controls. Isolated podocyte MPs expressed Nox5 and demonstrated increased ROS formation compared to unstimulated controls. Urinary MP formation was increased in $Nox5^{Pod+}$ mice compared to controls. Angiotensin II administration increased systolic blood pressure in both $Nox5^{Pod+}$ and nontransgenic mice. However, MP formation was further increased following angiotensin administration.

Conclusions: Nox5-expressing podocytes release MPs. These MPs contain Nox5 and are capable of producing ROS. Podocyte Nox5 expression in mice show enhanced urinary MP formation in the context of high blood pressure. Thus, Nox5 may be a contributing factor in the onset of damage in DKD and/or hypertension.

Funding: Government Support - Non-U.S.

FR-PO201

Coupling of Transient Receptor Potential Canonical Channel (TRPC6) and Phosphodiesterase 1 (PDE1) Activity in Diabetic Nephropathy

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Background: Diabetic Nephropathy (DN) is a major complication of diabetes and the incomplete understanding of its molecular mechanisms is highlighted by the limited treatments options. Our investigation focused on the link between TRPC6 and the calcium activated PDE1. Three isoforms of PDE1 are differentially expressed in vascular smooth muscle cells, renal tubular epithelial cells, podocytes, and mesangial cells. While TRPC6 renal expression is associated with DN and inhibition of PDE1 causes vasodilation, their interaction in the context of DN has not been studied. We hypothesized that the diabetic milieu stimulates TRPC6-mediated calcium flux which in turn activates PDE1and propagates kidney injury.

Methods: To investigate the role of PDE1 and TRPC6 mediated calcium flux and apoptosis, cultured primary human mesangial cells or isolated rat glomeruli were treated with TRPC6 agonist HYP9 with or without a pan-PDE1 inhibitor. Apoptosis was measured using high throughput imaging platform using caspase 3/7 as a marker. The role of PDE1 in hypertension and DN was evaluated in telemeterized spontaneously hypertensive rats (SHR) and in hypertensive type 2 diabetic (db/db) mice over expressing the renin gene.

Results: TRPC6 mediated calcium flux induced apoptosis in human mesangial cells and isolated rat glomeruli, which was attenuated by bothTRPC6 and PDE1 inhibitor thereby suggesting a functional coupling between TRPC6 (as a source of calcium) and PDE1 activation. Renal cell protection with PDE1 inhibition was tested in mouse model of DN, featuring a combination of diabetes, nephron loss and arterial hypertension. In this model a novel PDE1 inhibitor caused a significant reduction of albuminuria up to 69% after 6 weeks of treatment compared to vehicle. This was accompanied by a significant reduction in serum creatinine and several urine biomarkers of inflammation and injury. Histopathological analysis revealed substantial improvement in glomerular sclerosis, interstitial fibrosis and reduction in mesangial matrix compared to vehicle. Gene expression analysis of the kidney revealed changes the gene clusters associated with innate immunity and fibrosis.

Conclusions: The results demonstrates that TRPC6 mediated calcium flux is linked to the activation of PDE1 and its inhibition leads to renoprotective effects in DN.

Funding: Commercial Support - Eli Lilly and Company

FR-PO202

Hyperoside Inhibits Podocyte Epithelial-Mesenchymal Transition in Diabetic Kidney Disease via Regulating Insulin Resistance-Related Signaling Pathways, Compared with Rosiglitazone

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Background: Hyperoside (HYP), a bioactive component of *Abelmoschus manihot*, has been widely applied to clinical therapy in the diabetic kidney disease (DKD) patients. However, it remains elusive whether HYP can alleviate podocyte damage in DKD. The disordered activation of insulin resistance (IR)-related signaling pathways in the kidney induces podocyte epithelial-mesenchymal transition (EMT), further resulting in podocyte injury in DKD. Therefore, this study aimed to clarify the therapeutic effects of HYP on podocyte EMT in DKD and its underlying mechanisms, compare to rosiglitazone (ROS).

Methods: All rats were randomly divided into 4 groups, the Sham, the Vehicle, the HYP and the ROS groups. The appropriate doses of HYP, ROS and distilled water were administrated with oral for 6 weeks after the induction of DKD by high fat feed, mononephrectomy and streptozotocin intraperitoneal injection, respectively. The changes in podocyte EMT-related parameters in urine and blood were analyzed. The kidneys were isolated for histomorphometry, immunohistochemistry and Western blotting (WB) at sacrifice. *In vitro*, murine potocytes were used to investigate the inhibitory actions of HYP on IR-associated signaling pathways by WB, compared to ROS.

Results: For the DKD model rats, HYP and ROS ameliorated IR, glomerulosclerosis (GS), glomerular basement membrane (GBM) thickening and foot process effacement, and the effects of HYP on GS and GBM thickening were superior to ROS; HYP and ROS improved the protein expressions of podocyte EMT markers in the kidney including nephrin, P-Cadherin, collagen-1 and desmin, and the effects of HYP were similar to ROS; In addition, HYP and ROS regulated the protein expressions of the key signaling molecules in IR-related signaling pathways including TGF-β1/Smad3, GLUT4 and Erk1/2 pathways, respectively, and the targets of HYP were similar to ROS. *In vitro*, the disordered phosphorylation of TGF-β1/Smad3, GLUT4 and Erk1/2 pathways in podocyte induced by high-glucose was reversed by the treatment of HYP or ROS.

Conclusions: We expounded that HYP inhibits podocyte EMT in DKD via regulating IR-regulated signaling pathways including TGF-β1/Smad3, GLUT4 and Erk1/2 pathways in the kidney, respectively. Overall, this study provided the first evidence that HYP directly contributes to the prevention of podocyte lesion in DKD.

Funding: Government Support - Non-U.S.

FR-PO203

The COX 2-Thromboxane Axis Plays a Critical Role in Podocyte Injury Induced by High Glucose

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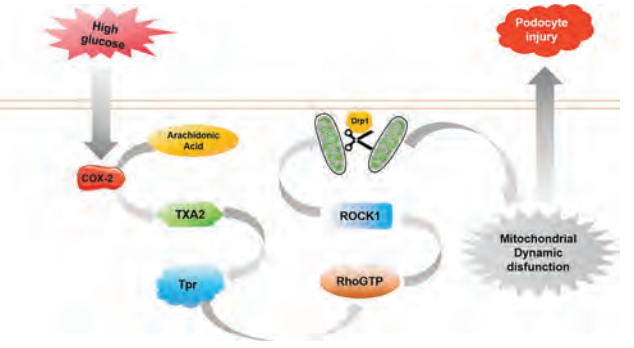
Background: Podocyte injury is a vital factor in the onset and progression of diabetic nephropathy (DN), thus is a promising therapeutic target to prevent DN. The cyclooxygenase 2 (COX 2)- thromboxane axis has been proved to play a critical role in podocyte injury whereas the underlying mechanism is still unknown. The aim of this study is to get a further insight of COX 2-thromboxane axis in podocyte injury.

Methods: In vitro study was performed with a high glucose medium of 30mmol/L to set up a podocyte injury model as previous described. Both the inhibitor and activator of the axis, small interfering RNA, ELISA, western blot and confocal were used to investigate the underlying mechanism of COX 2-thromboxane axis mediating podocyte injury.

Results: High glucose induced podocyte injury accompanied with increasing expression of COX 2 and excessive TXA_2, indicating that the COX 2-thromboxane axis was activated. Small interfering RNA was used to silence the thromboxane/prostaglandin receptors (TP-r) or block the TP-r with inhibitor SQ29548 alleviated the injury. Furthermore, the stimulation of high glucose led to the over-activation of Rho/ROCK1 pathway, resulting in an increased phosphorylation of Drp1, a critical protein regulating mitochondrial fission. As expected, pretreatment of Y26432 could block the ROCK1 release protective effect when the cells were exposed to high glucose. What's more, regulating of TXA2-TPr pathway with SQ29548, U46619 or small interfering RNA can affected the activity of Rho/ROCK pathway in podocytes stimulated with high glucose.

Conclusions: High glucose may activate the COX 2- thromboxane axis, leading to an activating activity of TP-r to induce the downstream effect of ROCK1 activated, resulting in excessive mitochondrial fission, and finally induced podocyte injury (Fig 1).

Funding: Government Support - Non-U.S.



FR-PO204

Puerarin Attenuates Diabetic Nephropathy by Promoting Autophagy in Podocytes

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Background: Puerarin, an active compound of *radix puerariae*, is a major compound used in Chinese herbal medicines to treat patients with diabetic nephropathy (DN). In the previous studies, we showed that puerarin exerts renoprotective effects in a mouse model of streptozocin (STZ) induced diabetic nephropathy (DN) through activation of Sirt1 and anti-oxidative effects. Here, we further investigated the underlying mechanism mediating the renal protective effects of puerarin in DN.

Methods: We tested the effects of puerarin in STZ-induced diabetic mice and in cultured immortalized mouse podocytes treated with either normal (NG) or high glucose (HG). We performed western blot analysis, PCR analysis, immunohistochemistry to determine the molecular mechanisms mediated by puerarin in DN using both vivo and in vitro models. Immunoprecipitation combined with western blot analysis was used to determine acetylation of LKB1. shRNAs were used to knockdown HMOX1 and Sirt1 in cultured podocytes.

Results: We found that puerarin ameliorated STZ-induced kidney injury as shown by kidney histology. We also found that puerarin restored podocyte differential markers such as P-cadherin and ZO-1 in diabetic glomeruli. We also found that expression of HMOX-1 and Sirt1 was suppressed in diabetic glomeruli but restored by puerarin treatment as shown by both real-time PCR, western blot analysis, and immunostaining. In conditionally immortalized mouse podocytes, puerarin inhibited HG-induced apoptosis and restored the protein and mRNA levels of ZO-1, P-cadherin, HMOX-1, and Sirt1. Interestingly, we showed that puerarin decreased LKB1 acetylation, thereby promoting AMPK-dependent autophagy. Knockdown of HMOX-1 and Sirt1 expression or treatment with the autophagy inhibitor 3-MA abolished the protective effects of puerarin in HG-treated podocytes.

Conclusions: Taken together, these results suggest that puerarin protects podocytes from diabetes-induced injury through HMOX1 and Sirt1-mediated upregulation of autophagy, a novel mechanism explaining its renal protective effects in DN.

Funding: Government Support - Non-U.S.

FR-PO205

Effect of Exosomes from High Glucose-Treated Mesangial Cells on Healthy Podocytes

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Background: Mesangial cells can communicate with podocytes *in vivo*, contributing to podocytes damage in the diabetic environment. This paracrine communication may have a relevant role in the diabetic nephropathy (DN). This study investigated whether exosomes secreted by high glucose-treated mouse mesangial cells (MMC) are able to induce dysfunction in normal podocytes.

Methods: MMC were cultured under standard (SG, 5 mM) or high glucose concentrations (HG, 30 mM) for 24 hr. Exosomes (Exos) secreted to the culture medium (SG-Exos or HG-Exos) were purified by ultracentrifugation. The vesicles size/concentration ratio was estimated by the particle tracking (NanoSigth). Vesicles characterization was performed by the presence of markers CD63 and CD81 by western blot. Podocytes in culture were exposed to either SG-Exos or HG-Exos for 24hr. In parallel, HG-MMC and podocytes were co-cultured using a transwell system. Exos secretion by MMC was inhibited by GW4869. Expressions of podocytes makers (actinin IV, p-cadherin and synaptopodin) and profibrotic markers (desmin, TGF-β1 and collagen IV) were analyzed by qPCR. Levels of synaptopodin, desmin, vimentin, podocin, alpha-actinin 4 and nephrin was determined by western blot. Expressions of ZO-1 and Nephrin were evaluated by immunofluorescence.

Results: HG stimulus induced a change in the amount, but not in the size of Exos released by MMC. HG-Exos induced phenotypic transition of podocytes that underwent epithelial mesenchymal transition, demonstrated by a downregulation of actinin 4, p-cadherin, synaptopodin together with an upregulation of desmin and TGF-β1. HG-Exos induced increases in vimentin and desmin proteins while protein expressions of nephrin, synaptopodin, alpha-actinin 4 and podocin were decreased. Levels of ZO-1 and nephrin were decreased in podocytes treated with HG-Exos by immunofluorescence. The co-culture experiments showed that the inhibitor of exosome secretion, attenuated the effects of HG-Exos on the expression of nephrin, synaptopodin, alpha-actinin 4 and podocin. These data suggest that Exos secreted by HG-MMC can cause dysfunction in health podocytes.

Conclusions: Results *in vitro*, demonstrated that exosomes can mediate the paracrine communication between MMC and podocytes, and suggest that high glucose stimulus in MMC can modified podocytes function contributing to DN.

Funding: Government Support - Non-U.S.

FR-PO206

Diabetic Nephropathy Is Associated with Reduced Fraction of Glomerular Basement Membrane Surface Area Opening into the Subpodocyte Space

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Background: Diabetic nephropathy (DN) is the leading cause of end stage kidney disease in the US and better understanding of mechanisms of kidney dysfunction in DN is needed. Current structural functional relationship models, including classical lesions are poor predictors of GFR decline, these imply the possible role of other factors involved in DN progression. Subpodocyte space (SPS) defined as the space between interdigitating foot processes covering GBM and the bottom surface of cell bodies has been characterized through serial sectioning and electron microscopy studies. The SPS is able to retain macromolecules and act as a resistance to fluid flow. However, knowledge about this space is very limited due to lack of validated methodologies for quantification of SPS properties. We developed unbiased quantitative approaches to quantify SPS properties using transmission electron microscopy and validated using SBF-SEM and 3D modeling. Our study will provide an approach to understand how SPS interplays with other structural changes in affecting kidney dysfunction in DN.

Methods: 9 Kidney biopsies of type 2 diabetes were selected and the results were compared with 5 normal controls. Structural studies were performed using these approaches: (1) segmentation of urinary spaces and identification of exit pores; (2) quantification of surface fraction and total surface of GBM opening into SPS/IPS/PUS and volumes of those spaces; (3) quantification of average in-flow areas and out-flow areas of SPS/IPS/PUS and lengths of outflow areas of those spaces

Results: Comparison of glomeruli from 9 T2D patients and 5 normal controls showed classical changes of DN. While the volume and the GBM surface exposed to each of the urinary space compartments were increased in DN, surface density of SPS and IPS were reduced and this reduction was more prominent for SPS (over 2 folds). Moreover, in DN patients, %GBM surface which is exposed to SPS was reduced and, in contrast, %GBM exposed to IPS was increased ($P=0.001$). The data indicates significant reduction in in-flow and widening of out-flow areas in DN compared to control ($P<0.05$).

Conclusions: Structural properties of urinary spaces are differentially regulated and reduced %GBM exposed to SPS may be a compensatory mechanism against GFR loss in DN.

Funding: NIDDK Support, Private Foundation Support

FR-PO207

The Mineralocorticoid Receptor Antagonist Finerenone Limits Podocyte Injury in High-Salt Loaded db/db Mice

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Background: Diabetic kidney disease (DKD) is a leading cause of end-stage kidney disease worldwide; however, the underlying mechanisms have not been fully elucidated. Previously, we identified cross-talk between mineralocorticoid receptor (MR) and the small GTPase Rac1, and found that activation of Rac1-MR pathway is implicated in proteinuric nondiabetic kidney disease (*Nat Med* 2008, *JCI* 2011). However, few mouse models of DKD hinder the progress of research on DKD.

Methods: We tried to establish the new mouse model of DKD with typical nodular lesion, in order to evaluate the involvement of Rac1-MR pathway in DKD. We performed uninephrectomy at young age (4-week postpartum) and fed a high-salt (HS) diet for 10 weeks to accelerate kidney damage in type 2 diabetic model of db/db mice. We evaluated urinary albumin excretion and kidney phenotype including Rac1-MR pathway, and the renoprotective role of the MR antagonist Finerenone in this DKD mouse model.

Results: HS loading induced prominent elevation of albuminuria and increased glomerular damage with typical nodular lesion in uninephrectomized db/db mice, which were accompanied by the podocyte injury. In db/m control mice, however, albuminuria and glomerular damage did not increase by uninephrectomy and HS loading. Expressions of active Rac1 and Sgk1, a downstream molecule of MR signaling, in the cortex and isolated glomeruli, were elevated in uninephrectomized and HS-treated db/db mice compared with the treated db/m mice. Of note, glomerular active Rac1 expressions were merged with podocyte specific markers including podocin, suggesting Rac1-MR activation in podocytes of the DKD model mouse. Finerenone inhibited the elevated Sgk1 expressions in glomeruli, associated with the improvement of the glomerular damage and podocyte injury, resulting in the significant reduction of albuminuria.

Conclusions: HS loading induces enhanced MR signaling, podocyte injury, and albuminuria in uninephrectomized db/db mice, which are ameliorated by the treatment of Finerenone, suggesting the involvement of activation of Rac1-MR pathway in the progression of DKD, and highlighting MR antagonism as a novel approach to treat DKD.

Funding: Commercial Support - Bayer Yakuhin

FR-PO208

Diabetic Condition Induces Hypertrophy and Mitotic Catastrophe in Parietal Epithelial Cells Through Cell Cycle Re-Entry

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Background: Parietal epithelial cells (PECs) have recently been reported to be involved in the pathogenesis of crescentic glomerulonephritis (GN) and focal segmental glomerulosclerosis (FSGS); however, little information is available about changes in PECs under the diabetic condition. Therefore, we performed a detailed analysis of the morphological changes of PECs in diabetic mice and in human.

Methods: Conditionally immortalized mouse PECs were exposed to 5 mmol/L glucose (LG), 30 mmol/L glucose (HG). Hypertrophy and cell cycle were assessed by flow cytometry. Apoptosis was ascertained by Annexin V/PI staining, and caspase 3/7 staining. ROS analysis was evaluated by fluorescent intensity of CM-H2DCFDA. Streptozotocin-treated mice, db/db mice were used as diabetic mouse models. In the analysis of human kidney biopsy samples, the renal histology of the patients with diabetic kidney disease (DKD) were compared with that in the patients with other diseases. Histomorphology of the renal tissue was examined by using light microscopy and transmission electron microscopy (TEM).

Results: In cultured PECs, HG induced hypertrophy and apoptosis in a dose-dependent manner as compared to LG. This effect is not through HG-induced ROS production. Flow cytometry showed that HG increased the percentage of cells in the S phase, indicating some PECs in G0/G1 phase re-entered into S phase. In TEM, PECs exhibited enlargement of cytoplasm at the ultrastructural level in all diabetic mouse models and in human DKD kidneys from early stage before the expression of CD44, which is activated PEC marker of crescentic GN and FSGS. Although rare, binuclear cells were observed in early diabetic model mice, which suggest mitotic catastrophe. PAX 8 staining revealed PEC nuclear hypertrophy in diabetic mice, whereas the cell number of PECs remained unaltered, suggesting that PECs in diabetic condition underwent DNA replication with a mitotic defect.

Conclusions: PECs in diabetic condition are in a state of dysregulation of proliferation similar to mitotic catastrophe from early stage without the expression of PEC activation marker CD44. As PECs are considered a precursor of podocytes, this injury to PECs might impair glomerular regeneration. Further studies are warranted to elucidate the potential pathological role of these morphological changes in PECs in DKD.

FR-PO209

Intraglomerular Cross-Talk Between Mesangial Cells and Podocytes Inhibits Normal Endoplasmic Reticulum-Associated Degradation Processes and Induces Podocyte Injury in Diabetes

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Background: Mesangial lesion and podocyte injury are essential for the progression of diabetic kidney disease (DKD). Although cross-communication between mesangial cells (MC) and podocytes is recently suggested by single cell RNA-seq analyses, its molecular mechanisms remain elusive. Our previous experiment on cDNA microarray of diabetic mice glomeruli suggested that ER stress might be involved in DKD progression. The aim of this study is to clarify the effects of MC-podocyte crosstalk on ER stress response of podocytes in diabetic conditions.

Methods: First, we conducted quantitative PCR array focused on ER stress-associated genes. Using cultured mouse podocytes (MPC5) and mouse macrophages (Mϕ) stimulated with MC-cultured medium (MC-sup) under high-glucose condition (HG), we evaluated podocyte-specific responses. Further evaluations of ER stress responses of MPC5 were made by Western blotting, real-time PCR and TUNEL staining. The effects of an ER-associated degradation (ERAD) inhibitor Eeyarestatin I (EerI) in MPC5 and db/db mice were also examined.

Results: In vitro, stimulation with HG MC-sup suppressed ERAD-related factors (XBP1, Derlin), and enhanced apoptotic responses in both protein and mRNA levels specifically in MPC5, but not in Mϕ. TUNEL staining of MPC5 also showed increased apoptotic cells by HG MC-sup. Those results were augmented by HG MC-sup compared to MC-sup under low-glucose condition. Of note, treatment with EerI recapitulated similar responses, namely suppressed IRE1α, spliced XBP1 and Derlin-2 in MPC5. In vivo, such alterations were also observed in isolated diabetic glomeruli. Administration of EerI significantly exacerbated albuminuria in db/db mice. Expression of genes related to inflammation and fibrosis increased, and immunohistochemistry showed lowered expression of Derlin-2 and nephrin in the glomeruli.

Conclusions: It is recently reported that ERAD pathway may play important roles in the maintenance of podocytes to avoid ER stress in several glomerular diseases including DKD. In this study, we first reveal that intraglomerular crosstalk between MC and podocytes inhibits normal ERAD processes, potentially causing podocyte injury in diabetic conditions.

FR-PO210

Calcitriol Plays a Protective Role in Podocytes of Diabetic Nephropathy Rats by Regulating Autophagy

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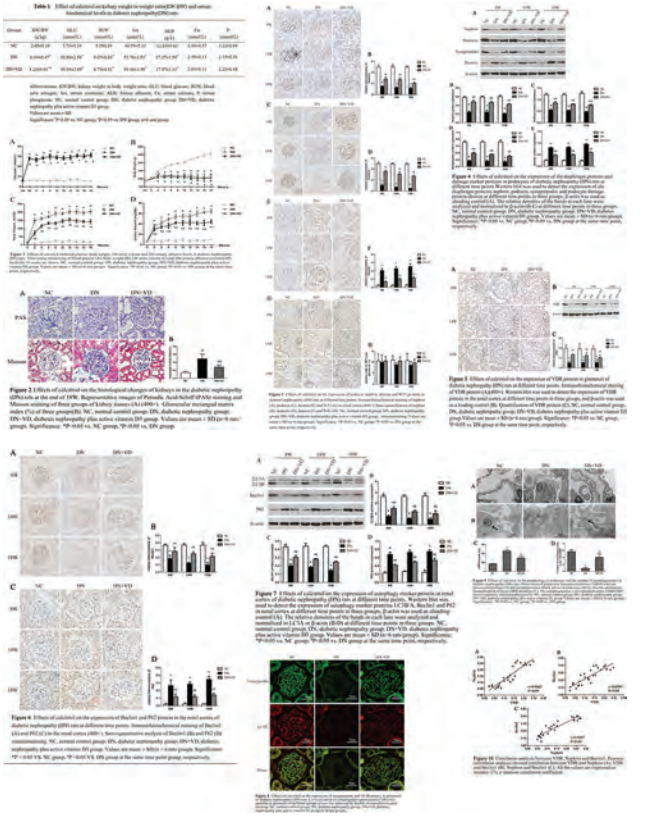
Background: Podocyte injury is the core link of the development of diabetic nephropathy(DN). The nature of podocyte proliferation determines the important role of intracellular degradation system in maintaining podocyte homeostasis. Evidences show that autophagy plays a critical role in the progression of podocyte disease. Previous research in our group has confirmed that calcitriol effectively reduce proteinuria and podocyte injury in DN rats. This study aimed to investigate whether calcitriol can reduce podocyte injury in DN rats by regulating autophagy.

Methods: DN model was established in male SD rats by intraperitoneal injection of streptozotocin(60mg/kg). The rats were subsequently given calcitriol or vehicle(0.1μg/kg/d) by gavage and then sacrificed at three time points(week8, 14, 18). Specimens were used for biochemical, histopathological and molecular biology tests.

Results: DN rats exhibited renal pathological damage accompanied by proteinuria. The expression of slit diaphragms proteins(low expression of nephrin, podocin, synaptopodin), VDR(low expression), autophagy-associated proteins(low expression of LC3B/A, Beclin1, overexpression of P62) were abnormal in DN rats. The number of autophagosomes in podocytes were significantly reduced. The fluorescence of LC3B and synaptopodin proteins were highly overlapping, the fluorescence intensity of both proteins in DN rats were significantly reduced. whereas calcitriol reversed these above changes.

Conclusions: Calcitriol reduces podocyte injury in DN rats by regulating autophagy, thereby reducing proteinuria.

Funding: Government Support - Non-U.S.



FR-PO211

Renal Olfactory Receptor 1393 Contributes to the Development and Progression of Type 1 Diabetes

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Background: Olfactory receptor 1393 (Olfr1393) is a G-protein coupled receptor with vital functionality outside of its native environment of the nose. Recently, we determined that this receptor is expressed in the renal proximal tubule where it aids in glucose reabsorption via the sodium-glucose co-transporters (Sglts). We also found that Olfr1393 is linked to the progression of type II diabetes in a diet-induced obesity mouse model. As Sglt inhibitors have emerged as a novel therapeutic option for type I diabetes (T1D), we sought to extrapolate the role of renal Olfr1393 in the context of this metabolic disorder.

Methods: To induce T1D in whole-animal Olfr1393 wildtype (WT) and knockout (KO) mice, low dose injections of Streptozotocin (STZ; 55 mg/kg BW) or vehicle control were administered for 5 consecutive days to deplete pancreatic β-cells and induce insulin deficiency in both male and female mice. Progression of diabetes was tracked by measuring 2 hour fasting blood glucose and glucose tolerance via intraperitoneal glucose tolerance tests at 2, 5, and 12 weeks post-STZ injections. Glomerular filtration rate was determined using transdermal measurement of FITC-Sinistrin and urinalysis was performed by dipstick.

Results: STZ administration induced phenotypes of hyperglycemia and impaired glucose tolerance in male, but not female, Olfr1393 WT mice. Notably, these diabetic phenotypes were significantly attenuated in the Olfr1393 KO males by 2 weeks post-STZ injection and the differences became more pronounced after 5 weeks. This improvement was accompanied with a reduction in proteinuria, glycosuria, and hemoglobinuria. No significant differences were detected in insulin sensitivity between diabetic WT and KO mice. One hallmark of T1D is the development of glomerular hyperfiltration; notably, neither diabetic WT nor KO mice presented with hyperfiltration 12 weeks post-STZ.

Conclusions: Collectively, this study indicates that diabetic phenotypes are attenuated in Olfr1393 KO mice suggesting that Olfr1393-mediated glucose handling is important for the progression of T1D. Efforts are currently underway to determine the expression and activity of the renal Sglts in the setting of T1D to elucidate the mechanism by which Olfr1393 contributes to the diabetic phenotype.

Funding: NIDDK Support

FR-PO212

A Novel All-Trans Retinoic Acid Therapy Directly Suppresses Bone Morphogenetic Protein 4 in Mouse Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) causes mesangial matrix expansion, resulting in glomerulosclerosis and renal failure. Collagen IV (COL4), a major component of the mesangial matrix, is positively regulated by bone morphogenetic protein 4 (BMP4)/ suppressor of mothers against decapentaplegic (Smad1) signaling. Treatment with all-trans retinoic acid (ATRA), a potent ligand of the retinoic acid receptor (RAR), shows a beneficial effect on kidney disease; however, its effects on glomerular matrix expansion in DN remain unclear. RAR/retinoid X receptor (RXR) heterodimer binds directly with retinoic acid (RA) response element (RARE) and regulates transcription of various genes. In the present study, we investigated the therapeutic potential of retinoids in DN, focusing on the regulatory mechanism of BMP4.

Methods: Diabetes was induced with streptozotocin in 12-week-old male Crl:CD1(ICR) mice. One month later, we initiated intraperitoneal injection of ATRA (15 μg/gBW) or corn oil three times a week, from 16 to 24 weeks of age. ATRA or specific agonists for each subtype of RAR were added to cultured mouse mesangial cells from 1 nM to 1 μM with or without advanced glycation end products (AGE, 200 μg/ml) for 24 hours. We analyzed glomerular matrix expansion, BMP4/Smad1/COL4 axis, RAR/RXR binding capacity, and putative RAREs.

Results: Glomerular matrix expansion, associated with increased BMP4, phosphorylated Smad1, and COL4 expression, worsened in diabetic mice at 24 weeks of age. ATRA administration alleviated DN and downregulated BMP4, phospho-Smad1, and COL4. In cultured mouse mesangial cells, treatment with ATRA or a retinoic acid receptor α (RARα) agonist significantly decreased BMP4 and COL4 expression, more so in AGE-treated cells. Genomic analysis suggested two putative RAREs for the mouse *Bmp4* gene. ChIP analysis and reporter assays indicated a putative RARE of *Bmp4*, located 11488–11501 bp upstream of exon1A, which bound to RARα and RXR in animals' kidney and in cultured cells, and the luminescence signal decreased after ATRA or RARα agonist addition.

Conclusions: ATRA suppressed BMP4 via binding of RARα/RXR heterodimer to a unique RARE, alleviating glomerular matrix expansion in diabetic mice. These findings provide a novel regulatory mechanism for treatment of DN.

Funding: Government Support - Non-U.S.

FR-PO213

A New Perspective on the Pathogenesis of Diabetic Nephropathy: Changes in Thyroid Hormone Signaling Trigger Diabetes-Induced Podocyte Pathology

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Background: In diabetic patients, hypothyroidism – both clinical and subclinical – is the most common diabetes-associated disorder, while thyroid dysfunction and low T_3 levels are strongly associated with worse renal clinical outcomes and increased mortality. Based on these data, we investigated the role of thyroid hormone (TH) signaling changes in diabetic nephropathy (DN).

Methods: ZSF1 rats were used as *in vivo* model of DN and human immortalized podocytes exposed to high glucose or H_2O_2 as *in vitro* model of diabetic stress. Rat systemic parameters were evaluated at different time-points. Immunohistochemical and western blot analysis were performed on rat renal tissue and human podocytes. Patient biopsies were analyzed using immunohistochemical assays.

Results: In ZSF1 rats, plasma T_3 levels decreased during DN, and this was inversely correlated with metabolic and renal disease worsening, and glomerular histological changes. We observed the re-expression of the fetal TH receptor (TR) isoform TRα1 in podocytes and parietal cells of diabetic rats and patients with DN, and increased glomerular expression of the TH-inactivating enzyme deiodinase 3 (DIO3). In ZSF1 rats, TRα1-positive cells also re-expressed fetal, mesenchymal and damage-related podocyte markers, such as Pax2, Six2, GDNF, desmin, Ret and GFRα1. Podocyte depletion and glomerular and podocyte hypertrophy were evident. *In vitro* studies showed that podocytes that were exposed to components typical of the diabetic milieu exhibited a significant increase in TRα1 and DIO3 expression, as well as cytoskeleton rearrangements, adult podocyte marker down-regulation and fetal kidney marker up-regulation, in addition to maladaptive cell cycle induction/arrest and TRα1-ERK1/2-mediated hypertrophy. Strikingly, T_3 administration significantly decreased TRα1 and DIO3 expression and reversed the above changes.

Conclusions: Our data show that diabetic stress induces the TH-TRα1 axis to adopt a fetal ligand/receptor relationship pattern that plays a key role in DN-associated podocyte pathology, and create a new perspective on the pathogenesis of DN, suggesting that TRα1 could be a new pharmacological target.

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FR-PO214

Salvianolate Ameliorates Oxidative Stress and Podocyte Injury Through Modulation of AMPK/NOX4 Axis in db/db Mice

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Background: Changes in podocyte morphology and function are associated with albuminuria and progression of diabetic nephropathy (DN). NADPH oxidase 4 (NOX4) is the main source of reactive oxygen species (ROS) in the kidney and NOX4 is upregulated in podocytes in response to high glucose.

Methods: In the present study, the effects of Salvianolate on DN and its underlying mechanisms were investigated in diabetic db/db mice and human podocytes.

Results: We confirmed that Salvianolate injection administration exhibited similar beneficial preventive results with the NOX1/NOX4 inhibitor, as reflected by attenuated albuminuria, reduced podocyte loss and mesangial matrix accumulation. We further observed that Salvianolate exerted its renoprotective role via reducing high-glucose induced NOX4-based NADPH oxidase activity, podocyte apoptosis and restoring podocyte differenation marker (synptopodin) expression in the isolated glomeruli of db/db mice. In human podocyte, NOX4 was expressed in the mitochondrial compartment and Salvianolate treatment blocked NOX4-derived mitochondrial superoxide generation and activated AMPK kinase expression, thereby ameliorating podocyte apoptosis. Therefore, Salvianolate possesses the renoprotective capabilities in part through AMPK-mediated control of NOX4 expression, confirmed by AMPK inhibitor (Compound C).

Conclusions: Taken together, our results identify that Salvianolate could prevent glucose-induced oxidative podocyte injury through modulation of AMPK/NOX4 axis in DN and have a novel therapeutic potential for DN.

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FR-PO215

Diabetic Milieu-Induced Mitochondrial Oxidative Damage and Loss of Mitochondrial Proteostasis in Glomerular Endothelial Cells

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Background: Oxidative stress and mitochondrial dysfunction are considered central mediators in the pathogenesis of diabetic complications including diabetic kidney disease (DKD). We have demonstrated that mitochondrial stress and dysfunction in glomerular endothelial cells precede and mediate in part albuminuria, podocyte defects and depletion, and glomerulosclerosis in DKD susceptible DBA/2J mice. We hypothesize that DKD-susceptibility is characterized by glomerular endothelial mitochondrial stress-dependent endothelial dysfunction and secretion of crosstalk factors required for podocyte injury and depletion. **Aim:** To examine mitochondrial oxidative stress and quality control mechanisms in glomerular endothelial cells exposed to a diabetic milieu and assess the impact of endothelial cell dysfunction on podocytes in co-culture.

Methods: We treated murine glomerular endothelial cells (mGECs) with high glucose media (HG) and 2.5% v/v of sera from non-diabetic control (CS) and diabetic (DS) DBA/2J mice. We measured mitochondrial function (oxygen consumption), fragmentation (mitotracker), mitochondrial ROS (mtROS; mitoSOX), accumulation of oxidized products (DNA lesion frequency, γ-H2AX, 8-oxoG, 3-Nitrotyrosine), mitochondrial unfolded protein response (UPR^{mt}), endothelial function (NOS activity) and cell death (Annexin/PI).

Results: Treatment of mGECs with HG or DS resulted in increased mtROS, oxidative mtDNA damage, mitochondria fission and reduced mitochondrial function compared to controls, this in turn impaired the synthesis of electron transport chain components. mtROS specific scavenger (mitoTEMPO) prevented these changes. Chronic exposure of mGECs to the diabetic milieu (up to 72h) resulted in accumulation of oxidized products due to inadequate clearance and loss of mitochondrial proteostasis, leading to cellular dysfunction. Co-incubation of podocytes with conditioned media from stressed mGECs resulted podocytes cell death.

Conclusions: Our results demonstrate that the diabetic environment can mediate GEC dysfunction by triggering mitochondria stress. Furthermore the inability to restore mitochondrial function and proteostasis, suggests a maladaptive response under chronic exposure to diabetic milieu and in turn the secretion of pro-apoptotic factors affecting podocytes in co-cultures.

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FR-PO216

Placental Growth Factor Deficiency Aggravates Diabetic Nephropathy

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Background: Placental growth factor (PlGF) is a member of the vascular endothelial growth factor (VEGF) family. PlGF exerts favorable angiogenenic and lymphangiogenic activity by binding to VEGF-R1 and -R3. Due to its functional synergy with VEGF-A, it is required for a correct neovascularization during pathological conditions while inactivation of PlGF contributes to decreased angiogenesis. Because reduced angiogenesis and lymphagiogenesis that contribute to defective lipid drainage are implicated in the

progression diabetic kidney disease (DKD), we investigated the role of PlGF in the development of DKD by using PlGF-knockout mice.

Methods: Diabetes was induced by a low-dose streptozotocin injection in 9-week-old male C57BL/6J PlGF-KO and wild-type mice and biochemical and morphological parameters were examined at 12 weeks later.

Results: In diabetic PlGF-KO mice, fasting blood glucose and HbA1c levels increased significantly and the development of glomerular sclerosis and mesangial area expansion were accompanied by albuminuria. They exhibited increased expression of type IV collagen, transforming growth factor-β1 and glomerular IHC staining for nephrin, PECAM-1 and WT-1-positive cells and VEGF-R1,-R2,-R3 expression decreased, suggesting decreased endothelial cell and podocyte structure. Intrarenal expression of pLKB1, and pAMPK decreased and that of PPARα, PGC1α, ERRα, p-eNOS, and urinary Nox concentration decreased while iNOS increased, indicating disturbed lipid metabolism and endothelial dysfunction in the same group. Diabetic PlGF-KO mice showed increased intrarenal FFA, TG, and cholesterol concentration representing presence of lipid accumulation and F4/80- and TUNEL-positive cells increased, suggesting increased inflammatory cell infiltration and apoptosis. CD68 and arginase-II increased indicating that macrophage subtype M1 polarization is involved in the inflammatory process. Expression of Bcl2/bax decreased and that of SOD1 and 2 decreased, indicating increased apoptosis and oxidative stress, respectively. Increased expression of intrarenal 8-OHdG and urinary isoprostane level indicates increased oxidative stress.

Conclusions: Impaired angiogenesis and lymphangiogenesis are implicated in PlGF deficiency and this promotes lipotoxicity-induced inflammation, oxidative stress and deteriorates renal functional and phenotypic parameters in DKD.

FR-PO217

Endothelial Nitric Oxide and the Podocyte NFAT2/Heparanase Axis in Diabetic Nephropathy

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Background: A reduction in endothelial nitric oxide synthase (eNOS) activity serves as a key driver in the development and progression of diabetic nephropathy (DN), which has been studied using global eNOS knockout (eNOSGKO) mice for a decade. However, eNOSGKO mice have several inherent problems including a tendency to develop progressive renal disease regardless of diabetic status. Diabetic eNOSGKO mice exhibit advanced podocytopathy, but the detailed mechanism is unknown. The calcineurin-nuclear factor of activated T cells (NFAT) signaling pathway has been reported to cause podocyte injury.

Methods: To determine the precise role of eNOS in DN, we created floxed eNOS mice. We conditionally deleted endothelial cell-specific eNOS expression (E-eNOSKO) after the onset of diabetes in mice to more closely represent the clinical course of human DN. Streptozotocin was used to generate diabetes. Tamoxifen was used to conditionally knock out endothelial cell-specific eNOS. To evaluate the role of NFAT2 in podocyte injury in diabetic eNOSKO mice, Podocin-Cre NFAT2 floxed eNOSGKO mice were also generated. A cyclin-dependent kinase 4-transformed podocyte line was treated with an NO donor in high glucose conditions.

Results: Diabetic E-eNOSKO mice showed significantly increased albuminuria with progressive glomerular lesion changes. We evaluated NFAT isoforms and found that NFAT2 was upregulated in podocytes in advanced DN patients and diabetic E-eNOSKO mice. NFAT2 activation in cultured podocytes was upregulated by high glucose and suppressed by NO donor treatment in a dose-dependent manner. Heparanase (HPSE), the only mammalian endoglycosidase that degrades heparan sulfate, was expressed in podocytes in both advanced DN patients and our model. HPSE was upregulated in cultured podocytes under high glucose conditions and was suppressed by NO donor treatment. Transfection of constitutively active NFAT2 increased HPSE in cultured podocytes. Podocyte-specific NFAT2-deleted diabetic eNOSGKO mice showed attenuated albuminuria with decreased HPSE expression in podocytes.

Conclusions: Our findings indicate that eNOS has a crucial role in the regulation of HPSE in podocytes through NFAT2 activation, which suppresses proteinuria in advanced DN.

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FR-PO218

The Mechanism of Mfn2 Regulating ABCG1-Mediated Cholesterol Efflux in Glomerular Endothelial Cells of Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD), is one of the most common microvascular complications of diabetes mellitus. Increasing evidence has shown that renal lipotoxicity plays an important role in the pathogenesis of DKD. The ATP-binding cassette transporter (ABC) G1 mediates intracellular cholesterol efflux. It has been found that overexpression of mitochondrial fusion protein 2 (Mfn2) in macrophages promotes ABCG1-mediated cholesterol efflux. In this study, we investigated the mechanism of Mfn2 regulating ABCG1-mediated cholesterol efflux in glomerular endothelial cell of diabetic kidney disease.

Methods: Glomerular endothelial cell specific knockout ABCG1 (ABCG1-GEC KO) mice and C57BL/6J (WT-N) mice were induced to type 2 diabetes. Another mice in each group were injected with Ad-Mfn2 adenovirus to establish diabetes model. After 8 weeks, mice were sacrificed and collected peripheral blood for detecting creatinine, lipids and glycosylated hemoglobin (HbA1c),and cholesterol efflux and mitochondrial function were detected. The kidney cortex tissue was taken freshly to extract the expression of ABCG1, inflammatory factors. In vitro, adenoviro-induced overexpression of Mfn2 and ABCG1 in glomerular endothelial cells were cultrued with high glucose to clearfy the relationship between Mfn2 and ABCG1. Specific inhibitors of PPAR-γ and PPAR-β were used to reveal the relationship of Mfn2 and ABCG1.

Results: In vivo experiments, cholesterol content increased significantly and mitochondrial respiratory was dysfunction obviously. Immunohistochemical demonstrated that the expression of inflammatory factors increased, while the expression of ABCG1 and Mfn2 decreased. The oxidative phosphorylation (OXPHOS) of kidney mitochondria complex I/II (CI/CII) and electron transfer ability (ETS) decreased significantly in experimental group ($P < 0.05$). In vitro experiments, the mitochondrial function regulated by Mfn2. The expression of ABCG1 was reduced and cholesterol efflux was blocked by specific inhibitors of PPAR-γand PPAR-β compared with control group.

Conclusions: Mfn2 mediated mitochondrial dysfunction plays an important role in cholesterol homeostasis incued by ABCG1 deficiency. In diabetic kidney disease, overexpression of Mfn2 could relieve the renal damage caused by cholesterol accumulation, which increased the expression of ABCG1 depending on PPAR-γ/PPAR-β.

FR-PO219

The Relative Roles of Nox4 vs. Nox5 in Diabetic Kidney Disease

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Background: Renal oxidative stress plays a crucial role in diabetic kidney disease (DKD). Recent studies have identified that Nox5 could be a main culprit in the context of human DKD. Nox5 is present in humans and rabbits but not in mice or rats. We examined the role of Nox4 vs. Nox5 in human DKD, in human renal cells as well as in rabbit and Nox5 transgenic (Tg) mouse model of DKD.

Methods: Expression of Nox5 was examined in human kidney biopsies. In vitro, Nox4 and Nox5 was silenced in human renal cells and were exposed to high glucose. In vivo, we have exposed the rabbits to high fat feeding (HF) as well as inducing insulin deficient diabetes using alloxan. We have generated a Nox5 knockout rabbit and a unique humanised Nox5 Tg mouse with concomitant Nox4 deletion.

Results: Expression of Nox5 was increased in kidney biopsies obtained from diabetic individuals. Nox5 shows the highest upregulation in response to high glucose in comparison to other Nox isoforms. Silencing of Nox5 reduces ROS formation and expression of proinflammatory and profibrotic cytokines and growth factors as well as putative elements that are implicated in DKD. Moreover, Nox5 is upstream of Nox4 and that Nox5 inhibition also downregulates Nox4, but not vice versa. HF and alloxan induced diabetic rabbits showed increased renal Nox5 expression in association with increased mesangial area and ECM accumulation along with upregulation of CTGF, fibronectin and MCP-1 as well as enhanced ROS production in the kidney. Expression of Nox5 in mesangial cells of Nox4KO diabetic mice demonstrated 30% increase in albuminuria, mesangial expansion, increased renal injury and inflammation via enhanced ROS production.

Conclusions: These findings suggest that Nox5 derived ROS accelerates renal injury in diabetes and provide proof of principle for the development of a new renoprotective agent in diabetes.

FR-PO220

YAP Activation in Renal Proximal Tubule Epithelial Cells Contributes to Development of Tubulointerstitial Fibrosis in Diabetic Nephropathy

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Background: Excessive production of CTGF in kidney has been implicated in the development and progression of DN. YAP (Yes-associated protein) is a transcription factor activator for multiple critical transcription factors. The goal of these studies is to determine the potential role and underlying mechanisms of YAP activation in renal proximal tubule epithelial cells (RPTC) during DN development and progression.

Methods: YAP activation in RPTC was evaluated in deidentified diabetic patient and control kidneys, type I and II diabetic mouse kidneys and cultured human renal proximal tubule epithelial cells (hRPTC). Unilateral nephrectomized (UNX) inducible RPTC specific YAP deletion (Yap^{ptiKO}) and wild type (Yap^{ptWT}) mice, FVB/NJ or $eNOS^{-/-}$ mice were subjected to streptozotocin injections to induce type I diabetes. The diabetic mice were treated with or without verteporfin (a YAP-TEAD association inhibitor), Y-27632 (a Rho association Kinase (ROCK) inhibitor). Mouse urinary albumin excretion and tubulointerstital fibrosis were evaluated. Expressions of YAP, CTGF and profibrotic or fibrotic proteins in RPTC were analyzed. hRPTC was exposed to 25mM glucose treated with or without verteporfin or Y-27632, or YAP, RhoA GTPase siRNA followed by analysis of YAP activation.

Results: YAP expression and nuclear translocation were upregulated in the RPTC of kidneys from diabetic patients and type I and type II diabetic mice, or in the hRPTC exposed to culture medium containing 25mM of glucose. RPTC specific YAP deletion, or treatment of the diabetic $eNOS^{-/-}$ or FVB/NJ mice with verteporfin or Y-27632

inhibited CTGF and α-SMA expression in diabetic renal cortical tissues and attenuated tubulointerstitial collagen I deposition. Proteinuria was ameliorated in verteporfin or Y-27632 treated mice but not in Yap^{ptKO} mice. Y-27632 treatment also decreased YAP activation in diabetic RPTC. In hRPTC, inhibition of YAP activation blocked CTGF and inhibition of RhoA GTPase attenuated YAP and CTGF expression in response to high glucose.

Conclusions: RhoA GTPase-dependent YAP activation and subsequent increases in CTGF and ECM production mediated myofibroblast transition may be potential underlying mechanisms for diabetic tubulointerstitial fibrosis and targeting YAP activation may serve as a therapeutic intervention in diabetic nephropathy.

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FR-PO221

Identification of Gene Signatures and Molecular Pathways Associated with Urine Albumin Creatinine Ratio Response to Renal Protective Drugs

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Background: Renal protective drugs reduce the risk of progression and urine albumin/creatinine ratio (UACR) in some but not all patients with type 2 diabetes and CKD. Previous studies showed that the response in each individual is consistent to different drugs. Here we aim to identify gene signatures and molecular pathways that are associated with the individual response to renal protective drugs.

Methods: ReninAAV db/db uNx mice were treated with the angiotensin-converting enzyme inhibitor Lisinopril, the angiotensin receptor blocker Losartan, the Janus-associated kinase inhibitor Ruxolitinib, the sodium glucose transporter 2 inhibitor Canagliflozin or vehicle control for 2 weeks (n=8 per group). ACR was measured at baseline and after treatment. RNAseq profiling of kidney cortex was performed. weighted gene co-expression network analysis and machine learning approaches were used to identify genes associated with UACR; ingenuity pathway analysis was used to identify enriched molecular pathways.

Results: The fraction of mice that responded to treatment, defined as >35% decline in UACR varied depending on the drug, with all mice responding to Lisinopril, 5/8 to Losartan, 4/8 to Ruxolitinib, and none to Canagliflozin. Network analysis identified 35 co-expression modules, several of which were distinctly associated with phenotype variables. Selecting 12 of the modules, a cross-validated logistic lasso regression model was able to predict responders with 83% accuracy (40/48). The cross-validated model was compared to results from 1000 random permutations of its class labels, and found to be significant ($p<0.001$). Enriched signaling pathways include genes involved in tight junction-, mTOR- and sirtuin signaling, as well as in nicotine degradation.

Conclusions: Our study identified gene signatures and molecular pathways associated with UACR response to renoprotective treatments, as well as pathways previously reported to be associated with human kidney disease progression. Results may increase our understanding of the molecular mechanisms underlying responses to treatment and help stratify patients to predict their response to treatment. Our findings will be compared to clinical trial data sets.

Funding: Commercial Support - Eli Lilly, Government Support - Non-U.S.

FR-PO222

Divergent Changes in Kidney Extracellular Matrix Stiffness in Different Mouse Models of Diabetic Nephropathy

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Background: The mechanical properties of the extracellular matrix (ECM) are important in regulating cell and tissue function, and changes in ECM stiffness contribute to a number of pathological conditions. Diabetes is characterized by dramatic changes in the structure of the kidney ECM. Glomerular and tubular basement membrane thickening and expansion of the mesangial matrix are hallmarks of diabetic nephropathy. It is not clear how structural alterations in the ECM translate into changes in the biophysical properties of the ECM in diabetic kidney disease. The goal of this work was to evaluate the stiffness of tubular basement membranes and glomerular ECM in multiple models of diabetic nephropathy of varying severity.

Methods: Tubules and glomeruli were isolated from db/db and eNOS$^{-/-}$ db/db mice. Tubules were subjected to tensile testing using a custom mechanical characterization method. Stress-strain response for tubular basement membrane was evaluated by measuring the force required to stretch the tubules a given length. Hyperelastic materials theory was used to model the tubular stress-strain response. Glomeruli were decellularized and subjected to compression testing to evaluate the compressive modulus of the glomerular ECM. A high deformation Hertzian contact model was used to determine glomerular stiffness.

Results: Biomechanical testing showed that tubular basement membrane stiffness was reduced in the db/db mouse at 16 weeks of age. At this time point, there was no evidence of tubulointerstitial fibrosis, but there were initial signs of renal functional declines based on increased urine albumin to creatinine ratio. In the eNOS$^{-/-}$ db/db mice, there was histologically evident glomerular sclerosis at 18 weeks of age. Glomerular ECM stiffness was significantly increased in a subset of glomeruli from these mice. The amount of stiffness may be related to the degree of glomerular fibrosis.

Conclusions: These data suggest that there are divergent changes in the stiffness of the kidney ECM in different animal models of diabetic nephropathy. These differences may be related to differences in the severity and/or progression of the disease in these different models. The pathophysiological consequences of these progression dependent changes in ECM stiffness will be the focus of future investigation.

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FR-PO223

Renoprotective Effects of Canagliflozin in CREDENCE May Be Independent of Glucose-Lowering Mechanisms

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Background: In the CREDENCE study, the SGLT2 inhibitor canagliflozin (CANA) improved renal and CV outcomes in patients with type 2 diabetes and CKD. Whether effects on CV and renal outcomes are explained by glucose lowering and how baseline kidney function modifies the glycemic effects of CANA are not completely understood.

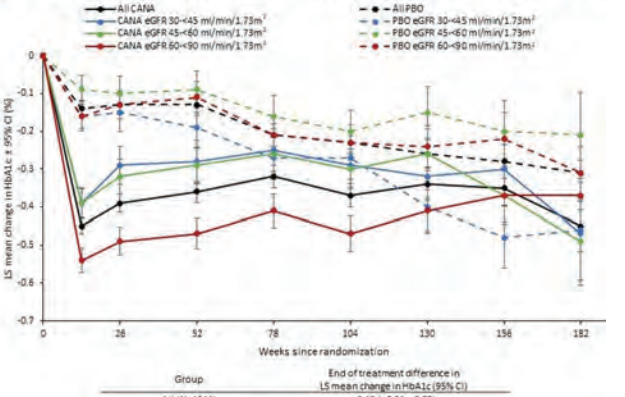
Methods: Analyses were performed in the 4401 patients randomized to CANA (N=2202) or placebo (N=2199). ANCOVA was used to analyze differences in HbA1c at end of treatment. Cox models stratified by screening eGFR and including HbA1c and systolic BP as time-varying covariates were used to analyze time to event.

Results: Least squares (LS) mean (SE) changes in HbA1c during treatment were small: –0.38% (0.03) for CANA vs –0.25% (0.03) for PBO. LS mean differences between CANA and PBO in HbA1c from baseline to end of treatment overall and in subgroups by screening eGFR are shown (Figure). Despite no reduction in HbA1c in the lowest eGFR group, risk reduction for the primary composite endpoint of ESKD, doubling of serum creatinine, or renal or CV death did not differ by screening eGFR (HRs of 0.75, 0.52 and 0.82 for eGFR 30-<45, 45-<60, and 60-<90 ml/min/1.73m^2, respectively; P-interaction=0.11). Risk reduction with CANA vs PBO after adjusting for running mean HbA1c (HR 0.74, 95% CI 0.63-0.88, P<0.001) was similar to the primary results (HR 0.70, 95% CI 0.59-0.82, P=0.00001). Running mean HbA1c was modestly associated with the primary outcome (HR per 1% change 1.13, 95% CI 1.06-1.21, P<0.001).

Conclusions: In patients with type 2 diabetes and CKD enrolled in CREDENCE, renoprotective benefits of CANA appear to be independent of HbA1c reduction and may be linked to non-glycemic properties of CANA.

Funding: Commercial Support - Janssen Research & Development, LLC

Figure. Effects of CANA vs PBO on HbA1c by eGFR strata (on-treatment).



Group	End of treatment difference in LS mean change in HbA1c (95% CI)
All (N=4244)	−0.13 (−0.21, −0.05)
eGFR 30-<45 ml/min/1.73m² (N=1252)	0.03 (−0.13, 0.18)
eGFR 45-<60 ml/min/1.73m² (N=1238)	−0.18 (−0.33, −0.03)
eGFR 60-<90 ml/min/1.73m² (N=1754)	−0.21 (−0.33, −0.08)

FR-PO224

Renal Efficacy and Safety of Canagliflozin by Baseline Medication Use: Results from the CANVAS Program

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Background: Canagliflozin is thought to confer renoprotection partly by enhancing natriuresis and intravascular volume status. We sought to assess the renal efficacy and safety of canagliflozin in patients using other medications that also alter sodium excretion or volume status.

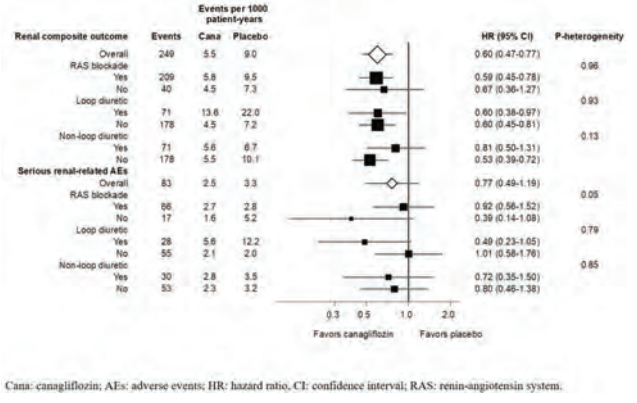
Methods: The CANVAS Program randomized participants with type 2 diabetes at high cardiovascular risk to canagliflozin or placebo. Other treatments, including the use of renin-angiotensin system (RAS) blockade, loop and non-loop diuretics were managed by treating physicians. Hazards ratios (HR) and 95% confidence intervals (CI) were estimated with Cox regression models, with selected medication by baseline treatment interaction terms added to test for heterogeneity. The primary renal composite outcome was sustained 40% reduction in eGFR, end-stage kidney disease or renal death.

Results: Of 10,142 participants in the CANVAS Program, 8116 (80%) were receiving RAS blockade, 1308 (13%) received loop diuretics, and 3182 (31.4%) received non-loop diuretics at baseline. The effect of canagliflozin on the primary renal composite outcome (HR 0.60, 95% CI 0.47-0.77) was consistent irrespective of baseline use of RAS blockade or diuretics (all *P*-heterogeneity>0.10; Figure). There was no evidence that the risk of renal-related serious adverse events was elevated by background use of medications that influence natriuresis or volume status, although few of these events occurred (Figure).

Conclusions: Canagliflozin appears to reduce the risk of progression of kidney disease in patients with type 2 diabetes, irrespective of use of some medications that also affect natriuresis or volume status, without additional renal-related safety concerns.

Funding: Commercial Support - Janssen Research & Development, LLC

Figure. Renal efficacy and safety of canagliflozin by baseline medication use



Cana: canagliflozin; AEs: adverse events; HR: hazard ratio, CI: confidence interval; RAS: renin-angiotensin system.

FR-PO225

Remission of Tubulointerstitial Nephropathy and Its Correlation to the Reduction of Albuminuria by SGLT2 Inhibitor in Patients with Advanced Stages of Diabetic Kidney Disease

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Background: The aim of this study is to examine the clinical advantages of SGLT2 inhibitor predominantly focusing on the amelioration of tubulo-interstitial nephropathy (TIN) through the prospective clinical study.

Methods: Patients with diabetic kidney disease were enrolled, and the patients were received 50 mg of Iplagliflozin. Their blood and urine were sampled at 0 M as baseline, 1 M and 12 M for measurement of parameters including urine Liver Fatty Acid Binding Protein (L-FABP), urine N-acetyl β-D-glucosaminidase (NAG), urine monocyte chemoattractant protein-1 (MCP-1), urine type IV collagen (T4C), 8-hydroxy-2'- deoxyguanosine (8OHdG) in addition to the regular biochemical parameters.

Results: All enrolled patients (n=25, 57.6 of mean age) showed no significant change in their blood pressure and body mass index during the observation period. Their eGFR was not changed either (57.7±21.3 at 0 M, 56.5±21.9 at 1 M, 58.0±24.4 mL/min at 12 M). Urine albumin-to-Cr ratio (ACR) was significantly reduced at 1 M and maintained until 12 M (median: 298.3 at 0 M, 136.0 at 1 M, 141.5 mg/gCr at 12 M). The reduction of ACR was even significant in xx patients who showed GFR<60 mL/min (median: 298.3 at 0 M vs 111.7 mg/gCr at 1 M, p=0.002). We also examined the correlation between baseline ACR and other parameters by single regression analysis, indicating that TIN-related parameters showed weak correlation (LFABP: R2=0.242, p=0.032, MCP-1: R2=0.252, p=0.029) but T4C and eGFR did not. When the patients were divided into two groups based on the ACR reduction responding to SGLT2 inhibitor by the median value of percent-reduction rate of ACR at 1 M, parameters related to TIN showed significant difference among the two groups (LFABP median: 6.58 vs 3.07 μg/gCr, NAG index median: 9.63 vs 7.19 U/gCr, MCP-1 median: 2.42 vs 1.77 pg/gCr) whereas T4C and eGFR were not different.

Conclusions: SGLT2 inhibitor significantly reduced the albuminuria even in patients with advanced renal damage. In these subjects, the reduction of ACR might be highly involved in the severity and restoring of TIN than glomerular damages.

FR-PO226

Acute Changes in Estimated Glomerular Filtration Rate and Related Factors and Subsequent Renal Function in Type 2 Diabetes Mellitus After Initiating Luseogliflozin

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Background: Acute fall in estimated glomerular filtration rate (eGFR), typical finding after initiating sodium glucose transporter 2 (SGLT2) inhibitors link to maintaining renal function among patients with diabetes mellitus. However, the relationship between magnitude of acute fall in eGFR and course of eGFR thereafter are not known.

Methods: A pooled analysis of four 52-week Phase III trials of luseogliflozin 2.5 mg daily (or up to 5 mg daily) in Japanese patients (N=941) with type 2 diabetes mellitus stratified according to the tertile of magnitude of acute changes in eGFR during 2 weeks after initiating it was conducted.

Results: The mean for age, HbA1c, estimated glomerular filtration rate, and urinary albumin were as follows: 60 years, 7.8%, and 79.6 ml/min/1.73m^2, 62.7 mg/gCr respectively. Acute changes in eGFR were widely varied among the patients with type 2 diabetes mellitus (mean,-2.3; min, -35.5; max, 27.6). Course of eGFR after 2 weeks of initiating luseogliflozin were rather recovered or maintained regardless of acute changes in eGFR. The patients with greater acute decline in eGFR, who were characterized by higher eGFR and body mass index, higher prevalence of using diuretics and lower uric acid, showed rapid recovery and maintenance of eGFR thereafter. Multivariate regression analysis revealed that higher body mass index, higher eGFR and use of diuretics were associated with greater acute decline in eGFR.

Conclusions: Although acute changes in eGFR widely varied among the type 2 diabetes mellitus with preserved renal function, the course of eGFR thereafter was maintained regardless of the degree of acute changes in eGFR. State of basal glomerular filtration rate and interaction of diuretics may relate to acute changes in eGFR after initiating SGLT2 inhibitor.

Funding: Commercial Support - Taisho Pharmaceutical Co., Ltd.

FR-PO227

Short-Term Changes in Albuminuria and Risk of Cardiovascular Outcomes in Type 2 Diabetes: A Post Hoc Analysis of the EMPA-REG OUTCOME Trial

Di Xie,[1] Simke W. Waijer,[1] Maximilian von Eynatten,[2] Audrey Koitka-Weber,[2,3] Silvio E. Inzucchi,[4] Bernard Zinman,[5] Christoph Wanner,[3] Hiddo J. L Heerspink.[1] *[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands; [2]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [3]Department of Medicine, Division of Nephrology, Wurzburg University Clinic, Wurzburg, Germany; [4]Section of Endocrinology, Yale University School of Medicine, New Haven, CT; [5]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada.*

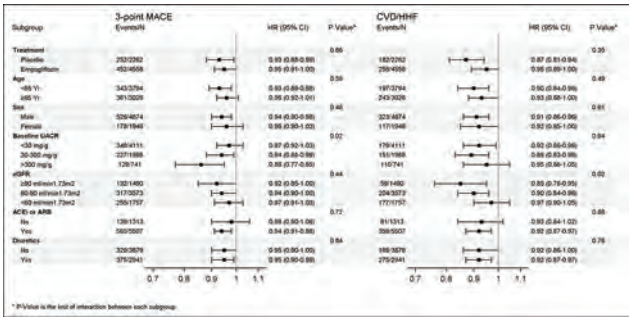
Background: Previous studies, primarily with RAAS inhibitors, have demonstrated that a reduction in albuminuria (UACR) during the first months of treatment is associated with improved long-term cardiovascular (CV) outcomes. Whether an early reduction in UACR with SGLT2 inhibition is also a positive indicator of long-term CV benefit is unknown. We therefore assessed the association between changes in UACR over the first 12 weeks of treatment with empagliflozin or placebo and subsequent long-term CV risk in a post-hoc analysis from the EMPA-REG OUTCOME trial.

Methods: We calculated UACR change as the percentage difference from baseline to week 12 in 6820 participants who did not experience a CV outcome during the first 12 weeks. Cox regression models were used to estimate the hazard ratio (HR) for the primary MACE outcome (non-fatal MI, non-fatal stroke, CV death) and CV death or hospitalization for heart failure (CVD/HHF) for each 30% reduction in UACR after adjustment for treatment assignment, laboratory measurements and medication use.

Results: Empagliflozin compared to placebo reduced UACR by 18% (95%CI 14-22%), and increased the likelihood of a ≥30% reduction in UACR at week 12 compared to placebo (odds ratio 1.42 [95%CI 1.27-1.58]). Over a median follow-up of 3.0 years, 704 (10.3%) primary CV and 440 (6.5%) CVD/HHF outcomes were observed. Each 30% reduction in UACR during the first 12 weeks was independently associated with an average 5% lower hazard for the MACE outcome (HR 0.95; 95%CI 0.91–0.98, p=0.002), and 8% lower hazard for the CVD/HHF outcome (HR 0.92; 95%CI 0.88–0.96, p<0.001). Results were consistent in subgroups by baseline characteristics or medication use, or empagliflozin/placebo treatment assignment(Figure).

Conclusions: Short-term reduction in UACR was more common with empagliflozin and was independently associated with a decreased risk of long-term CV outcomes. These results suggest that a change in albuminuria is a prognostic marker for CV outcomes.

Funding: Commercial Support - Boehringer-Ingelheim



FR-PO228

Change in Albuminuria and Renal Risk: A Post Hoc Analysis of the EMPA-REG OUTCOME Trial

Simke W. Waijer,[1] Di Xie,[1] Silvio E. Inzucchi,[2] Bernard Zinman,[3] Audrey Koitka-Weber,[4,5] Maximilian von Eynatten,[4] Christoph Wanner,[5] Hiddo J. L Heerspink.[1] *[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands; [2]Section of Endocrinology, Yale University School of Medicine, New Haven, CT; [3]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada; [4]Boehringer Ingelheim International GmbH, Mainz-Drais, Germany; [5]Department of Medicine, Division of Nephrology, Wurzburg University Clinic, Wurzburg, Germany*.

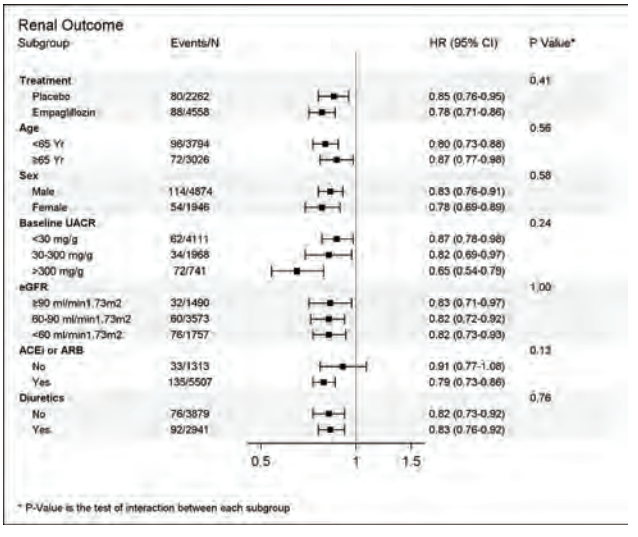
Background: Previous studies have shown that an early reduction in albuminuria (UACR) during RAAS inhibition is associated with improved renal outcomes. Empagliflozin is a SGLT2 inhibitor that decreases UACR. We assessed the association between an early reduction in UACR during treatment with empagliflozin or placebo and long-term renal risk in a post-hoc analysis from the EMPA-REG OUTCOME trial.

Methods: We calculated UACR change as the percentage difference from baseline to week 12 in 6820 participants who did not experience a renal outcome (>40% decrease in eGFR, end-stage renal disease or renal death) during the first 12 weeks. Cox regression models were used to estimate the hazard ratio (HR) for each 30% reduction in UACR with renal outcome after adjustment for treatment assignment, laboratory measurements and medication use.

Results: Empagliflozin, compared to placebo, reduced UACR by 18% (95%CI 14-22%) and increased the likelihood of a ≥30% reduction in UACR at week 12 (odds ratio 1.42 [95%CI 1.27-1.58]). Over a median follow-up of 2.9 years, 168 renal endpoints were observed. Each 30% reduction in UACR from baseline to week 12 was associated with an average 18% lower hazard for the renal outcome (HR 0.82 [95%CI 0.76-0.88]). The adjusted HR for each 30% reduction in UACR in patients with normo-, micro-, or macroalbuminuria at baseline was 0.87 (95%CI 0.78-0.98), 0.82 (95%CI 0.69-0.97) and 0.65 (95%CI 0.54-0.79), respectively (p for interaction 0.24). The association between change in UACR and renal outcomes was consistent in various subgroups and similar in the placebo and empagliflozin groups (Figure).

Conclusions: An early reduction in albuminuria was more common with empagliflozin and was independently associated with a reduced renal risk in patients with type 2 diabetes and cardiovascular disease.

Funding: Commercial Support - Boehringer-Ingelheim



FR-PO229

Early Dip in Estimated Glomerular Filtration Rate (eGFR) on the Efficacy of Ertugliflozin at Week 26

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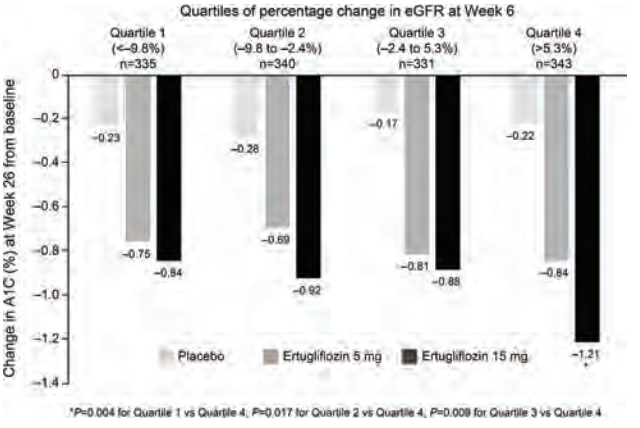
Background: In light of positive results from CREDENCE and previous cardiovascular outcome trials, sodium-glucose cotransporter 2 (SGLT2) inhibitors are frequently compared with renin-angiotensin-aldosterone system blockers, since some members of both drug classes reduce cardiorenal risk. The aim of this *post-hoc* analysis was to assess possible modulatory effects of the early eGFR dip observed with ertugliflozin on measures of treatment efficacy including changes in glycated hemoglobin (A1C), systolic blood pressure (SBP) and body weight (BW).

Methods: Data were pooled from three placebo-controlled studies of ertugliflozin 5 mg and 15 mg in adults with type 2 diabetes mellitus (N=1544). Patients were analyzed by quartiles (Q) of percent reduction in eGFR at Week 6 for changes from baseline in A1C, SBP and BW at Week 26. Pearson correlation was used to measure the strength of the linear relationship between the percent change in eGFR from baseline to Week 6 and changes in those endpoints.

Results: Patients in quartiles with the greatest eGFR decrease (Q1 and Q2) at Week 6 showed similar reductions in A1C at Week 26 compared with patients undergoing only small changes in eGFR (Q3) at Week 6 (**Figure**). Among patients with an increase in eGFR (Q4), those in the ertugliflozin 15 mg group, but not ertugliflozin 5 mg group, showed a greater reduction in A1C at Week 26 compared with other quartiles. Changes in SBP and BW were similar across all quartiles. A weak correlation (r=–0.138) between the change in eGFR at Week 6 and change in A1C at Week 26 was found in ertugliflozin 15 mg group.

Conclusions: Ertugliflozin causes an early decrease in eGFR but its degree has no meaningful impact on reductions in A1C, SBP or BW at Week 26. Ertugliflozin 15 mg may augment A1C reduction in patients with an eGFR rise during early treatment.

Funding: Commercial Support - This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and Pfizer Inc., New York, NY, USA.



Change in A1C at Week 26 from baseline by quartiles of eGFR change at Week 6

FR-PO230

Effects of Blood Pressure After Sodium-Glucose Cotransporter 2 Inhibitor Treatment on Renal Composite Outcomes in Japanese Type 2 Diabetes Patients with CKD

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Background: Previous large clinical trials using sodium–glucose cotransporter 2 inhibitors (SGLT2is) demonstrated improved renal outcomes in patients with type 2 diabetes mellitus (T2DM). Pleiotropic effects are considered important, but the mechanisms involved are not fully understood. The aim of this study is to clarify the mechanism by who the blood pressure (BP) after SGLT2i treatment influence renal composite outcomes in Japanese T2DM patients with chronic kidney disease (CKD).

Methods: We retrospectively assessed 626 Japanese T2DM patients with CKD who underwent SGLT2i treatment for over 1 year. The renal composite endpoint was the progression of albuminuria stage or a decrease in the estimated glomerular filtration rate (eGFR) by ≥15% per year. For comparative analyses, we included patients comprising

those with >92 mmHg in mean arterial pressure (MAP) after SGLT2i treatment and those with <92mmHg in MAP and used propensity score matching methods to address the imbalances in age, sex, body weight, hemoglobin A1c, eGFR, and urinary albumin–creatinine ratio (ACR) at baseline. The propensity score matching used an algorithm involving a 1:1 ratio of the nearest neighbor match with a ±0.025 caliper and no replacement.

Results: The standardized differences in the backgrounds for propensity-matched patients were calculated to be <0.1. Comparisons between the 210 propensity-matched patients in each group were performed. The incidence of renal composite outcomes was occurred in 42 cases totally and it was significantly lower in patients with <92 mmHg in MAP after SGLT2i treatment than in those with ≥92 mmHg in MAP (6.2% [n=13]and 16.0%[n=29], respectively, p=0.009 by chi-square test). The estimated hazard ratio for the renal composite outcomes, determined using a Cox proportional hazards model, was 1.361 (95% confidence interval, 1.011 to 1.832, p=0.042)in patients with ≥92 mmHg in MAP. There was no significant difference in the logarithmic value of ACR between the two groups.

Conclusions: The BP after SGLT2i treatment influenced renal composite outcomes in Japanese T2DM patients with CKD. These results reaffirmed the importance of BP management in T2DM patients with CKD, even during SGLT2i treatment.

FR-PO231

Pretreatment Extracellular Volume Expansion Predicts Body Fluid Response to SGLT2 Inhibitor in Diabetic Kidney Disease

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Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are an antihyperglycemic drug with diuretic action. We recently reported that SGLT2 inhibitor dapagliflozin ameliorates extracellular volume expansion with a mild increase in urine volume (Nephrology 2018). However, the predictors of fluid response to SGLT2 inhibitors remain unclear.

Methods: Thirty diabetic kidney disease (DKD) patients were treated with dapagliflozin (5mg/day). Body fluid volume including intracellular water (ICW), extracellular water (ECW) and total body water (TBW) was measured on days 0 and 7 using a bioimpedance analysis (BIA) device (InBody S10). Patients were divided into low and high responders by the median value of change in the ECW/TBW for 1 week, which is a marker of extracellular volume expansion. Baseline clinical parameters were compared between the low and high responders.

Results: The body weight significantly decreased (68.0±2.8 vs. 63.0±3.2 kg, p<0.001), but the estimated glomerular filtration rate (eGFR) was not significantly changed (29.2±2.7 vs. 26.1±2.3 mL/min/1.73 m^2, p=0.143) after 1 week. BIA showed that the median value of the change in the ECW/TBW for 1 week was -1.2% (0.416±0.005 vs. 0.400±0.012, p=0.054). The ECW (high responders 17.0±1.2 vs. low responders 14.2±1.2 L, p=0.056), the TBW (39.8±2.6 vs. 34.8±2.6 L, p=0.093), the ECW/TBW (0.426±0.001 vs. 0.406±0.001, p=0.021) and serum brain natriuretic peptide (318±53 vs. 92±50 pg/mL, p=0.003) in the high responders were higher than in the low responders. The eGFR (24.5±3.6 vs. 33.3±3.6 mL/min/1.73 m^2, p=0.046) and serum albumin level (2.9±0.2 vs. 3.4±0.2 g/dL, p=0.075) in the high responders were lower than in the low responders. Significant partial correlations adjusted for the eGFR were observed between the baseline ECW/TBW and changes in the ECW/TBW (r=-0.469, p=0.009) and the TBW (r=-0.528, p=0.027).

Conclusions: Extracellular volume expansion predicts body fluid response to SGLT2 inhibitor dapagliflozin in DKD patients. This result suggests that SGLT2 inhibitor may change its diuretic action depending on the pretreatment extracellular volume status.

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FR-PO232

How Does Canagliflozin Confer Renoprotection? Results From a Mediation Analysis of the CANVAS Program

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Background: Canagliflozin reduced renal risk in patients with type 2 diabetes participating in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program. This study explored potential mediators of the beneficial effects of canagliflozin on renal outcomes.

Methods: The percent mediating effect of 18 biomarkers, hypothesized to be likely changed by canagliflozin treatment and associated with renal risk, was determined by comparing the hazard ratios for the effect of randomized treatment from an unadjusted model and from a model adjusting for the biomarker of interest. Multivariable analyses assessed the joint effects of biomarkers that mediated most strongly in univariable analyses. The renal outcome was a composite of 40% eGFR decline, end-stage kidney disease, or renal death.

Results: Early changes after randomization in levels of 7 biomarkers (systolic blood pressure (9.5% of effect explained), urinary albumin:creatinine ratio [UACR] (18.2%), gamma glutamyltransferase (9.3%), hematocrit (40.7%), hemoglobin (29.1%), erythrocytes (40.5%), and serum urate (19.0%) were identified as individually mediating the effect of canagliflozin on the renal outcome. The same biomarkers and serum albumin were identified as significant mediators based on average post-randomization levels. In a parsimonious multivariable model, erythrocyte concentration, serum urate and systolic blood pressure were the three biomarkers that maximized cumulative mediation (115% [95%CI 72.96 to 203.66]). Mediating effects of UACR, but not other mediators, were highly dependent upon the baseline level of the mediator; UACR mediated 42% of the effect in those with baseline UACR >30 mg/g but only 8% in those with baseline UACR <30 mg/g.

Conclusions: The identified mediators support existing hypothesized mechanisms for the prevention of renal outcomes with SGLT2 inhibitors. The disparity in mediating effects across subgroups defined by baseline UACR suggests mechanisms of protection may vary in importance across patient subsets.

Funding: Commercial Support - Janssen Research & Development, LLC

FR-PO233

Renal and Cardiovascular (CV) Outcomes of Canagliflozin (CANA) According to Race and Ethnicity: A CREDENCE Secondary Analysis

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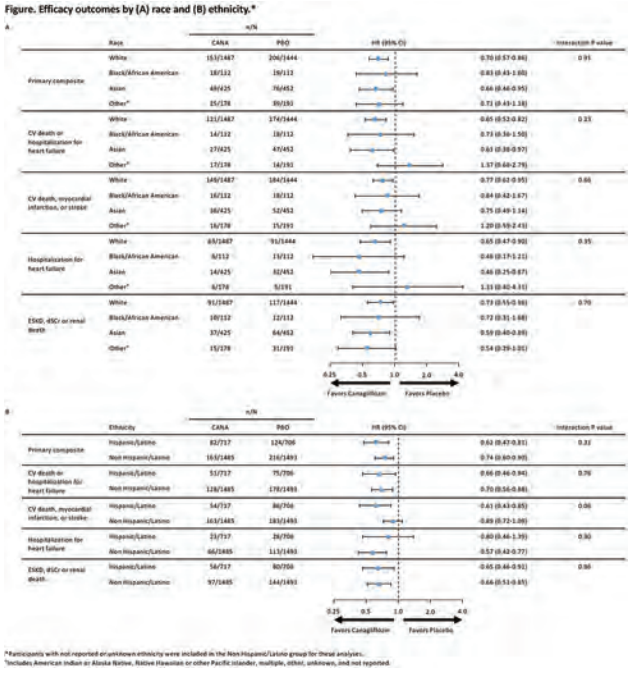
Background: CANA reduces kidney failure and CV events in people with type 2 diabetes who have chronic kidney disease. Given the international scope of the CREDENCE study, we assessed the efficacy of CANA according to self-reported race and ethnicity.

Methods: 4401 participants with eGFR 30-<90mL/min/1.73m^2 and urinary albumin:creatinine ratio >300-5000mg/g were randomized to CANA 100mg daily or matching placebo. Outcomes were analyzed in prespecified analyses by race and ethnicity, and results are reported without adjustment for multiplicity.

Results: The cohort enrolled were racially and ethnically diverse (n=2931 [67%] White, n=224 [5%] Black or African American, n=877 [20%] Asian, n=369 [8%] Other race, n=1423 [32%] Hispanic/Latino, n=2978 [68%] Non Hispanic/Latino [including not reported/unknown ethnicity]). CANA reduced the primary outcome of end-stage kidney disease (ESKD), sustained doubling serum creatinine (dSCr), or renal or CV death overall, with no evidence the effect differed in racial (P interaction=0.91) and ethnic subgroups (P interaction=0.31; Figure). Similarly, CANA reduced CV outcomes and the renal composite of ESKD, sustained dSCr or renal death, with no differences among the different racial and ethnic groups (all P interaction≥0.06).

Conclusions: CANA reduces the incidence of renal and CV events in people with type 2 diabetes and substantial albuminuria, with no evidence that effects differ in racial or ethnic groups, thereby supporting the breadth of use across a diverse group of patients.

Funding: Commercial Support - Janssen Research & Development, LLC



FR-PO234

Elevation of Hematocrit and Decrease in Hemoglobin A1c After the Administration of SGLT-2 Inhibitors Have Different Relation with Parameters Reflecting Diuretic Effect

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Background: Recently, sodium-glucose cotransporter 2 (SGLT-2) inhibitors were indicated to have hematopoietic effect, but it is still unclear whether the effect is independent from its anti-diabetic effect. In this study, we investigated changes in hematocrit and parameters reflecting diuretic change according to HbA1c reaction after administration of SGLT-2 inhibitors in patients with type 2 diabetes.

Methods: A total of 96 patients (male: n=59, age: 54.7±11.8 [mean±SD] years, BMI: 29.6±4.4 kg/m^2, HbA1c: 8.7±1.4 %) with type 2 diabetes who were newly administered SGLT-2 inhibitors from July 2014 to January 2018 were retrospectively identified. The patients were divided into two groups according to HbA1c change (responded [ΔHbA1c<-0.5 %] patients; group A: n=52 [male: n=32], age: 53.9±12.1 years, BMI: 29.9±4.5 kg/m^2; non-responded [ΔHbA1c≥0.5 %] patients; group B: n=44 [male: n=27], age: 55.5±11.5 years, BMI: 29.3±4.5 kg/m^2, HbA1c: 7.9±1.2 %). Changes in HbA1c, hematocrit, urine specific gravity, blood urea nitrogen, serum creatinine and plasma osmolarity levels between before and 30 days after the administration of the drugs were evaluated. Plasma osmolarity was calculated by the formula (2x(Na[mEq/l]+K[mEq/l]))+(BUN[mg/dl]/2.8)+(glucose[mg/dl]/18).

Results: HbA1c was significantly decreased in only group A (group A: -1.03±0.42 %; p<0.001, group B: -0.11±0.46; p=0.65) whereas both groups showed significantly increased hematocrit (group A: 1.8±2.0 %; p=0.007, group B: 2.0±1.8; p=0.035) and urine specific gravity (0.008±0.009 g/mL; p<0.001, 0.011±0.011; p<0.001). Blood urea nitrogen (0.86±3.52 mg/dL; p=0.31, 1.28±3.99; p=0.23), serum creatinine (0.04±0.08 mg/dL; p=0.35, 0.04±0.08; p=0.41), plasma osmolarity (1.11±3.82 mOsm/L; p=0.26, -1.16±5.66; p=0.12) and BMI (-0.61±0.48 kg/m^2; p=0.26, -0.51±0.51; p=0.58) did not change in both groups. Group A showed negative correlation between changes in BMI and plasma osmolarity (r=-0.28; p=0.04), whereas group B did not (r=0.14; p=0.36).

Conclusions: Our data suggest that the elevation of hematocrit and decrease in HbA1c after the administration of SGLT-2 inhibitors have different relation with parameters reflecting diuretic effect.

FR-PO235

The Study on the Transition of Renal Function of SGLT2 Inhibitors for Type 2 Diabetes with Moderate to Severe Renal Impairment

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Background: From the results of recent large-scale clinical trials, it has been clarified that SGLT2 inhibitors (SGLT2i) have protection of renal function independent of blood glucose. However, the renoprotective effect of SGLT2i in type 2 diabetes (T2DM) patients with advanced renal dysfunction less than eGFR 30 ml/min/1.73m^2 has not been studied. The aim of study is to investigate the effect of SGLT2i on renal function in patients with moderate to severe renal insufficiency, retrospectively.

Methods: We included Japanese T2DM patients less than eGFR 45 ml/min/1.73m^2, whose SGLT2i was administered for more than one year since October 2011 in Saitama madical center. We compared changes eGFR from 6 months before administration of SGLT2i to the start of administration, and from initiation of administration of SGLT2i to 6, 12 months after administration, and last month of administration (when SGLT2i is discontinued, just before discontinuation). We also examined safety.

Results: The subjects were 36 cases (12 cases were less than eGFR 30 ml/min/1.73m^2), and eGFR at the start of SGLT2i administration was 33.3 ± 12.2 ml/min/1.73m^2. The patients were received either ipragliflozin, canagliflozin, empagliflozin luseoglifrozin, tofoglifrozin or dapaglifrozin. The monthly change in eGFR from 6 months before to the initiation of SGLT2i administration, and from the initiation to 6, 12 months after administration, and to last chance (27 ± 13 months) were -0.7±1.3, -0.0±1.2, +0.1±0.6, and –0.0±0.4 ml/min/1.73m^2/month, respectively. The decrease in eGFR was significantly suppressed after SGLT2i administration (p <0.05, respectively). During the period, renal replacement therapy (RRT) was initiated only in 3 cases. Assuming that RRT is started when eGFR 6-8 ml/min/1.73m^2 remains unchanged from changes in eGFR before SGLT2i administration, it is predicted that 27 (75%) of the 36 cases could avoid RRT induction during the observation period. On the other hand, no adverse events related to SGLT2i other than RRT were observed during the period.

Conclusions: The administration of SGLT2i to T2DM with moderate to severe renal impairment can strongly and safely suppress the decline of eGFR, and can lead to enormous medical economic benefits by extending dialysis induction.

FR-PO236

The Effect of Oral Carnosine Supplementation on Urinary TGF-Beta in Diabetic Nephropathy: A Randomized Controlled Trial

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Background: Activation of TGF-beta pathway is a significant contributor to the pathogenesis of diabetic nephropathy. Carnosine is an amino acid that can inhibit TGF-beta synthesis. We tested the hypothesis that carnosine supplement added to a standard therapy will result in a reduction in urinary TGF-beta levels in patients with diabetic nephropathy.

Methods: We randomly assigned 40 patients with diabetic nephropathy and albuminuria 30-299 mg/day to treatment with carnosine (2 g/day) or placebo for 12 weeks. Urinary TGF-beta level by a solid-phase specific sandwich enzyme-linked immunosorbent assay (ELISA), urine albumin by immunonephelometric assay, renal function and metabolic profiles were determined at baseline and during 12 weeks of active treatment. Primary outcome was the decrease in the level of urinary levels of TGF-beta.

Results: The two groups were comparable for baseline characteristics, blood pressure, urine albumin, urine TGF-beta and renal function measurements. Urinary TGF-beta significantly decreased with carnosine supplement (-17.8% of the baseline values), whereas it tended to increase with placebo (+16.9% of the baseline values) (between-group difference P < 0.05). Whereas, blood urea nitrogen, serum creatinine, serum electrolytes and other biochemical parameters did not change during the study period including urinary albuminuria. The both groups were well tolerated with no serious side-effects.

Conclusions: These data indicate an additional renoprotective effect of oral supplementation with carnosine for decreasing urinary TGF-beta level that is marker of renal injury in diabetic nephropathy.

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FR-PO237

Dapagliflozin Stabilizes the Tubulointerstitial Fibrosis Marker Urinary Dickkopf-3

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Background: Urinary Dickkopf-3 (DKK3) is a stress-induced tubular epithelia-derived profibrotic glycoprotein that induces tubulointerstitial fibrosis through its action on the canonical Wnt/β-catenin signaling pathway. A previous study showed that DKK3 concentrations are higher in patients with CKD than in the general population, and that a

rise in urinary DKK3 was associated with significant eGFR decline. Prior experimental and clinical studies have suggested that SGLT-2 inhibition may reduce renal fibrosis. We therefore assessed the effect of the SGLT-2 inhibitor dapagliflozin on urinary DKK3.

Methods: 24hr urine samples were used from a double-blind, randomized, placebo controlled crossover trial in 31 patients with type 2 diabetes and albumin:creatinine ratio (UACR) >100 mg/g on a stable dose of an ACE inhibitor or angiotensin receptor blocker. Patients were assigned to 6-week treatment periods with dapagliflozin 10 mg/d or placebo in random order. Urinary DKK3 was measured by ELISA at the start and end of each 6-week treatment period. A mixed effects repeated measures model was used to assess the effect of dapagliflozin on urinary DKK3.

Results: Dapagliflozin decreased UACR by 43.9% (95%CI: 30.3 to 54.8) and eGFR by 5.1 (2.0 to 8.1) mL/min/1.73m^2 compared to placebo. At baseline, urinary DKK3 concentration was 574.8 [1st, 3rd quartile: 304.3, 1223.7] ng/24hr. After 6 weeks placebo treatment, urinary DKK3 levels increased by 41.7% (95%CI: 2.2 to 96.4), p=0.0373, whereas they remained stable after dapagliflozin treatment (-1.2% (-29.3 to 38.2), p=0.9421). Accordingly, dapagliflozin lowered DKK3 compared to placebo by 30.3% (2.0 to 50.3), p=0.0384. After dapagliflozin, change in urinary DKK3 was significantly correlated with change in UACR (r=0.41, p=0.0309). No correlations with changes in other clinical markers (HbA1c, eGFR, SPB, Hb, Hct) were observed.

Conclusions: Dapagliflozin stabilized urinary DKK3 after 6 weeks of treatment in patients with type 2 diabetes and increased albuminuria, while an increase was observed during placebo treatment, suggesting that dapagliflozin may lessen tubular stress and fibrosis. Future studies of longer treatment duration and clinical outcomes are needed to confirm the clinical impact of these findings.

FR-PO238

Effects of the SGLT2 Inhibitor Dapagliflozin on Plasma Volume in Patients with Type 2 Diabetes and Various eGFR Levels

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Background: Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce the rate of renal outcomes and heart failure events in patients with type 2 diabetes and chronic kidney disease possibly as a result of volume contraction. In this study we compare the effects of dapagliflozin on estimated and measured plasma volume and we investigate whether kidney function and other relevant characteristics modify effects of dapagliflozin on estimated plasma volume.

Methods: The Strauss formula was used to calculate changes in estimated plasma volume (ePV). Change in plasma volume measured with ^{125} I-human serum albumin (mPV) was compared with change in ePV in a study of patients with type 2 diabetes randomized to dapagliflozin 10 mg/day or placebo. Subsequently, changes in ePV were measured in a pooled database of 13 phase 2b/3 placebo controlled clinical trials involving 4533 patients with type 2 diabetes randomized to dapagliflozin 10 mg/day or placebo.

Results: Median change in ePV was similar to median change in mPV (-9.4 and -9.0 %) during dapagliflozin treatment. In the pooled analysis, dapagliflozin compared to placebo decreased ePV by 9.6 % (95% CI: 9.0 to 10.2%) after 24 weeks. This effect was consistent in various eGFR-groups (ePV changes of -9.5, -9.7 and -9.5 in eGFR subgroups <60, 60-90, and ≥90 ml/min/1.73m^2 [Figure 1]).

Conclusions: Dapagliflozin consistently decreased estimated plasma volume compared to placebo in a broad population of patients with type 2 diabetes underpinning heart failure benefits observed in patients with type 2 diabetes and chronic kidney disease.

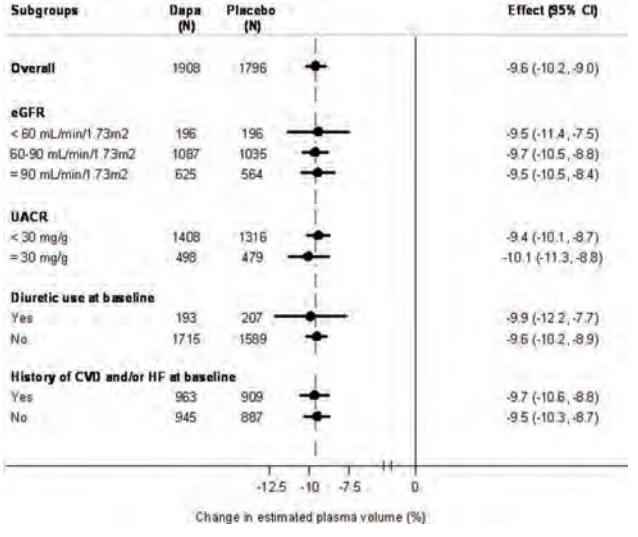

Figure 1: Changes from baseline in estimated plasma volume (%) during 24 week treatment with dapagliflozin relative to placebo in various subgroups

FR-PO239

The GLP-1R Agonist Liraglutide and Its Hypotensive and Natriuretic Effect in Diabetic CKD

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Background: The impaired sodium excretion with fluids retention, high activity of renin-angiotensin-aldosterone system (RAAS) are dominant pathogenetic factors in the development of hypertension in diabetic kidney disease. The GLP-1R agonist-liraglutide is an antidiabetic drug that has showed blood pressure lowering effect most probably mediated by increased natriuresis and inhibition of RAAS. The aim of the study was to investigate the hypotensive and nariuretic effect of a single dose of liraglutide compared to placebo in patients with type 2 diabetes mellitus and impaired renal function.

Methods: The study included 17 patients with eGFR below 30, and 17 patients with eGFR above 60 ml/min/1.73 m^2. In a cross-over study each subject received in a random order a single subcutaneous dose of 1.2 mg liraglutide and placebo with subsequent 24h blood pressure monitoring and 24h urinary samples collection to assess natriuresis. Before and after each medication the blood samples were collected to measure the serum concentration of renin, aldosterone and atrial natriuretic peptide (ANP).

Results: After 1.2 mg liraglutide 24h MAP increased from 97.8±8.1 to 102.4±8.6 mmHg, p=0.003 compared to placebo in patients with eGFR below 30 ml/min/1.73 m^2. In patients with eGFR >60 ml/min/1.73 m^2 no significant change of blood pressure was revealed. After liraglutide mean 24h urine sodium excretion increased in both groups (p=0.003) but the increase was significantly larger in patients with eGFR >60 ml/min/1.73 m^2 p=0.046. The difference of mean 24h sodium excretion between liraglutide and placebo correlated negatively with a difference of 24 mean arterial pressure (r=-0.7 p=0.01) in the group with eGFR >60 ml/min/1.73 m^2. The concentration of ANP increased after injection of liraglutide compared with placebo in both groups, but the increase was significantly larger in patients with worse kidney function (p=0.012). In the same group with eGFR <30 ml/min/1.73 m^2 significant decrease of the serum concentration of aldosterone was noted after liraglutide (p=0.013).

Conclusions: Liraglutide administration in the patients with advanced CKD may cause a transient increase of systemic blood pressure due to reduced natriuretic effect. The natriuretic effect of liraglutide in diabetic kidney disease depends on increased atrial natriuretic peptide and decreased aldosterone secretion.

FR-PO240

The Hemodynamic Effect of the GLP-1R Agonist Liraglutide in Diabetic Kidney Disease

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Background: The impact of GLP-1R agonists on blood pressure is a resultant of its vasodilatory and natriuretic effect and the increase of heart rate and sympathetic activity. The increased peripheral resistance resulting from the imbalance in factors regulating vascular tone and autonomic nervous system are important pathogenetic factors in the development of hypertension in diabetic kidney disease. The aim of the study was to investigate the hemodynamic effect of a single subcutaneous dose of 1.2 mg liraglutide compared to placebo in patients with type 2 diabetes mellitus and impaired renal function.

Methods: This cross-over study included 17 patients with eGFR below 30 ml/min/1.73 m^2 and 17 patients with eGFR above 60 ml/min/1.73 m^2. Blood pressure and heart rate were monitored noninvasively for 24 hours. Before and after each medication, systemic vascular resistance, heart rate variability, pulse wave velocity and central blood pressure were measured with signal morphology impedance cardiography and applanation tonometry.

Results: Significant increases of both 24h mean heart rate and cardiac output were noted in both groups. In patients with eGFR >60 ml/min/1.73 m^2 mean 24h heart rate was 73±8 after liraglutide compared with 68±5 beats per minute after placebo (p=0.005), whereas in patients with eGFR <30 ml/min/1.73 m^2 the respective values were 76±9 and 67±9 beats per minute (p<0.001). In the latter group it was additionally accompany by sympathetic predominance after GLP-1R agonist (p=0,005). The systemic vascular resistance was reduced after injection of liraglutide compared with placebo only in the study group with better preserved kidney function (p=0,002), whereas the pulse wave velocity was increased after GLP-1R analogue compared with placebo (p=0,0006), only in patients with eGFR <30 ml/min/1.73 m^2. Additionally also only in this group after liraglutide 24h mean arterial pressure significantly increased from 97.8±8.1 to 102.4±8.6 mmHg compared to placebo (p=0.003).

Conclusions: Liraglutide administration in the patients with advanced chronic kidney disease may cause a transient increase of systemic blood pressure probably due to the increase of cardiac output. Increased cardiac output mainly depends on an acceleration of heart rate, which is probably associated with a sympathetic predominance. The vasodilatory effect can be preserved only in earlier stages of CKD.

FR-PO241

Metformin Discontinuation in Type 2 Diabetes Patients Associated with Higher Risk of Diabetic Nephropathy: Finding from a Retrospective, Propensity Score-Matched, Common Data Model-Based Cohort Study

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Background: Metformin is a first-line drug in patients with type 2 diabetes (T2DM) worldwide. There are several evidences supporting benefits to T2DM patients in cardiovascular and renal outcomes with metformin, however, a long-term use of metformin is occasionally limited owing to risk of lactic acidosis or gastrointestinal side effects. This common data model-based study aimed to compare continuous metformin user with non-metformin user for risk of diabetic nephropathy (DN) in a real-world setting.

Methods: We performed a retrospective, propensity score matched, observational cohort study by using The Observational Medical Outcomes Partnership common data model version 5 (OMOP-CDMv5). We used medical data of 1.82 million patients in a tertiary hospital in South Korea from 2003 to 2017. Study participants were identified by drugs, diagnosis codes and laboratory test values in combination with event time. Among newly diagnosed T2DM patients without DN, more than one year ongoing of metformin treatment were considered as treatment group. Never use of metformin after four months since time of T2DM diagnosis were considered as comparative group. DN defined as onset of spot urine albumin to creatinine ratio (uACR)>30 mg/g, protein to creatinine ratio (uPCR)>150 mg/g or EPI-CKD eGFR<60 ml/min/1.73m^2. After 1:1 propensity score-based matching (PSM), the Cox proportional hazards model was used to analyze hazard ratio (HR) for DN events.

Results: A 2,003 of metformin using patients and a 222 of non-metformin using patients were identified. After 1:1 PSM, we matched each of 207 patients in both groups. Mean follow-up duration was 7.2 and 6.5 years, respectively. There were no significant differences of mean age, sex ratio, mean HbA1c, EPI-CKD eGFR, uACR and uPCR value between two groups at baseline. Metformin treatment group had lower risk for progression to DN (HR=0.66, 95% CI [0.47-0.93], p=0.018) than comparative group.

Conclusions: Continuous use of metformin in T2DM without DN was associated lower risk for progression of diabetic nephropathy. This longitudinal, real-world setting study may support protective effect of metformin for progression to diabetic nephropathy in T2DM.

FR-PO242

The Effects and Prognosis of Bariatric Surgery on Diabetic Nephropathy and Retinopathy in Obese Patients with Type 2 Diabetes Mellitus

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Background: The prevalence of obesity has increased dramatically during the past 3 decades, resulting in a large number of diabetes mellitus (DM) and its complications, including diabetic nephropathy (DN) and diabetic retinopathy (DR), the two most common microvascular complications. Bariatric surgery has been approved as an effective and potentially useful method to improve hyperglycemia condition in T2DM patients as well as reduce patient's body weight. However, the association between bariatric surgery and the onset and the progression of DN or DR in obese patients with type 2 diabetes mellitus (T2DM) hasn't been well studied.

Methods: A total of 127obese obese patients diagnosed with T2DM underwent bariatric surgery in Shanghai Jiao Tong University Affiliate Sixth People's Hospital from Jan. 2013 to Jan. 2018 and prospectively followed up for one year. The inclusion criteria included: (1) patients aged from 18-65 years old, (2) BMI over 28 kg/m2, (3)a diagnosis of T2DM, (4) a fasting C-peptide by the oral glucose tolerance test >1 ng/mL and a ratio of peak to fasting value >2 ng/ ml. Those with type 1 diabetes, latent autoimmune diabetes in adults, established diagnoses of non-diabetic nephropathy, malignancy, debilitating disease, unresolved psychiatric illness, or substance abuse were excluded from the study. Anthropometric and biochemical parameters were assessed at baseline and 1 year after surgery.

Results: In all patients, body mass index (BMI), blood pressure, fasting blood-glucose, HbA1c, uric acid, blood lipid, urine albumin creatinine ratio (UACR) all decreased significantly 1 year after surgery compared with baseline. 77 out of 127 patients (60.6%) had albuminuria at baseline, and the total remission of albuminuria was 57.9%, no patients had new-onset of albuminuria during the follow-up period. Logistic regression analysis showed that obesity, hypertension, glycemia, dyslipidemia and DR were associated with DN, and DR correlated with DN more strongly than other factors (OR=1.904). Preoperativesystolic pressure and UACR levels, as well as DR could be predictors for DN remission. However, there was no significant difference between baseline and 1 year after intervention in the changes in retinopathy.

Conclusions: Bariatric surgery could be a potential therapy in obese patients with T2DM and might have a protective role in diabetic kidney injury.

FR-PO243

Efficacy and Safety of Low-Dose Metformin for Improving Glycemic Control in Type 2 Diabetic Patients Receiving Maintenance Hemodialysis (HD): An Assessment by Continuous Glucose Monitoring (CGM)

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Background: Studies show that the use of metformin in HD patients may potentially increase the risk of lactic acidosis. The aim of our study was to evaluate the safety and effect of metformin with appropriate dose reduction to improve glycemic control in patients with type 2 diabetes (T2D) on HD.

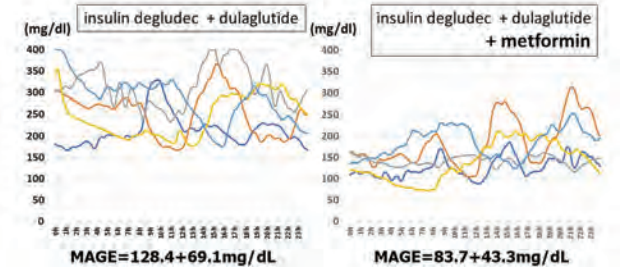
Methods: Subjects were six HD patients in our hospital, with T2D (av. BMI=29.7±5.9, glycoalbumin: GA>27%), treated with insulin degludec (8-35 units/day) + dulaglutide (0.75mg/week), with obesity and poor glycemic control. After adding low-dose metformin (250-500mg/day) to the medication, serum lactate level and pH of all six patients were monitored once in two weeks. Glycemic control (assessed by CGM) was calculated before and 4 weeks after the initial administration, and the mean amplitude of glycemic excursions (MAGE) was calculated.

Results: As shown in Figure (each color represents the mean glycemic profile of one patient), glycemic control improved by low-dose metformin as MAGE significantly decreased from 128.4±69.1 mg/dL to 83.4±43.3 mg/dL (p<0.05) without episodes of hypoglycemia. Mean GA significantly reduced from 32.0% to 22.62% (p<0.01), whereas there were no significant changes in the serum pH and lactate levels for 3 months.

Conclusions: After a single hemodialysis session, more than 90% of metformin and lactate were cleared, and the acid-base balance corrected. Unlike in pre-HD patients with impaired renal function, in patients on maintenance HD, metformin may potentially be safe and useful in controlling plasma glucose level when the dosage is appropriately reduced.

Funding: Private Foundation Support

Fig. Effects of low-dose metformin on plasma glucose control in HD patients with T2DM



FR-PO244

Metformin Use Is Associated with Asymptomatic Hyperlactatemia in Elderly Diabetic Men with Stage 3 CKD

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Background: Current recommendations allow metformin use in patients with chronic kidney disease stage 3 (CKD3). Whether metformin increases risk of hyperlactatemia in elderly CKD3 diabetic patients is unknown.

Methods: This was a case-control study including 92 stable CKD stage 3 male veterans attending Albany VAMC outpatient clinics in 2018. Patients were grouped according to presence of diabetes (D) and metformin use (M) into 3 groups: CKD3 and no diabetes (CKD3 -24pts), CKD3 and D with no M (CKD3/D -28 pts), and CKD3 and D on metformin (CKD3/D+M -40 pts). Hyperlactatemia was defined as lactic acid (LA)>2mmol/L and lactic acidosis as LA>4mmol/L in association with anion-gap metabolic acidosis. Characteristics associated with hyperlactatemia were evaluated in multivariable logistic regression analyses adjusted for age, race, BMI, eGFR, proteinuria, A1C, liver enzymes, Charlson comorbidity index, number of prescription drugs, and metformin and insulin use.

Results: In the total cohort, mean(SD) for age was 73.4(5.9) yrs and mean(SD) eGFR was 46.7(8.1)ml/min/1.73m^2. For CKD3, CKD3/D and CKD3/D+M groups mean(SD) LA levels were 1.3(0.3), 1.3(0.4) and 2.1(1.0)mmol/L (p<0.001) and eGFR were 43.2(7.8), 44.3 (8.7) and 50.6(6.1) ml/min/1.73m^2(p<0.001), respectively. Hyperlactatemia was present in 1(4.2%), 1(3.6%) and 17(42.5%) of CKD3, CKD3/D and CKD3/D+M patients, correspondingly. A single case of asymptomatic lactic acidosis was seen among CKD3/D+M group. Daily metformin dose correlated with LA levels (r=0.35, p=0.027). In multivariable adjusted regression analysis metformin use was significantly associated with hyperlactatemia (Figure 1).

Conclusions: Metformin use in elderly diabetic patients with CKD stage 3 was associated with high incidence of asymptomatic hyperlactatemia. Routine monitoring of LA levels may be warranted in diabetic CKD 3 patients treated with metformin.

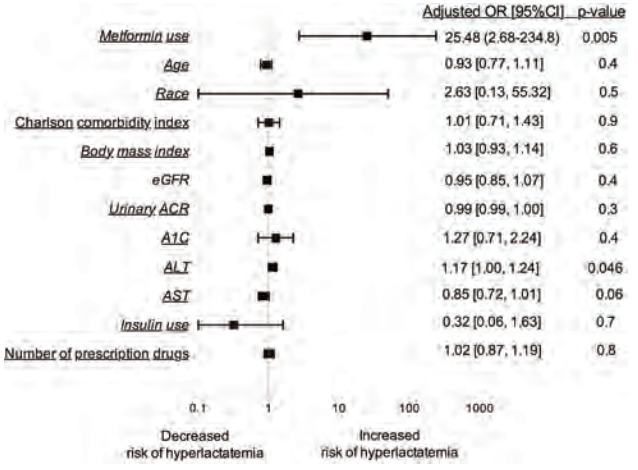

Figure 1

FR-PO245

A Safety Comparison of Metformin vs. Sulfonylurea Initiation in Patients with Type 2 Diabetes and CKD: A Retrospective Cohort Study

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Background: Metformin is the initial oral antihyperglycemic agent of choice in most patients with type 2 diabetes (T2D). However, in patients with chronic kidney disease (CKD), guidelines often recommend that metformin not be used due to slower clearance and risk of lactic acidosis. Sulfonylureas are a common alternative to metformin but have been associated with hypoglycemia, weight gain and cardiovascular events. We sought to compare the safety of metformin versus sulfonylureas in patients with T2D by CKD stage.

Methods: This retrospective cohort study included adults in Manitoba, Canada with T2D, an incident monotherapy prescription for metformin or a sulfonylurea, and a serum creatinine measurement from April 2006 to March 2017. Patients were stratified by estimated glomerular filtration rate (eGFR) into the following groups: eGFR ≥90, 60-89, 45-59, 30-44 or <30 ml/min/1.73 m^2. Outcomes included all-cause mortality, cardiovascular events, and major hypoglycemic episodes. Baseline characteristics were used to calculate propensity scores and perform inverse probability of treatment weights analysis and eGFR group was examined as an effect modifier for each outcome.

Results: The cohort consisted of 21,996 individuals (19,990 metformin users and 2,006 sulfonylurea users). Metformin use was associated with a lower risk of all-cause mortality (HR 0.48, 95% CI 0.40-0.58, p<0.001), cardiovascular events (HR 0.67, 95% CI 0.52-0.86, p=0.002), and major hypoglycemic episodes (HR 0.14, 95% CI 0.09-0.20, p<0.001), when compared to sulfonylureas. CKD was a significant effect modifier for all-cause mortality (p=0.002), but not for cardiovascular events or major hypoglycemic episodes.

Conclusions: Sulfonylurea monotherapy is associated with a higher risk of all-cause mortality, major hypoglycemic episodes and cardiovascular events compared to metformin. Although the presence of CKD attenuated the mortality benefit, metformin may be a safer alternative to sulfonylureas in patients with CKD.

Funding: Veterans Affairs Support, Commercial Support - Astra Zeneca

FR-PO246

Pleiotropic Effects of Oral Anti-Hyperglycemic Drugs on Renal and Cardiovascular Outcomes: A Meta-Analysis

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Background: Recently, there are a lot of data of novel oral anti-hyperglycemic drugs claiming to slow progression of kidney function decline and decrease cardiovascular events and all-cause mortality. Therefore, we performed the meta-analysis to explore the pleiotropic effects of oral anti-hyperglycemic drugs including sodium-glucose co-transporter-2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors on renal and cardiovascular outcomes.

Methods: A systematic literature search was performed in PubMed, Embase and Cochrane Central Register of Controlled Trials to identify randomized controlled trials examining the effects of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors on the incidence of new albuminuria, regression of albuminuria, doubling increase in serum creatinine, renal composite outcomes, renal replacement therapy (RRT), renal death, cardiovascular events and all-cause mortality. We used random effect model to compute the pooled adjusted hazard ratios (HR) for interested outcomes.

Results: Fourteen studies with 95,717 participants were included. SGLT2 inhibitors, GLP1 receptor agonists, and DPP4 inhibitors provided significantly lower HR of new incidence of albuminuria. SGLT2 inhibitors and DPP4 inhibitors had significantly higher HR of regression of albuminuria. In terms of renal composite for increasing in serum creatinine more than 40%, RRT, and renal death, there were significantly lower HR by SGLT-2 inhibitors and GLP-1 receptor agonists. In addition, significantly lower HR of doubling in serum creatinine was noted in SGLT-2 inhibitors. Regarding RRT events, HR was lower in SGLT-2 inhibitors. All-cause mortality was significantly reduced by SGLT-2 inhibitors. Finally, SGLT2 inhibitors had significantly lower HR of heart failure events.

Conclusions: SGLT-2 inhibitors exhibited nephroprotective effects in terms of regressing albuminuria, preventing the incidence of new albuminuria, doubling in serum creatinine, RRT events, renal composite outcome, heart failure events, and all-cause mortality. GLP-1 receptor agonists could attenuate the incidence of new albuminuria and renal composite outcomes, while DPP-4 inhibitors could only prevent the incidence of new albuminuria and regress albuminuria.

FR-PO247

Spironolactone for the Prevention of Microalbuminuria in High-Risk Type 2 Diabetes: Results from the Multicenter Randomized Double-Blind Controlled Trial PRIORITY

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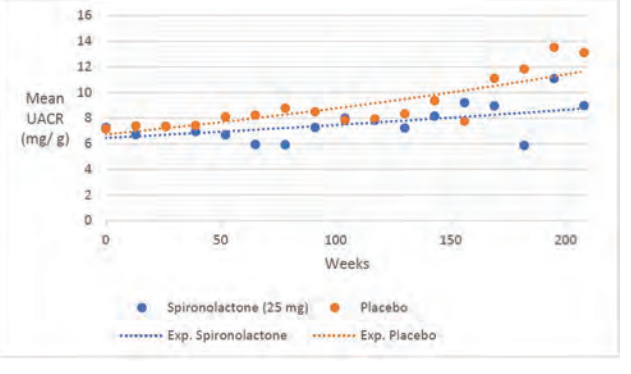
Background: The 'Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephRopathy In TYpe 2 diabetic patients with normoalbuminuria trial' (PRIORITY) tested if the aldosterone antagonist spironolactone (25 mg daily) could reduce progression to microalbuminuria in patients with type 2 diabetes (T2D) and normal urinary albumin creatinine ratio (UACR) (< 30 mg/ g) but at high risk for progression based on a urinary proteome-based classifier (CKD273).

Methods: Multicenter randomized double-blind controlled trial. The CKD273 classifier was assessed at baseline in 1775 subjects; 209 (12 %) had elevated risk and were randomized to spironolactone or matching placebo on top of ongoing treatment. Primary endpoint was development of confirmed microalbuminuria (moderate albuminuria) in 2 of 3 first morning urine samples (UACR) >30 mg/g and ≥30 % increase from baseline).

Results: Baseline mean ± SD: Age 63 ± 6.4 years, blood pressure 135 ± 12/ 79 ± 9 mmHg, eGFR 81 ± 17 ml/min/1.73m^2, and UACR 9.1 ± 7 mg/g, 88 % on ACEi or ARB. Mean follow up time was 2.5 years from 7 days to 4.3 years. Development of persistent microalbuminuria was seen in 35 (33 %) of placebo and 26 (26 %) spironolactone treated subjects, hazard ratio (HR) 0.81 (CI 95%: 0.49-1.34) p=0.41. In total 58 (28 %) did not complete the full follow up period, of which 16 had suspected side effects or safety considerations. Hyperkalemia was seen in 4 vs 13 and gynecomastia in 0 vs 3 subjects on placebo vs spironolactone, respectively, and 28 were excluded due to lack of adherence or lost to follow up. In 151 subjects treated per protocol HR was 0.71 (CI 95 %: 0.40 – 1.25) p = 0.23.

Conclusions: Treatment with spironolactone was not able to prevent or delay progression to persistent microalbuminuria in normoalbuminuric subjects with type 2 diabetes and high risk of kidney disease based on urinary proteomics risk score CKD273.

Funding: Government Support - Non-U.S.



FR-PO248

Direct Renin-Inhibitors for Preventing the Progression of Diabetic Kidney Disease: A Systematic Review and Meta-Analysis

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Background: Renin-angiotensin-aldosterone system blockade using angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) therapy is incomplete and may lead to compensatory rise in angiotensin precursors, including renin. Addition of direct renin-inhibitors (DRIs) to ACEI/ARB treatment might potentially slow down the progression of diabetic kidney disease (DKD). In this systematic review, we examined the benefits and harms of DRIs in preventing the onset or progression of DKD.

Methods: We searched CENTRAL, MEDLINE, and EMBASE (until Oct 2018) for relevant clinical trials that compared DRIs to placebo or other agents among those with type 1 or type 2 diabetes and kidney disease (defined by presence of UAER > 30 mg/d or urine albumin creatinine ratio (UACR) > 30 mg/g). Two authors independently screened studies for inclusion and extracted data. Following outcomes were included: all-cause and cardiovascular mortality, progression or regression of albuminuria, changes in blood pressure, and adverse events such as hyperkalemia. Treatment effects were summarized as relative risks (RR) or mean difference (MD) and 95% confidence intervals (CI) using random effects models.

Results: Nine clinical trials (n=10,051) were included. Addition of DRI to ACEI/ARB had no effect on all-cause mortality (2 studies, 9151 participants; RR 0.93, 95% CI: 0.4-2.19), cardiovascular mortality or change in GFR (2 studies, 638 participants, Mean difference 1.29, 95% CI: -0.44-3.02 ml/min/1.73 m^2) compared to ACEI/ARB use alone. Addition of DRIs to ACEI/ARB was associated with reduced progression to macroalbuminuria (RR 0.82, 95% CI:0.72-0.93) and improvement in regression to microalbuminuria (RR 1.19, 95% CI:1.19-1.29) in one study enrolling 8561 participants. Withdrawal due to adverse events or due to any other reason was similar in both groups. Risk of hyperkalemia was increased by the addition of DRIs to ACEI/ARB therapy (2 studies, 9153 participants, RR 1.34, 95% CI: 1.26-1.42).

Conclusions: Current evidence demonstrate that the addition of DRIs to ACEI/ARB therapy in patients with DKD doesn't reduce cardiovascular or all-cause mortality. However, it might impart kidney benefits by reducing albuminuria at the cost of higher risk of hyperkalemia.

FR-PO249

Five-Year Kidney Outcomes of Bariatric Surgery in Adolescents Compared with Adults

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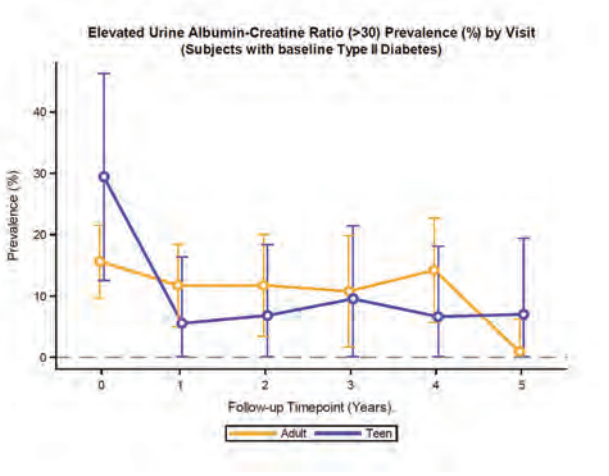
Background: Bariatric surgery improves markers of kidney health in severely obese adults and adolescents, yet it remains unclear whether kidney disease outcomes differ according to age at surgery.

Methods: We examined health effects of Roux-en-Y gastric bypass between adolescents (n=161; enrolled 2006-2012) and adults (n=396; enrolled 2006-2009) participating in two related but distinct studies. Estimated glomerular filtration rate (eGFR) by serum creatinine and cystatin C and urine albumin-to-creatinine ratio (UACR) were compared between cohorts through 5 years after surgery. Elevated UACR (≥30mg/g) and hyperfiltration (eGFR ≥ 135 ml/min/1.73m^2) were also compared. Analyses were stratified by the presence of pre-operative type 2 diabetes (pre-op T2D).

Results: The pre-op prevalence of elevated UACR was higher in adolescents than adults irrespective of pre-op T2D status. In adolescents with pre-op T2D, elevated UACR decreased from 29% prior to surgery to 6% 1 year after surgery (p=0.0041), whereas elevated UACR did not decrease significantly until year 5 after surgery in adults with pre-op T2D (p=0.0040) (**Fig 1**). The change in prevalence of UACR was not significantly different over time in adolescents vs. adults without pre-op T2D (p=0.95). Adolescents with pre-op T2D had an increased prevalence of hyperfiltration that remained throughout the study period (p=0.01), whereas hyperfiltration prevalence was similar in all study participants without T2D (p=0.94).

Conclusions: Adolescents with T2D experienced more hyperfiltration and earlier attenuation of elevated UACR after gastric bypass compared to adults and these differences were not observed in adolescents and adults without pre-op T2D.

Funding: NIDDK Support



FR-PO250

Testosterone Replacement Therapy (TRT) Delays Early Progression of CKD in Diabetes Mellitus (DM2)

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Background: We have previously shown that TRT provides significant survival benefits in hypogonadic men with kidney disease. Faster progression of chronic kidney disease (CKD) in DM2 is well known. Testosterone deficiency is common in both CKD and DM2. Here we examined if TRT slows CKD progression, cardiovascular disease and mortality in patients with DM2.

Methods: Data from a large cohort of veterans diagnosed with low total testosterone were used to determine the effect of TRT on the progression of CKD, cardiovascular diseases and all-cause mortality in patients with DM2. Increase in serum creatinine > 1.5 mg/dl was taken as a measure of progression of CKD. Data were extracted using the Veterans Administration Informatics and Computing Infrastructure (VINCI), and analyzed using SAS. Propensity matching for age, followup time and prior vascular disease was used to adjust groups. Results were compared by means tests, frequency tables, odds ratio and p values (p=<0.01).

Results: Of 57,985 patients with testosterone deficiency, 14,496 with DM2 had treatment (DM2_TRT) and 4319 had none (DM2_No_TRT), compared to controls without DM2 (Ctrl_TRT, N=29,938, Ctrl_No_TRT, N=9,232). Baseline DM2 age was higher (58.3 vs 61.6 yr). Followup and creatinine were was similar (Ctrl vs DM2 : 6.0 vs 5.7 yrs; 1.02 vs. 1.06 mg/dl). TRT provided significant reduction in all-cause mortality in both groups, (Odds DM2 0.69, 95% CI 0.65-0.74; Odds Ctrl 0.72, 95% CI 0.69-0.77). TRT reduced the progression of CKD (Odds DM2 0.71, 95% CI 0.67-0.75; Odds Ctrl 0.85, 95% CI 0.81-0.89). TRT reduced CVA (Odds DM2 0.86, 95% CI 0.76-0.98; Odds Ctrl 0.86, 95% CI 0.77-0.94). TRT reduced new MI in both groups (Odds DM2 0.74; Odds Ctrl 0.79). TRT reduced new retinopathy slightly. Prior cardiovascular disease was more common with DM2 (% difference Dx/Ctrl), e.g. CAD (158%), CHF (229%), CVA (89%), HTN (112%), MI (118%), PAD (185%).

Conclusions: TRT is associated with significant reductions in progression of early CKD[AG1], all-cause mortality and new cardiovascular diagnoses in patients with DM2 even while DM2 is associated with increased prior cardiovascular disease.

Funding: Veterans Affairs Support

FR-PO251

The Mechanism of Anti-Albuminuric Effect by Topiroxostat

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Background: In 2018, we demonstrated the anti-albuminuric effect of topiroxostat, a selective xanthine oxidoreductase inhibitor (XORi), in the ETUDE trial (24-week, multicenter, open-label, randomized trial; 1:1, high dose vs low dose) for hyperuricemic patients with diabetic nephropathy. XORis have been reported to have renoprotective power via reduction of oxidative stress, inflammation, and renin angiotensin system (RAS) activation. Therefore, we investigated reduction in oxidative stress (8OH-dG), inflammation (MCP-1) and RAS activation (angiotensinogen) in urine samples of patients actually administered topiroxostat.

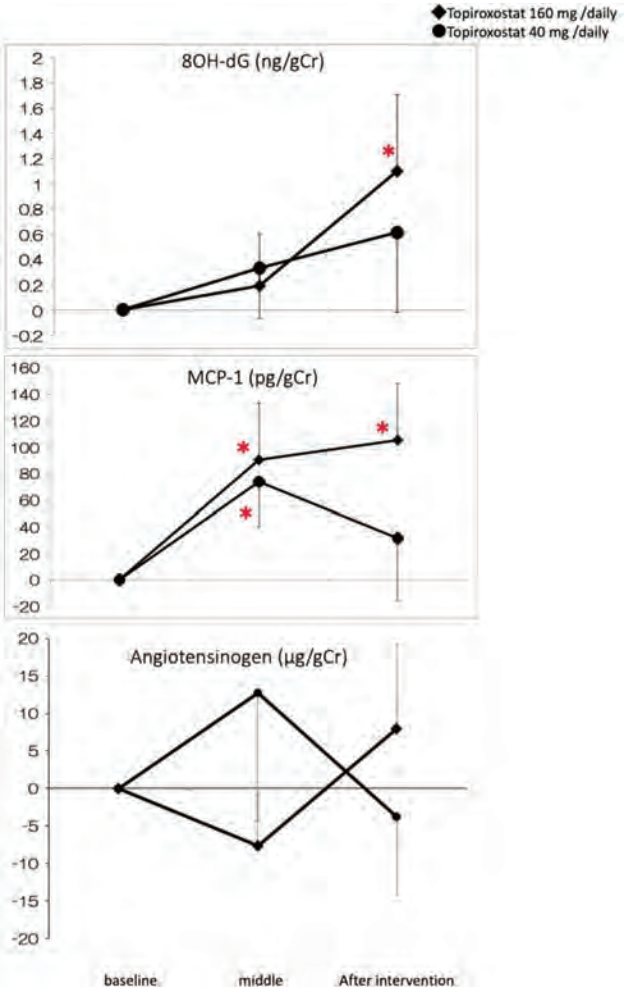
Methods: Urinary levels of 8OH-dG, MCP-1 and angiotensinogen in the samples collected in the ETUDE study were measured. We compared these parameters between high dose and low dose of topiroxostat by analysis of variance (ANOVA) using the treatment group, eGFR, age and gender and the baseline levels as fixed effects. In addition,

in each group of high dose and low dose of topiroxostat, the intra-group comparison was performed by t-test with the changes in these parameters after intervention relative to the baseline values.

Results: There was no significant differences in changes in 8OH-dG, MCP-1 and angiotensinogen between the two treatment groups by ANOVA (P = 0.69, 0.59 and 0.50, respectively). In comparison with the baseline values at the end of intervention, 8OH-dG (P = 0.08 high dose, 0.24 low dose) and MCP-1 increased in high dose group (P = 0.02 high dose, 0.51 low dose). The levels of angiotensinogen showed no statistically significant increase as well as decrease (P = 0.48 high dose, 0.72 low dose).

Conclusions: Our additional analysis failed to detect any suppressive effect of inflammation, oxidative stress and RAS activation with topiroxostat and could not reach an evidence that led to the mechanism of albuminuria lowering action.

Funding: Commercial Support - Sanwa Kagaku Kenkyusho



FR-PO252

Treatment of CKD Stage III-IV Diabetic Nephropathy Patients with Tripterygium wilfordii Hook F Extract and the Serum and Urine Metabolomic Analysis

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Background: Diabetic nephropathy (DN) is the most common cause of end-stage renal failure. Although angiotensin II receptor blockers (ARBs) can be used to attenuate proteinuria in DN patients, their efficacy remains limited in CKD stage III-IV DN. This study aimed to evaluate the efficacy of Tripterygium wilfordii Hook F (TwHF) extract in the treatment of type 2 DN patients with CKD stage III-IV and compare the serum and urinary changes of metabolic pathways after TwHF treatment using metabolomics.

Methods: From Oct. 2018 to Jan. 2019, type 2 DN patients with 25≤eGFR<60 ml/min/1.73m2 followed up in renal outpatient clinic of Peking Union Medical College Hospital, who were receiving ARBs and still suffered from severe proteinuria were enrolled as treatment group (TwHF extract 60mg daily). The patients matched by gender, age, proteinuria, and serum creatinine were selected as controls. treated with the maximum dose of ARBs. The urinary protein and eGFR levels were measured at one month after the commencement of treatment. The serum and urine metabolomic analysis before and after treatment in the TwHF group, using UPLC-LTQ-Orbitrap high-resolution mass spectrometry was performed to detect the changes in metabolic pathways.

Results: A total of 28 patients were included, 14 patients (52.9±15.2 ys, eGFR 45±16ml/min/1.73m^2) in the TwHF group and 14 patients in the control group (53.1±11.6 ys, eGFR 46±19ml/min/1.73 m^2). After 1 month treatment, the urinary protein of the TwHF group decreased significantly from 6.2±2.0g/24h to 3.4±1.7g/24h (P<0.05), and the control group decreased significantly from 5.0±1.8g/24h to 3.5±2.0g/24h (P<0.05). There was a significant difference in the reduction rate of proteinuria between the two groups (P=0.03). There were 18 metabolic pathways changed significantly in the urine metabolomic analysis after treatment, including leukotriene, peroxidase fatty acid, and eicosapentaenoic acid metabolic pathways which were associated with inflammation and oxidative stress. A similar change of metabolic pathways was found in the serum metabolomic analysis.

Conclusions: The TwHF extract can reduce the urine protein level of type 2 DN patients with CKD stage III-IV. The serum and urine metabolomic analysis implies TwHF extract may have anti-inflammation and attenuate oxidative stress effects.

FR-PO253

Association Between Individual Cholesterol and Albuminuria Response and Exposure to Atorvastatin or Rosuvastatin

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Background: The PLANET trials showed that atorvastatin 80 mg (ATOR) but not rosuvastatin at either 10 or 40 mg (ROSU) reduced urinary protein:creatinine ratio (UPCR) while effects on LDL cholesterol were similar. However, individual changes in both UPCR and LDL cholesterol to these statins varied widely between patients. This interindividual variability could not be explained by patients' physical or biochemical characteristics. We assessed whether the plasma concentration of the statins were associated with LDL cholesterol and albuminuria response.

Methods: the PLANET trials randomized patients with an urine protein:creatinine ratio of 500 – 5000 mg/g, fasting LDL cholesterol >2.3 mmol/L and stable treatment with ACE or ARB to a 52 week treatment period with ATOR 80 mg, ROSU 10 mg or 40 mg. For the current analysis patients with available samples at week 52 and treatment compliance >80% by pill count were included (N=295). Main outcome measurements were percentage change in UPCR and absolute change in LDL cholesterol (delta LDL), comparing baseline to week 52.

Results: Median (interquartile range) plasma concentration at week 52 for ATOR 80 mg was 3.9 (2.1 – 8.7); for ROSU 10 mg 1.0 (0.7 – 2.0) and for ROSU 40 mg 3.5 (2.0 – 6.8). Higher plasma concentration of statin was associated with larger LDL-cholesterol reductions at week 52 and not with UPCR change nor UACR change (Table). Serum albumin (β = 0.63, p = 0.05) and eGFR per 10 ml/min1.73m^2 (β = -0.09; p = 0.04) were independently associated with ROSU plasma concentration. Active metabolites concentration of either ROSU or ATOR did not correlate with LDL and UPCR changes.

Conclusions: Individual variation in plasma concentrations of rosuvastatin and atorvastatin explained the LDL-cholesterol changes of the patients. The individual variation in UPCR change was not explained by the plasma concentration of both statins.

Pearson correlations between plasma concentration of atorvastatin and rosuvastatin and delta LDL-cholesterol (mmol/L) and log Delta UPCR and UACR at week 52.

	LDL change		UPCR change		UACR change	
	Pearson correlation	P-value	Pearson correlation	P-value	Pearson correlation	P-value
Atorvastatin	-0.28	0.006	0.16	0.13	0.14	0.16
Rosuvastatin	-0.40	<0.001	0.07	0.30	0.03	0.70

FR-PO254

Efficacy and Safety of Patiromer by Baseline Serum Potassium Level <6.0 vs. ≥6.0 mEq/L: Pooled Results of Three Studies

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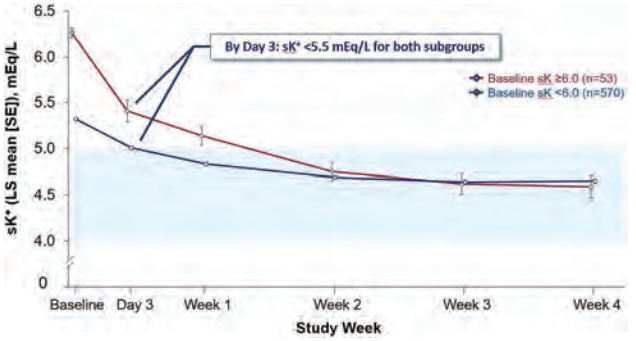
Background: Patiromer (PAT) is a sodium-free non-absorbed potassium (K^+) binder that uses calcium as the counter-exchange ion. In this post-hoc analysis, we assessed the efficacy and safety of PAT by baseline severity of hyperkalemia (HK).

Methods: We analyzed pooled data (patients with starting dose up to 25.2 g/day) through week 4 from 3 trials of PAT (AMETHYST-DN, OPAL-HK, TOURMALINE). Patients who took ≥1 PAT dose and had ≥1 post-baseline serum K^+ measurement (sK^+) were included, stratified according to sK^+ ≥6.0 mEq/L and sK^+ <6.0 mEq/L, and assessed for sK^+ change from baseline at week 4, sK^+ over time, and % with any sK^+ measurement in target range (3.8–5.0 mEq/L).

Results: 623 patients were evaluated; 53 had baseline sK^+ ≥6.0 mEq/L and 570 had baseline sK^+ <6.0 mEq/L. Mean (SD) baseline eGFR was 33.0 (16.6) and 40.2 (19.2) mL/min/1.73m^2 in those with sK^+ ≥6.0 and <6.0 mEq/L, respectively. >90% of patients in both groups were taking RAASi. Mean sK^+ was reduced to <5.5 mEq/L at Day 3 (48 hours after the first dose) in both subgroups (**Figure**). 97% of patients with sK^+ <6.0 mEq/L and 93% with sK^+ ≥6.0 mEq/L achieved any sK^+ measurement in the target range through week 4. Mean (95% CI) reductions from baseline at week 4 were -0.67 (-0.71, -0.63) and -1.67 (-1.91, -1.43) mEq/L in the sK^+ <6.0 and sK^+ ≥6.0 mEq/L subgroups, respectively. Adverse events (AEs) were reported in 31% of patients with sK^+ <6.0 mEq/L and 43% with sK^+ ≥6.0 mEq/L, with PAT-related AEs (most commonly constipation and diarrhea) reported in 13% and 19%, respectively.

Conclusions: Patiromer was effective and well-tolerated in patients with mild/moderate HK and severe HK. Regardless of the severity of HK, treatment with patiromer lowered sK^+ to 3.8–5.0 mEq/L in >93% of patients in 4 weeks. A higher rate of constipation occurred in the sK^+ ≥6.0 mEq/L subgroup and may be related to the fact that these patients appear to have worse overall health (e.g. lower eGFR).

Funding: Commercial Support - Funded by Relypsa, Inc., a Vifor Pharma Group Company



Serum K^+ Over 4 Weeks by Baseline Serum K^+ <6.0 vs ≥6.0 mEq/L: Pooled Analysis Across 3 Trials

FR-PO255

Patiromer Controls Serum Potassium for Up to 1 Year in Hyperkalemic Patients with Diabetes and Advanced Kidney Disease on RAAS Inhibitors Regardless of Age

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Background: Patiromer (PAT) is a sodium-free, non-absorbed potassium binder approved for the treatment of hyperkalemia (HK). Published data from the OPAL-HK study describes the efficacy and safety of patiromer in controlling serum potassium (sK^+) while maintaining RAAS inhibitor therapy in younger and older adult HK patients (pts) over 3 months of study treatment.

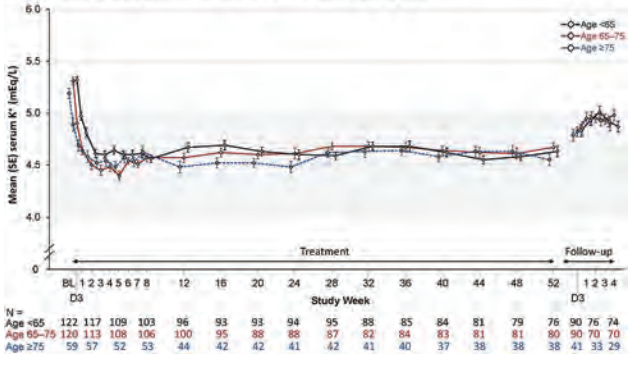
Methods: AMETHYST-DN was a 52-week, multicenter, open-label trial of 304 pts on RAAS inhibitors with eGFR 15–<60 mL/min/1.73m^2, type 2 diabetes, hypertension, and documented HK (sK^+ >5.0 mEq/L). PAT was titrated, if needed, to achieve and maintain sK^+ ≤5.0 mEq/L. Pts <65 (n=122), 65–74 (n=122), and ≥75 (n=60) years of age were randomized and received ≥1 dose of PAT.

Results: Baseline mean (SE) sK^+ levels were 5.32±0.35, 5.31±0.37, and 5.19±0.38 mEq/L in pts <65, 65–74, and ≥75 years of age respectively. By Day 3 (~48 hr after the first PAT dose), mean sK^+ levels were reduced in all 3 age groups (4.97±0.42, 4.90±0.44, 4.89±0.45 mEq/L respectively). The least squares (LS) mean (SE) changes in sK^+ from baseline to Week 4 were –0.67 mEq/L (*P*<0.0001), –0.82 mEq/L (*P*<0.0001), and –0.65 mEq/L (*P*<0.0001), respectively. After 52 weeks (end of treatment), the LS mean (SE) changes from baseline in sK^+ were –0.66 mEq/L (*P*<0.0001), –0.68 mEq/L (*P*<0.0001), and –0.61 mEq/L (*P*<0.0001), respectively. The figure shows mean sK^+ over 52 weeks for all age groups; patiromer cessation led to a rise in mean sK^+ during follow-up. Through 1 year, 18%, 23%, and 17% of pts reported ≥1 PAT-related AE (most common: constipation). There were few AEs leading to discontinuations through 1 year: 9%, 9%, and 10% of pts across the 3 cohorts.

Conclusions: Regardless of patient age, daily treatment with PAT reduced and maintained control of sK^+ for up to 1 year in hyperkalemic pts with advanced diabetic kidney disease receiving RAAS inhibitors. PAT was generally well tolerated.

Funding: Commercial Support - Funded by Relypsa, Inc., a Vifor Pharma Group Company

FIGURE. Mean (SE) serum potassium over time in AMETHYST patients by age group.



FR-PO256

Antidiabetic Medication Use in Patients with Type 2 Diabetes and CKD

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Background: Diabetes care and relevant clinical practice guidelines are continuously evolving, yet little is known about how to optimize type 2 diabetes mellitus (T2DM) care in patients with chronic kidney disease (CKD). We therefore sought to describe treatment approaches for glycemic control in patients with T2DM and CKD by examining patterns of newer (GLP1-ra and DPP-4i) and conventional (metformin, SU, TZD, and insulin) antidiabetic medication use in this patient population by using data from 2015.

Methods: We used data from a large claims and integrated database that includes employed and commercially insured patients in the United States (Optum). We selected adults age ≥18 years who had continuous enrollment between January 1, 2014 and January 1, 2015, restricting the cohort to patients who had T2DM and CKD prior to January 1, 2015. We defined medication use according to pharmacy fill information for two newer classes (GLP-1ra and DPP-4i) and four conventional classes of antidiabetic medications (metformin, SU, TZD, and insulin). We stratified our analyses by age, sex, race, ethnicity, income, geographic region, CKD stage, and prescribing provider specialty. The final cohort consisted of 38,577 patients.

Results: In 2015, metformin was the most common medication prescribed to patients in this cohort (49.2%). Among the newer medications, 3.4% of patients were prescribed GLP-1ra and 12.3% of patients were treated with DPP-4i. Among patients in CKD stage 1-3a, metformin remained the most commonly prescribed medication. The proportion of patients who were prescribed DPP-4i and insulin was higher in advanced CKD whereas the proportion of patients who were prescribed GLP-1ra was highest in patients with CKD stage 1. There were wide variations by sociodemographic factors. Generally, patients who received prescriptions for antidiabetic medications from nephrologists remained low (0.4-1.9%). Among patients who received prescriptions for GLP-1ra, most received their prescriptions from endocrinologists whereas patients treated with other classes of medications had their prescriptions written most frequently by PCPs.

Conclusions: Prescriptions for newer antidiabetic medications with known safety and efficacy remained low. Prescriptions for agents that are contraindicated in advanced CKD continued to be written. GLP-1ra were favored primarily by endocrinologists.

Funding: NIDDK Support

FR-PO257

Anti-Diabetic Medication Use and Kidney Function in US Adults

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Background: The concordance of diabetes mellitus (DM) and chronic kidney disease (CKD) constitutes a major public health problem. Though notable therapeutic advances have occurred in the last decade, diabetes medication patterns in the U.S. DM-CKD population remain poorly delineated, particularly associations with declining kidney function. Hence, we examined anti-diabetic medication (ADM) use among adult National Health and Nutrition Examination Survey participants (2001 to 2016) with self-reported diabetes or HbA1c ≥ 7.0%.

Methods: Comparisons were based on two thresholds of creatinine-based estimated glomerular filtration rate (eGFR, 60 and 45 ml/min/1.73m^2) and one threshold of urinary albumin to creatinine ratio (ACR, 30 mg/g).

Results: Renal function in US adults with DM was distributed as follows: eGFR ≥ 60 and ACR < 30 (≥ 60/<30~60.1%, ≥ 60/≥30~20.1%, 45-59/<30~7.4%,45-59/≥30~3.9%, <45/<30~3.1% and <45/≥30~5.4%. Use of ≥ 1 ADM was more prevalent with CKD than without kidney dysfunction (79.5% vs. 75.3%, *P*=0.004). Following these same eGFR and ACR categories, use of ≥ 1 ADM was associated with worsening kidney function category (75.3%, 75.4%, 82%, 84.5%,80.9%, and 86.7%, *P* < 0.001), as were sulphonylurea (26.3%, 33.3%, 29.5%, 29.9%, 36.7%, and 36.5%, *P*=0.002), insulin (23.3%, 27.3%, 30.9%, 41.0%, 40.6%, and 54.3%, *P* < 0.001) and amylin analog (0%, 0.6%, 0%, 0%, 0%, and 1.2%, *P*=0.03) use. Worsening kidney function category was associated with lower proportions of ≥ 2 ADM (35.6%, 41.5%, 34.0%, 38.9%, 26.4%, and 33.2%, *P*=0.032), biguanide (51.8%, 50.7%, 40.9%, 41.3%,16.4%, and 11.2%, *P* < 0.001) and SGLT-2 inhibitor (2.9%, 1.8%, 0.9%, 1.3%, 1%, and 0.1%, *P*=0.044) use. No association was present for thiazolidinedione, dipeptidyl peptidase-4 inhibitor, alpha-glucosidase inhibitor, GLP-1 receptor agonist and meglitinide use.

Conclusions: One in five in the U.S. DM-CKD population do not use anti-diabetic medications, and medication patterns vary substantially with kidney function.

FR-PO258

Temporal Trends in Pharmacologic Management of Diabetes Mellitus Among Patients with CKD in the United States

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Background: The nexus of diabetes mellitus and chronic kidney disease (DM-CKD) constitutes a major public health problem. Though substantial therapeutic advances have occurred in the last decade, diabetes management patterns in the US DM-CKD population remain poorly delineated. Hence, we examined trends in anti-diabetic medication use among adult National Health and Nutrition Examination Survey participants from years 2001 to 2016.

Methods: Eligible participants had self-reported diabetes or HbA1c ≥ 7.0 % and creatinine-based estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m2 or urinary albumin to creatinine ratio (ACR) ≥ 30 mg/g.

Results: Increases were observed in the proportions taking at least 1 anti-diabetic medication (1+ADM, 73.1% in 2001-2004, 79.2% in 2005-2008, 81.8% in 2009-2012 and 81.9% in 2013-2016, *P*=0.024). A biphasic pattern was observed for 2+ADM (33.6%, 43.7%, 42.0%, 31.9%, *P*=0.002). Regarding individual classes of ADM, values rose for biguanides (32.8%, 40.0%, 39.5%, 45%, *P*=0.048), insulin (26.9%, 27.8%, 38.7%, 39.4%, *P*=0.001) and meglitinides (0%, 3.5 %, 8.8%, 9.1%, *P* < 0.001); fell for sulphonylureas (35.9%, 38.3%, 37.1%, 23.6%, *P* < 0.001) and thiazolidinediones (19.2%, 21.1%, 9.8%, 3.6%, *P* < 0.001); exhibited a rise-and-fall pattern for alpha-glucosidase inhibitors (0.2%, 1.9%, 0.7% and 0.1%, *P*=0.015) and amylin analogs (0%, 1.9%, 0%, 0%, *P*=0.005) and remained statistically unchanged for dipeptidyl peptidase-4 inhibitors (6.5%, 6.5%, 4.5%, 3.7%, *P*=0.333) and SGLT-2 inhibitors 0%, 0.9%, 1.2% and 2.4%, *P*=0.091).

Conclusions: Thus, anti-diabetic medication use in the US DM-CKD populations has changed considerably between 2001 and 2016.

FR-PO259

Estimating the Effectiveness of Home-Based Kidney Care in Persons with Diabetes Using Propensity Scores

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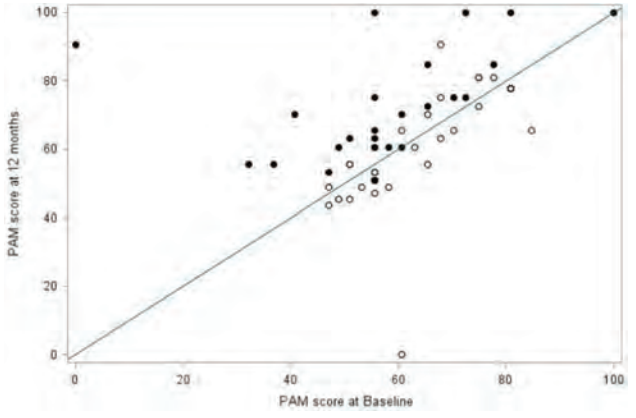
Background: Home-based kidney care (HBKC) is a pragmatic approach incorporating the healthcare preferences of individuals to address cultural barriers to standard kidney care. We carried out a 12-month randomized clinical trial (RCT) of HBKC in 72 American Indians, identified as having CKD with diabetes.

Methods: Participants were randomized to receive usual care (UC) or HBKC. After initial lifestyle coaching, the HBKC group received frequent additional reinforcement by CHWs about adherence to medicines, diet and exercise, self-monitoring, and coping strategies for living with stress. The primary outcome was the change from baseline to 12-months in the patient activation measure (PAM). Secondary outcomes included BMI, A1C, hsCRP, and KDQOL measures. Outcomes were compared between study groups using linear models with generalized estimating equations to account for household clustering and propensity scores to account for the fact that we did not randomize specifically for those with diabetes.

Results: Accounting for imbalances in group membership at baseline by applying propensity weights, the estimated average change in the difference in PAM scores was 15.6 points higher in HBKC compared to the UC while also adjusting for baseline PAM scores (Figure 1). When PAM score was categorized into PAM levels, we observed that participants in HBKC were 8.4 times more likely to be activated compared to the UC while adjusting for baseline PAM scores. Body mass index declined by 1.2 kg/m^2 (P=0.02) and hsCRP protein by 2.7-fold (P<0.001) more in HBKC group compared to UC. There was a modest decline in A1C by 0.8 % (P=0.14) in HBKC group relative to UC.

Conclusions: A home-based kidney care intervention improves the activation of participants in their own health care. It may also reduce risk factors for poor diabetes outcomes in a rural disadvantaged population.

Funding: Other U.S. Government Support



FR-PO260

Associations Between Facility Use of an Electronic Patient Care Plan and Foot Check Rates in Dialysis Patients

Hao Han, Sheetal Chaudhuri, Wendy Millette, Marta Reviriego-Mendoza, John W. Larkin, Len A. Usvyat, Jeffrey L. Hymes, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

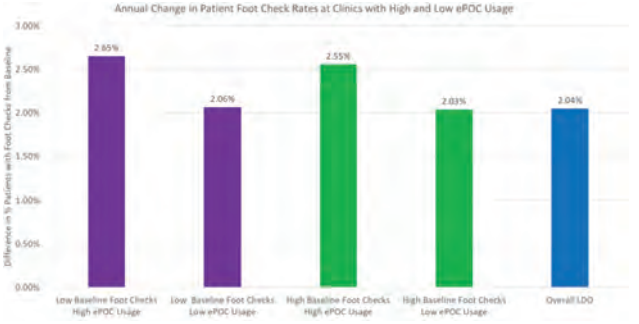
Background: Electronic care plans have the potential to streamline the management of patient meetings to create, follow, and optimize patient centric interventions for unstable conditions. A large dialysis organization (LDO) deployed an electronic Plan of Care (ePOC) tool for clinicians to improve and personalize care coordination. We assessed if use of the ePOC tool by facilities was related to improvements in the percentage (%) of patients receiving diabetic foot checks.

Methods: The ePOC application was deployed at an LDO in October of 2017. We analyzed monthly data from dialysis patients that had the ePOC application used by the care team during October of 2017 (baseline) and October 2018. We selected the top 15% of the clinics performing the highest % of diabetic foot checks, and the bottom 15% of clinics performing the lowest % of foot checks. Of those, we selected the top and bottom 33% of the clinics with the highest and lowest use of the ePOC tool, respectively. We compared the difference from baseline in % of patients receiving foot checks between facilities with high and low ePOC usage stratified by high and low achievement of baseline foot checks.

Results: We included data from 2432 dialysis facilities. We selected 400 clinics with care teams who were the highest and lowest users of the ePOC tool. Clinics starting with a low or high % of foot checks that were high ePOC users had greater increases in the % of foot checks after follow-up compared to clinics with low ePOC usage (Figure 1).

Conclusions: Use of the ePOC system in the dialysis setting may be have the potential to lead to improvements in the workflow of care in conducting diabetic foot checks. Further analyses are needed to support these findings as these may be confounded by clinics that are more compliant with internal policies.

Funding: Commercial Support - Fresenius Medical Care North America



FR-PO261

Developing Iron Thresholds to Predict Heart Failure Hospitalization Risk in Veterans with CKD

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Background: Iron deficiency is closely associated with heart failure (HF) risk. The specific thresholds for serum transferrin saturation (Tsat) or ferritin associated with HF are unknown in CKD.

Methods: We developed a historical cohort using the Veterans Affairs Informatics and Computing Infrastructure. We identified Veterans with pre-dialysis CKD (MDRD eGFR <60 mL/min/1.73m^2) with at least one set of iron indices between 2006-2015. Veterans with ESRD, genetic or chronic disorders affecting iron metabolism, or those who received intravenous iron or erythropoietin stimulating agents within 3 months of the iron indices were excluded. A generalized additive Cox model was applied to the cohort to explore the joint dose-response relationship of the hazard for HF hospitalization following the iron assay. A full 3-D response surface relating the HF covariate-adjusted hazard to both Tsat and ferritin was developed using cubic regression splines.

Results: Of the 1,159,371 Veterans with CKD, 141,477 met the inclusion criteria. The mean±SD for age and eGFR were 72±11 years and 43±11 mL/min/1.73 m^2, respectively. The median (IQR) Tsat and ferritin values were 22 (16, 28)% and 109 (55, 205) ng/mL. At the median values of Tsat and ferritin, 1-year cumulative incidence of HF hospitalization was 2.3%. Compared to the median value, Tsat ≤16% was associated with 25% increased risk for HF hospitalization while no specific threshold could be identified for ferritin. Tsat values ≤13% and ≤9% were associated with 50% and 100% increased risk of HF hospitalization at one year, respectively.

Conclusions: In Veterans with pre-dialysis CKD, decreased Tsat is closely associated with HF hospitalization risk, while serum ferritin levels do not provide a predictive value.

Funding: Veterans Affairs Support

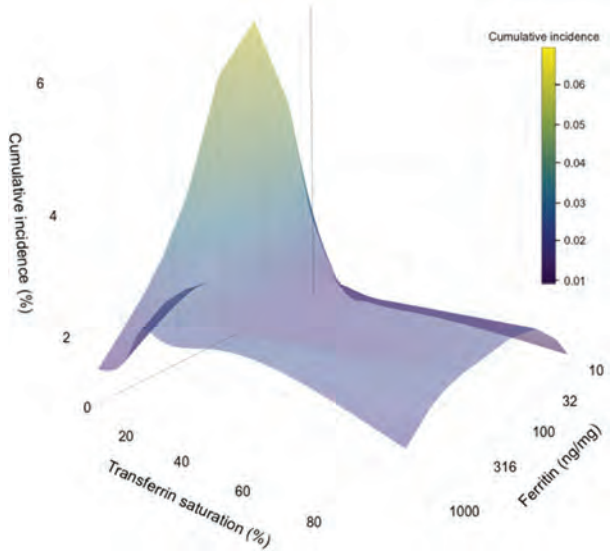

Figure. One-year cumulative incidence of HF hospitalization

FR-PO262

Coronary Artery Calcification but Not Aortic Pulse Wave Velocity Predicts CKD Incidence and Early Progression

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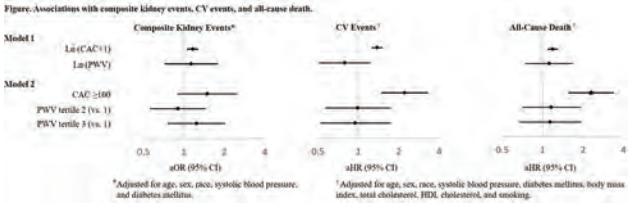
Background: Both aortic arch pulse wave velocity (PWV), a marker of medial arterial stiffness, and coronary artery calcification (CAC), a marker of coronary atherosclerosis, have been shown to be associated with all-cause death, cardiovascular (CV) events, and end-stage renal disease. We investigated whether CAC and PWV predict earlier kidney events, such as incident albuminuria and loss of estimated glomerular filtration rate (eGFR), when interventions targeting these measures may improve long-term outcomes.

Methods: We conducted a prospective, community-based cohort study of Dallas Heart Study participants who underwent PWV and CAC measurement. eGFR was calculated using the 4-variable MDRD formula. The primary outcome of composite kidney events after 7 years of follow-up was incident chronic kidney disease (CKD) (albuminuria or eGFR <60 mL/min/1.73 m^2) or a decrease in eGFR >2.5 mL/min/1.73 m^2 per year. Secondary outcomes were CV events (myocardial infarction, stroke, coronary revascularization, and CV death) and death at a median follow-up of 13 years. Associations with composite kidney events and CV events and death were measured using logistic and Cox Proportional Hazards regression, respectively.

Results: A total of 2,062 participants had a mean age 45±9.3 years, 56% were female, 47% were African American, 10% had diabetes mellitus, and 7% had CKD at baseline. There were 187 kidney events, 177 CV events, and 165 deaths. Log transformed CAC taken continuously was associated with composite kidney events, aOR (95% CI), 1.16 (1.06, 1.27), CV events, aHR (95% CI) 1.38 (1.27, 1.51), and death, aHR (95% CI) 1.19 (1.10, 1.29) (Figure). CAC ≥100 Agatston units was associated with CV events, aHR (95% CI), 2.21 (1.49, 3.28) and death, aHR (95% CI) 2.30 (1.57, 3.37), but not kidney events. PWV taken continuously or in tertiles was not associated with kidney events, CV events, or death.

Conclusions: CAC, but not PWV, was independently associated with CKD incidence and progression, CV events, and death. These results suggest that CAC may be a useful tool to predict clinically meaningful early kidney outcomes in addition to CV events and death.



FR-PO263

Association of Arterial Stiffness with Kidney Function Among Adults Without CKD

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Background: Associations of aortic stiffness with chronic kidney disease (CKD), including albuminuria and low estimated glomerular filtration rate (eGFR) have been reported in CKD patients. However, it is unclear that whether arterial stiffness is associated with an increased risk for kidney dysfunction among persons without CKD, and whether the association differs by sex.

Methods: We analyzed data from the national health check-up system in Japan, which enrolled persons who completed assessments of cardio-ankle vascular index (CAVI) and kidney function in 2005 and 2015. CAVI is a measure of arterial stiffness based on stiffness parameter β. We excluded participants who had CKD at baseline, defined as the presence of proteinuria or eGFR <60 mL/min per 1.73 m^2. The primary outcome was incident CKD events. Cox proportional hazards models were used to assess the associations between CAVI measurements, assessed as the highest versus lower quartile groups (CAVI measurements≧8.1 versus <8.1), and subsequent CKD events.

Results: The mean (±standard deviation) age of the 24,297 included participants was 46±13 years and 56% were female. Over a mean follow-up of 3.1 years, 1,435 CKD events occurred. In a multivariable analysis, the highest versus lower quartile of CAVI measurements was associated with an increased risk for CKD events (hazard ratio [HR], 1.3; 95% confidence interval [CI], 1.1, 1.5) with interaction by sex (p <0.001). Adjusted HR (95% CI) for CKD events was 1.5 (95% CI, 1.2, 1.9) in men and 1.1 (95% CI, 0.95, 1.4) in women for the highest versus lower quartile of CAVI measurements.

Conclusions: CAVI measurements ≧8.1 versus <8.1 was associated with an increased risk for CKD events, and the association was stronger in men than in women. CAVI measurements may help identify persons at higher risk for CKD events.

Funding: Private Foundation Support

FR-PO264

Aortic Valve Calcification (AVC) Is Associated with All-Cause Mortality Independent of Coronary Artery Calcification (CAC) in Patients with ESRD

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Background: AVC is common in ESRD patients (pts). However, the prognostic significance of the overlap between AVC and CAC in ESRD is not well established. We investigated whether AVC is associated with all-cause mortality independent of CAC in ESRD pts.

Methods: 259 ESRD pts (median age 55 years, 67% males) undergoing cardiac CT for AVC and CAC scoring (Agatston units) were included. Framingham's score (FRS), presence of cardiovascular disease (CVD), statin use, protein energy wasting (PEW, subjective global assessment), high-sensitivity C-reactive protein (hsCRP) and other relevant biochemistry and demographic data were determined at baseline. During follow-up for median 36 months, 44 (17%) pts died, and 68 pts underwent renal transplantation. Descriptive, multivariate logistic regression for determinants of AVC, and competing-risk regression analysis for AVC vs all-cause mortality, were performed to define the role of AVC in clinical outcome.

Results: Based on presence (+) or absence (-) of AVC and CAC at baseline, pts were divided into four groups: AVC (-) CAC (-), n=72, 28%; AVC (+) CAC (-), n=5, 2%; AVC (-) CAC (+), n=87, 33%; AVC (+) CAC (+), n=95, 37%. Pts with AVC had older age, higher BMI, more comorbidities, higher FRS, more statin use, lower hand grip strength, higher triglycerides and higher hsCRP. FRS (odds ratio [OR 2.25; 95% confidence interval [95%CI], 1.43 to 3.55] and CAC score (OR [95%CI], 2.18[1.34 to 3.59]) were identified as independent determinants of AVC. After adjustment for presence of CAC, inflammation (hsCRP >10 mg/L), PEW, CVD, 1-SD of FRS and statin use, AVC remained independently associated with all-cause mortality (subdistribution hazard ratio, SHR [95%CI] 2.57 [1.20 to 5.51]) while CAC lost its significant association with mortality (SHR [95%CI], 2.25 [0.46 to 11.01]).

Conclusions: The overlap of AVC and CAC was three times higher (37% vs 11 %) in this ESRD cohort than such overlap previously reported in general population. AVC associated with increased risk of all-cause mortality in ESRD pts, independent of presence of CAC, traditional risk factors and inflammation.

Funding: Commercial Support - Baxter Healthcare, Government Support - Non-U.S.

FR-PO265

Skin Autofluorescence as a Risk Factor for Cardiovascular Events and All-Cause Mortality in Persons with CKD Stage 3

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Background: Tissue advanced glycation end product (AGE) accumulation has been proposed as a marker of cumulative metabolic stress (glycation and oxidation) that can be assessed non-invasively by measurement of skin autofluorescence (SAF). SAF has been identified as an independent risk factor for cardiovascular events (CVE) and all-cause mortality (ACM) in the general population, persons with diabetes or on dialysis but data at earlier stages of CKD are inconclusive. We sought to investigate SAF as a risk factor for CVE and ACM in a prospective study of persons with CKD stage 3.

Methods: Participants with CKD stage 3 were recruited from primary care and assessed at baseline, 1 and 5 years. At each visit, SAF was measured using an AGE reader (DiagnOptics), alongside biochemical and biometric data. Data on subsequent hospital admissions with CVE (fatal and non-fatal myocardial infarction and stroke, transient ischemic attack, cardiac failure, peripheral vascular event and revascularisation; based on ICD-10 coding) and deaths were obtained from NHS Digital. Cox proportional hazards models were used to investigate determinants of CVE and ACM.

Results: 1,707 participants had measurements of SAF at baseline; mean age 72.9±9.0y, mean eGFR 53.5±11.9ml/min/1.73m^2, mean SAF 2.7±0.6 arbitrary units. We observed 319 deaths and 590 CVE during mean 5.1±2.2 years of follow-up. After multivariable analysis we identified SAF at baseline as an independent risk factor for CVE (HR 1.13 per standard deviation (SD) increase, 95% CI 1.04 to 1.24, p = 0.006) and ACM (HR 1.17 per SD increase, 95% CI 1.04 to 1.32, p = 0.007). There was no significant change in mean SAF over 5 years but change in SAF over 1 year was independently associated with CVE (HR 1.13 per SD increase, 95% CI 1.03 to 1.23, p=0.01) and ACM (HR 1.24 per SD increase, 95%CI 1.10 to 1.41, p=0.001).

Conclusions: We have identified SAF as an independent risk factor for CVE and ACM in persons with early CKD. These findings suggest that SAF measurements are clinically useful to risk stratify persons with CKD. Further, interventions to reduce AGE accumulation, such as dietary AGE restriction, may reduce cardiovascular risk in CKD but this requires testing in prospective randomised trials.

Funding: Private Foundation Support

FR-PO266

Continuous Ambulatory Blood Pressure Monitoring: A Viable Option in CKD?

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Background: Traditional cuff-based ambulatory blood pressure monitoring (ABPM) is cumbersome and fragments sleep. Continuous ABPM utilizes a simple pulse oximeter and 2-lead electrocardiogram to calculate blood pressure beat to beat from pulse transit time(PTT). While continuous ABPM overcomes the challenges of traditional ABPM, its validity in CKD—a population with a high burden of vascular disease—is unclear.

Methods: Two separate cohorts (20 Veterans and 20 University hospital-based) were enrolled for this study. Inclusion criteria were: age 18-89, MDRD eGFR 15-44, not on dialysis or transplant. Participants underwent simultaneous 24 hour cuff-ABPM (Spacelabs) and PTT-ABPM (Somnomedics). We determined the correlation between 24-hour blood pressure for cuff and PTT-ABPM. We used McNemar's test for correlated proportions to assess the degree of concordance between cuff and PTT-ABPM to determine dipping status (p<0.05 suggests lack of concordance).

Results: Among Veterans, mean age(SD) was 76(9) years, 95% male, mean BMI 31(5) kg/m^2, 95% hypertensive, 60% diabetic and 5% with peripheral vascular disease(PVD). At the University site, mean age(SD) was 67(11) years, 50% male, mean BMI 31(8) kg/m^2, 85% were hypertensive and 35% diabetic. None had PVD. The table below shows, by method, the average number of blood pressure readings, mean 24-hour blood pressure and the correlation between cuff and PTT-ABPM. Among Veterans, there was concordance with systolic dipping(McNemar's p 0.10) but not diastolic dipping(p=0.02). Among University participants, concordance was not observed for diastolic dipping(p=0.02) and the test could not be performed for systolic dipping as none of the PTT-ABPM had dipping though 8 were dippers by cuff-ABPM.

Conclusions: Among Veterans with CKD, PTT-ABPM correlates reliably with cuff ABPM for overall and systolic blood pressure as well as systolic dipping status. Among University CKD patients, PTT-ABPM does not correlate well with cuff-ABPM. Additional validation studies with larger sample sizes are required to confirm our findings.

Funding: Other NIH Support - UL1TR001427, Veterans Affairs Support

	Mean (SD) Number of BP Readings			Mean (SD) 24-hour BP (mmHg)				Correlation between Cuff and PTT ABPM								
	Cuff		PTT	Cuff		PTT		24-hour			Daytime			Nighttime		
Cohort	Day	Night	Overall	SBP	DBP	SBP	DBP	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR
VA	49(16)	19(5)	63,095 (18365)	132 (16)	71 (11)	137 (23)	77 (17)	0.76*	0.54**	0.95*	0.78*	0.54**	0.95*	0.70*	0.52**	0.92*
University	51(12)	17(6)	77136 (18344)	133 (18)	76 (13)	134 (19)	81 (16)	0.65*	0.64**	0.98*	0.63**	0.62**	0.98*	0.68*	0.63**	0.96*

*p<0.002; **p<0.02.

FR-PO267

Association of Low-Density Lipoprotein Cholesterol and Atherosclerotic CVD and Non-Atherosclerotic CVD Hospitalization Rate Across CKD Stages in 2 Million US Veterans

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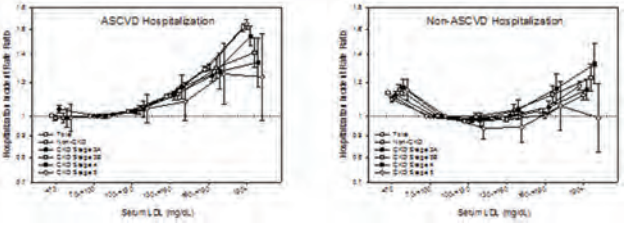
Background: A prior study has demonstrated that risk of myocardial infarction decreased with higher low-density lipoprotein cholesterol (LDL) levels across worsening estimated glomerular filtration rate (eGFR) category. It was postulated that this attenuated risk with progressing chronic kidney disease (CKD) may be attributed to competing risk of non-atherosclerotic cardiovascular disease events (ASCVD).

Methods: In 1,969,797 US veterans with a serum LDL between 2004 and 2006, associations between LDL and ASCVD and non-ASCVD hospitalizations were estimated using Poisson models adjusted for demographics, comorbid conditions, smoking status, use of statins and non-statins, body mass index and albumin across eGFR category (CKD stage).

Results: The cohort consists of 5% female, 14% African American, 19% diabetic, 32% statin-users, and 44% current smokers, with a mean patient age of 64±14 years. The median [IQR] of serum LDL level and eGFR were 103[81,128] mg/dL and 75[60,91] mL/min/1.73m2, respectively. Patients with higher LDL (>100 mg/dL) had an incrementally higher risk of ASCVD hospitalization rate across all CKD stages compared to the reference (LDL 70-<100 mg/dL); however, associations attenuated with higher CKD stage. Patients with low LDL (<70 mg/dL) had a higher risk of non-ASCVD hospitalization rate across all CKD stages. Patients with LDL≥190 mg/dL also had a higher non-ASCVD hospitalization risk across all CKD stages, except CKD stage 5. Risk of non-ASCVD hospitalization with higher LDL increased between non-CKD to CKD stage 4.

Conclusions: In US veterans, higher LDL level was associated with both higher ASCVD and non-ASCVD hospitalization rate across all CKD stages. The magnitude of association with high LDL for ASCVD events increased across worsening CKD stage, and decreased for non-ASCVD events. Further studies are need to understand why elevated LDL may be associated with higher risk of non-ASCVD events compared to risk of ASCVD events in chronic kidney disease.

Funding: Veterans Affairs Support



FR-PO268

Dietary Protein Intake and Outcomes in Patients with CKD

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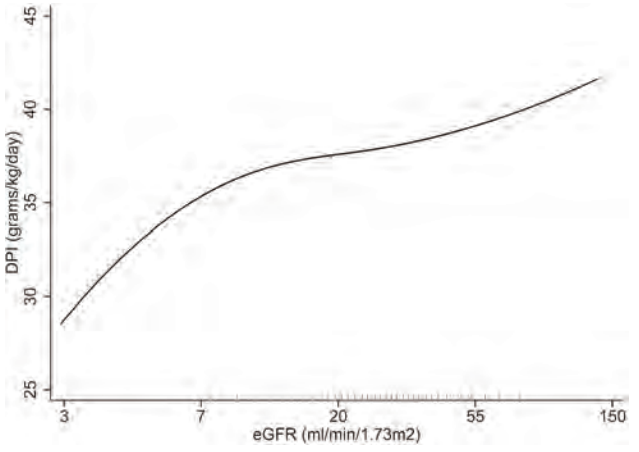
Background: Protein energy wasting is common in patients with CKD, but the trajectory of dietary protein intake (DPI) in patients with worsening CKD and the outcomes associated with DPI in this population are unclear.

Methods: We performed repeated collections of spot urine for the measurement of urine urea nitrogen and creatinine in 605 patients with non-dialysis dependent CKD followed at a single institution. We used the urine urea nitrogen-to-creatinine ratio to estimate daily excretion of urea nitrogen, and the Maroni formula to estimate dietary protein intake (DPI). We examined the association of DPI with estimated GFR using mixed effect models and penalized splines, and the association of baseline DPI with all-cause mortality and ESRD in multivariable adjusted Cox models with adjustment for demographic characteristics, smoking status, eGFR and comorbidities.

Results: Patients were 66±11 years old, 97% were men and 37% were African American. The baseline eGFR was 37±20 ml/min/1.73m^2, 210 patients died (mortality rate, 95%CI: 113/1000PY, 98-129) and 121 patients developed ESRD (65/1000PY, 57-78) over a median follow-up of 3.8 years. Patients underwent a median of 7 urine collections (range: 1-16). Lower eGFR was associated with a linear decrease in DPI (0.92 gm/kgBW/day lower DPI for every 15 ml/min/1.73m^2 lower eGFR, 95%CI: 0.38-1.46, p=0.001), with a steeper decline below an eGFR of ~20 ml/min/1.73m^2 (Figure). Higher baseline DPI was associated with higher mortality (adjusted hazard ratio associated with 1 gm/kgBW/day higher DPI, 95%CI: 1.015, 1.002-1.028, p=0.021) and higher ESRD risk (1.023, 1.006-1.041, p=0.009).

Conclusions: In patients with moderate to advanced CKD, DPI declines with progressive loss of kidney function, and higher DPI is associated with increased risk of all-cause mortality and ESRD.



FR-PO269

Insulin Sensitivity and Systemic Inflammation Are Potential Mediators of the Association Between Serum Uromodulin and Arterial Stiffness Among Nondiabetic Patients with CKD

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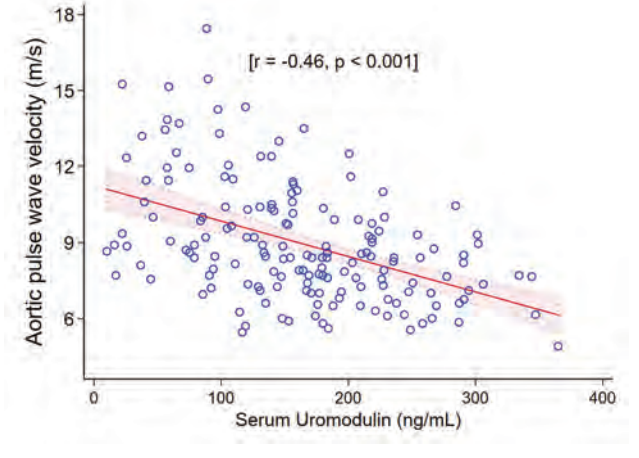
Background: Patients with chronic kidney disease (CKD) have an elevated risk of premature death due to cardiovascular disease (CVD) beyond what is predicted by traditional CVD risk factors. Serum uromodulin (sUmod) is a potential non-traditional CVD risk factor. The relationship between sUmod and subclinical CVD is not well described. We investigated the relationship between sUmod and aortic pulse wave velocity (PWV).

Methods: Participants included 73 CKD and 116 normal GFR patients who underwent a comprehensive clinical assessment including PWV measurement (via applanation tonometry) and clamp-derived insulin sensitivity index (ISI). Biomarkers included sUmod, creatinine-based eGFR and high sensitivity C-reactive peptide (hsCRP). Sequential linear models with robust standard errors were used to examine the relationship between sUmod and PWV and perform mediation analyses.

Results: Mean age was 55 (15) years; 45% were female, 34% African American. sUmod had a significant positive correlation with eGFR ($r = 0.65$; $p < 0.01$) and log ISI ($r = 0.27$, $p < 0.01$) and inverse correlations with log hsCRP ($r = -0.27$; $p < 0.01$) and PWV ($r = -0.46$, $p < 0.01$). A one interquartile range lower sUmod was associated with a 1.45 m/s increase (95% CI: 1.02, 1.89; $p < 0.01$) in PWV in the unadjusted model. Adjustment for demographics and mean arterial pressure attenuated the effect estimate [0.42 m/s; 95% CI: 0.05, 0.79; $p = 0.03$]. Additional adjustment for log hsCRP and log ISI further diminished the sUmod effect [0.18 m/s; 95% CI: -0.18, 0.53; $p = 0.3$].

Conclusions: Declining sUmod levels is associated with increased PWV, a subclinical marker of CVD that reflects arterial stiffness. This relationship appears to be mediated, in part, by systemic inflammation and insulin resistance.

Funding: Veterans Affairs Support



FR-PO270

Ambulatory Blood Pressure Patterns, Cognitive Function, and Frailty in CKD: Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: Hypertension (HTN) is highly prevalent in patients with chronic kidney disease (CKD) as is the risk of cognitive impairment and frailty. Our objective was to determine the association between ambulatory blood pressure (BP) patterns, cognitive impairment and frailty among patients with CKD.

Methods: We performed ambulatory BP monitoring (ABPM) on 1502 participants enrolled in CRIC. We evaluated the following exposures: 1) BP patterns: white-coat, masked, sustained HTN vs. controlled HTN and 2) dipping patterns: reverse, extreme, non dippers vs. normal dippers. Our outcomes included: 1) cognitive impairment: modified mini-mental status (3MS) score <85 for participants <65yrs, score <80 for 65-79 yrs and score <75 for >80yrs and 2) frailty: defined as meeting ≥3 of the following criteria - slow gait speed, muscle weakness, low physical activity, exhaustion and unintentional weight loss. Both outcomes were assessed at the time of ABPM and annually thereafter. Logistic regression models were used to assess the cross-sectional relationship between BP or dipping patterns and cognitive impairment and frailty. For longitudinal analysis, Cox discrete models were used.

Results: Mean age of the participants was 63 yrs, 56% were male, and 39% were Black. 9%(n=129) had cognitive impairment and 18%(n=275) were frail at the time of ABPM. After multivariable adjustment, there was no association between any BP or dipping patterns and prevalent cognitive impairment or frailty. 629 participants had incident frailty and 255 had incident cognitive impairment over a median follow up of 3 yrs. After adjustment, participants with white-coat HTN had 0.6 times the risk of incident frailty compared to controlled HTN [95%CI: 0.4, 0.9]. Participants with reverse dipping had marginally greater incident cognitive impairment compared to normal dippers (HR=1.5, 95% CI: 1, 2.3).

Conclusions: CKD patients with white-coat HTN have lower rates of incident frailty compared to controlled HTN. There was no consistent association between BP or dipping patterns and incident or prevalent cognitive impairment or prevalent frailty.

FR-PO271

Association Between Endogenous Sex Hormones and Kidney Function: Cross-Sectional Findings from the Hispanic Community Health Study/ Study of Latinos (HCHS/SOL)

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Background: The prevalence of end-stage renal disease is higher in males than females, despite the higher prevalence of chronic kidney disease (CKD) among females, suggesting that men are at higher risk of CKD progression. Sex steroid hormones have been proposed as a potential mechanism for these disparities. Few studies have examined the associations between endogenous sex hormone and kidney function.

Methods: We evaluated the cross-sectional associations between serum levels of endogenous sex hormones (luteinizing hormone (LH), follicle stimulating hormone (FSH), sex-hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), estradiol, and testosterone) and measures of kidney function among participants in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos Ancillary Study. The ancillary study inclusion criteria selected male and post-menopausal female participants with normal glucose or prediabetes at baseline. Sex-stratified survey-weighted linear regression models were used to examine if ranked quartile hormone concentrations were associated with estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR), after adjusting for age, ethnicity, body mass index, systolic blood pressure, and fasting blood glucose.

Results: The study included 1,854 participants (mean age 55 years, 33% post-menopausal female, 52% prediabetic, geometric mean UACR 7.8 mg/g, and mean eGFR 93 ml/min/1.73 m^2). Among females, LH and FSH were inversely associated with eGFR (β for highest versus lowest LH quartile= -8.7, 95% CI -13.9, -3.5, $p=0.001$; β for highest versus lowest FSH quartile= -12.4, 95% CI -19.0, -5.7, $p=0.0003$). Among males, LH was inversely associated with eGFR (β for highest versus lowest LH quartile= -5.5, 95% CI -9.4, -1.5, $p=0.01$), and LH and FSH were positively associated with UACR.

Conclusions: In our diverse subsample of Hispanics/Latinos that did not have diabetes, we observed associations of LH and FSH with kidney function measurements, after adjustment for multiple CKD risk factors. Our findings suggest that these gonadotropins may play a role in CKD.

Funding: Other NIH Support - NIEHS R01, NIOSH T42

FR-PO272

Vitamin D Replacement Improves Renal Function, Hemodynamics, and Inflammatory and Morphological Parameters in Vitamin D-Deficient Rats After Renal Ischemia-Reperfusion Injury

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Background: The initial damage after an ischemia/reperfusion injury (IRI) plays an important role in the pathogenesis of acute kidney injury (AKI) and predisposition to CKD. Vitamin D deficiency (VDD) is associated with hemodynamic changes, activation of inflammatory pathaways and renal disease progression following IRI-AKI. Conversely, vitamin D sufficiency may be considered a protective factor. We evaluated the effect of vitamin D replacement (VR) in IRI rats under VDD.

Methods: We performed bilateral 45 min IRI on day 30 in all groups. Male Wistar rats were randomized into three groups: **(1) IRI** [fed a standard diet (SD) for 120 days]; **(2) VDD+IRI** [fed a vitamin D-free diet (D) for 120 days]; and **(3) VDD+IRI+R (**fed a D diet for 30 days and just after IRI, on day 31, we reintroduced the SD). We evaluated inulin clearance (Cin); mean arterial pressure (MAP); renal blood flow (RBF); renal vascular resistance (RVR); proteinuria; plasma levels of 25(OH)D and aldosterone as well as renal tissue levels of collagen 3 (COL3) and MCP1 by ELISA; and immunoblotted for VDR.

Results: VDD+IRI+R animals had 25(OH)D levels restored (~42 ng/mL). VR improved renal function and hemodynamic parameters. Also, decreased proteinuria and the amount of MCP1 and COL3 in renal tissue (Table 1).

Conclusions: Our study suggests that VR improved the recovery of renal fuction, hemodynamics, inflammatory and morphologycal features in IRI-AKI associated with VDD. Thus, vitamin D monitoring and replacement should be considered in renal patients.
Financial Support: FAPESP 2018/04930-6, 2018/12297-1; CNPq 302599/2018-5.

Funding: Government Support - Non-U.S.

Table 1

	IRI	VDD+IRI	VDD+IRI+R
Cin (mL/min/100g BW)	0.47±0.02	0.46±0.03	0.57±0.02cf
MAP (mmHg)	124±2.5	142±3.7a	122±2.5d
RBF (mL/min)	7.9±0.43	6.0±0.03c	8.8±0.49e
RVR (mmHg/mL/min)	16.01±1.07	22.37±0.38a	13.93±0.85d
Aldosterone (pg/mL)	2172±328	3612±662c	1753±167e
Proteinuria (mg/24 h)	10.14±0.64	11.99±0.83	9.13±0.74f
VDR (%)	100.8±3.9	58.9±3.6a	148.3±5.5ad
COL3 (ng/ug protein)	2.15±0.13	2.64±0.27	1.95±0.06f
MCP1 (pg/ug protein)	2.82±0.25	3.76±0.38c	2.81±0.15f

Data are expressed as mean±SEM. BW: Body weight. a p<0.001, c p<0.05 vs IRI; d p<0.001, e p<0.01, f p<0.05 vs VDD+IRI.

FR-PO273

Association of Body Mass Index and Clinical Outcomes of Advanced CKD in T2DM: A Population-Based Analysis from the National Health Security System

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Background: The reversal of the obesity–mortality association has been very robust in patients with end-stage renal disease, but a limited number of studies show conflicting results in patients with non-dialysis-dependent chronic kidney disease (NDD-CKD). Several earlier studies found that the association of body mass index (BMI) with CKD is not straightforward in patients with type 2 diabetes mellitus (T2DM). The relationship of obesity with CKD has not been fully explored in Asian populations.

Methods: This study evaluated patients aged ≥18 years with T2DM obtained from the largest database of the National Health Security System (NHS) of Thailand from 2011to 2014. We aimed to determine the apparent optimum BMI range based on the World Health Organization's (WHO) criteria concerning the risk of advanced CKD (stages G4 and G5).

Results: With regard to the 27,392 patients, 62% were female, 3% had CKD stage G4 and 1% had CKD stage G5. The mean (±SD) age of the patients was 64±12years old. Mean BMI was 24.9±4.5 kg/m^2. The prevalence of having advanced CKD by BMI groups wasBMI (15–20 kg/m^2) 6.5%, BMI (20–25 kg/m^2) 4.3% (as reference), BMI (25–30 kg/m^2) 3.1%, and BMI (>30 kg/m^2) 2.6%. The multivariate analysis identified the odds ratio (OR) of BMI (adjusted OR; 95% confidence interval [CI]; *P*-value) as an independent risk factor for advanced CKD as 1.39; 1.15–1.6; 0.001, 0.8; 0.67–0.94; 0.008, and 0.75; 0.58–0.97; 0.03, respectively (**Figure 1**).

Conclusions: Patients with advanced CKD in public healthcare practices have strikingly higher rates of low BMI. The negative association of BMI with CKD could reflect reverse causality. This is the first epidemiological paradox that may of concern and be reported in a Southeastern Asian population.

Funding: Government Support - Non-U.S.

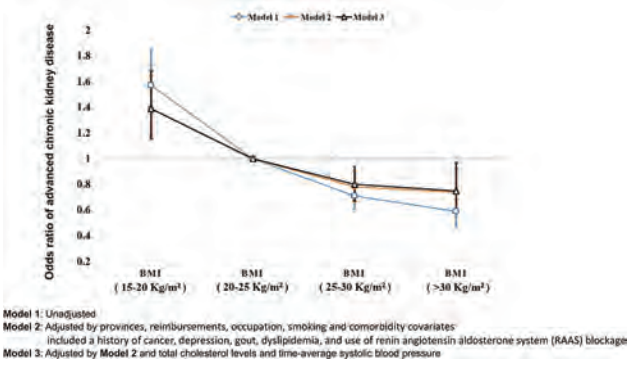

Figure1 The odds ratio (OR) of advanced chronic kidney disease between body mass index groups in Diabetes Mellitus type 2 patients by the three models adjustment.

FR-PO274

Metabolic Acidosis Is an Independent Predictor of Adverse Renal Outcomes and Higher Costs in Patients with CKD

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Background: Metabolic acidosis (MA) is a risk factor for chronic kidney disease (CKD) progression, but less is known about its effect on health care costs and resource utilization. We describe the association between MA, adverse renal outcomes and costs in non-dialysis patients with CKD stages 3-5.

Methods: De-identified medical records (Optum® EMR), 2007–2017 were used to identify non-dialysis CKD patients with ≥2 serum bicarbonate test values 28–365 days apart, ≥3 eGFR values >10 and <60 mL/min/1.73m^2 and ≥2 years of post-index data or death. Patients were followed for 2 years for the composite outcome (DD40) of death, dialysis, renal transplant, or eGFR decline ≥40%. Metabolic acidosis and normal serum bicarbonate groups were defined by 2 serum bicarbonate values between 12 and <22 mEq/L and 22–29 mEq/L, respectively. General linear regression models in a subset of patients with linked medical claims established predicted costs, which were applied to the larger EMR population based on demographic and clinical factors. Logistic and generalized linear regression models assessed serum bicarbonate as a predictor of DD40 outcomes and costs (log) respectively, controlling for age, sex, race, eGFR, log albumin-to-creatinine ratio, diabetes, hypertension, heart failure, and Charlson comorbidity score.

Results: 51,558 patients qualified for this longitudinal observational study. Compared to patients with normal serum bicarbonate, patients with MA experienced CKD progression at much higher rates, (DD40 rates 48% vs. 17%, p<0.0001) and significantly higher per patient per year costs, ($65,152 vs. $24,681, p<0.0001). This pattern was consistent across all stages of CKD, except stage 5. Serum bicarbonate independently predicted DD40 events and costs; odds ratio of CKD progression (DD40) for each 1 mEq/L increase in serum bicarbonate was 0.87, (CI: 0.866-0.879); parameter estimate -0.076 (p<0.0001) for costs.

Conclusions: In this analysis of >51,000 non-dialysis CKD patients followed for two years, patients with metabolic acidosis had higher rates of adverse renal outcomes and higher costs compared to patients with normal serum bicarbonate. Each 1 mEq/L increase in serum bicarbonate was associated with a 13% decrease in 2-year DD40 events and a 7% decrease in monthly costs.

Funding: Commercial Support - Tricida, Inc.

FR-PO275

Association of Total CO2 Levels with Albuminuria Progression in Patients with CKD: Results from the KNOW CKD Cohort

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Background: Metabolic acidosis is a common manifestation of CKD and contributes to various adverse effects. Although previous animal studies demonstrated that dietary acid induces an increase in proteinuria, the association between total CO2 and albuminuria progression have not extensively investigated in clinical studies. We aimed to identify the relationship between total CO2 levels and albuminuria progression in a multicenter prospective cohort.

Methods: A total of 503 patients with at least two urinary albumin-to-creatinine ratios (UACR) measurements 1 year apart and no change in the dose of ACEi/ARB were enrolled. Participants were divided into the quartiles based on the time-averaged total CO2 levels during the 1-year follow-up; Q1(<24.7 mmol/L), Q2 (24.7-26.6 mmol/L), Q3 (26.7-28.5 mmol/L), and Q4(>28.6 mmol/L). We examined the albuminuria progression which is defined as A1 (<30 mg/g Cr) to A2 (30-300 mg/g Cr), A2 to A3 (>300mg/g Cr), and A1 to A3 according to the quartiles of total CO2.

Results: At baseline, 159 patients had A1 albuminuria, and 344 patients had A2 albuminuria. After 1 year follow-up, 96 patients revealed albuminuria progression; 26 from A1 to A2, 62 from A2 to A3, and 4 from A1 to A3. The percentage of subjects

with albuminuria progression was higher in upper quartiles (P for trends <0.001). In multivariable logistic regression, the highest quartile of total CO2 was also significantly less likely associated with albuminuria progression compared with the lowest quartile (adjusted OR 0.31; 95% CI 0.13-0.77). In addition, multivariable linear regression using total CO2 as a continuous variable and UACR fold change also showed significant negative associations (β=-0.22, *P*=0.009).

Conclusions: In patients with CKD, total CO2 levels were independently associated with albuminuria progression over the 1-year interval. These results may suggest that high total CO2 levels could have beneficial effects on proteinuria progression in CKD patients even within the normal range of total CO2 levels.

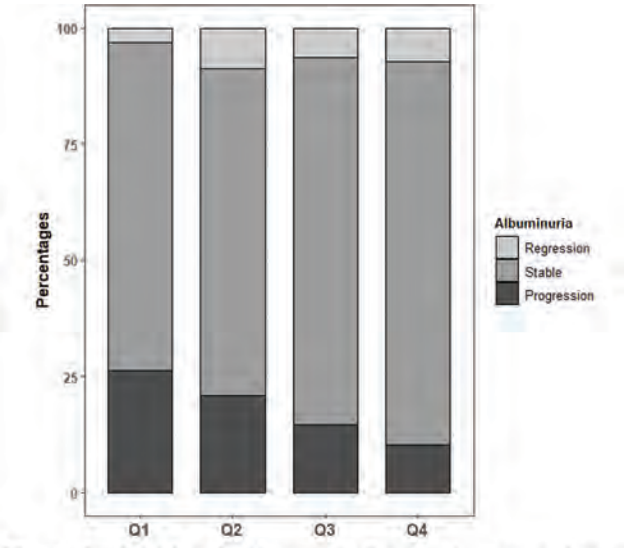

Figure 1. A higher incidence of albuminuria progression is associated with lower quartiles of total CO2 levels in patients with CKD. Q1 < 24.67 mEq/L, Q2=24.67-26.67 mEq/L, Q3=26.67-28.05 mEq/L, Q4>28.05 mEq/L.

FR-PO276

Interaction Between Alcohol Intake and Diabetes in Relation to the Risk of ESRD in the Singapore Chinese Health Study

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Background: The relationship between alcohol intake and risk of end-stage renal disease (ESRD) is controversial. Moreover, whether the association is modified by diabetes status is unknown.

Methods: We examined the association between alcohol intake and risk of ESRD in the Singapore Chinese Health Study, a prospective population-based cohort of 63,257 adults aged 45-74 years at recruitment (1993-1998). Information on alcohol intake, diet, medical history and other lifestyle factors was collected at recruitment. We identified 1,217 ESRD cases via linkage with National Singapore Renal Registry through 2015. Cox proportional hazards regression method was used to estimate hazard ratios (HRs) and 95% confidence interval (CI) of ESRD in relation to alcohol intake by diabetes status over an average 17.5 years of follow-up.

Results: Among the participants without diabetes at baseline, monthly to weekly alcohol intake was associated with a decreased risk of ESRD (HR 0.69, 95 % CI 0.55-0.88) compared to the non-drinkers, whereas the reduced risk was no longer significant among the participants with diabetes ($P_{interaction}$=0.21). Comparatively, alcohol intake with ≥2 drinks/day was significantly associated with an increased risk of ESRD compared to the abstainers among the diabetic patients (HR 2.12, 95% CI 1.19-3.78) but not associated with the risk among those without diabetes ($P_{interaction}$=0.02). Presence of heavy alcohol drinking and diabetes was associated with a 12-fold increased risk of ESRD compared with the absence of both factors (HR 12.0, 95% CI 7.00-20.7).

Conclusions: In conclusion, low-dose alcohol intake may have potential renal protective effect among individuals without diabetes. However, alcohol intake with ≥2 drinks/day could act synergistically with diabetes in increasing ESRD risk.

Funding: Other NIH Support - R01 CA144034 and UM1 CA182876, Government Support - Non-U.S.

FR-PO277

Progression of Diabetic Retinopathy and Declining Renal Function in Patients with Type 2 Diabetes

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Background: Diabetes mellitus (DM) causes microvascular complications that are major causes of morbidity and mortality. Diabetic retinopathy (DR) is an important microvascular complication and is the most common cause of preventable blindness in adults. Diabetic nephropathy is a leading cause of chronic kidney disease (CKD). The retina and the kidney share similar microvascular complications resulting from DM. Although many cross-sectional studies have reported associations between renal function and prevalent DR, this might be the result of enrolling patients with long disease durations. Therefore in this study, we investigated how declining renal function affects on DR progression of patients with type 2 diabetes and whether patients with decreased renal function need evaluation of DR status.

Methods: We enrolled 1527 patients with type 2 diabetes from the diabetes clinic in the Department of Endocrinology of Kangnam Sacred Heart Hospital who underwent fundus photographic examinations for DR and whose renal profiles were studied between August 2006 and February 2014. The presence of DR was assessed by an expert ophthalmologist using dilated fundoscopy. Patients were classified into the following categories: (1) normal: no apparent sign of DR; (2) non-proliferative DR (NPDR); (3) proliferative DR (PDR) according to the Global Diabetic Retinopathy Project Group. The presence and severity of DR in a participant were determined based on the eye showing the worst retinopathy. DR progression was defined as a change either from no DR progress to NPDR or from NPDR to PDR.

Results: The baseline prevalence of non-proliferative DR (NPDR) and proliferative DR (PDR) was 26.5% and 14.7%, respectively. The mean period for follow-up fundus exams was 4.0 ± 2.0 years. Among 1303 patients with no DR and NPDR, 134 (10.3%) patients progressed to NPDR or PDR. The progression group had longer duration of diabetes, higher fasting plasma glucose, higher HbA1c and a higher rate of > 20% decline in eGFR during the follow-up period. After multivariate analysis, > 20% decline in eGFR was an independent risk factor for progression of DR in patients with NPDR.

Conclusions: Decrease of renal function was associated with progression of DR, especially in patients with NPDR. This result supports the notion that an individualized screening schedule according to the individual patient's risk might be needed.

FR-PO278

Prevalence and Prognostic Significance of Systolic Orthostatic Hypotension in CKD

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Background: The prevalence of orthostatic hypotension (OH) and its prognostic significance is not well known in patients with chronic kidney disease (CKD). The aim of this study is to determine the prevalence and clinical factors associated with OH, and whether it is associated with risk of adverse kidney or cardiovascular outcomes in patients with CKD.

Methods: Data from the Chronic Renal Insufficiency Cohort study, a multi-center prospective study of subjects with mild to moderate CKD, were used. OH was defined as ≥20 mmHg decrease in systolic blood pressure in the standing compared to the seated position. Multi-variable logistic regression analyses were performed to identify factors associated with OH. Cox regression analyses were performed to examine the association between OH and renal outcomes (composite of end-stage renal disease [ESRD] and/or 50% decline in GFR), ischemic cardiovascular disease (CVD; composite of myocardial infarction, stroke, or peripheral artery disease), heart failure (HF) and all-cause mortality.

Results: The mean age of the study population (n=3873) was 58.2 (±11 SD) years, and mean estimated GFR was 42.9 ml/min/1.73m^2 (±13.5); 48.0% had diabetes. OH was present in 180 (6.9%) patients. In adjusted cross-sectional analyses, Hispanic ethnicity (odds ratio (OR): 1.75, 95% CI: [1.11,2.76]), diabetes (OR: 2.04, 95% CI: [1.37,3.06]), lower body mass index (OR: 0.92, 95% CI: [0.89,0.94] per 1 kg/m^2), elevated total cholesterol (OR: 1.01, 95% CI: [1.00,1.01] per 1 mg/dL), and beta-receptor blocker use (OR: 1.51, 95% CI: [1.05,2.2]) were associated with OH. After a median follow up of 8 years, models adjusted for demographic and clinical factors demonstrated that OH was independently associated with higher risk of renal outcomes (hazard ratio [HR]: 1.40, 95% CI: 1.10,1.78), but not ischemic CVD (HR: 1.18, 95% CI: 0.82,1.69), HF (HR: 1.37, 95% CI: 0.93,2.02) or all-cause mortality (HR: 1.00, 95% CI: 0.73,1.37).

Conclusions: Systolic OH was seen in 6.9% of participants in this study population with mild-moderate CKD. Several clinical and demographic factors were associated with higher prevalence of OH. The presence of OH was independently associated with higher risk of adverse renal outcomes, but not ischemic CVD, HF or mortality.

Funding: NIDDK Support

FR-PO279

Association of Pre-Diabetes with CKD Progression and Adverse Cardiovascular Outcomes in Patients with CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study

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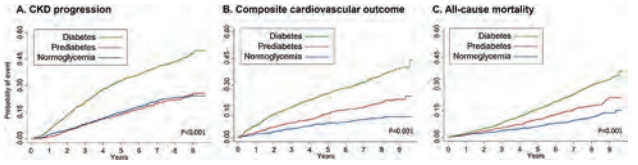
Background: Despite our understanding of diabetes (DM) as an established risk factor for renal and cardiac complications in CKD, the prognostic significance of prediabetes in this population remains largely unknown. We aimed to evaluate the association of prediabetes with CKD progression, adverse cardiovascular events and all-cause mortality in patients with CKD.

Methods: Participants of the Chronic Renal Insufficiency Cohort (CRIC) were categorized as having normoglycemia, prediabetes or DM according to fasting plasma glucose, HbA1c and treatment with anti-diabetic drugs at baseline. Adjusted Cox proportional hazards models (clinical variables, eGFR, 24-h urine protein, hematocrit and serum albumin) were fit to estimate the association of prediabetes and DM (versus normoglycemia) with CKD progression (development of ESRD or 50% decline in eGFR to ≤15 ml/min/1.73 m^2), a composite cardiovascular outcome (congestive heart failure, myocardial infarction or stroke) and all-cause mortality.

Results: Of the 3,701 individuals analyzed, 945 were classified as normoglycemic, 847 had prediabetes and 1909 had DM. Median follow-up was 7.5 years. While prediabetes was not associated with the risk of CKD progression (HRadj 0.96, 95% CI 0.76-1.21), it was associated with a 39% higher risk of the composite cardiovascular outcome (HRadj 1.39, 95% CI 1.06-1.83) (Figure 1) and a trend towards an increased risk of all-cause mortality (HRadj 1.28, 95% CI 0.99-1.67). Patients with DM had an increased risk of CKD progression (HRadj 1.38, 95% CI 1.12-1.70), composite cardiovascular outcome (HRadj 1.65, 95% CI 1.28-2.13) and all-cause mortality (HRadj 1.55, 95% CI 1.21-1.97).

Conclusions: In patient with CKD, prediabetes was not associated with CKD progression but was associated with an increased risk of adverse cardiovascular outcomes.



Kaplan-Meier curves for chronic kidney disease progression (A), composite cardiovascular outcome (B) and all-cause mortality (C) in participants with normoglycemia, prediabetes or diabetes.

FR-PO280

Association of Serum Triglycerides and Mortality Across Albuminuria Stages Among US Veterans

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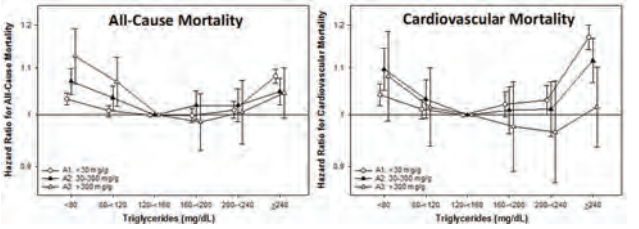
Background: Elevated serum triglycerides (TG) are a risk factor for mortality in the general population, however the relationship is less clear among chronic kidney disease (CKD) patients. Prior studies have evaluated the relationship of TG with mortality in CKD with estimated glomerular filtration rate (eGFR). However, data is lacking on how albuminuria, or urinary albumin-creatinine ratio (UACR), may impact the TG-mortality association.

Methods: Our cohort comprised 994,338 US veterans with a TG measurement between 2004-2006 and were followed until 2014. Albuminuria or UACR prior to TG measurement were extracted either as a calculated ratio, or via dipstick methods. We used Cox proportional hazard models with adjustments for demographics, comorbidities, body mass index and albumin levels to evaluate the association of TG with all-cause and cardiovascular (CV) mortality stratified by UACR groups.

Results: Mean (±SD) cohort age was 63±14 years old, with a median [IQR] TG of 128[87,192] mg/dL. A majority of patients had low levels of UACR <30 mg/g, whereas 2% had high levels of UACR >300 mg/g. The proportion of patients with UACR>300 mg/g increased with increasing TG. We observed a slight U-shaped association between TG and all-cause and CV mortality, among UACR <30 mg/g and UACR 30-300 mg/g stages. In particular, high TG ≥240 mg/dL were associated with the highest risk of CV mortality compared to TG 120-<160 mg/dL among those with UACR<30 mg/g [HR [95%CI]: 1.17[1.14, 1.20]]. These associations were incrementally lower for UACR 30-300 mg/g. Among UACR >300 mg/g patients, higher TG was associated with an even lower to null relationship with CV mortality. For low TG <80 mg/dL mortality risk estimates were higher for higher UACR stages, particularly for all-cause mortality.

Conclusions: We observed a U-shaped association between TG with all-cause and CV mortality among patients with UACR ≤300 mg/g, while TG-CV mortality associations for UACR>300 were weaker. Further studies are needed to evaluate how albuminuria may impact cardiovascular risk with elevated TG.

Funding: Veterans Affairs Support



FR-PO281

Trends of Obstructive Sleep Apnea (OSA) Among US Veterans with and Without CKD

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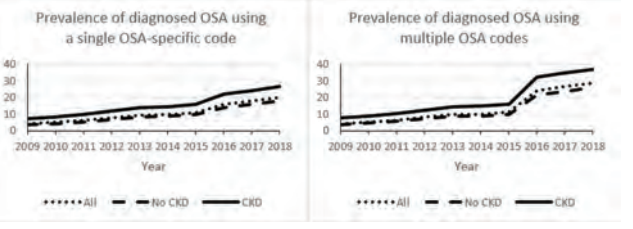
Background: Increasing attention has been paid to sleep problems among patients with CKD. OSA is one of the most common sleep-breathing disorders but is often under-recognized, particularly among persons with CKD. We examined trends in OSA by CKD status over the past ten years.

Methods: The study population were outpatients and inpatients in the Veterans Health Administration from FY2009-18, who were alive at the end of each fiscal year and aged >18 at the start of that year. Crude 1-year period prevalence (PP) of OSA was computed as the number of OSA cases identified from medical records in that year, divided by the number of persons in the study population that year. CKD was defined by at least one of 3 criteria: 1) a diagnostic ICD-9/10-CM code for CKD, 2) estimated glomerular filtration rate <60 ml/min/1.73m^2, or 3) albumin-to-creatinine ratio >30 mg/g. Two definitions of OSA were used: one based on a single ICD-9-CM or ICD-10-CM code (327.23 or G47.33); and one based on multiple ICD-9/10-CM codes, including CPAP treatment and organic sleep apnea.

Results: Throughout the study period, the 1-year PP of OSA was higher in CKD than non-CKD patients. Using either OSA definition, the PP in both groups increased gradually from FY2009 to FY2015, rose more sharply to FY2016, then increased gradually again to FY2018. The use of multiple ICD codes increased the PP by approximately15% throughout the decade. By FY2018, in patients with CKD, the PP rose to 26.5% using a single ICD code and to 36.8% using multiple codes

Conclusions: The gradual increase in the crude PP of diagnosed OSA in VA patients both with and without CKD may be attributable to the increasing incidence of OSA due to changes in OSA risk factors such as obesity and comorbidities, and likely to the increased detection of OSA due to greater awareness of the condition. The sudden increase in OSA PP in FY2015-16 probably resulted from the switch from ICD-9-CM to ICD-10-CM coding. Further studies are needed to document and explain OSA prevalence trends in veterans and other populations.

Funding: Other U.S. Government Support



FR-PO282

The Relationship Between Thyroid Status and Kidney Function Among 24 Million Patients in the National OptumLabs Data Warehouse

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Background: Experimental data suggest hypothyroidism contributes to the development of chronic kidney disease (CKD) due to alterations in kidney structure and function. We thus examined the relationship between thyroid status defined by serum thyrotropin (TSH) levels with estimated glomerular filtration rates (eGFRs) in a large US cohort.

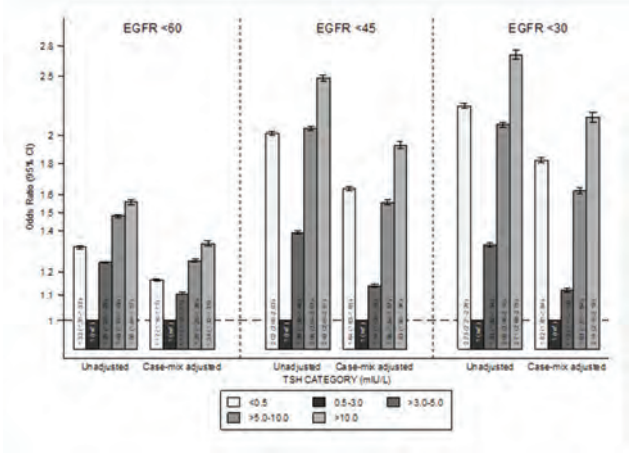
Methods: We examined the association of thyroid status with kidney function using the OptumLabs® Data Warehouse (OLDW), which contains administrative claims data

including medical claims and eligibility information from a large national US health insurance plan and electronic health record data from a nationwide network of provider groups. In patients who underwent ≥1 TSH and ≥1 eGFR measure(s) within 90-days over 2007-2017, we examined associations between TSH and severe, moderate-to-severe, and moderate kidney dysfunction (eGFR <30, <45, and <60 ml/min/1.73m^2, respectively) using logistic regression.

Results: In 24,103,735 patients who met eligibility criteria, 18.6% had eGFRs consistent with moderate, moderate-to-severe, or severe kidney dysfunction. Incrementally higher TSH levels of >3.0-5.0, >5.0-10.0, and >10.0mIU/L were associated with increasingly higher risk of severe kidney dysfunction (ref: 0.5-3.0mIU/L): adjusted ORs (95%CI) 1.12 (1.11-1.3), 1.63 (1.61-1.64), and 2.14 (2.10-2.18), respectively. Lower TSH levels in the hyperthyroid range (<5.0mIU/L) were also associated with severe kidney dysfunction: adjusted OR (95%CI) 1.82 (1.81-1.84). Sensitivity analyses showed similar findings for moderate-to-severe and moderate kidney dysfunction.

Conclusions: In a nationally representative cohort of patients, both hypo- and hyperthyroidism were associated with kidney dysfunction. Further studies are needed to determine underlying mechanisms, and whether correction of thyroid status improves kidney function in this population.

Funding: Commercial Support - OptumLabs



FR-PO283

Development of Malignant Disease Associated with Glomerular Hyperfiltration in Asian Population

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Background: Renal hyperfiltration (RHF) is associated with all-cause mortality. Herein, we evaluated the association between RHF and the development of malignant diseases, which is the most common cause of mortality.

Methods: We retrospectively reviewed the National Health Insurance Service (NHIS) database for a people who received nationwide health check-up in 2009. The population with age <18 years old, estimated glomerular filtration rate (eGFR) <60ml/min/m^2, presence of history for malignant disease or renal disease was excluded. RHF was defined as eGFR ≥95 percentile with age- and sex-matching. The primary outcome was a risk for development of the malignant diseases. Site-specific malignant disease was categorized according to body systems and organs using ICD-10 diagnostic codes. We used Cox regression analysis to identify relative risk ratio with multiple adjustments using age, sex, body mass index, income, and smoking status.

Results: A total of 1,953,123 examiners were included in this study with 1,853,114 (94.9%) and 100,009 (5.1%) in RHF negative and positive group, respectively. Overall cancer risk was significantly higher in the RHF group (adjusted HR 1.12, 95% CI 1.07-1.16, p <0.0001). Type-specific cancer risk was increased in digestive, stomach, colorectal, liver, uterus and ovary, multiple myeloma, and leukemia in RHF group. In the subgroup analysis according to sex, risks of cancer in digestive, stomach, colorectal, liver, respiratory and lung were higher in male with RHF. On the contrary, digestive, stomach, uterus and ovary, multiple myeloma, and leukemia showed significantly increased risk for female with RHF. After adjusting the variables including age, sex, smoking, drinking, physical activity, economic status, BMI, systolic blood pressure, eGFR, history of hypertension and diabetes, RHF was significantly associated with the development of digestive (aHR 1.12, 95% CI 1.05-1.19, p<0.001), stomach (aHR 1.16, 95% CI 1.05-1.29, p=0.005) and colorectal cancer (aHR 1.16, 95% CI 1.01-1.33, p=0.04).

Conclusions: The cancer risk in digestive organ was increased in an Asian population with RHF. Healthcare providers should consider the RHF could have a relationship with the development of malignant disease, especially in digestive organ.

FR-PO284

Determinants of Extracellular Volume Status in CKD Stage 3-5: A Cross-Sectional Study of Bioimpedance Analysis

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Background: Extracellular volume expansion predicts higher mortality and adverse cardio-renal outcomes in patients with chronic kidney disease (CKD). The higher value of the extracellular water (ECW) to total body water (TBW) ratio (ECW/TBW) measured by bioimpedance analysis (BIA) is a marker of extracellular volume expansion. However, the determinants of the ECW/TBW in CKD stage 3-5 have not yet been fully evaluated.

Methods: One hundred and one non-dialysis CKD patients (stage 3-5) were enrolled in this study. Body fluid volume including intracellular water (ICW), ECW and TBW was measured by bioelectrical impedance analysis device (InBody S10).

Results: Average values are the following: age 63.7±14.5 years, male 61.4%, body mass index (BMI) 24.8±4.7, systolic blood pressure 135±20 mmHg, estimated glomerular filtration rate (eGFR) 33.3±16.4 mL/min/1.73m^2, hemoglobin 11.6±2.3 g/dL, serum albumin 3.4±0.8 g/dL and the ECW/TBW 0.393±0.028 (normal range 0.36-0.39). The ECW/TBW correlated positively with age (r=0.373, p=0.0001), systolic blood pressure (r=0.248, p=0.014), and ECW (r=0.336, p=0.0006), while it correlated negatively with hemoglobin (r=-0.328, p=0.001), eGFR (r=-0.398, p<0.0001) and serum albumin (r=-0.533, p<0.0001). On the other hand, the ECW/TBW was not correlated with BMI (r=0.087, p=0.385), serum Na (r=-0.074, p=0.463), ICW (r=-0.146, p=0.146) and TBW (r=0.056, p=0.581), respectively. A stepwise multiple regression analysis revealed that serum albumin (p<0.0001), age (p=0.0002) and eGFR (p=0.0002) were independent determinants of the ECW/TBW.

Conclusions: Low serum albumin, high age and low eGFR are independently associated with higher extracellular volume status in CKD stage 3-5. Further prospective studies are needed to evaluate the impact of extracellular volume status and these factors on long-term outcomes.

Funding: Private Foundation Support

FR-PO285

Deoxycholic Acid (DCA) and Coronary Artery Calcification (CAC) in the Chronic Renal Insufficiency Cohort (CRIC)

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Background: Circulating levels of the secondary bile acid, DCA, are elevated in chronic kidney disease (CKD). In a small cohort of individuals with CKD 3b-4, higher plasma DCA was associated with prevalent CAC. Whether circulating DCA levels are associated with CAC prevalence, incidence, and progression in a large diverse CKD population is unknown.

Methods: We cross-sectionally and longitudinally evaluated the association between fasting serum DCA levels and CAC among 1057 CRIC participants using multivariable-adjusted regression models. CAC was measured in Agatston units at baseline and follow-up.

Results: Mean age was 57±12 years, 47% were female, and 41% were black. At baseline 676 (64%) had any CAC (CAC score >0 Agatston units), 405 (38%) had CAC ≥100, and 236 (22%) had CAC ≥400. In cross-sectional analyses, multivariable models adjusted for demographics and clinical factors including statin use showed no significant association between circulating DCA levels and CAC >0 compared to no CAC (CAC=0) (prevalence ratio per 1-SD increase in log DCA: 1.09, 95% CI 0.92-1.28). Similar results were observed when baseline CAC thresholds of ≥100, ≥200, ≥300, and ≥400 vs. no CAC (CAC=0) were used. 672 participants had follow-up CAC measurements. Over a mean follow-up of 3.2±0.6 years, of the 277 (41%) participants with no baseline CAC (CAC=0), 60 (22%) developed incident CAC (CAC >0). In the fully adjusted model, DCA was not significantly associated with incident CAC (CAC >0) (incidence ratio per 1-SD increase in log DCA: 1.06, 95% CI 0.83-1.34). Of the 395 (59%) participants with any baseline CAC (CAC >0), 20% and 7% had an increase of ≥100 and ≥200 Agatston units/year, respectively, at follow-up. In the fully adjusted model, DCA was not associated with CAC progression (risk ratio for increase in ≥100 and ≥200 Agatston units/year per 1-SD increase in log DCA: 1.08, 95% 0.87-1.34 and 1.18, 95% CI 0.77-1.82, respectively).

Conclusions: In CRIC participants, DCA was not associated with prevalent, incident, or progression of CAC.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO286

Increasing and Declining Estimated Glomerular Filtration Rates Predict Mortality Among a Community-Based Cohort

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Background: Serum creatinine based glomerular filtration rate (eGFR) is widely used to estimate the true glomerular filtration rate (eGFR) and as a tool for predicting risks of end-stage kidney disease (ESKD) and/or death in the field of public health. Most studies have focused on populations with a declining eGFR.

Methods: We enrolled a Japanese community-based cohort (N = 321,028; age 63.0 ± 7.8 years; men, 41.2%) via the public health check-up system. The follow-up period was 1,566 ± 501 days. The participants were classified into 12 annual eGFR change rate groups. Cox regression analyses were performed to calculate risks for all-cause mortality as the primary outcome measure. Stratified analyses were also conducted according to the level of dipstick proteinuria, annual body weight (BW) change of <0% and ≥0%, baseline eGFR ≥60 mL/min/1.73 m^2 and 15–59 mL/min/1.73 m^2, age ≤64 years old and >65 years old, sex, and the presence or absence of diabetes.

Results: There were 13.8% participants with an eGFR of 15–59 mL/min/1.73 m^2, and 8.9% reported a history of cardiovascular disease (CVD) Thus, our cohort was not at a high risk of both ESKD and CVD. During the study period, 2,604 (0.81%) died. Multivariable Cox regression analysis showed that increasing, as well as declining, eGFR was significantly associated with mortality when an annual eGFR change rate of 0%–4.9% was set as the reference range (U-shaped pattern). For example, the adjusted hazard ratio and 95% confidence interval of an annual eGFR change rate of ≥25% and ≤−25% was 14.17 (10.40–19.31) and 13.84 (9.69–19.76), respectively. Stratified analyses revealed that every stratification still demonstrated a significant U-shaped relationship, even though participants were grouped by dipstick proteinuria level, annual BW change, age, eGFR level, age, sex, and diabetes.

Conclusions: Increasing as well as declining eGFR is an important factor in patient mortality. Proteinuria, BW change, baseline eGFR level, age, sex, and diabetes did not affect this relationship.

FR-PO287

Albuminuria Is a Biomarker for Severity of White Matter Hyperintensities on Brain MRI in a General Elderly Population of Japanese: The Hisayama Study

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Background: White matter hyperintensities (WMH), which are often observed in brain magnetic resonance imaging (MRI) among the elderly, have been reported to be associated with an increased risk of symptomatic stroke. Albuminuria and reduced estimated glomerular filtration rate (eGFR) have been acknowledged to be independent risk factors for stroke, but the studies addressing the association of albuminuria and reduced eGFR with WMH volume in general Japanese elderly populations are limited.

Methods: A total of 1,214 community-dwelling Japanese subjects aged ≥65 years underwent brain MRI scans and a comprehensive health examination in 2012. Urine albumin-creatinine ratio (UACR) was categorized as normoalbuminuria (<30 mg/g),microalbuminuria (30-299 mg/g), and macroalbuminuria (≥300 mg/g). Subjects with normoalbuminuria were further divided into the following tertile categories: low-normal (≤7.3 mg/g), medium-normal (7.4-12.8 mg/g), and high-normal (12.9-29.9 mg/g). Reduced eGFR was defined as eGFR <60 mL/min per 1.73 m2. The severity of WMH was evaluated with the ratio of WMH volume to intracranial volume (WMHV/ICV). The association of UACR levels or reduced eGFR with WMHV/ICV ratio was estimated using the analysis of covariance.

Results: The age- and sex-adjusted geometric mean value of the WMHV/ICV ratio increased significantly with higher UACR levels (low-normal: 0.19%, medium-normal: 0.21%, high-normal: 0.25%, microalbuminuria: 0.25%; macroalbuminuria: 0.30%; P for trend <0.001). This association remained significant after additional adjustment for hypertension, diabetes mellitus, hypercholesterolemia, body mass index, eGFR, electrocardiogram abnormalities, smoking habits, alcohol intake, regular exercise, and cerebrovascular lesions on MRI (P for trend =0.001). In contrast, there was no clear association between reduced eGFR and WMHV/ICV ratio.

Conclusions: Our data suggest that albuminuria, even within the normal range, is a useful biomarker for estimating the severity of WMH in a general elderly population of Japanese.

FR-PO288

Body-Weight Fluctuation Is Associated with Rapid Kidney Function Decline

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Background: The association between body-weight fluctuation and renal outcomes is unclear. We aimed to evaluate the effects of body-weight fluctuation on the rate of renal function deterioration in a prospective cohort of individuals with normal renal function.

Methods: Data were obtained from the Korean Genome and Epidemiology Study (KoGES). Body-weight fluctuation was determined using average successive variability (ASV), which was defined as the average absolute body weight change using repeated measurements for all participants. The decline rate of estimated glomerular filtration rate (eGFR) over time was calculated using linear regression analysis of serial eGFR measurements for each patient. Rapid eGFR decline was defined an average decline in eGFR ≥3 ml/min/1.73 m^2 per year.

Results: In total, 7075 participants were analyzed. During a median follow-up of 11.7 (5.2-12.7) years, rapid eGFR decline was observed in 964 (13.6%) participants. When the participants were categorized into tertiles according to ASV, rapid eGFR decline was more prevalent in the highest ASV tertile group than in the lowest ASV group. Analyses using multiple logistic regression models revealed that the risk of rapid eGFR decline was significantly increased in the highest ASV tertile group compared to the lowest group (odds ratio, 1.51; 95% confidence interval 1.22-1.87). When ASV was treated as a continuous variable, an 1 kg increase in ASV was associated a 22% increased risk of rapid eGFR decline.

Conclusions: Body-weight fluctuation was significantly associated with an increased risk of rapid renal function decline in participants with normal renal function

FR-PO289

Reduced Serum Total CO2 Associates with Lower Urine Citrate Excretion in Clinic Outpatients

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Background: Emerging data supporting the GFR benefit of reducing the acid (H+) milieu of patients with CKD with serum total CO2 (STCO2) above that for which current KDIGO guidelines recommend alkali therapy suggest the need for a biomarker to identify candidate patients for treatment. Recent small-scale studies suggest that low urine excretion of the a pH-sensitive metabolite citrate (UcitrateV) predicts underlying acid (H+) retention in patients with CKD and serum [HCO3] > 24 mE/L and that dietary H+ reduction reduces H+ retention and increases UcitrateV in these patients (Goraya, et al. Kid Int 95:1190, 2019). Showing an association of low UcitrateV with low serum [HCO3] in a large database of unselected patients would further support the utility of UcitrateV for identifying patients with an increased H+ milieu.

Methods: We queried our electronic database for unique adult outpatients who had simultaneous values obtained for STCO2 (mM) and urine citrate (Ucitrate, mg/l) concentration. Because current KDIGO guidelines recommend alkali treatment for CKD patients with serum [HCO3] < 22 mEq/l and most clinical laboratories consider "normal" serum [HCO3] to be > 24 mEq/l, we compared Ucitrate among patients with serum [HCO3] < 22 mM and >24 mM.

Results: Our electronic database identified 264 unique patients, 55.3% male, with mean age ± SD = 50.7±20.3 years. Ucitrate was lower in patients with STCO2 <22 mEq/l compared to >24 mmEq/l (251±38 vs. 432±26 mg/l, respectively, p=0.003). Linear regression showed a significant relationship between Ucitrate and serum [HCO3] as continuous variables (p=0.025).

Conclusions: This database of unselected patients shows that reduced STCO2 associates with low Ucitrate and supports that an acid milieu promotes citrate conservation that is reflected by reduced urine citrate excretion. The data supports further investigation of urine citrate excretion as a biomarker of an increased acid milieu that might identify patients who are candidates for dietary H+ reduction as a kidney-protection strategy.

Funding: Private Foundation Support

FR-PO290

Plasma Renin Activity in CKD: A Descriptive and Prognostic Analysis

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Background: Elevated plasma renin activity (PRA) is associated with poor clinical outcomes including death and cardiovascular events. There is conflicting studies regarding associations of PRA with incident CKD, CKD stages, and renal prognosis.

Methods: We evaluated patients included in the Cleveland Clinic CKD registry with documented PRA values from 2005-2017. Patients with primary hyperaldosteronism or renal artery stenosis were excluded. PRA values were stratified into quartiles and adjusted

Cox models were utilized to evaluate survival. Adjusted mixed models were used to test the interaction between PRA and slope of eGFR over time.

Results: Among 1124 patients analyzed, PRA correlated inversely with eGFR (1.9 vs 1.2ug/L/hr for eGFR 15-29 vs 60-89 mL/min/ 1.73 m^2; p<0.001). Table 1 shows the patient characteristics by PRA quartiles. Patients in Q1 were older, more African American, had lower BMI, and more were on beta blocker therapy. They had higher systolic and diastolic blood pressures and were more likely to require 3+ blood pressure medications. All these associations were statistically significant (table 1). With median follow-up of 3.2 years, mortality was not different across PRA quartiles on adjusted Cox model analysis (P=0.16). On mixed model analysis, a significant association was noted between log PRA and time (slope of monthly eGFR decline = 0.02; p=0.014) suggesting a protective effect of higher PRA levels. In stratified analyses, this association was significant with baseline eGFR >50mL/min/ 1.73 m^2 but not lower eGFR.

Conclusions: While the mechanism remains unclear, PRA appears to correlate inversely with eGFR. Findings suggest a protective effect of higher PRA against CKD progression when eGFR is above 50 mL/min/1.73 m^2. Congruent with prior studies, lower PRA values are evident in older age, African Americans, and Beta Blocker therapy. Our study also suggests that lower PRA is associated with a more resistant hypertension. Whether this represents high salt intake or undiagnosed autonomous hyperaldosteronism is unclear.

Table 1. Patient Characteristics by PRA Quartiles

PRA Quartiles (ug/L/hr)	Q1: <0.1-0.7 (N=283)	Q2: 0.73-1.46 (N=270)	Q3: 1.5-3.5 (N=292)	Q4: 3.53-172 (N=279)	p-Value
Age (Years)*	70.2±10.5	69.0±11.3	69.0±11.5	66.1±11.9	<0.001
African American Race	41%	31.1%	24.3%	21.9%	<0.001
BMI*	30.5±6.7	31.0±7.3	31.0±7.2	32.7±7.4	0.003
eGFR (ml/min/1.73 m^2) *	53.0±15.0	49.4±15.3	47.1±15.3	47.3±13.7	<0.001
ACEi/ARB Therapy	88%	83.3%	82.9%	83.9%	NS
Diuretic Therapy	90.8%	87%	82.9%	89.2%	NS
Beta Blocker Therapy	87.6%	84.1%	77.7%	69.2%	<0.001
SBP (mmHg)*	153.6±28.2	147.3±26.6	140.1±23.8	138.1±23.4	<0.001
DBP (mmHg)*	81.6±14.7	79.0±13.4	76.3±14.5	75.9±13.8	<0.001
≥3 BP Meds	55.5%	43%	36.3%	36.9%	<0.001
Aldosterone (ng/dL) ¥	8.7[4.3,15.2]	9.2[5.1,14.5]	9.1[5.6,13.8]	10.8[5.4,20.4]	0.005

* Statistic presented as mean ± SD
¥ Statistic presented as median [P25, P75]
PRA: Plasma Renin Activity; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; ACEi: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; NS: Not Significant; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BP: Blood Pressure

FR-PO291

Glomerular Hyperfiltration Is Associated with Dementia: A Nationwide Population-Based Study

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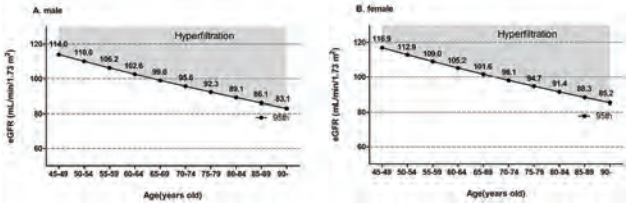
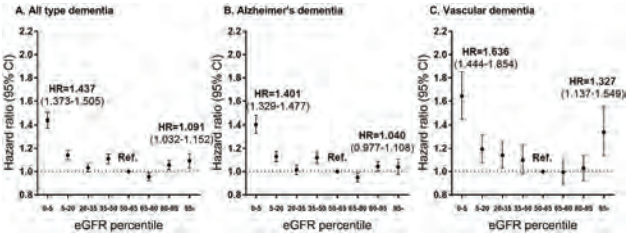
Background: Because prevention of dementia is critical before it occurs, identifying the risk factor of dementia is important. The object of this study is to identify the risk of dementia in people with glomerular hyperfiltration.

Methods: Using Korean National Health Information Database (NHID), we retrospectively reviewed total of 2,244,582 people, excluding ESRD patients and people with dementia before taking national health screening. Study population was divided into gender and age of five-years interval group. All eGFR≥95 percentile subjects in each group which was divided into sex and age of five-years were defined as hyperfiltration group. All 50 percentile≤eGFR<65 percentile subjects in each group which was divided into sex and age of five-years were defined as reference group. The hazard ratios (HR) for all type dementia, vascular dementia and Alzheimer's dementia were calculated within the study groups after adjustment for multiple variables.

Results: The corresponding eGFR values of hyperfiltration (95 percentile of eGFR) group were ≥114 mL/min/1.73m^2 in 45-49 years old male, ≥83 mL/min/1.73m^2 in ≥90 years old male and ≥117 mL/min/1.73m^2 in 45-49 years old female, ≥85 mL/min/1.73m^2 in ≥90 years old female. (Figure 1.) The hyperfiltration group (eGFR≥95percentile) showed a higher risk of all type dementia compared with the reference group (50percentile≤eGFR<65percentile), with the following HRs: 1.09 (95% CI: 1.032–1.152). The hyperfiltration group had higher risk of vascular dementia with the following HR: 1.33 (95% CI: 1.137–1.549). The relationship between hyperfiltration and Alzheimer's dementia was not statistically significant, with the following HRs: 1.040 (95% CI: 0.977–1.108). (Figure 2.)

Conclusions: Glomerular hyperfiltration is associated with increased risk of dementia, especially vascular dementia.





FR-PO292

Evaluation of Renal and Retinal Outcomes in the Northern Ireland Cohort of Longitudinal Ageing (NICOLA)

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Background: Microvascular pathology is a common feature of both eye and kidney diseases. Renal microvascular damage is not easy to identify without renal biopsy. Advances in imaging the retinal microvasculature may offer an alternative opportunistic evaluation of microangiopathic changes that correlate with kidney dysfunction. Retinal imaging might provide an earlier, non-invasive screening assessment for the presence of chronic kidney disease (CKD). We assessed retinal microvascular parameters for association with against measures of renal function measures in a prospective cohort study of older persons (>55 years): Northern Ireland Cohort of Longitudinal Ageing (NICOLA).

Methods: Retinal microvascular parameters (central retinal arteriolar/ venular equivalents (CRAE/CRVE) arteriolar to venular ratio (AVR), fractal dimension and tortuosity) were measured from optic disc centered fundus images and analysed using semi-automated software. Linear and logistic regression models were used to assess associations between microvascular parameters and the continuous variables of renal function (eGFR Creatinine (SeCr) and Cystatin C (Scys)) and the binary trait of CKD status, respectively. Minimally adjusted models included age and gender with fully adjusted models also including diabetes, smoking, alcohol, education, body mass index, antihypertensive medication, mean arterial blood pressure, triglycerides, high and low-density lipoproteins.

Results: Retinal and renal measures were available for 1,860 of the 3,518 NICOLA participants. In unadjusted, minimally adjusted and fully adjusted linear regression models, no significant associations were detected between CRAE, CRVE, AVR, fractal dimension or tortuosity and eGFRSeCr or eGFRScys. CKD status, defined by eGFRSeCr < 60 mL/ min per 1.73 m2, was significantly associated with venular tortuosity in all models (β=0.8; 95%CI: 1.3, 4.1; P=0.004). There was no significant associations detected between CKD status and any of the other retinal parameters assessed.

Conclusions: Our findings indicate that variation in retinal venular geometry is associated with renal dysfunction in an older population. These non-invasive retinal measures may help identify early mechanistic pathways for microvascular complications in individuals at high risk for future CKD.

Funding: Government Support - Non-U.S.

FR-PO293

Serum Albumin and All-Cause Mortality Across Varying Levels of Kidney Function

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Background: Serum albumin (sAlb) may be a strong predictor of longevity in the general population and in chronic kidney disease populations. Our objective was to determine the relationship between sAlb concentrations and mortality risk independent of kidney function.

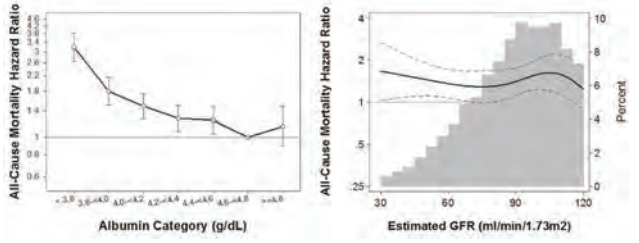
Methods: We analyzed a retrospective cohort of 31,274 adults from the 1999-2010 National Health and Nutrition Examination Survey. Estimated glomerular filtration rate (eGFR) was examined as both a confounder and modifier of the association of sAlb with mortality risk. We examined the association of sAlb categorized in 7 strata with mortality using Cox models. Covariates in the adjusted model included age, sex, race/ethnicity, level of education, diabetes, smoking status, systolic blood pressure, serum total cholesterol level, and eGFR. We then conducted spline analyses to estimate the association of sAlb with all-cause mortality across varying eGFR levels.

Results: In unadjusted analyses, participants with incrementally lower sAlb concentrations <4.6g/dL had increasingly higher mortality risk compared to those with sAlb ranging 4.6-<4.8g/dL (reference), whereas those with higher sAlb ≥4.8g/dL had lower mortality risk: HRs (95%CI) 3.88 (3.26, 4.62), 3.59 (3.01, 4.27), 2.79 (2.37, 3.29), 2.10 (1.79, 2.48), 1.72 (1.45, 2.03), and 0.71 (0.55, 0.92) for sAlb concentrations of <3.8, 3.8-<4.0, 4.0-<4.2, 4.2-<4.4, 4.4-<4.6, and ≥4.8g/dL, respectively. Case-mix + eGFR adjusted analyses showed similar findings, although the association of higher sAlb ≥4.8g/dL

with greater survival was attenuated to the null. Spline analyses showed participants with sAlb <4.6g/dL had higher mortality across all levels of eGFR ranging from 30 to 120 ml/min/1.73m^2 (reference: sAlb ≥4.6g/dL) [Figure].

Conclusions: Among a representative US cohort, there was a graded association between lower sAlb concentrations with higher death risk, which was robust across varying levels of kidney function.

Funding: NIDDK Support



FR-PO294

CKD in Patients with Pre-Diabetes from Two Large Healthcare Systems

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Background: Chronic kidney disease (CKD) in pre-diabetes (PDM) is not well-characterized. The study aim was to determine CKD prevalence and risk factors of patients with PDM treated at two large healthcare systems in the western United States.

Methods: The Center for Kidney Disease Research, Education and Hope (CURE-CKD) registry was created from clinical and administrative data in electronic health records of Providence St. Joseph Health and University of California Los Angeles Health (years 2006-2017). PDM, CKD, and hypertension (HTN) were identified by diagnostic codes and condition-specific criteria: PDM by HbA1c 5.7-6.4% or two measures of fasting (100-125 mg/dL) or random (140-199 mg/dL) blood glucose at least one day apart; CKD by two measures of serum creatinine-based estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2 (CKD-EPI), urine albumin-to-creatinine ratio ≥30 mg/g, or protein-to-creatinine ratio >150 mg/g at least 90 days apart; HTN by blood pressure ≥140/90mmHg on two measures at least 14 days apart.

Results: CKD was present in 20% of patients with PDM (101,868/497,233). Patients with CKD and PDM were predominately white (71%), women (58%), and older compared to those without CKD (72±15 years versus 56±17 years, p<0.001). HTN occurred in 72% of patients with CKD and PDM (73,788/101,868) with mean blood pressure of 131±17/70±10 mmHg. HbA1c was similar in those with and without CKD (5.8±0.3% and 5.8±0.4%). eGFR was 53±18 mL/min/1.73m^2 in patients with CKD and PDM versus 89±20 mL/min/1.73m^2 (p<0.001) in those without CKD. Among patients with PDM and CKD, individuals with HTN had higher eGFR compared to those without HTN (55±18 versus 50±21 mL/min/1.73m^2, p<0.001) and fewer had CKD stages 4-5 (7% versus 13%, p<0.001). Among small number of patients tested, albuminuria >30 mg/g or proteinuria >150 g/g occurred in 24% (3,027/12,470) and 42%(2,519/6,026), respectively.

Conclusions: CKD and major risk factors of HTN and albuminuria/proteinuria are often present in PDM without overt diabetes. In patients with PDM, CKD assessment and risk factor management are warranted

Funding: Private Foundation Support

FR-PO295

Mediation Analysis of Proteinuria and Serum Phosphate: Insight from the KNOW-CKD Study

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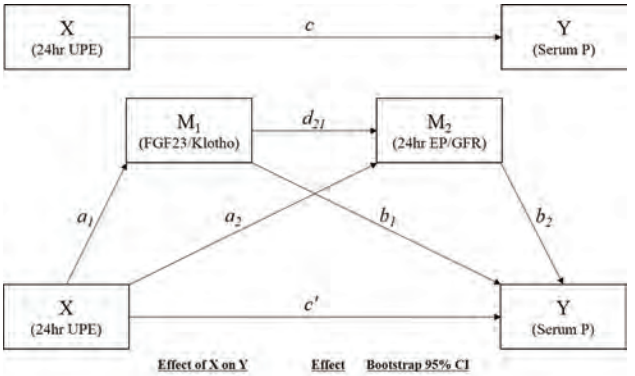
Background: Proteinuria and hyperphosphatemia are risk factors for cardiovascular disease in patients with chronic kidney disease (CKD). While experiencing the interaction between proteinuria and serum phosphate level, there is an insufficient mechanistic link between the two, particularly the extent to which is mediated by phosphate regulating factors. Therefore, we examined their association and potential mediators including circulating FGF23/Klotho and 24hr urinary excretion rate of phosphate to glomerular filtration rate (24hr EP/GFR) and 24hr tubular reabsorption rate of phosphate to GFR (24hr TRP/GFR).

Methods: We analyzed 1793 patients for whom 24hr urine protein and phosphate, serum phosphate, FGF23 and Klotho level were measured simultaneously using data from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD). Multivariable linear regression and mediation analyses were performed. Total, direct, and indirect effects were also estimated.

Results: The group of patients with high serum phosphate levels was likely to have higher proteinuria and FGF23 and lower Klotho levels. 24hr EP/GFR increased with increasing proteinuria and CKD progression, but 24hr TRP/GFR showed a tendency to decrease. Simple mediation analyses showed that 15.4% or 67.9% of the relation was mediated by FGF23/Klotho ratio or 24hr EP/GFR, respectively. In addition, 73.1% of the relation was mediated by two serial mediators.

Conclusions: These findings represents that proteinuria increases 24hr EP/GFR through FGF23/Klotho axis as a mechanism to regulate increased phosphate burden per unit nephron much earlier than reduction in renal function.



Effect of X on Y	Effect	Bootstrap 95% CI
Total effect (*c*)	0.078	(0.037 to 0.119)
Direct effect (*c'*)	0.021	(- 0.023 to 0.064)
Indirect effects		
a1b1+a2b2+a1d21b2	0.057	(0.034 to 0.081)
a1b1	0.010	(0.003 to 0.018)
a2b2	0.045	(0.025 to 0.066)
a1d21b2	0.002	(0.001 to 0.004)

Mediation analyses of the effect of 24hr UPE on serum phosphate level.

FR-PO296

Association of the Trajectories of Metabolic Component and Outcomes in Patients with CKD

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Background: Patients with chronic kidney disease (CKD) were known to increase the risk of chronic diseases including hypertension (HTN), diabetes mellitus (DM), dyslipidemia while they also affect deterioration of renal function. However, little is known about the relation of changeable aspect for metabolic component to CKD progression.

Methods: We assigned patients to be clustered High and Low group followed by trajectory analysis using K-means clustering on the basis of systolic and diastolic blood pressure (SBP,DBP), total cholesterol(TC), triglyceride(TG) and LDL cholesterol measurement at least two time point. The optimal number of clustering was selected by the Calinski-Harabasz index. Primary outcome was risk factor analysis by clustering group for eGFR decline, and death.

Results: The mean age of overall participants was 65.7±9.7 years, 50.4% for men and 11.8% for current smoker. The mean SBP was 127.8±15.8 mmHg, DBP was 83.6±8.4 mmHg. Total choresterol, TG and LDL was 196.4±40.9, 147.1±89.8, 115.5±37.2 mg/dl, respectively. The mean SBP of cluster High group was 138.9±13.2, and Low group was 118.9±10.9mmHg. In TC clustering, High group was 223.4 ± 33.0, and Low group was 167.5 ± 26.6 mg/dl. The mean TG in High group was 266.1 ± 116.7, and Low group was 118.8 ± 46.1 mg/dl. In LDL clustering, cluster High group was 139.7 ± 31.2, and Low group was 89.9 ± 24.3 mg/dl. In multivariate logistic regression, SBP high group (OR 1.13 95%CI 1.066-1.212), TG high group (OR 1.15, 95% CI 1.069-1.240) were independently associated with eGFR decline. And, also SBP high group (OR 1.82, 95%CI 1.070-3.123) and BMI lowest group (OR 2.19, 95%CI 1.07-4.38) were independently associated with death.

Conclusions: High SBP trajectory, and high TG trajectory have negative impacts on eGFR decline. And also, High SBP trajectory, and low BMI trajectory affected overall survival. In CKD patients, more meticulous following up was needed for better clinical outcomes.

FR-PO297

Examining the Characteristics of US Veterans on Triglyceride or HDL Altering Therapy Across Kidney Disease Stage Between 2004-2014

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Background: Current nephrology guidelines do not advocate for pharmacological therapy for triglycerides (TG) or high density lipoprotein (HDL) management in patients with chronic kidney disease (CKD), despite the fact that these lipids may be associated with a higher cardiovascular risk. Nonetheless some patients with CKD receive these medications. We sought to describe the characteristics of US veteran patients receiving fibrate or niacin and whether these characteristics differed by presence of CKD or across CKD stage.

Methods: We identified male veterans with an elevated TG(≥150 mg/dL) or low HDL (<40 mg/dL) who initiated a fibrate or niacin within 90 days of the lipid measurements between 2004-2014. We examined clinical characteristics at the time of fibrate or niacin initiation (N=78,957 and 100,356, respectively), stratified by CKD stage.

Results: In both treatment groups, there was a decreasing trend in fibrate and niacin initiation across higher CKD stage, where a majority of patients were non-CKD, with <1% of patients in stage 5 or end-stage renal disease (ESRD). Veterans with advanced CKD were more likely to be older at the time of fibrate or niacin initiation. In non-CKD and between CKD stage 3A-4, approximately 6-12% of patients on therapy were African-American, however that proportion more than doubled to 20-25% in ESRD/CKD stage 5. Across CKD stages, there was an increase in the proportion of concurrent statin users, with a peak at stage 4 or 5, and then a decline with ESRD. There were similar relationships of comorbidities across CKD stage among fibrate users, where the greatest proportion of cardiovascular conditions was among CKD stage 4 patients.

Conclusions: In US veterans, the proportion of patients with high TG or low HDL prescribed fibrate or niacin decreases with worsening CKD. In future analysis, we will investigate if use of these therapies in CKD patients with elevated TG or low HDL have a lower risk of cardiovascular events.

Funding: Veterans Affairs Support

		CKD Stage						
		Total	Non-CKD	3A	3B	4	5	ESRD
N,%	niacin	100356	71625(71.4%)	17717(17.7%)	8264(8.2%)	1915(1.9%)	184(0.2%)	651(0.7%)
	fibrate	78957	58166(73.7%)	12865(16.3%)	6071(7.7%)	1346(1.7%)	83(0.1%)	426(0.5%)
Age	niacin	64±11	61±10	70±9	73±9	72±10	69±10	62±10
	fibrate	61±12	59±11	69±9	72±9	72±11	68±12	61±11
Black	niacin	11	12	8	6	12	22	25
	fibrate	10	11	6	6	9	22	21
HDL (mg/dL)	niacin	34[29,39]	34[29,39]	33[29,38]	33[28,39]	32[27,36]	30[25,36]	32[27,38]
	fibrate	34[29,39]	34[29,40]	34[29,38]	33[28,38]	32[26,37]	31[26,37]	34[29,41]
Triglycerides (mg/dL)	niacin	198[138,290]	208[139,296]	193[136,275]	195[135,279]	195[136,290]	174[118,232]	208[134,317]
	fibrate	321[226,459]	330[234,473]	297[214,419]	298[210,422]	305[214,443]	319[200,464]	327[239,442]
Any Statin	niacin	58	56	62	66	66	73	58
	fibrate	48	45	55	59	61	49	51
MI	niacin	18	15	22	28	32	31	31
	fibrate	12	9	17	24	28	19	24
Angina	niacin	19	17	24	29	30	26	28
	fibrate	14	12	20	25	28	23	25
Atherosclerosis	niacin	21	16	28	39	46	40	45
	fibrate	16	12	24	35	42	34	37
Heart Failure	niacin	35	28	46	58	66	66	62
	fibrate	28	21	40	54	63	60	58

FR-PO298

Correlation Between Blood Pressure and Development of CKD in 5.6 Million Korean Adults with Normal Renal Function

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Background: Although hypertension is well known for a major risk factor of renal progression in patients with chronic kidney disease (CKD), there are few studies on whether hypertension is also a risk factor of renal progression in the population with normal renal function. So we analyzed correlation between blood pressure (BP) control and development of CKD in Korean adults with normal renal function.

Methods: We utilized medical checkup database of the Korean National Health Service (NHIS). We enrolled 5,638,320 subjects including people who underwent medical checkups both in 2009 & 2015 in a row and excluding people whose estimated glomerular filtration rates (eGFRs) were already less than 60 ml/min/1.73m^2 or whose urinalyses already showed proteinuria in 2009. New development of CKD was defined by the decline of eGFR to below 60 ml/min/1.73m^2 in 2015. We compared age, sex, obesity, and various medical illnesses such as hypertension, diabetes, and dyslipidemia between the CKD group (n=161,044) and the non-CKD group (n=5,477,276). We also stratified subgroups by initial systolic BP and diastolic BP by 10 mmHg, and investigated the risks of progression to CKD after adjusting these clinical factors.

Results: The CKD group showed higher incidence of old age, female, obesity, hypertension, diabetes, and dyslipidemia, compared with the non-CKD group. Subjects whose SBP were more than 120 mmHg or whose DBP were more than 70 mmHg showed higher incidence of progression to CKD, compared with subjects whose SBP were less than 120 mmHg and whose DBP were less than 70 mmHg, respectively (odds ratio 1.037, 95% confidence interval 1.014~1.061 / OR 1.021, 95% CI 1.004~1.038).

Conclusions: We suggest strict BP control is helpful for preventing CKD in the population with normal renal function.

Table 1. Odds ratio of development of CKD

	N	OR (95% CI)
SBP		
~99	2873	1.027(0.985~1.071)
100~109	10924	1
110~119	31362	1.011(0.988~1.034)
120~129	37067	1.037(1.014~1.061)
130~139	45336	1.064(1.041~1.088)
140~149	16235	1.122(1.093~1.152)
150~159	9960	1.192(1.157~1.227)
160~	7287	1.312(1.271~1.356)
DBP		
~59	2344	1.043(0.998~1.090)
60~69	20376	1
70~79	52764	1.021(1.004~1.038)
80~89	61125	1.061(1.043~1.079)
90~99	17629	1.141(1.116~1.166)
100~109	5598	1.225(1.186~1.264)
110~	1208	1.355(1.274~1.442)
PP		
~44	58602	0.986(0.974~0.998)
45~54	58472	1
55~64	29622	1.026(1.011~1.041)
65~	14348	1.137(1.114~1.160)
Total	161044	

Adjusted by age, sex, obesity, hypertension, diabetes, dyslipidemia, and eGFR

FR-PO299

Serum Bicarbonate Levels Are Not Associated with Total Kidney Volume in Patients with Polycystic Kidney Disease

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Background: Enhanced ammoniagenesis has been proposed as a potential mechanism of kidney cystic disease progression in patients with polycystic kidney disease (PKD). Animal studies have found that administration of sodium bicarbonate slows cyst enlargement and prevents development of interstitial inflammation and chronic fibrosis. We tested the hypothesis that higher serum bicarbonate levels in patients with PKD are associated with lower total kidney volume (TKV).

Methods: We included 383 patients from the HALT-PKD Study A with baseline serum bicarbonate levels and at least two measurements of TKV. Bicarbonate was examined as a continuous variable and in categories (≤ 24, 25-28 and >28 mEq/L, with 25-28 mEq/L as the reference group). Total kidney volume was measured using imaging from a 1.5T MRI scanner. The outcome was yearly change in slope of TKV. Linear regression models were used to examin the association between serum bicarbonate and change in TKV.

Results: The mean (SD) age was 37.4 (8.0) years. The mean (SD) serum bicarbonate and estimated glomerular filtration rate at baseline was 27.0 (2.4) and 90.0 (17.0) ml/min/1.73m,^{2} respectively. Participants with lower serum bicarbonate ≤ 24 mEq/L were more likely to be younger, female and to have higher systolic blood pressure than those with a serum bicarbonate > 28 mEq/L. There was no association between serum bicarbonate and change in annual slope of TKV when serum bicarbonate was examined as a continuous variable or in categories (Table 1).

Conclusions: Serum bicarbonate levels are not associated with total kidney volume in patients with PKD.

Funding: Other NIH Support - NHLBI

Annual Change in Slope of TKV (β Estimate (95% CI))

Serum bicarbonate (mEq/L)	Unadjusted	Model 1	Model 2
Per 1 mEq/L increase	3.6 (-0.9 to 8.1)	0.3 (-4.0 to 4.6)	1.1 (-3.1 to 5.4)
<25	-15.4 (-47.5 to 16.7)	-7.7 (-37.7 to 22.4)	-8.9 (-46.1 to 20.4)
25-28	REF	REF	REF
>28	9.6 (-15.2 to 34.5)	-3.3 (-26.9 to 20.4)	0.5 (-22.7 to 23.7)

Model 1: adjusted for age, gender, race

Model 2: adjusted for model 1 plus smoking, cardiac history, BMI, SBP, baseline eGFR and urine albumin to creatinine ratio

FR-PO300

Alteration of Physical Activity and Its Association with Cardiovascular Outcomes Among Pre-Dialysis CKD Patients

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Background: Cardiovascular disease is major cause of mortality among chronic kidney disease (CKD) patients, and it is fundamental to focus on reducing the potential risk factors. Regular physical activity is known to reduce the risk of cardiovascular disease in general population. However, whether the change of physical activity habits is beneficial for pre-dialysis CKD patients had not been examined thoroughly.

Methods: We performed a nationwide population based cohort study using the database of Korean National Health Insurance System. Among adult patients who received national health screening program ≥2 times between 2012 and 2016, CKD patients were identified using the serum creatinine and dipstick albuminuria measurements. Those who previously underwent dialysis or diagnosed cardiovascular disease were excluded. The frequency and the intensity of the physical activity were obtained at least twice, from self-reported questionnaire during the health examination. The study groups were divided according to the status of physical activity habit alteration; active, quit exercise, start exercise, and inactive group. Then, the development of myocardial infarction (MI), stroke or death was assessed using the multivariate Cox regression analysis.

Results: During the median follow up of 3.18 years, 549,187 CKD patients were examined for adverse outcomes. Compared to those who remained inactive, the active group patients who consistently continued physical activity exhibited lower risk of MI (hazard ratio (HR); 0.76, 95% confidence interval (95% CI); 0.69-0.85), stroke (HR (95%CI) 0.69 (0.62-0.78)), and death (HR (95%CI) 0.62 (0.57-0.67)). Moreover, those who newly started physical activity also showed lower risk of adverse outcomes, compared to the inactive group (HR (95%CI) 0.83 (0.76-0.89)).

Conclusions: Continuation of physical activity in pre-dialysis CKD patients is beneficial to reduce the risk of cardiovascular disease development. Therefore, clinicians should encourage even mild intensity of physical activity to CKD patients.

FR-PO301

Hyperuricemia Is Associated with Progression of CKD: Uric Acid Aggravates Renal Function

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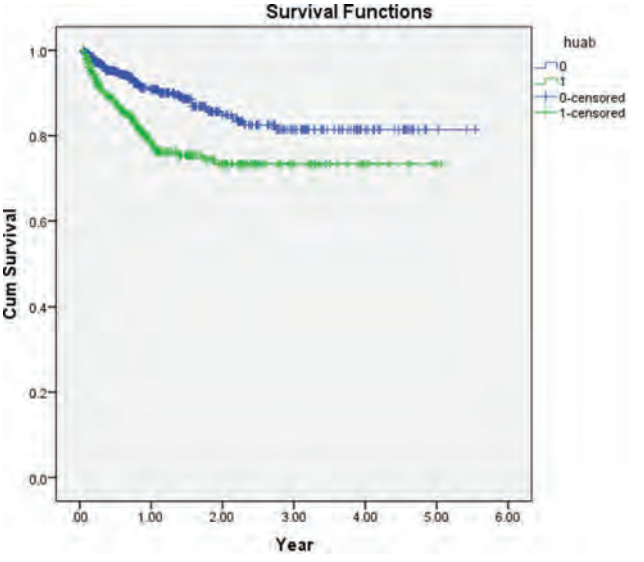
Background: Hyperuricemia (HUA) is common in chronic kidney disease (CKD). There is paucity of literature on the association between serum uric acid levels and the progression of CKD. This study aimed at assessing the effect of serum baseline uric acid level on the progression of CKD.

Methods: This retrospective study included 800 CKD patients in our center. The information on baseline and follow-up characteristics were collected from Renal Treatment System (RTS) database, including age, gender, serum uric acid (UA), glomerular filtration rate (eGFR), serum creatinine (Cr), urea, albumin (Alb), 24 hours urine protein quantitation (24h-u-pro) and blood pressure (BP). Cox regression analysis was used to evaluate the risk factors for CKD progression. The Kaplan–Meier analysis was used to test associations between serum uric acid levels and renal survival rates.

Results: A total of 800 patients were included in the study, and the mean age at entry was 36.6±14.4 years. There was no significant difference in gender distribution. The mean eGFR, Cr, serum uric acid at baseline were 99.23±31.54 ml/min/1.73m^2, 82.08±41.40 μmol/L, 371.60±103.18 μmol/L, respectively. 306 (38.3%) patients had HUA and 494 (61.7%) had non-HUA. We established different adjusted models and found that HUA was a risk factor for CKD patients to reach the composite endpoint after adjustment in six models. All models show that HUA was a risk factor for the progression of CKD. Among them, model 4 (adjusted for Cr+Alb+age+BP+gender) was the best model with the largest HR value (HR:2.010, 95%CI:1.310-3.084, P<0.05). The cumulative survival rate of non-hyperuricemia group was higher than that of hyperuricemia group (P=0.046).

Conclusions: HUA is prevalent in CKD and a risk factor for CKD progression. Anti-hyperuricaemic therapy may need to be considered in CKD patients to slow the disease progression, which needs to be tested further in clinical studies.

Funding: Government Support - Non-U.S.



Survival analysis

FR-PO302

The Association Between Serum Uric Acid Levels and Incidence of Proteinuria: A Large-Scale Cohort Study in a Community-Based Population

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Background: Hyperuricemia is associated with the development and the progression of renal disease. However, the threshold value of serum uric acid for the increased risk for proteinuria has not been determined. To clarify this point, we conducted a large-scale cohort study in a community-based population.

Methods: We used a nationwide database of 328,582 subjects without overt dipstick proteinuria at baseline (134,227 men, 194,355 women, aged 40–74) who participated in the annual "Specific Health Check and Guidance in Japan" check-up between 2008 and 2013, and were followed up for 6 years (median 3.0 years). We examined the association of serum uric acid levels at baseline with incident dipstick proteinuria (1+ or greater) in this population.

Results: During the follow-up period, 24,419 subjects (7.4%) newly developed dipstick proteinuria. In unadjusted Cox proportional hazard model, the hazard ratio (HR) for incident proteinuria was significantly increased both in men and women with high serum uric acid levels. In the adjusted model with possible confounders including age, renal function, smoking, alcohol consumption, and comorbidities, a similar significant trend was observed. The lowest HR was observed in men with serum uric acid 5.0-5.9 mg/dL and in women with 4.0-4.9 mg/dL, respectively. The significantly increased HRs for incident proteinuria was observed in the high range of serum uric acid in both men and women (≥ 8 mg/dL in men, ≥ 5 mg/dL in women, respectively). The adjusted HRs of the conventional cut-off point of hyperuricemia (> 7.0 mg/dL) for incident proteinuria was 1.10 (95% confidence interval [CI] 1.05-1.15) in men, and 1.75 (95%CI 1.58-1.93) in women, respectively.

Conclusions: In this community-based population, the high serum uric acid level was an independent risk for incident proteinuria in both men and women and the threshold values of serum uric acid for incident proteinuria might be different for men and women.

Funding: Government Support - Non-U.S.

FR-PO303

Relationship of Uric Acid with Cardiovascular Mortality: A Systematic Review and Meta-Analysis

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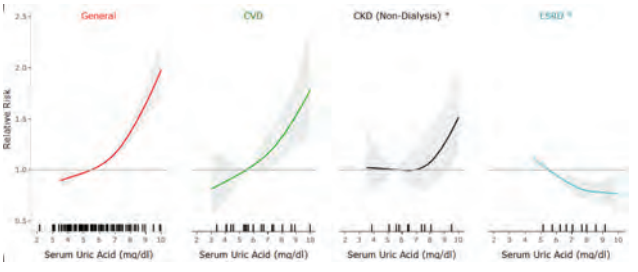
Background: Uric acid (UA) levels predict cardiovascular (CV) and all-cause mortality, but uncertainty remains regarding optimal threshold values for intervention. The aim of this systematic review and meta-analysis was to investigate risk thresholds for UA on CV mortality in four distinct populations: general population, cardiovascular disease (CVD), chronic kidney disease (CKD) and end stage kidney disease (ESKD).

Methods: We searched electronic databases up to 1 July 2018 for observational studies reporting associations for three or more groups of UA with all-cause and CV mortality in the four distinct populations:general, CVD, CKD and ESKD. Study-specific associations between UA and adjusted relative risks (RR) were estimated using restricted cubic splines with three knots at 10th, 75th and 90th percentile of the UA distribution and a generalised least squares method before pooling study estimates with a multivariate random-effects meta-analysis.

Results: We included 1,665,013 participants from 37 cohorts with 25,334 CV deaths. The overall pattern of association between serum UA and CV-mortality was non-linear (p-value, non-linearity < 0.001). Mortality risks increased beyond UA of 6.0 mg/dL [RR: 1.03 (1.01-1.05)], with an almost linear increase in risk for higher concentrations (7.0 mg/dL, [RR: 1.13 (1.08- 1.18)]) compared to a referent of 5.5 mg/dL. There was evidence of heterogeneity across studies (I^2=63.5). The shape of the UA-mortality association was similar for participants in the general, CKD, and CVD populations but differed significantly from ESKD (p<0.001). In ESKD, the pattern was completely reversed, with a reduced mortality for UA values above 5.5 mg/dL.

Conclusions: Uric acid exhibits a J-shaped association with CV mortality with increasing risk above 5.5 mg/dL in the general and CVD populations. This relationship was attenuated in CKD and completely reversed in ESKD. Large randomised clinical trials of urate-lowering therapy should test whether targeting this threshold will confer cardioprotection.

Funding: Government Support - Non-U.S.



Nonlinear dose-response analyses of UA and risk of CV mortality by population type

FR-PO304

Comparative Renoprotective Effect of Febuxostat and Allopurinol in Pre-Dialysis Stage 5 CKD Patients: A Nationwide Database Analysis

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Background: Hyperuricemia has been associated with chronic kidney disease (CKD) progression. Slowed CKD progression has also been observed in stage 1-3 CKD patients treated with the anti-hyperuricemic febuxostat. Large-scale studies comparing the renoprotective potential of febuxostat and allopurinol in pre-dialysis stage 5 CKD are lacking.

Methods: In our population-based retrospective cohort study, we used the National Health Insurance Research Database in Taiwan from 2012 to 2015 to select eligible pre-dialysis stage 5 CKD patients. Patients were included and grouped based on the prescription of allopurinol (n=3424) or febuxostat (n=2633) within 90 days after first-time erythropoiesis-stimulating agents (ESA) prescriptions. Long-term dialysis and all-cause mortality or dialysis (composite outcome) among febuxostat users and allopurinol users were analyzed and compared using the Cox proportional hazards model. Propensity-score matching and subgroup analysis were additionally performed.

Results: We identified 6057 anti-hyperuricemic users. 69.57% of allopurinol users and 42.01% febuxostat users required long-term dialysis (p<.0001). The adjusted hazard ratio was 0.65 (95% confidence interval, 0.60-0.70), indicating near 35% lower hazards of long-term dialysis from febuxostat compared with allopurinol use. The renal benefit of febuxostat use was consistent across most patient subgroups and/or using the propensity score-matched cohort. Similarly, the adjusted hazard ratio was 0.66 (95% confidence interval, 0.61-0.70) for the composite outcome of long-term dialysis or death.

Conclusions: Compared to allopurinol, febuxostat was associated with lower risk of progression to dialysis in pre-dialysis stage 5 CKD patients. Febuxostat's associated renal benefit does not compromise patient survival.

Funding: Private Foundation Support

Risks of study outcomes in patients using febuxostat and allopurinol

	No. of Events (%)		Incidence Rate Per 100 Patient-years		Study Outcome, Hazard Ratio (95% Confidence Interval)			
Treatment (No. of Patients)	Long-term dialysis	Dialysis or death	Long-term dialysis	Dialysis or death	Long-term dialysis		Dialysis or death	
					Unadjusted	Adjusted	Unadjusted	Adjusted
Febuxostat (n=2633)	1106 (42.01)	1388 (52.72)	49.60	62.24	0.59 (0.55-0.64)	0.65 (0.60-0.70)	0.64 (0.60-0.68)	0.66 (0.61-0.70)
Allopurinol (n=3424)	2382 (69.57)	2805 (81.92)	76.17	89.70	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)

FR-PO305

The Association Between Serum Uric Acid Levels and Cardiovascular Disease in Japanese Patients with CKD: The FKR Study

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Background: Growing evidence suggests that high serum uric acid (SUA) level is related to increased risk of cardiovascular disease (CVD). However, limited studies have investigated the influence of elevated SUA level on the prevalence of CVD in Japanese patients with chronic kidney disease (CKD). Besides, the nature of disease in Asian populations differs markedly from that in North American populations and European.

Methods: The Fukuoka Kidney disease Registry (FKR) is designed as one of the largest prospective, multicenter, observational cohort studies in non-dialyzed CKD patients. A total of 3,366 Japanese patients with CKD were eligible for this study. The association between SUA level and the prevalence of CVD was analyzed. CVD was defined as ischemic heart disease, hemorrhagic stroke, ischemic stroke, congestive heart failure, atrial fibrillation, and aneurism of thoracic or abdominal artery. The odds ratios (ORs) for the prevalence of CVD were estimated according to SUA levels as follows: ≤5.9 mg/dL, 6.0-7.9 mg/dL, and ≥8.0 mg/dL.

Results: The CVD was present in 857 (25.5%) patients. Mean serum uric acid was 6.2 ± 1.5 (standard deviation) mg/dL. The age- and sex-adjusted prevalence of CVD increased significantly (SUA ≤5.9 mg/dL: 22.9%, 6.0-7.9 mg/dL: 26.1%, and ≥8.0 mg/dL: 33.2%, [p for trend <0.05]). Compared with those with SUA ≤5.9 mg/dL, the multivariable-adjusted ORs for the prevalence of CVD were 1.11 (95% confidence intervals, 0.92-1.35) and 1.38 (1.04-1.84) in those with SUA 6.0-7.9 mg/dL and ≥8.0 mg/dL, respectively. Among CVD subtypes, higher SUA levels were associated with increased prevalence of atrial fibrillation (ORs [95% CI]: 1.38 [0.97-1.98] and 2.41 [1.50-3.89], respectively).

Conclusions: Higher SUA levels are associated with higher prevalence of CVD, especially with atrial fibrillation. The FKR study will prospectively clarify whether higher SUA levels increase risk for developing CVD in Japanese patients with CKD.

FR-PO306

Longitudinal Serum Uric Acid Level and Long-Term Outcome in CKD by Trajectory Analysis from the Korean Cohort Study for Outcomes in Patients with CKD (KNOW-CKD)

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Background: Hyperuricemia is an independent risk factor for microalbuminuria and decline of renal function. Though, it has not been proven whether high serum uric acid on longitudinal basis predicts renal outcome in chronic kidney disease patients.

Methods: Among the 2,238 patients enrolled in the KoreaN cohort study for Outcomes in patients With Chronic Kidney Disease (KNOW-CKD), 1,039 patients whose serum uric acid were measured more than 3 times were included. Patients were classified into three groups according to repeatedly measured uric acid levels by trajectory analysis using K-means. We investigated baseline characteristics and outcomes of each group. Renal events were defined as either doubling of creatinine, estimated glomerular filtration rate halving, or end-stage renal disease. Composite events were defined as either death, non-fatal cardiovascular disease, or renal event.

Results: Mean uric acid level was 4.91 ± 1.36 mg/dL for low uric acid group, 6.29 ± 1.28 mg/dL for middle uric acid group, and 8.53 ± 1.26 mg/dL for high uric acid group. Men accounted for 42.4%, 64.1%, and 70.4% in low, middle, and high uric acid group, respectively. Proportion of patients with hypertension (99.0%) and diabetes mellitus (DM) (24.2%) were the greatest in high uric acid group. The risk of renal event was 2.01-fold higher in high uric acid group (95% CI 1.43-2.84, P < 0.001) than middle uric acid group when adjusted for age, sex, hypertension and DM, and 2.16-fold higher (95% CI 1.24-3.75, P = 0.006) when additionally adjusted for other relative factors. The risk of composite event of high uric acid group was also significantly higher compared with middle uric acid group after adjustment for age, sex, hypertension, and DM (HR 2.37, 95% CI 1.62-3.47), and after adjustment for additional factors (HR 2.99, 95% CI 1.60-5.68, P <0.001).

Conclusions: High uric acid level in longitudinal aspect was associated with adverse renal outcome and composite outcome in chronic kidney disease patients.

Funding: Government Support - Non-U.S.

FR-PO307

Acid Retention Decreases Urine Citrate Excretion Through Reduced Kidney Clearance and Reduced Plasma Concentration of Citrate

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Background: Decreased urine excretion of the pH-sensitive metabolite citrate is a potential biomarker of H+ retention in patients with CKD and reduced eGFR but no metabolic acidosis (Goraya.KI 95:1190, 2019). We explored contributions of reduced plasma citrate (Pcit) and/or reduced kidney citrate clearance (UV/Pcit) to decreasing urine citrate excretion associated with increasing H+ retention over time.

Methods: We measured H+ retention, 8-hour urine citrate excretion (UcitrateV), Pcit, and UV/Pcit in macroalbuminuric, non-diabetic CKD 2 patients with hypertension associated nephropathy without metabolic acidosis (plasma total CO2 >24 mM) at baseline and after treatment with 0.5 meq/kg bw/day NaHCO3 (HCO3, n=40), 0.5 meq/kg bw/day NaCl (NaCl, n=40), or usual care (UC, n=40) and assessed after 5 years.

Results: Baseline H+ retention, UcitrateV, Pcit, and UV/Pcit were not different among groups. The 5-year vs. respective baseline value in HCO3 patients was not different for H+ retention (16.1±12.9 vs 18.1±14.8 mmol, p=0.46) or UcitrateV (1.063±0.244 vs 1.032±0.259 mmol, p=0.69). However, the 5-year vs respective baseline value in NaCl patients was higher for H+ retention (23.2±14.0 vs 19.2±16.7 mmol, p<0.01) and lower for UcitrateV (0.910±0.233 vs 1.021±0.275 mmol, p<0.01). Similarly, 5-year vs baseline value in UC was higher for H+ retention (22.1±11.2 vs. 17.4±9.9 mmol, p<0.01) and lower for UcitrateV (0.899±0.217 vs 0.989±0.212 mmol, p<0.01). Five-year vs.baseline value for Pcit was not different for HCO3 (0.050±0.016 vs. 0.048±0.016 mM, p=0.46) and NaCl (0.051±0.023 vs. 0.054±0.025 mM, p=0.08) but was lower for UC (0.050±0.020 vs. 0.052±0.020 mM, p<0.02). Five-year vs. baseline value for UV/Pcit was not different for HCO3 (0.048±0.011 vs. 0.047±0.008 ml/min/1.73m2, p=0.94) but was lower for NaCl (0.043±0.016 vs. 0.047±0.018 ml/min/1.73m2, p<0.002) and UC (0.045±0.024 vs. 0.048±0.024 ml/min/1.73m2, p<0.004)

Conclusions: Both reduced UV/Pcit and reduced Pcit mediated decreased UcitrateV in CKD patients without metabolic acidosis whose H+ retention increased after 5 years without alkali therapy but both parameters were unchanged in those treated with alkali in whom H+ retention did not increase. Increasing H+ retention initiates kidney and extra-kidney mechanisms for citrate conservation.

FR-PO308

A Serum Magnesium Concentration Lower Than 2 mg/dL Predicts Mortality in CKD Patients: A Propensity Score-Matching Study

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Background: Decreased serum mg may be associated with mortality and vascular calcifications. There is limited information on the impact of low mg (mg) in CKD stage 4 patients. We aimed to evaluate whether serum mg levels are associated with mortality in a matched population of CKD patients.

Methods: Patients were stratified into tertiles according to serum mg (T1<2.0 mg/dl, T2 =2.01-2.39 mg/dl and T3>2.4 mg/dl). For survival analysis, we used log-rank tests to compare Kaplan–Meier (KM) probability of death curves and performed uni- and multivariable Cox regression analysis. Given the comparable survival among T2 and T3 patients, serum mg <> 2 mg/dl was used to further perform propensity score matching (PSM) to minimize potential confounding and selection biases within tertiles. We used the derived propensity scores to match the groups in a 1:1 ratio. Further, KM analysis with the matched population was performed.

Results: This study included 1002 patients evaluated in the advanced-CKD outpatient clinic from 2009 to 2018. During the study follow-up, 158 died, 84 from T1, 34 from T2, and 35 from T3. Furthermore, 616 patients started dialysis, whereas 242 remained under follow-up in the outpatient clinic. KM showed that patients from T1 had a worse survival as compared with T2 and T3 (p<0.001; Figure 1A). Multivariate Cox proportional hazard showed that patients with mg <2 mg/dl had a higher mortality risk (HR 1.61, CI 1.05—2.46) as compared to the other groups. After matching, it was obtained an adjusted population of 343 patients with mg <2 mg/dl and 343 with higher concentrations of mg. Survival analysis with PSM-adjusted cohorts showed that patients with mg <2 mg/dl had worse survival compared to T2 and T3 (log-rank p=0.01; HR 1.73, CI 1.02—2.36, p=0.44; Figure 1B)

Conclusions: In appropriately-matched patients, a serum mg <2 mg/dl predicts mortality.

Funding: Government Support - Non-U.S.

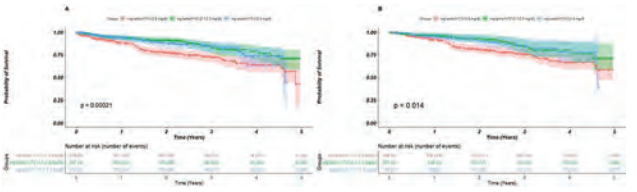

Figure 1. Survival analysis of not matched cohorts (A) and PSM-adjusted cohorts (B).

FR-PO309

Urine Hydroxyproline as a Marker of Renal Dysfunction in Patients with CKD

Jongho Son, Eun Sil Koh, Cheol Whee Park, Sungjin Chung. *The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.*

Background: Hydroxyproline (Hyp) is major component of the protein collagen in the tissues. Most of the Hyp released by the breakdown of collagen is degraded to free amino acid that circulates in plasma, is filtered, and is almost entirely reabsorbed by the kidney while some of the Hyp circulates in the peptide-bound form and are excreted in urine without further metabolism. This study was designed to examine whether the measurement of urinary Hyp could be useful for assessing renal function in the patients with chronic kidney disease (CKD).

Methods: A total of 298 patients with various stages of non-dialytic CKD were included in this study. Values of total and free Hyp were measured from 24 hours urine and urininary free-to-total Hyp ratio was calculated to compare with known renal functional parameters (from January 5th, 2016 to May 7th, 2018)

Results: Median levels of urinary free Hyp and total Hyp are 0.70 mg/day (IQR 0.30-2.10 mg/day) and 125.00 μmol/day (IQR 80.00-196.00 μmol/day), respectively. Univariate linear regression analysis showed that urinary free-to-total Hyp ratio was correlated with creatinine (β=0.399, P<0.001), estimated glomerular filtration rate (eGFR; β=-0.213, P=0.001), cystatin C (β=0.338, P<0.001), proteinuria (β=0.181, P=0.004) and fractional excretion of sodium (β=0.141, P=0.023). Results of multiple linear regression analysis showed that beta-coefficient of eGFR was –0.155 (P=0.084) for urinary free Hyp, 0.134 (P=0.091) for urinary total Hyp and –0.172 (P=0.042) for urinary free-to-total Hyp ratio, even after controlling for covariates, including age, gender and proteinuria.

Conclusions: Our results suggest that urinary free-to-total Hyp ratio would be used as a novel endogenous marker of renal dysfunction.

FR-PO310

Interaction Between Apolipoprotein L1 (APOL1) Genetic Risk and Air Pollution for Kidney Disease in African Americans

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Background: The *APOL1* high-risk genotype is frequent in African Americans (AAs) and is associated with increased chronic kidney disease (CKD). However, only a fraction of individuals with *APOL1* risk have CKD, indicating the presence of disease modifiers ('second hits'). Air pollution, measured by particulate matter ≤2.5 micrometers ($PM_{2.5}$) is an emerging risk factor for CKD and AAs are disproportionately exposed to higher levels. We assessed whether *APOL1* and environmental ($PM_{2.5}$) risk interact.

Methods: We used data from an urban biobanked cohort (Bio*Me* Biobank). This includes linked genotype, demographic and clinical data. We geocoded address level data from initial enrollment date and assigned a census track to link $PM_{2.5}$ estimates from EPAs Downscaler Model. We assigned annual average concentrations using daily $PM_{2.5}$ exposure from the 365 days before enrollment. We considered CKD after enrollment and fit a logistic model accounting for *APOL1*, $PM_{2.5}$ and their interaction, after adjusting for confounders.

Results: We had data on 4800 AAs and 675 (14%) had *APOL1* high-risk. Individuals with *APOL1* high-risk had lower baseline eGFR vs. low risk (75 vs. 81 ml/min). There were no other significant differences. The median $PM_{2.5}$ concentrations were 12.5 $\mu g/m^3$ and did not differ by *APOL1* risk. There were significant associations with CKD for both *APOL1* (adjusted OR 1.5; 95% CI 1.2-1.8) and with $PM_{2.5}$ (adjusted OR 1.09; 95% CI 1.08-1.10 per $\mu g/m^3$ increase) in fully adjusted models. In models accounting for interaction between *APOL1* and $PM_{2.5}$, although both significantly were associated with CKD, there was a possible interaction ($P_{interaction}$=0.06)

Conclusions: *APOL1* and $PM_{2.5}$ may interact for CKD. If validated, air pollution may be a novel environmental 'second hit' for baseline *APOL1* genetic risk.

Funding: NIDDK Support

Table 1. Logistic Regression Model including APOL1 and Air Pollution

	Adjusted Odds Ratio (95% Confidence Interval)	P Value
APOL1 Risk Genotype	1.51 (1.20-1.81)	<0.01
PM2.5 concentration (per μg/m3 increment)	1.09 (1.08-1.10)	<0.01
Interaction term between APOL1 and PM2.5 (continuous)	0.83 (0.7-1.02)	0.06
Age per year increment	1.03 (1.02-1.04)	<0.01
Body Mass Index per 1kg/m2 increment	1.02 (1.01-1.03)	<0.01
Baseline eGFR per 1ml/min decrease	1.06 (1.05-1.07)	<0.01
Education less than high school	0.82 (0.62-1.10)	0.19
African genetic ancestry	0.93 (0.45-1.93)	0.84

FR-PO311

The Effects of Serum Hemoglobin on Renal Survival in Pre-Dialysis CKD: Results from the Korean Cohort Study for Outcomes in Patients with CKD (KNOW-CKD)

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Background: The currently recommended hemoglobin (Hb) targets in CKD based on interventional studies using erythropoiesis stimulating agents (ESA) with outcomes such as cardiovascular events might be inappropriate for Hb target aiming for renal survival in CKD. Thus, we analyzed the effect of Hb on renal outcomes in a prospective pre-dialysis CKD cohort.

Methods: We analyzed the data from 2,197 subjects in KNOW-CKD which is a currently on-going prospective cohort study of CKD in Korea (NCT01630486 at www.clinicaltrials.gov). Renal event (RE) was defined by the doubling of serum creatinine or 50% decrease in estimated GFR (eGFR) by CKD-EPI equation from the baseline, or the initiation of renal replacement treatment. The subjects were grouped according to quartile value of Hb, with ranges of Q1 < 11.2 g/dL, Q2 11.3-12.7 g/dL, Q3 12.8-14.2g/dL and Q4 >14.3g/dL respectively.

Results: Out of 2,197 subjects, a total of 577 subjects (26.3%) developed RE during the mean follow up of 1,289.3±659.5 days. Cox regression analysis adjusted by sex, age, eGFR, urine albumin creatinine ratio, systolic blood pressure, medical history of diabetes mellitus(DM), hypertension, coronary artery diseases (CAD), hypercholesterolemia, smoking and alcohol revealed that each 1g/dL increase of Hb was associated with 19.4% risk reduction for RE (HR=0.806; 95% CI 0.758-0.858, p=0.000). Time dependent Cox regression adjusted by the same variables revealed that RE decreased along with Hb quartile groups (Q1: reference, Q2: HR=0.463; 95% CI 0.303-0.709; p=0.000, Q3: HR=0.176; 95% CI 0.094-0.328; p=0.000, Q4: HR=0.099; 95% CI 0.041-0.234; p=0.000, respectively). The favorable effects of Hb on RE were also consistent in subjects with higher cardiovascular risk factors such as DM, CAD, or coronary artery calcium score>100. ESA were used in only 167 subjects (7.6%) in which RE developed in 101 subjects (60.5%). It was also evident in ESA-receiving group in which each 1g/dL increase of Hb was associated with 21.1% risk reduction for RE (HR=0.799; 95% CI 0.677-0.943, p=0.000).

Conclusions: Targeting higher Hb level than current guideline was associated with the favorable renal outcomes in pre-dialysis CKD irrespective of the presence of higher cardiovascular risks or the usage of ESA.

FR-PO312

Clinical Factors, Non-Neoplastic Histological Variables and Kidney Function in Patients Undergoing Partial Nephrectomy in Solitary Kidneys or Bilateral Partial Nephrectomies

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Background: Significant nephron mass reduction after nephrectomies carries the risk of substantial worsening kidney function. We aimed to evaluate the relationship among clinical, non-neoplastic histological abnormalities and glomerular filtration rate (eGFR) after partial nephrectomy (PN) in solitary kidneys or bilateral PN.

Methods: We studied 57 patients, 24 with PN in a solitary kidney and 33 with bilateral PN. We used Pearson coefficient correlations and logistic regression analyses to evaluate the association between age, hypertension (HTN), diabetes, baseline eGFR, histological variables and post-nephrectomy eGFR at discharge.

Results: The mean age was 62 ± 13 years. The majority had HTN (81%), 23% had diabetes and 46% had chronic kidney disease. The baseline eGFR was 64 ± 26 ml/min/1.73m^2. Of the 36 patients with non-neoplastic histological data available, 75% had interstitial fibrosis (IF), 83% had global glomerulosclerosis (GGS) and 92% had arteriosclerosis (AS). Post-nephrectomy eGFR correlated with baseline eGFR (r=0.7; p<0.001) and IF% (r=-0.4, p<0.05), although not statistical significant, there was a trend in the correlation between post-nephrectomy eGFR and GGS% (r=-0.3; p=0.07). In multivariable-adjusted logistic regression analyses, post-nephrectomy eGFR < 45 ml/min/1.73m^2 was significantly associated with lower baseline eGFR (odds ratio [OR] per 10 units change in eGFR, 0.5[95% confidence interval (CI), 0.3-0.7)]) and PN in a solitary kidney compared to bilateral PN (OR, 6.6[95% CI, 1.3-34.2])

Conclusions: Lower baseline eGFR levels and PN in a solitary kidney compared with bilateral PN were independently associated with significant greater odds of post-nephrectomy eGFR < 45 ml/min/1.73m^2. IF% was significantly correlated with post nephrectomy eGFR.

FR-PO313

A Novel Single Domain, I-Body AD-114, Attenuated Kidney Fibrosis Through Targeting CXCR4

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Background: Kidney fibrosis, the final common pathway of various forms of chronic kidney disease (CKD), affects 10% of the world's population. However, the efficiency of current therapies is limited. The G-protein coupled C-X-C chemokine receptor 4, CXCR4, is a potential therapeutic target for tissue fibrosis. To date, the only approved CXCR4 antagonist (AMD3100) was terminated due to its off-target cardiotoxicity. Recently we have developed a fully human single-domain antibody-like scaffold termed i-body AD-114 with specific high binding affinity to CXCR4. AD-114 selectively blocks CXCR4 signaling and has shown anti-fibrotic effects in pulmonary fibrosis. The present studies have demonstrated the renoprotection of AD-114 in kidney fibrosis.

Methods: CXCR4 expression in the kidney biopsies from patients with diabetic kidney disease (DKD) and kidneys from three mouse models of CKD was detected using immunohistochemistry (IHC). To determine the preventive role of AD-114 in the development of CKD, a mouse model of folic acid (FA)-induced nephropathy was used. C57/BL6 mice (6-8 weeks, N = 10) were challenged with 250 mg/kg of FA followed by daily administration of AD-114(10 mg/kg) intraperitoneally for 21 day. Nonspecific i-body that doesn't bind CXCR4(10 mg/kg) and AMD3100(10 mg/kg) served as negative and positive controls. To assess the therapeutic role, i-body administration commenced when renal injury was established at Day 8 of FA injection and continued for 14 days. Renal function, histology and ECM deposition were assessed by urine creatinine/albumin kits, IHC and Masson's trichrome staining.

Results: CXCR4 expression was significantly upregulated in patients with DKD and fibrotic kidneys of three mouse models of CKD compared to control groups (P<0.001, N=6). In both prophylactic and therapeutic models, the results showed AD-114 markedly ameliorated renal function impairment (24h urine albumin/creatinine ratio) and fibrotic kidney remodeling (Masson's trichrome staining) and attenuated the FA-induced overexpression of collagen-4 (COL-4), fibronectin (FN), collagen-1(COL-1), collagen-3 (COL-3) and α-SMA (IHC) in kidneys compared to negative control i-body.

Conclusions: AD-114 effectively ameliorated fibrotic kidney remodeling through targeting CXCR4 signaling in a murine model of kidney fibrosis.

Funding: Government Support - Non-U.S.

FR-PO314

Assessment of the Feasibility of Measuring Salivary Urea by Attenuated Total Reflection-Fourier Transform Infrared Spectroscopy to Diagnose and Stage CKD

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Background: Attenuated total reflection Fourier-transform infrared (ATR-FTIR) spectroscopy has been shown to provide a straightforward, reagent-free method for the staging and diagnosis of different diseases including pancreatic cancer, and kidney stones. Recently, disposable ATR-FTIR internal reflection elements have been developed. It is plausible, given further advancements, for this technology to be miniaturised and utilised in portable diagnostic devices. Previous studies have shown a correlation between salivary and serum urea in chronic kidney disease (CKD) patients. However, these studies employed costly, labour-intensive commercial kits which limits wider applicability, therefore we assessed the feasibility of ATR-FTIR spectroscopy as an alternative method to measure salivary urea in patients with different stages of CKD.

Methods: The ATR-FTIR spectra of dried saliva samples from 6 healthy controls and 20 CKD patients (stage1-5) were recorded and analysed to provide their urea concentrations in the clinically-relevant range. The correlation between salivary urea and serum urea was also determined. The diagnostic performance of ATR-FTIR spectroscopy to diagnose CKD was assessed from the sensitivity and specificity parameters of a receiver operating characteristics (ROC) curve analysis.

Results: The limit of detection of salivary urea by ATR-FTIR spectroscopy is 2 mM. Statistically significant differences in salivary urea concentration were demonstrated between healthy subjects (4.6±1.4 mM) and CKD patients stages 3-5 (CKD 3: 6.8±0.7 mM, p<0.05; CKD 4: 9.1±1 mM, p<0.001; CKD 5: 14.8±1.6 mM, p<0.001). However, no significant differences were detected between CKD stage 1-2 and healthy controls. ROC analyses (the value ranging from 0.95-1) confirmed the suitability of the method for determination of salivary urea concentrations in the clinically-relevant range, with the sensitivities of 0.86-1 and specificities of 0.93-1.

Conclusions: This study showed that salivary urea can be measured by ATR-FTIR spectroscopy with significant differences in salivary urea levels between CKD stage 3-5 and normal subjects. The development of simple single-use ATR-FTIR spectroscopy devices may be a screening tool for rapid quantitation of salivary urea to diagnose CKD.

FR-PO315

CT Mapping of Spinal and Vascular Abdominal Urate Deposition with Correlation to Uric Acid Level

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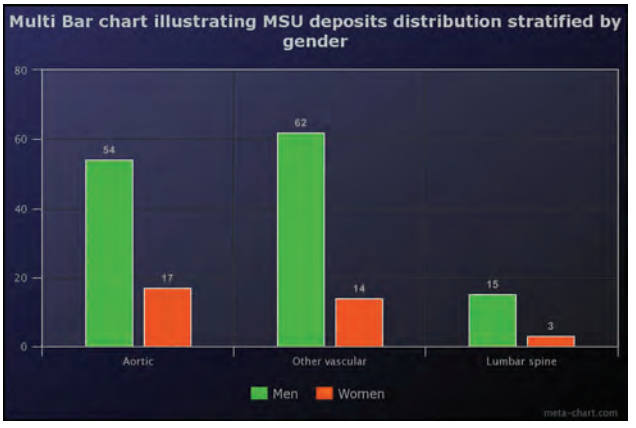
Background: Gout prevalence is about 1-5% in the western world, predominantly in elderly men. Monosodium urate (MSU) deposition outside extremities has been scarcely investigated yet may be a potential indicator of tophus burden and impending clinical deterioration.

Methods: After IRB approval, retrospective single center analysis of all Dual Energy CT abdomen and pelvis scans from January 2007 to July 2018 was conducted. The inclusion criteria were: age > 50 years, gout asymptomatic with high or normal uric acid level. All cases were then assessed by two radiologists using a validated software. The study was divided into two sub-cohorts based on gender, and assessed along three main parameters: aortic, other vascular (e.g. renal, iliac. etc) and lumbar deposits.

Results: 351 cases met the inclusion criteria (197 males, 56% and 154 females, 43.9%). Aortic, other vascular and spinal deposits were detected in 20.2%, 21.7% and 5.1% respectively. A statisical significant association between gender and gout deposits in all the three groups was detected with deposists more prevalent in men than women in all groups (27.4%, 31.5% and 7.6% for men and 11.0%, 9.1% and 1.9% for women in abdominal aorta, other vessels and lumbar spine respectively). Regression analysis showed that uric acid levels cannot predict aortic deposits in neither men (p = 0.91) nor women (p= 0.198) groups. On the other hand, uric acid level can significantly predict other vascular deposits in women only (r=0.005, p= 0,003) and the spinal deposits in both men (r= 0.01, p= 0.003) and women (r=0.002, p= 0.037) groups. Study limitations include retrospective analysis and feasibility sample.

Conclusions: MSU CT mapping was positive in gout-asympomatic patients with normal or high uric acid levels and are more prevalent in men than women. Uric acid level cannot predict aortic deposits but can predict other vascular deposits in women only and spinal deposits in both men and women.



FR-PO316

Pilot Study of Reloxaliase in Subjects with Severe Enteric Hyperoxaluria and Hyperoxalemia: A Pro Tem Analysis of Study ALLN-177-206

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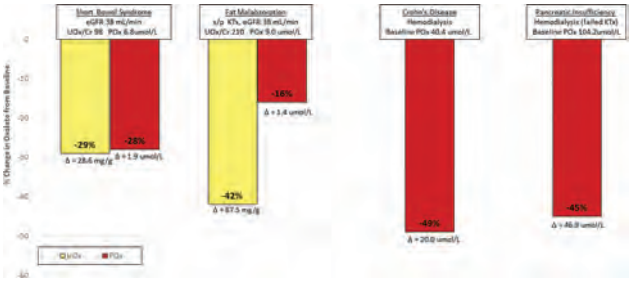
Background: Enteric hyperoxaluria (EH) refers to increased urinary oxalate (UOx) excretion as a complication of fat malabsorption due to GI surgery, or other gastrointestinal conditions. Hyperoxaluria, a major risk factor for kidney stones, can also lead to chronic kidney disease (CKD), including end-stage kidney disease. With decreasing kidney function, plasma oxalate (POx) levels can rise, resulting in oxalate deposition in the kidneys and other tissues. Reloxaliase is an oral enzyme which degrades oxalate in the GI tract. This study is enrolling patients with EH and CKD to examine the potential of reloxaliase to reduce UOx and POx.

Methods: This open label study is enrolling patients with EH, CKD and hyperoxalemia (UOx ≥40 mg/24h, eGFR <45 mL/min/1.73m^2 and POx >5 µmol/L), who receive reloxaliase 7,500U orally 5 x/d for 12 weeks. POx and 24h UOx are obtained monthly; in subjects on dialysis, POx is collected immediately before a dialysis session following the longest weekly interval between sessions. Efficacy is assessed based upon change from baseline to on-treatment average POx and UOx.

Results: To date, 4 EH subjects have completed the study; two have Stage 3 and 3bT CKD (short bowel syndrome, fat malabsorption s/p kidney transplant) and 2 are on hemodialysis (Crohn's disease, pancreatic insufficiency). Treatment compliance was >90% on average, and therapy was well tolerated. Reloxaliase reduced 24-hr UOx (normalized to creatinine) by 29-42%, and POx by 16-49%. The figure below provides high level case summaries, and the bars show the % change in UOx (yellow) or POx (red) from baseline.

Conclusions: In this population, reloxaliase was well tolerated and reduced both UOx and POx, suggesting the potential for reducing systemic oxalate deposition with chronic therapy. These preliminary data support further testing of reloxaliase in patients with severe EH. To our knowledge, this is the first therapeutic reduction in plasma oxalate in patients with EH and CKD with oxalosis.



FR-PO317

Association of Serum Alkaline Phosphatase with CKD and Cognitive Function in Patients with Diabetes and Acute Coronary Syndrome

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Background: Patients with diabetes and chronic kidney disease (CKD) have increased risk for cardiovascular disease events and vascular dementia. Alkaline phosphatase (ALP) is a risk marker and possible risk mediator for cardiovascular (CV) disease, Alzheimer's disease and vascular dementia. ALP has been reported to cross the blood brain barrier and to predict cognitive risk in CKD patients, potentially via vascular mechanisms or dephosphorylation of tau. Apabetalone is a bromodomain and extraterminal (BET) inhibitor selective for bromodomain 2, lowers ALP in a dose-response fashion and is being evaluated for prevention of CV disease events in the phase 3 BETonMACE trial. We examined baseline data from that trial to define the associations of ALP with CKD and cognitive function.

Methods: BETonMACE compares cardiovascular outcomes with apabetalone or placebo in 2425 patients with diabetes and acute coronary syndrome. CKD was defined by eGFR < 60 mL/min/1.73m^2. Cognition was assessed by the Montreal Cognitive Assessment tool (MoCA) in patients aged 70 and older at baseline (n=467) including in CKD patients (n=86).

Results: CKD was present in 11% (n=263) and was associated with age, female sex, longer history of diabetes, and higher ALP. Approximately half of the population showed MoCA score <26 suggesting early cognitive impairment. Lower MoCA score was associated with: a) higher ALP, and, b) with presence of CKD.

Conclusions: Elevated ALP is associated with poorer cognitive function and greater prevalence of CKD. Apabetalone, which lowers ALP, is being evaluated for effects on CV events, CKD, and cognitive function in the phase 3 BETonMACE trial reporting 2019.

FR-PO318

The KDIGO 2012 CKD Classification System Improves Physician Recognition and Management of Kidney Disease: A Randomized Vignette Study

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Background: Chronic kidney disease (CKD) is common worldwide with high morbidity and mortality rates. New international guidelines based on estimated glomerular filtration rate (eGFR) versus albuminuria were introduced 2012 to help with diagnosis, classification, referral, and treatment, but their clinical utility has not been evaluated. We therefore wanted to determine if KDIGO guideline helps physicians recognize and appropriately care for CKD patients.

Methods: We conducted a randomized vignette experiment with fractional factorial design based on 6 kidney-related scenarios and 3 laboratory presentation methods reflecting the KDIGO guideline. Participants evaluated one of three subsets of the 18 vignettes (i.e. 6 vignettes each with 4 answer alternatives). Kidney related results (serum creatinine and urine albumin) were presented as the "Old" (high/low levels), "Modern" (eGFR reported automatically), or "Future" (eGFR + albuminuria categorization + risk for complications = full 2012 KDIGO classification) laboratory report. Logistic regression modelled correct CKD management with laboratory presentation technique, clinical scenario, and other physician covariates. We included 249 interns, general practitioners, and residents/fellows from Norway and the US participating in post-graduate meetings and courses provided to physicians in training.

Results: When kidney laboratory data was presented as the "Modern report" (automatic eGFR calculation), there was a significantly higher probability for correct patient management compared to the "Old report" (OR 1.57, p<0.0001). Additional significant improvement was obtained with the "Future report" (OR 2.28 for correct answer, p<0.001 vs. "Old report"; OR 1.45, p=0.005 vs. "Modern report"). The 2012 KDIGO classification system improved physician management in 4 of the 6 clinical scenarios covering a wide range of kidney-related topics. Interaction analysis showed that GPs and those with 1-3 years of internal medicine experience had the strongest improvements with the new presentation techniques

Conclusions: Automatic GFR estimation, albuminuria categorization, and notification of the associated risk for complications improve most physicians' recognition and management of a wide range of CKD clinical scenarios.

Funding: Government Support - Non-U.S.

FR-PO319

Residential Greenness Improves Clinical Outcomes of Patients with CKD

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Background: As industrialization has progressed, green areas have been decreasing. The association between the distribution of green spaces and health outcomes is becoming global issues, especially regarding cardiovascular and respiratory diseases. However, little is known for relationship between residential greenness and survival of patients with chronic kidney disease (CKD).

Methods: 64,780 patients who visited 3 medical centers (Seoul National University Hospital, Seoul National University Bundang Hospital, Seoul National University Boramae Medical Center) from January 2001 to December 2016 were enrolled in the cohort study. Cox proportional hazard models were used to identify the association between long-term exposure of green space and mortality of patients with CKD, occurrence of end-stage renal disease (ESRD) and major adverse cardiovascular events (MACE) which were adjusted by age, sex, estimated glomerular filtration rate, hemoglobin albumin, hypertension, diabetes and mean particulate matter < 10 μm in aerodynamic diameter (PM_{10}). Green space was defined as average normalized difference vegetation index (NDVI) in summer (Jun-Aug) around patients' residence within 250m and 1250m area measured by MODIS satellite.

Results: The mean age of patients was 54 years, and 49 % of them were male. During the mean 6.75 follow-up years, 8,557 deaths (13%) occurred. Higher levels of residential greenness within 250m area (0.1 increases in residential NDVI) had lower HRs for all-cause mortality (HR 0.91, CI 0.89-0.94), MACE (HR 0.94, CI 0.90-0.97) and progression to ESRD (HR 0.88, CI 0.83-0.93), which were adjusted by PM_{10} of observation stations within 5km around the residence. Those who were highly educated, non-smokers and non-drinkers were more affected by residential greenness. These results were consistent for the 1,250m area which were adjusted by mean PM_{10} within 3km and 5km around residence.

Conclusions: CKD patients who lived in areas with higher levels of greenness had reduced risks of all-cause mortality, MACE and progression to ESRD.

FR-PO320

Role of Demographic Variables on Prevalence of Anxiety and Depression (AAD) in CKD Patients and Its Co-Relation with Quality of Life and CKD Outcome Parameters

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Background: Adapting with AAD in presence of CKD is challenging. Being multifactorial addressing AAD needs better etiological understanding. The purpose of this study is to find the relationship between different riders of demography with AAD and to investigate whether AAD has any correlation with quality of life(QOL) or overall CKD outcome.

Methods: 583 CKD patients (18-80yrs) of different stages and etiology, were enrolled in this prospective observational study. Any previous or ongoing treatment of psychiatric disorder, medical ailments or sorrowful events during recent past at the time of inclusion were excluded. The Hospital Anxiety and Depression Scale (HADS) were used as a tool to measure the AAD level. Demographic data, medical history, education level, professional details, nature composition and support from family, number of dependents, financial burden, and healthcare insurance coverage data were recorded. Baseline serum creatinine, estimated GFR(MDRD), routine clinical and lab data, QOL parameters, hospitalization, cardiovascular events and mortality data were captured quarterly until the end of study. HADS was recorded every 3 months to assess the severity of AAD. All patients were longitudinally followed up for 5 years. SPSS v 25.0 was used for statistical analysis, $p \leq 0.05$ were considered as statistically significant

Results: Out of 583 CKD patients [145(24.9%) dialysis and 438(75.1%) pre-dialysis], 59.3% were male and 40.6% were female. Mean age was 57.75 ±13.53 years. Anxiety was predominant in pre-dialysis patients whereas depression was prominent in dialysis subgroup. AAD were significantly more among male than female and in middle-aged than in elderly. Socioeconomic status, family support, dependent members in family and insurance coverage were variably associated with AAD. Maximum AS was observed while first encounter with nephrologist and when being advised for RRT. AS >8.0 and DS >7.0 was significantly correlated with poorer QOL parameters. Poorer blood pressure control, faster decline of GFR and frequent hospitalization were significantly correlated with AS >8. A positive trend toward association of all-cause mortality was observed with DS >7.

Conclusions: Different demographic variables has significant impact on AAD in CKD. AAD has variable impact on QOL, BP control, CKD progression and hospitalization or all-cause mortality.

FR-PO321

Location and Preference for Place of Death in Those Supported by a Kidney Supportive Care Clinic

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Background: Kidney supportive care (KSC) multidisciplinary clinics aim to improve quality of life and respect a person's wishes in death. One important outcome indicator of meeting a person's wishes is place of death (POD). The literature reports patients' preferred POD is most frequently their home or palliative care unit. Despite this body of literature, 54% of deaths in those aged over 65 occur in hospitals and 14% at home in Australia. We aim to assess if POD is concordant with actual POD in those known to KSC clinic.

Methods: Retrospective cohort study of patients attending a single center KSC clinic from February 2016 and who died prior to April 2019. Data including demographics, kidney replacement therapy pathway, prefered POD, actual POD, details of hospital deaths, timing of KSC clinic review were extracted from medical records. Early referal was defined as being seen in an out-patient setting and late referral defined as those not seen until the terminal hospital admission. Late and early group POD were compared using a Chi-Square test.

Results: 141 people were included in the analysis with the median age at death of 77 years (range 29-92 years), 40.4% female. Treatment pathways prior to death were haemodialysis (45.4%), peritoneal dialysis (6.4%) and conservative (48.2%). Referrals to KSC were early (73%) or late (27%). If seen early the preference for POD was in the community (80.6%; home or palliative care unit), hospital (9.7%) or it was unknown (9.7%). The preferred POD in those referred late was unknown (47.4%), community (36.8%) or hospital (15.8%). The early referral group were more likely to preference a community POD compared to late referrals (p=0.03). Concordance between preferred POD and actual POD in the early referral group was positive (63.1%), discordant (27.2%) or unknown (9.7%). Concordance in the late referral group was positive (31.6%), discordant (21%) or unknown (47.4%). The rate of concordance between groups was not statistically different.

Conclusions: Timely referral to a KSC clinic can assist with ensuring that death occurs in the preferred location. Late referrals do not allow adequate time for ascertaining or facilitating wishes. Ways to maximise quality of life and avoid medically futility need to be considered in this population.

FR-PO322

Experience of a Tertiary Center in the Training of Nephrology Fellows on Performing Real-Time Ultrasound-Guided Percutaneous Kidney Biopsy

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Background: Percutaneous kidney biopsy is a fundamental diagnostic tool in Clinical Nephrology, but there is concern as to whether it can be performed by Fellows. The aims of this study were to report a 10-year experience of a tertiary academic center in the qualification of Fellows to perform ultrasound-guided percutaneous biopsies of native kidneys.

Methods: This is a retrospective cohort study of native kidney biopsies performed between January/2009 and December/2018. The procedures were performed by Fellows and supervised by experienced Nephrologists. Predictors of complications, clinical outcomes and sample quality were analyzed.

Results: A total of 1387 biopsies was performed; the mean age was 40.7±16.2 years, with 60% of women (n=830) and the Body Mass Index was 25.2 kg/m^2. At the time of biopsy, lab exams were: serum Creatinine 2.2 ± 1.9 mg/dL, BUN 31±16 mg/dL, Hemoglobin 11.7±1.8 g/dL and Platelet count 262±95x10^3/mm^3. As to complications, 91.4% (n=1268) had none, 4.5% (n=63) had hematuria; 2% (n=28) had symptomatic hematoma; 2% (n=28) had majorcomplications, defined by the need for transfusion and/or arteriography. Independent predictors of major complications were female gender (OR 2.9; CI 1.01 to 8.1; p=0.049), hemodialysis (OR 8.0; CI 2.9 to 9.2; p<0.001), low platelet count (OR 0.99; CI 0.98 to 0.99; p=0.035) and hemoglobin level (OR 0.61; CI 0.40 to 0.96; p=0.032). The average sample contained18±10 glomeruli for light microscopy, 11±8 for immunofluorescence, while and 90% of samples contained at least 8 glomeruli.

Conclusions: Supervised kidney biopsies performed by Fellows in training were safe and efficient. Female gender, hemodialysis, low platelet count and hemoglobin levels were independent predictors for major complications.

FR-PO323

Online Peer Mentoring Is Associated with Improved Burden Score Among Caregivers of Patients with CKD

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Background: Caregivers experience significant burden resulting from providing care to patients with chronic kidney disease (CKD). Peer mentoring (PM) has been proposed as an effective strategy which may result in improvement in caregiver burden. This study evaluates the differences in the effect of online PM, face-to-face (FTF) PM, and usual care on burden among caregivers of patients with CKD.

Methods: A 16-hour structured program trained CKD patients and their caregivers to become peer mentors to newly diagnosed patients with CKD and their caregivers. Caregivers of patients with stage 4 or stage 5 CKD (n=86) were randomly assigned to online PM (n=29), FTF PM (n=29) or usual care (n=28). Online PM consisted of weekly communication through an interactive online platform, and more frequently through posts by the mentee. For the FTF group, the frequency of contact by a mentor was weekly by phone and monthly visit. PM was maintained for at least 6 months. Usual care participants received an information book about care of CKD patients. We used the 22-item Zarit Burden Interview (ZBI) to measure caregiver burden at baseline and months 12 and 18. Higher ZBI scores indicate heavier burden. We used linear mixed effect models to estimate the slope of change of ZBI score over time. SAS, version 9.4 was used for data analysis.

Results: A total of 70 caregivers completed the 18 month assessment. Baseline ZBI score and demographic characteristics (race, ethnicity, gender, age, marital status, education, employment status and rural/urban location) were similar among the groups. The online PM group showed a significant improvement in the mean ZBI score between baseline and 12 months (23.6±12.1 vs. 16.5±9.1); this improvement was sustained at 18 months (15.2±9.9) (Slope estimate [SE]:-3.44; 95% confidence interval [CI]:-6.31, -0.57 [P=0.02]). The decrease in ZBI was not significant in the FTF group (SE:-2.50;CI: -5.85, 0.87 [P=0.14]), or the control group (SE: -1.26;CI: -4.06, 1.54 [P=0.36]). Improved ZBI with online PM was independent of demographic characteristics.

Conclusions: Online PM is associated with a significant improvement in burden score among caregivers of patients with advanced CKD. The improvement is sustained at 18 months and is independent of demographic characteristics. Funding by: PCORI

Funding: Other U.S. Government Support

FR-PO324

Association of eGFR Slopes Before and After CKD Education with Renal Prognosis

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Background: Multidisciplinary education for patients with CKD plays a critical role in the prevention for CKD progression and development of ESRD. In this study, we thus aimed to determine the relationship between eGFR slopes before and after CKD education and renal prognosis.

Methods: This is a retrospective cohort study on 617 patients who underwent in-hospital CKD education in Nara Prefecture General Medical Center between Jan. 2013 and Dec. 2016. Baseline data were collected at the time of CKD education. Patients with acute kidney injury, urologic malignancies, or collagen disease were excluded, leaving 194 patients for analysis. We calculated two eGFR slopes before and after education with three eGFR levels which were measured at 3 months to 1 year before CKD education, baseline and at least 1 year after education. We divided into 4 slope categories according to median levels of two eGFR slopes before and after education: slope categories were defined as slow-slow, fast-slow, slow-fast, fast-fast eGFR decliner. Outcomes are ESRD and eGFR decline of > 30%. Kaplan-Meier curve and Cox proportional hazards model with propensity adjustment were used to assess the association between slope categories and incidence of renal events. Patients with fast-slow eGFR decline were used as a reference group.

Results: The median age of study participants was 68 (59-78) years and 130 (67%) were male. The median levels of baseline eGFR were 33 (21-48) mL/min/1.73m^2. During the median follow-up period of 35 months, renal events occurred in 53 participants. Crude Kaplan-Meier analysis showed patients with slow-fast and fast-fast eGFR declines were significantly associated with renal events compared with those with slow-slow and fast-slow eGFR declines (p<0.001). In adjusted Cox hazard analysis, hazard ratios for outcomes were 1.72 (95%CI 0.38-8.8) for slow-slow, 5.15 (95%CI 1.72-22.2) for slow-fast and 7.27 (95%CI 2.53-30.7) for fast-fast eGFR decliner. Additionally, c-statistics of eGFR slope before education for renal events was 0.596 but that of eGFR slope after education was 0.843 and the cut-off level was -2.5 mL/min/1.73m^2/year.

Conclusions: Improvement from fast to slow eGFR decline via CKD education was significantly associated with better renal prognosis. However, CKD patients with rapid eGFR decline of ≤-2.5 mL/min/1.73m^2 after education have poor renal outcomes.

FR-PO325

Are Patients' Needs for Shared and Informed Decision Making About Kidney Replacement Therapy Being Addressed?

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Background: Little is known about how patients perceive shared and informed decision making (SDM) about kidney replacement therapy.

Methods: As part of the PREPARE NOW trial, we asked adults with CKD if they desired shared decision making [SDM] about CKD treatments (i.e., "the doctor and I make the final decisions together"). We also asked participants to what extent they had discussed different kidney replacement treatments and potential treatment impacts with their kidney treatment teams as well as their satisfaction with discussions. We derived 2-year kidney failure risks from medical records. In multivariable models, we quantified associations of participants' characteristics with treatment discussions and associations of discussion quality with participant satisfaction.

Results: Among 456 participants, 322 (70.6%) desired SDM. These 322 had a mean (SD) age of 70.2 (12.7) years, 60% were female, 96% White, and 62% high school or less educated. They received nephrology care for a median (IQR) of 3.85 (1.94-6.49) years. Half (52%) saw their nephrologists at least every 6 months, and 17% had a 2-year risk of kidney failure >10%. Only a third (35%, n=113) of those desiring SDM had discussed any treatments (peritoneal dialysis [45%], in-center hemodialysis [86%], home hemodialysis [50%], kidney transplant [59%], and conservative management [70%]). Few discussed treatment impacts on their finances (26%), family's wellbeing (29%), need for help from family (37%), length of life (49%), or quality of life (60%). Still, a majority (64.6%) were 'completely' satisfied with discussions. After adjustment, those seeing nephrologists for longer had greater odds of having discussed transplant (OR [95% CI]: 1.16 [1.02-1.32] per 1-year increase, p=0.02). Those whose teams discussed more modalities (OR [95% CI]: 1.66 [1.19-2.33], p<0.01) or treatment impacts (OR [95% CI]: 1.69 [1.26-2.27], p<0.01) had greater odds of being 'completely' satisfied.

Conclusions: Most patients prefer sharing CKD treatment decisions with their physicians, but treatment discussions are infrequent and do not address key treatment aspects. More frequent and thorough discussions could improve patients' SDM experiences.

FR-PO326

Timing of Decisions About Conservative Management of Advanced CKD: Are We Adding to Patient Burden?

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Background: Non-dialytic, Conservative management (CM) is an increasingly prevalent option for the management of advanced chronic kidney disease (CKD) – especially in patients of advanced age or with high comorbidity. There is an increasing trend for making the CM decision earlier in the course of CKD. Whilst this offers an advantage in avoidance of unnecessary preparations for dialysis, there is a risk of subjecting some patients, with very low likelihood of progression to ESRF, to unnecessary distress.

Methods: In this retrospective study, we examined all patients who had the CM decision made in our regional renal centre.

Results: From 1 January 2006 to 31 December 2015, 338 patients had the CM recorded in their diagnosis list. Median age was 82.1 (IQR 92) years. 79.8% of patients

were judged as having moderate or high comorbidity. The median eGFR at the time of initiation of CM discussion with patients was 13.8 (IQR 5.7) ml/min/1.73 m^2. 281 (83.1%) had died at the date of last follow up. 46% of patients had a median eGFR > 10 ml/min/1.73 m^2 at last follow-up. Median eGFR at the time of death in CM patients was 9.1 ml/min/1.73 m^2 (IQR 7.0). 42% of those who died had a last recorded eGFR > 10 ml/min/1.7 m^2. 32 patients (9.4%) developed severe acute kidney injury during follow-up and 8 of these (2.4%) received dialysis. 15 patients (4.4%) changed their decision from CM to dialysis. The median rate of eGFR decline in the year before CM decision was 3.8 (IQR 6.5) ml/min/year in the whole group. eGFR at CM decision was inversely related to rate of eGFR decline in tertiles (tertile 1 [slowest decline] - 14.7 (IQR 6.7), tertile 2 -13.6 (IQR 5.4), tertile 3 – 12. 9 (IQR 5.3): p = 0.006). eGRF at CM decision was higher in patients with high comorbidity compared to those with low-moderate levels (14.7 [1QR 5.7] vs 13.5 [IQR 5.5]: p = 0.032)

Conclusions: Many patient on the conservative pathway die at relatively high levels of kidney function (eGFR >10 ml/min/1.73 m^2), probably related to extrarenal comorbidity. Decision making seems to focus more on age, comorbidity, and absolute levels of eGFR than on eGFR trajectory. As a result of this it is possible that some patients are unnecessarily burdened with decisions relating to choices between options of renal replacement therapy.

FR-PO327

Health-Related Quality of Life Is Associated with Disease Progression in Adults with Advanced CKD Not on Renal Replacement Therapy

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Background: Chronic kidney disease (CKD) is associated with reduced health-related quality of life (HRQOL). However, the association between HRQOL and disease progression prior to renal replacement therapy (RRT) is unclear. We examined the influence of HRQOL on disease progression in adults with Stage IV CKD (eGFR 15-29mls/min/1.73m^2) not on RRT.

Methods: Overall, 172 adults living in Tasmania, Australia provided data at baseline (2010-2012, 2016-2018). Of these, 152 participants attended a clinic where the Kidney Disease Quality of Life–Short Form was completed. Disease progression was examined using i) percentage annual change in eGFR [(eGFR at follow-up/eGFR at baseline)^(1/years elapsed between measurement)-1]*100 and ii) progression to CKD Stage V (eGFR<15mls/min/1.73m^2) or death. Generalized linear models were used to examine associations between HRQOL and disease progression adjusted for sociodemographic variables, comorbidities and laboratory factors.

Results: Overall, participants were predominantly male (63%) with a mean age of 72.2±10.2 years. At baseline, mean eGFR was 22.1±4.2 mls/min/1.73m^2 and serum creatinine was 242.3±56.4 μmol/L. Mean annual decline in eGFR was -4.2 mls/min/1.73m^2. Mean percentage annual change in eGFR was 8.8% with 61 (35%) participants progressing to CKD Stage V or death. Mean time to outcome was 446±289 days. Mean mental component summary (MCS) was 50.9±10.3 and physical component summary (PCS) was 38.6±10.4. Mean subscale scores were 81.8±17.5 for cognitive functioning and 74.0±24.9 for burden of disease. Improved cognitive functioning was positively associated with % annual change in eGFR (β=0.46, 95% CI 0.05-0.88, R^2=0.04,p<0.05). Both improved cognitive functioning (OR 0.98, 95% CI 0.95-0.99, R^2=0.23, p<0.05) and lower burden of disease (OR 0.98, 95% CI 0.96-0.99, R^2=0.24, p<0.05) were associated with lower odds of CKD Stage V or death. Baseline MCS and PCS were not associated with disease progression.

Conclusions: HRQOL involving self-reported cognitive functioning and burden of disease is associated with disease progression in adults with Stage IV CKD. Identifying modifiable risk factors is an important step in reducing the risk of RRT and premature death in this patient population and improving quality of life.

Funding: Private Foundation Support

FR-PO328

A Prospective Randomized Controlled Trial of Lifestyle Management for Preventing Respiratory Tract Infection in Patients with CKD

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Background: Respiratory tract infection (RTI) is a risk factor for progressive loss of kidney function. Lifestyle management has shown potential effect to prevent RTI in chronic kidney disease (CKD) patients. The study assessed the efficacy and safety of lifestyle management in reducing RIT of CKD patients.

Methods: In this prospective randomized controlled trial (RCT), 540 patients with CKD vulnerable to RIT were randomly assigned 1:1 to either lifestyle management group or control group for 48 weeks. Both groups received conventional care according to guideline recommendations, while patients in lifestyle management group additionally accepted health lifestyle management involving life behavior mission, acupoints massage and dietary guidance. The primary outcome was the interval of first occurrence of RIT. Secondary outcomes included the incidence of endpoint events, immunity indices, urinary protein creatinine ratio (PCR), liver and kidney function, cardiovascular events. This study was registered with Chinese Clinical Trials Registry, ChiCTR-IOR-17012654.

Results: 540 patients were screened, of whom 262 were randomly assigned: 161 to the lifestyle management group, 161 to the control group (30 patients were excluded) from January 1st, 2016 to December 31st, 2018. 77 (66.4%) patients in the life management group and 78 (67.2%) patients in the control group developed RTI over 48 weeks. Among them, 49 patients (42.2%) and 52 patients (44.8%) had RTI more than twice respectively. The interval of first occurrence of RTI in the life management group was 85.65±84.97 days, which was similar to the control group (84.36±90.63 days). The survival analysis showed that the patients with high frequency of RTI (>3 times within one year before enrollment) in the life management group had a lower risk of RTI than the control group (68 days vs. 65 days) (HR 0.87,95%CI 0.57-1.31). The level of IgA, C4, CH50, CD3CD4, CD3CD4/CD3CD8 in the life management group was higher than the control group, suggesting that immunity function of the patients was enhanced after lifestyle management. There was no significant difference in endpoint events, liver and kidney function, PCR and other safety indexes between the two groups.

Conclusions: Lifestyle management shows the effect to reduce the prevalence of RTI in CKD and slow CKD progression.

Funding: Government Support - Non-U.S.

FR-PO329

Dialysis vs. Conservative Care to Treat ESRD: A Systematic Review and Meta-Analysis

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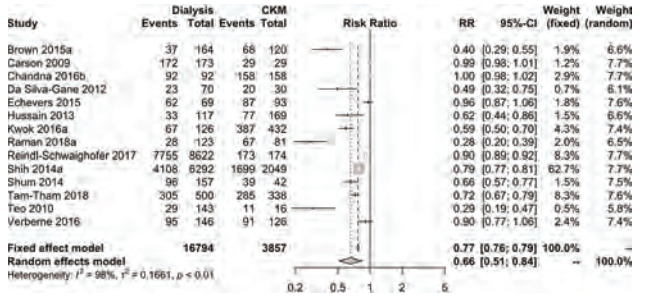
Background: The advantage of treating selected ESRD patients with dialysis over non-dialysis, conservative therapy, is unclear. We addressd this gap by providing a comprehensive evidence synthesis on the outcomes of dialysis vs. conservative care in ESRD patients.

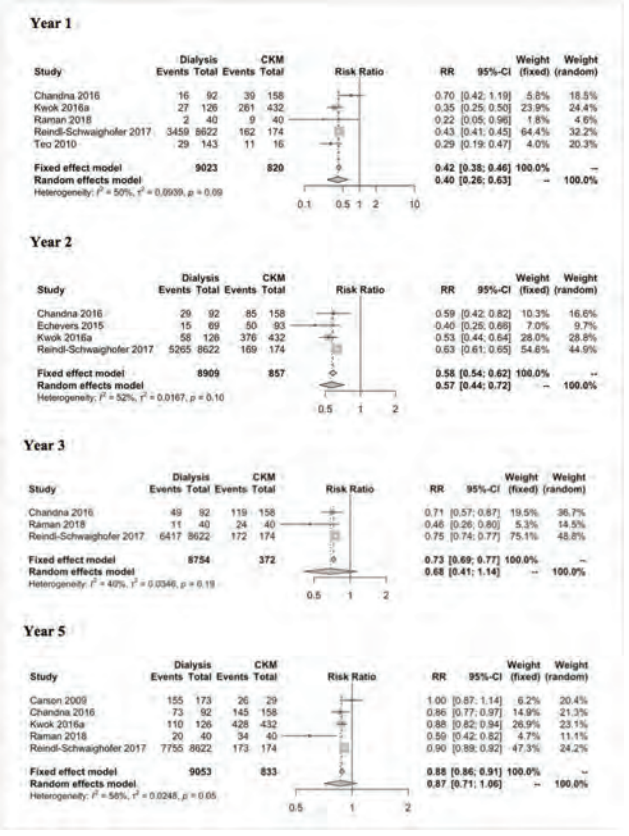
Methods: MEDLINE and EMBASE were searched from January 2009 to April 2019 for prospective and retrospective cohort studies that examined outcomes of ESRD patients receiving dialysis vs. conservative care. We calculated pooled risk ratios (RRs) and 95% confidence intervals (CIs) as well as statistical measures of variability in results across studies using random-effects models for all-cause mortality at years 1, 2, 3 and 5. Annual hospital inpatient days were pooled using standardized mean differences (SMD).

Results: Among 1,075 citations, 14 were included that involved 16794 and 3857 patients initially treated with dialysis or conservative care. Dialysis was associated with lower risk of all-cause mortality at year 1 (RR, 0.40, 95% CI, 0.26-0.63), year 2 (RR, 0.57, 95% CI, 0.44-0.72), and end of study (RR 0.66, 95% CI, 0.51-0.84), while no difference was detected at year 3 (RR, 0.68, 95% CI, 0.41-1.14) and year 5 (RR, 0.87, 95% CI, 0.71-1.06). There was no difference of annual hospital inpatient days (SMD, 14.64, 95% CI, -173.56-202.84).

Conclusions: Dialysis results in lower mortality in the short-term (the first two years) but may not improve survival thereafter (after the third year).



Forest plot: Mortality at end of study



Forest plot: Mortality at years 1, 2, 3, and 5

FR-PO330

Sustained Effect of Online Peer Mentoring on Activation of Patients with CKD

Korey Bartolomeo, Jose C. Romeu, George C. Ezeji, Eric Mark J. Lopez, Vernon M. Chinchilli, Nasrollah Ghahramani. *Penn State College of Medicine, Hershey, PA.*

Background: Peer mentoring (PM) has been proposed as a model for active patient engagement. This study evaluates the differences in the effect of online PM, face-to-face (FTF) PM and usual care on patient activation among chronic kidney disease (CKD) patients.

Methods: A total of 155 patients with stage 4 or stage 5 CKD were randomly assigned to online PM, FTF PM or usual care. Online PM consisted of weekly communication through an interactive online platform, and more frequently through posts initiated by the patient. For the FTF group, the frequency of contact by a mentor was weekly by phone and monthly visit. PM was maintained for 6 months. Usual care participants received an information handbook and were encouraged to discuss questions with their care team. We administered the 13-item validated Patient Activation Measure® (PAM) at baseline, at 12 months and at 18 months. We used linear mixed effect models to estimate the slope of change of PAM score over time. SAS, version 9.4 was used for data analysis.

Results: A total of 117 patients completed the 18 month assessment. Baseline PAM scores and demographic characteristics were similar among groups. The online PM group showed a significant improvement in mean PAM score between baseline and 12 months (67±15.7 vs. 77.5±12.7); improvement was sustained at 18 months (78.0±14.2) (Slope estimate [SE]:5.65;95% confidence interval [CI]:2.75, 8.52 [P=0.0001]). Among the FTF group, there was no significant change in PAM score in the 3 periods (SE:0.95;CI: -1.96, 3.86 [P=0.52]). Among the control group, there was no significant change in PAM score in the 3 periods (SE:0.02;CI:-3.03, 3.08 [P=0.99]). Slopes of change in PAM were significantly different between online and FTF groups (p=0.02), as well as online and control groups (p=0.009); there was no difference in the slopes of change in PAM between FTF and control groups (p=0.66). In subgroup analyses, the difference between the online group and other groups in slope of change in PAM was significant among male, but not female participants and among married, but not unmarried participants.

Conclusions: Online peer mentoring is associated with improved scores in Patient Activation Measure among patients with advanced CKD. This improvement is influenced by gender and marital status. Funding: PCORI

Funding: NIDDK Support, Other U.S. Government Support

FR-PO331

Online Peer Mentoring and Quality of Life Among Patients with CKD

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Background: Quality of Life (QOL) is an important medical outcome in patients with chronic kidney disease (CKD). Peer mentoring (PM) is a potentially effective intervention to improve QOL. This study evaluates the differences in the effect of online PM, face-to-face (FTF) PM and usual care on QOL patients with CKD.

Methods: A total of 155 patients with stage 4 or stage 5 CKD were randomly assigned either to online PM (n=52), FTF PM (n=52) or usual care (n=51). Online PM consisted of at least weekly communication through an interactive online platform, and more frequently through posts initiated by the patient. For the FTF group, the frequency of contact by a mentor was weekly by phone and monthly FTF visit. PM was maintained for at least 6 months. Usual care participants received a printed copy of an information handbook and were encouraged to discuss questions with their care team. All participants completed the Short Form Kidney Disease Quality of Life (KDQOL) tool designed specifically for patients with CKD, at baseline, at 12 months and at 18 months. We used linear mixed effect models to estimate the slope of change of subsets of KDQOL score over time. SAS, version 9.4 was used for data analysis.

Results: A total of 117 patients completed the 18 month assessment. Baseline KDQOL scores and demographic characteristics were similar among the 3 groups. Among the online PM group, there was a significant improvement in the following components of the KDQOL score: Effects of Kidney Disease (EKD) (Slope estimate [SE]:4.13; 95% confidence interval [CI]:0.87, 7.4 [P=0.01]); Burden of Kidney Disease (BKD) (SE:5.44; CI: 1.24, 9.64 [P= 0.01]);SF-12 Physical Composite (SE:2.50; CI:0.95, 4.06 [P=0.002]); SF-12 Mental Composite (SE:3.46; CI:1.78, 5.13 [P<0.0001]). In subgroup analyses, the improvements noted among the online PM in the EKD and BKD subscales were significant among white patients, but not among non-white patients. The improvements in the Physical and Mental Composite subscales were significant among non-white patients, but not among white patients. There were no statistically significant changes in KDQOL scores among the FTF PM group and the control group.

Conclusions: Online PM is associated with improved scores in subsets of the KDQOL among patients with advanced CKD. This improvement is influenced by race. Funding: PCORI

Funding: Other U.S. Government Support

FR-PO332

High Incidence of Adverse Drug Reactions in Patients with Advanced CKD

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Background: Little is known about adverse drug reactions (ADRs) in chronic kidney disease (CKD). We assessed the incidence rate and type of ADRs by CKD stage.

Methods: The CKD-REIN study includes 3033 outpatients (65% men) with CKD (eGFR<60mL/min/1.73m^2). ADRs were identified from medical records, hospital discharge reports, or patient interviews and adjudicated by pharmacist experts. A serious ADR is any event that is fatal, life-threatening, permanently/significantly disabling, requires or prolongs hospitalization or medically important. Determinants of first serious ADR-events were assessed by multivariate Cox regression model.

Results: At baseline, patients' median age was 69 (IQR, 60-76), median eGFR was 32 (IQR, 23-41) mL/min/1.73m^2 and the median number of medications was 8 per day. During a median follow-up of 2 years, 751 ADRs were reported in 536 patients, of which 150 were serious. The incidence rate of ADRs in patients with CKD stage 4 or 5 was 19.5[95%CI,17.6;21.4] per 100 person years (PY), against 10.9[9.7;12.1] per 100 PY in patients with CKD stage 3. We observed the same pattern for serious ADR with an incidence rate respectively of 4.0[3.2;4.8] per 100 PY in the former group and 1.8[1.3;2.2] per 100 PY for the latter one. Antithrombotics (34%), diuretics (12%) and renin-angiotensin system inhibitors (12%) represented the most frequent pharmacological classes associated with serious ADRs. Antithrombotics-linked serious ADRs were more common in patients with a low baseline eGFR (43% in CKD stages 4-5 vs. 20% in CKD stage 3). This marked difference between stages severity was not found for serious ADR related to diuretics or RAS inhibitors. On 10 deaths directly or indirectly related to an antithrombotic-linked serious ADRs, 8 occurred in CKD stage 4 or 5 patients, and 2 in CKD stage 3 patients. After adjusting for relevant covariates, hazard ratios for ADRs and for serious ADRs were significantly higher in patients with baseline eGFR < 30 vs. ≥30mL/min/1.73m^2 (respectively 1.6[13;1.9], 1.8[1.25-2.62]).

Conclusions: The burden of ADRs is high in CKD patients. A low eGFR appears as a risk factor of undergoing ADRs and serious ADRs. When taking care to CKD patients, especially advanced stages, antithrombotic agents need to be used with caution.

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FR-PO333

Physician-Guided CKD Self-Management via Smartphone App Is Associated with Proteinuria Reduction: A Retrospective Cohort Study

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Background: Smartphone apps are increasingly popular for chronic disease management. However, the feasibility and effectiveness of smartphone apps to manage Chronic Kidney Disease (CKD) are unknown. This study assessed the feasibility and effectiveness of a smartphone app for self-management of CKD.

Methods: "Kidney online" is a patient-facing, algorithm assisted, physician-guided, and interactive app in Chinese. Patients with a self-reported diagnosis of CKD used the app to track their symptoms, physical activities, vital signs, and laboratory test results. Patients received automatic recommendations by the proprietary algorithm and consulted their assigned tele-nephrologists on an ad-hoc basis. Patients who were enrolled in this app for more than 3 months between Dec. 2016 to Nov. 2018 with proteinuria ≥ 500mg/24hr were eligible for analysis. Changes in blood pressure (BP), estimated glomerular filtration rate (eGFR), and 24-hr proteinuria level were evaluated as outcomes between quartile groups, stratified by the total number of patient-physician conversations. Content analysis of the conversations was performed.

Results: Among the 2351 adult app users, 468 patients were identified for analysis. The total number of patient-physician conversations was 26 ± 10, 60 ± 10, 103 ± 16, and 259 ± 148 from the 1st to the 4th quartile respectively; and the reduction of 24-hr proteinuria was 162.2 ± 195.3, 859.8 ± 193.6, 676.4 ± 194.5, and 889.3 ± 194.5mg respectively (p=0.03). The odds ratio of <30% proteinuria reduction in the 4th quartile compared to the 1st quartile was 0.452 (p=0.007) after adjusting for age, sex, clinical parameters, and medications. Compared to the 1st quartile, the 4th quartile received more alerts in hypertension (43.6% vs. 24.1%, p=0.02), and hypotension (53.9% vs. 31.9%, p<0.0001). The textual analysis of the patient-physician conversations revealed themes on self-monitoring of BP, awareness of laboratory results, medication optimization and adherence, dietary modification, and education in CKD and the comorbidities.

Conclusions: More frequent patient-physician interactions via smartphone app are associated with better proteinuria control. A patient-friendly smartphone app for record keeping and communication is feasible and effective for physician-guided CKD self-management.

Funding: Commercial Support - Beijing Kidney Health Technology Company, China, Private Foundation Support

FR-PO334

Timing of Arteriovenous Access Creation in CKD Patients: The French CKD-REIN Study

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Background: Most guidelines on vascular access recommend to create an arteriovenous (AV) access in eligible patients when estimated glomerular filtration rate (eGFR) is 15-30 ml/min. We sought to assess whether clinical practices align with these recommendations.

Methods: We identified participants undergoing a first AV access creation in CKD-REIN, an ongoing prospective cohort study that includes 3033 adult patients under nephrology care for CKD in 40 clinics in France. We assessed the timing of AV access creation according to eGFR within a period of -90 to +30 days from surgery. We described patient characteristics and cumulative incidence of hemodialysis start and death according to the timing of AV access creation.

Results: Of the 335 participants who underwent a first AV access during a median follow-up of 2.6 years, 270 (81%) had contemporaneous information on eGFR level and were included in this analysis. Median eGFR at AV access creation was 13 ml/min (IQR 10-16). AV access creation at eGFR 15-30 ml/min (n= 83) vs <15 ml/min (n= 187) was more frequent in men then in women (78% vs 65%, p=0.03), and in patients with then without diabetes (63% vs 47%, p=0.02), cerebrovascular disease (26% vs 15%, p=0.04) and coronary artery disease (42% vs 24%, p=0.003). Conversely, participants with AV access creation at eGFR <15 had more nephrology visits over the last 6 months prior to surgery (29% vs 13% with ≥3 visits, p=0.001). The 2-year cumulative incidence of hemodialysis initiation was 79% in participants with eGFR 15-30 and 89% for participants with eGFR <15, with a median time from surgery of 11 (IQR 6-20) and 5 (2-11) months, respectively (p<0.001). Thirteen patients died before requiring hemodialysis. Cumulative incidence of death tended to be higher in the 15-30 (9%) vs <15 (4%) eGFR group, but this difference was not statistically significant (p=0.23).

Conclusions: In patients under nephrology care in France, later AV access creation seemed to be favored over the recommended earlier creation. This practice may limit unnecessary AV access creation (i.e. patients dying before requiring dialysis), but its impact on transitory catheter use is to be assessed.

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FR-PO335

Self-Rated Health Is Associated with Functional Limitations in Patients with CKD

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Background: In patients with chronic kidney disease (CKD), self-rated health (SRH, "In general, how do you perceive your health?") is associated with mortality. However, it is unclear how functional status associates with SRH. This study assessed the relationship between the SRH and functional status limitations in a cohort of patients with stages 3-5 CKD.

Methods: Adult patients with CKD seen at a nephrology outpatient clinic in Western Pennsylvania from Sept 2015 to Dec 2016 were invited to complete a survey as part of a quality improvement project. The survey included questions on patient's SRH (Likert scale, 1=Poor, 2=Fair, 3=Good, 4=Very Good, 5=Excellent) and activities of daily living (ADLs, Yes/No response). The five standardized ADL questions assessed physical- (ambulation, dressing, shopping) and cognitive- (executive and memory) based ADLs. The association of SRH with limitations to 3 or more total ADLs, physical ADL limitations only, or cognitive ADL limitations only were assessed using chi-square analysis.

Results: SRH was completed by 1310 participants (mean age 60 years), out of which 41% reported poor-to-fair health. Overall, 71% of those with poor-to-fair SRH had at least one ADL limitation. In the total cohort, the most commonly reported ADL limitation was difficulty with ambulation at 34%. Ambulatory limitations were seen in 58% of participants with poor-to-fair SRH versus 17% in persons with good-to-excellent SRH. Persons with poor-to-fair SRH were more likely to report ≥3 limitations of ADLs (26% vs. 3%, $p < 0.001$), ≥1 physical limitation (61% vs. 18%, $p < 0.001$), and ≥1 cognitive limitation (35% vs. 13%, $p < 0.001$), compared to those with good-to-excellent SRH, respectively. Older adults (age ≥65) were more likely to report good-to-excellent SRH compared to younger adults (63% vs. 56%, $p = 0.008$); however, in those with 31% of good-to-excellent older adults had at least one ADL limitation versus 22% of younger adults.

Conclusions: Lower self-perception of health is associated with a larger number of functional limitations in patients with CKD. Older CKD patients have better SRH despite a higher functional limitations burden and potentially greater frailty. Lower SRH may identify patients who could benefit from additional healthcare resources (e.g., physical therapy and rehabilitation) to improve person-centered outcomes.

Funding: Clinical Revenue Support

FR-PO336

Eliciting Patient and Caregiver Priority Outcomes in CKD: An International Nominal Group Study

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Background: Patients with chronic kidney disease (CKD) are at an increased risk of premature death and cardiovascular disease, and experience symptoms that impair quality of life. We aimed to identify patient and caregiver priority outcomes in CKD.

Methods: Patients with CKD (stages 1-5, dialysis or transplant) and caregivers were purposively sampled from seven centers (10 groups) across United States, Australia, and United Kingdom. Participants identified outcomes that were important in CKD Stages 1-5 (prior to commencing kidney replacement therapy (KRT)) and individually ranked their top 10 from most important to least important. A relative importance score (0 to 1) was calculated for each outcome based on frequency and rank.

Results: In total, 54 patients and 13 caregivers aged over 18 years participated, with 36 outcomes identified. The five top ranked outcomes for patients were: kidney function (importance score = 0.42; 95%CI 0.31-0.53), end stage kidney disease (0.29; 0.21-0.38), fatigue (0.26; 0.19-0.35), mortality (0.25; 0.17-0.35) and life participation (0.20; 0.14-0.27). For caregivers the top five outcomes were: life participation (0.38; 0.19 -0.59), kidney function (0.37; 0.18-0.59), mortality (0.23; 0.07-0.45), fatigue (0.21; 0.10-0.37) and anxiety (0.20; 0.08-0.35). Blood pressure, cognition and depression were consistently ranked in the top ten outcomes across role (patient/caregiver), country and stage of CKD (CKD vs KRT).

Conclusions: Patients and caregivers gave highest priority to kidney health, mortality, fatigue, life participation, and mental wellbeing. Consistent reporting of these outcomes in research can inform shared decision-making based on outcomes that are relevant and critical to patients and caregivers in CKD.

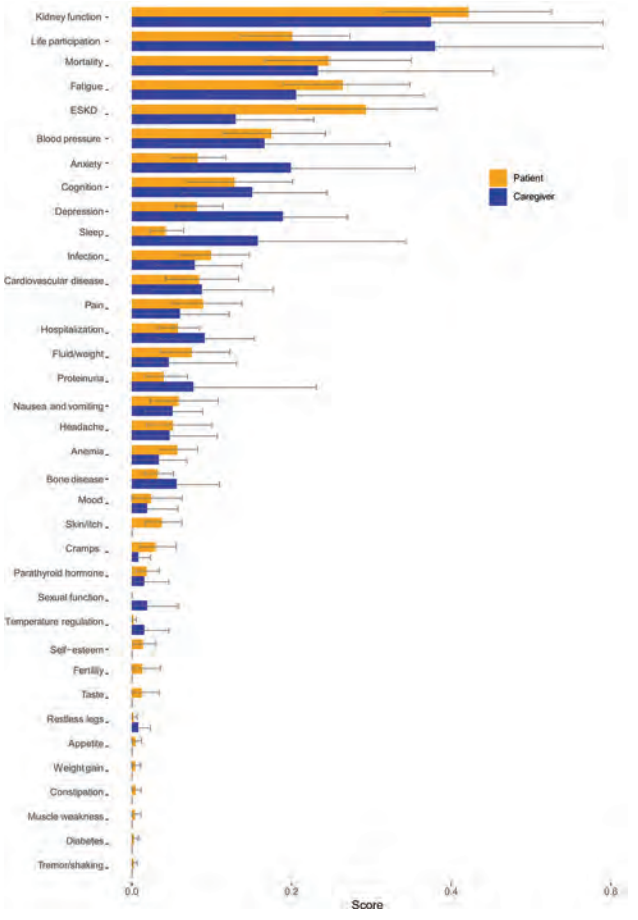

Figure 1. Top ranked outcomes by role

FR-PO337

Patients' Reliance on Non-Nephrologists for CKD Treatment and Advice

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Background: Chronic kidney disease (CKD) care is often fragmented across multiple health care providers, and it is unclear who patients rely on most.

Methods: We conducted a cross-sectional study of adults receiving nephrology care and enrolled in the PREPARE NOW trial to assess their reliance on their nephrologist, primary care provider (PCP), another specialist, or all their providers equally for CKD treatment and advice. We also asked participants about the frequency and patient-centeredness (range 0 [least] to 12 [most]) of their nephrology care. We assessed participants' kidney function and comorbidity (Charlson Comorbidity Index, range 0-37) using data from their electronic health records. In multivariable analyses, we quantified associations between participants' reliance on their nephrologists (vs. others) for their CKD treatment and demographics, comorbidity, kidney function, and perceived patient centeredness for their most recent nephrology visit.

Results: The 453 study participants had a mean (SD) age of 71.2 (12.1) years, 59% were female, 99% were White, and 66% had a high school education or less. Participants had seen nephrology for a median (IQR) of 3.8 (2.0-6.6) years, and 50% saw their nephrologist at least every 6 months. The median (IQR) patient-centeredness score was 11 (9-12). Participants' mean (SD) eGFR was 33.2 (11.7) mL/min/1.73m^2, and their median (IQR) Charlson score was 5 (3-7). Only half (56%) reported they relied primarily on their nephrologist for CKD treatment and advice, while 23% relied on their PCP, 18% relied on all providers equally, and 3% relied on another specialist. After adjustment, participants who saw their nephrologists for longer (OR [95% CI]: 1.09 [1.02-1.17] per additional year, p=0.01) and perceived nephrology visits as more patient centered (OR [95% CI]: 1.31 [1.17-1.47] per unit score increase, p<0.0001) had greater odds of relying mostly on nephrologists for CKD treatment and advice.

Conclusions: Many nephrology patients rely on non-nephrologists for CKD treatment and advice. Establishing longitudinal, patient-centered nephrology care and partnerships with patients' other physicians may help ensure patients adhere to nephrologists' CKD treatment and advice.

FR-PO338

Clinical Context for RBC Transfusions in CKD Patients: Results of the START-CKD Trial

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Background: Anemia is a common complication for patients with progressive CKD which untreated can lead to increased RBC transfusions (TX). Tx avoidance wherever possible is recommended in such patients to prevent the risk of allo-sensitization. Erythropoiesis-stimulating agents (ESA) have been used in CKD patients to reduce the need for Tx. The START-CKD trial evaluated an ESA treatment (darbepoetin) on the incidence of RBC Tx in anemic CKD subjects using either a hemoglobin (Hgb)-based titration algorithm (TD) or a fixed dose (FD). This study collected prospectively Tx data.

Methods: This was a US phase 3, multicenter, randomized, double-blind, parallel group study. 377 participants with stage 3-5 CKD were treated in the TD and in the FD arms for a period of up to 2 years. Tx, per protocol, were performed as deemed necessary by the treating physician and were prospectively adjudicated with the reasons and context for Tx recorded.

Results: The average age of the subjects, baseline Hgb and estimated GFR were balanced between the arms: 69 yrs, 9,0 g/dL and 22 ml/min//1.73m2. The primary endpoint of the study was similar between the TD and FD, 24% in both arms with an average Hgb at the time of first Tx of 7.4 vs 7.3 g/dL respectively. All Tx events are shown below:

Conclusions: The main reason for Tx was symptoms which were principally constitutional. Bleeding accounted for approximately 20% of Tx. The Hgb at the time of Tx was consistent with transfusion practice guidelines.

Funding: Commercial Support - Amgen

Primary Reason and Context	TD	FD
Number TF events	127	141
Primary Reason – n (%)		
Acute trauma	4 (3.1)	1 (0.7)
Planned	8 (6.3)	14 (9.9)
Critical illness	2 (1.6)	5 (3.5)
Worsening SX	66 (52.5)	75 (53.2)
Worsening Anemia	10 (7.90)	2 (1.4)
Clinical Situation – n (%)		
Bleeding	28 (22.0)	27 (19.1)
Trauma	3 (2.4)	0 (0.0)
Surgery/procedure	9 (7.1)	14 (9.9)
GI hemorrhage	15 (11.8)	9 (6.4)
Symptom	77 (60.6)	89 (63.1)
Chest pain	10 (7.9)	2 (1.4)
Dyspnea	35 (27.6)	49 (34.8)
Constitutional	50 (39.4)	57 (40.4)

FR-PO339

Kibow Multisite Hope Study-CKD IV Randomized Clinical Trial Protocol: A Unique Double-Blind Placebo-Controlled Cross-Over Design Using Renadyl™ with Standard-of-Care Therapy (n=500-600, 20-25 sites in the United States)

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Background: CKD patients experience poor quality of life due to high levels of uremic toxins in the blood. Treatment option for CKD patients are restricted diet and medications for primary comorbidities like hypertension and diabetes. Outcomes like fatigue pain and anxiety though major concerns and critically important to patients and clinicians may not be reported in clinical trials (Kid Int 2019; 95:1280-1283). The Standardized Outcomes in Nephrology (SONG) initiative 2014 established core outcome sets for nephrology trials (https://songinitiative.org/). An alternative regime to address some of these issues would benefit all stages of CKD patients. Renadyl™, a Pro/Prebiotic dietary supplement is proven to reduce several uremic toxins in 3 pilot clinical trials with no reports of adverse outcomes. We propose to carry out large scale RCT to validate it as a Live Bio-Therapeutic (LBT) drug with US FDA approval.

Methods: One-year RCT cross over design in an outpatient setting. Renadyl™ will be orally given at 90 B CFU/day.

Results: Measured end points: 1: eGFR, Quality of Life (QOL). 2: Uremic metabolite panel, CBC, liver function test 3**:** Biomarkers including KIM-1, NGAL, TMAO, IL-6 and CRP.

Conclusions: This is the first-ever RCT proposed using Renadyl™ as a Live Bio-Therapeutic (LBT) drug for CKD IV patients. Being noninvasive the intervention avoids any possible infection. As a rare unconventional crossover design, patients will be their own control for prudent data analysis. Secondly, every patient gets the interventional product, thus accelerating better patient recruitment. Significance of p-value alone does not help in the decision of the application of results to clinical care and its policy (Kid Int. 2019; 95:28-30). P < 0.05 and P > 0.05 can affect interpretation and lead to bias. The study design, quality of measurements, and the logical basis of assumptions are also important. (Kor J Pain 2017; 30(4): 241-242). Addition of Renadyl™ with standard care of therapy may possess excellent potential towards CKD applications worldwide. Seriously interested clinical PI's please contact: rangan@kibowbiotech.com

Funding: Commercial Support - Kibow Biotech Inc.

FR-PO340

Evolution of Patient Partner Roles in a Canadian, Patient-Oriented Kidney Research Network: A Qualitative Study

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Background: Engagement of patients as partners in health research is a mandate of the patient-oriented kidney research network, Can-SOLVE CKD. However, how patients assume and integrate their unique roles within the Network has not been examined. The aim of this study was to explore how researchers and patient partners characterize the roles and responsibilities of patients in the context of their individual projects and broader Network governance.

Methods: This study used a qualitative descriptive methodology informed by Role Theory. We purposively sampled across all research teams within Can-SOLVE CKD and conducted interviews and focus groups with researchers (i.e. project leads, co-investigators, and research coordinators) and patient partners (i.e. persons living with chronic kidney disease and their informal supports) from 17 of 18 Network projects. We conducted 4 focus groups (2 patient and 2 researcher groups; N=26) and 28 interviews (N=12 patients, N=16 researchers). We analyzed transcript data using an inductive, thematic analysis approach. Coding was done in duplicate (MJE, NF), and themes were developed in relation to the objectives.

Results: With increasing familiarity and comfort engaging together in research partnership, participants described an evolution of perspectives on patient partner roles within the Network and patient-oriented research more generally. We identified 3 themes to support this: 1) Receptivity to novel engagement opportunities – patient partners assume roles that align skills and interests with project needs; 2) Acknowledgement of role fluidity – roles and responsibilities evolve naturally with increasing experience and confidence; 3) Commitment to moving knowledge forward – patient partners increasingly engage in knowledge translation and moving research into practice.

Conclusions: The perceived roles of patient partners within the Can-SOLVE CKD Network have evolved since the Network's inception, as has participants' receptivity toward patient-oriented research. Future work will further characterize unique opportunities for patients to engage in kidney health research and the perceived impact of this engagement.

FR-PO341

Establishment of a Virtual Slide System Linking to the Japan Renal Biopsy Registry

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Background: A virtual slide is a high-resolution digital image created from scanning specimens on glass slides. Digital images are saved in a storage system and viewed on a computer screen using slide viewing software that is accessed via a web browser. These images can be assessed in the same way as with microscopy. The Japan Renal Biopsy Registry (J-RBR) has been operated since 2007 by the Japanese Society of Nephrology's Kidney Disease Registry Committee. As of December 2018, 143 facilities have joined the registry and data have been registered for more than 40,000 patients who underwent renal biopsy. The J-RBR is now one of the largest national registries in Japan and provides a wealth of information for examining actual conditions, conducting secondary research, and developing clinical practice guidelines. We attempted to establish a virtual slide system of renal biopsy specimens that is linked to the J-RBR in order to increase the registry's utility.

Methods: Installation of a server computer was made possible by a Grant-in-Aid for Intractable Renal Diseases Research, Research on Rare and Intractable Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan. The server computer was constructed at Niigata University, image view software was installed (Aperio eSlide Manager®, Leica Microsystems K.K.), and the server was connected to the J-RBR server. When logged into their J-RBR accounts, users can access the J-RBR server to view the histopathology images via a web browser.

Results: The virtual slide system was linked to the J-RBR in March 2019, and virtual slides from more than 100 patients were registered during the first 2 months of operation. The digital images are available to all researchers with a J-RBR account.

Conclusions: The virtual slide system enables renal biopsy specimens to be viewed and diagnoses made via teleconsultations, and it can help pathologists establish a clinical consensus for diagnosis. The system should also increase the reliability of J-RBR data, which in turn will promote more secondary research, including machine learning, to be undertaken and provide precise information for guideline development.

Funding: Government Support - Non-U.S.

FR-PO342

Electronic Health Record Based Population Health Management for Improving CKD Care: The Kidney-Coordinated Health Management Partnership (CHAMP) Study

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Background: Primary care providers (PCPs) care for most CKD patients but report limited knowledge, familiarity with guidelines, and time, leading to suboptimal care and clinical outcomes including progression to end-stage kidney disease (ESKD). CKD population health management (PHM) using electronic health records (EHRs) can be a sustainable, resource-efficient strategy to overcome clinician- and system-level barriers in the delivery of CKD care. **The Kidney CHAMP study will test the effectiveness of a multifaceted EHR-based PHM intervention to improve evidence-based CKD care in patients with high-risk CKD** (NCT03832595, www.kidneychamp.pitt.edu).

Methods: This is a 42-month pragmatic, cluster randomized controlled trial comparing an EHR-based PHM intervention versus usual care in 1,650 high-risk CKD patients. Patients are recruited using an opt-out approach from the University of Pittsburgh's PCP network (>330 PCPs; >480,000 patients). The CKD PHM dashboard uses risk prediction models to identify patients at high risk of CKD progression. The intervention combines timely PCP-targeted nephrology guidance (primarily as E-consults), pharmacist-led medication reviews, and patient-targeted CKD education. This builds on our prior work using EHRs to identify gaps in CKD care (e.g., suboptimal HTN control and RAASi use, unsafe medication use, late nephrology referrals). Primary outcome is a composite of 40% reduction in eGFR or ESKD.

Results: The CKD dashboard has been developed and includes the validated Kidney Failure Risk Equation, patient demographics, dates of PCP visits, lab values, and active medications. Additionally, an internal CKD risk prediction model has been developed and validated. The dashboard will be used to identify eligible patients, track the intervention components, and monitor CKD progression. Study enrollment began in May 2019. We have partnered with 80 practices and randomized the first 8. Enrollment will continue for 18 months, with 4 practices randomized each month.

Conclusions: Our study tests a novel approach to deliver CKD care that minimizes patient and PCP burden. This will inform efforts to use heath IT, risk prediction modeling, and PHM to augment evidence-based CKD care.

Funding: NIDDK Support

FR-PO343

Using Lean-Six Sigma Principles to Develop a Telenephrology Dashboard to Monitor Rural Veterans at Risk of Kidney Disease Progression

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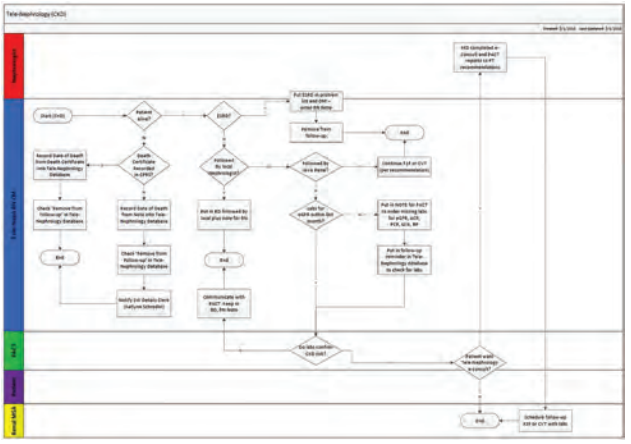
Background: Chronic kidney disease (CKD) affects about 14% of Americans, with a 34% greater prevalence in Veterans than the general population. Although early identification and consultation improves outcomes and lowers costs, access is challenging for rural Veterans. To improve access, we developed a telenephrology dashboard to monitor Veterans with CKD and intervene accordingly.

Methods: Lean Six-Sigma principles and the DMAIC (Define-Measure-Analyze-Improve-Control) framework were employed in this quality improvement project. During the "Define" phase, a project charter was drafted defining the scope and key stakeholders. This informed the "Measure" and "Analyze" phases, where the voice of the customer, current and future state maps, and process observation were utilized. In the "Improve" phase, PDSA (Plan-Do-Study-Act) cycles refined dashboard design. The "Control" phase is ongoing.

Results: A telenephrology dashboard was created to monitor patients with kidney disease within the Iowa City VA Health Care System. Voice of the customer (primary care providers and case managers) revealed 3 objectives: (1) timely identification of CKD risk and progression, (2) rapid access to specialty care, and (3) improvement of patient satisfaction. Process observation and mapping revealed opportunities for early identification and intervention for CKD using telenephrology protocols (Figure). From April 2018 to March 2019, 1080 charts were flagged and reviewed by the telenephrology case manager. Among these, e-consultations by nephrologists were performed for 364 Veterans (33.7%).

Conclusions: A telenephrology dashboard was created to monitor Veterans with CKD within the Iowa City VA Health Care system. This enables real-time access to nephrologists, thereby reducing wait-times to the next appointment and allowing for active surveillance of renal problems, and may improve overall quality of care.

Funding: Veterans Affairs Support



FR-PO344

Effect of Virtual Patient Simulation at Improving Management of Chronic Hyperkalemia

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Background: We sought to determine if an online, virtual patient simulation (VPS)-based continuing medical education (CME) intervention could improve performance of nephrologists related to identification of patients with hyperkalemia, and chronic management of hyperkalemia.

Methods: The intervention comprised two patients presenting in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments in a manner matching the scope and depth of actual practice. Tailored clinical guidance (CG), based on current evidence and expert recommendation, was provided following each decision, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user's baseline (pre-CG) decisions using a 2-tailed paired t-test to determine *P* values. The activity posted April 30, 2019; data for initial abstract submission was collected through May 22, 2019.

Results: To date after being live for 3 weeks, 37 nephrologists have participated (larger sample size expected by ASN conference). Significant improvements were observed after CG: Case 1: Initiate a loop diuretic: 24% absolute improvement (41% pre-CG vs 65% post-CG; P<.05) Order nutritional counseling: 19% absolute improvement (41% pre-CG vs 60% post-CG; P=.05) Initiate a potassium binder: 41% improvement (8% pre-CG vs 49% post-CG; P<.01) Discontinue spironolactone: 22% improvement (41% pre-CG vs 43% post-CG; P<.05) Case 2: Diagnose chronic kidney disease stage 3a: 43% absolute improvement (5% pre-CG vs 48% post-CG; P<.01) Diagnose heart failure, NYHA (WHO) Class II: 38% absolute improvement (14% pre-CG vs 52% post-CG; P<.01) Diagnose chronic hyperkalemia: 24% absolute improvement (29% pre-CG vs 53% post-CG; P=.05) Initiate potassium binder therapy: 57% absolute improvement (19% pre-CG vs 76% post-CG; P<.01)

Conclusions: VPS that immerses and engages specialists in an authentic and practical learning experience can improve evidence-based clinical decisions related to patient identification and management of hyperkalemia.

FR-PO345

Renal Hemodynamic Effects of Soluble Guanylyl Cyclase Activation vs. ACE Inhibition in a CKD Model in Conscious Rats

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Background: BP control using renin-angiotensin system (RAS) blockade is the current standard of care for CKD. However, outcomes remain suboptimal in part because adequate BP reductions are difficult to achieve in the volume expanded CKD states with RAS blockade even with additional antihypertensives. Given that endothelial dysfunction and/or NO loss accelerate the progression of diabetic and non-diabetic CKD, soluble guanylate cyclase (sGC) activators represent potential novel therapeutic interventions in CKD.

Methods: Two wks after 3/4 nephrectomy, male rats were instrumented for chronic BP radiotelemetry and RBF recordings and started on a 4% NaCl diet. Conscious BP and RBF recordings (1-2 hr; 2-4/wk) were initiated 1 wk later and continued over 3 wks while they were sequentially receiving: vehicle only by gavage (5 ml/kg), a low and a high dose of either the sGC activator (BR-11257) (3,10 mg/kg), enalapril (20,50 mg/kg) or the combination (3-4 days/wk with a ~3 day washout period). Effects on mean arterial pressure (MAP), RBF, renal vascular resistance (RVR) and the autoregulatory (AR) ability to buffer spontaneous BP fluctuations were assessed using a methodology developed in our lab.

Results: Table (mean ± SEM) In this CKD model with volume (salt) dependent hypertension (HTN), BR-11257 but not enalapril significantly reduced BP and RVR (high dose), but in combination the two were synergistic. Effects on RBF were more variable. No adverse effect on AR ability to buffer spontaneous BP fluctuations was observed with any of the regimens.

Conclusions: These data suggest that sGC activators may have significant therapeutic potential in CKD states with volume dependent and/or RAS blockade resistant HTN that merit further investigation.

Funding: Commercial Support - Bayer AG

Parameter	Vehicle (n=10)	BR-11257 (n-10)	Enalapril (n=10)	BR-11257 + Enalapril (n=9)
Baseline MAP (mmHg)	140 ± 4.7	131 ± 4.9	136 ± 3.9	127 ± 3.5
Low dose (Δ %)	↑ 9 ± 2.2	↓ 2 ± 3.1 δ	↑ 7 ± 3.5	↓ 15 ± 2.8 †
High dose (Δ %)	↑ 13 ± 3.1	↓ 9 ± 4.5 *	↑ 9 ± 3.9	↓ 20 ± 3.0 δ
Baseline RBF (ml/min)	16 ± 2.8	17 ± 2.5	16 ± 2.5	19 ± 3.8
Low dose (Δ %)	0 ± 7.1	↑ 11 ± 6.7	↑ 17 ± 8.2	↑ 13 ± 6.0
High dose (Δ %)	↑ 4 ± 6.5	↑ 11 ± 8.7	↑ 17 ± 5.0	↑ 21 ± 8.1
Baseline RVR (mmHg/ml/min)	11 ± 1.6	9 ± 1.2	11 ± 1.7	9 ± 1.3
Low dose (Δ %)	↑ 15 ± 10.4	↓ 7 ± 7.3	↓ 4 ± 7.9	↓ 23 ± 4.3 *
High dose (Δ %)	↑ 14 ± 8.1	↓ 12 ± 8.8 *	↓ 8 ± 5.7	↓ 30 ± 6.9 *

$p < 0.05$ maximum * vs vehicle; δ vs vehicle and enalapril; † vs. all other groups

FR-PO346

Increased Urinary Prostaglandin E_2 (PGE_2) Precedes Overt Albuminuria in Hyperfiltration-Induced Renal Injury in Children with Solitary Functioning Kidney (SFK)

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Background: Children born with SFK are at risk for end stage renal disease from hyperfiltration-induced injury. Urinary albumin and epidermal growth factor (EGF) are established biomarkers of glomerular and tubular injury, respectively. A biomarker to detect glomerular changes preceding microalbuminuria will be valuable in defining early effects of hyperfiltration. In a model of hyperfiltration as a continuum of glomerular changes caused by biomechanical forces, namely fluid flow shear stress (FFSS) and tensile stress, we showed that FFSS upregulates PGE_2, cyclooxygenase-2 and PGE_2 receptor EP2 in cultured podocytes as well as in unilateral nephrectomized mice. We hypothesized increased urinary PGE_2 in children with SFK.

Methods: Urine samples from children with SFK and controls were analyzed for PGE_2 by LC-MS/MS, albumin on VITROS autoanalyzer and EGF by ELISA. Patient characteristics of age, gender, Z-scores for height, weight, BMI, and BP were obtained. Wilcoxan-Mann-Whitney test was used group for comparisons and Spearman analyses for correlations.

Results: Children with SFK were comparable to controls except for having lower weight and BMI Z-scores. The median and interquartile range in control vs. SFK children were elevated for urine PGE_2 [5.7 (4.0, 8.8) n=72 *vs.* 9.1 (4.4, 16.7) n=57, p=0.009] ng/mgCr and albumin [7.0 (4.0, 10.3) n=41 *vs.* 7.6 (4.7, 24.0) n=40, p=0.085] µg/mgCr, but not for EGF [18637 (15298, 25622) n=44 *vs.* 20098 (13238, 30263) n=44, p=0.746] pg/mgCr. Urine albumin was within the normal reference range. A significant increase in urine PGE_2 (p=0.024) and albumin (p=0.019) but not EGF (p=0.412) was observed in SFK when sex, age, weight z-score, height z-score, DBP z-score, and SBP z-score were controlled for in regression modeling. Patient characteristics did not correlate with urine PGE_2, albumin or EGF. Urinary PGE_2 and albumin, PGE_2 and EGF, and EGF and albumin were not correlated.

Conclusions: Urinary PGE_2 and albumin, but not EGF, were elevated in children with SFK compared to controls, and were independent of each other reflecting distinct pathophysiologic mechanisms. Urinary PGE_2 is a potential biomarker for early glomerular injury caused by hyperfiltration associated increase in FFSS prior to overt microalbuminuria.

Funding: NIDDK Support

FR-PO347

Adaptive and Maladaptive Kidney Repair Models Reveal Distinct Pathways of Myeloid and Lymphoid Cell Recruitment and Activation

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Background: Incomplete repair after acute kidney injury (AKI) can lead to progressive fibrosis and development of chronic kidney disease (CKD). We have previously shown that unilateral ischemia-reperfusion kidney injury with contralateral nephrectomy (IRI/CL-NX) results in significantly less fibrosis in the injured kidney than does unilateral IRI with the contralateral kidney intact (U-IRI). Here, we investigated the mechanism of this difference by comparing an identical time of ischemic injury between mice subjected to U-IRI and those subjected to IRI/CL-NX.

Methods: Male wild-type mice were subjected to warm U-IRI or IRI/CL-NX (27 min). The injured kidney was removed on day 1, 7, 14 or 30 after IRI (n=10/group). Renal function was assessed by serum creatinine and BUN. Renal fibrosis and macrophage accumulation were assessed by Sirius red staining and IHC staining for F4/80. Kidney injury, inflammation, accumulation of myeloid and lymphoid cells, chemoattractant and survival factor expression levels were assessed by qPCR at each time point.

Results: This analysis revealed that initial recruitment and activation of macrophages, dendritic cells and T cells as well as myofibroblast activation and profibrotic gene expression were equivalent through day 7 in these two models. However, in the IRI/CL-NX model macrophage numbers declined after day 7 with tubule regeneration and only modest interstitial fibrosis on day 30. In contrast, macrophages persisted and expressed significantly higher levels of profibrotic growth factors *Pdgfb* and *Tgfb1* while dendritic cells and T cells significantly increased in numbers and expressed greater amounts of *Tnfa* and *Il1b*. These sustained immune responses correlated with progressive expression of collagen and fibronectin, sustained expression of *Havcr1* and *Lcn2*, less tubule regeneration and greater kidney atrophy. The persistence of macrophages, dendritic cells and T cells in injured U-IRI kidneys highly correlated with sustained expression of the chemokines *Ccl1*, *Ccl2* and *Cx3cl1*.

Conclusions: Abnormal accumulation of macrophages, dendritic cells and T cells may lead to progressive interstitial fibrosis, sustained inflammation and kidney injury in the setting of maladaptive kidney repair following IRI. Blocking homing chemokines may serve as a therapeutic target to attenuate CKD progression.

Funding: NIDDK Support

FR-PO348

Expression of an Anti-Fibrotic Molecule Smad Anchor for Receptor Activation (SARA) Is Differentially Regulated in Epithelial Cells and Fibroblasts at a Translational Level

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Background: We reported last ASN meeting that overexpression of SARA specifically in pericytes prevents them from transdifferentiating into fibroblasts, hence mitigates fibrotic changes in a mouse model of interstitial fibrosis. These findings suggest that SARA is a key molecule that regulates cellular phenotype. Here, we aimed to explore the mechanism by which SARA levels are regulated.

Methods: SARA protein and mRNA expression levels were evaluated in cultured epithelial cells and fibroblasts derived from rat kidney (NRK52E and 49F, respectively), with or without transfection of a plasmid expressing human SARA cDNA or HA-tagged focal adhesion kinase (FAK). RNA from NRK52E and 49F was subjected to RNA sequencing.

Results: SARA protein was abundantly expressed in NRK52E, while it was barely detected in NRK49F. In contrast, SARA mRNA levels were similar in NRK52E and 49F. When a plasmid expressing human SARA driven by a constitutive promoter was transfected, SARA protein overexpression was apparent in NRK52E cells, but not in 49F, while HA-FAK protein expression used as a control was equivalent both in NRK52E and 49F, indicating that the difference in 52E and 49F are not due to transfection efficiency. Indeed, human SARA RNA driven by SARA overexpression plasmid was significantly and equally increased in both NRK52E and 49F. RNA sequencing revealed 107,000 genes expressed both in NRK52E and 49F, and 922 and 754 genes were unique to NRK52E and 49F, respectively. KEGG enrichment analyses revealed that genes associated with metabolic pathways were most commonly differentially regulated (N=630), followed by those associated with PI3K-Akt signaling pathways (N=197) and endocytosis (N=176). Most significantly enriched genes were found in adherens junction related genes, and Hippo signaling and HIF-1 signaling pathway-related genes.

Conclusions: These results suggest that, in fibroblasts, a mechanism exists that keeps SARA levels low at a translational level. Some of the differentially expressed genes revealed by RNA sequencing in epithelial cells and fibroblasts are likely to be involved this regulation and could be a novel therapeutic target.

Funding: NIDDK Support

FR-PO349

Par1a Deletion Protects Against Folic Acid and Unilateral Ureteral Obstruction-Induced Fibrosis in Mice

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Background: We recently identifed Par1 serine threonine kinases as regulators of Notch signaling in the developing kidney: dual loss of Par1a/b led to impaired Notch activation and glomerular and proximal tubular development. Par1a expression increases following unilateral ureteral obstruction (UUO) and folic acid (FA) induced injury. However, the effect of Par1a deletion on renal fibrosis is not known. We hypothesized: Loss of Par1a would attenuate Notch signaling activation and renal fibrosis.

Methods: Immunoflorescence staining was used to examine the expression of Par1a/b and Notch signaling components. To test effect of Par1a deletion on fibrosis in vivo, FA (250 mg/kg dissolved in 300 mM NaHCO3) or vehicle was injected in 5 week old male *Par1a -/-* (Par1a KO) and *Par1a +/+* (Par1a) WT littermates. Kidney phenotype was assessed at 4 weeks post injection. UUO was performed in adult (10 week old) male Par1a KO and WT littermates; phenotype was examined at 7 days. 6-8 mice/group were studied. To detect renal fibrosis, Picrosirius red staining of collagen was performed. Polarized light and Image J was utilized to quantify fibrosis on 200 x images. Primary tubular cell cultures were generated from inducible Par1 knockout (Pax8rtTA:tetOCre: Par1flox/flox) mice. Cultures were exposed to TGFbeta (10 ng/mL) and examined at 72 hours. Doxycycline was used to induce Par1 deletion.

Results: Both Par1a and Jag1 expression increase following FA and UUO injury in mice. Par1a and Jag1 co-localized in kidney tubules following FA and UUO induced injury. Par1a deletion was protective against renal fibrosis in mice: as quantified by sirius red staining, % area of fibrosis was 1.4 ± 0.9 vs. 0.8 ± 0.5 in FA treated Par1a WT vs. KO kidneys. Following UUO, % area fibrosis was 2.75 ± 2.3 vs. 0.76 ± 0.29 in Par1a WT vs. KO kidneys.($p<0.01$) Par1 deletion was protective against TGFbeta induced renal tubular damage in vitro. Whereas E-cadherin expression was lost with TGFbeta treatment in control primary tubular cells, Par1 knockout cells had preserved E-cadherin expression following TGFbeta exposure.

Conclusions: Par1a deletion is protective against renal fibrosis in mice. Par1 deletion was protective against renal tubular injury in vitro, suggesting tubular Par1 mediates its protecitve effects. Colocalization of Par1 and Jag1 suggests Par1 may affect Jag1 mediated Notch activation.

Funding: NIDDK Support

FR-PO350

12/15-Lipoxygenase Knockout Mice Exhibit a Resistance to Kidney Damage in CKD

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Background: It has been reported that polyunsaturated fatty acids(PUFA) and their metabolites are related with inflammation and its resolution in several organs. The roles of these metabolites in kidneys, however, have been unclear. In addition, which metabolite is a key player in exacerbation and remission of chronic kidney disease (CKD) remains unknown. 12/15-Lipoxygenase (ALOX15) is one of the key molecules which has a function to produce bioactive lipid metabolites from PUFA. Although there are some reports to present linkage between ALOX15 and inflammatory diseases, it is still unknown whether and how ALOX15 has effects on the progression of CKD.

Methods: Kidney tissue from subtotal nephrectomy mice was analyzed with lipidomics to reveal lipid profiles of CKD kidneys. To establish CKD models, subtotal nephrectomy or oral administration of adenine was performed to C57BL/6J mice and ALOX15 knockout mice. Histologic examination, western blot and quantitative PCR were performed to investigate the phenotype of ALOX15 knockout mice.

Results: Lipidomics analysis revealed that ALOX15-mediated lipid metabolites were significantly decreased in kidneys of mice with subtotal nephrectomy in comparison with those of control mice. Therefore, we examined two CKD models of ALOX15 knockout mice, subtotal nephrectomy and adenine-induced nephropathy. Renal functions of ALOX15 knockout mice were more preserved than those of wild type mice in the both CKD models. Alfa-SMA and NGAL were also suppressed in ALOX15 knockout mice. Quantitative-PCR revealed that mRNA level of alpha-1 type I collagen in kidneys of ALOX15 knockout mice was reduced comparing with that of wild type mice in the both CKD models. Masson's trichrome staining revealed decreased interstitial fibrosis of ALOX15 knockout CKD mice in comparison with wild type mice. These results suggested that reduction of some ALOX15-mediated lipid metabolites which induce renal damage could have beneficial effects on CKD.

Conclusions: Lipidomics of the kidneys from subtotal nephrectomy mice revealed the significant change in the amount of ALOX15-mediated lipid metabolites. ALOX15 knockout mice exhibited a resistant phenotype to CKD. ALOX15 and some ALOX15-mediated lipid metabolites might be novel therapeutic targets of CKD.

FR-PO351

Erythrocyte Sphk1 Activation Coupled with PP2A Inhibition: A Missing Component to Counteract CKD

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Background: Hypoxia drives chronic kidney diseases (CKD) and promotes end organ damage. The erythrocyte is the only cell type delivering oxygen (O2) and O2 releasing capacity is finely regulated by hypoxia. However, its role and regulatory mechanisms in CKD remain unknown.

Methods: Untargeted metabolomics screening in the plasma and erythrocyte of mice infused with or without angiotensin II (Ang II) at 500ng/kg/min up to 14 days was conducted. Mice with specific ablation of Sphk1 in erythrocytes and patients with CKD were used to determine its function in CKD, potential mechanisms and human relevance.

Results: Genetic depletion of erythrocyte specific Sphingosine Kinase 1 (Sphk1, the only enzyme to generate S1P in erythrocytes) leads to severe renal hypoxia, persistently active HIF-1a, sustained inflammation, imbalanced vasoactive factors and fibrosis comparing to the Ang II-infused controls. Mechanistically, using untargeted erythrocyte metabolic profiling, we found that Ang II-infused controls but not erythrocyte Sphk1 knockout mice show highly active glycolysis, which fuels erythrocyte energy supply and O2 release mediator. These studies led us further discover that Sphk1 activation induces AMPK-mediated activation of BPG mutase and thus the production

of 2,3-biphosphoglycerate (2,3-BPG), an erythrocyte specific glycolysis metabolite negatively regulating hemoglobin-O2 binding affinity and eventually triggers O2 delivery to the kidney. Furthermore, we then provide both pharmacological and genetic evidence that AMPK phosphorylation and activation of BPGM in erythrocytes, is regulated by sphingolipid mediated protein phosphatase 2A (PP2A) inhibition. Finally, human translational studies validated mouse findings that erythrocyte BPG mutase and Sphk1 activity were significantly induced in the erythrocytes of CKD patients compared to normal controls and their elevations were correlated to disease severity.

Conclusions: Overall, our study elucidates that erythrocyte Sphk1 activation induced S1P production promotes 2,3-BPG production and O2 delivery via a PP2A-AMPK-dependent signaling cascade to counteract CKD. These findings add a significant molecular new insight to CKD and immediately suggest new therapeutic avenues.

Funding: Other NIH Support - NHLBI

FR-PO352

Complete Pik3c3 Deletion in Renal Proximal Tubule Cells Causes AKI Leading to CKD

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Background: Renal proximal tubules form the bulk of the kidney and are particularly sensitive to ischemic, toxic, and metabolic stress contributing to the pathogenesis of kidney disease. Class 3 phosphatidylinositol 3-kinase (Pik3c3) is the only PI3-kinase evolutionarily conserved from yeast to humans. However, the role of Pik3c3 in the proximal tubules in adult kidneys is unknown.

Methods: We generated a *Pik3c3* gene-floxed mouse and crossed it with *SLC34a1.CreER*^{T2} mice to produce tamoxifen (TAM)-inducible renal proximal tubule cell (RPTC)-specific Pik3c3 heterozygous (*Het*) and homozygous knockout (*KO*) mice for comparison with appropriate control (*Ctrl*) littermates. Pik3c3 deletion was not induced until the mice reached 8 weeks old.

Results: Our data revealed that the proximal tubule expresses the highest level of Pik3c3 among all renal tubule segments. The *Het* mice are fertile and normal. However, the *KO* mice exhibited marked RPTC injury, indicated by cytoplasmic vacuolization, nuclear condensation and fragmentation as well as TUNEL-positive cells in the proximal tubules, leading to cell death and infiltration of inflammatory cells (including neutrophils) within 13 days after TAM induction of Pik3c3 deletion. Subsequently, the *KO* mice developed chronic kidney disease (CKD), evidenced by marked proliferation of a-smooth muscle actin-positive myofibroblasts, persistent infiltration of inflammatory cells (including macrophages and lymphocytes), and tubulointerstitial fibrosis, with elevated serum creatinine and BUN, after 3 months of Pik3c3 deletion. Mechanistically, *in vivo* animal studies and *in vitro* RPTC culture studies unveiled strikingly increased levels of LC3II/I, LAMP1 and activation of the initiator caspase 12 and the effector caspase 3 in response to Pik3c3 inactivation.

Conclusions: Our data indicate that complete Pik3c3 deletion in RPTC disturbed the endocytic and autophagic pathways and disrupted the homeostasis of intracellular protein sorting, leading to intracellular vacuolation and cell death involving activation of caspases 12 and 3. This study not only reveals an essential role of Pik3c3 in maintaining the homeostasis and survival of proximal tubule cells, but also provides a new model of progressive CKD.

Funding: NIDDK Support

FR-PO353

Proximal Tubule-Specific KLF6-Mediated Amino Acid Metabolism Is Critical for the Progression of Kidney Injury

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Background: Transcriptional regulators of DNA-damage pathways leading to renal fibrosis are not well characterized. Krüppel-like factor 6 (KLF6), a zinc finger transcription factor, is expressed in the proximal tubule (PT) and highly upregulated in renal ischemia-reperfusion injury, sepsis, and DNA damage models, but its role in PT injury and tubulointerstitial fibrosis is unknown.

Methods: PT-specific *Klf6* knockdown (*Klf6*^{PTKO}) mice were generated by breeding *Klf6*$^{fl/fl}$ and *Pepck*-Cre mice (controls- *Klf6*$^{fl/fl}$ littermates). The "Tet-On" system was used to generate global inducible human *KLF6* (h*KLF6*) overexpressing mice (controls- TRE-h*KLF6*). Mice were given AAI or vehicle DMSO i.p. every 3 days for 2-3 weeks and euthanized 3 days after the final injection for functional, histological, RNA-Seq and ChIP-enrichment analysis of renal cortex.

Results: AAI-treated *Klf6*^{PTKO} mice had lower serum creatinine and urea nitrogen, preserved PT, and reduced inflammation and fibrosis, versus AAI-treated *Klf6*$^{fl/fl}$ mice. Conversely, AAI-treated h*KLF6* mice had worse renal function, more loss of PT, and increased inflammation and fibrosis versus AAI-treated control mice. RNA-Seq analysis identified 388 genes that were downregulated in *Klf6*$^{fl/fl}$ mice and significantly higher (preserved) in *Klf6*^{PTKO} mice after AAI. These were predominantly metabolic genes, including in amino acid metabolic and fatty acid oxidative pathways. ChIP-enrichment analysis of genes with KLF6 binding sites <1kb from a transcription start site (TSS) enriched for genes encoding enzymes critical to the essential branched-chain amino acid (BCAA) pathways, suggesting direct regulation by KLF6. AAI inhibits mitochondrial function causing production of reactive oxygen species, and the BCAA pathways preserved in *Klf6*^{PTKO} mice supply TCA cycle intermediates (e.g. succinyl-CoA), and enhance glutathione production, which may counteract the effects of AAI. Analysis of expression arrays of human CKD biopsies showed similar downregulation of BCAA genes with KLF6 binding sites close to the TSS, versus control samples.

Conclusions: Loss of PT KLF6 was associated with preserved BCAA metabolic enzymes that may help maintain the TCA cycle and increase glutathione, thus reducing injury after AAI. The potential role of transcriptional regulation of amino acid metabolism in driving PT injury has not previously been described.

Funding: NIDDK Support

FR-PO354

Genome-Wide Identification of Active Enhancers in Renal Aging

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Background: Aging is one of the major risk factors for acute kidney injury and chronic kidney disease. The aging kidney undergoes complex changes that predispose people to renal diseases. However, the regulatory circuitry governing the transcriptional network in renal aging is unclear. Here we aim to reveal specific transcriptional programs that underlie renal aging. In particular, enhancers are distal non-codingDNA elements that are crucial for spatiotemporal control of gene expression. Disease-associated SNPs are highly enriched within enhancers, highlighting the functionality. Bidirectional RNA transcription (referred to as eRNA) originates from enhancers.

Methods: The CAGE (Cap Analysis of Gene Expression) is a method used to comprehensively map transcription start sites (TSSs) using next-generation sequencing. Using CAGE, promoters and enhancers can be identified by analyzing TSSs of mRNAs and eRNAs, respectively. However, in the usual CAGE method, detection of eRNAs is inefficient, because these transcripts are actively degraded in the nucleus by the nuclear exosome complex soon after their synthesis. To overcome this issue, our group devised a simple and novel NET-CAGE technology, in which nascent RNA is used as input. We successfully achieved ultra-sensitive detection and quantification of active enhancers at single nucleotide resolution.

Results: We apply this NET-CAGE technology to describe active cis-regulatory landscape across renal aging and analyze differentially regulated enhancers and genes. NET-CAGE data for kidney show increased detection of enhancers in each age compared to CAGE data. In addition, we identify a number of kidney-specific enhancers.

Conclusions: Our comprehensiveanalysis of enhancers will provide key biological insights into cis-regulatory mechanism in renal aging.

FR-PO355

Follistatin-Like Protein 1 (FSTL1) Expression Is Correlated with Measures of Kidney Injury in the Nephrotic Syndrome Study Network (NEPTUNE) Cohort

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Background: The pathogenesis of progressive kidney injury has not been fully elucidated in chronic kidney disease (CKD). Gene expression profiling of renal cortical mRNA samples was performed in male Col4a3-/- and Col4a3+/+ mice at 4 and 7 weeks of age. Our microarray analysis showed that FSTL1 was one of only three genes upregulated at 4-weeks of age. FSTL1 is expressed in interstitial fibroblasts. It activates NFkB and increases COL1α1 expression in proximal tubule cells. There is limited data on FSTL1 in human CKD.

Methods: The NEPTUNE cohort was used to relate clinical variables to candidate gene expression to FSTL1 mRNA levels in the tubulointerstitial compartment of the kidney. Our study focused on patients with nephrotic syndrome due to primary focal segmental glomerulosclerosis (FSGS), immunoglobulin A nephropathy (IgAN), and membranous nephropathy (MN).

Results: Analysis revealed FSTL1 was inversely correlated with eGFR in the FSGS (r=-0.4473, p=<0.0001), IgAN (r=-0.6751, p=0.0011), and MN cohorts (r=-0.4122, p=0.0101). Additionally, FSTL1 correlated with proteinuria in FSGS (r=0.3368, p=0.0007) and IgAN (r=0.4352, p=0.0162) but less so in MN (r=0.2665, p=0.0515). In terms of histopathology FSTL1 was also related to interstitial fibrosis in FSGS (r=0.4477, p=<0.0001), IgAN (r=0.751, p=0.0001), and MN (r=0.5445, p=0.0004). FSTL1 was also related to tubular atrophy in FSGS (r=0.4465, p=<0.0001), IgAN (r=0.7523, p=0.0001), and MN (r=0.5246, p=0.0007). Finally, FSTL1 mRNA levels were also positively correlated with injury makers NGAL and KIM-1, extracellular matrix protein genes, cytokine gene expression (COL1α1 and TGFβ1), and genes involved in inflammation (CCL2 and TNF-α) in all three cohorts (p=<0.0026).

Conclusions: FSTL1 was inversely correlated with eGFR and positively correlated with interstitial fibrosis and tubular atrophy in all three of the cohorts. FSTL1 mRNA levels also correlated with injury markers and extracellular matrix protein gene expression. These findings support the hypothesis that FSTL1 may be a novel determinant of progressive CKD in primary nephrotic syndrome.

FR-PO356

Impact of Periostin in Aging Kidney

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Background: Periostin is a matricellular protein which plays important role in tissue adaptation to injury. In kidney disease, periostin is known to be highly expressed in tubulointerstitial fibrosis and correlated with renal function inversely. In this study, we investigated the effect of periostin in aging process and progressive renal interstitial fibrosis.

Methods: 1. UUO model We conducted unilateral ureteral obstruction (UUO) surgery in wild type (WT) mice and periostin knockout (KO) mice. And compared interstitial fibrosis and pericyte changes. 2. Aging model We compared interstitial fibrosis and changes of pericytes in 4 groups; WT young age group, WT old age group, periostin KO young age group and periostin KO old age group.

Results: In UUO model, periostin KO mice shows less interstitial fibrosis and increased number of pericytes. And periostin KO aging mice shows attenuated fibrosis and abundant pericytes compared to WT aging mice.

Conclusions: Periostin inhibition ameliorated renal interstitial fibrosis in UUO model and aging process. It is thought that it affects pericyte and shows a reno-protective effect.

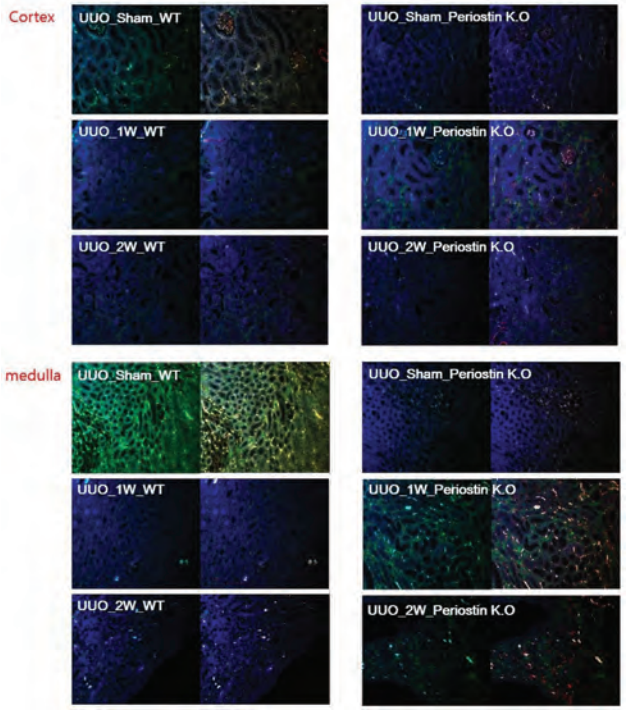
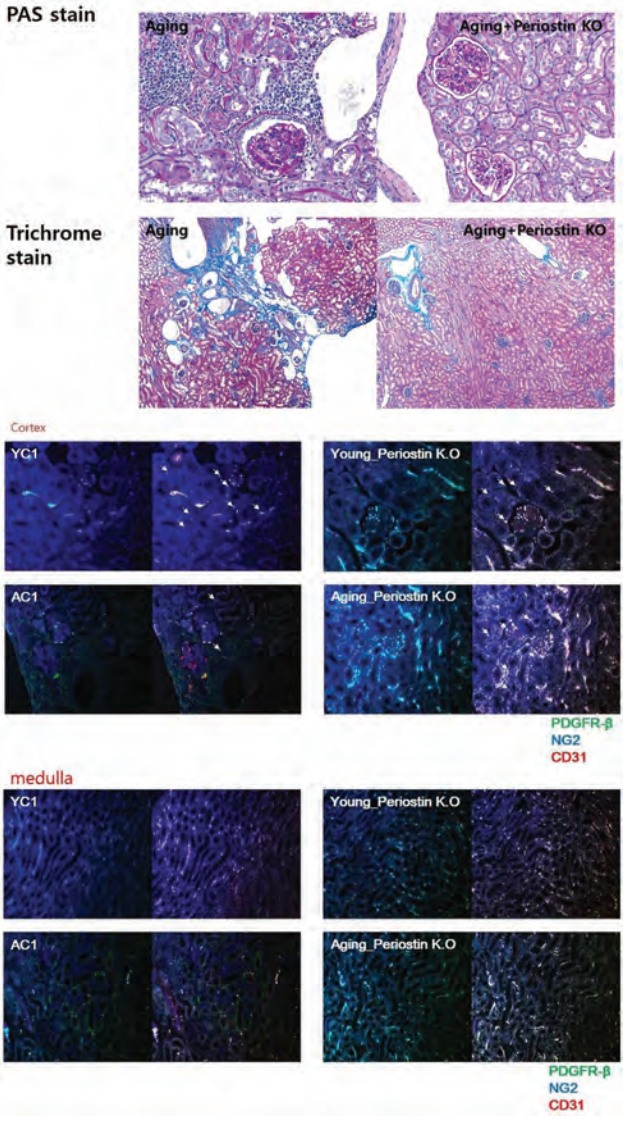


Figure 1. Changes of pericytes in UUO of periostin KO mouse



Figuer 2. Changes of fibrosis and pericytes in aging periostin KO mouse

FR-PO357

V1a Receptor-Mediated Kidney Tissue Oxygenation Is Independent of Vasopressin V2 Receptor Blockade

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Background: AVP binds to two subtypes of receptors in the kidney, the V1a and V2 receptors mediating different cellular effects. Selective V2 receptor antagonism induces aquaresis and is an efficacious decongestive approach. We showed that selective V1a receptor inhibition improves kidney oxygenation and kidney function which might be relevant for conditions of increased AVP levels such as chronic kidney disease. We investigated the potential interference of selective V2 antagonism with V1a antagonism on kidney oxygenation.

Methods: The effects of selective V2 antagonism (tolvaptan or satavaptan), selective V1a antagonism (relcovaptan) or a combination of both on renal blood flow (RBF) and tissue oxygenation (pO2) were investigated in isolated perfused rat kidneys (IPK) and in anesthetized Sprague Dawley rats (n=7 per group) via Laser Doppler Flowmetry in settings of increased AVP levels.

Results: Tolvaptan (0.3–100 nM) had no effect on the AVP-mediated (50 nM) reduction of perfusate flow while increasing urine excretion (p=0.07). *In vivo*, infusion of AVP (50 ng/kg/min i.v.) significantly increased mean arterial pressure (MAP) and reduced both RBF and tissue pO_2 (Table 1). Dose-dependent infusion of tolvaptan did not reduce the increased MAP values and did neither restore RBF nor kidney pO_2 levels. Similar results were achieved with satavaptan. Combination of V1a antagonism (relcovaptan) with V2 antagonism (tolvaptan) normalized AVP-increased MAP and restored RBF and pO2 back to basal values similar to the individual V1a antagonism (Table 1).

Conclusions: Selective V2 inhibition has no impact on renal oxygenation in settings of increased AVP levels and does not interfere with V1a receptor blockade-mediated beneficial effects on kidney oxygenation. Therefore, addressing the individual vasopressin

receptors alone or in combination in cardiorenal diseases is dependent on the presence of congestion and/or kidney hypoxia.

Funding: Commercial Support - Bayer AG

	MAP (mmHg) mean±SEM	Kidney pO2 (mmHg) mean±SEM	RBF (U) mean±SEM
Baseline	95±8$^{\#\#}$	29±8*	925±132
AVP (50 ng/kg/min)	131±4	15±2.5	762±115
Tolvaptan (1 µg/kg)	122±3	16±4	718±104
Tolvaptan (3 µg/kg)	118±3	16±4	721±112
Tolvaptan (10 µg/kg)	115±4	16.5±6	734±124
Tolvaptan (30 µg/kg)	112±4*	18±5	699±150
Baseline	98±3$^{\#\#\#\#}$	34±10$^{\#\#}$	1168±115$^{\#}$
AVP (50 ng/kg/min)	129±2	4±2	672±115
Relcovaptan (3 µg/kg)	97±2****	46±8*	1056±116
Relcovaptan (3µg/kg) Tolvaptan (10 µg/kg)	94±2****	37±9*	1046±134

*/**** p<0.05/0.0001 vs. AVP (One-way ANOVA)#/##/#### p<0.05/0.01/0.0001 vs. AVP (t test)

FR-PO358

Hypoxia Reduced Renal Injury and Inflammation in Rats with Chronic Nitric Oxide Inhibition

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Background: Chronic NO inhibition by Nω-nitroarginine methylester (NAME) leads to severe hypertension (HT) and Chronic Kidney Disease (CKD). Tissue hypoxia (HYP) has been postulated as a pathogenic factor in CKD, but we showed recent evidence that it may instead be renoprotective. We investigated whether this salutary effect would also be observed in NAME rats and whether it would involve NLRP3 and/or NFκB inhibition.

Methods: Male Munich-Wistar rats received NAME, 80 mg/kg/d in tap water. Ten Control (C) and 10 NAME rats were kept under 21% O_2 (NOR), while 12 C and 12 NAME rats breathed 12% O_2. After 4 wk, we assessed hemoglobin (Hb,g/dL), tail-cuff pressure (TCP, mmHg), urine albumin/creatinine (U_{Alb}/U_{Cr}), glomerulosclerosis (GS, %), % ischemic glomeruli (% IG), cortical density (mm^{-2}) of macrophages (MΦ), Angiotensin II+ (AII+) and NLRP3+ cells, cortical Collagen-1 (%Coll-1) and the renal content of nuclear p65, IL6, Casp1, HO1 and SOD2 (WB), and IL1β (pg/mg). HYP was confirmed by pimonidazole staining.

Results: HYP reduced HT, inflammation, o xidative s tress, r enal injury, a nd the content of NLRP3, CASP1, IL1β, nuclear p65 and IL6.

Conclusions: Tissue HYP exerted a protective effect in NAME, suggesting that it may influence a common pathogenic mechanism, which may relate to downregulation of the NLRP3 inflammasome/Casp1/IL1β and NFκB/IL6 pathways, and to limitation of oxidative stress. FAPESP/CNPq.

Funding: Government Support - Non-U.S.

	C_{NOR}	$NAME_{NOR}$	C_{HYP}	$NAME_{HYP}$
Hb	14±1	15±1	17±1*	17±1#
TCP	151±2	212±2*	154±4	188±6*#
U_{Alb}/U_{Cr}	0.2±0.1	1.8±0.4*	0.3±0.1	0.7±0.1#
%GS	0.1±0.1	1.1±0.3*	0.1±0.3	0.1±0.1#
%IG	0.5±0.3	6.9±0.9*	0.4±0.3	0.4±0.1#
MΦ	30±4	114±14*	32±3	46±6*#
AII+	2±1	5±1*	2±1	2±1#
%Coll1	2.4±0.2	6.1±0.3*	3.2±0.2	3.7±0.2#
Nuclear p65	1.1±0.2	3.2±0.5*	1.1±0.2	2.0±0.3#
IL6	1±0.1	6.1±1.7*	1.6±0.4	2.5±1.0#
NLRP3	1±1	4±1*	1±1	2±1*#
CASP1	1±0.2	5.6±2.0*	1.7±0.4	2.2±1.1#
IL1β	2.6±0.6	6.4±0.9*	3.8±0.7	2.9±0.3#
HO1	1±0.2	2.3±0.3*	1±0.2	1.9±0.2*
SOD2	1±0.1	0.5±0.1*	1±0.2	0.7±0.1

Mean±SE;*p<0.05 vs respect C, #p<0,05 vs N_{NOR}

FR-PO359

INO80 Inhibits Tubulointerstitial Apoptosis Under Hypoxia

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Background: Chronic kidney disease (CKD) is known to be caused by various kinds of factors including epigenetic factors. Among them we focused on the role of INO80. INO80 is an ATPase and nucleosome spacing factor. Biological function of INO80 is known to be ATP-dependent chromatin-remodeling, and it regulates transcription, DNA repair and replication. Our aim of this study is to clarify the pathophysiological role of INO80 in the kidney.

Methods: In order to investigate the expression levels of INO80 in the impaired kidney, we utilized 5/6 nephrectomy rats. To clarify the biological function of INO80 in the kidney, we performed *in vitro* experiments using HK2 (human kidney-2) cells in which INO80 was knocked down by using siRNA. In addition, genome-wide analysis using RNA-seq was performed to identify the downstream target genes of INO80 under hypoxia. Furthermore, we examined the effects of INO80 on apoptosis of tubular cells.

Results: In 5/6 nephrectomy rats, we found that the expression of INO80 was significantly suppressed at the mRNA level compared to sham rats. When HK2 cells were cultured under 1% hypoxic conditions for 24 hours, the expression level of INO80 significantly decreased. Genome-wide analysis by RNA-seq identified 32 downstream target candidate genes whose expressions decreased less than half compared with control siRNA when INO80 was knocked down by siRNA. While, knockdown of INO80 in HK2 cells promoted tubulointerstitial apoptosis by 24 hours, the expression of mRNA of tumor suppressor gene p53 and transcription factor E2F1 was significantly increased.

Conclusions: INO80 plays an important role in suppressing apoptosis in renal tubular cells, and it is considered that E2F1-mediated regulation may be involved in the apoptosis suppression pathway by INO80.

FR-PO360

Direct Inhibitory Effect of Sodium on Nrf2 Expression in Collecting Duct Cells

Mi Liu. *Southern Medical University Shunde Hospital, Foshan, China.*

Background: High salt is associated with the progression of CKD. High salt also contributes to oxidative stress in renal tissue and cells. However it remains unclear if high salt is involved in the pathogenesis of CKD through the regulation of oxidative stress. Nuclear factor E2-related factor 2 (Nrf2) is a transcriptional factor which regulates the expression of downstream antioxidant and detoxifying genes. The study was aimed at clarifying whether high salt will affect Nrf2 expression and Nrf2-dependent pathway.

Methods: Mice was treated with acute salt loading. Nrf2 expression in the kidney were detected by western blotting and immunostaining. mpkCCD cells were cultured in high osmolarity medium by adding NaCl. We measured the expression of Nrf2 and Nrf2-dependent genes via western blotting and qRT-PCR. Pretreatment with NAC, spironolactone or NS-398 in mpkCCD cells were performed and Nrf2 mRNA expression were monitored.

Results: Nrf2 protein levels in the kidney were markedly downregulated after acute salt loading. Nrf2 was remarkably downregulated in mpkCCD cells after NaCl treatment. Sodium gluconate had a similar effect on Nrf2 expression as NaCl, whereas neither Choline-Cl nor mannitol changed Nrf2 protein level. The mRNA levels of Nrf2-dependent genes were downregulated by NaCl mainly dependent on the effect of Na^+. The downregulation of Nrf2 was not affected by NAC, spironolactone or NS-398.

Conclusions: Sodium has a direct inhibitory effect on the expression of Nrf2 and Nrf2-dependent genes.

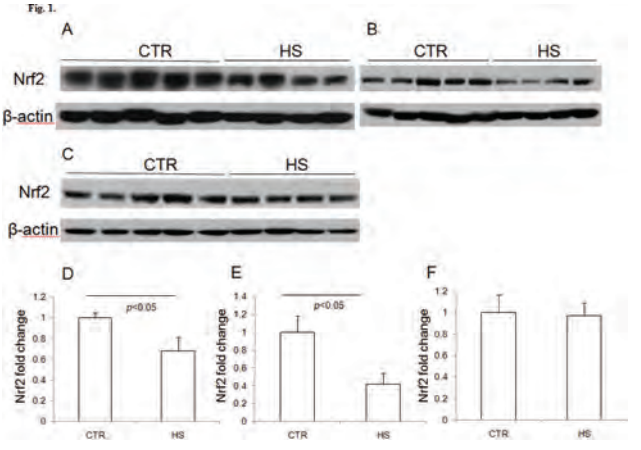
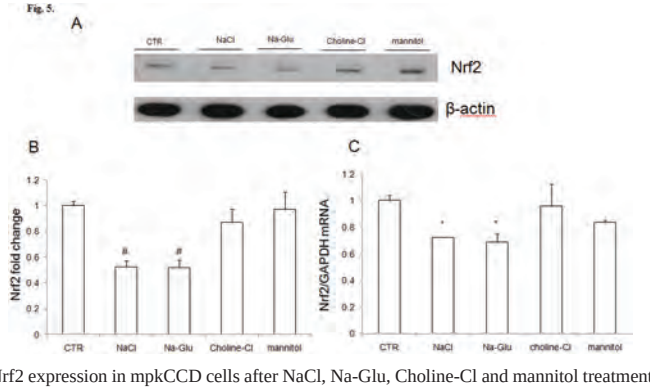


Figure 1. Nrf2 protein expression in kidneys after acute high salt loading.



Nrf2 expression in mpkCCD cells after NaCl, Na-Glu, Choline-Cl and mannitol treatment

FR-PO361

Abnormal Cytokine-Induced Responses in IgA1-Subpopulations Enhance Production of Galactose-Deficient IgA1, the Main Autoantigen in IgA Nephropathy

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Background: IgA nephropathy (IgAN), the most common primary glomerulonephritis in the world, is characterized by glomerular IgA1 immunodeposits enriched for galactose-deficient IgA1 (Gd-IgA1). Patients with IgAN have elevated blood levels of Gd-IgA1. Gd-IgA1 blood levels also predict disease progression. IgAN patients often present with synpharyngitic hematuria, and have elevated serum levels of IL-6, indicating ongoing inflammation. Some cytokines increase Gd-IgA1 production by IgA1-secreting cells from IgAN patients. We hypothesized that Gd-IgA1 overproduction induced by a cytokine stimulation may involve only a subpopulation(s) of IgA1-producing cells and used single-cell transcriptome analysis of cells from IgAN patients and controls to test that hypothesis.

Methods: A mixture of cytokines mimicking those of T-follicular helper (Tfh) cells (IL-4, IL-6, IL-21, CD40L; 50 ng/mL) was used to activate immortalized Ig-producing cells from IgAN patients and healthy controls (HC) for 30 min before single-cell transcriptomic analysis. IgA1-secreting cells were identified using a splice-variant analysis to differentiate membrane vs. secreted isoforms. Resultant data were normalized using Seurat V2.4 and the curated data were analyzed with Alteryx. Gd-IgA1 production was assessed after cytokine stimulation for 72 h.

Results: Gd-IgA1 production increased in Ig-producing cells from IgAN patients but not HC after stimulation with Tfh cytokines. Several subpopulations of IgA1-secreting cells from IgAN patients exhibited substantial repression of genes associated with regulation of cytokine responses (*e.g.,PTPN11, SOCS3, PTPN2,*) due to Tfh cytokine stimulation (N=3, p <0.05). The same subpopulations also exhibited abnormal changes in glycosyltransferase genes implicated in Gd-IgA1 production.

Conclusions: We identified subpopulations of IgA1-secreting cells from IgAN patients that exhibited differential regulation of expression of glycosyltransferases due to abnormal Tfh-cytokine signaling. These data suggest that there are subpopulations of IgA1-producing cells that may be primarily responsible for Gd-IgA1 overproduction.

Funding: NIDDK Support, Private Foundation Support

FR-PO362

Apolipoprotein C3 Induces Systemic Inflammation and Organ Damage in CKD by Alternative Inflammasome Activation via a Novel Pathway

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Background: CKD is associated with systemic sterile inflammation promoting the progression of CKD. Activation of the NLRP3 inflammasome plays an important role by inducing the release of the key alarminin Interleukin-1β (IL-1β). Identification of endogenous inflammasome activators in CKD patients is essential for the development of new anti-inflammatory treatment strategies.

Methods: Lipoproteins from CKD patients were fractioned. Their effect on IL-1b release was determined in human monocytes and in murine macrophages. Mechanistically, the NLRP3 activation by lipoproteins was studied in detail in vitro and several murine models. The relevance of these findings was studied in humanized mice subjected to unilateral ureter obstruction (UUO) or carotid perivascular injury.

Results: The VLDL fraction of lipoproteins from CKD patients substantially stimulated IL-1β release from human monocytes. Using proteomics, we found apolipoprotein-C3 (ApoC3) to accumulate within VLDL from CKD patients. ApoC3 stimulated pro-inflammatory activation of human monocytes in vitro and promoted a pro-inflammatory state in vivo in mice with accumulation of macrophages within the kidneys. Mechanistically, ApoC3 activated the NLRP3 inflammasome in human monocytes by inducing an alternative NLRP3 inflammasome via caspase-8 and dimerization of Toll-like receptor-2/4 leading to alternative inflammasome activation, a novel and previously unknown pathway. In general, we found that alternative inflammasome activation in human monocytes is mediated by Toll-like receptor adapter protein SCIMP. In humanized mice, ApoC3 activated human monocytes to impede endothelial regeneration and to substantially promote kidney injury. ApoC3 plasma levels were increased in patients with incipient CKD and associated with higher mortality in a large clinical trial (N=3,313) of patients undergoing coronary angiography after a median follow-up of 9.9 years.

Conclusions: These data provide novel insights into the regulation of the NLRP3 inflammasome activation in general and the pathophysiological role of triglyceride-rich lipoproteins containing ApoC3 in the progression of CKD and in CKD-associated cardiovascular disease. Targeting ApoC3 has the potential to prevent kidney damage and to provide an anti-inflammatory treatment strategy in patients with CKD.

FR-PO363

Effects of Bone Marrow Mesenchymal Stem Cell-Derived Exosomes on Renal Fibrosis by Regulating Macrophage Phenotypic Transformation

Xiaolan Chen. *The Affiliated Hospital of Nantong university, Nantong, China*.

Background: In recent years, bone marrow mesenchymal stem cells (BM-MSCs) have received extensive attention due to their biological characteristics such as self-replication, high proliferative potential and multi-directional differentiation. This hinders the clinical transformation of MSCs in the treatment of kidney disease. Recent studies have shown that homing of MSCs to the injury site in the circulatory system is not the main mechanism for their continued therapeutic effects.

Methods: Establishment of unilateral ureteral obstruction (UUO) model in mice and random grouping: (1) sham operation group; (2)UUO group; (3)UUO+PBS group; (4)UUO+MSC(1×10^6/animal); (5)UUO+ exosomes (30μg/animal) group. Stem cells and exosomes were injected intravenously in the caudal vein on the day of modeling. Specimen collection and detection: HE staining and Masson staining were used to detect the pathological changes of renal tissue in each group of mice. Western Blot was used to detect the expression of α-SMA protein. Immunohistochemistry was used to detect renal interstitial fibrosis, macrophage infiltration and phenotype in each group. Flow cytometry was used to detectmacrophage subtypes.

Results: In vivo: Compared with UUO group, the renal pathology of the two groups of mice intervened by MSC and exosomes tail vein injection was significantly improved. the expression level of CD86 was significantly decreased after MSC and exosomes intervention, while the expression level of CD206 was increased;the ratio M2/M1 of macrophage subtypes in MSC and exosomes intervention groups was significantly increased.**In vitro:** the proliferation ability of macrophages in LPS group was significantly decreased. the secretion of IL-12 by macrophages in LPS group increased significantly, but the secretion of IL-10 did not change significantly($P>0.05$).the expression of iNOS and ARG1mRNA in LPS group increased. Compared with LPS group, the proliferation ability of macrophages increased after exosomes intervention. the expression of IL-12 decreased and the expression of IL-10 increased after exosome intervention. iNOSmRNA expression was down-regulated and ARG1mRNA expression was up-regulated after exosomes intervention.

Conclusions: Exosomes derived from bone marrow mesenchymal stem cells can regulate macrophage phenotypic transformation, thus improving renal fibrosis.

FR-PO364

The Expansion and Phenotype of HLA-DR^{hi} Intermediate Monocytes in CKD

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Background: A chronic microinflammatory state occurs in CKD, one aspect of which is monocyte subset dysregulation. Monocytes are comprised of one major ("classical") and two minor ("intermediate" and "nonclassical") subsets. The intermediate monocyte (IM) subset is pro-inflammatory and numerically increased in CKD. Having recently reported that human IM may be further subdivided into HLA-DR^{mid} and HLA-DR^{hi} subpopulations and that IM increase in CKD is specific to the HLA-DR^{hi} IM subpopulation, we aimed to determine whether HLA-DR^{hi} IM display distinctive expression of surface proteins required for endothelial adhesion and transmigration in health and in CKD.

Methods: Adult outpatients with CKD or healthy controls (HC) provided blood samples by informed consent. Peripheral blood mononuclear cells (PBMC) were isolated and analyzed by multi-colour flow cytometry for monocyte subpopulation numbers and surface protein expression levels (CD45, CD14, CD16, HLA-DR, CCR2, CCR5, CCR7, CX3CR1, CD11a, CD11b, CD11c, CD62L, CD49d and CD162).

Results: Consistent with prior results, higher numbers of total IM ($p=0.03$) and in HLA-DR^{hi} IM ($p=0.015$) were present in PBMC from CKD vs HC. IM had higher expression of CCR5 than classical and non-classical monocytes ($p<0.0001$). Among the IM, high CCR5 was specific to HLA-DR^{hi} IM ($p=0.002$). Surface expression of the integrin chains CD11b and CD11c was also highest among HLA-DR^{hi} IM ($p<0.001$). For CCR5, CD11b and CD11c, HLA-DR^{hi} IM surface expression was similar for CKD and HV. In contrast, HLA-DR^{hi} IM surface expression of CX3CR1 (the receptor for fractalkine/CX3CL1) was higher in CKD vs. HV ($p=0.02$). Finally, we also observed that surface expression of the selectin ligand PSGL-1/CD162 was higher on classical monocytes ($p=0.008$) and HLA-DR^{mid} IM ($p<0.001$) in CKD compared to HC. Other surface proteins analyzed also showed distinctive patterns of expression among the monocytes subsets that were not modulated in CKD.

Conclusions: Among circulating monocyte subpopulations, several surface proteins which mediate endothelial adhesion and transmigration are highly expressed by HLA-DR^{hi} IM, a distinctive subpopulation that is numerically increased in CKD. Functional analyses may help to determine whether CKD-associated expansion of HLA-DR^{hi} IM contributes to microvascular inflammation and progressive fibrosis.

Funding: Private Foundation Support

FR-PO365

Comparative Analysis of Regulatory T Cell Subpopulations in CKD Outpatients and Healthy Controls

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Background: Regulatory T cells (T-reg) suppress autoimmunity/inflammation and allo-antigen-specific immune response in transplantation. Consequently, ex vivo-expanded T-reg are a promising immunomodulatroy therapy. In CKD/ESRD, circulating T-reg numbers are peserved and can be culture-expanded. Nonetheless, T-reg sub-phenotypes and their relevance to CKD pathophsiology are not fully characterised. We aimed to compare relative proportions and surface phenotype characteristics of circulating T-reg subpopulations in adult CKD outpatients and healthy adults.

Methods: Blood samples and clinical information were provided by CKD outpatients without immune-mediated disease (n=35, eGFR:11-64) and by healthy volunteers (HV, n=20). Multi-color flow cytometry was performed on fresh PBMC for CD4, CD25, CD127 and FoxP3 (to identify T-reg) and for CD45RA, HLA-DR, TNFR2, CCR7, CD62L and CD39 (to define subpoulations and their functional markers).

Results: Peripheral blood $CD4^+$ $CD25^+$ $CD127^{lo}$ T-reg (confirmed to be $FoxP3^+$) were identified and subdivided into 3 subpopulations based on expression of CD45RA and HLA-DR [RA^+ DR^-, RA^- DR^+, RA^- DR^-]. No difference in T-reg frequency (expressed as % of total CD4+ T-cells) was seen between CKD and HV. However, RA^- DR^- T-reg were proportionately increased and RA^+ DR^- T-reg were proportionately decreased in CKD ($p<0.0001$), consistent with a relative expantion of "antigen experienced" T-reg. In regard to surface proteins of potential functional importance, the selectin CD62L was expressed at higher level on total T-reg of CKD vs. HC (average MFI 3810 vs 1299, p=0.0002) as well on each of the 3 T-reg subpopulations. In contrast, surface expression of the ectonuclease CD39 (which dephosphorylates ATP and ADP) was lower on total T-reg (average MFI 665 vs 6936, $p<0.0001$) and was present on lower proportions of RA^- DR^+ T-reg (average 53.0% vs 87.1%, p=0.001) and RA^- DR^- T-reg (average 36.6% vs 73.8%, $p<0.0001$) in CKD vs. HV. Expression of CCR7 and TNF receptor 2 (TNFR2) did not differ for T-reg and T-reg subpopulations of CKD and HV.

Conclusions: Although adults with CKD had comparable blood T-reg numbers compared to HV, they differed in the relative frequencies of CD45RA/HLA-DR-defined T-reg subpopulations and in expression of proteins that could reflect alterations in migration patterns (CD62L) and specific regulatory functions (CD39).

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

FR-PO366

Klotho Restrains RIG-1/NF-κB Signaling Activation and Monocyte Inflammatory Factor Release Under Uremic Conditions

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Background: Systemic inflammation is a main hallmark of chronic kidney disease (CKD). However, the mechanisms underlying the pathogenesis of CKD-associated systemic inflammation are unclear. Our study aimed to investigate the relationship between indoxyl sulphate (IS) and CKD-associated systemic inflammation, and the protective effect of Klotho against IS-induced systemic inflammation in CKD.

Methods: Serum Klotho was measured by ELISA. Heterozygous *kl/kl* (*kl/*$^+$) mice or WT mice were treated with 5/6 renal damage and then injected with recombinant Klotho protein.

Results: It shows that in 286 CKD patients, the serum levels of inflammatory factors are positively related with IS, but negatively related with Klotho. Klotho can significantly inhibit IS-induced retinoic acid-inducible gene I (RIG-I) /NF-κB activation and the productions of IL-6 and TNF-α in cultured monocytes. *In vivo*, RIG-I/NF-κB activation is observed in monocytes in both CKD mice and patients. Notably, higher levels of IL-6 and TNF-α are detected in $kl^{+/-}$ mice with CKD. Klotho administration can evidently attenuate RIG-I/NF-κB activation in monocytes and systemic inflammation in CKD mice.

Conclusions: These results suggest that Klotho can suppress CKD-associated systemic inflammation through inhibiting IS-induced RIG-1/NF-κB activation and monocyte inflammatory factor release.

The basic information of 286 CKD patients

CKD stage	CKD 2(n=36)	CKD 3(n=51)	CKD 4(n=55)	CKD 5(n=144)	P
Age, years	39.86±11.9	49.88±13.88	47.27±14.89	46.29±14.18	＜0.05
Male gender, n(%)	19(53)	22(43)	34(62)	60(42)	＜0.001
eGFR(ml/min/1.73m2)	71.16(67.41,82.22)	42.79(36.04,53.27)	19.71(16.99,25.22)	8.14(6.39,10.45)	＜0.001
BMI(kg/m2)	24.06±2.89	24.50±3.50	23.23±2.99	22.34±3.43	＜0.001
ALB(g/L)	41.50(34.43,45.28)	39.00(35.30,42.40)	40.40(35.30,43.80)	38.85(36.40,42.08)	>0.05
Uric acid(μmol/L)	434.50±90.46	429.24±94.02	500.60±113.53	539.04±123.22	＜0.001

Klotho inhibits IS-induced monocyte activation by restraining RIG-1/ NF-κB signaling

FR-PO367

Single-Cell Genomics Applied to Unilateral Ureteral Obstruction Kidneys with Lymphatic Vessel Knockdown Identifies the Key Role of Adaptive Immunity in Renal Fibrosis

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Background: Lymphangiogenesis in chronic kidney disease has been reported in a large number of literatures. However, it is still unclear how the lymphatic vessels (LVs) act as a transport channel regulating the infiltration of immune cells in the kidney. The purpose of this study was to clarify the mechanisms by which LVs regulate the infiltration of immune cells and the following chronic kidney disease and fibrosis.

Methods: We constructed four lymphatic knockdown mouse models. The new-born proliferated LVs were knockdown by injection of Ganciclovir after unilateral ureteral obstruction (UUO) in Lyve-1-tk and Prox-1-tk mice, and resident LVs were knockdown by injection of DT in Lyve-1-DTR and Prox-1-DTR mice. Then, we performed RNA-Seq and single-cell transcriptomics on the kidneys of lymphatic knockdown group and control group.

Results: It showed that the UUO kidney had less LVs, less inflammatory cell infiltration and reduced fibrosis after new-born proliferated LVs or resident LVs knockdown. The ischemia reperfusion injury model yields the similar results. Both differentially expressed genes (DEGs), GO and KEGG pathway analysis identified that DEGs are mainly enriched in chemokine related genes. The heat map showed that chemokines and renal extracellular matrix deposition related genes were significantly down-regulated after lymphatic knockdown. The single-cell transcriptomics showed that lymphatic knockdown attenuated UUO induced intrarenal inflammatory infiltration (from 60% to 25%) and preserved renal tubular epithelial cells (from 40% to 75%). The main reduced inflammatory cells were T cells and DCs. Interestingly, the reduction in T cells included all subpopulations, while the subpopulation reduced in DCs was lymphoid DCs, but not myeloid DCs. The other immune cells, such as macrophages, B cells, and neutrophils, were not altered. In addition, we found that B cells expressed more abundant genes associated with cell senescence such as p21cip1 and p16ink4a after lymphatic knockdown.

Conclusions: We verified that lymphatic knockdown alleviates renal inflammation and fibrosis in UUO kidneys. The decreased immune cells after lymphatic knockdown are T cells and lymphoid DCs, accompanied with B cell senescence, suggesting the adaptive immunity participates in UUO induced renal inflammation and fibrosis.

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FR-PO368

Heritability Enrichment Analyses in Kidney Function Genome-Wide Association Study Identifies Trait-Specific Kidney Cell Types

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Background: Identifying relevant tissues and cell types underlying kidney function and disease informs experimental follow-up studies to understand disease biology. Novel statistical methods allow for unbiased identification of trait-relevant cell types by incorporating RNA-seq data with GWAS summary statistics.

Methods: We used LD score regression for specifically expressed genes (LDSC-seg) to partition heritability in GWAS summary statistics of European ancestry participants from the CKDGen Consortium of estimated glomerular filtration rate (eGFR, n=567,460), urinary albumin-to-creatinine ratio (UACR, n=547,361), blood urea nitrogen (BUN, n=243,031) and serum urate (n=288,666). GWAS of asthma (UK Biobank, n=452,264), and schizophrenia (CLOZUK+PGC Consortia, n=105,318) were used as negative controls. Publicly available kidney single-cell RNA-seq datasets (human, 24 cell types; mouse, 16 cell types) were used to construct the top 10% specifically expressed genes per cell type followed by testing heritability enrichment in each trait. For examination at tissue level, the same procedure was applied using GTEx V7 data.

Results: Across tissues, we found significant enrichment of heritability in trait-associated loci containing genes that are highly expressed in kidney (eGFR: 2.2-fold enrichment, p=9.1e-8; urate: 2.1-fold enrichment, p=1.2e-5); liver was also enriched. Within the kidney, enrichment was observed in regions containing genes specifically expressed in proximal tubule cells in human (eGFR 2.3-fold, p=8.5e-5; BUN 1.7-fold, p=0.005; urate 2.3-fold, p=7.8e-6) and mice (eGFR 2.3 fold, p=0.0003; BUN 1.8-fold, p=0.02; urate 2.3-fold, p=0.0002), as well as in human podocytes (UACR 1.7-fold, p=0.009). Both asthma and schizophrenia did not show significant enrichment of heritability in regions with genes that are highly expressed in kidney cell types, but instead in brain tissues (schizophrenia, smallest p=9.8e-16).

Conclusions: GWAS signals of kidney function traits are enriched for genes that are highly expressed in relevant tissues and cell types such as proximal tubular cells for eGFR, BUN and urate, and glomerular cells for UACR. These results allow for identifying relevant cell types for experimental research to translate GWAS loci into a mechanistic understanding.

FR-PO369

The Antioxidant Activity of Neurotropin Contributes to the Kidney Protective Effect

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Background: Neurotropin (NTP) is an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus and contains various non-protein components. NTP has long been used for the treatment of neuropathic pain such as postherpetic neuralgia. Recently, NTP have been reported that various organ protective effects by its antioxidant action. Furthermore, it is also suggested that NZ-419, which is one of the components of NTP, has the antioxidant activity and contributes to the renoprotective effect. Therefore, the aim of this study is to evaluate the antioxidant activity and renoprotective effect of NTP by in vitro and in vivo.

Methods: The radical scavenging ability for reactive oxygen species (ROS) was examined by electron spin resonance (ESR) method, chemiluminescence method or fluorescence analysis. The effect of NTP on oxidative stress induced by uremic toxins was evaluated using human renal proximal tubule epithelial cells (HK-2). Furthermore, 5/6 nephrectomized rats (CKD) were divided into 3 groups (CKD, CKD + NTP, and CKD + aspirin) and were orally administered each drug once daily for 4 weeks. Survival rate, kidney function parameters, oxidative stress marker, and kidney fibrosis were measured.

Results: NTP had concentration-dependent $O_2^{\cdot-}$ and $ONOO^-$ scavenging ability and scavenged $OH^{\cdot}$ at high concentrations. The inhibitory effect on intracellular ROS production was observed in only H_2O_2 under the simultaneous addition of NTP and irritant. On the other hand, the irritant-induced ROS production was inhibited under the preincubation of NTP for 9 hour. Survival rate of CKD rats was shown a trend of decreased in the aspirin group. NTP didn't affect survival rate and had a tendency to suppress kidney damage. Also, compared to the CKD group, the NTP group was observed that thiol concentration, antioxidant marker, increased in blood and decreased in fibrotic area in kidney.

Conclusions: In this study, it is considered that NTP has the direct radical scavenging ability and alters intracellular signal transduction to suppress oxidative stress. In conclusion, NTP may contribute to the renoprotective effect by not only the antioxidant effect but also the antifibrosis.

FR-PO370

Regulation and Role of NADPH Oxidase 4 in CKD

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Background: While low-levels of reactive oxygen species (ROS) are important for physiological signaling, excessive ROS production has been implicated in CKD progression. Therefore, understanding the contribution of renal redox signaling in physiological and pathological context is essential to develop new therapeutics. NADPH oxidase 4 (NOX4) catalyzes the formation of hydrogen peroxide (H_2O_2). NOX4 is highly expressed in the kidney, but its role in renal damage is unclear and may depend on its specific tissue localization.

Methods: We performed immunostaining with a specific anti-NOX4 antibody and measured *NOX4* mRNA expression in human renal biopsies encompassing diverse renal diseases. We generated transgenic mice specifically overexpressing mouse Nox4 in renal tubular cells and subjected the animals to acute and chronic unilateral ureteral obstruction (UUO) model of fibrosis.

Results: In normal human kidney, NOX4 protein expression was at its highest on the basolateral side of proximal tubular cells. NOX4 expression increased in mesangial cells and podocytes in diabetic nephropathy. In tubular cells, NOX4 protein expression decreased in all types of chronic renal disease studied. This finding was substantiated by decreased *NOX4* mRNA expression in the tubulo-interstitial compartment in a repository of 176 human renal biopsies. Overexpression of tubular NOX4 in mice resulted in enhanced renal production of H_2O_2, increased NRF2 protein expression and decreased glomerular filtration, likely via stimulation of the tubulo-glomerular feedback. Tubular NOX4 overexpression had no obvious impact on kidney morphology, apoptosis, or fibrosis at baseline. Under acute and chronic tubular injury induced by UUO, overexpression of NOX4 in tubular cells did not modify the course of the disease.

Conclusions: NOX4 expression was decreased in tubular cells in all types of CKD tested. Tubular NOX4 overexpression did not induce injury in the kidney, and neither modified microvascularization, nor kidney structural lesions in fibrosis.

FR-PO371

Hypoxia Attenuates Tubulointerstitial Injury, Inflammation, and Oxidative Stress in the Adenine Overload Model

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Background: Adenine excess (ADE) leads to renal deposition of crystals (Crys) and tubulointerstitial nephritis via NFκB. Tissue hypoxia (HYP) has been considered a pathogenic factor in Chronic Kidney Disease (CKD). We showed recently that chronic HYP was renoprotective in rats with 5/6 renal ablation (Nx). Here we investigated a possible beneficial effect of HYP in ADE.

Methods: Male Munich-Wistar rats received standard (C) or 0.5% ADE chow. Six C and 8 ADE rats breathed 21% O_2 (NOR), while 8 C and 8 ADE rats were kept under 12% O_2 (HYP). After 2 wk, we assessed hemoglobin (Hb, g/dL), tail-cuff pressure (TCP, mmHg), urine albumin/creatinine (U_{alb}/U_{cr}), left kidney/body weight (x100), crystal density (Crys/mm^2), urine KIM1 (ng/mL), cortical macrophages (MΦ) and angiotensin II+ (AII+) cells/mm^2 and collagen-1 (%Coll-1), as well as the renal content of nuclear p65, IL6, CASP1, HO1, SOD1 (WB) and IL1β (pg/mg). Renal HYP was confirmed by pimonidazole staining.

Results: HYP reduced renal hypertrophy, tubular injury, interstitial inflammation/fibrosis and the content of p65 and IL6, but not CASP1 or IL1β, suggesting specific NFκB inhibition, while lowering HO1 and increasing SOD1.

Conclusions: As in Nx, breathing 12% O2 limited renal injury in the ADE model and attenuated NFκB and oxidative stress, suggesting the existence of a common pathogenic mechanism and the need to review the role of tissue hypoxia in CKD. FAPESP/CNPq.

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	C_{NOR}	ADE_{NOR}	C_{HYP}	ADE_{HYP}
Hb	13±1	14±1	16±1*	16±1#
TCP	148±3	162±3*	146±2	161±3*
U_{ALB}/U_{CR}	0.1±0.1	0.4±0.1*	0.2±0.1*	0.2±0.1#
LKW/BW	0.5±0.1	0.9±0.1*	0.4±0.1	0.7±0.1*#
Crys	-	44±4	-	40±4
KIM-1	0.2±0.1	10.2±1.6*	0.2±0.1	4.6±1.8#
MΦ	27±5	366±20*	24±2	201±14*#
AII	3±1	7±1*	2±1	3±1#
%Coll-1	2.5±0.1	8.8±0.3*	2.5±0.2	5.2±0.3*#
p65	1.0±0.1	2.5±0.4*	1.3±0.1	1.2±0.2#
IL6	1.0±0.1	3.1±0.3*	1.1±0.2	2.4±0.2*#
CASP1	1.0±0.1	2.8±0.3*	1.7±0.4	2.3±0.3
IL1β	2.1±0.3	18.4±1.7	1.8±0.2	17.5±2.3
HO1	1.0±0.1	2.6±0.3*	0.8±0.1	1.9±0.2*#
SOD1	1.0±0.1	0.2±0.1*	0.9±0.2	0.4±0.1*#

Mean±SE;*p<0.05 vs C, #p<0.05 vs ADE_{NOR}

FR-PO372

The Analysis of Chaperone-Mediated Autophagy in Hypertensive Kidney Disease

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Background: Three different types of autophagy coexist in mammalian various cells. Chaperone-mediated autophagy (CMA) in kidney disease such as acute kidney injury and diabetic nephropathy has been reported. However, it is unclear whether CMA is involved in hypertensive kidney disease. So we examined whether CMA is involved in hypertensive renal disease and its mechanism.

Methods: First, we examined CMA levels in WKY (Wister Kyoto Rat) and MSHRSP (Malignant Stroke-Prone Spontaneously Hypertensive Rat) and treated with antihypertensive therapy by extracting lysosome fractions and using immunoprecipitation. In fact analysis of hypertensive model rats revealed that Lamp2A was strongly expressed in the proximal tubule and collecting duct, and co-staining with Hsc70 was also observed and could confirmed CMA. Therefore by using HK2 cells treated with endoplasmic reticulum stress (ERS) chemical inducer tunicamysin (Tun), we examined cell damage and mitochondrial injury if CMA was regulated by siRNA, Trichostatin A (TSA) and Humanin (HMN).

Results: First, compared with WKY, lysosome-Lamp2A expression was significantly increased in the renal medulla of MSHRSP but not in the renal cortex of MSHRSP. By antihypertensive therapy, ly-Lamp2A expression was significantly increased and CMA activity upregulated, so CMA failure was confirmed. Second, in HK2 cell with treated Tun, CMA was rapidly increased at 1 hour of administration and lasted for 3 hours. After12 hours, CMA activity returned to the initial condition, and at 24 hours, it decreased to about 50 percentages. When expression was reduced in Hsc70 and Lamp2, CMA decreased and cell induced apoptosis. In addition, in TSA treatment which involved in Hsc70 transport, ly-Lamp2A did not change and almost no CMA occurred. In HMN treatment such as CMA enhancer, pAKT was increased, but Bax and pJNK were also increased in lysosome, we would be able to consider that ERS induced CMA ameliorates cell damage, but it also seems to increase apoptosis of unnecessary abnormal mitochondria and damaged cells.

Conclusions: We found CMA induced ERS pathway was associated with cell apoptosis and mitochondria injury in hypertensive kidney disease.

FR-PO373

Niban Protein Regulates Apoptosis in HK-2 Cells via Caspase-Dependent Pathway

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Background: To investigate whether Niban protein plays a role in renal interstitial fibrosis by regulating apoptosis of renal tubular epithelial cells.

Methods: Unilateral ureteral obstruction (UUO) model was established by using 24 C57B / 6J mice, which were divided into sham operation group, UUO 3 day group, UUO 7 day group and UUO 14 day group. Renal pathological changes were observed by HE staining and Masson staining, Immunohistochemistry was used to detect the expression of Niban, collagen I, collagen III and E-cadherin, Western blot was used to detect the expression of Niban, E-cadherin, collagen I, caspase3, P53, Bip and Chop, TUNEL assays were used to detected apoptosis; Niban siRNA were transfected in HK-2 cells to silence the expression of Niban, Niban plasmid were transfected in HK-2 cells to overexpresse the expression of Niban, Angiotensin II (Ang II) is used to induce apoptosis in HK-2 cells, while tunicamycin (TM) induces endoplasmic reticulum stress response, Western blot was used to detect the expression of Niban, α-SMA, E-cadherin, caspase8, caspase9, caspase12, Bip and Chop.

Results: 1. Apoptosis increased in the UUO model, with the development of obstruction, Niban's expression decreased gradually, the expression of P53, Bip and Chop gradually increased, reached the peak on days 7, and the expression decreased to the normal level on days 14. 2. After AngII stimulates HK-2 cells, Niban expression is decreased and apoptosis is increased. Silencing of Niban up-regulated the levels of caspase 8, caspase 9, α-SMA and apoptosis, while down-regulated the level of E-cadherin. Overexpression of Niban down-regulated the level of caspase 8, caspase 9, α-SMA, and apoptosis, while up-regulated the levels of E-cadherin. 3. After tunicamycin stimulated HK-2 cells, the expression of Niban decreased, compared with the control group,while the endoplasmic reticulum stress marker proteins Bip and Chop increased significantly. Inhibition of Niban expression, the expression of Bip and Chop in HK-2 cells increased, but it was not statistical difference; after stimulation with tunicamycin, the expression of Bip and Chop in HK-2 cells was significantly increased, and there was a statistically significant difference between the two groups compared with Niban siRNA group.

Conclusions: Niban protein is involved in apoptosis regulation in HK-2 cells, and most likely via Caspase-dependent pathway.

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FR-PO374

SIRT3 Regulates the Mitochondrial Lysine Acetylation and Metabolic Networks in Proximal Tubular Epithelial Cells in Renal Fibrosis

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Background: Proximal tubular epithelial cells (PTCs) are high energy demanded relying on mitochondrial oxidative phosphorylation as the main energy source which is disturbed in renal fibrosis. Acetylation is recognized as an important posttranslational modification for mitochondrial function. SIRT3 is the major mitochondrial protein deacetylase and regulates mitochondrial metabolic function. In this study, we investigated whether SIRT3 could mediate the progress of renal interstitial fibrosis by regulating mitochondrial acetylation.

Methods: In vivo, unilateral ureteral obstruction (UUO) or ischemia-reperfusion (I/R) were used to induce renal fibrosis. In vitro, primary tubular epithelial cells were stimulated by TGF-b1. Proteomics and acetylation proteomics were performed on PTCs separated from UUO-operated mice at day 1. Westernblot and immunofluorescence staining were used to detect the SIRT3 expression and the acetylation levels in mitochondria. Immunoprecipitation was used to analyze the acetylation level of the PDHA. Honokiol was used as SIRT3 activator. SIRT3 shRNA adenovirus was used to knockdown SIRT3 expression.

Results: SIRT3 expression was decreased and mitochondrial protein acetylation was increased in tubular epithelial cells in the early phase of renal fibrosis. We identified 1900 unique acK site across 895 proteins between sham and UUO mice. The majority of proteins with 91.84% were hyper-acetylation. The increased acetylized proteins with 26.76% were mitochondrial protein. Notably, all proteins involved in mitochondrial oxidative phosphorylation were acetylated. We found pyruvate dehydrogenase a1(PDHA1) which provides the primary link between glycolysis and the TCA cycle was hyper-acetylation at K63, K149, K267, K277, K385. Immunoprecipitation analysis further confirmed that PDHA1 was acetylated under pro-fibrosis stimulation. And the PDH activity was decreased. Inhibiting SIRT3 could amplify the acetylation of PDHA1, inhibit PDH function and aggravate mitochondrial dysfunction. Activation SIRT3 could inhibit the acetylation of PDHA1, restore the PDH activity, improve the mitochondrial function, and further ameliorate renal fibrosis.

Conclusions: SIRT3 as a regulator of lysine acetylation in mitochondria and present a mechanism for regulating metabolic pathway through PDHA1 in Proximal tubule in renal fibrosis.

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FR-PO375

Leukaemia Inhibitory Factor Promotes Fibroblast Activation via ERK-Egr-1 Pathway and Increasing Mitochondrial Biogenesis

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Background: Fibrosis is the common pathway of various progressive kidney diseases. Fibroblasts are major players in the pathogenesis of renal fibrosis. Recent researches have shown that Leukemia Inhibitory Factor (LIF) exerts beneficial effects on various diseases. However, the role of LIF in the pathogenesis of kidney diseases remains largely unknown. Our study is to investigate the role of LIF in renal fibrosis.

Methods: Animal model of renal fibrosis was induced by unilateral ureteral occlusion (UUO) and ischemia reperfusion injury (IRI). Western blot (WB) and real time PCR were performed to evaluate the expression of LIF, LIF receptor (LIFR) and GP130, etc. Immunofluorescence staining was performed to evaluate the localization of LIF, LIFR and GP130. LIF neutralizing antibody was subcutaneously injected to evaluate the role of LIF in renal fibrosis induced by UUO. H&E, Masson and Sirius red staining were used to estimate renal pathology. Transforming growth factor β1 (TGF-β1) was used to stimulate cultured NRK-49F cells and primary mouse fibroblasts.

Results: LIF and its receptors (LIFR and GP130) were mainly expressed in interstitial fibroblasts, and significantly upregulated in fibrotic renal tissues induced by both UUO and IRI. LIF promoted the activation and proliferation of both NRK-49F cells and primary mouse fibroblasts through ERK-Egr-1 pathway. ERK inhibitor U0126 or silencing endogenous Egr-1 significantly inhibited LIF-induced fibroblast activation in NRK-49F cells. LIF stimulates mitochondrial biogenesis in both NRK-49F cells and primary mouse fibroblasts. LIF neutralizing antibody significantly inhibited TGF-β induced fibroblast activation in vitro, attenuated interstitial fibrosis induced by UUO.

Conclusions: Our experimental results indicate that LIF-LIFR/GP130-ERK-Egr-1 pathway plays a detrimental role in fibroblasts activation and thus contributes to interstitial fibrosis. LIF stimulates mitochondrial biogenesis to promote the activation and proliferation of both NRK-49F cells and primary mouse fibroblasts. Blocking LIF production is a plausible strategy for therapeutic intervention of chronic kidney disorders.

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FR-PO376

PGC-1α Inhibits the NLRP3 Inflammasome via Preserving Mitochondrial Viability to Protect Kidney Fibrosis

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Background: NOD-like receptor, pyrin domain containing-3 (NLRP3) contributes to inflammation, cell death, and fibrosis in animal models of kidney disease. The NLRP3 inflammasome is activated by mitochondrial damage. However, it is unknown whether PPARγ-coactivator 1α (PGC-1α), a key mitochondrial biogenesis regulator, can modulate NLRP3 pathway. Here, we demonstrated that PGC-1α inhibits activation of NLRP3 inflammasome via preserving mitochondrial viability.

Methods: We isolated primary tubular epithelial cells (TECs) from C57BL/6 mice. The NLRP3 inflammasome pathway, mitochondrial dynamic proteins and morphology, oxidative stress marker, and profibrotic markers were examined after the TECs were treated with TGF-β1 (5 ng/ml) alone, TGF-β1+PGC-1α plasmid DNA (1 ug), TGF-β1+siPGC-1α (50 nM), and TGF-β1+PGC-1α activators (Metformin, AICAR, and Resveratrol). For animal study, C57BL/6 mice underwent unilateral ureteral obstruction (UUO) and were treated with PGC-1α activators.

Results: *In vitro*, TGF-β1 treatment suppressed PGC-1α, dysregulated mitochondrial dynamics, and impaired mitochondrial morphology. In addition, the NLRP3 inflammasome pathway was activated and the expression levels of profibrotic markers and oxidative stress marker were increased in TGF-β1-treated TECs. These changes were further accentuated by PGC-1α knock-down. In contrast, restoration of PGC-1α with the activators and the plasmid improved mitochondrial dynamics and morphology and attenuated the NLRP3 inflammasome activation and profibrotic marker expression. The release of mtDNA in the cytosol, the expression of TNFAIP3 and the increased degree of oxidative stress, which are inducers of the NLRP3 inflammasome after mitochondrial damage, were increased by TGF-β1 and PGC-1α knock-down. Restoration of PGC-1α significantly reversed these alterations. *In vivo*, UUO resulted in the decreased expression of PGC-1α and mitochondrial defects, while the NLRP3 inflammasome was activated and fibrosis was increased by UUO. These changes were significantly improved by PGC-1α activators.

Conclusions: This study demonstrates that kidney injury is ameliorated by PGC-1α-induced inactivation of the NLRP3 inflammasome.

FR-PO377

Oligomerization of APOL1 Risk Variants After Mitochondrial Translocation

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Background: Inheriting two copies of APOL1 risk variants (G1 and G2) increases susceptibility to chronic kidney disease in African Americans. G1 and G2 are toxic, gain-of-function variants despite their recessive mode of inheritance. APOL1 multimerization has been proposed as an explanation for recessive gain-of-function.

Methods: Immunoprecipitation experiments were performed in HEK293 cells with co-transfection of constructs expressing APOL1 (G0, G1, or G2) tagged with FLAG or MYC. Oligomerization of untagged APOL1 was assessed in tetracycline inducible APOL1-expressing HEK293 TRex cells using blue native PAGE. Mitochondrial-enriched and cytosolic fractions were prepared by differential centrifugation. TOMM20 was knocked down with siRNA 48 hours prior to induction of APOL1 expression. APOL1-induced cytotoxicity was determined using the Muti-Tox Fluor Mutliplex cytotoxicity assay kit from Promega.

Results: After co-transfection of FLAG- and MYC-tagged APOL1, immunoprecipitation of FLAG followed by Western blot for MYC demonstrated APOL1-APOL1 binding. Blue native PAGE of APOL1 expressing cell lines revealed that G1 and G2 tend to form large oligomers whereas G0 remains mostly monomeric. When we fractionated cells via differential centrifugation, we found that the oligomers were present mostly in the mitochondrial-enriched fractions. Knockdown of the mitochondrial outer membrane protein TOMM20 blocked APOL1 mitochondrial import and eliminated both APOL1 oligomer formation and APOL1-induced cytotoxicity.

Conclusions: APOL1 molecules can interact with other APOL1 molecules and risk variants have a greater tendency to form large oligomers. The oligomers are mostly located in the mitochondrial-enriched cell fraction and inhibiting mitochondrial import of APOL1 dramatically reduces the formation of oligomers, suggesting that mitochondrial import of APOL1 is necessary for subsequent oligomerization of G1 and G2. Whether these APOL1 oligomers directly cause cytotoxicity remains to be answered.

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FR-PO378

Energy Production System Is Suppressed in Kidneys of Low-Birth-Weight Rats, Which Develop FSGS

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Background: Intraglomerular hypertension should be associated with the pathogenesis of FSGS lesion of low-birth-weight (LBW) related nephropathy, because LBW is significantly associated with a decreased number of nephrons. However, there is a possibility that other mechanisms participated in the pathogenesis of LBW-related nephropathy. We purposed to investigate innate factors which should be involved in the pathogenesis of LBW-related nephropathy at adulthood.

Methods: Low-birth weight rats (N = 7) were obtained by intra-peritoneal injection of dexamethasone into pregnant rats. Normal-birth weight rats (N = 7) were obtained by saline injection. At 4 weeks of age, left kidneys were removed. After that, until 9 weeks of age, rats were fed with high salt diet.

Results: At 9 weeks of age, serum creatinine levels of LBW rats were significantly higher than NBW rats (p=0.03). Furthermore, at 9-week-age, focal segmental sclerosis (FSGS) lesions were observed in 7.43% of glomeruli in LBW rats, but only 0.48% in NBW rats. On the other hand, at 4 weeks of age, there were no sclerotic lesions and any other pathological changes both in LBW rats and in NBW rats. A quantitative proteomics by using histologically normal cortexes at 4-week-age revealed marked suppression of energy metabolism in kidneys of LBW rats. For examples, 15 proteins related to TCA cycle, 15 proteins of fatty acid metabolism, 14 proteins glycolysis, and 12 proteins of mitochondrial oxidative phosphorylation were significantly suppressed in LBW rats. Bioinformatics analysis by using Ingenuity Pathway Analysis revealed RICTOR should be key regulator of these proteomic changes.

Conclusions: Kidneys in low-birth-weight rats should have suppressed energy production system before the occurrence of histological kidney damage. Not only intraglomerular hypertension, but also such innate defects of energy production, might to form FSGS lesions in LBW-related nephropathy.

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FR-PO379

Effect of Magnesium on the Processes of Inflammation and Oxidative Stress Associated with CKD

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Background: The development and progression of vascular calcifications (VC) is a prevalent complication in advanced stages of chronic kidney disease (CKD). Previous observations show that magnesium (Mg) may be beneficial in preventing the development of VC. Uremia is considered to be an inflammatory state, and both chronic inflammation and oxidative stress appear to have a causal effect in VC by directly affecting vascular smooth muscle cells (VSMC). The main goal of this work was to assess, through both *in vivo* and *in vitro* approaches, the effect of Mg on inflammation and oxidative stress associated with CKD.

Methods: *In vitro* studies were based on the culture of VSMC in the presence of high phosphorus (P), with or without Mg. *In vivo* experiments were performed in an experimental model of uremic rats feeding with high P diet and Mg dietary supplementation during 14 days. All experimental protocols were reviewed and approved by the Ethics Committee for Animal Research of the University of Cordoba (Cordoba, Spain) and adhered to the recommendations included in the Guide for Care and Use of Laboratory Animals (US Department of Health and Human Services, NIH) and European laws and regulations on protection of animals, under the advice of specialized personnel.

Results: VSMC incubated with high P exhibited an increase in pro-inflammatory mediators, the inflammatory cytokines and the levels of oxygen reactive species (ROS). The addition of Mg prevented the elevation in inflammatory markers. Uremic rats receiving normal dietary Mg showed elevated levels of ICAM-1 and high oxidative stress By contrast, dietary Mg supplementation abolished all these processes.

Conclusions: Taken together, these results suggest the protective role of Mg in the generation of oxidative stress and inflammation in the context of renal disease.

FR-PO380

Therapeutic Approaches in Mitochondrial Dysfunction, Inflammation, and Autophagy in Uremic Cachexia: The Role of Aerobic Exercise

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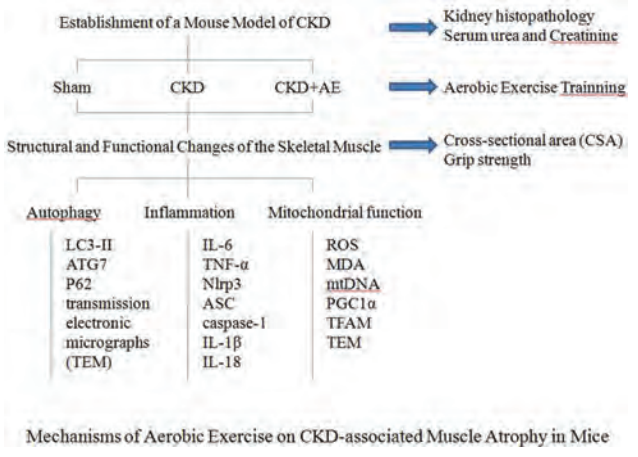
Background: Chronic kidney disease (CKD) causes several systemic changes, including muscular homeostasis, and eventually results in muscle atrophy. CKD-induced muscle atrophy is highly prevalent, and exercise is well known to enhance muscle function, although the exact mechanism remains unclear. Here, we aimed to assess whether the protective effect of aerobic exercise in CKD mice was associated with mitochondrial dysfunction, autophagy or inflammation.

Methods: C57BL/6J mice were randomly allocated into 3 experimental groups: Sham, CKD, and CKD+aerobic exercise (CKD+AE). Renal function was assessed via serum creatinine and urea levels, and histological PAS and Masson staining were performed. Muscle wasting was determined based on grip strength, cross-sectional area (CSA), and MyHC protein expression. We measured mitochondrial dysfunction by assessing mtDNA, ROS and ATP production, and mitochondrial configuration. Autophagy was determined via assessments for Atg7, LC3, and SQSTM1 on western blotting. Inflammation was identified via pro-inflammatory cytokines and NLRP3 inflammasome components using real-time PCR and western blotting.

Results: CKD mice exhibited higher BUN and creatinine levels and more severe glomerulosclerosis and tubulointerstitial fibrosis, relative to the Sham group; all these effects were relieved by aerobic exercise. Moreover, grip strength, CSA, and MyHC protein expression were improved after 8 weeks of aerobic exercise. Furthermore, aerobic exercise significantly decreased MDA levels, increased SOD2 activity and ATP production, and improved mitochondrial configuration, relative to the CKD group. In addition, aerobic exercise down-regulated the overexpression of pro-inflammatory cytokines and NLRP3 inflammasome components, and balanced the mitochondrial biogenesis and autophagy.

Conclusions: Aerobic exercise may ameliorate CKD-induced muscle wasting by improving mitochondrial dysfunction, inflammation and autophagy in uremic cachexia.

Funding: Government Support - Non-U.S.



Mechanisms of Aerobic Exercise on CKD-associated Muscle Atrophy in Mice

FR-PO381

Markers of Mitochondrial Mass and Biogenesis Are Reduced in Non-Dialysis-Dependent CKD and Not Restored Following Exercise

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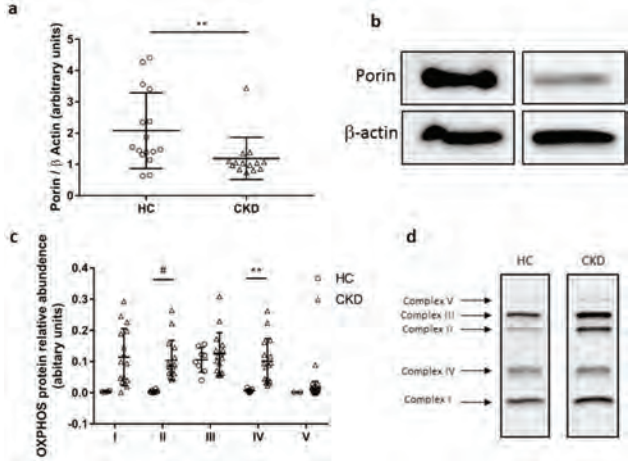
Background: Patients with non-dialysis dependent chronic kidney disease (NDD-CKD) exhibit reduced exercise capacity, poor physical function and symptoms of fatigue. The mechanisms that contribute to this are not clear but may involve mitochondrial dysfunction. We investgated the effect of NDD-CKD on mitochondrial mass and the expression of transcription factors involved in mitochondrial biogenesis compared to healthy controls, and the effect of 12-weeks of exercise on these markers.

Methods: Skeletal muscle biopsies were collected from the vastus lateralis of 16 NDD-CKD patients (Stage 3b-5) and 16 matched healthy controls (HC). To investigate the effect of exercise training VL biopsies were collected from 17 NDD-CKD patients stage 3b-5 pre and post a 12-week exercise intervention. Mitochondrial mass (porin/β-actin ratio) was analysed by western blotting and the expression of transcription factors involved in mitochondrial biogenesis was investigated by real-time PCR.

Results: NDD-CKD exhibited significantly reduced porin/β-actin ratio (86%, $p<0.001$) and reduced mRNA expression of PGC-1α, NRF-1/2, TFam, mfn2 and SOD1/2 compared to HC ($p\leq0.05$). 12-weeks of exercise training resulted in a significant increase in PGC-1α expression only ($p=0.04$), but no change in mitochondrial mass was observed ($p>0.05$).

Conclusions: NDD-CKD patients exhibit a reduction of skeletal muscle mitochondrial mass and suppression of mRNA expression of transcription factors that are involved in mitochondrial biogenesis, which may contribute to the detrimental muscle related symptoms experienced in this population. After 12-weeks of exercise training no improvement was observed. Reasons for this lack of improvement warrant further investigation in NDD-CKD.



CKD results in a reduction in mitochondrial mass within skeletal muscle. a) Western blot of porin/β-actin ratio; b) Densitometry of porin/β-actin ratio. **denotes $P<0.001$ vs healthy controls; c) Western blot analysis of OXPHOS proteins, relative to loading control; d) Densitometry analysis of OXPHOS complex abundance.

FR-PO382

PET Imaging of Renal Mitochondria in Acute and Progressive Kidney Disease Models Using a Novel PET Probe ^{18}F-BCPP-BF

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Background: The kidney is a highly energy-demanding organ and rich in mitochondria. In addition to physiological importance of mitochondria as a powerhouse, mitochondrial dysfunction is often associated with overproduction of ROS, which is believed to play a critical role the pathogenesis of kidney diseases. Nonetheless, only a few studies have reported the renal mitochondrial status in the clinical settings partly due to a paucity of methodologies. Recently, Ohba et al. developed a novel PET probe ^{18}F-BCPP-BF specifically binding to mitochondrial complex I (MC-I). ^{18}F-BCPP-BF has a favorable pharmacokinetic property for kidney imaging, which enables us to non-invasively visualize and quantitate the amount of MC-I in whole kidneys in vivo (EJNMMI Research 2016; 6: 82).

Methods: In this study, we demonstrated high-resolution animal PET analyses for kidneys in glomerulonephritis and AKI model animals using ^{18}F-BCPP-BF.

Results: In anti-GBM glomerulonephritis model rats, the uptake level of ^{18}F-BCPP-BF in kidney showed only slight decrease at the acute phase (74% vs. normal control), while it became more remarkable at the later phase (33% vs. normal control). The significant decrease in the PET signal was accompanied with robust reduction of mitochondrial complex proteins including MC-I, demonstrated by Western blotting analysis. The slight change in PET signals at acute phase despite massive protein urea may reflect less damage in tubular epitheliums. In rat acute renal I/R model, the renal uptake of ^{18}F-BCPP-BF was slightly decreased at 3 hours after reperfusion (75% vs. sham), when kidney function was slightly declined accompanying morphological abnormality of mitochondria in S3 proximal tubular cells though the loss of proximal tubular epithelial cells was still minimal.

Conclusions: The novel PET probe opens up new possibilities for studying pathophysiological meanings of mitochondrial status in kidney disease, which may be applicable to new clinical diagnosis for patients with various types of kidney diseases.

FR-PO383

APOL1 Alternative Splice Isoforms Localize to the Endoplasmic Reticulum with Distinct Topologies and Do Not Associate with Endosomes

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Background: Two risk variants of the *APOL1* gene, G1 and G2, are associated with chronic kidney disease in African Americans. APOL1 risk variants have been proposed to cause podocyte toxicity by a variety of pathways, including inhibition of endosomal maturation via direct binding to cytoplasmic VAMP8 on endosomes. APOL1 G0 (wild type), G1 and G2 variants all localize to the endoplasmic reticulum (ER) and the cell surface of podocytes, suggesting that direct interaction with VAMP8 is unlikely. However, those studies utilized isoform APOL1.vA, whereas three minor splice isoforms (vB1, vB3 and vC) exist, with different N-termini and so may be not be secreted. While transient transfection of all four isoforms leads to their apparent secretion, this may be an overexpression artifact. We therefore aimed to determine the localization of APOL1 isoforms stably expressed in podocytes.

Methods: We generated inducible *APOL1* stable podocytes and determined the localization of each isoform by immunofluorescence and flow cytometry. We assessed APOL1 isoform levels in immortalized human podocytes by qRT-PCR, immunofluorescence and western blotting.

Results: By immunofluorescence with Triton X-100 permeabilization, all four isoforms localized to the ER, but selective permeabilization of the plasma membrane with digitonin revealed topological differences: isoforms vA and vB1 are inside the ER lumen, while vB3 and most of vC are on the outer face of the ER, like APOL2. Consequently, only vA and vB1 are appreciably detected on the cell surface by flow cytometry, indicating those two isoforms are secretory, while vB3 and vC are cytoplasmic. Wild type podocytes express the three splice isoforms at much lower levels than vA by RT-PCR, but *APOL1* mRNA and protein levels are notoriously poorly correlated. Western blotting of endogenous podocyte APOL1 with sensitive in-house APOL1-specific antibodies revealed the major band was vA, but a minor upper band became detectable upon gamma interferon stimulation. This could represent vB3 or a post-translational modification.

Conclusions: APOL1 isoforms vA and vB1 are secretory, whereas vB3 and most of vC are cytoplasmic, but on the outer ER membrane, not endosomal. APOL1 is therefore unlikely to directly interact with VAMP8 to interfere with endosomal trafficking.

Funding: Commercial Support - Genentech (a member of the Roche group)

FR-PO384

Integrative Omics Reveal Molecular Signatures of Endoplasmic Reticulum Stress in Tubular Epithelial Cells

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Background: Over the past decade, dysregulated and prolonged endoplasmic reticulum (ER) stress has been observed in acute kidney injury and chronic kidney disease (CKD). However, how ER stress contributes to disease pathophysiology in the kidney remains unclear. Here we take an unbiased approach to identify potential modulators of ER stress pathways in human proximal tubular epithelial cells.

Methods: We performed bulk RNA sequencing (RNA-seq) and untargeted LC-MS metabolite profiling on HKC-8 proximal tubular epithelial cells cultured with and without 2.5 uM of tunicamycin, an inducer of ER stress. Single-cell RNA-seq (scRNA-seq) was performed on kidney organoids differentiated from induced pluripotent stem cells, grown to day 25, and treated with tunicamycin.

Results: RNA-seq revealed 2912 differentially expressed genes after 4 hours and 2436 differentially expressed genes after 24 hours of tunicamycin treatment. These genes were enriched for pathways relevant to inflammatory response ($P < 0.001$), Wnt signaling (P=0.015), protein processing in the ER (P=0.022), and extra-cellular matrix receptor interaction (P=0.04). A subset of the most highly differentially expressed genes were validated in tubular cells profiled in scRNA-seq of tunicamycin-treated 3D kidney organoids. Thirty genes differentially expressed in HKC-8 cell ER stress were also genes at kidney trait loci identified in recent genome-wide association studies; these genes are involved in cellular differentiation (PAX8) and fibrosis pathways (ACVR2A, SMAD3, TRIB1). Although network analyses identified known ER stress protein ATF4 as the main upstream transcriptional regulator, ATF4 target genes comprised only a small fraction of the differential expression gene set. Our metabolite profiling revealed decreased 2-HG (FC -2.25, P=0.021) and a-KG (FC -1.63, P=0.002) levels in ER stress: these metabolites are known epigenetic modulators, with implications for differential methylation activated by ER stress. Decreased abundance of these metabolites is also consistent with the commensurate increase in PHGDH expression (FC 2.87, P<0.001).

Conclusions: Taken together, these results demonstrate pervasive injury-relevant and ER stress induced transcriptional changes in kidney cells, with potential modulation by genetic variation and intermediate metabolites.

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FR-PO385

Renal Failure Induced by Deletion of the Gene Encoding Canonical Transient Receptor Potential 1 (TRPC1) Channels: A Mouse Model of Normotensive CKD

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Background: TRPC1 plays a key role in cardiac hypertrophy, vascular smooth muscle proliferation & glomerular mesangial cell contractility. It is reduced in diabetes, but exact relationship is unknown. Since TRPC1 deletion produces diabetes & cardiomyopathy, we tested for renal phenotypes in TRPC1 deficiency.

Methods: In age-matched wild types, +/- & null males, from 1 - 20 mon, we measured serial blood glucose, blood & urine creatinine (Cre) by HPLC. Renal ultrasound was done at 7, 11, & 20 mon. Glomerular filtration rate (GFR) was estimated by Cre clearance (C) & confirmed by inulin C. Blood pressure (BP) was measured directly by arterial cannulation.

Results: Despite hyperglycemia from 3 mon on & diabetes at 6 mon, kidney volume at 7 mon (0.38 vs 0.46 cc) & kidney weight (KW) to body (B) W (1.2 vs 1.5 %) were 17% lower in null. From 11- 20 mon, kidney volume (0.4 vs 0.5 cc) stayed 16% lower & KW:BW (1.1 vs 1.5 %) 28% lower. Renal echogenicity was similar at 7 & 11 mon but increased by 37% at 20 mon, sugggesting injury & scarring. Normal at 12 mon, serum Cre (0.1 vs. 0.06 mg%) was elevated at 17 mon. Cre C fell by 42% (0.66 vs. 1.13 ml/min/mouse) & by 50% when factored for BW (1.7 vs. 3.4 ml/min/100g). Renal failure was confirmed by 44 to 48% reduction in GFR (214 vs 384 µl/min per mouse; 603 vs 1,155 µl/min per100 g BW; 362 vs 681 µl/min/ per g KW). There was no hypertension based on systolic BP (in torr) (113 vs. 121), diastolic (77 vs. 86) or mean (89 vs. 98). Urine concentration ability was intact by osmolality after 17 h dehydration. Urine acidification was impaired in null based on urine pH (6.0 vs 5.2). Urine albumin was increased in null (12 vs 7 µg/d or 23 vs 14 µg/mg Cre). Haploid deletion prduced similar renal phenotypes.

Conclusions: 1. Both haploid & diploid TRPC1 deletion produces nephropathy based on 50% GFR loss, reduced kidney volume, and increased echogenicity. It offers an excellent model to study non-hypertensive CKD. 2. Though renal failure emerges ~12 mon after diabetes, the small kidney size at the outset & the minimal proteinuria favor hypoplastic over diabetic nephropathy. 4. We propose that the TRPC1 protein is key in normal growth & development for the kidney (as for the heart) & a possibl role in hyperfiltration in response to diabetes.

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

FR-PO386

Functional Impact of Endogenous ATRAP, a Novel Angiotensin II Type 1 Receptor-Associated Protein, on Human Renal Proximal Tubule Cells

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Background: The proximal tubule is a particularly important site for aging-related kidney damage. Sirtuin 1 (SIRT1), an NAD^+-dependent deacetylase in the proximal tubule, is involved in renal damage associated with aging. However, the mechanisms of SIRT1 regulation remain to be elucidated. We recently reported that ATRAP-deficient mice displayed an exacerbation of age-associated renal function decline and tubulointerstitial fibrosis. Although the molecular mechanisms by which ATRAP deficiency exacerbates age-associated tubulointerstitial fibrosis has not yet been defined, renal SIRT1 protein expression was more decreased in aged ATRAP-deficient mice compared with aged wild type mice. Further investigations of ATRAP-dependent SIRT1 protein expression are important to resolve aging-associated kidney dysfunction. in this study we aimed to establish an ex vivo model of the proximal tubule to determine the role of ATRAP in SIRT1 protein expression.

Methods: We established an immortalised RPTEC line by expressing hTERT and shRNA-targeted CDKN2A. Next, we cloned this immortalized RPTEC and then characterised the cells based on the expression of a proximal tubular marker (SGLT2, DPP4). We call this cloned immotarised RPTEC, ciRPTEC. To analyze the ATRAP function in the proximal tubule cells, we use siRNA-mediated ATRAP knockdown in ciRPTEC and CRISPR-CAS9 mediated ATRAP knockout.

Results: *SIRT1* mRNA expression, which was induced by serum starvation, was unaffected by transient ATRAP knockdown. On the other hand, SIRT1 protein expression was not induced by serum starvation in our ciRPTEC cells, although transient ATRAP knockdown reduced the expression of SIRT1 protein under both normal and serum-starved conditions. Like ATRAP knockdown, ATRAP knockout did not affect *SIRT1* mRNA expression under either the normal or serum-starved condition. However, SIRT1 protein expression was significantly decreased by serum starvation in ATRAP knockout cells, while no significant reduction in SIRT1 protein was observed in control cells.

Conclusions: These results indicate that ATRAP mediates SIRT1 protein abundance in ciRPTEC by regulating its synthesis and/or stability but does not affect the level of *SIRT1* mRNA transcription or stability.

FR-PO387

Combined Treatment with Losartan and an NF-κB Inhibitor Affords Better Renoprotection Than AT1R Blockade Alone in Aging Rats

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Background: The mechanisms underlying aging nephropathy (AN) are unclear. Renal angiotensinII (AII) and NF-κB activation are important factors in the pathogenesis of Chronic Kidney Disease (CKD). We investigated whether combined treatment with Losartan (L) and the NF-κB inhibitor Pyrrolidine Dithiocarbamate (PDTC) would attenuate experimental AN.

Methods: Male Munich-Wistar rats were divided in 4 groups: **12M** (n=10), 12-month-old rats; **15M** (n=10), 15-month-old rats; **15M+L**(n=8) rats receiving L (50 mg/kg/d) and **15M+L+PDTC** (n=8), rats receiving L and PDTC (15 mg/kg/d). Both compounds were given orally from 12 to15 mo of age. We assessed body weight (BW, g), tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/24h), serum creatinine (Scr, mg/dL), glomerulosclerosis (GS,%), cortical macrophages (MΦ, cells/mm^2) and AII+ (cells/mm^2), Collagen-1 (Coll-1, %), as well as renal TLR4 and IL-6 (WB).

Results: Group 15M exhibited mild hypotension, creatinine retention, albuminuria, glomerulosclerosis, Coll-1 deposition and cortical infiltration by MΦ. Renal abundance of TLR4 and IL-6 was also increased, suggesting activation of the NF-κB pathway. L decreased cortical MΦ and Coll-1, but not TLR4 or IL-6, failing to reduce ALB or GS%. Combined L+PDTC prevented the increase of renal TLR4, IL-6 and MΦ, reduced AII+ and strongly attenuated ALB and GS%.

Conclusions: Simultaneous inhibition of renal AII and of the NF-κB system can contribute to reduce the decline of renal function with age. FAPESP/CNPq

Funding: Government Support - Non-U.S.

	12M	15M	15M+L	15M+L+PDTC
BW	383±4	378±15	370±16	369±15
TCP	148±5	135±5 [a]	123±3 [a]	129±3 [a]
ALB	27±5	75±18	76±29	32±14 [b]
Scr	0.5±0.1	0.7±0.3 [a]	0.6±0.1	0.6±0.1
GS%	2.6±0.8	8.8±1.7 [a]	5.0±1.9	2.4±0.9 [b]
Coll-1%	4.4±0.5	9.8±0.2 [a]	6.2±0.2 [a]	5.3±0.2 [abc]
AII+	5±1	7±1	5±1	5±1 [b]
MΦ	25±1	69±6 [a]	47±3 [b]	35±6 [b]
TLR4	1.0±0.1	1.5±0.3	1.1±0.1	0.8±0.1 [b]
IL-6	1.0±0.1	2.0±0.3 [a]	2.1±0.3	1.1±0.1 [bc]

Mean±SE;[a] $p<0.05$ vs 12M, [b] $p<0.05$ vs 15M, [c] $p<0.05$ vs 15M+L

FR-PO388

Progression of Established CKD Is Halted by Metformin Treatment in Rats

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Background: Metformin, the first-line drug for type-2 diabetes mellitus, also exerts multiple benign pleiotropic actions on different organs. Recent preclinical and clinical data point towards a beneficial impact of metformin on the kidney. Chronic kidney disease (CKD) is a worldwide recognized public health problem and represents a progressive loss of renal function over a period of months or years. Current treatment strategies for CKD mainly focus on controlling important risk factors. To date, effective treatment directly targeting the kidney is lacking. Here, the efficacy of metformin to attenuate progression of already established CKD was investigated.

Methods: A rat model of adenine-induced CKD (n=64) was used. Metformin (200 mg/kg) or vehicle (1% carboxymethylcellulose) treatment, by daily oral gavage (7 days/week), was initiated after 4 and 5 weeks of adenine (0.25%) administration; *i.e.* after CKD had developed. Treatment was continued during 4 weeks until the end of the study (*i.e.* week 8 and 9, respectively). A constant dose volume of 10 mL/kg was used. The effect of metformin on renal function and histopathology was studied.

Results: Serum creatinine levels dramatically rose in vehicle-treated CKD rats: from 0.6 ± 0.1 mg/dL (week 0) to 1.3 ± 0.2 mg/dL (week 4) and 2.6 ± 1.2 mg/dL (week 5) and further to 5.7 ± 0.6 mg/dL (week 8) and 4.8 ± 1.1 mg/dL (week 9). This increase from week 4 and 5, respectively, was almost completely prevented by metformin treatment as indicated by serum creatinine levels after 8 (2.0 ± 0.5 mg/dL) and 9 (2.9 ± 0.5 mg/dL) weeks respectively ($p<0.05$ vs. vehicle). Histological examination of periodic acid–Schiff-stained renal sections revealed less tubular dilation, epithelial flattening, brush border loss and, basement membrane thickening in metformin-treated rats in comparison to vehicle-treated animals. The renal tubulointerstitial area percentage, consisting of both extracellular matrix and infiltrating cells, in metformin treated CKD rats, was significantly lower, as compared to vehicle treatment (33% and 23% lower in rats receiving metformin from week 4 and 5, respectively, as compared to vehicle).

Conclusions: Metformin is able to attenuate the progression of pre-existing adenine-induced CKD in rats.

Funding: Government Support - Non-U.S.

FR-PO389

Latent Transforming Growth Factor Beta Biding Protein 4 (LTBP4) Attenuates Tubulointerstitial Fibrosis and Ameliorates Inflammation and Mitochondrial Dysfunction in CKD

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Background: Transforming growth factor beta (TGFβ) has been well known as a key factor for fibrosis and inflammation. LTBPs regulate TGFβ signaling in complicated ways. Disruption and loss of LTBP4 expression is associated with abnormal accumulation of extra-cellular matrix (ECM) and altered TGFβ activation. However, the role of LTBP4 in chronic kidney disease remains largely unknown.

Methods: To investigate the impact of LTBP4 on tubulointeresitial fibrosis (TIF), we generated LTBP4-overexpression and LTBP4-deficiency human renal proximal tubule cells (HK-2), treated with exogenous TGFbeta and established a fibroblasts-HK-2 co-culture system using rat fibroblasts (NRK-49F) and HK-2 cells. Moreover, to create TIF model, we performed unilateral ureteral ligation (UUO) in *Ltbp4S*-/- mice and wild-type (WT) mice to check ECM deposition and phenotypic alterations.

Results: Up-regulation of Ltbp4 in fibrotic kidney was noted in TIF model with UUO. Markers and mediators of fibrosis, α-SMA, fibronectin, collagen I, Pdgfrβ and TGFβ in gene and protein levels were reduced significantly in LTBP4-knock down HK-2 cells treated with additional TGFbeta. LTBP4-overexpression enhanced epithelial-mesenchymal transition (EMT) with showing decreased epithelial-cadherin, increased vimentin and collagen I in the co-culture system. In addition, lower expression of Pdgfrβ with higher expression of Nrf2 signaling was noted in fibrotic kidneys in *Ltbp*4S-/- mice compared with changes in WT mice, suggesting inflammation condition could be altered by the absence of Ltbp4S. Ltbp4-deficiency also reduced inflammatory gene expression such as IL-6 and altered IL-6-associated mitochondrial biogenesis.

Conclusions: Ltbp4 acts as a regulator of fibrosis and inflammation. Ltbp4 appears to inhibit antioxidant Nrf2 pathway and enhance fibrosis in a TGFβ-related manner in a murine UUO model of TIF and in a cell co-culture system. In addition, LTBP4 deficiency ameliorates mitochondrial dysfunction and alleviates renal fibrosis.

FR-PO390

Tolvaptan and Bardoxolone Methyl Synergistically Activate the Nrf2/HO-1 Pathway

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Background: Tolvaptan, a vasopressin type2 receptor antagonist, has been approved for the treatment of autosomal dominant polycystic kidney disease. Furthermore, tolvaptan has been shown to improve the renal function in rodent models of chronic kidney disease (CKD); however, the underlying molecular mechanisms remain unknown. CKD is characterized by increased levels of oxidative stress, and an antioxidant transcription factor-nuclear factor erythroid 2-related factor 2 (Nrf2)-has been gaining attention as a therapeutic target. Therefore, we investigated the effects of tolvaptan and a well-known Nrf2 activator, bardoxolone methyl (BARD) on Nrf2.

Methods: We investigated the effect of tolvaptan and bardoxolone methyl on Nrf2 using mouse cortical collecting duct (mpkCCD) cells and mice kidneys.

Results: Tolvaptan led to Nrf2 nuclear translocation and induced mRNA and protein expression of heme oxygenase 1 (HO-1) in mpkCCD cells and the outer medulla of mice kidneys. Phosphorylation of unfolded protein kinase RNA-like endoplasmic reticulum kinase (PERK) by tolvaptan played an important role in activation of Nrf2/HO-1 pathway. Moreover, tolvaptan and BARD synergistically activatied Nrf2/HO-1 antioxidant pathway in mpkCCD cells.

Conclusions: We found the novel pharmacological property of tolvaptan that activated the PERK/Nrf2/HO-1 signaling pathway. Nrf2-regulated antioxidant systems were synergistically activated by tolvaptan and BARD. Tolvaptan is a potential therapeutic candidate in renal disease.

Funding: Government Support - Non-U.S.

FR-PO391

Adipose Tissue Macrophage Infiltration in CKD

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Background: Patients with advanced chronic kidney disease (CKD) present higher levels of inflammatory markers, associated with significant morbidity and mortality. Increased adipose tissue macrophages (ATM) may play an important role in a state of chronic inflammation seen in CKD patients. Historically, macrophages were divided into two main phenotypes, M1 or pro-inflammatory, and M2 associated with tissue repair. The aim of this study is to examine the degree of macrophage infiltration and macrophage characteristics of adipose tissue in patients and mice models with CKD.

Methods: We studied adipose tissue from 4 pairs of control-advanced CKD patients undergoing kidney donation or transplantation the same day. Stromal vascular fractions (SVF) were isolated from subcutaneous (SCF) and visceral (VF) adipose tissue. Macrophage populations were studied by flow cytometry. In a model of advanced CKD mice, macrophage populations were studied in adipose tissue SVF and peripheral blood. The same experiment was replicated in a model of advanced CKD in IL-6 knock-out (KO) mice.

Results: Patients with CKD had higher number of macrophages in adipose tissue compared to controls [fold change 1.9 for SCF and 2.7 for VF $p<0.01$]. In CKD mice, there was an increase in total number of macrophages in SCF versus control [42.24% vs 5.96%; $P<0.01$]. SCF of CKD mice also had lower CD301-/CD11c+ macrophages [1.5% vs 16.15%; $P=0.005$] and higher CD301+/CD11c-macrophages versus controls [96.6% vs 71.4%; $P<0.001$]. No difference was seen between the CKD and controls in VF. When SVF were studied in an IL-6 KO mice CKD model, there were no differences in ATM numbers in SCF or VF. In peripheral blood and despite lower total number of leukocytes [CD45+ 10.5% vs 16%; $P<0.05$], CD163+, CD11c+ and CD206+ macrophages were significantly increased in CKD mice compared to controls [47% vs 27%, 4.3% vs 2.6%, and 2% vs 1.3% respectably; $P<0.05$ for all]. There was also a higher number of T-cell sub-populations seen in CKD mice compared to controls [CD4+ 13.6% vs 11.4% and CD8+ 7.5% vs 5.4%; $p<0.001$ for both].

Conclusions: In humans, there was higher macrophage infiltration in adipose tissue. This was reproduced in a mice model of CKD. The lack of increased ATM numbers in the IL-6 KO mice model, suggest IL-6 may play a role in the recruitment of macrophages to adipose tissue in advanced CKD.

FR-PO392

Kidney Injury Molecule-1 (KIM-1) Promotes Tertiary Lymphoid Tissue (TLT) Development in the Kidney Through LTaβ/LTβR Signaling

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Background: TLTs, inducible ectopic lymphoid tissues formed in chronic inflammatory conditions, have been described in various pathologic kidney diseases. However, the links between activation of the inflammation and the triggering cascade of B/T-cell clusters in the kidney are not understood. Here we investigated the role of KIM-1 on tubular epithelial cells (TECs) in affecting the formation of TLTs and modulation of the immune response in kidney injury.

Methods: The immune response associated with TLT formation was investigated using a kidney injury model induced by aristolochic acid (AA) in wild-type (WT) or

KIM-1$^{\Delta}$ (functional knockout of KIM-1) mouse. Studies in vitro were also done using renal primary TECs isolated from WT or KIM-1$^{\Delta}$ mouse kidney, or macrophage cells. Cells were treated with AA and incubated with endothelial cells (ECs, primary mouse kidney endothelial cells and bEND3), followed by measurement of the lymphotoxin pathway, lymphoid chemokines and pro-inflammatory characteristics.

Results: Under AA treatment, WT, but not KIM-1$^{\Delta}$, mice developed multiple TLTs in the kidney, morphologically characterized by high endothelial venules (HEVs) expressing PNAd, germinal centers within B cell follicles and T cells infiltration. These characteristics were associated with higher expression of lymphorganogenic chemokines (CXCL13-CXCR5, CCL21/CCL19-CCR7 axes), adhesion molecules (ICAM1, VCAM1), and IFN-γ in WT mice. Furthermore, in KIM-1$^{\Delta}$ mouse IF and qPCR revealed significantly less LTβ expression both on TECs and interstitial inflammatory cells than WT. LTα expression also showed the same trend. However, there was no obvious difference on LTβR expression of ECs. PNAd expression on ECs was induced by incubation with TECs substituted for macrophages or without co-culture conditions in the presence of AA treatment. Compared with WT, KIM-1$^{\Delta}$ TECs also displayed reduced expression of LTα, LTβ and induction of HEV marker PNAd following AA stimulation, similar to in vivo.

Conclusions: KIM-1 plays a critical role in initiation of the inflammatory response by activating HEV through LTαβ/LTβR signaling, providing inflammatory milieu to enhance immune cell infiltration. These findings provide a new insight that TECs modulate immune reaction in kidney injury and can be a therapeutic target for inflammatory renal diseases.

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FR-PO393

Experimental CKD Reduces Tubuloglomerular Feedback Synchronization and Impairs Autoregulation

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Background: Tubuloglomerular feedback (TGF) is an important component of autoregulation of renal blood flow and can prevent transmission of high blood pressure to glomeruli. We have previously shown that the TGF mechanism operates in a network fashion, leading to TGF synchronization. Eventually, this ensures that each nephron receives appropriate perfusion to match the energy-intensive reabsorption of Na^+. We have shown that loss of synchronization impairs autoregulation which is implicated in chronic kidney disease (CKD). We hypothesized that structural damage to the nephron-network would impair TGF-synchronization.

Methods: Male Lewis rats underwent uni-nephrectomy followed by partial nephrectomy to induce CKD (n=6) or underwent sham-operations (n=6). Six weeks later, the rats were anesthetized and mean arterial pressure (MAP), renal blood flow (RBF), and glomerular filtration rate (GFR) were assessed. Renal cortical perfusion was recorded with laser speckle contrast imaging (LSCI; Moor Instruments). After filtering to isolate TGF frequencies, we quantified phase coherence (PC) and used graph analysis to provide information about TGF synchronization between nephrons.

Results: Within the CKD group, RBF (8.0±0.6 to 6.7±1.0 mL/min) and GFR (0.89±0.33 to 0.37±0.7 mL/min) were decreased compared to controls (7.4±1.3 to 7.0±1.4 mL/min), (0.63±0.38 to 0.55±0.14 mL/min) respectively, although this did not reach significance. MAP showed no differences between CKD (102±7 to 89±5 mmHg) and controls (104±6 to 91±4 mmHg). Strength of TGF-synchronization between nephrons is indicated by higher values for phase coherence (PC). PC values were decreased for CKD rats (0.3±0.02) versus controls (0.5±0.03) which indicates weaker synchronization ($p<0.005$). Each pixel in the image is treated as a node and connected to other nodes via edges with significant PC; the CKD group had a lower number of connecting edges (780±532) compared to controls (36932±22589) ($p<0.005$). The number of synchronized regions (clusters) decreased for CKD rats (1±0.08) compared to controls (2±0.3) ($p<0.005$).

Conclusions: In this model of CKD, we demonstrate an impaired ability of nephrons to synchronize TGF in the renal cortex as assessed by LSCI. Since this network synchronization could prevent hypertensive injury further investigations are on improving network function.

Funding: Government Support - Non-U.S.

FR-PO394

CKD of Unknown Etiology (CKDu) in Sri Lanka (SL): A Tissue Analysis

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Background: CKDu is a leading cause of kidney disease in Central & North Central SL. Based on a prospective renal biopsy study, we hypothesized that higher acuity reflects recent exposure to a putative toxin. Tissue evidence of hypothesized causes was sought in high acuity CKDu biopsies.

Methods: Forty-three patients had biopsy-confirmed CKDu (10/2016-9/2017); activity index (AI: tubulitis & interstitial inflammation in nonatrophic cortex) and chronicity index (CI: global glomerulosclerosis, periglomerular fibrosis, tubular atrophy, interstitial fibrosis) (scale 0-3) were scored. Thirteen biopsies met our definition of AI≥ 2 & CI ≤ 4 for active tubulointerstitial nephritis (AIN). A subset of AIN was analyzed for semiquantitative element content by mass spectrometry (MS) (n= 4) and electron microscopy (EM) (n=2). Non-CKDu SL biopsies were controls for histology (n=5) and MS (n=2).

Results: CKDu patients with AIN were 45 yrs old (mean; ±10.8), mostly men (75%), all born in endemic areas and drank well water as a primary source. Only 4 (33%) had dysuria, but 9 (75%) reported acute symptoms (fever, back/joint pain) within 6 mo prior to biopsy. None had hematuria, proteinuria was rare (8%) & mean sCr was 1.9 mg/dL. Rare silver stained dense granules visualized in tubular epithelial cells of both CKDu (67%) and controls (40%) corresponded to atypical lysosomes on EM. MS revealed no cadmium or arsenic; lead was minimal, lower than in control paraffin (Table). A high-throughput shotgun sequencing approach to detect infectious pathogens is underway.

Conclusions: We confirm an active phase in a subset of CKDu patients. Rare tubular atypical lysosomes were noted in both cases and controls. No lead, cadmium, or arsenic deposition was seen in the kidney. Further advanced tissue techniques may help elucidate causes of CKDu.

Content of select elements (of 70 analyzed) in SL Kidney Biopsies

Mean Content (ug/g)	Paraffin (1)	AIN (4)	Controls (2)
Arsenic	0.106	0.226	0.4325
Cadmium	<0.001	<0.001	<0.001
Copper*	2.116	12.52	0.2805
Iron*	25.02	127.3	<0.001
Lead	1.841	0.295	2.108
Mercury	<0.001	<0.001	<0.001
Nickel	1.829	1.77	8.01
Vanadium	0.112	0.389	0.409

*Histochemical stains neg

FR-PO395

Gut Flora-Dependent Metabolite Trimethylamine-N-Oxide Accelerates Kidney Aging Through p53/p21/Rb Pathway and Age-Related CircRNAs

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Background: Gut microbiota can influence the aging process and may modulate aging-related changes in cognitive function. Trimethylamine-N-oxide (TMAO), gut microbiota-dependent metabolites, has been shown to be associated with kidney diseases and other disease. However, the relationship between TMAO and aging, especially renal aging, has not been fully elucidated.

Methods: We analyzed age-related palsma levels of TMAO and circRNAs in 3-month-old and 24-month-old C57BL/6 mice. Then HK-2 and TCMK-1 cell were incubated with different concentrations of TMAO (0, 1uM, 10uM, 100 uM, 1mM, 10mM, 100mM, 200, 500mM) for 24h, 48h and 72h to measure cell viability using a cell counting kit-8. Western blotting and qRT-PCR was used to detect the changes of related proteins and RNA after exposure to TMAO (100mM) for 48h and 72h.

Results: In the present study, we found that circulating TMAO increased with age in mice. In vitro, we demonstrated that prolonged TMAO treatment induced senescence in HK-2 and TCMK-1 cell, characterized by reduced cell proliferation, increased expression of senescence-associated β-galactosidase (SA-β-gal). Meanwhile, TMAO increased the expression of p53, p21, p16 and decreased phosphorylation of Rb expression. Furthermore, TMAO changed the expression of circRNAs.

Conclusions: In summary, these data suggest that elevated circulating TMAO during the aging process may deteriorate HK-2, TCMK-1cell senescence and renal aging, which is probably associated with the activation of the p53/p21/Rb pathway and the change of circRNAs.

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FR-PO396

CircRNA_15698 Exacerbates Folic Acid-Induced Renal Interstitial Fibrosis via the miR-185/TGF-β1 Pathway

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Background: Circular RNAs (circRNAs) are a novel type of noncoding RNAs that modulate the pathogenesis of multiple diseases. A study reports that circRNA_15698 aggravates the renal mesangial extracellular matrix of diabetic nephropathy via miR-185/TGF-β1. However, the role of circRNA_15698 in renal tubulointerstitial fibrosis remains unclear. In this study, we aim to investigate whether circRNA_15698 plays an important role in folic acids (FA)-induced renal interstitial fibrosis and its corresponding mechanism.

Methods: Male CD1mice were peritoneally injected 250 mg/kg of FA or its vehicle. We collected kidney tissue after removing blood by PBS perfusion on day 30 after FA injection and evaluated renal interstitial fibrosis by PAS and Masson staining. We measured mRNA levels of pro-inflammatory cytokines such as interleukin-6 (*Il6*), tumor necrosis factor-α (*Tnfα*), and inflammatory cells including T lymphocytes and macrophages in the kidneys. We also examined the expression of pro-fibrosis factors, alpha smooth muscle actin (a-SMA), Collagen I (COL-1), and Fibronectin. Finally, we examined the renal expression of circRNA_15698, miR-185, transforming growth factor-beta (Tgfb) and analyzed the math seeds between circRNA_15698 and miR-185 as well as between miR-185 and Tgfb on TargetScan and miRanda.

Results: Peritoneal injection of FA induced obvious renal interstitial fibrosis (RIF) seen on PAS and Masson staining on day 30 after the injection. Pro-inflammatory cytokines, both *Il6* and *Tnfα* elevated remarkably in FA-injected mice compared to normal control mice. The infiltration of T lymphocytes and macrophages were seen in the kidneys. Pro-fibrosis factors, a-SMA, COL-1, and Fibronectin were increased in renal FA-injected mice on both mRNA and protein levels of the above factors. In addition, the

renal expression of circRNA_15698 was upregulated, renal miR-185 was downregulated and *Tfgb* was *also* upregulated. Finally we found perfect match seed displayed between circRNA_15698 and miR-185 as well as between miR-185 and *Tgfb* on TargetScan and miRanda analysis.

Conclusions: Our results suggested that circRNA_15698 might play an important role in FA-induced renal interstitial fibrosis by sponging miR-185 and increasing production of profibrotic TGF-β1. This is a novel pathway in pathogenesis of renal fibrosis and circRNA_15698 might be a new therapeutic target for renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO397

Racial/Ethnic Disparities in Atrial Fibrillation Treatment and Outcomes in US Dialysis Patients

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Background: Stroke prevention is a major goal in the management of end-stage renal disease (ESRD) dialysis patients with atrial fibrillation (AF). In the general AF population, racial/ethnic minorities have higher stroke rates, lower rates of anticoagulation and higher anticoagulation complication rates. We desribe differential treatment patterns by race/ethnicity and their association with racial/ethnic disparities in stroke outcomes among dialysis patients with AF.

Methods: We used the United States Renal Data System to identify ESRD patients diagnosed with AF who initiated hemodialysis from 2006-2013 with Medicare Part A, B, and D coverage. Patients were followed for all-cause stroke, mortality, prescription of oral medications for AF, and cardiovascular disease procedures (CVD) for AF. We used a causal inference mediation approach that accounts for time varying mediators and confounders to quantify what proportion of excess strokes can be attributed to lower use of AF therapies by race/ethnicity.

Results: The study included 56,587 ESRD dialysis patients with AF. Black, non-Hispanic White, Hispanic, and Asian patients accounted for 19%, 69%, 8%, and 3% of the population, respectively. In adjusted analyses, Black, Hispanic, and Asian patients were 13%, 18%, and 22% more likely to experience stroke within 1 year and 10%, 17%, and 28% times less likely to fill a prescription for warfarin compared to White patients, respectively. Prescription of warfarin was associated with decreased stroke rates (HR=0.82). Mediation analyses suggested that 7%, 10%, and 12% of excess strokes among Black, Hispanic, and Asian patients could be prevented if the warfarin distributions in these groups were equalized to that in the White population. We did not find racial/ethnic disparities for all-cause mortality or use of CVD procedures. All results achieved $p<0.05$.

Conclusions: Increased racial/ethnic disparities in stroke rates among ESRD dialysis patients with AF are partially explained by lower use of oral anticoagulants among Blacks, Hispanics, and Asians. The reasons for these racial disparities in practice are unknown, but the results support the development of strategies to maximize stroke prevention in minority populations that address patient, physician, and system barriers to optimal treatment.

FR-PO398

Dialysis Modality and Cardiac Function at the Time of Kidney Pre-Transplant Patients' Evaluation

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Background: Hemodialysis (HD), peritoneal dialysis (PD) and pre-emptive kidney transplant are different options at the time of the pre-transplant patients' evaluation; however, it is not clear how each dialysis modality affects cardiac structure and function. This study explores the association of different dialysis modalities and the cardiac function in this patient population.

Methods: This is a single-center, retrospective and descriptive study for patients who had completed pre-transplant cardiac evaluation in the renal transplant program at University of Kentucky between January 2010 and December 2015. We classified patients into 3 groups according to the dialysis modality. Group 1 included pre-emptive patients (n=74), group 2 included PD patients (n=61), and group 3 included HD patients (n=144). We analyzed the echocardiographic parameters for all patients and correlated them with the different dialysis modalities.

Results: There were no differences in demographic parameters between the 3 groups. Pre-emptive patients had a lower rate of diabetes mellitus (p=0.046) and marginally lower coronary artery diseases (p=0.055). There was no significant difference between the three groups regarding the left ventricular ejection fraction or right ventricular systolic function as measured by end diastolic and systolic dimensions, severity of tricuspid and mitral regurgitations and diastolic function as measured by E/e'. Moreover, the pulmonary artery pressures as measured by velocity of tricuspid regurgitation and pulmonary artery acceleration time were not significantly different between groups. Left ventricular mass index was significantly higher in patients on hemodialysis and lower in patients on peritoneal dialysis (p=0.010).

Conclusions: Patients being evaluated for kidney transplantation and not yet on dialysis had lower rates of diabetes and a trend toward lower coronary artery disease compared to patients who are already on dialysis. The left ventricular mass index was the highest in HD patients and the lowest in PD patients.

FR-PO399

Association of CPR Duration with Discharge Outcomes in Maintenance Dialysis Patients

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Background: Cardiopulmonary resuscitation (CPR) is associated with high mortality rates in patients receiving maintenance dialysis. There are no large studies to date that relate the duration of CPR to discharge outcomes in these patients.

Methods: Using electronic medical records, we identified all the adult patients (≥18years) who underwent CPR and were admitted to the hospital from January 2006 to December 2014 and then used chart review to select patients who were on maintenance dialysis. The charts documented CPR duration, CPR characteristics, in-hospital mortality, and discharge to home. In multivariate analyses, candidate variables were patient demographics, dialysis duration, number of co-morbidities, in-hospital vs out-of-hospital CPR, and initial heart rhythm.

Results: Of the 402 ESRD patients who had undergone CPR, duration of CPR was documented in 296 patients. Among these, CPR duration was ≤10 minutes in 111 patients and >10 minutes in 185 patients. Of those who had received CPR ≤10 minutes, 46.2% died within the same hospitalization; of patients receiving CPR >10 minutes, 83.2% died within the same hospitalization. Those receiving CPR for >10 minutes had higher odds of in-hospital death (OR 8.91 4.44, 17.89, p=<.0001) and survivors had lower odds of discharge to home (OR 0.08, 0.01,0.63, p=0.017) after adjusting for confounding variables.

Conclusions: Longer CPR duration was independently associated with poor discharge outcomes. These data may help clinicians determine prognostic information to guide discussions with families. Moreover, It may be appropriate to limit the CPR duration in patients deemed to have a poor prognosis.

FR-PO400

Pericardial Effusions in Patients with Renal Disease: A Single-Centre Experience

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Background: Pericardial effusions are common in renal patients and frequently thought to be uraemia related. However alternative aetiologies do exist and the best management approach remains unclear.

Methods: All renal inpatients with pericardial effusions at a tertiary renal centre from 2010-2018 were identified, and data was collected on patient factors, investigation results, treatment, interventions, and outcomes. This was used to compare cases undergoing pericardiocentesis versus those that did not, identify causes of pericardial effusion and create diagnostic groups for comparison.

Results: Fourty-six patients with pericardial effusions were identified, aged 18-83, 63% male. Renal modalities included haemodialysis (72%), peritoneal dialysis (9%), CKD (6%), transplant (6%), and AKI requiring renal replacement therapy (RRT) (7%). Twenty-four patients underwent pericardiocentesis. The commonest reason for this was cardiovascular compromise, with 21/24 cases having a large effusion (>2cm) on imaging. The commonest cause of pericardial effusion was uraemia related (15), followed by idiopathic/incidental (10), surgical (7), tuberculosis (Tb) related (6), autoimmune (4), pyogenic (3) and unknown (1). Pericardial fluid microbiology culture was positive in only 3 cases, and no positive Tb cultures were obtained. Of the drained cases 13 had fluid protein levels measured; in all cases the protein level was >35g/L. Fluid LDH was measured in 15 patients; in 11 cases this was >2/3 the upper reference range.

Conclusions: In our cohort uraemic pericardial effusions were the commonest cause, in keeping with previous studies. This uraemic group included patient's pre-RRT initiation, RRT non-compliant patients, and patients switching modality, suggesting that poor dialysis contributed to effusion development. Other aetiologies did exist and so a wide differential must be maintained. Pericardiocentesis was only necessary for therapeutic relief, as drainage did not aid diagnosis, therefore it should be reserved for cases with clinical compromise. Although fluid LDH and protein levels in our cohort suggested mostly exudative effusions, current literature states that these factors do not reliably distinguish between pericardial effusion types nor help in establishing the cause. Our findings have revealed diagnostic groups that will be further analysed to help identify differentiating factors between these effusions.

FR-PO401

Electrocardiogram Findings at the Initiation of Hemodialysis and Types of Future Cardiovascular Events

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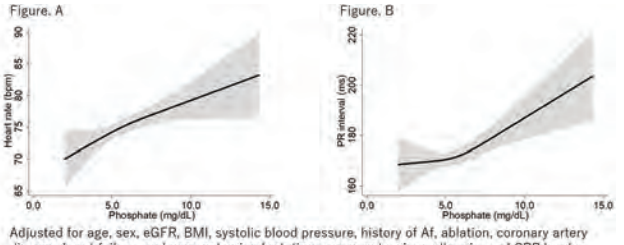
Background: Prognostic value of electrocardiogram (ECG) was reported in pre-dialysis patients. However, it remains to be revealed in hemodialysis (HD) patients. Since

incident HD patients suffer from volume overload and electrolyte abnormalities, ECG at the initiation of HD is thought to be a kind of "stress ECG test".

Methods: We performed a retrospective multicenter cohort study of incident HD patients. We collected the latest data just before the initiation of HD. The primary outcome was atherosclerotic and non-atherosclerotic cardiovascular diseases (CVD) after the initiation of HD. Using Cox proportional hazards models, we examined whether ECG parameters (PR, QRS, QT interval, heart rate, and left ventricular hypertrophy [LVH] by voltage criteria) predict the primary outcome.

Results: Among the enrolled 683 patients, 21 and 16% of the patients showed LVH and PR interval >200 ms (PR prolongation), respectively. Serum phosphate levels were positively associated with heart rate and PR interval (Figure). Over a median follow-up period of 3 years, 19 and 16% of the patients developed atherosclerotic and non-atherosclerotic CVD, respectively. Backward stepwise multivariate Cox regression models including ECG parameters and baseline characteristics of patients revealed that LVH predicted atherosclerotic CVD (hazard ratio [95% CI: Confidence Interval]): 1.96 [1.24-3.11]). In contrast, PR prolongation was a significant risk factor of non-atherosclerotic CVD (hazard ratio [95%CI]: 2.00 [1.17-3.42]).

Conclusions: LVH and PR prolongation were significant risk factors of atherosclerotic and non-atherosclerotic CVD, respectively. Fibroblast growth factor 23 might explain the positive association of serum phosphate levels with heart rate and PR interval.



Adjusted for age, sex, eGFR, BMI, systolic blood pressure, history of Af, ablation, coronary artery disease, heart failure, and pacemaker implantation, serum potassium, albumin, and CRP levels, corrected calcium levels, hemoglobin levels, prescription of β-blocker, and calcium channel blockers, heart rate (only in Figure.B), and hospital.

FR-PO402

Impact of Electrolytes and Acid-Base Changes During Hemodialysis Session on Incidence of Arrhythmia

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Background: Patients on hemodialysis (HD) have a high incidence of sudden cardiac death. Since we often observed increasing incidence of arrhythmia during and just after dialysis session, drastic changes in electrolytes and/or acid-base may prolong QTc interval and cause arrhythmia. To investigate occurrence and frequency of arrhythmias chronologically and to examine the effects of electrolyte and acid base change on QTc interval during dialysis session.

Methods: We recorded ECG by 24-hour Holter and simultaneously measured changes in serum electrolytes and acid-base during a single hemodialysis session in 50 patients (F/M=15/35, 64% were diabetes, 1993 days of mean HD vintage, 70.1 years of mean age). HD parameters were: 3h (n=1), 3.5hr (n=1) or 4hr×3/week, dialyzer; polysulfone, QB=150-200ml/min. Concentration of electrolytes in dialysate were Na^+ 140 mmol/l, K^+ 2.0 mmol/l, Ca^{2+} 3.0 mmol/l, Mg^{2+} 1.0 mmol/l, Cl^- 110 mmol/l, CH_3COO^- 8 mmol/l and HCO_3^- 30 mmol/l.

Results: ECG was recorded from the start of dialysis session. The highest incidence of SVPC and VPC was recorded during 1st 4-hour(during dialysis; 25%) and 2nd 4-hour (right after dialysis; 26%). QTc did not increase in 18 patients and increase in 32 patients during dialysis session. Between these two groups, mean initial QTc was not different but logistic regression revealed that serum HCO_3^- (odds=0.64) and pH (odds=1.05E+009) were strong determinants among others (Ca^{2+}, K^+, Mg^{2+}, Na^+ and QTc). Multiple regression analysis revealed not only initial QTc but also QTc change during single dialysis session was affected by initial level or changes in serum Ca^{2+}(p=0.0001/0.01), K^+ (p=0.0007/0.03) and HCO_3^- (p=0.02)/pH(<0.0001) among others (Mg^{2+} and Na^+) by weighted least squares multiple regression (r=0.83/0.85).

Conclusions: These results suggest that QTc prolongation during dialysis session is caused by not only magnitude of changes in serum Ca^{2+} and K^+ as reported previously but also magnitude of alkalization in our dialysate composition. In order to prevent prolongation of QTc and arrhythmia, changes in acid-base should be minimized specifically.

FR-PO403

Silent Arrhythmias In Hemodialysis Patients Does Not Increase Major Cardiovascular Events over Short-Term Follow-Up

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Background: This study was conducted to know the incidence and outcome of silent cardiac arrhythmias in hemodialysis patients.

Methods: A total of 25 patients on regular hemodialysis (HD) were enrolled for studying cardiac arrhythmias. At screening phase, all HD patients were subjected to fluid optimization and adjustment in the BP medicines over a period of 2 weeks. Only those patients, who had no history of or evidence of arrhythmias in baseline electrocardiogram were enrolled. Holter monitoring for evidence of arrhythmia was done for 24 hours, including 4 hours of hemodialysis session on two occasions: long interdialytic (LIDP) and short interdialytic period (SIDP). Incidence and types of arrhythmia was noted. Factors associated with arrhythmias and effect of interdialytic period on arrhythmia were studied. All these patients were followed for a period of 12 months to study the impact of cardiac arrhythmias to adverse cardiovascular events.

Results: Out of 25 patients studied, 17 patients (68%) developed arrhythmia. Of all the arrhythmias, sinus bradycardia was the most common type, which occurred in 60% of patients. Incidence of supraventricular tachycardia (SVT) was 24% followed by atrial tachycardia 16%, premature ventricular complex 12%, atrial fibrillation 8%, premature atrial complex 4% and ventricular tachycardia 4%. The baseline demographic parameters of patients with or without arrhythmias were similar. In laboratory parameters, serum creatinine was higher in arrhythmia group (9.2 mg/dl vs 6.9 mg/dl, P=0.003). Mean ultrafiltration was higher in arrhythmia group after long inter-dialytic period (2.86 ± 0.68L vs. 2.12 ± 0.93L, P = 0.036). Incidence of arrhythmia was higher after LIDP as compared to SIDP (64% vs. 52%, p=0.004). A total of 4 patients died over 1 year of follow up - three patients died in non-arrhythmia group while one in the arrhythmia group. One patient in arrhythmia group developed heart failure. None of the patients developed symptomatic cardiovascular event over 12 months of short observational period.

Conclusions: Asymptomatic silent arrhythmia is a common complication seen in patients on maintenance hemodialysis (68%) with bradycardia being the commonest (60%). Impact of arrhythmia on long term cardiovascular outcome needs long term follow up of these patients.

FR-PO404

Cardiac Arrest in Hospitalized Maintenance Hemodialysis Patients

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Background: Sudden cardiac death accounts for half of cardiac-related deaths in maintenance hemodialysis (HD) patients. Data regarding the frequency of shockable rhythms at presentation to or during a hospital stay is limited.

Methods: A retrospective cohort study was performed to evaluate the characteristics, laboratory values and treatment of HD patients with a hospital stay due to or complicated by cardiac arrest between 2015-2018. Arrests following continuous renal replacement therapy were excluded (n=4). Differences in predictors of interest according to the use of defibrillation during cardiac arrest were analyzed by chi^2 tests or t-tests.

Results: Of the 34 subjects included, mean age was 64 years, 83% were male, 29% were black, 53% had heart failure and 44% had atrial fibrillation. 25 arrested during admission, while 9 had out-of-hospital arrests. 71% died during their admission. 29% had ventricular tachycardia (VT) or fibrillation (VF) during their arrest; 70% of these received at least one shock. 50% had asystole/pulseless electrical activity (PEA) without VT or VF. The remaining 21% rhythms were not described; one of these had no documentation regarding whether or not defibrillation was used. The median duration since the preceding HD session was 24 hours (25-75th percentile:12-45) with pre-arrest serum electrolytes as follows: potassium 4.9±0.7mmol/L, bicarbonate 22±4.6mmol/L, phosphorus 4.6±1.9mg/dL and calcium 8.8±0.8mg/dL. Comparisons according to receipt of defibrillation are presented in Table 1.

Conclusions: Asystole/PEA appear to be more frequent than VT/VF in HD patients with a hospital stay due to or complicated by cardiac arrest. Of patients with VT/VF, 30% were not defibrillated. Further studies are needed to better understand the etiology and treatment of cardiac arrest in HD patients during hospitalization.

Characteristic	Defibrillated (n=7)	Not Defibrillated (n=26)	P
Mean Age (years)	58.7 ± 15.6	64.6 ± 16.4	0.40
Male	6 (86%)	21 (81%)	0.76
Black	2 (29%)	8 (31%)	0.91
Median Duration Since Preceding HD session (hours)	24 (21-61)	24 (12-45)	0.63
Heart Failure	4 (57%)	13 (50%)	0.74
Mean Left Ventricular Ejection Fraction	50 ± 19%	54 ± 17%	0.34
Atrial Fibrillation	4 (57%)	10 (39%)	0.37
Mean Serum Potassium (mmol/L)	4.6 ± 0.4	5.0 ± 0.7	0.26
Mean Serum Bicarbonate (mmol/L)	24.0 ± 7.4	22.1 ± 4.1	0.54
Mean Serum Phosphorus (mg/dL)	5.0 ± 2.6	4.7 ± 1.8	0.80
Mean Serum Calcium (mg/dL)	8.5 ± 0.6	8.8 ± 0.8	0.51
Died During Admission	5 (71%)	18 (69%)	0.91
Out of Hospital Arrest	4 (57%)	5 (19%)	0.046

Table 1. Characteristics of Defibrillated vrs Not Defibrillated Patients

FR-PO405

Effects of Spironolactone (SPL) on Arrhythmias in Hemodialysis Patients: Secondary Results of the SPin-D Trial

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Background: Aldosterone may contribute to the development of arrhythmias in HD patients. Whether treatment with SPL affects the risk of arrhythmias in this setting is unknown.

Methods: The Spironolactone in Dialysis (SPin-D) trial evaluated the safety of SPL for 36 weeks at 12.5 mg, 25 mg, or 50 mg vs placebo in maintenance HD patients. We analyzed data from a subset of participants with arrhythmia monitoring for 7 days at baseline (N=35), 6-weeks (N=37), and end of study (N=53). Adjusted Poisson models including treatment, time point and randomization stratification factors were used to analyze associations of SPL, SPL dose, and serum potassium (K) with the incidence rates of arrhythmias during follow-up.

Results: Conduction blocks or bradycardia and atrial fibrillation or flutter (AF) were common while ventricular arrhythmia was infrequent (Table). Conduction defects or bradycardia were more frequent with SPL compared with placebo in unadjusted and adjusted models. Reduction in AF risk with SPL vs. placebo was less robust at higher SPL dose: (adjusted rate ratios [RR], 95% CI) SPL 12.5 mg (0.09, 0.01-0.77), 25 mg (0.40, 0.06-2.72) and 50 mg/daily (0.89, 0.21-0.80), and conduction block or bradycardia was more frequent at higher SPL dose: (adjusted RR, 95% CI) SPL 12.5 mg (1.56, 0.93-2.52), 25 mg (1.45, 1.06-1.97) and 50 mg (3.00, 1.73-5.20). The RR per 1 mEq/L increase in serum K was 1.54, 95% CI: 0.89-2.65 for AF and 1.20, 0.78-1.86 for bradycardia/block.

Conclusions: Arrhythmias occur with a high incidence in maintenance HD patients with AF and bradycardias/conduction blocks occurring more frequently than ventricular arrhythmias. SPL may reduce AF but increase conduction blocks and bradycardia. Additional studies are needed to confirm these findings, evaluate the effects of SPL dose, and determine if increased K mediates SPL-associated arrythmias.

Funding: NIDDK Support, Other NIH Support - NCATS

Arrhythmia Rate at Baseline and Follow-Up

	Overall Rate at Baseline	Placebo	SPL 12.5 mg	SPL 25 mg	SPL 50 mg	Combined SPL During Follow-Up
Arrhythmia Type						
Atrial Fibrillation or Flutter	5.6	13.2	1.2	5.3	11.7	6.3
Conduction Block or Bradycardia	3.4	15.5	24.4	22.3	46.5	33.6
Ventricular Tachycardia or Fibrillation	0.4	0.8	0.0	0.0	0.7	0.2
Sinus Bradycardia or Asystole	0.7	1.4	1.4	0.0	15.4	6.1
Sinus Tachycardia, Supraventricular Tachycardia, or Wide Complex Tachycardia	14.9	13.7	12.5	10.9	15.3	13.0

Rates are provided as events per 100 patient-days and are show for combined placebo and spironolactone group at baseline and by randomized treatment group during follow-up.

FR-PO406

Arrhythmia in Chronic Hemodialysis as a Function of Pre-Dialysis Electrolytes and Interdialytic Interval

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Background: Sudden cardiac death is a leading cause of death in hemodialysis patients. For patients on thrice weekly dialysis, these deaths are most common before and during dialysis following the three day interdialytic period. Cummulative fluid, electrolyte, and metabolite accumulation during the longer interdialytic period have been correlated with increased arrhythmia, but the specific imbalances that are driving this cardiac instability have not been identified.

Methods: 60 stable patients on chronic thrice weekly hemodialysis with a tendency to hyperkalemia provided informed consent. Cardiac rhythm was continuously monitored for one week starting at the midweek dialysis session (day 1). Pre-dialysis chemistries and 12 lead EKG were determined at the pre and post weekend dialysis session (days 3 and 6). Frequency of ventricular ectopy, superventricular ectopy, bradycardia, and average QTc were reported in 4 hour blocks. Rates of arrhythmias through the week and correlation with individual clinical parameters were analyzed using standard statistical methods.

Results: Total arrhythmia frequency was low and did not correlate with dialysis in the whole population. Neither ventricular ectopy nor bradycardia correlated with dialysis or interdialytic interval. Superventricular ectopy showed peaks during dialysis on both days 3 and 6, but these did not reach statistical significance. None of the arrhythmias correlated with pre-dialysis electrolytes, BNP or ultrafiltration volumes. Pre-dialysis PR intervals, QRS duration, and QTc did not correlate with arrythmias or with electrolytes. QTc, one known risk factor for ventricular arrhythmia, was significantly prolonged during dialysis on both days 3 and 6: ΔQTc pre- to intra-dialysis 18.6 ± 38.9 ms (P=0.0007) and 13.6 ± 53.6 (P=0.031) on days 3 and 6, respectively. Patients with lower pre dialysis serum Ca were more likely to prolong QTc during dialysis.

Conclusions: In this cohort of 60 stable chronic hemodialysis patients, there was significant prolongation of the QTc during each dialysis session which was more prominent in patient with lower pre-dialysis serum Ca. However, prolonged QTc was not correlated with observed arrhythmia and we did not find a significant increase in arrhythmia related to pre-dialysis electrolytes or intradialytic period.

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FR-PO407

Natural History of Atrial Fibrillation in Patients with ESKD on Hemodialysis

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Background: Anticoagulation for nonvalvular atrial fibrillation (AF) is controversial in patients with end-stage kidney disease (ESKD) maintained on hemodialysis (HD). Reserving anticoagulation for periods of highest stroke risk and lowest bleeding risk may help maximize the benefits of anticoagulation while minimizing the risks. To identify any such periods, we examined the natural history of untreated AF among those with ESKD maintained on HD.

Methods: We reviewed Medicare claims for HD patients aged >65 years that developed AF from 2011 to 2013 that did not have prescription claims for warfarin or direct oral anticoagulants in the months prior and post the AF diagnosis. Incident AF was defined as no prior claim for atrial fibrillation for at least a year before the index AF claim. Examining the twelve months following the AF diagnosis, we calculated the instantaneous hazard rates of ischemic stroke, major bleeding, and all-cause mortality. Patients were censored at date of death, date of kidney transplantation, or end of follow-up.

Results: We included 14,803 HD patients who had incident AF claims from 2011 to 2013 but no anticoagulation prescription claims. Almost all (99.9%) had a $CHADS_2$-VASC score of 2 or higher with 34% of all patients having a score of 7 or higher. The majority of patients did not have a stroke or major bleed in the year prior to the index AF date (61% and 64%, respectively). We found low rates of ischemic stroke (40 events per 1000 person years); intermediate rates of major bleeding (232 events per 1000 person years); and high rates of all-cause mortality (739 events per 1000 person years). Hazard function plots illustrated that both ischemic stroke and bleeding rates were high immediately after the AF diagnosis but that both rates declined and stabilized around 30 days post-AF diagnosis.

Conclusions: Our results suggest that the risk of major bleeding may be highest immediately after the diagnosis of AF and that major bleeding may occur more frequently in this time period than ischemic stroke. The risks for both ischemic stroke and major bleeding appear to then decline and stabilize over time. Further research is needed to determine if reserving anticoagulation until one month post-AF diagnosis helps maximize the benefits of anticoagulation while minimizing the risks.

FR-PO408

Hypocalcemia-Induced Bradycardia Is More Pronounced in Male Hemodialysis Patients

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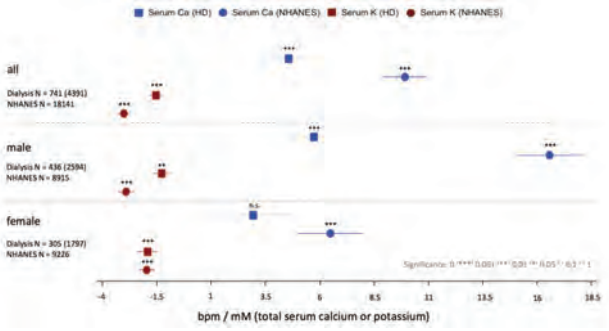
Background: The risk of sudden cardiac death (SCD) is increased 14-fold in chronic hemodialysis (HD) patients compared to patients with normal kidney function suffering from cardiovascular diseases. This high rate is not explained by traditional cardiovascular risk factors. Recently, severe bradycardia has been implicated in SCD in HD patients. Mathematical modelling suggests an electrophysiological link between low serum calcium (Ca) levels and bradycardia. Therefore, we analyzed the correlation between heart rate (HR) and Ca as well as potassium (K).

Methods: Data were obtained from 18,141 individuals taken from the NHANES 2011-16 US cross-sectional survey and 741 chronic HD patients. To determine the correlation between HR (dependent variable), Ca and K, respectively, linear mixed effects models for HD patients included dialysis vintage as random effect. For NHANES subjects simple linear regression was employed.

Results: In HD patients, a significant inverse correlation was found between HR and Ca. The effect was statistically significant only in males. The same effect with a similar factor of approximately 2 between the results for males and females was seen in the NHANES subjects. K had a significant inverse correlation with HR in both sexes.

Conclusions: Our results corroborate predictions of physiology-based mathematical models regarding the relation between HR and serum levels of K and Ca, respectively. In addition, we observed that the effect size of the HR-to-Ca relationship was larger in males. This unexpected finding warrants further investigation in other cohorts. If confirmed, the modulatory effects of sex on cardiac electrophysiology need to be explored.



FR-PO409

Association of Functional Outcomes of Sleep and Intermediary Cardiovascular Outcomes in Incident Hemodialysis Patients

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Background: Prior studies show that sleep conditions are associated with an increased risk of cardiovascular (CV) disease and mortality in adults initiating hemodialysis (HD). It is not known whether functional outcomes of sleep (fatigue, concentration difficulty, and memory impairment) are associated with CV morbidity in incident HD patients. We sought to examine whether functional outcomes of poor sleep were associated with intermediary cardiovascular outcomes in incident HD.

Methods: In 228 incident hemodialysis patients from the Predictors of Arrhythmic and Cardiovascular risk in ESRD (PACE) study, Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10), a validated questionnaire that assesses the functional effect of daytime sleepiness through 5 domains (general productivity, activity level, social outcomes, vigilance and intimacy and sexual relationship), was administered within 6 months of enrollment. Baseline comorbidities, including history of CV disease and diabetes, were ascertained by chart review, and baseline cardiac testing, including ECG and echocardiogram, was obtained. Intermediary cardiovascular outcomes included (QTc [ms], heart rate variability [ms^2], left ventricular mass index [g/m^2, LVMI], and left ventricular hypertrophy [LVH]). Associations of log transformed FOSQ-10 scores with intermediary outcomes were examined using linear regression.

Results: Mean age was 55 years, median body mass index was 28 (IQR 24,33), median Charlson comorbidity index was 5 (IQR 4,6), with 68% African American. Lower FOSQ-10 scores, indicating greater impairment from sleep disturbances, were associated with greater QTc duration and lower heart rate variability after adjustment for clinical factors.[Table] There were no significant associations of FOSQ-10 score and LVMI or LVH.

Conclusions: In adults initiating hemodialysis, poor functional outcomes of sleep are associated with increased risk of intermediary CV outcomes. Screening for sleep disturbances in incident hemodialysis patients may identify individuals at increased risk for adverse CV outcomes.

Funding: NIDDK Support

Table. Association of FOSQ-10 score and intermediary CV outcomes

FOSQ-10 score, per 0.1 log increase	QTc (ms)	Heart rate variability (ms^2)	LVMI (g/m^2)	LVH
	β (95% CI)	β (95% CI)	β (95% CI)	PR (95% CI)
Unadjusted	-0.49 (-0.85, -0.13)	16.0 (3.22, 28.9)	0.02 (-0.11, 0.16)	1.00 (0.99, 1.01)
Adjusted	-0.42(-0.79, -0.05)	14.7 (1.44, 27.9)	0.04 (-0.10, 0.19)	1.00 (0.99, 1.01)
Model adjusted for age, sex, and ethnicity, comorbidity index, QT-prolonging medication use, beta blocker use, alpha blocker use, DBP, and serum potassium				

FR-PO410

Functional Outcomes of Sleep Predict All-Cause Mortality in Incident Hemodialysis Patients

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Background: Patients with ESRD commonly experience sleep disturbances. Fatigue, difficulty concentrating, and memory impairment are functional outcomes of poor sleep measurable by validated questionnaire. Although sleep disturbances are associated with increased risk of mortality in patients initiating hemodialysis, it is unclear if functional outcomes of sleep impact mortality risk. We sought to examine whether functional outcomes of poor sleep are associated with an increased risk of mortality in patients initiating hemodialysis.

Methods: In 228 participants enrolled in the Predictors of Arrhythmic and Cardiovascular risk in ESRD (PACE) study, the validated Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10), which assesses functional outcomes of daytime sleepiness through 5 domains (productivity, activity level, social outcomes, vigilance and sexual relationship), was administered within 6 months of enrollment. Proportional hazards regression was used to examine the association of FOSQ-10 score with all-cause mortality. Effect modification was tested using multiplicative interaction terms.

Results: Mean age was 55 years, median body mass index was 28 (IQR 24,33), with 68% African American. During 816 person-years of follow-up, there were 95 deaths. Each 0.1 log decrease in FOSQ-10 score was associated with increased risk of mortality (HR 1.09, 95%CI 1.01-1.18), independent of clinical covariates. [Figure] This association was not modified by age, sex, race, or history of diabetes.

Conclusions: In adults initiating dialysis, poor functional outcomes of sleep are associated with increased risk of overall mortality. Future studies should assess the impact of screening for sleep disturbances in ESRD patients to identify individuals at increased risk of death.

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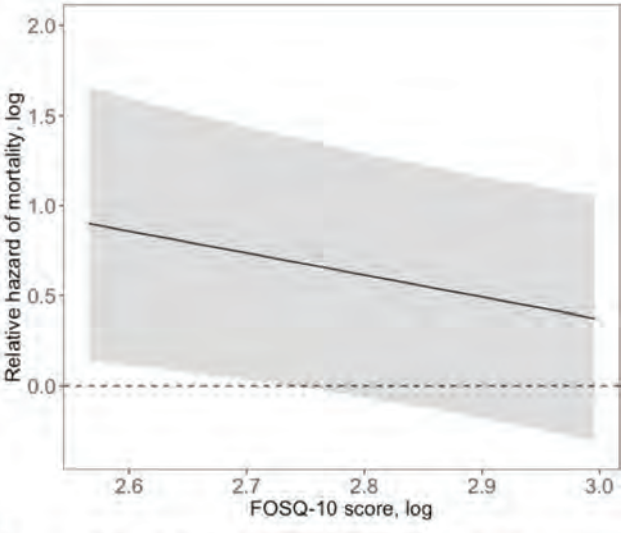

Figure. Association of FOSQ-10 score with all-cause mortality among adults initiating hemodialysis.

FR-PO411

Hypomagnesemia with High FGF-23 Is a Significant Risk Factor for Cardiovascular Disease in Hemodialysis Patients

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Background: In patients with chronic kidney disease, cardiovascular disease is the major cause of mortality and morbidity. Magnesium has been shown to impact cardiovascular health positively. Most previous cohort studies and their meta-analysis have shown a link between high serum phosphate levels and high FGF23 levels and an increased cardiovascular risk. However, few studies have investigated parameters associated with magnesium levels in hemodialysis (HD) patients. Accordingly, we examined the clinical significance of magnesium (Mg) cross-sectionally, and investigated the relationship between Mg levels and FGF23 levels.

Methods: Eighty-nine HD patients were enrolled. Their mean age was 66.9 ± 11.3 years, and the mean duration of HD treatment was 10.9 ± 8.1 years. Twenty-six patients had diabetes mellitus (DM) and eighteen patients had cardiovascular diseases. We analyzed their medical history, echocardiography, computed tomography, biochemical measurements, cardiovascular morbidity, mortality, etc. We identified prospective studies reporting associations between Mg and FGF23 concentrations and parameters. Statistical significance of the difference between groups was determined by the chi-square test. All statistical analyses in this study were performed with SPSS statistics software 22 for Windows.

Results: The number of cardiovascular disease patients was significantly higher in the group with a serum Mg level of less than 2.5 mg/dl (P = 0.015) but was not correlated to serum Mg level. The serum FGF23 level was related to cardiovascular disease (P = 0.04). There was no relationship between cardiovascular disease and serum P level. Comparing high FGF23 to low FGF23, cardiovascular disease was significantly increased in the low Mg group (P = 0.021) but not in the high Mg group (P = 0.426). The odds ratio for cardiovascular disease in the high FGF23 group compared with the low FGF23 group was 3.38. The association between FGF23 and cardiovascular disease was modified significantly by Mg level.

Conclusions: We suggest that in cardiovascular disease, FGF23 and serum Mg levels are more influenced by the serum P level. High serum FGF23 was associated with cardiovascular disease in hemodialysis patients with low Mg level, but not in those with high Mg level. In particular, the combination of low Mg level and high FGF23 level is a risk factor for cardiovascular disease.

FR-PO412

Fibrate Therapy in Hemodialysis Patients: A Prospective 10-Year Study

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Background: KDIGO guideline suggests that statin should not be initiated in hemodialysis (HD) patients. Fibric acid derivative (fibrate) is another lipid-lowering drug class capable of reducing plasma triglyceride (TG), cholesterol and LDL-cholesterol (LDL-C), but has been rarely used in HD patients due to potential adverse events, namely myositis and transaminitis. Recent study demonstrated that low-dose fenofibrate (100 mg) was safe in HD patients. The efficacy of low-dose fenofibrate (LF) and gemfibrozil (G), two most commonly-used fibrates, has not been compared before in patients with advanced CKD. This research aims to study the lipid-lowering effect and safety profiles of LF and G in HD patients with hyperlipidemia.

Methods: This was a prospective study of all HD patients with hyperlipidemia who were initiated on fixed-dose fibrates at Vajira Hospital between January 2009 and December 2018. The data collected were baseline characteristics, kidney function, body mass index and type of fibrate. All patients were followed for 6 months. Changes in fasting lipid profiles were recorded and compared at 3 and 6 months after initiating treatment. Liver function tests and muscle enzyme were monitored at the beginning and two months after starting drug.

Results: There were overall 94 HD patients recruited to receive fibrate therapy (33 LF and 61 G) without additional lipid lowering drug. At 6 month, LF 100 mg effectively lowered both fasting TG and LDL-C (-34% and -21%; p=0.004 and 0.01 respectively) whereas G 600 mg significantly reduced fasting TG (-29%, p=0.003) but not LDL-C level (-11%; p=0.06). Myalgia and myositis were reported in 5 patients (13.7%) in LF group and 6 patients (11.3%) in G groups. No patient experienced rhabdomyolysis or severe myositis requiring discontinuation of fibrate. Transaminitis occurred in 5 patients from each LF and G group (15.2% and 8.2% respectively). Only 1 patient receiving LF had significant transaminitis (ALT>3 x upper limit of normal) that required fenofibrate discontinuation. Three patients died (2 in F group and 1 in G group) from causes determined not to be fibrate-related.

Conclusions: Both low-dose fenofibrate and gemfibrozil were effective in lowering plasma TG but only fenofibrate could significantly reduce LDL-C in HD patients. Both drugs were well-tolerated and could be useful alternatives to statin in HD patients with hyperlipidemia.

Funding: Government Support - Non-U.S.

FR-PO413

Statin Dose Prior to Dialysis Transition with Post-Transition Hospitalization Frequency

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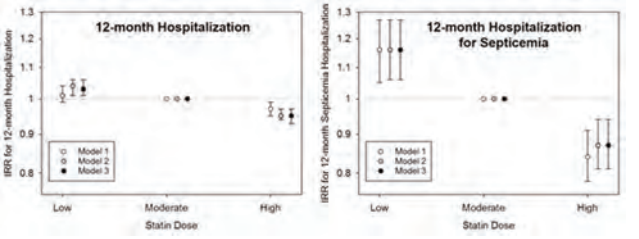
Background: In a prior study, we demonstrated that statin use prior to dialysis start was associated with lower mortality and hospitalization risk. Although current guidelines advocate for initiation of a moderate dose statin in late stage chronic kidney disease (CKD), we sought to examine whether risk of hospitalization, in particular septicemia, in the year after dialysis start differed according to statin dose in the year prior to transition.

Methods: In a cohort of veterans transitioning to dialysis from 2007-2015, we identified 32,439 patients on low-, moderate- and high-dose statin therapy for at least 181 days in the year prior to dialysis start. Poisson models with adjustment for demographics, comorbidities and use of other lipid altering medications were used to examine associations between statin dose of hospitalization incidence.

Results: Cohort mean±SD age was 72±10 years old, 4% were female, 21% African American, 6% Hispanic, 80% diabetic and 39% had a prior myocardial infarction. High-dose patients were more likely to be younger, African American and diabetic but less likely to have liver disease or cancer. In unadjusted and adjusted analyses, statin dose had a linear association with hospitalization rates. Compared with moderate statin dose (reference), low- and high-dose statin therapy were associated with higher and lower hospitalization rates, respectively [IRRs (95% CIs) 1.03 (1.01, 1.06) and 0.95 (0.93, 0.97), respectively]. Associations were similar for septicemia hospitalizations.

Conclusions: Risk of hospitalization, particularly septicemia, in the year after transition to dialysis was lower with higher statin dose therapy. Statins are known to have anti-inflammatory benefits and further studies are needed to investigate whether the use of higher dose statins confers benefits that outweigh risk of adverse events in patients transitioning to dialysis.

Funding: NIDDK Support, Veterans Affairs Support



FR-PO414

A Scoring System for Predicting Individual Effects of Statin Treatment in Type 2 Diabetes Mellitus Patients on Hemodialysis

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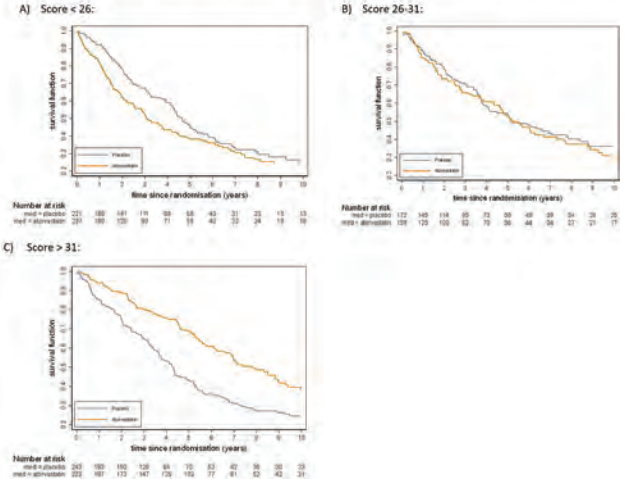
Background: Randomized clinical trials did not show a benefit of statins in hemodialysis (HD) patients. However, post-hoc analyses of the German Diabetes Dialyse (4D) study indicated that there are subgroups defined by theragnostic markers showing heterogenous treatment effects. We combined the information of multiple markers to a score predicting individual treatment effects.

Methods: We used data from the 4D study, a randomized trial including 1,255 HD patients with type 2 diabetes, randomized to atorvastatin or placebo. We calculated two scores, score 1 (23 predictive markers) and score 2 (17 clinically available markers) and classified patients in groups based on score cut-points indicating changes in effect. In each group we calculated effect estimates with respect to a composite cardiovascular endpoint and all cause death using both trial follow-up (FU) (median: 4 yrs) and long-term FU data (median: 11.5 yrs).

Results: The groups based on score 1 showed completely differential treatment effects: G1) (score < 26, 458 (36%) pts) showed harm: HR=1.54 (95%CI: 1.16-2.03) [Fig. 1a]; G2) (score 26-31, 331 pts (26%)) showed no effect: HR=1.03 (95%CI: 0.72-1.48) [Fig. 1b] and G3) (score>31, 466 pts (38%) showed benefit: HR=0.43 (95% CI: 0.30-0.60) [Fig. 1c]. In G3 statins also reduced all-cause mortality: HR=0.63 (95% CI: 0.48-0.83). Results for score 2 were similar with a smaller group G3 (N=360 pts). For long-term FU the effects were less heterogenous among groups.

Conclusions: The effect of statins in patients on HD is heterogenous and can be predicted by markers that relate to plausible effect modifying mechanisms including cholesterol metabolism, atherosclerosis, protein energy wasting or competing risks. The score will be useful in clinical practice not only to select patients that benefit from statins but also to identify those where treatment is harmful.

Fig. 1) Survival curves with respect to cardiovascular endpoint in patient groups identified by prediction score, N=1,255 HD patients with type 2 diabetes (adjusted for age, sex and coronary heart disease).



FR-PO415

The Target Cholesterol Level for Favorable Prognosis in Hemodialysis Patients: 10-Year Outcomes of the Q-Cohort Study

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Background: The prevalence of atherosclerotic diseases is higher in hemodialysis patients. The aim of the current study was to determine the target cholesterol level for the best prognosis in patients undergoing long-term hemodialysis.

Methods: A total of 3,517 participants undergoing maintenance hemodialysis were followed up for 10 years. The outcomes were the incidences of cardiovascular disease (CVD) and mortality. Total cholesterol (TC) in mg/dL was divided into the following quartiles derived from baseline data: Q1 < 131, Q2 ≥ 131 and < 152, Q3 ≥ 152 and < 178, and Q4 ≥ 178. To determine the cholesterol level of the best prognosis, we used a multivariable-adjusted restricted cubic spline model.

Results: During the follow-up period 1,033 patients had CVD, and 1,742 patients died. Compared with Q1, the respective multivariable-adjusted hazard ratios and associated 95% confidence intervals for ischemic heart disease (IHD), peripheral artery disease (PAD), and CVD in Q4 were 1.40 (1.05–1.85), 1.35 (0.93–1.98), and 1.28 (1.07–1.54). The incidences of IHD, PAD, and CVD were significantly positively associated with higher cholesterol levels after adjustment for confounding factors (p for trend < 0.05). Compared with Q4, the respective multivariable-adjusted hazard ratios and associated 95% confidence intervals for CVD mortality, infection-associated mortality, cancer-associated mortality, and all-cause mortality in Q1 were 1.13 (0.89–1.43), 1.09 (0.82–1.45), 1.69 (1.14–2.51), and 1.24 (1.07–1.43). The TC level at which all-cause mortality risk was lowest was 179 mg/dL.

Conclusions: Higher TC predicts IHD, PAD, and CVD events, and lower TC predicts cancer-associated mortality and all-cause mortality in patients undergoing hemodialysis. We determined the favorable value of serum cholesterol level was 179 mg/dL.

FR-PO416

Circulating Levels of CD34⁺ Cells Predict Long-Term Cardiovascular Outcomes in Patients on Maintenance Hemodialysis

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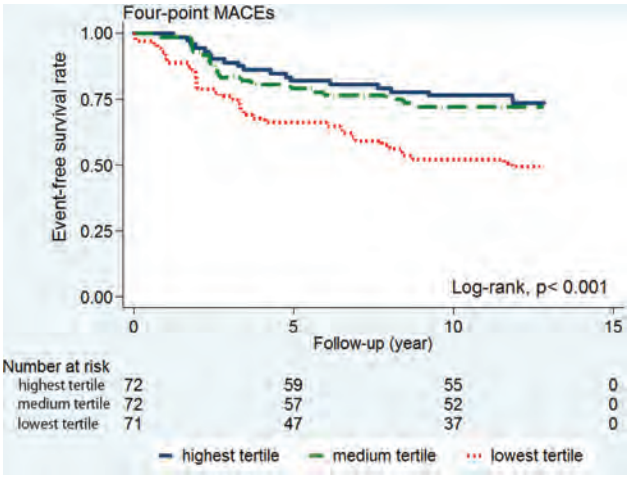
Background: CD34⁺ cells maintain vascular homeostasis and predict cardiovascular outcomes. We previously evaluated the association of CD34⁺ cells with cardiovascular disease (CVD) events over 23 months, but long-term CVD outcomes in relation to levels of CD34⁺ cells in patients on maintenance hemodialysis are unclear. Herein, we analyzed the long-term predictive potential levels of CD34⁺ cells for CVD outcomes and all-cause mortality.

Methods: Between March 2005 and May 2005, we enrolled 215 patients on maintenance hemodialysis at Nagoya Kyoritsu Hospital and followed them up to 12.8 years. According to the CD34⁺ cell counts, patients were classified into the lowest, medium, and highest tertiles. Levels of CD34⁺ cells were analyzed in association with four-point major adverse CV events (MACEs), CVD death, and all-cause mortality.

Results: The mean CD34⁺ cell count was 0.09 (range, 0.01 to 0.35 for all study patients). Patients in the lowest tertile were more likely to be older, have higher prevalence of cardiovascular disease, and to smoke than patients in the medium and highest tertiles. Age, smoking habit, lower geriatric nutrition risk index, lower calcium × phosphate product, and lower intact parathyroid hormone were significantly associated with the lowest tertile. Among 139 (64.7%) patients who died during a mean follow-up period of 8.0 years, 39 (28.1%) patients died from CVD. Patients in the lowest tertile had a significantly lower survival rate than those in the medium and highest tertiles (p ≤ 0.001). Using multivariable analyses, the lowest tertile was significantly associated with four-point MACEs (hazard ratio 1.80, p = 0.023) and CVD death (hazard ratio 2.50, p = 0.011).

Conclusions: our long-term observational study revealed that a low level of CD34⁺ cells in the circulation predicts CVD outcomes among patients on maintenance hemodialysis.

Funding: Private Foundation Support



FR-PO417

Oral Mucosal Lesions and Association with Mortality in Hemodialysis Patients: A Prospective Cohort Analysis (ORAL-D Substudy)

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Background: Impaired oral health is prevalent and frequently severe for adults treated with long term hemodialysis. We aimed to evaluate the prevalence of oral mucosal lesions and association with mortality outcomes among hemodialysis patients.

Methods: We did a planned analysis of ORAL-D. ORAL-D is a prospective multinational cohort study evaluating a standardized oral and dental examination among 4726 hemodialysis. Oral mucosal lesions included ulceration, red lesion, white lesion, geographical tongue, fissured tongue, candidiasis and herpes using WHO recommended methods. The association between mucosal lesions and all-cause and cardiovascular mortality was estimated using a Cox proportional hazard regression model adjusted for age, sex, education, smoking history, prior myocardial infarction, diabetes, hemoglobin, serum albumin, serum phosphorus, time on dialysis and body mass index. Analyses were clustered by country. The outcomes were prevalence and all-cause and cardiovascular mortality.

Results: 4205 adults (mean age 61.6 ± 15.6 years) had a complete oral examination. 40% had at least one oral lesion. The point prevalence of oral lesions was (in ascending order of frequency): oral herpes 0.5%, mucosal ulceration 1.7%, neoformation 2.0%, white lesion 3.5%, red lesion 4.0%, oral candidiasis 4.6%, geographical tongue 4.9%, petechial lesions 7.9%, and fissured tongue 10.7%. During median follow-up of 3.5 years, 2114 patients died (1013 from cardiovascular causes). Oral candidiasis was associated with all-cause mortality (adjusted hazard ratio (aHR) 1.37, 95% CI 1.00 to 1.86) and cardiovascular mortality (aHR 1.64, 95% CI 1.09 to 2.46). There was no association observed for any other oral mucosal lesion with mortality.

Conclusions: Oral mucosal lesions are prevalent in hemodialysis patients. Oral candidiasis appears to be a risk factor for death.

Funding: Veterans Affairs Support

FR-PO418

Oral Symptoms and Salivary Function and Association with Mortality in Hemodialysis Patients: A Prospective Cohort Analysis (ORAL-D Substudy)

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Background: Oral symptoms and impaired salivary function are frequently reported by adults treated with long term hemodialysis. We evaluated the association of oral symptoms and salivary function and with all-cause and cardiovascular mortality.

Methods: We did a planned sub-analysis in the ORAL-D study, a multinational cohort study involving a standardized oral and dental examination among 4726 hemodialysis patients. We assessed oral mucosal self-reported symptoms (thirst and xerostomia) and salivary characteristics (pH, buffer capacity, flow rate pre/post dialysis). The association with all-cause and cardiovascular mortality was estimated using a Cox proportional hazard regression model adjusted for country, age, sex, education, smoking history, prior myocardial infarction, diabetes, and time on dialysis.

Results: In 4205 adults (mean age 61.6±15.6 years), the mean salivary pH was 7.45 (SD 1.35), with more than 60% of patients (n=1621) with high salivary buffering capacity. The mean pre-dialysis salivary flow rate was 0.83 (SD 0.74) ml/min, and slightly decreased at the end of dialysis (0.76 ± 0.80 ml/min). During median follow-up of 3.5 years, salivary flow rate was associated with lower all-cause (adjusted hazard ratio (aHR) 0.85, 95% CI 0.76 to 0.95 for pre-dialysis flow rate and aHR 0.84, 95% CI 0.75 to 0.94 for post-dialysis flow rate) and cardiovascular mortality (HR 0.74, 95% CI 0.62 to 0.90 for pre-dialysis flow rate and HR 0.74, 95% CI 0.61 to 0.90 for post-dialysis flow rate). When considering the risk of mortality associated with Xerostomia Inventory items, requiring to sip a drink to swallow better was associated with all-cause and cardiovascular mortality (HR 1.26, 95% CI 1.07 to 1.48 and 1.30, 95% CI 1.02 to 1.66, respectively). Similarly, Thirst Inventory items were associated with all-cause mortality.

Conclusions: Oral symptoms are prevalent in haemodialysis patients. Salivary characteristics and related symptoms are associated with mortality.

FR-PO419

Development and Application of Sequential Enrichment Approach for ApoL1 Purification

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Background: Apolipoprotein L1 (ApoL1) is associated with either HDL3 or the Trypanolytic Factor (TLF) complex. The TLF complex also includes Haptoglobin-Related Protein (HRP) and Apolipoprotein A1 (ApoA1). Both human and transgenic mouse data suggest genotype is insufficient to cause renal disease. We hypothesized that circulating ApoL1 variants undergo PTM that promote renal disease progression or severity. To test address this hypothesis, a method for the selective enrichment of ApoL1 containing lipoprotein particles would be essential for ApoL1 characterization by mass spectrometry. Our objective here was to develop a affinity enrichment method that enabled selective TLF purification from patient plasma and serum samples.

Methods: Serum lipoproteins were isolated from healthy controls (HC) and from diabetic-/non-diabetic-African American (AA) dialysis patients using differential dextran-sulfate precipitation. TLF enrichment methods were based on known high affinity interaction of hemoglobin (Hb) with Hb-savaging receptors haptoglobin (Hp) and haptoglobin-related protein (Hpr). Ligands tested for TLF enrichment included Hb-agarose, hemin- (Hm-) agarose, and control agarose resins. Analysis of the enriched TLF was based on ApoL1, ApoA1, and Hpr immunoblot (IB) analysis or proteomic analyses.

Results: ApoA1, Hpr, and ApoL1 IB and proteomic studies demonstrate both Hb-agarose and Hm-agarose enrich ApoL1, ApoA1 and Hpr from serum HDL. IB data suggest enhanced enrichment of ApoL1, ApoA1 and Hpr using Hm-agarose beads compared to Hb-agarose beads. IB analysis of control, diabetic, and non-diabetic AA serum samples suggests specific enrichment of Hpr protein in AA TLF samples. Proteomic studies identified (1) a significant decrease of ApoL1 in Hm-bead TLF isolates of 2-fold for diabetic and 6-fold for non-diabetic AA dialysis patients as compared to healthy controls and (2) decreased phosphorylation of ApoL1 Ser-327 and Ser-S330 in dialysis patients samples.

Conclusions: An affinity-isolation method based on Hm-agarose was developed to enrich Hpr-containing lipoproteins from dilute solutions. This method may be parallelized into 96-well plates to enables higher throughput processing of patient samples. TLF ApoL1 abundance is decreased in non-diabetic AA ESRD patients versus diabetic AA ESRD patients versus healthy controls.

Funding: NIDDK Support

FR-PO420

Asymptomatic Cerebral Microbleeds in Hemodialysis Patients with a History of Stroke

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Background: T2*-weighted magnetic resonance imaging (MRI) is an extremely sensitive technique for detecting hemorrhagic lesions. It is especially superior for detection of previously asymptomatic cerebral microbleeds (CMBs), compared to other MRI methods. T2*-weighted MRI has increased the detection rate of CMBs, and as a consequence, the prevalence of CMBs has attracted attention in various patient populations. Clinically, CMBs are a risk factor for stroke, and especially intracerebral hemorrhage, and are also often detected after stroke, including in cases of intracerebral hemorrhage and ischemic cerebrovascular disease. They are also highly prevalent in hemodialysis (HD) patients. In this study, we examined CMBs in HD patients with a history of stroke.

Methods: A cross-sectional study of the prevalence of CMBs and related factors was performed in 309 HD patients (45 with and 264 without a history of stroke) who underwent T2*-weighted MRI at Osaka City University Hospital and affiliated hospitals from 2005 to 2017. The study protocol was conducted in accordance with the Principles of the Declaration of Helsinki and was approved by the ethics committee of Osaka City University Graduate School of Medicine (No. 1415). Informed consent was obtained from all subjects prior to their participation in the study.

Results: CMBs were detected in 103 patients (33.3%). The prevalence of CMBs was significantly higher in patients with a history of stroke compared to those without this history (57.8% vs. 29.2%, p<0.001). In multivariate analysis adjusted for background characteristics, a history of stroke was a significant independent factor related to CMBs (OR: 3.7, 95%CI: 1.7-8.8), as were age and hypertension. A history of intracerebral hemorrhage was more strongly associated with CMBs compared to cerebral infarction (OR: 29.3, 95%CI: 3.4-253.0 vs. OR: 2.1, 95%CI: 0.9-5.3).

Conclusions: Our results show a high prevalence of CMBs in HD patients with a history of stroke, and indicate that a history of stroke is significantly associated with CMBs in HD patients. In particular, a history of intracerebral hemorrhage has a strong association with CMBs.

FR-PO421

Outcome of Hemorrhagic Stroke in Patients on Hemodialysis

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Background: Patients on maintenance hemodialysis (MHD) on greater risk of hemorrhagic stroke or ischemic stroke. There is paucity of literature on outcome of hemorrhagic stroke (HS) in patients on MHD. Hypertension (HTN) and use of heparin during dialysis could be risk factors. We performed this study to identify risk factors associated with hemorrhagic stroke in patients on maintenance hemodialysis and outcome of such patients.

Methods: This study is a retrospective analysis of patients admitted with acute hemorrhagic stroke on MHD at our center. Study population comprised of 28 patients of hemorrhagic stroke with intracerebral hemorrhage. Study duration was from January 2008 to December 2018. All patients were on MHD for > 3 months. Hemorrhagic stroke was diagnosed with clinical examination and CT scan. Their demographic data, relevant investigations and clinical parameters were recorded. Student t test was used to compare data between survivors and non survivors.

Results: We had 28 patients (15 males and 13 females). Mean age of patients was 51.4± 16 .5 years. Comorbidities were Hypertension (100%), diabetes (12 of 28),CAD (9 of 28), hyperlipidemia (8of 28) and history of cerebrovascular accidents (5 of 28). Duration of HD was 27± 9.2 months. All patients had severe hypertension at presentation (BP > 200/110). Mean GCS at presentation was 9.8± 4.1. Site of intracerebral hemorrhage (ICH) was putamen (11 of 28), Thalamus (7 of 28), brain stem (4 of 28), massive (3 of 28) and others (3 of 28). Mortality was 68%(19 of 28). Mean time to death was 9.2± 5.2 days. Neurological deterioration was cause of mortality. GCS at presentation and serum albumin were factors influencing survival. GCS was 13.8± 3.7 in survivors and 4.7± 1.9 in non survivors. S. albumin was 3.8 ± .4 gm% in survivors and 2.7±.5 gm% in non survivors.

Conclusions: Patients of hemorrhagic stroke on hemodialysis had dismal outcome with mortality of 68% and survivors had better GCS and s. albumin at presentation.

FR-PO422

Intradialytic Hypoxemia In ESRD Patients on Hemodialysis

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Background: Mortality rates amongst end- stage renal disease (ESRD) patients on hemodialysis (HD) are high and death is most often due to cardiovascular disease. Based on previously published retrospective data, low oxygen levels during HD have been associated with all-cause hospitalization and mortality. We aimed to explore this association in our two university managed HD units.

Methods: We looked at HD patients with central venous catheters (CVC) and those with arterio-venous access (AVA). We measured oxygen levels using crit-line monitors (CLM) for 3-4 routine dialysis sessions. For those with CVC, we considered those with mean ScvO2 <63% to have intradialytic hypoxemia. Amongst patients with AVA, we identified those with prolonged intradialytic hypoxemia (PIH) as having SaO2 <90% for > 1/3 of the session. We then examined the differences in clinical characteristics between

these high-risk groups with hypoxemia and their control cohorts without desaturation. These characteristics include demographic, session- related, laboratory and CLM parameters.

Results: We enrolled 222 patients, of which 35 had CVC and 187 had AVA. Amongst those with CVC, 22 (62.8%) experienced mean ScvO2 <63% and they had an average 1.4 g/dl higher hemoglobin (95% confidence interval [CI], 0.3 to 2.5, P=0.014). However, they did not have any other significant differences from those with higher mean ScvO2. Amongst those with AVA, 5 (2.7%) experienced PIH and they tolerated 11.2% smaller change in blood volume per hour, (95% CI, 1.1 to 21.3, P= 0.030). No other statistically significant differences were observed. We did however note that amongst patients with either access type, those with intradialytic hypoxemia tended to have higher hospitalization rates in the preceding 6 months and had more C- curve profiles on CLM.

Conclusions: We did identify patients who experienced low oxygen levels during HD. However, the proportion of our AVA cohort with PIH was almost one quarter of that previously reported by Meyring-Wosten, 2016. Desaturation rates among those with CVC were similar to previously published studies. We intend to further determine if the use of supplemental oxygen during dialysis can correct the intradialytic hypoxemia. If this can be successfully accomplished, it may be worthwhile to conduct larger prospective studies to evaluate the impact of this intervention on patient outcomes.

FR-PO423

Feasibility of an Electronic Neurocognitive Battery for Assessing Cognitive Function in New-Start Hemodialysis Patients: A Pilot Study

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Background: Hemodialysis (HD) is the dominant form of renal replacement therapy used in Canada and around the world. It provides effective management of uremia, however, it is associated with significant morbidity and mortality. Cognitive abnormalities are almost universal in HD patients and appear early after treatment. Impaired cognition leads to functional decline and reduced quality of life. Despite the prevalence of cognitive impairment in HD patients, it is not well characterized or a major focus of care. The purpose of this study is to confirm feasibility of utilizing the well-validated, culturally-independent Cambridge Brain Sciences (CBS) battery in this population. Additionally, we aim to assess need for assisstance in completing these tests, refine the process and provide initial data on the performance of CBS assessment in this population to allow planning of a large-scale study.

Methods: We included patients from eight HD centres across the London Health Sciences Centre program. Adult patients (age > 18 years), with no pre-existing dementia or communication impairment, receiving HD treatment for more than 30 days and less than 12 months were included. Cognitive function was assessed using the CBS cognitive test series. This consists of 12 tests that assess a broad range of cognitive abilities. Individual patients cognitive scores were compared against age and sex matched normal values.

Results: Thirty patients completed a full set of testing and were included in our analysis. Across all measured domains, patients on HD scored significantly lower scores than their age and gender matched controls.

Conclusions: In hemodialysis patients, the CBS is a feasible tool that can be used in large-scale studies to identify domain-specific cognitive impairment. Preliminary results from this pilot study suggest significant cognitive impairment within the first year of hemodialysis.

Funding: Clinical Revenue Support

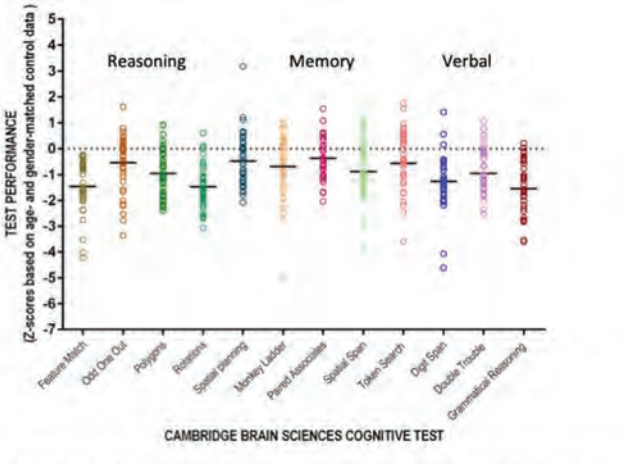

Figure 1: Patient performance on the 12-test CBS neurocognitive battery. Individual patient (circles) and cohort average (solid lines) test performance presented as z-scores compared to gender and age matched controls.

FR-PO424

Evaluation of Screening Tests for Severe Cognitive Impairment in Maintenance Hemodialysis Patients

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Background: Detailed neurocognitive testing shows that cognitive impairment is common among patients requiring maintenance hemodialysis. Identification of a well performing and easy to administer test for cognitive impairment could facilitate broader screening in dialysis units.

Methods: In 150 hemodialysis patients, we performed a comprehensive battery of neurocognitive tests (considered the "gold standard" for this study). Participants were classified as having normal cognitive function versus mild, moderate, or severe cognitive impairment by comparing scores in multiple cognitive domains to normative data. We examined the predictive screening ability of the Mini-Mental State Examination (MMSE), the Modified Mini-Mental State Examination (3MS), the Montreal Cognitive Assessment (MoCA), Mini-Cog, Clock Drawing test, Trails Making B (Trails B), and Digit Symbol Substitution tests to identify participants with severe cognitive impairment using area under the curve analysis.

Results: Mean age was 64 years; 61% were men, 39% were black and 94% had at least a high school education. Of the 150 participants, 21% had normal cognitive function, 17% mild cognitive impairment, 33% moderate impairment, and 29% severe impairment. The MoCA had the best predictive ability for severe cognitive impairment (AUC = 0.81 [0.73, 0.89]). A score on the MoCA of less than 21, which maximized the sum of sensitivity and specificity, displayed a sensitivity of 86% and specificity of 55% for severe impairment. The Trails B and Digit Symbol tests also performed reasonably well with AUC of 0.73 [0.59, 0.87] and 0.78 [0.68, 0.88], respectively. The MMSE, 3MS, Mini-Cog, and Clock Drawing tests had the lowest predictive performance.

Conclusions: Nearly one third of participants had severe cognitive impairment. The MoCA, a widely available, brief assessment that requires relatively simple training to administer, showed high sensitivity and moderate specificity in detecting severe cognitive impairment in prevalent hemodialysis patients.

Funding: NIDDK Support, Private Foundation Support

Table. Performance of Screening Tests in Predicting Severe Cognitive Impairment

Screening test	Cognitive Battery (Gold standard)	N	n	AUC	95% CI
Montreal Cognitive Assessment	Complete Battery	148	43	0.81	(0.73, 0.89)
Digit Symbol Substitution	Battery minus Digit Symbol	144	36	0.78	(0.68, 0.88)
Trail Making Part B	Battery minus Trails B	141	19	0.73	(0.59, 0.87)
Mini-Cog	Complete Battery	148	43	0.73	(0.65, 0.81)
Modified Mini Mental State Examination	Complete Battery	148	44	0.72	(0.61, 0.82)
Mini Mental State Examination	Complete Battery	148	44	0.69	(0.58, 0.80)

Complete battery = Wechsler Memory Scale-III (WMS-III) Word List Learning Subtest,[8] the Wechsler Adult Intelligence Scale-III (WAIS-III) Block Design[9] and Digit Symbol-Coding Subtests,[9] Digit Span (forwards and backwards),[9] the Mental Alternation Test,[10] and the Controlled Oral Word Association Test (COWAT)[11] and the Trail Making Tests A and B (Trails A and B).[12]
N = total number of participants with sufficient data
n = number of participants with severe impairment
AUC = Area under the curve

FR-PO425

Cognitive Impairment and Mortality in Maintenance Hemodialysis (HD) Patients: A Longitudinal Study

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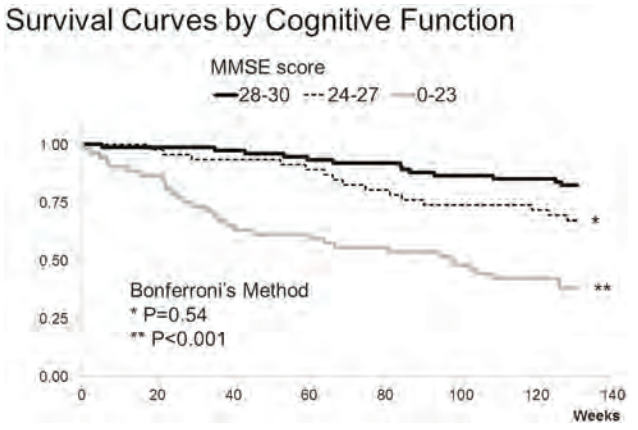
Background: We examined the transition of the Mini-Mental State Examination (MMSE) results and the mortality rate of maintenance HD patients in our hospital over a 130-week period, in order to compare the cognitive functions and mortality.

Methods: Using the longitudinal cohort of 181 HD patients aged ≥65, we examined the MMSE in March 2016, and a follow-up MMSE was conducted on 112 surviving patients in September 2018. We also tracked the serological data during this period. MMSE score of 28 to 30 was classified as the normal group, 24 to 27 as mild cognitive impairment (MCI) group, and less than 23 as dementia group.

Results: In 2016, 76 patients were within the normal group(41.9%, mean age 72.1), 48 were within the MCI group(26.5%, mean age 77.9), and 57 were within the dementia group(31.5%, mean age 80.2). As shown in figure 1 below, compared to the normal group, mortality rate decreased significantly as the severity of dementia further deteriorated. There was no significant difference in the nutritional status index such as albumin or Cholinesterase among these groups. The pneumonia-associated death in patients with dementia was twice as high as among those without dementia or MCI (64% vs 36%, 39%; $p < 0.05$).

Conclusions: This longitudinal study indicated that the presence of dementia is an independent predictor of mortality in patients on HD.

Funding: Private Foundation Support



FR-PO426

Hemodialysis Can Contribute to Acute Changes in Cerebral Volume and White Matter Structure

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Background: Cerebral atrophy, silent cerebral infarcts, and leukoaraiosis are common brain injuries in chronic kidney disease (CKD) patients undergoing hemodialysis (HD), but their etiology is poorly understood. To elucidate the acute effects of HD on the brain, we used a novel system designed in-house to perform magnetic resonance (MR) imaging during HD. Diffusion tensor imaging (DTI) is an MR modality used to characterize white matter (WM) structure. Mean diffusivity (MD) is a DTI metric associated with cellularity and edema in WM. We predict that HD will induce a transient increase in MD and cerebral volume volume, potentially due to osmotic stress and edema.

Methods: 12 CKD patients receiving hemodialysis ≥3 times/week underwent diffusion and T1 weighted MR scans (Siemens 3T Biograph mMR) prior to and in the last 60 minutes of HD. The MR data were processed to correct for noise, motion, and artifacts prior to tensor fitting. Spatially normalized scalar maps were compared pairwise using tract-based spatial statistics (TBSS) and a general linear model with threshold-free contrast enhancement. Cerebrospinal fluid (CSF), WM, and gray matter (GM) volumes were extracted from T1 maps in CAT12 and compared before and during HD by Wilcoxon paired t-tests (α=0.05).

Results: During dialysis, MD was elevated (p<0.05) in regions of the superior corona radiata (fig. A) and peripheral WM near the cingulate gyrus (fig. B). CSF volume decreased by an average of 50.2 ± 12.2 ml (p<0.05) while the GM volume increased by an average of 28 ± 11.1 ml (p<0.05), as shown in figure C.

Conclusions: Increased MD in conjunction with increased brain volume suggests cerebral edema, potentially caused by osmotic stresses associated with HD. Further investigations are ongoing to determine if edema contributes to the brain injury and cognitive impairment observed in HD patients.

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

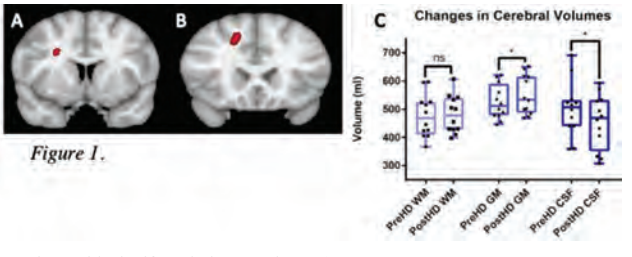

Figure 1.

The regions with significantly increased MD (p<0.05) during HD are shown in red in A and B. C gives the volumes of WM, GM, and CSF before and during HD.

FR-PO427

Depression Screening Is Associated with Lower Mortality and Hospitalization Among Adults Initiating Chronic Hemodialysis

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Background: Transitioning to chronic hemodialysis (HD) continues to be a vulnerable period for adults with end-stage renal disease (ESRD). Depression commonly develops among these patients and negatively impacts quality of life, treatment adherence, hospitalization, and mortality. Depression screening may be an important tool in identifying depression and improving outcomes. Among a large national cohort of Veterans, we examined whether depression screening in the year prior to chronic HD transition led to lower mortality and hospitalization in the first year of HD.

Methods: Using data from the USRDS Transition of Care in CKD study, an observational study that focuses on Veterans who transitioned to chronic dialysis between 2007 to 2015, we identified adults with an outpatient nephrology, geriatric or primary care visit in the year prior to transition to HD. Pre-ESRD depression screening was defined as completion of a Patient Health Questionnaire-2 (PHQ-2) in the 12 months prior to transition. The main outcomes were all-cause mortality and hospitalization in the 12 months post transition. Associations were examined with Cox proportional hazards models (mortality) and Poisson regression models (hospitalization). Hierarchal adjustment models were used to account for sociodemographics, comorbidity and laboratory values, pre-ESRD care intensity, and post-ESRD dialysis characteristics.

Results: After excluding adults with a diagnosis/treatment of depression, bipolar disease, or dementia prior to the index outpatient visit, the final analytic cohort consisted of 30,013 Veterans who transitioned to HD. Sixty-one percent of patients had PHQ-2 screening during the 12 months prior to HD transition. During the 12 months post-transition, the crude all-cause mortality rate was 32/100 person-year for those screened and 35/100 person-year for those not screened, while the median (IQR) hospitalizations were 2 (2,2) per year for both groups. In fully adjusted models, PHQ-2 screening was associated with a significantly lower risk of mortality (HR 0.94, 95% CI: 0.90-0.98) and hospitalization (IRR 0.97, 95% CI: 0.95-0.99).

Conclusions: Screening for depression among adults with ESRD in the year prior to transition to chronic hemodialysis was associated with improved outcomes after dialysis initiation.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO428

An Analysis of Delirium in Elderly Patients with ESRD During Hospitalization for Starting Maintenance Hemodialysis

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Background: Delirium is an acute and usually reversible disturbance in mental abilities that causes confused thinking and emotional disruption. It has recently been reported that delirium is an independent predictor of death in patients undergoing maintenance dialysis for end-stage renal disease (ESRD). Although it is well known that delirium occurs much more easily in the elderly, it remains unproved whether the occurrence of delirium during hospitalization for starting dialysis is associated with early mortality after the start of dialysis in elderly populations.

Methods: We conducted a retrospective cohort study to investigate the association between delirium and early mortality after starting dialysis in the elderly. The cohort consisted of patients aged 75 years old or older who started hemodialysis for ESRD at the National Center for Global Health and Medicine from 2010 to 2017 and at Yokosuka Kyosai Hospital from 2007 to 2011. Delirium was defined as patients who, during hospitalization for starting dialysis, newly showed confused thinking and reduced awareness of their environment and were prescribed anti-psychotic medications. The primary outcome was death within a year of the start of dialysis. Data were analyzed using Cox proportional hazard models with adjustments for baseline characteristics. To assess underlying characteristics of the patients with delirium, we identified the determinants using a multinomial logistic regression.

Results: We enrolled 264 patients (males, 59%); 34 patients were diagnosed with delirium. The primary outcome was observed in 19 patients with delirium (55%) and 26 patients without delirium (11%) (p < 0.01). In a Cox proportional hazards model, delirium was independently associated with a higher risk of all-cause mortality within a year of the start of dialysis (hazard ratio 6.96, 95% confidence interval 3.84-12.63; adjusted hazard ratio 5.78, 95% confidence interval 2.93-11.41). In a multinomial logistic regression, delirium was positively correlated with “cognitive impairment” and “the use of steroid” and inversely correlated with “the presence of arteriovenous fistula”.

Conclusions: Delirium predicts early mortality after starting dialysis in the elderly.

FR-PO429

Patient Treatment Adherence in the ASCEND Trial for Depression in Patients Undergoing Maintenance Hemodialysis

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Background: The multi-center clinical trial, ASCEND, demonstrated a modestly larger effect of 12-week treatment with sertraline (SER) on depression scores, compared with cognitive behavioral therapy (CBT).

Methods: We undertook a *post-hoc* analysis to characterize patient adherence to these treatments and to examine the association of patient treatment adherence with depression scores at the end of the intervention.

Results: The average age of participants (n=120) was 51 ± 13 years, 57% were male, and 43% were white. Among those randomized to CBT, 82% completed at least 7 of the 10 sessions, 72% were rated by the therapist as engaged in at least 7 CBT sessions and 47% of the participants attempted/completed CBT homework > 50% of the time. SER dose titration was done algorithmically; 73% of participants randomized to drug, took their prescribed dose for at least 8 weeks. Depression was assessed by the Quick Inventory of Depression Scores, Clinician Rated (QIDS-C) at 12 weeks. There was a weak negative association between number of CBT sessions attended and QIDS-C score (R=-0.19) and number of days SER was taken and QIDS-C score (R=-0.27). We examined the association of baseline parameters (demographics, depression diagnosis, severity, and history, participation in a pre-enrollment motivational interviewing session, and initial treatment preference) with treatment adherence separately for CBT and SER. The only significant predictor for CBT adherence was a history of depression; participants with no history of depression attended on average 1.8 more sessions and were 26% more likely to attend a session (p=.02) than participants with a history of depression. There was no relationship between baseline parameters and SER use.

Conclusions: High levels of treatment adherence for depression, with both CBT and SER, can be achieved in patients on maintenance hemodialysis. Baseline characteristics are generally poor predictors of future adherence to treatment. The identification of patient and treatment level factors that promote adherence to treatments for depression are needed.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO430

Retrospective Analysis of Serum Albumin and Other Biomarkers in Chronic Hemodialysis Patients Dialyzed with the Optiflux F180NR Dialyzer

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Background: Optiflux® dialyzers are commonly used in US ESRD patients. Considering that low serum albumin (sALB) levels are associated with increased risk of mortality, albumin loss during hemodialysis (HD) should be minimized, especially in patients (pts) with hypoalbuminemia. A retrospective analysis was conducted to assess changes in sALB and other biomarkers in pts dialyzed with the Optiflux F180NR (OPTI).

Methods: In-center HD pts (n=284) treated with OPTI dialyzers for 6 months were analyzed. Pts maintained the same vascular access type and were without a diagnosis of liver disease or cancer. Changes in pre-dialysis (Pre-HD) labs at month 1 (M1) and month 6 (M6) were compared using paired t-tests. A sub-analysis of pts with hypoalbuminemia (sALB ≤3.5 mg/dL) was conducted.

Results: After 6-months of HD treatments, significant increases in mean sALB (0.07 g/dL), nPCR (0.05), and hemoglobin (0.42 g/dL) were observed with increased mean ultrafiltration volume (UFV) and adequacy (Table). A sub-analysis of 47 pts with hypoalbuminemia at M1 showed increases in sALB (0.36 g/dL) at M6 for 44 pts. Three pts had concomitant decreases in sALB (0.4 g/dL) and nPCR (0.44) during the same period.

Conclusions: During a 6-month follow-up, HD patients dialyzed with Optiflux F180NR dialyzers showed increased levels of serum albumin, nPCR, hemoglobin, ultrafiltration volume, and Kt/V.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	Month 1 (M1) Mean	Month 6 (M6) Mean	Difference	p-value*
Pre-HD sAlb, in g/dL	3.84	3.91	0.07	< 0.0001
Normalized protein catabolic rate (nPCR), in g/kg/day	1.01	1.06	0.05	0.002
Pre-HD Hemoglobin (Hgb), in g/dL	10.66	11.08	0.42	< 0.0001
Ultrafiltration volume (UFV) in L	2.57	2.67	0.10	0.03
spKt/V	1.64	1.68	0.04	0.01

* from paired t-test

FR-PO431

Low Proteinuria Is Associated with Increased Mortality in Incident Dialysis Patients: Results from the CRIC Study

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Background: In multiple studies, increased levels of proteinuria are associated with worse outcomes. However, in individuals with glomerular filtration rate <30 ml/min, some studies have reported a J-shaped association of proteinuria with mortality. However, this association has not been examined in incident dialysis patients.

Methods: Among 725 incident dialysis participants in the CRIC Study (mean age 60.1 [SD 11.4] years, 32.4% White, 54.2% Black, 59.0% men), we evaluated the association of pre-dialysis urinary protein-to-creatinine ratio (PCR) within two years of dialysis initiation (<0.5, 0.5- 0.9, 1.0- 3.4, ≥3.5 [g/g]) with mortality (333 deaths during the median follow-up of 3.5 years) using Cox models adjusting for potential confounders (e.g. blood pressure, serum albumin, history of cardiovascular disease including heart failure).

Results: Participants with the lowest PCR level, <0.5 g/g, were likely to be older and had lower blood pressure compared to those with higher proteinuria. We observed a J-shaped association with the highest mortality risk in the lowest PCR category (<0.5 [g/g]) (crude hazard ratio 2.69 [95%CI 1.79-4.04] vs. PCR of 0.5- <0.9) followed by the highest PCR category (1.46 [1.01-2.10]) (Table). The excess risk in persons with the lowest PCR level was attenuated but still statistically significant after accounting for potential confounders.

Conclusions: Among incident dialysis patients, there was a J-shaped association between pre-dialysis proteinuria and elevated risk of mortality, with the highest risk in the lowest PCR category. While the reasons for this association are uncertain, our findings suggest that healthcare providers should be aware that low protein excretion, not just high protein excretion, is a marker for an increased risk of mortality in patients who start dialysis.

Funding: Private Foundation Support

Table. Hazard ratios (95% CI) of all-cause mortality according to PCR (g/g) levels

	<0.5 (n=88)	0.5- 0.9 (n=90)	1.0- 3.4 (n=266)	≥3.5 (n=281)
All-cause mortality (333 deaths)	62 deaths	30 deaths	104 deaths	137 deaths
Model 1	2.69 (1.79-4.04) **	ref	1.13 (0.78-1.65)	1.46 (1.01-2.10) *
Model 2	2.62 (1.74-3.95) **	ref	1.20 (0.82-1.74)	1.58 (1.10-2.28) *
Model 3	2.48 (1.64-3.75) **	ref	1.21 (0.83-1.76)	1.49 (1.03-2.16) *
Model 4	1.78 (1.08-2.93) *	ref	1.14 (0.72-1.80)	1.23 (0.75-2.02)

Model 1 was unadjusted
Model 2 adjusted for age and gender
Model 3 additionally adjusted for a clinical history of diabetes mellitus, CVD history, heart failure, stroke
Model 4 further adjusted for systolic blood pressure, total cholesterol, eGFR, serum albumin, hemoglobin, white blood cell, diuretics, and angiotensin-converting-enzyme inhibitor/angiotensin receptor blockers.

FR-PO432

Elevated $PM_{2.5}$ Increases Daily Hospital Admission and Readmission Risk in Chronic Hemodialysis Patients

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Background: Fine particulate matter (diameter < 2.5 um, $PM_{2.5}$) increases the risk of hospitalization through acute exacerbations of underlying conditions. We examine the role of $PM_{2.5}$ on all-cause and cause-specific admissions and readmissions among hemodialysis patients, a population with elevated hospital and 30-day readmission rates.

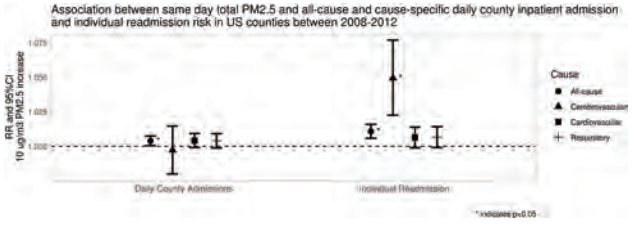
Methods: Health data from the United States Renal Data System included individual-level inpatient hospitalizations and events classified as rehospitalizations between 2008 and 2012 in 552 US counties. Admission rates were calculated for 1,799,928 inpatient hospitalizations. We evaluated immediate (same day) and delayed effects of a 10$\mu g/m^3$ increase in $PM_{2.5}$ on all-cause and cause-specific (cardiovascular, respiratory, and cerebrovascular) health associations. Daily county admission risk was measured with admission counts and expressed as a risk ratio (RR) using Conditional Poisson models stratified by county-day. This time stratified case crossover approach adjusted for changes in population size and risk characteristics by design, where each population served as its own control. Patient readmission risk was expressed as a RR and evaluated using Cox proportional hazard models with time-dependent environmental covariates controlling for meteorology, patient-specific, and event-specific variables.

Results: Same day elevated $PM_{2.5}$ was associated with a 0.4% (95%CI: 0.05-0.7%) increase in the RR of all-cause daily county admissions and even greater risk for increased 30-day readmission. Daily RRs associated with same day $PM_{2.5}$ were increased by 1.1% (0.6-1.6%) for all-cause and 4.9% (2.3-7.7%) for cerebrovascular readmissions. At delayed

exposure times cardiovascular and respiratory readmission risks were also observed but are not shown due to space constraints.

Conclusions: Our results show increased risk of hospital admission and 30-day readmission associated with elevated $PM_{2.5}$ for patients receiving chronic hemodialysis. These findings suggest that daily ambient air quality may impact morbidity and healthcare costs for patients with End Stage Renal Disease. This abstract does not reflect EPA policy.

Funding: Other U.S. Government Support, Clinical Revenue Support



FR-PO433

The Predictive Role of Serum MRP8/14 (S100A8/A9) on Mortality in Hemodialysis Patients

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Background: The inflammatory mediator myeloid-related protein 8 (MRP8: S100A8), which forms a heterodimeric complex with a binding partner MRP14 in the bloodstream, plays important roles as an endogenous ligand in various diseases. Serum MRP8/14 reportedly became a potential biomarker in patients with acute coronary syndrome and ANCA-associated vasculitis. The aim of this study was to investigate the predictive role of serum MRP8/14 levels on all-cause mortality in hemodialysis patients.

Methods: We conducted a multicenter, observational cohort study of 388 Japanese subjects undergoing maintenance hemodialysis in Kumamoto, Japan. Serum MRP8/14 levels were measured using an ELISA. The potential associations between serum MRP8/14 levels and clinical variables were examined in a cross-sectional study. Multivariable Cox regression was used to estimate the association between serum MRP8/14 levels and mortality, adjusting for possible confounding variables including age, sex, diabetes and others. Median follow-up was 6.6 years.

Results: The mean age of the subjects was 65.3 years, 36.9% were female, and the median vintage was 5.8 years. The median MRP8/14 level was 6108 ng/ml [normal range in healthy subjects: 500–3500] at baseline. Serum MRP8/14 levels positively correlated with white blood cells (ρ=0.54, P<0.0001) and high-sensitivity C reactive protein (hs-CRP) values (ρ=0.34, P<0.0001). We classified MRP8/14 and hs-CRP into tertile, and estimated the hazard ratios (HR) for all-cause mortality in comparison with the lowest tertile. As for hs-CRP, the middle tertile (HR, 1.90; 95%CI, 1.04–3.61) and the highest tertile (2.87; 1.54–5.54) were each significantly associated with all-cause mortality in the low-phosphate group (cut-off, 6.0 mg/dl), after adjustment for relevant confounding factors. In contrast, elevated MRP8/14 levels were evidently associated with all-cause mortality in the middle tertile (12.3; 1.64–271.6) and in the highest tertile (26.8; 3.49–610.4) in the high-phosphate group, but not in the low-phosphate group.

Conclusions: High serum MRP8/14 levels should give a potential predictive marker on mortality in hemodialysis patients with high-phosphate levels, which characteristic differs significantly from that of a conventional inflammatory marker, hs-CRP.

FR-PO434

Trimethylamine N-Oxide and Cardiovascular Outcomes in Hemodialysis Patients

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Background: Trimethylamine-N-Oxide (TMAO) has a definite role in promoting atherosclerosis, which is an independent risk factor of cardiovascular disease. Cardiovascular disease is the leading cause of death in hemodialysis patients. The plasma level of TMAO in hemodialysis patients increases significantly, which is more than 20 times over the non-dialysis patients, but the relationship between TMAO and the cardiovascular outcomes in hemodialysis patients has not been well defined.

Methods: A prospective cohort study design was adopted. 252 patients who were eligible for the inclusion criteria were enrolled, and baseline clinical data were collected. Then these patients were followed for 9 years, the primary endpoints were all-cause and cardiovascular death, and the secondary endpoints were cerebrovascular death. The plasma TMAO concentration was determined, the Kaplan-Meier method and Cox proportional risk model were used to analyze the relationship between TMAO concentration and cardiovascular mortality and all-cause mortality.

Results: Median follow-up was 73.4 (42.9-108) months. During the follow-up, there were 123 cases of death totally, among them 39 cases of cardiovascular death, 19 cases of cerebrovascular death, 65 cases of other causes death. 20 cases transferred to other dialysis centers, and 15 cases received kidney transplantation. The median plasma TMAO concentration was 63.1μmol/L. Based on the median concentration of TMAO, the patients were categorized as High TMAO group (TMAO > 63.1μmol/L) and Low TMAO group (TMAO ≤ 63.1μmol/L). Kaplan-Meier analysis found that the incidences of all-cause death (Log-Rank P < 0.001) and cardiovascular death (Log-Rank P = 0.006) in High TMAO group were significantly higher than those of Low TMAO group. Multivariate Cox regression demonstrated that plasma TMAO was significantly associated with all-cause death (TMAO as continuous variable : HR 1.123, 95%CI(1.067-1.183), P < 0.001; TMAO as dichotomous variable : HR 2.147, 95%CI(2.149-3.117), P < 0.001) and cardiovascular death (TMAO as continuous varible : HR 1.126, 95%CI(1.027-1.235), P = 0.011; TMAO as dichotomous variable: HR 2.517, 95%CI(1.275-4.969), P = 0.008). After adjustment of conventional and non-conventional risk factors, the relationship of plasma TMAO and all-cause and cardiovascular death remained significant.

Conclusions: Plasma TMAO is an independent risk factor of cardiovascular outcomes in hemodialysis patients.

Funding: Government Support - Non-U.S.

FR-PO435

Circulating PCSK9 Level Predicts Risk of Cardiovascular Events and Death in Hemodialysis Patients

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Background: The proprotein convertase subtilisin/kexin type 9 (PCSK9) is a promising new target for prevention of cardiovascular event (CVE). However, the clinical significance of circulating PCSK9 is unclear in HD patients

Methods: A total of 353 patients were prospectively enrolled from June 2016 to May 2018 in K-cohort study groups. Serum PCSK9 level was measured at the time of study enrollment. Serum levels of high-sensitivity C-reactive peptide (hsCRP), monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6, osteoprotegerin and receptor activator of nuclear factor kappa-B ligand (RANKL) were also measured. The primary endpoint was defined as composite of CVE and death from any cause.

Results: Serum PCSK9 level was positively correlated with total cholesterol level, but not with inflammatory (hsCPR, MCP-1 and IL-6) and calcification-related markers (osteoprotegerin and RANKL). Multivariate linear regression analysis revealed that statin treatment, serum albumin and total cholesterol levels at baseline were independent determinants of circulating PCSK9 levels. In multivariate Cox-regression analysis, PCSK9 tertile 3 was associated with 1.99-fold risks for composite event (95% confidence interval [CI], 1.08-3.66), and it was independently associated with 2.26-fold risks for CVE (95% CI, 1.11-4.62). PCSK9 tertile 3 also provides additional prognostic significance to predict composite event in subgroups with higher level of hsCRP and LDL, and no statin treatment.

Conclusions: Circulating PCSK9 level independently predicts CVE and death in HD patients, and these results anticipate future studies for the effect of PCSK9 inhibition in HD patients.

FR-PO436

Sex-Specific Association Between Serum Uric Acid and Cause-Specific Mortality in Maintenance Hemodialysis Patients: A Multicenter Prospective Cohort Study

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Background: Studies have shown inconsistent results about the association between serum uric acid (SUA) and mortality in maintenance hemodialysis (MHD) patients. Moreover, no studies have explored the possibilities of the relationship between SUA and non-cardiovascular (CVD) mortality.

Methods: We conducted a multicenter prospective cohort study among 1039 MHD patients. The blood samples of all participants were obtained prior to the hemodialysis session at baseline. Multivariable adjusted Cox proportional hazards models were used to estimate the HRs and 95%CIs for the risk of all-cause mortality, CVD mortality and non-CVD mortality associated with SUA.

Results: Over a median follow-up of 28 months, 230 deaths were recorded, of which 140 (60.9) were due to cardiovascular disease. overall, a U-shaped relationship was found between SUA and all-cause mortality. Moreover, the patients in the lowest SUA showed a higher risk of CVD mortality (HR: 1.57, 95%CI: 1.03-2.40), whereas no significant association was found with non-CVD mortality. By contrast, the patients in the highest SUA group showed a higher risk of non-CVD mortality (HR:1.82, 95%CI: 1.04-3.17) and no significant association was found with CVD mortality. The association between SUA and all-cause mortality were consistent across different subgroups.

Conclusions: There was a U-shaped relationship between SUA and all-cause mortality. Furthermore, lower SUA had an increased risk of CVD mortality and higher SUA had a higher risk of non-CVD mortality. Whether SUA reduction therapy is beneficial to the MHD patients should be the subject of the future research work.

The association between sex-specific serum uric acid levels and mortality

SUA, mg/dl	No. events(%)	Adjusted HR(95%CI)	P
All-cause mortality			
Tertile 1	100 (28.9%)	1.45 (1.04, 2.03)	0.029
Tertile 2	61 (17.6%)	1.0(Ref)	--
Tertile 3	69 (19.9%)	1.46 (1.02, 2.11)	0.040
CVD mortality			
Tertile 1	68 (19.7%)	1.57 (1.03, 2.40)	0.035
Tertile 2	37 (10.7%)	1.0(Ref)	--
Tertile 3	35 (10.1%)	1.24 (0.76, 2.01)	0.384
Non-CVD mortality			
Tertile 1	32 (9.2%)	1.22 (0.71, 2.13)	0.476
Tertile 2	24 (6.9%)	1.0(Ref)	--
Tertile 3	34 (9.8%)	1.82 (1.04, 3.17)	0.036

FR-PO437

Erectile Dysfunction Is Associated with increased Coronary Artery Calcification But Not Mortality in Incident Dialysis Patients

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Background: Erectile dysfunction (ED) is prevalent among the hemodialysis population. Increasing age, diabetes and nonuse of ACE inhibitors has been associated with a higher incidence of ED in our previous work. ED predicts mortality in the general population likely through its association with CVD risk factors.

Methods: Objective: To determine the relationship between ED, coronary artery calcification and mortality in incident dialysis patients without prior coronary events using the Dialysis, Heart and Bone Study. **Methods:** Sixty-three male participants were enrolled in this prospective study and completed the fifteen-item validated questionnaire, the IIEF-15 as well as MSCT to measure coronary artery calcification. Subjects having a score 25 or less in the self-administered questionnaire were considered to have ED. Detailed information regarding demographics, medical history, and medication usage was obtained by self-report.

Results: The mean age of participants was 49.2 (13.1) years and two-thirds were AA. Forty-four percent of participants had severe ED, 23.8% had moderate ED, 15.8% had mild ED and 15.8% had no ED. The median (IQR) Agatston score was 56.8(0.5-406.5) for those with ED and 0(0-0) for those without ED [p=0.007]. Twenty-three percent of the participants died during an average follow-up of 5 (1.5) years. Twenty-one percent of the participants with ED died compared to ten percent of people without ED (p=0.4). Using a proportional hazard model with covariate adjustment by propensity score, ED was not significantly associated with mortality (p=0.64)

Conclusions: ED is common in new to dialysis patients. ED was significantly associated with increased CAC score. However, it was not associated with increased mortality in incident dialysis patients.

FR-PO438

Relationship Between Serum Uric Acid and Vascular Calcification in Patients Treated with Hemodialysis

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Background: Vascular calcification (VC) is highly prevalent among hemodialysis (HD) patients and predicts cardiovascular mortality. The level of serum uric acid (SUA) may be related with endothelial dysfunction, which may involve in VC. However, whether uric acid concentrations are associated with VC in HD patients is unknown. The aim of our study was to assess the association of SUA and VC in HD patients.

Methods: This was a cross-sectional study including 313 patients receiving HD therapy for at least 3 months between January 2014 and December 2018. The simple vascular calcification score (SVCS) in plain X-rays of the pelvis and hands was used to evaluate VCs.

Results: Mean age was 57.1±14.0 (SD) years, and 32.2% had diabetes. Mean uric acid level was 476.06±111.68 umol/L, 73.8% had hyperuricemia. The SVCS detected VC in 179 (57.1%) patients, including 160 patients presenting VC of pelvis arteries and 95 patients presenting VC of hands arteries. In total of patients, a SVCS≥ 3 was present in 104 (33.2%) patients. By binary logistic regression, age (P<0.001), HD duration (P<0.001), diabetes (P<0.001) were independently associated with a SVSC≥ 3, the levels of SUA was not associated with a SVSC≥ 3. Adjusted logistic regression models showed that the ORs per 1umol/L higher uric acid level for VC of pelvis arteries was 0.996 (95% CI, 0.994-0.999; P=0.015) in total patients and 0.995 (95% CI, 0.991-0.999; P=0.010) in non-diabetic HD patients. However, there was no association between SUA and VC of hands arteries.

Conclusions: Higher uric acid levels were associated with lower risk of VC of pelvis arteries in patients treated with HD.

FR-PO439

Atheromas and Peripheral Vessel Physiology in Relation to Culinary Habits in ESRD: Diversion Between Peritoneal Dialysis and Hemodialysis Population by Adopting the Mediterranean Diet Regime

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Background: End stage renal disease (ESRD) relates to atheroma formation and typically amplifies cardiovascular risk. Patients on hemodialysis (HD) impose strict dietary restrictions. On the contrary, patients on peritoneal dialysis (PD) may consume a wide variety of alimentary goods.

Methods: 92 male ESRD patients, 52 of them on HD and the rest 40 on PD without apparent cardiovascular disease were matched to enroll the study. The 2 groups did not differ statistically in age, (64,9 ± 15.2 vs 64 ± 11.4) prevalence of hypertension, diabetes mellitus, smoking and lipid profile. All underwent common carotid ultrasound examination for detecting plaque formation and intima –media thickness (IMT) evaluation as indices of subclinical atheromatosis. Peripheral vessel rheology was assessed by the SHIM-5 score that grades erectile potency. A lower score indicates severe erectile dysfunction unmasking thus endothelial dysfunction. Dietary habits were evaluated through a special diet score (Med-Diet score, range 0-55), which assesses adherence to the Mediterranean diet. Lower values indicate poor adherence to this alimentary pattern.

Results: Patients on HD had statistically higher IMT (1.5 ± 0.7 vs 0.85 ± 0.2), lower SHIM-5 score grading (8.8 ± 6.9 vs 12.8 ±4.5) and lower Med-Diet score(22 ± 4 vs 29 ±3) as compared to PD patients (all P<0.05). Carotid IMT and carotid plaque formation were inversely associated (r=-0.32, P<0.01) and SHIM-5 was positively correlated (r=0.29, P<0.01) to the Med-diet score. The associations remained significant in linear regression analysis after adjustment for age, body mass index, presence of hypertension, diabetes mellitus, tobacco use and statin therapy (all P<0.01).

Conclusions: ESRD male patients on peritoneal dialysis may exhibit lower atheromatic load and enhance peripheral vessel rheology by adopting the Med-diet regime. Healthy dietary choices may improve quality of life and cardiovascular outcome in this specific ESRD population.

FR-PO440

Association of Serum Indoxyl Sulfate Level with Peripheral Artery Occlusive Disease in Patients with Hemodialysis

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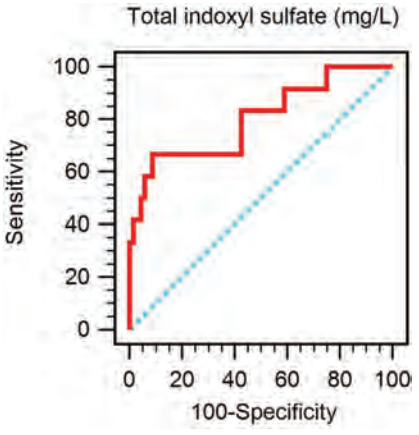
Background: Indoxyl sulfate (IS) can be considered as a cardiovascular toxin and a nephrotoxin that has been associated with intima media thickness, vascular disease, coronary artery disease, progression of kidney disease and increased mortality. Peripheral arterial occlusive disease (PAOD) is associated with an increased risk of death in hemodialysis (HD) patients. The aim of this study was to evaluate the relationship between IS level and PAOD by ankle-brachial index (ABI) in HD patients.

Methods: Blood samples were obtained from 80 chronic HD patients. Serum total IS level was performed with high-performance liquid chromatography and mass spectrometry. ABI values were measured using the automated oscillometric method (VaSera VS-1000). ABI values that were < 0.9 were included in the low ABI group.

Results: Among the 80 HD patients, 12 of them (15.0%) were in the low ABI group. Compared with patients in the normal ABI group, the patients in the low ABI group had higher prevalence of diabetes (P = 0.010), higher serum C-reactive protein (P < 0.001), and IS (P < 0.001) levels, while lower had statin used (P = 0.042). In addition, the multivariable logistic regression analysis showed that serum IS (Odds ratio [OR]: 1.115, 95% confidence interval [CI]: 1.015-1.225, P = 0.023) and CRP levels (each increase 0.1 mg/dL, OR: 1.187, 95% CI: 1.046-1.346, P = 0.008) were the independently associated with PAOD in HD patients. The area under the receiver-operating characteristic (ROC) curve predicting PAOD by serum IS level in HD patients was 0.800 (95% CI: 0.696-0.881, P = 0.0002).

Conclusions: In this study, serum total IS level was found to be associated with PAOD in HD patients.



FR-PO441

Tumoral Calcinosis in Hemodialysis Patient

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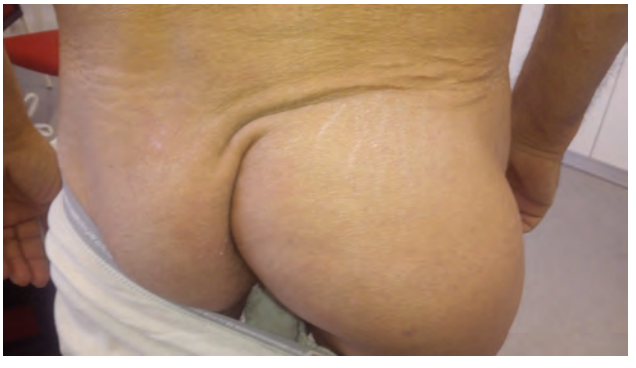
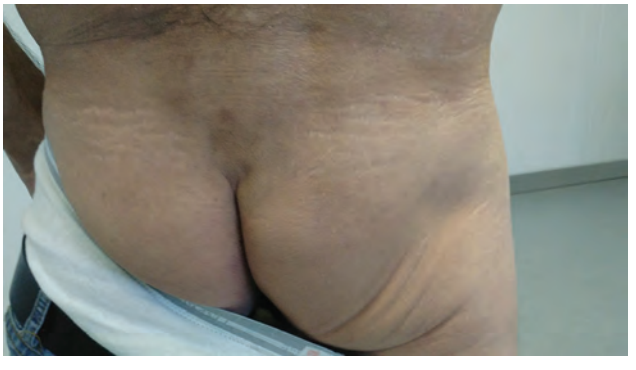
Introduction: Uremic tumoral calcinosis is an uncommon but serious complication of end-stage renal disease. It is characterized by massive extraosseous calcification in periarticular tissues, leading to limited range of joint movement, pain, and skin ulceration.

Case Description: A 52-year-old man developed a progressively enlarging painless mass on the posterior surface of the right leg and on the back surface of the right shoulder with limited range of flexion following 5 years of hemodialysis. Magnetic resonance showed amorphous, cystic, and multilobulated calcification. Pathology report revealed tumoral calcinosis. We started intensifying hemodialysis program (5 days per week, 4 hours each session), low calcium bath, aggressive control of hyperphosphatemia, initiation of cinacalcet, antibiotics and administration of sodium thiosulfate 25 mg i.v per each session. After 6 weeks we noticed significant reduction in the magnitude of the masses and in 8 weeks complete resolution. We turned hemodialysis schedule to 3 times a week and continued to have close monitoring of the patient.

Discussion: Effective treatment options for tumoral calcinosis remain elusive. The primary focus of therapy should be to optimize calcium and phosphate homeostasis. Avoidance of a positive calcium balance should be a high priority. Experienced nephrologists recommend a course of dialysis 5–7 days per week for the first couple weeks of treatment, with the duration of this intensified dialysis therapy depending on clinical response. Sodium thiosulfate is a chelating agent that has antioxidant activity and increases activity of endothelial nitric oxide synthetase. Sodium thiosulfate is believed to act by dissolving insoluble tissue calcium salts to form calcium thiosulfate, which is many thousand times more soluble than many other calcium salts.





FR-PO442

Effectiveness and Safety of Modified Sodium Thiosulfate Therapy for Calciphylaxis in Chinese Patients

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Background: Calciphylaxis is a generally fatal condition without acknowledged effective treatment. Some case reports and clinical studies have described intravenous sodium thiosulfate (STS) prevent the progression of calciphylaxis. Nevertheless, this therapy for individuals presented serious complications resulting in withdrawal of treatment in our experience. Based on the ethnic diversity, we modified the usage of STS and evaluated the effectiveness and safety of modified STS therapy for calciphylaxis in Chinese patients.

Methods: 20 patients who were diagnosed calciphylaxis and treated with STS in our center were enrolled. Evaluation of effectiveness and safety was based on items including demographics, clinical data and laboratory measurements. Therapeutic schedule were named Zhongda Therapy with 5 course of treatment and 2-3weeks of interrupt between 2 courses. STS from the initial dose (3.2g) were administered intravenously in 100 ml once a day gradually increasing day by day up to the highest dose (6.4g). Patients maintained the condition of highest dose for 2-3 weeks and finished one course of treatment.

Results: The Mean age of the cohort was 45.50±14.95 years, 75% of patients was male and the median time span was 87 (52, 120) months range from entering the dialysis to diagnosed as calcipylaxis. In our research, 90% patients got improved and 12/20 patients were follow-up more than 12 months with 100% one-year survival rate. Of these patients, lesions involved different body parts such torso, limb, fingertips or compound type and throughout the body were 20% with powerful pain. The therapy relieved pain and promote early healing of skin lesions, even help one avert amputation. Reduction of phosphorus ($P=0.035$) and the NPRS ($P<0.001$) correlated significantly with STS treatment courses. Although adverse events occurs up to the 35% (nausea/vomiting 10%, hypotension 10%, infection 5% and multi-complication 10%), no one interrupted treatment due to mild discomfort. And if the incidence rate were calculated according to frequency divided by the total course, it will reduced to 14%.

Conclusions: Chinese patients need to modified the usage of STS to treat the calciphylaxis. And Zhongda Therapy offered a safe and effective treatment.

FR-PO443

Impact of Hemodialysis on the Concentrations of Sodium and Potassium During Infusion of Sodium Thiosulfate Using an In Vitro Hemodialysis Model

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Background: The purpose of this study was to evaluate the impact of hemodialysis on the concentrations of sodium and potassium in the blood when a 25 g dose of sodium thiosulfate injection is infused over 60 minutes in combination with hemodialysis.

Methods: Sodium thiosulfate (25 g) was prepared by diluting 100 mL of 250 mg/mL Sodium Thiosulfate Injection with 800 mL of 5% dextrose. This was added to the circulating blood surrogate solution at a rate of 15 mL/minute using an infusion pump of an *in vitro* model of dialysis machine [Figure]. Serial samples were collected before the administration of the sodium thiosulfate solution, after 15 minutes, 30 minutes, and 60 minutes of infusion from pre-and post-dialyzer ports in both the dialysate circuit and the extracorporeal circuit.

Results: The concentration of sodium thiosulfate in pre-dialyzer and post-dialyzer samples of the circulating blood surrogate solution peaked at 30 minutes and 15 minutes, respectively and then remained relatively unchanged during the remainder of the infusion. Mean sodium concentrations (mEq/L) in the circulating blood surrogate solution collected after exposure to a dialyzer were 103.2 ± 12.2, 114.2 ± 18.8, 117.2 ± 7.5, 93.5 ± 5.9 at 0, 15, 30, and 60 minutes, respectively ($p=0.248$). Mean potassium concentrations (mEq/L) in the circulating blood surrogate solution collected after exposure to a dialyzer were 1.4 ± 0.3, 1.6 ± 0.3, 1.5 ± 0.1, 1.2 ± 0.1 at 0, 15, 30, and 60 minutes, respectively ($p=0.365$). Sodium and potassium concentrations in dialysate increased marginally after exposure to the dialyzer.

Conclusions: Our study demonstrates that neither potassium nor sodium accumulated in a circulating blood surrogate solution when a dose of sodium thiosulfate was infused in conjunction with hemodialysis.

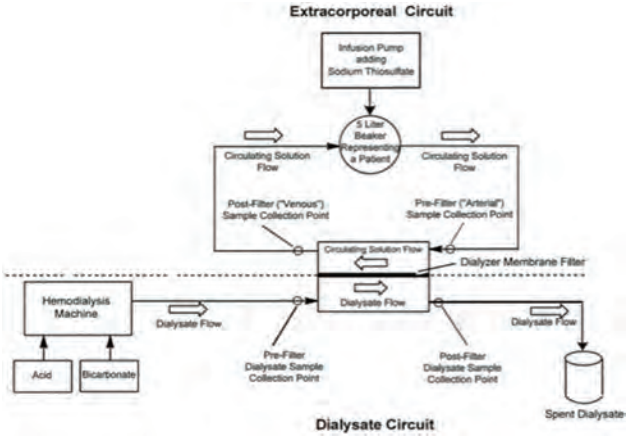

Figure. Schematic diagram of in vitro hemodialysis model used in this study

FR-PO444

Avoidance of the Third Amputation with Remission of Intolerable Pain by Sodium Thiosulfate Administration in a Severe Calciphylaxis Patient

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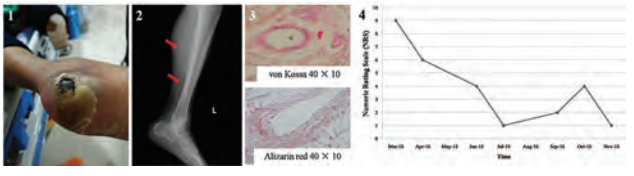
Introduction: Calciphylaxis is a rare but fatal vascular calcification disease characterized by ischemic skin damage and severe pain, often leading to amputation. Currently, there is no specific therapy, but sodium thiosulfate (STS) shows potential curative effects in many related reports. We report a calciphylaxis patient with recurrent skin necrosis which seems the third amputation is inescapable. STS significantly relives the sharp pain and delays deterioration of skin ulcer.

Case Description: A 64-year-old Chinese male with 23-year hemodialysis history had recurrent and progressively worsen acro-skin ulcer accompanied by extremely pain. His highest pain score for numeric pain rating scale (NRS) was 9, which made him behave suicidal tendency. He had twice amputations of left fingers and right lower limb, there is still an emerging ulcer on his left heel (Fig.1) with unmanageable pain. His previous amputating wound was also poor-healed after half a year of surgery. X-rays showed the large vessel calcification (red arrows) which suspected of supplying blood at the necrotic site(Fig.2). A skin biopsy on his amputated right lower leg showed extensive calcium deposition in small vessel walls(Fig.3). He was diagnosed as severe calciphylaxis and we conducted a comprehensive therapy based on intravenous STS with the daily increasing dose from 3.2 g/d to maintain with 6.4 g/d after 5 days. After one-week treatment, the patient felt pain significantly relieved (Table) and 3 months later, his amputating wound gradually crusted so that a third amputation was avoided.

Discussion: Although there is no large randomized clinical trial to confirm the effect of STS in calciphylaxis patients, the use of STS significantly reduces pain and the patient avoids the third amputation. It is suggested that STS also has a certain therapeutic effect on severe calciphylaxis, which mainly relies on relieving pain and delaying the progression of skin ulcers.



FR-PO445

Dialysis Initiation Improves Calcification Propensity

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Background: Cardiovascular morbidity and mortality is high in patients starting dialysis and could be related to modifications of calcification inducers and inhibitors by dialysis, promoting cardiovascular events. The impact of dialysis initiation on serum calcification propensity evolution and arterial stiffness is however not known. We therefore, prospectively determined the evolution of the T_{50}-value and its main determinants, as well as pulse wave velocity (PWV) over the first three months of dialysis initiation.

Methods: We analyzed the evolution of T_{50}, fetuin-A and phosphocalcic parameters before dialysis initation (M0), and monthly until month three (M3) of incident patients starting hemodialysis (HD) or peritoneal dialysis (PD) in two tertiary Swiss University Hospitals. Arterial stiffness was assessed by pulse tonometry at M0 and M3, and biological parameters were compared between M0 and M3 and before/after HD. Linear mixed models were used to assess parameter evolution over time taking into account repeated measures and other influencing variables.

Results: Forty-six patients on HD and 12 on PD were followed. Among them, 45 were male (78 %) with median age of 67 years (25^{th}-75^{th}: 54-77). T_{50} significantly increased between M0 and M3 from 183 (120-266) to 246 (175-330) minutes, p<0.001. Fetuin-A, calcium and magnesium also increased while phosphate decreased. Factors associated with T_{50} changes over time were fetuin-A, phosphate and magnesium (p<0.001). Fetuin-A changes were associated with inflammation-related factors (albumin, crp) but not phosphocalcic parameters. Arterial stiffness was not significantly modified over 3 months. PD and HD initiation showed similar trends.

Conclusions: Dialysis initiation significantly improves calcification propensity and fetuin-A levels. These modifications do not explain the high mortality related to dialysis initiation. The clinical relevance of using T50 values to initiate dialysis awaits further studies.

Funding: Government Support - Non-U.S.

FR-PO446

Acid-Base Dynamics in Allo-Hemodialysis Treatments: Quantitative Insights from a Novel Physiology-Based Mathematical Model

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Background: In some areas of the world access to conventional hemodialysis (HD) is elusive, resulting in millions of premature deaths every year. Allo-hemodialysis (alloHD) is a substantially simplified and less costly dialysis modality, in which the blood of a healthy subject ("buddy") flows counter-current to the patient's blood through the dialyzer. Solutes, including bicarbonate, are transferred across the membrane. In this study, we proposed a physiology-based mathematical model to explore the impact of alloHD on the patient's and buddy's acid-base status.

Methods: A dynamic model of physiological regulation of HCO_3^-/CO_2 buffering system with Henderson-Hasselbalch mass-action kinetics is used to describe a coupled transfer between patient and buddy via alloHD. The model incorporates production of CO_2 and H^+, loss due to non-bicarbonate buffering, and ventilation. In addition, we assume a normal renal function and regulation of HCO_3^-/CO_2 in the buddy, but not in the patient. The patient model is parameterized to yield various degrees of metabolic acidosis, while the buddy model is parameterized to physiological values.

Results: Figure 1 shows an example of acid-base dynamics. AlloHD is able to correct patients' acid-base status. Interestingly, there are only minimal changes to the buddy's acid-base status. The buddy's kidney function affects the extent to which the patient's acid-base status is corrected. Furthermore, since buddy's renal function is fully intact, we observe a secondary compensation where HCO_3^-, pCO_2 and pH initially decrease before regulatory compensations restore the buddy's acid-base status.

Conclusions: Our findings indicate that an alloHD session can restore the patient's acid-base status. Our modeling suggests that there is minimal disturbance in buddy's acid-base status while providing substantial corrective regulation of patient's acid-base homeostasis. Although our modeling results are promising, there is a need for further empirical investigation to verify the predictive power of the model.

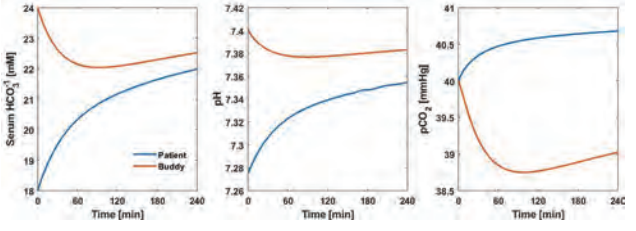

Figure 1: Temporal dynamics of acid-base status in patient and buddy during alloHD

FR-PO447

Cardiac Stunning During Haemodialysis: The Therapeutic Effect of Intradialytic Cycling

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Background: Cardiovascular risk is elevated in end stage renal disease (ESRD). Left ventricular dysfunction is linked to repetitive transient ischemia occurring during maintenance haemodialysis (HD); cardiac stunning can subsequently occur defined as myocardial regional wall motion abnormalities (RWMA). Ischemic RWMA have been documented during HD resulting in maladaptive cardiac remodelling and increased risk of heart failure. Intra-dialytic exercise is well tolerated and can improve quality of life and physical function. It may also attenuate HD induced cardiac stunning. The aim of this exploratory study was to assess the effect of intra-dialytic cycle ergometry on cardiac stunning.

Methods: Twenty exercise naïve participants on maintenance HD (59 ± 11 yrs) underwent resting echocardiography and maximal cardiopulmonary exercise testing.

Subsequently, cardiac stunning was assessed with myocardial strain derived RWMAs at four time-points during 1) standard HD, and 2) HD with 30 mins of sub-maximal intra-dialytic cycle ergometry at a workload equivalent to 90% of oxygen uptake at the anaerobic threshold (VO_2AT).

Results: Compared to HD alone, HD with intra-dialytic exercise significantly reduced RWMAs after 2.5hrs of HD had elapsed (Total 110 ± 4, mean 7 ± 4 segments vs. total 77 ± 3, mean 5 ± 3 respectively; p = 0.008). Global cardiac function, intra-dialytic haemodynamics and left ventricular volumetric parameters were not significantly altered with exercise.

Conclusions: Intra-dialytic exercise, completed after one hour of maintenance HD, significantly reduced cardiac stunning. Thirty minutes of sub-maximal exercise at 90% VO_2AT was sufficient to elicit this acute cardio-protective response.

Funding: Commercial Support - Coventry University Phd funded project

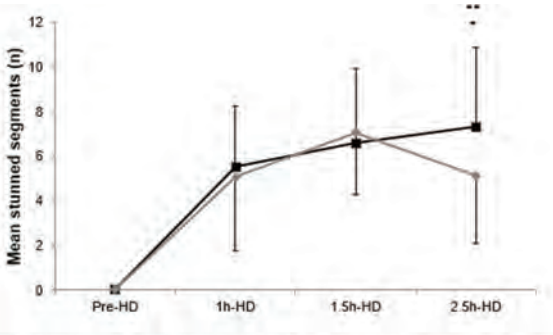

Figure 1: Summary of mean regional wall motion abnormalities during HD and HD+CLE conditions. ⟶ indicates HD+CLE condition; ⟶ indicates HD condition. * significant difference between HD+CLE and HD conditions; ** significant difference from 1.5h-HD. LV, left ventricular; CLE, constant load exercise; HD, hemodialysis.

Regional wall motion abnormalities during haemodialysis. At 2.5h-HD, the number of regional wall motion abnormalities was significantly reduced with intradialytic exercise (HD+CLE).

FR-PO448

Examining Mortality in the Multinational Observational Study of Continuous Renal Replacement Therapy (CRRT) Practices

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Background: Risk-stratification of patients receiving CRRT to guide practice is direly needed. Utilizing data from a registry of critically ill adults receiving CRRT, we report mortality and kidney recovery rates and examine clinical parameters associated with mortality.

Methods: Multi-national observational registry study including critically ill adults (age ≥18 and ≤89 years) receiving CRRT. Patients who received CRRT for <48 h or other type of acute RRT before CRRT were excluded. Moderate and severe kidney disease at baseline were defined as baseline serum creatinine >265 μmol/L and ESKD/kidney transplant, respectively.

Results: 566 critically ill patients receiving CRRT were included. Mean (SD) age was 58.7 (14.3) yrs., 58.5% were male. Mean BMI was 31.1 (8.0) kg/m^2. Median [range] Charlson and APACHE-II scores were 2.0 [0.0-18.0] and 29.0 [9.0-50.0], respectively and 106 (18.7%) patients had moderate/severe kidney disease at baseline. Median days from ICU admission to CRRT initiation was 1.0 [0.0-52.0] and 213 (37.6%) patients had fluid overload (FO%) ≥10% at CRRT initiation. Median SOFA at CRRT initiation was 15.0 [6.0-23.0]. Mean delivered CRRT dose was 33.1 (14.1) ml/kg/h and the median FO% per CRRT-day was 1.4% [0.3%-7.0%]. ICU mortality rate was 48.4%. In a multivariable Cox model, age (>60 vs ≤60), BMI (>29.7 vs ≤29.7), moderate/severe kidney disease at baseline, FO% per CRRT-day (>1.4% vs ≤1.4%), the absence of circuit anticoagulation, diagnosis of sepsis or acute-on-chronic liver failure, and serum bicarbonate at CRRT initiation (≤20 vs >20 mmol/L) independently associated with higher ICU mortality. Among 217 survivors without moderate/severe kidney disease at baseline, 142 (65.4%) recovered kidney function no longer needing RRT at hospital discharge.

Conclusions: Approximately one of two critically ill adults receiving CRRT died in the ICU. However, almost two-thirds of survivors recovered kidney function sufficiently enough to be independent of RRT. We identified clinical parameters independently associated with ICU mortality. This registry can help develop and validate risk-stratification tools in this susceptible population, and identify modifiable risk factors for evaluation in clinical trials.

Funding: Private Foundation Support

FR-PO449

Predictors of Hypophosphatemia and Outcomes During Continuous Renal Replacement Therapy

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Background: Hypophosphatemia occurs in up to 80% of patients undergoing continuous renal replacement therapy (CRRT) and is associated with poor outcomes. Whether pre-emptive phosphate supplementation is warranted in select patients has not been adequately explored. This single-center, retrospective cohort study evaluates predictors of hypophosphatemia and characterizes treatment approaches in adult patients undergoing CRRT.

Methods: Patients requiring CRRT for at least 12 hours were divided into two groups based on the presence or absence of hypophosphatemia as defined by serum phosphorus <2.5 mg/dL. Select laboratory values at baseline and during CRRT, medications and nutritional sources affecting phosphorus, and CRRT parameters were compared. Patient outcomes including acute kidney injury (AKI) resolution, freedom from renal replacement therapy (RRT) at hospital discharge, duration of intensive care unit (ICU) and hospital stay, duration of mechanical ventilation, and ICU mortality were evaluated.

Results: Seventy-two patients were included. The group was 43% female and 51% African American. CRRT was ordered for AKI in 83% and for end-stage renal disease in 15% of patients. Hypophosphatemia occurred in 45 patients (63%). Mean time to development of hypophosphatemia was 34 ± 22 hours. Patients who developed hypophosphatemia received a longer duration of CRRT (p=0.001), were more likely to have a diet ordered (p=0.005), less likely to have received calcium infusions (p=0.045), and had lower phosphorus (p=0.017) and potassium levels (p=0.038) and higher calcium levels at baseline (p=0.048). Development of hypophosphatemia was associated with an increased duration of ICU stay (p=0.014) but not with the other patient outcomes evaluated. Twenty-seven of the 45 patients (60%) who developed hypophosphatemia received phosphorus supplementation with near equal use of intravenous, oral, and combination routes. Only 16 patients (36%) achieved resolution of hypophosphatemia while on CRRT.

Conclusions: Hypophosphatemia is common, difficult to correct, and contributes to longer ICU stays in patients requiring CRRT. A pre-emptive approach to address hypophosphatemia including aggressive supplementation strategies to correct phosphorus is warranted in patients requiring CRRT.

FR-PO450

Development and Validation of a Predictive Model for Delivered Dose in Continuous Renal Replacement Therapy

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Background: Continuous renal replacement therapy (CRRT) has become one of the most relevant therapies for acute kidney injury and critical patients. Since the beginning there has been controversy about delivering, measuring, and defining ideal dose. Measuring effluent volume related to body weight has been the method of choice for the last years. It's well known that prescribed dose and delivered dose differ significantly, mainly because of down time, the effect of pre-dilution replacement, and the dialyzer capacity to saturate the effluent. Current practice recommends prescribing 25% more dose to achieve the desired goal. A tool that could account for the three main factors that lower the dose and could predict de delivered dose, could be of great help for the daily prescription of CRRT. The objective of this study is to validate the results of the proposed model in our Institution.

Methods: We developed an app-based model programed in Xcode® for IOS, with a prescription step method, and patient based format, that considers: down time, pre-dilution replacement, and effluent saturation. The model is given a desired therapy, and then calculates the simulated delivered dose. For validation we evaluated since March 2019, 5 treatments of CRRT in CVVHDF mode, and run 15 dose evaluations by measuring simultaneously: BUN pre-filter pre-dilution, BUN pre-filter post-dilution, and UN of the effluent solution. We then compared the delivered dose with the results of the predictive model.

Results: We found good correlation compared to the delivered dose. We conducted a Pearson correlation that showed: r =0.91, 95% CI= (0.74 - 0.97), R^2=0.82, and a P value of <0.0001. To evaluate agreement we conducted a Bland Altman plot we demonstrated that 100% of results where between the 11% error: (Bias= -2, SD of Bias 4.2,95% Limits of agreement (-11– 5.5).

Conclusions: Even though the sample was small, the delivered dose predictor computes accurate results as compared to the delivered dose. The App based tool can help predict de delivered dose given to a patient, it can be of great utility to simulate different therapies with different prescriptions, and compare different results. At present more patients and treatments are being continuously evaluated to strengthen even further the results.

FR-PO451

Prognostic Potential of Calcitriol in the Patients Requiring Postoperative Continuous Renal Replacement Therapy After Liver Transplantation

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Background: The mortality of the patients with End-Stage Liver Disease and renal dysfunction is high. It is important to know and correct the predicting risk factors of mortality in the patients requiring continuous renal replacement therapy (CRRT) after liver transplantation (LT). lmmunomodulatory and anti-inflammatory effects of calcitriol, produced by liver and kidney, improved survival rate in the animal experiment underwent solid organ transplantation. We investigated whether lower calcitriol level is associated with the mortality in in the patients requiring CRRT after LT.

Methods: We conducted a retrospective study consisted of 65 patients requiring CRRT after LT. Their demographic data and biochemistry parameters were obtained at the initiation of CRRT by reviewing electronic medical records. The deficiency of calcitriol was defined as its plasma level < 10 pg/ml. Primary end point was 180-day mortality from the initiation of CRRT after LT.

Results: The subjects were divided into calcitriol deficient group (CDG, n=36) and calcitriol non-deficient group (CNDG, n=29). There were no significant differences in demographics between two groups. Compared with CDG, hematocrit (26.3 ± 2.3 vs. 20.5 ± 5.1 (%), p=0.045) and 25(OH)D3 (7.2 ± 2.8 vs. 2.8 ± 1.2 (ng/ml), p=0.011) were higher in CNDG at the initiation of CRRT. In contrast, 180-day mortality in CDG (30.6%, 11/36) was higher than that of CNDG (3.4%, 1/29, p=0.005). By Cox regression analysis, calcitriol deficiency (OR 25.9, 95% CI 2.72-246.9, p=0.005) and Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification (OR 0.4, 95% CI 0.16-0.99, p=0.046) was risk factor of mortality after adjusting Model for End-Stage Liver Disease (MELD) score, RIFLE and 25(OH)D3.

Conclusions: Calcitriol deficiency is associated independent risk factor with the mortality in the patients requiring CRRT after LT. In the future, randomized interventional trial is necessary to confirm whether calcitriol is a correctable risk factor to improve the survival in them.

FR-PO452

Accelerated Venovenous Hemofiltration (AVVH): Piloting a Transitional Renal Replacement Therapy in the Intensive Care Unit

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Background: The need for continuous renal replacement therapy (CRRT) is associated with high mortality and resource use in the ICU. There are no guidelines establishing optimal timing of transition from CRRT to intermittent hemodialysis (iHD). AVVH is a form of CRRT that allows for higher blood flows, increased hemofiltration rates, no anticoagulation, and a 10 hour treatment period, as a transition between CRRT and iHD, and assessed treatment characteristics.

Methods: Quality improvement pilot aimed to achieve a safe and effective transition between CRRT and iHD using AVVH at large academic medical center between October 2017 and August 2018. AVVH treatment doses, blood flows, clearances, filter clotting, and patient outcomes were recorded.

Results: 51 patients received a total of 142 complete AVVH treatments. 11 (8%) patient treatments were not completed due to inadequate blood flows (3), filter clotting (7), and change to comfort measures (1). Average prescription was: treatment time 9.3 (± 1.6) hours, blood flow 350 (± 22) mL/min, replacement fluid rate 4.1 (± 0.3) L/hr, ultrafiltration volume 2.0 (± 1.1) L/treatment, urea reduction ratio 28 (± 17)%/10 hrs. 32/51 (69%) patients received sequential daily treatments (range 2-13 treatments). In-patient mortality was 31%, length of stay 53 (± 49) days. 36/51 (70%) patients successfully transitioned to iHD, 10/51 patients (20%) recovered renal function after AVVH, and 4/46 (8%) patients required readmission to the ICU after developing hypotension on iHD.

Conclusions: AVVH was successfully integrated into our ICU program as an innovative transition therapy between CRRT and iHD. It has tremendous potential to reduce ICU readmission and healthcare costs. Further study is needed to determine its impact on resource utilization and patient outcomes.

Patient Characteristics

AKI Cases	44 (86%)
Age (years)	61 (±15)
Apache Score	25 (±7)
Use of Vasopressors	43 (30%)
In-Hospital Mortality	16 (31%)
Pre-AVVH BUN (mg/dL)	44 (±17)
Post-AVVH BUN (mg/dL)	31 (±14)

FR-PO453

Efficacy and Safety of High-Volume Hemofiltration (HVHF) in Patients with Septic Shock and AKI: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Septic Shock is among the most common causes of death in the intensive care unit (ICU). The underlying pathophysiology involves an overactive immune response. It has been theorized that blood purification technique that reduces the levels of inflammatory cytokines and/or bacterial toxins could mitigate this response. High-volume hemofiltration (HVHF) is a blood purification technique that has been studied to improve outcome associated with septic shock. Our aim is to do a systematic review of randomized controlled trials that assessed the use of HVHF in septic shock.

Methods: A comprehensive literature search from the PubMed, Embase, Cochrane Library, and Ovid was performed with the following search terms: Hemofiltration, Septic Shock, Acute Kidney Injury. The search was limited to randomized-controlled trials that compared HVHF to Conventional (as dictated by the Surviving Sepsis Guidelines) and/or Standard-Volume Hemofiltration (SVHF). Six prospective clinical trials were selected and analysed using Cochrane Revman v5.3. The primary outcome was 28-day mortality. Other outcomes assessed were dialysis dependence, length of ICU and hospital stay, vasopressor requirement and adverse events.

Results: Six trials comprising 745 patients were selected. 373 patients treated with HVHF and 372 patients in the control group were included. Pooled analysis of the 6 trials for 28-day mortality did not show a statistically significant difference between HVHF and control (745 participants, OR: 0.90, 95% CI 0.67-1.21). There were no noted significant difference between groups for any of the secondary outcomes. Adverse events, including electrolyte abnormalities and secondary infections, were more commonly observed in HVHF-treated patients, although reporting was inconsistent across studies.

Conclusions: There is insufficient evidence to support the therapeutic benefit for routine use of high-volume hemofiltration in patients with septic shock. Larger trails are needed to fully assess clinically relevant outcomes as well as cost-effectiveness.

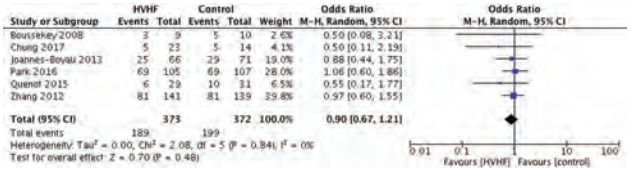

Figure 1. Forest Plot for 28-Day Mortality

FR-PO454

Effectiveness of Implementation of Hemodiafiltration and Achieving Target Convective Volume: Results from HDFit Trial

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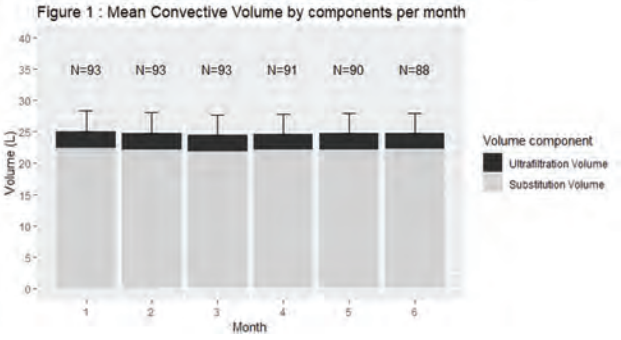
Background: Hemodiafiltration (HDF) is associated with better outcomes compared to hemodialysis (HD), provided adequate convective volumes (CV) are achieved. Implementation of protocols targeting optimal CV have not been well described.

Methods: HDFIT was a randomized controlled trial studying the impact of postdilution high-volume online HDF versus high-flux HD on measured physical activity (NCT02787161). HDFIT included stable patients (Kt/V ≥1.2, permanent access, vintage ≥3 to ≤24 months). Clinic staff were trained to use Fresenius 5008 CorDiax® HDF machines the day before/morning of randomization visit. HDF was performed in 6-month follow-up with a CV target of 22L/treatment. We assessed implementation of HDF with a median achieved CV >22L across treatments.

Results: HDFIT randomized 195 patients (HDF n=97, HD n=98) at 13 clinics with mean age 53±15.1 years and 11% used a permanent catheter. There was an 8% and 11% dropout rate in HDF and HD groups. HDF group had 95 patients with CV data recorded (median=70 treatments/patient). Median treatment time was 235 (IQR 232 to 240) and 235 (IQR 233 to 240) minutes for HD and HDF. Median CV >22L was achieved in 86% (82 of 95) of HDF patients during follow-up. Monthly mean CV ranged from 24L to 25L (Figure 1). At 3-months, distinctions were found in mean Kt/V (HDF=1.8±0.4, HD=1.6±0.4; p<0.001) and phosphate (PO4) (HDF=4.8±1.3, HD=5.2±1.4 mg/dL; p=0.022). Distinctions were maintained at 6-months in mean Kt/V (HDF=1.8±0.5, HD=1.7±0.4; p=0.028), yet not PO4.

Conclusions: HDF was successfully implemented in the HDFIT trial with 86% of patients achieving protocol CV target. Monthly mean CV was consistently >22L in follow-up. HDF provided higher Kt/V throughout follow up and more PO4 removal at 3 months. HDF appears to be an easily implementable technique with brief training required.

Funding: Private Foundation Support



FR-PO455

Improved Survival with High-Volume Hemodiafiltration in Argentina: A Propensity Score-Matched Cohort Study

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Background: While hemodialysis (HD) is the current standard of care, hemodiafiltration (HDF) adds high convective volume to remove middle molecules. We compared all-cause mortality in Fresenius Medical Care Argentina patients treated with either HDF or high-flux HD.

Methods: Data were extracted from Fresenius EuCliD® database and comprise treatments between 11/2011 and 05/2018. Pts were divided patients into those treated with HD (control group), high-volume (HV) HDF (>70% of treatments with >23 L substitution volume), and low-volume (LV) HDF (< 23 L substitution volume). The baseline period comprised 3 months before the HD-to-HDF switch, it was followed by 1 month washout period. Pts were for 1 year, death, or lost to follow-up. To minimize bias by indication, HDF pts were propensity score matched to HD pts by age, gender, diabetes, vintage, fluid status (determined by bioimpedance), vascular access, systolic blood pressure, phosphate, and albumin.

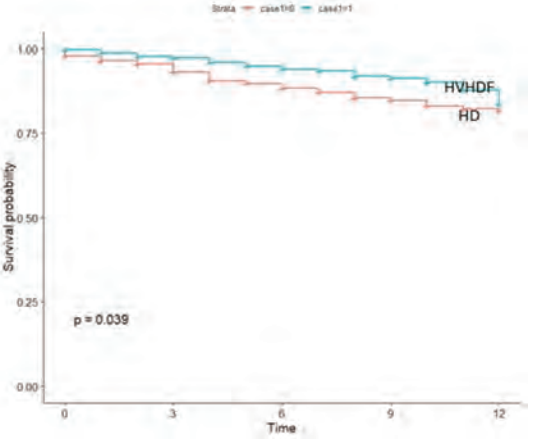
Results: We selected 12,911 pts from 73 centers (11,111 HD; 1,800 HDF). Propensity score matching resulted in 537 HD and 545 HDF patients (Table 1). Kaplan-Meier analysis showed a survival benefit of HV-HDF vs. HD (11.46 vs 22.5 deaths/100 pt-years, p=0.039, figure 1), but not for LV-HDF (23.4 vs 22.5 deaths/100 pt-years).

Conclusions: Within the known limitations of observational trials (patient selection bias, residual confounding) our propensity score matched multicenter study shows a survival benefit of HV-HDF, but not LV-HDF, over HD in Argentinian patients.

Table 1:

	HD	HDF	
	Mean (SD)	Mean (SD)	p
Age (yrs)	57.9 (16.9)	56.2 (15.7)	0.14
Male %	60	70	0.03
DBT %	30	30	0.75
Vintage (months)	20.5 (14.8)	28.6 (23.0)	0.00
Hydration	1.5 (2.4)	1.8 (2.1)	0.07
Catheter (%)	20	10	0.04
SBP (mmHg)	128.4 (18.0)	129.4 (19.5)	0.40
P (mg/dl)	5.0 (1.20	5.2 (1.2)	0.06
Alb (g/dl)	3.9 (0.4)	3.9 (0.5)	0.30

Figure 1:



FR-PO456

Safety and Efficiency of Low-Molecular-Weight Heparin (LMNH) Administered in the Venous Line of Patients Treated by Online Hemodiafiltration and High Flux Hemodialysis

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Background: Removal of low molecular weight heparin (LMWH) occurs during high flux hemodialysis (HF-HD) and online hemodiafiltration (OL-HDF) if administered before the dialysis session in the arterial line of the extracorporeal HD circuit. It is recommended to administer (LVMH) through the venous line to improve anti-coagulation efficacy. The goal of our study is to evaluate efficacy, and safety of LMWH administered through the venous line in OL-HDF and HF-HD patients

Methods: We enrolled 49 OL-HDF and 48 HF-HD patients from February to October 2018 (mean age 66 yrs.arteriovenous fistula 90%, the average dialysis time 240 min). Three consecutive 6-week periods (i.e. 5400 dialysis sessions) were analyzed according to the path and dose of (LMWH) administration: Phase I (arterial line), phase II (venous line), phase III (reduced dose). Phase I and II involved HF-HD + OL-HDF patients, and phase III involved only Ol-HDF patients. In each session we evaluated filter and chamber clotting (semi-quantitative visual scale), venous pressure, KT/V, volume infused in OL-HDF. The 3 periods were done with FX membranes (90%), BK, BG

Results: 34 %, 63 % and 66% of membranes were scored as "clean" during phases I, II, III respectively (p<0.05). 9%, 0.6% and 0.4 % of membranes clotted during phases I, II, III respectively. 75%, 93% et 95% of venous chambers were clean during phases I, II, III respectively (p<0.05). 1%, 0%, 0% were clotted with loss of circuit during phases I, II, III respectively (p<0.05). Average LMWH doses were: 0.43 ml (0.2-0.6) and 0.3 ml (0.2-0.6) of Nadroparin during phases I, II respectively (p<0,001). During phase III, LMWH dose decreased from 33 to 50% for 58% of patients with an anti-Xa target = 0.3ui/ml. Between phases I -III, KT/V improved from 1.71 to 1.83 (p<0.005), Infused volume from 20.7 to 23.7 l. Bleeding time was identical during Ph I - Ph III. In the HF-HD sub-group during phases I and II, venous LMWH administration decreased the average LMWH dose from 0.55 ml to 0.34 ml respectively and improved the quality of blood restitution.

Conclusions: Venous line administration of LMWH at the start of dialysis allows a dose reduction and improvement of dialysis adequacy parameters.

FR-PO457

Hemodialysis (HD) Using Super High-Flux Dialyzer Provides Comparable Efficacy with High-Volume Post-Dilution Online Hemodiafiltration (ol-HDF): A Prospective Crossover Randomized Controlled Trial

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Background: Although high volume post-dilution online hemodiafiltration (ol-HDF) that could remove large toxin such as beta-2 microglobulin (B2M, MW 11.8 kDa) as well as protein-bound toxins especially indoxyl sulfate (IS) and subsequently improve survival of HD patients is now accepted as the best modality for chronic HD patients, the procedure is sophisticated and expensive. The present study was conducted to compare the efficacy in term of large and protein-bound uremic toxin removals between HD using novel super high-flux (SHF) dialyzer which has large pore size close to albumin, PES 17D alpha (Nipro, Japan) and ol-HDF in a non-inferiority fashion.

Methods: A prospective cross-over randomized controlled trial included twelve prevalent HD patients who were randomly allocated into 2 sequences of treatment period of SHF-HD treatment and later ol-HDF period or vice versa. Each treatment period took 12 weeks and divided by wash out phase of 4 weeks of HD using regular high-flux (HF) dialyzer. The primary outcome was removal of B2M in term of reduction ratio (RR). Other small, protein-bound and large uremic toxin removals, albumin loss, and nutritional parameters were also compared.

Results: SHF-HD provided comparable B2M RR with ol-HDF (78.8±4.7 and 76.8±8.1 respectively, p=0.152). In addition, B2M clearance, alpha-1 microglobulin (A1MG, MW 33 kDa) RR, A1MG clearance, and IS RR were also comparable. The spKt/Vurea was not different. Although the albumin loss in dialysate was higher in SHF-HD than ol-HDF(4.2±2.8 and 0.6±0.8 g/session, respectively), the serum albumin levels at baseline and after 12 weeks of SHF-HD treatment were significantly improved from 3.71±0.38 to 3.88±0.22 g/L (p<0.001) while they did not change during ol-HDF period. In addition, normalized protein catabolic rate was significantly increased in SHF-HD compared to ol-HDF (p=0.012) with no significant changed of lean tissue index after 3-month period of the study.

Conclusions: SHF-HD that lower cost and accessibility was non-inferior efficacy to ol-HDF in term of large, protein-bound and small uremic toxin removals without adverse effect on serum albumin which potentially improve long-term survival.

Funding: Private Foundation Support

FR-PO458

High-Volume Postdilution Online Hemodiafiltration Is Possible Even at Low Blood Flow Rates

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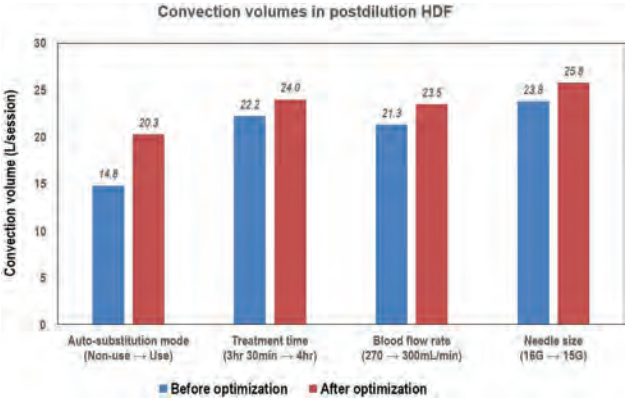
Background: Recent evidence suggests that high-volume hemodiafiltration (HDF) improves patient survival. However, in patients with low blood flow rate (BFR), it is not easy to obtain a high convection volume (CV) with postdilution online HDF. The aim of this study was to investigate whether it is possible to achieve high CV, defined as ≥22 L/session, with postdilution HDF even for patients with low BFR.

Methods: A total of 33 consecutive patients undergoing thrice-weekly postdilution HDF were included. In order to obtain a high CV, we optimized treatment parameters such as treatment time (TT), BFR, needle size and filtration fraction (FF) in all patients according to a stepwise protocol, depending on patent's condition. All dialysis machines were equipped with auto-substitution system. Data of 2592 sessions for one month before and after completion of optimization of treatment parameters were analyzed. The mean CV was determined.

Results: The mean age of patients was 62.5±12.5 years, and 45.5% male. Before the initiation of a stepwise protocol, TT was 233.6±10.9 min, BFR was 267.1±11.1 mL/min, and 84.8% of needles were 16G and 15.2% were 15G. The mean CV was 23.8±2.4 L/session and 75.8% of patients reached CV of ≥22 L/session. After completion of optimization, 90.9% of patients reached a high CV with mean of 24.4±2.3 L/session. Of note, TT was 241.8±16.1 min, BFR was 293.6±12.5 mL/min, and 69.7% of needles were 16G and 30.3% were 15G. Interestingly, in 96.70% of patients who reached a high CV, BFR was less than 300 mL/min with mean of 293.5±12.5 mL/min. In addition, 90.0% of patients with BFR of less than 300 mL/min reached a high CV. The changes of CV after optimization of parameters is shown in the figure.

Conclusions: The high convection volumes could be achieved by increasing of BFR and treatment time and optimization of FF even if high BFR was not obtained. High-volume postdilution HDF is possible in routine clinical practice even for patients with low BFR less than 300 mL/min.



FR-PO459

Predilution Online Hemodiafiltration Improves Health-Related Quality of Life (HRQoL) in Patients Undergoing Hemodialysis

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Background: Sarcopenia and frailty condition cause aggravation of the health-related quality of life (HRQoL) including physical, psychological, and social aspects. Furthermore, these conditions are associated with a high risk of hospitalization and mortality of mantenance hemodialysis (MHD) patients. The effect of OL-HDF on the HRQoL has not been established. In this study, we compared the effect of nutritional conditions and HRQoL between patients treated by OL-HDF and conventional HD using a superflux dialyzer.

Methods: Thirty-eight MHD patients were enrolled in this crossover study. All patients were treated with conventional HD using a superflux dialyzer for first the 4 months (1st CHD period), were switched to predilution OL-HDF for 4 months (OL-HDF period) and then were returned to conventional HD using the superflux dialyzer for the next 4 months (2nd CHD period). We evaluated clinical parameters, the fat mass and muscle mass, and HRQoL using the KDQOL-SF™

Results: No significant difference in serum albumin in the patients with a higher serum albumin level was observed. However, in patients with low albumin, the levels significantly increased (3.6±0.1 to 3.8±0.1 g/dL) during the OL-HDF period. Moreover, although there was no significant difference in the patients with a higher fat mass, fat mass significantly increased (8.0±2.1 to 8.6±2.4 kg) in patients with a lower fat mass during the OL-HDF period. Increased serum albumin and fat mass values during the OL-HDF period returned to baseline levels during the 2nd CHD period. No significant difference in the mental health and body pain score was found during the study period. Although there was no significant difference in the patients with a higher score of physical functioning (PF), role physical (RP), vitality (VT), and social functioning (SF), the patients with a lower score during the 1st CHD period showed significantly increased in these scores (PF: 28.3 ±11.7 to 30.3±11.5, RP: 33.5±9.5 to 37.9, VT: 41.4±5.6 to 43.8±7.4, and SF: 32.4±7.5 to 36.7±8.3, respectively) during the OL-HDF period. These scores decreased to base line levels during the 2nd CHD period.

Conclusions: In this crossover study, we revealed that compared with conventional HD using a superflux dialyzer, OL-HDF significantly improved the nutritional conditions and score of HRQoL in MHD patients with sarcopenia.

FR-PO460

A Comparative Analysis of Clinical Outcomes in Hemodiafiltration and High Flux Hemodialysis: A Retrospective Cohort Study

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Background: Conventional Hemodialysis is the most common treatment modality of renal replacement therapy. It clears uremic toxin by diffusion with insufficient removal of middle sized molecules. Online hemodiafiltration was introduced to increase its clearance. olHDF is considered to have more clinical benefits due to its combined diffusive and convective mechanism. It has better clearance of phosphate, improves erythropoietin response, better intradialytic hemodynamic stability and quality of life. Primary objective was to compare the effectiveness of HDF and HFHD among ESRD patients on maintenance hemodialysis at SLMC-Global City and SLMC-QC in terms of survival rate, dosage requirement of Erythropoietin Stimulating Agent, rate of patients who achieved the target hemoglobin, phosphorus and Kt/V. Secondary outcome determined the substitution volume that provides survival benefits among patients on online hemodiafiltration.

Methods: This is a retrospective cohort study of all adult patients who underwent two to three sessions a week of high flux HD and hemodiafiltration. The study population included all ESRD patients aged 19 and above, on maintenance dialysis for more than or equal to 3 months on January 2015- March 2017. Online hemodiafiltration at SLMC-Global City uses auto-substitution volume for each treatment session.

Results: A total of 171 patients were included. 83 patients on HDF and 88 patients on HFHD group. There is a higher survival rate for patients on HDF at 1st and 2nd year of dialysis 93.97 and 92.77% respectively. No significant difference in dosage requirement of ESA, rate of patients who achieved target hemoglobin, phosphorus level and kt/V at 3rd, 6th and 12th month. Substitution volume of 15-19 Liters has higher survival rate that those with

20-25 liters. For every unit increase in substitution volume at 12 months, the odds of mortality decreases by 21.46%.

Conclusions: The result showed that there is higher survival rate for patients on HDF than on HFHD, no significant difference on requirement of ESA dose, achieving target phosphorus, hemoglobin and dialysis adequacy between the two modality. There is a trend of survival benefit and improvement in Kt/V for patients with higher substitution volume. We recommend caution in interpretation of these retrospective data. A randomized clinical trials is still needed to validate findings.

FR-PO461

Impact of Hemodiafiltration on Serum Interferon Levels in Patients with CKD: Results from the HDFIT Study

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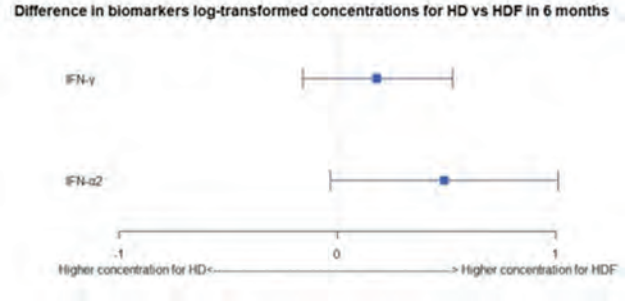
Background: Interferons are cytokines that play an important role in immunomodulatory processes. Hemodiafiltration (HDF) optimizes the removal of medium-sized molecules, and although HDF has been associated with a reduction in pro-inflammatory biomarkers, its effect on serum interferon levels have not been described until the present.

Methods: HDFIT was a multicenter randomized controlled trial comparing HDF to high flux hemodialysis, in which biosamples were collected at baseline and after 6 months (HD n=67; HDF n=63). Cytokines measurement was performed through Milliplex® Human Cytokine Magnetic Bead Panel (IFN-g and IFN-a2) (EMD Milipore Corporation, USA).

Results: There was no significant difference in patients demographic characteristics between groups regarding age (53 years old in HD ± 15 vs 53 ± 16 in HDF), gender (68% male in HD vs 71% in HDF) and diabetes (44% in HD vs 28% in HDF). The mean difference (95% confidence interval) between HDF and HD in 6 months was 0.18 (-0.16 — 0.53) and 0.49 (-0.03 — 1.01) for IFN-g and IFN-a2, respectively (Figure 1). This effect was mainly driven by a reduction in interferons observed in the HD group (IFN-a2 0.35 ± 1.8 vs 0.07 ± 1.8 and IFN-g 1.21 ± 1.08 vs 1.11 ± 1.08) and their maintenance on HDF group (IFN-a2 0.78 ± 1.79 vs 0.78 ± 1.79 and IFN-g 1.55 ± 1.12 vs 1.46 ± 1.12).

Conclusions: This study demonstrates that after 6 months of treatment, patients on HDF maintained the concentrations of circulating interferons (IFN-a2 and IFN-g) compared to HD, where the concentration of IFN decreased over time. Based on the knowledge of IFN actions and functions, these findings suggest that HDF may have immunomodulatory effects that could be beneficial to patients with CKD.



FR-PO462

Flexitrate Regional Citrate Anticoagulation in Continuous Venovenous Hemodiafiltration

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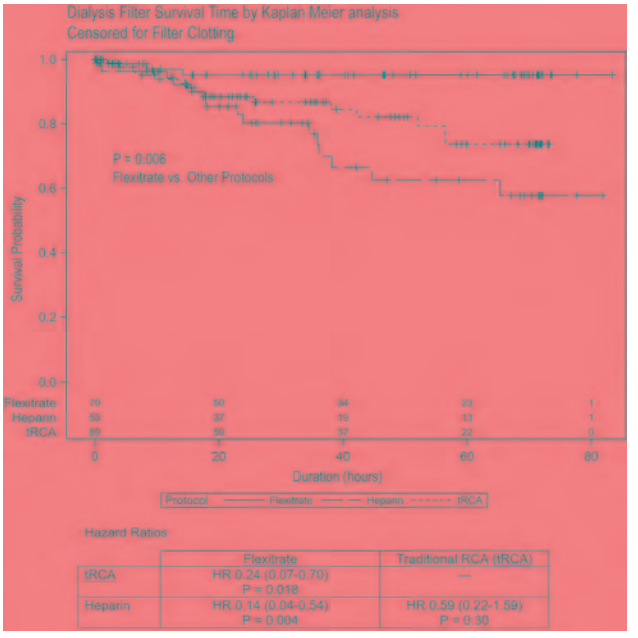
Background: This study compared Flexitrate, an innovative regional citrate anticoagulation (RCA) protocol, to traditional RCA (tRCA) and Heparin anticoagulation protocols in intensive care patients treated with continuous renal replacement therapy (CRRT).

Methods: A single-center, retrospective, cohort study, was conducted in a 26-bed ICU in a large community hospital. Consecutive patients from a 6 month pilot of Flexitrate CRRT were compared to consecutive patients from the preceding 9 months receiving tRCA and Heparin CRRT anticoagulation. 80 dialysis sessions (Flexitrate = 2,852 hours, tRCA = 3,580 hours and Heparin = 2,026 hours), performed in 53 patients, were evaluated for filter life, RCA control, and metabolic control.

Results: Filter survival was significantly improved with Flexitrate compared to tRCA (HR 0.24, p=0.018) and Heparin (HR 0.14, p=0.004); see attached Figure. Anticoagulation control was superior with Flexitrate with Patient Ionized Calcium out of target a median of 16% of the time, compared to 27% for tRCA (p<0.001). Filter Ionized Calcium was out of target a median of 6.8% of the time, compared to 23% for tRCA (p= 0.03). Flexitrate produced significantly less alkalosis, hypernatremia, and hypocalcemia than tRCA, and was comparable to Heparin anticoagulation. The only adverse metabolic outcome with Flexitrate was more Hypomagnesemia.

Conclusions: The Flexitrate protocol extended filter life, delivered more consistent anticoagulation, and provided superior metabolic control compared to a tRCA protocol. Filter life was also superior to Heparin anticoagulation, with similar metabolic control. A randomized control trial comparing these protocols is recommended.



Dialysis Filter Survival for the three protocols, censored for filter clotting.

FR-PO463

Haemodialysis (HD) vs. Online Haemodiafiltration (HDF) and Mixed Haemodiafiltration (MHDF): What Place?

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Background: HD has been a gold standard of dialysis. High-efficiency on-line HDF is recognised as an advanced modality of treatment improving patient outcome. Yet post-dilution HDF has limitations like increased blood viscosity, protein concentration, high transmembrane pressure impairing uraemic solute removal. Pre-dilution method can partially overcome this but the price to pay is decreased overall efficiency. Joining both modalities can potentially improve conductive and convective solute removal and maintain patients haemodynamic stability.

Methods: Eighteen ESRD adults established on HD for at least one year were chosen. They received 6 months conventional HD, followed by 6 months HDF (with 1.2 HDF factor), then 6 months MHDF. Fresenius 5008 machines were used with FXCorDiax1000 dialysers and therapy monitoring system (TMON). A central delivery system supplied 3 types of fluid and ultrapure water direct to the machines. All patients had cardiovascular instability. Various parameters were measured monthly as per standard UK Renal Association guidelines. SF24 Quality of Life questionnaire was analysed by an independent observer.

Results: Results are summarised in the table with mean values. The increased urea reduction rate on HDF and MHDF over conventional HD was statistically significant, p=0.002 and 0.003 respectively. There was no difference between HDF v MHDF. Similarly the difference in Kt/V between HD v HDF and MHDF was significant, p=0.005 and 0.009 with no difference between HDF and MHDF. Differences in pre-dialysis phosphate level between the 3 modalities was not statistically significant although the post-therapy phosphate value between HD v HDF and MHDF showed a p value of 0.003. The haemoglobin and PTH had no significant differences between modalities. We measured β2 microglobulin and proBNP in the MHDF group, the diffence in 6 months was insignificant. HDF and MHDF patients had higher physical and mental component scores.

Conclusions: On-line HDF and MHDF are superior to conventional highflux dialysis, we could not observe additional benefit between HDF and MHDF. Perhaps using a higher HDF factor for dilution and substitution fluid is required to achieve better results.

Funding: Government Support - Non-U.S.

	URR %	Kt/V	Phosphate (mmol/l)	Haemoglobin (gm/l)	PTH (pmol/l)
HD	64±4.5	1.25±0.43	1.93±0.35	107	31.2±20.3
HDF	71±2.5	1.53±0.40	1.67±0.41	104	25.1±19.4
MHDF	68±3.6	1.41±0.36	1.90±0.38	110	24.1±16.4

FR-PO464

Removal of Middle Molecules Using Medium Cut-Off Membranes in Hemodialysis Mode vs. High-Flux Membranes in Post-Dilutional Online Hemodiafiltration Mode: The REMOC Study

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Background: Medium-cut off (MCO) dialyzers were shown to provide better clearance of larger middle molecules compared to high-flux HD and hemodiafiltration (HDF). Whether this results in lower predialysis levels in decreased exposure is not clear.

Methods: In this randomized, open-label, cross over study, 27 HD patients were randomized to either 12 weeks of HD with MCO dialyzers (Theranova 400, Baxter) or online post-dilution HDF with high-flux dialyzers (FxCorDiax 800, Fresenius medical care) using maximally achievable substitution volumes. After 12 weeks, patients were crossed-over to the other treatment modality for 12 weeks. Pre-dialysis serum levels of middle molecules (λ- and κ-free light chains [FLC] were assessed at the beginning and end of each treatment period. The primary outcome was efficiency as assessed by predialysis treatment levels of λ- and κ-FLC, as well as safety (serum albumin levels and frequency of adverse events). A mixed linear model based on the delta value to baseline was used to compare the effect of MCO-HD and HDF on FLC levels. Here, treatment modality and randomization order were assumed as fixed effects, the patient as random effect.

Results: Twenty-seven patients were randomized, six dropped out doe to unability to receive randomized study treatment. Twenty-one patients completed the study and were included in the analysis (14 [66.7%] males; mean age 56.9±14.9 years; mean BMI 28.2±7.4; median dialysis vintage 16 [8-40] months). For κ- and λ-FLC, the delta to baseline after 12 weeks of MCO-HD compared to HDF (κ: -0.8±52.3 vs. -8.0±61.0 mg/dL; λ-FLC: 4.2±24.1 vs. -4.2±26.6 mg/dL) was not significantly influenced by treatment modality or order (κ-FLC: p=0.29; λ: p=0.37) but rather by the patient (κ-FLC: p=0.004; λ-FLC: p=0.02). There was no difference in AE incidence or delta serum albumin levels (MCO-HD vs. HDF: 0.0±0.2 vs 0.0±0.3 g/dL) between treatment modalities.

Conclusions: Twelve weeks of MCO-HD treatment compared to twelve weeks of HDF did not signifantly change pre-dialysis levels of κ- and λ-FLC in prevalent dialysis patients. This suggests that MCO-HD clears larger middle molecules as effectively as high-efficiency HDF, which may allow to extend the benefits of HDF to patients and areas where this treament modality is not available.

FR-PO465

In Vitro Cytokine Removal: Comparison of Conventional High-Flux Dialyzers and Middle-Cut-Off Dialyzer (Theranova HDx)

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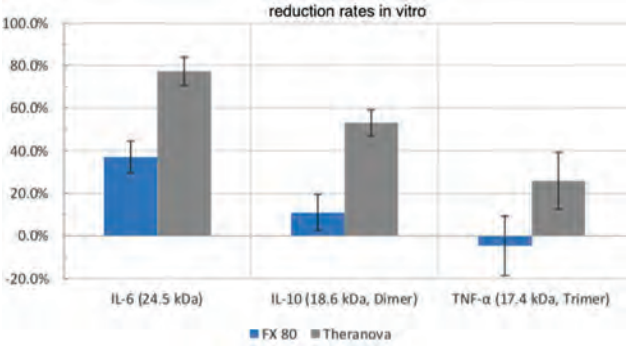
Background: The removal of inflammatory mediators is important for the treatment of acute (ARF) or chronic renal failure (CRF). In ARF and sepsis, attempts is made to achieve removal through the use of high-volume treatments or adsorbers. In CRF, this has so far not been sufficiently addressed, but is important for mortality (MIA syndrome). By using new MCO filters (Baxter Theranova (HDx)), an improvement of cytokine status seems to be possible in both areas. The effectiveness of HDx in the removal of interleukins (interleukin 6, interleukin 10 and TNFalpha in hemodialysis treatments will be assessed.

Methods: The efficacy of HDx was compared to conventional high-flux dialyzers (Fresenius FX80). The measurements were performed in vitro in a 3l pool of fresh frozen plasma (citrate and heparin anticoagulation). IL6 (24.5 kDa) IL10 (18.6 kDa, dimer)) and TNFalpha (17.4 kDa, trimer) were added to plasma (1.5 µg/l each). Samples were taken before and after the dialyzer (after 5, 15, 30, 60, 120 and 180 minutes). In addition to cytokines, albumin and total serum protein concentrations were measured (LEGEND MAX Human IL-6/IL-10/TNF-α; Cobas Mira Plus; Roche LT-AB0103, LT-TP0253). Every test was repeated 5 times.

Results: Theranova HDx showed significantly higher removal rates of all tested cytokines over a period of 180 minutes. A comparison of the concentrations at the beginning and end of the measurements showed: IL-6 reduction - HDx about 80% / FX80 about 40%. IL-10 reduction - HDx about 50% and FX80 about 10%. TNF-αReduction - HDx about 25%; FX80 no reduction The concentration of albumin and total serum protein was not significant different during the treatment in both groups.

Conclusions: Hemodialysis therapy with Theranova HDx appears to be a superior therapy option for the removal of cytokines. This opens up new treatment options for both acute and chronic dialysis patients. However, clinical studies are still necessary to assess the significance in patient treatment.



FR-PO466

Easy, Simple, and Effective Pressure Control by Pinch Valve in CRRT Directly Connected to Extracorporeal Membrane Oxygenation

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Background: The simultaneous use of continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) is increasing in the patients with AKI coexisting with respiratory or circulatory failure in ICU. However, there are no recommended techniques to combine them. Pinch valve is suitable for handling flow capacity by throttling line without corrosion or contamination. Therefore, we investigated whether the external use of pinch valve on the blood lines of CRRT connected to ECMO is helpful to maintain the pressures of CRRT lines in the acceptable pressure range without modifying ECMO settings or inhibiting pressure alarms of CRRT.

Methods: We conducted a prospective observational study in 14 patients (M:F=8:6, age median 50.5 (range 21~75) years, SOFA score 12 (4~16)) requiring CRRT (blood flow rate 150 ml/min) and ECMO (veno-arterial:veno-venous=12:2, FiO_2 60 (40~100) %, cardiac support 90 (70~125) % of normal cardiac index, blood flow rate 3.8 (2.9~5.0) L/min, sweep gas flow 3.0 (1.0~5.0) L/min) between Aug and Oct 2018. The connections of CRRT to ECMO were performed 41 times. Inflow CRRT line is connected after the oxygenator and the outflow CRRT line, before the blood pump in the ECMO circuit. Pinch valve was externally used on inflow and outflow lines of CRRT.

Results: The initial blood flow rate of CRRT was 150 ml/min. Any reduction of blood flow in CRRT on ECMO was not necessary. Before the application of pinch valve, the pressures of CRRT were too high or too low to maintain CRRT directly connected to ECMO circuit. However, after the application of pinch valve, the pressures of CRRT were tolerable and significantly different ($^{*}p<0.05$, $^{**}p<0.001$) from those before the use of pinch valve. CRRT alarms disappeared owing to pinch valve. The changes of CRRT pressures were summarized in Table(Mean±SEM). The median life span of CRRT filter was 63 (range 10~72) hours.

Conclusions: Management of line pressures in CRRT connected to ECMO could be easy, simple and effective by the external application of pinch valve without inhibiting CRRT alarms.

CRRT Pressures on ECMO (mmHg)	Tolerable Range by company	Before use of pinch valve	After use of pinch valve			
			0 hour (n=41)	24 hours (n=32)	48 hours (n=28)	72 hours (n=19)
Access	-150 ~ -50	165 ± 15	51 ± 11**	40 ± 14**	58 ± 14**	52 ± 16**
Filter	+100 ~ +250	-11 ± 9	127 ± 5**	148 ± 6**	158 ± 8**	146 ± 9**
Effluent	-150 ~ +50	-96 ± 9	27 ± 5**	2 ± 5**	-27 ± 10**	-45 ± 17*
Return	+50 ~ +150	-62 ± 9	83 ± 4**	85 ± 9**	87 ± 5**	70 ± 8**
Transmembrane	~ +450	47 ± 3	61 ± 3**	97 ± 5**	129 ± 10**	134 ± 17**

FR-PO467

Outside-In Filtration Technology for Prolonged Filter Life

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Background: Maintaining circuit patency is a prerequisite for optimal treatment efficacy and is essential for continuous renal therapies. In currently marketed dialyzers, blood flows in the intra-luminal (IL) space where formation of thrombi inside the fibers leads to filter blockage. This effect limits set life in continuous acute therapies. NovaFlux is developing Outside-In (OI) hemodialyzers in which blood flows in the inter-fiber (IF) space and dialysate flows in the IL space.

Methods: In a simulated extracorporeal circuit we measured pressure drop and filter life using both bovine and donated human blood. Clearance of small and middle solutes were measured in the Outside-In and Inside-Out filter configurations using standard methods. Clotting of different zones of the filter was made by disecting the filter and estimating the number of clots in each zone.

Results: In-vitro data using a conventional dialyzer in an OI configuration (blood outside fiber) reveals significantly lower membrane clogging and extended filter life. OI increases filter life to over 100 h vs ~24 h with standard filter flow with statistically

equivalent clearance[i]. These advantages are due to new hydrodynamics where blood flows in 3-D interconnected flow channels created in the IF space. When a conventional hemodialyzer is used in the OI configuration, we discovered that stagnant zones are created within the filter. Such zones can be eliminated with a modified filter housing that maintains an optimal blood shear rate and uniform velocity distribution. NovaFlux is developing prototype housings to overcome such limitations. [i] Dukhin SS, Labib ME, et al. OI HF for prolonged operation. Jour Mem Sci, 464 (2014) 173–178.

Conclusions: Two key refinements are required for completing commercial OI dialyzers, namely: modified membrane and housing design. Current membranes are characterized by an asymmetrical membrane structure with a smooth tight inner luminal skin (active membrane layer). This membrane structure is reversed for OI so that the blood contacts a smooth active membrane layer on the outer surface of the fiber. We have made progress in developing a hemocompatible OI PES hollow fiber with an outer active hydrophilic membrane layer. OI dialyzers with these modifications should be able to be produced by current production equipment with relatively minor modifications, enabling longer set life and lower anticoagulation.

FR-PO468

Study of Dilution Modes Under Different Operational Conditions in Continuous Venovenous Hemofiltration

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Background: The landmark CRRT dose trial (Ronco et al, Lancet 2000) was performed in the post-dilution CVVH mode. The clinical benefits provided by different CRRT modes may influence MM clearance. The purpose of this experimental CVVH study was to measure the clearance of small solutes (urea, creatinine) and MM surrogates (vancomycin, inulin) in different dilution modes, degree of pre-dilution, and flow conditions along with MM sieving coefficient (SC) values over extended periods.

Methods: The Prismaflex (Baxter) machine was used to deliver replacement fluid at different dilution points [pre-blood pump dilution (PBP), pre-dilution (PRE) and post-dilution (POST)]. Simulated treatment involved 6 liters of bovine blood (Hct ~ 35%) processed at zero net ultrafiltration for a duration of 240 minutes. A 1.4 m^2 hemofilter (HF 1400) was used. The three experimental conditions were: 1) blood flow rate (Q_B): 190 mL/min; replacement flow rate (Q_R): 2 L/hr, 2) Q_B: 290 mL/min; Q_R: ~3 L/hr, 3) Q_B: 380 mL/min; Q_R: ~4 L/hr. These conditions were chosen to maintain filtration less than 25% in POST. Solute clearance at various times were calculated based on mass balance.

Results: There were significant differences ($p < 0.001$) in urea & creatinine clearance for the different experimental conditions. There was a significant decrease ($p < 0.01$) in urea and vancomycin clearance from POST to PRE and from POST to PBP, although there were no significant differences between PRE and PBP for any of the solutes. Neither urea nor creatinine clearance changed significantly over time for any of the operational conditions and dilution modes. There were significant differences ($p < 0.001$) in inulin and vancomycin clearance in these 3 experimental conditions. No significant differences ($p > 0.05$) in inulin clearance between post-dilution and pre-dilution mode, post-dilution and pre-pump-dilution mode, and pre-dilution and pre-pump-dilution mode were observed. A significant decrease in inulin and vancomycin SC occurred over time under all conditions was most evident in POST.

Conclusions: 1) Small MW solute clearance increased as the extent of pre-dilution decreased 2) MM SC decreased substantially (especially in POST) with time, most likely due to secondary membrane effects. 3) The data obtained by varying pre- and post-dilution percentages are predictable for small solutes but are not entirely consistent for MMs.

FR-PO469

Urea Transfer Kinetics in Allo-Hemodialysis: Results from an Ex Vivo Study

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Background: Allo-hemodialysis (alloHD) is a novel, low-cost extracorporeal dialysis modality where the conventional dialysate is replaced by blood from a healthy subject ("buddy"). We are not aware of literature reporting urea transfer across hemodialyzer membranes with counter-current blood flow through the conventional blood and dialysate compartments.

Methods: We developed a mathematical model of alloHD setup comprising the patient and the buddy beaker, the extracorporeal circuit, and the dialyzer. To calibrate the model, we conducted an *ex vivo* alloHD experiment with human whole blood. We dialyzed a 500-mL patient bucket against a 500-mL buddy bucket for 60 minutes. Heparin (5,000 U/L) was used as anticoagulant. Average blood flow rate of 110 mL/min on both sides was achieved by peristaltic pumps. The patient side was initially spiked with urea to simulate pre-dialysis conditions. Blood samples from both sides were collected at multiple time-points into the experiment. Serum urea was measured using automated spectrophotometry.

Results: The urea concentrations on the patient and buddy sides equilibrated rapidly (**Figure 1**). The estimated urea mass transfer coefficient (K_oA) was 853 mL/min. Using this estimated K_oA, the model-based urea concentrations predicted the observed concentration profiles very well.

Conclusions: The estimated urea K_oA of 853 mL/min is similar to a typical urea *in vivo* K_oA reported for conventional hemodialysis (~1000 mL/min). The presence of blood on both sides of the dialyzer membrane did not appear to affect the urea mass transfer capacity of the dialyzer in a clinically meaningful way, and rapid urea equilibrium was achieved in this *ex vivo* alloHD setup. These findings are an important step towards validation of the alloHD concept and planning of future animal experiments.

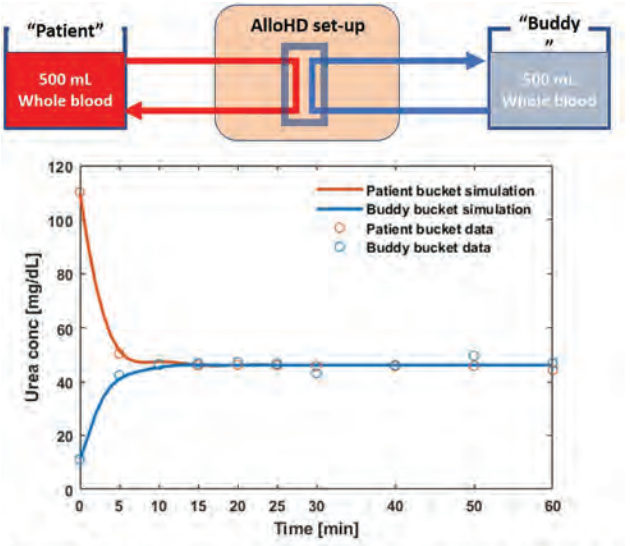

Figure 1: Time-course of urea concentration in the patient and buddy bucket during alloHD. On the patient side, we used two pumps, and their flow rate differential was used to target zero net ultrafiltration.

FR-PO470

A Single-Center Experience Piloting the Tablo Hemodialysis System for Intermittent Hemodialysis (IHD) in an Acute Hospital Setting: A Quality Improvement Project

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Background: The TABLO hemodialysis system integrates on-demand dialysate production, reverse osmosis (RO) water purification and computerized data collection into a single mobile unit. The system provides a maximum dialysate flow rate (Qd) of 300ml/minute. Kinetic modeling and outpatient clinical experience show that adequacy targets (urea reduction ratios [URR] greater than 65%) can be achieved. This Quality Improvement project was undertaken to evaluate the performance of TABLO in patients undergoing intermittent hemodialysis (IHD) in an acute care setting.

Methods: Between January and February 2019, 25 hospitalized patients with acute (17) or end stage renal failure (8) received hemodialysis therapy with the TABLO. Treatment parameters including URR, ultrafiltration (UF) accuracy, serum potassium and treatment complications were recorded.

Results: TABLO was used for a total of 46 hemodialysis treatments. Thirty two % of patients had weights greater than 100 kg. Vascular access was tunneled catheter (57%) AV fistula (21%) non-tunneled catheter (14%) and AV graft (8%). Ninety two percent used an Opti 180 and 8% used an Opti 200 dialyzer. The average URR was 68% (SD11) with an average dialysis time of 3.7 hours. Pre-dialysis potassium averaged 4.5 mmol/L. Potassium obtained the day after dialysis averaged 4.1 mmol/L. Blood flow rates averaged 371 (SD54) cc/minute. Average prescribed and achieved UF for patients was 1.7 L. Six treatments were terminated early due to access problems, hypotension or clotting. Seven therapies required a second setup due to clotting. These runs were subsequently completed.

Conclusions: This QI project demonstrates that the TABLO provides adequate URR with Qd 300ml/min and accurately meets UF targets in the majority of patients requiring IHD in the acute care setting. Water pressure problems frequently encountered with Fresenius 2008T machines were not encountered with TABLO. The TABLO's small footprint (size of a dormitory refrigerator) facilitates travel to multiple ICUs. The TABLO was welcomed within the space constraints of ICU rooms. Low dose heparin and/ or periodic saline flushes may be required to prevent clotting. Further studies will be required to assess potassium removal in highly catabolic patients.

Funding: Clinical Revenue Support

FR-PO471

Ten Thousand Consecutive Treatments Using the Tablo Hemodialysis System in Hospitals and Clinics

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Background: The Tablo® Hemodialysis System is an all-in-one system indicated for use in clinic and hospital settings. Features include an integrated water purification system, the ability to produce dialysate on demand, a simplified user interface, and two-way wireless connectivity for data transfer. This study reports on the clinical experience using Tablo for 10,000 treatments (txs) in the clinic and hospital settings.

Methods: Data on treatment performance and clinically significant alarms (air in venous bloodline, high/low venous pressure, low systolic blood pressure, and blood leak in dialyzer) for 10,000 consecutive dialysis txs was collected using the Tablo system and transmitted wirelessly in real-time to a cloud-based, HIPAA compliant platform.

Results: Tablo was used to treat hemodialysis patients in the clinic and hospital settings using a wide range of treatment times and ultrafiltration rates. The average number of clinically significant alarms was 1.1 and 2.5 per treatment in the clinic and hospital settings, respectively.

Conclusions: In 10,000 treatments within the clinic and hospital settings, Tablo can successfully complete dialysis and ultrafiltration with minimal interruption from clinically significant alarms. This data can be successfully transmitted wirelessly to Tablo's cloud-based, HIPAA compliant server. This extensive clinical experience with Tablo confirms earlier reports of its successful use in smaller studies.

Funding: Commercial Support - Outset Medical

Results for patients treated in the clinic and hospital settings

CLINIC	RESULTS
Txs	5758
Txs ≤ 4 hr (mean tx time ± sd) (%)	5402 (3.4 ± 0.6) (93.8%)
Txs > 4 hr (mean tx time ± sd) (%)	356 (4.6 ± 0.3) (6.2%)
Blood flow rate (mean ± sd)	383.3 ± 33.0 mL/min
Dialysate flow rate (mean ± sd)	299.5 ± 8.8 mL/min
Fluid removed (mean ± sd)	1796.8 ± 1130.9 mL
Avg # of clinically significant alarms (per tx)	1.1
HOSPITAL	RESULTS
Txs	4265
Txs ≤ 6 hr (mean tx time ± sd) (%)	4242 (2.8 ± 1.0) (99.5%)
Txs > 6 hr (mean tx time ± sd) (%)	23 (7.8 ± 1.0) (0.5%)
Blood flow rate (mean ± sd)	325.8 ± 48.6 mL/min
Dialysate flow rate (mean ± sd)	297.8 ± 20.0 mL/min
Fluid removed (mean ± sd)	1758.8 ± 1096.5 mL
Avg # of clinically significant alarms (per tx)	2.5

FR-PO472

Reuse of Dialysis Reverse Osmosis System Reject Water for Aquaponics and Hydroponics

Eason Chang, Chun leong Low. *Nephrology Unit, Hospital Sultan Abdul Halim, Sungai Petani, Malaysia.*

Background: Hospital Sultan Abdul Halim hemodialysis unit located in the district of Sungai Petani in Kedah, Malaysia has started operation since 1998. The dialysis unit has 19 hemodialysis machines and is located in 2 separate buildings which caters to about 90 patients. Hemodialysis is provided by single-pass, proportioning dialysis systems paired with reverse osmosis (RO) system water filtration that rejects 60–70% of the presented mains at the RO system membrane. This reject water is discarded to drain almost universally.

Methods: In our unit, the reject water is used for aquaponics and hydroculture since July 2018. The reject water from one of the building has been repiped and the reject water is then pumped into fish tanks. The amount of reject water is estimated to be between 10000 – 12000 litres per day. The state fisheries department collaborated with us by supplying fish tanks, fingerlings and feed for the fishes. Four 1800 litres capacity tanks, three 700 litres capacity tanks and one 1000 litres capacity tank were used.

Results: The fisheries department performed water testing to determine the suitability of the water for aquaculture. The test revealed water temperature of 31 degrees celcius (25-35), pH of 7.76 (6.5-8.5), ammonia level of 0.001 (<0.02 ppm/mg/l) and dissolved oxygen level of 5.84 (>4ppm). The species of fishes that were bred include Oreochromis aures x Oreochromis mossambicus (Red Tilapia), Oreochromis niloticus (Genetically Improvised Farmed Tilapia), Scortum barcoo (Jade Perch) and Oxyeleotris marmorata (Marble Goby). The fries released were initially 2-3 inches long and weighed about 20-30 grams in average. After a period of 5 months, the fishes grew to an average of 10-11.5 inches and weighed about 400-470 grams. The nutrient rich water from the fish tanks are then recirculated to the vegetable pots via deep water culture. The vegetables that were grown included Amaranthus dubius (red spinach), Sissoo (brazillian spinach), Brassica juncea (mustard), Mentha (mint) and Allium schoenoprasum (chives). These vegetables were harvested and given to patients for consumption.

Conclusions: Reject water that is actually clean and uncontaminated water can be reused to promote water conservation and used for aquaculture and hydroponic activities with encouraging results. It also provides a good biosecurity enviroment for the fishes to grow.

FR-PO473

Hybrid Conductivity/Urea Kinetic Modeling Approach to Calculate Kt/V and Normalized Protein Catabolic Rate with Reduced Need for Postdialysis BUN

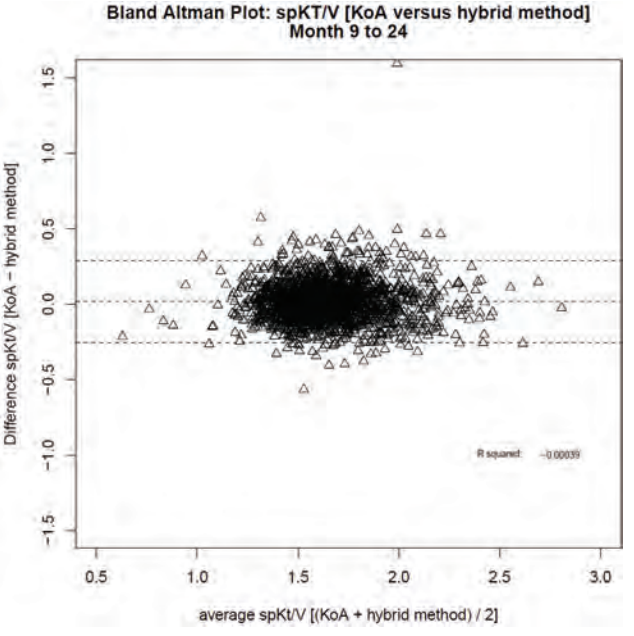
Jochen G. Raimann,[1] Xiaoling Ye,[1] Peter Kotanko,[1] John T. Daugirdas.[2] *[1]Renal Research Institute, New York, NY; [2]University of Illinois College of Medicine, Chicago, IL.*

Background: We present a novel hybrid conductivity /urea kinetic modeling (UKM) method to calculate Kt/V and normalized protein catabolic rate (nPCR) that markedly reduces the need for routine post-dialysis BUN measurement.

Methods: Data from midweek dialysis sessions of patients monitored over a 2-year period were studied. During the initial 8 months (baseline), measured average conductivity clearance, Kecn, and URR were entered into a UKM program to calculate a median patient-specific modeled solute distribution volume, Vcal. During months 9–16 (period 1) and 17–24 (period 2) Kt/V was computed by UKM using URR and estimated dialyzer clearance (conventional method) as well as by the proposed method, which can compute Kt/V using Vcal along with the treatment-specific average Kecn without the need for a postdialysis SUN.

Results: In 1087 patients, the mean (SD) of the median single-pool Kt/V by the conventional method were 1.62 (0.245), 1.66 (0.24) and 1.67 (0.25) during baseline, periods 1 and 2, respectively. During periods 1 and 2, median Kt/V with the new method averaged 1.64 (0.24) and 1.65 (0.24), respectively; differences between the new method and conventional method averaged –0.6% (8.0) and –0.8% (8.4), respectively. nPCR rate was comparable between the two methods. **Figure:** Bland-Altman plot of the bias in median (single-pool) Kt/V using the proposed method compared to the KoA based classic method during Months 9 to 24.

Conclusions: The novel hybrid conductivity-UKM based method of monitoring hemodialysis adequacy is non-inferior to the standard approach. It has the potential to avoid Kt/V errors related to improper peridialytic BUN sampling.



FR-PO474

Clinical Study to Assess the Performance of a Novel Dialyzer with Endexo™ in ESRD Subjects

Jill M. Meyer,[1] Dylan Steer,[1] Lisa A. Weber,[3] Abeer A. Zeitone,[2] Mayuri Thakuria,[2] Chiang-Hong Ho,[2] Sharanya Vemula,[2] Shakil Aslam,[2] Claudy Mullon,[2] Robert J. Kossmann.[2] *[1]Balboa Nephrology Medical Group, La Jolla, CA; [2]Fresenius Medical Care North America, Waltham, MA; [3]Kansas Nephrology Physicians, P.A., Wichita, KS.*

Background: Surface modifying macromolecules (SMM) may improve the hemocompatibility of hemodialyzers in the development of heparin free hemodialysis (HD). The aim of this clinical trial was to assess the performance and safety of a new dialyzer using a novel fluorinated SMM additive (Endexo™) in ESRD Subjects.

Methods: This prospective, sequential, multi-center, open-label study (NCT# 03536663) was designed according to the FDA's Guidance for the premarket testing of hemodialyzers. Adult subjects, prescribed thrice-weekly HD for at least 180 days, were enrolled at 3 HD clinics in the US. After completing 12 HD sessions (4 weeks) with an Optiflux® F160NR dialyzer (Opti), subjects received 36 HD sessions with the dialyzer with Endexo (EndX). Evaluated parameters included spKt/V, URR, albumin, β2-microglobulin (β2M), complement activation for Opti and EndX, and hemoglobin and platelet count for EndX only.

Results: A total of 23 subjects (60.5±15.1 yr., BW 70.9±17.4 kg, 17 males) were enrolled and 17 subjects completed the study, 6 subjects were withdrawn due to missed visits not related to the dialyzers. Mean treatment times (208 vs. 207 min), blood flow rates (447.7 vs. 447.5 ml/min), dialysate flow rates (698.5 vs. 698.0 ml/min), URR (80%± 8 vs. 80.2%±4.8) and spKt/V (2.0±0.43 vs. 1.9±0.31) were comparable for EndX and Opti, respectively. There was no evidence of overt complement activation as C5a and C3a levels remained unchanged from pre-HD, and a slight trend for increase in sC5b-9 levels at 30 min was observed for both dialyzers. Comparable increase in serum albumin was observed from pre to post HD, 7.45%±8.5 Opti and 7.40%±7.4 EndX, however, β2M removal rate was 67% higher with EndX vs. Opti. Post-HD hemoglobin increased by 4.75%±8.2 vs. pre-HD (EndX), and post-HD platelet count decreased by 2.7%±5.6 vs. pre-HD (EndX). Three serious adverse events were reported, none of them were device related.

Conclusions: In a prospective, sequential, multi-center, open-label clinical trial, the Optiflux dialyzer and the novel dialyzer with Endexo were well tolerated with high URR

and spKT/V. The β2-microglobulin removal efficiency was 67% higher with the dialyzer with Endexo.

Funding: Commercial Support - Fresenius Medical Care North America, Renal Therapies Group, Waltham, MA, United States

FR-PO475

High-Volume Predilution Online Hemodiafiltration (HVPO-HDF) Is the Ideal Blood Purification Method from an Amino Acid Nutritional View

Motoko Kato,[1] Shunichiro Urabe,[1] Toru Hyodo,[2] Makoto Kitamura,[3] Miho Hida,[3] Yasuhisa Kurata,[3] Keiichiro Sakashita,[5] Kenichi Kokubo.[4] *[1]Eijin Clinic, Hiratsuka, Kanagawa, Japan; [2]Eijin Clinic and Cambodian Association of Nephrology, Hiratsuka, Japan; [3]Kurata Hospital, Hiratsuka, Kanagawa, Japan; [4]Kitasato University School of Allied Health Sciences, Sagamihara, Japan; [5]Laboratory of Dialysis Medical Care and Technology, Nagoya-city, Aichi, Japan.*

Background: Elderly ESRD patients with sarcopenia and frailty have been recently increased in Japan. It was reported the amino acid losses were up to 6 to 12 g per HD session (Kidney Int. 1994;46: 830-7). It seems to be important to restrain these amino acid losses during dialysis session from the point of nutritional view. We analyzed the amino acid losses that occur on performing high volume pre-dilution on-line HDF (HVPO-HDF) and HD.

Methods: We compared the amino acid and albumin amount into the total waste fluid, reduction rate of β_2-microgloblin (β_2-MG) and Kt/V (urea) in same 9 patients (7 males, 4 diabetics, mean age: 71.4±2.5 years) when they received HVPO-HDF and HD. The treatment time is 4 hours, respectively. The mean blood flow rate was 200 mL/min, respectively. The dialysate flow rate was 200 and 500 mL/min, respectively. The replacement fluid flow rate was 400 mL/min and total replacement fluid volume was 90 in HVPO-HDF. Hemodiafilter MFX-21Meco(Nipro, Ltd) was used for HVPO-HDF and Dialyzer FX-220(Fresenius Ltd) was for HD. These hemodiafilter and dialyzer were designed to suppress albumin leakage as possible as during dialysis session.

Results: In the O-HDF group, the total amino acid, total non-essential, essential, branched-chain amino acid losses (4511±797* mg, 2892±772* mg, 1619±286* mg, 739±167* mg, respectively) were significantly lower than in the HD group (6309±1072mg, 4008±772mg, 2301±414mg, 1058±263mg, respectively) (* $p < 0.01$). The albumin losses of both methods were almost same and extremely low (HVPO-HDF: 0.15±0.0 g, HD: 0.12±0.0). In the HVPO-HDF group, the β_2-MG reduction rate (69.8±5.0** %) was higher than in the HD group (65.3±5.0%) (** $p < 0.05$). The Kt/V (urea) values in the former and latter were 1.33±0.17** and 1.45±0.23, respectively. The HVPO-HDF can restrain the amino acid loss more effectively than HD. Both of hemodiafilter and dialyzer which were used in this study showed extremely low albumin leakage. In the HVPO-HDF group, the β_2-MG reduction rate was higher than in the HD group. The Kt/V (urea) of HVPO-HDF was within favorable range (>1.2).

Conclusions: This method is most powerful method to restrain amino acid and albumin losses in order to keep nutritional condition to avoid sarcopenia and frailty in elderly ESRD patients.

FR-PO476

Variability Between Prescribed and Measured Dialysate Sodium in the Acute Care Hemodialysis: Effects of Additives and Other Electrolytes

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Background: Significant variance in ordered versus measured dialysate Na has been noted in the outpatient HD setting. We examined this variance in a large hospital acute care hemodialysis program.

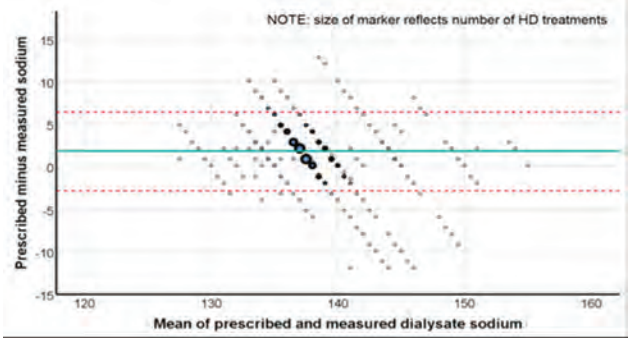
Methods: Dialysate electrolyte panels (DEP) were examined with point of care concentrates in an inpatient HD unit (Fresenius machines). DEP labs included Na, K, HCO3, PO4, and Mg. Ordered versus measured values for each electrolyte were analyzed by linear mixed model that included the particular HD machine for random effect. Logistic regression modeling was used to determine factors associated with significant variance between ordered and measured values.

Results: 5416 HD treatments identified. Significant differences noted between ordered and measured Na, HCO3 and Mg, but not K (Table 1). We focused on Na; 94% of HD's had differences of ± 5 mEq/L between ordered and measured dialysate Na levels. Bland-Altman plot showed skew towards a lower delivered versus ordered dialysate Na concentration. In 694 HD treatments, dialysate Na was manually corrected based on the first out of range measured Na. On repeat, 86.3% of treatments were within ± 3 mEq/L of the ordered Na. On logistic regression modeling for factors associated with measured dialysate Na >5 mEq/L out of range, phosphorus added to the dialysate and ordered dialysate Na > or < 140 were both statistically significant; 2.63 (1.38 - 5.02) and 1.10 (1.04 - 1.15), respectively.

Conclusions: There were significant differences between prescribed and measured dialysate Na, HCO3 and Mg, but not with K. Measured Na was on average 1.75 mEq/L lower than ordered; a difference of >5 mEq/L was found in 6% of HDs. Manual adjustment of dialysate Na setting, when performed, corrected this difference 86% of instances when rechecked on the same HD. Additives to the dialysate solution and ordered dialysate Na > or < 140 were associated with out of range measured Na

Funding: Clinical Revenue Support

Ordered - Measured	Mean	95% CI	2-tailed p-value
Na	1.75	1.68 to 1.82	<0.001
K	0.0053	0.0040 to 0.013	0.191
HCO3	0.30	0.26 to 0.35	<0.001
Mg	-0.030	-0.033 to -0.028	<0.001



FR-PO477

A 1-Year Study on the Effects of Hemodialysis Using Dialyzer with Medium Cut-Off Membrane

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Background: Medium cut-off (MCO) membrane is a dialyzer with enhanced sieving properties for soultes. An internal filtration of MCO membrane facilitated filtration of large middle molecules, and enhanced fitration of small molecules withtout replacement fluid. A long-term study for several markers after use of MCO membrane is few. We evaluated the various effects related with MCO membrane for 1 year in patients with ESRD.

Methods: Total 40 patients were analyzed for 1 year. The enrolled patients were > 18 years old and were on hemodialysis (HD) using high flux (HF) membrane for >3 months before enrolment. We prospectively collected serum samples with 3-month interval for 1 year. All patients were divided into control (HF, n=20) and MCO (MCO, n=20) group. The patients with serum albumin of > 3.5 g/dL and clinical sign, such as uncontrolled hyperparathyroidism or hyperphosphatemia, were included in MCO group. We measured and calculated serum markers, including parathyroid hormone (PTH), C-reactive protein (CRP), phosphate, hemoglobin (Hb), total protein, albumin, and spKt/V with 3-month interval.

Results: Compared to control group, patients in MCO group were younger and showed higher values of serum albumin and phosphate. In MCO group, serum protein and albumin decreased significantly over time (p <0.05), but serum albumin compared with serum protein did not decrease significantly since 6 months (p =0.056). Serum albumin increased significantly after 6 months in MCO group (p =0.012). The spKt/V increased until 6 months, but it didnot increased significantly since 6 months in MCO group (p =0.072). Several markers such as serum phosphate, calcium, CRP and Hb except for PTH did not show significant changes in both groups. Unexpectedly, PTH increased singnificantly in both groups. In analysis of differences between two groups over time, there was a significant difference only in change of serum phosphate (p =0.030).

Conclusions: Baseline levels of serum phosphate and albumin were high in MCO group due to selection bias. However, this study showed that albumin loss in MCO group was not significant after 6 months, and the spKt/V value in MCO group increased until at least 6 months. Moreover, we could recognize the possibility for hyperphosphatemia reduction in MCO group. Thus, HD using MCO membrane may be superior in clearance of small solutes and be not inferior in albumin loss for 1 year.

FR-PO478

Clinical and Operational Results of In-Center Nocturnal Hemodialysis (INHD) Programs in a Large Dialysis Organization (LDO)

Martin J. Schreiber, Sean Muir, Lillian Mecum, Brooke Bowlby, Bram Van hout, Zachariah W. Peterson. *DaVita Inc, Denver, CO.*

Background: INHD offers a combination of efficacy, safety, and improved treatment tolerability. Recognizing the specific clinical and laboratory results that indicate INHD might be beneficial for a given patient requires an understanding of modality-specific therapeutic differences. Here, we report the operational characteristics and clinical laboratory results of INHD programs in an LDO.

Methods: All patients admitted to LDO INHD programs during 2017 and 2018 were included in the analysis. Patient demographic information, dialysis prescription data, laboratory markers, blood pressure, target weight, and hospitalization rates were assessed and compared to those for in-center hemodialysis (ICHD) patients treated at the LDO during the same period.

Results: Data from 2747 patients treated in 176 INHD programs were assessed. Across the LDO, 19 INHD programs started operation during 2018, 24 closed; the most common closure reasons were transition of patients to the working shift (82%) and staffing constraints (9%). Mean INHD program census was <10 patients, mean operating time was 8.9 hours/shift, and staff retention rate was 83%. Mean age of INHD patients was

52 years; 29.5% were female; access use was 68.9% AVF, 15.1% AVG, 10.6% CVC, and 5.4% other. Laboratory and clinical parameters for INHD vs ICHD patients are shown.

Conclusions: INHD was associated with improved solute clearance, lower ultrafiltration (UF) rates, improved nutritional parameters, and lower hospitalization rates compared to ICHD. Patients receiving standard ICHD who are not achieving risk factor control, are experiencing increased organ stunning risk with elevated UF rates, or with hemodynamic instability should be considered for transition to INHD.

Funding: Commercial Support - DaVita Inc

	INHD n=2747	ICHD n=268,572
Kt/V > 1.2	98.8%	97.1%
Albumin > 3.5 g/dL	85.4%	71.4%
Albumin > 4 g/dL	33.3%	19.0%
Phosphorus < 5.5 mg/dL	58.1%	58.9%
Calcium ≤ 10.2 mg/dL	97.2%	97.4%
URR ≥ 65%	94.4%	91.3%
PTH 150-600 pg/mL	53.3%	61.0%
BP pre-dialysis (mm Hg)	146.0	147.4
BP post-dialysis (mm Hg)	132.9	137.4
UFR (mL/kg/hr)	5.3	7.2
Hospitalization rate (admissions per patient per year)	1.40	1.82

FR-PO479

Controlling High Pre-Dialysis Serum Total Carbon Dioxide Concentration with Low Dialysate Flow Systems During Frequent Nocturnal Hemodialysis

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Background: Although use of low dialysate bicarbonate concentration ([bicarbonate]) during in-center, thrice weekly in-center hemodialysis (ICHD) is a common strategy to control high serum predialysis serum total carbon dioxide concentration ([TCO2]), such an approach is not always possible with commercial lactate dialysates. We used clinical data in patients who transferred from ICHD using bicarbonate dialysate to 6 times per week hemodialysis during the FREEDOM Study and the H^+ mobilization model (Sargent et al, Semin Dial 31:468-78, 2018) to calculate the effect of using 30 L versus 60 L of dialysate volume per treatment to reduce [TCO2] during frequent nocturnal hemodialysis (NHD).

Methods: The H^+ mobilization model was first used to simulate ICHD treatments using dialysate [bicarbonate] of 34, 37 & 40 mEq/L at [TCO2] of 22, 24 & 26 mEq/L to calculate a weekly acid generation rate. Assuming a constant weekly acid generation rate, patients were assumed transferred to NHD with treatment (Tx) frequencies of 3.5 (every other day), 4 & 5 times per week and dialysate volumes per Tx of 30 L & 60 L. Blood flow rate was assumed as 300 mL/min, Tx time of 420 min, and dialysate [lactate] was 40 mEq/L during NHD.

Results: Summary results are tabulated. Lowering dialysate volume per Tx from 60 to 30 L resulted in lower [TCO2] by approximately 2-3 mEq/L.

Conclusions: Patients who may achieve excessively high [TCO2] during NHD using lactate as dialysate buffer can use of 30 L instead of 60 L per treatment to reduce [TCO2]. Such reductions in dialysate volume during NHD are not expected to substantially lower dialysis adequacy.

Funding: Commercial Support - NxStage Medical Inc. (Fresenius Medical Care)

[TCO2] During NHD (mEq/L)

	3.5 Tx/wk		4 Tx/wk		5 Tx/wk	
[TCO2] during ICHD	DV=30 L	DV=60 L	DV=30 L	DV=60 L	DV=30 L	DV=60 L
22	20	23	21	24	24	26
24	21	24	23	25	25	27
26	23	26	25	27	27	28

All values averaged during ICHD treatments (Tx) using dialysate [bicarbonate] of 34, 37 & 40 mEq/L; the standard deviation of all values was 1 mEq/L. (DV denotes dialysate volume per treatment.)

FR-PO480

Plasma Viscosity Can Explain the Marked Reduction in Dialyzer Mass Transfer Area Coefficient for Urea and Other Solutes In Vivo Compared with In Vitro Values

Daniel Schneditz,[1] John T. Daugirdas.[2] *[1]Division of Physiology, Otto Loewi Research Center, Medical University of Graz, Graz, Austria; [2]University of Illinois College of Medicine, Chicago, IL.*

Background: The dialyzer area membrane transfer coefficient product (K_0A) characterizes the diffusive performance of a dialyzer and is one of the key components to prescribe a dialysis dose. However, in-vivo dialyzer K_0A for urea is always much smaller and only 50 to 60% of in-vitro K_0A tabulated in dialyzer manufacturer sheets and typically obtained from clearance measurements using crystalloid water solutions. The reason for this reduction has not been clearly determined. We hypothesized that the known effect of viscosity on solute diffusivity might partially or fully account for this reduction.

Methods: In-vitro dialyzer clearance of urea and glucose was measured in low- and high-flux dialyzers under different operating conditions using crystalloid solutions as well as bovine blood with different hematocrit and plasma viscosity. Viscosity of plasma, blood, and aqueous solutions was measured at 37°C. Diffusivity and relative K_0A values were computed for each solute under these different conditions.

Results: Relative K_0A was negatively correlated to relative plasma viscosity ($p<0.001$, $r^2=0.38$) and solute diffusivity ($p<0.001$, $r^2=0.48$) for urea and glucose (Fig. 1). Plasma was 1.84±0.31 times more viscous compared to crystalloid test solutions with a viscosity of 0.72 mPa.s, suggesting a correction multiplier of 0.54 (=1/1.84) for in-vivo solute diffusivity and K_0A relative to the in-vitro value. The average multiplier based on individual measurements was 0.67±0.09.

Conclusions: The known effect of viscosity on solute diffusivity is sufficient to explain the reduction of dialyzer K_0A for urea and glucose in-vivo compared to in-vitro measurements. The residual scatter in the K_0A to viscosity relationship suggest that additional mechanisms may be operative.

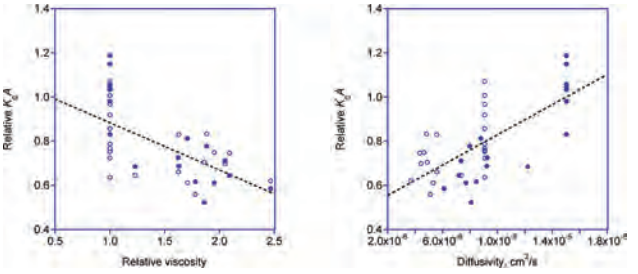

Fig. 1 Relative K_0A for urea (closed circles) and glucose (open circles) as function of relative plasma viscosity (left panel) or solute diffusivity (right panel). Dashed lines show the linear regressions for both urea and glucose.

FR-PO481

Hemoperfusion Associated with Impairment in Hemostasis in Patients with Acute Pesticide Intoxication

Samel Park, Eun-Young Lee. *Soonchynhyang University, Cheonan, Korea, Cheonan, Republic of Korea.*

Background: Hemoperfusion is one of the important treatment modalities in extracorporeal therapy for patients with acute intoxication. Its use has declined during the past 20 years despite its efficacy due to bleeding.

Methods: Twenty-five patients who underwent hemoperfusion due to acute pesticide intoxication participated. The changes in CBC, platelet function, platelet shape by SEM, platelet glycoprotein expression by FACS, and coagulation profiles were evaluated.

Results: After initiation HP, platelet count decreased by 40%. Delayed closure time that represents platelet dysfunction was observed; however, SEM showed activated shape-changed platelets adhered to activated charcoal. Platelet expressing CD61 (fibrinogen receptor) significantly decreased, while those expressing CD42b (vWF receptor) did not show significant change; however, platelet expressing CD49b (collagen receptor) significantly increased. Thrombin-antithrombin complex (a marker for thrombin generation) appeared to decrease without significance. FDP and d-dimers (markers for fibrinolysis) increased significantly during HP.

Conclusions: Our data suggest that hemoperfusion leads to increased platelet adhesion with decreased platelet aggregation, which might be associated with reduced thrombin generation and increased fibrinolysis.

Funding: Government Support - Non-U.S.

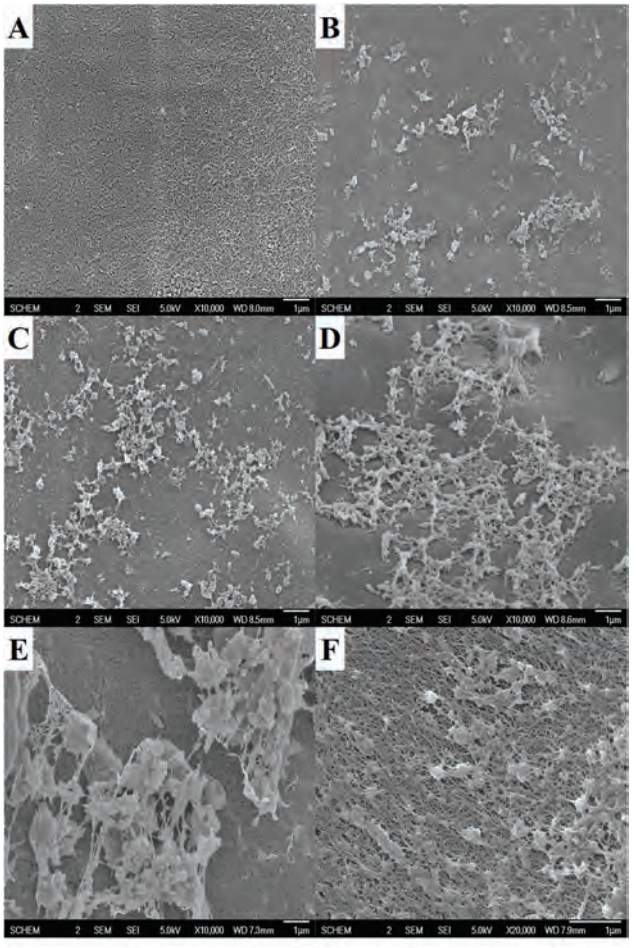

Figure 1. Scanning electron microscopy of the surface of activated charcoal from hemoperfusion cartridge. (A) Clear surface of the activated charcoal coated with cellulose, obtained from a non-used HP cartridge. Activated platelets adhered to the surface of activated charcoal after (B) 30 min, (C) 60 min, and (D) 120 min of shaking *in vitro*. (E), (F) Surface of activated charcoal obtained from a HP cartridge used in a patient with pesticide intoxication. (E) Red blood cells and activated platelets adhered to the surface of activated charcoal. (F) The activated platelets and fibrin clots adhered to the surface of activated charcoal.

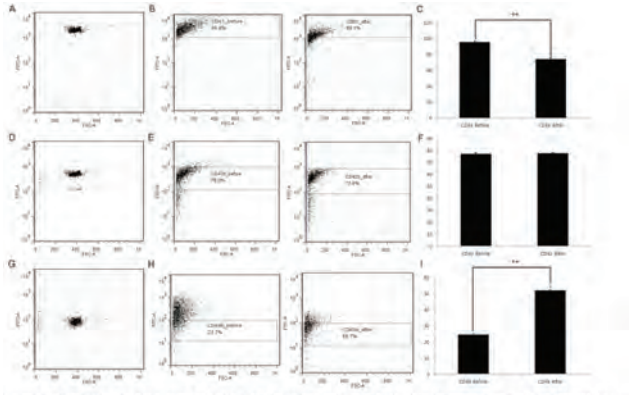

Figure 4. Changes in the expression of platelet surface glycoprotein after *in vitro* exposure to activated charcoal. (A) Identification of CD61-positive control platelets. (B) Gating of CD61 expression on platelets. CD61 expression was decreased after treatment. (C) CD61 content of platelet shown as a percentage of total platelets. (D) Identification of CD42b-positive control platelets. (E) Gating of CD42b expression on platelets. CD42b expression was not changed after treatment. (F) CD42b content in platelets shown as a percentage of total platelets. (G) Identification of CD49b-positive control platelets. (H) Gating of CD49b expression on platelets. CD49b expression was increased after treatment. (I) CD49b content in platelet shown as a percentage of total platelets. *, $p < 0.05$; **, $p < 0.01$.

FR-PO482

The Proteome of Hemodialysis Membranes: A Discovery Proteomic Pilot Study

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Background: Hemodialysis (HD) membranes have been continuously upgraded during the past decades. Nevertheless, little is known about the real pattern of protein removal among different HD membranes. We aimed to explore the proteome of depuration from a mid-cut-off HD membrane (Theranova, Baxter, IL, USA) and from a high flux membrane in HD and hemodiafiltration (HDF) (FX1000, Fresenius Medical Care, Bad Homburg, Germany).

Methods: 9 HD patients were separated in 3 groups: Theranova, FX1000 in HD and FX1000 in HDF. During their mid-week session, 1 liter of dialysate was sampled and 30 ml were freeze-dried. Additionally, the dialysis membrane was eluted and both dialysate and eluate were prepared for LC/MS-MS analysis (liquid chromatography coupled with a tandem mass-spectrometer). Samples were analyzed using an nano-RSLC (high performance liquid chromatographer, Thermo Fischer, Waltham, MA, USA) coupled on line with a Q-Orbitrap mass spectrometer. Data were processed by database searching using SequestHT with Proteome Discoverer 2.2 software against a human Swissprot database and quantified with a TMT-labeling approach. Semi-quantitative analysis was expressed as a ratio. Proteins were analysed using STRING tool for reactome pathway analysis.

Results: 526 proteins were found in the dialysate samples from all the membranes and 360 onto dialysis membranes. 455 proteins were found in the dialysate from FX1000 HDF group, 437 for Theranova and 410 for FX1000 HD. 360 proteins were also found adsorpbed onto the membranes. For Theranova, 45 proteins were found significantly more depurated by diffusion and/or convection than adsorption and 101 more by adsorption than diffusion/convection. For FX1000 HD, 56 and 100. For FX1000 HDF, 61 and 56 respectively. With Reactome pathway analysis, numerous removed proteins were involved in innate immune system, hemostasis, extra-cellular matrix organization, platelet aggregation, lipid metabolism and molecular signaling pathways.

Conclusions: More than 500 proteins were identified in the proteome of depuration from HD and HDF membranes among which a significant number are specific from each membrane and modalities. Further analysis are required to understand the issues of the depuration of these proteins in improving HD patients outcomes.

Funding: Commercial Support - Baxter S.A.

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Ex Vivo Validation of Allo-Hemodialysis for Removal of Creatinine and Protein-Bound Uremic Toxins

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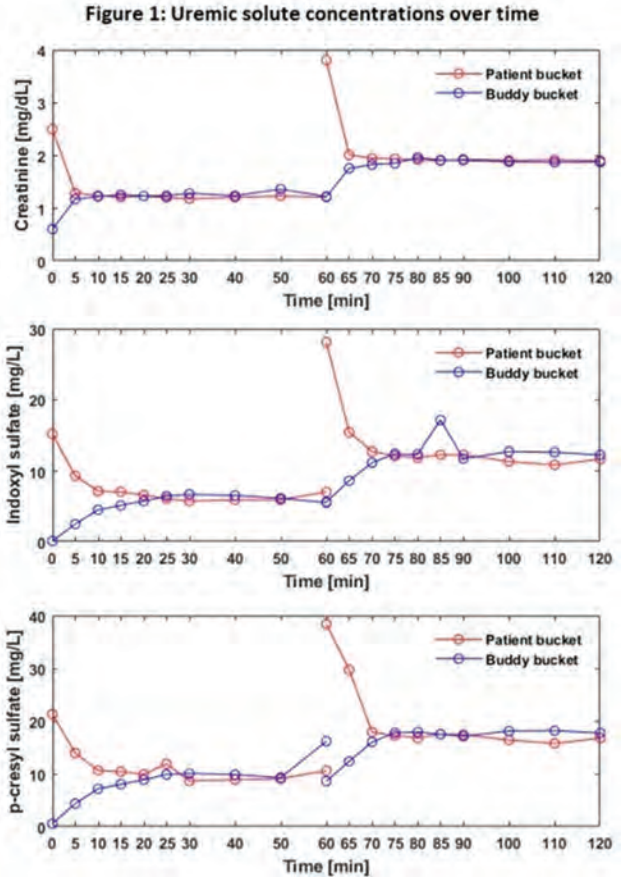
Background: Unlike conventional hemodialysis, allo-hemodialysis (alloHD) has a patient dialyzed against a healthy subject ("buddy"). This *ex vivo* study aimed to explore the feasibility of removing creatinine and protein-bound uremic toxins (PBUTs) with alloHD, where whole blood constitutes the "dialysate".

Methods: Two buckets of whole blood (anticoagulated with 5,000 U/L heparin) were designated as "patient" and "buddy" and dialyzed against each other for 2 hours with initial flow rates of 110 mL/min for both circuits using a high-flux cellulose triacetate dialyzer (Nipro Cellentia 17H, surface area 1.7 m^2) and targeting zero net ultrafiltration. The "patient" bucket was initially spiked with creatinine, indoxyl sulfate (IS), and p-cresyl sulfate (pCS) to establish a diffusion gradient between patient and buddy. This was followed by a 2nd spike 1 hour into the experiment. After each spike, blood samples from both sides were collected after each spike every 5 min for 30 min, then every 10 min for the next 30 min. IS and pCS were measured via liquid chromatography–mass spectrometry after liquid-liquid extraction, while creatinine was determined via spectrophotometry.

Results: Solute concentration differences between "buddy" and "patient" dissipated rapidly (**Figure 1**). As expected, creatinine concentrations equilibrated faster (within about 5 min), while PBUT concentrations equilibrated more slowly (within 15 to 25 minutes), presumably due to their high degree of protein binding. No blood clots were present even after 2 hours of *ex vivo* recirculation.

Conclusions: This bench experiment demonstrates the ability of alloHD to not only remove water-soluble unbound solutes but also PBUTs. These findings support alloHD's viability as a potential alternative to conventional hemodialysis.

Funding: Commercial Support - Fresenius Medical



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Dialysate Citrate and Mortality in the Dialysis Outcomes and Practice Patterns Study

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Background: Metabolic acidosis is a common threat for hemodialysis patients, managed by alkaline dialysis baths. The main base is bicarbonate, to which small amounts of acetate or citrate may be added. These additives are metabolized to bicarbonate, mostly by the liver. In view of uncertainties about benefits and potential harms associated with citrate-containing dialysate we assess here whether citrate dialysate is associated with mortality in the international Dialysis Outcomes and Practice Patterns Study (DOPPS).

Methods: Detailed patient-based information on dialysate composition was collected in DOPPS phases 5 and 6 (2012 to 2017). Cox regression was used to model the association between dialysate containing bicarbonate with versus without citrate and mortality among DOPPS country/phases with at least 15 patients using citrate containing dialysate.

Results: Citrate-containing dialysate use was most common in Japan, Italy, and Belgium (25, 23, 21% of DOPPS phase 6 patients) and used in < 10% of patients in other countries. Among 10,618 patients in DOPPS country/phases with at least 15 patients using citrate-containing dialysate, patient demographics, comorbidities, and labs were similar among patients using (14%) vs. not using (86%) dialysate citrate. After accounting for case mix, we did not observe an association between citrate containing dialysate use (any vs. none) and mortality, HR (95% CI) = 1.03 (0.85-1.23). Nor did we find evidence of a dose-dependent relationship when parameterizing dialysate citrate concentrations as 1, 2, and 3+ mEq/L.

Conclusions: The use of this emergent practice of citrate-containing dialysate was not associated with the risk of all-cause mortality in hemodialysis patients participating in the DOPPS. Clinical indications for the use citrate dialysate deserve further investigation in future studies.

Funding: NIDDK Support, Commercial Support - The DOPPS Program support and additional support for specific projects and countries can be found here: https://www.dopps.org/AboutUs/Support.aspx, Private Foundation Support, Government Support - Non-U.S.

Table 1: Dialysate citrate and mortality by progressive adjustment

		Mortality Hazard Ratio (95% CI)			
Exposure	Patient N (%)	Model 1	Model 2	Model 3	Model 4
No D. citrate (ref)	86	1.00	1.00	1.00	1.00
D. Citrate=1 mEq/L	2	1.06(0.76-1.48)	1.03(0.74-1.42)	1.02(0.73-1.43)	1.05(0.74-1.48)
D. Citrate=2 mEq/L	9	1.31(1.01-1.70)	1.24(0.95-1.61)	1.23(0.94-1.60)	1.22(0.92-1.61)
D. Citrate=3+mEq/L*	3	1.02(0.73-1.42)	0.88(0.64-1.21)	0.90(0.65-1.23)	0.79(0.57-1.10)
Any D. Citrate (vs. none)	**14 (86)**	**1.16(0.97-1.38)**	**1.07(0.90-1.27)**	**1.07(0.90-1.27)**	**1.03(0.85-1.23)**

* Upper limit of dialysate citrate = 10 mEq/L
- Each column shows 2 separate models: (1) categories of dialysate citrate vs. no dialysate citrate and (2) any dialysate citrate vs. no dialysate citrate
- Restricted to countries/phases (Belgium/5 and 6, Canada/6, Germany/5 and 6, Italy/5 and 6, Japan/5 and 6, Spain/6, Sweden/6, UK/5 and 6) with at least 15 patients prescribed dialysate citrate
- n=10,618 patients and 1,758 deaths
- Model 1: stratified by country and phase; accounting for facility clustering
- Model 2: additionally adjusted for age and sex
- Model 3: additionally adjusted for diabetes
- Model 4: additionally adjusted for total dialysate base concentration (sum of bicarbonate + acetate or citrate), albumin, phosphorus, calcium, PTH

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Hemodialysis with Citrate Dialysate Does Not Harm Patients: Results from an European NephroCare Cohort

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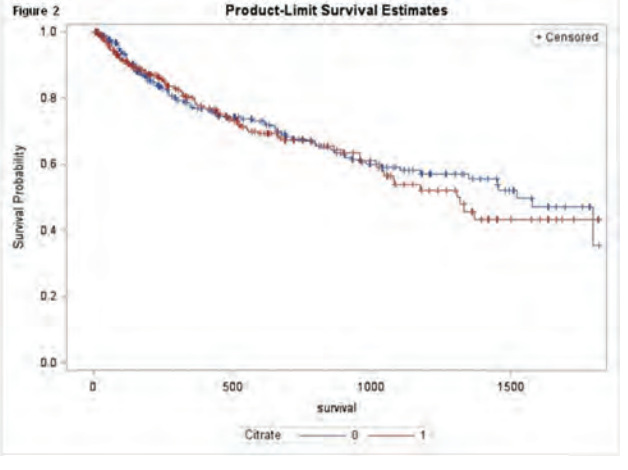
Background: Chronic hemodialysis (HD) using citrate dialysate is prescribed for improving dialysis tolerance and reducing heparin needs. Recently the safety of citrate (Ci) has been challenged by a French retrospective study. We report a mortality analysis in incident HD patients treated in the NephroCare dialysis centers in France, Turkey and Czech Republic in which citrate concentrate were prescribed.

Methods: This a retrospective study including 10020 incident HD patients between 2014 and 2018. Data were extracted from the EuCliD5 database. Patient survival was analyzed from three cohort studies designed to address different potential sources of biases. Patients were considered Ci+ if 70% of dialysis sessions were performed with Ci all along their lifetime (Study 1) or during the first 3 months of dialysis (Study 2). Study 3 included time-varying Ci exposure and time-varying PS score (monthly and 6-monthly averages) in a proportional hazard Cox regression to address variation in dialysate composition and patients' characteristics.

Results: Among 10020 enrolled patients, 435 were classified as Ci+. These patients were older with more severe comorbidities. In Study 1, the mortality was higher in Ci+ patients (p<0.0001). After propensity score matching (PSM; 345 patients Ci+ and Ci-) mortality remained strictly superimposable (Figure 1). In Study 2, no difference in survival was found before or after PSM. The monthly exposure analysis (Study 3), including 3671 patients with 835 deaths, clearly showed that the risk of mortality was related to the propensity score reflecting more sever condition (HR:5.06 (2.05-12.51)) but not with the Ci (HR:0.83 (0.67-1.03)).

Conclusions: In the European NephroCare experience, no significant impact on survival was found in chronic HD patients under Ci+ dialysate as compared to standard dialysate treated patients.



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Impact of Dialysate Calcium Concentration on Clinical Outcomes in Incident Hemodialysis Patients

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Background: The association between dialysate calcium (DCa) concentration and mortality in hemodialysis (HD) patients is controversial. In this study, we evaluated the impact of DCa concentration on mortality in incident HD patient.

Methods: Incident HD patients were selected from the Clinical Research Center registry—a prospective cohort study on dialysis patients in Korea. Patients were categorized into 3 groups according to the prescribed DCa concentration at the time of enrollment. High DCa was defined as a concentration of 3.5 mEq/L, mid-DCa as 3.0 mEq/L, and low DCa as 2.5 to 2.6 mEq/L. The primary outcome was all-cause mortality and secondary outcomes were cardiovascular or infectionrelated hospitalization.

Results: A total of 1182 patients with incident HD were included. The number of patients in each group was 182 (15.4%) in high DCa group, 701 (59.3%) in the mid-DCa group, and 299 (25.3%) in the low DCa group. The median follow-up period was 16 months. The high DCa group had a significantly higher risk of all-cause mortality compared with the mid-DCa group (hazard ratio [HR] 2.23, 95% confidence interval [CI] 1.28–3.90, P=0.005) and the low DCa group (HR 3.67, 95% CI 1.78–7.55, P<0.001) after adjustment for clinical variables. The high DCa group was associated with higher risk of cardiovascular and infection-related hospitalization compared with the low DCa group (HR 3.25, 95% CI 1.53–6.89, P=0.002; and HR 2.77, 95% CI 1.29–5.94, P=0.009, respectively). Of these 1182 patients, 163 patients from each group were matched by propensity scores. In the propensity score matched analysis, the high DCa group had a significantly higher risk of all-cause mortality compared with the mid-DCa group (HR 2.52, 95% CI 1.04–6.07, P=0.04) and the low DCa group (HR 4.25, 95% CI 1.64–11.03, P=0.003) after adjustment for clinical variables.

Conclusions: Our data showed that HD using a high DCa was a significant risk factor for all-cause mortality and cardiovascular or infection-related hospitalization in incident HD patients.

FR-PO487

A High Magnesium Concentration in Citrate Dialysate Prevents Oxidative Stress and Damage in Human Monocytes

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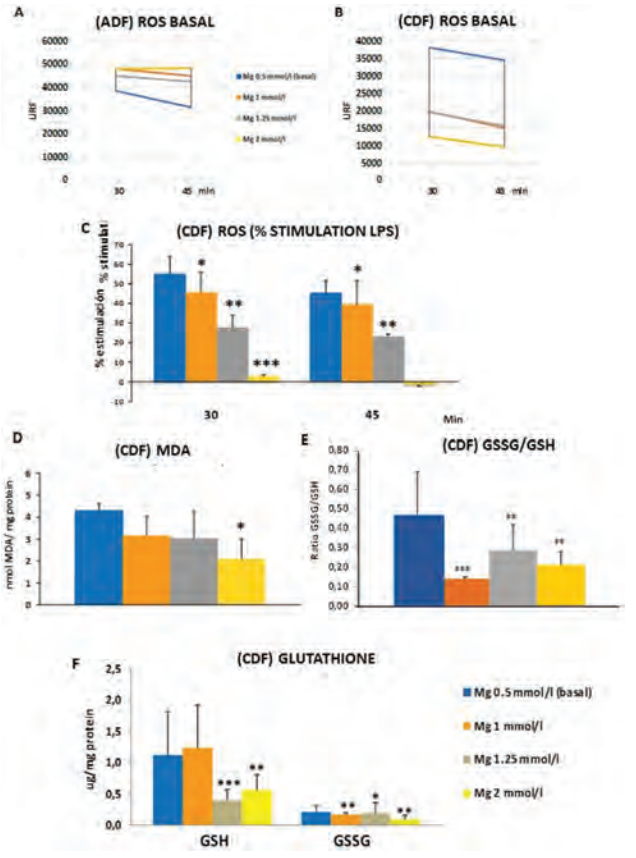
Background: The use of dialysis fluids (DF) during haemodialysis has been associated with an increased oxidative stress and reduced serum levels of magnesium (Mg), contributing to inflammation and immune system disorders. Since it has been demonstrated the role of Mg in modulating immune function and reducing oxidative stress, in this study we have characterized whether higher Mg concentrations in DF could protect from oxidative-inflammatory stress in immunocompetent cells.

Methods: The effect of citrate (CDF, 1 mmol/L) or acetate (ADF, 3 mmol/L) dialysates with 0.5 mmol/l Mg (routinely used) or with higher Mg concentrations (1, 1.25 and 2 mmol/L) were assessed in human monocyte culture (THP-1). The levels of reactive oxygen species (ROS), malondialdehyde (MDA) and reduced (GSH) and oxidized (GSSG) glutathione were quantified under basal and/or inflammatory conditions (stimulation with lipopolysaccharide, LPS, 1 μg/ml).

Results: In monocytes, 0.5 mmol/L Mg CDF produced lower basal ROS production in relation to ADF (p<0.05). Moreover, the increase of Mg in CDF resulted in a significant reduction of ROS production under basal and inflammatory conditions, which was extremely marked in 2 mmol/L Mg (p<0.001). These effects were not observed in ADF. Interestingly, in a dose-dependent manner, high doses of Mg in CDF reduced the oxidative stress observed in monocytes under basal conditions. In fact, 2 mmol/L Mg significantly decreased the levels of GSH, GSSG and MDA and the GSSG/GSH ratio in relation with 0.5 mmol/L Mg.

Conclusions: The CDF produces a lower ROS production compared to ADF. Increasing the concentration of Mg in the DF, especially in CDF, could have a positive and protective effect reducing oxidative stress and damage in immune cells.



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Efficacy and Safety of Expanded Hemodialysis Enabled by a Medium Cut-Off Membrane: A Randomized Control Trial

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Background: End stage kidney disease patients suffer high morbidity and mortality. Evidence suggests that accumulated uremic toxins, including larger middle molecules poorly cleared with conventional hemodialysis (HD), have a significant role in inflammation, cardiovascular disease and immune modulation. Expanded HD with a medium cut off membrane may effectively and safely remove middle molecules compared to conventional HD.

Methods: A 24 week, open-label RCT in thrice weekly in-center HD patients assessed whether a medium cut-off dialyzer (Theranova 400) compared to a high flux dialyzer (Elisio-17H) was superior in reduction ratio (RR) of lambda free light chains (λ FLCs) as a representative larger middle molecule (primary efficacy outcome) and non-inferior in maintaining pre-dialysis serum albumin levels (primary safety outcome). Primary analyses used an ANCOVA model with fixed effects for treatment and site, with multiple imputation for missing values performed using all post-baseline values. Secondary outcomes (shown in the table) used a mixed-effects repeated measures model.

Results: Among 172 patients randomized at 21 sites, mean age was 59 years, 39% were women and 40% African American. Median vintage was 4 years and 45% had diabetes as the cause of ESRD. The λ FLC reduction ratio was significantly higher with the Theranova membrane, while albumin levels were similar between groups (Table). Adverse and serious adverse events also were similar between groups.

Conclusions: The Theranova 400 dialyzer provides superior removal of larger middle molecules as compared to a similar size high flux dialyzer while maintaining serum albumin level without adverse safety signals. Larger studies of longer duration are needed to to assess if better larger middle molecule clearance is associated with improvements in clinical outcomes, including vascular disease, quality of life and mortality.

Funding: Commercial Support - Baxter

Primary* and Secondary‡ Outcomes

	Theranova 400	Elisio 17H	Theranova 400 - Elisio 17H	
Outcomes	Mean (SD)	Mean (SD)	Mean Estimated Treatment Difference (SE)	95% CI or p-value
λ FLC (% RR)*	32.2 (12.6)	17.5 (12.7)	14.8	10.5, 19.2
Serum Albumin (g/dL)*	4.03 (0.28)	4.02 (0.39)	-0.015	-0.098,0.069
Complement Factor D (% RR)‡	38.1 (11.2)	14.6 (11.3)	23.5 (2.0)	<0.001
κ FLC (% RR)‡	59.3 (13.1)	43.9 (14.9)	15.4 (2.5)	<0.001
IL-6 (% RR)‡	-0.9 (46.2)	-14.8 (43.6)	14.0 (7.9)	0.08
TNFα (% RR)‡	44.5 (10.2)	34.5 (10.7)	10.0 (1.8)	<0.001
β2-microglobulin (% RR)‡	73.6 (10.4)	65.4 (9.4)	8.2 (1.8)	<0.001

RR, reduction ratio

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The Comparison of Vancomycin Removal Between Medium Cut-Off (Theranova®) and Other Dialyzers

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Background: For more perfect treatment of *Staphylococcus aureus* infection in patients with end-stage renal disease (ESRD) on hemodialysis (HD), the maintenance of the target level of vancomycin (molecular weight 1,448 Dalton), 15~20 mg/L, is very important. Recently developed medium cut-off dialyzer, Theranova®, revealed superior clearance of waste product with large middle molecular weight (~ 45,000 Dalton). Hence, Theranova® may cause the suboptimal level of vancomycin in HD patients. The aim of this study is to investigate whether the reduction ratio of vancomycin (RRoV) in HD patients on Theranova® is greater than that on low-flux/high-flux dialyzer.

Methods: We analyzed prospectively collected vancomycin levels between April 2018 and April 2019. HD dialyzer was randomly assigned to the patients underwent intravenous vancomycin. In the first study (n=31, M:F=21:10, age 66 (55~73) years, dry body weight (DBW) 55.0 (50.8~63.5) Kg), RRoV by Theranova® was compared with that by low-flux dialyzers (FX 10®, Fresinius or Polyflux 17L®, Baxter). In the second study (n=24, M:F=15:9, age 63 (46~75) years, DBW 52.0 (46.0~63.0) Kg), RRoV by Theranova® was compared with that by high-flux dialyzers (FX 80®, Fresinius or Polyflux 170H®, Baxter).

Results: In two studies, there were no significant differences in the total amount of vancomycin, dosing interval, the level of vancomycin just before HD, the time of HD session, and the net ultrafiltration between two groups, respectively. The RRoV by Theranova® was greater than that by low-flux (45.5 (36.4~51.2) % vs. 33.3 (28.8~41.7) %, p=0.001). However, there was no significant difference in RRoV between Theranova® and how-flux dialyzer (50.6 (41.4~54.5) % vs. 46.4 (40.5~55.1) %, p=0.597).

Conclusions: Although the RRoV by Theranova® was significantly greater than that of low-flux dialyzer, there was no significant difference between Theranova® and high-flux dialyzer. Therefore, existing vancomycin dosing protocol on high-flux dialyzer could be valid in treatment of *Staphylococcus aureus* infection in patients with ESRD on HD using Theranova®, too.

FR-PO490

Effect of Different Dialysis Procedures on Monocyte Subsets

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Background: In cardiovascular and end-stage kidney disease, monocyte subsets are associated with cardiovascular events and mortality. The aim of the present study was to monitor monocyte subsets over a 6-week period in individuals on different extracorporeal dialysis procedures.

Methods: In a prospective, randomized, controlled, cross-over study enrolling 15 maintenance dialysis patients (*DRKS00010788*), low-flux and high-flux hemodialysis (HD) were compared to high convective volume (≥25 L) postdilution hemodiafiltration (HDF). Each patient was subjected thrice weekly to each treatment mode for 6 consecutive weeks. Dialysis membrane material was always identical (PUREMA® L and H, resp.). Dialysate flow rates differed in HD and HDF (500 vs. 700 mL/min). Blood flow rates and treatment time were kept identical for individual patients. Monocyte subsets were determined at baseline (t0), after 3 (t3) and 6 weeks (t6) of each treatment period. Monocytes subtypes were differentiated in classical ($CD14^{++}/CD16^{-}$), intermediate ($CD14^{++}/CD16^{+}$) and non-classical ($CD14^{+}/CD16^{++}$) by flow-cytometric analysis. In addition, highly sensitive serum CRP was monitored by ELISA.

Results: While there were no differences in monocyte subsets over time within and between treatment modes, ANOVA revealed a lower number of total monocytes at t6 in HDF compared to low-flux HD (885±245 vs. 993±349 cells/µl; P=0.019). Classical monocytes ranged between 677±191 (high-flux HD, t3) and 763±297 (low-flux HD, t6) cells/µl, intermediate monocytes between 91±31 (HDF, t3) and 125±89 (HDF, t0) cells/µl, and non-classical monocytes between 83±39 (HDF, t3) and 109±54 (low-flux HD, t3) cells/µl. Furthermore, no differences in CRP levels were found within and between treatments (range 5.12±7.18 mg/L in HDF at t6, and 11.42±19.17 mg/L in low-flux HD at t6). CRP correlated with total monocytes (r=0.638, P<0.001) as well as with classical (0.608, P<0.001), non-classical (0.216, P=0.017) and intermediate (0.520, P<0.001) subtypes.

Conclusions: Over a 6-week period, large differences in toxin removal of extracorporeal dialysis therapies have no impact on monocyte subsets and inflammation. Monocyte phenotypes may be useful to characterize inflammation in patients on maintenance dialysis.

Funding: Commercial Support - 3M Deutschland GmbH

FR-PO491

Experience with a Novel Hemodialysis System: User Satisfaction and Clearance

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Background: The need for IHD in hospitalized patients with AKI and ESRD has been increasing. Delivery of this care has a significant cost. An inpatient hemodialysis unit requires a large financial outlay for water treatment and performing IHD in an ICU room involves transporting heavy equipment and often ties up a dialysis nurse. Outset Medical's Tablo is an easily transportable, all-in- one system with a user-friendly touch screen interface that requires minimal training. This pilot project was designed to assess whether the Tablo system was both easy to use and provided adequate urea clearance.

Methods: 25 hospitalized patients with AKI or ESRD requiring IHD were treated using the Tablo system. 15 of these patients were in the ICU and 10 patients were in the inpatient dialysis unit. Tablo was set up and run by a hemodialysis nurse or technician using a Revaclear 300 dialyzer. Blood flow was between 300-400 ml/min and dialysate flow rate was 300 ml/min. Dialysis prescription, duration and ultrafiltration rate were left to the discretion of the attending nephrologist. Nursing satisfaction was assessed by a Likert scale questionnaire. Dialysis adequacy was estimated by KT/V (Daugirdas) and Urea reduction ratio (URR).

Results: The majority of nurses/technicians found Tablo easier to use than a conventional dialysis machine (average score 5/5), most nurses felt comfortable providing treatment with this system after a short training session (average score 4.9/5) and they were also satisfied with Tablo as a treatment option (average score 4.9/5). Several participants also reported that the system was easy to transport and took up less space in an ICU room. Mean Kt/V was 1.18 (0.68 - 2.37), mean URR was 62.39 (44.44 - 87.04), mean patient weight was 81.98 kg (53.50 - 187.60), mean time and blood flow were 3.6 hours (3.5 – 4.5) and 366 ml/min (300 - 400) respectively.

Conclusions: Most of the operators found the Tablo system easy to use and transport. Although urea clearance was less than goal, we attribute this both to the shorter treatment time used in our center and the fact that treatment time was not adjusted for patient weight. Previous small studies have confirmed this system can deliver adequate clearance despite lower dialysate flow; larger randomized controlled trials are needed to validate this.

Funding: Commercial Support - Outset medical provided the Tablo machines.

FR-PO492

Optimizing Serum Total Carbon Dioxide Concentration During More Frequent Hemodialysis Using Low Dialysate Flow and Lactate Dialysate

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Background: There have been few studies to determine the optimal dialysate lactate concentration ([lactate]) during more frequent hemodialysis (MFHD) at low dialysate flow rates using the NxStage System One dialysis delivery system to achieve a predialysis serum total carbon dioxide concentration ([TCO2]) of 22-26 mEq/L. We used clinical data in patients who transferred from in-center, thrice weekly hemodialysis (ICHD) using bicarbonate dialysate to 6 times per week hemodialysis using lactate dialysate during the FREEDOM Study and the H^+ mobilization model (Sargent et al, Semin Dial 31:468-78, 2018) to calculate the effect of dialysate [lactate] during MFHD on [TCO2] after transfer from ICHD.

Methods: The H^+ mobilization model was first used to simulate ICHD treatments using dialysate bicarbonate concentration ([bicarbonate]) of 34, 37 & 40 mEq/L at [TCO2] of 20, 22 & 24 mEq/L to determine a weekly acid generation rate. Assuming a constant weekly acid generation rate, patients were assumed transferred to MFHD with treatment (Tx) frequencies of 4, 5 & 6 times per week with dialysate volume per Tx &Tx times of 40 L & 210 min, 30 L & 180 min, and 25 L & 170 min, respectively. Blood flow rate was assumed as 450 mL/min and dialysate [lactate] as either 40 or 45 mEq/L during MFHD.

Results: Summary results are tabulated. After transfer from ICHD, [TCO2] during MFHD increased when using a dialysate [lactate] of 45 mEq/L but not when using a dialysate [lactate] of 40 mEq/L. [TCO2] during MFHD was higher at higher [TCO2] during ICHD. Calculated results were predominantly dependent on the weekly dialysate volume (150-160 L/wk) and relatively independent of Tx frequency.

Conclusions: KDOQI guidelines suggest that [TCO2] should be ≥22 mEq/L; therefore, these results suggest that patients transferring from ICHD with [TCO2] ≤24 mEq/L should initially be prescribed a dialysate [lactate] of 45 mEq/L when using 150-160 L/wk of dialysate volume during MFHD.

Funding: Commercial Support - NxStage Medical Inc. (Fresenius Medical Care)

[TCO2] During MFHD (mEq/L)

	Dialysate [Lactate] of 40 mEq/L			Dialysate [Lactate] of 45 mEq/L		
[TCO2] During ICHD	4 Tx/wk	5 Tx/wk	6 Tx/wk	4 Tx/wk	5 Tx/wk	6 Tx/wk
20 mEq/L	18	19	20	22	23	24
22 mEq/L	20	21	22	24	24	25
24 mEq/L	22	22	23	25	26	27

All values averaged for dialysate [bicarbonate] during ICHD of 34, 37 and 40 mEq/L; the standard deviation of all values was 1 mEq/L.

FR-PO493

Patient-Reported Outcome Measures (PROMs) and Expanded Hemodialysis (HDx) with Medium Cut-Off Dialyzers in a Large Cohort of Patients in Colombia: The COREXH Study

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Background: Increasing importance and focus have been directed towards quality of life measures (QoL) and patient experience in end stage kidney patients on hemodialysis (HD). A new therapy, expanded hemodialysis(HDx) with Theranova membane improved clearance of middle molecular uremic toxins but to date its effects of QoL are lacking

Methods: Historical cohort, multicenter study in prevalent patients older than 18 years under the HDx therapy with MCO membrane that complete the twelve months of follow up in the COREXH Registry, in Renal Therapy Services (RTS) Colombia network. PROMs were assessed by KDQOL-36, Dialysis Symptoms Index (DSI), and diagnostic criteria for Restless Legs Syndrome (RLS) tools. The ANOVA and Cochran's Q test was used.

Results: Out of 992, the 619 men (62.4%) with mean age 60.4±15.7 years. For KDQoL 36 domains, symptoms, burden and effects of kidney disease and mental component, significant increase in score at 6 and 12 mos was noted (Table1). ANOVA for DSI shows statistically significant differences in mean severity scores over the follow-up with improvement from 30.7, 29.9 and 28.5 at baseline, six months and one year respectively, ($F(2, 1450) = 6.92$, $p = 0.0087$)). The proportion of patients with RLS scores improved from 22.11% at baseline, to 12.47% at 6 m and 9.98 at 12 m (Cochran's Q, 2 df) = 145.42, $p < 0.0001$.

Conclusions: In this large multicenter study, HDx with Theranova resulted in improved patients' related outcomes.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.

Patient Reported Outcome Measures

KDQoL – 36 domains	Baseline (N=971) Mean (SD)	At Six Months (N=808) Mean (SD)	At Twelve Months (N=642) Mean (SD)	p-Value
Sympton/Problem Domain	78.6 (15.8)	81.0 (15.4)	81.5 (14.9)	< 0.0001 *
Effect of Kidney Disease	69.7 (22.03)	72.8 (22)	75.1 (21)	< 0.0001*
Burden of Kidney Disease	46.2 (27.5)	48.9 (29.9)	50.2 (32.3)	< 0.0012*
SF-12 Physical	41.1 (11.1)	41.0 (11.2)	41.7 (10.5)	0.27*
SF-Mental	51.1 (11.6)	51.9 (11.3)	52.3 (11.1)	< 0.0016*
DSI	30.7 (22.3)	29.9 (32)	28.5 (21.7)	0.0087 *
RLS				
% of patients with RLS	22.1	12.47	9.98	< 0.0001**

* Anova test

** Cochran's Q test

KDQOL-36: Kidney Disease Quality of Life-36

DSI: Dialysis Symptoms Index

RLS: Diagnostic criteria for Restless Legs Syndrome

FR-PO494

What Is the Most Cost-Effective Strategy to Rinse a Re-Processed Dialyser Before a Dialysis Session?

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Background: Dialyser reuse is practised in developing countries to reduce cost. The Indian Society of Nephrology (IndSN) Hemodialysis Guidelines recommend using 2L of Normal Saline (NS) to flush the blood compartment of a dialyser before each reuse to ensure elimination of air and residual sterilant. It is also recommended that the dialysate compartment of the dialyser be rinsed for 5 minutes. In this study, we tested several strategies to determine the smallest volume of NS that could lead to elimination of residual sterilant from a reprocessed dialyser and thereby lead to cost savings.

Methods: We pilot tested combinations of flushing (after draining the dialyser completely) with different volumes of NS (2L, 1L and 500 ml) and 0 or 10 minutes dialysate compartment rinsing in 5 sessions each. After determining the smallest flush volume that consistently eliminated the sterilant (4% peracetic acid, 21% hydrogen peroxide and 10% acetic acid), we reduced the rinsing time in decrement of 2 minutes, starting from 10 minutes. Residual sterilant was checked with a commercial strip (Serim Research Corporation, IN, USA) that detected the presence of >1 ppm of hydrogen peroxide. We also noted the time taken for the entire process and the cost. The final selected strategy was compared with the 'IndSN gold standard' in 150 sessions each.

Results: The first step of the pilot showed us that the smallest volume of NS that was able to consistently get rid of the sterilant from the reprocessed dialyser was 500 ml. Next, we found that a minimum of 8 minutes of rinsing was needed to eliminate the sterilant completely. Adding 2 minutes as a safety margin, we then compared 500 ml flush + 10 min rinsing with the strategy recommended by the IndSN in 150 sessions each. This strategy showed no residual sterilant in any session. The cost (INR 30 versus INR 100) and the time taken (15 min vs 25 min) were less than that with the protocol recommended by the IndSN.

Conclusions: Flushing of the dialyser blood compartment with 500 ml of NS followed by 10 minutes of rinsing of the dialysate compartment leads to complete removal of sterilant prior to initiating dialysis using a reprocessed dialyser. This strategy results in a significant saving in terms of cost and time taken to initiate dialysis compared to currently recommended protocol.

FR-PO495

Glycosaminoglycan Modified-Dialysis Membranes Improve Blood Biocompatibility In Vitro

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Background: The number of patients requiring renal replacement therapies is increasing with an estimated number of 5.4 million a year in 2030. Most patients use (hemo)dialysis (HD) therapy. Major drawbacks of HD are: (i) poor removal of toxic larger middle-sized molecules and protein-bound uremic solutes; (ii) large fluctuations in water balance and uremic waste, potassium and phosphate of the patients, since it is non-continuous (iii) not fit for prolonged use due to clogging and coagulation of the membranes. Recently, we showed *in vitro* that combining dialysis and adsorption in one step using mixed matrix membranes (MMM) improves removal of protein-bound uremic solutes from human plasma as compared to conventional dialysis membranes. Although the results with MMM are promising, for continuous use further optimization is required. Due to the well-known contribution of glycosaminoglycans (GAGs) to the barrier and anti-fouling properties of the natural filtration barrier in the kidney, this work aimed to improve hemo- and biocompatibility of MMM by application of novel GAGs either as coatings post membrane fabrication or by incorporation of the GAG into the membrane polymer via blending.

Methods: Flat MMM were coated or blended with the following GAG sources: Heparin, GAGs from porcine intestine (GPI), heparan sulphate (HS) isolated from cultured glomerular endothelial glycocalyx, HS from bovine kidney (HSBK), and heparinase III digested HSBK. Both GAG coating and blending showed a high stability on the MMM. Water permeance, and a panel of anti-coagulation and platelet adhesion assays were studied in all cases.

Results: The new MMM with 3 out of 5 GAGs have higher water permeance in comparison to non-modified MMM whereas heparin and GPI modified MMM were superior in their anti-coagulation and platelet adhesion properties.

Conclusions: GAG-modified MMM have superior biocompatible properties that may improve current dialysis treatment and ultimately enable incorporation into future portable artificial kidney devices.

Funding: Government Support - Non-U.S.

FR-PO496

Discrepancy Between In Vivo and In Vitro (Dialyzer Mass Transfer-Area Coefficient) KoA in Patients on Chronic Intermittent Hemodialysis (IHD): A Retrospective Analysis

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Background: KoA is a measure of the dialysis membranes clearance efficiency. Manufacturer KoA values are determined from in-vitro studies. The achieved in-vivo KoA using these membranes in IHD is not known.

Methods: We retrospectively reviewed measured hemodialysis kinetic results in 70 patients receiving IHD at an outpatient free-standing dialysis unit. Over a 2-month period, we reviewed 140 dialysis sessions. Age, Gender, Weight, Height, length of session, blood flow rate (Qb), dialysate flow rate (Qd), pre-BUN, post-BUN, urea reduction rate (URR), type of dialyzer and manufacture KoA, UF, pre-weight, post-weight and spKt/V were recorded. Specimens were obtained according to specifications of the dialysis unit. We then calculated the Kt/V using Daugirdas 2 equation (D2), body surface area (m^2) calculated using Mostellar equation (M-BSA), and total body water (L) calculated using Watson's formula (W-TBW). MS Excel® was used for mathematical calculations ("what if analysis") and IBM SPSS® v22 was used for statistical analysis – correlations and t-tests. In-vivo KoA was back calculated from D2 using AS Michaels equation: Clearance (K) = Qb ((exp(KoA(1-Qb/Qd)/Qb) -1)/(exp(KoA(1-Qb/Qd)/Qb) -1)-b/Qd))

Results: There were 70 patients, 39 females, mean age 58.9±13.4 years, mean time on HD 233±18 minutes, mean Qb 404±44.8 mL/min, mean Qd 800±0 mL/min, mean

pre-BUN 53.7±21.3 mg/dL, mean post-BUN 14.6±7.2 mg/dL. Of the 140 IHD sessions, 2 were excluded for incomplete data. When comparing Kt/V, calculated using manufacture KoA with Michaels equation, we found a moderate correlation to UKM (r = 0.5646, p=0.0001). When comparing D2 to UKM, we found a strong positive correlation (r=0.97, p=0.0001). When compared, the in vitro KoA (1231±116ml/min) was 72.8% lower than in vivo KoA (340±156ml/min), mean difference 891±17mL/min (p=0.0001). The reduction in KoA (rKoA) was calculated using equation: 1-(in-vivo KoA/ in vitro KoA). rKoa had a strong positive correlation to body surface area (r=0.8, p=0.0001) and W-TBW (r=0.83, p=0.0001), but no other significant correlations could be discovered.

Conclusions: Our study showed a significantly lower in vivo KoA as compared to in vitro KoA. Larger studies are needed to further evaluate the variables affecting the in-vivo KoA.

FR-PO497

A Randomised Study Investigating the Effect of Medium Cut-Off Haemodialysis on Markers of Vascular Health Compared with Online Haemodiafiltration (MoDal Study)

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Background: Medium Cut-Off (MCO) Haemodialysis (HDx) provides improved clearance of larger middle molecules (up to 45kda) compared with high-flux haemodialysis. Inflammation and cardiovascular (CV) disease, characterised by endothelial dysfunction (ED) are intimately linked in this patient group. Expanded solute removal, through HDx could be biologically significant in modifying endothelial function and CV risk. Endothelial microvesicles (EMV) are a marker of ED and each log increase correlates with a 20-fold increase in CV and all-cause mortality in HD patients. The primary aim of this study was to investigate the effects of HDx treatment on EMV compared with haemodiafiltration therapy(HDF).

Methods: A single-centre, pilot, open-label, randomised controlled study with 1:1 simple randomisation to 6 months MCO therapy or continue on existing HDF therapy(NCT03510520). Pre-dialysis EMV (CD144+) was measured at baseline (T0), 3 months (T12) and 6 months (T24). Secondary outcome measures included inflammatory cytokines, a panel of larger middle molecules, body composition monitoring and patient-reported outcome measures.

Results: 63 participants were randomised to either MCO or HDF and 50 participants (25 each group) completed the full protocol. Mean age was 62.8±16 years, 70% male, 60% Caucasian, 34% diabetic, 68% AVF/G as AV access with no significant difference between groups in these domains. Mean substitution volume in the HDF group was 20.8L±2.84 per session. There was a rise in EMV in the HDF group (change in mean EMV 0.145 logCD144+ EMV/ml at T12 [p>0.05], 0.269 at T24 [p<0.05) and fall in EMV in the MCO group (-0.18 T12 [p<0.05], -0.145 T24 [p<0.05]). Mean albumin change in the MCO group was -1.8±2.93 g/l vs 0 ±1.89g/l in the HDF group (p<0.05).

Conclusions: Switching from HDF to HDx therapy is associated with a reduction in plasma EMV levels at 3 months with a sustained reduction at 6 months. This is in contrast with a rise in plasma EMV levels seen within the same time period in those remaining on HDF. A fall in serum albumin is seen with HDx treatment within the limits expected. Mechanisms behind the changes seen require further exploration. In an era where equipoise still exists between diffusive and convective treatment modalities, HDx could be an important future direction.

Funding: Commercial Support - Baxter Healthcare

FR-PO498

The Relationship of Frequency of Hemodialysis Treatments per Week to Improved Clinical Outcomes in Patients in Skilled Nursing Facilities

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Background: Dialysis patients residing in a skilled nursing facility (SNF) are characterized by advanced age, frailty, and hemodynamic instability, with multiple comorbid conditions. Based on previous increased frequency studies it was postulated that SNF residents could benefit from frequent hemodialysis (HD) when compared to conventional therapy. Given the potential for less traumatic treatments we compared the effects of HD performed 5 times per week (MFD5) with 4 times per week (MFD4) on mortality and hospitalization rates for patients in skilled nursing facilities.

Methods: We studied patients enrolled in Dialyze Direct staff-assisted, on-site SNF home HD programs in five states: OH, TX, FL, NY, PN, analyzing 1177 patients under care for 260 patient-years. 83% were dialyzed MFD5 (77,745 patient-days) and 17% (15,545 patient-days) were dialyzed) using NxStage technology for approximately 2.7 and 3.1 hrs per treatment respectively.

Results: Patient characteristics of MFD4 vs MFD5 were comparable with respect to age (69y vs 70y), gender (49% F vs 45% F), HD vintage (3.14 vs 2.79 yrs), and mean blood pressure upon program entrance (135 vs. 130 mmHg). Weekly time on HD differed (3.1 vs 2.7 hrs => 12.2 vs 13.4 hours per week). Patients were divided into length of stay quartiles: 15, 33, 90, and 1127 days. Mortality: relative risk in MFD5 patients was lower for per patient-year (0.25 vs 0.54 p<0.05); significant differences were present in quartile one (0.15 vs 0.28) and four (0.07 vs 0.21). Hospitalizations: relative risk in MFD5 was lower per patient year (2.64 vs 4.88 p<0.05); a significant difference in hospitalization was present in quartile one (1.78 vs 4.25). Blood Pressure: MFD5 and MFD4 pre-hemodialysis systolic blood pressure were (136 vs 132 mmHg); for both groups pre-HD.

Conclusions: Five times a week dialysis significantly reduces mortality and hospitalization rates in patients confined to nursing homes, possibly related to more effective and gentler fluid management strategy, that with better blood pressure control and fewer episodes of intradialytic hypotension may have protected organ systems. Its success in this frail population confirms the importance of volume control.

Funding: Private Foundation Support

FR-PO499

Circulating Angiopoietin-Like Protein 2 Levels and Mortality Risk in Patients Receiving Maintenance Hemodialysis: A Prospective Cohort Study

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Background: Prognosis of patients undergoing hemodialysis treatment is poor, as many of them exhibit premature aging. Systemic inflammatory conditions often underlie premature aging phenotypes of the uremic population. Thus, we asked whether Angiopoietin-like protein (ANGPTL) 2, a factor that accelerates progression of aging-related and non-infectious inflammatory diseases, was associated with mortality of hemodialysis patients.

Methods: We conducted a multicenter prospective cohort study of 412 patients receiving maintenance hemodialysis treatment and evaluated relationships between circulating ANGPTL2 levels and risk for all-cause mortality. Circulating ANGPTL2 levels were log-transformed to correct for skewed distribution, and analyzed as continuous variable.

Results: Of 395 subjects analyzed statistically, time-to-event data analysis revealed high circulating ANGPTL2 levels associated with increasing risk for all-cause mortality after adjustment for age, sex, hemodialysis vintage, nutrition status, metabolic parameters, and circulating high sensitivity C-reactive protein values [HR: 2.04, 95%CI (1.10, 3.77)]. High circulating ANGPTL2 levels were also strongly associated with increased mortality risk, particularly in patients with a relatively benign prognosis [HR: 3.06, 95%CI (1.86, 5.03)]. Furthermore, the relationship between circulating ANGPTL2 levels and mortality risk was especially strong in populations showing less senescent phenotypes, such as younger patients [HR: 7.99, 95%CI (3.55, 18.01)], short hemodialysis vintage [HR: 3.99, 95%CI (2.85, 5.58)], or non-diabetes [HR: 5.15, 95%CI (3.19, 8.32)].

Conclusions: We conclude that circulating ANGPTL2 levels are positively associated with mortality risk of patients receiving maintenance hemodialysis, and that ANGPTL2 may uniquely reflect progression of premature aging and subsequent mortality risk in that population.

Funding: Government Support - Non-U.S.

FR-PO500

Risk Factors and Clinical Impact of Early-Onset Peritonitis in Peritoneal Dialysis Patients

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Background: Peritoneal dialysis (PD) related peritonitis is a serious complication of PD and the leading cause of technique failure. However, the impact of early peritonitis on PD survival is not clearly proven. This study aims to analyze the risk factors and outcomes of early-onset peritonitis.

Methods: We retrospectively reviewed 1336 patients who performed PD catheter implantation between 1996 and 2017. Of the 1336 patients, 614 patients who had at least one episode of peritonitis were enrolled. According to time from start of PD to first episode of peritonitis, patients were divided into early-onset (≤6 months) and late-onset (>6 months) peritonitis group.

Results: Among 614 patients, 164 (26.7%) patients developed their first episode of peritonitis within 6 months. The early-onset peritonitis group had more prevalence of diabetes mellitus (P = 0.004), lower serum albumin level at initiation of PD (P = 0.002) and higher peritonitis rate (P < 0.001) than the late-onset peritonitis group. Multivariate logistic regression analysis showed that risk factors associated with early-onset peritonitis were diabetes mellitus (OR 1.510, 95% CI 1.036-2.201, P = 0.032) and a lower serum albumin level at the start of PD (OR 0.629, 95% CI 0.434-0.910, P = 0.014). In multivariate Cox regression analysis, early-onset peritonitis was not an independent risk factor for technical failure and mortality. However, a negative correlation was observed between the time to first peritonitis and technical failure (HR 0.995, 95% CI 0.991-0.999, P = 0.023) and mortality (HR 0.991, 95% CI 0.987-0.997, P = 0.001). In the Spearman analysis, the time to first peritonitis was negatively correlated with the incidence of peritonitis (r = -0.437, P = 0.000).

Conclusions: Diabetes mellitus and a lower serum albumin level at initiation of PD were independent risk factors of early-onset peritonitis. Early-onset peritonitis was associated with higher incidence of peritonitis, technical failure and mortality.

FR-PO501

Microbiology Laboratory Practices Influences a Capacity of Pathogen Identification from Peritoneal Effluent in PD Patient with Peritonitis: A Result from the Thailand PDOPPS

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Background: Effective treatment of peritonitis relies mostly on the identification of pathogenic organisms from the PD effluent. However, culture-negative peritonitis is common in Thailand, a country with "PD First" policy.

Methods: This prospective case-cohort study was conducted in 21 PDOPPS centers in Thailand during May 2016 to October 2017. All cloudy PD bag prior to starting antibiotic from consented PD participants who had peritonitis were submitted to local and central laboratories. Facility practices regarding culture technique and microbiology laboratory practices were collected via survey of microbiology laboratory directors in each facility.

Results: During the cohort period, there were 360 peritonitis episodes (241 participants). The crude peritonitis rate was 0.40 episodes/year. Only 202 episodes (169 participants) had specimen submitted to both laboratories. By local laboratory result, Gram-positive bacteria were accounting for 26.2% of episodes followed by Gram-negative bacteria (23.4%), polymicrobial infection (2.5%), and fungal infection (5.0%). Of note culture negative rates was 42.5%. Central laboratory culture additionally identified organisms in 26 episodes whose local laboratory culture was negative, increasing positive culture rate to 70.3%. Central laboratory culture provided additional yield mainly in fungal, mycobacterium, and polymicrobial infections. Only 1 facility had complete equipment, reagents, and media to culture mold and mycobacteria while obligate anaerobe could be isolated from 4 facilities. None but one performed large volume culture.

Conclusions: Microbiology laboratory practices influence a capacity of pathogen identification from the PD effluent in PD patient with peritonitis and should warrant a competency assessment program.

Funding: Other U.S. Government Support

FR-PO502

Reduction of Peritonitis in an Integrated Health Care System: Collaboration Between Nephrologists, Dialysis Provider, and Health Plan

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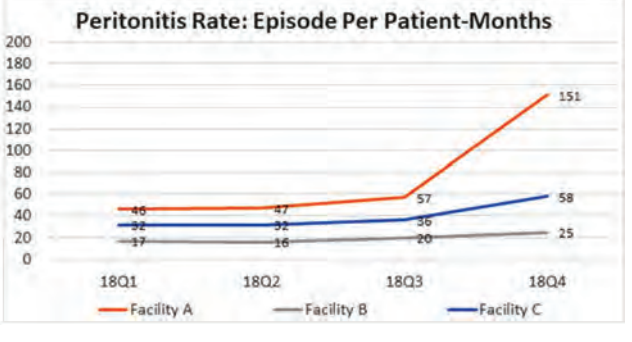
Background: Peritonitis is a serious complication in patients on peritoneal dialysis (PD). Centers for Medicare and Medicaid Services (CMS) has set peritonitis rates as a performance metric for PD clinics. Kaiser Permanente (KP) Northern California is an integrated health care system with 4.4 million members. In 2018, a workgroup was created to monitor and reduce peritonitis rates in 3 non KP PD clinics with high rates.

Methods: A KP workgroup was formed consisting of 3 non KP PD Medical Directors, a RN Clinical Practice Consultant, and a Regional Health Plan Director. The work group outlined performance improvement tools: 1. The facility's P&Ps were aligned with ISPD guidelines and adherence to P&P monitored; 2. Workflow for patient education and training; 3. Root cause analysis for peritonitis. After an initial site visit, monthly conference calls were held with the work group and facility staffs to review all peritonitis episodes and perform a Root Cause Analysis.

Results: The work group identified several factors that had contributed to peritonitis: 1. Patients that experienced peritonitis were not incident patients, but with a vintage of 2+ years; 2. Patient training and retraining was not consistent; 3. The education and training was not done in an organized manner and there was no enforcement and oversight of this process. The following actions were taken by KP in conjunction with the facility team- 1. P&Ps were reviewed, and staff informed of goals; 2. Staff and management buy-in was obtained to empower and drive improvement. As a result, of the initiative, there was a reduction in the peritonitis rates in all the three facilities (Figure).

Conclusions: In an integrated health care system, creating a dialysis provider and health plan partnership to implement a culture of cooperation is a unique approach to improve patient care. The partnership led to collaboration of care for better outcomes.



FR-PO503

Influence of Season and Climatic Conditions on Peritoneal Dialysis-Associated Peritonitis in a Subtropical Monsoon Climate Region of China

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Background: Peritoneal infections are a common complication in patients undergoing peritoneal dialysis (PD) and are frequently the cause of the failure of the technique. Knowing the factors that can lead to theirappearance helps to establish preventative measures. The aim of this research is to understand the influence of season, temperature and humidity on peritoneal dialysis-associated peritonitis in the subtropical monsoon climate region(Hunan provence) in China.

Methods: A retrospective observational study of all peritoneal dialysis-associated peritonitis that occurred in our PD center over a period of 9 years (2009-2017). Our PD center is located in hunan province, China which has the subtropical monsoon humid climate. Demographic data of patients, biochemical indicators at the time of onset, culture results of dialysate fluid, and data of the humidity and temperature of the months from 2009 to 2017 in hunan province were collected.

Results: There were 448 cases of peritonitis(0.17episodes/patient/year) in 885 patients (47±13 years, 56.4% males, 8.7% diabetics, 50.2±19 months on technique). There was significant seasonal variation in the rate of overall peritonitis and gram-negative bacteria peritonitis, with peak incidence in June. When comparing the incidence of peritonitis in different seasons, we found the incidence rates of overall peritonitis and gram-negative bacteria peritonitis were the highest in summer, respectively($p<0.05$). But we did not find this variation upon analysing the incidence rates of peritonitis caused by gram-positive bacteria. There was significant correlation between monthly peritonitis rate and the average monthly temperature ($r=0.258$, $p=0.018$). There was significant correlation between monthly gram-negative bacteria peritonitis rate and the average monthly temperature ($r= 0.278$, $p=0.010$) either. Butwe did not find correlation between the incidence rates of peritonitis and average humidity.

Conclusions: The rates of overall peritonitisand and gram-negative bacteria peritonitisperitonitis are the highest in summer. The higher the temperature, the higher the risk of overall peritonitis and especially of gram-negative bacteria.

FR-PO504

Prophylactic Oral Antibiotics for Post-Endoscopic Peritonitis in Peritoneal Dialysis Patients

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Background: Gastrointestinal endoscopy (GIE), especially lower GIE, is a risk factor for peritoneal dialysis (PD)-related peritonitis. However, there are currently no recommendations regarding preventive antibiotic regimens for GIE-associated peritonitis.

Methods: We retrospectively reviewed the association between prophylactic oral antibiotic administration and GIE-associated peritonitis.

Results: Among 140 patients who received PD treatment in our hospital from April 2008 to March 2018, 91 patients underwent a total of 360 GIEs, excluding patients who received therapeutic antibiotics for exit-site or other infections. None of the 30 GIEs (0%) (1 upper, 29 lower) accompanied by prophylactic oral antibiotic use led to PD-related peritonitis. The oral antibiotics included levofloxacin (n=24, 80%), amoxicillin-clavulanic acid (n=4, 13%) and others (n=2, 7%). In contrast, two of the 330 GIEs (0.6%) conducted without prophylaxis (1/289 upper, 0.3%, 1/41 lower, 2.4%) resulted in PD-related peritonitis, including one upper GIE procedure involving biopsy and one lower GIE involving oral double-balloon enteroscopy for suspected small intestinal bleeding. The incidence of peritonitis following upper GIE with invasive procedures was 1.0% (1/104), similar to past reports, and the incidence of peritonitis following lower GIE with or without invasive procedures was 2.4%, which was lower than previously reported.

Conclusions: Although it was not possible to show any significant effect of prophylactic oral antibiotics on the frequency of total GIE-associated peritonitis because of the small numbers, we could not conclude that prophylactic antibiotics were not beneficial in patients undergoing lower GIE. The administration of prophylactic oral antibiotics covering *Enterobacteriaceae* may thus be a convenient and promising option for preventing GIE-associated peritonitis.

FR-PO505

Dialysate and Plasma Meropenem Concentrations in Continuous Intraperitoneal Regimen During Peritoneal Dialysis-Related Peritonitis

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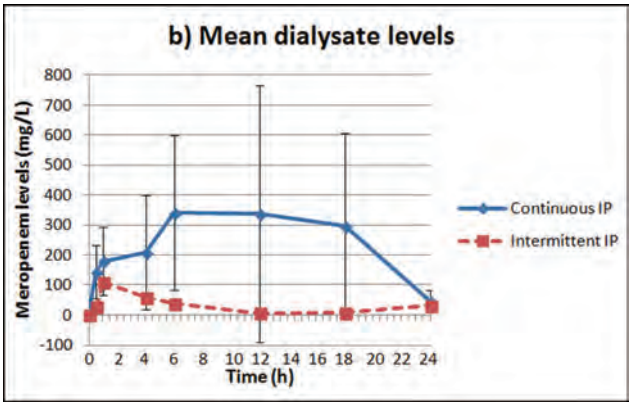
Background: Peritonitis is a major complication in peritoneal dialysis (PD) patients. Currently, the increase of intraperitoneal (IP) meropenem used regarding the rise in resistant organisms. A single dose of IP meropenem was recommended. However, data on the continuous regimen of IP meropenem is still limited. We examined plasma and dialysate meropenem level in the continuous IP meropenem in PD related peritonitis.

Methods: A prospective, descriptive study was performed in 8 patients with PD related peritonitis. Seven patients received a loading dose of meropenem 500 mg IP followed by meropenem 125 mg/L IP (4 exchanges daily). Another patient received the recommended intermittent IP meropenem 1 g daily. Concentrations of meropenem in plasma and dialysate were measured at specified intervals over 24 h with a high-performance liquid chromatography method.

Results: In the continuous group, the mean of maximum meropenem level was 340.6 mg/L (standard deviation [SD] ± 21.5) and 28.7 mg/L (SD ± 21.5) in dialysate and plasma, respectively. At 24 hour, mean dialysate drug level was minimum at 45.3 mg/L (SD ± 36.2). Dialysate meropenem concentrations from this regimen exceeded MIC of the pathogenic resistance organism (MIC > 8 mg/L) at every time points. For the intermittent regimen, mean plasma and dialysate meropenem levels were 11.8 mg/L (SD ± 8.2) and 34.2 mg/L (SD ±35.7), respectively. Interestingly, dialysate meropenem concentration at 12 hours after 1 g of meropenem was 4.9 mg/L which may not provide adequate drug level for resistant organisms. Five patients (71%) responded to the treatment, but two patients (29%) developed treatment failure from fungal peritonitis. No major side effect was observed.

Conclusions: Meropenem loading 500 mg and continue with 125 mg/L provide adequate dialysate meropenem concentration and could be considered for effective treatment in PD related peritonitis.

Funding: Government Support - Non-U.S.



Dialysate meropenem level

FR-PO506

A New Workflow Using Artificial Intelligence to Reduce Peritonitis for Patients Treated with Peritoneal Dialysis

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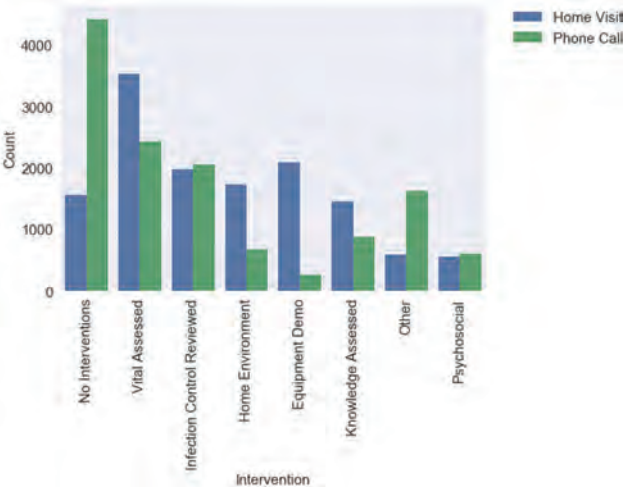
Background: ~10% of patients with kidney failure are treated with peritoneal dialysis (PD). To reduce peritonitis risk (a major complication of PD), we trained a model to predict which patients were at risk of peritonitis in the next month. The model was trained with an XGBoost classifier and had an area under the receiver operating characteristic curve of 0.66. This abstract outlines a new workflow implemented by a large dialysis provider.

Methods: Starting in Dec 2018, we used the peritonitis predictive model to generate risk scores on a monthly basis for the entire PD population treated by Fresenius Medical Care North America. We scheduled a home visit for patients within the first 30 days and a phone call for patients on dialysis between 30 and 90 days. For the remaining patients, we used the model to segment into three groups: high risk (~10%), medium risk (~10%) and low risk. Those patients with high risk were scheduled for a home visit and those with medium risk were scheduled for a phone call. An assessment was created in Feb 2018 to track specific interventions.

Results: We have performed over 14000 phone calls and over 7000 home visits due to this personalized care effort. Many of the home visits resulted in reviews of infection control, home environment or equipment. More of the phone calls resulted in no intervention than the home visits, which is logical given that those patients have lower risk scores. Analysis of outcomes such as peritonitis rates and modality changes is underway.

Conclusions: Integrating artificial intelligence into clinical decision support allows us to intervene with the right patient at the right time for the right reason. Future work must be conducted to improve the model to include additional reasons for intervention such as psychosocial or educational needs.

Funding: Commercial Support - Fresenius Medical Care North America



FR-PO507

Does Single-Dose Conjugated Pneumococcal Vaccine Provide Enough Antibody Response in Peritoneal Dialysis Patients?

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Background: Dialysis patients have 10-100 fold-increased risk of sepsis and pneumonia related mortality. The incidence of pneumonia increased and over half of reported pneumonia cases in dialysis patients are caused by Streptococcus pneumonia. Immunization against infectious diseases is a fairly simple, prevention strategy in dialysis patients. Implementation of polysacharidde pneumococcal vaccination (PPSV23) has led to an considerable decrease in pneumonia incidence. In accordance to PPSV23, conjugated pneumococcal vaccine (PCV13) has an increased and sustainable immunogenic response. In dialysis patients, antibody response to vaccination is decreased. This is the first study that investigates whether PCV13 vaccination provides enough antibody response in peritoneal dialysis (PD) patients.

Methods: Participants received a single dose of 0.5 ml of PCV13 administered intramuscularly. Blood samples were drawn prior to vaccination and at 1 month after vaccination. Serum antipneumoccal antibody level is measured by ELISA method.

Results: 69 PD (39 male, 30 female) patients and 10 healthy volunteers were inrolled in our study. Mean age was 52,6 ± 12,9 years (Image 1). In PD patients and control groups, first month antibody levels were increased statistically significant than prevaccination (p=0,001, p=0,008, respectively). First month antibody levels were higher in control group compared to patients (p=0,013). In PD group, statistically significant relationship were observed between antibody levels and serum albumin, CRP, Kt/V, weekly CrCl, nPCR parameters (Image 2).

Conclusions: In PD patients, PCV13 vaccination resulted enough but lower antibody levels than control group. Malnutrition, inflammation and lower dialysis adequacy were associated with lower antibody response.

Image 1. Demographic and clinical characteristics of patients

	PD Patients
Mean ± SD age (year)	52,55 ± 12,9
Sex: males/females (%)	39/30 (%56,5/43,5)
Duration of dialysis (Months)	30,2 ± 41,5
ESRD etiology, n (%)	
Diabetes mellitus (DM)	22 (%31,9)
Hypertension (HT)	24 (%34,8)
Vesicoureteral reflux	7 (%10,1)
Glomerulonephritis	6 (%8,7)
Polycystic kidney disease	4 (%5,8)
Others	6 (%8,7)
Urea: mg/dL (Mean ± SD)	112 ± 33,44
Cr: mg/dL, (Mean ± SD)	9,67 ± 7,6
Albumin: g/dL, (Mean ± SD)	3,57 ± 0,5
White blood cell: x10³/mL, (Mean ± SD)	8034,45 ± 2249,6
Hemoglobin: g/dL, (Mean ± SD)	10,62 ± 1,7
CRP: mg/dL (Mean ± SD)	1,43 ± 1,4

Image 2. Comparison of anti pneumococcal antibody titres and laboratory parameters before and after vaccination

		0. month Median (25.p-75.p) U/mL	1. month Median (25.p-75.p) U/mL	p
Controls (n=10)		527 (486,5-678,5)	933,5 (821,8-996)	0,005
PD patients (n=69)		660,5 (563-734,8)	837 (723-851)	0,001
Albumin (gr/dL)	<3,5 (n=28)	694,5 (607,5-796,75)	795,5 (653-846)	0,387
	≥3,5 (n=41)	651 (556,5-722)	842 (739,5-855)	0,001
CRP (mg/dL)	<1,14 (n=34)	677 (555,75-750,75)	846 (746,75-855)	0,004
	≥1,14 (n=36)	663 (572-716)	792 (639-846)	0,105
Kt/V	≤1,7 (n=17)	671 (592-743,5)	811 (658,5-853)	0,246
	>1,7 (n=52)	660 (555,25-751,5)	838 (723-851)	0,004
Creatinine clearance (L/week/1,73m²)	≤50 (n=17)	671 (592-736,5)	842 (715-855)	0,093
	>50 (n=52)	666 (556,25-748,5)	837 (715-851)	0,009
nPCR (gr/kg/day)	≤1,2 (n=21)	671 (602,5-850)	811 (685,5-851)	0,435
	>1,2 (n=45)	666 (555,25-721,25)	841 (717-852,5)	0,001

FR-PO508

Is Peritoneal Dialysis a Good Technique for Patients with Autosomal Dominant Polycystic Kidney Disease?

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most frequent genetic cause of Chronic Kidney Disease, progressing in most cases to End-Stage Renal Disease. Initially, Peritoneal Dialysis (PD) was contraindicated in this kind of patients, because it was thought that an already elevated abdominal volume would decrease the tolerance and promote a higher incidence of complications. However, this trend is in reverse and every day there are more patients with ADPKD in PD without showing more complications, with good tolerability and adequacy.

Methods: Descriptive, retrospective, unicentric study design; we selected all the patients with a diagnosis of ADPKD and that entered our PD program between April 1st, 1999 and March 31st, 2018. Every one of these patients was matched with 2 non-ADPKD patient who also entered our PD program in the same time period. We proceed to compare the incidence of dialysate leaks, eventrations, peritonitis; the number of hospitalizations and technique failures, and the PD adequacy in both groups through their Kt/V and nPCR at 6, 12, 18 and 24 months of beginning the technique.

Results: Comparing the basal characteristics of both groups, there was only significant difference in the Charlson index score. The ADPKD group had a mean of 2.9 ±1.07, while the non-ADPKD group had 4.2 ± 1.97. The most common cause to enter on PD program was patient choice. The mean technique survival was similar in both groups 969.6 ± 667.4 vs 847.5 ± 666.4 days. The proportion of patients in APD was higher in the ADPKD group, 71 vs 46% (p = 0.1). The means of episodes of peritonitis, dialysate leaks and hospitalizations were similar. The most common cause of withdrawal from the program was transplant (50 vs 32%); the percentage of infradialysis was higher in the non-ADPKD group (7 vs 18%). Kt/V mean was > 1.7 in both groups, but it was overall lower in the ADPKD group. A value of p < 0.0.5 was only achieved when the peritoneal Kt/V was contrasted.

Conclusions: ADPKD patients not show higher risk of PD complications or technique failure when compared with non-ADPKD with similar characteristics. PD is an effective treatment modality for ADPKD patients, and ADPKD should not be taken as an absolute contraindication. PD adequacy thresholds are achievable in ADPKD patients.

FR-PO509

Peritoneal Dialysis Outcomes of Patients with Nephrotic Syndrome: A Propensity Matched Study

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Background: Whether or not nephrotic syndrome (NS) patients developed to end stage renal disease (ESRD) stage could be treated by peritoneal dialysis (PD) were not clear. The aim of this study is to investigate the outcomes of PD treatment on ESRD patients with or without NS.

Methods: In this retrospectively cohort study, all incident PD patients with NS who started PD during February 1, 2006, to December 31, 2017, were identified and matched with patients who without NS by using propensity scores based on age, gender, diabetes mellitus and serum albumin. Both the mortality and technique failure on PD were compared.

Results: A total of 53 NS PD patients and 53 matched control non-NS PD patients with a median follow-up of 3.32(0.84, 5.95) years were included. The median survival of NS PD patients (6.60 years, 95% CI 4.95-8.25 years) was comparable to that of non-NS PD patients (5.20 years, 95% CI 4.05-6.34 years, p=0.261). An interaction effect was observed between survival time and baseline NS status. Thus, patients' outcomes within 1.5 years and after 1.5 years were analyzed separately. Both the mortality rate (log-rank test, p=0.235) and technique failure (log-rank test, p=0.543) within 1.5 years in the patients with NS were comparable to those of non-NS group. However, after 1.5 years, as compared to patients without NS, NS status at baseline had both lower all-cause mortality (p=0.020) and lower technique failure rate on PD (p=0.008). Multivariable Cox regression analysis showed that as compared to non-NS patients, PD patients with NS (HR 0.38, 95% CI 0.17-0.86, p=0.019) were significantly associated with both lower all-cause mortality adjusting for age (HR 1.05, 95% CI 1.02-1.08, p<0.001) and serum albumin levels at baseline (HR 0.86, 95% CI 0.75-1.00, p=0.047) and lower technique failure rate after adjusting for age (HR 1.03, 95% CI 1.00-1.05, p=0.020) and hypertension.

Conclusions: Our study demonstrated that both the short and long-term PD outcomes of ESRD NS patients were not inferior to their matched control, which indicated that PD could be considered as a long-term renal replacement therapy for ESRD patients with baseline NS.

FR-PO510

Impact of Obesity in Peritoneal Dialysis Patients

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Background: Some studies reveal that obesity is associated with a decrease in mortality in hemodialysis patients. However, few studies have addressed the association between BMI in peritoneal dialysis (PD) patients.

Methods: We performed this longitudinal, retrospective study, to evaluate the impact of obesity in PD patients, using data from the Registry of Renal Patients of Catalonia from 2002 to 2015 (n = 1573). Obesity was defined as BMI> 30; low weight: BMI <18.5; normal range: BMI 18.5-24.99; and pre-obesity: BMI 25-29.99. Variations in BMI were calculated during follow-up. The main variables evaluated were the technique and patient survival.

Results: Obesity was observed in 20% of patients starting PD. We did not find differences in sex or PD modality, being older the obesity group (65.9% are ≥55 years versus 59% non-obese p=0.003) and presenting more DM and cardiovascular disease (47.9% obese versus 25.1% non obese and 41.7% versus 31.5% respectively). We did not observed differences in hemoglobin, albumin and KTV in obese patients. Concerning peritonitis rate we did not find any difference between groups, presenting more peritonitis patients on CAPD and ≥65 years (subhazard ratio (SHR) 1.75 (p= 0.000) and 1.56 (p=0.009)). Related to technique survival, we found higher transfer to HD in obese group in the univariate analysis that was not confirmed in the multivariate analysis (SRH 1.12 (p=0.4)), and we did not found differences in mortality rate. In relation to be transplanted, underweight group, olders and patients with cardiovascular disease or diabetic nephropathy presented less probability (SHR 0.65, 0.24. 0.5 and 0.54 p <0.05). Obese patients did not present differences in survival with weight changes, but in non-obese patients, the gain of 7% of the basal weight during the first year supposed a protective factor of dying (HR 0.6 p=0.034).

Conclusions: We did not observe differences in PD adequacy parameters, technique and patient survival or probability of being transplant in obesity group. However, we found that obese patients presented more DM and cardiovascular diseases that are related to higher morbi-mortality in the multivariate analysis.

FR-PO511

Long-Term Patient Survival Was Not Influenced by the Initial Modalities in Peritoneal Dialysis Patients: A Propensity Score-Adjusted Single-Center Study

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Background: The association between the modalities of peritoneal dialysis (PD) and long-term patient survival considerably differs among countries and remains unknown.

Methods: We retrospectively investigated the long-term survival rate of 146 Japanese patients, including those who switched from PD to hemodialysis (HD), and evaluated the correlation between survival time and clinical features at PD initiation, and the effect of using different dialysis modalities, continuous ambulatory peritoneal dialysis (CAPD) or automated PD (APD), on patient survival and their associated factors.

Results: The following patient characteristics were as follows: age (median, interquartile range), 65.0 (55.0–73.5) years; body mass index (BMI), 22.6 (20.8–25.9) kg/m^2; diabetes, 35.0%; serum albumin level, 3.4 (2.9–3.8) g/dL; serum creatinine level, 8.3 (6.2–9.9) mg/dL; dialysate-to-plasma creatinine concentration ratio (D/PCr), 0.66 (0.54–0.77); and urine volume, 700 (305–1000) mL. Time on PD was 36.0 (17.0–64.5) months, and time on patient survival was 53.0 (20.0–103.0) months. The 5- and 10-year patient survival rates were 65.4% and 40.0%, respectively. Cox proportional hazard analysis revealed that patient survival was significantly affected by age (hazard ratio [HR], 1.08; 95% confidence interval [95% CI], 1.05–1.11; p < 0.001), diabetes (HR, 2.07; 95% CI, 1.18–3.63; p = 0.011), and D/PCr (HR, 8.31; 95% CI, 1.38–49.9; p = 0.021). When comparing CAPD (n = 57) with APD (n = 84), the Kaplan–Meier analysis showed the values for patient survival time as 61.0 (45.1–76.9) months for CAPD versus 140 (76.9–203.0) months for APD, log-rank test; p < 0.001. Baseline characteristics showed significant differences between CAPD and APD in age (70.0 vs. 60.5 years), ACE-I/ARB intake (41% vs. 68%), icodextrin (39% vs. 16%), and serum creatinine levels (8.1 vs. 9.0 mg/dL), respectively. After propensity score adjustment for choosing CAPD, the superiority for APD over CAPD disappeared (p = 0.756).

Conclusions: We conclude that patient survival in this population was superior to that in previous worldwide reports. Moreover, the selection of CAPD or APD for initial dialysis was not associated with long-term patient survival, following adjustment of the baseline characteristics.

FR-PO512

Outcome Measures for Technique Failure Reported in Randomized [AT1] Trials in Patients on Peritoneal Dialysis: A Systematic Review

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Background: Peritoneal dialysis (PD) technique failure (TF) has been identified as a core outcome by the Standardized Outcomes in Nephrology - Peritoneal Dialysis (SONG-PD) initiative to be reported in trials. However, the definition and measures used for TF are not standardized. We aimed to assess the scope and consistency of definitions and measures used for TF in trials in patients on PD.

Methods: MEDLINE, Embase and CENTRAL databases were searched for randomized trials conducted in patients on PD that reported TF as an outcome up until July 2018. The definition and measures used were extracted and independently assessed by two reviewers.

Results: We included 23 from 187 trials involving 41 to 371 participants, with follow-up durations ranging from 6 weeks to 4 years. The duration of hemodialysis required to define TF was reported in 6 (26%) trials, specifically: 30 days (2 trials), "permanent" without further definition (2 trials), continuing HD until censoring (1 trial) and "any duration" (1 trial). In 9 trials it was unclear how transfer to HD/death/transplant was accounted for in the analysis of TF. Eight trials reported only "transfer to HD" without further definition regarding transplantation/death, whereas death was a cause of TF in 4 trials and censored in the remaining 2 studies. No study included transplant in their definition of TF. TF was reported as a frequency in 21 trials. Eighteen trials compared TF rates in the intervention and control groups, with 15 using a hazard ratio and the remaining 3 using unclear methodology. Attribution of TF was reported in 14 trials. Three trials reported only peritonitis-related TF without mentioning other causes of TF, with the remaining 11 studies reporting different reasons in each case.

Conclusions: There is substantial heterogeneity in how PD technique failure is defined and reported, likely contributing to substantial variability in reported rates. Standardized measures for reporting technique failure in PD trials are required.

FR-PO513

IoT (Internet of Things) Follow-Up vs. Conventional Care in Patients with Continuous Ambulatory Peritoneal Dialysis: A Retrospective, Case-Control Study

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Background: Peritoneal dialysis (PD) has been accepted as a home-based, more cost-effective renal replacement therapy worldwide. Increasing evidence indicates that patients on PD have clinical outcomes that are not optimistic than those on hemodialysis. The reasons for these observations are multifactorial and include lack of experience on self health-care and limited modality of follow-up. Internet of things (IoT), a novel technology that would improve access to and compliance in PD patients, has been designed and deployed to PD patients in our center for the nursing follow-up.

Methods: A retrospective, case-control study enrolled 30 patients on continuous ambulatory peritoneal dialysis (CAPD) in our center from 2018.09 to 2018.10. The patients were categorized into IoT group (15 patients) and conventional group in which patients was selected by propensity score matching for the gender, age, dialysis age and basic nephropathy. All the patients had been followed up for 3 months to assess their quality and compliance of PD. IoT follow-up was defined as the framework of home-based sphygmomanometer, electronic scale, weighing scale and portable application description (PAD) via bluetooth and the nurses in PD group could review the data timely over the internet and provide care management advice. Conventional care was defined as telephone or outpatient follow-up monthly.

Results: There were no differences among gender, age, dialysis age, and basic nephropathy distribution between the two groups. After 3-month follow-up, the weight compliance rate in IoT group seemed better than that in conventional group, with rate of 100% and 80%, p=0.068; the blood pressure compliance rate in IoT group seemed higher than that in conventional group, with rate of 60% and 46.7%, p=0.464. Nine patients (the rate of 60%) in IoT group, while only 2 patients (13.3%) in conventional group, had got alterations of hypotensive drugs, p=0.008. Eight patients (53.3%) in IoT group had acquired adjustments of PD doses, while no patient in conventional group had any changes, p=0.001.

Conclusions: Our preliminary results had indicated that IoT technology could provide innovations and timeliness for basic nursing care in PD follow-up. IoT devices would help to improve the availability and effectiveness of peritoneal dialysis.

FR-PO514

Thirty-Day Readmissions in the Peritoneal Dialysis Population Have High Clinical Variability

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Background: Dialysis facilities are evaluated on their all-cause 30-day readmission rate. We investigated the clinical heterogeneity of 30-day readmissions in the peritoneal dialysis (PD) population and the relatedness of readmissions to index hospitalizations.

Methods: In adults with Medicare receiving PD in the United States from 1/1/2013-12/31/2014, we classified index hospitalization and 30-day readmission pairs as "related" if the principal diagnoses were of the same organ system. Using multinomial logistic regression and adjusting for the patient, facility, and geographic factors, we studied whether prior hospitalization burden was associated with a higher likelihood of related readmission. For each of the most common index hospitalization diagnoses, we summarized the most likely reason for 30-day readmission.

Results: The adjusted probability of an unrelated 30-day readmission was 19.2% (95% CI: 18.7%, 19.7%) in patients with 0-1 hospitalizations in the prior year and 26.3% (95% CI: 25.0%, 27.2%) in patients with 4 or more hospitalizations (relative increase 1.4, 95% CI: 1.3, 1.5). Cardiovascular index hospitalizations were most likely followed by a related 30-day readmission (11.8%, 95% CI: 11.3, 12.4%), while renal index hospitalizations were least likely (3.4%, 95% CI: 2.4, 4.3%). For the most common index hospitalizations (peritonitis, sepsis, hypertension, and pneumonia), the most common reason for 30-day readmission was the same as the index hospitalization. Rates of these readmissions varied widely: 43% of peritonitis admissions were followed by peritonitis, sepsis, or peritoneal catheter complications; 34% of sepsis admissions by infections; 21% of hypertension admissions by hypertension or volume overload; and 21% of pneumonia admissions by pneumonia, sepsis, or pulmonary complications.

Conclusions: High background hospitalization rates were associated with increased unrelated 30-day readmissions. When stratifying by index hospitalization diagnosis, there was substantial variability in the rate of and reason for 30-day readmission. Medicare could improve 30-day readmission metrics in PD by accounting for clinical heterogeneity and background hospitalization burden.

FR-PO515

The Transition Care Programme: Our Experience in the Last 10 Years

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Background: Home therapies including peritoneal dialysis (PD) & home haemodialysis (HHD) are associated with better outcomes in patients with end stage kidney disease (ESKD) as compared to in-centre dialysis. Home therapies allow patients autonomy and flexibility with proven improved quality of life. Treating end-stage kidney disease at home means less travel & its associated cost. The cost of HHD to the health care system is the lowest of all dialysis modalities while incentre dialysis is the most expensive. 'Home, Independent dialysis and Transition Service' (HITS) was commenced in July 2009 within the Kidney Health Service. Since its inception, the uptake of home therapies has increased over the 10 years.

Methods: A retrospective analysis of patients referred to HITS and incident patients requiring kidney replacement therapy (KRT) between Jan 2009 and Dec 2018 with 6 months follow-up after their chosen modality. Incident home therapies pre- HITS and all prevalent dialysis patients via HITS were also analysed.

Results: Incident Home therapies increased from 44% in 2006 (pre-HITS) to 69% in 2018. There was an increased uptake of PD by 13.5% with 25 patients choosing PD in 2006 and 45 patients in 2018. The uptake of HHD remained at 20%. From the prevalent dialysis pool there was an increase in patients choosing HHD from transplant, incentre dialysis and PD from 28.6% in 2013 to 50% in 2018. Patient were followed up for 6 months and due to reasons including PD peritonitis, technique failure, haemodynamic instability rendering HHD unsafe, between 5-15% patients transitioned from home therapies to incentre haemodialysis.

Conclusions: Home therapies was relocated to the suburbs and away from the main hospital campus in 2006. The Transition unit followed in 2015. Since this initiative, the uptake of home therapies has increased which is largely due to the increased availability of pre-dialysis and specific home therapies nurses, medical support and a dedicated multi-disciplinary team. However, KRT modality in home therapies at 6-months are still not being maintained which necessitates stringent patient selection criteria with rigorous and intense education. Our transition unit has seen the increase in the uptake of home therapies however more work is required to keep patients on these modalities.

FR-PO516

Effect of Switching Dialysis Modalities on Metabolic and Nutritional Parameters: Analysis from USRDS

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Background: The effect of renal disease and the two dialysis modalities (hemodialysis (HD), and peritoneal dialysis (PD)) on metabolic and nutritional parameters has been well-studied. Compared to HD, PD is associated with low parathyroid hormone and calcium (Ca) levels, low albumin (alb) and increased BMI. In 2011, the prospective payment system dialysis bundle provided incentive for providers to place patients (pts) on PD, leading to more pts switching from HD to PD. To our knowledge, the impact of switching modalities on these parameters has not been described. We aim to elucidate the effect of switching dialysis modalities and the direction of the switch on metabolic and nutritional parameters in end-stage renal disease (ESRD) pts.

Methods: Using USRDS data, we reviewed 2,955,601 pts and analyzed 16,203 pts who switched modalities from 2012 to 2016. Pts were included if they were age >18, were switched from HD to PD or PD to HD after being on the first modality for at least 2 months, and had data available in Crownweb records before and after switch. Transplant pts and pts who switched modalities more than once during the research period were excluded. After excluding data for the last 3 months of the first modality and the first 3 months of the second, we used t-test to compare average Ca, phos, alb, BMI, and normalized protein catabolic rate (NPCR). We further used linear models to show differences between the two groups, adjusting for demographics and time on first modality.

Results: In both groups, phos and Ca increased after switch. In the HD to PD group, alb decreased (0.25mg/dL) and BMI increased (0.42kg/m2); NPCR did not change significantly. In the PD to HD group, alb (0.26) and NPCR (0.06) increased, though BMI decreased (2.1kg/m2). Compared to HD to PD switch patients and after adjusting for demographics and time on initial dialysis modality, PD to HD pts had higher phos (0.15mg/dL), Ca (0.09mg/dL), alb (0.41mg/dL), and NPCR (0.07g/kg/d), and lower BMI (2.23 kg/m2). All results were significant ($p<0.0001$).

Conclusions: Regardless of the direction of the switch, HD was associated with a higher alb and lower BMI. After adjusting for demographic variables and time on initial dialysis, switching from HD to PD results in lower phos, Ca, alb, but higher BMI than PD to HD pts.

FR-PO517

Prospective Follow-Up of Peritoneal Function in New PD Patients: Comparison Between a Conventional and a More Biocompatible Dialysis Solution

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Background: Preservation of peritoneal membrane function is essential for patients on long-term peritoneal dialysis (PD). Biocompatible dialysis solutions characterized by a higher pH and a lower concentration of glucose degradation products, are hypothesized to prevent or postpone the membrane alterations that result in ultrafiltration failure and consecutive morbidity and mortality. The objective of this study was to make an in vivo comparison between conventional and biocompatible solutions and the time course of peritoneal solute and fluid transport.

Methods: We analyzed prospectively collected peritoneal transport data from 251 incident patients treated between 1994 and censoring in 2016. The maximal follow-up was 5 years. 135 patients were treated with conventional and 116 with biocompatible solutions. Linear mixed models including change point analyses were performed to compare the time course of peritoneal transport between both groups. Adjustment was made for comorbidity. The interaction with peritonitis was examined

Results: 67% (conventional) and 64% (biocompatible) of the patients underwent minimally 3 transport measurements during follow up. Follow-up during the first years was characterized by consistently faster solute transport and lower ultrafiltration in the biocompatible group. After a change point at 3 years in the conventional group an increase in small solute transport occurred in these patients group ($p=0.01$). Thereafter solute transport increased progressively in the conventional compared to the biocompatible group. This was accompanied by a marked decrease in net ultrafiltration, which became lower in the conventional group between 3 and 4 years. Patients with a previous peritonitis in the conventional dialysis group, showed a significant decrease of transcapillary ultrafiltration already after 2 years on PD ($p=0.02$) while this was not present in the biocompatible dialysis group or in patients without peritonitis. The decrease in ultrafiltration was caused by both reduced free water transport ($p=0.08$) and small pore fluid transport ($p=0.06$).

Conclusions: this study emphasizes the detrimental relationship between conventional dialysis solutions, peritonitis and the acceleration of peritoneal transport abnormalities in long-term PD patients.

FR-PO518

"We Try Not to Let PD Control Us": Patient and Caregiver Perceptions of Empowerment in Managing Peritoneal Dialysis

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Background: While peritoneal dialysis (PD) can offer patients more independence and flexibility compared with hemodialysis, the demanding regimen can impose a burden on patients. Patient empowerment can strengthen capacity for self-management and improve outcomes. We aimed to describe patient and caregivers' perceptions, attitudes and experiences of empowerment in PD.

Methods: Adult patients on PD (n = 81) and their caregivers (n = 45) from nine dialysis units in Australia, Hong Kong, and the United States participated in 14 focus groups. Transcripts were thematically analyzed.

Results: We identified six themes: *lacking clarity for self-management* (limited understanding of rationale behind necessary restrictions, muddled by conflicting information); *restricted flexibility and freedom in doing dialysis regimen* (burden in budgeting time, confined to be close to home); *strength with supportive relationships* (gaining reassurance with practical assistance, comforted by considerate health professionals, alleviated with involvement of friends and family); *defying constraints* (reclaiming the day, undeterred by treatment, refusing to be defined by illness); *regaining lost vitality* (enabling physical functioning, restoring energy life participation) and *personal growth through adjustment* (building resilience and enabling positive outlook, accepting the dialysis regimen). Illustrative quotations are provided in Table 1.

Conclusions: For patients and caregivers, understanding the rationale behind lifestyle restrictions, practical assistance and family support in managing PD facilitated empowerment, whereas being constrained in time and capacity for life participation outside the home undermined it. While some refused to allow PD to control their lifestyle, education and counseling enhancing practical skills and time management can help patients accept and minimize the disruption of PD, and may improve treatment satisfaction and outcomes.

Table 1. Selected quotations

Theme	Quotations
Lacking clarity for self-management	*Yeah, and if not, why not? I want to know the physics, the mechanics behind why it's going to damage this, and if I'm going to get hurt... that's what I need to know. So then I understand. Not just tell me "you can't do that". Why?* *The dietitian for my kidneys says you can't do this and you can't do that, and I say hang on, I'm a diabetic. I say this and you say that, which is right and which is wrong? Then they said, as long as you don't overdo anything, just do what you do. So it's confusing, I mean one dietitian says you do this, another one says that, and they conflict.*
Restricted flexibility and freedom in doing dialysis regimen	*Before, I can go out whenever I want. But now I have to schedule every day... the only thing is that I have no time anymore for everything. Every time must be budgeted.* *Like I was working, I've been working for how many years? And just for two years I am not working, so it could be affecting me, staying home, seeing everybody going, working, and I'm at home and staying there doing my dialysis and things like that... At the moment it's like a full stop. I can't move forward in my life. It's like you have to stay home, you have to do this.*
Strength with supportive relationships	*I made the trip with no hassle whatsoever. The people in the center, they have got lots of tricks up their sleeve, like you know, when you're doing travelling you find yourself in all sorts of situations. Doing an exchange may be something you need to take care of, but the setting is not something that you can choose, so they gave me a couple of tricks up my sleeve.* *So I think that what's important to me is the relationship with me and the PD unit has really helped, like all the nurses are really compassionate and really get to know me. They sort of help me along through the journey.* *So they know I have to be back home or I can't stay out, if I'm going somewhere in the morning or whatever. So they all work with me, and everybody is just like, it is what it is.*
Defying constraints	*Since you're sleeping while your machine is on at night - I do the automated - I'm done as soon as I wake up, and make sure the hours are taken care of. Then I'm free to go about my day just like I regularly did before. So there's really no change in my activities during the day, basically.* *We try not to let the dialysis control us, you know. I say forget about the time, you do it whenever, as a family together we go out, but we come back on the time. We don't lose the time, but we just, six hours away from the machine, and in that time, that is where we find to put what we want to do as a family.* *Most people don't even know I'm on dialysis unless I tell them. Because I don't feel like it's a big deal to me.*
Regaining lost vitality	*First of all I thank God and the doctors. I had been swollen for about three years, I couldn't walk, and I ended in the hospital and I thank God again and the doctors that are helping me and I feel fine now. [translated]* *Since she's been on dialysis, at least it's giver her a bit of pep in her step again nowadays. I can see, from my point of view, she was going downhill rapidly until the diagnosis. At least now we can get out and enjoy the grandkids.*
Personal growth through adjustment	*As crazy as it may sound, I feel like being on dialysis really pushed me more in life, of becoming independent. Through dealing with my personal issues, my self-issues, it really helped me. It made me see life better by being on dialysis, it's crazy but that's how it made me.* *The hardest is acceptance... I used to think that I wasn't going to do dialysis. I didn't want to do that. "Why would I want a life where I'm going to be slave to a machine?" I had to be in treatment to accept that it is life changing. I we all should go through that. [translated]*

FR-PO519

Physician-Led CKD Education Improves Quality and Reduces Cost of Care in Patients with ESRD

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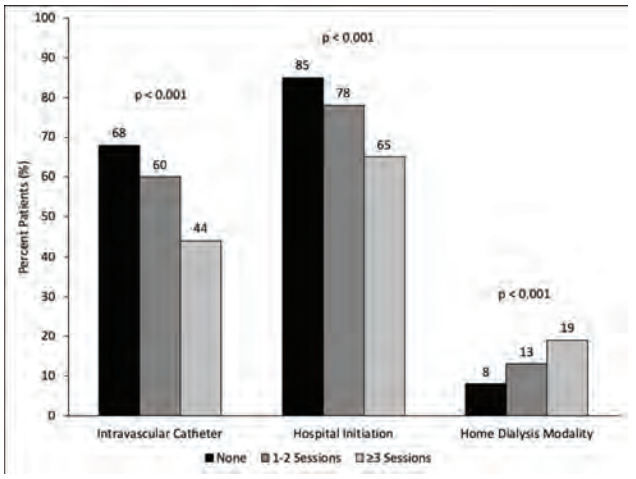
Background: Healthcare providers are tasked with reducing costs and improving patient awareness of chronic kidney disease (CKD). Patient educational initiatives may reduce costs and improve outcomes.

Methods: We developed a large-scale physician-led CKD education program. We performed a retrospective review of all dialysis initiates over a 24-month period and evaluated outcomes based on participation in educational programs.

Results: A total of 1294 dialysis initiations were analyzed and 621 patients (48%) attended at least one class. No differences in participation were observed based on gender, race, or primary language spoken. Overall participation in educational workshops was associated with decreased intravascular catheter use, increased home dialysis modalities, and decreased hospitalization for dialysis initiation ($p<0.001$). Attendance when stratified by no participation vs. 1-2 sessions vs. ≥ 3 sessions revealed a progressive trend towards decreased intravascular catheters, in-center dialysis modalities, and hospitalization for dialysis initiation ($p<0.001$; Figure). In multivariate analysis, the associations between participation in CKD education and decreased likelihood of intravascular catheter access (OR 0.55; $p<0.001$), decreased in-center hemodialysis modality (OR 0.48; $p<0.001$), and increased in-center hemodialysis initiation vs. hospital (OR 2.02; $p<0.001$) were independent of race, gender, age, or primary language spoken.

Conclusions: Patients with CKD who participate in physician-led educational programs are less likely to need urgent dialysis, which results in decreased use of intravascular catheters, and hospitalization for dialysis initiation. They are also more likely to utilize home dialysis modalities. Development of patient educational programs could significantly reduce costs and improve outcomes in this population.



CKD Edu - Outcomes; n=1294

FR-PO520

Lower Utilization of Home Dialysis in Non-White and Dual-Eligible Dialysis Patients

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Background: Past studies have associated non-white race with lower utilization of home dialysis. We aimed to assess the joint influence of race and dual eligibility (*i.e.*, concurrent enrollment in Medicare and Medicaid), a surrogate for poverty, on home dialysis utilization in each state.

Methods: Using Medicare Limited Data Sets, we identified all patients with Medicare Part B claims documenting outpatient dialysis from January 2014 to December 2017. For each calendar week (Monday to Sunday), we identified patients with at least one day of either home hemodialysis or peritoneal dialysis treatment. Within each of the 50 states, we modeled utilization of home dialysis with logistic regression, using a generalized estimating equation. Risk factors comprised non-white race, dual eligibility (DE), the interaction of race and DE, age, sex, and calendar year. We applied a Bonferroni correction to the set of tests of race, DE, and the interaction thereof ($\alpha = 0.05/150$).

Results: The cohort comprised 633,288 patients and 61,522,192 patient-weeks. Overall, 1.8% of patient-weeks were marked by home hemodialysis and 8.9% were marked by peritoneal dialysis. Relative to white patients without DE, state-specific adjusted odds ratios (AORs) of home dialysis in non-white patents without DE were centered at 0.58; among 34 states in which the effect of race was significant, AORs ranged from 0.28 to 0.76. State-specific odds ratios of home dialysis in white patients with DE were centered at 0.42; among 43 states in which the effect of DE was significant, AORs ranged from 0.25 to 0.78. Relative to white patients without DE, state-specific AORs of home dialysis in non-white patients with DE were centered at 0.25. However, interactions of race and DE were significant in only 2 states. In 46 states, non-white patients with DE were less likely to undergo home dialysis than both non-white patients without DE and white patients with DE.

Conclusions: Both non-white race and DE are associated with lower likelihood of home dialysis utilization in most states. The effects are generally log-additive, thus placing non-white patients with DE at profoundly lower likelihood of home dialysis utilization. Substantial growth in home dialysis will necessitate identifying and addressing the reasons for these disparities.

FR-PO521

Early Peritoneal Dialysis Start: Is There Room for More?

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Background: Despite educational care, a considerable number of End Stage Renal Disease (ESRD) patients present to Nephrology without a plan for dialysis and in the urgent need of it. Most of them could be suitable for Peritoneal Dialysis (PD), but concerns with PD access placement, makes hemodialysis (HD) through a central venous catheter as the only viable option. Early PD start (in the first 14 days after catheter placement) could be an option in this subset of patients and favor the increment of PD programs. The purpose of our study was to demonstrate that early PD start could be a safe option for patients in the urgent need of dialysis.

Methods: Retrospective, single-center study, with 18 ESRD patients without a dialysis care plan, who started PD in the first 14 days after catheter placement (Early start group - ESG) and 34 patients who started PD after planned dialysis care (Late start group - LSG). For each group we collected demographic data, previous nephrology follow up, type of catheter placement and initial PD prescription. We also measured short-term (90-day) clinical outcomes (Kt/V, creatinine clearance, daily ultrafiltration (UF), hemoglobin, ferritin, parathyroid hormone, phosphorus, calcium and albumin), as well as PD related complications (peritonitis, exit-site infections, leaks and catheter dysfunction).

Results: Patients on ESG begun PD in about 4.9 days after catheter placement, mainly due to overhydration. These patients were predominantly of male gender (88 vs 59%, p= 0.025) and without previous follow-up by Nephrologist (67 vs 97%, p=0.001). Although there weren't any differences in PD modality and type of catheter placement, exchange volumes were lower in the ESG (p=0.001). Short term outcomes were equal among groups, except for daily UF (higher in ESG; p= 0.013). Concerning mechanical complications, the number of leaks and episodes of catheter dysfunction were also similar, as well as the rate of infectious complications.

Conclusions: Despite being a single center study, with a small number of patients enrolled, our results demonstrate the safety and feasibility in beginning PD in patients with kidney failure, without a previous plan for renal replacement therapy. Early PD start in patients with the urgent need of dialysis could be an important step to improve PD worldwide, overcoming the initiation of HD through a catheter and its well known risks.

FR-PO522

Evaluation of a Wearable Artificial Kidney for Peritoneal Dialysis in a Uremic Pig Model

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Background: A WEarable Artificial KIDney (WEAKID – H2020 SC1) for peritoneal dialysis (PD) was designed that recirculates dialysate *via* a tidal mode using a single lumen peritoneal catheter. We hypothesize that continuous dialysate regeneration by the WEAKID system containing sorbents, will maintain a high plasma-dialysate concentration gradient and increase the mass transfer area coefficient (MTAC). Thereby, WEAKID may enhance clearance while reducing the number of exchanges. Application is envisaged at night as a bedside device (12 kg, nighttime system). A wearable system (1.6 kg, daytime system) may further enhance clearance during the day.

Methods: The day- (n=3) and nighttime system (n=8) were tested separately for 8 h/treatment in a uremic pig model for PD (n=2). Plasma clearance and the MTAC of urea, creatinine and phosphate with the day- and nighttime system were compared with a standard peritoneal membrane permeability analysis (SPA, n=13).

Results: The daytime system caused a 2.0-fold (p=0.01) and 1.6-fold (p=0.07) increase in creatinine and phosphate clearance and 1.9-fold (p=0.01) and 1.6-fold (p=0.04) increase in MTAC creatinine and phosphate, resp., *vs* a SPA (Table 1). With the nighttime system, creatinine clearance and MTAC increased by a factor of 1.2 (p=0.002) and 1.4 (p=0.01), resp.

Conclusions: WEAKID increases small solute clearance compared with a SPA. This provides a rationale for a first in human clinical trial to evaluate safety and efficacy of WEAKID in PD patients.

Funding: Government Support - Non-U.S.

Table 1. Plasma clearance and the MTAC of urea, creatinine, phosphate during WEAKID and SPA experiments.

	Peritonitis	SPA (n=13)	Daytime (n=3)	Nighttime (n=8)	Daytime *vs* SPA	*p**	Nighttime *vs* SPA	*p**
Plasma Clearance (mL/min)								
Urea	NO	5.8±1.0		5.8±0.3			≈1.0	0.97
	YES	7.3±1.3		9.9±4.5			≈1.4	0.30
Creatinine	NO	3.4±0.6		4.0±0.4			≈1.2	0.002
	YES	5.2±1.1	10.7±2.0	9.1±5.0	≈2.0	0.01	≈1.7	0.17
Phosphate	NO	2.7±0.4		2.8±0.0			≈1.1	
	YES	4.7±1.2	7.2±1.4	5.8±5.4	≈1.6	0.07	≈1.2	0.69
Mass Transfer Area Coefficient (mL/min)								
Urea	NO	8.7±1.4		11.3±2.4			≈1.3	0.08
	YES	16.8±2.1	18.2±6.2	20.7±11.0			≈1.2	0.51
Creatinine	NO	3.8±0.6		5.3±0.8			≈1.4	0.01
	YES	8.9±2.3	16.8±3.2	13.8±8.9	≈1.9	0.01	≈1.6	0.32
Phosphate	NO	2.8±0.8		3.1±0.0			≈1.1	
	YES	7.1±1.3	11.1±2.0	8.6±9.0	≈1.6	0.04	≈1.2	0.79

*Independent T-test.

FR-PO523

Assessing the Impact of Dialysis Modality on Hospitalization in a Large Population of ESRD Patients

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Background: Hospitalizations and readmissions pose a significant burden to ESRD patients and result in significant costs to the US health care system. There is increasing focus on patient outcomes and cost advantages for patients starting ESRD treatment on a home dialysis modality. Understanding the impact that specific modalities can have on hospitalizations may assist in changing physician behavior regarding initial modality selection.

Methods: Data were derived from adult patients receiving dialysis treatments in a large dialysis organization between 01 March 2016 and 31 March 2019. Hospitalization rates (overall and cause-specific), length of stay, and readmission rates were assessed

separately for in-center hemodialysis (ICHD), peritoneal dialysis (PD), and home hemodialysis (HHD) patients. All outcomes were considered monthly and as 12-month rolling averages.

Results: As of March 2019, 12-month rolling average hospitalization rates were 1.24, 1.41, and 1.80 admits/year for PD, HHD, and ICHD patients, respectively; 30-day readmission rates were 26.2%, 24.3%, and 32.1% and mean length of stay was 6.62, 6.60, and 6.52 days, respectively. Significant variability was observed across geographic regions, with PD hospitalization rates ranging from 0.95 to 1.42 admissions/year and HHD hospitalization rates ranging from 1.13 to 1.66 admissions/year. Causes of hospitalization differed across modalities and programs: ICHD patients had higher rates of respiratory-related admissions and lower rates of admissions for gastrointestinal- and infection-related causes than patients on home modalities.

Conclusions: There is a pressing need to reduce hospitalization rates among ESRD patients to limit rising health care costs and improve outcomes. Here we demonstrate that hospitalization and readmission rates are consistently lower, and length of stay shorter, for patients using home dialysis modalities (PD and HHD) than those receiving ICHD. However, significant variability was observed across home programs, by program size and geographic location. Findings from this study have been used to develop a proactive approach to decreasing hospitalizations and readmissions based on program characteristics.

Funding: Commercial Support - DaVita Inc

FR-PO524

Timing of Peritoneal Dialysis Initiation and Mortality: A Retrospective Clinical Study

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Background: The impact of timing of peritoneal dialysis (PD) initiation on mortality is controversial. We conduct this study to investigate the association between timing of PD initiation and mortality.

Methods: In this single-center cohort study, incident PD patients from January 1, 2006, to December 31, 2016 were enrolled. All patients were followed up until December 31, 2018. Patients were categorized into 3 groups according to the estimated glomerular filtration rate (eGFR) at the initiation of PD using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation. Defined early, mid, and late starts as eGFR ≥ 7.5, 5-7.5 and < 5 ml/min/1.73 m^2, respectively. Cox regression analysis was used to compare mortality (overall and cardiovascular [CV]) among the 3 groups.

Results: A total of 2,151 incident PD patients were enrolled. The number of patients in early group was 319, mid group was 726, and late group was 1,106. Compared with the early-start group, the overall and CV mortality rates were not lower for the mid- (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.69-1.12 and HR 0.89, 95% CI 0.63-1.25) or late-start (HR 0.82, 95% CI 0.64-1.05 and HR 0.78, 95% CI 0.55-1.11) groups. In age-stratified model, elderly patients (age≥65 years) showed a significant lower risk of overall and CV mortality in late-start group (HR 0.65, 95% CI 0.45 – 0.95 and HR 0.50, 95% CI 0.30-0.83) and a significant decreased risk of CV mortality in mid-start group (HR 0.55, 95% CI 0.33-0.92) compared with early-start group; however, there was no significant difference in overall or CV mortality between the 3 groups in younger patients (<65 years).

Conclusions: Lower eGFR at PD therapy initiation was not associated with lower mortality risk. However, an eGFR < 5 ml/min/1.73m^2 at the initiation of PD was associated with lower risk of mortality among elderly patients, while not among younger patients.

FR-PO525

The Effect of Hemodialysis with Central Venous Catheterization on Urgent-Start Peritoneal Dialysis

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Background: Urgent-start peritoneal dialysis(USPD)has received worldwide attention. A number of clinical studies have shown that USPD has great advantages in early complications, technical survival, and medical economics. Due to differences in economic conditions and acceptance, there is no pre-dialysis preparation in most ESRD patients in China. So most patients accept hemodialysis with central venous catheterization (HD-CVC) before deciding on long-term dialysis alternatives. Patients who eventually choose peritoneal dialysis will begin USPD treatment. Whether HD-CVC has effect on USPD that has not been studied. So we investigated the effects of the HD-CVC on USPD.

Methods: Retrospective analysis was performed on patients who received USPD from 2008/08/01 to 2017/03/31 in our hospital. According to whether the patient had HD-CVC before USPD, it was divided into USPD group (HD-CVC was not performed before peritoneal dialysis) and HD-PD group (HD-CVC was given first, and then peritoneal dialysis catheterization was performed within 2 week). The follow-up time was 1 year. The differences in clinical biochemical indexes, dialysis dose, urine volume, residual renal function, dialysis adequacy, peritoneal dialysis complications and technical survival rate between the two groups were observed.

Results: 1. A total of 482 patients were included in this study, including 315 patients in the USPD group and 167 patients in the HD-PD group. The gender, age, the proportion of diabetic nephropathy patients, creatinine, glomerular filtration rate, blood potassium before admission were similar between the two groups(P>0.05). 2. At 1 month of peritoneal dialysis, residual renal function, UKt/V and TKt/V in the USPD group were significantly higher than those in the HD-PD group, blood urea nitrogen and creatinine were significantly lower than those in the HD-PD group(P<0.05). At 6 months, the urine volume in the USPD group was significantly higher than those in the HD-PD group(P=0.002). 3. The export infection rate, peritonitis infection rate, mechanical complications and technical survival rate were similar between the two groups(P>0.05).

Conclusions: HD-CVC before USPD may affect the residual renal function and dialysis adequacy of patients. Therefore, HD-CVC is not recommended for ESRD patients who need peritoneal dialysis but have no indication of emergency dialysis.

FR-PO526

Perceived Exercise Barriers and Benefits in Haemodialysis and Peritoneal Dialysis Patients

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Background: Patients receiving dialysis are extremely inactive. This may be due to uncertainty and lack of appropriate guidance about exercise, or due to a number of barriers that patients may perceive. Understanding dialysis patients' perceived exercise barriers and benefits can inform interventions to address the barriers and promote the benefits, and increase exercise participation.

Methods: Perceived exercise barriers and benefits of 1017 haemodialysis patients (HD) [age: 63.1 (15.3) years; males: 653 (64%); white: 585 (58%)] and 124 peritoneal patients (PD) [age: 62.1 (15.2) years; males: 86 (69%); white: 95 (77%)] were assessed using the 'Dialysis Patient-perceived Exercise Benefits and Barriers Scale' (DPEBBS). Barriers and benefits to exercise were classed as binary variables (i.e. yes and no). Frequency analysis and chi-squared tests were conducted to compare the barriers and benefits perceived by HD and PD patients.

Results: The proportion of HD and PD patients who reported barriers and benefits to exercise is displayed in Figure 1. Significantly more HD patients than PD patients reported 'reduces body pain' (p=.013), 'delays decline in body function' (p=.010), and 'improves quality of life' (p=.033) as benefits. No significant differences in barriers were observed between the groups. Tiredness was the most commonly reported barrier by both groups.

Conclusions: The findings suggest that HD patients are more aware of the physical benefits of exercise than PD patients. This may be due to HD patients being better informed about the benefits and more actively encouraged to exercise than PD patients via regular contact with healthcare professionals. However, more evidence is needed to determine factors that may influence HD and PD patients' physical activity levels prior to developing exercise interventions.

Funding: Private Foundation Support

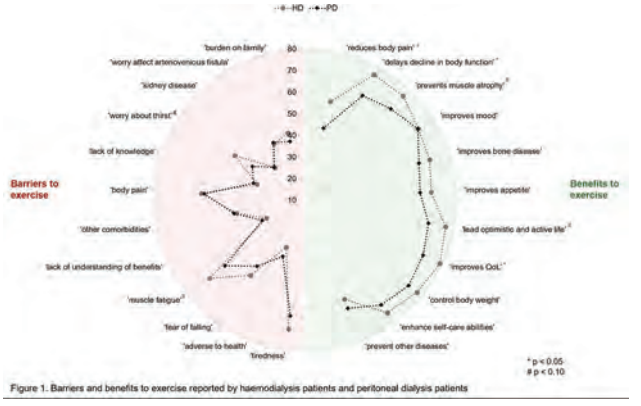

Figure 1. Barriers and benefits to exercise reported by haemodialysis patients and peritoneal dialysis patients

FR-PO527

Pilot of Assisted PD in an Integrated Health Care System

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Background: Peritoneal dialysis (PD) is a home based modality that has many benefits. However, it can be challenging for patients with physical disabilities and psychosocial barriers, particularly the elderly. Assisted PD can provide support to overcome these barriers and promote PD utilization and retention. Assisted PD programs have been in use worldwide for over 20 years and have demonstrated good results. There are no such programs in the US. Kaiser Permanente Northern California (KPNC) is an integrated health care system that serves over 4.4 million members. Our PD unit in the Greater Southern Alameda Area is an internal PD program in KPNC, serving over 150 patients. In 2018 a pilot program of assisted PD was developed by the our unit to help overcome common barriers to PD and expand it as modality of choice.

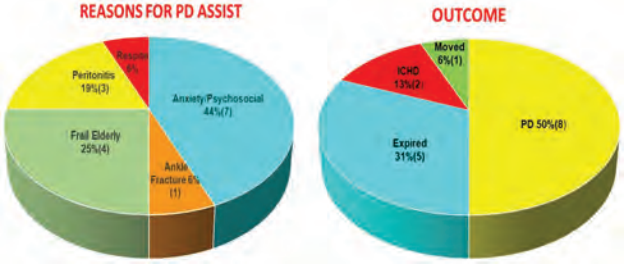
Methods: A seven month pilot of temporary assisted PD was completed from April to October 2018. Patients were identified using certain selection criteria and assisted PD was offered for a time limited period of 90 days per patient. A single PD RN was designated as the assist PD nurse. The assistance included cycler set up and connections; lifting bags; performing CAPD exchanges; adding antibiotics; retraining and psychosocial support.

Results: Sixteen PD patients (7 incident, 9 prevalent) were assisted with a total of 59 visits. Reasons were anxiety/psychosocial (7); ankle fracture (1); frail elderly (4);

peritonitis (3) and respite (1). Visits per patient ranged from 1-10. 50% (8) stayed on PD; 13% (2) switched to hemodialysis (HD); 31% (5) expired and 1 relocated.

Conclusions: Assisted PD provides an effective means to support frail or functionally limited PD patients, encouraging them to select it as a modality and/or remain on PD. In our pilot, providing this assistance enabled us retain 50% of our patients on PD, who would otherwise have had to transfer to in center HD. Assisted PD is a valid and safe alternative to in center HD and should be used to expand modality choices, overcome barriers to PD and shift care to home.

Funding: Clinical Revenue Support



FR-PO528

Comparison of Outcomes Between Percutaneous and Surgical Placement of Peritoneal Catheters in Dialysis Patients: A Meta-Analysis

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Background: The successful insertion of the peritoneal dialysis catheter (PDC) ensures effective catheter function and technique survival. The most commonly used technique is the surgical approach by laparotomy or laparoscopy. Minimally invasive techniques are currently developing and seem to be an alternative. We evaluated the efficacy and safety of the percutaneous insertion methods compared to conventional surgical methods.

Methods: Studies comparing percutaneous and surgical methods of PDC insertion were identified through databases of PubMed, EMBASE, Cochrane and Web of Science. Catheter survival, dialysate fluid leakage, mechanical and infectious complications were analyzed using random effects model and results were presented as odds ratio (OR) and 95% confidence intervals (CIs).

Results: Sixteen studies were finally identified. The pooled data demonstrated no differences in catheter survival, dialysate fluid leakage and mechanical complications between percutaneous and surgical way (OR = 1.24, 95% CI = 0.81–1.91, *P*= 0.33; OR =1.49, 95% CI = 0.98–2.26, *P*= 0.06; OR = 0.65, 95% CI = 0.39–1.08, *P*= 0.08, respectively). Infectious complications occurred less in percutaneous group (OR = 0.56, 95% CI = 0.32–0.96, *P*= 0.04). The malposition incidence was obviously lower in percutaneous method compared with surgical method (OR = 0.51, 95% CI = 0.32–0.82, *P*= 0.005). The detailed analysis on bleeding, omental wrapping, hernia, exit site infection, peritonitis and tunnel infection did not show difference.

Conclusions: The percutaneous method is a safe and effective alternative to insert peritoneal catheters and could be an optimal choice besides the conventional surgical way.

Funding: Government Support - Non-U.S.

Main Outcomes	No. of studies	No. of patients	Mean Difference [95%CI]	P value	I^2(%)
survival	13	2,375	1.24[0.81,1.91]	0.33	74
leakage	14	1,972	1.49[0.98,2.26]	0.06	30
mechanical complications	13	1,991	0.65[0.39,1.08]	0.10	76
infectious complications	14	2,436	0.56[0.32,0.96]	0.04	74

FR-PO529

Local Anaesthesia Peritoneal Dialysis Catheter Insertion: A Single-Centre Tertiary Care Renal Unit Experience from the United Kingdom

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Background: Peritoneal dialysis [PD] is one of the modalities for renal replacement therapy and requires inserting a PD catheter[PDC] into the peritoneal space and is traditionally a surgically assisted PD catheter insertion[SPDCI] under general anaesthesia[GA]. CKD5 patients are at high risk for GA. Local anaesthesia PDC insertion [LPDCI] has been done in those without previous abdominal surgery[PAS]. Peritoneal adhesions due to previous surgery can complicate insertions. We share our experience of LPDCI vs SPDCI from a tertiary care renal unit in the UK.

Methods: Retrospective data was collected from April 2017 to April 2018 and retrieved from electronic patient records and peritoneal dialysis unit notes. The analysis was performed using Microsoft Excel 2010.

Results: A total of 86 catheters were inserted in 83 patients. 35% (29) have diabetes. Figure 1 shows the procedure group characteristics.

Conclusions: Physician-led LPDCI is usually performed in patients without PAS. In our cohort, 43% who underwent LPDCI had PAS. Some of these cases were performed under fluoroscopy guidance. There was no significant difference in immediate complications and catheter function. Peritonitis after six months of LPDCI was higher but unrelated to PAS and LPDCI. PDC loss and modality change were high due to patient choice and infections and is being addressed by further improvements in patient education on hand hygiene and assessment of PDC care. Peritonitis should be treated promptly and where possible PDC should be reconsidered if clinically appropriate. LPDCI is a safe and effective way of providing definitive access to PD. It is cost-effective, performed in a shorter time, spares surgical theatre time and space, improves patient satisfaction by reducing patient stay and avoids the risk of GA.

Type of PDC insertion	LPDCI [n=63] (%)	SPDCI [n=23] (%)
Sex [M:F]	38:25	9:11
Previous abdominal surgery	27(43)	19(83)
Failure of the procedure	2(3.2)	1(4.3)
Bleeding	1(1.6)	1(4.3)
Mechanical failure	6(9.5)	4(17.4)
Tunnel infection	2(3.2)	1(4.3)
Peritonitis after 6 months	17(27)	3(5)
Pleural leak	4(6.4)	0
Bowel, bladder & blood vessel injury	0	0
PDC still in use	23(36.5)	9(39.1)
Transplantation	5(7.9)	1(4.3)
Switched to HD	25(39.7)	5(21.7)
Procedure switch	1 had SPDCI (1.6)	2 had LPDCI (8.7)
Death due to non PDC related cause	2(3.2)	2(8.7)
Duration of PDC in-situ days in PDC removed cases [Mean; Median; SD]	232.7; 140.8; 196.4	181.7; 196.9; 84.7

Comparative analysis of physician-led [LPDCI] vs surgeon-led [SPDCI] peritoneal dialysis catheter insertions has been shown in figure 1.

FR-PO530

Point-of-Care Ultrasound in Peritoneal Dialysis Catheter-Related Infection: An Observational Study

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Background: Peritoneal dialysis (PD) catheter-related infection (PD-CRI) is the most common complication of this form of renal replacement therapy. The diagnosis of PD-CRI is made with physical examination (PE), but the physical findings lack sensitivity or specificity. Point-of-care ultrasound (POCUS) is an emerging discipline in the Nephrology community that allows the physician to incorporate real-time information from the ultrasound into his clinical evaluation. POCUS could improve the diagnostic accuracy of PD-CRI and reduce patient exposure to antibiotics. This single-center observational study aimed to compare the accuracy of POCUS and PE for the diagnosis of PD-CRI.

Methods: POCUS was performed by a Nephrology fellow using a linear transducer when PD-CRI was suspected. POCUS was repeated in every patient visit. PD-CRI was defined as purulent discharge with or without inflammatory signs, and a positive microbiological culture collected from the exit-site. We considered a positive POCUS as an anechoic collection around the external cuff, and its largest dimension was recorded. PE findings were coded using a validated clinical score.

Results: A total of 25 patients (58 % male) were enrolled. We also recruited nine patients with no signs of PD-CRI as controls. A total of 13 PD-CRIs were diagnosed, from 22 suspected cases. The most common isolated agent was *Corynebacterium spp.* In this population, the diagnostic accuracy of PE was low, with an area under the ROC curve (AUROC) of 0,6 (95% CI 0,37-0,84). Purulent drainage alone, although highly specific (100%), showed a low sensitivity (61,9%) for the diagnosis of PD-CRI. In contrast, POCUS had an AUROC of 0,91 (95% CI: 0,73-1) for PD-CRI diagnosis. All the PD-CRI cases had a positive POCUS evaluation, and we did not find this sonographic sign in controls ($p < 0,001$). The optimal cut-off point of the collection dimension was equal to or greater than 1,4 mm (Sensitivity 100%; Specificity 89%). Suspected PD-CRI cases with negative POCUS and not exposed to antibiotic therapy, had similar PD-CRI rates in one-month follow-up as the control group ($p = 0,929$).

Conclusions: POCUS is superior to PE for the diagnosis of PD-CRI and should be considered by nephrologists with access to an ultrasound machine. POCUS may decrease unnecessary antibiotic exposure in PD patients due to an increase in PD-CRI diagnostic sensitivity.

FR-PO531

Quality Improvement Strategies to Reduce Peritoneal Dialysis Catheter Insertion Wait Times: A 10-Year Experience

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Background: Bedside peritoneal dialysis (PD) catheter insertions have been effective in reducing wait-times, however laparoscopic insertions are still needed in patients with prior abdominal surgeries, high risk of leaks and hernia repairs. Our study aim was to assess the impact of local quality improvement initiatives on wait-times for laparoscopically inserted PD catheters over a 10-year period.

Methods: We reviewed our database at the Toronto General Hospital for laparoscopic wait-times for PD catheter insertions between January 1, 2008 to December 31, 2018. Wait-times for catheter removals, manipulations and hernia repairs were reviewed. Buried PD catheters were excluded from analysis. A control chart analysis of mean quarterly wait-times for laparoscopically inserted PD catheters was performed. We captured the effect of three local interventions on wait times: interventional radiology program (fluoroscopic-guided), bedside insertion program and transition to becoming a centre of regional practice, wherein patients from other parts of the province were referred to us for more complex catheter procedures.

Results: A total of 379 new patients had laparoscopically inserted catheters between 2008 and 2018. Quarterly mean wait-time for catheter insertion was between 21.3 to 28.5 days (Figure 1). After becoming a regional centre of practice in 2016, mean wait-time for new insertions increased dramatically to 39.3 days. There was no change in access to operating room (OR) time during this period. After 2016, there was a 56.4 % increase in external patients receiving procedures at our institution without increase in access to OR time. 51% of procedures were hernia repairs, catheter manipulations along with removal and reinsertion.

Conclusions: Quality improvement strategies may initially help to reduce wait-times for PD catheter insertions. However, long-term success of these improvement strategies must be supported with administrative policies that lead to proportional increases in access to OR time.

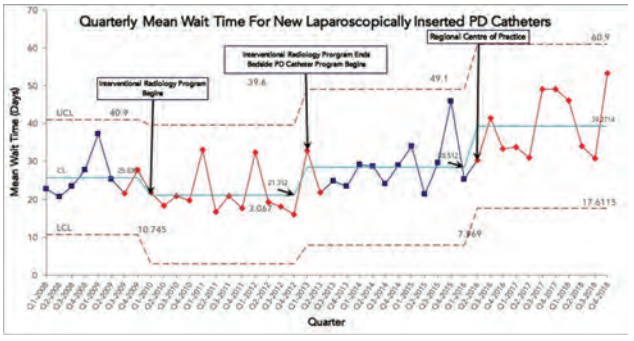

Figure 1

FR-PO532

Barriers to Peritoneal Dialysis in Saskatchewan Canada: Results from a Province-Wide Survey

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Background: Peritoneal dialysis (PD) offers similar clinical outcomes to hemodialysis (HD) at a fraction of the cost. PD remains underutilized as remote HD patients in Saskatchewan often relocate or travel hundreds of kilometers weekly in order to receive dialysis related care. The purpose of this study was to determine the barriers to receiving PD in our province.

Methods: We conducted a cross sectional survey of in center HD patients across the province of Saskatchewan. 740 in center HD patients at two academic sites and 7 satellite units were approached by study coordinators. 421 patients (n=268 in the main units and n=153 in the satellite units) agreed to participate in the study. A questionnaire using a five-point Likert scale was created to identify barriers to PD with questions addressing PD awareness and knowledge, accessibility, and risks/fears/beliefs surrounding PD. Responses were anonymous and tabulated using a data collection tool.

Results: Only 82% of patients were aware of PD as a treatment option. 35% of patients felt they had no understanding of the benefits or risks of PD. Prominent barriers to PD that we identified were: excellent care in the HD unit (62%), proximity to dialysis unit (41%), unwilling to dialyze daily (36%), and unwilling to learn a new technique (34%). Beliefs held by patients that figured prominently in their decision to choose HD over PD included not wanting to take their disease home (32%), fear of being a burden on family (32%), lack of space (28%), risk of infection, issues with self-image while on PD, and PD being an inferior modality to HD (all approximately 24%).

Conclusions: In this study, we identified patient specific barriers to PD in a prevalent cohort of HD patients. Several barriers were identified with a few consistent themes being identified, including deficiencies in knowledge, patient specific beliefs and poor patient education. The most frequently reported knowledge barrier was a lack of understanding of benefits and risks of PD. While the study does not reflect the views of all patients, the information gained will be valuable in designing an educational program to improve adoption of PD within our province.

FR-PO533

Early Start Peritoneal Dialysis: How to Increment This Modality?

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Background: Despite the increasing incidence of end-stage renal disease (ESRD), peritoneal dialysis (PD) is offered to a minor subset of patients. One way to increment PD rates is the early start of technique after catheter placement without the usual break in times but there are concerns with mechanical and infectious complications that could compromise PD outcomes. The aim of this study was to compare the outcomes and safety of early PD start, after 12 and 24 months.

Methods: Retrospective analysis performed in a single-center; 52 patients: 34 started PD after planning (late start group - LSG) and 18 in the first 14 days after catheter placement (early start group - ESG). Demographic data, comorbidities, Charlson comorbidity index (CCI) were collected. PD related complications and dropout cases were identified.

Results: ESG present a male predominance (88.2 vs 58.8%; p=0.025) and higher CCI (35.9 vs 59.4% estimated 10-year survival) with a significantly prevalance of cardiovascular diseases (p=0.03). Average time between catheter placement and PD starting in the ESG was 5 days. LSG stayed longer under PD (813 vs 555 days). Kidney transplantation was the main cause of dropout in the LSG group whereas in the ESG the causes were mechanical issues and death. First episode of peritonitis (FP) occurred earlier in the ESG (478 vs 831 days) but this difference was not statistically significant among the 2 groups. Unadjusted Kaplan-Meier estimated that the difference in dropout-free survival was statistically significant in bouth groups (p=0.006, long rank test). Multivariate analysis with Cox regression demonstrated that, even though the risk of dropout was higher during the first 12 months in the ESG (HR=5.503; p=0.014), this decreases after 24 months (HR=2.363; p=0.036) of PD. The frequency of dropout was higher in the ESG (77.1% versus 61.8%) but this difference was not significant (p=0.242). When comparing the frequency of dropout after excluding patients that were transplanted, results were similar.

Conclusions: Urgent-start PD can be a valid and safe alternative to hemodialysis via central venous catheter and should be offered to patients without contraindications. Other factors not related to the early start of technique (age and higher CCI), can have a negative impact on the morbidity and mortality of those patients influencing the outcomes of DP technique.

FR-PO534

International Variation in Outcomes After PD-Related Peritonitis

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Background: Peritoneal dialysis (PD)-associated peritonitis is a major source of morbidity, mortality, and technique failure for patients receiving PD. We sought to understand if there were regional differences in peritonitis outcomes.

Methods: We used Peritoneal Dialysis Outcomes and Practice Patterns Study phase 1 (2014-2017) data from Australia and New Zealand (A/NZ), Canada (CA), Japan (JP), Thailand (TH), the UK, and the US to report variation in peritonitis outcomes (up to 50 days after peritonitis) by country and to estimate associations with organism type using logistic regressions adjusted for country, age, sex, diabetes, and serum albumin. Cure was defined as the lack of any outcome except hospitalization. Technique failure (TF) was defined as permanent transfer to hemodialysis or failure to resume PD within 12 weeks.

Results: We observed 2270 peritonitis episodes in 6949 patients during 7816 years of follow-up (crude rate: 0.29 episodes/year). Cure proportion was 64% (range by country: 54-68%), and death occurred in 6% (JP: 2%; TH: 16%, others: 4-5%). Hospitalization was common for both peritonitis-related causes (55%, range: 41-75%) and for any cause (72%; range: 59-91%), with >80% occurring within 14 days. Relapsing/recurrent peritonitis occurred in 9% (range: 7-14%), and concurrent exit-site infection occurred in 12% (JP, UK: 19-21%; TH: 6%; others: 9-10%). Catheter removal occurred in 21% (TH, JP, UK: 24-29%; others: 18-20%), and TF occurred in 16% (TH: 10%; others: 16-19%). Higher odds of death, TF, or catheter removal were seen for Gram-negative (OR=2.78, 95% CI=2.03, 3.8), culture negative (OR=1.3, 95% CI=0.92, 1.83), polymicrobial (OR=4.43, 95% CI=2.89, 6.79), and missing/unknown peritonitis (OR=2.64, 95% CI=1.89, 3.69), compared to Gram-positive peritonitis.

Conclusions: High proportions of peritonitis resulting in death (Thailand) and TF (all countries) suggest novel interventions to prevent peritonitis are needed. Emphasis on

identification methods and development of organism-specific treatment strategies may help reduce morbidity associated with these episodes.

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Organism type	N peritonitis	Death*	Technique failure*	Catheter removal*	Recurrent/relapse peritonitis	Concurrent exit-site infection*	Hospitalization (peritonitis-related)	Hospitalization (all-cause)
Gram-positive	864	2%	10%	13%	9%	12%	36%	53%
S. aureus (coagulase-negative)	344	1%	8%	8%	12%	5%	20%	37%
S. aureus (other)	197	6%	8%	20%	9%	25%	37%	58%
Streptococcus	183	1%	9%	9%	5%	11%	54%	72%
Other Gram-positive	140	1%	16%	20%	9%	10%	52%	69%
Gram-negative	876	7%	21%	28%	12%	11%	53%	72%
E.coli	91	7%	19%	22%	6%	7%	56%	75%
Klebsiella	56	11%	17%	22%	14%	11%	54%	70%
Pseudomonas	55	8%	33%	40%	15%	21%	48%	74%
Other Gram-negative	174	6%	19%	28%	14%	9%	51%	69%
Culture-negative	399	6%	11%	17%	9%	10%	38%	59%
Polymicrobial	126	8%	29%	40%	8%	11%	54%	76%
Yeast	36	17%	64%	69%	6%	9%	67%	89%
Other/unknown	469	10%	21%	23%	6%	13%	38%	73%

*Excluding US large dialysis organizations.

FR-PO535

Declining Peritonitis Rates Incompletely Translate into Improved Technique Survival in Australian Peritoneal Dialysis Patients

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Background: Peritoneal Dialysis (PD) peritonitis rates are declining, but not matched by a uniform reduction in technique failure (TF) rates. Understanding the reasons for this disconnect will potentially help identify new targets for intervention.

Methods: 13653 incident PD patients undergoing first PD treatment episodes in Australia between 2003 and 2017 were analysed for TF in 3-year cohorts. Instances of TF were segregated into infective or non-infective causes and cumulative incidences (CI) calculated at 1- and 2 years of death-censored technique failure (transfer to HD for >30 days) with death as competing risks. CI calculated using the Fine and Grey method.

Results: The peritonitis rate in Australia halved over the observation period. There were substantial improvements in death rates during PD treatment. However, there were minimal or no changes in death-censored PD technique failure (DCTF). Adjustment for age and diabetes made of DCTF events at 1 year, the proportion attributed to infection fell from 44% to 28%, with a similar fall at 2 years. After adjustment for age and diabetes, there was a suggestion of moderate improvement among the most recent cohort.

Conclusions: PD peritonitis rates have declined substantially over the study period as have death rates, but overall technique survival has changed only modestly. Non-infective causes of DCTF are proportionately higher; identification of modifiable risk factors provide the next target to enhance PD outcomes.

Results

Year of PD start	2003-2005	2006-2008	2009-2011	2012-2014	2015-2017
n	2426	2809	2449	2977	2992
CI (DCTF) at 1 year (95% CI)	.21 (.20-.23)	.21 (.19-.22)	.21 (.20-.23)	.19 (.18-.21)	.17 (.16-.19)
CI (DCTF) at 2 years (95% CI)	.35 (.33-.37)	.34 (.32-.35)	.34 (.32-.36)	.33 (.31-.35)	.32 (.30-.35)
Subhazard ratio (adjusted for age / diabetes)	1.0	0.99 (0.91-1.06)	1.0 (0.92-1.08)	0.93 (0.86-1.00)	0.80 (0.72-0.88)
Peritonitis rate (per p-year)	0.60 (0.57-0.62)	0.54 (0.53-0.56)	0.43 (0.41-0.45)	0.38 (0.37-0.40)	0.30 (0.29-0.32)
Proportion infective DCTF 1yr (%)	44	40	30	24	28
Proportion infective DCTF 2yr	46	44	32	28	30
CI (death) at 1 year	.10 (.09-.12)	.08 (.07-0.9)	.08 (.07-.09)	.05 (.04-.06)	.06 (.05-.07)
CI (death) at 2 year	.20 (.18-.22)	.17 (.15-.18)	.14 (.13-.16)	.13 (.11-.14)	.13 (.12-.15)

FR-PO536

Risk Factors for Early Mortality After Switch from Peritoneal Dialysis to Hemodialysis: A Multinational Registry Study

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Background: Transfer to hemodialysis (HD) is frequent in peritoneal dialysis (PD), and mortality risk is highest in the early transition period to HD. We sought to identify risk factors of mortality after a PD to HD transition.

Methods: Incident PD patients (started on PD within 180 days of RRT initiation) who switched to HD for ≧1 day between 2000 and 2014 were identified, using registries from Australia/New Zealand (ANZDATA), Canada (CORR), Europe (ERA-EDTA), and the United States (USRDS). Separate multivariable Cox models were built for early (<90 days), medium (90-180 days) and late (>180 days) periods after switch to HD. Patients were followed after switch from PD to HD from the first day (model 1), day 90 (model 2) or day 180 (model 3) until death, censoring at time of kidney transplantation and end of follow-up.

Results: Overall, 6,669, 5,848, 21,574, and 80,459 patients were included from ANZDATA, CORR, ERA-EDTA and USRDS, respectively. Risk of mortality after switch to HD was lower in the most recent cohorts. Older patients were at increased risk of death, particularly during the first 90 days after switch. Similarly, the mortality risk associated with longer PD vintage was highest during the early periods after switch to HD, but attenuated afterwards. Males experienced lower risk of mortality early after transition to HD, but higher mortality risk after 180 days on HD.

Conclusions: In this multinational registry study, mortality risk factors varied by time period after switch from PD to HD. Females, older patients and patients with PD vintage >3 years before switching to HD were at greater risk of early mortality and should be followed more closely when transitioned to HD.

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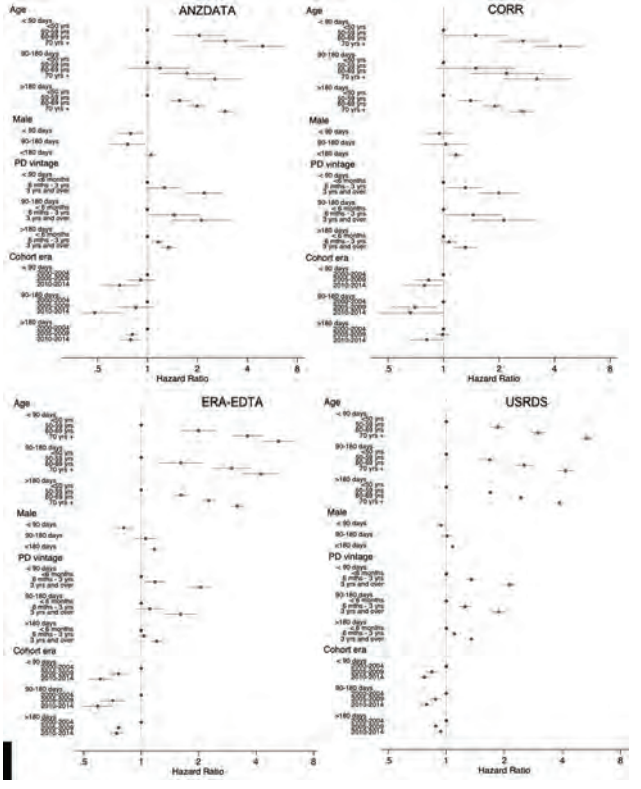

FR-PO537

Interesting Relationship Between Levels of Thioredoxin and Vitamin D on Antioxidant System in Peritoneal Dialysis Patients

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Background: The reactive oxygen species produced continuously during oxidative metabolism are generated at very high rates in chronic kidney failure. Therefore, defending against oxidative stress is an essential task with the patients who suffering from that disease. An important cellular system against oxidative stress is the cytosolic mammalian thioredoxin system (TS) which consist of thioredoxin (trx), nicotinamide adenine dinucleotide phospate (NADPH) and thioredoxin reductase (TrxR) has emerged as a major anti-oxidant which involved in the maintenance of cellular physiology and survival. Vitamin D is also an other strong antinflammatory molecule and it has a growing of number of studies revealing its pleiotropic roles beyond the bone and calcium metabolism. The aim of this study is to find a significant relation between these two systems.

Methods: We conducted a study of 69 patients with end stage of kidney disease who were under the treatment of continuous ambulatory peritoneal dialysis or automated peritoneal dialysis. Serum thioredoxin level were measured. Measurements were corrected according to comorbid diseases, medications, duration and type of peritoneal dialysis and residual renal function. In addition, they were also evaluated for the correlation between hemoglobin, uric acid, CRP, albumin, ferritin, lipid parameters and iPTH levels. Our aim was to prove the effect of the use of Vitamin D supplementation on thioredoxin as an anti-oxidant system. 40 out of 62 patients were already under the vit D supplemantation but the rest of the group was not eligible.

Results: There was no statistically significant difference between Thioredoxin measurements according to PD type, etiology and drugs ($p > 0.05$) but Thioredoxin levels in patients with vit D supplemantation were significantly higher than those without vit D supplemantation. ($p < 0.01$). The results were evaluated in a confidence interval of 95% and a significance level of $p < 0.05$.

Conclusions: This result of study was not suprising but important because it emphasized that Vit D anti-inflammatory effect especially in chronic kidney failure patients except the bone-mineral metabolism and pointed to strict follow –up vit D level in this group which is already under the inflamatory situation to reduce complications related to oxidative stress by contributing the augmentation of thioredoxin serum level.

FR-PO538

A Case of Scleroderma Renal Crisis in a Patient with Systemic Sclerosis Sine Scleroderma

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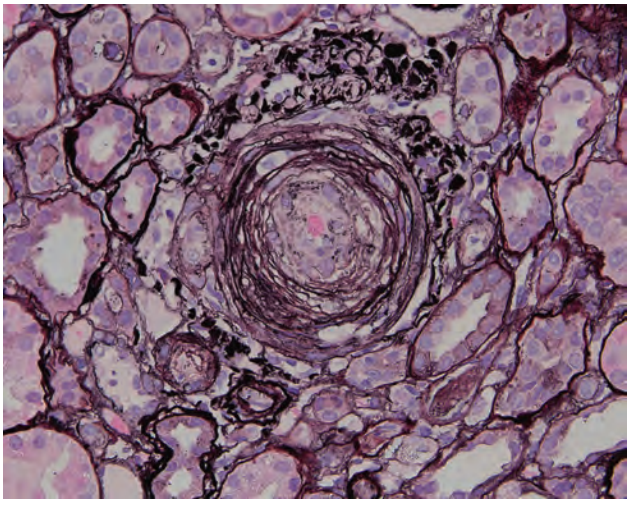
Introduction: Scleroderma renal crisis (SRC) typically presents with abrupt onset of accelerated hypertension (HTN) and acute kidney injury (AKI) usually in patients with diffuse cutaneous Systemic Sclerosis (dcSSc). We report a case of SRC in a patient with systemic sclerosis sine scleroderma (ssSSc), a rare form that presents with visceral involvement in the absence of skin manifestation.

Case Description: A 64 year old female with a history of Raynaud's phenomenon, seronegative rheumatoid arthritis and HTN was admitted to Northwestern Memorial Hospital with shortness of breath, uncontrolled HTN and AKI. Her blood pressure (BP) ranged from 165/94 to 194/100 mmHg. She had bilateral crackles, no lower extremity edema and no skin manifestations of scleroderma. Anti nuclear antibody was positive >1:1280 with a negative serologic work up including anti-SCL-70, anti-centromere and RNA polymerase III antibodies. Urinalysis was without protein or blood. HTN was uncontrolled and captopril was started with good BP response. AKI worsened and a kidney biopsy was performed (Fig). Pathology showed ischemic glomerulopathy, marked arteriosclerosis with onion skinning and vascular lesions suspicious for thrombotic microangiopathy concerning for SRC. Her clinical course deteriorated rapidly with the development of severe pulmonary HTN, heart and renal failure.

Discussion: ssSSc is a rare form of systemic sclerosis. Two types of ssSSc patients have been described and the course can follow either limited scleroderma or dcSSc. The latter can have delayed sclerodactyly and early vital organ involvement similar to our case. Clinicians need high degree of suspicion to diagnose ssSSc given the lack of skin findings. While serologic testing can help with diagnosis, SRC is a clinical diagnosis that can be enhanced by renal biopsy. This case highlights the difficulty in diagnosing patients with SRC in the setting of ssSSc.



Arteriosclerosis with onion skinning

FR-PO539

Scleroderma Renal Crisis in a Patient with Paraneoplastic Syndrome

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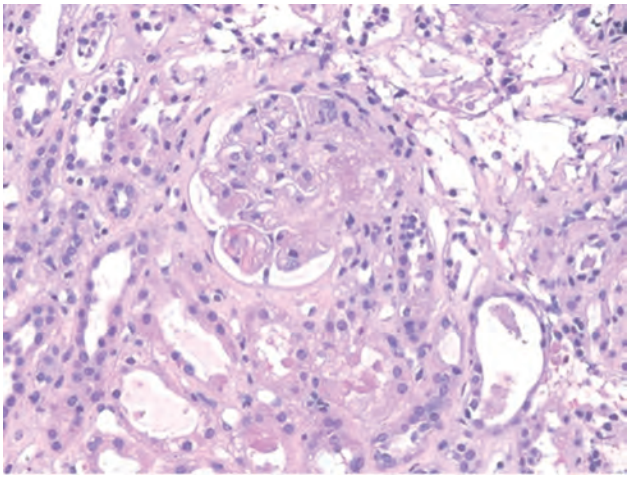
Introduction: Scleroderma renal crisis affects 5-10% of patients with systemic sclerosis, with 5-year survival rate of 59%. Anti-RNA polymerase IIIAb are associated with risk of SRC and cancer. We describe a patient with paraneoplastic scleroderma who presented with AKI and HTN after steroid use and diagnosed with SRC.

Case Description: A 55-year-old woman with h/o HTN, Endometrial cancer (3/ 2017) s/p TAH-BSO, tumor debulking, paraneoplastic scleroderma (diagnosed a month back with + autoantibodies to RNA polymerase III) was sent to ER for worsening creatinine(2 mg/dl to 4.6 mg/dl in 2 weeks). Of note patient was noted to have worsening liver enzymes 2 months back and underwent liver biopsy which showed ductopenia and fibrosis. Given suspicion of an autoimmune process prednisone was initiated. On admission, patient was in acute respiratory distress requiring intubation, hypertensive (SBP 180mmHg) and in renal failure. Diagnosis of SRC was made, Captopril was initiated and steroid was discontinued. Renal biopsy showed TMA with extensive involvement of arteries, arterioles, extensive (50%) ischemic glomerular alteration, segmental duplication of glomerular capillary wall and moderate tubular injury. No significant interstitial fibrosis/tubular atrophy. She was discharged on dialysis.

Discussion: SRC is characterized by presence of high blood pressure with variable degrees of renal insufficiency.5-20% of patients with diffuse scleroderma are at risk of developing SRC. A positive RNA Pol IIIAb, present in our patient, further increases the risk of developing renal crisis. SRC associated with paraneoplastic scleroderma is even rarer. An extensive review of the literature showed only 4 cases of SRC in patients with ovarian, lung, breast and renal carcinoma. Given that SRC is a potentially life-threatening disease, we should have a high degree of suspicion in patients with scleroderma who present with hypertension and acute renal failure.



Glomerular microthrombi

FR-PO540

Systemic Sclerosis Sine Scleroderma Renal Crisis: An Atypical Presentation

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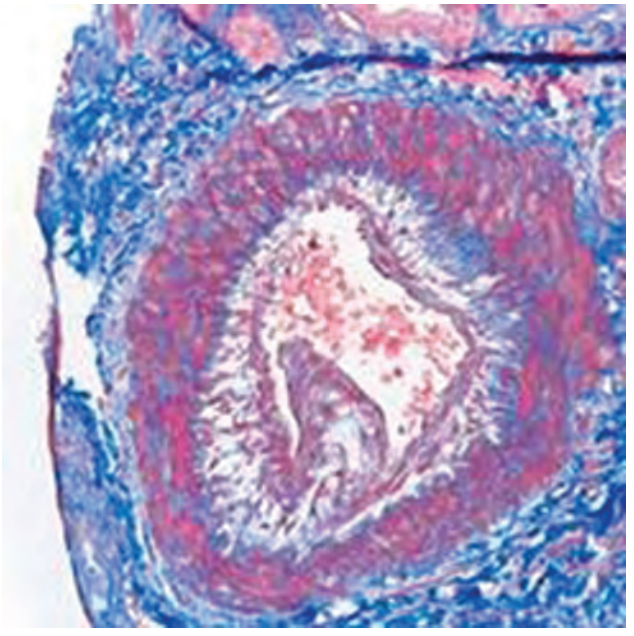
Introduction: Scleroderma renal crisis (SRC) is a rare complication that occurs in 5% of all systemic sclerosis (SSc) patients. Previously reported one-year mortality of 76% decreased to 15% when captopril became the preferred treatment. Usually, SRC is triggered by high dose steroids in patient with SSc. Our patient instead, presenting with signs of Hemolytic Uremic Syndrome (HUS) diverting the workup towards infectious/ autoimmune/genetic causes of HUS until, renal biopsy and response to captopril became the key elements of diagnosis.

Case Description: This is a 19-year-old female presenting with vomiting, diarrhea and abdominal pain that progressed into dyspnea, oliguria, anasarca, malignant hypertension and renal failure. No evidence of skin or joint manifestations. Lab tests: low platelets, low Hg with schistocytes, stools (-)ve for E. coli and Shiga-toxin, normal ADAMTS13 activity and (-)ve Scl-70 antibodies. But, positive antinuclear antibody (ANA) and Sjogren's antibody (SsA) implied an autoimmune process. After failing a course of steroid pulse, plasmapheresis and plasma exchange transiently increased platelets and Hg. But, anuria persisted, requiring daily dialysis. Renal biopsy: onion peel lesion in medium sized arterioles, likely scleroderma renal crisis, prompted the decision to start captopril. After one dose, she had 2 liters of urine and eventually, renal function returned to normal.

Discussion: This is the first case report of a suspected HUS, later being diagnosed as SSc sine SRC based on clinical findings, positive ANA and SsA, renal arteriolar vasculopathy and response to captopril treatment without cutaneous manifestations and negative Scl-70 panel. Thus, it is important to consider SSc sine SRC when presenting with such clinical picture to attain complete renal recovery and decrease mortality.



FR-PO541

Low Alanine Aminotransferase in Hemodialysis Patients: A Marker for Pyridoxine Deficiency

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Introduction: Hemodialysis (HD) patients often have lower serum alanine aminotransferase (ALT) levels than those with normal kidney function. There are multiple proposed mechanisms with controversy surrounding the contribution of pyridoxine (vitamin B6) deficiency, a cofactor for liver aminotransferase synthesis. We present a remarkable case of pyridoxine deficiency diagnosed in a HD patient by an undetectable ALT.

Case Description: A 71-year-old woman on HD for 6 years was admitted for an infected hand wound. She also had a duodenal switch surgery for obesity 17 years prior. Home medications included a dialysis multivitamin and pyridoxine 100 mg daily, though she hinted at variable adherence to both due to insurance issues. Admit labs incidentally showed an undetectable ALT level, confirmed on repeated testing. Bilirubin and AST were normal. She had a normal ALT 4 months prior and past imaging showed no cirrhosis. Subsequent pyridoxine testing, measured in its active form of pyridoxal 5'-phosphate, was low at 7.3 nmol/L [Normal 20-125 nmol/L]. Other water-soluble vitamin levels including thiamine and cobalamin were normal. She was given 10 mg pyridoxine IV daily for one week with maintenance 100 mg oral daily. Follow up 4 weeks later revealed improved pyridoxine levels to 29.3 nmol/L and a now detectable ALT level of 9 U/L. She remains on a dialysis multivitamin and oral pyridoxine 100 mg daily.

Discussion: Aminotransferases are often drawn with routine labs in the dialysis population, with elevations signaling concern for pathology such as infectious hepatitis. However, undetectable or borderline levels may not alarm practitioners, particularly as aminotransferases are known to be lower in HD patients. This poses a risk of missing a diagnosis of pyridoxine deficiency, which may ultimately cause progressive anemia, neuropathy, and confusion. Vitamin B supplementation in HD is accepted as routine due to a restrictive diet and dialytic removal, though insurance coverage may be sporadic. Our patient had an additive risk factor of malabsorption due to her bariatric surgery. This case highlights a noteworthy presentation that should prompt providers to investigate water-soluble vitamin levels and adherence to supplementary vitamins. Our patient showed that dramatically low ALT levels may be an early and only sign of pyridoxine deficiency in HD patients.

FR-PO542

Perils of Renal Revascularization for Severe Hypertension

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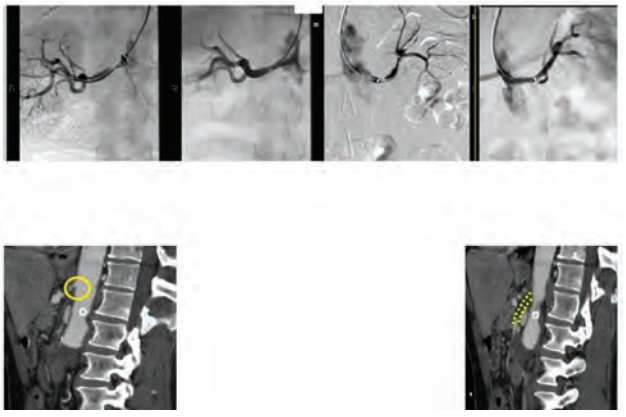
Introduction: Revascularization is not superior to medical therapy in atherosclerotic renal artery stenosis (RAS). This may be partly attributed to renal complications from revascularization but also from extra renal complications due to the drop in systemic blood pressure (BP). We highlight this with a case of a man who developed an extrarenal complication following renal angioplasty.

Case Description: A 58 year old man was referred to the hypertension clinic at a tertiary care hospital. He was on 5 BP lowering drugs with a 5-minute office resting BP of 213/99 mm Hg. Magnetic resonance angiogram showed extensive atherosclerotic disease of the aorta and branches including bilateral (B/L) RAS, 80 % on right and 50% on left. In view of this and resistant hypertension, he underwent B/L renal angioplasty and stenting. Post intervention BP in the clinic was 123/89 mmHg despite a 50% decrease in BP medications. On day 3, he developed diffuse, progressively worse abdominal pain, along with nausea and vomiting. Laboratory tests showed leukocytosis and elevated lactate. Computed tomography scan confirmed diagnosis of subacute mesenteric ischemia due to superior mesenteric artery (SMA) occlusion and progressive stenosis of celiac trunk. He underwent stenting and angioplasty of the latter which resolved his symptoms. At 1 month, his BP was 106/68 on 3 drugs.

Discussion: Renal artery stenting for drug resistant hypertension improved this patient's BP. However, the decrease in systemic BP made the hitherto non-critical stenoses of aortic branches clinically critical, thus precipitating bowel ischemia. This highlights some of the mechanisms behind the morbidity associated with renal revascularization. Our data also suggests that critical review and awareness of the extent of extrarenal atherosclerosis prior to renal angioplasty may prevent or at least hasten the diagnosis of post-revascularization complications.



Upper panel-renal artery stentingLower panel-stenosis in celiac artery(left), SMA(right)

FR-PO543

Unique Cause of Renal Infarction: A Case of Pheochromocytoma

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Introduction: Pheochromocytomas (PHEOs) are rare chromaffin cell derived neuroendocrine tumors. Common presentations include paroxysmal episodes of headache, palpitation, sweating and hypertension. Life threatening complications including renal artery stenosis, and acute myocardial infarction had been reported from the possible mechanism of catecholamine-induced vasospasm and/or extrinsic compression of renal artery in some reported cases. Here, we report an interesting case of PHEOs associated with renal infarction, unrelated to artery thrombosis/stenosis.

Case Description: A 48 year old male with no significant past medical history presents to the emergency room (ER) with sudden onset headache and blurring of vision. Vital signs revealed blood pressure of 215/120 mm of Hg. No focal neurological deficits were noted. Laboratory work was unremarkable. CT head and CT angiogram of head and neck obtained revealed no evidence of intracranial hemorrhage. He left against medical advice at that time, but returned two days later to the ER with left flank pain. This time his vital signs showed blood pressure of 100/60 mm of Hg, and he had left sided abdominal tenderness. Laboratory work revealed troponin of 23.65 ng/mL [normal, <0.04ng/ml]. Abdominal and chest CT scan showed large wedge like non-enhancing region in the lateral mid to upper pole of left kidney and solid heterogeneous 4.9 cm right adrenal gland mass. PHEOs was suspected, and he was started on doxazosin plus apixaban. Cardiac catheterization was deferred. Specific laboratory work revealed high levels of total plasma catecholamine, plasma metanephrine, nor metanephrine, and chrmogranin A respectively. Twenty-four hour total urinary metanephrines, normetanephrines, and catecholamines were also markedly raised. The patient underwent uncomplicated laparoscopic right adrenalectomy few weeks after this admission. Surgical pathology confirmed the diagnosis of PHEOs.

Discussion: The workup and definitive diagnosis of PHEOs continue to be challenging. We present a case of PHEOs with renal infarction. Renal infarction from renal artery stenosis/thrombosis has been well documented in the literature. Our case is unique in its presentation, in that his renal infarct was independent of renal artery stenosis or thrombosis. We hypothesize, this was most likely from wide variation in blood pressure, and possible hypotensive episode, in the absence of renal artery pathology.

FR-PO544

Renal Artery Aneurysm in Dialysis Patients

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Introduction: Renal artery aneurysms(RAAs) are rare(less than 1% in the general population), with most found incidentally on abdominal imaging. Aneurysm rupture has a high mortality and morbidity if not recognized in a timely manner

Case Description: We present two case-both end stage renal disease(ESRD) patients who presented with RAA rupture. The first patient was a 56 year old African American male on intermittent hemodialysis who presented with complaints of right sided flank pain for one day, without associated trauma, fevers, hematuria and hemoglobin of 7.7mg/dl on labs. A CT scan showed a right retroperitoneal hematoma. CT angiogram revealed two small pseudoaneurysms in the right renal artery with active extravasation that was successfully coiled. The second patient, a 72 year old Hispanic male, on peritoneal dialysis, was admitted to the critical care unit after an ischemic stroke. He was found to have Atrial fibrillation and started on a heparin drip for anticoagulation. His anti hypertensive medications were held to allow for permissive anti-hypertension. However, his hemodynamics worsened shortly afterwards requiring pressor support and stat labs revealed a drop in hemoglobin to 3.6mg/dl from 9.9mg/dl. Point of care ultrasound demonstrated a hypoechoic area around the left kidney. CT angio showed multiple areas of contrast blush in the left kidney consistent with active bleeding. IR guided coil embolization of the left renal artery was performed successfully and bleed was stopped.

Discussion: RAAs are associated most commonly with hypertension, followed by connective tissue diseases like fibromuscular dysplasia, Ehler–Danlos syndrome, Marfan syndrome, and vasculitis(such as polyarteritis nodosa and chronic granulomatosis with polyangiitis). Atherosclerosis is also associated with RAA but exact causative mechanism is not known. RAA rupture may present with back pain, abdominal pain, ileus, and hemorrhagic shock with CT showing retroperitoneal hematoma. Patients with chronic kidney disease and end stage renal disease have several risk factors for development of RAAs and rupture. Clinicans should have high suspicion for RAA rupture in dialysis patients presenting with abdominal pain, uncontrolled hypertension and sudden drop in hemoglobin. Endovascular treatment is a minimally invasive option available to treat renal artery aneurysm even in setting of aneurysmal rupture and bleeding as is gaining favor over open surgical repair.

FR-PO545

MobiusHD® Device: Controlling Refractory Hypertension in ESRD

Spencer Hodgins, Michael J. Germain. *Nephrology, UMMS Baystate Medical Center, Springfield, MA.*

Introduction: We discuss an interesting case of a patient on dialysis with severe hypertension. As a life saving measure we were granted compassionate use of the MobiusHD device, a baroreflex modulator implanted in the carotid artery. We discuss the outcomes and potential benefits of this device seen in this case.

Case Description: The patient is a 22-year old female with history of ESRD due to FSGS. She was diagnosed at a young age and underwent kidney transplantation at 11. She unfortunately went back on dialysis in 2016 at age 19 due to recurrent rejection and obstruction from a ureteric stricture. On dialysis she was noted to have extremely labile BP. In the 12 months prior to MobiusHD implantation, she had 22 admissions. Most were for hypertensive emergency requiring clevidipine. She also had an admission for PRES syndrome with seizures. Work up for secondary causes of hypertension was negative. Given the severity of her illness the MobiusHD device was implanted in Feb. 18 through Compassionate Use approval granted by the FDA. In the 12 months following MobiusHD implantation she had only 9 admissions (Fig. 1). We also evaluated her dialysis flowsheets and pre-dialysis systolic BP in her unit dropped from an average of 169.1 in the 6 months prior to the device to 152.5 in the 6 months following (Fig 2).

Discussion: Our case highlights the potential benefits of the MobiusHD device in a patient with life-threatening complications due to hypertension. It is noted that up to 50% of dialysis patients have a blunted baroreflex response which suggests that this device may be helpful in this population.[1,2] Since implantation of this device the patient has had a drastic improvement in quality of life and we are hoping to get her back on the transplant list with maintained stability.

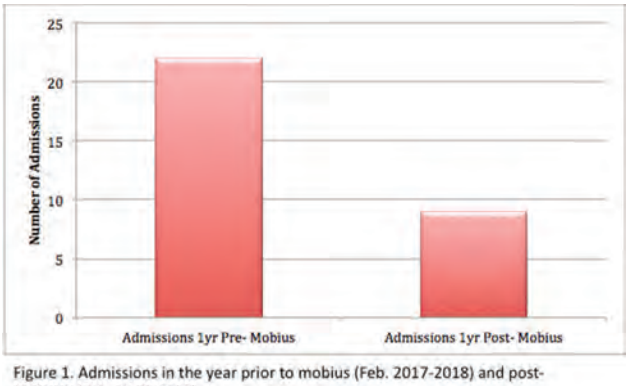

Figure 1. Admissions in the year prior to mobius (Feb. 2017-2018) and post-MOBIUS (Feb. 2018-2019).

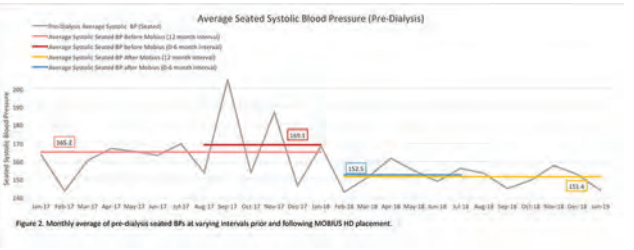

Figure 2. Monthly average of pre-dialysis seated BPs at varying intervals prior and following MOBIUS HD placement.

FR-PO546

Secondary Hyperoxalemia Causing Cardiac Failure in an ESRD Patient

Samuel J. Peeples,[1] Manish K. Saha,[2] Vimal K. Derebail,[3] Lucia Balos,[4] Alan L. Hinderliter,[1] Rocco C. Venuto.[5] University of North Carolina Kidney Center *[1]University of North Carolina Health Systems, Chapel Hill, NC; [2]UNC Kidney Center, Chapel Hill, NC; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Jacobs School of Medicine, Buffalo, NY; [5]Erie County Medical Center, Buffalo, NY.*

Introduction: Secondary hyperoxaluria is a known complication of bariatric surgery due to impaired fat absorption. Oxalate deposition leading to organ dysfunction is poorly defined outside of primary oxalosis. We describe a case of cardiac and renal oxalosis with end-organ failure secondary to gastric bypass surgery.

Case Description: A 65-year-old male on hemodialysis for 3 years with history of heart failure with preserved ejection fraction (EF), jejunoileal bypass at age 18 and right nephrectomy due to cystic mass presented for exertional dyspnea and orthopnea after newly establishing care with us. His ESRD was presumed due to chronic nephrolithiasis after his jejunoileal bypass surgery. Electrocardiogram demonstrated atrial fibrillation and low QRS voltage. Transthoracic echocardiography (TTE) showed mildly thickened left ventricular wall with granular, sparkling texture to the myocardium, preserved EF, and biatrial enlargement concerning for cardiac amyloid. Serum immunofixation revealed an IgA lambda spike of 0.9 g/dL with kappa and lambda serum free light chains of 19mg/dL and 28mg/dL (ratio 0.67). Bone marrow aspiration showed 5-10% plasmacytosis, a lambda predominance and negative Congo red stain. Fat pad biopsy was negative for amyloid. Myocardial biopsy demonstrated diffuse cardiac oxalosis and interstitial fibrosis; Congo red stain was negative. Retrieval and staining of frozen tissue from prior nephrectomy revealed diffuse oxalosis with interstitial fibrosis. Serum oxalate levels before and after dialysis were 27 and 8 mcmol/L (normal <1.6), respectively, with an oxalate reduction ratio of 67%.

Discussion: Cardiac and renal oxalosis may have resulted from jejunoileal bypass, a now uncommon surgery. Oxalate is well cleared by HD, but long-standing hyperoxalemia prior to ESRD and between dialysis sessions likely led to myocardial deposition. Patients with ESRD due to secondary hyperoxalemia should continue to adhere to a low oxalate diet and regular dialysis sessions to prevent extra-renal oxalate deposition. Our case also illustrates that low QRS voltage in association with increased left ventricular wall thickness and a sparkling, granular appearance of the myocardium on TTE is not specific for cardiac amyloid, but may suggest cardiac oxalosis in the appropriate setting.

FR-PO547

Different Faces of PRES in Adolescent Lupus Nephritis on Hemodialysis

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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a neurologic condition characterized by seizures, altered mental status, headache, visual changes and specific findings on MRI. For pediatric PRES atypical involvement of frontal lobes, basal ganglia or cerebellum is not rare. Risk factors include SLE, renal disease, dialysis, hypoalbuminemia, hypertension, immunosuppression. Recurrent PRES and status epilepticus (SE) have rarely been described in children.

Case Description: We analysed all cases of PRES in pediatric renal patients in our hospital in the last 5 years and found only 3 cases. All of them are adolescents with active lupus nephritis (LN) on hemodialysis (HD).

Discussion: All our patients had multiple risk factors for PRES: LN, new onset HD, cyclophosphamide, hypoalbuminemia, hypertension. Despite the common predisposing factors, they all had different but atypical course of PRES. Case 1 had PRES one year after an initial lupus cerebritis and had a concurrent pulse therapy following seizure event because of concern for recurring cerebritis. Case 2 had recurrent PRES while she was on nicardipine drip. Case 3 had SE associated with PRES, a very rare condition. Both cases 2 and 3 received the cycle#2 of cyclophosphamide 2 weeks before onset of PRES. However, there was no PRES with the subsequent cycle#3. Current hypothesis of PRES involves vasogenic edema due to an endothelial injury. Hypertension is a consequence rather than the cause of the disorder; and it may be absent in PRES. LDH was suggested as a useful marker for identification of patients before onset of clinical symptoms. Unfortunately, in our cases LDH was not done. Further studies are needed on the role of LDH as a predictive tool for establishing potential preventive measures such as strict BP control, empirical antiepileptic drug, and optimal fluid control in high risk individuals.

Clinical characteristics during the PRES episode with seizures

	1st case	2nd case 1st episode/2nd episode		3rd case Status Epilepticus
Age/Sex	18/F	16/F		19/M
LN class	III + V	IV		IV + V
SLE duration	5 y	2 y		3 m
HD duration	3 m	1 m		2 m
Immunosuppression	Azathioprine	Cyclophosphamide #2		Cyclophosphamide #2
BP medications	Amlodipine, clonidine, quinapril, minoxidil	Furosemide, nifedipine, labetalol	1 week after 1st episode on nicardipine drip	Amlodipine, metoprolol, lisinopril
BP during PRES	180/100	160/110	140/95	180/100
PRES area	Frontal, parietal, temporal, occipital lobes	Frontal, parietal, occipital lobes	Thalamus, frontal, parietal, occipital lobes	Frontal, occipital lobes, basal ganglia
Antiepileptic medications	levetiracetam* (for 1 y) due to lupus cerebritis, currently on	Levetiracetam started	levetiracetam*, currently on	2 weeks of valproic acid after PRES, currently without
Follow up	6 m	2 m		2 m

*questionable adherence

FR-PO548

An Unusual Vaginal Discharge: The First Reported Case of Peritoneal Dialysis Catheter-Fallopian Tube Fistula

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Introduction: Complications of peritoneal dialysis(PD) include obstructions and fistulas. Obstructions can result from various reasons including omental or fallopian tube wraps while communications/fistulas between the bladder and colonic walls are also possible. Vaginal discharge of PD fluid with an anatomically intact pelvis is not yet reported.

Case Description: The patient is a 42-year old African American woman with a past medical history of Lupus Nephritis and End-Stage Renal Disease on Peritoneal Dialysis(PD) for the past 5 years with poor compliance and repeated episodes of peritonitis. The patient reported an episode of abdominal pain and reported intermittent incontinence with painless vaginal discharge. These symptoms were not initially considered to be related to PD. She was treated for repeat peritonitis and vaginitis/cervicitis. She also reported that the discharge happens only during the fills on PD. She was admitted for peritonitis and PD was resumed. Within an hour of resuming dialysis, she had a large amount of fluid leak from the vagina. Obstetrics and Gynecology performed a pelvic examination that did not reveal an overt fistula or any abnormal findings. CT scan with contrast showed PD catheter coiled in the pouch of Douglas. The contrast went through the catheter to the right fallopian tube, entered the uterus and extended through the cervix into the vagina. It appears that the patient had formed collections on the pelvic floor, and one had PD Cath in direct communication with the fallopian tube. The patient underwent an open exploratory lap with salpingectomy. She transitioned to hemodialysis electively.

Discussion: This case highlights the differentials of vaginal discharge in a woman on PD. The patient had reported various concerns like possible intermittent incontinance, sudden vaginal discharge. All these symptoms were not considered to be related to PD, thus delaying diagnosis. Her abdominal pain was related to peritonitis and loculating collection in the abdomen. The painless vaginal discharge was happening through natural communications between the peritoneum, fallopian tube, and vagina. Abnormal fistulas are possible with excoriations and infections leading to friable organs, as also through natural orifices. Vaginal discharge in PD patient should lead to detailed exam and imaging.

FR-PO549

A Queer Case of Rapidly Progressive Metastatic Pulmonary Calcification (MPC) in a Patient with ESRD: Are We Doing Enough?

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Introduction: Metastatic pulmonary calcification (MPC) is a metabolic lung disease which is poorly understood and can prove fatal. Despite its high prevalence, it remains undetected. We describe a case of MPC in a young female patient with ESRD which ultimately lead to patient's demise.

Case Description: A 32 year old female with history of end stage renal disease (ESRD) secondary to autosomal dominant polycystic kidney disease presented with generalized weakness for 2 months. She had been on hemodialysis (HD) for 3 years but was not compliant with dialysis. Physical exam was grossly unremarkable and vital signs were within normal limits. Relevant laboratory findings included BUN of 73 mg/dl, Cr of 11.7 mg/dl, phosphorus of 8.2 mg/dl, calcium of 11.1 mg/dl and PTH was 1284 pg/ml. Broad spectrum antibiotics were initiated. Few hours into admission, she rapidly deteriorated, became confused and was subsequently intubated and transferred to the Intensive Care Unit. High Resolution CT scan of the chest showed very dense airspace opacification (measuring a mean attenuation of 329 HU), involving the right middle lobe and left upper lobe (including the lingula) with patchy dense opacification elsewhere. Patient remained afebrile. Blood cultures, sputum cultures, tuberculosis quantiferon and bronchoalveolar lavage were negative for any infection. Technetium (Tc) 99 bone scan disclosed diffuse activity in the pulmonary parenchyma, strongly supporting metastatic pulmonary calcification Despite escalating supportive measures, the patient became increasingly hypoxic and died 4 days later.

Discussion: In contrast to other conditions leading to death in ESRD patients, metastatic pulmonary calcification does not usually cause symptoms, can result in quick respiratory decline and is often identified only at autopsy as routine chest X-rays are mostly negative. MPC may remain undiagnosed and untreated, at times progressing to severe acute respiratory failure. It is of paramount importance that we not only do timely detection and treatment but also explore new diagnostic and therapeutic methods for MPC to decrease overall mortality in ESRD patients.

FR-PO550

The Heart of Calcium

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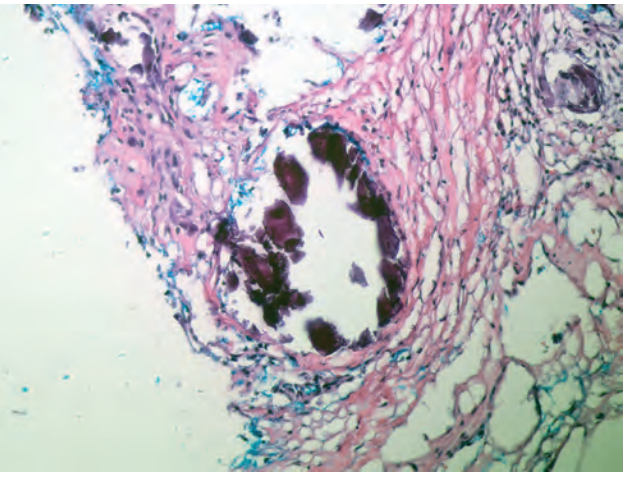
Introduction: Calciphylaxis or calcific uremic arteriopathy is a rare disorder causing diffuse calcification of arterioles in dermis and subcutaneous tissue. We here by present a case of systemic calciphylaxis presenting as non infective endocarditis with stroke.

Case Description: 59 year old Caucasian female with End stage Renal disease secondary to Microscopic polyangitis (with only renal involvement +PANCA) for 2 years initially on hemodialysis for a year and then switched to peritoneal dialysis, presented to the hospital with subjective fever and shortness of breath concerning for multifocal pneumonia. Echo showed 1.5 x 2 cm mitral valve vegetation and PFO. Her infectious work up was persistently negative including blood cultures for bacterial, fungus and AFB. She did not have fever during hospitalization. Hospital course was complicated by stroke thought to be embolic from valve vegetation. With worsening clinical conditions she underwent mitral valve replacement and mitral valve pathology showed myxoid degeneration, with no inflammation or organism but calcification and cultures remained negative. On presentation patient also complained of painful hard nodules from ankle to knee of posterior bilateral lower extremities for 6 months. Biopsy was diagnostic for calciphylaxis. She had elevated phosphorus to 11 and PTH of 780 on presentation The mobile masses seen on echocardiography were likely to represent healed vegetations that had calcified as a result of calciphylaxis. She was started on intensive daily dialysis and sodium Thiosulfate with good outcome.

Discussion: High clinical suspicion is warranted to make the diagnosis of calciphylaxis. Despite a multi-interventional approach for calciphylaxis, the disease remains associated with a high morbidity and mortality. To our knowledge this is the first reported case of non infective endocarditis with complication of stroke as the initial manifestation of calciphylaxis followed by further work up showing skin involvement, with ultimate good outcome.



FR-PO551

Osteitis Fibrosa Cystica in Renal Osteodystrophy Masquerading as Malignancy

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Introduction: High bone turnover in renal osteodystrophy is a rare clinical entity nowadays due to early diagnosis and treatment of secondary hyperparathyroidism. Since it is a diagnosis of exclusion, a formidable diagnostic challenge exists when the likelihood of malignancy is high in an elderly ESRD patient.

Case Description: A 64-year-old African American man with a history of HTN, cardiomyopathy with ICD and ESRD on hemodialysis was admitted for pathological fracture of L2 with no neuro deficit. Imaging showed generalized osteopenia, burst fracture of L2, radiolucent foci all over the spine. Preliminary diagnosis of malignancy was made, and cord compression was ruled out. Biopsy from L2 revealed- i. reactive bone with prominent peri-trabecular fibrosis, ii. patchy hemosiderin-laden macrophages and iii. increased number of multinucleated osteoclasts indicative of bone resorption. Skeletal survey was inconclusive for malignancy or myeloma. Contrast CT abdomen and pelvis reported cortical erosion of symphysis pubis by a mass measuring 3.7 cm x 4.3 cm.

Biopsy from the mass revealed- focal granulation tissue and hemosiderin-laden macrophages. Blood work for myeloma showed only polyclonal gammopathy on SPEP. Serology for tumor markers was negative and TB was ruled out. Meanwhile, the patient received multiple units of PRBC, periodic filgrastim and darbepoetin injection for pancytopenia. Bone marrow biopsy reported high normocellular marrow, polyclonal plasma cells, hemosiderin-laden macrophages, extensive peri-trabecular fibrosis and bony remodeling with osteoblasts. Then the PTH level was checked and found to be 2020 pg/ml. Neck ultrasound showed all four parathyroid hyperplasias. Finally, the patient underwent parathyroidectomy. The patient improved slowly and was sent home after a while. On follow up visit, the patient reported an increased sense of well-being. Follow up lab revealed- normalization of CBC requiring no further PRBC transfusion or filgrastim injection.

Discussion: This case illustrates the importance of considering secondary hyperparathyroidism as the possibility of a lytic bony lesion in the ESRD population. High bone turnover in hyperparathyroidism can manifest as osteitis fibrosa cystica (lytic lesion), brown tumor (both lytic and expansile mass) and/or peri-trabecular bone marrow fibrosis. Clinical and histopathological co-relation is crucial for such a diagnosis.

FR-PO552

Metastatic Calcinosis of Gastric Mucosa

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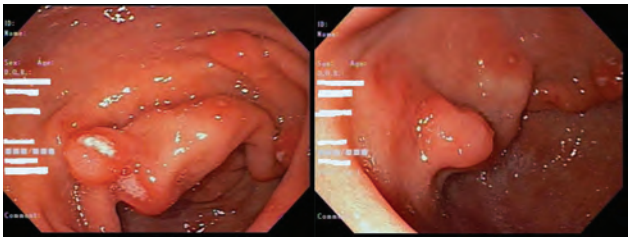
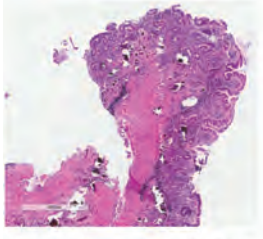
Introduction: Metastatic calcinosis is a rare and serious complication of chronic renal failure. The striking feature is the calcification seen around large joints. While it mostly involves the blood vessels and dermis, it can also rarely affect the mucosal layers of the gastrointestinal tract.

Case Description: A 49-year-old African-American male with history of chronic GN leading to ESRD followed by an initial renal transplant in 1980 with subsequent graft failure in 1991, requiring re-initiation of dialysis. Had a second transplant in 2016 with stable graft function. Two years later, he started experiencing persistent worsening dysphagia and weight loss despite normal appetite. Labs and vitals were stable. He was referred for EGD, which showed extensive patchy exudates with underlying friable ulceration of upper esophagus, erythema of antrum and few nodular regions in pre-pyloric area. Duodenal Villi showed extensive whitish tips. The pathology was consistent with Candida esophagitis and Helicobacter pylori gastritis that was treated appropriately. The biopsies also revealed mucosal calcinosis in the gastric antrum and body, which could be explained by the long-standing history of dialysis and could also be supported by the evidence of extensive calcification of common iliac and external iliac arteries, bilateral native kidneys and prior transplanted kidney. The symptoms improved with the treatment of Candida esophagitis and H. pylori gastritis.

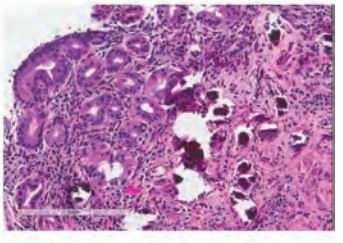
Discussion: Metastatic calcinosis is a severe consequence of chronic renal failure, as there is a disruption in calcium and phosphorus metabolism. Failure of management of hyperphosphatemia in chronic renal failure leads to secondary hyperparathyroidism and precipitation of calcium products in multiple organs. Though Calcinosis of vascular media is the common finding, it can rarely involve the mucosal layers of the GI tract causing ulcerations.



Pre pylorus and Antrum



Hematoxylin and Eosin stain 100x. Calcium deposits distributed along the lamina propria and under foveolar epithelium.



Hematoxylin and Eosin stain 200x. Prominent cyanophilic calcium crystals arising from lamina propria vasculature. Concomitant chronic gastritis is present with increased lymphoplasmacytic infiltrates.

FR-PO553

Dialysis-Related Amyloidosis with Fever

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Introduction: Although dialysis-related amyloidosis (DRA) is generally afebrile, literature shows that some cases of DRA manifest fever and its treatment has not been well established. Herein, we report a case of 74-year-old woman with febrile DRA, and discuss optimum treatment for this condition with a review of literature.

Case Description: A 74-year-old woman with 34-year history of hemodialysis due to end-stage renal disease caused by chronic glomerulonephritis presented with four months of intermittent fever of 99-102°F coinciding with recurrent bilateral shoulder and hip joint pain. Laboratory testing revealed WBC 6,300/μL, Neut 76%, Hb 8.0 g/dL, CRP 17.0 mg/dL, and β_2-microglobulin (β_2M) 21.0 mg/L. Blood cultures were negative. Imaging studies of the shoulder and hip joints revealed periarticular soft-tissue thickening, bone cysts, and intense accumulation of ^{99} mTc and ^{67} Ga in scintigraphy. Biopsy of the articular synovial membrane of the right shoulder joint revealed amyloid deposition, leading to the diagnosis of DRA. Hemodialysis was switched to online hemodiafiltration (HDF) and then to combination use of β_2M adsorption column with online HDF, where the latter modality yielded a higher clearance (76, 84, 102 mL/min) and reduction rate (67, 77, 80%) of β_2M. Intermittent fever and joint pain decreased remarkably in frequency and intensity but were still present after two months. Promptly after starting prednisolone 10 mg/day, her fever and joint pain disappeared, CRP level normalized, and anemia alleviated. The prednisolone dosage is gradually decreased without exacerbation.

Discussion: Our case and three reported cases of DRA with fever all manifested polyarticular pain with amyloid deposition in articular synovial membrane. Three of the four cases were prescribed with prednisolone and achieved prompt normalization of temperature and CRP level within ten days, while the remaining case without steroids had fever for five months. One case with early use of prednisolone but with no change in β_2M clearance initially achieved normalization of temperature but experienced a relapse of the symptoms, which ceased by using β_2M adsorption column. These cases imply that increasing β_2M clearance is crucial to control this condition in the long run, while concurrent early use of steroids has the advantage of promptly alleviating fever, joint pain, and progression of anemia.

FR-PO554

Activation of Blood Leak Alarm During Hemodialysis Secondary to Hydroxocobalamin Therapy of Cyanide Toxicity

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Introduction: Toxic levels of cyanide, which may develop with prolonged infusions of sodium nitroprusside, can be treated with hydroxocobalamin. A noted side effect of hydroxocobalamin is red discoloration of plasma and urine. Hydroxocobalamin may also lead to red discoloration of dialysate with activation of blood detector alarms during conventional hemodialysis.

Case Description: 61 year old female with advanced renal disease due to poorly controlled hypertension presented with severe blood pressure elevation of 247/125 mmHg with imaging findings concerning for 5.6 cm abdominal aortic aneurysm with impending rupture. Sodium nitroprusside was started for blood pressure control at low dosages for 9 days. On the 9th day, she developed a wide anion gap metabolic acidosis: sodium 145, potassium 4.5, chloride 96, bicarbonate 18, BUN 24, SCr 2.52, and anion gap 31. Cyanide toxicity was diagnosed and treated with intravenous hydroxocobalamin. Conventional hemodialysis was initiated with a Fresinius FMC machine, but could not be performed due to activation of blood leak dectector alarms with visibly reddish colored dialysate. CVVHD was subsequently initiated through use of NxStage machine. The red discoloration of the dialysate gradually resolved over a 48 hr period, at which time intermittent hemodialysis was reinitiated with no further blood leak alarms.

Discussion: Blood leak detection alarms on dialysis machines have been designed to cease operations when blood is detected in the dialysate. Fresenius dialysis machine contains blood leak alarm consisting of two-color light source transmitter/sensor (red light and green light) that monitor clarity of effluent dialysate. The photodetector is triggered when green light (wavelength 562–575 nm) is absorbed by blood. A leak detector is placed in dialysis solution outflow line, using sensor in dialysate effluent path. When blood leaks are detected, the alarm is activated and blood flow through dialyzer stops. NxStage CRRT machine does not have hydroxocobalamin-related false blood leak alarms. The blood leak detector of NxStage machine uses a single optical emitter with 880-nm wavelength designed to detect light scatter. It does not depend on light absorption, and, therefore, was not activated by discoloration of the dialysate by hydroxocobalamin, such that renal replacement therapy could be administered.

FR-PO555

Use of CardioMEMS in Dialysis Patients with Heart Failure

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Introduction: Volume overload is a major problem in patients with chronic kidney disease (CKD) and heart failure (HF). Fluid removal during dialysis treatment is the cornerstone management in these conditions but, assessing the amount of volume that

should be removed is a challenge. We present two cases of remote ambulatory pulmonary artery (PA) pressure measurements in dialysis patients with HF using cardioMEMS.

Case Description: Case 1. Heart Failure with Preserved Ejection Fraction 65-year-old Caucasian female, history of type II diabetes, hypertension, CKD, hepatitis C, liver cirrhosis, NYHA class III diastolic HF. Echocardiogram left ventricular ejection fraction was (LVEF) >55%. CardioMEMS was implanted in 2016. Patient was started on intermittent hemodialysis (iHD) via a tunneled catheter in 2018. Patient was switched to continuous cyclic peritoneal dialysis (CCPD) in 2019. Her PA pressure by CardioMEMS increased after initiation of the HD but decreased significantly after CCPD was established (Figure 1). **Case 2. Heart Failure with Reduced Ejection Fraction** 73-year-old Caucasian male with history of type II diabetes, hypertension, and CKD, NYHA class III systolic HF. Echocardiogram LVEF <20%. CardioMEMS was implanted in 2016. Patient had declining kidney function and a right upper arm arteriovenous fistula was placed, iHD was initiated in 2018. His PA pressure readings by CardioMEMS gradually declined after initiation of dialysis (Figure 2).

Discussion: Hemodialysis resulted in significant changes in the PA pressure in HF patients. Remote ambulatory monitoring of PA pressures is a promising strategy in dialysis patients with HF since it might guide the management of volume status and allowing early interventions.

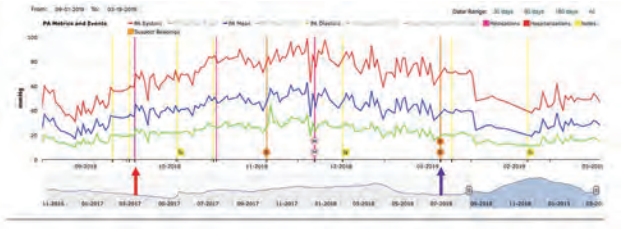

Figure 1. PA pressures. Red arrow indicated when HD was initiated and the purple arrow indicated when CCPD was established.

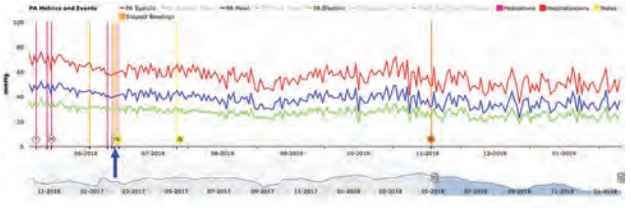

Figure 2. PA pressures. Arrow indicated when hemodialysis was started.

FR-PO556

Striking Radiological Findings of Visceral Arteries Calcification in a Severe Calciphylaxis Patient

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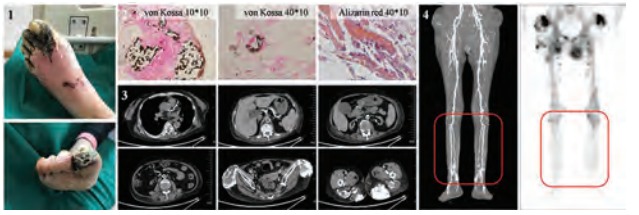
Introduction: Calciphylaxis is a rare complication of end stage renal disease characterized by calcification, fibrointimal hyperplasia, and thrombosis in the subcutaneous adipose tissue and dermis. Skin biopsy is the standard method for confirmed diagnose but it's still controversial for creating new wounds. The imaging characteristics of calcification may help diagnose calciphylaxis. This article reports a severe visceral calciphylaxis patient confirmed by skin biopsy with striking calcification of the visceral vessels.

Case Description: A 45-year-old female with systemic lupus erythematosus have a 14-year medication history of oral glucocorticoids and 10-year maintenance hemodialysis. She had an erythema on toes and deteriorated into painful dry gangrene with infection 1 month before admission (Fig.1). Skin biopsy (Fig.2) confirmed the diagnosis of severe calciphylaxis. Interestingly, her imaging fingdings showed striking calcification of visceral blood vessels. Extensive calcification of arteries of pancreas, kidneys and intestinal canal can be seen in the computed tomography scan (Fig.3). Although she doesn't have symptoms of visceral ischemia such as chronic abdominal pain or gastrointestinal bleeding, it may be a predictor of visceral calciphylaxis and she may show symptoms of visceral ischemia or bleeding one day. Computed tomography angiopraphy (CTA) of the lower limbs shows diffuse calcification the lower extremity arteries and soft tissues. Exactly, bone scintigraphy scan proved abnormal diffuse high uptake of subcutaneous soft tissue in crus that is in consistence with what shown in CTA (Fig.4). The efficacy of therapies based on sodium thiosulfate is still in follow-up.

Discussion: Characteristic histological features of calciphylaxis include medial arterial calcification and thrombosis in arterioles. This patient has typical clinical manifestations of severe calciphylaxis and striking imaging features of visceral vascular calcification. Biopsy in visceral arterioles is difficult, so that the combination of multiple imaging methods is valuable to early diagnosis of visceral calciphylaxis.



FR-PO557

Effluent Colors in Continuous Hemodiafiltration

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Introduction: Continuous venovenous hemodiafiltration (CVVHDF) is widely used as a renal replacement therapy modality on patients with acute kidney injury. It usually generates a yellow citrine outflow that is stored as effluent. Bellow we describe 2 cases of unusual effluent color changes due to special clinical situations in our center.

Case Description: Case Report 1- Red effluent fluid: An 38 year- old female patient admitted to the ICU after mitral valve replacement surgery developed Acute Kidney Injury (AKI). CVVHDF was attempted and on the 14th day after surgery, effluent fluid was red colored, concomitant with the spike of CPK and the diagnosis of rhabdomyolysis. Dipstick analysis revealed the presence of hemoglobin (false positive). Microscopic evaluation of the effluent fluid was negative for the presence of red blood cells, thus excluding the possibility of rupture of the filter. Myoglobin concentration on the effluent was 1765 UI/L. Case report 2- Green effluent fluid :An 50 year-old male patient admitted to the ICU after myocardial revascularization surgery developed AKI and CVVHDF was attempted. Due to refractory shock methylene blue was added to the vasoactive drugs arsenal and 30 minutes later the effluent fluid removed by CVVHDF was green colored.

Discussion: Changes on the CVVHDF effluent color to red should alert the nephrologist to the possibility of hemolysis or dialyzer membrane compromise. Because of it's high molecular weight and a Sieving coefficient of less than 0,1% hemoglobin is not expected in the dialysate. However myoglobin has a much smaller molecular weight and a Sieving Coefficient of 40%, therefore it should be considered as a possible cause of red dialysate. Blue colored effluent occurred most likely due to and additive effect of the methylene blue with the usual citrine yellow effluent color.

FR-PO558

Acquired Autoimmune Hemophilia A After Initiation of Hemodialysis

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Introduction: Acquired hemophilia A is a rare autoimmune disorder in which circulating IgG antibodies inhibit and deplete coagulation factor VIII. It is common in patients with congenital hemophilia A after factor VIII transfusions but rare without preexisting hemophilia. Presentation in adults is similar to the congenital form, with spontaneous hemarthroses or bleeding in the setting of isolated PTT prolongation. No consistent triggers have been identified, though associations have been suggested with connective tissue disorders, malignancies, and immunomodulators, among others.

Case Description: A 60 yo man was admitted for painful unilateral thigh swelling and severe anemia with hemoglobin nadir 3.5 g/dL. PMH included ESRD due to hypertension, hemodialysis (HD) had been initiated 1-month prior. Family history negative for bleeding or autoimmune disorder. Laboratory values were significant for leukocytosis (17.8 K/uL) and prolonged PTT (107.8 s) with normal PT, INR, platelets, and reticulocytes. Iron studies were consistent with anemia of chronic disease. On hospital day 2 he developed an unprovoked right upper extremity hematoma requiring emergent fasciotomy on the side of his tunneled HD catheter. A naïve left arm AV fistula was unaffected. Concern for factor VIII inhibitor was raised, and confirmed with circulating anticoagulant screen and undetectable factor VIII level. Recombinant factor VIIa & factor VIII inhibitor bypassing agent were utilized to control bleeding, concurrent with high-dose prednisone, cyclophosphamide, and plasmapheresis to decrease inhibitor activity. After a complicated course, he was discharged on prednisone, cyclophosphamide, and tranexamic acid with a PTT of 45.2s.

Discussion: We suspect that the recent initiation of HD triggered this autoimmune response. The right IJ catheter was the presumed bleeding site. A small series of HD-associated hemophilia is reported in the literature, though the mechanism of this association is speculative. HD is known to activate the complement system and trigger cytokine release, though the severity of this effect is decreasing with improved biocompatible dialyzer membranes. Autoantibody formation in ESRD or due to HD is not well described or recognized. Acquired hemophilia is a hematologic emergency with high mortality and should be considered for patients presenting with bleeding complications and coagulation abnormalities after HD initiation.

FR-PO559

Hypereosinophilia in Haemodialysis Patients

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Introduction: The incidence of hypereosinophilia (>2 x 10^9/L) in our haemodialysis population in London over the last 13 years is 9.7 per 100 patients per year. We present 9 cases of significant hypereosinophilia which occured alongside significant haemodynamic instability during haemodialysis (HD) sessions.

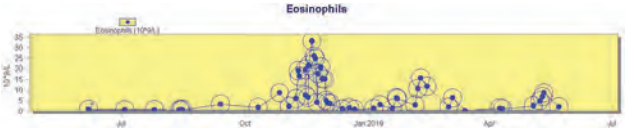
Case Description: All the patients survived these episodes; 7 of 9 had prompt reduction in eosinophil counts following high dose corticosteroids. All patients were on haemodiafiltration, with ultra-pure water. There was a high recurrence rate following wean of steroid treatment. Adaptations to the HD circuits including changing the line lock, dialyser type and dialyser surface area were made, but the inconsistent response suggests more than bioincompatibility. We did specific allergy testing for ethylene oxide (ETO), latex and chlorhexidine in 3 patients, 1 of which raised to latex. All 9 patients were ANCA negative, Hepatitis B, C and HIV negative. 1 patient had positive strongyloides serology.

Discussion: The reason for the hypereosinophilia is unclear, but it has made HD challenging in these patients. It is possible that there may be other precipitants not related to the HD circuit. Joint management between nephrologists, haematologists and HD unit staff is important for the management of hypereosinophilic patients experiencing severe haemodynamic instability during HD.

Investigations for patients 1-9

Patient	Peak eosinophil count (X10<9>/L) Normal range: <0.4 X10<9>/L	Mast cell tryptase (µmol/L) Normal range: 2- 14 µmol/L	Total IgE (kUA/L) Normal range: <75 kUA/L	BMAT, FIP1L1-PDGRFA performed (Y/N)	Cause of end stage renal failure	Dialysis access	ACEi or ARB therapy (Y/N)	CT scan performed (Y/N)
1	11.6			N	Presumed diabetes	AVF	Y	N
2	20.9	7.9		Y - no clonal abnormality	Presumed diabetes	RIJTL	N	Y
3	15.5	16.2	864	N	Presumed diabetes	AVG	Y	N
4	36.1	14.7		Y - no clonal abnormality	MPGN	RIJTL	N	Y
5	7.9	11.9	<2	Y - no clonal abnormality	Unknown	RIJTL	Y	N
6	33.1	10	1220	Y - no clonal abnormality	Unknown	RIJTL	N	Y
7	5.6	8.2	238	N	Unknown	RIJTL	Y	N
8	20.1			N	Amyloidosis	AVF	Y	Y
9	20.3	20.3	1628	Y - no clonal abnormality	FSGS	RIJTL	Y	N

BMAT: bone marrow aspirate trephine, ACEi: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, MPGN: membranoproliferative glomerulonephritis, FSGS: focal segmental glomerulosclerosis, RIJTL: right internal jugular tunnelled line, AVF: arteriovenous fistula, AVG: arteriovenous graft



Patient 6

FR-PO560

Erythropoietin Stimulating Agent (ESA)-Resistant Vitamin B6 Deficiency Anemia in a Pediatric Patient on Hemodialysis

Sagar Patel, Leah E. Goswick, Majed Jeroudi, Radhakrishna Baliga. *LSU Health Sciences Center, Shreveport, LA.*

Introduction: Vitamin B6 is a water soluble vitamin, the active form of which is Pyridoxal 5'-phosphate, that functions as a coenzyme of erythroid specific 5-aminolevulinate synthase (ALAS2) which is involved in the synthesis of heme. Vitamin B6 deficiency is often associated with inflammation as observed in chronic kidney disease, particularly those requiring dialysis. Administration of an ESA has also been shown to be associated with increased erythrocyte consumption of vitamin B6. We report here a pediatric patient who developed an ESA resistant anemia that significantly improved following vitamin B6 supplementation.

Case Description: 16-year-old African American male with end stage renal disease secondary to obstructive uropathy, on chronic hemodialysis, experienced a decrease in his hemoglobin over a 3-month period from 11 to 6.5 g/dL, while receiving darbepoietin alfa (ESA) [0.9mcg/kg/week] intravenously for one month. His transferrin saturation was 41%, ferritin level 706 [80-388] ng/mL, mean corpuscular volume (MCV) 87 [78- 98] fL. His corrected reticulocytes count was 2.3% [0.2-1.8%]. Additional laboratory data included the following: Direct antiglobulin testing and stool for occult blood were negative; Vitamin B12, 635 [193-986] pg/ml; folate, 8.4 [3.1-17.5] ng/mL; copper, 1413 [665-1480] mcg/l; zinc, 77 [60-120] mcg/dL and Ceruloplasmin, 31.4 [15-30] mg/dL. PTH was elevated at 258 [9-69] pg/ml. Vitamin B6 level was low at 1.2 [5.3-46.7] ug/L. Bone marrow biopsy was normocellular (65%) with erythroid hyperplasia and rare dyserythropoiesis. Prussian blue staining showed increased iron storage. Supplemental Vitamin B6 (100mg daily) was initiated, at which time his hemoglobin was 7.3 g/dL. Three months later, his hemoglobin was 11.6 g/dL with transferrin saturation of 18%.

Discussion: Vitamin B6 clearance is increased with standard hemodialysis and a further 50% increase in vitamin clearance is noted when receiving high flux high efficiency hemodialysis as seen in our patient. Vitamin B6 deficiency anemia should be considered in any pediatric patient on high flux hemodialysis who is not responding to standard ESA and iron therapy.

FR-PO561

Role of Extracorporeal Treatments in Management of Massive Bee Attack

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Introduction: Bee stings can cause severe allergic reaction which can be triggered by a single sting, prognosis worsening with increasing number of stings. More than half of the victims who experience multiple bee stings develop Acute Kidney Injury (AKI), which is due to multiple factors, such as intravascular hemolysis, rhabdomyolysis, hypotension and direct renal tubular toxicity of the venom components. We present a case of anuric acute renal failure due to massive bee attack, managed by renal replacement therapy and plasmapheresis.

Case Description: 53 year old male with history of hypertension, presented to our facility after an attack from killer bees (reportedly > 2000 bees). Upon initial presentation(16 hours after attack); he was intubated, in shock requiring vasopressors despite fluid resuscitation, and noted to be anuric. Patient was initiated on a high dose

continuous renal replacement therapy (CRRT) with CVVHDF promptly after arrival, in conjunction with Plasmapheresis (PLEX), circuits connected in parallel, to manage renal failure as well as potentially assist with bee venom removal. He received 2 sessions of PLEX (days 1, and 3); CRRT for a week, followed by intermittent hemodialysis (iHD) for another two weeks. Partial renal recovery was noticed and patient was discharged home with a Cr of 4.9 mg/dl. Upon follow up 2 weeks later, further improvement of Cr to 2.5 mg/dl was noted.

Discussion: Massive bee stings is a rare cause for hospital admission and AKI. Patients could also present with cardiomyopathy, and multi-organ dysfunction, perpetrated by shock and/or direct toxicity of venom. Short term mortality could approach 25%, particularly in setting of AKI. Bee venom is a heterogenous toxin with molecular weight of toxins ranging from 2.8 to 43 KDa. One of the major toxins, Mellitin (2.8Kda) is water soluble, and potentially dialyzable. Prompt initiation of dialysis with PLEX could offer benefits in removal of bee venom as well as inflammatory mediators. While there is no consensus in the literature regarding mode of dialysis in such setting, a large case series suggested a higher rate of renal recovery in patients who received CRRT (+/-PLEX) versus iHD. Our patient showed promising trend towards full recovery of renal function.

Initial labs

NA (mmol/L)	K (mmol/l)	Cl (mmol/L)	Co2 (mmol/L)	BUN (mg/dL)	Cr (mg/dL)	PH	Myoglobin (ng/mL)
137	4.8	108	20	20	2.54	7.27	> 1000

FR-PO562

Getting Off on the Wrong Foot: Trichosporon inkin Peritonitis

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Introduction: Peritonitis is a serious complication of peritoneal dialysis and 3-6% are fungal in etiology. Trichosporon inkin, a yeast-like fungus associated with the superficial hair shaft infection "white piedra," seldom causes invasive infections. Treating invasive Trichosporon spp. can be challenging given limited data. We present a rare case and describe the treatment of resistant T. inkin peritonitis in an end stage renal disease (ESRD) patient on automated peritoneal dialysis (APD).

Case Description: A 56 year old man with ESRD from membranoproliferative glomerulonephritis on APD presented with abdominal pain and cloudy dialysate. PD fluid cultures were drawn and he was empirically treated for bacterial peritonitis with intraperitoneal cefazolin + ceftazidime, while nystatin was used for fungal prophylaxis. 6 days later, pain and cloudy fluid persisted, and his fluid culture grew Trichosporon inkin. The patient, who also had onychomycosis, later admitted to picking at his right 2nd toenail to remove a splinter prior to handling his PD catheter. The PD catheter was removed due to his fungal infection, and he was converted to HD. Initial use of IV micafungin failed to improve his symptoms. Testing showed the T. inkin to be resistant to Echinocandins, but susceptible to voriconazole. Voriconazole was given for 10 weeks with resolution of his symptoms and onychomycosis. Now off antifungals for 2 months, he is waiting re-evaluation to return to PD.

Discussion: The etiology in our case was likely poor hand hygiene after manipulation of his toe. Multiple cases of Trichosporon spp. onychomycosis have been described but only 3 prior T. inkin peritonitis cases have been reported, the last in 2003 and treated with caspofungin. Voriconazole, FDA-approved in 2002, was used in our case as it performed best in vitro against T. inkin, which is typically resistant to echinocandins. Therapy duration is not as clear and has ranged from 2-8 weeks in the literature, often being anecdotal. T. inkin is also associated with biofilm formation, causing up to a 1000x higher MIC required by voriconazole in 1 in vitro model. With these concerns, the patient was treated with a lengthy course to give the best hope for cure and to restart PD eventually. This is the first case to describe voriconazole treatment in T. inkin peritonitis, with further research needed to define optimal therapy duration.

FR-PO563

Treating Resistant Mycobacterium abscessus in Peritoneal Dialysis-Associated Infection

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Introduction: Mycobacteria-associated peritoneal dialysis (PD) infections should be considered in culture-negative or refractory cases. Non-tuberculous mycobacteria (NTM) are abundant in soil and water, and can rarely cause PD infections. NTM are associated with high rates of catheter loss and hemodialysis (HD) conversion. Of the NTM, *Mycobacterium abscessus* grows rapidly and is resistant to standard therapies. We present a challenging case of an exit site infection (ESI) due to multidrug-resistant *M. abscessus* that progressed to peritonitis despite antibiotics and PD catheter revision.

Case Description: An 80-year-old man on PD was treated for ESI and a culture collected by his dialysis unit showed gram-variable bacilli requiring outside lab send out for identification. On day 8, he developed a tunnel track abscess necessitating drainage and catheter revision. On day 15, abscess cultures grew acid-fast bacilli (AFB), thus doxycycline was added. On day 21, *M. abscessus* was identified from the original ESI culture. Antibiotics were broadened to clarithromycin and moxifloxacin. PD fluid analyses were previously negative. However, by day 33, the patient developed recurrent tunnel infection and cloudy PD fluid with AFB. The PD catheter was removed, and he transitioned to HD. On day 41, the original culture finally reported that the *M. abscessus* was resistant to multiple antibiotics including aminoglycosides, cephalosporins, doxycycline, and fluoroquinolones. A four-drug treatment regimen of eravacycline, imipenem, clarithromycin, and linezolid was ultimately selected.

Discussion: PD-associated infections due to NTM are difficult to distinguish from more common organisms, with our patient initially showing gram-variable bacilli. A delay in appropriate treatment occurs frequently because a minimum of 3-5 days on special medium is necessary for NTM to grow and speciation lags for weeks, as was seen in our case. *M. abscessus* causes less than 10% of PD-associated NTM infections, thus therapy guidelines are based on limited experience. Macrolides are the most reliable option and should be combined with a parenteral antibiotic tailored to susceptibility data. Our case highlights the difficulty faced with very resistant strains. A high index of suspicion and early catheter removal remain the cornerstone for successful management of *M. abscessus* and other NTM infections.

FR-PO564

A Twisted Fate: A Case of PD Catheter Malfunction due to Fallopian Tube Migration

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Introduction: Management of peritoneal catheter malfunction is an important aspect of peritoneal dialysis care. Most often peritoneal catheter dysfunction is related to omental wrapping, but rarely other intraperitoneal structures can cause outflow obstruction. We report a case of PD catheter dysfunction secondary to fallopian tube migration and wrapping, managed by conversion to hemodialysis.

Case Description: 27 y.o.female with ESRD secondary to Class- IV Systemic Lupus Erythematous (SLE) Nephritis initiated peritoneal dialysis (PD) 14 days following catheter insertion. From the outset, she reported severe abdominal pain and cramping associated with filling and draining, occasionally noting blood tinged PD effluent. She was sent to IR for a catheter check, found to have a small non-occlusive filling defect inside the PD catheter around 10 cm from the catheter tip. tPA was instilled in the catheter with transient resolution of the filling defect but no impact on pain symptoms. 6 weeks post catheter insertion she underwent exploratory laparotomy to further evaluate catheter dysfunction. Intraoperative findings were notable for left oviductal fimbriae adherence to the PD catheter in the pouch of Douglas. The fallopian tube was gently separated from the PD catheter and the catheter was removed due to concern about recurrence, as the patient wished to preserve fertility. The patient converted to hemodialysis.

Discussion: Fallopian tube migration, although cited as a rare cause of PD catheter dysfunction, is an important consideration when managing PD associated abdominal pain in female patients. To date, there are 12 reported cases of PD catheter outflow obstruction due to fallopian tube entanglement in the literature, with three reports of oophoropexy resulting in ongoing successful use of the peritoneal catheter. In our case, the decision was made intraoperatively not to attempt oophoropexy or oophorectomy due to the patient's inability to consent and her prior wishes to preserve fertility.

FR-PO565

An Unusual Presentation of an Unusual Disease: Cryptococcus Neoformans Peritonitis in a Patient on Peritoneal Dialysis

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Introduction: Mexico is the country with more peritoneal dialysis (PD) patients in the world, and it's used by the majority of the patients requiring RRT. Cryptococcus neoformans is an opportunistic infection in the immunocompromised population. The central nervous system is the most common organ affected. Peritonitis is an unusual complication of infections caused by C. neoformans and has rarely been reported in patients on PD. We present a case of peritonitis due to C. neoformans in a patient on PD in Mexico.

Case Description: A 36-year old Mexican female came to the ED with headaches and photophobia for about one week. These symptoms were associated with weight loss (60 pounds), for about 5 months. The patient had ESKD secondary to DM. She lived in a rural area located in the central western coast of Mexico. She owned chickens, cats, and dogs. She reported three sexual partners with no condom use. On admission, she had fever, photophobia, bilateral Babinski, hyperreflexia of upper and lower extremities and nuchal rigidity. The initial labs didn't reveal significant abnormalities; except for a positive-HIV test. We performed a lumbar puncture (LP) and also obtained PD fluid samples. Both were positive for C. neoformans. We started therapy with liposomal amphotericin B (6mg/kg/day) and fluconazole; the nephrology team removed the PD catheter, and transitioned her to HD. Her hospital course was complicated with hospital-associated infections, and despite all efforts, the patient died after 20 days of therapy.

Discussion: To our knowledge there are around 4 cases of C. neoformans's peritonitis associated to PD since 1988 when the first case was reported. The previously case presented is the first one reported in Mexico and Latin America. The reported cases had a predominance of female gender and comorbidities such as HIV infection, hypertension, DM and 25% had fatal outcome. C. neoformans is a deadly and underdiagnosed pathology worldwide. The diagnosis can often be challenging in areas with limited access to healthcare, and thus, the treatment is delayed. The determination of peritonitis by C. neoformans must be considered in patients on PD and must lead to the suspicion of a disseminated infection.

FR-PO566

Actinomyces neuii Peritonitis in Peritoneal Dialysis

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Introduction: Due to impaired immunity and increased microbial exposure, peritonitis is the most common complication seen in peritoneal dialysis (PD). Although staphylococcal infections are most common, a variety of other microorganisms can colonize and subsequently infect the peritoneal cavity. We report a case of continuous ambulatory peritoneal dialysis (CAPD) peritonitis due to Actinomyces neuii.

Case Description: A 71-year-old female with end-stage renal disease on home continuous cycler peritoneal dialysis and prior history of clostridium difficile colitis presented with two days of severe watery diarrhea and severe abdominal cramps. Vital signs were stable and examination was notable for abdominal distention and cloudy PD fluid. Stool samples were positive for C. diff and gram-positive bacteria were identified in PD fluid. She was prescribed oral metronidazole and intraperitoneal vancomycin. Final fluid cultures were positive for Actinomyces neuii susceptible to Vancomycin and have been successfully treated with 2 weeks of vancomycin. We educated her on the importance of hand hygiene and sterile technique.

Discussion: Actinomyces is a gram-positive bacillus comprising normal gut flora. It is rarely associated with soft tissue infections, but may occur in those with impaired immunity. Because the peritoneal cavity lacks robust innate immune responses, it is a favored site for infection. We speculate that increased bacterial translocation from the gut due to colitis or contamination of the PD catheter may have contributed to the peritonitis. Actinomyces is a likely underrecognized cause of peritonitis in PD patients due to its fastidious nature, but identification is important because actinomyces infections may be indolent and may not respond to repeated short courses of antibiotics. If left untreated, sinus tracts and abscesses may form, which can lead to secondary infections.

FR-PO567

Compounded Amino Acid Peritoneal Dialysate as an Alternative Volume Management Strategy in a Diabetic Patient

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Introduction: Volume control in diabetic patients with end stage renal disease (ESRD) on peritoneal dialysis (PD) can be challenging. Common glucose sparing volume control strategies for these patients include dietary sodium restriction, diuretics, and the use of icodextrin dialysate. Another potential strategy is the use of amino acid based dialysate, which may maintain ultrafiltration by avoiding hyperglycemia and loss of the osmotic gradient between dialysate and blood. In the United States amino acid peritoneal dialysate is often not covered by insurance, leading to limited experience.

Case Description: A 63 year old female diabetic with history of ESRD treated with continuous cycler PD developed increasing challenges to maintain dry weight with frequent use of 4.25% dextrose along with a 2L icodextrin day dwell. On exam the weight was 86.5 kg (dry weight 83 kg) and blood pressure was 173/59, with bilateral crackles and trace edema in the extremities. Daily peritoneal ultrafiltration was between 500-700 ml with no residual urine output. Labs showed BUN 47, creatinine 12.4 mg/dl, albumin 3.4 g/dl, glucose 104 mg/dl, sodium 136 meq/L, HgA1c 6.0%, total weekly Kt/V 2.45. Given hypoalbuminemia and worsening volume status despite frequent use of 4.25% dextrose and icodextrin, the decision was made to substitute a compounded dialysate with amino acids (1.0% amino acids in 5L of 2.5% dextrose) during CCPD with continued daytime 2L icodextrin dwells. Daily ultrafiltration improved to an average of 1L per day. Weight decreased to 79.2 kg, edema resolved, and blood pressure improved with a reduction from 5 to 4 antihypertensives. Due to insurance, the amino acid supplemented dialysate was lost in September with a subsequent increase in weight and blood pressure. In October the next year, insurance reauthorized the amino acid solution, which was restarted with similar improvement in weight and blood pressure.

Discussion: Volume control can be challenging despite typical glucose sparing strategies in diabetic PD patients. Our patient had improvements in volume control during periods when an amino acid based solution was used in place of standard dextrose solutions. We hypothesize that the tonicity of the above solution allowed for superior ultrafiltration and volume control compared to 4.25% dextrose due to avoidance of hyperglycemia and loss of osmotic gradient.

FR-PO568

It Is Never Too Late: A Case of Renal Artery Angioplasty for Resistant Hypertension in ESRD

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Introduction: Atherosclerotic renovascular disease is an important and potentially treatable cause of secondary hypertension. In patients with end-stage renal disease, common contributors to uncontrolled hypertension include volume overload, sympathetic overactivity, and erythropoietin-stimulating agents. It is therefore challenging to identify ESRD patients who could benefit from angioplasty for renal artery stenosis.

Case Description: A 65 year old patient with ESRD due to BK nephropathy on peritoneal dialysis developed uncontrolled hypertension requiring multiple medications, including hydralazine 50 mg qAM and 100 mg qPM, isosorbide mononitrate 30 mg qAM and 60 mg qPM, labetalol 200 mg BID, amlodipine 10 mg daily, valsartan 160 mg BID, torsemide 40 mg BID, and doxazosin 8 mg BID. He also had extensive atherosclerosis of the aorta, bilateral common iliac and external iliac arteries requiring multiple stents. He developed resistant hypertension on PD, which was uncontrolled on the above regimen and required several hospitalizations with BP in the 200s/100s. Workup revealed a 99% stenosis of the proximal left renal artery, which was stented. After angioplasty, he had improvement in his blood pressures to 120-130/60-80 on valsartan 160 mg BID and metoprolol succinate 100 mg daily. His 24 hour urine collections for creatinine clearance confirmed increase in urine output, with a urine volume of 508 cc on the final collection pre-angioplasty and 2000 cc on the first collection post-angioplasty. In addition, his weekly Kt/V from residual renal function alone increased from 0.54 before angioplasty to 2.7 after angioplasty. He developed volume overload with a trial off PD which could not be managed with diuretics alone. PD was resumed, with a reduced frequency of four sessions per week.

Discussion: Our patient demonstrated significant improvement in blood pressure control, with a substantial reduction in the number of medications and the stabilization of his blood pressure after angioplasty for renal artery stenosis despite being dialysis-dependent. Residual renal function improved, with fewer PD sessions required weekly to maintain adequate clearance and euvolemia. Particularly in patients with other manifestations of peripheral vascular disease, the possibility of renal artery stenosis should be investigated, and perhaps treated, in ESRD patients with resistant hypertension.

FR-PO569

Pleuroperitoneal Leak in Peritoneal Dialysis Patients: Experience of a Single Center

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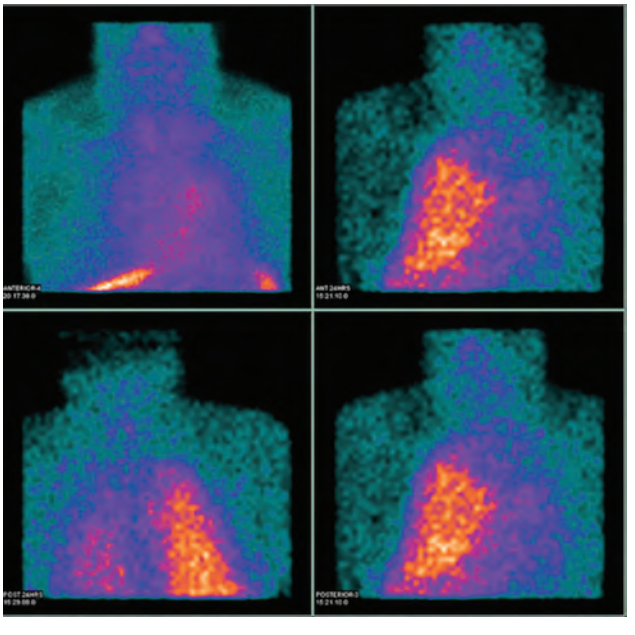
Introduction: Pleuroperitoneal leak (PPL) is a rare complication, incidence reported between 1.6-10%. Etiology include congenital and acquired defects in the diaphragmatic muscle fibres, favored by increase intraabdominal pressure due to peritoneal dialysis solutions. The objective is to report the incidence, diagnosis, treatment and evolution of PPL.

Case Description: Descriptive, retrospective study. We analyzed all cases of PPL in the last 3 years.

Discussion: We found 5 patients with the diagnostic of PPL (Table 1). The male gender predominated, vintage of peritoneal dialysis (5-22 months) Diagnosis was suspected with clinical presentation, chest x –ray, difference between plasmatic and pleural effusion glucose (the pleural higher than plasmatic), and confirmed with scintigraphy. All patients required endopleural tube and peritoneal cavity rest with change of modality to hemodialysis. In 4 of the 5 patients an attempt was made to return to peritoneal dialysis (PD), but PPL recurred in all. The prognosis is discouraging due to the high recurrence rate. We included biompedance data, none of the patients had sarcopenia, ruling out this condition as a risk factor to develop diafragmatic defect, the only biochemical association was with hypoalbuminemia.

Characteristics of all patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Modality	CAPD	APD	CAPD	CAPD	APD
Time in peritoneal dialysis until diagnosis (months)	5	22	10	5	5
Albumin (g/dL)	2.74	3.28	3.03	2.35	3.32
Appendicular lean body mass index (kg/m2)	8.82	6.7	7.2	7.5	8.4
Sarcopenia (Reference Values Healthy Mexican Population)	No	No	No	No	No
Location	Bilateral	Right	Bilateral	Right	Right
Peritoneal Scintigraphy Report	Positive	Negative	Positive	Positive	Positive
Initial Treatment	Endopleural Tube	Endopleural Tube	Endopleural Tube	Endopleural tube + Pleurodesis	Endopleural Tube
Cavity Rest (weeks)	6	4	8	7	32
Final Renal Replacement Therapy	HD	HD	HD	HD	HD + Kidney Transplant



FR-PO570

Peritoneal Dialysate Tamponading a Massive Retroperitoneal Hemorrhage

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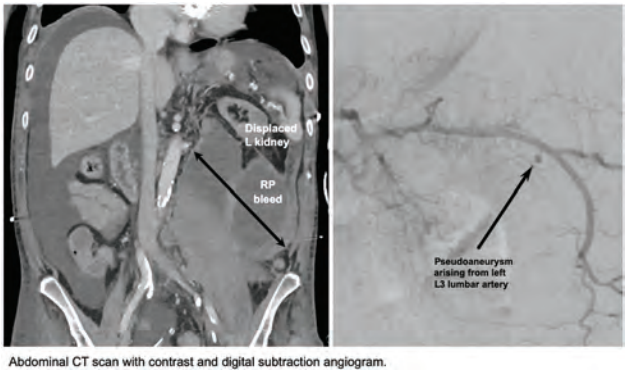
Introduction: Spontaneous retroperitoneal (RP) bleeding is a rare but potentially fatal event. Due to its late manifestations, diagnosis is often delayed until blood loss is profound. We describe a patient in whom an RP bleed was suspected due to hypotensive episodes during peritoneal dialysis (PD) drainage.

Case Description: We describe a 47-year-old male with end stage renal disease (ESRD) on PD, on warfarin with a goal INR of 2.5-3.5 for mechanical mitral and aortic valves, who underwent a total hip arthroplasty for a left femoral fracture. Postoperatively he was continued on his home PD regimen (2L dwell, 2.5% dextrose, 5 exchanges per day) and restarted on warfarin. On postoperative day 17 he became unresponsive during PD drainage, with a blood pressure of 62/34 mm Hg. Hemoglobin dropped from 8.4 to 4.5 g/dL, and the INR was 2.2. Packed red blood cells and norepinephrine were administered, and he was transferred to the cardiac care unit, where he had a PEA arrest requiring CPR and intubation. Following return of spontaneous circulation, his blood pressure recovered and vasopressors were discontinued. Subsequent PD exchanges on the same day were complicated by repeated hypotensive episodes requiring vasopressors. This was observed only during PD drainage and resolved when fluid was re-infused. A CT scan showed a large left RP hematoma (14x11x23 cm). Angiography demonstrated a left L3 lumbar artery pseudoaneurysm as the source of bleeding. Coil embolization was performed, bleeding was well-controlled, and subsequent PD exchanges were well-tolerated.

Discussion: We report an unusual case of spontaneous RP hemorrhage in a patient with ESRD for whom PD drainage led to life-threatening hypotension. We speculate that the RP bleed was partially tamponaded by PD fluid via transmission of pressure retroperitoneally.



Abdominal CT scan with contrast and digital subtraction angiogram.

FR-PO571

PD Peritonitis from Cat Mouth Flora: Pasteurella, Not the Only Thing You Need to Worry About

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Introduction: Neisseria weaveri, previously known as CDC group M-5, is an aerobic gram negative non-motile rod normally found in animal oral flora and associated with infections related to dog bites. We present a case of peritonitis in a patient on peritoneal dialysis (PD) due to this microorganism after a cat bit the PD tubing.

Case Description: A 61 year old female with end stage renal disease (ESRD) due to diabetes and hypertension on PD presented to the emergency department after her domestic cat bit and punctured the PD tubing while undergoing an exchange. She had no evidence of peritonitis and was discharged with prophylactic doxycycline for Pasteurella multocida peritonitis. Eight days later, she returned to the emergency department with abdominal pain and cloudy effluent. A diagnosis of peritonitis was made after peritoneal fluid studies revealed an elevated neutrophil count of 2,248 cells/mcL. The patient received IV loading doses of vancomycin and cefepime and then transitioned to intraperitoneal vancomycin, cefepime and oral metronidazole. Her peritoneal cell counts and symptoms quickly improved on antibiotics. The peritoneal fluid culture isolated Neisseria weaveri however blood cultures did not yield any bacterial growth. After all cultures finalized, antibiotics were narrowed to a two week course of oral ciprofloxacin. Resolution of peritonitis was confirmed after completion of antibiotics with negative peritoneal fluid studies.

Discussion: Neisseria weaveri is found in the normal canine oral flora and has been found in wounds from infected dog bites. A previous case report has been documented of peritonitis from Neiserria weaveri but no mechanism of infection was identified. While cats are less likely to carry Neiserria weaveri, the organism has been isolated from feline oral flora. Care and sterility of peritoneal dialysis equipment is paramount to preventing peritonitis as infection can be devastating for patients on home dialysis modalities. Consideration of the multitude of organisms that have been isolated from feline oral flora (Neisseria, Pasturella, Pasteurellaceae, Moraxella amongst others) must be kept in mind when wet contamination of PD fluid with feline oral flora occurs, with appropriate antimicrobial coverage.

FR-PO572

Anterior Cutaneous Nerve Entrapment in a Patient on Peritoneal Dialysis

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Introduction: Anterior cutaneous nerve entrapment syndrome (ACNES) is a commonly underdiagnosed cause of abdominal pain and has been implicated in 15-30% of cases of chronic abdominal pain. It is caused by the entrapment of the cutaneous branches of the intercostal nerves at the lateral border of the rectus abdominis muscle that supply the abdominal wall. ACNES should always be considered in the differential in patients with chronic unilateral abdominal pain.

Case Description: 55-year-old man with history of end stage renal disease secondary to hypertension on peritoneal dialysis (PD) for ~ 4 months and diabetes developed 5/10, intermittent sudden onset shooting and burning right sided abdominal pain. It was not associated with nausea, vomiting, fever or changes in bowel habit. PD fluid analysis revealed clear effluent with total nucleated white cells ≤20 and negative culture. Liver function tests were normal except for mild elevation in lipase at 133 with normal amylase. Noncontrast CT of abdomen and pelvis was unrevealing except for persistent defect in the left rectus abdominis muscle with overlying surgical scar. As Liraglutide can cause elevation in lipase in the absence of pancreatitis, it was discontinued with decrease in lipase to 81. However, his pain persisted and Pregabalin was prescribed with some efficacy. He was seen by neurologist where careful history and physical examination yielded the diagnosis of ACNES. Persistent defect in the left rectus abdominis muscle with overlying surgical scar noted on abdominal CT was thought to be the likley culprit of ACNES. He was treated with a compounded lidocaine gel with resolution of his pain and discontinuation of pregabalin.

Discussion: ACNES is commonly overlooked or confused with visceral pain, often leading to extensive diagnostic testing with negative results before an accurate diagnosis is established. Diagnosis of ACNES is based on the presence of well-localized abdominal pain often along the lateral aspect of the rectus abdominis muscle sheath, increase in tenderness to palpation during muscle tensing on examination (Carnett's sign) and response to trigger point injection of a local anesthetic. Although ACNES can be quite painful and disabling, it is typically nonprogressive with no long-term sequelae. Mainstay of treatment is reassurance, activity modification, physical therapy, and pain relief with analgesics or trigger point injections.

FR-PO573

Peritoneal Dialysis-Associated Peritonitis Presenting as Catheter Dysfunction

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Introduction: Catheter dysfunction is a common complication among peritoneal dialysis (PD) patients. Most common causes of one-way dysfunction include constipation, catheter tip migration, kinks in external tubing, omental wrapping, intraluminal obstruction from fibrin or a clot, and peritoneal occlusion via adjacent organs. Catheter obstruction presents a major morbidity to PD patients and is a significant risk factor for modality failure. Up to 20% of patients are transitioned at least temporarily to hemodialysis when they experience catheter obstruction. We report an unusual presentation of a usual pathology, a case of peritonitis that presented initially as catheter obstruction.

Case Description: A 69-year-old man presented for to clinic because he was unable to drain his PD catheter the night prior. He had no issues with lost dwell or prolonged drain on prior treatments. On presentation he felt weak, fatigued and lethargic. On further questioning he had decreased appetite, crampy abdominal pain, diarrhea and abdominal bloating. On arrival, he was afebrile, had scattered rhonchi on lung exam, no granulation tissue or erythema at the exit site, and mild LLQ tenderness. We were able to freely instill dialysate but unable to drain. Alteplase was instilled sequentially for 30 minutes then 2 hours and large strands of fibrin cleared, permitting drainage of 50cc of cloudy effluent from which gram stain, cell count and cultures were sent. This sample returned a cell count of 2007 cells/μL with 43% PMNs, and eventual culture speciating MRSA. He was treated for staphylococcus aureus induced peritonitis with 3 weeks of intraperitoneal vancomycin. His course was complicated by CDiff enterocolitis, necessitating the addition of oral vancomycin.

Discussion: Catheter dysfunction and peritonitis are both complications of PD with significant morbidity. Here we present an atypical presentation of peritonitis, as the presenting symptoms were purely catheter dysfunction without initial complaint of abdominal pain. While fibrin can cause both one-way or two-way obstruction and is associated with peritonitis, there are no cases in the literature of peritonitis presenting this way. It is important to recognize this potential presentation as peritonitis events should prompt quality improvement efforts for both the individual patient and the PD program.

FR-PO574

Cat Bite-Induced Pasteurella multocida Peritonitis

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Introduction: Peritoneal dialysis (PD) patients are at an increased risk of developing peritonitis, necessitating the importance of proper sterile technique. While, the majority of peritoneal infections arise from skin flora, an important, but often under-recognized

risk factor for peritonitis is pet ownership. This case report will examine an incident of zoonotic infection induced peritonitis.

Case Description: A 70-year-old PD dependent female presented with one day of progressively worsening abdominal pain and cloudy peritoneal fluid, without associated fevers. Physical examination revealed diffuse abdominal tenderness with guarding. There were no concerning findings at the catheter entry site. Initial blood work was unremarkable, except for a mild leukocytosis. A sample of peritoneal fluid was sent for analysis, but returned a nucleated cell count of 0. However, despite a lack of PMNs, the fluid culture grew Pasteurella multocida. This was an unexpected result that prompted further investigation into the patient's home environment and PD machine. The patient owns 4 cats and 1 dog, but was not restricting pet access to her bedroom with her dialysis machine. Although the fluid cell count was negative, further investigation showed inadequate dwell time in the ED. The patient was ultimately treated with IP Ceftriaxone. Careful inspection of the PD machine by the PD unit revealed several bite and scratch marks on the tubing. The patient was re-educated on sterile technique and has restricted pet access to her bedroom. She now protects her PD tubing by encasing it with a pool noodle.

Discussion: As PD patients are at an increased risk of infection, education on proper sterile technique and home environment is critical. This case illustrates several key points in the prevention and diagnosis of peritonitis. Clinical suspicion of peritonitis should remain high despite unimpressive fluid cell count. Peritoneal fluid culture should always be checked if clinical suspicion is high. Pet ownership should be assessed in all patients and the importance of restricting pet access to PD machine should be emphasized during initial training. If pets are present, patients should be instructed to limit pet access to the bedroom and storage space for PD equipment. Furthermore, patients should wrap tubing if needed. By addressing pet ownership with patients, we hope to further reduce peritonitis incidence.

FR-PO575

Hemodialysis Access Failure Caused by Hyperviscosity due to Secondary Polycythemia in Polycystic Kidney Disease

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Introduction: Hemodialysis (HD) access failure is one the gravest complications that can lead to morbidity and mortality in End Stage Renal Disease (ESRD) patients. We present a rare case of an Autosomal Dominant Polycystic Kidney disease (ADPKD) patient with ESRD on HD who developed overt secondary polycythemia that led to hyperviscosity, recurrent hemodialysis access clotting and hemodialysis failure.

Case Description: A 44-year-old male with ADPKD on HD presented with dyspnea following several missed HD sessions. He was found to have respiratory failure secondary to pulmonary edema and required intubation. His laboratory studies revealed potassium of 6.9 mmol/L (non-hemolyzed), hemoglobin level of 18.1mg /dl and hematocrit of 58%. EKG showed widened QRS complex with peaked T waves. Emergent HD was planned but multiple attempts at hemodialysis were unsuccessful due to clotted arteriovenous fistula followed by recurrent clotting of three temporary dialysis catheters. Repeated phlebotomy was attempted with no significant drop in hemoglobin. He received multiple doses of intravenous calcium gluconate, insulin and kayexalate. Eventually, the patient developed refractory hyperkalemia of 8.7 mmol/L leading to arrythmia and cardiac arrest. Further laboratory evaluation revealed erythropoietin level (EPO) was 139.0 mIU/ml (normal range 2.6-34 mIU/ml). JAK 2 mutation was negative. There was no history of obstructive sleep apnea, smoking or use of performance enhancing agents. Autopsy confirmed ADPKD and did not reveal any evidence of malignancy. There was no evidence of abnormal cardiopulmonary physiology or chronic lung disease.

Discussion: Patients with ADPKD tend to have excess EPO production by renal cysts. Secondary polycythemia can occur in these patients as a result. In this case, patient's hyperviscosity from secondary polycythemia caused clotting of hemodialysis access sites despite treatment with repeat phlebotomy. Hemodialysis was therefore unsuccessful. In literature, there are few cases of hemodialysis access failure caused by secondary polycythemia due to ADPKD which led to such serious intractable hyperviscosity leading to the ultimate death of the patient. This case illustrates that early recognition of this complication in patients with ADPKD is essential for appropriate management and avoid subsequent complications in this population.

FR-PO576

Case of Acute Pseudo-Aneurysm Formation in a Clotted and Abandoned Brachial-Cephalic Arteriovenous Fistula

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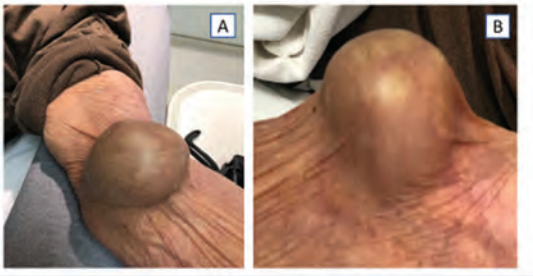
Introduction: Pseudo-aneurysm formation is a known complication of dialysis arteriovenous access. Pseudo-aneurysms typically form at the site of needle puncture or at the arteriovenous anastomosis. Here we present a case of acute pseudo-aneurysm formation in a clotted and abandoned arterio-venous fistula (AVF)

Case Description: An 88-year old male on chronic hemodialysis via a right femoral vein catheter presented to the dialysis unit with sudden onset of swelling in his left arm. The swelling was in the ante-cubital fossa, near the arteriovenous anastomosis of a clotted left arteriovenous fistula (AVF) that had not been cannulated in over 6 years. He denied any trauma at the site of the swelling and attested to a significant increase in the size of the swelling over the past 48 hours. On examination the swelling was firm, pulsatile and non-tender. Vascular surgery was consulted, and same day intra-operative findings confirmed the presence of a pseudo-aneurysm which was resected. The histology and cultures of the resected tissue did not reveal any malignancy or infection

Discussion: Pseudo-aneurysms are hematomas that form due to a defect in the vessel wall. They are devoid of the endothelium or the vessel wall. In other words, they are hematomas communicating with the lumen of the vascular access, and therefore rupture of a pseudo-aneurysm can be life-threating. Typically, the pseudo-aneurysms form at the site of repeated needle cannulation. Pseudo-aneurysm formation is very rare in a clotted or abandoned AV access. It is not clear what caused the pseudo-aneurysm formation in this patient, but this case highlights the importance of continued monitoring of 'abandoned and clotted' dialysis vascular access



Pseudo-Aneurysm at the Arteriovenous Anastomosis of a Clotted Brachial-Cephalic fistula
'A' Front View
'B' Side View

FR-PO577

A Successful Ultrasound-Guided Percutaneous Transluminal Angioplasty for a Patient with Arteriovenous Graft Failure Within 24 Hours of Its Creation and After 3 Months Since Failure

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Introduction: The primary purpose of any hemodialysis access is to provide adequate, long-term and repeated access to the circulatory system with minimum complications. Arteriovenous graft (AVG) rarely fails acutely within the postoperative period causing graft loss with the need for subsequent creation of new hemodialysis access. We describe the rescue of the AVG which immediately failed following its creation, there was no hope for its future use, so consequently was abandoned for over three months.

Case Description: The 63 years old woman with end stage renal disease has been on chronic hemodialysis since 2014. Her right distal arteriovenous fistula was functional until November 2018 when it failed. The right elbow brachial-basilic graft was created successfully which also failed within 24 hours following its creation.3 months later after creation, this patient was referred to our centre. Ultrasonography visualized stenosis at the peripheral draining vein, severe stenosis at venous-graft anastomosis and intragraft stenosis with no flow of blood through the entire graft. Ultrasound guided Percutaneous transluminal angioplasty was performed with immediate restoration of good graft patency, good patency of brachial artery and basilic vein. The next day, patient used the AVG for hemodialysis successfully for the first time. The AVG remained patent and chronically usable for hemodialysis up to 4 months.

Discussion: Our case demonstrates the feasibility of repairing an immediately failed arteriovenous dialysis graft following its creation with restoration of good patency adequate for chronic hemodialysis by ultrasound guided percutaneous transluminal angioplasty, even after 3 months since failure.

FR-PO578

Successful Insertion and Use of Arteriovenous Graft (AVG) After Left Ventricular Assist Device (LVAD) Implantation

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Introduction: A subset of patients requires long-term renal replacement therapy (RRT) after LVAD implantation. The success of using AVG for RRT access in these patients has not been established.

Case Description: [Fig1] Case A: A 68-year-old man developed acute kidney injury (AKI) requiring RRT 2 days after LVAD implantation. He remained RRT dependent. A brachiobasilic AVG was placed 55 days after LVAD implantation and successfully used 28 days later. Subsequent course was notable for *S. bovis* bacteremia complicated by infected AVG pseudoaneurysm requiring AVG excision. A second brachiobasilic AVG was placed and functioned well, requiring a thrombectomy 98 days after placement. Case B: A 67-year-old man developed septic shock with AKI 18 months after LVAD implantation. He remained RRT dependent and brachiobasilic AVG was placed 584 days after LVAD implantation. Balloon angioplasty of the AVG was required for stenosis at the arterial anastomosis, and AVG was successfully used 32 days after placement. He required no subsequent vascular access procedures and had no access or bloodstream infections. Case C: A 71-year-old man with stage 3b CKD developed AKI requiring RRT 4 days after LVAD implantation. He remained RRT dependent and brachiobasilic AVG was placed 107 days after LVAD implantation. Failed first cannulation attempt led to hematoma requiring evacuation and AVG revision. AVG was successfully used 40 days after placement.

He later developed polymicrobial bacteremia from a driveline infection, and AVG was excised due to concern for seeding. A second brachiobasilic AVG was placed and functioned well, requiring a thrombectomy 147 days after placement.

Discussion: AVG can be successfully used for long-term RRT access in LVAD patients. Infection and thrombosis rates need further study in larger cohorts. Outcomes between AVG, AV fistula, and dialysis catheters should be evaluated.

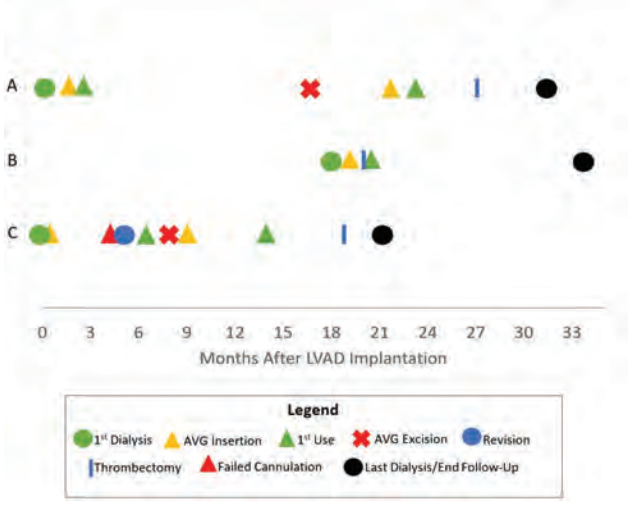

Figure 1.

FR-PO579

Treatment of Refractory Hyperammonemic Coma with CRRT in a Patient with Ureterosigmoidostomy

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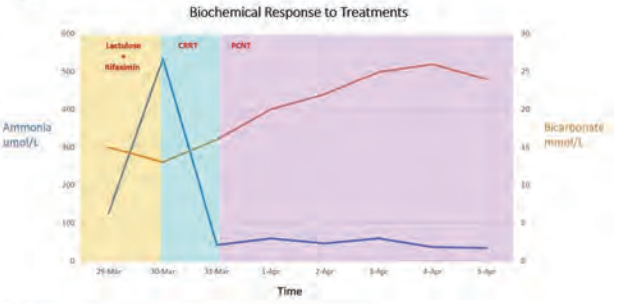
Introduction: Hyperammonemia is most common in liver disease but other rare causes exist. Serum ammonia (NH3) concentrations >150umol/L is linked to poor neurological outcomes and even death. In severe cases, extracorporeal removal of NH3 can be lifesaving.

Case Description: A 64-year-old female was admitted to the ICU with coma & NH3 level of 534umol/L with normal liver & renal function. She had ureteosigmoidestomy as a child for bladder extrophy. The high NH3 was attributed to increased colonic absorption from urine & increased NH3 production from bacterial splitting of urea in the colon. She did not respond to Lactulose & Rifaximin. Urology was consulted for percutaneous nephrostomy, however, her clinical status declined, so an urgent decision was made to remove NH3 by CVVHDF. NH3 level & coma improved in 8 hours. Next day, nephrostomy tubes were placed, the NH3 levels remained low, and her mental status improved.

Discussion: Patients with ureterosigmoidostomy can present after many years with hyperammonemia. The treatment is a new urinary diversion to avoid contact with the colon. Nephrostomy is a temporary solution followed by a permanent procedure, such as an ileal conduit. NH3 level >150 is related to cerebral edema, increased intracranial pressure (ICP) and brain herniation. Therefore, in severe cases, urgent extracorporeal removal should be considered. While the use of renal replacement therapy to remove NH3 has been reported, there is no definite guideline. Some reports favor HD over CRRT due to higher clearance. However, when the NH3 is continuously produced at a high rate, CRRT may be more beneficial since it offers fewer interruptions, less rebound, & less rapid fluid shifts which can worsen ICP. This case highlights that CRRT can be an effective bridging strategy in patients with severe hyperammonemic encephalopathy.

Figure



Table

Lab Results	Pre-treatment	Post-treatment
Ammonia(NH3)	534	47
pH	7.26	7.44
pCO2	34	36
HCO3-	13	22
AG	15	9
Na+	142	146
K+	3.7	3.7
Cl-	114	115
BUN	18	11
Cr	0.64	0.60

FR-PO580

Familiar Hyperkalemic Hypertension Genotype with a Negative Phenotype: A CUL3 Mosaicism

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Introduction: The Familiar Hyperkalemic Hypertension (FHHt) is an inherited disease featuring arterial hypertension with hyperkalemia, metabolic acidosis, and hypercalciuria, that is mainly due to overactivation of the thiazide-sensitive renal NaCl cotransporter in the distal convoluted tubule, as a consequence of mutations in four different genes: two encoding the kinases known as WNK1 and WNK4 and two encoding proteins that are components of a Ring type ubiquitin ligase complex, known as KLHL3 and CUL3. Mutations in CUL3 produce the more severe phenotype that in all 36 reported cases result in a shorter protein due to skipping of exon 9 and has been described as *de novo* mutation or as autosomal dominant inherited from one parent.

Case Description: Here we report on a 12 year-old boy with arterial hypertension (150/100mmHg), hyperkalemia (7 mEq/L) metabolic acidosis (pH 7.0; HCO_3^- 17.8 mEq/L) and hyperchloremia (108 mEq/L). Two months after hydrochlorothiazide was initiated the blood pressure was 129/76 and serum electrolyte values were normal (K^+, 4.5 mEq/L; Cl^- 98 mEq/L, pH 7.37 and HCO_3^- 25.8 mEq/L). DNA from the proband and his parents were obtained with their consent to evaluate the cause of the FHHt. The proband's DNA analysis revealed a CUL3 mutation resulting in exon 9 deletion. The mutation was present in the mother's blood DNA, but not in the father's. The mother, however, exhibits no FHHt phenotype. Her blood pressure and serum electrolytes were normal. The CUL3 mutation was found in DNA extracted from the mother's oral mucosa but at lower levels than in the blood. The mother of the proband is a unique occurrence of CUL3 FHHt genotype, with no phenotype, due to a mosaicism.

Discussion: Mosaicism refers to the presence of two genetically distinct cells lines with distinct karyotype or genotype in the same individual and results from postzygotic mutational events. Individuals may present gonadal mosaicism (found only in the gametes), somatic mosaicism, or a combination of both. In somatic mosaicism, it is frequent to find different proportions of the two cell lines across tissues, even within the same embryonic lineage (ectoderm, endoderm or mesoderm). In the proband's mother, the mutation exhibits presumably little to no effect on renal tubular cells, but is present in the oocytes and was inherited by her child.

FR-PO582

Customized Renal Replacement Therapy in a Patient with a Serum Sodium of 97 mEq/L

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Introduction: Hyponatremic patients requiring continuous veno-venous hemofiltration (CVVH) offer a unique challenge as commercial replacement solution contain physiologic concentrations of sodium. Use of such fluids may cause rapid correction of hyponatremia resulting in osmotic demyelination. We present a patient with

Acute kidney injury (AKI) and severe hyponatremia who was successfully treated using custom made CVVH solutions.

Case Description: A 55-year-old male with no significant medical history was found unconscious. He suffered cardiac arrest with return of spontaneous circulation after CPR. He was diagnosed to have sepsis secondary to diarrheal illness and severe rhabdomyolysis. Patient was found to have oliguric AKI, severe anion gap metabolic acidosis and multiple electrolyte abnormalities. Labs included serum sodium of 97 mEq/L, CO2 of 8, potassium of 6.2 and pH of 7.2. He received 100 mL of 3% sodium chloride with improved serum sodium to 105 mEq/L. CVVH was initiated for oliguric AKI, hyperkalemia and metabolic acidosis. On days 1 and 5 CVVH prefilter replacement solutions were compounded by draining fluid from a Prismasol bag and replacing with 5% dextrose (D5W) to dilute the sodium. On days 2, 3 and 4 solutions were compounded by pooling 2L of D5W and 2L of normal saline and adding potassium, magnesium, and chloride to achieve a concentration of 4 mEq/L, 2 mEq/L, and 81 mEq/L respectively. Sodium acetate was then added to adjust the sodium concentration and osmolarity based on the daily serum target. Other electrolytes were replaced separately due to compatibility risks. Incremental serum sodium targets were achieved on each day. The patient achieved serum sodium target on day 6 and was started on standard CVVH fluid containing 140 mEq/L sodium. The patient was later discharged home with no need for further renal replacement therapy.

Discussion: Rapid correction of severe hyponatremia can cause osmotic demyelination syndrome. CVVH to treat oliguric AKI with severe hyponatremia using commercial premixed replacement fluid bags is a challenge. This case illustrates the utility of customized CVVH solutions as a method for the correction of severe hyponatremia in critically ill patients requiring CVVH.

FR-PO583

Management of Critical Hypernatremia During Continuous Renal Replacement Therapy and Septic Shock

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Introduction: The concept of osmotic stability in the critically ill during continuous renal replacement therapy is insufficient explored. Herewith, we are reporting a case of extreme hypernatremia (serum sodium [$SeNa^+$] 182 mEq/L) with septic shock and acute kidney injury addressed with continuous renal replacement therapy (CRRT) and simultaneous hypertonic saline (HTS) administration.

Case Description: A 52-year-old male suffered a motor bicycle accident with subarachnoid hemorrhage and traumatic right below-the-knee amputation[FT1]. On the 17th day of hospitalization he suffered acute decompensation with increased work of breathing and decreased alertness. He required emergency intubation with mechanical ventilation and 3 pressor agents to maintain acceptable BPs. Initial laboratory studies revealed acute kidney injury with serum creatinine (SeCr) 3.6 mg/dL (normal baseline), BUN 142 mg/dL and sodium 177 mEq/L. With intravenous fluids, SeCr improved to 3 mg/dL while $SeNa^+$ rose to 182 mEq/L. Due to subsequent anuria, resistant hypoxia and escalating vasopressor requirements, a decision was made to start CRRT in continuous hemofiltration modality. To address co-morbid hyperosmolar state, HTS with 3% saline was added to ensure a predictable rate of $SeNa^+$ correction; correction for serum protein content (5 mg/dL) was achieved by multiplying predicted $SeNa^+$ by 0.95 to calculate *in vivo* $SeNa^+$. Recovery was complicated by hypotonic polyuria and central diabetes insipidus (DI), attributable to subarachnoid hemorrhage.

Discussion: While presence of DI was difficult to recognized with anuria and AKI but undoubtedly was responsible for hypernatremia on presentation. Premixed CRRT fluids are hypotonic (Na^+ 140 mEq/L) by default, when considering the presence of serum protein content. Excessive drops of $SeNa^+$ and BUN likely would have caused harm in our index case without concurrent HTS administration. Management of dysnatremic CRRT protocols represent an important and emerging field of critical care nephrology.

CVVHD and Electrolytes

Days on CVVHD	BFR/Therapy fluid dose	Hypertonic (3%) saline infusion	SeNa+	SeOsm	SeCr	BUN	UOsm	UNa+
Day-1	250 mL/min 4L/hrs	250 mL/hr	182 mEq/L	443 Mosm/kg	3 mg/dL	139 mg/dL	Anuric	Anuric
Day-2	250 mL/min 4L/hrs	200 mL/hr	169 mEq/L	372 Mosm/kg	2.9 mg/dL	119 mg/dL	Anuric	Anuric
Day-3	250 mL/min 4L/hrs	150 mL/hr	160 mEq/L	343 Mosm/kg	2.6 mg/dL	93 mg/dL	Anuric	Anuric
Day-4	250 mL/min 4L/hrs	100 mL/hr	152 mEq/L	312 Mosm/kg	0,8 mg/dL	21 mg/dL	Oliguric	Oliguric
Day-5	CRRT stop	3% saline stop	144 mEq/L	318 Mosm/kg	0.6 mg/dL	11 mg/dL	122 mOsm/kg	<20 mmol/L
Day-6	DDAVP 1 mcg Q12 hrs	D5W 100 mL/hr	149 mEq/L	320 Mosm/kg	0.6 mg/dL	9 mg/dL	544 mOsm/kg	130 mmol/L

FR-PO584

Hyponatremia in a Hemodialysis Patient: A Common Problem with an Uncommon Cause

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Introduction: Hyponatremia is a common electrolyte disturbance in hospitalized patients and is associated with increased mortality and morbidity. It occurs in ~9-29% of hemodialysis patients. The importance of this finding in pre dialysis labs is often overlooked and assumed to be due to excessive free water intake and diminished kidney dilution capacity in the setting of ESRD.We present a case of hyponatremia in a hemodialysis patient secondary to adrenal insufficiency

Case Description: A 66-year-old Korean male presented after a flight from Korea with headache and abdominal pain. Last hemodialysis(HD) was 3 days prior. Pain resolved spontaneously, but hospitalization prolonged to establish outpatient HD.PMH of ESRD due to HTN, renal transplant(Korea 2007), that failed 6 months prior with return to HD.Admission creatinine8.5mg/dL and sodium140. Over 1 week, his sodium declined. By day 6, pre dialysis sodium was 125 and he developed malaise, anorexia, chest and abdominal pain. Fluid restriction to <750cc/day instituted but sodium further declined, with dialysis complicated by hypotension and fever. Blood cultures, QuantiFERON Gold were negative. Serum calcium increased to 10.7(8.4-10.2mg/dL) and CBC differential noted eosinophilia 0.64(0-0.5).8 am cortisol sent was 1.2mcg/dL and ACTH stimulation test showed poor adrenal reserve indicative of adrenal insufficiency. Repeated questioning done on medication and Methylprednisone found in examined pill bottles, which was absent in admission list. After restarting steroids, he clinically improved to baseline, with sodium improved to 130 at discharge

Discussion: Hyponatremia has been associated with increased mortality in numerous patient populations. In ESRD patients, it is commonly seen and attributed to poor compliance with fluid restriction, hence may not be investigated. Potentially life-threatening causes such as AI, as in our patient, can be missed. Arreggar et al, noted in their study that 6 of 15 ESRD-H patients with sustained hypotension on dialysis had secondary AI, and BP normalized with steroid administration. Our patient was found, with more careful history, to have secondary AI from long term corticosteroid use. Our case suggests that a higher index of suspicion is appropriate in hyponatremic hemodialysis patients, especially if dialysis is complicated with other signs such as intra-dialytic hypotension, as diagnosis and treatment may have benefits in mortality reduction

FR-PO585

Loss of NCC Impairs the Outgrowth of the Renal Distal Convoluted Tubule (DCT) During Renal Development

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Background: Gitelman syndrome is an autosomal recessive renal tubulopathy characterized by hypokalemic alkalosis, hypomagnesemia and hypocalciuria. The syndrome is caused by loss-of-function mutations in the NaCl co-transporter (NCC) in the renal distal convoluted tubule (DCT). Data from NCC ko mice suggest that DCT atrophy contributes to the pathogenesis of the disease. Since Gitelman patients are usually diagnosed during adolescence or early adulthood, we tested the idea that the late clinical onset of Gitelman syndrome is related to a progressive regression of the DCT during adolescence.

Methods: Immunofluorescent detection of distal tubule marker proteins as well as morphometric analyses of DCT fractional volume and investigation of DCT specific gene expression with real time quantitative PCR were used to analyse the structure and protein expression pattern of the DCT at different ages and stages of development (day 1, 4, 10 and 6 weeks after birth) in NCC wt and NCC ko mice.

Results: Mice of both genotypes developed normal and showed a similar body weight gain. Plasma aldosterone levels and renal renin mRNA expression were higher in NCC ko mice than in NCC wt mice already at day 10. In contrast, plasma ion levels did not differ between genotypes at age 10 days, but a significant hypomagnesemia was observed in NCC ko mice at 6 weeks. Immunofluorescent detection of parvalbumin (an early DCT marker) revealed that the fractional cortical volume of the early DCT is almost similar for mice of both genotypes at day 4, but gets significantly lower at day 10 and is almost zero at 6 weeks in NCC ko mice. The DCT atrophy correlates with a marked reduction in the protein abundance of the DCT-specific Mg^{2+} channel TRPM6 and an increased proteolytic cleavage and hence activation of the alpha- and gamma subunit of the epithelial Na^+ channel (ENaC).

Conclusions: Thus, after an initial outgrowth of the DCT up to day 4, DCT development lacks significantly behind in kidneys of NCC deficient mice. The impaired DCT development associates already at day 10 with clear signs of volume contraction with elevated renin and aldosterone levels and an activation of ENaC, suggesting that Gitelman syndrome might be present much earlier during life than usually expected. Despite an early downregulation of TRPM6, hypomagnesemia is a rather late symptom.

Funding: Government Support - Non-U.S.

FR-PO586

Aldosterone Activates NCC Through the Resulting Hypokalemia and Chloride-Sensing Mechanism of WNK4

Jen-Chi Chen, Chih-Jen Cheng. *Tri-Service General Hospital, Taipei City, Taiwan.*

Background: Aldosterone increases the expression and apical abundance of ENaC via binding to the mineralocorticoid receptor (MR). However, the underlying mechanism of aldosterone-induced NCC activation is still unclear. Earlier studies have shown that a high potassium diet reversed NCC phosphorylation in aldosterone-treated mice, and vice versa for the NCC dephosphorylation in MR knockout mice. We recently demonstrated that hypokalemia reduces intracellular chloride concentration, which releases WNK4 from chloride-mediated inhibition. We hypothesized that hypokalemia resulting from aldosterone activates WNK4 via the chloride-sensing mechanism.

Methods: Aldosterone solution (100 g/kg/day) or vehicle control (5% DMSO in physiological saline) was administered to chloride-insensitive L319F/L321F WNK4 knockin mice and their control littermates using Alzet osmotic pumps. *In vivo* NCC activity was reflected by the protein abundance of total and phosphorylated NCC and also by thiazide-sensitive urinary sodium excretion rate. Moreover, other plasma and urine biochemistries were compared.

Results: After two-week aldosterone infusion, both wild-type and chloride-insensitive WNK4 knockin (KI) mice developed a similar metabolic alkalosis (HCO_3^- 25 vs. 25 mM) and hypokalemia (K^+ 2.4 vs. 2.6). Compared with wild-type mice, KI mice had higher urine output (2.1 vs. 3.2 ml/day), urinary sodium excretion (144 vs 221 mmol/day), and blood pressure. Of note, aldosterone increased the total and T58-phosphorylated NCC in wild-type mice. However, aldosterone did not further enhance the already high NCC phosphorylation in KI mice.

Conclusions: In sum, our results support the notion that aldosterone enhances NCC activity via the resulting hypokalemia and chloride-sensing mechanism of WNK4. Moreover, chronic aldosterone infusion induces natriuresis, compatible with aldosterone escape phenomenon, probably related to pressure natriuresis or natriuretic peptides.

Funding: Government Support - Non-U.S.

FR-PO587

Sympathetic Nervous System Regulation of the NCC in Dahl Salt-Sensitive Hypertension

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Background: Studies suggest that sympathetic nervous system (SNS) release of norepinephrine (NE) influences the activity of the sodium chloride cotransporter (NCC) via α_1 and β adrenoceptor pathways. Regulation of the NCC involves a complex network of kinases including WNK1, SPAK, and OXSR1. Hypothesis**:** NE stimulates an α_1 adrenoceptor pathway to drive increases in NCC activity that contribute to the development and maintenance of Dahl salt sensitive (DSS) hypertension (SSH).

Methods: Groups of naïve DSS rats and DSS rats given a continuous subcutaneous (s.c.) infusion of terazosin/DMSO (α_1 antagonist, 10mg/kg/day), or propranolol/DMSO (β antagonist, 10mg/kg/day) were placed on a 21 day normal salt (0.6% NaCl, NS) or high salt (4% NaCl, HS) diet. Separate groups of DSS rats were fed a 42 day HS diet; and on day 21, rats were treated with s.c. saline or terazosin for the remaining 21 days of the diet. Basal MAP, NCC activity (peak natriuresis to hydrochlorothiazide [HCTZ]; 2mg/kg), and the expression of the NCC and its regulatory kinases were assessed via immunoblot on day 21 or day 42 of experimental diet (N=5-6/gp).

Results: DSS rats fed a 21 day HS diet develop SSH and show increases in NCC activity, expression, and its regulatory kinases expression compared to rats on a NS diet. DSS rats fed a 21 day HS diet and treated with α_1 antagonist, terazosin, show attenuated SSH, reduced NCC activity, and expression of NCC and WNK1. A β antagonist, propranolol, did not attenuate DSS SSH. Critically, α_1 adrenoceptor antagonism attenuates SSH, NCC activity/expression, and WNK1 expression in DSS rats with established hypertension.

Conclusions: SNS release of NE activates an α_1 adrenoceptor pathway to drive the development and maintenance of Dahl SSH. Significantly, α_1 adrenoceptor antagonism attenuates the development and maintenance of SSH by evoking downregulation of NCC activity, expression, and regulatory kinase WNK1 expression. Collectively, these findings suggest that NE stimulates an α_1 adrenoceptor pathway involving WNK1 signaling to drive increases in NCC activity and the development and maintenance of SSH in DSS rats.

Funding: Other NIH Support - NHLBI

	Dietary Salt Intake	MAP (mmHg)	Peak ΔUNaV to HCTZ (μeq/min)	NCC Expression (Fold Change)	Total pNCCT53 (Fold Change)	WNK1 Expression (Fold Change)	SPAK Expression (Fold Change)	OxSR1 Expression (Fold Change)
Naive DSS rat 21-day	NS	127 ± 3	9.4 ± 0.6	1 ± 0.14	1 ± 0.17	1 ± 0.08	1 ± 0.11	1 ± 0.05
	HS	162 ± 4*	11.4 ± 0.4*	1.09 ± 0.14	1.05 ± 0.17	1.04 ± 0.12	0.96 ± 0.15	0.96 ± 0.06
DSS rat 21-day sc Terazosin	HS	143 ± 3#	5.9 ± 0.6#	0.27 ± 0.09#	0.44 ± 0.17#	0.26 ± 0.1#	0.29 ± 0.11#	0.68 ± 0.08#
DSS rat 21-day sc Propanolol	HS	157 ± 4	10.4 ± 0.6	0.95 ± 0.09	1 ± 0.11	1.03 ± 0.07	0.36 ± 0.09#	1.05 ± 0.08
DSS rat 42-day sc Saline	HS	207 ± 5	14.4 ± 0.6	1± 0.10	1± 0.20	1± 0.18	1± 0.19	1± 0.05
DSS rat 42-day sc Terazosin	HS	191 ± 3@	9.3 ± 2.0@	0.69 ± 0.08@	0.42 ± 0.15@	0.48 ± 0.09@	0.97 ± 0.11	0.88 ± 0.09

Table 1: *p<0.05 vs. respective naive Normal Salt (NS, 0.6% NaCl) group; #p<0.05 vs. naive DSS 21 Day High Salt (HS, 4% NaCl) group; @p<0.05 vs. 42 day subcutaneous (sc) saline group.

FR-PO588

Fructose Increases the NCC Activity Through the Calcium-Sensing Receptor-WNK4-SPAK Pathway

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Background: We have recently shown that the Calcium Sensing Receptor (CaSR) activates NCC via the WNK4-SPAK pathway (JASN 2018). It is known that glucose and other sugars behave as positive allosteric modulators of CaSR. The effect of glucose on CaSR is particularly relevant in the apical membrane of distal convoluted tubule (DCT), which is not exposed to glucose, except during diabetic glycosuria. The exposure of DCT to fructose varies from low to high because it occurs in an intake-dependent manner. Thus, we hypothesize that sugar delivery to the DCT, by their allosteric effect on the CaSR, might activate NCC via the CaSR-WNK4-SPAK pathway.

Methods: To test if glucose or fructose induce SPAK phosphorylation, we used HEK-293 cells cotransfected with CaSR + SPAK +/- WNK4 cDNA. Expression and phosphorylation of SPAK were assessed using a constant low-calcium medium (0.5mM), but varying the glucose or fructose concentration from 0, to 5.5 or 25mM. The calcimimetic R568 was used as a positive control. To corroborate NCC activation in vivo, we analyzed WNK4-SPAK-NCC pathway in kidneys of mice subjected to a 3h treatment with vehicle, oral calcilytic NPS2143, 20% fructose (in drinking water) *ad libitum*, or 20% fructose *ad libitum* + NPS2143.

Results: Exposure of HEK-293 cells to glucose or fructose increased SPAK and ERK phosphorylation ($p<0.001$). In contrast, when WNK4 cDNA was not transfected, ERK phosphorylation (as a surrogate of CaSR activation) increased, but there was no effect on SPAK phosphorylation ($p<0.01$). In mice, 20% fructose intake resulted in increased NCC phosphorylation ($p<0.01$). Moreover, fructose intake activated WNK4 and SPAK ($p<0.05$). The effect of fructose was abrogated by coadministration of the calcilytic NPS2143 ($p<0.01$).

Conclusions: Our results show that glucose and fructose induce SPAK phosphorylation in cells in a WNK4-dependent manner. In vivo, fructose intake increased NCC phosphorylation via WNK4 and SPAK, which were in turn activated by CaSR, since the calcylitic compound NPS2143 prevented the effect. Our observations suggest that activation of NCC by glucose or fructose via CaSR could be one of the mechanisms involved in the development of increased salt reabsorption and hence hypertension in diabetes mellitus or during high fructose consumption.

Funding: Government Support - Non-U.S.

FR-PO589

Regulation of PKC-Dependent WNK4 Phosphorylation by Extracellular Potassium: Insight into Familial Hyperkalemia and Hypertension Pathophysiology

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Background: Familial Hyperkalemic Hypertension (FHHt) is caused by mutations in genes such as KLHL3 and WNK4, which result in higher protein levels of the kinase WNK4 and thus upregulation of the phosphorylated renal NaCl cotransporter NCC (pNCC), increasing its activity. Because NCC activity is inversely proportional to plasma K^+ in physiological conditions, it is puzzling that NCC activity is not suppressed by hyperkalemia in FHHt. We have shown that WNK4 phosphorylation by PKC/PKA at S64 is important for kinase activity and that it is increased by hypokalemia. Here we investigated how this site is regulated in hyperkalemia and FHHt.

Methods: Wild-type (WT) mice were fed with low (LKD-0%), normal (NKD-1.2%) or high (HKD-5%) K^+ diets for 7 days. Transgenic $KLHL3^{R528H/+}$ mice (with FHHt phenotype) were fed with LKD or NKD for 4 days. Blood samples were obtained to measure electrolyte levels. Western Blot assays with kidney lysates were performed to analyze total and phosphorylated WNK4 and NCC levels. WNK4-transfected HEK293 cells were incubated in low (1mM), normal (5mM) or high (10mM) K^+ media. *Ex vivo* kidney slices from WT mice were exposed for 30 min to control solutions followed by 30 min to low, normal or high K^+ media.

Results: We observed that phosho-S64 in WNK4 is increased in WT mice by LKD, but not affected by HKD, while in the same samples, we corroborated that pNCC is increased by LKD and decreased by HKD. Accordingly, in $KLHL3^{R528H/+}$ mice, WNK4-S64 phosphorylation was not suppressed by hyperkalemia as phosphorylation levels increased in a similar amount than WNK4 total levels. In these mice, both pNCC and pWNK4-S64, were further increased by LKD, showing that DCT cells can still respond to low $[K^+]$ via de $[Cl^-]$-WNK4 pathway. In addition, consistent with the observations *in vivo*, in WNK4-transfected HEK293 cells and in *ex vivo* kidney slices, we found that pWNK4-S64 was increased by incubation with low K^+, but not decreased by high K^+.

Conclusions: WNK4 phosphorylation at S64 is increased by low $[K^+]_e$. However, we did not observe the opposite process by high $[K^+]_e$. Since WNK4 remains phosphorylated at S64 in this setting, this might help to explain why elevated WNK4 levels in FHHt are enough to maintain higher NCC activity in spite of hyperkalemia.

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FR-PO590

WNK Bodies Enable WNK4-Dependent Phosphorylation of SPAK/OSR1 for Their Apical Trafficking

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Background: The distal convoluted tubule (DCT) is vital for K^+ homeostasis. Low plasma $[K^+]$ stimulates the apical Na^+, Cl^--cotransporter (NCC), limiting electrogenic K^+ loss in the downstream tubule at the expense of increased NaCl retention and blood pressure. NCC is activated via phosphorylation by Ste-20-related proline/alanine-rich kinase (SPAK) and oxidative-stress-responsive kinase 1 (OSR1), two homologous substrates of with no lysine (WNK) kinases. During hypokalemic NCC activation, the human and rodent DCT develop cytoplasmic structures containing WNKs and SPAK/OSR1, termed WNK bodies. Their function is unclear. We hypothesized that WNK bodies serve as sites of SPAK/OSR1 activation, followed by trafficking of SPAK/OSR1 towards NCC.

Methods: To explore this hypothesis, we analyzed cellular distribution and phosphorylation of SPAK/OSR1 in different rodent models of hypokalemia (dietary K^+

deprivation, genetic WNK4 deletion, and furosemide treatment) using high-resolution immunofluorescence and electron microscopy.

Results: Feeding mice (n=5) a K^+-deficient diet for 10 days increased abundance of phosphorylated (p) SPAK/OSR1 at the apical DCT membrane and induced formation of WNK bodies enriched in pWNK and pSPAK/OSR1, suggesting that WNK bodies may facilitate phosphorylation steps. In contrast, only unphosphorylated WNK1 and SPAK/OSR1 were detected in WNK bodies of WNK4-deficient mice (n=3), which emphasizes the importance of WNK4 for SPAK/OSR1 activation in hypokalemia. Enlargement of WNK bodies along with reduction of apical SPAK/OSR1 in the WNK4-deficient DCT suggested that pSPAK/OSR1 might exit WNK bodies for apical trafficking towards NCC. To confirm this, we disrupted cellular trafficking machinery using the microtubule assembly inhibitor colchicine in rats receiving furosemide (n=4). Compared to rats receiving only furosemide (n=4), concomitant colchicine treatment resulted in accumulation of pSPAK/OSR1 in WNK bodies, along with reduced apical abundance of pSPAK/OSR1. Electron microscopy revealed that WNK bodies are membraneless, hypodense structures closely associated with microtubules.

Conclusions: In sum, our results indicate that WNK bodies are membraneless organelles performing SPAK/OSR1 activation for their subsequent apical trafficking, thereby linking plasma [K^+] to NCC phosphorylation, NaCl balance and blood pressure.

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FR-PO591

Renal TNFα Activates WNK Phosphorylation Cascade and Contributes to Salt-Sensitive Hypertension in CKD

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Background: The inappropriate over-activation of with-no-lysine kinase (WNK)–STE20/SPS1–related proline/alanine-rich kinase (SPAK)–NaCl cotransporter (NCC) phosphorylation cascade increases sodium reabsorption in distal kidney nephrons, resulting in salt-sensitive hypertension. Although chronic kidney disease (CKD) is a common cause of salt-sensitive hypertension, the involvement of WNK phosphorylation cascade is unknown. Moreover, the effect of immune systems on WNK kinases has not been investigated despite the fact that immune systems are important for salt sensitivity.

Methods: WNK phosphorylation cascade and its contribution to salt sensitivity was evaluated in three CKD mouse models (aristolochic acid nephropathy (AAN), adenine nephropathy and subtotal nephrectomy). The regulator of WNK signaling in CKD was also explored focusing on immune systems.

Results: Immunoblotting and immunofluorescent study revealed that the protein abundance of WNK1, but not of WNK4, was increased at the distal convoluted tubules (DCT) in the AAN kidney. Accordingly, the phosphorylation of SPAK and NCC was also increased. Moreover, a high-salt diet did not adequately suppress the activation of WNK1–SPAK–NCC phosphorylation cascade in AAN, leading to salt-sensitive hypertension. WNK1 also was increased in adenine nephropathy, but not in subtotal nephrectomy, models. By comparing the transcripts of these three models focusing on immune systems, we hypothesized that TNFα regulates WNK1 protein expression. In fact, TNFα increased WNK1 protein expression in cultured cells by reducing the transcription and protein levels of NEDD4-2 E3-ligase, which degrades WNK1 protein. Furthermore, the TNFα inhibitor etanercept reversed the reduction of NEDD4-2 expression and upregulation of WNK1–SPAK–NCC phosphorylation cascade at DCT *in vivo* in the AAN kidney.

Conclusions: TNFα activates WNK1–SPAK–NCC phosphorylation cascade in the kidney, leading to salt-sensitive hypertension in CKD. These observations provide the new mechanism how immune systems regulate salt-sensitivity in CKD.

Funding: Government Support - Non-U.S.

FR-PO592

The Novel Role of 14-3-3 Gamma in the Pathogenesis of Deoxycorticosterone Acetate Salt Hypertensive Mouse Model

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Background: Sodium chloride cotransporter (NCC) plays a key role in the regulation of blood pressure and electrolyte homeostasis. 14-3-3 γ belongs to a family of multifunction regulatory proteins. Previous data have shown that 14-3-3 proteins regulate renal ion channel and transporter such as ENaC. Our preliminary data showed that 14-3-3γ inhibits NCC. Thus, we hypothesized that 14-3-3 γ plays a role in affecting blood pressure regulation through NCC. The purpose of this study is to investigate the role of 14-3-3 γ in NCC regulation in DOCA-salt hypertensive mouse model.

Methods: DOCA salt mouse, western blot analysis, cell culture, siRNA knock-down experiments, and tail-cuff blood pressure (BP) measurement were used in this study.

Results: To determine whether 14-3-3 γ has a role in the pathogenesis of hypertension, we first established the DOCA salt hypertensive mouse model. Systolic blood pressure was significantly higher in DOCA salt hypertensive mice than that in control mice (148 ± 25 vs 119 ± 20, $p < 0.01$, n=4). Western blot analysis from the kidney tissues harvested from these mice showed that 14-3-3 γ protein abundance was significantly reduced in DOCA salt hypertensive mice compared to the control mice group (100 ± 11.3 % vs 58.2 ± 11.8 %, $p < 0.01$, n=4). Total NCC and phospho-NCC were significantly increased in DOCA salt group compared to the control group (1.0 ± 0.12 vs 1.4 ± 0.25; 1.0 ± 0.17 vs 1.34 ± 0.10, respectively, $p < 0.05$, n=4). ERK 1/2 phosphorylation was significantly reduced in DOCA salt group compared to the control group. To further investigate the role of ERK 1/2 signaling pathway in the 14-3-3 γ-mediated NCC regulation, we performed the 14-3-3 gamma knock-down experiments in Cos-7 cells transfected with 14-3-3 γ siRNA and NCC. Knocking down 14-3-3 γ expression significantly increased total NCC protein expression while reducing ERK 1/2 phosphorylation. Overexpression of 14-3-3γ significantly reduced NCC protein expression while enhancing ERK 1/2 phosphorylation. In the presence of knock-down ERK 1/2, 14-3-3 γ-mediated inhibition of NCC was reversed.

Conclusions: Taken all data together, we concluded that 14-3-3 γ plays an important role in NCC regulation through ERK 1/2-mediated signaling pathway in DOCA salt hypertensive mouse model, which provides a novel mechanism underlying pathogenesis of DOCA salt hypertension.

Funding: Veterans Affairs Support

FR-PO593

Generation and Analysis of Pseudohypoaldosteronism Type II Knockin Mice Caused by Nonsense Mutation in the Kelch Domain of KLHL3

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Background: Mutations in Kelch-like 3 (*KLHL3*) are the most common causative genes detected in patients with pseudohypoaldosteronism type II (PHAII). Although *Klhl3*$^{R528H/+}$ knock-in (KI) mice carrying a missense mutation in kelch repeat domain has been reported, the nonsense *KLHL3* mutation-causing PHAII in the same domain have not been fully investigated *in vivo*.

Methods: We generated and analyzed mutant *Klhl3* KI mice harboring a nonsense *W523X* mutation in the kelch domain (corresponding to human *KLHL3 W470X* mutation). The associated protein expression of their kidney tissue was evaluated by western blot and immunofluorescence. The co-immunoprecipitation (co-IP) method was conducted to clarify the role of *KLHL3* kelch repeat domain.

Results: Both heterozygous and homozygous *Klhl3*$^{W523X/+}$ KI mice exhibited a significantly elevated systolic blood pressure ($p < 0.05$), secondary hyporeninemia ($p < 0.05$), a higher serum potassium level (K^+) ($p < 0.05$) with decreased fractional excretion of K^+ (FE_K; $p < 0.05$) and a higher serum chloride level but lower bicarbonate level ($p < 0.05$). Their kidney tissues showed decreased levels of KLHL3 protein along with an enhanced downstream WNK1/4-SPAK/OSR1-N(K)CC phosphorylation. *In vitro*, co-IP demonstrated human KLHL3 harboring the PHAII-causing *W470X* mutation resulted in a decreased expression of total KLHL3 protein with truncated KLHL3 protein, leading to impaired binding affinity of KLHL3 to WNK1/4.

Conclusions: *Klhl3*$^{W523X/+}$ KI mice feature typical PHAII with a simultaneous increase of WNK1 and WNK4 through impaired binding of the KLHL3 kelch domain to WNKs.

FR-PO594

Effects of Extreme Dietary Potassium Restriction and K+ Loading on Blood Pressure and Renal Tubular Na+ Transport

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Background: For almost a century it has been known that dietary potassium intake inversely correlates with blood pressure. Yet, it is unclear how potassium restriction leads to hypertension, or how potassium excess causes a natriuresis despite elevated aldosterone levels. Our goal was to study the effects of dietary potassium on blood pressure, acid/base balance, and ion transport.

Methods: Wild-type SV129 mice were fed K+ deficient, control, high K+ basic, and high KCl diets for 10 days. We monitored BP using radiotelemetry probes, urine electrolyte excretion via metabolic cages, and transporter expression via immunofluorescence, western blots, and diuretic challenges.

Results: Interestingly, despite the induction of hypokalemia, extreme K+ depletion had no effect on blood pressure. In contrast, K+ loading resulted in a progressive ~10 mmHg increase in blood pressure. To determine whether these effects were dependent on NaCl intake, we challenged mice with 1% saline. The K+ deficient mice developed an increase in blood pressure (~8 mmHg), whereas K+ replete mice exhibited no significant change in blood pressure with saline challenge. Notably, just 10d of K+ restriction was associated with diabetes insipidus, evidenced by polyuria and a decrease in AQP2 expression. This was associated with an increase in sodium transporters in the upstream tubule, likely the cause of salt sensitivity. The elevated blood pressure on the K+ loaded diet correlated with elevated aldosterone levels and increased ENaC activation. During K+ loading, the type of anion (basic vs. chloride-rich) had a considerable effect on key transporters along the tubule, despite no differences on blood pressure.

Conclusions: In our model, the effect of dietary K+ on blood pressure was linked to NaCl intake, due to differential effects of K+ loading and restriction on sodium transport pathways along the nephron. The inverse relationship between dietary K+ intake and blood pressure was only observed in the setting of NaCl loading, though our data strongly suggest that AQP2 expression should be closely monitored to accurately interpret such

results. Further, the accompanying anionic content should be taken into consideration when modeling the physiologic effect of K+ intake on tubular salt transport and blood pressure.

Funding: NIDDK Support

FR-PO595

Kidney-Specific and Sex-Dependent Action of the Circadian Clock Protein BMAL1 in the Renal Response to Dietary Potassium Deprivation

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Background: BMAL1 is a core mammalian circadian clock transcription factor responsible for the tissue-specific regulation of thousands of genes. Male, but not female, kidney-specific BMAL1 knockout (KO) mice exhibit lower blood pressure compared to control mice (CNTL). The goal of this study was to determine the BMAL1-dependent response to five days of dietary potassium (K) deprivation in males and females.

Methods: We generated the KO using floxed exon 8 BMAL1 mice crossed with kidney-specific cadherin Cre+ mice. Floxed Cre- littermates were used as CNTL. Metabolic cages were used for 12 hr urine collections.

Results: There was not a genotype difference in food intake in either sex, however, males displayed a transient decrease throughout the treatment (M: P<0.05) but females had no change (F: P=0.4). Similarly, neither sex had a genotype difference in body weight. Body weight of males did not change from treatment (M: P=0.8) but females increased in weight (F: P<0.0001). K excretion throughout treatment was comparable between CNTL and KO in both sexes. The K excretion rate in males decreased within 24 hours of the start of treatment from baseline and remained low for the full 5 days (CNTL: 0.65±0.05 to 0.012±0.002; KO: 0.64±0.02 to 0.015±0.004 mmol; P<0.0001). Females exhibited a similar response in K excretion rates (CNTL: 0.38±0.09 to 0.03±0.009; KO: 0.42±0.08 to 0.003±0.01 mmol; P<0.0001). After an initial decrease in sodium (Na) excretion in males, rates remained lower than baseline throughout treatment in CNTL whereas KO increased back to baseline levels by day 5 of treatment (CNTL: .29±0.02 to 0.19±0.01; KO: 0.29±0.01 to 0.26±0.01 mmol; P<0.0001). Genotype-dependent differences in Na excretion were not apparent in females, however, there was a transient increase following treatment in CNTL and KO reaching its peak at day 4 (CNTL: 0.21±0.06 to 0.26±0.05; KO: 0.21±0.03 to 0.24±0.03 mmol; P<0.05). Male CNTL had greater cumulative Na compared with male KO (P<0.001) and both female groups.

Conclusions: Male kidney-specific BMAL1 KO mice exhibited a decrease in renal Na retention in response to a low K diet. Thus, BMAL1 functions in the sex-dependent response of the kidney to dietary K restriction.

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FR-PO596

Role of Ammonia in the Renal Potassium Response to Dietary K^+ Deficiency

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Background: Previous studies have shown that glutamine administration simultaneously increases ammonia excretion and decreases K^+ excretion. The current studies determined whether increased ammonia metabolism is necessary for the normal kaliuretic response to hypokalemia.

Methods: We used NBCe1-A KO mice, which have decreased ammonia response to metabolic acidosis, and WT littermates. We determined whether NBCe1-A KO blocked the ammonia response to hypokalemia and whether this response was necessary for normal changes in K^+ excretion. Lastly, we incubated tissue slices with defined solutions to determine direct effects of ammonia on NCC phosphorylation.

Results: In WT mice exposed to a K^+-free diet for 4 days, as compared to mice provided K^+-control diet, there was increased ammonia excretion, increased expression of cortical ammoniagenic enzymes, PDG and PEPCK, and decreased expression of the ammonia recycling enzyme, glutamine synthetase. In KO mice each of these responses was blunted significantly. NBCe1-A KO mice have a genetic mutation affecting only cortical proximal tubule segments, which is not thought to regulate K^+ excretion, yet when exposed to a K^+-free diet developed a significantly lower serum K^+, measured on day 4, and they excreted significantly more urinary K^+ on each day than did WT littermates. Distal nephron K^+ transporter, ROMK, BK channel, and H^+-K^+-ATPase $\alpha1$ and $\alpha2$, expression did not differ detectably between hypokalemic WT and KO mice. ENaC α, β and γ expression increased with K^+-free diet similarly in WT and KO mice. NCC phosphorylation, which has a key role in the renal response to hypokalemia, however, was significantly less in hypokalemic KO than in hypokalemic WT mice. Ex vivo incubation of kidney slices for 1 hour in defined solutions showed that decreased extracellular K^+ increased phospho-NCC expression over the tested range of 2-8 mM K^+. Addition of ammonia, 2 mM, also increased phospho-NCC expression. Total NCC expression was not altered by changes in extracellular K^+ or by ammonia addition.

Conclusions: The renal kaliuretic response to dietary K^+-deficiency-induced hypokalemia requires an NBCe1-A-dependent increase in cortical proximal tubule segments ammoniagenesis, which then leads to an ammonia-dependent stimulation of NCC phosphorylation that is necessary for normal K^+ conservation.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO597

Insulin Stimulates V-ATPase on Renal Proximal Tubules via the Akt/mTORC2 Pathway

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Background: Maintaining an acid-base balance is essential for homeostasis. Acid-base transport in renal proximal tubules (PTs) is mainly sodium dependent and conducted coordinately by apical Na^+/H^+ exchanger (NHE)3, vacuolar H^+-adenosine triphosphatase (V-ATPase) and basolateral Na^+/HCO_3^- cotransporter (NBC)e1. V-ATPase on the PTs well-known to play an important role in proton excretion. Previously, we reported stimulation of PT sodium transport by insulin was mediated via Akt2 mTORC2 pathway. However, it is unclear whether insulin is involved in acid-base balance on the renal PTs. We hypothesized insulin may regulate V-ATPase on PTs.

Methods: We measured luminal V-ATPase activity in freshly isolated, split-opened mouse PTs by using a pH-sensitive dye BCECF. To uncover the signaling mechanism, we examined the effect of bafilomycin, Akt1/2 inhibitor VIII, an mTORC1 inhibitor rapamycin and an mTORC1/2 inhibitor, PP242. The measurement of V-ATPase activity was as follows; Freshly isolated and split-opened PTs in the chamber were first perfused in HEPES, and then the perfusate was switched to Na^+- free HEPES. The intracellular pH recovery rates during perfusing with Na^+-free HEPES were measured, and intracellular pH change was calculated during the initial 30 seconds as V-ATPase activity. To confirm the protein expression, protein phosphorylation was analyzed by Western blotting.

Results: V-ATPase activity in PTs was markedly stimulated by insulin, and this stimulation was almost completely inhibited by bafilomycin, Akt inhibitor VIII, and PP242, but not by rapamycin. In freshly isolated mouse PTs, V-ATPase activity was increased approximately 20% by 1nM insulin above baseline and this stimulation was completely suppressed by Akt 1/2 inhibitor VIII. While PP242 completely suppressed the insulin-mediated V-ATPase stimulation in mouse PTs, rapamycin failed to affect the insulin effect. Insulin-induced phosphorylation of Akt in mouse renal cortex was completely suppressed by Akt1/2 inhibitor VIII and PP242, but not rapamycin.

Conclusions: Our results indicated that stimulation of V-ATPase activity by insulin in PTs is mediated via Akt2/mTORC2pathway. These results implicate the complex signaling in the proximal tubule acid-base balance, providing treatment targets for renal disease.

Funding: Government Support - Non-U.S.

FR-PO598

Secretin Activates Pendrin-Dependent HCO_3^- Secretion in β-Intercalated Cells

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Background: The secretin receptor is expressed in the intercalated cells (IC) of the collecting duct. Using *in vivo* mice experiments, we have recently shown that secretin triggers a pronounced and rapid increase of urinary HCO_3^- excretion. Importantly, this secretin effect was completely absent in pendrin (SLC26A4) KO mice and strongly reduced in CFTR KO mice. We hypothesize that secretin directly activates β-intercalated cells (β-IC) of the collecting duct (CD) via stimulation of basolateral secretin receptors.

Methods: We used isolated perfused cortical collecting ducts and intracellular pH measurements in β-ICs to quantify the transport rate of pendrin upon fast removal of luminal chloride in the presence of 24 mM luminal HCO_3^-. Tubules were loaded with the pH indicator dye BCECF-AM from the luminal side to achieve selective IC dye loading. The experiments were done in WT and CFTR KO mice. The initial alkalization rate ($\Delta pH/\Delta t$) upon luminal chloride removal was taken as measure of pendrin activity in β-ICs. Secretin (10 nM) was applied for 10 min to the basolateral side. Analysis was performed in a strictly paired fashion in the single β-IC before and after secretin and this was compared to time controls with no secretin stimulation.

Results: Mean $\Delta pH/\Delta t$ was markedly increased with secretin (0.20±0.038 pH/min vs. 0.43±0.044 pH/min (24 cells, 4 CDs, 4 mice), p<0.0001). This increase was significantly different from time controls without secretin (p=0.0022, 20 cells, 4 CDs, 4 mice).

Conclusions: These results show that basolateral secretin directly activates pendrin-dependent HCO_3^- secretion in β-ICs. Importantly, HCO_3^- secretion in β-IC is markedly reduced in CFTR KO mice. Thus, our previously demonstrated *in vivo* effects of secretin align well with those reported here in the isolated perfused CD. This shows that secretin triggers urinary HCO_3^- excretion by activating the β-ICs.

Funding: Government Support - Non-U.S.

FR-PO599

The Molecular Chaperone GRP170 Regulates ENaC Biogenesis and Salt and Water Homeostasis in the Kidney

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Background: The epithelial sodium channel (ENaC) is expressed in a variety of epithelial tissues. In the distal nephron, ENaC is responsible for Na^+ reabsorption and regulates salt and water homeostasis and blood pressure. ENaC is a heterotrimeric channel composed of an α, β, and γ-subunit. Unassembled ENaC subunits are recognized by the

ER associated degradation (ERAD) machinery and degraded. Using cellular models, we determined that the ER localized molecular chaperone, GRP170, regulates both ENaC quality control and trafficking. We determined that GRP170 is required for the degradation of the unassembled αENaC subunit, but not the β or γ-subunits. However, when all three ENaC subunits are present, GRP170 promotes trafficking of ENaC to the cell surface. Therefore, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 knock-out (KO) mouse. A GRP170 allele flanked by LoxP sites ("floxed") was generated, and crossed to a mouse that expresses Cre recombinase in kidney tubules upon doxycycline treatment. Adult mice were treated for 10 days with doxycycline to deplete GRP170 and given either a standard or high-salt diet. Mice were placed in metabolic cages and weight, water intake and urine output were monitored. Animals were sacrificed and blood, kidneys, lungs, and liver were harvested.

Results: GRP170 KO mice lose weight after doxycycline treatment (~20% body weight in three weeks), whereas control mice do not. Rapid weight loss is consistent with volume loss. Because Na^+ reabsorption by ENaC promotes water reabsorption, loss of volume is consistent with decreased ENaC activity. Indeed, a significant increase in plasma aldosterone, a decrease in plasma Na^+, and an increase in plasma K^+ are observed in the GRP170 KO mouse. When experiments were repeated with a high-salt diet, changes in plasma Na^+ and K^+ levels were no longer observed. Because a high-salt diet partially rescues the GRP170 KO phenotype, these data are consistent with Na^+ depletion and reduced ENaC activity.

Conclusions: The GRP170 chaperone regulates ENaC expression or activity in the mouse kidney, consistent with its effect *in vitro*. Ongoing experiments will examine whether GRP170 regulates other ion channels or transporters.

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FR-PO600

Low ENaC Expression Abolishes Furosemide-Induced K^+ Excretion

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Background: In the collecting duct (CD) ENaC-mediated Na^+ absorption drives K^+ excretion. Acute K^+ excretion is dependent on the regulated delivery of Na^+ to the aldosterone-sensitive part of the distal nephron (ASDN) and acute activation of ENaC. Furosemide is considered a K^+ wasting diuretic as it greatly enhances Na^+ delivery to the ASDN. Here, we study the magnitude of acute furosemide-induced kaliuresis under various states of CD ENaC expression.

Methods: C57/Bl6J mice were subjected to different dietary regimens altering molecular ENaC expression levels. The animals were anesthetized and bladder-catheterized. Diuresis was continuously measured before and after furosemide (2μg/gBW) was administered. Flame photometry was used to measure urinary Na^+ and K^+ and ENaC expression levels were determined by semi-quantative Western Blotting.

Results: A high K^+ and a low Na^+ diet greatly increased ENaC protein expression and furosemide-induced kaliuresis. In contrast, furosemide-induced kaliuresis was greatly reduced in animal fed a low K^+ diet and absent in animals on a high Na^+ diet, conditions with markedly reduced ENaC expression. No significant differences in furosemide-induced natriuresis were found when comparing the dietary groups but it tended to by higher in the low ENaC expressing groups. The furosemide-induced diuresis was similar in all dietary groups.

Conclusions: Acute furosemide-induced kaliuresis differs greatly and markedly depends on the *a priori* molecular expression level of ENaC. Remarkably, it can be even absent in animals fed a high Na^+ diet, despite a marked increase of tubular flow. This study provides auxiliary evidence that acute CNT/CCD dependent K^+ secretion requires both functional and molecular activation of ENaC.

Funding: Government Support - Non-U.S.

FR-PO601

Chronic Fluid Shear Stress (FSS) Induces ERK Dependent Sodium Transport in Principal Cells (PCs)

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Background: Nephron loss by disease or nephrectomy lead to compensatory hemodynamic and cellular effects on the remaining nephrons. Increases in single nephron glomerular filtration rate and tubular flow rate, exert FSS on tubular epithelia. Rising tubular flow rate have acute and chronic effects on epithelial Na channel (ENaC) dependent Na absorption. Acute (minutes) increase in cortical collecting duct (CCD) flow rate augments Na absorption; however, chronic (hours) flow, as in unilateral nephrectomy, is expected to augment Na excretion and increase fractional excretion of Na. *In vitro* FSS induces ERK phosphorylation in murine CD cells and ERK has been shown to be a regulator of ENaC. Thus, we hypothesize that chronic FSS-induces ERK activation in the CCD to inhibit amiloride sensitive Na transport.

Methods: To test this, murine PCs (mpkccd) were grown on snapwells under static conditions or exposed to 0.4 dynes/cm^2 of FSS for 24 hrs and amiloride sensitive Na current (*Iasc*) measured in an Ussing chamber. Kidneys from sham control and unilateral nephrectomized mice were used for immunohistochemistry (IHC) and immunofluorescence (IF).

Results: *Iasc* was 23.4±1.4 μA/cm^2 (n=6) in static PCs, but in cells exposed to 24 hours of FSS the *Iasc* was reduced to 12.9±1.0 μA/cm^2 (n=9; p<0.01). Next, we tested whether U0126, a MEK inhibitor, could recover the FSS mediated reduction in *Iasc*. PCs exposed to FSS and U0126 exhibited a lower *Iasc* of 6.9±0.3 μA/cm^2 (n=4, p<0.01 vs static and FSS without inhibitor), suggesting ERK stimulates ENaC dependent transport and that non-ERK factors repress *Iasc*. To identify ERK expression *in vivo*, we performed IHC and IF in kidneys of mice post-unilateral nephrectomy and in sham controls. IHC, in control and nephrectomized mice, showed heterogenous expression of phospho-ERK (pERK) in the CCD. Sham and nephrectomized kidneys were labelled with dolichos biflorus agglutinin (DBA), a PC marker, and anti-pERK antibody. In sham kidneys pERK co-localized with PC cells; however, in nephrectomized mice pERK chiefly co-localized with DBA and in a minority of cells localized with non-DBA stained cells of the CCD.

Conclusions: Chronic FSS induces ERK to stimulate ENaC dependent Na transport *in vitro*, and *in vivo* pERK is expressed primarily in PCs, suggesting ERK may play an identical role *in vivo*

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO602

Regulation of Rhcg Protein in the Intercalated Cells of the Outer Medullary Collecting Duct by Aldosterone

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Background: Rhcg, an ammonia transporter, is expressed mainly in the intercalated cells (ICs) of the collecting duct. Serum potassium level regulates the expression of Rhcg. Aldosterone level is increased in metabolic acidosis; however, direct effects of aldosterone on the Rhcg expression remain obscure.

Methods: C57BL/6J mice were divided into four groups: 1) sham-operation, 2) sham and NH_4Cl drinking (Sham-NH_4Cl), 3) adrenalectomy and NH_4Cl drinking (ADX-NH_4Cl), and 4) adrenalectomy with continuous administration of aldosterone and NH_4Cl drinking (ADX-Aldo-NH_4Cl). Mice were sacrificed three days after NH_4Cl drinking. Urinary ammonium excretion and localizations of Rhcg and ubiquitin were examined. For *in vitro* experiments, IN-IC cells, which we previously established as an intercalated cell-derived cell line, that stably express flag-tagged Rhcg (Rhcg-flag) were generated. The effects of aldosterone, spironolactone, Go6983 (a PKC inhibitor) and MG132 (a proteasome inhibitor) on the expression of Rhcg-flag were examined.

Results: NH_4Cl-induced increase in urinary ammonium excretion was less in ADX-NH_4Cl mice than that in Sham-NH_4Cl mice. Aldosterone increased ammonium excretion in ADX-Aldo-NH_4Cl mice as much as that in Sham-NH_4Cl mice. Immunohistochemical study revealed that NH_4Cl drinking increased the accumulation of Rhcg at apical membrane of the ICs of the outer medullary collecting duct in Sham-NH_4Cl mice. Adrenalectomy and aldosterone decreased and increased the accumulation of Rhcg at apical membrane of the ICs in ADX-NH_4Cl and ADX-Aldo-NH_4Cl mice, respectively. Ubiquitin expression was not changed between in PCs and ICs of Sham-NH_4Cl mice, while it was less in ICs than in PCs in ADX-NH_4Cl mice. Aldosterone restored the ubiquitin expression in ICs. In *in vitro* experiment, Western blotting showed that aldosterone increased the expression of Rhcg-flag in the membrane fraction of IN-IC cells. Spironolactone and Go6983 each inhibited the expression of Rhcg-flag. Treatment with MG132 increased the expression of Rhcg-flag in whole cell lysate.

Conclusions: Aldosterone could directly regulate Rhcg expression through the mineralocorticoid receptor-PKC pathway. Furthermore, aldosterone could modulate Rhcg expression through the ubiquitin-proteasome pathway.

Funding: Government Support - Non-U.S.

FR-PO603

Effect of Loading NH_4Cl in $P2Y_2$ Receptor Knockout and Wild-Type Mice

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Background: Chronic lithium (Li) administration for bipolar disorder causes renal tubular acidosis. In animal models, Li invokes collecting duct remodeling (CD-R) resulting in an increased proportion of $[H^+]$-ATPase-positive intercalated cells, presumably to increase kidney H^+ excretion. We reported that genetic deletion of $P2Y_2$ receptor blunts this Li-induced CD-R response, suggesting that $P2Y_2$ receptor facilitates H^+ elimination in response to an acid load. To investigate the role of $P2Y_2$ receptor in acid-base regulation, we evaluated the effect of NH_4Cl loading on blood and urinary acid-base indices in $P2Y_2$ knockout (KO) and wild type (WT) mice.

Methods: Groups of WT or KO mice (B6D2; N=5-6/group) were fed standard rodent chow and given tap water with/without 0.28 M NH_4Cl for 9 days and humanely euthanized. Terminal urine and blood samples were collected and analyzed for indices of acid-base homeostasis.

Results: Table shows the terminal data. NH_4Cl loading induced a more severe metabolic acidosis in $P2Y_2$ receptor KO than WT mice as evidenced by the markedly lower blood pH, HCO_3 and BE, and increased water intake (not shown here). Urinary NH_3 excretion was slightly lower in KO than WT mice despite having more severe metabolic acidosis, suggesting that kidney NH_3 production or excretion is impaired in KO. The higher than expected pCO_2 (expected pCO_2 ~ 26 mm Hg) for the degree of metabolic acidosis induced by NH_4Cl loading, and the higher pCO_2 in KO than WT under basal conditions suggests that $P2Y_2$ receptor may regulate respiratory ventilation.

Conclusions: $P2Y_2$ receptor seems to have an important role in the maintenance of acid-base balance. This may be through facilitating CD-R in response to an acid load and participating in respiratory ventilation.

Funding: Veterans Affairs Support, Clinical Revenue Support

Parameter	WT-CNT	KO-CNT	WT-NH4Cl	KO-NH4Cl
Blood pH	7.40 ± 0.01	7.33 ± 0.04	7.32 ± 0.02	7.16 ± 0.03*
Blood pCO2 (mm Hg)	31.78 ± 1.68	41.82 ± 4.37**	35.57 ± 4.48	34.22 ± 0.62
Blood HCO3 (mEq/L)	19.48 ± 0.97	20.26 ± 0.98	18.23 ± 2.06	12.28 ± 0.92*
Blood BE (Base Excess)	-5.20 ± 0.86	-5.80 ± 0.73	-7.67 ± 1.91	-16.30 ± 1.41*
Blood Urea Nitrogen (mg/dl)	19.68 ± 0.37	24.92 ± 1.21	27.04 ± 1.02	29.12 ± 1.78
Urine NH3 (µmol/day/20 g bw)	8.45 ± 1.87	9.77 ± 1.62	82.08 ± 8.19***	69.99 ± 12.82***

*significantly different ($P < 0.05$) from the corresponding value in WT-NH4Cl group; **significantly different ($P < 0.05$) from the WT-CNT group; ***significantly different from the corresponding control (CNT) groups.

FR-PO604

Adaptation to a High-Salt Diet Requires A-Type Intercalated Cell-Dependent NaCl Secretion

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Background: The kidney controls the extracellular volume and the blood pressure because of its ability to excrete efficiently Na+ and Cl- ions. We have recently identified a novel pathway that mediates the secretion of Na+ in the collecting duct (Morla, et al. 2016). This system involves A-type intercalated cells (AIC), NKCC1 and the H,K-ATPase type 2 (HKA2), which is known to be able to transport Na^+. Here, we investigated the AIC implication in NaCl renal secretion and the physiological relevance of this pathway *in vivo*. We speculate that this pathway may help the kidney to excrete large amounts of salt when needed.

Methods: Collecting ducts from control kidneys following a normal and a high-salt diet (8% NaCl, HS) were isolated and analyzed by RT-qPCR and immunofluorescence followed by 3-dimensions reconstruction. To assess the physiological relevance of this novel pathway, we placed HKA2 knockout mice (HKA2KO mice) under HS diet.

Results: On isolated collecting ducts, we observe an increase of the total AIC number under HS diet (+10%). This adaptive proliferation of AIC in response to HS diet suggests a relevant role of AIC in NaCl secretion. RT-qPCR reveal that HS diet leads to a 4- and 1.6-fold increase of HKA2 and NKCC1 expressions, respectively. Altogether these results support the role of HKA2 and NKCC1 in mediating the secretion of NaCl in AIC. Under HS diet, HKA2KO mice display increased urine output and water intake associated with a decreased urinary osmolarity compared to control mice. HKA2KO mice also display a decrease of plasma K^+ and a hypochloremic metabolic alkalosis. This phenotype, induced by salt load, resembles Bartter syndrome, a salt-losing pathology due to thick-ascending limb dysfunction. Under HS diet, furosemide induces an 80% increased natriuresis in control mice but only a 30% increase in HKA2KO demonstrating that NKCC2 is less functional in HKA2KO mice. We, therefore, propose that the absence of Na^+ secretion through HKA2 is compensated by a stronger inhibition of NaCl reabsorption through NKCC2, leading to a mild Bartter-like syndrome.

Conclusions: In conclusion, we demonstrate that AIC participate to the regulation of Na+ balance through the stimulation of the NaCl secretion pathway under HS diet *in vivo* and we highlight the critical role of HKA2 in the fine adaptation to a HS diet.

Funding: Government Support - Non-U.S.

FR-PO605

The Renal AE4 Transporter (Slc4a9) Prevents Life-Threatening Hypochloremic Metabolic Alkalosis During NaCl Restriction and Base Loading

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Background: The renal transporter AE4 (Slc4a9) is localized to the basolateral membrane of type B intercalated cells (β-ICs) in the collecting duct. Recently, it has been shown that β-ICs contribute to renal sodium (Na^+) reabsorption during dietary salt restriction. Currently it is generally assumed that AE4 constitutes the primary basolateral Na^+ extrusion pathway in β-ICs, but there is still no direct evidence of such a role.

Methods: We subjected AE4 knockout mice and their wildtype littermates (WT) to either a salt (NaCl) deficient diet alone (10 days) or a salt deficient diet combined with an additional base load (230 mM $NaHCO_3$, 7 days). We analyzed the effects of each diet on plasma volume, renal Na^+ and Cl^- handling, renal protein expression levels of NHE3, NCC, ENaC and pendrin, plasma renin and aldosterone levels, and acid-base homeostasis.

Results: Surprisingly, AE4 knockout mice did not show any signs of Na^+ loss or volume contraction or compensatory activation of other renal Na^+ reabsorption pathways under salt deficient diet. However, we observed that AE4 knockout mice developed a mild hypochloremic metabolic alkalosis under these conditions, which severely aggravated when the animals were additionally subjected to a base load ($NaHC0_3$). In contrast, WT littermates maintained normal Na^+ and acid-base balance under both diet regimes. While WT mice markedly increased pendrin expression during the base load, this response was completely absent in AE knockout animals.

Conclusions: The findings show that the renal transporter AE4 (Slc4a9) is dispensable for Na^+ homeostasis during salt restriction, but is essential for the stimulatory effect of alkalosis on the upregulation of the apical Cl^-/HCO_3^- exchanger pendrin. Insufficient function of AE4 can cause life threatening hypochloremic metabolic alkalosis during base loading conditions (e.g. vomiting).

FR-PO606

MAGE-D2 Is Required for a Normal Cell Surface Expression of NHE3 Protein

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Background: We recently showed that mutations in *MAGE-D2* cause polyhydramnios leading to preterm birth and a severe but transient form of antenatal Bartter's syndrome (transient aBS). Reduced expression of the sodium–chloride transporters NKCC2 and NCC was shown in vivo and in vitro and explains massive salt losing (Laghmani et al, N Engl J Med. 2016). The absence of metabolic alkalosis however, which is pathognomonic feature of aBS, suggests that additional transporters may be affected. One possible explanation is that MAGE-D2 also regulates NHE3, the predominant isoform responsible for apical membrane Na(+)/H(+) exchange in the proximal tubule and thick ascending limb. Consequently, the aim of the present study was to investigate the potential role of MAGE-D2 in NHE3 biogenesis.

Methods: Protein-protein interaction was assessed by co-immunoprecipitation (COIP) assay and proximity ligation assay (PLA). NHE3 protein expression was monitored in transiently transfected HEK293 cells by immunoblotting. Stability of NHE3 protein was assessed by cycloheximide chase assay. We studied the effects of wild type MAGED2 and mutant R446CMAGE-D2 on total and cell surface expression of NHE3. In addition, the role of endogenously expressed MAGE-D2 role was investigated by small interfering RNA.

Results: CO-IP assays in renal cells showed that MAGE-D2 WT interact physically with NHE3. Accordingly, PLA revealed that MAGE-D2 is close to NHE3 in renal cells. Interestingly, R446CMAGE-D2, a missense mutation identified in a transient aBS patient, co-expression significantly decreased NHE3 cell surface expression (48.8% from the control, *P value* = 0.0172). Analogous to R446CMAGE-D2, knockdown of endogenous MAGE-D2 by small interfering RNA also decreases NHE3 cell surface abundance. Interestingly, in contrast to NKCC2 and NCC, MAGE-D2 co-expression did not affect total NHE3 protein expression. Moreover, cycloheximide chase assays (CHX) showed that in cells over expressing MAGE-D2, stability of NHE3 is not affected.

Conclusions: Our findings show that MAGED2 specifically promotes the cell surface expression of NHE3. Importantly, our data indicate that MAGED2 differentially affects multiple salt transporters in the nephron, thus explaining the severe phenotype as well as the absence of metabolic alkalosis.

FR-PO607

14-3-3 Epsilon Regulates NPT2a Activity in the Renal Proximal Tubule

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Background: 14-3-3 is an adapter protein implicated in the regulation of a large spectrum of signaling pathways. We have demonstrated an increased association between the Na-phosphate cotransporter type 2a (NPT2a) and 14-3-3 epsilon in the absence of the Na-H Exchanger Regulator Factor 1 (NHERF1) in proximal tubule cells. We hypothesize that 14-3-3 epsilon associates with a phosphorylated residue in the carboxy-terminal PDZ-1 binding motif of NPT2a and inhibits NHERF1-mediated Npt2a forward trafficking to the apical membrane.

Methods: We generated cDNA constructs modifying the threonine residue in the NPT2a PDZ-1 binding motif "TRL" to either mimic phosphorylation (T635D, T635E) or prevent phosphorylation (T635A). We combined these wild type and mutant NPT2a cDNAs with NHERF1 FL or 14-3-3 epsilon FL in IRES-containing bicistronic mammalian expression vectors. We then transiently transfected these constructs in NHERF1-deficient opossum kidney (OKH) cells and assessed membrane expression with confocal fluorescent microscopy and sodium-dependent phosphate cotransport activity with ^{32} P phosphate uptake assays.

Results: NPT2a FL and NHERF1 FL exhibited membrane co-localization. Phosphomimic NPT2a (DRL) appears as cytosolic punctate regions with no NHERF1 FL co-localization. Phosphomimic NPT2a (ERL) and non-phosphomimic NPT2a (ARL) exhibit both reduced membrane localization (compared to NPT2a FL) and cytosolic punctate regions but neither co-localized with NHERF1 FL. ^{32} P uptake assays corroborated the confocal immunofluorescence with a 7-fold increase in phosphate uptake in OKH cells expressing NPT2a FL and NHERF1 FL versus water-transfected OKH cells. NPT2a ERL and NPT2a ARL with NHERF1 had a 2-fold increase in phosphate uptake versus water-transfected OKH cells. NPT2a FL and 14-3-3 epsilon FL do not exhibit cytosolic co-localization. NPT2a phosphomimics (DRL & ERL) both exhibit reduced membrane localization and cytosolic punctate expression, but no co-localization with 14-3-3 epsilon.

Non-phosphomimic NPT2a (ARL) exhibits no membrane expression or co-localization with 14-3-3 epsilon FL.

Conclusions: These studies demonstrate that the phosphorylation state of T635 in the PDZ binding motif of NPT2a is a determinant in the molecular switch between NHERF1 and 14-3-3 epsilon regulation of the trafficking and functional activity of the cotransporter.

Funding: Veterans Affairs Support

FR-PO608

The Diuretic Actions of SGLT2 Inhibitors and Loop Diuretics Induce Different Compensating Mechanisms

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Background: We recently reported that SGLT2 inhibitor ipragliflozin (Ipra) exhibits a sustained diuretic and natriuretic tone that activates compensatory increases in fluid and food intake, and solute-free water reabsorption to stabilize body fluid volume (Am J Physiol Renal Physiol 2018, ASN Kidney Week 2018). Here we determined whether loop diuretics activate similar compensatory mechanisms.

Methods: Sprague-Dawley rats were treated by oral gavage with vehicle (Veh), loop diuretic furosemide (FR) [50mg/kg] or Ipra [5mg/kg] (n= 4-8) in metabolic cages for 1 week. Bioimpedance spectroscopy (ImpediVet) was used to assess body water on days 0 and 7.

Results: FR and Ipra increased urine volume (Veh 18±2, FR 27±3, Ipra 31±2 mL/day [average of 7 days], ANOVA p=0.006), but FR did not increase fluid intake (41±4, 37±6, 51±5 mL/day, p=0.188) and food intake (23±1, 8±3, 23±3 mL/day, p=0.009). As a result, FR significantly decreased fluid balance (fluid intake-urine volume) (23±2, 10±3, 21±4 mL/day, p=0.010). Urine vasopressin (1.5±0.3, 0.7±0.3, 2.4±0.4 ng/day, day 3, p=0.024) and renal solute-free water reabsorption (84±10, 42±11, 128±7 mL/day, day 7, p<0.001) were decreased in the FR group and increased in the Ipra group. Serum osmolality was similar among the groups (307±3, 311±3, 305±2 mOsm/kgH_2O, day 7, p=0.357). The change in total body water (+8±7, -34±8, -5±3 mL, from day 0 to day 7, p<0.001) and creatinine clearance (5.8±0.3, 2.7±0.6, 5.6±0.2 L/day, day 7, p=0.025) were significantly decreased in the FR group.

Conclusions: The SGLT2 inhibitor maintained body fluid volume and renal function. The loop diuretic decreased both parameters with the impaired solute-free water reabsorption unexpectedly being associated with a lack of compensatory increases in vasopressin secretion and fluid intake.

Funding: Government Support - Non-U.S.

FR-PO609

The Stimulatory Role of SPAK Kinase in the Regulation of the Large Conductance Ca^{2+}-Activated Potassium (BK) Channels Protein Expression in Kidney

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Background: SPS1-related proline/alanine-rich kinase (SPAK) and the oxidative stress-responsive kinase 1 (OSR1) have been shown to be the downstream kinases of with-no-lysine (WNK). SPAK/OSR1 has been shown to mediate the regulation of WNK kinase in cation-chloride cotransporter including sodium chloride cotransporter (NCC) and potassium chloride cotransporter (KCC), etc. In addition, previous studies reported that WNK4 inhibits BK channel activity and protein expression by enhancing BK degradation through stimulating ERK 1/2 and p38 signaling pathway. One previous study showed that SPAK/OSR1 suppressed BK channel activity in *Xenopus* oocytes over-expressing SPAK/OSR1. It remains largely unknown whether SPAK/OSR1 modulate the BK protein expression in kidney tissues. Thus, in this study we have investigated the effects of SPAK kinase on renal BK protein expressions in both mammalian cells and mouse kidney.

Methods: SPAK KO mice, ERK1 global KO mice, western blot analysis, cell culture, and siRNA knock-down experiments were used in this study.

Results: When Cos-7 and HEK 293 cells were over-expressed with SPAK plasmids, BK protein expressions were increased while decreasing ERK 1/2 phosphorylation in a dose-dependent manner, whereas the cells were transfected with SPAK siRNA, BK protein expressions were decreased while increasing ERK 1/2 phosphorylation in a dose-dependent manner. In SPAK mice, BK protein abundance was decreased while increasing ERK 1/2 phosphorylation. In addition, in ERK 1 KO mice BK protein abundance was increased while dramatically increasing SPAK phosphorylation. In addition, WNK4 inhibited BK protein expression while increasing ERK 1/2 phosphorylation.

Conclusions: These data suggested that SPAK signaling positively regulates BK protein expression through negatively modulating ERK 1/2 phosphorylation, potentially by reducing BK degradation.

Funding: Veterans Affairs Support

FR-PO610

The Impact of TRPV-1 Genetic Polymorphisms on Serum Sodium Concentration in Elderly Patients

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Background: Disorders of water balance, reflected as serum sodium concentration, are common in clinical practice but their pathophysiology remains incompletely understood. An N-terminal variant of transient receptor potential vanilloid-1 (delta N-TRPV-1) is important for mammalian central osmosensory transduction in hypothalamic magnocellular neurosecretory cells (MNCs) and is activated by hypertonicity, thus stimulating pituitary AVP secretion. Nevertheless, TRPV-1 single nucleotide polymorphisms (SNPs) have not yet been studied in relation to human osmoregulation.

Methods: We genotyped four common TRPV-1 SNPs in 507 acutely admitted elderly patients and 2480 ambulatory elderly patients, who were respectively at high- and low risk for hyponatremia. These SNPs include rs8065080 (I585V), rs224534 (T469I), rs222748 (H167H) and rs222749 (P91S). The effect of TRPV-1 SNPs on serum sodium concentration and the risk of hyponatremia was examined using multiple linear regression analysis and multiple logistic regression analysis. Haplotype analysis was employed to test the effect of combinations of TRPV-1 SNPs.

Results: In both cohorts, carriership of rs8065080, rs224534 and rs222748 did not significantly influence serum sodium concentrations. In acutely admitted elderly patients, univariate analysis demonstrated that serum sodium levels of rs222749 carriers were lower than of non-carriers, both in the entire cohort (133.9 ± 6.0 versus 135.7 ± 6.4 mmol/L, p=0.049) and in Western-European patients (133.7 ± 6.0 versus 135.7 ± 6.1 mmol/L, p=0.028). Acutely admitted patients rs222749 carriers were more likely to be included in the lowest sodium tertiles (serum Na <137 mmol/L; OR 2.54; 95% CI 1.18 - 5.34). In multiple linear regression analysis, carriership of the rs222749 allele was an independent predictor of serum sodium concentration in acutely admitted elderly patients but not in ambulatory patients.

Conclusions: In view of data from previous in vitro studies we hypothesize that rs222749 involves a gain-of-function mutation through enhanced delta N-TRPV-1 expression in MNCs, leading to increased pituitary AVP release and lower serum sodium levels in vulnerable patients.

Funding: Clinical Revenue Support

FR-PO611

ARL15 Regulates CNNM2-Dependent Mg^{2+} Transport by Modulating Its N-Linked Glycosylation

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Background: A large genome-wide association study identified that ARL15, a small GTP-binding protein, is associated with urinary Mg^{2+} excretion. Within the kidney, ARL15 is highly expressed in the thick ascending limb (TAL) and distal convoluted tubule (DCT), where Mg^{2+} reabsorption is tightly regulated. However, the exact function of ARL15 and the mechanism by which ARL15 regulates renal Mg^{2+} handling are still unknown.

Methods: To identify protein-interaction between ARL15 and Cyclin M (CNNM) proteins, proximity-dependent biotin identification (BioID) and co-immunoprecipitation were performed. Immunohistochemistry were used to investigate co-localization in mouse kidney and human embryonic kidney (HEK293) cells. Furthermore, cell surface biotinylation and $^{25}Mg^{2+}$ uptake assays were used to assess cell surface expression of CNNM2 and Mg^{2+} transport activity. The glycosylation pattern of CNNMs was determined by far lectin Western blot and glycosidase assays.

Results: We identified members of the CNNM family as direct interaction partners of ARL15 by BioID. Immunoprecipitation with truncated CNNM2 proteins indicated that ARL15 interacts with CNNM2 at its carboxyl-(C)-terminal conserved CBS domain. CNNM2 and ARL15 co-localize in the DCT. Interestingly, overexpression of ARL15 in HEK293 cells showed subcellular localization in the Golgi-apparatus and resulted in an increased N-glycosylation of CNNM proteins. This ARL15-mediated glycosylation was Mg^{2+}-sensitive and encompassed hybrid and complex glycosylation. The functional consequences of ARL15-dependent glycosylation were examined by $^{25}Mg^{2+}$ uptake experiments. ARL15 increased $^{25}Mg^{2+}$ uptake via CNNM2 by increasing its cell surface expression.

Conclusions: ARL15 increases CNNM2 plasma membrane expression by regulating its N-glycosylation pattern. Altogether, our results establish ARL15 as novel regulatory mechanism of Mg^{2+} transport within the DCT.

Funding: Government Support - Non-U.S.

FR-PO612

Phenotype of Ksp-Cadherin Deficient Mice: Normal Kidney Development but Delayed Maturation of Maximal Urinary Concentrating Ability

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Background: Ksp-cadherin is a largely kidney-specific member of the cadherin superfamily of cell adhesion molecules. Despite ubiquitous basolateral expression throughout the tubular nephron its function remains unknown.

Methods: To address this question we have generated Ksp-cadherin deficient mice (Ksp-null) by introducing a premature stop codon into the second exon of the Ksp-cadherin gene.

Results: Homozygous Ksp-null animals were born at expected frequencies and were not overtly different from age- and gender-matched wild-type (WT) controls. Kidneys from neonate and adult Ksp-null and WT mice had no discernible differences in the ultrastructural organization of nephrogenic progenitors or mature nephrons. Analysis of E-cadherin and Na/K-ATPase indicate that E-cadherin expression is not modified to compensate for Ksp-cadherin loss and that epithelial cell polarity is unaffected. Serum electrolytes, total CO_2, BUN, and creatinine levels were not significantly different between the two groups. Under basal conditions 10 week-old Ksp-null animals produced a urine that was significantly less concentrated than that from a matching WT cohort (1463 ± 219 vs 2184 ± 164 mOsm respectively; P=0.0249). After 24 hrs of water deprivation, similarly aged Ksp-null animals were unable to concentrate their urine to the same extent as their WT counterparts (3283 ± 69 vs 3840 ± 112 mOsm respectively; P=0.0017). Expression analysis of NKCC2, UTA1-3, UTB, AQP1+2, V2R, ROMK, CLCK1, and UMOD indicated that the concentrating defect was not due to altered expression of the principal proteins involved in the generation of the cortico-medullary osmotic gradient. Immunolocalization studies suggested that the defect may be due to misexpression of AQP2 in the IMCD of the Ksp-null mutants. Under both baseline and water-restricted conditions 10 month-old Ksp-null mutants were able to concentrate their urine to the same extent as similarly aged WT animals, suggesting that the defect in urinary concentrating ability in the 10 week-old Ksp-null mice is due to a developmental delay.

Conclusions: In conclusion Ksp-cadherin is not essential for nephron formation or nephron segment delineation. Its null mutation does, however, significantly delay the maturation of maximal urinary concentrating ability.

Funding: NIDDK Support

FR-PO613

Tacrolimus Improved Symptoms of Type 4 Bartter Syndrome Model Mice

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Background: Type 4 Bartter syndrome (BS) is a hereditary tubular disease characterized by salt-losing polyuria, hypokalemia, and metabolic alkalosis. Because barttin (coded by *Bsnd* gene, which is a disease causing gene of type 4 BS) is expressing from thick ascending limbs of Henle's (TAL) to collecting ducts, the function of distal nephron is widely impaired and the symptoms of type 4 BS are generally very severe. Although potassium replacement therapy has been mainly used for hypokalemia, there is no fundamental treatment for type 4 BS. It has been reported that calcineurin inhibitors enhance phosphorylation of sodium (Na) -potassium (K) -2 chloride (Cl) cotransporter (NKCC2) and Na-Cl cotransporter (NCC), which are key sodium transporters in TAL and distal convoluted tubule, respectively. In this study, we hypothesized that tacrolimus, a calcineurin inhibitor, would increase in phosphorylation of NKCC2 and NCC, and improve symptoms of type 4 BS.

Methods: *Bsnd*$^{neo\,/\,neo}$ mice, which is hypomorphic of barttin, were used as a model of type 4 BS. *Bsnd*$^{neo/neo}$ showed severe polyuria, hypokalemia, and metabolic alkalosis. Tacrolimus was administered subcutaneously once a day. After a week administration of tacrolimus, blood sampling and kidney harvest were performed. Phosphorylation of NKCC2 and NCC was evaluated by Western blotting. For the investigation of urine volume and urinary K excretion, urine was collected in a urine collection cage after a single intraperitoneal administration of tacrolimus.

Results: After a week administration of tacrolimus, serum potassium levels were significantly increased in *Bsnd*$^{neo\,/\,neo}$ mice. However, improvement of metabolic alkalosis was not observed after tacrolimus treatment. After single administration of tacrolimus, urinary K excretion was significantly reduced, and urine volume also tended to be decreased. Phosphorylation of NKCC2 and NCC was significantly increased in *Bsnd*$^{neo\,/\,neo}$ mice.

Conclusions: Tacrolimus administration ameliorated hypokalemia in type 4 BS model mice by suppressing urinary K excretion. Increase in phosphorylation of NCC and NKCC2 would contribute to the improvement of hypokalemia in type 4 BS. Tacrolimus might be effective for the treatment of type 4 BS.

Funding: Government Support - Non-U.S.

FR-PO614

Different NKCC2 Amino Acid Sequences Between 129/Sv and C57BL/6 Mice Affect Analysis of NKCC2 Phosphorylation with Phosphoform-Specific Antibodies

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Background: The furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) of the thick ascending limb is critical for the renal control of electrolyte and fluid homeostasis. The activity of NKCC2 is regulated via phosphorylation of several serine and threonine (T) residues in the N-terminal tail of the co-transporter. To study NKCC2 function, phosphoform-specific antibodies directed against these phosphorylation sites (e.g. T96 and T101) have been developed and applied in studies on mouse models. The most frequently used mouse strains are 129Sv and C57BL/6 mice. Surprisingly, when we tried to detect phosphorylated NKCC2 (pNKKC2) with anti pT96/pT101 NKCC2 antibodies, we detected a strong pNKCC2 signal only in kidneys from 129Sv mice but not in kidney from C57BL/6 mice. In the latter, only some unspecific cross-reactivity of the pNKCC2 antibodies with the phosphorylated thiazide-sensitive NaCl cotransporter was seen.

Methods: To address this unexpected finding, we compared 129Sv and C57BL/6 mice via database analysis, metabolic cage experiments, quantitative RT-PCR and immunoblotting.

Results: Database analysis revealed that C57BL/6 mice have a five amino acid deletion (ΔT96-N100) in NKCC2, which lies in the region of the epitopes recognized by most anti-pNKCC2 antibodies. Although we observed strain differences in urinary Ca^{2+} and Mg^{2+} excretion and in the expression of several renal ion transporters and channels between 129Sv and C57BL/6 mice, these differences are likely not related to the five amino acid deletion in NKCC2. When we crossbred 129Sv and C57BL/6 mouse strains, mice of the F2 generation with the deletion (ΔT96-N100 mice) and mice without the deletion (control mice) were phenotypically similar. In particular, there were no differences in NKCC2 mRNA and protein abundances between the ΔT96-N100 and control mice. Nevertheless, pNKCC2 remained barely detectable in ΔT96-N100 mice using the antibodies against the full-length epitope.

Conclusions: Our study reports an important difference between the NKCC2 amino acid sequences of 129Sv and C57BL/6 mice that does not appear to significantly affect NKCC2 function, but strongly interferes with the detection of NKCC2 phosphorylation via phosphoform-specific antibodies. This needs to be considered when studying NKCC2 regulation in different mouse strains and when cross-breeding mice.

FR-PO615

MAGE-D2 and HSP40 Protect NKCC2 Against Hypoxia-Induced Endoplasmic Reticulum-Associated Degradation

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Background: We recently showed that *MAGED2* mutations cause polyhydramnios with prematurity and a severe but transient form of antenatal Bartter's syndrome associated with inappropriate expression of the sodium–chloride transporters NKCC2 and NCC (Laghmani et al, N Engl J Med. 2016 May 12;374(19):1853-63). However, the transient nature of the disease remains unclear. We speculated that through its interaction with HSP40, MAGE-D2 protects the co-transporters from endoplasmic reticulum (ER) associated degradation activated by ER stress due to tissue hypoxia during early pregnancy, an effect that becomes less relevant later. In support of this notion, we found that HSP40 interacts with NKCC2 at the ER. Consequently, the aim of the present study was to investigate the effect of hypoxia on NKCC2 biogenesis and explore the potential role of MAGE-D2 and HSP40 in this process.

Methods: Cellular hypoxia was induced chemically by incubating HEK cells for 16-24 hours with cobalt chloride ($CoCl_2$). NKCC2 protein expression was monitored by immunoblotting in HEK cells transfected with the co-transporter. NKCC2 stability was assessed by cycloheximide chase assay.

Results: Similar to MAGE-D2, HSP40 co-expression increases also NKCC2 biogenesis. Subjecting HEK cells, transfected either stably or transiently with NKCC2, to a hypoxic microenvironment chemically induced by $CoCl_2$ (200-600 μM) significantly decreased total NKCC2 protein expression in a dose-dependent fashion. Cycloheximide chase assay revealed that in cells subjected to chemical hypoxia, NKCC2 stability and maturation are decreased. Interestingly, the effect of hypoxia on NKCC2 maturation was more severe following HSP40 or MAGE-D2 knockdown. Even more impressive, simultaneous knockdown of MAGE-D2 and HSP40 strikingly aggravated the effect of cellular hypoxia on NKCC2 maturation (> 99%).

Conclusions: Our data indicate that cellular hypoxia chemically induced by CoCl2 alters NKCC2 stability and maturation. Most importantly, our findings strongly suggest that MAGE-D2 cooperates with HSP40 to protect NKCC2 against ER associated degradation induced by cellular hypoxia, which could explain, at least in part, the transient nature of antenatal Bartter's syndrome in carriers of *MAGED2* mutations.

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FR-PO616

Actinin-4 (ACTN4) Interacts with ALMS1 and NKCC2 in Thick Ascending Limbs (TAL) to Regulate NKCC2 Trafficking

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Background: Loss-of-function mutations in the *ALMS1* gene cause Alström syndrome, characterized by hypertension, early onset obesity, type 2 diabetes and progressive loss of renal function. Single nucleotide polymorphisms (SNPs) in the *ALMS1* gene are associated with decreased renal function (lower GFR) and increased pulse pressure in the general population. However, the role of ALMS1 in the control of renal function is unclear. We recently found that ALMS1 physically interacts with the apical renal Na/K/2Cl cotransporter NKCC2 in the TAL, where it mediates its endocytosis. However, the molecular mechanisms by which ALMS1 mediates NKCC2 endocytosis are unclear. We hypothesized that ALMS1 is part of a protein complex that binds apical NKCC2 and promotes its endocytosis and recycling.

Methods: To begin studying these mechanisms we used a targeted proteomics screen to identify new binding partners for ALMS1 in the TAL as well as immuno-precipitation.

Results: GST-pull down with the C-terminus of ALMS1 identified several trafficking proteins. One of them, Actinin-4 (ACTN4), is involved in endocytosis and its mutation causes focal segmental glomerular disease. GST-ACTN4 (full length) pulled down both ALMS1 and NKCC2 from TALs. Immunoprecipitation of NKCC2 followed by mass spectrometry identified ACTN4. The role of ACTN4 in the nephron is unclear so we studied its localization. ACTN4 was abundant in glomeruli but also localized in cells along the nephron in a punctate vesicular pattern. ACTN4 was located in TALs (co-labeled with NKCC2) and co-localized with ALMS1 n the subapical space. To study the role of ALMS1 and ACTN4 we generated a mouse line with doxycycline (Dox) inducible nephron-specific deletion of ALMS1 (Dox-inducible-Pax8-Cre-ALMS1fl/fl). 4 weeks after finishing Dox treatment, ALMS1 expression in medullary tubules was decreased by 78±14% ($p<0.05$). Interestingly, ACTN4 expression was also decreased by 45±9% ($p<0.05$) in nephron specific ALMS1 KO, compared to doxycycline treated controls (ALMS1fl/fl). In isolated mouse TALs, the surface to total NKCC2 ratio was increased by 55±19% ($p<0.05$), suggesting decreased retrieval from the surface.

Conclusions: We conclude that ACTN4 binds both ALMS1 and NKCC2 and ALMS1 is required for proper NKCC2 trafficking. Our data suggest that ACTN4 plays a role in tubular Na absorption in addition to its role in podocytes.

Funding: NIDDK Support

FR-PO617

N-Terminal Phosphorylation of Kidney Na-K-2Cl-Cotransporter Attenuates Its Endocytosis

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Background: The renal Na-K-2Cl-cotransporter (NKCC2) of the thick ascending limb (TAL) is critical for renal salt handling. Its activity is stimulated by phosphorylation of conserved N-terminal threonine and serine residues (T96, T101, T114, and S126), although the underlying mechanisms are not entirely clear. We hypothesized that NKCC2 phosphorylation interferes with its clathrin-mediated endocytosis.

Methods: Cellular distribution of NKCC2 and its phosphorylated form (pNKCC2) was evaluated in rat kidney and cultured rat TAL cells by high-resolution immunofluorescence, electron microscopy and biochemical tissue fractionation by sucrose gradient. Association of NKCC2 and pNKCC2 with clathrin was studied by binding assays.

Results: Labeling of rat kidney sections for NKCC2 revealed its even distribution between the luminal membrane and apical vesicular compartment, whereas pNKCC2 resided predominantly in the luminal membrane. Analysis of NKCC2, pNKCC2 and clathrin distribution in apical membrane fragments obtained from cultured TAL cells using the rip/flip technique showed regular co-localization of NKCC2- and clathrin immunogold signals, whereas pNKCC2 signal localized to clathrin-negative electron-dense membrane domains containing the lipid raft marker flotilin-1. In line with this, isolation of detergent-resistant membrane rafts from rat kidney tissue using extraction with Triton X-100 and subsequent sucrose gradient centrifugation revealed co-distribution of pNKCC2 and flotilin-1 signals in rafts-containing low-density gradient fractions, whereas clathrin signal was present in non-raft high-density fractions. GST pull down assays showed interactions of clathrin with recombinant N-terminal NKCC2 mutants mimicking its dephosphorylation (S/T->A), whereas mutants mimicking the phosphorylated N-terminus (S/T->D) did not bind clathrin. Acute *in vivo* stimulation of NKCC2 phosphorylation by treating vasopressin-deficient Brattleboro rats with desmopressin (1ng/kg body weight for 30 min) attenuated its co-immunoprecipitation with clathrin (-72%, $p<0.05$) and increased NKCC2 surface expression (+24%, $p<0.05$).

Conclusions: In sum, these results suggest that NKCC2 phosphorylation inhibits its clathrin-mediated NKCC2 endocytosis resulting in increased NKCC2 surface expression and activity.

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FR-PO618

Role of Vasopressin V2 Receptor Signaling in NKCC2 Regulation in Diabetes Mellitus

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Background: Previous studies have reported that vasopressin V2 receptor is present in thick ascending limb (TAL) of loop of Henle and can regulate the abundance of Na-K-2Cl cotransporter (NKCC2). Nonetheless, the upstream signaling and the pathological significance in a disease state remains obscure. We aimed to address the role of vasopressin V2 signaling in TAL in diabetic kidney disease.

Methods: We compared the levels of aquaporin 2 and NKCC2 in the membrane fraction of the kidney between db/+ and db/db mice. We then orally administered tolvaptan, vasopressin V2 receptor antagonist, to db/+ and db/db mice for two weeks and evaluated the changes in aquaporin 2 and NKCC2. To test the role of V2 signaling in humans, we obtained urinary exosomes from diabetic subjects treated with tolvaptan and compared the levels of aquaporin 2 and NKCC2 before and after the treatment.

Results: The administration of tolvaptan reduced aquaporin 2 abundance in db/+ mice. We also found that NKCC2 abundance was reduced by tolvaptan in this model. To evaluate the role of vasopressin signaling in diabetic kidney, we compared their levels between db/+ and db/db mice, and found that both aquaporin 2 and NKCC2 were significantly elevated in db/db mice (1.87-fold increase for aquaporin 2; $P = 0.03$, and 1.90-fold increase for NKCC2; $P<0.001$). Moreover, these levels were significantly reduced by tolvaptan administration, indicating the contribution of vasopressin V2 signaling in the kidney in db/db mice. To extend these observations into humans, we evaluated NKCC2 levels in urinary vesicles in subjects with diabetic kidney disease who received tolvaptan. Among 15 subjects examined, six showed response to tolvaptan, resulting in reduced aquaporin 2 levels in urinary exosome. In these cases, NKCC2 levels tended to reduce after the treatment.

Conclusions: Vasopressin V2 receptor signaling is involved in the regulation of NKCC2, which can be dysregulated in the kidney of diabetes mellitus.

FR-PO619

Functional Substrates of Vasopressin-Responsive PARylation in Kidney Collecting Duct Cells

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Background: Poly (ADP-ribose) polymerases (PARPs) regulate cellular progress, such as cell cycle, cell proliferation and differentiation, through molecular regulation of protein-protein interactions and protein stability. In our previous study, cellular poly ADP-ribosylation (PARylation) was induced by vasopressin treatment in mpkCCD cells. The present study aimed to examine regulation of PARylation as a part of vasopressin signaling in renal collecting duct (CD) cells.

Methods: We examined 1) vasopressin-responsive PARylation in mpkCCD cells using pulldown assay of biotin-conjugated NAD^+ and immunoprecipitation assay using PAR (poly ADP-ribose) antibody; 2) immunoblotting for PARP1 abundance in nuclei and cytoplasm. Substrate proteins of PARP1 in kidney CD cells were identified from data mining in multiple public databases. Functional enrichment of PARP1 substrates was analyzed using Metascape.

Results: dDAVP (10^{-9} M, 24 h) remarkably increased abundance of total PARylated proteins in mpkCCD cells in biotin-NAD^+ pulldown and PAR immunoprecipitation assays. Interestingly, the cleavage of PARP1 was induced by both short-term (2 h, 6 h) and long-term (24 h, 48 h) dDAVP (10^{-9}M) treatment, suggesting that vasopressin signaling affects PARP1 action. Immunoblots using subcellular fractions of mpkCCD cells confirmed the cleaved form of PARP1 produced by dDAVP treatment was exported to the cytosolic fraction. dDAVP-induced AQP2 mRNA and protein expression was significantly attenuated under siRNA-mediated PARP1 knockdown conditions in mpkCCD cells. From a data mining approach, we identified 752 substrate proteins of PARP1 and 171 proteins interacting with PARP1 in kidney CD cells. Among them, 72 proteins were found across all the matches, suggesting as putative targets of PARP1 in the kidney collecting duct. Functional enrichment analysis revealed that these PARP1 substrates are involved in DNA damage repair, gene transcription, insulator function and DNA methylation, which have been known as cellular functions of PARP1.

Conclusions: Vasopressin-responsive PARylation is accompanied with remarkable changes in protein abundance and cleavage of PARP1 in kidney CD cells. Bioinformatic approaches identified putative PARP1 substrates and functional clustering of the identified substrates that could be involved in vasopressin signaling in the kidney CD cells.

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FR-PO620

SNX27, Interacting with AQP2 in a PDZ-Dependent Manner, Regulates the Stability of AQP2 Protein

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Background: Sorting nexin 27 (SNX27), a PDZ domain-containing protein, is known to cooperate with a retromer complex, regulating the trafficking and stability of membrane proteins. The carboxyl-terminus of aquaporin-2 (AQP2c) has the class I PDZ-interacting motif (X-T/S-X-Φ), however, interaction between SNX27 and AQP2 has

not been studied. We aimed to examine the interaction of SNX27 for the regulation of AQP2.

Methods: GST-SNX27 constructs [SNX27-Full Length, Δ(PX+FERM), ΔFERM, ΔPDZ, and Δ(PDZ+PX)] were generated, and the purified proteins were incubated with His-tagged AQP2c protein *in vitro*. Coimmunoprecipitation (Co-IP) assay was performed using rat kidney inner medullary collecting duct (IMCD) tubule suspension. Immunoblotting and immunolabeling were carried out in SNX27 siRNA-transfected mpkCCD cells. Autophagy was examined using autophagosome marker (mRFP-GFP-LC3).

Results: Co-IP and GST pull-down assays demonstrated that PDZ domain of SNX27 directly interacted with AQP2c. Immunocytochemistry of HeLa cells co-transfected with Flag-SNX27 and HA-AQP2 revealed that AQP2 co-localized with the intact SNX27, suggesting that a PDZ domain of SNX27 is required for the interaction with AQP2. Removal of PDZ domain (SNX27-ΔPDZ) induced accumulation of AQP2 at the perinuclear region in HeLa cells. Immunohistochemistry revealed colocalization of SNX27 and AQP2 at both cytoplasm and plasma membrane in rat kidney CD cells. Subcellular redistribution of SNX27 under dDAVP stimulation/withdrawal was almost identical with AQP2 in rat kidney. Cell surface biotinylation assay showed that dDAVP-induced AQP2 translocation to the apical plasma membrane of mpkCCD was not affected by SNX27 knockdown. Immunoblotting revealed that dDAVP-induced AQP2 up-regulation was significantly blunted by SNX27 knockdown, whereas qRT-PCR showed no change of AQP2 mRNA expression. During dDAVP withdrawal, decrease of AQP2 expression in mpkCCD cells with SNX27 knockdown was significantly attenuated by chloroquine, but not by MG132. Moreover, SNX27 knockdown remarkably induced autophagy in mpkCCD cells expressing LC3.

Conclusions: SNX27, directly interacts with AQP2 in a PDZ-dependent manner, is likely to regulate stability of AQP2 protein. It acts as a component of the AQP2 controlling machinery, at least in part, through regulation of autophagy-lysosomal degradation of AQP2.

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FR-PO621

Possible Involvement of Upregulated Arginine Vasopressin in Fluid Retention on Peritoneal Dialysis

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Background: Fluid retention is a typical complication of peritoneal dialysis (PD), and interferes with the safety and long-term delivery of PD. Arginine vasopressin (AVP), which is synthesized in the hypothalamus, is involved in water reabsorption in the collecting ducts and could be involved in fluid retention. Here, we examined hypothalamic AVP synthesis during PD in both basic and clinical research.

Methods: 1) First, after administration of 3% hypertonic saline (HTN) as dialysis solution for a short-term dwell or polyethylene glycol (PEG) as dialysis solution for a long-term dwell, we evaluated the fluorescence intensity of AVP-enhanced green fluorescent protein (eGFP) in the hypothalamus. The intensity of eGFP offers a quantitative indicator of AVP synthesis in transgenic rats. Second, we quantified Fos-like immnoreactive (IR) cells in several brain regions known to be involved in maintaining fluid homeostasis by control of AVP synthesis and/or having interactions with the hypothalamus. 2) We measured plasma AVP levels, plasma osmolality and urinary osmolality in 20 PD patients during visits.

Results: 1) Fluorescence intensities for eGFP were significantly increased in the hypothalamus after administration of HTN and PEG. Immunohistochemistry for Fos revealed activation of several brain areas after administration of HTN and PEG. 2) Plasma AVP levels (5.5 ± 0.6 pg/mL) and plasma osmolality (303.4 ± 1.6 mOsm/kgH_2O) increased significantly in PD patients, and these values were correlated (Rho = 0.56, P = 0.02, n= 20). In addition, a positive correlation was observed between plasma AVP levels and urine osmolality (Rho = 0.65, P = 0.03). Given these findings, we considered that the physiological function of AVP remained in PD patients.

Conclusions: To the best of our knowledge, this represents the first report to reveal an upregulation of hypothalamic AVP during PD by performing both basic and clinical research. Upregulation of hypothalamic AVP could induce fluid retention. These findings provide potential insights into fluid management for PD patients.

FR-PO622

WNK1 as a Central Osmosensor for Vasopressin Release and Water Homeostasis

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Background: The brain circumventricular organs organum vasculosum lamina terminalis (OVLT) and subfornical organ (SFO) lack blood-brain barrier and function as sensors for systemic osmolality. Hyperosmolality activates neurons in OVLT and SFO, leads to vasopressin production in cell bodies of magnocellular neurons in the paraventricular and supraoptic nuclei of hypothalamus and release through axonal termini in the posterior pituitary. Previous work focused on cell membrane resident proteins such as mechanosensitive channels TRPV1 and V4 as candidates of osmosensors. Results of knockout animal studies yet are conflicting. Compared to membrane proteins by responding to stretch, intracellular proteins may be better positioned to sense cell water content in response to changes in extracellular osmoles. WNK kinases are activated by hyperosmolality. We investigated the role of WNK1 in central osmosensing.

Methods: *Wnk1*-floxed mice were bred with synapsin-Cre mice to generate neuronal-specific *Wnk1*-knockout (KO) mice.

Results: Under *ad lib* water and food intake, average daily urine output was higher in KO mice (n = 6) than in control mice (n = 8) (1.57 ± 0.17 ml vs 1.03 ± 0.15 ml, $p < 0.05$). Daily water intake was also higher in KO than in control (4.84 ± 0.25 ml vs 4.14 ± 0.21 ml, $p < 0.05$). Serum osmolality in KO mice trended higher but not statistically significantly different from control (314 ± 4 vs 307 ± 3 mOsm/kg, p = 0.18). Urine osmolality was lower in KO than in control mice. The pattern of serum and urine osmolality suggests that defects in vasopressin release or action (i.e., diabetes insipidus) rather than primary polydipsia or osmotic diuresis as the cause of polyuria. To further distinguish between these possibilities, mice were water-deprived for 24 hrs. Urine output remained elevated in KO than control mice under water deprivation (1.17 ± 0.13 ml vs 0.63 ± 0.08 ml, $p < 0.05$). Serum osmolality was increased and the difference between KO and control was amplified by water deprivation (329 ± 4 vs 312 ± 3 mOsm/kg, $p < 0.01$). To support the hypothesis of blunted vasopressin release in neuronal *Wnk1*-KO, work is ongoing to measure serum vasopressin and copeptin levels in KO & control mice.

Conclusions: Our results suggest that WNK1 protein may function as an intracellular osmosensor for regulating vasopressin release.

Funding: NIDDK Support

FR-PO623

Functional Characterization of Gain-of-Function Mutations of the V2 Vasopressin Receptor Leading to Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD)

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Background: Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD) is a chromosome X-linked disease associated to gain-of-function mutations of the V2 vasopressin receptor (V2R), a G protein-coupled receptor. NSIAD can be quite severe in affected male children. It is characterized by inability to excrete a free water load, hyponatremia, and undetectable vasopressin circulating levels.

Methods: In this study, we have expressed the wild type V2R and three constitutively active V2R mutants, the R137L, R137C and the F229V in MCD4 cells, a cell line derived from renal mouse collecting duct, stably expressing the vasopressin-sensitive water channel Aquaporin-2 (AQP2).

Results: In cells expressing each active mutant, AQP2 was constitutively localized to the apical plasma membrane, in the absence of vasopressin stimulation. Conversely, in cells expressing the wild type V2R, AQP2 was localized in intracellular vesicles and redistributed to the apical membrane in response to vasopressin. In line with these observations, under basal conditions, osmotic water permeability of each constitutively active mutant was significantly higher compared with that of cells expressing the wild type V2R. Interestingly, specific inhibition of PKA reduced the basal osmotic water permeability only in F229V expressing cells, indicating the activation of a PKA-dependent pathway. Conversely, for the R137L and R137C mutants a PKA-independent signalling leading to redistribution of AQP2 and consequent increase in osmotic water permeability is predicted.

Conclusions: Our findings demonstrate, for the first time, a direct link between the activating mutations of the V2R and the alteration of water permeability in cells expressing V2R mutants providing a rationale for the water balance disturbance observed in NSIAD.

Funding: Government Support - Non-U.S.

FR-PO624

UT-A2-Mediated Water Transport Is Regulated by N-Glycosylation

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Background: Urea transporters (UTs) are transmembrane glycoproteins that facilitate the diffusion of urea across cell membranes, and play a crucial role in the urinary concentrating mechanisms, important for maintaining nearly constant blood plasma osmolality. Renal UTs include: UT-A1 and UT-A3, which are expressed on the apical and basolateral membranes of the inner medullary CD, respectively; UT-A2, localized in the thin descending limb of the inner and outer renal medulla; and UT-B, expressed in the endothelial cells of the descending vasa recta and red blood cells. The X-tal structure of bovine UT-B shows that three monomers assemble to form a homotrimer. Each monomer contains 10 transmembrane helices folded into independent urea channels. Helices 5 and 6 are connected by an extracellular loop that can be glycosylated. Indeed, protein glycosylation is known to modulate protein structure/activity. UT-A2 is glycosylated at Asparagine-210, yielding 45 kDa and 55 kDa glycoforms. Previously, we showed that wild-type mouse UT-A2 (mUT-$A2^{WT}$) enhances water transport when expressed in *Lithobates catesbeianus* oocytes, and that two conserved Threonine residues (T176 and T338) are required for this transport. Here, we investigated the role of glycosylation on UT-A2-mediated water transport.

Methods: First, the N210 residue of mUT-A2 was mutated to glutamine (Q), generating UT-$A2_{N210Q}$. Next, mUT-$A2^{WT}$ and UT-$A2^{N210Q}$ (c-Myc tagged) cRNA, or H_2O was injected into *Lithobates* oocytes. UT-A2 cell surface expression was assessed by biotinylation and western blot analyses, with and without PNGase F. P_f was assessed by placing the oocytes in a hypotonic solution and monitoring the rate of cell swelling with video microscopy.

Results: We observed an immunoreactive band at 34 kDa after treating mUT-$A2^{WT}$ with PNGase F, a molecular weight consistent with unglycosylated monomer. No bands

were detected in the 45-55 kDa range with mUT-A2^{N210Q}, indicating lack of glycosylation. The P_f value for mUT-A2^{WT} (0.0013±0.0001, n=27) was significantly greater than UT-A2^{N210Q} (0.0005±0.00004, n=25) and H_2O oocytes (0.0006±0.00004, n=30).

Conclusions: These results indicate that the oocytes were not only capable of adding N-linked glycans to membrane proteins, but also that this post-translational modification affects activity. This observation is relevant to urine concentration mechanisms.

Funding: Government Support - Non-U.S.

FR-PO625

Drug-Induced Hyponatremia: Vasopressin-2 Receptor-Dependent and -Independent Pathway

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Background: Drugs associated with hyponatremia were traditionally classified into those enhancing vasopressin release and those potentiating the renal action of vasopressin. For the latter mechanism to act, vasopressin-2 receptor would have the pivotal role in activating aquaporin-2 in the collecting duct. However, vasopressin-2 receptor-independent pathways might be activated as well by drugs that induce renal water retention. This preliminary study was undertaken to find antidiuretic drugs acting through vasopressin-2 receptor-independent pathways.

Methods: Five drugs or active metabolites were treated in inner medullary collecting duct suspensions prepared from male Sprague-Dawley rats. The intracellular cAMP levels were determined using a competitive enzyme immunoassay kit to compare the responses with and without tolvaptan (100 nM) cotreatment. Also, dDAVP (10 nM) was used as positive control.

Results: As expected, dDAVP induced an increase in cAMP production (20.7 ± 2.0 vs. 11.4 ± 0.6 pmol/mg protein, P<0.05) Similarly, haloperidol (14.7 ± 0.9 pmol/mg protein, P<0.05), sertraline (18.7 ± 0.9 pmol/mg protein, P<0.05), and carbamazepine (17.3 ± 0.7 pmol/mg protein, P<0.05) had higher levels of cAMP. These responses were almost completely blocked by tolvaptan cotreatment (haloperidol, 8.5 ± 0.5 pmol/mg protein; sertraline, 12.6 ± 1.2 pmol/mg protein; carbamazepine 12.5 ± 0.7 pmol/mg protein, all P<0.05). Notably, the cAMP level was increased by vincristine treatment (16.7 ± 1.6 pmol/mg protein, P<0.05), but not reversed by tolvaptan cotreatment. On the other hand, chlorpropamide did not induce any change in cAMP with and without tolvaptan cotreatment.

Conclusions: As known before, chlorpropamide appears to enhance vasopressin release. Contrary to a previous notion, vincristine may induce water retention via vasopressin-2 receptor-independent pathways. Activation of vasopressin-2 receptor has a role in hyponatremia induced by haloperidol, sertraline, and carbamazepine.

Funding: Government Support - Non-U.S.

FR-PO626

Intracellular Sites of AQP2 S256 Phosphorylation in the Plasma Membrane, Cytoplasmic Vesicles, and the Trans Golgi Network Identified Using Inhibitors of the AQP2 Recycling Itinerary

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Background: Vasopressin-regulated trafficking of aquaporin 2 between cytoplasmic vesicles and the plasma membrane of kidney principal cells is essential for body water homeostasis. VP-induced phosphorylation of AQP2 at serine residue S256 is required for its accumulation at the cell membrane, but the intracellular location(s) where this phosphorylation occurs remains poorly understood. Here, we used strategies to block AQP2 trafficking at different cellular locations in LLC-PK1 cells, and we monitored phosphorylation of AQP2 S256 at these sites using anti-phospho S256 antibodies after vasopressin/forskolin (VP/FK) stimulation.

Methods: Phosphorylation extent and location were assessed by western blotting and immunocytochemistry, respectively.

Results: Methyl-b-cyclodextrin (MBCD) treatment blocks endocytosis, and recycling AQP2 accumulates at the cell surface without an increase in S256 phosphorylation. However, VP/FK applied to MBCD treated cells resulted in a significant increase in S256 phosphorylation, indicating AQP2 can be phosphorylated when present in the plasma membrane. Taxol, an inhibitor of microtubule function, results in AQP2 containing vesicles being scattered throughout the cytoplasm, and inhibits VP-induced membrane accumulation of AQP2. Taxol alone did not affect AQP2 phosphorylation, but VP/FK treatment of taxol exposed cells caused a significant increase in S256 phosphorylation, indicating that AQP2 can be phosphorylated on scattered cytoplasmic vesicles. Finally, AQP2 trafficking is blocked in the peri-nuclear, trans-Golgi network both by incubating cells at 20°C for 2 h or by using the V-ATPase inhibitor bafilomycin. VP/FK stimulated AQP2 phosphorylation significantly under both conditions.

Conclusions: These findings suggest that the VP/FK induced phosphorylation of AQP2 at S256 can occur at various locations during its recycling itinerary to and from the cell surface; at the plasma membrane itself, on cytoplasmic vesicles, or in the trans-Golgi network. Whether protein kinase A is involved in AQP2 S256 phosphorylation in all these locations is unclear, but the ability to dissect different intracellular phosphorylation stations may help to uncover new strategies to regulate AQP2 trafficking in conditions such as nephrogenic diabetes insipidus and hyponatremia.

Funding: NIDDK Support

FR-PO627

Urinary Net Endogenous Acid Production: A Reliable Predictor of Net Acid Excretion

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Background: High acid production and positive acid balance have been associated with progression of chronic kidney disease (CKD) and degenerative aging processes. Endogenous acid production (EAP) equations that most accurately represent net acid excretion (NAE) require analyses of diet and stool unmeasured anions and a research lab to measure titratable acids and bicarbonate, a somewhat complicated research protocol. Being able to evaluate only urinary analytes might be easier. Here, we evaluate the predictive value of urinary measured (EAP) and unmeasured anions (UNEAP) to the measured value of NAE.

Methods: 24 hour urine collections from metabolic balance studies from 15 patients for repeated intervals were performed at the control period (baseline), diet intervention phase, and the recovery phase. Each phase was at least 3 days. NAE was calculated from measured values (= titratable acid + ammonium – bicarbonate). UNEAP was calculated from urinary [(phosphate+chloride)-(sodium+potassium+calcium)] + sulfate (SO4) + total organic acid (OA) production. EAP = urinary SO4+ OA salts. We used mixed effects model with repeated measures to assess agreement between the estimated and measured value of NAE.

Results: Assessment between these measures showed a high correlation between UNEAP and NAE (r=0.85, p<0.001). EAP underestimated the measured value of NAE by 9.7 mEq/d and the difference in the means was statistically significant (p=0.003) with the 95% limits of agreement between the differences being -32.5 mEq/d to 12.9 mEq/d. On the other hand, there was a non-significant difference in the means (3.24 mEq/d) between UNEAP and NAE with the 95% limits of agreement being -25.5 mEq/d to 32.0 mEq/d.

Conclusions: Using only urine measures, UNEAP was a more reliable estimate of NAE compared to EAP. Measures for estimating UNEAP may be less cumbersome than measuring NAE and help promote research into treatments that affect acid balance, such as alkali treatment for CKD.

Funding: Clinical Revenue Support

FR-PO628

Pseudohypobicarbonatemia Induced by Severe Hypertriglyceridemia

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Background: Reports of falsely low serum carbon dioxide (sCO_2) concentration, i.e., pseudohypobicarbonatemia (psHypoHCO$_3^-$) in patients with severe hypertriglyceridemia (hyperTG) have emerged. This phenomenon results from lipid interference in some spectrophotometric analyzers. Our aim was to assess the magnitude and implications of psHypoHCO$_3^-$ in a tertiary care hospital.

Methods: We searched for cases of serum triglycerides (TG) > 1000 mg/dL with a concomitant (measured <24 hrs apart) sCO_2, between 2017 and 2018. We extracted those with $sCO_2 \leq 12$ mEq/L to focus on the more clinically relevant cases. Each measured sCO_2 was compared with the calculated bicarbonate (HCO$_3^-$) from an arterial blood gas (ABG) obtained within 6 hrs of the venous blood draw. PsHypoHCO$_3^-$ was defined as: erroneous HCO$_3^-$ (eHCO$_3^-$) gap = (calculated HCO$_3^-$ - measured sCO_2) > 5 mEq/L.

Results: We identified 1698 events (652 patients) of TG > 1000 mg/dL and a sCO_2 measured on the same day. TG inversely correlated with sCO_2 (R=-0.38, p=0.00001). We found 179 events (59 patients) with sCO_2 < 12 mEq/L. In 104 of those, an ABG was either not available or performed > 6 hrs apart from the venous blood draw. The remaining 75 events included 30 instances (11 patients) of true hypobicarbonatemia and 45 instances (24 patients) of psHypoHCO$_3^-$. Among those with psHypoHCO$_3^-$, the median values of sCO2, calculated HCO$_3^-$, anion gap and eHCO$_3^-$ gap were 8 (<5 – 12), 20 (10 - 28), 21 (15 – 29) and 13 (5 – 19) mEq/L, respectively, whereas the median pH was 7.37 (7.14 - 7.56). True metabolic acidosis was either absent (42%) or spuriously magnified (58%). TG directly correlated with the eHCO$_3^-$ gap (R=0.59, p=0.00004). Acute pancreatitis (56%) and diabetic ketoacidosis (38%) were the most common concomitant disorders but they did not fully account for the eHCO$_3^-$ gap in the psHypoHCO$_3^-$ cases. Additionally, unnecessary HCO$_3^-$ therapy was initiated in 16% and serum lactate was measured in 80% of the psHypoHCO$_3^-$ events (lactate was normal in 72%).

Conclusions: Severe hyperTG can lead to spuriously low sCO_2. The degree of hyperTG correlates with the magnitude of PsHypoHCO$_3^-$. Clinicians and laboratory personnel should be aware of this phenomenon to prevent incorrect interpretation of acid-base status and medical mismanagement.

FR-PO629

Spurious Low Serum Bicarbonate Level due to Severe Hypertriglyceridemia: A Clinical Challenge

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Introduction: A low serum bicarbonate level (SBL) in the presence of a high anion gap (AG) generally indicates presence of metabolic acidosis secondary to an increase in unmeasured anions. Herein, we report 2 patients with profound hypertriglyceridemia (HTG) who presented with low measured SBL and a high AG. Evaluation revealed that the low SBL was spurious and resulted from extremely high serum triglyceride (TG) levels; once HTG was treated, the reported SBL was corrected.

Case Description: The first patient is a 48-year old man with a history of chronic pancreatitis secondary to severe HTG. He was admitted for acute pancreatitis and was found to have a serum TG of 3267 mg/dl. He had normal renal function and electrolytes but SBL was reported <5 mmol/l on chemistry panel with an AG of >28. However, arterial blood gas (ABG) revealed absence of acidemia with PH 7.4, PCO2 35, PO2 84, and bicarbonate 23 suggesting presence of spurious low SBL. Therapeutic plasma exchange (TPE) resulted in rapid improvement of HTG to 731 mg/dl the next day; SBL rose simultaneously to 18 mmol/l confirming the diagnosis. The second patient is a 26-year old woman with a history of diabetes who was admitted for acute pancreatitis. She was found to have a serum TG level of 10,950 mg/dl. SBL on routine chemistry panel was reported 9 mmol/l with an AG of 27. ABG showed pH 7.4, PCO2 37, PO2 75 and bicarbonate 23.7. She underwent 3 sessions of TPE, which lowered her serum TG to 1420 mg/dl and raised measured SBL to 18 mmol/l within 3 days with no additional intervention.

Discussion: Accurate assessment of bicarbonate is essential for the diagnosis of acid-base disturbances. Bicarbonate can be "measured" in serum as total carbon dioxide (tCO2) or "calculated" from ABG analysis (Henderson-Hasselbalch equation). In most instances, tCO2 and bicarbonate are closely related due to the constancy of the apparent dissociation constant of blood carbonic acid (pK'). Presence of a marked difference between the two values creates a clinical challenge that should prompt identification of a cause. Severe HTG interferes with laboratory testing in several ways (e.g. turbidity) and should be considered in the settings where there is no clinically apparent reason for low SBL. These 2 cases highlight the need for the clinicians to keep severe HTG in the differential diagnosis of SBL to avoid management errors.

FR-PO630

Medications Containing H^+ Salts Are Associated with Lower Serum Total CO_2 and Higher Serum Anion Gap in Patients With Non-Acidotic Diabetic Kidney Disease

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Background: Metabolic acidosis (MA) is associated with adverse clinical consequences in CKD. Many medications contain H^+-salts which could contribute to development of MA. This study determined the association between H^+ load from medications (med-H^+ load) and acid-base indices in patients with diabetic kidney disease (DKD) but without MA.

Methods: We conducted this cross-sectional study in 74 US veterans with DKD (eGFR 51±18 ml/min/1.73m^2) and serum tCO_2 24±2 meq/L. None were treated with alkali. The daily H^+ load from medications containing H^+-salts was determined using the daily dose, molecular weight, and valence of the agents. Participants were categorized into a low or high med-H^+ load group using a threshold of 7.7 meq/d, which is the equimolar amount of HCO_3^- in one 650mg $NaHCO_3$ tablet required to mitigate this H^+ load. We compared serum (tCO_2 and anion gap) and urinary (NH_4^+, titratable acids [TA], and pH) acid base indices between groups using linear regression models adjusted for eGFR, ACR, protein intake, and other potential confounders.

Results: 40 of 123 (33%) medications prescribed contained H^+-salts. Two agents contributed ≥1 meq/d of H^+, metformin (9.7±3.3 meq/d) and gabapentin (5.9±3.7 meq/d). 29 of 74 (39%) participants were in the high med-H^+ load group. In the high and low groups, 93% vs 13% received metformin and 55% vs 18% received gabapentin. Mean±SD med-H^+ load was 14.2±4.3 in the high and 1.6±2.4 meq/d in the low group. Those in the high group had significantly lower tCO_2 and higher serum anion gap after adjustment (table). Metformin use and gabapentin use (irrespective of dose) were modestly associated with lower serum tCO_2 and higher anion gap. Med-H^+ load did not seem to impact urinary acid excretion.

Conclusions: Medications containing H^+-salts, particularly metformin and gabapentin, contribute to meaningful differences in serum tCO_2 and anion gap in patients with non-acidotic DKD, suggesting that these agents may be novel risk factors for MA in DKD.

Funding: Veterans Affairs Support

Variable	High vs Low Acid Load	Metformin Use vs No	Gabapentin Use vs No
Serum total CO2 (meq/L)	-1.74 (-3.02 to -0.45)	-1.18 (-2.41 to 0.04)	-0.99 (-2.24 to 0.25)
Serum anion gap (meq/L)	2.16 (0.88 to 3.44)	1.69 (0.47 to 2.91)	1.19 (-0.08 to 2.46)
Urinary NH4+ (meq/hr)	0.15 (-0.20 to 0.50)	0.16 (-0.16 to 0.49)	0.11 (-0.22 to 0.44)
Urinary Titratable Acids (meq/hr)	0.00 (-0.25 to 0.25)	-0.12 (-0.35 to 0.11)	-0.11 (-0.35 to 0.12)
Urine pH	-0.08 (-0.33 to 0.17)	0.00 (-0.23 to 0.24)	-0.04 (-0.27 to 0.20)

FR-PO631

A Validated Anion Gap Threshold for High Anion Gap Metabolic Acidosis

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Background: The anion gap (AG), calculated by AG = $[Na^+]$–$[Cl^-]$–$[HCO_3^-]$, is often used to screen for acid-base disorders but cut-off levels used by clinical texts were based on empirical data. We recently sampled 300 healthy volunteers and the mean AG was 13±2mEq/L (manuscript in preparation). The proposed reference range (±2SD; central 95th percentile) was 9-17mEq/L. This study was to define a cut-off value for high AG metabolic acidosis (HAGMA).

Methods: Data from ICU patients from a prior study was used. Blood samples were classified into 2 groups: no HAGMA, or HAGMA present due to lactic acidosis, ketosis, citrate toxicity or severe uremia. The association of AG and HAGMA was tested by the Mann-Whitney U test. ROC analysis of AG was undertaken with optimal cut-off determined by Youden index.

Results: From 1,545 blood samples, 400 had adequate data. The median age was 64.7yrs, weight 60.1kg, 31.6% were females and 170 had HAGMA. With HAGMA, median AG was 19mEq/L (IQR 17–22) vs 15mEq/L (IQR 13–17) without HAGMA (P<0.001). AG has an AUC of 0.802 and the optimal cut-off was ≥17mEq/L (Fig. 1). The false negative rate (FNR) was 19.5%; false positive rate (FPR) 32.1%. Other AG thresholds were analysed (Table 1). As HAGMA may be life-threatening, a lower FNR is desired. The best FNR of 13.2% was with AG ≥13mEq/L, corresponding to mean AG of healthy persons, but FPR increased to 53.0%.

Conclusions: The recommended AG cut-off for HAGMA is ≥13mEq/L. This provides the best sensitivity but at the expense of specificity. As false negatives can still occur, acid-base status should be evaluated clinically, aided by repeated measurements of AG.

Table 1: Sensitivity & Specificity of AG Thresholds for HAGMA

AG cut-off	Specificity	False Positive	Sensitivity	False Negative
≥13 (Population Mean)	20.0%	53.0%	53.0%	13.2%
≥15 (Population Mean + 1SD)	44.3%	45.9%	45.9%	15.7%
≥17 (Population Mean + 2SD)	73.5%	32.1%	32.1%	19.5%

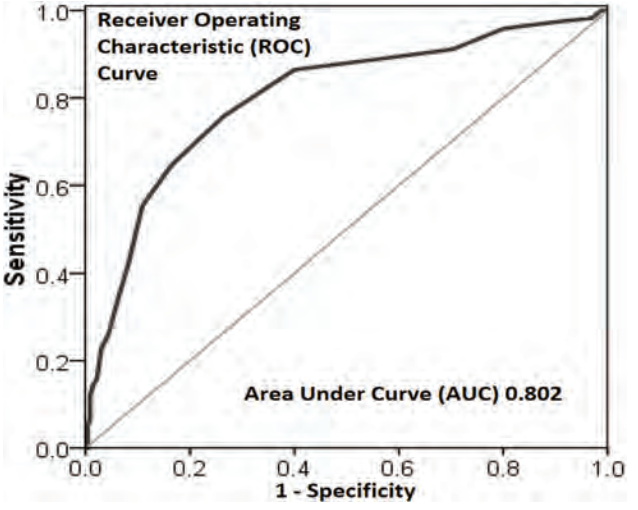

Fig. 1: ROC curve of AG for HAGMA

FR-PO632

Metabolic Acidosis Is Underdiagnosed and Undertreated in Patients with CKD

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Background: Metabolic acidosis is a common complication of chronic kidney disease (CKD) and is associated with adverse effects on physical function, accelerated CKD progression and increased mortality. Although chronic metabolic acidosis can be easily identified using routinely collected laboratory tests, there is limited data on its recognition and treatment.

Methods: We integrated laboratory data from 36 million US adults with de-identified longitudinal claims and prescription data from 280 million de-identified individuals included in the Symphony Health Solutions IDV® (Integrated Dataverse). Patients who met stringent laboratory criteria indicative of CKD and chronic metabolic acidosis were included: ≥2 eGFRs <60 ml/min/1.73m^2 with no intervening eGFR ≥60 ml/min/1.73m^2; ≥2 serum bicarbonates ≥12 to <22 mEq with no intervening bicarbonate <12 or ≥22 mEq/L; qualifying values ≥28 days apart. No patients with a diagnosis of acute kidney injury (AKI) within 28 days prior to either qualifying bicarbonate value were included. A physician diagnosis of metabolic acidosis was based on administrative claims, and treatment of metabolic acidosis was defined as a prescription for oral alkali therapy.

Results: Approximately 2.4 million individuals met laboratory criteria for CKD, 118,620 of those also met laboratory criteria for metabolic acidosis. Claims and prescription data were available for 86,782 individuals with both CKD and chronic metabolic acidosis. In this population, a diagnostic code for metabolic acidosis was present in only 21% of patients (N=19,038). The overall frequency of oral alkali therapy use was 15% (N=13,272) ranging from 10% in those without a diagnostic code for acidosis to 34% in those with the appropriate diagnostic code.

Conclusions: Metabolic acidosis is underdiagnosed and undertreated in US adults with CKD. Disease specific educational efforts as well as development of novel treatments is needed to improve outcomes for this important complication.

Funding: Commercial Support - Tricida Inc.

FR-PO633

Dietary Protein Intake and Urinary Citrate Excretion in Asians

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Background: Dietary protein intake (DPI) is associated with acid loading. We hypothesize that urinary citrate excretion rate (UCER) is lower in patients with chronic kidney disease (CKD) having higher DPI. We examine the relationship between DPI and UCER in a multi-ethnic Asian population in patients with CKD and participants without kidney disease.

Methods: We used data from patients with stable CKD from the Asian Kidney Disease Study and normal participants without diabetes or hypertension from the Singapore Kidney Function Study. Participants fasted overnight, and provided a 24hr urine collection, blood sample, and underwent measured glomerular filtration test (mGFR; mL/min/1.73m^2) using ^{99m}Tc-DTPA. Daily protein intake (DPI, g/day) was calculated from 24-hour urine urea using Maroni's formula. Non-normal data was natural log-transformed for analysis. We performed univariate analysis of Ln UCER against the factors of age, gender, ethnicity, presence of CKD, Ln mGFR, and DPI. A multiple linear regression model was constructed including these variables to assess the association of DPI with UCER after adjusting for kidney disease and function.

Results: Complete data were available from 187 CKD patients (48.7%male) and 89 non-CKD participants (47.2% male) (p=NS). The mean ages were 59±12.8 years and 42±14.3 years in the CKD and non-CKD groups, respectively (p<0.001). The median mGFR in the CKD and non-CKD groups were 45 (IQR: 29-63) and 100 (IQR: 88-113), respectively (p<0.001). The median UCER (mmol/day) was lower in the CKD group (46, IQR: 11-106 vs. 303, IQR: 206-446) (p<0.001). No participant was on sodium bicarbonate supplementation. On univariate analysis, lower UCER was associated with increased age, presence of CKD, decreased mGFR, and decreased DPI (all p<0.001). Indians had higher UCER compared to Chinese and Malays (p<0.01). Gender was not associated with UCER. In a multiple linear regression model including these variables (RSq=0.53, p<0.001), daily protein intake is not significant (estimate 0.0084, p=0.0511).

Conclusions: After adjusting for presence of CKD, kidney function, age, ethnicity and gender, DPI is not significantly associated with UCER.

Funding: Government Support - Non-U.S.

FR-PO634

A Comparison of the Effect of Sodium Bicarbonate on Acid-Base Indices in CKD Patients with and Without Diabetes: A Secondary Analysis of the BASE Pilot Trial

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Background: In CKD, those with diabetes mellitus (DM) tend to have higher urinary NH_4^+ (u-NH_4^+) excretion, lower urinary pH (u-pH), and in some studies, higher serum total CO_2 (s-tCO_2) than those without DM at the same level of eGFR. The comparative effect of $NaHCO_3$ supplementation on acid-base indices in those with and without DM is uncertain.

Methods: This was a secondary analysis from the Bicarbonate Administration to Stabilize eGFR (BASE) Pilot Trial, which was a randomized, double-blinded, placebo-controlled study to determine the safety and tolerability of two doses of $NaHCO_3$ in 194 CKD patients over 28 weeks. 90 participants received higher dose $NaHCO_3$ (0.8 meq/kg-lean/d), 52 received lower dose $NaHCO_3$ (0.5 meq/kg-lean/d; n=52), and 52 received placebo. The BASE Pilot Trial found that both doses were safe and well tolerated (Kidney Week 2018, SA-OR036). In this study, we compared the mean change in u-NH_4^+ excretion, u-pH, and s-tCO_2 from baseline between the treatment groups, stratified by DM status, using linear mixed models adjusted for demographics, eGFR, ACR, diuretic use, ACE/ARB use, protein intake, and clinical center.

Results: Mean±SD age was 67±12 years and eGFR was 36±9 ml/min/1.73m^2; 54% had diabetes. In DM vs. non-DM, baseline s-tCO_2 was 24±2 vs. 24±3 meq/L (p=0.95); u-NH_4^+ was 22±14 vs. 20±10 meq/d (p=0.19), and u-pH was 5.7±0.5 vs 5.9±0.5 (p=0.03). The lower dose reduced u-NH_4^+ excretion and increased u-pH similarly in non-DM and DM (Table). With the higher dose, additional effects on u-NH_4^+ excretion and u-pH were more robust in non-DM, however the interaction p-values were not significant. In both DM and non-DM, statistically significant increases in s-tCO_2 were only observed in those treated with the higher $NaHCO_3$ dose.

Conclusions: In individuals with CKD, $NaHCO_3$ may have an attenuated dose-response effect on urinary acid excretion in DM. However, the effect of $NaHCO_3$ on s-tCO_2 seems to be similar for those with and without DM, and only the higher dose significantly increased s-tCO_2

Funding: NIDDK Support

Measurement	Urinary NH4+ (% change)			Urinary pH			Serum total CO2 (meq/L)		
Comparison	Non-DM	DM	p-interaction	Non-DM	DM	p-interaction	Non-DM	DM	p-interaction
Lower dose vs. placebo	-28% (-48% to 0%)	-39% (-57% to -15%)	0.47	0.5 (0.1 to 0.8)	0.5 (0.2 to 0.9)	0.77	-0.3 (-1.5 to 0.9)	0.6 (-0.7 to 1.9)	0.31
Higher dose vs. placebo	-56% (-68% to -40%)	-46% (-60% to -27%)	0.34	0.9 (0.6 to 1.2)	0.6 (0.3 to 0.9)	0.27	1.2 (0.1 to 2.4)	1.6 (0.5 to 2.8)	0.64
Higher dose vs. Lower dose	-40% (-56% to -17%)	-11% (-33% to 19%)	0.07	0.4 (0.1 to 0.7)	0.1 (-0.2 to 0.4)	0.14	1.5 (0.3 to 2.8)	1.0 (-0.1 to 2.1)	0.54

FR-PO635

Alkalinization by Urologists and Nephrologists (AlcalUN): Does Oral Sodium Bicarbonate ($NaHCO_3$) Affect Extracellular Volume?

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Background: Oral alkalinization with $NaHCO_3$ or citrate is widely prescribed in numerous situations from metabolic acidosis to nephrolithiasis. Most of nephrologists/urologists use it on a regular basis, while extracellular volume (ECV) increase is the main feared adverse event for $NaHCO_3$. To date, no clinical trial has specifically studied this aspect in clinical routine.

Methods: AlcalUN (NCT03035812) is a French multicentric prospective open trial aiming at determining the impact on ECV of a chronic oral alkalinization by $NaHCO_3$ during nephrologists or urologists use. Patients receiving oral alkalinization without $NaHCO_3$ composed a control group. The main criterion was the ECV increase as judged on body weight (BW), blood pressure (BP), and edema at first visit.

Results: From 01/2017 to 12/2018, 20 investigators included 122 patients whom 92 (75%) had at least one follow-up and 74 (61%) received $NaHCO_3$. If both groups were comparable as judged on demographic data, patients in the $NaHCO_3$-group had more chronic kidney diseases (74 *vs.* 28%, p<0.001) where patients in the non $NaHCO_3$-group (citrate) had more nephrolithiasis (23 *vs.* 94%, p<0.001). At baseline (inclusion), BW, BP, and presence of edema were comparable in both groups. After a mean of 98±48 days of follow-up, 70 patients (76%) had an ECV increase but the repartition was highly similar in both groups (77 *vs.* 72%, p=0.76), especially BW did not differ (*cf.* **Figure 1**).

Conclusions: Oral alkalinization with $NaHCO_3$ does not increase ECV more than citrate while it is used in a more risky population. These results should be confirmed in a widest population (recruitment continues) and now in a randomized controlled trial.

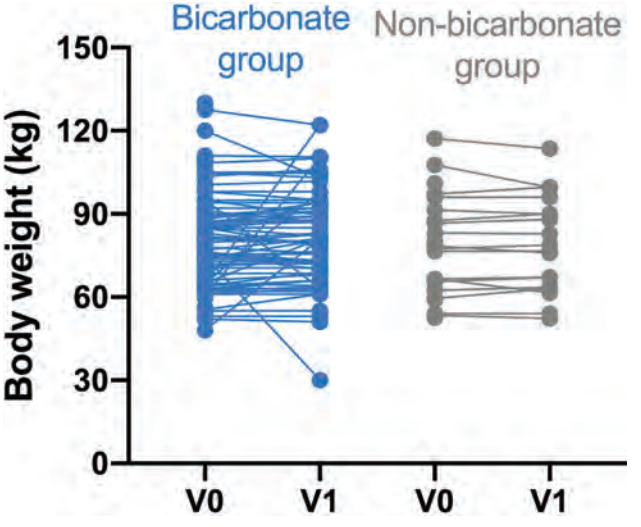

Figure 1. Evolution of body weight between inclusion (V0) and first follow-up (V1).

FR-PO636

Drug Therapy Choices for Acquired Distal Renal Tubular Acidosis by US Nephrologists and Rheumatologists

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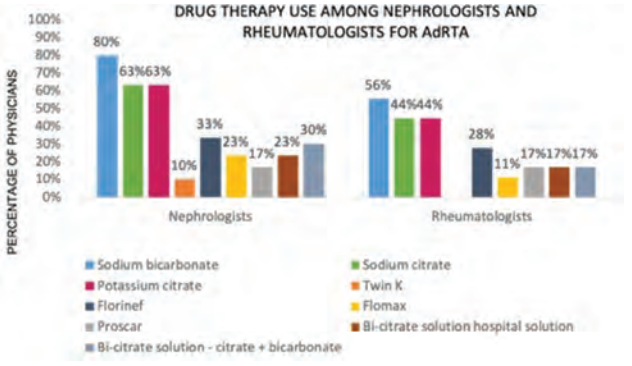
Background: Drivers of drug therapy choices for acquired distal renal tubular acidosis (dRTA) are not well understood. AdRTA, which is linked with Sjogren's disease, systemic lupus erythematosus (SLE), primary biliary cirrhosis (PBC) and autoimmune hepatitis, is often encountered by rheumatologists and nephrologists. To better understand the drug therapy approaches for AdRTA patients, a quantitative market research study was undertaken

Methods: Between March 25th–April 15th, 2019, an online survey was conducted with 30 nephrologists and 20 rheumatologists in the USA on the subject of dRTA, with a focus on AdRTA. All screened respondents had direct clinical experience of AdRTA patients

Results: Sodium bicarbonate (SB) is the most commonly prescribed treatment for AdRTA, prescribed by 80% of nephrologists (Nph) and 56% of rheumatologists (Rhm), followed by sodium citrate (SC) and potassium citrate (PC). In potassium depleted patients, however, PC is the most commonly prescribed agent (Nph 55%, Rhm 57%). The majority of Rhms and Nephs consider the Neph is the most likely to prescribe all of the available treatments (range: 56% Flomax to 78% PC). 67% of Nphs report high satisfaction with SB and 53% with PC, fewer than their Rhm colleagues (high satisfaction: SB-90%, PC-100%). However, 70% of Nphs and 40% of Rhms indicate treatments for AdRTA are sub-optimal and only 60% of Nphs and 40% of Rhms considered the available treatments effective and easily accessible. Many nephrologists expressed that:*"More effective therapies that are less burdensome to patients."* and *"More new treatment options"* are needed. [Figure]

Conclusions: Most nephrologists and rheumatologists have direct experience prescribing drug therapy for AdRTA with sodium bicarbonate being the most commonly prescribed treatment. However, while they express overall satisfaction with available treatments, many believe that they are sub-optimal, not effective or/and not easily accessible

Funding: Commercial Support - Advicenne S.A.



FR-PO637

Outcomes of Correcting Metabolic Acidosis in CKD with Cirrhosis: A Retrospective Study

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Background: Chronic Kidney Disease complications include metabolic acidosis. There is evidence of mortality benefit to correcting acidosis to bicarbonate levels of around 22 meq/L. Conversely, in chronic liver disease, respiratory alkalosis is the most common acid-base disorder, which manifests as low serum bicarbonate on labs. Physiologically, it appears that correcting metabolic acidosis to a reasonable level may provide benefit to CKD with cirrhosis, however most practices do not get a venous or arterial blood gases to first identify the cause of low serum bicarbonate. The impact of identifying and managing metabolic acidosis in patient with cirrhosis has not been studied well. Correcting acidosis commonly requires using sodium containing salts, which can lead to sodium overload resulting in increased need for paracentesis procedures. Our hypothesis is that adding oral sodium bicarbonate (NaHco3) targeting bicarbonate 22 meq/L would lead to increased ascites and more frequent paracentesis so we should target lower bicarbonate levels in cirrhosis.

Methods: We conducted a single center retrospective chart review of all patients with CKD and Cirrhosis, managed at University of Arkansas for Medical Sciences, over a period of 5 years to study incidence of paracentesis correlated with oral bicarbonate therapy.

Results: Out of 366 patients with the diagnosis of CKD and cirrhosis, 200 patients did not get paracentesis. Out of these 31(15.5%) were on oral bicarbonate.166 patients recieved paracentesis out of which 41 (24.7%) were on bicarbonate. However, this difference was not statistically significant (P value 0.0383).

Conclusions: KDIGO guidelines recomend correcting metabolic acidosis with oral bicarbonate supplementation to prevent CKD progression targeting serum bicarbonate of about 22 meq/L. However, it is not clear if we can extend this to the population with cirrhosis and CKD. Purpose of our study is to address this question and to study the effects of bicarbonate supplementation with regard to its effect on incidence of paracentesis procedures that can lead to increased complications for these patients. Our retrospective data suggests that patients on oral NaHco3 require frequent paracentesis, but has not met statistical significance. We plan a prospective randomized control study to address this question better.

FR-PO638

A Case of Tubulointerstitial Nephritis Complicated by Primary Biliary Cirrhosis with Renal Tubular Acidosis and Nephrogenic Diabetes Insipidus

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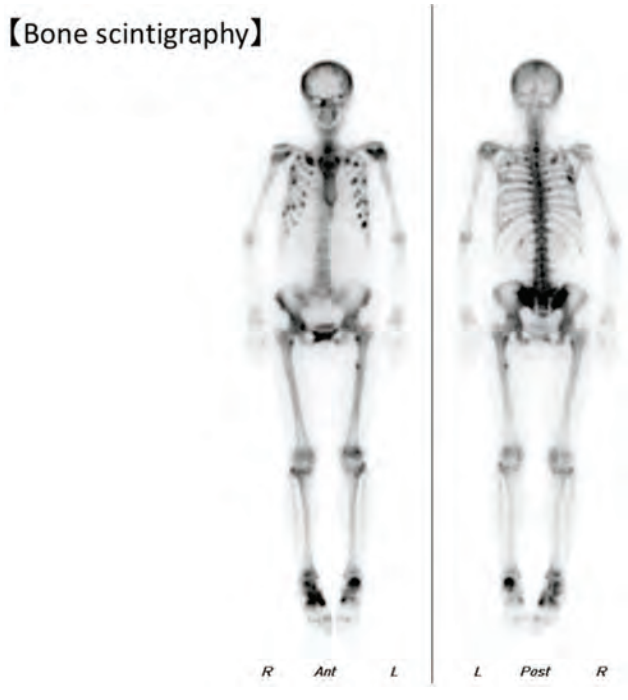
Introduction: Tubulointerstitial nephritis is often caused by drugs, infections, autoimmune disorders. We report a case of tubulointerstitial nephritis associated with primary biliary cirrhosis, which developed renal tubular acidosis and nephrogenic diabetes insipidus.

Case Description: A 50-year-old woman presented with a four-month history of left shoulder pain, back pain, dry mouth, polydipsia, polyuria. She hospitalized for weakness of limbs. Her lab studies revealed serum creatinine 2.72 mg/dL, serum potassium 1.5 mg/dl, and normal anion gap metabolic acidosis which suggested distal and proximal renal tubular acidosis. She had multiple fractures which suggested the presence of osteomalacia. Her urine output exceeded 10L/day, and urine osmolarity was low. After corrected serum potassium weakness of limbs improved, but polyuria did not improve. She was thought to nephrogenic diabetes insipidus because of resistant to antidiuretic hormone. Kidney biopsy was performed to clarify the cause of these findings. The major histologic changes were interstitial infiltration by mainly lymphocytes, tubulitis, and interstitial edema. The presence of antimitochondrial M2 antibodies suggested primary biliary cirrhosis. She was treated with oral steroids and a thiazide diuretic. Her polyuria resolved, and serum creatinine level improved to 0.9 mg/dl.

Discussion: In conclusion, our patient with tubulointerstitial nephritis and primary biliary cirrhosis had a favorable outcome from oral steroids and a thiazide diuretic. Previous studies have demonstrated Fanconi syndrome in patients with primary biliary cirrhosis, and our patient suggested that tubulointerstitial nephritis complicated by primary biliary cirrhosis could develop renal tubular acidosis and nephrogenic diabetes insipidus.



FR-PO639

Mortality and Magnesium Levels in CKD

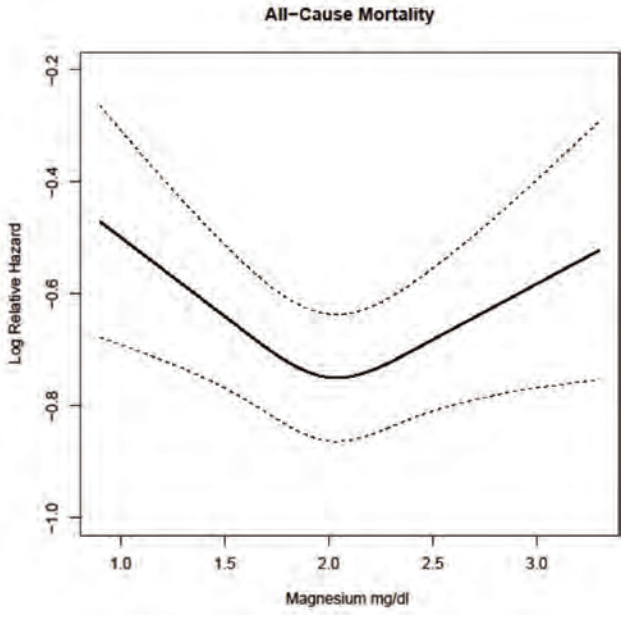
Rami M. Azem,[1] Remy Daou,[3] Susana Arrigain,[1] Jesse D. Schold,[1] Georges Nakhoul.[2] *[1]Cleveland Clinic, Cleveland, OH; [2]Cleveland Clinic Foundation, Cleveland, OH; [3]Saint Joseph University, Beirut, Lebanon.*

Background: Magnesium disorders are common in Chronic Kidney Disease (CKD) and are typically a consequence of decreased kidney function or use of medications such as diuretics. While hypomagnesemia has been linked with increased mortality, the association between elevated magnesium levels and mortality is not clearly defined. Additionally, associations between magnesium disorders and risk of different types of death have not been reported.

Methods: Using our Electronic Health Record-based CKD registry, we identified patients with eGFR 15 to < 60 ml/min/1.73m2 who had magnesium levels within the prior year. We examined associations between magnesium levels and all-cause, cause-specific mortality and progression of CKD while adjusting for demographic factors and comorbidities using Cox models, Competing Risks regression and mixed models.

Results: Out of 10,568 CKD patients, 12.4% (N=1,314) had hypomagnesemia (Mg < 1.7 mmol/L) while 1.9% (N=205) had hypermagnesemia (Mg > 2.6 mmol/L). We observed a U-shaped association between serum magnesium levels and mortality, with both hypomagnesemia (HR=1.14, 95% CI: 1.04, 1.24) and hypermagnesemia (HR=1.23, 95% CI: 1.03, 1.48) having higher all-cause mortality. Our results showed increased subhazard of non-cardiovascular, non-malignancy deaths for hypomagnesemia (SHR=1.29, 95% CI: 1.12, 1.49), but no significant differences in other causes of death. In a sensitivity analysis excluding patients with malignancy, results were similar. Hypomagnesemia was not associated with stronger eGFR decline (P = 0.10).

Conclusions: Hypomagnesemia and hypermagnesemia were both associated with increased mortality. Hypomagnesemia was associated with increased non-cardiovascular, non-malignancy death.



FR-PO640

Serum Magnesium, Mortality, and Cardiovascular Disease in CKD and ESRD Patients: A Systematic Review and Meta-Analysis

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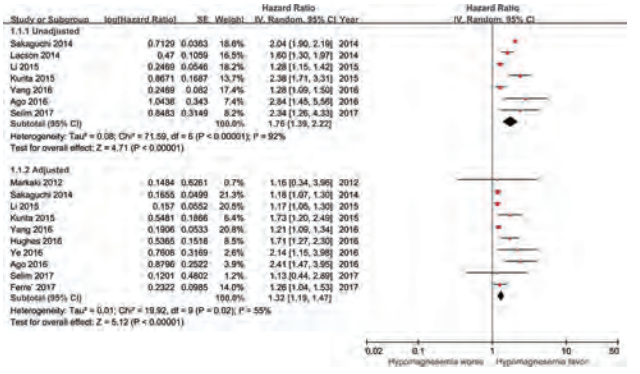
Background: Magnesium plays an independent pathogenic role in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients. However, the results of these studies were somewhat underpowered and inconclusive.

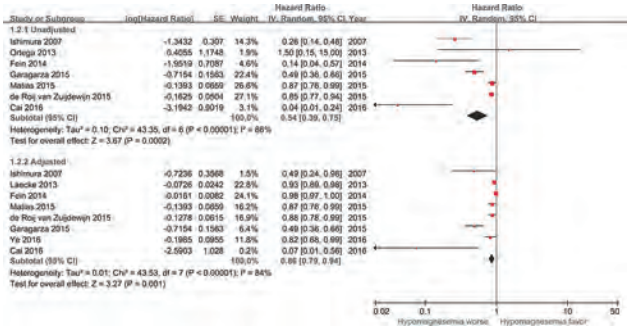
Methods: Literature was identified by searching PubMed, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL). Unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) were pooled.

Results: The results showed that there was a strong association between hypomagnesemia and the risk of all-cause mortality in patients with CKD and ESRD (HR 1.32; 95% CI1.19–1.47; p < 0.00001) after multivariable adjusted. On the contrary, hypermagnesemia was inversely associated with all-cause mortality in patients with CKD and ESRD (HR 0.86; 95%CI 0.79–0.94; p = 0.001). Moreover, a significant association between hypermagnesemia and decreased risk of cardiovascular mortality was observed (HR 0.71; 95% CI 053–0.97, p = 0.03) in the adjusted model. In addition, subgroup analysis found that hypomagnesemia was strongly associated with increased all-cause mortality in hemodialysis patients (HR 1.29; 95% CI 1.12–1.50; p = 0.0005).

Conclusions: Our results indicate that hypomagnesemia is significantly associated with cardiovascular and all-cause mortality in patients with CKD and ESRD.



The association between hypomagnesemia and all-cause mortality for dichotomous variables (hypomagnesemia vs. normal magnesium or hypermagnesemia group) Fig.



The association between hypermagnesemia and all-cause mortality for continuous variables (hypermagnesemia vs. normal magnesium or hypomagnesemia group)

FR-PO641

Impact of Serum Calcium Level Fluctuations on In-Hospital Mortality

Charat Thongprayoon,[1] Wisit Cheungpasitporn,[2] Michael A. Mao,[1] Stephen B. Erickson.[1] *[1]Mayo Clinic, Rochester, MN; [2]University of Mississippi Medical Center, Jackson, MS.*

Background: Calcium concentration is strictly regulated at both the cellular and systemic level, and changes in serum calcium levels can alter various physiological functions in various organs. This study aimed to assess the association between changes in calcium levels during hospitalization and mortality.

Methods: We search our patient database to identify all adult patients admitted to our hospital from January 1st, 2009 to December 31st, 2013. Patients with ≥2 serum calcium measurements during the hospitalization were included. The serum calcium changes during the hospitalization, defined as the absolute difference between the highest and lowest calcium levels, was categorized into five groups: 0-0.4, 0.5-0.9, 1.0-1.4, 1.5-1.9, ≥2.0 mg/dL. Multivariable logistic regression was performed to assess the independent association between calcium changes and in-hospital mortality, using the change in calcium category of 0-0.4 mg/dL as the reference group.

Results: Of 9,868 patients included in analysis, 540 (5.4%) died in the hospital. The in-hospital mortality progressively increased with higher calcium changes, from 3.4% in the group of 0-0.4 mg/dL to 14.5% in the group of ≥2.0 mg/dL (p<0.001). When adjusted for age, sex, race, principal diagnosis, comorbidity, kidney function, acute kidney injury, number of serum calcium measurements, and length of hospital stay, the serum calcium change of 1.0-1.4, 1.5-1.9, and ≥2.0 mg/dL were significantly associated with increased in-hospital mortality with OR of 1.67 (95% CI 1.24-2.25), 2.11 (95% CI 1.48-3.01), and 3.96 (95% CI 2.95-5.30), respectively. The association remained statistically significant when further adjusted for either the lowest, highest, or admission serum calcium.

Conclusions: Larger serum calcium changes in hospitalized patients were progressively associated with increased in-hospital mortality.

FR-PO642

Changes in Serum Phosphate Levels Associated with In-Hospital Mortality

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Background: Fluctuations in serum phosphate levels have recently been shown to be associated with coronary calcification and increased mortality in end-stage renal disease (ESRD) patients. However, the impacts of serum phosphate changes in hospitalized patients remain unclear. This study aimed to test the hypothesis that serum phosphate changes during hospitalization were associated with in-hospital mortality.

Methods: We included all adult hospitalized patients from January 2009 to December 2013 that had at least two serum phosphate measurements during their hospitalization. We categorized the hospital serum phosphate change, which was defined as the absolute difference between the highest and lowest phosphate, into 5 groups: 0-0.6, 0.7-1.3, 1.4-2.0, 2.1-2.7, ≥2.8 mg/dL., Using the phosphate change group of 0-0.6 mg/dL as the reference group, the adjusted odds ratio of in-hospital mortality for various phosphate change groups was obtained by multivariable logistic regression analysis.

Results: A total of 28,149 patients were studied. The in-hospital mortality in patients with phosphate change of 0-0.6, 0.7-1.3, 1.4-2.0, 2.1-2.7, ≥2.8 mg/dL was 1.5, 2.0, 3.1, 4.4, and 10.7%, respectively ($p<0.001$). When adjusted for potential confounders, a larger phosphate change was associated with progressively increased in-hospital mortality with ORs of 1.35 (95% 1.04-1.74) in 0.7-1.3 mg/dL, 1.98 (95% CI 1.53-2.55) in 1.4-2.0 mg/dL, 2.68 (95% CI 2.07-3.48) in 2.1-2.7 mg/dL, and 5.4 (95% CI 3.94-6.45) in ≥2.8 mg/dL compared to the phosphate change group of 0-0.6 mg/dL. A similar result was noted when we further adjusted for either the lowest, highest or admission phosphate.

Conclusions: Greater serum phosphate changes during a patient's hospitalization were progressively associated with increased in-hospital mortality.

FR-PO643

Granger Causality Analysis of Regulatory Network of Phosphate Metabolism in Healthy Individuals

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Background: Basic and clinical studies reveal that the homeostasis of phosphate is maintained by a regulatory network. The aim of our study was to explore the variation of phosphatoninin with the change of diet.

Methods: 6 healthy volunteers were treated with regular Pi diet (NPD) and high Pi diet (HPD) for 5 days. Their blood and urine specimens at 10 fixed time points on the 5th day of intervention were collected. In order to reveal the causality relationship in the phosphorus metabolism network, this study used the Granger causal analysis to determine time series relationship.

Results: HPD resulted in a significant increase in serum Pi and urinary Pi excretion. There was a significant increase in PTH. FGF23 was upward trend. By using Granger causal analysis, we found PTH was earliest change in RPD, which was the initiation factor. The change of FGF23 appeared at the latest that was the passive factor. In HPD, FGF23 was initiation factor. Serum Ca and Pi were passive factors.

Conclusions: With the traditional comparison, it was difficult to reveal the caucality relationship of phosphate network. By Granger causality analysis, we found in RPD kidney was the most significant organ in keeping serum Pi stably. In HPD, FGF23 was the main hormone to maintain homeostasis of phosphate regulatory network.

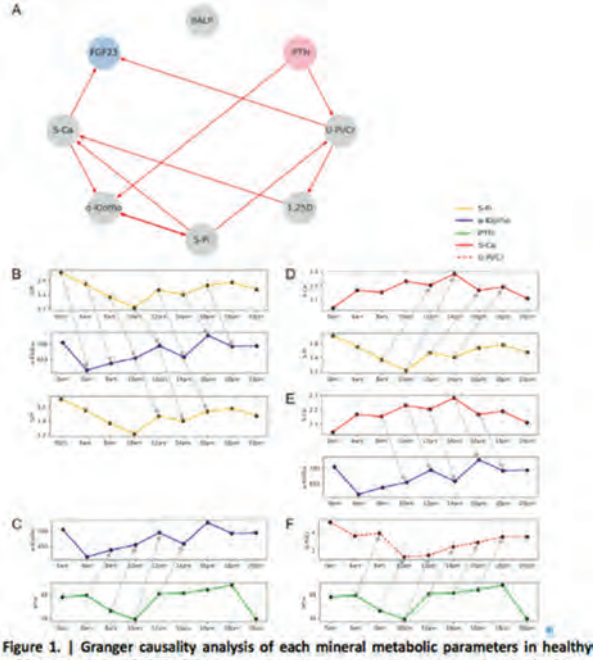

Figure 1. | Granger causality analysis of each mineral metabolic parameters in healthy subjects treated with RPD. (A) Here we show Granger causality analysis network of subjects treated with regular-phosphate diet intervention. The arrowhead points to the result of two mineral metabolic parameters' Granger causality. Double-arrowhead reflects reciprocal Granger causation of two mineral metabolic parameters. iPTH (pink) is the cause of network, and FGF23 (blue) is the result of the regulatory network. iPTH regulates FGF23 indirectly by influencing urinary phosphate excretion, $1,25(OH)_2D_3$, serum Ca, serum Pi and α-Klotho, which keeps serum Pi level stable and maintains phosphate regulatory network homeostasis. (B)(C)(D)(E)(F) Show Granger causality between α-Klotho and serum Pi, iPTH and α-Klotho, Serum Pi and serum Ca, α-Klotho and serum Ca, iPTH and urinary Pi excretion of time series analysis, respectively. Grey arrowhead reflects the "cause" of the earlier periods leads to the "result" of latter periods. For example, the decline of serum Pi level from 8 a.m. to 10 a.m. (cause) results in increased of α-Klotho expression from 10 a.m. to 12 p.m. (result) in Granger causality analysis.¶

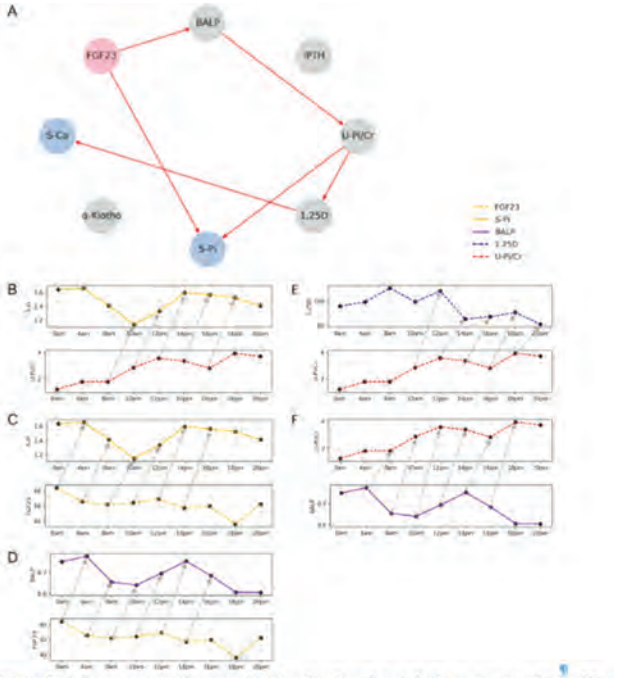

Figure 2. | Granger causality analysis of each mineral metabolic parameters in healthy subjects treated with high-phosphate diet intervention. (A) Here we show Granger causality analysis network of subjects treated with high-phosphate diet intervention. The arrowhead points to the result of two mineral metabolic parameters' Granger causality. FGF23 (pink) is the cause of network, serum Ca and serum Pi (blue) are the results of the regulatory network. (B)(C)(D)(E)(F) Show Granger causality between serum Pi and urinary Pi/Cr, FGF23 and serum Pi, FGF23 and BALP, $1,25(OH)_2D_3$ and urinary Pi/Cr, BALP and urinary Pi/Cr of time series analysis, respectively. Grey arrowhead reflects the "cause" of earlier period results in the change of "result" at latter periods. Pi, serum Pi; Ca, serum Ca; 1,25D, $1,25(OH)_2D_3$; U-Pi/Cr, Urinary Phosphate/Creatinine; 1,25D, $1,25(OH)_2D_3$.¶

FR-PO644

Hyperphosphatemia in a Patient with Mucormycosis and AKI

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Introduction: Hyperphosphatemia may arise from ingestion, extracellular shifts (e.g. cell death or alterations in acid-base status), bone resorption, hormonal dysregulations leading to reduced renal excretion, and/or poor kidney function. Pseudohyperphosphatemia has been well-described but may be under-recognized and/or not commonly seen in clinical practice.

Case Description: A 35-year-old 7-week-pregnant woman with type 1 diabetes mellitus was admitted for mucormycosis involving the clivus and cervical vertebrae. On day 1, she was initiated on liposomal amphotericin (10mg/kg) with normal saline support. On day 4, sulfamethoxazole/trimethoprim and ampicillin/sulbactam were added for methicillin-sensitive *Staphylococcal Aureus* and *Prevotella Buccae* from her fungating mass. On day 6, patient was noted to have acute kidney injury (AKI) when her creatinine increased from 0.4-0.5 mg/dL to 1.25 mg/dL. Nephrology was consulted for AKI and concurrent multiple electrolyte abnormalities. See Table for laboratory findings. Chart review was notable for a hypotensive episode when her blood pressure dropped from a baseline of 100/80 mmHg to 79/50 mmHg over 4 hours. Physical exam was unremarkable. Primary team replaced her potassium and magnesium and started sevelamer carbonate 2400 mg tidac.

Discussion: While the etiologies of AKI, hypokalemia, and hypomagnesemia were straightforward, hyperphosphatemia was out of proportion to the degree of AKI. A full investigation for contributing factors of hyperphosphatemia other than AKI revealed that she had pseudohyperphosphatemia due to liposomal amphotericin. Methods for measuring Pi may differ among commonly used clinical analyzers, where some may read the organic phosphate contained in the lipid bilayer of the liposomes as Pi. Repeat phosphorus level on a different analyzer revealed a level of 5.8 mg/dL. Erroneous treatment of pseudohyperphosphatemia would have been detrimental in current case.

Laboratory findings

Liposomal amphotericin	Creatinine (mg/dL)	Potassium (meq/L)	Magnesium (mg/dL)	Calcium (mg/dL)/Albumin (g/dL)	Phosphorus (mg/dL)	Alkaline phosphatase (IU/L)
Day 1	0.4	3.8	1.9	8.5/3.0	2.6	278
Day 4	0.5	3.1	1.3	8.0/2.0	5.0	245
Day 6	1.25	2.7	1.2	7.8/2.5	6.0	396
Day 10	1.46	3.9 (after repletion)	1.9 (after repletion)	8.1/2.3	10.7	

Others: Parathyroid hormone 26 pg/ml, vitamin D, 25-OH 33 pg/mL, lactate dehydrogenase 106 U/L, creatine phosphokinase 21 U/L, urinalysis was without protein, blood, or cellular casts.

FR-PO645

A Simple Equation to Estimate Urinary Flow Rate Using Urine Creatinine

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Background: Accurate assessment of urine flow is critical to clinical care, but challenging to estimate. We hypothesized we could dervie an equation that would accurately estimate urine flow rate.

Methods: We derived a new equation to estimate urine flow rate (eV) using the Cockcroft-Gault and the measured creatinine clearance (UV/P) equations. Accuracy was evaluated by comparing eV to measured urine flow rate (V) in persons with CKD who participated in the AASK and COMBINE trials. Participants with concordant estimated and measured creatinine excretion rates were included to define a subset with highly accurate 24 hour urine volumes.

Results: The eV equation required only urine creatinine, age, sex, and weight data. In AASK, we evaluated 570 participants who had mean GFR of 46.7 ± 15.1 ml/min/1.73m^2 and measured urine flow rate (V) 94.9 ± 34.2 ml/hour over 24 hours. A high correlation was found between eV and V (r = 0.91, p< 0.001), however Bland Altman plots showed that eV was 9.6 ml/hour lower than V, on average, in AASK. Thus a correction factor was added to the eV equation and externally evaluated in COMBINE, wherein 123 participants had mean eGFR of 34 ± 8 ml/min/1.73m^2. EV and V were highly correlated (r = 0.91, p< 0.001) and bias was improved (5.3 ml/hr). Overall, 80% of individuals had eV that was within 20% of V.

Conclusions: A simple equation using urine creatinine and demographics can accurately predict urine flow rate and may have clinical utility in situations where the accuracy of timed collections is uncertain.

Funding: NIDDK Support, Other NIH Support - U01 - COMBINE U01DK097093.

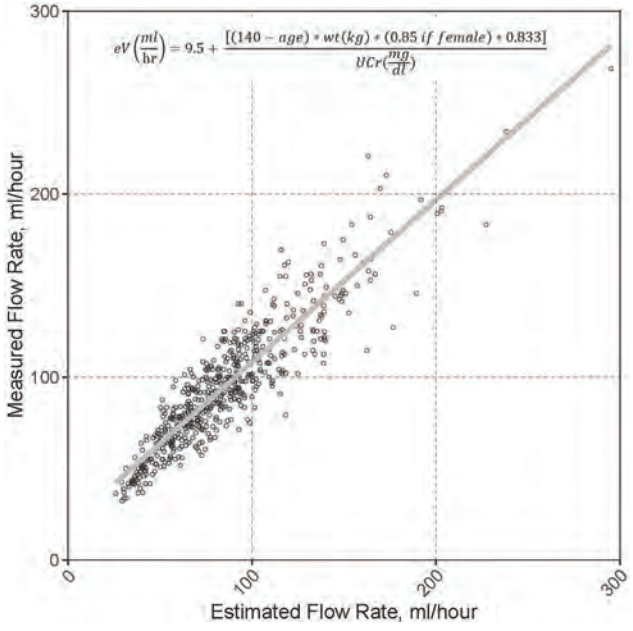

Figure 1 shows the correlation of measured vs. estimated flow rate using eV equation (top of graph) in AASK participants who had measured creatinine excretion rates within 20% of estimated excretion rates (N=570). r = 0.91, p< 0.001.

FR-PO646

Insulin Use for the Treatment of Acute Hyperkalemia

Toby J. Humphrey, Ian Wilkinson, Thomas F. Hiemstra. *University of Cambridge, Cambridge, United Kingdom.*

Background: Insulin has been the cornerstone of treatment for hyperkalaemia (HK) for many decades and remains in wide clinical use. Despite this, there is a paucity of data on the efficacy and safety of this approach. To investigate this, we interrogated a large electronic health record (EHR) dataset to explore the characteristics and consequences of insulin treatment for HK.

Methods: Patients receiving insulin for the treatment of HK were identified from a complete EHR database of all admissions to a UK tertiary hospital over 3.5 years. Variables extracted included demographics, comorbidities, concomitant medications, biochemistry results including all blood potassium values, and all in-hospital prescribing. Factors associated with the need for insulin retreatment were explored using a mixed-effects logistic regression model and odds ratios are reported.

Results: Insulin was administered to 1,284 adult patients(2,541 total administrations). Insulin-treated patients were aged 72 (IQR 59.5-84.5) years and had significant comorbidity (Charlson index 5, IQR 3 to 7). At the end of the follow-up period, only 60.3% remained alive. Potassium concentration immediately (≤ 60 min) pre-treatment was 6.34±1.2mmol/L. The mean reduction in potassium at 4-hours post infusion was 0.86±0.92mmol/L. Multiple doses were given to 542 patients (42.2%), of whom 209 (16.2%) were retreated within 4 hours of the first infusion. Patients receiving multiple insulin infusions were more likely to have chronic kidney disease (44.5% vs 36.5%, p=0.002) or heart failure (22.9% vs 17.4%, p=0.009) and to have been exposed to ACE inhibitors (33.2% vs 27.9%, p=0.02) or potassium sparing diuretics (19.4% vs 15.5%, p=0.04), although only CKD remained significantly associated with retreatment in a regression model adjusted for age, gender and co-morbidity (OR 1.4, 1.1-1.7, p=0.01). Dysregulation of glucose metabolism occurred in 672 patients (53%) following insulin. Hypoglycaemia (plasma glucose<4mmol/L) occurred in 133 patients (10.4%) within 4 hours of insulin administration, and 16 patients (1.2%) experienced a glucose < 2mmol/L.

Conclusions: HK requiring insulin treatment occurs most commonly in a more elderly and comorbid population, is associated with CKD, requires re-treatment in 4 out of 10 patients, and is associated with dysregulated glucose metabolism (either high or low) in 53%. There is an unmet need for improved emergency treatments for HK.

Funding: Commercial Support - AstraZeneca

FR-PO647

Treatment of Hyperkalemia with Insulin: Comparative Evaluation of Patient Characteristics

Toby J. Humphrey, Ian Wilkinson, Thomas F. Hiemstra. *University of Cambridge, Cambridge, United Kingdom.*

Background: Hyperkalaemia (HK) is a comon and serious medical emergency and current standard of care consists of an insulin infusion. Here, we report characteristics of HK patients treated with insulin in a tertiary hospital in the UK, compared with HK patients not treated with insulin.

Methods: HK patients (at least 1 potassium measurement ≥6mmol/L) were identified from electronic health records of patients admitted to a tertiary hospital between April 2015 and August 2018. All HK patients treated with insulin (K-I) were identified and compared with HK patients not treated with insulin (K-noI). Categorical variables were compared by X^2-test and continuous variables by Student's *t*-test or Mann–Whitney *U*-test. Associations with insulin treatment were explored using a mixed effects logistic regression model with insulin use as the dependent variable, odds ratios (OR) are reported with associated 95% confidence intervals.

Results: HK ≥6mmol/L was identified in 5,272 of 211,993 patients (1.9%) attending the Emergency Department. Of these, 1284 received insulin for HK (K-I). Compared to K-noI patients, K-I patients were older (72 years(59.5-84.5) vs 71(53-83), p<0.001), more likely to be diabetic (35% vs 25.2%, p<0.001) and have chronic kidney disease (CKD) (39.9% vs 18.6%, p<0.001). Median length of hospital stay was longer in K-I patients (11.7 days (4.9-24.7) vs. 6.0 (1.2-17.3), p<0.001). A higher proportion of K-I patients were taking ACE Inhibitors (30.1% vs 23.1%, p<0.001), Angiotensin-2-receptor blockers (12.3% vs 9.2%, p=0.001) or potassium-sparing diuretics (17.1% vs 9.6%, p<0.001). In a mixed-effects logistic regression model, insulin treatment was associated with CKD (OR 2.4, 2.1-2.8), male sex (OR 1.6, 1.4-1.8), potassium-sparing diuretics (OR 1.6, 1.3-2.0) and hypertension (OR 1.3, 1.1-1.5). At the end of follow up, 575/1,284 patients (44.8%) in K-I vs 1,089/3,988 patients (27.3%) had died (p<0.001). In a logistic regression model adjusting for age, gender and co-morbidity, the risk of death remained higher in the K-I group (OR 1.9, 1.6-2.2). Exact cause of death was not assessed.

Conclusions: Patients that receive insulin for HK are older, more likely to be male and have hypertension, CKD, diabetes and exposure to medications that increase potassium than those that do not. Receiving insulin for HK is associated with longer hospital stay and a higher risk of death.

Funding: Commercial Support - AstraZeneca

FR-PO648

Hyperkalemia Progression Rates Among Patients with Mild Hyperkalemia

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Background: To describe time to progression from mild hyperkalemia (HK) to moderate-to-severe or severe HK among patients with mild HK and pre-specified subgroups.

Methods: Adults with at least one mild HK event (i.e. serum potassium [K^+] > 5.0 and ≤ 5.5 mEq/L) were identified using electronic medical records from the Research Action for Health Network (2012-2018). Index date was defined as the date of the first mild HK event. Patients were required to have at least one additional serum K^+ lab value during the study period (2 years post-index date). Progression to moderate-to-severe and to severe HK was defined as the first occurrences of a serum K^+ lab > 5.5 mEq/L and > 6.0 mEq/L, respectively. Kaplan-Meier analyses were conducted to estimate the rates of HK progression over the study period for the overall population and patient subgroups including those with and without chronic kidney disease (CKD in stages 3-5), heart failure (HF), hypertension, or type 2 diabetes (T2D).

Results: A total of 35,369 patients with mild HK were included in the analysis. Mean age was 65.6 years, and 47.5% were women. At 2 years post-index, 16.9% and 8.7% of patients progressed to moderate to severe HK and to severe HK, respectively (**Table**). Patients with CKD, HF, hypertension, and T2D experienced higher rates of HK progression compared with patients without those conditions (all log-rank $p < 0.001$) (**Table**). HK progression rates also increased significantly as CKD stage increased ($p < 0.001$) (**Table**).

Conclusions: A total of 16.9% of patients with mild HK experienced HK progression during the 2-year follow-up period. HK progression rates increased significantly with CKD stage and were also higher among those with HF, hypertension, or T2D.

Funding: Commercial Support - AstraZeneca

Table. Progression to Moderate-to-severe and Severe HK among Patients with Mild HK

Progression outcome	HK progression among all patients	HK progression by subgroup (n)										
		CKD Stage					HF		Hypertension		T2D	
		No CKD	Stage 3	Stage 4	Stage 5 without dialysis	Stage 5 with dialysis	Yes	No	Yes	No	Yes	No
	(n=35,369)	(23,777)	(7,792)	(1,892)	(1,377)	(531)	(5,132)	(30,237)	(20,540)	(14,829)	(11,197)	(24,172)
Moderate-to-severe	16.9%	12.0%	21.7%	32.2%	43.6%	50.2%	32.7%	19.4%	25.0%	16.7%	29.0%	18.1%
Severe	8.7%	3.9%	7.5%	12.4%	22.8%	31.3%	15.7%	7.3%	10.1%	6.7%	12.3%	6.9%

FR-PO649

Compared Effects of Calcium and Sodium Polystyrene Sulfonate on Mineral, Bone Metabolism, and Acid-Base Equilibrium in CKD Patients with Hyperkalemia

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Background: Hyperkalemia is prevalent in end-stage renal disease patients, being involved in life-threatening arrhythmias. Although polystyrene sulfonate (PS) is commonly used for the treatment of hyperkalemia, direct comparison of effects between calcium and sodium PS (CPS and SPS) on mineral, bone metabolism and acid-base equilibrium has not yet been studied.

Methods: This study was designed as a prospective, open-labeled, randomized, and crossover study (n=40). Patients were orally administered CPS (ARGAMATE® 89.29 % GRANULE 5.6 g; powder 5 g) or SPS (KAYEXALATE DRY SYRUP 76%® 6.54 g; powder 5 g) after each meal. After 4 weeks treatment, each PS was immediately switched to another PS without washout interval, and followed-up for further 4 weeks. To investigate the cation-absorption capacity of CPS and SPS, we constructed an artificial colon fluid (ACF) based on the data of human diarrhea as described previously. One gram of CPS or SPS was added into the 50 ml of ACF (n=6, respectively). After filtration, the concentrations of K, Ca, Na, Mg, and NH_3 in the supernatant were determined.

Results: After 4 week-treatments, there was no significant difference of changes in serum potassium (K) from the baseline (ΔK) between the two groups. However, SPS significantly decreased serum calcium (Ca) and magnesium (Mg) and increased intact parathyroid hormone (iPTH) values, whereas CPS reduced iPTH. ΔiPTH was inversely correlated with ΔCa and ΔMg (r=-0.53 and r=-0.50, respectively). Furthermore, sodium (Na) and atrial natriuretic peptide (ANP) levels were significantly elevated in patients with SPS, but not with CPS, whereas ΔNa and ΔANP were significantly correlated with each other in all the patients. We also found that SPS, but not CPS treatment significantly increased plasma HCO_3^- and serum Na levels, while serum NH_3 levels were not changed by either PS treatment. ΔNa and Δ(Na to Cl ratio) but not ΔNH_3 were positively correlated with ΔHCO_3^- (r=0.75, p<0.0001, r=0.84, p<0.0001, and r=0.06, p=0.75, respectively). In artificial colon fluid, CPS increased Ca and decreased Na. Furthermore, SPS more decreased K, Mg, and NH_3.

Conclusions: Compared with SPS, CPS may be safer for the treatment of hyperkalemia in pre-dialysis patients, because it did not induce hyperparathyroidism or volume overload.

Funding: Private Foundation Support

FR-PO650

Reflex Ordering of Polystyrene Sulfonate for "Red-Flagged" Mild Hyperkalemia: A Problem of Perception

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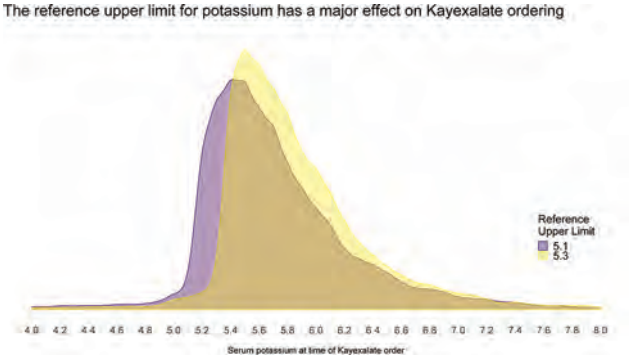
Background: Lab test results, typically reported with reference ranges, are often flagged and red when abnormal. For potassium (K), while treatment recommendations have not changed, reference limits may have. How the reference upper limit (RUL) impacts provider responsiveness to hyperkalemia treatment with polystyrene sulfonate (PS, Kayexalate) is unknown.

Methods: We queried the EHR at 14 hospitals in a large integrated health system, for orders of PS between 2012-2018. The serum K at the time of an order was deemed the result that occasioned treatment. We extracted the RUL for the result, which changed from 5.1 to 5.3 mEq/L in December, 2015. We compared PS ordering based upon RUL using a two-sample Kolmogorov–Smirnov (KS) test. KS is a nonparametric test to determine if two samples are drawn from the same distribution; the null hypothesis is that the distribution of orders by K level remains the same regardless of RUL.

Results: There were 43,497 orders for PS, almost evenly split between RUL 5.1 and 5.3. The two distributions were statistically different (D = 0.17478, p-value < 0.0001). For results with RUL 5.1, the initial peak in PS ordering occurred at K 5.2, whereas it occurred at 5.4 with RUL 5.3. The maximum absolute difference between the two cumulative curves (D statistic), 0.17, occurs at K 5.3, falling within the "high" range for RUL 5.1, but normal for RUL 5.3. For RUL 5.1, approximately 10% of results between 5.2-5.3 led to a PS order, whereas only 2% led to an order for RUL 5.3.

Conclusions: While the physiologic understanding of K and its serum levels have not changed, we found that modifying the RUL led to major changes in PS prescribing for hyperkalemia. This abrupt and sustained shift suggests a reflexive approach to treatment, whereby providers are ordering PS based upon an abnormal flag or red-colored value, rather than clinical indication. Educating providers and using appropriate nudges or defaults can lead to more thoughtful approaches to management of K and other electrolyte disorders.



FR-PO651

Efficacy and Safety of Sodium Zirconium Cyclosilicate for Reducing the Incidence of Hyperkalemia in Patients with ESRD: A Japanese Subgroup Analysis of the DIALIZE Study

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Background: Patients with end-stage renal disease (ESRD) are at increased risk of developing hyperkalemia (HK), despite receiving hemodialysis (HD), even if with use of lower dialysate potassium concentration (2.0mEq/L). DIALIZE (NCT03303521), a randomized, double-blind, placebo (PBO)-controlled, phase 3b, international study, determined the efficacy and safety of sodium zirconium cyclosilicate (SZC) for the treatment of HK in ESRD patients undergoing HD. Here, we report an exploratory analysis of the Japanese subgroup.

Methods: Patients were adults on stable HD with HK, and were randomly assigned (1:1) to receive PBO or SZC. Study drugs were administered orally, starting at a dose of 5g once daily on non-dialysis days and titrated at 5g increments to a maximum of 15g daily, to maintain normokalemia (serum K: 4.0-5.0mmol/L). Primary endpoint was the proportion of responders (i.e., patients who maintained a pre-dialysis serum K between 4.0 and 5.0mmol/L on at least 3/4 dialysis treatments after a long inter-dialytic interval without requiring rescue therapy during the evaluation period), and secondary was the proportion of patients requiring rescue therapy for severe HK. Adverse events and inter-dialytic weight gain (IDWG) were evaluated for safety.

Results: A total of 56 Japanese patients were randomly assigned: 28 received SZC, and 28 PBO; 96.4% completed the study in the SZC group and 100% in the PBO group. Patients in the SZC and PBO groups had a mean age of 60.7 and 64.4 years, respectively; all other baseline characteristics were balanced between groups. 71.4% (n=20) and 0% were responders (nominal p<.001) in the SZC and placebo group, respectively. Further, 3 subjects in the placebo group but none on SZC required rescue therapy. AEs were reported in 53.6% (n=15) and 57.1% (n=16). Two SAEs were reported, one in SZC group (gastrointestinal hemorrhage) and one in placebo group (arteriovenous fistula site complication); both events were deemed unrelated to the study drug. IDWG was similar in both groups.

Conclusions: This exploratory analysis showed that the safety and efficacy profile of SZC in the Japanese subgroup is in line with that observed in the global study population.

Funding: Commercial Support - AstraZeneca

FR-PO652

Additional Benefit of Patiromer Under Real-Life Conditions

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Background: Patiromer was placed on the market in Germany in April 2018. Additional Benefit was not affirmed by regulatory authorities (GBA-Gemeinsamer Bundesausschuss). In the OPAL-HK trial, in patients that were treated with Patiromer, mean serum potassium levels declined by 1.01±0.03 mmol/L and after 4 weeks 76% of the patients reached potassium levels below 5.1 mmol per liter. We sought to evaluate, whether these promising results can be achieved under real-life conditions outside of clinical trials.

Methods: We analysed potassium levels in all patients treated with patiromer in a large chronic kidney disease cohort including patients with and without renal replacement therapy. In addition, the number of patients that reached the target range below 5.1 mmol/l was evaluated. Data extraction and analysis were performed using an multi-factorial Algorithm-based approach.

Results: 7222 Patients that were treated between 1.1.2018 and 15.4.2019 were screened. 49 Patients (20 females) were treated with Patiromer (24 hemodialysis, 2 peritoneal dialysis, 23 CKD). For 37 patients at least one potassium value was available before and after initiation of Patiromer. Mean potassium levels were 5.85±0.56 mmol/L before and 5.45±0.77 mmol/L on treatment with Patiromer (p<0.01). However, only 13 out of 37 patients (35%) reached a potassium level in the target range below 5.1 mmol/l.

Conclusions: With only 35% of patients in the potassium target range below 5.1 mmol/l, additional benefit of Patiromer under real-life conditions was small compared to OPAL-HK where 76% reached the target range.

FR-PO653

Long-Term Healthcare Cost and Resource Use in Patients with Hyperkalemia

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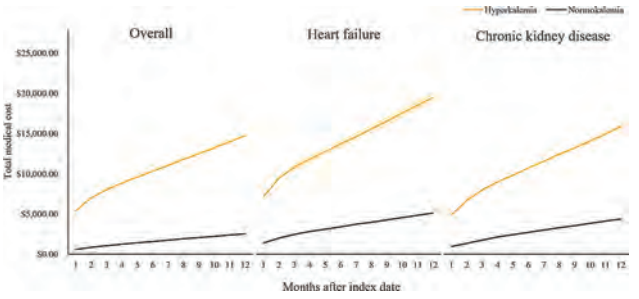
Background: Few studies provide information on economic burden of hyperkalemia (HK) especially regarding long-term healthcare cost and resource use.

Methods: A retrospective cohort study was done with a Japanese hospital claims database, Medical Data Vision. We extracted data for patients aged ≥18 years with ≥2 serum potassium (S-K) values ≥5.1 mmol/L; from April 1, 2008, to September 30, 2018 for patients with HK, and normokalemic patients without any record of S-K ≤3.5 mmol/L or ≥5.1 mmol/L. Direct healthcare cost and resource use over 1 year after the first HK episode and during follow-up after 1 year were separately assessed.

Results: 27,534 HK cases and 233,098 normokalemic controls were identified from a total of 1,208,894 patients who had at least one S-K value. Mean length of follow-up was 2.90 years in cases and 3.68 years in controls. Compared with controls, median inpatient and outpatient costs per visit over 1 year were significantly higher in HK (inpatient: $6,614 vs. $4,046; outpatient: $231 vs. $116) (p <0.001) and after 1 year (inpatient: $6,072 vs. $4,042; outpatient $253 vs. $130) (p <0.001). Median total costs in HK and controls were $7,617 (interquartile range [IQR] $3,119-$19,733) and $938 (IQR $345-$2,359) over 1 year, and $4,335 (IQR $1468-$1,1620) and $779 (IQR $269-$2,079) after 1 year, respectively. Median total costs were higher in subgroups of heart failure ($11,147) and chronic kidney disease ($8,407) (Figure). HK cases had higher resource use including incidences of hospitalization (62.6% vs. 14.4%), rehospitalization (10.0% vs. 1.1%), and emergency room (ER) visit (26.9% vs. 3.2%) over 1 year. Higher resource use continued after 1 year with cumulative incidences of hospitalization (73.7% vs. 49.7%), rehospitalization (29.3% vs. 7.3%), and ER visit (50.4% vs. 16.3%). HK cases had longer hospital stay (mean 22.97 days vs. 11.05 over 1 year, and 21.06 vs. 10.94 days after 1 year).

Conclusions: The results showed that HK is associated with significant long-term economic burden and needs careful medical attention.

Funding: Commercial Support - AstraZeneca K.K.



Mean cumulative cost over 12 months after hyperkalemia

FR-PO654

Hyperkalemia and Progression of CKD

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Background: To compare rates of chronic kidney disease (CKD) progression between CKD patients with and without hyperkalemia (HK).

Methods: Adult patients with CKD stage 3-4, with or without HK, were selected from electronic medical records from the US Research Action for Health Network (2012-2018). CKD stage was identified by diagnosis codes or estimated glomerular filtration rate (eGFR). HK was defined as having ≥1 serum K^+ lab value >5.0 mEq/L and confirmed by another HK event. Index dates were defined as 30 days after the first K^+ lab >5.0 mEq/L for HK patients and after a randomly selected K^+ lab ≤5.0 mEq/L for patients without HK. Patients were required to have ≥1 eGFR value in both the baseline (6 months pre-index date) and study period (up to 5 yrs post-index date). Two outcomes were evaluated separately: 1) progression to CKD stage 5; 2) ≥10 unit decline in eGFR. Kaplan-Meier analyses and multivariable Cox models adjusted for baseline eGFR, demographic characteristics, relevant comorbidities, and treatment use were performed. Sensitivity analyses were performed adjusting for albumin-creatinine ratio (ACR), stratifying by baseline CKD stage, and excluding patients with baseline acute kidney injury (AKI).

Results: Patients with HK (n=9,220) vs. those without HK (n=36,764) (mean age 72.3 vs. 72.7 yrs) had higher rates of CKD stage 4 (33.9% vs. 9.7%), heart failure (31.7% vs. 15.0%), and AKI (33.8% vs. 11.5%), and a higher ACR value (393.9 vs. 154.4 mg/g). In the 5-yr study period, 16.7% of HK patients and 3.5% of those without HK progressed to CKD stage 5, and 31.7% and 17.0%, respectively, had an eGFR decline ≥10 units (both log-rank p<0.001). In Cox models, patients with vs. without HK had a statistically significant higher risk of CKD progression to stage 5 (adjusted hazard ratio [aHR] 2.20; 95% confidence interval [CI], 2.02-2.38) and eGFR decline (2.40; 2.28-2.52) (both p<0.001). Cox model results were consistent when adjusting for ACR, stratifying by baseline CKD stage, or excluding AKI patients.

Conclusions: Even after adjusting for relevant comorbidities and treatments, HK was significantly associated with higher risk of progression to CKD stage 5 and eGFR decline among patients with CKD stage 3-4. Associations were robust in all sensitivity analyses.

Funding: Commercial Support - AstraZeneca

FR-PO655

Detection of Hypoglycemia Incidents After Hyperkalemia Treatment with Dextrose 50% and Insulin

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Background: Hypoglycemia is a potential complication following hyperkalemia treatment with insulin. Most of the previous trials studied this risk in patients with decreased GFR. Our study assessed the incidence of hypoglycemia and its associated risk factors in patients with normal and decreased kidney function.

Methods: We conducted a retrospective study of hospitalized adult patients at a large community hospital who had hyperkalemia [potassium >5.4mmol/L] and were treated with intravenous insulin and dextrose 50%. We identified the incidence of hypoglycemia [blood glucose<70mg/dL] within six hours of insulin administration.

Results: 142 patients were eligible for analysis. 25 patients (17.6%) developed hypoglycemia. Hypoglycemia was detected at a median of 105 minutes after insulin administration. Factors associated with a higher risk of hypoglycemia included lower body mass index mean(25.2±8.2vs.30.3±9.2)p=0.01, no history of diabetes OR 5.16, 95%CI:1.67-16.0;p=0.002, and patients who didn't receive co-treatment with Polystyrene sulfonate [p=0.047]. Patients with hypoglycemia had lower pre-treatment glucose levels compared to patients who did not mean(96.9±50.5vs.154.7±87.8)p=<0.0001. Previous trials showed a lower risk of hypoglycemia in patients who received co-treatment with

albuterol. Our study showed a non-significant trend toward higher risk of hypoglycemia in patients who received albuterol co-treatment [n=19 (20.3%) vs.n=10 (14.7%);p=0.384]. There was no difference hypoglycemia incidents in patients with normal kidney function versus patients with decreased kidney function, [normal kidney function vs. acute kidney injury p=0.98; normal kidney function vs. ESRD p=0.93]. There was no significant difference in the mean eGFR in hypoglycemic versus non-hypoglycemic patients (24.75±32.4vs.24.89±26.0)p=0.98.

Conclusions: Patients with lower BMI and no history of diabetes were at a significantly higher risk for hypoglycemia. This is maybe explained by a lack of insulin resistance associated with low BMI and non-diabetic status. Lower pretreatment glucose levels were associated with hypoglycemia. Hypoglycemia was most likely to develop within 1-3 hours of treatment. This study supports the recommendations of frequent blood glucose monitoring following hyperkalemia treatment with intravenous insulin. Identifying risk factors is crucial

FR-PO656

TolvaThirst: Is Thirst Triggered to Adapt to an Acute Natremia Increase in Chronic Hyponatremic Patients?

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Background: Water body content is tightly controlled by both input (mostly, thirst-driven intake) and output (mostly, renal aquaresis). The osmotic-driven thirst threshold is 10 mOsm/kgH_2O higher than that of arginine vasopressin (AVP) secretion; it takes over when AVP-induced antidiuresis fails to limit water loss. In chronic hyponatremic patients, both AVP release and/or thirst could be impaired. However, their ability to maintain natremia within a narrow range in response to acute water loss has never been reported.

Methods: We submitted chronic hyponatremic patients (n=31) to acute water loss through a single oral 15 mg tolvaptan administration, a type 2 AVP-receptor antagonist. We then monitored hourly plasma sodium and osmolality, urine output and osmolality, and water intake, as well as thirst scales.

Results: Overall, tolvaptan induced a significant weight loss (-1.2±1.2%, p<0.001) and natremia increase (+3.0±2.9mM, p<0.001). In 18 "isonatric" patients, natremia remained steady (+1.1±1.6 mM) during the first 6 hours (*cf.* **Figure 1**), whereas in 13 "dysnatric" patients, it significantly increased (+5.8±1.7 mM, p<0.001). Even if all patients had no difference in minimum urine osmolality (*i.e.* no difference regarding to the pharmacological intervention), "isonatric" patients had a better water balance (+1.22±7.2 *vs.*-16.4±7.0 mL/kg, p<0.001), mostly driven by a better water intake during the first hour (13.4±7.5 *vs.*8.8±10.0 mL/min, p=0.009).

Conclusions: Acute aquaresis-triggered water intake prevented changes innatremia in about 60% of the reported patients, whereas in 40% this mechanism was impaired. Further studies are needed to address the (patho)physiology of thirst adaptation and acute water intake in chronic hyponatremic patients, then to develop tools for identifying patients at risk for wide changes in natremia.

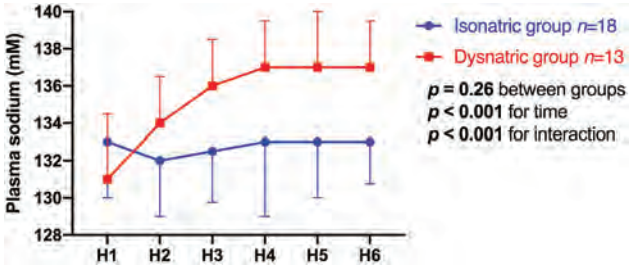

Figure 1. Evolution of natremia after a single tolvaptan administration during the first 6 hours (H1 to H6): 13 "dysnatric" patients significantly increased their natremia, when 18 "isonatric" did not.

FR-PO657

De Novo Central Diabetes Insipidus Abruptly Unmasked by Discontinuation of Intravenous Vasopressin

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Introduction: Central diabetes insipidus (CDI) is an uncommon disorder during septic shock. Hyponatremia is also an uncommon adverse effect of intravenous (IV) vasopressin (AVP). Rapid correction of hyponatremia is associated with ominous neurological sequelae. We describe a rare case of abrupt onset of polyuria mimicking CDI following cessation of IV AVP vasopressor use that led to rapid correction of hyponatremia.

Case Description: A 64-year-old woman admitted with small bowel obstruction developed a purulent surgical site infection 6 days post adhesiolysis that required a washout procedure, 13 L of crystalloid fluid resuscitation and transfer to intensive care unit (ICU) for shock management with IV AVP as vasopressor. In the ICU, her serum Na (sNa) gradually dropped from 134 to 121 mEq/L over a 6-day period. Kidney function remained normal. As an attempt to correct the sNa, she received 40-mg IV furosemide and the Na content in parenteral nutrition was increased to 170 mEq/L, but the sNa did not improve. On ICU day 7, she returned to the operating room for additional washout and debridement. IV AVP was discontinued post-Op. Within 2 hours, the urine output (UOP) drastically increased to 600 ml/hr for a total of 11 L of UOP in 24 hrs. At that time, her urine osmolality (uOsm) decreased from 463 to 61 mOsm/kg. Her sNa rapidly corrected from 120 to 135 in 24 hours. To slow the rate of sNa correction, she received 4 L of 5% dextrose in water (D5W) and DDAVP. Her UOP decreased to 150 ml/hr, uOsm rose to 342 mOsm/kg and sNa fell back to 130 mEq/L. Two days later, DDAVP was stopped and sNa remained stable at 137 mEq/L.

Discussion: The case highlights the importance of careful vigilance of UOP and onset of water diuresis in the context of hyponatremia in septic shock treated with IV AVP. In addition to hyponatremia itself, we speculate that prolonged exposure to IV AVP may suppress endogenous release of AVP, leading to abrupt onset of CDI following discontinuation of IV AVP. Discontinuation of IV AVP in hyponatremic patients should be executed cautiously with close monitoring of UOP and uOsm and consideration for concomitant administration of D5W or DDAVP as needed.

FR-PO658

Tolvaptan in Portal Hypertension: Real-Life Experience

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Background: Tolvaptan (TVP) is an antagonist of V2 ADH receptors, used for hyponatremia in SIADH, congestive heart failure (CHF) and cirrhosis.

Methods: Retrospective review of TVP use between 2012 and 2017 to study the use of TVP in real life in patients with portal hypertension (PHT) (past history of non-malignant ascites or variceal bleed).

Results: 81 patients received TVP. Of them, 19 had PHT. CHF was more frequent in patients with PHT (53 vs 26%, p=0.03). There were no differences in natremia at the start of treatment (126±1.3 vs 128±0.6mEq/l). There was a delay in the correction of hyponatremia in the PHT subgroup over the first month, being the final serum sodium concentration 135±1.6 vs 139±0.8mEq/l (p=0.02). We found no difference in survival. In the PHT subgroup, 8 had confirmed cirrhosis and 11 severe CHF. The cause of cirrhosis was hepatitis C (n=3), alcohol (n=4) and unknown (n=1). 4 had hepatocellular carcinoma. Mean MELD score at the time of receiving tolvaptan was 12±2.3. Only one patient received a liver transplant 4 months after treatment with TVP. Cirrhotics had significant comorbidities (13% CHF; 13% microcytic lung cancer; 75% squamous cell carcinoma; 25% SIADH) and polypharmacy (13% antidepressants; 38% diuretics; 13% antiepileptics; 38% benzodiazepines; 13% cytostatics; 13% antipsychotics). Cirrhotics had fewer episodes of hyponatremia (8.4±1.1 vs 10.6±2.8), although not statistically significant. There was a trend for TVP treatment to be longer in cirrhotics (23.2±7.4 vs7.3±2.6 days, p=0.07). We studied the delay in hyponatremia correction observed in patients with PHT: it was attributable to patients with CHF, in whom the mean increase in serum sodium concentration over the first month was 1.4±1.9 vs 7.2±1mEq/l in cirrhotic patients (p=0.03). Median survival time was 105 weeks (CI95% 0-239) in CHF vs 5 weeks (CI95% 3-7) in cirrhotics, but was not statisticallt significant.

Conclusions: Even though TVP is approved for its use in hyponatremia associated to advanced cirrhosis as a bridge to liver transplant, in our centre its use is reserved to patients with significant comorbidities that can contribute to the development of hyponatremia and worsen its prognosis. Presence of ascites in CHF as a surrogate for PHT complicates management, delaying the correction of hyponatremia.

FR-PO659

Use of Selective Serotonin Reuptake Inhibitors and Risk of Hyponatremia in a Large Health Care System

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Background: Selective serotonin reuptake inhibitors (SSRIs) use may increase the risk of hyponatremia. We aimed to quantify hyponatremia risk associated with SSRIs compared to that of serotonin-norepinephrine reuptake inhibitors (SNRIs) and determine whether it differs by eGFR and thiazide diuretic use.

Methods: Among primary care patients prescribed SSRIs between January 1, 2004 and January 30, 2017 in the Geisinger Health System, we defined mild and moderate hyponatremia as outpatient blood Na<135mEq/L and <130mEq/L in the 3 months after medication initiation. We then used propensity score matching to pair patients prescribed SSRIs with those prescribed SNRIs and evaluated differences in hospitalizations for hyponatremia (defined by ICD-9 and -10 codes) during the entire course of medication use, overall and stratified by demographic factors, level of eGFR, and thiazide diuretic use.

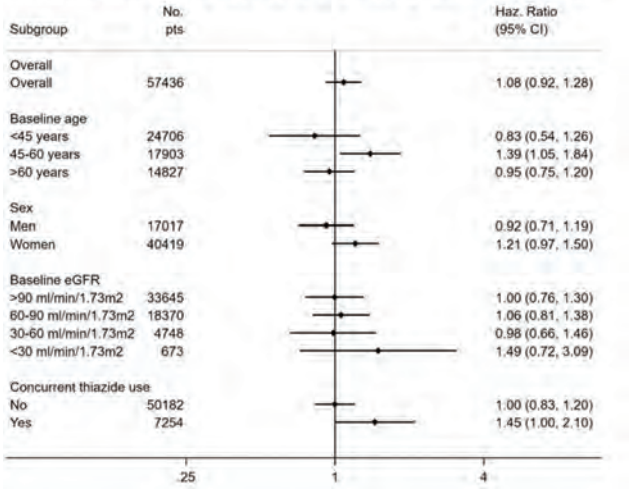
Results: Among 69,551 patients prescribed SSRIs, 25% had a blood sodium measurement within 3 months after initiation. The risk of mild and moderate hyponatremia was 11% and 3%. In comparison, 25% of the 30,089 patients prescribed SNRIs had monitoring, and the risk of mild and moderate hyponatremia was 7% and 1% (p<0.01 for both comparisons to SSRIs). In the propensity matched cohort, there was no difference in

hyponatremia hospitalization overall (1.1% in SSRIs vs. 0.9% in SNRIs; HR=1.08, 95%CI 0.92-1.28; p=0.35), but higher among those with thiazide diuretic use (1.7% in SSRIs vs. 0.9% in SNRIs; HR=1.45, 95%CI 1.00-2.10; p<0.05)(**Figure**). There was no difference in risk of hospitalized hyponatremia by level of eGFR.

Conclusions: Patients prescribed SSRIs had infrequent monitoring but were at risk for short-term outpatient hyponatremia. Thiazide diuretic use may potentiate the risk of hospitalized hyponatremia with SSRI use.

Funding: NIDDK Support

Figure. Risk of hospitalized hyponatremia comparing propensity-score matched patients prescribed SSRIs and those prescribed an SNRIs.



FR-PO660

Leveraging Electronic Medical Records to Expedite Hyponatremia Management

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Background: Hyponatremia is defined as serum sodium (Na) ≤135 mmol/L[1]; values ≤125 mmol/L are considered severe. Guidelines suggest Na correction should not exceed 6–8 mmol/L in 24 hours for either acute or chronic hyponatremia, regardless of clinical presentation[6,7]. We analyze the impact of electronic medical record (EMR) alerts to improve the diagnosis of hyponatremia, expedite appropriate management and prevent errors; this has never been described in the literature.

Methods: 2-cohort retrospective chart review conducted on inpatients before and after the implementation of two novel alerts. The first alert informed the physician of severe hyponatremia. The second alert displayed for nurses when the Na rose more than 1.5 mmol/L for two consecutive Na, prompting them to contact the provider. Cohort 1 comprised all inpatients at UHealth Tower in the 3 months before the alert's implementation. Data was collected for patients experiencing at least one Na of ≤125, and included pertinent blood and urine levels, as well as patterns of physician response. Cohort 2 comprised every patient who provoked a BPA in the 3-month period after go-live. Using the Mann-Whitney test and Fisher's Exact test for data analysis, primary endpoints were the percent of patients treated for hyponatremia, percent whose Na was normalized, and overcorrection difference. Secondary endpoints included time to intervention and treatment types.

Results: 41 patients had a Na ≤125 in cohort 1 vs 5 patients in cohort 2 (p<0.05). Na overcorrection was not seen in cohort 2; and was 9% in cohort 1 (p=1). 85% in cohort 1 received treatment for hyponatremia vs 80% in cohort 2. Na returned to normal in 75% of cohort 1 vs 40% in cohort 2, which could be due to the small sample size. Faster treatment intervention was seen in cohort 2: 76 mins vs. 24 mins (p=0.2798). Treatments in both cohorts primarily comprised normal saline and fluid restriction.

Conclusions: The implementation of EMR alerts significantly reduce the incidence of severe hyponatremia and may improve response provider response time, with lower overcorrection rates. These unique alerts, geared to assist in the timely management of hyponatremia, could be expanded to other tests and conditions. A follow-up study to explore standardizing management is ongoing.

FR-PO661

Severe Hypernatremia from Sea Water Ingestion Treated with Continuous Renal Replacement Therapy

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Introduction: Severe hypernatremia is uncommon and conventional management of patients with severe hypernatremia is unpredictable. Too rapid or too slow correction can both lead to catasthrophic outcome. We report a case of a patient who was lost at sea for 3 days and presented with serum sodium of 174mmol/L. He was managed with continuous veno-venous hemodiafiltration (CVVHDF) for controlled reduction of sodium.

Case Description: A 59 year-old gentleman was found at sea 3 days after being reported missing. On presentation, he was dehydrated, lethargic with first degree sun burnt over his body. He was tachycardia (heart rate of 118 bpm), BP 104/74mmHg. His weight was 80kg and height 170cm. His sodium was 174mmo/L, chloride > 140mmo/L, bicarbonate 10.3mmol/L, Creatinine 118micromol/L, urea 14.8mmol/L, glucose 5.5mmol/L and serum osmolality of 357mOsm/kg. His urine sodium 221mmol/L, urine potassium 69mmol/L and urine osmolality 1100mOsm/kg. His urine output ranged between 40-50mls/hour. He was managed initially at the emergency department with Dextrose 5% drip and kept nil by mouth. His sodium drops from 174mmol/L to 168mmol/L over the next 6 hour. Due to risk of unpredictable changes in sodium level, decision was made to initiate CVVHDF with citrate anticoagulation. His dialysis prescription was as follows: Qb of 150mL/min, Qd of 1L/hour, QR of 1.6L/hour via a left femoral dialysis catheter. Customization of dialysate and replacement fluid was performed by addition of 3% sodium chloride solution. His sodium levels decreased as expected. and achieved normal sodium level over 4 days. He was weaned off CVVHDF on day 5. (Figure 1) Patient subsequently was transferred to a private hospital for further management.

Discussion: Extreme hypernatremia is rare and changes in sodium level with conventional treatment can be unpredictable. Correction of severe hypernatremia with CVVHDF provide a slow reduction of serum sodium in a controlled manner with positive outcome.

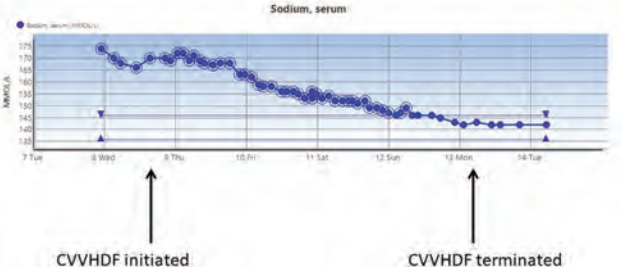

Figure 1: Serum sodium trend prior, during and after CVVHDF

FR-PO662

Acid-Base Disturbances in Multiple Myeloma

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Introduction: Multiple myeloma (MM) can be associated with several acid/base abnormalities that may not be as frequently appreciated as other clinical manifestations such as renal insufficiency, anemia, hypercalcemia, lytic bone lesions.

Case Description: A 62-year-old man with relapsed IgA kappa monoclonal MM presented with confusion and malaise. Labs showed: serum bicarbonate 13 mEq/L, serum chloride 102 mEq/L, anion gap (AG) 19, albumin 1.6 g/dL. Beta-hydroxybutyrate and lactic acid were not elevated. Additional labs included: blood urea nitrogen 29 mg/dL, creatinine 1.1 mg/dL, eGFR 72 mL/min/1.73m^2. Arterial blood gas demonstrated pH 7.50, pCO2 18 mmHg, pO2 95 mmHg. Head imaging and infectious work-up were unremarkable. Although renal function normalized with supportive care, symptoms did not improve and these acid/base abnormalities persisted. Despite no history of liver disease and normal liver function tests, serum ammonia was elevated at 142 umol/L. MM-associated hyperammonemic encephalopathy leading to hyperventilation was felt to be the cause of his respiratory alkalosis. In addition, the elevated AG was attributed to presumed negatively charged IgA. Ultimately, plasma exchange was started, and he received carfilzomib, pomalidomide, and dexamethasone. His acid/base abnormalities subsided with treatment of his MM, and mental status returned to baseline.

Discussion: This case demonstrates unusual acid/base disturbances associated with MM. Respiratory alkalosis from hyperammonemic encephalopathy is thought to be due to excess ammonia production by myeloma cells.[1] Several cases report failure with standard treatments for hyperammonemia but response to chemotherapy.[2-3] Furthermore, inpatient mortality is reduced in patients who received MM-targeted therapy compared to those who did not.[4] The AG metabolic acidosis is presumed due to negatively charged IgA immunoglobulins. An increased AG has been reported in up to 30% of patients with IgA monoclonal gammopathy, in contrast to a decreased AG that is more commonly seen in IgG gammopathy.[5] Of note, however, the magnitude of AG elevation does not correlate with monoclonal protein concentration, and AG abnormalities are not a sensitive test for screening for monoclonal gammopathies.[5] It is important for clinicians to recognize and understand these potential acid/base disturbances in MM, as early identification may expedite proper therapy.

FR-PO663

Tolvaptan Resistance in Severe SIADH

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Introduction: Approaches to treat euvolemic hyponatremia include: 1) minimizing input of hypotonic solutions (restricting positive free water); 2) administering hypertonic solutions (giving negative free water); 3) decreasing the driving force for electrolyte-free water reabsorption by a) increasing the urinary solute load (oral urea, NaCl, KCl) and b) decreasing medullary concentration (loop diuretics); and 4) decreasing the permeability for electrolyte-free water reabsorption (demeclocycline, vaptan aquaretics). The recent introduction of tolvaptan provides a molecular tool to essentially treat the syndrome of

inappropriate anti-diuretic hormone (SIADH) secretion with "nephrogenic DI in a bottle." We present a case where all of these approaches were utilized.

Case Description: A 48-year-old man developed severe hyponatremia (serum [Na] 107 mM) due to SIADH in the setting of recurrent metastatic small cell lung cancer. He was asymptomatic. Oral fluid restriction and 3% NaCl were employed to gradually increase his serum [Na] to 125 mM over 4 days. He was then placed on tolvaptan 15 mg daily without effect, so the dose was increased to 30 mg daily and he was discharged home 2 days later with a serum [Na] of 131 mM. Over the next 4 days, serum [Na] decreased to 127 mM and 3 days later he felt "off" and was re-admitted with serum [Na] 117 mM. Tolvaptan was increased to 60 mg daily—and ultimately to 60 mg twice daily—without effect, as urine osmolality remained >900 mosm/kgH_2O. Serum [Na] increased sluggishly to 122 mM two days later but then decreased again to 117 mM. Tolvaptan was discontinued and he was placed on NaCl tablets 2 g tid, KCl 20 mmoles twice daily, and furosemide 40 mg twice daily. Over the next 3 days, serum [Na] increased to 124 mM. Oral urea 15 g twice daily was started and serum [Na] only increased to 126 mM, so the dose was increased to 30 g twice daily, and over the next 4 days serum [Na] increased to 140 mM. The patient has since maintained isotonicity on twice daily use of urea 30 g, NaCl 2 g, KCl 20 mmoles, and furosemide 40 mg.

Discussion: This case illustrates that a patient with severe SIADH may be resistant to a maximal dose of tolvaptan yet still respond to traditional measures. Therefore, while aquaretic therapy aimed at the underlying free water permeability defect may be more physiologically elegant, maneuvers that modify the driving force for electrolyte-free water reabsorption may be more practical.

FR-PO664

Dysnatremia and Crude Mortality Rates: Evidence from the Sodium Metabolism and Management Experience (SoMME) Study

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Background: Few studies have evaluated the association of dysnatremia with mortality among hospitalized patients. It is unclear if there is a reduced mortality rate among hospitalized patients with deranged sodium levels. We evaluated the association between sodium levels on admission with in-patient mortality, 30 day mortality and long term mortality. We hypothesized that mortality rates will vary by sodium levels with worse mortality outcomes at both extremes of sodium levels.

Methods: We obtained data from 39261 patients admitted between 2012-2016 patients who had a serum sodium on admission at a tertiary referral hospital in Central Wisconsin. We classified them into five categories based on their admitting serum sodium as severe low (<125), moderate low (125-129), mild low (130-134), normal (135-145) and high (>145). We obtained their vital status (alive or deceased) at end of hospital stay, within 30 days of admission and at the end of study period on December 31, 2017. Data were stratified by age and sex.

Results: There were 39261 patients (53% males, 97% whites) with age groups: <45 (12%), 45-64 (30%), 65-84 (44%) and >=85 years (14%). A U-shaped distribution of mortality is associated with serum sodium levels with mortality associated with high sodium levels being the greatest. Mortality associated with moderate low sodium levels almost approximate that of severe low sodium levels. These results were consistent across age and sex.

Conclusions: Higher crude mortality was seen in all patients with dysnatremia. Hypernatremia was associated with the worst mortality. Exploring mechanisms that contribute to death in dysnatremia, and researching if correcting sodium levels may prevent further deaths in the future.

Funding: Private Foundation Support

Mortality during admission, within 30 days of admission or at end of study period by levels of admitting serum sodium level

Sodium on admission mmol/L	Number of admissions N	Deceased during admission* N (%)	Deceased during admission or within 30 days of admission* N (%)	Deceased at end of study* N (%)
Severe low (<125)	506	26 (5.1)	61 (12.1)	240 (47.4)
Moderate low (125-129)	1210	71 (5.9)	152 (12.6)	580 (47.9)
Mild low (130-134)	8724	282 (3.2)	592 (6.8)	2935 (33.6)
Normal (135-145)	27813	625 (2.3)	1148 (4.1)	5227 (18.8)
High (>145)	1008	97 (9.6)	187 (18.6)	489 (48.5)
Total	39261	1101 (2.8)	2140 (5.4)	9471 (24.1)

*p-value for trend is <0.0001 using the chi-square statistic for all outcomes.

FR-PO665

Hypernatremia Induced by Treatment for Hypokalemia in a Patient with Sjögren Syndrome and Renal Tubular Acidosis

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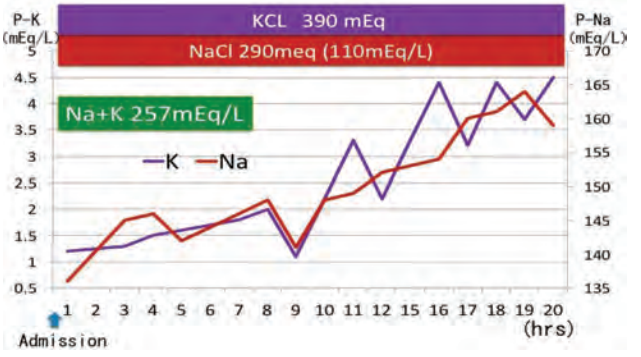
Introduction: Hypokalemia and metabolic acidosis are severe complications of renal tubular acidosis (RTA) in Sjögren's syndrome. The concentration of sodium in the plasma water should equal the concentration of sodium plus potassium in the total body water. The sodium concentration is not always considered when treating hypokalemia.

Case Description: A 60-year-old women presented with general weakness, hypotension, hypokalemia, metabolic acidosis, and acute kidney injury. Her blood pressure was 60/44mmHg, and her heart rate was 89/min. Na^+ 144 K^+ 1.5 mEq/L, Cl^- 114 mEq/L, glucose 166 mg/dL, BUN 65.9 mg/dL, Cr 2.34 mg/dl, pH 7.052, P_{CO2} 36.2, P_{O2} 321, and HCO^{3-} 9.6 mEq/L. Urinary electrolytes Na^+ 41 mEq/L, K^+ 12.2 mEq/L, Cl^- 32 mEq/L, pH 6.5, Osmolality 244 mOsm/kg. The patient was intubated because of respiratory muscle weakness from severe hypokalemia. She was treated with intravenous potassium chloride (KCl 400 mEq) and isotonic fluid for the treatment of hypovolemic shock. This solution was actually hypertonic because of its high potassium concentration: Na^+ 110 mEq/L, and K^+ 147 mEq/L, in a total of 2.6 liters. After 18 hours the patient developed hypernatremia (Na^+ 161 mEq/L), but her serum potassium had normal sized (K^+ 4.6 mEq/L). Her urinary measurements were as follows: Na^+ 40 mEq/L, K^+ 52.7 mEq/L, Cl^- 82 mEq/L, and osmolality 405 mOsm/kg. After the hypertonic fluid was changed to a hypotonic type, she recovered. She was also found to have Sjögren's syndrome after a positive screen for anti-Lo, and anti-Ra antibodies. A positive Schirmer's test and a renal biopsy also suggested Sjögren's syndrome. She was discharged without complications. There is no physical examination or other vital signs.

Discussion: This case indicates that serum sodium concentration should be carefully monitored in patients with hypokalemia and acute kidney injury induced by distal RTA receiving intravenous potassium chloride therapy and hypertonic fluid, which contain high levels of potassium. We should keep this complication in mind when treating severe hypokalemia.



Clinical Course

FR-PO666

Symptomatic Hyponatremia: SIADH or NSIAD): Diagnostic Challenge, Surprise Diagnosis, and Successful Management with Tolvaptan for 6 Years

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Introduction: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of euvolemic hyponatremia. In the absence of any identifiable cause after extensive investigations, and especially in the presence of low or undetectable serum ADH level, diagnoses such as nephrogenic syndrome of inappropriate antidiuresis (NSIAD) caused by gain-of-function mutations in the V2 vasopressin receptor (V2R) have to be entertained. Chronic management of symptomatic hyponatremia can also be a challenge.

Case Description: A 17 year old previously healthy girl presented with dizziness, and short-term memory loss. Blood tests revealed serum sodium 128 mEq/L. Clinical picture was suggestive of SIADH (euvolemic state, low serum osmolality, increased urinary osmolality, and increased urinary sodium level) but extensive investigations/imaging studies failed to delineate any underlying cause for SIADH. Review of old medical records revealed normal serum sodium (142 mEq/L) over a decade ago. She was managed as possible SIADH, with water restriction that resulted in modest improvement in her serum sodium level. A month later her symptoms recurred with recurrence of hyponatremia. Serum ADH levels returned undetectable on both occasions and were confirmed to be low 3rd time from two different labs. Later, her serum sodium acutely dropped to 119 mEq/L when she drank water prior to a renal ultrasound. She was suspected having NSIAD but DNA sequencing of V2R gene did not show any mutation. She was managed with combination of moderate fluid restriction and daily Tolvaptan. Five years later, she had seizures with severe hyponatremia (109 mEq/L) after taking SSRI for depression. 1½ year later she had another episode of unexplained hyponatremia (118 mEq/L), and a head MRI was repeated for headache after correction of hyponatremia which revealed a small enhancing mass in the right osteomeatal infundibulum. The mass turned out to be small blue cell tumor esthesioneuroblastoma, a relatively rare nasal tumor that is rarely associated with SIADH. She underwent complete tumor resection with clear margins, and now has normal serum sodium without any fluid restriction or medications.

Discussion: Patients with chronic unexplained hyponatremia should be followed very closely and reevaluated periodically with high index of suspicion for unusual tumors.

FR-PO667

Is There a Role for Concomitant Administration of Albumin and Diuretics? A Meta-Analysis

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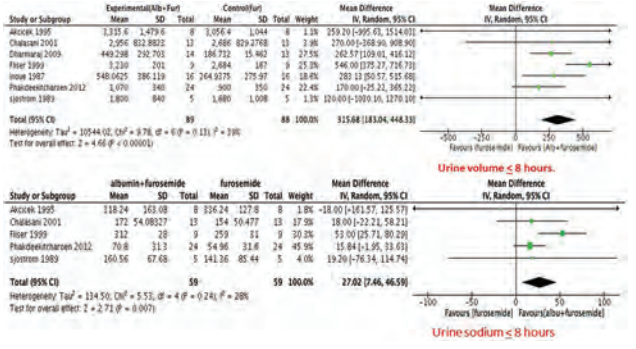
Background: Diuretics are the cornerstone of volume management in patients with disease states such as heart failure, nephrotic syndrome and cirrhosis. Diuretic resistance is commonly encountered in such patients and is often attributed to hypoalbuminemia. Albumin is sometimes empirically used to increase diuretic efficacy in these patients. We sought to systematically study the effect of albumin combined with diuretics on urine volume and urine sodium in patients with hypoalbuminemia.

Methods: Systemic search of electronic databases from inception until June 2018 was performed. We included clinical studies in patients with hypoalbuminemia that included more than 5 subjects, comparing co-administration of albumin and diuretics versus loop diuretics alone. A total of 754 records were screened independently by two investigators. 26 full text articles were assessed for eligibility. Synthesis of data was done using meta-analysis techniques using Revman Software.

Results: There were 9 eligible studies which met the criteria and had the required data. All of them were cross over studies. 6 of the studies were done exclusively in nephrotic syndrome patients, one of which included pediatric subjects. There was a statistically significant increase in urine volume of 315 ml (95% CI 183.04, 448.33) and urine sodium of 27 meq (95% CI 7.46, 46.59) at 8 hours with co-administration of albumin and furosemide compared to furosemide alone[fig]. There was no statistically significant increase in the 24 hour urine output 385 ml (95% CI -141.92, 911.68).

Conclusions: Our results suggest that in patients with hypoalbuminemia, co-administration of albumin and furosemide increases urine output and sodium excretion at 8 hours. There were no differences in urine volume at 24 hours, but most these studies used single doses or few hours of diuretic infusions. Randomized controlled trials in patients with defined diuretic resistance is required to confirm the efficacy of co-administration of albumin and furosemide.



FR-PO668

A Case of IgG4-RD Manifesting as Kidney Disease: Idiopathic or Lymphoproliferative Etiology?

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Introduction: IgG4-RD is a systemic inflammatory disorder characterized by infiltration of IgG4+ plasma cells into affected tissues. When IgG4-RD involves the kidneys it manifests most frequently as tubulointerstitial nephritis and/or membranous nephropathy. Imaging often demonstrates bilateral cortical nodular lesions.

Case Description: A 61-year-old male with hypertension presented for evaluation of elevated serum creatinine to 1.89 mg/dL. He noted NSAID use 2-4 times/week for back pain for much of the year prior, and home systolic BP readings 140-150mmHg. Additional workup revealed 378mg protein on 24-hour urine; and elevated free kappa and lambda light chains. SPEP showed hypergammaglobulinemia, with immunofixation electrophoresis negative for monoclonal bands. Bone marrow biopsy demonstrated multilineage hematopoiesis and 3% polytypic plasma cells without evidence of clonality; Congo red stain was negative for amyloid. Spine MRI showed no lytic lesions, but did identify a 2cm L thyroid nodule. PET/CT revealed markedly enlarged and hypermetabolic kidneys bilaterally. A diagnosis of plasma cell disorder was made. Renal biopsy showed severe lymphoplasmacytic tubulointerstitial disease with abundant IgG4+ plasma cells. Molecular analysis of the plasma cell infiltrate detected a clonal IgH gene rearrangement in a polyclonal background. Thyroid tissue from a left hemithyroidectomy for the above nodule was negative for IgG4, but an included adjacent lymph node was diffusely IgG4+. The patient's serum creatinine demonstrated a stable improvement to 1.3-1.4 mg/dL since initiation of workup.

Discussion: This is an unusual presentation of an uncommon disease, IgG4-related disease. Immunohistochemical staining indicated a polytypic plasma cell infiltrate on renal biopsy, while molecular testing identified a clonal cell population with IgH gene rearrangement, raising the possibility of multiple populations of plasma cells: one polyclonal, another IgG4+, and a third that is clonal and producing paraprotein. Further workup is needed to determine the etiology.

FR-PO669

Curious Case of Hypercalcemia

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Introduction: Hypercalcemia is a well-known phenomenon in malignancy. There is humoral hypercalcemia of malignancy mediated by increased parathyroid hormone-related peptide PTHrh(80%), local osteolytic hypercalcemia(20%) but in hematological tumors, another pathway of overproduction of 1, 25(OH) 2 D3 from tumor cells can cause this accounting for 1% of cases. Hereby we present a case where the only finding was mild splenomegaly and positive 1, 25(OH)2D3 leading to ultimate diagnosis of primary splenic large B cell lymphoma.

Case Description: 71-year-old male with past medical history of neuroendocrine tumor of right middle lobe of lung resected 15 years ago with no evidence of recurrence to date, history of mild elevation in PSA with biopsy showing no prostate cancer on 12/12 cores, presented to emergency department with weakness, nausea. Found to have hypercalcemia and AKI. He received pamidronate as an inpatient. His inpatient work up included CT scans (non-contrast), bone scan, skeletal survey that was negative for malignancy. However there was mild splenomegaly (14.1 cm) noted on CT. There were several calcified lymph nodes in the mediastinum as well calcified pleural plaques. Multiple myeloma screening labs were negative. PTHrh was not elevated. Flow cytometry of peripheral blood revealed no abnormalities. TB testing is negative. ACE for sarcoidosis was in normal range. PTH was suppressed. Vit D 1, 25(OH) 2 D3 was elevated at 133. Although no malignancy was found on extensive work up, we strongly felt that it was the most likely cause and referred to oncology. He was discharged after his calcium stabilized around 11. Bone marrow biopsy was done showing no evidence of disease. Finally, PET CT was performed showing a hypermetabolic spleen. He underwent splenectomy on 7/25/2018. Pathology was consistent with primary splenic large B cell lymphoma. His hypercalcemia has completely resolved. He has recovered well from his surgery. He was given standard therapy for diffuse large B cell lymphoma, which is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). He received 6 cycles of R-CHOP. Post treatment PET scan showed no evidence of disease.

Discussion: Hypercalcemia is rare in patients with B cell NHL, with its insidious presentation requiring urgent treatment. Dedicated evaluation is required in these cases. The presentation with hypercalcemia has a serious impact on prognosis and survival.

FR-PO670

Glomerulopathy, Lymphomatous Kidney Infiltration, and AKI as the First Sign of Relapsed Mantle Cell Lymphoma

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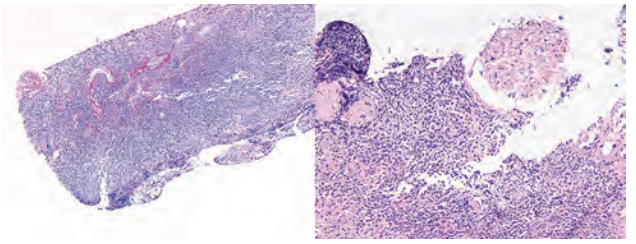
Introduction: Paraneoplastic glomerulopathy may be an early sign of malignancy. Membranous nephropathy (MN) is the most common glomerular disease reported with solid tumors and is rare in liquid tumors. We report a case of concomitant MN, lymphomatous infiltration, and acute kidney injury as the first sign of Mantle Cell Lymphoma (MCL) relapse.

Case Description: 70-year-old male with Chronic Kidney Disease stage 3 and in remission from MCL treated with autologous stem cell transplant in 2011 presented with new shortness of breath for one week. His blood pressure was 160/90, pulse 110bpm, and oxygen saturation 96% on room air. He had pitting edema to the thighs and crackles at the lung bases. Significant laboratory values included serum creatinine of 8.0 (0.7-1.3)mg/dl, baseline of 3.0mg/dl, and serum albumin of 2.2 (3.8-5.0)g/dL. Urinary protein to creatinine (UPC) ratio was 22. Urine sediment showed 5RBCs and 0WBCs per HPF. Serum immunofixation was positive for IgM kappa. Serum kappa/lambda light chain ratio was 2.0 (16/8mg/dl). Patient underwent kidney biopsy which showed widespread lymphoma infiltration (figure below) and 8/11 glomeruli globally sclerosed, the remaining had capillary wall spikes, and subepithelial deposits on electron microscopy. Immunoflourescence showed inflammatory cells positive for IgM and kappa. PLA2R staining was weakly positive. The patient recieved methylprednisolone 1 gram for 3 days and acalabrutinib for his relapsed MCL. One week later, UPC was 12, but creatinine was unchanged likely due to ongoing lymphomatous infiltration.

Discussion: This case highlights the importance of clinician suspicion for relapsed disease in patients presenting with nephrotic syndrome and prior history of liquid tumor. This case is unique since the kidney biopsy showed two distinctive pathologic findings including subepithelial deposits consistent with secondary MN and lymphomatous infiltration of the parenchyma. Treatment should focus on the underlying malignancy where earlier detection may improve outcomes.



Infiltrating lymphoma and glomeruli with capillary wall thickening.

FR-PO671

Unique Presentations of Post-Renal Transplant Gamma Delta T Cell Lymphoma

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Introduction: Post-transplant lymphoproliferative disorder (PTLD) is serious complication occurring in up to 10% of solid organ transplant recipients (R). In monomorphic PTLD, the majority of cases arise from B cells (good prognosis) and rarely from T cells. Less than 5% of T-cell lymphomas express gamma delta T-cell receptors. Gamma delta T cell lymphomas (GDTL) are outlined into two groups: hepatosplenic (HSGDTL) and primary cutaneous (PCGDTL). We present 2 recipients that developed PCGDTL and HSGDTL.

Case Description: R1 was a 67-year-old male who received a living, unrelated renal transplant, induced with Simulect. He was EBV IgG + and mismatched CMV IgG -. He presented 1-year post transplant with 20lb weight loss, pruritic skin rash, no EBV DNAemia, and diffuse lymphadenopathy on body PET CT. Biopsy of left axillary lymph node, skin, and bone marrow revealed a mature stage 4 T-cell lymphoma (CD2+, CD3+, CD4+, CD5+, CD7+, CD8-, CD45+, TCR gamma-delta TCR+, and alpha-beta TCR-). This case of PCGDTL had an unusual phenotype of CD4 positivity with presentation in lymph nodes and bone marrow. Immunosuppression was discontinued. Following treatment with 6 cycles of EPOCH regimen with complete resolution, his disease relapsed 2 months later and he died with a functioning allograft within 1 year of diagnosis. R2 was a 44-year-old male who received a deceased donor renal transplant, induced with Thymoglobulin. He was EBV IgG+ and non-mismatched CMV IgG-. He presented 7 years post transplant with abdominal pain, abnormal liver function tests, no EBV DNAemia, and moderate hepatosplenomegaly on abdominal CT. Peripheral blood flow cytometry and bone marrow biopsy revealed HSGDTL (CD2+, CD3+, CD4-, CD5-, CD7+, CD8 (dimly positive), CD25-, gamma/delta TCR+, and alpha/beta TCR-). Immunosuppression was discontinued. He was treated with 2 cycles of CHOEP regimen with treatment failure and 3 cycles of salvage therapy (Gemcitabine, Decadron, Carboplatin) with complete resolution. He relapsed with leukemic conversion 2 months later and died with a functioning allograft.

Discussion: Our cases demonstrate that GDTL is an aggressive neoplasia with rapid onset and poor prognosis. Despite initial response, both recipients died within 1 year of diagnosis. PCGDTL seems to clinically present earlier than HSGDTL. Also, neither of our patients had CMV/EBV viremia, suggesting GDTL development is potentially independent of virology.

FR-PO672

Renal Microangiopathy and Tubulitis Following Haploidentical Stem Cell Transplant with α/β T Cell and CD19 B Cell Depletion

Amber Hertz-Tang, Vaishalee P. Kenkre, Weixiong Zhong, David Yang, Arjang Djamali, Gauri Bhutani. *University of Wisconsin Madison, Madison, WI.*

Introduction: Selective depletion of α/β T-cells and CD19 B-cells in haploidentical (haplo) hematopoietic stem cell transplantation (HSCT) is being investigated as a strategy to avoid graft versus host disease (GVHD) while preserving immune reconstitution. We describe 4 cases of renal dysfunction following haplo-HSCT.

Case Description: All cases were Caucasian males who underwent non-myeloablative peripheral blood haplo-HSCT using fludarabine, cyclophosphamide and total nodal irradiation (7Gy). All reached engraftment and received mycophenolate (MMF) for GVHD prophylaxis (30 days). All are living at last follow up. The table summarizes their presentations.

	Case 1	Case 2	Case 3	Case 4
Diagnosis	Chronic Lymphocytic Leukemia	Marginal Zone Lymphoma	Peripheral T-Cell Lymphoma	Mantle Cell Lymphoma
Age at HSCT	52	57	55	65
Baseline serum creatinine (mg/dl) (eGFR mL/min/1.73sqm) pre-HSCT	1.06 (85)	1.63 (46)	0.89 (93)	1.03 (72)
Total follow up post-HSCT (days)	1021	491	315	301
Time to 50% GFR loss (days)	127	199	277	155
Renal pathology	Thrombotic microangiopathy (TMA) and active tubulointerstitial nephritis (TIN)	Severe chronic active TIN and TMA	Mild chronic and active TMA and acute tubular necrosis (ATN)	ATN, TIN, TIN and chronic active TMA
Infections [pre-immuno-suppression (IS)]	CMV	None	•CMV •C.diff	C.diff
Other organ dysfunction (days post-HSCT)	Skin-GVHD confirmed (29)	None	•Skin-GVHD presumed (33) •Gut-GVHD confirmed (176) •Pulmonary hypertension (308)	•Skin-GVHD confirmed (45) •Lung-GVHD presumed (129) •Pulmonary hypertension (82)
GVHD treatment	•Prednisone •MMF •Rituximab •Eculizumab -Renal indication	•Prednisone •MMF •Etanercept -Renal indication	Prednisone -GI indication	•Prednisone •Sirolimus -Pulmonary indication
Infections (post-IS)	•Aspergillus •Pseudomonas •Influenza A	•Strep pneumo •C.diff •Parapertusis •Adenovirus	•H.influenza •RSV	•MSSA •Pseudomonas •E.coli sepsis
Renal response	Partial response (PR) to IS. Progressed to ESRD with infections.	PR to IS. Progressed to ESRD with infections.	PR to IS. Last known serum creatinine:2.36 eGFR:29	No IS given for renal disease. Progressed to ESRD in setting of infections and cardiac disease

Discussion: All patients had endothelial injury and most (3/4) had inflammatory tubular pathology. Given the setting of haplo-HSCT with selective T-cell depletion, timeline and degree of renal insult, as well as response to IS, renal complications were most concerning for alloimmune response (GVHD). Chemotherapy and pre-IS infections may also have contributed to endothelial/tubular injury in early post-HSCT period. Our series highlights (1) GVHD is likely an important factor in post haplo-HSCT endothelial injury and direct/indirect tubular injury; (2) This condition is difficult to treat due to high risk of infections post-HSCT. Renal risks in haplo-HSCT need further investigation.

FR-PO673

Crystalglobulinemia in Multiple Myeloma: A Rare Case of Survival and Kidney Recovery

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Introduction: Crystalglobulinemia is a rare complication of monoclonal gammopathy wherein crystallised immunoglobulins deposit in various organs causing occlusive vasculopathy, endothelial damage and thrombosis. The reported mortality in this disease is extremely high.

Case Description: We report a case of a 74-year-old female presenting with polyarthralgia, chest pain, petechial rash and rapidly progressive oliguric acute kidney injury requiring dialysis. The serum creatinine on admission was 368 μmol/L, which peaked at 763 μmol/L on day 5 of admission. Troponin-T was 447ng/L (normal <14 ng/L), peaking at 1,223ng/L 7 days later. There were no ischemic changes on ECG. Serum protein electrophoresis showed IgG kappa paraprotein of 25.7 g/L and κ/λ ratio 21.8 (normal 0.26-1.85). Kidney biopsy revealed crystalline eosinophilic casts in the lumens of medullary tubules. Similar crystalline deposits were present in some interlobular arteries with luminal occlusion. Several glomeruli showed similar mainly crystalline deposits in glomerular capillary loops occluding lumens. Ultrastructure showed widening of subendothelial spaces of glomerular capillary loops with subendothelial flocculent material consistent with a thrombotic microangiopathy. Tubular crystal deposits had an organised parallel linear ultrastucture. Bone marrow biopsy confirmed immunoglobulin G (IgG) κ plasma cell multiple myeloma. This patient was successfully treated with 5 sessions of plasmapheresis and clone reduction chemotherapy with 11 cycles of cyclophosphamide, bortezomib and dexamethasone. This resulted in complete resolution of her symptoms, normalisation of troponin-T, reduction of paraprotein levels to <1 g/L and overall excellent kidney and hematological recovery. In 2 months, she was no longer dialysis dependent and in 32 months her latest creatinine had improved to 100 μmol/L.

Discussion: Crystalglobulinemia is a rare and life-threatening illness that should be suspected in patients with rapidly progressive acute kidney injury and monoclonal gammopathy. It can mimic other clinical entities, such as acute coronary syndrome, vasculitis and rheumatological disease due to the deposition of crystalglobulins in various organs. Our case demonstrates that timely investigation with kidney biopsy and appropriate treatment can lead to remission of multiple myeloma and excellent recovery of kidney function.

FR-PO674

Is This the Real Lyse? Is This Just Fantasy? Pseudohyperkalemia with Concurrent Tumor Lysis Syndrome in Extreme Leukocytosis

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Introduction: Hyperkalemia is a potentially dangerous electrolyte imbalance encountered in hematological malignancies, often seen in tumor lysis syndrome (TLS) and renal failure. It is increasingly recognised that potassium can be spuriously elevated in severe leucocytosis.

Case Description: A 74-year-old Chinese gentleman presented to the emergency room with 3 days of giddiness and was diagnosed with Chronic Myeloid Leukemia with blast crisis. Notable serum laboratory results included marked leucocytosis of 710x 10^9/L, platelets of 680x10^9/L, hemoglobin of 5.5 g/dL, creatinine of 289 μmol/L, potassium of

7.2 mmol/L (unlysed), phosphate of 1.69 mmol/L and markedly elevated uric acid and lactate dehydrogenase levels of 1572 µmol/L and 10,761 U/L respectively. Electrolyte abnormalities were attributed to spontaneous TLS with KDIGO Stage 3 acute kidney injury (AKI). Emergent medical therapy was instituted with insulin/dextrose, intravenous hydration and hydroxyurea. Rasburicase was withheld pending glucose-6-phosphate dehydrogenase status. Urgent renal consult was obtained for the consideration of renal replacement therapy (RRT) in view of oliguria. Simultaneous serum and whole blood potassium sample analysed via direct potentiometry subsequently revealed significantly discordant results of >8.0mmol/L and 4.7mmol/L respectively. Pseudohyperkalemia was suspected and corroborated by the absence of typical hyperkalemia changes on electrocardiographs. Serial paired samples yielded similar results, confirming the diagnosis. Despite this, decision was made to proceed with RRT in view of anuric AKI, ongoing TLS in the setting of large tumor burden, with anticipated delay of rasburicase administration and definitive chemotherapy.

Discussion: Pseudohyperkalemia occurring with extreme leucocytosis is multifactorial. It results from lysis of fragile leukocytes during clotting, compounded by mechanical stress during venepuncture, pneumatic transport and centrifugation. This phenomenon may go unrecognised in the setting of concurrent TLS and high index of suspicion is required. Diagnosis can be made by evaluating samples with direct potentiometry or sent in heparin-lithium tubes. While management of isolated pseudohyperkalemia in the absence of AKI is conservative, threshold to initiate dialysis should be lowered if there is concurrent TLS and oliguria.

FR-PO675

Solitary Renal Mass in Waldenström Macroglobulinaemia

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Introduction: Waldenström macroglobulinaemia is a rare B-cell lymphoproliferative disorder characterised by the presence of an IgM paraprotein and bone marrow infiltration by lymphoplasmacytic lymphoma. WM is more commonly found in men with a median age of onset of 60- 70 years and has an incidence of 0.3/100,000. WM may present with symptoms related to disease burden such as cytopenias, lymphadenopathy, and constitutional symptoms. Direct renal involvement by WM is a very rare occurrence. Here, we describe a WM case presenting with a large solitary renal mass.

Case Description: A 68 year old Caucasian male was referred with a persistent anaemia and weight loss. On examination, there was no evidence of palpable lymphadenopathy, or organomegaly. Initial investigations revealed a normocytic anaemia with a haemoglobin of 11g/dL, white cell count of 4 x 10^9/L, platelet count of 314 x10^9/L and normal renal function. He was referred to haematology as serum protein electrophoresis detected an IgM paraprotein band. Computed tomography of his thorax, abdomen and pelvis revealed an infiltrative mass expanding from the left pelvicalyceal system with invasion of the renal parenchyma anteriorly. There was prominent left retroperitoneal adenopathy without evidence of metastatic disease. CT-guided biopsy of the renal mass revealed cells with plasmacytoid morphology admixed with intermediate size lymphoid cells. The cells were diffusely positive with CD79 and most cells stained for CD20, consistent with lymphoplasmacytic lymphoma. Investigations at this point quantified his IgM paraprotein band to 9g/L. Serum free light chain assay revealed free kappa and lambda chains of 43.5mg/L and 19.7mg/L respectively. His ß2 microglobulin was 7.2 mg/L. Urinary Bence-Jones protein was not detected. A bone marrow aspirate and trephine confirmed infiltration by lymphoplasmacytic lymphoma. He was commenced on the dexamethasone, rituximab and cyclophosphamide regimen.

Discussion: This case describes a rare manifestation of WM. Renal involvement by lymphoma is thought to occur by direct infiltration from retroperitoneal adenopathy or haematogeneous dissemination. Our review of the literature identified only six previous cases of renal masses in association with this B-cell lymphoproliferative disorder. This case illustrates the importance of consideration of WM and other lymphomas in the differential diagnosis of a renal mass and the necessity of prompt biopsy.

FR-PO676

A Case of ANCA-Associated Glomerulonephritis Accompanied by Membranous Lesions During the Course of Recurrent Renal Cancer

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Introduction: ANCA-associated glomerulonephritis (ANCA-GN) has been classified as a pauci-immune type of crescentic glomerulonephritis since glomerular immune complex deposits are not demonstrable by immunofluorescent study and electron microscopy. ANCA-GN and membranous nephropathy (MN) has been rarely reported. We report an ANCA-GN accompanied by membranous lesions during the course of recurrent renal cancer.

Case Description: A 70-year-old male was referred to our hospital because of worsening renal function and persistent hematuria and proteinuria of around 0.5-1 g/gCr. He had underwent left nephrectomy for renal cancer at the age of 49 and also left lung cancer at 60 years. Laboratory examination revealed positive MPO-ANCA titers in the serum (148.4 U/ml) and an elevated serum creatinine level (1.5 mg/dl). There were no other findings that suggest organ involvement of systemic vasculitis. CT and PET-CT scans revealed nodular lesions of the right lower lung and mediastinal mass suspected of malignancy. A renal biopsy revealed necrotizing extracapillary proliferative glomerulonephritis with fibrocellular crescents, compatible with ANCA-associated glomerulonephritis (ANCA-GN). However, immunofluorescent study showed granular depositions of IgG along the glomerular capillary walls, with IgG subclass being positive for IgG1, weak positive for IgG2 and negative for IgG3 and IgG4, suggesting secondary membranous nephropathy. Interestingly, electron microscopy showed deposits along glomerular basement membranes and also paramesangial areas. There were few deposits in the subepithelial areas. He was finally diagnosed with metastatic renal cancer to the lymph node of the mediastinum and chemotherapy with sunitinib was begun. Thereafter, the serum creatinine did not change and MPO-ANCA decreased to 32.6 U/ml without using corticosteroids.

Discussion: Although ANCA-GN accompanied by MN has been rarely reported, the present case showed atypical membranous lesions suggesting unique etiology of immune complex formation.

FR-PO677

Hypophosphatemia from a Liver Spindle Cell Tumor: A Novel Site for FGF23-Related Tumor-Induced Osteomalacia

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Introduction: Tumor induced osteomalacia(TIO), presenting with hypophosphatemia driven by fibroblast growth factor 23(FGF23) production is a paraneoplastic phenomenon. We present a liver tumor with demonstrated FGF23 production, a previously unreported site.

Case Description: A 58 y/o female with a history of lupus and osteoporosis presented with fatigue, weight loss and joint pains. Medications include alendronate, plaquenil and vitamin D. She was found to have 3.6g of 24 hour urine protein and low phosphorous for four years. Fractional excretion of phosphate ranged between 40-60 % (normal 10-20%) on several occasions during a period of 3 months. Renal biopsy was performed and revealed proximal tubule vacuolation, without evidence of lupus activity. C-terminal FGF23 levels were tested at multiple points and elevated to 97 and 770 RU/ML at a serum phosphorous of 1.7 and 3.4 mg/dL respectively on high dose supplementation. Parathyroid hormone and vitamin D levels were normal. FGF23 levels remained elevated. Ga-68 dotatate PET scan revealed an irregular enhancing liver mass which upon resection was a spindle cell tumor with clear margins. **Immunohistochemical stain of the pathologic tissue was positive for FGF23 when compared to normal liver. Cell culture of tumor cells versus the patients normal liver cells showed two-fold higher FGF23 expression.** The intra-op & post-op period was uneventful except worsening of hypophosphatemia as expected with increase in FGF23 to 800-1400 RU/ml. 3 months post-op, she had a minor fall with an avulsion fracture of the 5th metatasrsal base. 5 months later the patient remains hypophosphatemic, but requires less oral supplementation. Symptoms have improved significantly, however her FGF 23 remains elevated.

Discussion: While the liver has been shown to express FGF23, TIO has not been previously described as a consequence of a liver neoplasm. TIO is a potentially curable paraneoplastic etiology of symptomatic hypophosphatemia. Symptoms usually remit quickly in tumors in which resection is possible. This adds to potential sites to explore when evaluating for TIO. Repeat PET scan will be required to evaluate our patient for residual disease given continued FGF23 elevation. Recombinant FGF23 antibody is another potential intervention if other methods of cure are impossible.

FR-PO678

Heavy Chain Deposition Disease Unmasked After Treatment of Sjogren Syndrome-Associated Glomerular Disease

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Introduction: Diagnosis of heavy chain deposition disease (HCDD) is often challenging. We present a case of a patient who had 2 kidney biopsies and treatment of one disease unmasked the diagnosis of HCDD.

Case Description: A 69 year old female was diagnosed with smoldering myeloma (IgG-lambda clone). Treatment was not planned. She was also recently diagnosed with Sjorgen syndrome. Few weeks later, she presented with AKI with Scr of 1.4mg/dl (baseline of 1mg/dl) and proteinuria (4gm/24hours). Serology showed positive ANA, positive SS-A antibody, antidsDNA, low C3 and C4 levels. A kidney biopsy confirmed MPGN pattern with diffuse nodular sclerosis having polyclonal IgG and IgM lambda deposits, and EM showing focal organized deposits. There was also a diffuse interstitial lymphoplasmacytic infiltrate. Based on the IF findings, the diagnosis of mixed cryoglobulinemia-associated GN was made, but a paraproteinemia related disease could not be ruled out. A Hepatitis C PCR was negative. Since the kidney disease was related to rheumatologic findings, steroids were initiated. Despite steroids, her creatinine worsened over 6 weeks and proteinuria increased to over 8gm/24 hours. A repeat kidney biopsy was diagnostic for gamma-3 heavy chain deposition disease, with a nodular sclerosing glomerulonephritis and strong (4+) IgG and C1q reactivity in the mesangium and along glomerular and tubular basement membranes; no significant reactivity for kappa and lambda light chains or C3 was noted on routine IF microscopy. IgG subclass staining showed strong (4+) gamma-3 reactivity, in the same areas corresponding to the IgG staining. Electron microscopy reveals diffuse powdery deposits along all the basement membranes and in the mesangium, supporting the diagnosis of HCDD. The steroid treatment might have unmasked the underlying HCDD, following resolution of the autoimmune mediated renal lesions. A repeat bone marrow

showed no change in percent of plasma cells. Regardless, she was started on bortezomib based therapy. Four months later, she still remains dialysis dependent.

Discussion: Diagnosis of HCDD is challenging. In this case, the initial pathology of an autoimmune process causing kidney disease masked a chronic HCDD related kidney disease. High index of suspicion is required for diagnosis of HCDD. Prognosis remains guarded.

FR-PO679

AKI from Polytypic Plasma Cell Interstitial Infiltration in Sjogren Syndrome

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Introduction: 57-year-old woman with a history of extensively treated Marginal Zone Lymphoma diagnosed with concomitant pulmonary AL Amyloidosis on lung biopsy in 2011 as well as remote history of Sjogren Syndrome, referred for acute kidney injury (AKI). She was last treated with rituximab for lymphoma 6 months ago.

Case Description: During initial evaluation (1/22/19), she was found to have a relatively brisk worsening of creatinine (Cr) from 0.9 to 2mg/dL over a 2- week period. She had new onset microscopic hematuria, glycosuria and pyuria with proteinuria quantified as 1.3g (albumin/cr of 66mg/g). Ultrasound showed edematous bilateral kidneys with serial CT imaging highlighting an insidiously worsening loss of corticomedullary differentiation over the last year. Ancillary studies showed a stably abnormal k/l ratio of 3.5 and IgG- k M- spike of 0.1g/dL, with these serologies showing chronic and fluctuating elevated titers since the diagnosis of Lymphoma. There was also a gradually worsening total serum protein of 11.1g/dL and IgG titer of 5925mg/dL (normal < 1616). Native kidney biopsy was undertaken on 2/1/19 that showed extensive interstitial infiltration with polytypic plasma cells with no morphologic or immunophenotypic evidence of lymphoma. Just prior to kidney biopsy, Cr peaked at 2.96mg/dL and prednisone 1 mg/kg was initiated for empiric management. Given absence of lymphomatous renal involvement, chemotherapy was not entertained. Renal function improved with Cr dropping to 0.7mg/dL following a tapering course of prednisone. This was accompanied by resolution of pyuria and stabilization of IgG titer to 3725mg/dL on last check. She tested positive for serum ANA (positive ss-A and ss-B) with negative double- stranded DNA.

Discussion: Patient experienced AKI from a non-lymphomatous polycloncal plasmacytic interstitial infiltrate concomitant with a severe hypergammaglobulinemia that responded briskly to prednisone. In the context of worsening sicca symptoms over the last 6 months and positive serologies, the plasmacytic infiltration was deemed a manifestation of Sjogren syndrome, which was first diagnosed in 2005 following biopsy of minor salivary glands. This presentation of renal failure from Sjogren syndrome is a rare occurrence and even more intriguing in a patient with extensive history of lymphoma. Accurate diagnosis in this case was essential to avoid unnecessary use of chemotherapy.

FR-PO680

Karyomegalic Interstitial Nephritis in a Woman with Hodgkin Lymphoma on Brentuximab Therapy

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Introduction: Karyomegalic interstitial nephritis (KIN) is a rare form of chronic interstitial nephritis that can lead to end stage renal disease. It is characterized histologically by hyperchromatic, abnormally enlarged nuclei of tubular epithelial cells, as well as interstitial fibrosis and tubular atrophy. KIN has an autosomal recessive form, associated with mutations in the FAN1 gene. Other potential etiologies include toxins (e.g. ochratoxin A), heavy metals (e.g. busulfan, lead), alkylating agents (e.g. ifosfamide), and viral infections. We present a case of KIN in a woman with Hodgkin's lymphoma on brentuximab vedotin (trade name: Adcetris) therapy. To our knowledge, this is the first case report of KIN associated with this medication.

Case Description: A 50 year-old Hispanic female was diagnosed with anaplastic high-grade Hodgkin's lymphoma with metastasis to the liver, large intestine, and adrenal gland. She had poor response to 4 cycles of ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine) and 3 cycles of ICE (Ifosfamide, Carboplatin, Etoposide). She then received two doses of Brentuximab vedotin. She had a normal renal function prior to the infusion of Brentuximab vedotin, which declined rapidly afterwards. Urinalysis showed 3+ glucose, 3+protein, 1 WBC, 0RBC and 6-10 granular casts/LPF. Urine protein to creatinine ratio was 2.8 g/g. Kidney biopsy showed KIN. Despite discontinuation of brentuximab vedotin, her kidney function continued to worsen, and she was prepared for dialysis.

Discussion: Brentuximab vedotin is an antibody-drug conjugate (ADC) which targets tumor cells expressing CD30, followed by internalization and release of monomethyl auristatin E (MMAE), which binds to tubulin and disrupts the microtubule network. This results in cell cycle arrest, and may explain the markedly enlarged and hyperchromatic nuclei seen in renal tubular epithelial cells, which did not undergo apoptosis as tumor cells do. The present case is the first report of KIN association with brentuximab vedotin. While there is the possibility that KIN may be a late consequence of ifosfamide administration, the temporal relationship between treatment with brentuximab vedotin and the onset of kidney injury suggests that brentuximab vedotin was the most likely responsible agent in this case.

FR-PO681

A Unique Case of Hyponatremia

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Introduction: Immune check point inhibitors(ICI) have revolutionized cancer treatment. They promote activation of T cells causing programmed death of tumor cells. However they can cause life threatening immune related adverse events (irAEs) including autoimmune endocrinopathies, such as hypophysitis, thyroiditis, adrenalitis, insulinitis, and parathyroiditis. We present a case of hypophysitis caused by the use of iplimumab and nivolumab, presenting with severe hyponatremia.

Case Description: A 60 y.o. lady with metastatic renal cell carcinoma was started on treatment with ICI- Iplimumab and Nivolumab. After two cycles of treatment, patient developed thyromegaly, was diagnosed with immune thyroiditis manifesting as hyperthyroidism followed by hypothyroidism, requiring levothyroxine. Two months into ICI therapy she presented to the hospital with complaints of left-sided flank pain. A CT scan of abdomen revealed increase in growth of the left renal mass. Laboratory data revealed serum sodium (Na) level of 127 mmol/L (Na was 142 a week prior). She was placed on fluid restriction of 1.2 liters per day and salt tablets 1 gram 3 times daily. Yet Na level continued to drop to 118 by 3rd day of hospitalization. Urine osmolality was 504 mosm/kg with urine sodium of 24 mmol/L. Her TSH level was low at 0.023 (0.400 - 4.000 mcU/mL) with free T4 levels of 0.69 (0.70 - 1.90 ng/dl), A.M. cortisol level was very low at 1 mcg/dl (6.0 - 18.4 mcg/dl). Patient was diagnosed with adrenal insufficiency and central hypothyroidism thought to be secondary to immune related adverse effects resulting from the use of Ipilimumab and Nivolumab. She was started on methylprednisone 70 milligrams IV daily, her serum Na improved from 119 to 126 mmol/l in 24 hours and normalized over 3 days. She was switched to oral tapering dose of hydrocortisone.

Discussion: The combined treatment of iplimumab (anti-CTLA4 Ab) and nivolumab (anti-PD-1 Ab) increases the tumor efficacy but also increases the risk for autoimmune hypophysitis, which can cause secondary adrenal insufficiency through complement deposition, mononuclear cell infiltration and production of antibodies to adenohypophysial endocrine cells resulting in adrenal insufficiency induced hyponatremia. In this case, hyponatremia did not respond to fluid restriction and salt tablets but responded to steroids. Hyponatremia induced by ICI should be recognized and treated promptly.

FR-PO682

Mantle Cell Lymphoma Resulting in Paraneoplastic Immune Complex Mediated Glomerulonephritis

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Introduction: Glomerulonephritis (GN) can result from paraneoplastic effect of certain malignancies. Here we report a case of a gentleman with Mantle cell lymphoma (MCL) who developed GN necessitating treatment of his cancer that otherwise did not meet hematological criteria for treatment.

Case Description: A 63-year Caucasian male with a newly diagnosed MCL, not on treatment, came in for evaluation of lower extremity edema within two weeks of diagnosis. His edema was associated with a weight gain of ten pounds, and acute kidney injury with a creatinine rise from a baseline of 1.08 to 1.72, peaking at 3.14 mg/dL over the next few weeks. Initial evaluation consisted of a normal renal ultrasound, a urinalysis with 3+ blood, positive leukocyte esterase. A microscopic evaluation of his urine sediment showed dysmorphic red blood cells (RBCs), 5 white blood cells, and no bacteria. A spot urine protein to creatinine ratio of 5.3g/g creatinine of which 3.3g was albumin. Serological work up demonstrated a normal or negative serum and urine electrophoresis, serum free light chains, complements, anti- neutrophilic cytoplasmic antibody, anti-double stranded DNA, anti-glomerular basement membrane antibody, erythrocyte sedimentation rate, C-reactive protein, hepatitis serologies, lactate dehydrogenase, haptoglobin and cryoglobulin. His anti-nuclear antibody was weakly positive. He underwent a kidney biopsy showing acute tubular necrosis with immune complex GN with a focal proliferative and mesangioproliferative pattern of injury. There was no paraprotein deposition or parenchymal infiltration with the lymphoma cells. His GN was attributed to a paraneoplastic process resulting from his underlying MCL. His GN prompted treatment with high dose steroids, bendamustine, and rituximab with improvement in creatinine to 1.2 mg/dL, and complete resolution of proteinuria. A subsequent positron emission tomography scan showed marked regression of his MCL.

Discussion: Renal involvement in mantle cell lymphoma is a rare complication. Mantle cell lymphoma is often an indolent condition that does not require treatment. However, organ-threatening GN such as that reported in our case can only respond to treatment. Serological studies are often insufficient and kidney biopsy is required for definitive diagnosis. Rituximab-based regimens are effective for treatment of paraneoplastic GN resulting from MCL.

FR-PO683

Hypophosphatemia and Fibroblast Growth Factor 23 Producing Metastatic Breast Cancer

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Introduction: Fibroblast growth factor-23 (FGF23) is a key regulator of phosphate metabolism and downregulates expression of cotransporters in the kidney essential for phosphate reabsorption. FGF23 mutations cause inherited renal phosphate wasting diseases leading to osteomalacia in adults. In the paraneoplastic setting, FGF23 over secretion leads to tumor-induced osteomalacia (TIO) also known as oncogenic osteomalacia.

Case Description: 47-year-old woman with metastatic breast cancer was evaluated for persistent hypophosphatemia. First diagnosed with left mammary duct carcinoma in 2013, she underwent partial mastectomy followed by chemotherapy. She had a reoccurrence in 2016 and failed multiple lines of chemotherapy with new metastasis to the liver and several osseous lesions. Patient was initiated on monthly denosumab one year prior to current visit, with last dose one month ago, for metastatic bone involvement. Phosphorous level on consultation was <0.9 (2.5-4.5)mg/dl with no prior laboratory values. Calcium level was 7.4 (8.5-10.5)mg/dl and Alkaline Phosphatase level was 738 (< = 130)U/L. The fractional urinary excretion of phosphate was elevated at 56%. Etiology for hypophosphatemia was initially thought to be secondary hyperparathyroidism given elevated PTH 488 (12-88)pg/ml due to hypocalcemia in the setting of recent denosumab administration. Phosphorous levels remained low despite aggressive oral calcium and phosphate repletion and oral calcitriol. Given persistent hypophosphatemia, FGF23 was checked and levels returned strikingly elevated at 2430 (< = 180)RU/ml suggesting an FGF23 secreting tumor as the most likely cause for severe hypophosphatemia. Oral phosphate supplementation was continued, though unfortunately, given progression of disease, palliative measures were chosen with a focus on comfort care.

Discussion: TIO is a rare paraneoplastic syndrome, but when present, downstream effects of phosphaturia can lead to profound weakness and skeletal collapse. Though prior reports have identified bone or soft tissue as the primary site, the case above is unique since the syndrome occurred in metastatic disease with a primary breast cancer. Recognition of TIO is essential since patients that have solitary lesions may undergo resection which may be curative. In patients with several lesions or metastatic cancer, medical therapy can be attempted to improve the quality of life.

FR-PO684

Vascular Renal Amyloidosis with Waldenstrom Macroglobulinemia (WM)

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Introduction: Several kidney diseases have been associated with WM; they include lymphoplasmacytic lymphoma infiltration, immunoglobulin light chain (AL) amyloidosis and cryoglobulinemic glomerulonephritis. AL amyloidosis classically presents with nephrotic syndrome. We present a rare case of renal vascular AL amyloidosis in a patient with WM

Case Description: A 82-year-old white woman with history of WM presented with worsening kidney function. Nine years prior, she was diagnosed with WM and was treated with Bendamustine and Rituximab for 6 monthly cycles and then Rituximab maintenance for 2 years. She remained stable for six years. Over the last year, she was noted to have worsening anemia, rising serum creatinine from 1.3 mg/dl to 1.8 mg/dl and new onset of subnephrotic range proteinuria (1 gm/day). Her urinalysis did not reveal any blood or dysmorphic RBC. In addition, for several months, her blood pressure was harder to control. At baseline, her serum immunoglobulin free light chain ratio (Kappa/Lambda) was close to 9 and had risen to 45 at the time of presentation. Her immunofiixation was positive for IgM and IgG kappa. Physical exam was remarkable for a BP of 170/90 mm hg and trace lower extremity edema. Her serological work up was negative except for a low C4 (8 mg/dl). A kidney biopsy was performed which revealed significant non-specific chronic injury, with global glomerulosclerosis and tubulointerstitial scarring in about 50% of cortex. The better preserved glomeruli showed signs of hypoperfusion, but there was no amyloid, other paraprotein deposition, or hypercellularity in any of the glomeruli. Amyloid deposition, characterized by positive Congo red stain, was noted in a single arcuate artery with perivascular tissue involvement. Immunofluorescence revealed equal kappa and lambda staining on frozen tissue, but on paraffin sections, kappa staining was positive in the involved artery. Electron microscopy did not reveal amyloid fibers in the glomeruli. Based on these results, a diagnosis of WM associated renal vascular amyloidosis was made and she was started on treatment with bortezomib and rituximab and is currently doing well

Discussion: In a patient with WM presenting with kidney dysfunction and or proteinuria, vascular amyloidosis involving only the large vessels should also be considered in the differential diagnosis.

FR-PO685

Thrombotic Microangiopathy Following Y^{90}-Dotatate Treatment

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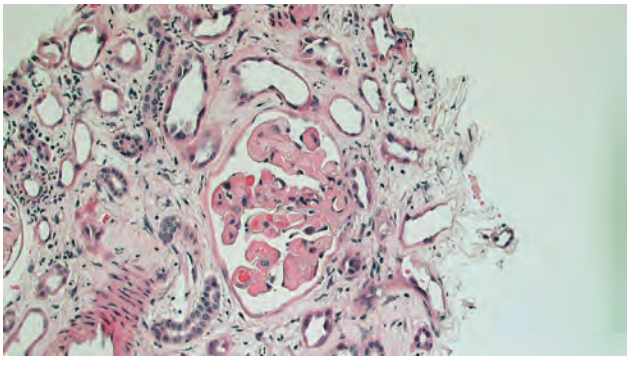
Introduction: Gastro-entero-pancreatic neuroendocrine tumours are rare; the expression of somatostatin receptors enables treatment with radiolabelled somatostatin analogues such as Yttrium labelled octreotide (Y^{90}-dotatate). Patients are routinely consented for non-specific renal toxicity prior to treatment.

Case Description: We present the case of a 49 year old woman with a well differentiated neuroendocrine tumour. She was treated with lanreotide (long acting somatostatin analogue) but follow up scans demonstrated progressive disease and she was then treated with three cycles of Y^{90}-Dotatate therapy (4.0 GBq). Four months later she presented with shortness of breath with a haemoglobin of 69 g/L, platelet count of 132 x 10^9/L and creatinine of 145 umol/L. She had previously normal renal function. Over the following days the platelet count fell further to 55 x 10^9/L at the lowest and she was hypertensive. A blood film demonstrated fragments. Three stool cultures were negative for shigella toxin and e.coli. An ADAMST13 demonstrated >10% activity. She was commenced on plasma exchange, receiving five 1.5L cycles with fresh frozen plasma. The case was discussed with the National Renal Complement Therapeutics Centre, Newcastle, UK. It was thought that this was not in keeping with a complement driven process amenable to Eculizumab treatment. The platelet count gradually increased to normal range with the haemoglobin remaining stable around 80g/L during plasma exchange. A renal biopsy was performed which demonstrated morphological features compatible with a TMA. Since stopping plasma exchange, the patient has been followed up in the renal clinic, with focus on good blood pressure control but renal function appears to be declining slowly.

Discussion: TMA has been described in association with Y^{90}-Dotate therapy and this case demonstrates this rare complication which carries a poor renal prognosis.



Renal biopsy: glomerulus showing thrombi in capillary loops and basement membrane thickening; mesangiolysis; aneurysmal dilatation of capillary loops; background acute tubular necrosis.

FR-PO686

Hypercalcemia Secondary to Malignancy-Associated Ectopic PTH Secretion: A Rare Mimicker of Primary Hyperparathyroidism

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Introduction: Hypercalcemia affects nearly 30% of patients with cancer, and malignancy-related hypercalcemia is the most common cause of hypercalcemia in hospitalized patients. In most cases, hypercalcemia is due to tumor secretion of PTHrP, osteolytic metastases or increased production of 1,25 $(OH)_2D$. We present a very rare case of malignancy-related hypercalcemia due to ectopic production of intact PTH in a patient with hepatocellular carcinoma.

Case Description: A 61-year-old man with history of hepatocellular carcinoma and hepatitis C infection complicated by cryoglobulinemia and CKD stage 4 was admitted with complaints of malaise, abdominal pain, dyspepsia, constipation, and inability to ambulate after suffering a left femoral fracture. Labs upon admission were notable for ionized calcium 12.7 mg/dL (normal 8.5-10.1), PTH 397 pg/mL (normal 14-72), PTH-rp 16 pg/mL (normal 14-27), and 1,25OH-vitamin D 12 pg/mL (normal 18-72). Further hypercalcemia workup included a parathyroid ultrasound and Sestamibi scan that were negative for parathyroid adenoma or carcinoma. An abdominal ultrasound revealed known liver mass attributed to his HCC and a new left upper quadrant mass adjacent to the spleen. The para-splenic lesion was FDG-avid on PET/CT. CT-guided biopsy of the left upper quadrant mass was consistent with HCC and stained positive for parathormone, confirming the diagnosis of intact PTH-secreting HCC. He was not a surgical candidate. Hospital course was complicated by refractory hypercalcemia (serum Ca as high as 14 mg/dL) despite generous intravenous normal saline, calcitonin, furosemide, and high dose cinacalcet (90 mg BID). The patient responded to 60 mg pamidronate. His serum calcium at discharge was 10.7 mg/dL.

Discussion: This patient had hypercalcemia due to ectopic intact PTH secretion, which is exceedingly rare. Very few case reports have been described, mostly involving solid tumors, including neuroendocrine, ovarian, rhabdomyosarcoma, gastric, hepatocellular,

kidney, lung, parotid, and breast cancers. Because of elevated PTH, hypercalcemia in this setting could be mistaken for primary hyperparathyroidism, which could lead to an unnecessary neck exploration as an attempt to identify a parathyroid adenoma. Hypercalcemia in the setting of elevated PTH and non-parathyroid malignancy should thus raise suspicion for this entity.

FR-PO687

Lung Cancer Before and Acute Myeloid Leukemia (AML) After the Diagnosis of IgG4-Related Disease

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Introduction: IgG4-related disease (IgG4-RD) is a multi-organ immune mediated fibro-inflammatory condition. The common diagnostic features of IgG4-RD are tumefactive lesions of involved organs, lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells and storiform fibrosis. Elevated serum concentrations of IgG4 are present in 70% of cases. Glucocorticoids are first line therapy. Recurrent and refractory cases are common and may benefit from steroid sparing maintenance therapy. This case illustrates the association of IgG4-RD with an increased risk of malignancy.

Case Description: A 53 -year old woman with history of epithelioid neoplasm of the lung s/p wedge resection in 2016 presented 10 months later with dyspnea. Diagnostic work up was significant for an exudative pleural effusion without malignant cells and bilateral hydroureteronephrosis with Scr of 3.5 mg/dl and urine PCR 1.1g/g despite stent placement. Kidney biopsy showed extensive dense fibrosis with one focus of positive IgG4 staining (20cells/hpf). Archived lung tissue from wedge resection as well as thyroid tissue from remote partial thyroidectomy stained positive for IgG4. Serum IgG4 was 106 mg/dl. Remission was successfully achieved with glucocorticoids. Scr improved to 1mg/dl and IgG4 level to 30.9mg/dl. However her IgG4-RD relapsed once prednisone was tapered below 10 mg/dl. Rituximab 1g q 14 days x2 doses along with prednisone taper did not help. PET scan showed hypermetabolic activity in the cervical and chest lymph nodes, thyroid, right lung, right hepatic lobe and both kidneys. Bone marrow biopsy with flow cytometry was negative for malignancy. Oral cyclophosphamide plus rituximab and prednisone were trialed without success. While on this regimen, she continued to deteriorate and was readmitted with fever and worsening shortness of breath. The plan was to exclude infection and consider a plasma cell inhibitor for refractory IgG4-RD. Repeat work up including bone marrow biopsy was notable for AML for which she is now being treated.

Discussion: Malignancy is associated with subsequent development of IgG4-RD. Some studies also suggest that prior IgG4-RD is associated with increased risk of developing malignancy. Our patient had cancer pre- and developed a different cancer post-IgG4-RD diagnosis. This case sheds light on the importance of cancer screening in IgG4-RD.

FR-PO688

Severe Hypophosphatemia in a Patient with a Relapsing Lymphoma

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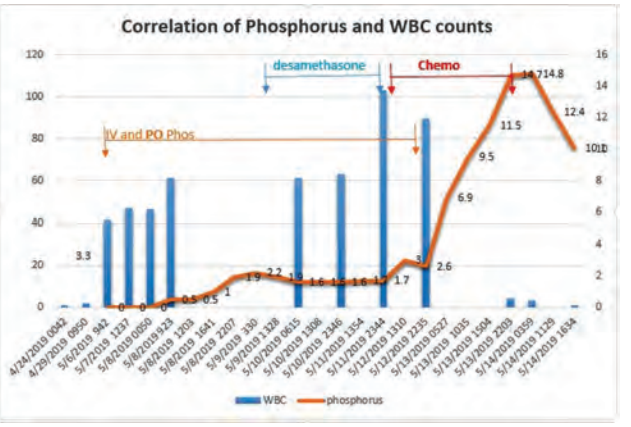
Introduction: Hypophosphatemia in cancer patients is commonly ascribed to chemotherapy, renal wasting or malnutrition from anorexia and poor oral intake. We report a case of hypophosphatemia caused by rapid cancer cell proliferation.

Case Description: Hypophosphatemia was observed in a 61-year-old woman with history of marginal zone lymphoma diagnosed in 2017 presenting with fatigue and undetectable phosphate (phos) levels. Her symptoms started 5 days prior with reported decreased oral intake, but no other gastrointestinal symptoms. Blood work showed phos <1 mg/dl; iPTH level was 17. Her medications included Acyclovir 400mg daily and Allopurinol 100mg daily. Her phos further dropped to <0.3 mg/dl on admission. This severe hypophosphatemia required aggressive intravenous phos treatment and simultaneous oral phos supplementation thereafter. 24 hr urinary fraction excretion of phos was only 1.8%, ruling out renal loss of phos, including acyclovir induced phos wasting. Initial white blood count (WBC) was 41 B/L, phos was <0.3 mg/dl, compared to phos of 3.3 mg/dl with WBC of 0.9 B/L a week prior to this admission. She then developed hyperphosphatemia upon re-initiation of chemotherapy, after repeated computerized tomograhy scan and flow cytometry confirmed lymphoma relapse. She received 4 days of Dexamethasone where the hypophosphatemia converted to hyperphosphatemia, likely from tumor lysis, then further worsened by chemotherapy. Her phos peaked at 14.8 mg/dl. Acyclovir was resumed and it did not cause recurrent hypophosphatemia. A similar hypophosphatemia-hyperphosphatemia pattern was also observed in her previous hospitalization, and correlated with her WBC (Figure 1).

Discussion: The hypophosphatemia correlated with hyperproliferation of cancerous cells. Therefore, hypophosphatemia might be a surrogate biomarker of recurrence of rapidly proliferating hematological malignancy. Phos levels can serve as an excellent adjuvant, widely available, non-invasive and cost-effective biomarker.



FR-PO689

Recurrent Laryngeal Cancer with Uncommon Kidney Metastasis

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Introduction: Laryngeal cancer is the fourteenth most common malignancy worldwide, where squamous cell carcinoma (SCC) is the most prominent subtype. Distant metastases occur in less than ten percent and involve the lung, liver, and bone but kidney metastases are seldomly reported. We report a rare case of recurrent laryngeal cancer with infiltrative kidney metastases.

Case Description: 64-year-old man with recurrent metastatic laryngeal carcinoma was evaluated for worsening kidney function. First diagnosed with laryngeal carcinoma in 2011, managed with radiation therapy, with reoccurrence in 2017 requiring laryngectomy. Follow-up scans showed new metastatic lung disease treated with left upper lobe resection and cisplatin chemotherapy. Creatinine rose to 2.5 (0.7-1.3)mg/dl (baseline of 1.0mg/dl) over 3 months. He denied use of nonsteroidal anti-inflammatory drugs, and had not received intravenous contrast. He was recently started on ramipril for hypertension. Urinalysis showed no protein, with bland urine sediment. Renal ultrasound revealed enlarging kidneys, right 12.3cm (increased from 9.8cm 4 months prior) and left 11.9cm, without hydronephrosis. Positron emission tomography (PET) revealed several new areas of increased uptake by both kidneys, pulmonary nodules and diffuse hilar and retroperitoneal lymphadenopathy. Renal biopsy showed diffuse infiltrative moderately to focally well differentiated SCC replacing most of the cortical and medullary tissue. Four of 29 glomeruli were globally sclerosed, minimal changes in remaining glomeruli, with diffuse tubular atrophy and interstitial fibrosis. Immunofluorescence microscopy was not performed due to diffuse renal tissue infiltration. The patient's creatinine remained elevated at 2.5mg/dl with plan by head and neck oncology for combination carboplatin, taxol, and cetuximab given the rapidly progressive nature of the disease.

Discussion: Kidney dysfunction in the setting of malignancy is often attributed to nephrotoxic chemotherapy as a potential cause. It is important to recognize that kidney infiltration is also possible where treatment can be aimed at addressing the underlying malignancy. The above case is unique in that it highlights the rare entity of laryngeal carcinoma metastasizing to the kidneys and should be considered in patients presenting with kidney dysfunction and large kidneys.

FR-PO690

Hyponatremia Secondary to CTLA-4 Inhibition-Induced Hypophysitis

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Introduction: Ipilimumab is a cytotoxic T-lymphocyte associated antigen 3 (CTLA-4) inhibitor which is used in therapy of multiple types of cancers, including malignant melanoma. One side effect of ipilimumab, reported in nearly 17% of patients receiving it in clinical trials, is autoimmune hypophysitis. We present a case of a patient with a history of melanoma treated with ipilimumab and hypophysitis, who presented with symptomatic hyponatremia after being treated with CTLA-4 inhibitor therapy.

Case Description: This is a 73 year old man with history of hypertension, DM, invasive melanoma of the right earlobe requiring wide excision and sentinel lymph node biopsy, pT4a N0 M0 Stage IIIA. He completed 3 cycles of adjuvant ipilimumab and nivolumab. Patient presented to the hospital with dizziness and weakness. He was fully oriented on presentation, normotensive and euvolemic on exam. The serum sodium was 119 meq/L and calculated serum osmolality was 246 mOsm/kg, BUN 3 mg/dl and sCr 0.4 mg/dl, with a normal uric acid. UA was unremarkable, with urine sodium 29 mmol/L and osmolality 134 mOsm/kg. Further workup showed low TSH, low morning cortisol, and brain MRI showed signs of hypophysitis, confirming the diagnosis of CTLA-4 inhibitor-induced hypophysitis. He was treated with thyroid hormone and adrenocorticoid

replacement, his hyponatremia improved. He was discharged from the hospital few days later with serum sodium 130 meq/L.

Discussion: In cases of hypophysitis, hyponatremia has been shown to occur due to secondary adrenal insufficiency with loss of ACTH-secreting corticotrophs. While the cause of hypophysitis is suspected as treatment-induced autoimmune lymphocytic hypophysitis, which results in anterior hypophyseal necrosis, this can only be definitively determined on postmortem. The present case illustrates that the hypophysitis which occurs may be permanent, and requires lifelong adrenal hormone replacement. Physicians and nephrologists should be aware of the diagnosis of CTLA-4 inhibitor-induced hypophysitis and include it in the differential diagnosis of hyponatremia when there is relevant chemotherapy history.

FR-PO691

Intravascular Lymphoma of the Kidney and AKI

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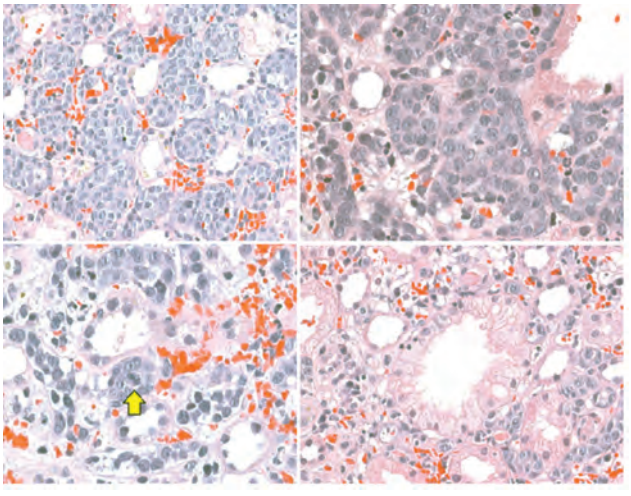
Introduction: Intravascular lymphoma of the kidney (ILK) is an extremely rare condition characterized by malignant infiltration of small vessels.

Case Description: A 66-year-old woman presented with fatigue, altered mental status, and acute onset diarrhea. On exam, she was pale with abdominal tenderness. CBC showed leukocytosis, anemia, and thrombocytopenia. Basic chemistry showed creatinine: 2.1 mg/dL (baseline: 0.8), BUN:15 mg/dL, Na:122 mmol/L, HCO_3:17 mmol/L, markedly elevated LFTs, and lactic acid levels. Urinalysis showed: hematuria, mild proteinuria, and granular casts. Multiple studies including cancer work-up from blood, CSF, and BAL was only notable for high ESR. Pan CT scan revealed no lymphadenopathy. Bone marrow biopsy, flow cytometry, and genetic studies were also unmarkable. Despite the treatment with fluids and broad-spectrum antimicrobials, her clinical status continued to be poor with encephalopathy and acute kidney injury requiring dialysis. A kidney biopsy revealed heavy neoplastic cell infiltration of the renal cortex (nests surrounding renal tubules with marked interstitial hemorrhage) and prominent small vessel infiltration. Immunohistochemical staining showed that all malignant cells expressed CD45, PAX5, CD79a, CD20, BCL6, and MUM1, whereas staining for CD3, CD5, CD10, TdT, CD34, AE1/AE3, CAM 5.2, and MART1 was negative. Diagnosis of ILK was made. The patient was emergently treated with Rituximab, Cyclophosphamide, Etoposide, and steroids. Nevertheless, after a prolonged hospital course complicated by septic shock, and disseminated opportunistic infections, the patient expired.

Discussion: ILK is a devastating condition with a median survival of less than a year. Ante-mortem diagnosis is often missed due to the lack of detection of malignant cells in peripheral blood. Biopsy is mandatory whenever possible. Renal hemorrhage, and acute tubule-interstitial nephritis may be a presentation of this condition.



FR-PO692

Primary Large B Cell Lymphoma Mimicking Renal Cell Carcinoma

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Introduction: Primary renal lymphoma is extremely rare and accounts for less than 1% of all kidney tumors. The prognosis is poor and the median survival is less than a year. It is extremely difficult to differentiate between renal cell carcinoma and primary renal lymphoma on initial imaging without biopsy. Primary renal lymphoma is a debated topic due to the kidneys not containing any lymphatic tissue.[1] Here we present a 81 yo CF who presented with nonspecific abdominal finding and was eventually diagnosed with a rare primary diffuse large B-cell lymphoma on CT guided biopsy.

Case Description: An 81 year-old- CF with PMHx of HTN, HLD presented with insidious onset dull epigastric dull and right sided abdominal pain. The pain was nonradiating, and nothing made it better or worst. It was associated with nausea, dry heaving, loss of appetite and weight loss. Otherwise ROS were negative. Vital signs were within normal range. Physical exam was unremarkable except minimal tenderness on palpation in the epigastric area and the right abdomen. A CBC was unremarkable, CMP was suggestive of AKI. Persistent nagging abdominal pain resulted in a CT abdomen and pelvis with contrast that was suggestive of renal mass with encasement of the IVC. She underwent CT guided renal biopsy instead of resection due to high risk of surgical removal that came back positive for a rare primary diffuse non hodgkin's B cell lymphoma. Her metastasis workup was negative. Oncology and the surgical team were consulted for further management.

Discussion: Primary Diffuse large B cell lymphoma of kidney is infrequent and management is completely different than RCC but needs renal biopsy to diagnose. With better technique and advancement in minimally invasive renal biopsy there is now a low complication rate. The use of percutaneous renal mass biopsy has expanded considerably in the last decade making it easier to differentiate between primary vs. secondary renal malignancy. We postulate that this advancement would stratify the malignant risk which could help in decreasing the number of needless extirpative therapies like nephrectomy.

FR-PO693

Use of Anti-FGF-23 Monoclonal Antibody for the Treatment of Severe Hypophosphatemia Secondary to Tumor-Induced Osteomalacia

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Introduction: Hypophosphatemia in patients with cancer may be due to poor oral intake or more commonly from drug-induced tubulopathies leading to renal phosphate wasting. Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic cause of hypophosphatemia and hyperphosphaturia, as a result of constitutive release of fibroblast growth factor-23 (FGF-23). Here we present a case of profound hypophosphatemia secondary to oncogenic osteomalacia that improved with administration of burosumab, a monoclonal IgG1 antibody against FGF-23.

Case Description: A 68-year-old man with history of metastatic prostate cancer s/p prostatectomy, presented with several months of generalized weakness, worsening fatigue, muscle cramps and paresthesia. A whole-body bone scan showed extensive osseous metastatic disease. Laboratory data revealed serum phosphorus of 0.9mg/dL and inappropriately elevated random urinary phosphate (125 mg/dL; FEPO4 70%), indicative of renal phosphate wasting. His renal function was normal (serum creatinine 0.9 mg/dL) and ionized calcium was 1.07 mmol/L (normal 1.15-1.32mmol/L). Further work up revealed 25(OH)-Vitamin D level of 40 ng/mL and 1,25 $(OH)_2$Vitamin D level of 28 pg/mL. His serum FGF-23 levels were remarkably elevated (812 RU/mL, normal <180 RU/mL). Patient was diagnosed with oncogenic osteomalacia and was initially treated with oral phosphate and active vitamin D supplementation, which was unsuccessful (serum phosphorous persistently <1.0 mg/dL). He was then started on burosumab 90 mg every 2 weeks. After three doses, his phosphorus levels increased to 2 mg/dL and 1,25 $(OH)_2$Vitamin D level increased to 62 pg/mL.

Discussion: Burosumab is a human IgG1 monoclonal antibody directed against FGF-23 that has been approved for X-linked hypophosphatemia. By decreasing levels of FGF-23, burosumab increases both renal reabsorption and gastrointestinal absorption of phosphorus. Although burosumab is not yet approved for the treatment of hypophosphatemia in oncogenic osteomalacia, our case reveals another application for burosumab in this setting, specially in patients with refractory and symptomatic hypophosphatemia.

FR-PO694

Early-Stage IgG4-Related Tubulointerstitial Nephritis Incidentally Detected with a Tumor Lesion of the Ureteropelvic Junction

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Introduction: Histological examination of IgG4-related kidney disease (IgG4-RKD) is typically performed when kidney function decreases or when multiple low-density lesions are found in enhanced computed tomography (CT) images; thus, advanced-phase rather than early-phase IgG4-TIN is often detected. Here, we report a case of very early-stage IgG4-related tubulointerstitial nephritis (TIN) incidentally detected with involvement of the ureteropelvic junction (UPJ).

Case Description: A 72-year-old Japanese man was admitted to our hospital for progressive renal dysfunction. He had been followed-up for 18 years after surgical resection of a bladder tumor. Six months prior to presenting at our hospital, periodic CT showed a mass lesion on his right UPJ. He was clinically diagnosed with right ureter cancer and received neoadjuvant therapy followed by a right nephroureterectomy. Histology revealed IgG4-positive cell ($IgG4^+PC$) infiltration, obliterative phlebitis, and storiform fibrosis in the removed mass, leading to the diagnosis of IgG4-RKD. Notably, $IgG4^+PCs$ also infiltrated the tubulointerstitium of the cortex of the right kidney without storiform fibrosis, although no imaging abnormality was viewed in preoperative CT, indicative of very early-phase IgG4-TIN. In addition, mononuclear cells gathered only beneath the kidney capsule and around arteries and veins, and based on immunofluorescence, most of these aggregations were composed of T cells, B cells, and CD21-positive follicular dendritic cells, suggestive of mature tertiary lymphoid tissue (TLT). $IgG4^+PCs$ surrounded the TLT. Because renal function gradually worsened, the patient was admitted. Although neither extra-renal organ involvement nor an imaging abnormality of the left kidney was

noted, glucocorticoids were initiated and prevented renal deterioration, suggesting that IgG4-TIN was also present in the left kidney.

Discussion: IgG4-TIN was incidentally detected with involvement of the UPJ regardless of a lack of abnormalities in images of the kidney. $IgG4^+PC$ was distributed beneath the kidney capsule and around arteries and veins accompanying TLT. This case suggests that IgG4-TIN develops from common sites of TLT with TLT formation prior to the appearance of imaging abnormalities.

FR-PO695

A Case of Concurrent Multiple Myeloma and LECT2 Amyloidosis

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Introduction: Multiple myeloma is a cancer of plasma cells that can lead to kidney problems. Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is one of the most recently described forms of amyloid with unknown etiology, strong ethnic predominance and manifests as slow progressive renal failure.

Case Description: 44-year-old Hispanic female with no prior past medical history, presented to the ER with headache, nausea, fatigue and RLE pruritic rash x2 months and lab values concerning for acute kidney failure. Symptoms worsened 2 weeks prior to presentation with persistent headaches, emesis, hypersomnia and dyspnea on exertion. Physical exam with mild diffuse abdominal tenderness and dry RLE rash. Initial labs with BUN 58 mg/dL & Cr 5.40 mg/dL (1.1 mg/dL 5 months prior). Urine studies revealed UA with 1+ protein, protein/Cr ratio 4.52 g; CBC remarkable for anemia and thrombocytosis. Abdominal ultrasound unremarkable except moderate hepatomegaly. Work-up remarkable for positive ANA, SPEP with kappa light chain monoclonal peak in gamma region and abnormal serum & urine K/L ratio. Renal biopsy showed amyloidosis with positive congo red stain for amyloid deposits suspicious for LECT2 Amyloid and focal atypical kappa light chain dominant casts; 30% IFTA. Skeletal survey with multiple skull lytic lesions. Bone marrow biopsy and staining consistent with IgG Kappa multiple myeloma. Patient started on Velcade/Dex for IgG kappa multiple myeloma. Discharged with outpatient follow up

Discussion: Renal LECT2 amyloidosis is an uncommon form of amyloidosis of unknown etiology that causes slowly progressive renal failure with affinity to kidney and liver and more commonly seen in Hispanic patients. No available treatment except renal transplantation once end stage kidney disease is established. There are different types of myeloma, classified by the type of immunoglobulin produced by the abnormal plasma cells. IgG kappa type is the most common abnormal M protein. There has been overlap between multiple myeloma and amyloidosis with patients frequently diagnosed with both myeloma and AL amyloidosis, which is not the case in our patient with multiple myeloma and LECT2 amyloid. Thus, thorough categorization of patients presenting with renal amyloidosis should be encouraged to broaden the understanding of these subtypes and afford appropriate therapy and accurate prognosis to avoid unnecessary treatment.

FR-PO696

Cinacalcet-Induced Permanent Hypocalcemia in a Patient with Primary Hyperparathyroidism and Normal Kidney Function

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Introduction: Cinacalcet (C) increases sensitivity of calcium (Ca) sensing receptor to extracellular Ca and suppresses parathyroid hormone (PTH) secretion. C is used in patients with primary hyperparathyroidism (PHPT) who are not surgical candidates. We report a case of irreversible hypocalcemia after 6 months of C administration in a patient with PHTP.

Case Description: A 58-year-old Caucasian male with PHPT, recurrent nephrolithiasis, osteopenia in femoral neck and normal kidney function (eGFR>90ml/min/1.73m^2) underwent surgical resection of 2 parathyroid glands. Postoperatively, PTH remained elevated (iPTH 227pg/mL, normal level [30-69]) in association with albumin-corrected Ca (aCa) 10.4mg/dL [8.2-10.2], ionized Ca (iCa) 1.4mmol/L [1.15-1.35]) and hypercalciuria (24-hr urinary Ca 427mg). Due to persistent PHPT and refusal of further surgery C 30 mg daily was initiated. C resulted in resolution of hypercalcemia, normalization of Pi and iPTH fall to 139pg/dL in 4 weeks. However, 6 months later the patient presented to the hospital with newly developed widespread paresthesia and hypocalcemia (aCa 7.2mg/dL, iCa 0.96 mmol/L), hyperphosphatemia (4.6mg/dL) and suppressed PTH (7pg/dL). C was discontinued and Ca supplements were initiated leading to normalization of iCa (1.17mmol/L) and PTH (38pg/ml). However, the patient continued to have hypercalciuria and required continuous oral Ca supplementation to avoid paresthesia and maintain eucalcemia even 12 months later. Repeat DXA showed improvement in bone mineral density.

Discussion: Reversible hypocalcemia due to C was mainly reported in patients with advanced CKD and it usually responds to a reduction or discontinuation of C. The present case has several novel features. Firstly, C-induced hypocalcemia developed in a patient with normal kidney function. Secondly, because PTH has normalized after temporal C exposure, we suggest that C can induce apoplexy of PTH-overproducing parathyroid cells. Lastly, we suspect the development of a defect resembling renal PTH resistance based on the presence of persistent hypercalciuria despite normal PTH levels with resultant hypocalcemia requiring continuous Ca supplementation. Further clinical investigations are needed to understand whether in some patients cinacalcet can cause or unmask renal PTH resistance.

FR-PO697

Calcium Maldistribution: A Case of Calcium Nephrolithiasis, Aortic Calcification, and Osteopenia

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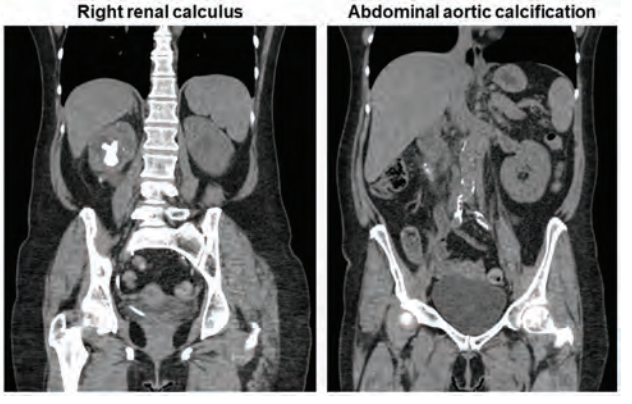
Introduction: Epidemiologic studies show that patients with nephrolithiasis have a higher prevalence of aortic calcification and bone demineralization compared to those without nephrolithiasis. We present a case of calcium nephrolithiasis with concomitant aortic calcification and osteopenia.

Case Description: A 62-year-old post-menopausal woman was seen for evaluation of nephrolithiasis. She was a smoker, but had no significant past medical history. Work up revealed serum K 4.8 mEq/L, CO_2 26 mEq/L, creatinine 0.8 mg/dL, calcium 9.6 mg/dL, phosphorous 3.9 mg/dL, intact parathyroid hormone 31 pg/mL, 25-hydroxy vitamin D 42 ng/mL and urinary pH ≥6.2 on all urinalyses (n=4), suggesting possible incomplete renal tubular acidosis. Stone analysis showed 100% calcium phosphate. Urine supersaturation showed marked hypocitraturia (235 mg/day) without hypercalciuria (153 mg/day). On computed tomography, she had numerous right kidney stones and significant abdominal aortic calcification [figure]. Dietary history revealed low calcium intake. Dual-energy x-ray absorptiometry (DEXA) was performed and showed osteopenia in the lumbar spine (T score: -2.3, Z-score: -0.7) and left femoral neck (T score: -1.4, Z-score: -0.2). As per Fracture Risk Assessment Tool, her 10-year fracture risk for a major osteoporotic fracture was 8.4%. Given above findings, we recommended smoking cessation, increasing dietary intake of calcium, fruits and vegetables, and to continue monitoring bone density.

Discussion: This is a case of calcium maldistribution, in which there was extraosseous deposition of calcium in the right kidney and aorta, and bone demineralization. The presence of nephrolithiasis and arterial calcification prompted us to perform a DEXA scan, which led to a more comprehensive treatment plan. More importantly, the case highlights an important need to better understand the pathophysiology underlying the maldistribution and extraosseous deposition of calcium.



FR-PO698

Case Study: A Report on the Efficacy of Hydroxychloroquine in Treating Hypercalcemia

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Introduction: Sarcoidosis is a rare autoimmune disease resulting in the formation of non-caseating granulomas. Hypercalcemia occurs in 10 to 30 percent of sarcoidosis cases due to 1-alpha-hydroxylase over expression in granulomas. This enzyme increases 1,25-dihydroxy vitamin D levels, by conversion of 25-OH to 1,25-OH vitamin D. Hypercalcemia may be seen in any granulomatous disease. If hypercalcemia is uncontrolled it may lead to complications including nephrocalcinosis, renal lithiasis, and irreversible renal failure. Glucocorticoids are the mainstay of treatment of sarcoidosis, including the complication of hypercalcemia. Antimalarial agents such as chloroquine and hydroxychloroquine are known to impair production of 1,25-OH Vitamin D by blocking 1-alpha--hydroxylase activity. We report a case of a 56 year old caucasian female with sarcoidosis complicated by hypercalcemia successfully treated with hydroxychloroquine.

Case Description: A 56-year-old caucasian female with history of diabetes mellitus, hypothyroidism, and hypertension was referred for management of recent onset of worsening hypercalcemia. Her electrolytes were notable for serum calcium of 12.4 mg/dL (baseline 9.1-9.7), ionized calcium 1.49 mmol/L (NR 1.11-1.30), and serum creatinine of 1.7 mg/dL (baseline 0.9-1.1). Her calcium level remained elevated in spite of stopping daily Vitamin D3 supplementation and treatment with Denosumab injections. Differential diagnosis; included lymphoma and sarcoidosis: sarcoidosis was confirmed by tracheobronchial lymph node biopsy. Since pulmonary function was normal, there was a desire to avoid systemic steroid treatment. The patient was started on 200 mg hydroxychloroquine twice a day to control her hypercalcemia without the use of steroids. Within 2 months after initiation of hydroxychloroquine, calcium normalized and renal function returned to baseline. Hydroxychloroquine was then decreased to once a day and calcium remained normal over a period of greater than 2 years.

Discussion: This case uses hydroxychloroquine as a steroid sparing alternative in the treatment of hypercalcemia. This case demonstrates the efficacy of hydroxychloroquine in the treatment of hypercalcemia, by directly inhibiting the 1-alpha-hydroxylase activity. Based on this mechanism of action it should be considered as a treatment strategy in any disease resulting in 1-alpha hydroxylase overproduction.

FR-PO699

Overcorrection of Severe Hyponatremia in a Chronic Alcoholism Patient: A Case Report of Osmotic Demyelination Syndrome

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Introduction: Patient with chronic alcoholism can have chronic hyponatremia from multiple mechanisms. Both chronic alcoholism and severe hyponatremia predispose patient to the osmotic demyelination syndrome. Rapid correction of serum sodium can lead to severe neurological damage.

Case Description: 45-year-old man with chronic alcoholism presented with confusion, generalized weakness, nausea, and vomiting for 3 days. He had history of heavy alcohol drinking for 3 years. Initial labs showed serum sodium level of 99 mmol/L. He was given intravenous 3% NaCl of the rate of 30 ml/hr to correct hyponatremia. Three hours later lab result showed a sodium level of 113 mmol/L. The patient was more lethargic and was found to have anisocoria. CT head showed diffuse atrophy but no acute abnormality. FLAIR MRI showed hyperintensity of supratentorial white matter, likely due to mild chronic microangiopathy. He was given intravenous 5%Dextrose at 100 ml/hr for overcorrection of hyponatremia. Later in hospital course he was more alert. His sodium level later increased to 127 mmol/L over the next 4 days. Patient was discharged to the nursing facility. He presented to hospital again with dysphagia, generalized weakness and spastic quadriparesis. His sodium level is 134 mmol/L. MRI showed abnormal restricted diffusion in the pons and bilateral thalami. There was subtle abnormal enhancement in the abnormal area in the pons which suggested osmotic demyelination syndrome.

Discussion: Patients who are high-risk for osmotic demyelination syndrome should raise awareness when correcting hyponatremia. Rapid sodium correction in this group of patients may lead to deterioration of neurological status due to neuronal shrinkage. The rate of sodium correction should not exceed 6-8 mEq/L in 24 hours period. Clinical manifestations of osmotic demyelination syndrome includes lethargy, dysarthria, dysphagia and seizure. Patients usually presented 2-6 days after correction. Our patient developed symptoms during the next 8 days. Even though it was later than the average onset, the risk factors and his symptoms are typical. MRI may not become positive until four weeks after onset. If the initial MRI is negative, it does not exclude osmotic demyelination syndrome.

FR-PO700

Peculiar Case of Life Threatening Hypokalemia

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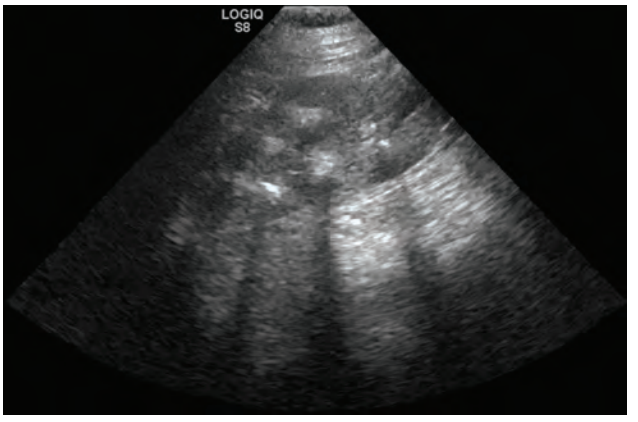
Introduction: Severe hypokalemia causes muscle weakness and cardiac arrhythmias. We present a case of life threatening hypokalemia due to RTA.

Case Description: 32-year-old woman presented with subacute weakness and muscle pain. She denied personal or family history of nephrolithiasis, autoimmunity, malignancy, deafness, growth retardation, fracture, anorexia, diarrhea, medication, illicit drug or heavy metal exposure. EKG showed QTc 756 ms and U waves. Labs revealed creatinine 0.75 mg/dL, K+ 1.7 mEq/L, Mg2+ 2.9 mg/dL, HCO3- 13 mEq/L, pH 7.28, urine pH 7.5, trace urine albumin, urine anion gap 7 mmol/L and urine osmolal gap 39 mOsmol/kg. 24 hour urine showed K+ 133 mEq, calcium 863 mg, phosphate 1150 mg, protein 690 mg and citrate <60 mg. Her imaging was notable for nephrocalcinosis. Calcidiol was 6.5 ng/ml and peak CPK was 5145 U/L. PTH decreased from 205.8 pg/mL (calcium 7.5 mg/dL) to 42.9 pg/mL (calcium 8.9 mg/dL). Chest imaging without hilar adenopathy. SS-A and SS-B antibodies were negative. Genetics screen was obtained and pending. After 880 mEq of K, her plasma K reached > 4. K citrate was started at 120 mEq daily and her acidosis resolved after 3 days. She was discharged with 80 mEq of K Citrate daily with stable chemistries.

Discussion: Distal RTA (dRTA) is characterized by inability to secrete H+ in the distal tubule. It is associated with hypokalemia if non-voltage mediated. It can lead to hypercalciuria, hyperphosphaturia, hypocitraturia and consequent nephrocalcinosis. dRTA yields alkaline urine but urinary pH is maintained <6.5 because bicarbonate is not significantly lost. However, this patient had urinary pH 7.5 and tubular proteinuria suggesting proximal tubule injury. The etiology of the patient's proximal tubule injury is unclear, but the hypovitaminosis D is glaring. Overall, this case represents a peculiar presentation of RTA, with likely long-standing dRTA and sub-clinical nephrocalcinosis coupled with proximal injury resulting in life threatening hypokalemia. Clinicians should consider RTA as the cause of hypokalemia.



Nephrocalcinosis

FR-PO701

Hyponatremia due to Primary Adrenal Insufficiency Treated by Cortisol Replacement

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Introduction: Hyponatremia complicating malignancy is most commonly seen due to the syndrome of inappropriate antidiuretic hormone secretion. We present a unique case in which metastatic non-small cell lung cancer (NSCLC) led to primary adrenal insufficiency and hyponatremia

Case Description: A 66-yr-old man was admitted for symptomatic hyponatremia. He was evaluated at an outside facility for a month history of blood-streaked sputum and weight loss. He was hypotensive with initial serum sodium (SNa) 125 mEq/L, potassium 5.3 mEq/L, bicarbonate 22 mEq/L, chloride 86 mEq/L and Creatinine 0.5 mg/dL. After receiving 1 L of normal saline, he became confused with an associated fall in SNa 116 mEq/L, prompting transfer to our institution. On arrival, he was lethargic and disoriented. His vital signs were normal. Physical examination revealed a disoriented man with digital clubbing. Laboratory studies revealed a serum osmolality 235 mOsm/kg, urine osmolality (UOsm) 271 mOsm/kg and urine sodium 74 mmol/L. CT of head showed superior cerebellar mass with vasogenic edema. Further imaging revealed right upper lobe lung mass and bilateral adrenal nodules. He was treated with dexamethasone 6 mg every 6 hours for vasogenic edema and suspicion for adrenal insufficiency. Repeat laboratory studies showed improvement of SNa to 123 mEq/L and decrease in UOsm to 129 mOsm/kg. The SNa decreased to 120 mEq/L while the UOsm increased to 382 mOsm/kg after tapering of dex. A cosyntropin stimulation test was consistent with primary adrenal insufficiency. Hydrocortisone therapy at replacement doses resulted in normalization of SNa

Discussion: Adrenal glands are commonly involved in metastatic cancer but primary adrenal insufficiency uncommonly ensues, unless majority of the adrenal cortex is destroyed. Although it has been reported with advanced breast cancer and colon carcinoma, to our knowledge only a handful of cases of adrenal insufficiency leading to hyponatremia due to NSCLC have been reported. The pathogenesis is related to loss of negative feedback of cortisol on vasopressin which acts as a secretagogue for ACTH. The rate of rise of sodium is ideally 6-8 mEq/24 hours, but needs cautious monitoring since erratic changes may be seen (observed in our case). Dex is the initial corticosteroid of choice as it doesn't interfere with cortisol assay during cosyntropin stimulation test

FR-PO702

Pseudohyperphosphatemia in Multiple Myeloma

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Introduction: Hyperphosphatemia commonly occurs in renal failure or hypoparathyroidism. If severe it can cause severe hypocalcemia leading to cardiac or neurologic symptoms. Pseudohyperphosphatemia is rarely seen and it is due to interference by other serum elements in the phosphorous assay.

Case Description: We present here a 58 year old woman with refractory IgG kappa multiple myeloma. SCr was 0.6 mg/dL, eGFR >60 ml/min, Pi 34 mg/dL, iCa 1.06 mmole/L, PTH 32 pg/mL, uric acid 6.2 mg/dL, LDH 212 U/L, IgG 7888 mg/dL, total protein 13.2 g/dL, serum globulin 10.3 g/dL In the setting of normal renal function, normal PTH, no laboratory evidence of tumor lysis syndrome and discrepancy between serum phosphorus and calcium levels we suspected this was a case of pseudohyperphosphatemia.

Discussion: It has been stated that paraproteins interfere with spectroscopic measurement of phosphomolybdate which is the actually measured adduct in the routine laboratory phosphorous (P) assay. The inherent flaw in the design of this test is its dependence on light penetration into the sample, thus any condition that increases the turbidity of the sample would falsely elevate the reading. Also, the abnormal serum proteins may themselves bind phosphate which may spuriously increase the total serum

phosphate, but not the biologically active form of phosphate. The level of serum phosphate returns to normal when it is measured after deproteinization with sulfosalicylic acid or trichloroacetic acid. Instead of precipitating the proteins we performed a mixing study using normal serum with a Pi of 1.3 mg/d and performed serial dilutions. The patient's serum diluted fourfold only increased the Pi level of the mixture to 2.1 mg/dL indicating that the upper bound of our patient's true Pi level is around 4.5 mg/dL. We can also calculate the free Pi concentration from association constant of calcium and phosphorus, which is $2.3x10^{-7}$ $mole^2/L^2$. When the ionized calcium is 1 mmole/L the free serum Pi level has to be 0.23 mmol/L. Using an activity coefficient of Pi of 0.23, the patient's actual plasma Pi is about 1 mmole/L or ~ 3mg/dL. It is interesting that a falsely elevated Pi level does not occur in every patient with paraproteinemia thus it is likely that the type of paraprotein produced by the clone may have specific chemical attributes that leads to the spurious measurement.

FR-PO703

A Case of Spurious Hyponatremia in Hyperleukocytosis

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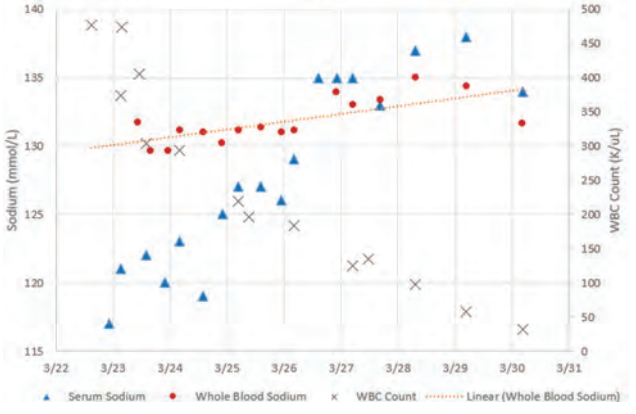
Introduction: Hyponatremia is commonly seen in the oncology population. Here we report a case of discordance between serum sodium and whole blood sodium measurements in the setting of severe leukocytosis.

Case Description: A 72-year-old male with blastoid variant mantle cell lymphoma presented with fatigue and nausea. He appeared hypovolemic on exam. Laboratory evaluation revealed a WBC count of 476 K/uL. Serum sodium (SNa) was 117 mmol/L, potassium > 10 mmol/L, BUN 27 mg/dL and creatinine 1.36 mg/dL. Whole blood potassium was 3.73 mmol/L. Glucose was 96 mg/dL and total protein was 5.2 g/dL. Urine chemistry showed sodium < 10 mmol/L, chloride < 15 mmol/L, potassium 66.0 mmol/L, osmolality 722 mosm/kg. SNa initially improved with normal saline hydration to 121, but did not improve further over the next 24 hours. No alternative causes for hyponatremia were identified. SNa at our institution is measured by the direct ion-specific electrode method which makes pseudohyponatremia from lipids or proteins unlikely. Whole blood sodium (WBNa) checked on day two was 131.7 mmol/L while concurrent SNa remained 121. With leukopheresis and R-CHOP the WBC count improved from 476 to 31.5 K/uL. Serial WBNa measurements remained stable (129.6 – 135) during treatment while SNa gradually increased from 117 to normal levels (Fig. 1). The gap between WBNa and SNa diminished as WBC burden was reduced and these measurements correlated well when WBC count decreased below 150 K/uL.

Discussion: This case identifies a disparity between SNa and WBNa measurements in the setting of severe leukocytosis. Psuedohyperkalemia has been previously described in this population and is thought to be due to leukocyte membrane fragility and mechanical stress during blood tube handling leading to cell lysis and leakage of intracellular contents into plasma. This case suggests that SNa measurements are also distorted by this mechanism. Whole blood sodium measurements may be more reliable than serum measurements in the setting of severe leukocytosis.



FR-PO704

Mycobacterium Chimaera: An Unusual Cause of Hypercalcemia and Kidney Injury

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Introduction: Mycobacterium Chimaera is an indolent nontuberculous mycobacterium that has been recently associated with outbreaks of prosthetic valve endocarditis throughout Europe and the United States. Contaminated heater-cooler devices in the cardiothoracic operating rooms have been implicated as the cause of the outbreak. Hypercalcemia and kidney involvement have rarely been reported as part of the disease presentation. We hereby present a case of M. Chimaera prosthetic valve endocarditis presenting with hypercalcemia and kidney dysfunction.

Case Description: A 63-year-old male with a history of bicuspid aortic valve status post bioprosthetic AVR presented with generalized weakness, fatigue, and altered sensorium. MRI of the brain revealed small embolic events that prompted a TEE which was suspicious for vegetations on the bioprosthetic valve along with valve dehiscence and perivalvular abscess. He was thus transferred to our facility for evaluation of re-do surgery. On evaluation, he was found to have an AKI with a creatinine of 1.7 mg/dl (baseline around 1). He was also notably hypercalcemic at 12 mg/dl with an undetectable PTHrP level. Creatinine and calcium trended down slowly with hydration and the patient was eventually taken to the OR for AVR. While 25-OH vitamin D level was low (20.8 ng/ml), the 1,25-OH vitamin D level was elevated at 65.4 pg/ml. Microbiologic evaluation of the explanted valve revealed moderate acid-fast bacilli by Ziehl-Neelson stain and the cultures were positive for Mycobacterium Chimaera. The patient was also found to have multifocal choroiditis on ophthalmic evaluation, which was indicative of disseminated mycobacterial infection. He was thus treated with a prolonged course of rifampin, ethambutol, and azithromycin. The patient was eventually discharged home in good condition with complete normalization of creatinine and calcium levels.

Discussion: Mycobacteria are associated with elevated 1,25-OH Vitamin D levels due to production of 1-alpha-hydroxylase enzyme by activated macrophages. The ensuing hypercalcemia can certainly lead to kidney dysfunction but M. Chimaera has also been associated with granulomatous interstitial nephritis. Treatment focuses on antibiotic therapy and in the case of prosthetic valve endocarditis, surgical treatment whenever possible.

FR-PO705

Linezolid-Induced SIADH: A Rare Cause of Hyponatremia

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Introduction: Linezolid is a oxazolidinone antibiotic against gram-positive organisms that inhibits bacterial protein synthesis. Thrombocytopenia is common, but hyponatremia is rare after linezolid use.

Case Description: An 89-year old woman with MRSA wound infection after lumbar laminectomy required prolonged linezolid therapy. She was admitted to the hospital for acute anemia and hyponatremia, with a hemoglobin drop from 8gm/dl to 6.8gm/dl and a sodium level of 127meq/l on admission over a 3-week period. Patient was hypotensive with blood pressure of 90/50 mm Hg, but her sodium levels failed to improve with isotonic fluids. Labs showed serum sodium of 122meq/l, serum osmolality 255mOsm/kg, urine osmolarity 389mOsm/kg, urine sodium 125mmol/l and serum uric acid level of 2.6 mg/dl. Rest of the work-up including serum cortisol and TSH were normal. All labs were suggestive of SIADH and as further investigations towards finding the underlying etiology did not reveal any other cause, linezolid was considered to be the culprit. Linezolid was stopped, and patient was started on fluid restriction and salt tablets, her sodium improved from 122meq/l to 130meq/l over 4 days. Anemia was attributed to myelosuppression caused by linezolid, which is one of its serious side- effects.

Discussion: This case was given 6 points using Naranjo adverse drug reaction (ADR) probability score indicating an association between hyponatremia and Linezolid use. Linezolid has previously been reported to cause hyponatremia with a frequency of 18% in a retrospective cohort study. Exact mechanism remains unknown but could be secondary to ADH release due to the medication or from underlying inflammation. There are 3 other cases published to date reporting hyponatremia from linezolid use. Interestingly, most of these reports have been on Asian population, possibly hinting towards a higher incidence in this group. However, more research is needed to explore this hypothesis. It is important to increase awareness of this side-effect as new drug-resistant bacteria emerge and use of Linezolid increases. Close monitoring of serum sodium is important for those on prolonged treatment with Linezolid, since it also lowers the seizure threshold. The use of Linezolid can lead to neurologic side effects of hyponatremia, ranging from mild effects such as tremor, incoordination to severe such as seizures.

FR-PO706

Guess the "Glucose"

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Introduction: Hyponatremia is the most common electrolyte abnormality encountered in clinical practice. Proper interpretation of the various laboratory tests helps to differentiate the various types of hyponatremia. Treatment varies with the nature of onset, acute or chronic, severity and symptoms.

Case Description: 39 year old male who recently immigrated from Guatemala 1 week ago was admitted for seizures witnessed by his family. Review of systems was positive for urinary incontinence and tongue biting. Vital signs showed Temperature 97.3F, BP126/97, HR 112, RR 16. Physical exam was notable for Tongue trauma, dry mucous membranes and decreased skin turgor. Laboratory data was significant for Sodium of 102, Glucose > 4000, BUN 50 and Serum Osmolality 350. A diagnosis of Hypertonic Hyponatremia due to Hyperglycemia was made. Patient was treated in the ICU for 2 days with Insulin and Isotonic Intravenous fluids and was discharged from the hospital on day 5.

Discussion: Scenario 1 - If the Glucose from the lab value were true at 4000, corrected sodium would be 164 meq/L, using the correction factor of 1.6 mEq per L decrease in serum sodium for every 100 mg per dL increase in glucose concentration. Scenario 2 - We calculated the estimated glucose using the formula for serum osmolality. Assuming an osmolal gap of 10, calculated osmolality was set at 340. This resulted in an estimated glucose of 2100. Based on the estimated glucose, the corrected sodium level was calculated at 134 meq/L. Take home teaching points - Extreme laboratory values should be cautiously examined. Corrected Sodium values in both the scenarios have very different managements with extremely improtant clinical implications. Fun fact - Guiness World Record for the highest blood glucose survived by a human being was 2656 mg/dL.

CBC	
WBC	11
HgB	12.3 (MCV 97)
PLT	322

Urine lytes	
Na	60
K	14
Cl	54
Cr	13.6
UPC	1.69

UA	
SG	1.016
pH	7
Protein	1+
Glucose	3+
UPC	1.69

BMP	
Na	102
K	3.6
Cl	56
HCO3	26
BUN	50
Cr	2.7
Glucose	>4000

Other	
Serum Osm	350
Beta-OH Butyrate	0.3
UDS	Negative

What's the corrected Na?

$$\textit{Serum Osmolality (calculated)} = 2\,[Na^+] + \frac{[BUN]}{2.8} + \frac{[Glucose]}{18}$$

FR-PO707

Characterization of ADPKD-Like Patients Monoallelic for ALG8 Mutations

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Background: Although *PKD1* and *PKD2* are the common ADPKD genes, recently monoallelic *GANAB* and *DNAJB11* mutations have been associated with an ADPKD-like phenotype. These studies showed genic overlap between ADPKD and the related disorder, autosomal dominant polycystic liver disease (ADPLD). Our aim was to further determine the etiology of genetically unresolved ADPKD-like patients.

Methods: Here we screened 723 ADPKD-like patients without mutations in the known ADPKD genes employing a 137 gene panel of described ADPKD, ARPKD, ADPLD, ADTKD and ciliopathy genes, plus candidate loci. Identified families were characterized by segregation, imaging and analysis of the clinical phenotype.

Results: One gene, *ALG8*, stood out due to a high number of truncating variants across multiple families. *ALG8* encodes a glucosyltransferase, and biallelic mutation have been associated with a congenital disorder of glycosylation, CDG1H, while monoallelic mutations have been described to cause ADPLD in 5 families. Nine families were identified with likely significant *ALG8* pathogenic variants: 2 missense and 7 truncating, with 14 mutation proven cases. The kidney involvement was mild with normal function and small to medium sized cysts, predominantly in the left kidney, and few liver cysts. The presentation was often sporadic, but in one family two sibs had similar asymmetric disease. The relatively high frequency of *ALG8* truncating changes in the normal population (gnomAD database) indicates that it may be a common cause of renal cysts, but additional modification may be required for clinically significant disease. Consistent with this, a patient with Stage 4 CKD also had a rare *PKD1* missense variant, while his sister with only the *ALG8* variant had just a few cysts. Further, in a described unlinked (PKD3) Spanish family, significantly affected individuals had splicing variants to one or two known ciliopathy genes segregating with the *ALG8* mutation.

Conclusions: *ALG8* is a gene associated with multiple cyst development in the kidney and screening will likely explain a significant number of mildly affected cases. Oligogenic inheritance with additional gene variants may be required to trigger clinically significant PKD.

Funding: NIDDK Support

FR-PO708

Expanding the Variability of the ADPKD-GANAB Clinical Phenotype: A New Family of Italian Ancestry

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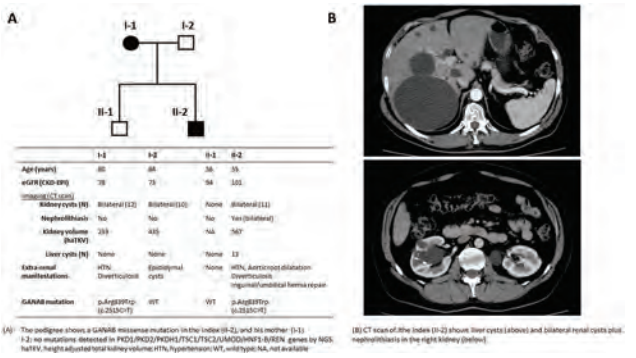
Introduction: Causative GANAB mutations have been described reported in only 12 families, 9 diagnosed with late-onset mild ADPKD and 3 with ADPLD. We describe a new family with mild, late-onset ADPKD due to p. R839W GANAB mutation, previously reported in an ADPLD patient requiring liver transplantation.

Case Description: Diagnosis of ADPKD was made in a 45-year old man during pre-surgical screening for umbilical and inguinal hernia repair. Hematuria, hypertension and aortic root dilatation were documented. At age 52, he experienced acute flank pain. Abdomen CT scan showed bilateral renal cysts (TKV 565 cc), nephrolithiasis, normal-sized liver with multiple cysts, and colonic diverticuli; renal function was normal. PKD1-PKD2 NGS and MLPA analyses were negative; analysis of additional PKD related genes showed a heterozygous p. R839W GANAB mutation. Familial study revealed p. R839W GANAB mutation in the mother. The elderly parents had normal renal function, normal-sized kidneys with multiple bilateral kidney cysts (mainly parapelvic in the father). The ADPKD-GANAB affected mother had no liver cysts on CT scan. The father has been studied for PKD related genes and no mutation was found.

Discussion: Since ADPKD-GANAB is a rare condition, we need further families to better characterize the phenotypic features of this new cystic disease. In our family, the p. R839W GANAB mutation, previously associated with severe ADPLD, was associated with a mild ADPKD, although showing several renal and extrarenal manifestations. The overlapping cystic phenotype and the plethora of renal and extrarenal manifestations are in agreement with the hypothesis that in GANAB disease, hepatic and renal cysto-genesis is the result of the common defective polycystin-1 pathway.



FR-PO709

ADPKD: Rare PKD1 and PKD2 Complex Genotypes May Explain Intrafamilial Phenotypic Variability

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Background: Discordant affected relative-pairs are seen in nearly 10% of ADPKD families. Complex genotypes may result in renal disease variability beyond that predicted by the sole effect of a PKD mutant allele, leading to the discovery of biallelic or digenic disease. Here we illustrate such complexity in 6 ADPKD pedigrees showing a marked intrafamilial phenotypic variability.

Methods: Among our single-center ADPKD cohort (186 patients), we selected pedigrees (P) in which marked phenotypic variability was investigated by NGS analysis of PKD1 and PKD2 genes.

Results: In P1 and P2, the index cases (IC), presented with very early onset (VEO) disease. In P1, with neonatal onset, the ADPKD affected father transmitted a PKD1 truncating (T) mutation, whereas the mother, without cystic phenotype, transmitted a PKD1 hypomorphic mutation. In P2, the ADPKD-PKD2 mother's pregnancy was complicated by Potter sequence. Parent's PKHD1 gene analysis was negative. Two non truncating (NT) mutations in PKD1/PKD2 genes were detected in the healthy father. Therefore, a complex PKD inheritance was suspected in the fetus. P3: early onset (EO) ADPKD in two monozygous twins was underpinned by a PKD1 NT mutation on their inherited paternal allele and by a de-novo PKD1 T mutation. In P4 a digenic ADPKD was diagnosed in the two most severely affected siblings: a PKD2 T mutation and a PKD1 NT mutation were detected. Elderly parents in P5 and P6 had few kidney cysts and preserved eGFR, whereas IC showed moderate/severe CKD due to ADPKD. In P5 the IC carried a homozygous PKD1 NT mutation; in P6 the IC harbored 2 PKD1 mutations (in trans).

Conclusions: Our study illustrates the genetic complexity in an otherwise "simple" Mendelian disorder, providing insights into the genetic basis of ADPKD intrafamilial disease variability.

Funding: Government Support - Non-U.S.

PKD1 and PKD2 alleles involved in biallelic and digenic ADPKD complex genotypes

P	Index Mutant Alleles		Phenotype of the Index Case	Phenotype of the Family Members
1	PKD1 c.12691C>T (p.Gln4231*) Paternal allele	PKD1 c.3994G>A (p.Asp1332Asn) Maternal allele	**VEO**: EHK in utero; enlarged palpable kidneys at birth HTN, ?; y; ESRD, 15 y	Father: ADPKD; ESRD (after right traumatic nephrectomy), 44y Mother: no renal/liver cysts; normal eGFR, 64 y External aunt: ADPKD; CKD IV, 60 y
2	PKD2 c.1045T>C (p.Ser349Pro) Mother allele (Index DNA not available)	PKD1 c.9610G>A (p.Gly3844Arg) PKD2 c.608C>T (p.Thr203Ile) Father alleles (Index DNA not available)	**VEO**: EHK in utero, oligohydramnios. Termination of pregnancy	Mother: ADPKD; HTN, 15 y; fibrosis; normal eGFR, 38 y Father: no renal/liver cysts; normal eGFR, 35 y Parents: wild-type PKHD1 sequence
3	PKD1 c.5852G>A (p.Arg1951Gln) Paternal allele	PKD1 c.7204C>T (p.Arg2402*) De novo	Twin 1[a]-**EO**: ADPKD; HTN, 12 y; CKD II and TKV 693cc, 15 y Twin 2-**EO**: ADPKD; HTN, 14 y; CKD II and TKV 586cc, 19 y	Father: ADPKD; HTN, 30 y; normal TKV/eGFR, 50 y Sibling 1 (harboring paternal PKD1 allele): ADPKD; normal TKV/eGFR, 20 y
4	PKD2 c.1094+1G>A (p.Ala365Ile) Maternal allele	PKD2 c.77G>A (p.Cys26Tyr) Maternal allele	Sibling 1: ADPKD; HTN, 36 y; CKD IIIb and TKV 3429cc, 50y Sibling 2: ADPKD; HTN, 31 y; CKD IV and TKV 3315cc, 54 y	Sibling 3 (harboring maternal PKD 2 allele): ADPKD; CKD II and TKV 2780, 48 y Mother: CKD, ? ?4 y Maternal grandfather: ESRD, 80 y
5	PKD1 c.12460C>T; c.12460C>T (p.Arg4154Cys); (p.Arg4154Cys)		ADPKD: HTN 40 y; CKD IV, 65 y	Parents: BCK; never teached ESRD, 36-65 y Daughter (PKD1 c.12460C>T heterozygous): ADPKD; no liver cysts; normal eGFR, 28 y
6	PKD1 c.7490-5C>G (p.Gly2497fs) Paternal allele	PKD1 c.8293C>T (p.Arg2765Cys) Maternal allele	ADPKD with multiple liver cysts, CKD IIIa, TKV 347cc, 57 y	Father: <5 kidney cysts; normal TKV/GFR, 69 y Mother: <5 kidney cysts; multiple liver cysts; normal TKV/GFR, 65 y

P, pedigree; VEO, very early onset; EHK, enlarged hyperechoic kidneys; HTN, hypertension; y, years old: ESRD, end stage renal disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; EO, early onset; ?, deceased; BCK, bilateral cystic kidneys
[a]Monozygous twins

FR-PO710

Clinical Variability in PKD2-Linked Families with the Same Germ-Line Mutation

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common inherited renal cystic disease. It is genetically heterogeneous:72-75% of ADPKD cases are related to mutations in the PKD1, 15-18 % to PKD2 and the remaining 7–10% of affected are genetically unresolved (GUR). Both genes are characterized by high level of allelic heterogeneity. It is rare to identify the same germ-line mutation in different families, since mutations are "private". The age at disease onset, the severity, and the clinical outcome contribute to the intra and interfamilial variability. Aim of the study was to evaluate the clinical characteristics of PKD2 gene-linked families with the same germ-line mutation.

Methods: Patients (pts) with ADPKD were enrolled and followed prospectively. Diagnosis of ADPKD was made upon the revised Ravine's criteria. Complete clinical details were recorded, including family history and pedigree. We performed Sanger sequencing analysis to identify mutations. The eGFR was calculated CKD-EPI equation. The progression of CKD was determined by the change in eGFR per year. Data were shown as mean ± sd or median (min-max).

Results: Twenty-five pts (14male) were included in the analysis, belonging to 10 PKD2gene-linked families with the same germ-line nonsense mutation (c.2533C>T, p.Arg845Ter). 7/10 families had their origin from the same geographical area. The other three families originated from an area 100 km away. Four of them reached ESRD (61 ± 9 yrs) belonging to different families. In 3/4 families at least one relative of ESRD pts did not required RRT at the same age. Moreover, in one family 2 relatives are not even CKD. Nine patients (43 ± 14yrs) are still not affected by CKD; 6/9 pts have at least one ESRD relative. Eleven patients (61 ± 9.6 yrs) have CKD stage 2-3 and a progression rate estimated of 2.3 ml/min/year (0.73-5.1). One of them is a fast progressor and he is in treatment with Tolvaptan.

Conclusions: We found the same PKD2 germline mutation in 10 families maybe due to a founder effect in our region. High intra-interfamilial variability in ADPKD pedigrees was observed, despite the same germline mutation. This could be explained by other clinical or genetic factors (environmental, SNPs, modifier genes, etc) that may affect disease severity.

FR-PO711

Diagnostic Utility of Whole-Exome Sequencing in Autosomal Dominant Polycystic Kidney Disease

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Background: Whole exome sequencing (WES) is increasingly being used to screen for certain genetic conditions, including some genetic forms of kidney disease. However, there are challenges in sequencing adult polycystic kidney disease (ADPKD) due to *PKD1* having 6 pseudogenes. Our goal was to examine WES accuracy in individuals with clinical diagnosis of ADPKD, as well as in an unselected cohort.

Methods: We examined data from 31,391 subjects in the Geisinger-MyCode population as part of the Regeneron-DiscovEHR collaboration. WES was performed using a modified version of the IDT xGen Exome Research Panel. Average depth of coverage for PKD1 and PKD2 were 27X and 33X, respectively. We identified subjects with *PKD1* or *PKD2* putative loss-of-function (pLoF) mutations (stop-gain, frameshift, canonical splice) as well as large deletions encompassing *PKD1*or *PKD2* detected in WES-based CNV analysis. ADPKD phenotyping was done by identification of individuals who had a diagnosis code for polycystic kidney disease, followed by confirmation by chart review.

Results: Out of the 31,391 subjects, we identified 22 (0.07%) patients with clinical diagnosis of ADPKD using a phenotype-first approach, and 26 (0.08%) pLOF mutation carriers using a genotype-first approach. With a phenotype-first approach, we found pLOF mutations in 21/22 (95.5%) patients with clinical diagnosis of ADPKD (13 *PKD1* and 8 *PKD2* carriers). Of the 26 pLoF carriers, there were 18 *PKD1* carriers and 8 *PKD2* carriers. All 8 *PKD2* carriers had clinical diagnosis of ADPKD by chart review. Of the 18 *PKD1* carriers, 12 had ADPKD by chart review although 2 of the remaining 6 patients without evidence of ADPKD were in their 30s and lacked adequate abdominal imaging.

Conclusions: When conducted with a sequencing platform that achieves sufficient depth of coverage of *PKD1*, WES provided 100% diagnostic accuracy in *PKD2* pLoF carriers and showed high sensitivity but limited specificity for *PKD1* pLoF carriers. WES may have diagnostic value in a genotype-first approach in identifying ADPKD patients, but additional confirmation of *PKD1* mutations may be needed.

Funding: NIDDK Support

FR-PO712

Clinical Whole-Genome Sequencing Enables Diagnostic Certainty in Polycystic Kidney Disease

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is predominantly caused by pathogenic-variants in *PKD1* or *PKD2* and is the most common cause of Polycystic Kidney Disease (PKD). Diagnosis is usually by age-dependent ultrasound criteria, which is challenging in those without family history, with atypical clinical features or younger patients. ADPKD diagnosis has also become more complex with recent identification of additional genes that mimic the phenotype. However, new treatments require definitive diagnosis to appropriately prescribe. Whole Genome Sequencing (WGS) can diagnose PKD, including ADPKD and its gene mimics, and provide prognostic information, but has not been validated for clinical use.

Methods: In this study, we first validated WGS for ADPKD diagnostic testing using a blinded cross-over method. Forty-two adult ADPKD patients underwent sequencing of *PKD1* and *PKD2* by both WGS and Sanger sequencing. We then examined the first 85 samples referred to a clinically-accredited diagnostic laboratory for WGS, with variant analysis targeted to a PKD gene-panel (*PKD1, PKD2, GANAB, HNF1B, PKHD1, UMOD, TSC1, TSC2, OFD1).*

Results: WGS identified all *PKD1* and *PKD2* germline disease-causing variants in the validation study, without false-positive results (sensitivity and specificity 100%). In the unselected, real-world diagnostic cohort (42 males:43 females; median-age 39years (0-79years); 46% with family history of PKD), the overall diagnostic rate was 71%, with a 91% diagnostic rate in patients with typical clinical features of ADPKD (100% with *PKD1/PKD2* variants) and 56% in those with atypical clinical features (63% with *PKD1/PKD2* variants*;* 37% with *PKHD1, HNF1B, GANAB, TSC2* variants). Most patients with atypical PKD did not have clinical features that predicted likelihood of genetic diagnosis, highlighting the value of genomic testing in this group.

Conclusions: The high diagnostic rate in both typical and atypical PKD suggests clinicians should consider diagnostic genomics in their approach to PKD diagnosis.

Funding: Private Foundation Support

FR-PO713

Prevalence of Diagnosed Polycystic Kidney Disease by Race/Ethnicity Among a Large Diverse United States Population, 1998-2018

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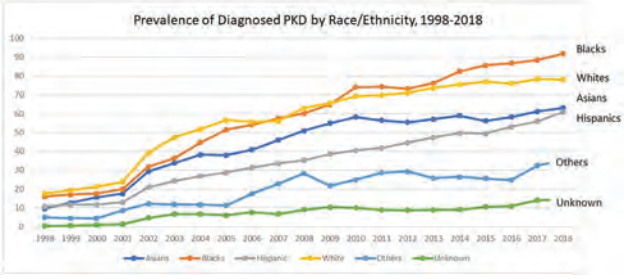
Background: While polycystic kidney disease (PKD) is considered a rare disease, it accounts for the 4th most common cause of ESRD in the United States (US). Estimates of PKD prevalence in Europe and the US are similar (30-50 per 100,000 persons) but whether differences exist across race/ethnicities is relatively unknown. We examined trends in the prevalence of diagnosed PKD overall and by race/ethnicity in a large, diverse healthcare delivery system with over 4.6 million members in the US.

Methods: Diagnosed PKD was identified among members aged ≥15 years in each calendar year from 1998 through 2018. PKD was defined as ≥2 separate encounter diagnoses for PKD (ICD9 codes 753.12, 753.13, 753.14, and ICD10 code Q61.2, Q61.19, Q61.3). Race/ethnicity was determined by self-report. Temporal trends in diagnosed PKD was examined overall and by race/ethnicity.

Results: A total of 7,580,947 members were included in the study period. Between 1998 and 2018, 3,524 members were identified as PKD with an overall prevalence of 46.5 cases per 100,000 people. The mean age of the PKD population was 49 years and comprised of 50% females with 10% Asians, 13% Blacks, 20% Hispanics, and 43% Whites. Prevalence (per 100,000) by race/ethnicity was 58.7, 84.5, 47.7, and 71.7 among Asians, blacks, Hispanics, and whites, respectively (p<0.001). Diagnosed prevalence of PKD increased among all racial/ethnic groups over the 20-years (Figure).

Conclusions: These data demonstrate sizeable differences in PKD prevalence by race/ethnicity. This information can help tailor strategies for identifying and managing this important population, based on the underlying population. Moreover, these data point to the potential to generate additional insights on the natural history/clinical course of this potentially modifiable genetic kidney disease.



FR-PO714

Tubular Basement Membrane Duplication and Cell Interposition Are Distinctive Histological Findings in the Adult Patients Genetically Diagnosed with Nephronophthisis-Related Ciliopathies

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Background: Unlike pediatric patients, nephronophthisis-related ciliopathys (NPHP-RCs) are often suspected only after renal biopsy in adult patients, because they usually have no specific extra-renal complications of NPHP-RCs. However, histological findings of NPHP-RCs, such as microcyst and interstitial fibrosis, are also commonly seen in any chronic tubulointerstitial disorders in general. In addition, comprehensive genetic testing is not easily available. Therefore, identification of representative histopathologic pattern of NPHP-RCs is useful for precise diagnosis of adult patients.

Methods: We analyzed 16 adult patients who were suspected as NPHP-RCs by renal biopsy. All patients had no extrarenal findings (retinitis pigmentosa and liver function disorder) and no family history of NPHP-RCs. Comprehensive genetic testing was performed using capture-based next-generation sequencing for 69 genes that cause nine types of hereditary cystic kidney diseases, including NPHP-RCs.

Results: Through the analysis, six patients were genetically diagnosed with NPHP-RCs, including three patients with homozygous *NPHP1* mutations and three patients with a compound heterozygous mutation in *NPHP3*, *NPHP4*, or *CEP164*, respectively. At the time of renal biopsy, the patients diagnosed genetically as NPHP-RCs were significantly younger than those without mutations (median, 30 years old vs 69 years old, $P = 0.02$). Regarding the pathological findings, tubular basement membrane (TBM) duplication and cell interposition in TBM of intact tubules were significantly more common in the patients with NPHP-RCs (83% vs 20%, $P = 0.035$, 83% vs 10%, $P = 0.008$, respectively).

Conclusions: Our study revealed that disorders of TBM could be specific findings in the adult patients genetically diagnosed with NPHP-RCs. These findings are potentially beneficial for optimal diagnosis of adult NPHP-RCs and are suggestive of the pathogenesis of the diseases.

Funding: Government Support - Non-U.S.

FR-PO715

Therapeutic Targeting Strategies in Pkd1 Loss-of Function Mouse Model: Insights into Pkd1 Regulation

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Background: Autosomal dominant polycystic kidney disease (ADPKD) causes renal and extrarenal phenotypes, mainly due to PKD1 mutations. As a therapeutic strategy, CRISPR-Cas is attractive but the high frequency of off-targets precludes clinical application. Because microscopic cysts are likely formed *in utero* in ADPKD kidneys, we targeted at early renal stage wild type *Pkd1/Pc1* protein from 3 series of transgenic (Tg) lines in *Pkd1*$^{-/-}$ mouse, to assess for long-term cure/improvement of severe renal and pancreatic cysts and neonatal death.

Methods: Re-expression of Pc1 was generated via three Tg matings: a) a systemic $Pkd1_{TAG}$ mouse (16 Tg copy) b) 2 renal-specific $SBPkd1_{TAG}$ mice (2 and 20 Tg copy) or c) a novel Tg line targeting Pkd1 cDNA with renal-specific elements, *SBP* (16 Tg copy). Longitudinal molecular and histologic analyses were performed on kidneys and pancreas.

Results: $Pkd1_{TAG}$;*Pkd1*$^{-/-}$ mice expressing 7-fold over the endogenous Pkd1 gene are totally rescued from renal or pancreatic phenotypes. From 8 mo onwards, $Pkd1_{TAG}$;*Pkd1*$^{-/-}$ mice, relative to parental Tg line, display later renal cysts consistent with gene-dosage increase pathogenic mechanism. $SBPkd1_{TAG}$;*Pkd1*$^{-/-}$ mice with mild ~0.64 or notable 7-fold renal Pc1 overexpression are rescued from neonatal death. In the mild expressor with Tg copies comparable to endogenous, renal and pancreatic cysts are detected at P5 and deaths occurs at P10-P15 whereas the high expressor display renal cysts later at P15 but no pancreatic cysts and survive up to ~3 mo. Renal cysts develop likely from differential tubular and temporal regulatory response to Pc1 either insufficient or over-expression. *SBP;Pkd1*$^{-/-}$ mice with 0.87-fold Pkd1 endogenous level exhibit very mild renal cyst formation at P0 and escape neonatal lethality. This targeting strategy required multiple SBP Tg copies to produce Pkd1 therapeutic levels similar to the $SBPkd1_{TAG}$ and provided evidence for regulatory region within the Pkd1 gene-body. Identification of cystic nephron segments will shed light on the mechanism.

Conclusions: Our results demonstrate that Tg foetal Pc1 expression can substantially delay cystogenesis and extend mouse lifespan. This study shows that Pc1 re-expression not only requires high spatiotemporal regulation by the Pkd1 upstream region but also by regulatory elements within the Pkd1 gene-body.

Funding: Government Support - Non-U.S.

FR-PO716

Betaine Supplementation Ameliorates Renal Disease Severity in Experimental ADPKD

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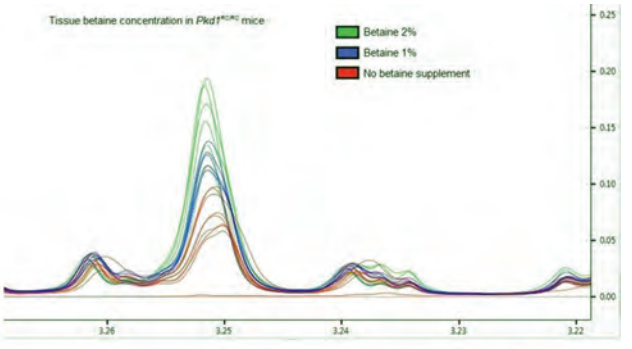
Background: We have recently shown that kidney tissue levels of the methyl donor betaine and betaine dependent remethylation are lower in ADPKD, and correlate with disease severity. However, the effects of betaine supplementation have not been explored in ADPKD. We hypothesized that chronic betaine supplementation would increase renal betaine concentration and ameliorate disease progression in murine ADPKD.

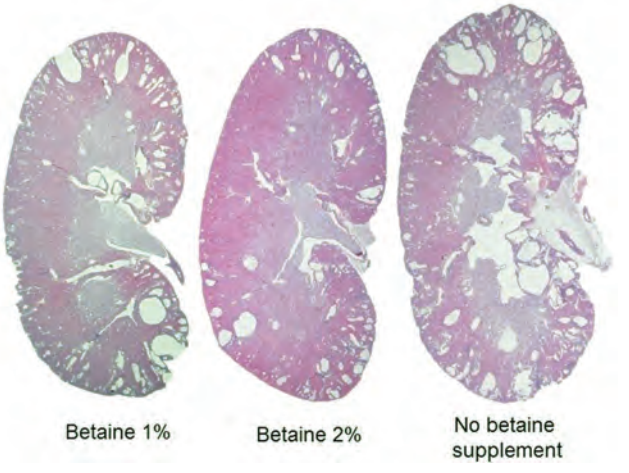
Methods: One month old *Pkd1* $^{RC/RC}$ mice were divided into three groups and started treatment with regular water or regular water supplemented with 1 or 2% betaine for 5 months (n=16 per group). All mice were euthanized at 6 months of age, and kidneys were harvested. Cystic index was determined from histological sections. [1] H-NMR-based metabolomics analysis was performed from kidney tissue, urine and plasma samples.

Results: One and 2% betaine supplementation increased plasma and tissue betaine concentrations (p<0.001), reduced kidney/body weight to 1.82 and 1.85 vs 2.25 (p<0.01), and cystic index to 11.1 and 9.4 vs 21.1 (p<0.01) (Fig. 1). Tissue betaine concentrations correlated inversely with kidney/body weight (R^2=0.386, p<0.01). Metabolomics analysis from tissue and plasma identified significant differences in mitochondrial fatty acid oxidation and TCA cycle pathways among the groups.

Conclusions: Chronic betaine supplementation ameliorates disease severity in murine ADPKD possibly through improving mitochondrial function. These observations may represent a promising intervention from early stages of the disease.

Funding: NIDDK Support, Other NIH Support - DK118391





FR-PO717

Metformin Improves Relevant Disease Parameters in the Hypomorphic Pkd1$^{RC/RC}$ ADPKD Mouse Model

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Background: Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in *PKD1* or *PKD2*, presents with progressive development of renal cysts and eventual end-stage kidney disease and has limited treatment options. Previous work showed that metformin treatment reduces cyst growth in two early, rapid ADPKD mouse models, potentially through inhibition of CFTR-mediated fluid secretion, mTOR signaling and cAMP production. Here we tested whether metformin treatment ameliorated ADPKD manifestations in a relevant, slowly progressive ADPKD mouse model.

Methods: Using the slowly developing ADPKD mouse model with an R3277C knock-in point mutation in both alleles of the *Pkd1* gene (*Pkd1$^{RC/RC}$* mice), male and female mice were treated ± metformin (300 mg/kg/day in drinking water) from 3 months through 9-12 months of age. During this treatment period, we periodically measured tail cuff blood pressures, glomerular filtration rates (GFR) by the FITC-sinistrin technique, and blood studies by i-Stat. At euthanasia, we assessed kidney histology (e.g., cystic index), total kidney weight/body weight ratio (TKW/BW), and mRNA and protein expression by qPCR and immunoblotting of key cell signaling, injury and inflammatory markers.

Results: As previously reported, *Pkd1$^{RC/RC}$* females had a more severe disease phenotype as compared with males. Metformin treatment reduced TKW/BW relative to age- and sex-matched controls at both 9 and 12 months of age. Metformin treatment also improved systolic blood pressures and increased GFR relative to controls at 9 months in both sexes. Moreover, metformin improved anemia (increased hematocrit) at both 9 and 12 months of age and generally lowered blood urea nitrogen (BUN) levels relative to controls in both sexes. Finally, metformin treatment also reduced the gene expression of key kidney injury markers, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), and the inflammation markers tumor necrosis factor-α and interleukin-6 in these mice, along with KIM-1 protein expression.

Conclusions: Metformin improves various key ADPKD disease parameters in a relevant, slowly progressive ADPKD model. Additional studies to examine effects of metformin in PKD clinical trials and the potential additivity of these metformin effects with other mechanistically distinct ADPKD therapies are underway.

Funding: Other U.S. Government Support

FR-PO718

2-Deoxy-D-Glucose Effectively Retards Kidney and Liver Cysts Growth in the Mouse at a Plasma Concentration That Is Safe in Humans: A Bridge Study to Design a First Safety Trial in ADPKD Patients

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a genetic disorder characterized by renal and liver cysts. The first therapy, tolvaptan, was recently approved. However, the presence of side effects and low tolerability calls for development of alternative approaches. We previously showed that inhibition of glycolysis by 2-deoxy-glucose (2DG) significantly retards disease progression (Rowe et al Nat Med, 2013; Chiaravalli et al, JASN, 2016). To translate the results for application in humans, we studied long term oral administration of 2DG and precise pharmacokinetic (PK) parameters.

Methods: We used a slowly progressive murine model by inactivating Pkd1 at P45 (Pkd1flox/-TmCre). Cohorts of 13 mice were treated for 4.5 months with oral administration of 2DG (100mg/kg) daily, for 5 days a week followed by 2 days of washout. Total kidney volume (TKV) was monitored by MRI, renal function by blood urea nitrogen and creatinine. At sacrifice kidney/body weight and histological analysis were performed. Liver cysts were identified by Cytokeratin-19 staining. Body weight, water and food intake as well as serum levels of ALT, AST, ALB and CK were detected for safety analysis. For the PK study of 2DG blood was collected after gavage at different time points (15, 30, 45, 60, 120, 180 min, 12 h, 24 h) and detected with HPLC pre-column fluorescent derivatization.

Results: 100mg/kg of 2DG significantly reduces TKV and restores renal function in the Pkd1flox/-TmCre mice. Biliary cysts were significantly reduced in number, length and area after 2DG treatment (n=8). Importantly, no sign of toxicity can be detected neither in Pkd1flox/- TmCre-nor in wt mice. PK analysis revealed that 100mg/kg 2DG oral administration in mice corresponds to/is slightly lower than the dose of 30mg/kg in humans based on published studies, a dosage extensively shown to be safe with no adverse events reported.

Conclusions: Our data show that 2DG is efficacious on renal and liver cysts, it improves renal function and shows no signs of toxicity at a dose that corresponds to a well tolerated dose in humans. Our data build a strong rationale for designing a first study with 2DG in ADPKD patients.

Funding: Private Foundation Support

FR-PO719

Correcting the Trafficking of CFTR, NHE3, and ENaC in ADPKD Reduces Cysts and Improves Renal Function

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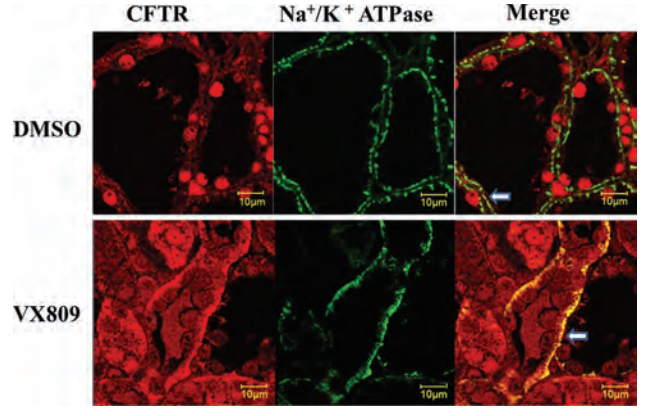
Background: Autosomal dominant polycystic kidney disease (ADPKD), caused by malfunction of either PC1 or 2, is associated with progressive enlargement of cysts, leading to a decline in function and renal failure. We demonstrated previously that VX-809, a CFTR corrector, used to rescue CFTR trafficking, reduces cyst growth in mouse models.

Methods: To address the mechanism of how this occurs, we used proximal tubule-derived, cultured *Pkd1*-knockout cells and the *Pkd1$^{fl/fl}$; Pax8^{rtTA}; TetO-cre* mouse model. Treating the mice with doxycycline (doxy), ablates PC1 in renal tubular epithelial cells and causes the development of multiple large cysts which leads to a decline in renal function.

Results: We found that cysts are reduced when the mice are treated with VX-809 and renal function improved. VX-809 treatment of cultured *Pkd1*-knockout cells increased the activity of NHE3. We assessed the location of NHE3 and ENaC in the cystic kidneys using confocal microscopy. In the mice treated with doxy, NHE3 and ENaC were present in large cysts, but not at the apical membrane. NHE3 and ENaC primarily colocalized with Rab11, a marker of recycling endosomes. In the mice treated with doxy and VX-809, NHE3 and ENaC colocalized with a plasma membrane marker consistent with an increase in NHE3 and ENaC activity and protein expression. In the mice were treated with doxy large cysts developed and the CFTR was colocalized with the ER marker, and to a small amount with apical membrane marker. When mice were treated with doxy and VX-809, most of the CFTR was rescued from the ER and colocalized with the basolateral membrane (Fig.1) and total protein levels increased. Interestingly, basolateral localization of CFTR occurs in the sweat duct, a normally Cl^- absorbing epithelium.

Conclusions: The data suggest that VX-809 reduces cyst size in the PC1-null mice by promoting an absorptive phenotype. Given that administration of VX-809 is safe, this drug potentially offers a new way to treat patients with ADPKD.



FR-PO720

β$_3$-Adrenergic Receptor: Possible New Drug Targets for the Treatment of Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a genetic condition caused by mutations in either Polycystin 1 or Polycystin 2 genes and characterized by the formation of fluid filled cysts in the renal parenchyma. Elevations of intracellular cAMP are a major driver of cyst growth. Inhibition of cAMP accumulation in vasopressin-sensitive nephron segments currently constitutes the only approved therapy for ADPKD. Interestingly, sympathetic nerve activity is elevated in patients with chronic kidney disease and this over-activity has been implicated in cystogenesis. Since β$_3$-adrenoreceptors (β$_3$-ARs) are expressed in multiple nephron segments we wished to characterize their signaling pathway in ADPKD and their potential role in its pathogenesis.

Methods: Murine cell lines heterozygous (Pkd1$^{+/-}$) or homozygous (Pkd1$^{-/-}$) for a deletion in Pkd1 gene were stably transfected with β$_3$-AR, then seeded in 3D matrix and stimulated with Mirabegron, a selective β$_3$-AR agonist. Cyst size and number were measured using ImageJ. cAMP levels in treated cells were measured via Fluorescence Resonance Energy Transfer (FRET). β$_3$-AR expression was studied via WB on total kidney lysates from an ADPKD mouse model (Pkd1$^{fl/fl}$; Pax8^{rtTA}; TetO-Cre). Mice were treated with either β$_3$-AR antagonist SR59230A (4mg/kg/day) for 4 weeks or saline. Finally animals were sacrificed and kidney parameters measured.

Results: We found that, upon treatment with Mirabegron, Pkd1$^{-/-}$+β$_3$-AR cells form larger and more numerous cysts than untransfected Pkd1$^{-/-}$ cells. FRET analysis confirmed that this effect is associated with a significant increase in cAMP levels elicited by β$_3$-AR activation. Using our ADPKD mouse model we found that renal β$_3$-AR expression is up-regulated in cystic animals *versus* healty littermates. Most importantly, treatment of

these mice with SR59230A leads to improved kidney/body weight ratios and Blood Urea Nitrogen levels in the treated animals *versus* controls.

Conclusions: Our *in vitro* data indicate that modulating the activity of β_3-AR has a direct effect on cystogenesis. Our *in vivo* data further suggest that β_3-ARs are potentially interesting therapeutic targets in the treatment of ADPKD in that antagonizing β_3-AR activity may reduce cAMP accumulation and thus cyst growth in both vasopressin-sensitive and insensitive nephron segments.

Funding: NIDDK Support

FR-PO721

Chronic Exercise Ameliorates the Progression of Renal Dysfunction in Polycystic Kidney Disease Model Rats

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Background: Autosomal Dominant Polycystic Kidney Disease (PKD) is the most frequent hereditary renal disease, but the exact mechanisms of cystogenesis remain to be elucidated. PKD leads to renal dysfunction, and it is a major cause of ESRD. Several clinical studies have shown that chronic exercise (Ex) exerts beneficial effects in CKD patients. However, the beneficial effects of Ex on renal function have not been reported in PKD. The present study investigated the effects of Ex in polycystic kidney (PCK) rats with PKD.

Methods: Five-week-old male PCK rats were divided into the sedentary (Sed) group and Ex group. Ex underwent forced treadmill exercise (28m/min, 60 min/day, 5 days/week) for 12 weeks. Plasma and urinary parameters and renal histology were examined. Expression of Ki67, desmin, TGF-β and PGC-1α and phosphorylation of AMPK were assessed by immunohistochemistry and western blotting.

Results: Ex significantly decreased the body weight, kidney weight, urine volume, urinary protein excretion, plasma creatinine and ameliorated renal cystic formation and interstitial fibrosis. Ex significantly decreased the Ki67 and TGF-β expressions in tubulointerstitial cells and the desmin expression in glomeruli. Ex also increased the PGC-1α expression and stimulated the phosphorylation of AMPK in the kidney.

Conclusions: Chronic exercise ameliorates renal dysfunction with inhibition of cystic formation and podocyte injury via an AMPK-PGC-1α-mediated metabolic switch in PCK rats. Ex may be a novel therapeutic approach for the development of renal dysfunction in PKD patients.

Funding: Government Support - Non-U.S.

FR-PO722

Pioglitazone and Tolvaptan in a Mouse Model of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is characterized by fluid-filled cyst formation and mainly caused by mutations in the *PKD1* gene. Currently, the only treatment option for ADPKD is the vasopressin V2 receptor antagonist tolvaptan (TVP). However, due to unfavourable side effects, the drug is not well tolerated by all patients, leaving a need for alternative approaches. We hypothesized that a combination treatment can result in a better therapy, as the complex intracellular signalling involved in ADPKD is then targeted from various angles simultaneously. We conducted a preclinical study in an adult onset ADPKD model to investigate the effects of a combination treatment of TVP and pioglitazone (PIO), a peroxisome proliferator-activated receptor gamma (PPARγ) agonist. This drug slows disease progression in two PKD rat models (Blazer-Yost et al., PPAR Res 2010 & Flaig et al., J Trans Int Med 2016), and is now tested in a clinical trial for ADPKD.

Methods: *In vitro*: PIO was tested in a 3D cyst model for PKD (mIMCD3-*Pkd1*$^{-/-}$ cells) to evaluate its efficacy on reducing cyst swelling. *In vivo:* An inducible adult onset model for ADPKD (P18Ksp*Pkd1*^{del} mice) was used. Following *Pkd1* inactivation by tamoxifen on postnatal day 18/19, mice (n = 20 males per group) were fed with food pellets containing 0.1% TVP and/or 0.1875% PIO. Mice were treated until 50% of the untreated group had renal failure (blood urea levels > 20 mmol/l).

Results: PIO was effective in reducing cyst swelling *in vitro*. TVP was able to improve renal survival in mice (86% vs. 41% in the untreated group, $p<0.01$) and reduced 2KW/BW% by 2-fold ($p<0.001$). Plasma adiponectin, a surrogate drug marker for PIO treatment, was higher in PIO-treated mice, to a similar extent as in humans after PIO treatment. However, PIO had no effect on renal survival and on downstream PPARγ signalling in the kidney. Also, *Pparg* gene and PPARγ protein expression was very low in wildtype, cystic and PIO-treated kidneys.

Conclusions: TVP improved renal survival and reduced cyst growth, confirming our model's relevance to ADPKD. Despite *in vitro* efficacy and using a clinically relevant dose, PIO had no therapeutic benefit *in vivo*, possibly due to low expression of PPARγ in mouse kidneys. Further research on the expression levels of the *Pparg* gene and the PPARγ protein in relevant rat models and patients are ongoing.

Funding: Private Foundation Support

FR-PO723

Dual Targeting of the G Protein-Coupled Receptors CaSR and V2R for Treating Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Annarita Di Mise,[1] Xiaofang Wang,[2] Hong Ye,[2] Lorenzo Pellegrini,[3] Vicente E. Torres,[2] Giovanna Valenti.[1] *[1]University of Bari, Bari, Italy; [2]Mayo Clinic, Rochester, MN; [3]Palladio Biosciences, Newtown, PA.*

Background: ADPKD is the 4th leading cause of end stage renal disease in the US. It is caused by mutations in *PKD1* or *PKD2* genes, which lead to excessive cell proliferation and fluid secretion, and ultimately cyst formation and growth. Reduced resting cytosolic calcium (Ca^{2+}) and increased cAMP levels, associated with the tonic action of vasopressin, are two central biochemical defects in ADPKD. Currently there is no cure for the disease. The vasopressin V2 receptor (V2R) antagonist tolvaptan is the only drug approved to delay the progression of ADPKD, however it causes serious idiosyncratic hepatocellular toxicity. Simulations on a multiscale computational model of drug-induced liver injury indicate that the novel V2R antagonist lixivaptan has a safer liver profile. Here, we show that co-targeting two GPCRs, the Calcium Sensing Receptor (CaSR), which finely regulates Ca^{2+} homeostasis, and the V2R, using the calcimimetic R-568 in combination with lixivaptan, reduced cyst progression in two animal models of human PKD.

Methods: PCK rat and *Pkd1*$^{RC/RC}$ mouse littermates were fed ground rodent chow without or with lixivaptan (0.5%) and R-568 (0.025% for rats and 0.04% for mice), alone or in combination, for 7 (rats) or 13 (mice) weeks.

Results: In PCK rats, lixivaptan induced a significant reduction in kidney weight, cyst and fibrosis volumes by 20%, 31% and 60%, respectively, compared to animals fed with standard diet. The combined treatment strongly decreased the same parameters by 24%, 46% and 73%, respectively. R-568 alone induced a significant reduction only in kidney weight by 9% and fibrosis volume by 52%. Similar results were obtained in *Pkd1*$^{RC/RC}$ mice.

Conclusions: These data suggest an intriguing new application for two known drugs. The potential for synergy between these two compounds suggested in these animal studies warrants further investigation in clinical settings.

Funding: Commercial Support - Amgen Inc.; Palladio Biosciences, Inc.

FR-PO724

New Therapeutic Approach Based in Inhibition of Metalloproteases in Polycystic Kidney Disease

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Background: Polycystic Kidney Disease (PKD) is a group of genetic disorders characterized by the presence by multiple cysts in the renal parenchyma, as well as others extrarenal manifestations such as hepatic cysts (Polycystic Liver Disease or PLD). Mutations in genes PKD1 and PKD2 caused the dominant form called ADPKD, by other band mutation in PKHD1 caused the recessive form or ARPKD. To this day, it have been reported several altered molecular pathways in the PKD but the key mechanism of cystogenesis (process by which cysts are formed) remains unmask. In that studio, with the use of animal models we reported a study about metalloproteases or MMPs of Extracellular Matrix (ECM) in the renal and hepatic cystogenesis and its therapeutic potential.

Methods: We use the rodent models *Pkd1*$^{cond/cond}$ *TamCre* y *Pkdh1*$^{del3\text{-}4/del3\text{-}4}$, models of ADPKD and ARPKD respectively, as well as for the study at molecular level of the role of the MMPs, as models for the testing of a new therapeutic approach, called MTT. Furthermore, the understanding of the disease has been addressed by histological (immunofluorescent and immunohistochemical), pathophysiological (renal and/or hepatic function) and transcriptomic (RT-qPCR) techniques.

Results: We have realized a complete study of the MMPs present in kidney and liver of our animal models, as well as have studied different pro-fibrotic and inflammatory markers related to the enzymatic activity of MMPs. Our study indicates that in renal and hepatic cystogenesis the levels of these markers and genetic expression of MMPs are increased, and therefore that this molecular pathway may be a possibility of therapeutic approach. MTT is an inhibitor of the extracellular matrix metalloproteinases that our group wanted to test as a possible therapy for ADPKD and ARPKD. We have seen that MTT inhibits the gene expression of several MMPs, reduces renal and hepatic fibrosis, improves renal function and inhibits renal and hepatic cystogenesis.

Conclusions: In this work, we evaluate the role of matrix metalloproteases (MMPs) in the cystogenesis of PKD. In addition, the MMP inhibitor MTT was examined in two different rodent models reducing hepatic and renal cystogenesis, and offering a new possible approach.

FR-PO725

Development and Implantation of Novel Morphometric 3D Capsule Device to Constrain Structural Change of Polycystic Kidney: A Feasibility Study in a Rat Model

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Background: Polycystic kidney disease is characterized by progressive enlargement of kidneys as a consequence of uninhibited formation and expansion of numerous kidney cysts. Current therapeutic options for polycystic kidney disease are limited in their effectiveness at halting disease progression. The objectives of the study were (1) to develop and implant a computed tomography (CT) image-derived morphometric 3D capsule device to encase a kidney and (2) to demonstrate experimental outcome of the device to constrain structural change of polycystic kidney in a rodent model.

Methods: Kidney capsule devices were designed from CT images of wild-type and Cy/+ rats. Capsule devices were surgically implanted on kidneys in six surgical sessions over a period of 14 months in 7 wild-type rats 6.5-8 weeks of age (3 sham operation, 2 right, 2 left) and 6 Cy/+ rats 6.5 weeks of age (2 sham, 3 left, 1 bilateral). After operation, rats were followed for 5.4-12.4 weeks to grow and sacrificed to retrieve kidneys. During the follow-up, serum creatinine was measured. Retrieved kidneys were weighed. Histological analysis including cystic area measurement and immunohistochemistry was performed.

Results: Morphometric capsule devices were configured and developed by image processing technique and produced using 3D printing technique. Encapsulated Cy/+ kidneys (n=5; mean weight 3.64g) were consistently smaller in size (by 21-36%; $p<0.001$) than unencapsulated Cy/+ kidneys (n=7; mean weight 5.52g). Encapsulated Cy/+ kidneys (mean %cyst area: 29.4%) showed smaller histologic cystic area (by 28-58%; $p<0.001$) than unencapsulated Cy/+ kidneys (mean %cyst area 48.6%). Cell proliferation and macrophages were also markedly reduced in encapsulated Cy/+ kidneys, compared to unencapsulated Cy/+ kidneys.

Conclusions: We developed a CT image-derived morphometric 3D capsule device to encase a kidney and demonstrated that the device constrained structural change of polycystic kidney in a rodent model as a feasibility study toward a novel potential therapeutic avenue for halting progression of polycystic kidney disease.

FR-PO726

Anti-Polyamine Therapy Restrains Polycystic Kidney Disease in Orthologous Mice

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Background: Autosomal-dominant polycystic kidney disease (ADPKD) is caused by mutations in *PKD1* or *PKD2* and is characterized by cysts derived from renal tubules. Cysts slowly expand due to aberrant proliferation and secretion of cyst-lining epithelial cells, ultimately destroying the kidney by compression and resulting fibrosis. Only one FDA-approved drug is available for ADPKD, so there is a critical need for new therapies for this disease. The polyamines are metabolites of the amino acid ornithine and are produced by all cells. These metabolites are involved in a large number of cellular processes, including proliferation, for which they are essential. Polyamine production is often elevated in proliferative diseases, including multiple types of cancer, and inhibition of polyamine synthesis has been shown in some cases to restrain cancer progression. We hypothesized that polyamines promote cyst cell proliferation and disease progression in ADPKD. We tested this by treating an ADPKD-orthologous mouse model with DiFluoroMethylOrnithine (DFMO), an inhibitor of the rate-limiting enzyme (ornithine decarboxylase) responsible for polyamine biosynthesis.

Methods: *Pkd1*$^{RC/RC}$ mice ("RC"), which have a missense mutation [*Pkd1*(p.R3277C)] that matches an allele found in a human ADPKD family, were used. RC mice were given DFMO in the drinking water (665 mg/l) to achieve a dose of 133 mg/kg starting at PN28. Mice were sacrificed at 6 mo, and serum and kidneys were collected for assessment of 2 kidney/body weight (2K/BW), cystic index, fibrosis, proliferation, apoptosis, and BUN. RNA was collected from kidneys in control, DFMO-treated, and wild-type (C57Bl/6 at 6 month) mice for expression profiling by RNA-Seq.

Results: DFMO treatment had no effect on overall body weight but significantly lowered 2K/TBW and cystic index. There was no effect on BUN, which does not become elevated in RC mice until ~9 months. Assessments of other disease parameters are in progress. RNA-Seq analysis indicates inhibitory effects of DFMO on c-Myc and mTOR, as well as inflammatory pathways.

Conclusions: Inhibition of polyamine production by DFMO restrains kidney growth and cyst expansion in an orthologous model of ADPKD, potentially through effects on c-Myc and mTOR+1187 pathways. These data suggest that DFMO, which has been approved for use in humans, is a potential therapy for ADPKD.

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FR-PO727

Computational Drug Screening Identifies the Androgen Receptor Antagonist Flutamide as a Potential Treatment Option for Polycystic Kidney Disease

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Background: Treatment options for patients with autosomal dominant polycystic kidney disease (ADPKD) are limited and novel therapies are needed. A key hallmark of ADPKD is enhanced tubular epithelial cell proliferation.

Methods: We constructed a network-based molecular model of ADPKD using ADPKD-associated molecular features from scientific literature, the OMIM database, clinical trials on ADPKD, and a human ADPKD transcriptomics dataset. We computationally screened compound libraries with the ADPKD molecular model using data from the Connectivity Map and a constructed library of literature-based drug mechanism of action molecular models. We finally evaluated the impact of top-ranked compounds on cell viability and proliferation in two ADPKD cell lines and HK2 cells.

Results: Five compounds - flutamide, mifepristone, spironolactone, troglitazone, and vorinostat - were identified in the computational drug screen being capable of inversing the ADPKD gene signature and showing significant positive overlap with the ADPKD molecular model. Four compounds had a significant negative impact on cell viability in ADPKD cell lines as compared to treated HK2 cells. Flutamide had the strongest impact on ADPKD cell viability (65.4% in WT9-7, 67.8% in WT9-12, 92.0% in HK2 cells). Flutamide on top significantly reduced cell proliferation in ADPKD cells (41.1% in WT9-7 and 41.9% in WT9-12) as compared to HK2 cells (92.8%).

Conclusions: Flutamide significantly hampers cell viability and cell proliferation of ADPKD cells and warrants follow-up studies to investigate its potential as novel treatment option for patients with ADPKD.

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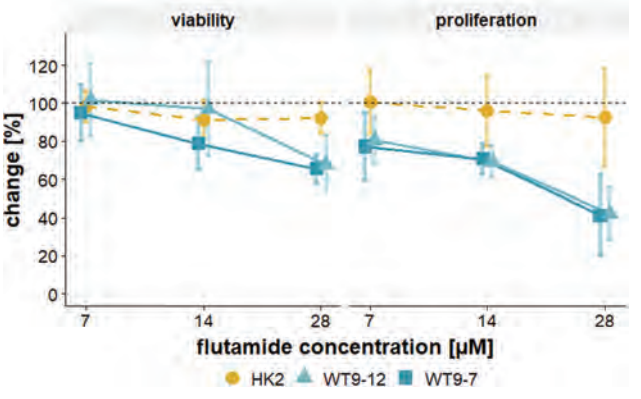

The impact of flutamide on cell viability and cell proliferation in the two ADPKD cell lines WT9-7 and WT9-12 as well as in control human renal proximal tubular (HK2) cells is displayed. Data are presented as mean and standard deviation

FR-PO728

Ciclopirox-Olamine Alters Ferritin Trafficking and Plays a Protective Role in Polycystic Kidney Disease

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Background: The search for safer and better drugs for Polycystic kidney disease (PKD) continue despite successful lauch of Tolvaptan. We have recently shown that the Notch3 signaling pathway is activated in renal cyst epithelial cells. To determine *in vivo* role of Notch inhibition, we used Ciclopirox-olamine (CPX). CPX can inhibit Notch and other pathways by its property to chelate iron and thus inhibit the activity of iron dependent enzymes such as gamma secretase (involved in Notch pathway activation).

Methods: We used primary normal human kidney (NHK) cells of collecting duct origin and primary cells from cysts of ADPKD patients (ADPKD cells). The effect of CPX on cell viability, ability to form cAMP dependent 3D cysts *in vitro* and cellular ferritin status was evaluated by both Western blotting and immunocytochemistry. CPX was also injected into a mouse model of PKD (*PKD1*$^{RC/PC2}$) for 27 consecutive days and disease was analyzed and compared to the vehicle injected controls for Notch signaling and ferritin (another target of CPX).

Results: CPX (0.2micro molar) inhibited cyst formation in ADPKD cells and resulted in a 40% reduction in cyst area. *In vivo* use of CPX in an orthologous mouse model of PKD also resulted in amelioration of cyst progression. A significant reduction in cystic index and kidney to body weight ratio was observed. However, the disease rescue did not involve Notch3 inhibition. We then focused on iron metabolism, because CPX is an iron chelator. First, we found that ferritin levels were significantly elevated in the kidney lysates from PKD mice and CPX significantly down regulated that to the level of WT mice. Human ADPKD cells were highly enriched in ferritin and CPX reduced the ferritin

levels in a dose dependent manner. Since ferritinophagy is one of the known mechanisms of ferritin degradation, consistent with that we found that an autophagy marker (LC3B) and ferritinophagy marker (NCO4) dose dependently increased in ADPKD cells upon CPX treatment.

Conclusions: Our data suggest that CPX confers protection against ADPKD pathology and increased ferritinophagy is one of the mechanisms. These data also indicate that CPX, a drug used to treat skin infections and currently in clinical trials for cancer, may have the potential to treat ADPKD.

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FR-PO729

Targeting Axoneme Polyglutamylation as a Potential Therapeutic Approach for ADPKD Treatment

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Background: ADPKD is the most common inherited renal disorders mainly caused by mutations of *PKD1* or *PKD2*, which encodes Polycystin 1 (PC1) and Polycystin 2 (PC2) respectively. PC1 and PC2 co-localize to the primary cilium of kidney epithelial cells and have been proposed to form a receptor/channel complex to sense environmental cues. Recently, the structural mapping of ADPKD pathological mutations indicates that the pathogenic mechanism of *PKD* mutations are mainly associate with the incorrect folding or trafficking of PC1/PC2 complex. Thus, theoretically, correcting the proper cilia localization of PC1/PC2 complex could restore its functional dosage and holds strong potential for being developed as a therapeutic avenue to delay or even prevent the renal cystogenesis. However, perusing this strategy is impeded by the lack of understanding of how the ciliary targeting/maintenance of polycystins are controlled. Polyglutamylation is one of the tubulin posttranslational modifications (PTMs) that occur predominantly on cilia axoneme. We recently discovered a novel paradigm that axoneme polyglutamylation is essential for the ciliary anchoring of polycystins, indicative of its potential for being used as a drug target.

Methods: 1. Imaging-based drug screen. 2. Immunofluorescent. 3. 3D culture. 4. Embryonic kindney culture.

Results: Here, by implementing axoneme polyglutamylation as readout, we performed an imaging-based small molecule screen and discovered several hits that can increase PC2 dosage and restore the ciliary localization of PC2 in PKD cell model by promoting axoneme hyperglutamylation. Mechanistically, these drugs strongly promote the ciliary trafficking of TTLL5 and TTLL6, the key tubulin polyglutamylases that localize to primary cilia. We also have pinpointed the real molecular target of identified hits for inducing axoneme hyperglutamylation, which is overexpressed in ADPKD patients. Remarkably, inhibition of the identified molecular target by its selective inhibitor significantly suppressed the cyst growth in *in vitro* and *ex in vivo* models of renal cystogenesis, suggesting its strong potential for being developed as drug target for ADPKD treatment.

Conclusions: Targeting axoneme ploy glutamylation could be a effective way to restore the functional levels of polycystins and hold a strong potential for being developed as a therapeutic approach for ADPKD.

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FR-PO730

Early Cyst Initiation Transcriptional Changes in a Novel Porcine Model of Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD), the most common genetic renal disease leading to renal failure in adulthood, starts in utero. However, most studies of transcriptional changes have been done either in late human disease or in mouse models that do not mimic the autosomal dominant pattern (AD) of genetic disease in humans. In this early study, we examine the feasibility of single cell RNA-seq (scRNA-seq) to identify transcriptional changes in specific cells types in an AD porcine PKD1 model.

Methods: We characterized 1928 cells from a wildtype littermate and 3702 cells from two PKD1 +/- littermates using unbiased scRNA-seq. We determined cell identity by performing differential gene expression analysis using the Seurat package, creating principle component analysis (PCA) and t-Distributed Stochastic Neighbor Embedding. Marker genes from PCA analysis were compared to previously reported renal marker genes for mouse. Differential gene expression between case and control was calculated using the Wilcoxon rank sum test in Seurat.

Results: Ten clusters were definitively identified as tubular in nature using marker genes. PKD1 was not differentially expressed between cases and controls, consistent with previous bulk RNA-seq studies. 85 genes were upregulated in PKD1 +/- cystic areas compared to controls, eleven of which were identified as part of the PKD signature in previous metaanalysis by Almeida, et al. Twenty-seven genes were upregulated in wildtype tissue, three of which were identified as part of the PKD signature in a previous metanalysis.

Conclusions: This study provides the first characterization of porcine PKD1 +/- population cell populations using scRNA-seq and provides a preliminary look at differential gene expression within the tubular component of cells between wildtype and PKD+/- tissue. Given the low power to detect change due to small sample size and lack of single cell transcription datasets for ADPKD comparison, we still identified differential expression of several genes previously reported to play a role in ADPKD. We are currently validating our findings on an additional 12 different pigs with up to 4 samples per animal.

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FR-PO731

miR-210-3p Inhibition Prevents Macrophage M2-Like Polarization and Decreases Fibrosis in Murine ADPKD

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common life-threatening hereditary renal disease with an incidence of 1 in 400 to 1 in 1000 individuals. The decline in renal function in ADPKD correlates with the development of renal fibrosis in the peri-cystic local micro-environment (PLM) along withincreased expression of miR-210-3p. A large proportion of the cells in PLM are identified as macrophages (MØs). These MØs undergo a phenotypic switch from M1-like (INOS +) M2-like (arginase +) as fibrosis progresses.

Methods: LNA enhanced anti-miR's(Qiagen) is administered IP from PN14 to PN 28 or PN42 at a dose of 10 um/gm/ Q 4 days. At harvest (PN28 or PN42), one halves of each kidneyis formalin fixed paraffin embedded (FFPE) while the other halves are analyzed by flow cytometry. Serial FFPE sections are analyzed for fibrosis (trichrome staining) and proliferation (PCNA) by Image J software, macrophage phenotyped with IHC or IF.MØphenotypic changes areassessed by flow cytometry and IF or IHC of serial sections. Both wild-type and cystic kidneys are used to obtain MØs, WT-Mac, and C-Mac, respectively, as well as epithelial cells, WTEC and CEC, respectively that were co-cultured in transwells.

Results: *In vivo* targeting of miR-210-3p with an anti-miR reduces both fibrosis and proliferation in PLM areas and significantly improved renal function at PN42. MØ phenotype assessment of anti-miR-210-3p treated kidneys demonstrates a significant reduction in M2 (from 1900 cells to 1000, $p < 0.05$). Data from co-culture experimentsdemonstrate C-Macs show an increased change to M2, assessed by flow cytometry and express increased levels of Arg1, Mrc1, Egf, Retnla and decreased levels of Tnf transcripts when co-cultured with CEC in comparison to WTEC.

Conclusions: We demonstrate that *in vivo*miRNA inhibition of miR-210-3p significantly reduced fibrosis by reducing MØ phenotypic change to M2-like. In agreement with published studies miRNAs regulated transcription factors associated with MØ phenotype change to M2. Induction of MØphenotypic change to M2-like by the CEC via miRNA changes within the MØshas not been studied in depth and requires further investigation. miRNAs are an attractive target as these molecules are small in size and exogenously administered anti-miR concentrates in the kidney.

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FR-PO732

Urinary CD206+ Cells Correlate with Rate of Renal Function Loss in Autosomal Dominant Polycystic Kidney Disease

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Background: We showed that tissue-resident macrophages promote renal cystic disease severity in mice; however, the relevance of this observation to ADPKD patients was unknown. While key markers that define these resident macrophages in mice cannot be used in humans (e.g., mouse marker F4/80 is encoded by gene *Emr1*; it is expressed exclusively by human eosinophils), we recently identified CD206 as a candidate marker of human resident macrophages.

Methods: We evaluated CD206+ immune cell populations in kidneys from ADPKD patients (vs non-ADPKD controls) using flow cytometry and confocal immunofluorescence microscopy approaches. We used similar analyses for analyses of CD206+ cells in urine samples from ADPKD patients.

Results: We found that CD206+ cells accumulated in regions adjacent to renal cysts. While the average number of intrarenal CD206 cells was higher in ADPKD kidneys (vs controls), the variability was high and this difference did not reach statistical significance (0.0252 vs. 0.006 percent of total renal cells; $p = 0.170$). Also, we found that the urinary CD206+ cell-based index (e.g., after adjustment for urine creatinine concentration) correlated moderately with a rate of GFR decline (over 5 years) in a small cohort of ADPKD patients (n=30). This effect was independent of kidney length (KL), recently described CKD stage 3B predictor in ADPKD with similar AUC 0.88 as height-adjusted total kidney volume. The correlation between average GFR decline rates and KL was comparably strong ($r = 0.400$; $p = 0.029$), the correlation between the eGFR decline rates and urine albumin to creatinine ratio was weaker (ACR; $r = 0.192$) in this cohort.

Conclusions: Together with studies on resident macrophages in animal models, these data suggest that resident renal macrophages participate in the disease pathogenesis in ADPKD patients. They also point to urinary CD206+ cells as a novel candidate marker of the disease activity in ADPKD.

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FR-PO733

Global MicroRNA Profiling in Human Urinary Exosomes Reveals Novel Disease Biomarkers and Cellular Pathways for ADPKD

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Background: ADPKD is the most common genetic kidney disease and the fourth most common cause of end-stage renal disease (ESRD) world-wide. Although PKD1 and PKD2 patients present different phenotypes, a high intra-familial variability in disease progression has been observed, suggesting that other genetic or environmental factors have major influences on progression of ADPKD.

Methods: Spot urine specimens were collected from patients with ADPKD and healthy controls. Global miRNA-sequencing was conducted in urine exosome-derived miRNAs from healthy volunteers, ADPKD patients with early (eGFR > 60 mL/min) or late (eGFR < 60 mL/min) disease in a discovery cohort (n=22). TaqMan qPCR was carried out in a clinically phenotyped validation cohort (n=60) and in a *Pkd1* mouse model. In silico bioinformatic analyses identified altered miRNA target genes and disease pathways.

Results: Discovery phase RNA-seq identified a number of dysregulated miRNAs in ADPKD derived exosomes. Two candidate miRNA families identified (miR-192/miR-194-2 and miR-30) were selected for testing by qPCR in a validation cohort (n=60) and in an established mouse *Pkd1* model. We confirmed that miR-192-5p, miR-194-5p, miR-30a-5p, miR-30d-5p and miR-30e-5p were significantly downregulated in human urine exosomes and in *Pkd1* cystic kidneys. Expression levels of all five miRNAs showed significant correlations with baseline eGFR-EPI and ultrasound-mean kidney length (MKL) and improved the diagnostic performance (AUC) of MKL for the rate of disease progression. Finally, by analysing inverse correlations of these two miRNA families with the increased expression of their predicted target genes, we identified several dysregulated pathways and transcriptional networks. These included novel miR-194-5p interactions with the 3'UTR of *ANO1* and *PIK3R1*. Inhibition of these two candidate genes in human *PKD1* cystic cells significantly reduced cyst growth in vitro, confirming their functional significance.

Conclusions: Our results demonstrate that urine exosome global miRNA profiling can be a powerful tool to identify ADPKD patients with rapid disease progression who could benefit from disease modifying treatment. We have identified a subset of urinary exosomal miRNAs that could serve as novel biomarkers of disease progression and also suggest potential new therapeutic targets in ADPKD.

Funding: Government Support - Non-U.S.

FR-PO734

Exosomes Generated from Cystic Renal Epithelial Cells Regulate Cellular Communication and Cystogenesis in ADPKD

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Background: The exosomes have recently drawn considerable interest as they are implicated in many pathophysiological processes of human diseases, including ADPKD. Cells can use these vesicles to communicate with both adjacent cells via the molecules present on the surface of these vesicles and distant cells via the circulation. Urinary exosomes have been proposed as a potential diagnostic tool in ADPKD. However, the basic cell biological understanding of the exosomes in cellular communication and the role of circulating exosomes in ADPKD is lacking.

Methods: To investigate if exosomes regulate cell-to-cell communication and cystogenesis, we isolated exosomes from urine of ADPKD patients and normal individuals (control) as well as from culture media of $Pkd1^{+/+}$ and null renal epithelial cells. The isolated exosomes were used to treat $Pkd1^{+/+}$ renal epithelial cells for a cell proliferation assay and cystogenesis in 3D cultures. Circulating exosomes was isolated from blood to evaluate if exosomal PD-L1 is associated with disease progression of ADPKD and with response to treatment in PKD animals.

Results: We found that treatment with exosomes isolated from ADPKD patient urine and from media of cystic renal epithelial cells increased cell proliferation of NRK-52E cells and mIMCD cells compared to those cells treated with exosomes isolated from normal individuals and wild type renal cells in an exosome concentration dependent manner. In addition, we found that NRK-52E cells treated with ADPKD urinary exosomes developed cysts-like structures in collagen gels within 2 days, which continued to grow progressively up to day 8, whereas NRK-52E cells treated with normal urinary exosomes only developed tubule-like structures in collagen gel up to day 8. We further found that urinary ADPKD exosomes induced the activation of ERK and mTOR signaling in treated cells. The expression of PD-L1 was increased in cystic renal epithelial cells and we are now evaluating if the increase of PD-L1 in exosomes isolated from bloods of PKD animals and ADPKD patients can be used as a biomarker for ADPKD.

Conclusions: Urinary ADPKD exosomes and exosomes from cystic renal epithelial cells regulate renal epithelial cells proliferation and cystogenesis. The levels of PD-L1 in circulating exosomes may be a potential biomarker for ADPKD.

Funding: NIDDK Support

FR-PO735

Diverse Receptor Tyrosine Kinase Phosphorylation in Urine-Derived Immortalized Tubular Epithelial Cells of ADPKD Patients

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Background: Clinical features of autosomal dominant polycystic kidney disease (ADPKD), including responses to drugs, differ among patients even if they have the same gene mutation in PKD1 or PKD2. This suggests that there is diversity in the expression of other modifier genes or in the underlying molecular mechanisms of ADPKD, but these are not well understood. In this study, we analyzed the diversity in receptor tyrosine kinase (RTK) phosphorylation in tubular epithelial cells of ADPKD patients.

Methods: Urine-derived epithelial cells were primarily cultured, and immortalized cell lines were established by SV40 large T gene transfection. SLC12A3-positive colonies, which is a specific marker of distal tubules, were used for experiments. RTK phosphorylation and its downstream signaling were analyzed in established cell lines. Three-dimensional culture of MDCK cells was used as a cyst formation model of ADPKD.

Results: Comprehensive analysis of RTK phosphorylation in immortalized tubular epithelial cells from 8 ADPKD patients and 4 healthy controls revealed diversity in the activation of several molecules, such as Axl (Gas6 receptor) and Met (HGF receptor), and there were differences even among patients from the same family. Golvatinib, a selective Met inhibitor, or transduction of siRNA for Met suppressed cell proliferation as well as downstream signaling, such as phosphorylation of Akt, only in the cell lines in which hyperphosphorylation of Met was observed. In three-dimensional culture of MDCK cells, HGF activated Met and its downstream signaling, such as Akt or Erk, resulting in an increased total cyst number and total cyst volume. Golvatinib treatment inhibited these phenotypes in MDCK cells.

Conclusions: The analysis of urine-derived tubular epithelial cells demonstrated diverse RTK phosphorylation in ADPKD, and Met phosphorylation was noted in some patients. Given the difference in the effects of golvatinib on immortalized tubular epithelial cells among patients, this analysis may aid in determining suitable drugs for individual ADPKD patients as "precision medicine".

FR-PO736

3D In Vitro Cystogenesis Assays Utilizing Human Patient-Derived ADPKD Kidney Cells for Drug Screening

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a slowly progressive genetic renal disorder that is caused by mutations in either the PKD1 gene (polycystin 1) or the PKD2 gene (polycystin 2). ADPKD is characterized by the formation of fluid filled cysts in both kidneys leading eventually to end-stage renal disease. Several *in vivo* and *in vitro* models of ADPKD exist, although many of them fall short of fully recapitulating the human disease phenotype, driving the failure of most therapeutic candidates in human clinical trials.

Methods: We have developed a unique 3D Biogel-based platform in 384-well tissue culture format utilizing cells isolated from individual cysts on human ADPKD donor kidneys. Cultures from each individual cyst are genotyped to determine the PKD1 or PKD2 mutation. Interestingly, from 9 human ADPKD donor tissues to date (8 with PKD1 mutations, 1 with a PKD2 mutation), we have discovered that only a subset of donors are prone to second somatic hits in single cyst-derived cultures, in addition to the germline mutation. These cells form cysts over days to weeks in culture that can be tracked by high-content imaging with cyst size and number being quantified through algorithm-based image analysis. This platform can be used for screening or validation of candidate drugs and provides significant advancement in throughput and pathophysiologic relevancy.

Results: Here, we show the effects of proprietary small molecules derived from a pre-clinical Cystic Fibrosis (CF) drug discovery program. In human bronchial epithelial cells, these compounds confer a dual effect of CFTR correction and ENaC inhibition. In our system, they are capable of reducing both the size and total number of cysts present after more than a week in culture.

Conclusions: The exact mechanism of action remains to be elucidated, but our data suggests two key findings. First, primary cultures of human cyst cells can be derived from individual cysts of ADPKD kidney tissues and can form cysts in 3D Biogel in a medium-throughput screening system to profile candidate PKD therapeutics. Second, treatments once reserved for CF and other genetic diseases might open new avenues for treatments of PKD. *DBM acknowledges the Mayo Clinic PKD Center Genotyping Core for genotyping services.*

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FR-PO737

Vascular Disease in PKD: A Novel Role for MLL1 in the Hedgehog-GLI1 Regulated Pro-Angiogenic Genes in Endothelial Cells

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Background: We have previously reported that activation of the Hedgehog (Hh) pathway is severely impaired in Polycystic Kidney Disease Endothelial Cells (PKD-ECs), leading to endothelial dysfunction and development of vascular defects. Furthermore, the severity of vascular dysfunction cannot be completely accounted for by the genetic defects, suggesting that other factors play a role. Here, we hypothesized that epigenetic changes modulating PKD-ECs transcriptome are responsible for the abnormal endothelial phenotype.

Methods: We studied the expression and regulation of pro-angiogenic molecules, such as vascular endothelial growth factor A (VEGFA), Angiopoietin 1 (ANG1) and Angiopoietin 2 (ANG2) using Chromatin Immunoprecipitation (ChIP) and gene expression assays in ECs stimulated with Smoothened Agonist (SAG, 100 nM for 24 hrs).

Results: ChIP studies demonstrated that VEGFA, ANG1 and ANG2 are direct targets of the transcription factor GLI1, after activation of the Hh pathway. Furthermore, PKD-ECs displayed lower binding of GLI1 (Fig. 1A) and histone methyltransferase MLL1 (Fig. 1B) to the promoter region of those pro-angiogenic genes, compared to WT-ECs. Importantly, analysis of Histone 3 Lysine 4 methylation revealed a lower enrichment of methyl groups in PKD-ECs compared to WT (Fig. 1C).

Conclusions: Our data suggest that there is a specific epigenetic pathway affected in PKD controlling the ECs phenotype. These studies provide the base for the development of novel therapeutic strategies that, through modulation of epigenetic mechanisms, focus on the vascular aspects of PKD.

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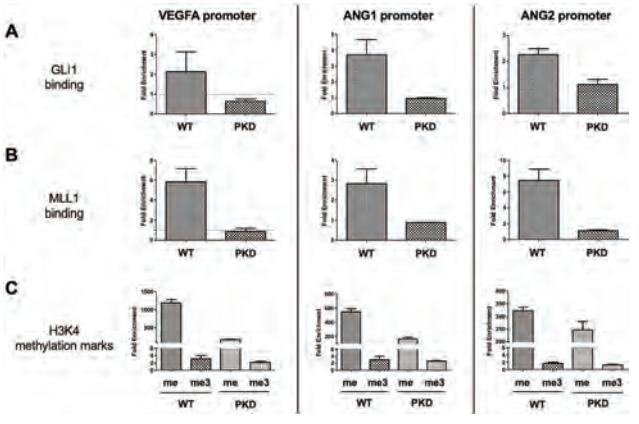

FR-PO738

Serum Global Metabolic Profiling Identifies Key Metabolic Networks Dysregulated in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a monogenetic disorder, caused by mutations in either the *PKD1* or *PKD2* gene, that eventually leads to end-stage renal disease. Despite this prognosis, treatment options for ADPKD are limited. Total kidney volume has been qualified by both FDA and EMA as a prognostic enrichment biomarker for selecting patients at high risk for progressive decline in renal function for inclusion in interventional clinical trials for ADPKD. However, an ADPKD-specific, easily-accessible and reliable biofluid biomarker for identification, stratification and monitoring of disease progression is lacking.

Methods: As several signaling and metabolic pathways are known to be dysregulated during ADPKD progression, we examined the global metabolic profiles of serum samples from a *Pkd2*-KO mouse model of ADPKD (n=6) and WT normal (n=6) mice; as well as ADPKD patients (n=22) and healthy volunteers (n=15) to investigate whether a metabolic profile could be established to aid in assessing disease progression. Dysregulated metabolites were identified and interrogated for their correlation to BUN, eGFR or HtTKV.

Results: Global metabolic profiling carried out in mouse and human serum samples detected a total of 841 and 1156 metabolites, respectively. In human serum samples, principal component analysis showed a clear separation of serum global metabolic profiles between ADPKD and healthy populations. Sex and age were also contributing factors, accounting for 20% and 25% of the metabolite differences observed between the respective human populations. As anticipated, serum creatine and urea were among the dysregulated metabolites increased in ADPKD samples and were highly correlated to eGFR (R^2=0.949) and BUN (R^2=-0.078), respectively. Importantly, we have identified a targeted list of serum metabolites (including those involved in lipid metabolism) that showed differential abundance in both human and mouse ADPKD compared to their respective healthy cohorts.

Conclusions: Our comprehensive evaluation of the global metabolic profiles of serum samples from a mouse model of ADPKD as well as ADPKD patients have identified significant dysregulation in several key metabolic networks. Our results point to the potential use of serum metabolites as translational biomarkers for ADPKD.

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FR-PO739

Global DNA Hypomethylation in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) affects an estimated 600,000 individuals in the United States. We have previously demonstrated that the serum level of s-adenosyl methionine (SAM): s-adenosyl homocysteine (SAH), an indicator of cellular methylation potential, is decreased in ADPKD patients with normal to mildly decreased kidney function. As the alteration in the methylation potential may influence DNA methylation, we hypothesized that global DNA hypomethylation may occur in ADPKD.

Methods: Global DNA methylation status was assessed in DNA extracted from whole blood and from kidney tissue by measurement of 5-methylcytosine content by ELISA (Epigentek, Farmingdale, NY). Blood samples were obtained from 17 subjects with ADPKD and normal or near normal kidney function and 12 age- and sex-matched healthy control subjects. Kidney tissue was available from 2 ADPKD patients and 2 control subjects.

Results: Global DNA methylation was significantly lower in the ADPKD subjects compared to healthy subjects (Table 1). Similarly, global DNA methylation was lower in the ADPKD kidney tissue (2.54% vs 5.80%). Renal blood flow decreases early in the course of disease and we show that SAM:SAH (methylation potential) is significantly correlated with renal blood flow ($r = 0.45$, $p = 0.02$). These findings suggests that decrease in methylation potential may be an early event in ADPKD.

Conclusions: Global DNA hypomethylation is present in ADPKD both in peripheral blood cells and in kidney tissue. As DNA hypomethylation might play a role in disease progression, agents that increase global DNA methylation might have therapeutic potential in ADPKD.

Funding: Private Foundation Support

Global DNA methylation in ADPKD and healthy subjects

Parameter	ADPKD (N =17)	Healthy Controls (N=12)	P
Age (years)	41 ± 11	45 ± 11	0.32
Male/Female	9/8	6/6	0.14
eGFR (ml/min/1.73m^2)	77 ± 27		
Height corrected total kidney volume (ml)	616 ± 190		
% Methylated DNA (blood cells)	1.1 ± 0.5	3.5 ± 2.0	< 0.0001

data presented as mean and standard deviation

FR-PO740

Identification of Cystogenic Signaling Pathways in a Newly Developed, Inducible-Kidney Epithelial Cell Model of Pkd2-Mediated Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder. Loss-of-function mutations of *Pkd1* and *Pkd2* genes cause the disease. However, initiating signaling events, most proximal to the polycystins, have not been precisely identified. Here, we developed in vitro inducible *Pkd2* gene knockout (KO) model to explore the immediate consequences of *Pkd2* KO and to identify the initiating factors that drive cystogenesis.

Methods: A doxycycline (Dox)-inducible *Pkd2* KO renal medulla epithelial cell line was established from Pkd2 $^{flox/flox}$/Pax8-rtTA/LC1 KO mice crossed with the SV-40 LTA "immorto mouse". For RNA-Seq, Dox treated cells were compared to isogenetic controls. 4 replicates from two different passages were analyzed. Libraries were constructed from mRNA and sequenced (2×75 bp, paired-end). Sequence reads were aligned on the mouse genome GRCm38p6, and downstream analyses were performed with R packages and multiple bioinformatics tools.

Results: The inner medulla epithelial cell line forms a polarized, electrically-tight, monolayer on filter supports, and as assessed by Western blot analysis, allows complete PC2 KO within 4 days of Dox treatment. Hierarchical clustering analysis of RNA-Seq corroborated renal medullary origin. Differential expression (DE) analysis of RNA-seq showed revealed 3243 genes changed significantly (FDR<0.05) in response to the rapid repression of *Pkd2*. Chief among them were other Cystic Disease genes, *Muc1*, *Ganab*, *Pkhd1*, *Dzip1l*, and *Dnajb11*, but not *Pkd1*. The other DE genes were significantly enriched in the sonic hedgehog (SHH) signaling pathway and cilia structure components. *Evc*, *Evc2*, *Gli3*, and *Prkacb* of the SHH signaling pathway were downregulated, implicating

suppression of SHH and alter cilia as cytogenetic drivers. In addition to *Gli3* of SHH, 108 other transcription factor (TF) genes were significantly changed, including TF associated with cilia (*Glis3* and *Pax8*), Wnt signaling and ER stress.

Conclusions: RNA-Seq analysis of our newly established inducible *Pkd2* KO kidney epithelial cell line identified gene networks that are rapidly changed in response to PKD2 repression, providing clues about the proximal cytogenetic signaling events in PKD.

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FR-PO741

A Human Organoid-on-a-Chip Model Reveals Effects of Flow on Polycystic Kidney Disease Cystogenesis

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Background: Polycystic kidney disease (PKD) is caused by the loss of polycystin proteins that are posited to act as flow-sensitive mechanosensors on primary cilia, but the effects of flow on cystogenesis are difficult to study *in vivo*. Human kidney organoids differentiated from pluripotent stem cells provide a genetically specific model of PKD cystogenesis *in vitro*. We hypothesized that adding flow to this model would exacerbate cyst growth resulting from PKD mutations.

Methods: Kidney organoids were derived from stem cells with bi-allelic, truncating mutations in *PKD1* or *PKD2*, and subjected to fluid shear stress at physiological levels (0.2 dynes/cm^2) in microfluidic chips. A static culture condition in the same chips that allowed for simple diffusion of nutrients was used to control for the effects of flow. Fluorescence-labeled glucose was introduced and monitored in time-lapse videos over a 12 hour period, and absorption was quantified using image intensity analysis. Cyst polarity was determined by immunofluorescence for cilia and tight junctions. Cyst expansion was quantified in the presence or absence of transporter modulators such as SGLT2 inhibitors and mannitol.

Results: Cysts in PKD organoids were highly dynamic and increased in size rapidly under flow, compared to static controls. Flow could also be substituted by a diffusive static condition that exposed organoids to an equivalent volume of culture media to achieve a similar effect. PKD cysts in organoids polarized with the apical ciliated surface facing outwards towards the media and exposed to flow, modeling the interior of a tubule *in vivo*. Expansion of PKD cysts was coupled to glucose transport into epithelial structures and their lumens, while inhibition of glucose transport decreased cyst expansion in a dose-dependent manner.

Conclusions: Our findings suggest that flow, volume, and glucose transport are positive regulators of cyst expansion. Cystogenesis can be enhanced through mechanisms of tubular reabsorption in addition to secretion, and glucose transporters may be crucial to this effect. Collectively, our data support a role for polycystins in regulating the delicate balance of renal transporter function. Therapeutics that reduce flow through the kidney may therefore be beneficial in reducing cyst growth in PKD.

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FR-PO742

Microinjection-Based Analyses in a 3D Cyst Model

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Background: ADPKD is characterized by continuous cyst growth. Hereby fluid secretion into the cyst lumen plays a major role. We could show that in addition to cAMP-mediated chloride secretion also ATP- and Ca^{2+}-dependent chloride secretion contributes to cyst enlargement. Hereby the binding of luminal ATP to P2Y2-receptors leads to activation of the apical chloride channel Anoctamin 1. Functional studies in our established *in vitro* cyst model are partly restricted, since applied pharmaceuticals and substances only reach the basolateral side of the cysts. In addition, the quantification of the apical secretion rate of various molecules such as ATP is not possible. Our goal was to establish a micro puncture technique for *in vitro* cysts, which would allow us to inject or withdraw substances into or out of the cyst lumen.

Methods: In our *in vitro* 3D-cyst model, principal-like MDCK collecting duct cells (plMDCK) form cysts within a collagen matrix. Those cysts get punctured and substances injected utilizing a microinjector in combination with a micromanipulator and a high-resolution macroscope. Successful injection can be monitored by co-injection of a dye into the cyst's lumen. Injected cysts can then be tracked over time in a live cell imaging chamber.

Results: With this new technique we are able to puncture cysts and inject substances into *in vitro* cysts starting at a size of >100μM. Correct application can be visualized by applying a coloured dye in addition and visualizing the cyst thereafter in a live cell imaging chamber. Therefore, we are able to apply various substances of interest at the apical side of the cysts and analysing their direct effect on cyst growth. In addition, small amounts of fluid can be extracted from the cysts and further analysed. This technique will be used to test for luminal ATP concentrations under different culture conditions.

Conclusions: We have established a new method, allowing us to puncture *in vitro* cysts and applying substances luminally or measuring concentrations of different molecules in the cyst lumen such as ATP by extracting cyst's fluid. In addition, the punctured cysts can be imaged over time in our live cell imaging setup.

FR-PO743

A Novel CRISPR/Cas9 eGFP Knockin Mouse for Characterizing Endogenous Polycystin 1

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Background: Mutations in *Pkd1* are identified in the majority of cases of autosomal dominant polycystic kidney disease (ADPKD). This gene encodes a large trans-membrane protein, Polycystin 1 (PC1), which undergoes complex processing that results in multiple cleavage products. The complexity and low abundance of PC1 makes investigation into the functions of endogenous protein extremely challenging, and most of our knowledge of PC1 comes from study of recombinant protein over-expressed in heterologous systems. In order to investigate PC1 function under physiological conditions, we generated a knock-in mouse model that expresses a chimeric PC1-eGFP-3HA fusion protein under the control of its native promoter using the CRISPR/Cas9 method.

Methods: We characterized the expression of PC1-eGFP-3HA by immunoblot (IB), immunoprecipitation(IP), and immunofluorescence(IF) in mouse tissues and in Murine Embryonic Fibroblasts (MEFs) and Renal Epithelial Cells (REC) derived from the mouse line. The*Pkd1-eGFP-3HA/Pkd1* and *Pkd1/KO* mouse lines were intercrossed to test if the fusion protein was functional.

Results: Genomic PCR and sequencing results confirmed the successful insertion of eGFP and 3HA tag sequences into the *Pkd1* locus. Offspring of *Pkd1-eGFP-3HA/Pkd1* X *Pkd1/KO* crosses were obtained at mendelian ratios. Neither the kidneys nor livers of *Pkd1-eGFP-3HA homozygotes* were cystic at 1 year, and they remain healthy at >1.5 years without other apparent abnormality. The PC1-eGFP-3HA fusion protein can be reliably detected by IB and IP in various tissues and cell lines. Multiple previously reported PC1 cleavage products were detected in a variety of tissues. However, we have not yet been successful in detecting PC1-specific signal above background by IF in any tissues. Live cell imaging and IF in MEF cells using various antibody, fixation and microscopy methods failed to detect PC1. So far, we can only visualize the fusion protein unambiguously by IF in primary cilia of REC.

Conclusions: The PC1 fusion protein function appears to be as functional as untagged protein and could be detected more easily and reliably. Using GFP-nanobody magnetic beads, the affinity purification–mass spectrometry (AP-MS) for endogenous PC1 fusion protein is also more efficient. This model will be a helpful resource for studying endogenous PC1 trafficking in live cells and how it interacts with other proteins.

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FR-PO744

Primary Patient Material as Model for a High Content 3D In Vitro Screening Assay to Study ADPKD

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by the formation of fluid-filled cysts in the kidney. Currently only one drug is on the market for ADPKD, a vasopressin receptor 2 inhibitor Tolvaptan. However, Tolvaptan does not prevent cysts from forming but slows down cyst swelling. Identifying the mechanisms involved in cystogenesis and identification of treatments is hampered by the lack of pathophysiologically relevant *in vitro* models. Here, we report the development of an *ex vivo* 3D cyst screening assay that uses primary cells from resected kidneys from ADPKD patients to facilitate *in vitro* studies for ADPKD.

Methods: Patient tissue was harvested directly from resected kidneys and cultured in 3D in an optimized hydrogel and culture medium until cryopreservation. Short expansion culture was performed in similar culture conditions. Compound testing was done in 384 well plates. After 24h pre-culture, compounds were added for 48h. Plates were fixed and stained for nuclei and F-actin. Plates were imaged and using Ominer ™ high throughput image analysis software the entire z-stack of each well was recapitulated for 3D quantification and morphometric analysis.

Results: Cultures propagated from cryopreserved tissue developed a cystic phenotype that was stably maintained in 3D culture. Swelling of these cysts could be induced using forskolin, which activates adenylyl cyclase and using desmopressin, which activates the vasopressin 2 receptor. Effect of Metformin, Rapamycin, Roscovtine and Tolvaptan was examined in combination with desmopressin or forskolin. Compound effects were visualized with high content imaging. Using Ominer ™ images were analyzed. Measurement of phenotypic characteristics such as nucleus morphology and thickness of the cyst wall enabled discrimination of compounds that reduced cyst swelling and compounds that were cytotoxic. All reference compounds showed the expected decrease in cyst swelling.

Conclusions: We have developed a 3D screening assay that uses low-passage patient material as model of renal cysts. With this assay, we have successfully tested a panel of reference compounds. Using our image-based approach we are able to discriminate between efficacy or toxicity inducing compounds. This assay offers a powerful tool for future drug and target discovery as well as mechanistic studies for ADPKD.

Funding: Commercial Support - OcellO

FR-PO745

Heterozygous Inactivation of PKD1 in Miniature Pigs Induces Embryonic Cyst Formation and Progressive Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Murine models do not faithfully recapitulate important features of human ADPKD or its dominant inheritance. Gene editing and somatic cell nuclear transfer in large animals have provided superior models for human genetic disorders that have improved our understanding of disease mechanisms and the translational value of pre-clinical studies for novel therapies. Porcine anatomy, development, physiology, genetics and body size are like those of humans. We generated a new ADPKD model in the Yucatan miniature pig to monitor renal cyst formation *in utero* and postnatal PKD progression.

Methods: Gene targeting methods were used to insert a blasticidin cassette into intron 30 of *PKD1*, which resulted in a null allele, and somatic cell nuclear transfer to generate *PKD1*$^{+/-}$ cloned pigs. Breeding colonies were established to generate *PKD1*$^{+/-}$ and wildtype littermates. Kidneys were collected at embryonic days 30, 60, 90, newborn (~120 embryonic days) and 3, 6, 9 and 12 months postnatal to evaluate cyst development. Embryonic kidneys were imaged by micro-CT and larger kidneys were sectioned using a tissue slicer for measurement of cystic index. Thin tissue sections were stained with antibodies to AQP-2 to identify collecting ducts and PCNA, a marker of cell proliferation.

Results: Embryonic *PKD1*$^{+/-}$ pig kidneys had sporadic cysts and cystic dilations that appeared to form in clusters, consistent with the proposed mechanism of early cyst development in human ADPKD. The number of cysts and total cystic area progressively increased after birth; however, changes in kidney weight relative to body weight were not significantly different between *PKD1*$^{+/-}$ and wildtype pigs. Many, but not all, cysts stained positive for AQP-2, indicating the involvement of multiple segments of the nephron. There were increased PCNA-positive cells in cystic epithelia compared to non-cystic tissue in embryonic and adult *PKD1*$^{+/-}$ kidneys.

Conclusions: Our results demonstrate that inactivation of one *PKD1* allele induces renal cyst formation *in utero* and progressive ADPKD in a new porcine model ADPKD.

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FR-PO746

Kidney and Cystic Volume Imaging for Disease Presentation and Progression in the Cat ADPKD Large Animal Model

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Background: Persian cats have a variant in *polycystin – 1* (*PKD1*) causing autosomal dominant polycystic kidney disease (ADPKD). The variant (c.10063C>A) causes a protein truncation (p.C3284X) and is the only known variant in cats. As in humans, the variant is lethal *in utero* when in the homozygous state. Affected cats can have a wide range of progression and severity of disease. However, cats are an overlooked biomedical model and have not been used to test therapeutics and diets that may support human clinical trials. To reinvigorate the cat as a large animal model for ADPKD, the efficacy of imaging modalities in cats was demonstrated and supported robust estimates of kidney and fractional cystic volumes.

Methods: Three imaging modalities, ultrasound, computed tomography (CT), and magnetic resonance imaging, were used to examine variation in disease presentation and disease progression in 11 felines with *ADPKD*. Imaging was compared to well-known biomarkers for chronic kidney disease and glomerular filtration rate. Total kidney volume, total cystic volume, and fractional cystic volume (FCV) were determined for the first time in *ADPKD* cats. A few cats had follow-up examinations to evaluate progression.

Results: The size of the cat's kidney supported the determination of FCV measurements. CT was a rapid and efficient modality for evaluating therapeutic effects that cause alterations in kidney volume and/or FCV. Biomarkers, including glomerular filtration rate and creatinine, were not good indicators of kidney function. The wide variation in cystic presentation suggested genetic modifiers likely influence disease progression in cats. All imaging modalities had comparable resolutions to those acquired for humans, and software used for kidney and cystic volume estimates in humans can be used in cats.

Conclusions: Veterinary-based imaging protocols are as robust and efficient for evaluating *ADPKD* in cats as in humans. Cats can be identified as fast and slow progressors, thus, could assist with modifier discovery. Software to measure kidney and cystic volume in human ADPKD kidney studies is applicable and efficient in cats. The longer life span, similar genetics, disease presentation and progression, and the large kidney size suggest cats as an efficient biomedical model for evaluation of *ADPKD* therapeutics.

Funding: NIDDK Support

FR-PO747

Angiomotin Knockout Causing Glomerulotubular Nephropathy May Be via an Activated Hippo Signalling Pathway

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Background: Angiomotin (Amot) is an angiostatin binding protein involved in endothelial cell migration. Using CRISPR/Cas9, we created Amot knockout (KO) rats that developed cysts from 1 month and proteinuria by 6 months. Histology revealed dilated tubules, podocyte hypertrophy, foot process effacement, thick glomerular and tubular basement membranes. We aimed to elucidate the pathomechanism of Amot KO with iTRAQ (isobaric tags for relative and absolute quantitation) based quantitative proteomics.

Methods: Kidney cortex from 1-mth rats were homogenized and labelled with iTRAQ. Quantitative proteomic analysis was performed using 2D-nLC-MS/MS. Peptide identification and quantification was carried out on ProteinPilot 5.0 software using Paragon database search algorithm (5.0.0.0.4767) and integrated false discovery rate(FDR) analysis function. Data were searched against UniProtKB protein sequence databases. Statistically significant differences were based on fold change ≥1.5 and p-value <0.05. Rat glomeruli were isolated for ex vivo podocyte culture or total RNA extraction. Immunofluorescence(IMF) and western blot(WB) were performed on podocytes for Yap (Yes-associated protein) nucleus translocation analysis. Real-time PCR were performed for Yap target genes.

Results: 5030 proteins were quantified with confidence corresponding to peptide and protein FDR <0.01 and with ≥2 unique peptides per protein. We identified 101 up-regulated and 209 down-regulated proteins in KO compared to WT rats. Expression of TEAD1, a major YAP target transcription factor, was significantly decreased. IMF and WB showed increased Yap nucleus deposition. Transcriptional expression of YAP target genes (Ankrd1, Cyr61, Diaph3, Anln and Ctgf) were increased.

Conclusions: *In vivo* Amot KO caused Yap nuclei translocation and activated the Hippo/Yap pathway.

Funding: Government Support - Non-U.S.

FR-PO748

Notch Overexpression in a Mouse Model of Polycystic Kidney Disease

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Background: Polycystic kidney disease (PKD) is a major cause of end stage renal disease and characterized by enlarged kidneys containing numerous fluid-filled cysts, hypertension, anemia, and progressive loss of kidney function. PKD is autosomal dominant (ADPKD), caused by mutations in the *PKD1* or *PKD2* genes, or autosomal recessive (ARPKD), caused by mutations in the *PKHD1* gene. While the genetic basis of PKD is known, the downstream molecular mechanisms which lead to deregulation of proliferation, apoptosis, and differentiation remain poorly understood. Previous work has demonstrated Notch activation in mouse models of ADPKD and ARPKD. In addition, we have shown that aberrant Notch signaling during kidney development leads to an alterations in cell fate. Thus, we hypothesize that Notch overexpression during kidney development may play an important role in PKD pathogenesis.

Methods: We generated transgenic mice with overexpression of *Notch1* in renin lineage cells using the Cre-lox system. Specifically, we crossed mice which express Cre recombinase under the control of the renin locus (*Ren1*$^{dcre/+}$) with transgenic mice containing a sequence encoding an intracellular portion of the mouse *Notch1* gene inserted into the ubiquitously expressed *Rosa26* locus (*Rosa*$^{Notch/+}$). Control mice (*Ren1*$^{d+/+}$;*Rosa*$^{Notch/Notch}$) and mutant mice (*Ren1*$^{dcre/+}$;*Rosa*$^{Notch/+}$) were studied at 3, 6, and 9 months of age.

Results: Mutant mice developed large kidneys with numerous cysts by 3 months of age and this phenotype worsened with advancing age. Histologic examination confirmed the presence of numerous cysts throughout the kidney cortex of mutant mice. Mutant animals had decreased *Renin* expression shown by PCR and decreased RENIN protein levels in the kidney and plasma as shown by immunohistochemistry and ELISA respectively. In addition, mutant animals developed anemia and worsening renal function with age. Finally, mutant animals did not live beyond 9 months of life, likely dying secondary to renal failure and/or anemia.

Conclusions: Mice with overexpression of *Notch1* in renin lineage cells develop numerous renal cysts, enlarged kidneys, anemia, progressive renal insufficiency and early death – recapitulating many features of human PKD. To our knowledge, this is the first model of PKD resulting from overexpression of Notch signaling, and this work highlights the importance of aberrant Notch signaling in PKD.

Funding: NIDDK Support

FR-PO749

Sprouty1 Regulates FGF Signaling-Mediated Nephron Progenitor Maintenance

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Background: Nephron progenitors maintain and differentiate with various signaling cascades. FGF9 and FGF20 play pivotal roles in generating and maintaining nephron progenitors during kidney development. However, molecules regulating FGF signaling during nephron progenitor development is not known. Sprouty (Spry) is an antagonist of receptor tyrosine kinases. In developing kidney, Spry1 is expressed in the ureteric buds

and regulates Ret-GDNF-dependent renal branch morphogenesis. Although Spry1 also expressed in the nephron progenitors, function of Spry1 in this population is still elusive.

Methods: To understand whether Spry1 antagonize function of FGF9/20 induced nephron progenitors, we generated Spry1, Fgf9, Fgf20 triple mutant animals and evaluated kidney phenotypes.

Results: Deletion of Spry1 rescues bilateral renal agenesis caused by deletion of both Fgf9 and Fgf20. In addition, deletion of Spry1 normalizes number of nephron progenitors in Fgf9 and Fgf20 hypomorphic kidneys. Nephron progenitor specific deletion of Spry1 also rescues loss of Fgf9 and Fgf20 induced bilateral renal agenesis. Further genetic analyses identified Fgf8 compensates loss of Fgf9 and Fgf20 at the background of Spry1 mutant.

Conclusions: This data demonstrate that Spry1 expressed in nephron progenitors antagonize FGF signaling to balance nephron progenitor maintenance.

Funding: NIDDK Support

FR-PO750

Fibroblast Growth Factor Signaling Mediates Progenitor Cell Aggregation and Nephron Regeneration in the Adult Zebrafish Kidney

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Background: The zebrafish kidney regenerates after injury by development of new nephrons from resident adult kidney stem cells. Although adult kidney progenitor cells have been characterized by transplantation and single cell RNA seq, signals that stimulate new nephron formation are not known.

Methods: Adult wild type and Tg(*lhx1a:EGFP*) and Tg(*hsp70:dn-fgfr1*) transgenic zebrafish kidneys were injured by gentamicin injection. Regeneration was observed by in situ hybridization, immunofluorescence, and qPCR analyses.

Results: We demonstrate that fibroblast growth factors and FGF signaling is rapidly induced after kidney injury and that FGF signaling is required for recruitment of progenitor cells to sites of new nephron formation. Chemical or dominant negative blockade of Fgfr1 prevented formation of nephron progenitor cell aggregates after injury and during kidney development. Implantation of FGF soaked beads induced local aggregation of *lhx1a:EGFP+* kidney progenitor cells.

Conclusions: Our results reveal a previously unexplored role for FGF signaling in recruitment of renal progenitors to sites of new nephron formation and suggest a role for FGF signaling in maintaining cell adhesion and cell polarity in newly forming kidney epithelia.

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FR-PO751

SIX2+CITED1+ Cells: The Culprit of Wilms Tumor Development?

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Background: Wilms tumor (WT) accounts for 95% of renal pediatric malignancies and is characterized by uncontrolled proliferation of nephron progenitors (NP) without generation of functional nephrons. Due to the inability of isolating these human NP, little is known about WT initiation and growth. In this study, we isolated NP expressing SIX2 and CITED1 (the master genes regulating nephrogenesis) from WT samples and from human fetal kidneys (hFK) and performed in vivo and in vitro experiments to study the regulation of self-renewal vs differentiation of NP.

Methods: WT and hFK samples were histologically analyzed, digested to single cell suspension, incubated with Smartflare-probe and SIX2+CITED1+ cells immediately sorted and processed for RNA-seq, single-cell RNA-seq and for other analysis. Xenografts of WT-NP and FK-NP were generated and tumor formation was assessed. Using a nephrogenic specific media, we established conditions for long-term culture of NPs and studied mechanisms that regulate self-renewal vs differentiation were performed.

Results: Histology confirmed a different pattern of expression for SIX2 and CITED1 across WT with different prognosis and stages compared to hFK. Our RNA-seq analysis confirmed of mechanisms overexpression of tumorigenic genes in WT-NP compared to WT-NP. When transplanted in vivo WT-NP demonstrated marked capacity of tumorigenesis, which in some instances induced metastasis, while hFK-NP did not. Single-cell RNA-seq after xenotransplantation of WT-NP defined precise cancer-associated cellular identities compared to WT-NP. In vitro experiments confirmed that modulation of integrin signaling leads to blockade of self-renewal in NP by decreasing CITED1 expression, activating b-catenin and inducing specification by stimulating the activation of LEF1.

Conclusions: This work evidenced that SIX2+CITED+ cells in WT represent a population of cancer stem cells with tumorigenic ability. Our characterization also highlights differences in self-renewal potential between favorable and unfavorable WT samples, with b-catenin playing a key role in regulating this biological process. These studies can help to increase our knowledge of human nephrogenesis and the development of new strategies aimed at halting tumor progression.

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FR-PO752

In Utero Exposure to Maternal Diabetes Impairs Nephron Progenitor Differentiation

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Background: The incidence of diabetes mellitus has significantly increased among women of childbearing age worldwide and infants exposed to maternal diabetes *in utero* are at increased risk of congenital renal anomalies. In this study, we utilized a genetic model of maternal type 1 diabetes, the *Akita* (*Ins2*$^{+/C96Y}$) mice, to evaluate its effect on kidney development.

Methods: Diabetic *Ins2*$^{+/C96Y}$ females were bred with wildtype *C57BL/6J* males and, wildtype offspring exposed to maternal diabetes *in utero* (DM_Exp) were assessed. Wildtype offspring from *C57BL/6J* dams were used as controls. Kidneys were collected at different postnatal days (P0, P2 and P34). Nephron numbers were estimated using the gold-standard physical dissector/fractionator method. The expression of nephron progenitor and developing nephron markers was analyzed by qPCR, immunohistochemistry and/or Western blot.

Results: Adult DM_Exp mice (P34) exhibited a nephron deficit of approximately 20% with no association with growth restriction. At P2, the rate of apoptosis and cell proliferation in nephron progenitors was unchanged. However, the expression of the nephron progenitor markers, *Six2* and *Cited1*, was increased in DM_Exp kidneys. In association with this, there was a significant reduction in the total number of early developing nephrons (i.e., renal vesicle, comma- and S-shaped body structures) in DM_Exp kidneys compared to control kidneys. This was associated with reduced expression of the intracellular domain of Notch 1 (NICD) and the canonical Wnt target lymphoid enhancer binding factor 1 (Lef1).

Conclusions: Together, these data suggest that the diabetic intrauterine environment impairs the differentiation of nephron progenitors into nephrons, which may be mediated by diminished Wnt/β-catenin and Notch signaling pathways.

FR-PO753

Development of a New Nephron Progenitor Cell Replacement System for Application in Human Induced Pluripotent Stem (iPS) Cell-Derived Nephron Progenitor Cells (NPCs)

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Background: Previously, we generated a transgenic mouse model that enabled diphtheria toxin (DT)-induced ablation of Six2-positive NPC s (Six2-iDTR mouse). After eliminating host NPCs, we transplanted allogenic or xenogeneic NPCs into the metanephric mesenchyme. Donor NPCs were differentiated into neo-nephrons, which have the ability to filter and produce urine, and were connected to the host mouse ureteric bud. In the future, we aim to use this system in kidney regeneration using human iPS cell-derived NPCs. However, human cells permanently express diphtheria toxin receptors and can undergo apoptosis when treated with DT. Therefore, a new NPC elimination system is warranted. In this study, we developed a new transgenic mouse model to ablate NPCs without affecting human cells using tamoxifen instead of DT (six2 CreERT2-DTA mouse) for application in human cells.

Methods: Six2-CreERT2 mice were crossbred with Rosa26-floxed stop DTA mice to obtain Six2CreERT2-DTA mouse offsprings, which were used as hosts. We attempted regeneration from dissociated cells derived from E13 mice and E15 rats metanephros, and NPCs differentiated from human iPS cells. We injected these dissociated cells below the renal capsule of the E13 transgenic mice metanephros. The injected metanephros were isolated, and the organs were cultured for 7 days with 4OH-tamoxifen. After culturing, the metanephros were analyzed using immunofluorescent staining. To verify the blood-inducing ability of the regenerated nephrons in vivo, we additionally transplanted Six2CreERT2-DTA mice metanephros injected with dissociated cells derived from E13 mice into immunodeficient mice under tamoxifen administration and evaluated the results.

Results: We successfully eliminated Six2-positive NPCs from the cap mesenchyme by this system and regenerated nephrons derived from mouse or rat metanephros. In vivo, we successfully regenerated chimera kidneys that have blood-inducing ability from mouse metanephros. Human iPS cell-derived NPCs were engrafted in the Six2CreERT2-DTA mouse metanephros cap mesenchyme.

Conclusions: We developed a new nephron progenitor cell elimination and replacement system that can be utilized in human cells.

FR-PO754

ZEB2 Controls Ureteral Smooth Muscle Cell Fate

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Background: ZEB2 is a SMAD-interacting transcriptional factor and loss-of-function *ZEB2* mutations are associated with Mowat-Wilson Syndrome (MWS), a genetic disease with multiple congenital defects including hydroureter and hydronephrosis. Ureteral smooth muscle cells (SMCs) derive from TBX18^{+} mesenchymal progenitors and abnormal

development of ureteral SMCs can lead to hydroureter and hydronephrosis. However, the molecular role of ZEB2 in ureteral SMCs development from TBX18^{+} mesenchymal progenitors is not known.

Methods: We analyzed *Zeb2* ureteral mesenchyme-specific conditional knockout mice *Zeb2$^{flox/flox}$;Tbx18Cre^{+}* (*Zeb2* cKO) and their wild-type littermate controls for urinary tract phenotypes by gross and histological examination. Cell specific marker studies were carried out to determine abnormal ureteral cellular and molecular phenotypes and ureteral SMCs development.

Results: We found that at P0 and E16.5, *Zeb2* cKO mice developed hydroureter and hydronephrosis with dilated ureter devoid of ureteral smooth muscle cells as compared to wild-type littermate controls. Cell marker study showed that TAGLN^{+} ACTA2^{+} ureteral SMCs did not appear but there was an expanded layer of FOXD1^{+} POSTN^{+} ureteral tunica adventitia in *Zeb2* cKO mice during early ureter development. At E14.5-E15.5, there was an increase in SOX9 expression in ureteral mesenchymal cells but a decrease in TBX18 expression in *Zeb2* cKO mice, suggesting an early abnormal development of ureteral SMCs. We also found that both apoptosis and proliferation were increased in ureteral mesenchyme cells, and the SMAD signaling was disturbed in *Zeb2* cKO mice.

Conclusions: ZEB2 is expressed in ureteral mesenchymal cells. In the absence of ZEB2, ureteral inner mesenchymal cells differentiate into FOXD1^{+} POSTN^{+} ureteral tunica adventitia rather than ureteral SMCs. These data suggest that ZEB2 controls ureteral smooth muscle cell fate in ureteral mesenchymal cells. Loss of ZEB2 leads to depletion in the ureteral smooth muscle layer formation, which eventually causes hydroureter and hydronephrosis phenotype in *Zeb2* cKO mice.

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FR-PO755

A Hedgehog (Hh)-TGFb Signaling Axis Controls Murine Stromal Cell Development and Ureteropelvic Junction Patency

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Background: Signaling mechanisms that control stromal differentiation from *Osr1*+ progenitors during normal and malformed renal development are largely undefined. Hh proteins bind cell surface PTCH1, thereby disabling PTCH1-mediated inhibition of SMO and increasing Hh-mediated transcriptional activity. We showed that Cre-mediated *Ptch1* deletion in *Osr1*+ progenitor cells at mouse E9.5 increased Hh signaling and induced formation of an ectopic population of *Foxd1*+*Raldh2*+ cells that block the ureteropelvic junction (UPJ) and are present in obstructing tissue in human UPJO (Shebani-Deloui et al, 2018). Here, we investigated molecular mechanisms that function downstream of Hh in this developmental disease context.

Methods: Hh and TGFb signaling was investigated in mice with Tamoxifen (TM)-induced deficiency of either *Ptch1*, *Tgfbr2*, or both. *EGFP*+*Osr1*+ cells were isolated by flow sorting and analyzed by RNASeq. Kidney tissue was analyzed by histology, immunostaining, and light sheet fluorescence imaging. TGFbRII deficiency was induced with ITD-1, which causes proteosomal degradation of TGFbRII (Willems et al, 2012), at the stage of cell aggregation in human kidney organoid tissue.

Results: RNASeq of *Osr1*+ cells isolated from urogenital ridge of *Osr1-EGFP-Cre^{ERt2};Ptch1$^{loxP/-}$* mice at E11.5, 2 days post TM, demonstrated increased *Tgfb2* expression compared to controls (P=0.02). Yet, TM-dependent Cre-mediated *Tgfbr2* deficiency induced in *Osr1*+ cells at E9.5 revealed normal renal structural development and cell differentiation. In contrast, promotion of TGFbR2 degredation with ITD-1 in BiPS-derived human kidney organoid tissue treated from the stage of aggregation inhibited organoid growth, a finding consistent with nephron deficiency in mutant mice with *Tgfbr2* deficiency in both *Foxd1*+ and *Six2*+ cell (Rowan et al, Development, 2018). Analysis of mice at E18.5 with both *Tgfbr2* and *Ptch1*-deficiency (*Osr1-EGFP-Cre^{ERt2};Ptch1$^{loxP/-}$;Tgfbr2$^{loxP/-}$*), induced at E9.5, demonstrated a marked rescue of hydronephrosis (5/11 *Ptch1;Tgfbr2*-deficient vs. 13/15 *Ptch1*-deficient mice; P=0.02) and a major decrease in ectopic peri-ureteric RADH2-positive stromal cells.

Conclusions: Increased Hh signaling in *Osr1*+ cells increases TGFB signaling that controls formation of ectopic *Raldh1*+ stromal cells and obstruction of the UPJ.

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FR-PO756

Loss of Dicer in the Peri-Wolffian Duct Stroma Leads to Aberrant Ureteric Budding and Increased Rates of Vesicoureteral Reflux

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Background: Vesicoureteral reflux (VUR) is associated with urinary tract infections, hypertension, and reflux nephropathy, a leading cause of pediatric end-stage renal disease. Formation of the vesicoureteral junction is determined largely by the induction site of the ureteric bud from the Wolffian duct, which depends on signals from the surrounding stroma. VUR is heritable, but no single genetic mutation causes most known cases of VUR. miRNAs are small noncoding RNAs, processed by Dicer, that regulate gene expression post-transcriptionally. We hypothesize that miRNAs are necessary for vesicoureteral junction development and prevention of VUR.

Methods: We generated a transgenic mouse model with loss of Dicer in the peri-Wolffian duct stroma (mutant=Tbx18cre; Dicer$^{Fl/Fl}$). We performed euthanized cystograms and 3D reconstructions of the ureters and bladder on mutants and controls (control=Tbx18Cre negative littermates). We performed immunostaining and 3D reconstructions at E11.5 to assess ureteric bud induction, common nephric duct apoptosis, and metanephric mesenchyme positioning.

Results: Euthanized cystograms demonstrated higher rates of VUR in the mutant mice compared to control [44% (8/18) of mutants as opposed to 4.0% (3/77) of controls ($p < 0.01$)] at postnatal day 0 (P0). 3D reconstructions showed lower ureteral insertions into the bladder and shorter intravesicular tunnel lengths on the side of VUR in mutants compared to control and non-refluxing mutant ureters ($p < 0.05$) at P0. Calbindin immunostaining revealed that the ureteric bud induction site was cranially shifted in embryonic day 11.5 (E11.5) mutants compared to controls ($p < 0.05$). Cleaved caspase-3 and TUNEL staining at E11.5 showed no difference in apoptosis patterns between mutant and control.

Conclusions: These data suggest a requirement for miRNAs in peri-Wolffian duct stroma for normal ureteric bud induction, subsequent ureter insertion into the bladder, and prevention of VUR. This does not appear to be due to abnormal apoptosis. Current work is evaluating the metanephric mesenchyme position. Future work will elucidate which miRNAs and mRNAs in the peri-Wolffian duct stroma are critical for normal ureteric bud induction to prevent VUR.

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FR-PO757

Identification of TAZ as a Regulator of TGF-β Mediated Fibrosis in iPSC-Derived Organoids

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Background: Chronic kidney disease (CKD) progresses by replacement of functional tissue compartments with fibrosis, a maladaptive repair process. Shifting kidney repair away from fibrosis is key to blocking CKD progression. Much research into the mechanisms of fibrosis is performed in rodent models, outside of the human genetic context and time consuming and expensive. By contrast, reductionist two-dimensional cell culture systems consist of single cell types and lack physiological context. Recently, human induced pluripotent stem cell (iPSC)-derived organoids have shown promise in avoiding some of these limitations. We used iPSC-derived organoids to study fibrogenesis and identify anti-fibrotic mechanisms of bile acid receptor agonists acting downstream of TGF-β1.

Methods: Renal organoids were derived from human iPSCs using a modified feeder-free Takasato protocol. Organoids showed glomeruloid (nephrin/podocalyxin-positive), tubular (E-cadherin/lotus lectin-positive), and vascular compartments. TGF-β1 treatments at 0, 5, 10, and 20 ng/mL were tested. FXR, TGFR5 and TAZ targets and extracellular matrix elements were assessed by qPCR, imunoblotting and confocal microscopy.

Results: TGF-β1 treatment of mature organoids induced extracellular matrix elaboration within 48-72 h in a dose-dependent manner with complete disruption of the organoids at the highest. Previously, we have shown that INT767, a dual TGR5/FXR bile acid receptor agonist, blocks TGF-β1-induced fibrogenesis. To understand the intersect between bile acid receptor agonism and TGF-β1-mediated fibrosis, we focused on transcription factors predicted to interact with the collagen 1 locus. TGF-β1 treatment increased tafazzin (TAZ) and TEA domain transcription factor 1 (TEAD1) expression in the organoids with TAZ and TEAD1 nuclear co-localization in tubules. INT767 decreased TAZ and TEAD1 expression and attenuated TGF-β1-induced fibrosis with preservation of mature nephron architecture.

Conclusions: Treatment of iPSC-derived renal organoids with TGF-β1 recapitulated important aspects of kidney fibrosis over a short period compared to traditional model systems. We demonstrated a mechanism downstream of TGF-β1, involving TAZ and TEAD1 transcription factors, with translational therapeutic potential.

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FR-PO758

Differentiated Expression of Biomarkers for Interstitial Cells During Kidney Development

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Background: Recently, the development of renal fibrosis is thought to involve 3 more cell types in addition to renal epithelial and endothelial cells. They are pericytes, mesangial cells, and fibroblasts, which are all derived from mesenchymal cells and possess the potential to differentiate into ECM-secreting cells. According to literature, the biomarkers for them are PDGFR-β, α-SMA, and desmin, however they can not be specifically identified with alone immunostaining. Therefore, a systematic study of the relationship among three biomarkers for the differentiation of the mesenchymal cells is helpful for the cytological study of renal fibrosis.

Methods: In this study, we utilized serial kidney sections with multiple developmental timepoints (E12.5, E15.5, E17.5, P1, P3, P5, P7, P14, P21, P28, and P40) and localized PDGFR-β, α-SMA, and desmin combined with CD34 by immunostaining.

Results: 1. Druing the early development, PDGFR-β and α-SMA were expressed in reticular mesenchymal cells, which were perpendicular to scanty bundles of tubules and ureteric buds, while desmin was mainly expressed in cap-mesenchyme in early stage. 2. As more and more tubules extended into medulla, their expressions were decreased and confined to interstitial cells in the mature kidney, while peritubular vessels expressed CD34 instead. PDGFR-β was expressed at both fibroblast and pericyte, while α-SMA and desmin were respectively expressed at fibroblast and pericyte. 3. Through the kidney development, both PDGFR-β and α-SMA were expressed in the structure, closely associated with the artery and arteriole, with former in the outer layer (adventitia) while latter in smooth muscle cells of inner layer, next to CD34 positive endothelial cells. No co-localization was observed. 4. All of them were expressed in young glomeruli, while α-SMA vanished in the mature glomeruli.

Conclusions: Although the expressions of PDGFR-β and α-SMA are associated with renal vasculogenesis and angiogenesis, their expressions are related with different vascular structures, respectively participating in differentiation of endothelial and subendothelial smooth muscle cell, while desmin is related to the differentiation of renal progenitor cells. Among the three, PDGFR-β is the most reliable biological marker of grown renal interstitial cells, including pericytes.

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FR-PO759

Optimal Generation of Mesangial Cells and the Stromal Progenitor Cell Lineage from a Platelet-Derived Growth Factor Receptor Alpha Fraction of Fetus Cells

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Background: We previously transplanted a cell population comprising several heterogenic types of renal progenitor cells (RPCs) from mouse metanephros into the nephrogenic zone of other mouse metanephros and regenerated nephrons derived from the transplanted RPCs. However, mesangial cells of the regenerated glomeruli comprised cells derived from the host. We could not confirm the regeneration of mesangial cells by the transplanted cells. Therefore, we optimized the RPC cell composition via cell sorting and examined the possibility of regenerating the mesangial cells.

Methods: Metanephros was harvested from GFP mice, and an enzymatic treatment extracted the dissociated single cells (DSCs) from the metanephros. Stromal progenitor cell components were extracted via cell sorting by targeting the platelet-derived growth factor receptor alpha (PDGFRa) fraction from the DSCs. Three groups of cells, i.e., the PDGFRa-sorted cells, non-sorted cells, and fibroblasts as controls, were transplanted into the nephrogenic zone of B6 mice metanephros. Then, these groups were transplanted under the retroperitoneum of the para-aortic region of adult B6 mice and harvested after 2 weeks. Specimens were assessed via immunofluorescence staining. Furthermore, the regenerative cells were counted to the extent to which the transplanted cells reached.

Results: In the fibroblast group, the cells transplanted to the nephrogenic zone did not colonized in the metanephros. In the non-sorted group, although some cells colonized, there was negligible regeneration of the mesangial cells. However, in the PDGFRa-fraction sorted group, we confirmed regeneration of the mesangial cells from the exogenous cells in 92% of glomeruli (n=13). Furthermore, the proportion of the exogenous mesangial cells with a single glomerulus unit was 67.5%. We also confirmed regeneration of other stromal progenitor cell lineages, such as interstitial fibroblasts, vascular pericytes, and juxtaglomerular cells.

Conclusions: When we increased the ratio of the stromal progenitor cells via cell sorting targeting the PDGFRa fraction from DSCs, we succeeded in efficiently regenerating the mesangial cells and other stromal progenitor cell lineages, such as interstitial fibroblasts, pericytes, and juxtaglomerular cells, in the kidney of the mouse embryos.

FR-PO760

Endothelial-Specific Phosphatase VEPTP/PTPRB Is Essential for the Development of the Renal Mesangium

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Background: The angiopoietin-Tie2 signaling pathway plays an essential role in vascular development and homeostasis while its dysregulation is associated with a number of diseases including pathological neovascularization, glaucoma, diabetic nephropathy, and acute kidney injury. The endothelial-specific phosphatase VEPTP/PTPRB plays a major role in the negative regulation of Tie2 receptor phosphorylation. We genetically inactivated the *Ptprb* gene in mice in order to elucidate its significance in renal vascular development.

Methods: Global genetic inactivation of a conditional floxed allele of *Ptprb* was accomplished using a tetracycline-inducible Cre-based recombination system. Mouse kidney sections were processed for histology and immunostaining while glomerular ultrastructure was analyzed by transmission electron microscopy.

Results: Inactivation of *Ptprb* at E13.5 results in glomerular maldevelopment. *Ptprb* deficiency results in notable simplification of the glomerular tuft and glomerular aneurysms in neonatal (P0) kidneys due to the impaired establishment of the mesangium reminiscent of genetic loss of components of the PDGFB signaling system (*Pdgfb, Pdgfrb*, and *Nrp1*). Immunofluorescence for mesangial markers and ultrastructure analysis corroborate the absence of the renal mesangium in *Ptprb*-knockout mice. In contrast, postnatal (P0) deletion of *Ptprb* does not overtly affect mesangial cell recruitment but causes the development of renal capsule hemorrhages and sporadic thrombotic vascular anomalies in other organs of adult mutant animals which resemble hereditary venous malformations due to hyperactivating mutations of the Tie2 receptor in patients.

Conclusions: The renal mesangium is the *de facto* pericyte of the glomerular endothelium. Our findings indicate that *Ptprb* may play a pivotal and time-dependent role in pericyte recruitment and investment in different vascular beds. During gestation, *Ptprb* regulates the recruitment of mesangial cells into the glomerulus. Postnatally, *Ptprb* deficiency results in vascular anomalies reminiscent of venous malformations and poor pericyte investment caused by constitutive Tie2 activation.

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FR-PO761

Defining the Role of Vascular Endothelial Growth Factor 3 (VEGFR3) in the Fenestrated Microvasculature Beds of the Kidney

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Background: The vasculature of the mammalian kidney is heterogeneous due to the need to carry out highly specialized functions such as glomerular filtration, urinary concentration and electrolyte homeostasis. The vascular endothelial growth factor tyrosine kinase receptor 3 (VEGFR3) is best known for its essential role in lymphatic endothelial cell proliferation however it is also highly expressed in fenestrated microvascular beds in several tissues including the kidney. In contrast to VEGFR2, functions of VEGFR3 in kidney vasculature are poorly understood but have been implicated in a number of kidney pathologies including cystogenesis and renal fibrosis. We hypothesize that VEGFR3 is required for proper maturation of renal microvascular beds and that loss of VEGFR3 will accelerate progression of kidney disease.

Methods: We generated a new conditional transgenic mouse model to study *Vegfr3* function in the kidney vasculature (*Vegfr3*^{flox}). This model allows for endothelial-specific excision of the floxed *Vegfr3* allele using the vascular-specific Cre driver strain *Cdh5-Cre/ERT2*. We evaluated a *Vegfr3*-YFP reporter mouse to analyze expression of *Vegfr3* within the microvascular beds of the kidney. Mouse kidney sections were processed for histology and immunofluorescence.

Results: Analysis of *Vegfr3-YFP* reporter mice demonstrates that *Vegfr3* is expressed in multiple fenestrated microvascular beds of the kidney including the glomerulus, ascending vasa recta, and peritubular capillaries. Twenty percent of mice heterozygous for the intact neo-cassette-containing floxed *Vegfr3* allele (*Vegfr3*$^{+/neo}$) exhibit chylous ascites suggesting disruption of the neo-cassette containing VEGFR3 allele. These mice demonstrate reduced viability and exhibit several vascular pathologies including blood filled lymphatic capillaries and hemorrhage of intestinal Peyer's patches.

Conclusions: VEGFR3 is expressed in many specialized microvascular beds within the kidney and may play an important role in their development and maintenance. We have generated a novel conditional mouse model to comprehensively study the role of VEGFR3 in renal vasculature. Using this model to perform time dependent endothelial-specific knockout of *Vegfr3* through development will provide valuable insights into specialized functions of fenestrated microvascular beds in the kidney.

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FR-PO762

Modeling Vascular Diseases Using Organ-Specific Endothelial Cells

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Background: The establishment of vascular network initiates with the specification of endothelial cells and the formation of primitive vascular network. While primitive vascular network supplies nutrients to the developing embryo, postnatal vascular system mainly originates from aorta-gonad-mesonephros (AGM) that eventually gives rise to both endothelial and hematopoietic lineages. During development, homogeneous endothelial cells further differentiate to acquire organ-specific identities to accomplish diverse functions of different organs. Endothelial cells may also be derived from multipotent progenitor cells within certain mesodermal organs. Recent study has shown that renal progenitors could at least partially contribute to renal vasculature. We established a kidney organoid differentiation platform that can generate renal-specific endothelial cells from human pluripotent stem cells. This differentiation platform enables us to study vascular development and diseases in an organ-specific manner.

Methods: Kidney Organoid Differentiation Single Cell RNA Sequencing Disease Modelling

Results: We established a kidney organoid differentiation platform that can generate renal-specific endothelial cells from human pluripotent stem cells.

Conclusions: Recent study has shown that renal progenitors could at least partially contribute to renal vasculature. We established a kidney organoid differentiation platform that can generate renal-specific endothelial cells from human pluripotent stem cells. This differentiation platform enables us to study vascular development and diseases in an organ-specific manner.

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FR-PO763

Vascularized Kidney Organoids for Modeling PKD

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Background: Various models of 3D culture have been developed to model PKD cystogenesis. While recent studies demonstrated the utility of hPSC-derived kidney organoids for modeling ADPKD, even control organoids exhibited cyst formation when forskolin was administered. Moreover, those organoid models displayed cyst formation in both proximal and distal nephrons, which may not fully recapitulate cyst pathogenesis of PKD patients. We postulate that vascularized kidney organoids developed in vitro under flow may provide a better model for in vivo cystogenesis via activation of ciliary signals without the need for forskolin.

Methods: PKHD1-mutant hPSCs were generated by CRISPR/Cas9 genome editing. Hetero and homozygous mutants with frameshift mutations were selected with deep-seq. Kidney organoids were generated following our reported protocol and cultured in vitro under static or flow conditions. Forskolin was tested for cyst formation. cAMP activation was evaluated by ELISA. Control and cystic organoids were characterized by immunostaining and transcriptome analyses. To evaluate differential gene expression profiles, microarray (3D-Gene®) and Metacore™ were used.

Results: CRISPR-mutant kidney organoids (static culture) with homozygous mutations in PKHD1 exhibited cyst formation in both proximal and distal nephrons when treated with forskolin, while a heterozygous mutant did not form cysts. Forskolin significantly increased cell proliferation marked by Ki67 in both tubular cells and interstitial cells in homozygous mutant organoids. Further, microarray analysis revealed differential gene expression induced by forskolin and/or PKHD1 homozygous mutations, which was associated with >50 signal pathways. Some signal pathways have been implicated in PKD cystogenesis, yet others, apparently altered by forskolin, appeared to be non-specific to PKD cystogenesis. By contrast, CRISPR-mutant, vascularized kidney organoids cultured under flow exhibited cyst formation and Na, K-ATPase mislocalization solely in distal nephrons without addition of forskolin, which are consistent with clinical findings.

Conclusions: The fluidic chip model of PKD organoids demonstrated clinically relevant phenotypes of PKD patients, which would complement current PKD models to better understand PKD pathomechanisms for new therapeutic development.

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FR-PO764

Uremic Vasculopathy Modeling with Induced Pluripotent Stem Cells and Uremic Toxin Mixtures

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Background: Cardiovascular complications remain as major causes of morbidity and mortality in end-stage renal disease (ESRD) patients. Although uremic vasculopathy substantially contributes to the development of cardiovascular complications in ESRD, it is difficult to simulate uremic vasculopathy with current research methods like animal models or cell culture experiment. In this study, we aimed to develop a simplified uremic vasculopathy model using uremic toxin mixtures on endothelial cells differentiated from induced pluripotent stem cells (iPSCs-ECs).

Methods: Peripheral blood mononuclear cells from a normal control and an ESRD patient was reprogrammed to iPSCs using Sendai virus, then iPSC-ECs were differentiated from iPSCs. Uremic toxin mixtures comprised of diverse combination of urea, creatinine, uric acid, indoxyl sulfate, and advanced glycation end-product were tested in a cell culture model of iPSC-ECs. Reactive oxygen species (ROS), apoptosis, and tube formation or scratch migration assay were measured to evaluate dysfunction of iPSC-ECs. Media alone was used as a negative control and 15% serum from ESRD patients receiving hemodialysis was used as a positive control.

Results: Urea, uric acid, and indoxyl sulfate significantly suppressed the tube formation of iPSC-ECs, while creatinine alone did not affect ROS levels or the tube formation of iPSC-ECs. Uremic toxin mixtures comprised of high concentration of urea, creatinine, uric acid, and indoxyl sulfate increased ROS production and apoptosis, whereas decreased tube formation of iPSC-ECs similarly with ESRD patients' uremic serum. ESRD patient-specific iPSC-ECs showed impaired wound healing potential which was partially restored by losartan and TGF-β inhibitor.

Conclusions: We developed a simplified uremic vasculopathy model using uremic toxin mixtures comprised of urea, uric acid, and indoxyl sulfate and iPSC-ECs. This novel model may be used as a new research tool of uremic vasculopathy and drug screening system.

FR-PO765

Generation of Kidney Branching Ureteric Bud Organoid from Human Pluripotent Stem Cells

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Background: The repetitive reciprocal interactions between metanephric mesenchyme (MM) and ureteric bud (UB) lay the basis for kidney organogenesis. Nephron progenitor cell (NPC) within the MM generates the nephrons, while UB branches to generate the collecting duct network. Human pluripotent stem cell (hPSC)-derived NPCs and nephron organoids have been well established. However, currently available hPSC-derived UB still lack their definitive features – they had very limited branching ability and did not interact with NPCs. Here we present a novel method to generate a branching UB organoid from hPSCs. Our platform will advance the kidney regeneration field and it will also provide a novel platform for modeling diseases in the collecting duct.

Methods: We first developed a robust culture medium, named UB culture medium (UBCM), to support the long-term expansion of mouse UB as three-dimensional (3D) branching organoid. Meanwhile, we employed *SOX9*-GFP reporter hPSC line to monitor and optimize our UB differentiation protocol. After differentiation, the *SOX9*-GFP+ UB progenitor-like cells were purified via flow cytometry. Aggregated *SOX9*-GFP+ cells branched out in UBCM and can be passaged as 3D organoid. The identity of the UB organoids were confirmed by gene expression, ability to interact with NPCs and the potential to generate mature collecting duct.

Results: The expandable mouse UB organoid cultured in UBCM showed homogenous expression of broad UB markers (Lhx1, Gata3, Pax2, Pax8) and UB progenitor markers (Ret, Etv5, Sox9). By qPCR, our hPSC-derived UB showed the expression of various UB markers at similar levels to that in the primary UB obtained from human fetal kidney. Immunostaining also confirmed the homogeneous expression of RET, GATA3, SOX9, PAX2, CDH1 and KRT8 in the hPSC-derived UB organoids. More importantly, when the hPSC-derived UB were reconstructed with hPSC-derived NPCs, kidney organogenesis was restored, generating nephrons from the NPCs and collecting duct from the UB.

Conclusions: 1. Novel UBCM supports the long-term expansion of mouse UB 2. Novel directed differentiation protocol generates UB progenitor-like cells from hPSCs 3. Aggregated hPSC-derived UB branches in UBCM and can be passaged as 3D organoids 4. Restored kidney organogenesis in vitro when hPSC-derived NPC and UB are reconstructed

Funding: Private Foundation Support

FR-PO766

Fibrotic Kidney Organoids and Human CKD Samples Demonstrate Loss of Homologous Recombination as a Critical Mediator of Maladaptive Repair

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Background: Myofibroblasts are a hallmark of maladaptive repair that have been demonstrated in injured kidney organoids and kidney tissue *in vivo*. Tubular epithelial DNA damage potentiates myofibroblast generation. Mechanisms for DNA repair include genome-conserving homologous recombination (HR) and mutation-generating non-homologous end joining (NHEJ). Here we hypothesize that DNA damage repair between HR and NHEJ in tubular epithelial cells governs maladaptive repair, which could be examined using kidney organoids and human kidney tissue.

Methods: Kidney organoids were generated from hPSCs by our established protocol. Organoids were treated with repetitive cisplatin to induce tubular epithelial DNA damage, ascertained by γH2AX positivity. Stromal cells were monitored for the advent of the myofibroblast marker, αSMA. DNA damage repair was modulated to inhibit either HR or NHEJ in cisplatin treated organoids. FANCD2, a crucial HR element, was used as a surrogate for HR activity. HR and NHEJ activities were evaluated by qPCR for multiple genes of DNA repair. Findings in organoids were confirmed in patient biopsy samples of CKD and minimal change disease (MCD) with tubular injury.

Results: Cisplatin treatment induced DNA damage to tubular epithelial cells. HR activity increased in injured tubules, yet repetitive cisplatin treatment downregulated HR-related genes wheras NHEJ activity persisted. Suppression of HR activity by RAD51 inhibition hastened nephron loss and the evolution of myofibroblasts, while inhibition of the critical NHEJ enzyme, DNA ligase IV, delayed maladaptive responses. Human CKD patient samples with moderate to severe parenchymal scarring demonstrated little HR activity in injured tubules, whereas non-fibrotic MCD patient samples with tubular injury displayed activation of HR.

Conclusions: Human kidney organoids model maladaptive repair upon recurrent DNA damage in tubular epithelial cells. Mechanistic analysis of maladaptive repair in kidney organoids revealed loss of HR as a pathologic process. As opposed to non-fibrotic human kidney tissue, CKD patient samples demonstrated little HR activity in DNA damaged tubular epithelial cells. Human kidney organoids represent a novel model to decipher pathophysiologic processes in human kidney injury and repair.

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FR-PO767

Development of Novel Real-Time Biosensor Kidney Organoids to Study AKI

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Background: Kidney disease is on the rise worldwide. Persistent acute kidney injury and chronic kidney disease inevitably both lead to tubular atrophy, kidney fibrosis and eventually end-stage renal disease. The exact mechanisms are poorly understood and there are currently no treatments. Recent advances in generating human kidney organoids *in vitro*, have provided an invaluable tool to study kidney disease and injury, and a new tool for small molecule screening. We utilize a recently developed human kidney organoid protocol from induced pluripotent stem cells (iPSCs) to generate a new kidney biosensor to deepen our understanding of acute kidney injury and fibrotic tissue development in this model.

Methods: As a real-time readout of acute injury and to test the efficacy of new compounds we developed an early apoptosis reporter, CytochromeC-GFP iPSC line. Healthy cells in the organoids express green GFP in the mitochondria, upon injury the GFP signal loses mitochondrial localization and becomes cytoplasmic before activating the Caspase 3 apoptotic pathway. We establish optimal dosage with known nephrotoxins and a real-time response using CytochromeC-GFP organoids to validate our biosensor.

Results: Using the CyochromeC-GFP biosensor iPSC line we show that the healthy iPSCs and organoids exhibit mitochondrial CytochromeC-GFP expression as shown by co-labelling with MitoTracker Red CMXRos. Upon injury with nephrotoxins the GFP signal in the injured cells loses localization to the mitochondria and becomes cytoplasmic. Co-labelling with apoptotic Caspase 3/7 stains showed that it co-localizes with the injured cells (cytoplasmic CytochromeC-GFP expression) in the tubules.

Conclusions: Using the CyochromeC-GFP biosensor iPSC line we show that the health of organoids can be monitored in real-time, and can be used to study cytotoxic response. It provides a new way to examine kidney health in a human based model that can be utilized in examining nephrotoxic effects during drug and small molecule compound screening.

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FR-PO768

Optimizing Human Kidney Organoids for Modeling Nephrotoxicity, Kidney Injury, and Kidney Diseases and for Screening to Identify Therapeutic Options

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Background: To optimize their potential in modeling nephrotoxicity and kidney disease, pluripotent stem cell-derived kidney organoid protocols are being optimized for enhancing reproducibility, differentiation, scalability and reducing costs.

Methods: Organoids were generated by modifications of our laboratory's prior published techniques. Importantly, organoids were generated without use of undefined matrices. Cell types and structures were identified by immunostaining for LTL, PODXL, NPHS1, CDH1, GATA3, PDGFR-β and CD31. Protocols were modified to generate organoids to contain different compositions of specific cell types and structures, and they were tested for nephrotoxicity and kidney injury response by exposure to stimuli including cisplatin and LPS. The degree of kidney injury was assessed by various markers including KIM-1, αSMA, $cPLA_2$, and γH_2AX. The protocols enable high throughput analyses.

Results: Our novel method to generate human kidney organoids without undefined matrices yields all major cell types including proximal and distal tubules, podocytes, collecting duct, stromal cells, and endothelial cells in anatomically juxtaposed contexts. Avoidance of undefined matrices facilitates potential use of these organoids for more clinically relevant applications. Variation on the simplified and cost-effective protocols results in variation in composition of cell types and structures along with varying connectivity among cell types. Immunostaining for markers including KIM-1, LTL, αSMA, $cPLA_2$, and γH2AX showed that kidney organoids containing multiple distinct structures present together were more sensitive to nephrotoxicants compared to organoids generated to have predominant amount of proximal tubules lacking other cell types.

Conclusions: Protocols have been developed to generate human kidney organoids without undefined matrices in a more streamlined cost effective manner with programmed relative amounts of distinct kidney component structures. Proximal tubule susceptibility to toxicity is altered by adjustments in the organoid generation that change the surrounding contextual environment of other kidney structures.

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FR-PO769

Modeling Renal Manifestations of Tuberous Sclerosis Complex with iPSC-Derived Kidney Organoids

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Background: Renal manifestations are the second most common clinical finding in patients with TSC. Here we tested the ability of human induced pluripotent stem cell (iPSC) lines carrying heterozygous or homozygous mutations in the *TSC2* locus, to differentiate into human kidney cells and to model the cellular pathophysiology of TSC kidney lesions.

Methods: An iPSC cell line derived from a patient carrying a heterozygous microdeletion in the *TSC2* locus (*TSC2*$^{+/-}$), and a TALEN-engineered isogenic line carrying the microdeletion in both *TSC2* alleles (*TSC2*$^{-/-}$), were incubated with CHIR99021 (CHIR), Activin and FGF9, presented in a sequential fashion. The same concentration and stimulation duration for each growth factor were used for both iPSC lines.

Results: After modifications to the original chemically defined differentiation protocol developed by Morizane *et al.*, both iPSC lines successfully generated SIX2$^+$, PAX2$^+$ nephron progenitor cells with high efficiency by day 9 of differentiation. By day 14, self-organized renal vesicles had formed in the cultures of both cell lines, albeit visible cyst-like structures were observable in *TSC2*$^{-/-}$ vesicles but not in *TSC2*$^{+/-}$ vesicles. In low attachment 3D culture conditions, *TSC2*$^{-/-}$ organoids but not *TSC2*$^{+/-}$ organoids, presented expanding spheroidal cysts. Histological analysis of *TSC2*$^{-/-}$ and *TSC2*$^{+/-}$ organoids on day 21 of differentiation showed the presence of major kidney cell types including glomerular PDXL1-expressing podocytes, ECadherin-expressing distal tubules, and proximal tubules with brush borders. Cyst-like, dilated proximal and distal tubules with increased phosphorylation of p70-S6-kinase were observed in *TSC2*$^{-/-}$ organoids but not in heterozygous ones.

Conclusions: We have established a protocol for directed differentiation of TSC iPSCs into 3D organoids containing multi-segmented nephron structures that recapitulate TSC-specific cystic phenotypes. This novel bioengineering tool will provide valuable insight into the cellular and molecular mechanisms of renal abnormalities and set the basis for patient-specific phenotypic drug screens

FR-PO770

Kidney Organoid Model of Selective Podocyte Injury

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Background: Podocyte injury triggers progressive loss of kidney function. Determining the mechanisms involved in the progression of podocyte damage is critical to developing renoprotective therapies. We previously generated a transgenic mouse line, NEP25, which expresses human (h) CD25 on podocytes. Selective podocyte injury can be induced by the hCD25-targeted immunotoxin, LMB2. In addition, we analyzed podocyte-specific gene expression profiles utilizing RiboTag mice, which selectively express hemagglutinin (HA)-tagged ribosomal protein in podocytes. In the present study, to efficiently investigate the function of altered genes during podocyte injury, we aimed to generate NEP25/RiboTag kidney organoids and establish an *in vitro* model of podocyte injury.

Methods: Nephron progenitor cells (NPCs) were established by culture-dependent purification (CDP) method from 12.5 dpc NEP25/RiboTag mouse kidneys (*Cell Stem Cell*. 2016, 19, 516-29). Kidney organoids were generated by transient stimulation with FGF2 and CHIR99021 of NPC aggregates and subsequent 6–8 day culture. Podocyte-specific polysomes were obtained via immunoprecipitation using an anti-HA antibody.

Results: We confirmed that the organoids show glomerulus-like and tubule-like structures. Immunostaining revealed that the former expressed nephrin, WT1, podcalyxin, and synaptopodin and the latter expressed LTL and megalin. Nephrin-positive podocytes also expressed hCD25 and HA. Q-PCR confirmed that *Nphs1* (33.3), *Nphs2* (21.2), *Wt1* (24.9), and *Dach*1 (6.2) were concentrated in HA-immunoprecipitated RNA by the indicated fold. When organoids were incubated with LMB2 (20 nM) for 4 days, podocalyxin and WT1 staining disappeared. *Nphs1* and *Nphs2* mRNAs became undetectable, *Wt1* (0.05 fold) and *Dach1* (0.37) decreased, and *Cxcl1* (4.2) and *Epha8* (55.6) increased, thus reproducing *in vivo* injured podocytes.

Conclusions: We established kidney organoids in which podocytes can be selectively injured and podocyte mRNA can be selectively obtained. This organoid system will be a powerful tool for investigating mechanisms underlying podocyte injury.

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FR-PO771

A Drug-Specific Nephrotoxicity Prediction System Using Kidney Organoids

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Background: Drug-induced nephrotoxicity is increasingly recognized as a serious clinical problem, leading to acute kidney injury (AKI) and chronic kidney disease. Lack of reliable models with physiological function of human kidneys results in the difficulty to predict nephrotoxicity of new drugs in preclinical trials. Here, we demonstrate kidney organoids containing multi-segmented nephron epithelial cells generated from human pluripotent stem cells (hPSCs) as a new technology for pre-clinical nephrotoxicity assessment.

Methods: We generated kidney organoids from hPSCs by a directed differentiation protocol and validated the maturation of organoids using immunostaining and transcriptome analyses. Organoids were treated with various nephrotoxicants which cause injury in a segment-specific manner via specific drug transporters. Injury responses were analyzed by immunostaining, qPCR, and biomarker assays. We also generated reporter organoids to evaluate the toxicity with a real-time biosensor of ATP/ADP ratio in 384-well culture plates.

Results: We confirmed increased expression of drug transporters including OAT1, OAT3, OCT2 and PMAT with matured gene expression profiles in kidney organoids during 5 to 7 weeks of differentiation. Organoids simulated various drug-induced injury such as biomarker upregulation, DNA damages, and morphological changes specifically in the tubules or in the glomeruli by low concentration of nephrotoxicants mediated by these transporters (OATs: tenofovir and aristolochic acid [AA], OCT: cisplatin, PMAT: puromycin aminonucleoside). The injuries induced by tenofovir and AA, or cisplatin were ameliorated by OATs inhibitor probenecid or OCT2 inhibitor cimetidine, respectively. On the other hand, high concentration of these nephrotoxicants resulted in widespread injury to all nephron compartments and interstitial cells. In addition, nephrotoxicants significantly reduced the ATP/ADP ratio within 24 hours of treatment.

Conclusions: Kidney organoids faithfully recapitulate drug-induced AKI by reflecting the toxicity characteristics of the drugs, allowing to distinguish between drug-specific and generalized toxicity responses. The reporter organoids may realize high-throughput and real-time nephrotoxicity screening, providing a new platform to evaluate nephrotoxicity as preclinical trials.

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FR-PO772

Modeling a Recurring Wilms Tumor-Associated Mutation in Kidney Organoids

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Background: Wilms tumor (WT) is the most common pediatric kidney cancer and blastemal-predominant tumors represent a more lethal, chemotherapy-resistant form of WT. This tumor subtype expresses markers found only in the nephrogenic niche of the fetal kidney, suggesting it arises from a malignant transformation of these cells. Sequencing of blastemal-predominant tumors has identified a recurring single amino acid mutation, Q177R, within the conserved DNA binding domains of the closely related transcription factors SIX1/SIX2. These factors are critical for the maintenance of nephron progenitors during mammalian kidney development. Therefore, we hypothesize that this recurring mutation disrupts the regulatory networks controlled by SIX1/SIX2 resulting in the malignant transformation of nephron progenitors. Efforts to model WT in mice have proven challenging and differences in gene expression dynamics between mouse and human nephrogenesis, specifically the temporal expression of SIX1, necessitates a novel system in which to investigate the tumorigenic potential of the Q177R mutation.

Methods: IPSC-derived kidney organoids recapitulate key stages of human kidney development *in vitro*, resulting in the formation of complex nephron-like structures. Building upon established protocols, we have developed a modified, minimal 3D protocol to reproducibly generate kidney organoids for use as a model system. To investigate the transformative potential of the SIX1-Q177R mutation within the context of our kidney organoid system, we generated an isogenic iPSC line expressing a FLAG-tagged, mutant SIX1-Q177R protein from the endogenous SIX1 locus.

Results: ChIP-qPCR revealed proper targeting of SIX1 to its canonical DNA targets by day 5 of differentiation with significantly increased binding by day 8, recapitulating the *in vivo* activities of SIX1 during human nephrogenesis. Analysis of gene expression changes over the course of differentiation also revealed proper temporal expression patterns of many canonical nephron progenitor markers in our kidney organoids.

Conclusions: By combining modern genome editing techniques with our defined kidney organoid differentiation system, we have enabled the in-depth characterization of the altered regulatory landscape brought about by the SIX1-Q177R mutation throughout the earliest stages of human kidney development in a relevant *in vitro* model system.

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FR-PO773

Comprehensive Gene Expression Analysis Using Renal Coloboma Syndrome Patient-Derived iPSCs

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Background: Renal coloboma syndrome (RCS) is characterized by kidney hypoplasia or dysplasia and abnormality of the optic nerve. PAX2 mutation is one of the major genetic abnormalities of RCS. PAX2 is an essential transcription factor for kidney development. In mouse, Pax2 homozygous deficient mouse shows kidney agenesis and neonatal lethal. It is reported that Pax2 involved in ureteric bud branching via the regulation of Gdnf expression. However, the role of PAX2 gene during human kidney development is not clear. In this study, PAX2 regulated genes during human kidney development were evaluated using RCS patient derived induced pluripotent stem cells(iPSC)with PAX2 gene mutation.

Methods: Three RCS patient derived iPSCs with PAX2 gene mutation were established. Control iPSC and RCS patient derived iPSC were differentiated into kidney lineage cells with reported methods (Taguchi, et al. Cell Stem Cells 2014). The differentiated kidney organoid from iPSC were evaluated by immunocytochemistry and qPCR. Furthermore, to detect PAX2 regulated genes, comprehensive gene expression analysis was performed.

Results: Kidney lineage cells were inducible from both control and RCS patient derived iPSC. The expression patens of kidney lineage markers (such as WT1, SIX2, AQP1, PODXL) were almost similar among three RCS patient derived iPSC with PAX2 gene mutation and control iPSC. PAX2 gene expression in control iPSC was peaked on day 14 in our protocols. In immunocytochemical analysis and qPCR, PAX2 was highly expressed in INTEGRINα8+/PDGFRα- cells, which was known as the surface marker as nephron progenitor cells. These cells were collected by flow cytometry. By comprehensive gene expression analysis using control and RCS patient derived INTEGRINα8+/PDGFRα- cells, 189 upregulated genes were detected in control samples. Some upregulated genes were confirmed by qPCR in control iPSC derived INTEGRINα8+/PDGFRα- cells. The gene expression was also confirmed in mouse embryonic kidney. Additionally, *in silico* study using FANTOM database also indicate that some of our candidate genes were upregulated during the kidney development.

Conclusions: Comprehensive analysis using RCS patient derived iPSC with PAX2 gene mutationis is useful for identification of PAX2 regulated genes during human kidney development.

FR-PO774

Percutaneous Intrarenal Transplantation of Differentiated Induced Pluripotent Stem Cells into Newborn Mice

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Background: The reprogramming of adult cells to generate iPSCs may provide an unprecedented opportunity to elucidate disease mechanisms *in vitro*; for disease-modifying bioassays, and to advance cell-replacement therapy. The *in vivo* engraftment and survival of patient-derived iPSCs following allogenic transplantation into host kidneys remains a challenge. Here we investigate the survival and engraftment of human dermal derived iPSCs using a newborn mouse model, which represents a receptive immuno-privileged host environment.

Methods: iPSCs were generated from skin biopsies of patients using Sendai virus reprogramming. Differentiation of iPSCs to podocytes (iPSC-POD) was performed in *Nphs1* (Nephrin)-green fluorescent protein (GFP) iPSCs by the addition of activin A, bone morphogenetic protein 7 (BMP7) and retinoic acid over 15 days of culture. To assess *in vivo* integration, undifferentiated iPSCs and iPSC-POD differentiated for 10 or 15 days were labeled with either carboxyfluorescein succinimidyl ester (CFSE) or long term cell tracking Qtracker® 705 probe. Thereafter, 1 x 10^5 of differentiated iPSC-POD were resuspended and injected in 10 ul of phosphate buffered saline solution directly into the kidneys of mouse pups at postnatal day one (P1). A timecourse analysis of cell integration was assessed in differentiated iPSC-POD, compared to undifferentiated cells, using confocal fluorescence microscopy and the co-expression of glomerular and podocyte-specific markers.

Results: D10 differentiated iPSC-PODs, that were positive for podocyte markers including podocin, were detected following direct kidney injection in newborn mice after P3. Undifferentiated iPSC-PODs were not detected at the same timepoint. The transplanted cells were viable and located in the developing kidney cortex including the tubulointerstitium and localised adjacent to developing glomeruli in the outer nephrogenic zone where they were found to co-localise with glomerular-specific markers including podocin, synaptopodin and Wilms tumour 1 (WT1).

Conclusions: This study provides proof-of-principle that transplanted differentiated iPSC–POD can survive and integrate into recipient newborn mouse kidneys, and represents an ideal *in vivo* environment due to the immature and immunoprivileged nature of the developing postnatal kidneys.

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FR-PO775

Low Nephron Number Resulting from SIRT3 Deficiency Increases Susceptibility to Renal Dysfunction Later in Life

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Background: Low nephron endowment is a risk factor for chronic kidney diseases (CKD) in adulthood but no causal correlation has been formally proved. We have demonstrated that mice lacking the mitochondrial protein Sirtuin 3 (SIRT3) are more susceptible to acute kidney injury than wild type (WT) mice. Here, we explored whether *Sirt3*$^{-/-}$ mice can be used as a low nephron number model and are more susceptible to CKD.

Methods: Metanephroi were isolated from WT and *Sirt3*$^{-/-}$ mice to study nephrogenesis. The susceptibility of *Sirt3*$^{-/-}$ mice to CKD was studied in adriamycin (ADR)- or bovine serum albumin (BSA)- induced progressive nephropathies.

Results: We demonstrated that, at the embryonic day 12.5, *Sirt3*$^{-/-}$ mice had less ureteric bud branching and fewer metanephric SIX2^{+} progenitor cells. Impaired nephrogenesis in *Sirt3*$^{-/-}$ mice resulted in a nephron deficit compared to WT mice (40% reduction at post-natal day 7, P<0.001), due to altered mitochondrial dynamics, biogenesis, mitophagy and energetic metabolism. Notably, low nephron endowment at birth is not enough to cause renal disease in adulthood, but enhances the susceptibility of *Sirt3*$^{-/-}$ mice to renal damage. Specifically, when *Sirt3*$^{-/-}$ mice were exposed to ADR or BSA overload, they experienced more severe proteinuria, podocyte loss (% reduction in WT-1^{+} cell density: *Sirt3*$^{-/-}$, 68% vs WT, 30%, P<0.01) and vascular rarefaction than WT mice (% reduction in MECA-32^{+} cell density: *Sirt3*$^{-/-}$, 57% and WT, 43%, P<0.05). We also proved that nephron deficit can be corrected through prenatal SIRT3 boosting. Indeed, in a model of low nephron number and reduced renal SIRT3 levels – WT mice born to mothers fed a low protein diet – nephron number was restored through NAD^{+} precursor nicotinamide riboside (NR) treatment.

Conclusions: Our results provide evidence that low nephron endowment is a critical determinant of susceptibility to CKD when the kidney is challenged by additional hits, and support the use of SIRT3 boosting during nephrogenesis as a therapeutic option for increasing nephron number.

Funding: Private Foundation Support

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Loss of Hypoxia-Regulated MicroRNA-210 Results in Decreased Nephron Number

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Background: Low nephron number increases an individual's risk for developing hypertension and chronic kidney disease, which affect approximately 30% and 15% of American adults, respectively. Intrauterine growth restriction and fetal hypoxia are significant causes of low nephron number; however, the underlying molecular mechanisms that drive this are unknown. Nephron number, in turn, is determined prior to birth in humans. *microRNA-210* (*miR-210*) is the most consistently induced microRNA in hypoxia and regulates various processes including metabolism, cell cycle progression, and apoptosis. We hypothesize that loss of *miR-210* results in abnormal kidney development.

Methods: To test this hypothesis, we obtained a global *miR-210* knockout (KO) mouse. We used the "gold standard" physical dissector/fractionator combination method to estimate nephron number at postnatal day 30 (P30). We collected wildtype (WT) and KO littermates right before the burst in nephrogenesis at P0 and right before the end of nephrogenesis at P2. To measure changes in gene expression in nephron progenitors and their derivatives, we performed qPCR, immunofluorescent staining, and Western blot assays.

Results: We found an approximately 35% reduction in nephron number in *miR-210* KO male kidneys and a 28% reduction in both WT and KO female kidneys, compared to WT males. Analysis of nephron progenitor proliferation, apoptosis and differentiation markers showed no discernable difference in kidney development at P0. However, we observed decreased expression of the differentiation marker Jag1 by Western blot at P2, as well as fewer total Lef1-, Jag1, and Nicd1-positive differentiating nephron structures. We observed no difference in nephron progenitor proliferation nor apoptosis at P2. However, there was an approximately 35% increase in the total number of cleaved-Casp3-positive cells and its immunofluorescent staining suggests that there is an increase in apoptosis in differentiating nephron structures. Furthermore, we found increased mRNA expression of several pro-apoptotic *miR-210* target genes (*Casp8AP2/FLASH*, *Ptpn2*, and *Bnip3*).

Conclusions: *miR-210* KO kidneys have a nephron deficit, which is associated with decreased differentiating nephron structures and increased apoptosis within those structures.

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FR-PO777

Caloric Restriction During Pregnancy Reduces Nephron Endowment and Impairs Adult Kidney Function by Inactivating mTOR and the Methionine Salvage Pathway

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Background: Maternal malnutrition during pregnancy correlates with lower nephron numbers and higher risk of chronic kidney disease (CKD) in adulthood, but the underlying molecular mechanisms are still unknown. The nephron progenitor pool exhausts abruptly in third postpartum day in mice with no nephrogenesis at later stages. We used a mouse model to study the effects of maternal caloric restriction on kidney development and nephron progenitor cells (NPCs).

Methods: Pregnant CD1 mice were monitored in metabolic cages and their daily caloric intake was reduced by 30% compared to the average consumption of the control group at the same gestational age. The effect on kidney morphology and function was measured by immunostaining, kidney biomarkers analysis and nephron count. Six2^{+} GFP^{+} NPCs were extracted from Six2 Cre$^{tg/+}$ E18.5 embryos of calorically restricted pregnant dams or controls and isolated by FACS. mRNA expression and metabolomic activity in sorted NPCs were evaluated by bulk RNAseq and mass spectrometry, respectively. Key findings were validated using western blotting.

Results: Animals exposed to caloric restriction in utero had 50% fewer nephrons after birth and throughout adulthood as well as lower kidney function, as demonstrated by higher serum urea levels. Nephrogenesis was shorter by at least 24 hours. Calorically restricted E18.5 Six2^{+} NPCs had decreased expression of mTOR pathway genes, and lower overall mTOR activity, reflected in lower levels of phosphorylated ribosomal protein S6. Mass spectrometry of metabolites from isolated NPCs identified a strong reduction in the methionine salvage pathway.

Conclusions: Reduced mTOR signalling and methionine salvage activity in NPCs from fetuses carried by malnourished mothers led to a premature end of nephrogenesis, reduced nephron numbers, and the associated increased risk for CKD in adulthood.

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FR-PO778

Ontogeny and Phylogeny: Our Evolutionary History and Bioenergetics Explain High Variation in Nephron Number (NN) at Birth

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Background: Low NN at birth is recognized as a major lifetime risk factor for chronic kidney disease (CKD), but its origin is poorly understood. Recent studies based on the Barker hypothesis suggest that epigenetic downregulation of nephrogenesis modulated by maternal-fetal stressors (e.g. hypoxia, undernutrition) contributes to CKD in adulthood. Application of evolutionary biology to medicine has led to new approaches in cancer and infectious disease research, and shows promise in nephrology (Chevalier, Kidney Int Rep 2:302, 2017; J Am Soc Nephrol 29:705, 2018).

Methods: Data abstraction: Medline searches including the terms "kidney, evolution, physiology, genetics, bioenergetics, and development" 1970 to the present.

Results: The rapid evolution of hominids was a product of increased nutrient quality and availability ~2 million years ago, resulting from transition of the east African environment from forest to savannah. Natural selection favored doubling brain size from *Homo habilis* to *Homo sapiens* over a period of 1 million years. Our brain consumes 90% of basal metabolic rate (BMR) at birth, 50% at 1 year of age, and 20% in adulthood. Maternal energy consumption in pregnancy and during breastfeeding increases BMR by 20%, which must be balanced by high kidney oxygen consumption tied to BMR. Maternal protein restriction during pregnancy in mice resulted in 75% reduction in NN; offspring of mice lacking DNA methyltransferase 1 (Dmt1) in nephron progenitor cells developed 50% reduction in NN. Nutrients and oxygen signal energy metabolism to mitochondria through the hypoxia-inducible factor (HIF) pathway to regulate nephron morphogenesis. This epigenetic response is driven by metabolic reprogramming of nephron progenitor cells from glycolysis (maintenance of self-renewal) to differentiation (cessation of nephrogenesis) mediated by the Wnt pathway.

Conclusions: Energy, the currency of evolution, is constrained by the environment. Selection pressure favors allocation of available energy from kidney to brain growth in early development. Through epigenetic regulation of bioenergetics, reduction of nutrients available during pregnancy proportionately restricts nephrogenesis. Since only 18% of children with congenital kidney anomalies develop end-stage CKD before 15 years of age, this evolutionary strategy favors reproductive fitness in the majority of cases.

FR-PO779

Cell Turnover Dynamics in the Human Kidney Using Radiocarbon Dating

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Background: Kidney cell turnover is fundamental to maintain organ homeostasis and to replace lost cells in response to injury. This study aims to define regeneration in the human kidney and explore turnover kinetics in health and disease. Proximal tubular epithelial cells are known to turnover, however questions remain about the dynamics and source of replacement cells. Podocytes were traditionally considered irreplaceable, however reports of putative progenitors have sparked interest in podocyte regeneration. The novel method of radiocarbon dating DNA to determine human cell age (Spalding et al. 2005) has been used to answer fundamental questions about human regeneration in the brain, heart and adipose tissue. This study adapts the method to address these important questions in the kidney.

Methods: Human kidney nuclei sorting was developed for this study. The method is effective for whole kidney tissue and isolated glomerular fraction analyses, from either fresh or frozen tissue from both nephrectomy and postmortem sources. Podocyte, endothelial and proximal tubule nuclei were isolated, antibody-labeled and sorted by flow cytometry. This method yields over 10 million cell-type specific nuclei per sample with over 95% sort purity required for radiocarbon dating. DNA was extracted using carbon-clean methods and sent for carbon isotope analysis using accelerator mass spectrometry.

Results: Preliminary results from a cohort of 10 kidneys, collected from nephrectomy, indicates human proximal tubules have an average age of 13.3 years (±2.6), turning over at a rate of 7.7% per year. This was not impacted by patient age. Endothelial and podocyte dating is ongoing. DNA content analysis, via flow cytometric analysis of DAPI-labeled nuclei, indicates limited endoreduplication.

Conclusions: Radiocarbon dating has the potential to definitively answer questions regarding kidney regeneration in humans. Nuclei-based sorting provides an unbiased method to efficiently sort large numbers of cell-specific nuclei for a range of downstream analyses. Preliminary results of proximal tubules and ongoing successful sorts of podocytes and endothelial cells provides proof-of-principle that human kidney cell age can be determined. From physiological turnover, this study forms the basis for ongoing examination of kidney regeneration in pathology.

Funding: Commercial Support - AstraZeneca, Government Support - Non-U.S.

FR-PO780

Using Next-Generation Imaging Technologies to Construct 3-D Multi-modal Molecular Atlases of the Human Kidney

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Background: Little is known about the integration, interactions, and molecular cross-talk between the different cell types and cellular compartments in normal kidneys. As part of the Human BioMolecular Atlas Program (HuBMAP), we are developing an ultra-high content imaging mass spectrometry (IMS)-based 3-D imaging pipeline to characterize the molecular signatures of different cell types at high resolution in normal, intact human kidneys.

Methods: Fresh discarded human kidneys obtained from surgical nephrectomy specimens were frozen on dry ice/isopentane slurry. Sequential sections were obtained through tissue blocks, scanned for autofluorescence (AF), and alternate sections prepared for IMS and multiplexed immunofluorescence (MxIF). IMS data was collected using a prototype MALDI timsTOF Pro Mass Spectrometer. Two cycles of MxIF were performed using a panel of validated, fluorophore-conjugated antibodies, and image fusion used to integrate information from IMS-generated molecular maps with autofluorescence and MxIF images. Sequential 2-D IMS/AF/MxIF images were then registered and mapped to the 3-D coordinate system using data from sequential sections with in house tools.

Results: A preliminary lipidomics study of human kidney tissue has been performed using our custom 3-D multimodal molecular imaging platform. The data set consists of 32 serial sections collected from the cortex of the kidney. Each 2-D tissue section is ~4x8 mm and they were imaged using IMS at 20 μm spatial resolution, resulting in ~150,000 pixels per section. AF/IMS and MxIF image registration pipelines enabled the construction of high-spatial resolution ion volumes. The entire 3-D volume was ~4x8x0.32 mm and contains ~4.8 million voxels (20x20x10 μm). The fully constructed 3-D molecular atlas enabled the visualization of various lipids to specific substructures in the kidney, including the proximal and distal tubules and glomeruli. For example, C24 Sulfatide and PI-Cer(42:0) (putative identifications) were found to track with distal tubules throughout the 3-D volume.

Conclusions: We have developed a novel pipeline for 3-D biomolecular multimodal tissue imaging that will enable the construction of high-resolution molecular atlases of the human kidney.

Funding: Other NIH Support - HuBMAP consortium

FR-PO781

Phenotype Expansion of Heterozygous FOXC1 Mutations Towards Involvement of CAKUT

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Background: Heterozygous *FOXC1* mutations have been identified as the cause of Axenfeld-Rieger syndrome type 3 and anterior segment dysgenesis 3. Patients present with variable eye malformations. Syndromic cases may present with abnormalities in brain, heart, blood vessels, and hearing loss. Congenital anomalies of the kidney and urinary tract (CAKUT) have not been associated with mutations in *FOXC1*.

Methods: In order to identify novel monogenic causes of CAKUT we performed whole exome sequencing (WES) in 514 families with CAKUT.

Results: By WES analyses, we discovered 7 *FOXC1* heterozygous mutations in 8 CAKUT families. Five of the families have isolated CAKUT, while the other 3 families have syndromic CAKUT with anomalies in eyes, blood vessels, brain, bones, or facial dysmophologies. CAKUT phenotypes include renal agenesis, renal dysplasia, multicystic dysplastic kidney, ureteropelvic junction obstruction, hydronephrosis, vesicoureteral reflux, and posterior urethral valve. None of the 7 mutations were reported in patients with Axenfeld-Rieger syndrome or anterior segment dysgenesis before. Two of the mutations are absent, and the others are present in <5 individuals as heterozygote of 125,000 healthy controls in the gnomAD database. We thereby discovered CAKUT as a new phenotype of heterozygous *FOXC1* mutation. Interestingly, mouse models for *FOXC1* (Green, 1970; Kume et al., 1998; Kume et al., 2000; Motojima et al., 2016) show severe CAKUT with extra-renal malformations. The mode of inheritance is autosomal dominant with incomplete penetrance and variable expressivity. To evaluate whether the presence of CAKUT in heterozygous *FOXC1* mutation is due to allelism, we conducted genotype-phenotype correlations. There are 40 truncating and 34 missense mutations known in Axenfeld-Rieger syndrome or anterior segment dysgenesis. All 34 missense mutations are in the forkhead domain. In contrast, in the 8 CAKUT families, we did not find any truncating mutations and only 1 out of 4 missense mutation is in the forkhead domain.

Conclusions: We propose a phenotype expansion of *FOXC1* to include CAKUT, potentially explained by allelism.

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FR-PO782

PLXNB2 Mutations Are a Likely Cause of Congenital Anomalies of the Kidneys and Urinary Tract in Humans and Mice

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) constitute the most common cause of end-stage renal disease in children, but the genetic causes of CAKUT remains largely elusive. Gene mutant mouse models are important research tools for human CAKUT, to date, 185 genes that if mutated causes murine CAKUT phenotypes is in the MGI database (http://www.informatics.jax.org). Most of them could also be a potential cause of CAKUT in humans.

Methods: To identify novel monogenic causes of CAKUT in humans, we performed whole exome sequencing (WES) in a worldwide cohort of 703 individuals with CAKUT. Based on the mode of inheritance in mice and pLI scores (Loss of function intolerant) in the ExAC database for the 185 murine CAKUT genes, we screened for variants in these genes in our CAKUT WES data to discover novel human candidate CAKUT genes. Functional studies were carried out to verify the pathogenesis of variants in these candidate genes.

Results: We identified 6 different heterozygous mutations in *PLXNB2* in 7 individuals from 6 unrelated families, one heterozygous mutation occurred *de novo*. Affected individuals exhibited a broad spectrum of CAKUT phenotypes, while, 77% of individuals exhibited syndromic features. With functional studies, we found mutations in *PLXNB2* destabilized the PLXNB2 protein, damaged the synthetic PLXNB2 protein transport, weakened the binding ability of the PLXNB2 protein to its receptor, Semaphorin 4, and influenced the cells migration and the activity of CDC42 and Ras in cells.

Conclusions: Our results support that mutations in *PLXNB2* are a novel cause of human syndromic CAKUT through defective cell migration via influencing the activity of CDC42-Ras or through defective Semaphorin-Plexin signaling.

FR-PO783

Mutations in UMOD Are Associated with FSGS and Can Be Mistaken for a Glomerular Disease

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Background: Focal segmental glomerulosclerosis (FSGS) is a common histopathologically defined kidney lesion that can be observed with various underlying causes, including highly penetrant gene mutations. We recently identified pathogenic variants of *UMOD*, a gene encoding the tubular protein uromodulin, in seven families with suspected or biopsy proven FSGS.

Methods: We reviewed the clinical and pathology reports of seven families identified to have pathogenic variants of UMOD. Sanger sequencing of affected and unaffected to verify co-segregation with disease.

Results: Review of clinical records and pathology reports confirmed biopsy-proven cases of FSGS in 33% of patients with *UMOD* variants. The *UMOD* variants seen in these families were mutations previously reported in association with uromodulin associated kidney disease (UAKD). Consistent with the features for UAKD, most patients in our study presented with autosomal dominant inheritance, subnephrotic range proteinuria, minimal hematuria, and renal impairment. These patients with *UMOD* associated kidney disease did not have the classic clinical characteristics of gout, hyperuricemia, or presence of renal cysts on renal ultrasound. Kidney biopsies showed histologic features of glomerular injury consistent with secondary FSGS including focal sclerosis and podocyte foot process effacement.

Conclusions: Our study demonstrates that using our standard clinical testing using a kidney biopsy, patients with UAKD can be mistaken for FSGS since there are no specific histopathological features for UAKD. Genetic testing can clarify the diagnosis of UAKD with secondary FSGS. Genetic testing should be considered for families diagnosed as familial FSGS or hereditary glomerulonephritis of unclear etiology.

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FR-PO784

Whole-Exome Sequencing Identifies Mutations in ARHGEF6 as a Potential Novel Monogenic Cause of Congenital Anomalies of the Kidney and Urinary Tract

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Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease in the first 3 decades of life. Although over 40 monogenic genes have been implicated in human CAKUT so far, many causes remain elusive.

Methods: In order to identify novel monogenic causes of CAKUT we performed whole exome sequencing (WES) in 514 families with CAKUT.

Results: By WES, we discovered a missense mutation (p.I444N) in the X-linked gene *ARHGEF6* in 3 affected male subjects of family A5124 with CAKUT. Evaluation of our WES data of 514 unsolved CAKUT families revealed 3 further hemizygous *ARHGEF6* mutations in 3 families (family GM1: p.R191*; B1185: p.L387Afs*58; GM2: c.2135+4A>G, splice). Affected individuals exhibited a spectrum of CAKUT phenotypes that correlated in severity with the underlying mutation: renal agenesis, bladder exstrophy, VUR, PUV with hydronephrosis, renal hypoplasia and hypospadias. The 2 patients with loss-of-function mutations also had extrarenal features (cardiomyopathy; extra vertebra). No pathogenic variants in *ARHGEF6* were present in a control cohort of 100 NS and 258 NPHP cases. All variants, except p.I444N, were absent from gnomAD. *ARHGEF6* encodes a guanine nucleotide exchange factor for the small GTPases CDC42 and RAC1, and has been implicated in various biological functions including cell migration. Both small GTPases play a role in kidney development, such as the requirement of Cdc42 for normal tubulogenesis in ureteric bud and metanephric mesenchyme development (*J Cell Sci*; 128:4293, 2015). Overexpression in HEK293 cells of *ARHGEF6* wildtype cDNA, but not of patient mutants, activated CDC42 and RAC1, while *ARHGEF6* knockout cells reduced CDC42 activity.

Conclusions: We identified likely disease-causing mutations in *ARHGEF6* in 4 unrelated families with CAKUT. Our findings suggest that dysregulation of CDC42 or RAC1 via *ARHGEF6* dysfunction may cause CAKUT.

Funding: NIDDK Support

FR-PO785

Recessive Mutations in TLN1, PAX, or ARHGEF17 Are Potential Novel Causes of Nephrotic Syndrome in Humans

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Background: Steroid resistant nephrotic syndrome (SRNS) almost invariably progresses to end-stage kidney disease. Although more than 60 single-gene causes of SRNS are known, a large proportion remains unexplained. Recently, we identified mutations in *MAGI2*, *TNS2*, *DLC1* and *CDK20* genes as novel causes of NS (Ashraf *Nat Commun* 17:1960, 2018). Study of these proteins provided new insights into the pathogenesis of NS, linking into small GTPase 'RhoA' function.

Methods: We performed whole exome sequencing (WES) to identify novel monogenic causes of NS in >1,000 individuals with NS.

Results: We identified 4 different recessive mutations in 3 different genes *TLN1* (Talin1), *PAX* (Paxillin) and *ARHGEF17* (Tem4) in 4 unrelated families with NS. Specifically, in two individuals with NS, we identified a highly conserved homozygous *TLN1* mutation (family B3328, I1989del), or compound heterozygous mutations (family A3788, M79V and S1164W) in *TLN1*, which is known to interact with integrins and actin, and plays a role in activating integrins *via* its F3 N-terminal domain at focal adhesions. Knockout mice of *Tln1* have been previously shown to develop severe proteinuria, foot process effacement, and kidney failure. Additionally, we also discovered recessive homozygous mutations in *PAX* (family A3995, Y281H, conserved to *D. rerio*) and *ARHGEF17* (family A3658, V1883M, conserved to *C. elegans*). Interestingly, *TLN1*, *PAX* and *ARHGEF17* are highly expressed in podocytes and directly interact with *TNS2* and *DLC1*, which are both known to cause NS, if mutated. Talin1 and Tem4 are also known to specifically affect RhoA function *in vitro*.

Conclusions: We have identified mutations of *TLN1*, *PAX* and *ARHGEF17* as novel causes of NS. Our findings confirm that Rho-like small GTPase signaling is part of NS pathogenesis.

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FR-PO786

Nos1ap-/- Mice Replicate the Human Nephrotic Syndrome Phenotype Potentially via a CDC42-Diaphanous-Related Mechanism

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. We previously identified causative recessive mutations in *NOS1AP* in two SRNS families and demonstrated that *NOS1AP* mutations impaired CDC42 activation, podocyte migration rate (PMR) and filopodia formation (Majmundar, *JASN* 29:682, 2018). To further delineate the pathogenesis of SRNS due to *NOS1AP* loss-of-function, we generated a mouse model and performed additional cell culture studies.

Methods: Homozygous *Nos1ap*$^{ex3-/ex3-}$ C57Bl/6 mice, lacking *Nos1ap* exon 3 (*Int Heart J* 57:341, 2016), were screened monthly for proteinuria, and urine albumin-creatinine-ratios, BUN and serum creatinine levels were determined. We conducted live cell imaging in a human podocyte cell line under shRNA-mediated downregulation of *NOS1AP* and cDNA over-expression of *NOS1AP*, *CDC42* or *DIAPH3* as well as pharmacologic inhibition of DIAPH proteins (by SMIFH2).

Results: We examined *Nos1ap*$^{ex3-/ex3-}$ mice carrying biallelic *Nos1ap* Exon 3 deletion alleles for albuminuria. Mice developed albuminuria starting at the age of 5 months when compared to their wild-type and monoallelic littermates but had not developed renal failure by the age of 12 months. In a podocyte cell culture system we further studied the role of NOS1AP within the signaling pathway of CDC42 and its downstream effectors, the diaphanous proteins. Filopodia formation upon *NOS1AP* cDNA overexpression was assessed in the presence of the DIAPH protein inhibitor SMIFH2 and reduced in a dose-dependent manner similarly to prior CDC42 inhibiton by CASIN. Reversely, defective PMR, an established intermediate phenotype of SRNS, in *NOS1AP* shRNA-mediated knock-down podocytes was rescued by overexpression of *DIAPH3* cDNA and constitutively active CDC42.

Conclusions: We show that the human SRNS phenotype due to recessive *NOS1AP* mutations is replicated in *Nos1ap*$^{ex3-/ex3-}$ mice. We demonstrate that DIAPH function is part of the CDC42 mediated pathogenesis of SRNS due to *NOS1AP* loss-of-function.

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FR-PO787

Mutations in the Diaphanous Related Formin DAAM2 as a Novel Cause of Nephrotic Syndrome

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Background: Steroid Resistant Nephrotic Syndrome (SRNS) is the second most frequent cause of end-stage renal disease in the first 3 decades of life. Identification of >55 monogenic causes of NS has rendered insights into disease mechanisms of NS (*Nat Rev Nephrol.* 12:133, 2016). Diaphanous related formins (DRF) regulate actin polymerization, filopodia and lamelipodia formation. The basal state interaction of the N-terminal DID domain with the C-terminal DAD domain is autoinhibitory and is relieved by conformational changes induced by GTPases. Accordingly, mutations in the DID domain of the formin gene, *INF2*, cause NS (*Nat Gen* 42:72, 2010).

Methods: To identify novel monogenic causes of NS we performed whole exome sequencing (WES) in a worldwide cohort of ~600 individuals with NS.

Results: In the three unrelated families (B1068, HN-F25, and HN-F627) with SRNS, we discovered three different homozygous mutations in the formin *DAAM2*: p.R335Q (located in the DID domain), p.S1027L (in the DAD domain), and p.R445* (terminating DAAM2 after the DID domain). All mutations are deemed disease causing by prediction programs and are absent homozygously and very rare heterozygously in the gnomAD database. We show that DAAM2 localizes to podocyte foot processes by immunofluorescence. In the podocyte migration rate assay (PMR), *DAAM2* knockdown by shRNA reduced PMR. PMR was rescued by overexpressing WT-DAAM2 cDNA but not by the cDNA representing the human missense mutations. In podocytes, filopodia formation was induced by overexpressing GFP-WT-DAAM2 cDNA but not by the cDNA representing the human missense mutations. Applying the formin activating small molecule IMM-01 caused filopodia formation in shRNA DAAM2-k.d. podocytes in a dose-dependent manner, and overcame the filopodia formation defect of mutant cDNA overexpression.

Conclusions: We here discovered mutations in the formin *DAAM2* as a novel monogenic cause of NS. We demonstrate that mutations of DAAM2 cause loss of filopodia formation and reduced PMR as intermediate phenotypes in NS, linking the pathomechanism to formin regulation. DAAM2 is likely a potential target for formin activating drugs.

Funding: NIDDK Support

FR-PO788

Recessive Mutations in Bassoon (BSN) Are a Potential New Cause of Nephrotic Syndrome

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Background: Steroid-resistant nephrotic syndrome (SRNS) is the second most frequent cause of chronic kidney disease in children and young adults. Major insights into its pathogenesis came from discovery of ~60 monogenic causes, contributing to ~12-30% of SRNS with onset <25 years of age. However, a significant proportion remains without a genetic diagnosis.

Methods: To identify novel pathogenic genetic variants, we performed whole-exome sequencing (WES) in a world-wide cohort of >800 individuals from different families with SRNS. We evaluated potential pathogenicity of genetic variants by in-silico prediction scores, evolutionary conservation and allele frequency in public genome sequencing databases.

Results: We identified 6 individuals from different families with recessive deleterious mutations in the *BSN* gene (bassoon). Two individuals harbored different homozygous mutations (p.S1481T and p.P3888L), while 4 had compound heterozygous mutations (p.R519W / p.T2829M; p.R3664Q / p.R1193H; p.P620L / p.K2697E; and p.P2503Afs*15 / p.H3716N). Age of SRNS onset was 7 months to >21 years old. Of 4 patients who underwent renal biopsies, 3 had focal segmental glomerulosclerosis, and 1 had minimal change disease. Four patients had extra-renal manifestations (microcephaly, atrial septal defect, short stature, seizures, and intellectual disability). Bassoon is a scaffolding protein found in the neuronal presynaptic plasma membrane, involved in priming of synaptic vesicles, assembly of active zones and localization of voltage-gated calcium channels (*Front Synaptic Neurosci* 7:19, 2015). Podocytes have been shown to contain structures resembling synaptic vesicles. Bassoon was previously identified in cultured podocytes and in kidney glomeruli by Western blot and immunohistochemistry (*FASEB J.* 20(7):976, 2006).

Conclusions: By WES, we here identify recessive mutations of *BSN* in 6 affected individuals, revealing a potential novel monogenic cause of SRNS.

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FR-PO789

Recessive Mutations in TNS1 Are a Potential Novel Cause of Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. Using WES, we demonstrated that mutations in one of the 59 known SRNS genes can be identified in 25% of patients (*NDT*, 2019 doi: 10.1093/ndt/gfz028).

Methods: To discover additional monogenic causes of NS, we performed WES in a cohort of 600 families with childhood onset SRNS.

Results: We identified rare compound heterozygous missense mutations in the *TNS1* gene in five individuals from four unrelated families with NS: family **B2014:** p.R1198Q and p.R940Y; **A1226:** p.I224N and p.D66V; **A4619:** p.S1098R and S920C, **A4580:** p.T218I and p.A1685T. TNS1 is known to interact with actin, to bind to β1-integrin and serve as a scaffold for adhesion-related signaling. Specifically, it enhances RhoA activity in a DLC1-dependent manner through its multiple domains (*BBA* 1853:3258, 2015). We found that the p.T218I (PTEN_C2 domain) and p.A1685T (PTB domain) mutations are predicted to reduce overall protein domain stability, while the highly conserved p.D66V mutation is predicted to destabilize the PTEN_C2 domain (http://cupsat.tu-bs.de/). The two siblings in our index family (B2014) presented with a history of proteinuria. In addition, sibling B2014_21 had renal hypoplasia and lack of corticomedullary differentiation on renal ultrasound, while B2014_22 had increased renal echogenicity with prominence of the renal papillae. Notably, *tensin*$^{-/-}$ mice have renal failure, proximal tubule cysts with disrupted cell-matrix junctions in non-cystic areas, tubulointerstitial nephritis, glomerulosclerosis, and abnormal renal papillae (*JCB* 136:1349, 1997). Employing immunofluorescence in sections of healthy rat glomeruli, we demonstrated primarily mesangial localization of TNS1, which is corroborated by single-cell RNA expression data in mice glomeruli (*JASN* 29:2060, 2018).

Conclusions: We identified likely disease-causing mutations in *TNS1* in four unrelated families with NS, revealing a novel monogenic cause of human glomerular disease.

Funding: NIDDK Support

FR-PO790

Recessive Mutations in SYNPO2 May Cause Nephrotic Syndrome via Mesangial Cell Dysfunction

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. So far mutations in 60 genes were identified to cause steroid resistant nephrotic syndrome (SRNS).

Methods: To identify novel monogenic causes of NS we performed whole exome sequencing (WES) in a cohort of 1,200 NS patients. To study the functional significance of mutations found, podocyte migration rate (PMR) and active Rac1 GLISA assay were performed in a human podocyte cell line.

Results: In 3 unrelated patients with childhood onset nephrotic syndrome (NS) we discovered 1 homozygous truncating and 2 homozygous missense mutations in *SYNPO2* (p.K1124*, p.G413S, and p.A1134T). From the 3 types of renal glomerular cells, the *SYNPO2* transcript is expressed 10 fold higher in mesangial cells than in podocytes or endothelial cells (*JASN* 29: 2060, 2018). Accordingly, by immunofluorescence (IF) in adult rat sections, SYNPO2 localized most strongly to mesangial cells. By IF, on the subcellular level, SYNPO2 colocalizes with F-actin. Upon overexpression in podocytes, SYNPO2 colocalizes also with ACTN4, a gene that is mutated in autosomal dominant SRNS in humans. *SYNPO2* shRNA knockdown reduced podocyte migration rate (PMR) in a human podocyte cell line. PMR was rescued by transfection of wild type mouse *SYNPO2* cDNA but not by cDNA representing any of the 3 mutations from patients with NS. *SYNPO2* shRNA knockdown in the podocyte cell line decreased active Rac1, which was rescued by transfection of wild type *SYNPO2* cDNA but not by cDNA representing any of the 3 mutations from patients with NS.

Conclusions: We here discovered recessive *SYNPO2* mutations as a novel monogenic cause of nephrotic syndrome, leading to mesangial cell dysfunction through Rac1-GTPase dysregulation.

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FR-PO791

First Identification of a Rare PODXL Splice Site Mutation in a Case of Focal Segmental Glomerulosclerosis

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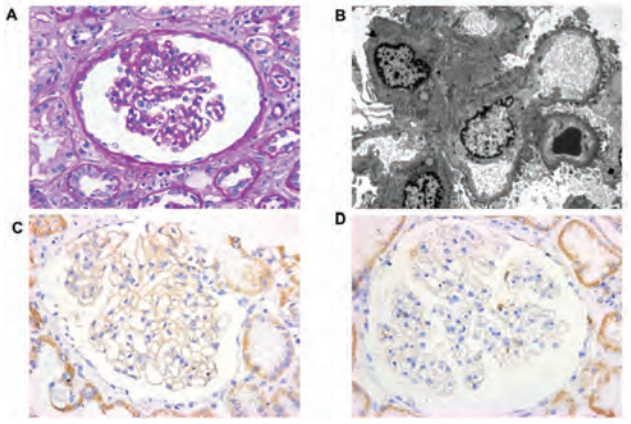
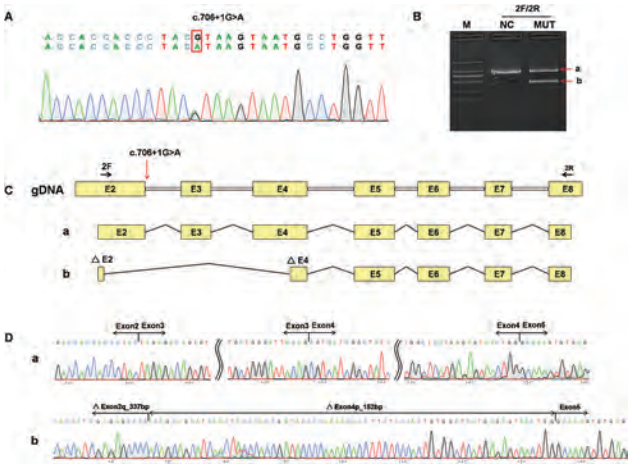
Introduction: Podocalyxin plays an important role in the regulation of podocyte morphogenesis and function. We recently identified heterozygous *PODXL* nonsense mutations linked to autosomal dominant focal segmental glomerulosclerosis (FSGS). Here, we reported the first heterozygous *PODXL* splice site mutation identified in FSGS.

Case Description: A 63-year-old Chinese female was admitted to the ward in December 2018 for persistent proteinuria (maximum 2500mg/24hr) and hypertension (140/90mmHg) for three months. Serum creatinine and albumin were within normal range and renal ultrasound revealed normal sized and echogenic kidneys. Renal biopsy suggested FSGS (Figure 1A-1B). Father of the patient was died of renal failure and no history of renal disease found in other close relatives. Whole exome sequencing performed on the patient revealed a *PODXL* heterozygous donor splice site variant (c.712+1G>A, rs137907090, allele frequency 0.0002) (Figure 2A), leading to the 585bp deletion including exon 3, the last 337 nucleotides on exon 2 and the first 152 nucleotides on exon 4 (Figure 2B-D). This mutation removed 195 amino acids in-frame in the sialomucin domain. Immunohistochemical showed decreased podocalyxin expression along glomerular capillary (Figure 1C) compared with that of normal control (Figure 1D). Losartan was started and at last follow up in May 2019, 24hr proteinuria was 1500mg and serum creatinine remained within normal range.

Discussion: This case expands the genetic spectrum of *PODXL*-associated FSGS and further supported that down-regulation of podocalyxin expression linked to FSGS.



Representative microscopic images of the patient.



Mutation and its consequences.

FR-PO792

Nephrin Mutation in Childhood-Adult Onset Nephrotic Syndrome (NS)

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Background: Nephrin, a slit diaphragm protein, is essential to integrity of podocyte structure. Mutations in the nephrin gene, *NPHS1*, typically result in *congenital* NS. Variants causing similar disease in later childhood and adults are rare. We believe our family is the first case report in which all members of the family have this mutation. A 18-year-old Caucasian female was referred for steroid and calcineurin inhibitor resistant NS. Her first renal biopsy was at age 7 due to proteinuria with normal renal function and blood pressure. All 18 sampled glomeruli and interstitium appeared normal by light microscopy (LM), but electron microscopy (EM) showed partial foot process effacement. Repeat biopsy at age 18 when eGFR < 30 ml/min/1.73m^2 showed focal segmental glomerulosclerosis, not otherwise specified (FSGS-NOS). She received Rituximab as attempted salvage therapy. Renal function deteriorated further and she reached end-stage disease by age 19. Her brother, at age 16, was evaluated and had nephrotic range proteinuria with preserved renal function. His renal biopsy showed 37 normal glomeruli by LM, with global activation of foot processes and effacement by EM. With consent, both patients and their parents (without proteinuria) were tested for a podocyte mutation

Methods: Genomic DNA was extracted from peripheral blood cells and genotyped for coding sequence variants in the *NPHS1* gene in 9 healthy controls and the current family.

Results: No homozygous variants in *NPHS1* were detected in 9 healthy controls. The 2 children were homozygous for a pathogenic variant in *NPHS1* c.2928G>T [p.Arg976Ser]. Both parents were heterozygous for this variant, representing a possible carrier-state. This mutation, a missense single nucleotide variation in exon 22, may affect mRNA splicing in the fibronectin domain of nephrin

Conclusions: We report two cases of childhood-onset proteinuria due to a *NPHS1* missense mutation, with autosomal recessive inheritance. Renal pathology probably begins as a podocytopathy that slowly progresses to segmental glomerular sclerosis and renal impairment. NS due to genetic mutations may be resistant to conventional immunosuppressive therapy. Genetic testing may direct limitation of immunosuppression with minimal therapeutic benefit and inform counseling to future progeny

FR-PO793

Whole-Exome Sequencing in 33 Families with VACTERL or VACTERL-Like Phenotype Identifies Potential New Candidate Genes

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Background: VACTERL association describes the combination of congenital anomalies including vertebral defects (V), anorectal malformations (A), cardiac defects (C), tracheoesophageal fistula with or without esophageal atresia (TE), renal malformations (R), and limb defects (L). Involvement of genetic factors in its pathogenesis is supported by reports of familial segregation, but only four likely monogenic causes have been suggested (*FOXF1, HOXD13, PTEN, ZIC3*).

Methods: We performed unbiased whole exome sequencing (WES) to identify monogenic or digenic causes in 33 families with VACTERL or VACTERL-like phenotype.

Results: We evaluated the WES data for causative mutations in 3 different groups of known or candidate VACTERL genes: i) mutations in the 4 known VACTERL genes *FOXF1*, *HOXD13, PTEN* and *ZIC3*, ii) in 108 VACTERL candidate genes of the Shh or Wnt pathway, and iii) in 58 syndromic human CAKUT genes. In addition, we evaluated WES data for mutations in potential novel VACTERL genes under 5 different monogenic hypotheses: iv) recessive, v) dominant, vi) *de novo*, vii) digenic dominant or viii) digenic recessive mutations. We detected no mutation in any of the 4 known VACTERL genes (above group i). In group ii we detected potential mutations in 11 different genes. In group iii we detected potential mutations in 13 genes. When evaluating for potential novel VACTERL genes, we identified recessive (group iv, n=4, *B9D1, CORO7, TTLL11, NKX2-3*), dominant (group v, n=5), *de novo* (group vi, n=1), digenic dominant (group vii, n=11) and digenic recessive mutations (group viii, n=3). Overall, we detected mutations in 25/33 families in 44 genes (17 had more than one potential gene). Interestingly, in 7 individuals at least one mutation in a known gene for syndromic CAKUT together with a second mutation in another syndromic CAKUT or VACTERL candidate gene could be found. Array-based molecular karyotyping revealed no copy number variants in any of the 33 families.

Conclusions: This study establishes that WES can identify mutations in potential candidate genes in 76% of families with VACTERL or VACTERL-like phenotype. Furthermore, WES shows a potential digenic mode of inheritance in 51% of our cohort.

FR-PO794

Variable Penetrance of the Therapy-Resistant Phenotype Among Children with the Genetic Form of Nephrotic Syndrome

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Background: Currently, genetic forms of nephrotic can be classified as highly penetrant, pathogenic variants in single genes ("monogenic") or common risk alleles contributing to the diseases pathogenesis such as *APOL1* high-risk (HR) genotypes. Monogenic NS is thought to be therapy-resistant, with an inability to achieve complete remission (CR) and *APOL1* NS has a lower odd of achieving CR. However, there have been reports that some patients with monogenic diseases may achieve CR. Factors associated with remission among genetic NS is still unclear. Therefore, this study used a large North American cohort of children with NS to (1) describe the prevalence of CR as a function of genetic profile and (2) identify factors potentially modifying the CR phenotype.

Methods: 70 genes implicated in monogenic forms of NS and the two *APOL1* risk alleles were analyzed in 215 children from the Nephrotic Syndrome Study Network (NEPTUNE) who had undergone whole genome sequencing. A variant pathogenicity pipeline was applied to identify patients with putative monogenic NS and *APOL1* HR genotypes. General characteristics and CR were compared among patients classified with putative monogenic NS, *APOL1*-attributed NS, and no know genetic form of NS.

Results: Monogenic NS was found in 15 patients (7%) and *APOL1* attributed NS was found in 28 patients (13%). Compared to no known genetic NS, monogenic and *APOL1* attributed NS had lower rate of ever achieving CR (83% vs 43% and 59%, p=0.002 and 0.01, respectively) and lower likelihood to achieve remission (Hazard ratio 0.4 for both, p = 0.02 and 0.009, respectively, at 6 months of follow up). Loss of function Mendelian variants and those co-existing with other Mendelian variants or *APOL1* HR genotype, tended to result in lack of CR.

Conclusions: Children with monogenic or *APOL1* attributed NS were significantly less likely to achieve CR. Despite this, a substantial proportion of children with genetic forms of NS still achieved CR. Mendelian variants and *APOL1* HR alleles in this North American, population-based NS cohort appear to increase risk of not achieving CR, rather than being fully penetrant for this phenotype. Further functional analysis is essential in increasing the accuracy of classifying patients with monogenic NS and making subsequent clinical correlations.

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FR-PO795

Genotype-Phenotype Correlation for the COL4A3 2881+1 G>A Founder Mutation in the Croatian Population

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Background: Alport syndrome (AS) and thin glomerular basement membrane nephropathy (TBMN) are genetically heterogenic disorders caused by mutations in COL4A3, COL4A4 and COL4A5 genes. Genetic heterogeneity with various types and number of mutations with no mutational "hot spots" can make diagnostic process challenging. Some type of mutations increase the likelihood of a severe phenotype but recent studies also showed that same mutations can result in different clinical presentation.

Methods: Total of 26 patients from 10 unrelated families with heterozygous for COL4A3 splice donor 2881+1 G>A mutation detected by next generation sequencing (Illumina MiSeq platform) for COL4A3, COL4A4 and COL4A5 genes mutations was tested as part of a project "Genotype-Phenotype correlation in Alport's syndrome and Thin Glomerular Basement Membrane Nephropathy" founded by the Croatian Science Foundation. There were 11 females and 15 male patients, age range 5-72 years (median 44 years).

Results: According to available clinical data majority of patients (88,5%) presented with haematuria and 72,7% with proteinuria. Decline in kidney function was present in 65% of patients; 40% being mild, 15% severe and 10% suffered from end stage renal disease (2 transplanted patients). Three patients had sensorineural hearing impairment. Kidney biopsy was performed in 50% of cases. On light microscopy focal segmental sclerosis was present in 30% of specimens, whereas, electron microscopy showed TBMN in 40%, TBMN with focal lamellation in 20% and changes suggestive of AS (Figure 1) in 40% of patients.

Conclusions: Here we present genotype-phenotype correlation for COL4A3 2881+1 G>A founder mutation in Croatian population showing clinical and pathohistological heterogeneity. Therefore, identification of modifiers causing such heterogeneity is of grave importance for better understanding of collagen IV nephropathies.

Funding: Government Support - Non-U.S.

FR-PO796

A Case of Autosomal Dominant Alport Syndrome with a Gene Variant of ESPN, a Hearing Loss-Causative Gene, That Was Diagnosed by Whole-Exome Analysis

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Introduction: Alport syndrome (AS) is a rare hereditary disease that presents with chronic kidney disease and sensorineural hearing loss and is diagnosed by its clinical features, pathological features on renal tissue, and mode of inheritance. AS has three genetic modes of heredity: X-linked, autosomal recessive, and autosomal dominant. Because the clinical and pathological features of autosomal dominant AS are much milder than those of the other two modes of heredity, definitive diagnosis is difficult.

Case Description: We report a woman in her 20s who exhibited persistent haematuria with normal renal function and sensorineural hearing loss. Her family members exhibited the same clinical findings among three generations and were suspected of having autosomal dominant AS (ADAS). Renal biopsy showed minor glomerular abnormalities on light microscopy and extensive thinning of the glomerular basement membrane on electron microscopy. Whole-exome analysis revealed a missense variant on c. 2510 G > C (p. Gly837Ala) in COL4A4 (type IV collagen α4). Two cases with the same variant have been reported previously, one as ADAS and the other as autosomal recessive AS. However, these two cases exhibited no sensorineural hearing loss. The analysis in the present case revealed another missense variant in ESPN (Espin), an actin-bundling protein, which is a causative gene for sensorineural hearing loss. Although the pathophysiological significance of such missense variant needs to be clarified, computational analysis predicted that the variant creates a new phosphorylation site for protein kinase C.

Discussion: By applying whole-exome analysis, we confirmed the diagnosis of ADAS for the present case. Our case suggests a possible association of hereditary sensorineural hearing loss with ADAS. When a suspicious hereditary disease exists, direct sequencing of the gene is usually performed. Although direct sequencing of the specific gene is crucial for diagnosis, other possible mutations may be missed. Whole-exome analysis should be considered as a method to diagnose hereditary and multiple-organ disorders.

FR-PO797

Reassessing the Pathogenicity of p.G953V in COL4A5 Gene: Report of 19 Chinese Families

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Background: X-linked Alport syndrome (XLAS) is an inherited renal disease caused by mutations in *COL4A5* gene. The p.G953V variant in *COL4A5* gene is considered pathogenic previously. However, there is conflicting of its pathogenicity recently. Here we reported 19 Chinese families with the p.G953V in *COL4A5* to evaluate its pathogenicity.

Methods: Families were selected from the on-line registry database of hereditary kidney diseases in children in China, according to the following two criteria a) cases with gene mutations tested by targeted next generation sequencing (NGS); b) cases with the p.G953V in *COL4A5*. The clinical data and genetic findings were collected and analyzed.

Results: Fifty-one individuals from 19 families were enrolled, out of which 36 (18 probands and 18 family members) carried p.G953V. We found there were no clinical features of XLAS not only in the 6 probands with p.G953V and pathogenic variants in other genes (e.g. *WT1*, *ADCK4*, *NPHP1*, *TRPC6*, *COL4A4* and *PAX2*) but also in another 6 probands with only the p.G953V. The other 6 probands, with a combination of p.G953V and another pathogenic variant in *COL4A5* had XLAS. Eleven family members (11/18, 9 females and 2 males) who had the p.G953V variant only were asymptomatic. These two males had normal result of urine analysis (at age of 42 and 35 years) and no more clinical traits of Alport syndrome.

Conclusions: The p.G953V in *COL4A5* gene is not a pathogenic mutation for XLAS. Individuals should not be diagnosed as XLAS only based on the detection of p.G953V in *COL4A5* gene.

FR-PO798

β2 Adrenergic Signaling Regulates a New OPN-LDLR-βPix-Rac1 Multimolecular Complex in Alport Syndrome

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Background: Alport syndrome is a rare hereditary renal disorder with no cure. Our group showed that Osteopontin (OPN) and low density lipoprotein receptor (LDLR) are highly expressed in the renal tubular epithelial cells (TECs) of the *Col4a3*$^{-/-}$ Alport mouse and play causative pathological roles. We showed that Alport kidneys had more epithelial to mesenchymal transition (EMT) and cholesterol accumulation in TECs, both phenotypes ameliorated by OPN deficiency. However, the molecular mechanisms involved are unknown.

Methods: Immunoprecipitation and cholesterol influx assays were used in human renal TEC line (HK2) with β_2AR agonism/antagonism. *Ksp*-Cre mosaic analysis with double marker (MADM) mice were used to track EMT in Alport mice. CD44 was measured by immunostaining in Alport Kidneys, and by western blot in HK2 cells treated with OPN monoclonal antibody (mAb) to quantify EMT. PBMCs from Alport patients and healthy donors were used to generate iPSCs which were differentiated into KSP+ve TECs.

Results: In HK2 cells, OPN interacts with LDLR and the Rac1 guanine exchange factor βPix to form a multi-molecular complex controlled by β_2AR signaling. Stimulating HK2 cells with adenylate cyclase activator forskolin or β_2AR selective agonist salbutamol, decreased cholesterol influx by 15.4% and 17.4%, respectively-p<.0001. Conversely, treating HK2 cells with Rac1 inhibitor NSC23766, PKA inhibitor H89, or selective β_2AR antagonist butoxamine significantly increased cholesterol influx -p<.05. OPN mAb blocked the Rac1 inhibitor effect, indicating the role of OPN in this complex. MADM mice showed that EMT in Alport kidneys is of tubular origin as was confirmed by excessive staining of interstitial CD44 (N=3 mice/group-p<.05). OPN mAb caused a 30% decrease in CD44 protein levels (N=3/group-p<.05). iPSC-TECs were functional in the cholesterol assay.

Conclusions: We conclude that elevated OPN in Alport TECs blocks cAMP production and reduces OPN binding to LDLR, thereby freeing LDLR to increase LDL cholesterol influx and drive EMT. OPN knockout or β2AR stimulation increases cAMP-mediated sequestration of LDLR by OPN-βPix complex that blocks LDLR function. Alport patient iPS-TECs may be a useful screening platform to identify β2AR stimulants regulating cholesterol influx.

Funding: Other NIH Support - NIH RO1, MHRI

FR-PO799

Antenatal Membranous Nephropathy and Axonal Charcot-Marie-Tooth Type 2 with c.466delC Mutation in the Metallo-Membrane Endopeptidase Gene: A Warning Signal About Long-Term Use of Neprilysin Inhibitors

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Background: First cases of truncating mutations in the *neprilysin/metallo-membrane endopeptidase (MME)* gene were identified in 2002 as the cause of alloimmunization during pregnancy, resulting in moderate to severe forms of antenatal membranous nephropathy (MN). Ten years later, two sisters and one brother of the originally reported Moroccan family, found homozygous for the c.466delC mutation in the *MME* gene, developed rapid motor and sensory neurological disorders, leading to the diagnosis of axonal Charcot-Marie-Tooth (CMT2). We report here the description of clinical and electrophysiologic investigations.

Methods: Clinical features and ancillary test results were collected from laboratory database and patient charts. Electrodiagnostic tests were carried out by standard techniques with surface electrode recording.

Results: Patient 1 had experienced antenatal MN during her second pregnancy at the age of 23 years. She presented with vasomotor painful episodes and progressive muscle weakness of the lower limbs at the age of 33 years. Two years later, she developed progressive gait disturbances, distal lower limb weakness with foot drop and frequent falls. This was improved by foot orthotics. Neurological examination revealed moderate muscle atrophy of the 4 limbs associated with distal sensory loss. Patient 2, her sister, had a prior history of antenatal MN (at the age of 31 years) and autoimmune thrombocytopenic purpura with a long-term corticosteroid treatment. She presented with falls at the age of 44 years and subsequently broke her foot needing osteosynthesis. First neurologic manifestations of Patient 3, their brother, were painful nocturnal cramps at the age of 30 years. All these patients had normal kidney function parameters and exhibited a typical CMT2 phenotype being demonstrated by the clinical picture and electrodiagnostic test results.

Conclusions: This is the first family associating renal and neurological abnormalities linked to *MME* gene mutation. This observation confirms that neprilysin/*MME* is involved in peripheral nerve functioning. Neurological surveillance is recommended in prolonged treatment with neprilysin inhibitors.

FR-PO800

Renal Lesions Associated with MYH9 Disorder (5773delG Mutation): Clinical and Pathological Analyses

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Introduction: *MYH9* mutations at C-terminal, such as exon 40, have not been reported to cause renal injuries. This is the first report of renal phenotype with *MYH9* exon 40 5773delG mutation. Of note, focal segmental glomerulosclerosis (FSGS) could occur even in association with *MYH9* exon 40 5773delG mutation. Accumulation of abnormal Non-muscle myosin heavy chain IIA (NMMHC-IIA) in podocytes may lead to podocyte injuries and development of FSGS lesions.

Case Description: A 37-year-old Japanese man with persistent urine abnormalities and gradually progressive renal dysfunction was admitted to hospital; his mother and two sons had giant platelets. Renal biopsy was postponed 8 years ago because he had thrombocytopenia. Laboratory data showed serum creatinine, 2.45 mg/dL; urine protein, 6 g/gCr; urine red blood cells, 36 /high-power field; and platelets, 47,000 /μL. May–Hegglin anomaly was suspected owing to macrothrombocytopenia and cytoplasmic Döhle-like inclusion bodies in granulocytes; he had bilateral cataracts and hearing loss in the 4000-Hz range. On renal biopsy, 13 glomeruli were microscopically examined: 6 showed global sclerosis and others showed mild mesangial proliferation with segmental glomerulosclerosis. On immunofluorescence examination, IgG, IgA, IgM, C1q, and C3 deposits were observed in the mesangium; α2, 5 chain staining in basement membranes showed normal pattern. Foot process effacements and intense bleb-like morphological changes in podocytes were observed via electron microscopy. Electron dense deposits in certain mesangial areas and no Alport's basement membrane changes were found. NMMHC-IIA staining in spots pattern was observed via immunofluorescence examination of granulocytes. *MYH9* 5773delG (G1924fs) mutation was found via genomic DNA sequencing. These findings and ineffective steroid therapy led to the possible diagnosis of FSGS associated with MYH9 disorder.

Discussion: On further pathological analyses, double staining of vimentin and NMMHC-IIA showed decreased colocalization of NMMHC-IIA in cell bodies and primary processes of podocytes. Podocytes were significantly stained by an antibody specific to abnormal NMMHC-IIA produced by *MYH9* 5773delG mutation; this was not observed in glomeruli of patients without the mutation. We finally diagnosed the patient with FSGS associated with MYH9 disorder.

FR-PO801

Features of Glomerulopathy with Fibronectin Deposits

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Background: Glomerulopathy with fibronectin deposits (GFND; OMIM: 601894) is a rare inherited kidney disorder characterized by massive fibronectin deposits, leading to end-stage renal disease (ESRD). Differential diagnosis of GFND from other immunotactoid glomerulopathy is important in treatment. We systematically reviewed and analyzed clinical features and genotypes of patients with GFND.

Methods: Electronic databases were searched using related terms (till May 30th, 2019). This report adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Results: From 1633 articles searched, there were 23 eligible studies with 86 patients with GFND from 44 families. Female patients were 40% (34/86) and most (70/83, 84%) patients had family history. 33 patients (38%) had hematuria and 38(47%) had nephrotic proteinuria. Median age at onset was 14.5 years for hematuria and 24 for proteinuria. Half of the patients had hypertension (18/35, 51%). ESRD was reported in 22 out of 68 patients (26%) at 34 median years. Of the 50 patients available for pathology reports, most patients showed negative immunofluorescence stains and fibrillary deposit in the electon-microscopy with the fibrils sized 9-14 nm in diameter. 42 patients underwent genetic tests for *FN1* and 3(8%) had no mutation. Of the 39 with *FN1* mutation, and 35 (35/39, 89%) had a missense mutation, 3 (8%) had deletion, and 1 had an intronic mutation. Mostly affected was the heparin-binding site where 92% (32/39) of the mutations occurred. c.2918A>G was the most commonly reported mutation. There was no genotype-phenotype correlation in this study.

Conclusions: GFND may proceed to ESRD at third decade of life. Hypertension and nephrotic syndrome are often accompanied. Some patients with GFND may present without family history and may be negative for *FN1* mutation.

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Table 1. Clinical features of patients with GFND

	Total (N = 86)
	N° (%)
Ethnicity	
Caucasian	57/81 (70%)
Asian	24/81 (30%)
N/A	5
Sex	
Male	52/86 (60%)
Female	34/86 (40%)
Family	
Family Hx	70/83 (84%)
No family Hx	13/83 (16%)
Renal manifestation	
HU	33/86 (38%)
PU	83/83 (100%)
Nephrotic PU	38/83 (47%)
Nephrotic syndrome	18/38 (49%)
Hypertension	18/35 (51%)
CKD	27/68 (31%)
ESRD	22/68 (26%)
TPL	6/86 (7%)
Age at (median, years)	
Visit	33
Diagnosis	34
HU	14.5
PU	24
CKD	36.5
ESRD	34
TPL	37
Last F-U	38
Laboratory findings (mean)	
eGFR	83.3
SCr	2.73
SAlb	3.2
PU	2.7 (g/day)
SBP	151.9 mmHg
DBP	94.5 mmHg
Genotype	
Gene study	Performed in 42/86 (49%): 39 with mutation, 3 without mutation
Types	35 Missense, 3 deletion, 1 intronic splicing mutation
Region	19 HEP-II, 17 HEP-III, 2 integrin binding site, 1 intronic

FR-PO802

Prednisone Reduced Proteinuria and Stabilized Serum Creatinine in a Patient with Familial Fibronectin Glomerulopathy

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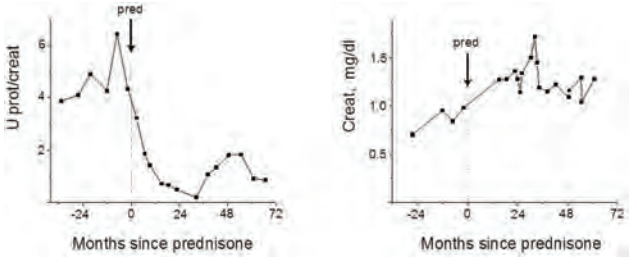
Introduction: Fibronectin Glomerulopathy (FNG) is a rare, autosomal dominant disease characterized by proteinuria, hematuria and progressive renal failure associated with glomerular deposition of fibronectin, typically leading to ESRD in the 2nd to 6th decade. There is no established treatment for this condition beyond conservative measures such as blood pressure control and use of ACE inhibitors. We present a case of FNG associated with progressive CKD and nephrotic range proteinuria showing a sustained response to prednisone treatment.

Case Description: A 27 year old G_2P_2 female presented with 3 g of proteinuria, serum creatinine 0.7 mg/dl, inactive urinary sediment and normotension without medication. She was part of a large family with glomerular disease, including 3 members who died of cerebral hemorrhage or stroke in their thirties. The patient's kidney biopsy showed mesangial deposition of fibronectin consistent with FNG. No interstitial fibrosis was seen. Genotyping revealed the Y973C fibronectin gene mutation. Despite maximal tolerable ACE inhibition, proteinuria increased to 4-6 g/g creat and serum creatinine increased to 1.0 mg/dl. Based on its use in IgA nephropathy, she was treated with prednisone 60 mg (~1 mg/Kg) for 2 mos, tapering by 20 mg every 2 mos. Proteinuria decreased to ~1 g/g creat for > 5 yrs and creatinine stabilized in the 1.2 mg/dl range with treatment. No significant side effects were encountered.

Discussion: Prednisone induced a sustained response in this patient. This is one of the first reports of effective treatment of FNG with immunosuppressive therapy. In conclusion, this protocol should be considered in FNG patients with nephrotic range proteinuria despite maximal ACE/ARB inhibition who have relatively preserved renal function.



Prednisone reduced proteinuria and stabilized serum creatinine

FR-PO803

Mechanism of Mutation of AarF Domain-Containing-Kinase 4 (ADCK4) Glomerulopathy

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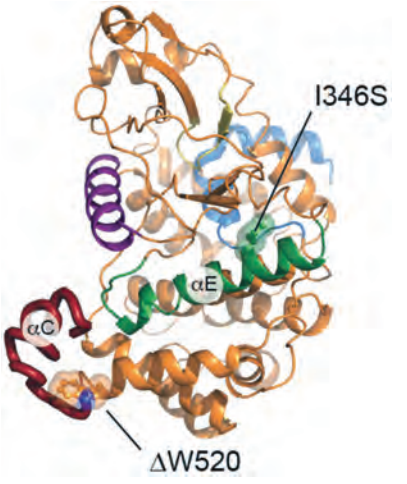
Introduction: AarF domain-containing-kinase 4 (ADCK4) is a mitochondrial resident protein kinase belonging to the UbiB protein kinase-like family. ADCK4 is thought to facilitate the ATP dependent biosynthesis of coenzyme Q10 (CoQ10). Mutations in *ADCK4* cause early-onset proteinuria, focal segmental glomerulosclerosis/nephrotic syndrome, followed by end-stage renal disease (ESRD). The regulation of ADCK4 in CoQ10 biosynthesis is not well understood

Case Description: We report a patient who was discovered with proteinuria on routine screening at age of five-year-old. Renal biopsy showed FSGS. Renal functions and proteinuria continued to worsen over the years. Whole exome sequence revealed a novel compound heterozygous for two mutations in the aarF domain-containing-kinase 4 (ADCK4) gene. Her father has proteinuria related to fibrillary GN and bilateral duplicated collecting system, brother with right ureteropelvic junction obstruction and sister with unilateral duplicated collecting system. Genetic analysis using whole exome sequencing for this family with proteinuria and structural anomalies of the kidney and urinary tract revealed a novel compound heterozygous mutation in the *ADCK4*.

Discussion: We generated a computational model to understand the mechanism of action of 2 novel identified mutations: I346S in the C-lobe of the ADCK4 kinase domain, and a termination at W520 that leads to the truncation of the C-terminal a5 helix. The alterations of ADCK4 c.1560G>A and c.1037T>G are novel mutations. the model suggests potential mechanisms for alterations in protein function through either destabilization of important allosteric interactions necessary for kinase activation and/or conformational changes that facilitate enzyme activity (Figure 1).



FR-PO804

Sanger Sequencing Pitfall Exists in Hereditary Thrombotic Microangiopathy with Homozygous Mutation Identified in Only One Biological Parent

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Background: The aim of this study was to elucidate the underlying etiology of a mutation appeared to be homozygous which was identified in only one of parents in one boy with hereditary thrombotic microangiopathy.

Methods: One boy was diagnosed as steroid-resistant nephrotic syndrome at 2.4 years old. Urinary protein recurrence occurred 1.5 years later, while serum creatinine (Scr) increased to 83 umol/L and platelet (PLT) decreased to 40×109/L. One point eight years later, hemoglobin (Hb) was 72 g/L, PLT 29×109/L, Scr 120 umol/L. Five point nine years later, his renal function was normal. Light microscopy, electron microscopy and immunofluorescence of renal biopsy indicated thrombotic microangiopathy. Genetic analysis revealed he had homozygous DGKE (NM_003647) missense variant c.1420G>A (p. Asp474Asn) which was identified in only his father. Six short tandem repeats (STR) were selected to confirm biological relationships between the boy and his parents. Quantitative PCR was performed to detect the deletion by Bio-Rad CFX real time PCR system using SYBR Green I qPCR SuperMix (TransGen Biotech, China, AQ131).

Results: Six loci alleles in different chromosomes demonstrated typical Mendelian inheritance with paternal and maternal alleles being detected in the patient, which indicated that biological relationship of the boy and his parents exist. The gDNA quantity in *DGKE* exon 11 of the boy was half of the normal control while normal in his parents. Further analysis showed the breakpoints in *DGKE* were exon 1 and exon 12. It may be a *de novo* heterozygous deletion.

Conclusions: The case was demonstrated to be homozygous due to a large deletion encompassing a missense/small deletion in DGKE gene.

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FR-PO805

Clinical and Genetic Characteristics of Pregnancy-Associated aHUS in Japan

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Background: Complement dysregulations mostly by the genetic alterations of the complement related factors are involved in the pathogenesis of atypical hemolytic uremic syndrome (aHUS). Pregnancy can impact on the onset of aHUS. Clinical courses and pathogenesis of pregnancy-associated aHUS is not yet fully clarified.

Methods: Blood samples of aHUS patients were analyzed by hemolytic assay, anti-CFH antibody test and whole exome sequences. Pregnancy-associated aHUS was defined as aHUS that occurs during pregnancy or perinatal period. TMA cases with active underlying diseases were excluded.

Results: Out of 264 cases consulted to our division, 6 cases were associated to the pregnancy. All the cases developed TMA immediately after delivery within 12 hours, and no TMA events during pregnancy were observed. The ages of the patients ranged from 25 to 33 years old, and all the cases were primipara. 2 cases underwent Caesarean sections. 5 cases showed both liver and kidney dysfunctions, leading to the diagnoses of aHUS and HELLP syndrome. Hemolytic assays were negative to weak positive, and anti-CFH antibody tests were all negative. Whole exome sequencing detected diverse mutations in complement related factors (C3 V555I, C3 S562L, CFH R1215G, CFI R201S, CFB K533R, MCP S13F). Each mutation corresponds to each case, and there are no common mutations to them. 4 mutations are found in the idiopathic aHUS patients in our cohort, one (CFB K533R) is previously described as an aHUS causing mutation and one (C3 V555I) is novel. One case (CFI R201S) required temporary hemodialysis for severe acute kidney injury. 5 cases recovered the kidney function, while one case (CFB K533R) reached to the end stage kidney disease 1.5 years after the onset of the disease.

One case (CFH R1215G) continued eculizumab therapy every two weeks until now. All the cases were followed up for up to 5 years and one case had the second pregnancy with successful delivery. No recurrence of TMA was observed during follow-up period.

Conclusions: The clinical and genetic characteristics of pregnancy-associated aHUS in our cohort are; 1) postpartum TMA with HELLP syndrome is typical, 2) the recurrence rate of aHUS is low, 3) the recovery of kidney and liver functions is generally good, 4) diverse mutations in complement related factors were detected, but they might not be the sole factors responsible for the onset of the disease.

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FR-PO806

Genotype and Phenotype Correlation in a Chinese Cohort with Autosomal Dominant Tubulointerstitial Kidney Disease

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Background: Autosomal dominant tubulointerstitial kidney disease (ADTKD) characterized by tubulointerstitial damage and progressive chronic kidney injury might be an important cause of chronic kidney disease for patients with family aggregation of ESRD. *UMOD, HNF1B, MUC1, REN* and *SEC61A1* were reported to be the disease causing genes. In this study, we screened genetic variations and did a follow-up study in a Chinese suspected ADTKD cohort.

Methods: 80 individuals from 53 families suspected with ADTKD were enrolled. Demographic data, clinical data and family history of the 53 probands were obtained from clinical record. Genetic testing for *UMOD, HNF1B, REN, MUC1* and *SEC61A1* were performed with suitable method of direct sequence, multiple ligation-dependent probe amplification (MLPA) or next-generation sequencing (NGS). We performed a 1-5 years' flow-up study for the 53 probands.

Results: According to the genetic variants identified in the cohort, 11 persons were diagnosed as ADTKD-UMOD, 1 as ADTKD-REN and 1 as ADTKD-HNF1B. Pathogenic variant in *MUC1* and *SEC6lA1* genes were not confirmed. The mean age of diagnosis was 30±11years, and numbers of males and females were almost equal. Hyperuricemia and decreased kidney function were the common features. But clinical features were similar between patients with genetic variants and without variants (ADTKD-NOS). Flow-up study data from 35 probands were available while 18 probands lost. According to the flow-up study, ADTKD-NOS patients had better outcome than those patients identified genetic variants (p=0.011). Among the 11 variants in *UMOD*, 5 effected cysteine and 6 effected other amino acid. 80%ADTKD-UMOD patients with pathogenic variants lead to cysteine substitution did not develop to ESRD while 83.3% ADTKD-UMOD patients with other amino acid substitution developed ESRD.

Conclusions: 24.5% patients diagnosed ADTKD in a Chinese suspected ADTKD and *UMOD* was the mainly disease causing gene. Clinical features are not specific in patients carried pathogenic mutations compared to those without mutations. Renal survival of ADTKD-NOS is better than patients identified genetic variants. ADTKD-UMOD patients with pathogenic variants lead to cysteine substitution tend to have better outcome.

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FR-PO807

Quality of Life in Patients with Autosomal Dominant Tubulointerstitial Kidney Disease

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Background: The reaction to diagnosis and quality of life (QOL) in autosomal dominant tubulo-interstitial kidney disease (ADTKD) due to *UMOD* and *MUC1* mutations from the time of diagnosis until treatment for end-stage kidney disease (ESKD) has not been characterized. It is unclear how asymptomatic patients react to a positive genetic test result.

Methods: A cross-sectional survey concerning QOL and genetic testing was delivered to 622 individuals who had undergone genetic testing from families with known ADTKD.

Results: 286 of 622 individuals completed the survey, including 61(21%) genetically unaffected, 3(12%) with stage 1, 2 CKD, 51(18%) Stage 3, 41(14%) Stage 4 pre-dialysis, 50(17%) receiving dialysis, and 47(16%) s/p kidney transplantation. Of 55 respondents who thought they had normal kidney function at the time of testing and were found to have ADTKD, 51(93%) were happy testing was performed (Figure 1), 3(5%) neutral, and 1(2%) neutral/unhappy. Forty-two of 183(23%) affected individuals stated that ADTKD "has a substantial effect and I think about it daily," 47(26%) think about ADTKD weekly, 48(26%) monthly, and 48(26%) less than monthly. The mean PROMIS anxiety score was similar between unaffected and affected individuals and the general population. Depression was present in 41% of affected vs. 23% of unaffected individuals (p=0.01).

Conclusions: Genetic testing of presymptomatic patients for ADTKD is reasonable when requested. This study provides reassurance regarding the impact on QOL of the increased use of genetic testing to diagnose kidney disease. ADTKD has a significant impact on QOL, with depression, not anxiety, being more prevalent in affected individuals.

Funding: NIDDK Support

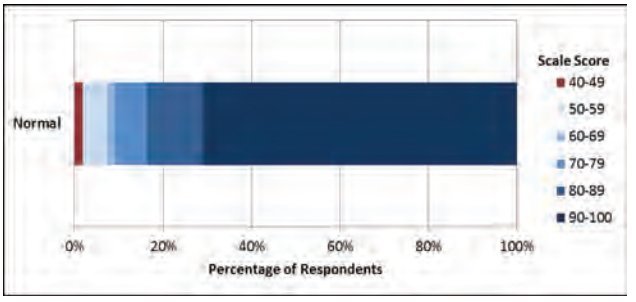

Figure 1. Response of 49 asymptomatic respondents who had undergone positive genetic testing for ADTKD to the question, "Are you happy that you underwent testing?" Patients responded on a scale with a score of 0=unhappy, 50=neutral, and 100=happy.

FR-PO808

Predictors of Age of ESRD in Autosomal Dominant Tubulointerstitial Kidney Disease due to UMOD Mutations

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Background: The aim of this work was to identify parameters that may explain the significant intra- and interfamilial variation in the age of onset of ESRD in patients with ADTKD-*UMOD*. The minor rs4293393 variant residing in the *UMOD* promoter has an allele frequency of 19% and decreases uromodulin synthesis by approximately 50%. It was postulated that if the minor variant was present in cis with the disease-causing mutation of *UMOD (mUMOD)*, it would result in decreased mUMOD production and improved survival. A Mendelian randomization experiment was therefore attempted.

Methods: The study included 983 individuals with 127 different *UMOD* mutations, with 722 undergoing genetic testing and 261 being historically affected. An *in vitro* score was created for 29 prevalent mutations based on transit time through the endoplasmic reticulum. Other parameters included in the evaluation were parental age of ESRD, median age of ESRD for the patient's family, BMI, history of gout, age of gout.

Results: The rs4293393 minor variant allele frequency was 16.4% when trans to *mUMOD* and 5.4% when cis to *mUMOD*, resulting in Hardy Weinberg equilibrium being present (p=0.03) and precluding a Mendelian randomization study. The following factors were found to be significantly associated with age of ESRD: age of gout (p<0.001), parental age of ESRD (p<0.001), body mass index (p=0.033), and median age of ESRD for the family (p=0.007). The *in vitro* score was also significant (p=0.03).

Conclusions: The minor variant was significantly less commonly linked to the *mUMOD*. The minor variant may lead to decreased mUMOD production and milder disease that was less frequently identified. An *in vitro* score was an excellent predictor of age of ESRD according to mutation. Parental age and age of gout were highly predictive of age of ESRD.

Funding: NIDDK Support

FR-PO809

Prevalence and Clinical Features of ADTKD-UMOD in Hemodialysis Patients in a Geo-Referenced Population in Southeastern Brazil: The REGENT Study

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Background: Autosomal dominant tubulointerstitial kidney disease due to *UMOD* mutations (ADTKD-*UMOD*) is a rare genetic kidney disease whose prevalence is not well known. We studied the prevalence and clinical aspects of ADTKD-*UMOD* in hemodialysis (HD) patients in a metropolitan health region of Southeastern Brazil (Metro-II).

Methods: The REGENT study (Familiar Renal Disease, Epidemiology and Genetics in Niteroi) was designed to study familial renal diseases in Metro-II (2 million inhabitants). Between 2017/2018, we evaluated HD patients geo-referenced in Metro-II. Each patient was asked whether any other family members had developed ESRD. If affirmative, after clinical exclusion of other known diseases (such as ADPKD, Fabry's, Alport's, Familial glomerulonephritis, etc.), blood was collected for *UMOD* genetic analysis.

Results: 209 of 1308 patients (16%) indicated a family history of kidney disease. After exclusions, 70 remained as index cases of an unknown familial disease (5.4% of the total). These patients reached ESRD at a younger age ($p < 0.05$), did outpatient treatment before dialysis ($p < 0.001$), and were on dialysis for more years ($p < 0.01$). Family pedigrees showed a dominant pattern in 35%. Three of the index cases were found to have unique *UMOD* variants, consisting of 3 heterozygous missense mutations (c.163 G>A; p.Gly55Ser) (c.667 T>G; p.Cis223Gly) and (c.263 G>A; p.Gly88Asp). The first family consisted of 3 HD, 1 CAPD, 1 transplant and 2 outpatients. Genotyping in the 3 families revealed a total of 18 UMOD affected individuals, regardless of HD, age or symptoms. Metro-II calculated prevalence was 10 ppm. Juvenile gout was not present, simple cysts were present in a few cases. There was no proteinuria or hematuria. Some cases showed hyperuricemia, episodes of urinary tract infection, anemia in childhood and a history of hypothyroidism without specific antibodies. Patients started HD on average between 51.7±9.4 years. A decline in eGFR first occurred between 32.7±4.4 years. Renal biopsy in 3 patients revealed interstitial nephritis.

Conclusions: Familial renal disease without diagnosis constitutes a significant proportion of ESRD patients in Brazil. ADTKD is rare, but frequently underdiagnosed.

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FR-PO810

Molecular Genetic Investigations Identify New Clinical Phenotypes Associated with BCSL1-Related Mitochondrial Disease

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Introduction: The human *BSC1L* gene encodes a homolog of the *Saccharomyces cerevisiae* bcs1 protein, which has a known role in the assembly of Complex III of the mitochondrial respiratory chain. Several human disease phenotypes have been reported in association with pathogenic *BCS1L* variants, including severe presentations with Growth Retardation, Aminoaciduria, Chloestasis, Iron overload, Lactic acidosis and Early death (GRACILE syndrome) and the relatively mild Björnstad syndrome, characterised by abnormal flattening and twisting of hair shafts (*pili torti*) and hearing problems.

Case Description: Here we describe a patient who presented as an adult with aminoaciduria, seizures, bilateral sensorineural deafness and learning difficulties. He also exhibited progressive chronic kidney disease and is approaching end stage renal disease age 49 years. The diagnosis was not obvious. Whole genome sequencing revealled bi-allelic variants in *BCS1L;* the first with a previously reported c.166C>T, p.(Arg56*) heterozygous variant together with a novel pathogenic heterozygous variant c.205C>T, p.(Arg69Cys). Characterisation of cellular consequences of *BCS1L* variants confirmed a decrease in BCS1L protein levels. Biochemical analysis of Complex III revealed normal respiratory chain enzyme activities in the muscle but a decrease in Complex III assembly was detected in cultured fibroblasts.

Discussion: Together, these data support the pathogenicity of the novel *BCS1L* variants identified in our patient and emphasise the importance of consideration of a mitochondrial disease in unexplained CKD with multisystem features.

FR-PO811

A Case of Hereditary Amyloidosis

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Introduction: Amyloidosis is a condition caused by improperly folded proteins causing end organ damage as the result of tissue deposition. The gold standard of diagnosis is by Congo red staining and fibril deposition on electron microscopy. Although both AL and AA amyloidosis are the most common presentations, inherited forms of the disease occur. A case of Fibrinogen A alpha type (Afib), a form of hereditary renal amyloidosis, is presented.

Case Description: A 72-year-old Spanish male with history of hypertension presented for evaluation of chronic kidney disease and proteinuria. At time of presentation he reported a family history of amyloidosis in his maternal cousin. Other family members affected by kidney failure included the patient's mother, maternal aunt and maternal uncle. Assessment for monoclonal protein was negative. A kidney biopsy revealed hypertensive arteriosclerosis and amyloid deposits. Staining for AA and Lect2 were negative. Fibrinogen A amyloid was suspected given predominant glomerular fibrinogen deposits. Testing by liquid chromatography tandem mass spectrometry confirmed presence of Fibrinogen A alpha-type amyloid. Single gene analysis of the FGA gene was positive for a variant of undetermined significance. The patient was referred for genetic counseling. Genetic testing of his maternal cousin in Spain is in process.

Discussion: Hereditary amyloidosis is a group of conditions inherited in an autosomal dominant fashion and includes Afib amyloidosis. Characterized as a renal disorder, systemic disease can be present. It may occur more commonly than previously thought, mischaracterized as AL disease and occurring in dialysis cohorts. The disease occurs as a result of hepatic production of the amyloid protein with renal deposition and progressive decline in renal function. Treatment options are limited but simultaneous liver and kidney transplant appear to be curative. Amyloidosis presents most commonly as AL or AA forms. Hereditary amyloidosis must be considered anytime a diagnosis of systemic amyloidosis is made, as systemic involvement does occur in this disease commonly identified as renal limited. Identification of hereditary amyloidosis is important for prognosis and treatment of the disease.

FR-PO812

A Novel ELISA Allows Exact PLA2R1 Domain-Specific Autoantibody Quantification in Sera from Patients with Membranous Nephropathy

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Background: Phospholipase A2 Receptor 1 (PLA2R1) is the major antigen, which is recognized by autoantibodies in about 80% of patients with membranous nephropathy (MN). Total PLA2R1-antibody (PLA2R1-ab) levels are closely associated with disease prognosis and treatment response. The aim of the study was to investigate the clinical relevance of PLA2R1 domain-specific antibody levels in patients with PLA2R1-associated MN.

Methods: Individual CysR, CTLD1, CTLD7 and CTLD8 domains of the PLA2R1 were fused N-terminal to the rabbit Fc unit. The purified fusion proteins were used to establish novel PLA2R1 domain-specific ELISA. A prospective cohort of 149 untreated patients with newly-diagnosed PLA2R1-associated MN as well as a control cohort of 50 individuals (10 FSGS, 10 minimal change disease, 10 MPGN, 11 IgA nephropathy, 9 healthy donors) was analyzed. Results were validated using Western blot techniques.

Results: The ELISAs of the N-terminally located CysR and CTLD1 domains were highly sensitive and specific for the detection of domain-specific antibodies, as shown by the validation experiments using Western blot techniques. The CysR domain was recognized by 145 (97.3%) out of 149 MN patients, and the CysR-specific antibody level was highly correlated with the total PLA2R1-ab level (Spearmans rho = 0.949, $p<0.001$). In addition, CTLD1-ab were detected in 78 (52.3%) patients of the cohort. Again, a close correlation with the total PLA2R1-ab level was observed (Spearmans rho = 0.641, $p<0.001$). In contrast, the ELISA of the C-terminally located CTLD7 and CTLD8 domains exhibited a lower level of sensitivity compared to the Western blot technique. Precisely, all 149 MN patients of the cohort recognized the C-terminal CTLD7-8 domain in Western blot, while only 57 (38.2%) and 15 (10.1%) patients were tested positive in the CTLD7- and CTLD8-specific ELISA, respectively. A week correlation was observed between the CTLD7-ab level and the PLA2R1-ab level (Spearmans rho = 0.398, $p=0.002$). After adjustment for the total PLA2R1-ab levels, PLA2R1 domain-specific antibody levels could not predict the clinical outcome of patients in our cohort.

Conclusions: The total PLA2R1-ab levels, but not the PLA2R1 domain-specific antibody level, are predictive for the clinical outcome of patients with MN.

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FR-PO813

Discrepancy of Serum Ant-PLA2R and Podocyte PLA2R Expression in Taiwan Patients with Membranous Nephropathy

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Background: Anti-phospholipase A2 receptor (PLA2R) autoantibodies could be found in 60~85% patients with idiopathic membranous nephropathy, first discovered in 2009. Enhanced expression of podocyte PLA2R protein in these patients was also postulated later. There are some patients, however, have serum anti-PLA2R antibodies only without enhanced expression of podocyte PLA2R protein, vice versa. Currently, patient with membranous nephropathy have one of each will be diagnosed as PLA2R-associated membranous nephropathy. The mechanism of this discrepancy existing is not clearly known yet. To date, there are few articles reporting prevalence of serum anti-PLA2R and podocyte PLA2R expression in Taiwan patient with membranous nephropathy. We conduct a study to investigate this issue.

Methods: This investigation was prospectively performed in a tertiary hospital. From 2016/8-2018/5 period, patients with biopsy-proved membranous nephropathy will received blood test of plasma anti-PLA2R ELISA (Euroimmune®) before initiation of glucocorticoid or immunosuppressants. In addition, pathologic slides of these patients are

proceeded to IHC stain for PLA2R (Atlas®). Clinical parameters and pathologic findings are collected for analyzed.

Results: During the study period, totally 60 patients were diagnosed with membranous nephropathy. 58 patients received blood test for plasma anti-PLA2R, and 55 patients' pathologic slide were successfully proceeded to IHC stain of podocyte PLA2R. Within patients receiving both evaluation (n=53), there are 24 patients with double positive results (45.3%), and 19 patients with double negative results (35.8%). 3 patients have plasma anti-PLA2R antibody but got negative results of podocyte PLA2R enhanced expression (5.7%). 7 patients have no plasma anti-PLA2R antibody but got positive results of podocyte PLA2R enhanced expression (13.2%). Discrepancy of serum ant-PLA2R and podocyte PLA2R expression account for totally 18.9% of enrolled patients.

Conclusions: The reason of discrepancy of serum ant-PLA2R and podocyte PLA2R expression is still not known yet. Further studies are still needed Currently, serum anti-PLA2R ELSIA assay and tissue IHC stain for PLA2R expression are both useful tools for diagnosis of PLA2R-associated membranous nephropathy.

FR-PO814

Complement in Membranous Nephropathy

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Background: Approximately 70% of patients with membranous nephropathy (MN) have autoantibodies against the PLA2 receptor and biopsy specimens generally show positivity for C3 and IgG4 in immune deposits. However the pathway of complement activation in MN remains unclear.

Methods: We examined a cohort of patients with PLA2R positive (n=10) and negative (n=9) idiopathic MN. Cases of secondary MN were excluded. Biopsies were stained for PLA2R, complement components (C3c, C3d, C4d, C5b9, FHR5) and IgG4. Staining intensities were graded categorically as 0, 1+, 2+ and 3+. Electron microscopy was performed and the presence of subepithelial electron dense deposits (EDD) was graded according to the percentage of stage 1 and 2 EDD present. More than 80% of stage 1 and 2 EDD was marked 3+, 50-80% was marked 2+, less than 50% was 1+ and absent stage 1 and 2 EDD was scored zero. Clinical and laboratory characteristics were reviewed.

Results: Both cohorts had similar clinical and laboratory characteristics. The PLA2R positive group had intense staining for all complement factors assessed. In contrast, complement staining in the PLA2R negative group was overall less intense. IgG4 staining was strong in PLA2R positive cases but varied in the PLA2R negative cases. In the PLA2R positive group the majority of the EDD were stage 1 and 2 and this was associated with intense staining particularly for C3c, C5b9, FHR5 and IgG4.

Conclusions: We have identified differences in the intensity of staining of complement factors C3c, C3d, C4d, C5b9 and FHR5 between PLA2R positive and negative patients possibly suggesting differences in disease mechanism that could affect prognosis and influence stratification for complement inhibiting therapies.

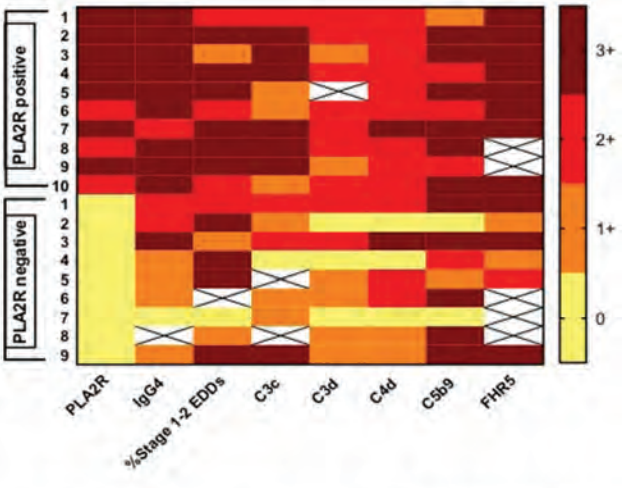

Figure 1. Heatmap of glomerular staining intensity of PLA2R, IgG4, % stage 1and 2 EDDs and complement factors in the two groups

FR-PO815

Clinical and Genetic Feature of Membranous Nephropathy in Patients with Primary Sjögren Syndrome

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Background: In our previous study, membranous nephropathy (MN) was the most common pathological patterns of glomerular involvement in patients with primary Sjögren's Syndrome. In this pilot study, we try to observe the clinical features and genetic background of MN patients with primary Sjögren's syndrome (pSS-MN).

Methods: Data from pSS-MN patients (n=73) confirmed by renal pathology were retrospectively collected from Peking Union Medical College Hospital, from Jan 30, 1993, to January 30, 2018. The serum anti-PLA2R antibody and renal tissue PLA2R antigen were tested by ELISA and immunofluorescence respectively. Idiopathic MN (iMN) patients were used as controls (n=150). Eight SNP sites, four high-risk sites for pSS and four high-risk sites for MN, as well as 3 HLA class II sites (HLA-DQA1, HLA-DQB1and HLA-DRB1) were typed by Sanger test in 23 pSS-MN patients. Genetic data of MN and normal people from Peking University First Hospital cohort and of pSS and normal people from Peking Union Medical Hospital cohort was used as control.

Results: pSS-MN patients were significantly older than iMN patients (mean age 53.3±14.1 vs 46.4±14.3, p<0.001) with predominantly female (78.1% vs 44.7%, p<0.001). Laboratory test showed significantly higher ESR (58.4±31.8 vs 35.0±26.5, p<0.001) but lower 24h urine protein (4.13±2.96 vs 6.02±5.71, p<0.001) in pSS-MN patients. There was no significant difference in eGFR and albumin level between the two groups when the biopsy was performed. pSS-MN and iMN patients had a similar positive rate of anti-PLA2R antibody (61.8% vs 74.0%, p=0.205). In pSS-MN patients, the mutation rates of 3 SNP (linked rs35771982- rs3749117 and rs9271588) were significance higher than normal control (30.1% vs 8.7%, p<0.001; 46.8% vs 21.7%, p=0.001, respectively), without significance when compared with iMN (p=0.30) or pSS patients (p=0.13). When compared with normal control, both HLA-DRB1*1501 (p=2.6×10^-5) and the haplotype (HLA-DRB1*1501-DQA1*0102DQB1*0602, 39.13% vs 9.00%, p=9.6×10^-8) in pSS-MN patients were identified as risk alleles, but the difference was not significant between the pSS-MN and iMN patients (p=0.09).

Conclusions: pSS-MN and iMN patients shared similar clinical and genetic feature, as well as PLA2R positive ratio. HLA-DRB1*1501 was the most significant HLA allele in pSS-MN patients.

Funding: Government Support - Non-U.S.

FR-PO816

Can Multidrug Resistance-Associated Protein-1 and P-Glycoprotein Expression on Peripheral Blood Lymphocytes Be Used as Biomarkers to Predict Steroid Resistance in Idiopathic Nephrotic Syndrome?

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Background: Steroid remains mainstay therapy for Idiopathic Nephrotic Syndrome (INS). Other than histological changes, pharmacogenomic factors may also affect steroid response. Overexpression of P-glycoprotein (P-gp) and Multidrug resistance-associated protein 1 (MRP-1) modulate the pharmacokinetics of steroids and may contribute to steroid resistance.

Methods: P-gp, and MRP-1 expression were evaluated on whole blood and functional activity on PBMCs in steroid-sensitive nephrotic syndrome (SSNS) (n=170, M=103, age=8.54±4.3 yrs); steroid-resistant nephrotic syndrome (SRNS) (n=81, M=43, age=7.43±4.6 yrs) patients. The genetic variants G2677T/A of MDR-1 gene were genotyped by PCR-RFLP technique.

Results: Biochemical difference were found in 24hrs urinary protein/Creatinine ratio (SSNS=0.13±.0.06, SRNS=3.67±0.91, p<0.001), total cholesterol (SSNS=144.21±34.61, SRNS=460.52±201.09, p<0.001). Percentage expression of P-gp (9.80±3.44 and 4.36±2.05, p<0.001); and MRP-1 (13.46+4.80 and 7.75+3.22, p<0.001) was significantly higher in SRNS than SSNS. P-gp expression on CD4+ (6.08±2.06 v/s 4.34±1.97, p=0.008); and CD8+cells (8.65±2.19 v/s 3.99±1.72, p<0.001) was high in SRNS than SSNS respectively. MRP-1 expression on CD4+ and CD8+cells was higher in SRNS (12.06±2.91 v/s 3.35±1.83, p=0.043); (5.11±2.68 v/s 1.59±0.99, p<0.001) respectively. Functional activity of P-gp and MRP-1 was significantly increased in SRNS as compared to SSNS (66.26±+15.77 and 30. 82±9.87, p<0.001); (67.62+14.67 and 32.97+11.36, p<0.001) respectively. ROC curve predictive cut-off values percentage of P-gp (7.13%) and MRP-1 (9.62%) was found to be predictive of steroid resistance with a sensitivity of 90% and 80.7%, and specificity of 90% and 80%, respectively. Moreover, homozygous mutant allele TT+AA was significantly associated with a resistant population of nephrotic syndrome (p=0.025, OR = 2.86 CI=1.14-7.14). The expression of P-gp (9.68±4.99 v/s 5.88±3.38, p=0.002) was significantly higher in the patients of homozygous mutant alleles compared to wildtype GG.

Conclusions: Overexpression of P-gp and MRP-1 on peripheral blood lymphocytes may be used as biomarkers for SRNS with high sensitivity and specificity. Use of P-gp and MRP-1inhibitors may prevent steroid resistance.

FR-PO817

Preclinical Studies of N-Acetylmannosamine (ManNAc) for Glomerular Diseases

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Background: Glomerular hyposialylation of glycoproteins and glycolipids has been implicated in human and experimental nephrotic syndromes. In this study we assessed the prevalence of glomerular hyposialylation in human nephrotic syndromes and explored

therapeutic potential of the sialic acid precursor *N*-acetylmannosamine (ManNAc) in three different nephrotic mouse models.

Methods: We created neuraminidase-induced and adriamycin-induced nephrotic mice and a nephrotic knock-in mouse model deficient in *Gne*, a central enzyme in sialic acid biosynthesis. ManNAc was administered in drinking water (~1 g/kg/d) to all three mouse models and clinical/biochemical parameters were assessed at different timepoints. Human glomerular sialylation was assessed by lectin histochemistry and confocal imaging in kidney biopsies of 123 well-phenotyped subjects with focal segmental glomerulosclerosis (FSGS; 69 subjects), minimal change disease (MCD; 29 subjects), or membranous nephropathy (MN; 25 subjects) supplied by the Nephrotic Syndrome Study Network (NEPTUNE).

Results: In all three mouse models, ManNAc administration increased glomerular sialylation and markedly reduced proteinuria and podocyte injury within a week of treatment. Hyposialylation was detected in an unexpectedly high percentage (>60%) of human kidney biopsies across all three disease entities, indicating that this condition may occur frequently, remains greatly unexplored and, importantly, may be treatable. Analysis of the association of sialylation status to clinical, pathological or other documented subject data showed a trend of correlation of severe glomerular hyposialylation with decreased eGFR, increased interstitial fibrosis and increased tubular atrophy, in particular in FSGS subjects.

Conclusions: These encouraging preclinical data, together with minimal toxicity of oral ManNAc therapy in humans (demonstrated in Phase 1 and 2 clinical trials for the rare hyposialylation disorder GNE myopathy) led to obtaining an Investigational New Drug approval to start a Phase 1 clinical trial to evaluate the safety, tolerability and pharmacokinetics of ManNAc in subjects with primary podocyte diseases (ClinicalTrials.gov NCT02639260). Preliminary results of this ongoing study are promising regarding safety and tolerability in subjects with glomerular disease.

Funding: NIDDK Support, Other NIH Support - NHGRI Support

FR-PO818

Nuclear Magnetic Resonance Metabolomic Profiling in Distinguishing Primary from Secondary FSGS

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Background: FSGS is a renal histologic lesion with diverse etiologies that cause podocyte injury and depletion. Subclasses of FSGS include primary, genetic, and secondary forms. These subclasses differ noticeably in management and prognosis. Without an accepted biomarker that discriminates among these FSGS types, classification of patients is often challenging. NMR-based urine metabolomics has shown potential in biomarker discovery. We hypothesized that urine metabolites can distinguish such patients.

Methods: We used high resolution NMR spectroscopy to study urines of 12 patients with primary FSGS and 14 patients with secondary or genetic FSGS. NMR spectra were binned and normalized by total spectrum area. Using non-specific feature selection, we analyzed the top 50% ranked bins in the dataset by partial least squares discriminant analysis (PLS-DA). Cross-validation was used to choose tuning parameters and to estimate predictive performance. The 95% confidence interval was estimated using the score test.

Results: PLS-DA score plot demonstrated considerable overlap within the secondary/genetic group relative to the primary group (Figure). When comparing these two groups, the top 5 spectra bins corresponding to highest variable importance included the following metabolites: choline, acetyl-carnitine, histidine, betaine, taurine *N*-phenylacetyglutamine and two unknown metabolites. Estimated predictive accuracy was 65.4% (95% CI 46.2-80.1%). Sensitivity was 58.3% (95% CI: 32.0-80.7%) and specificity was 71.4% (95% CI: 45.4-88.3%).

Conclusions: This study found that a panel of urine metabolites could potentially discriminate primary from secondary FSGS. Further studies are needed to identify the unknown compounds. Understanding the differential expression of these metabolites could shed new insights into the biology of FSGS.

Funding: Private Foundation Support

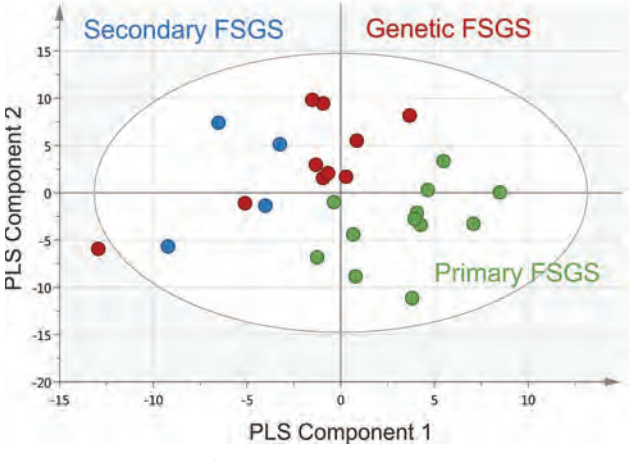

Figure. PLS-DA score plot of NMR spectra showing separation between patients with Primary and Secondary/Genetic FSGS.

FR-PO819

Tar Sequence (Double-Stranded-RNA)-PKR Activation Mediated Podocyte Injury with HIV-1 Infection

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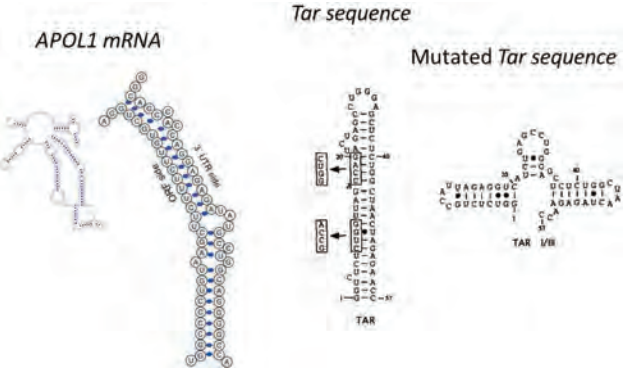
Background: Podocyte damage by Human Immunodeficiency Virus (HIV-1) is critical to the pathogenesis of HIV-1 associated nephropathy (HIVAN). There is an evidence that viral RNA and proteins detected in podocytes, but there is no productive infection. While APOL1 risk genotypes for FSGS is also the risk for HIVAN. We reported that activated PKR (interferon-induced double-stranded RNA-activated protein kinase) by double-stranded-RNA (dsRNA) of APOL1 mediates APOL1 nephropathy (Figure). HIV-1 also has dsRNA structures called *tar sequence*. Our hypothesis is that activated PKR by *tar sequence* could be cause of podocute injury in HIVAN.

Methods: We prepared virus stocks were prepared by transfecting 293T cells with lymphocyte tropic pNL4-3 and Macrophage-Tropic pNL(AD8) tittered by p24 ELISA assay. Differentiated conditionally immortalized human podocytes were cultured a 6 well plate and infected with virus (p24 100 ng/6-well).

Results: After 6 hours incubation, activated PKR signal was observed and prominent in podocyte cell line from APOL1 risk genotype with pNL(AD8). WT-1 signal was decreased in Podocyte cell line after 96 hours incubation. Virus RNA (rev, vpu, env, and nef) was detected in podocytes by RNA sequence analysis, however, there is no productive infection. Next we generate *tar sequence* mutated virus (Figure). Activated PKR signal was not observed with mutated *tar sequence*. Specific PKR inhibitor demonstrated that PKR inhibitor reduced activated PKR and ameliorate WT-1 decline.

Conclusions: HIV-1 direct infection on podocyte cell line providing mechanism by which tar sequence of HIV-1 contributes to cell injury via PKR. Targeting *tar* sequence - PKR opens novel therapeutic approaches to treating HIVAN.

Funding: NIDDK Support



FR-PO820

Akt Downregulation Induces Tubular Apoptosis via FoxO-1-Induced BIM Activation in Proteinuric States

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Background: Proteinuria induces tubular apoptosis preceding tubular atrophy but the underlying molecular mechanism remains undetermined. We demonstrated that cell survival protein, protein kinase B(Akt) is downregulated in proximal tubule epithelial cells in response to albumin overload. We hypothesize that inhibition of Akt expression decreases phosporylation and activation of its downstream targets Forkhead box(FoxO) transcriptional factors leading to mitochondrial apoptosis in proteinuric states.

Methods: *In-vitro* albumin overload: Human kidney proximal tubule epithelial cells(HKC-8) were incubated with 10mg/ml endotoxin free human albumin for 6, 16 and 24 hours. Chromatin immunoprecipitation(CHIP) assay was used to probe protein-DNA interactions. *In-vivo* albumin overload: Wild type and Akt1/2 $^{lox/lox}$ SGLT2 cre+ mice underwent daily intraperitoneal albumin injections(10mg/g) for 6 weeks. Human kidney biopsies with minimal change disease and focal segmental glomerulosclerosis (FSGS) were investigated for Akt activation.

Results: Expression of phosphorylated Akt-Ser 473 and Akt-Thr 308 was downregulated in association with increased caspase-3 activity and BIM expression in HKC-8 cells with albumin overload. Treatment of HKC-8 cells with pan Akt inhibitor MK-2206 and constitutively active(CA-Akt) Akt resulted in down regulation and upregulation of apoptosis respectively with albumin overload. *In-vivo* albumin overload decreased active p-Akt expression in association with tubular apoptosis. Akt1/2 $^{lox/lox}$ SGLT2 cre+ mice displayed increased BIM/Bax expression in mitochondrial isolates in association with tubular apoptosis in response to albumin overload indicating a close causal link between inhibition of Akt and mitochondrial apoptosis in proximal tubule epithelial cells. Furthermore, patient kidney biopsies (n=5) with FSGS displayed decreased proximal tubule PSer473 Akt expression. Albumin overload caused decreased Akt phosphorylation of FoxO-1 and 3 and nuclear translocation of FoxO-1. CHIP assay revaled transcriptional activation of BIM by Foxo-1.

Conclusions: We concluded that Akt and its downstream targets play an important role in mediating mitochondrial apoptosis leading to tubular injury in glomerular diseases. We propose that discovery of novel treatment options targeted for activation of Akt can ameliorate tubulointerstitial injury and progression in proteinuric states.

FR-PO821

Network-Based Assessment of Minimal Change Disease Identifies Glomerular IL7 Pathway Activation as Potential Mechanism for Biomarker Discovery and Drug Testing

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Background: Minimal change disease (MCD) is a major cause of the nephrotic syndrome. With a substantial number of patients requiring long-term immunosuppression leading to significant morbidity, our study aim was to determine the glomerular transcriptome of MCD to serve as base for biomarker discovery and drug target identification. Respective animal work showed podocyte injury induced by IL7/IL7R signaling *(Zhai S, BBRC, 2018)*.

Methods: Renal biopsies from adult patients representing the following groups were selected from the Norwegian Kidney Biopsy Registry: MCD (n=14), as well as normal tissue (n=8) and primary membranous nephropathy (MN; n=12) as two reference groups. Glomerular RNA for 75 base-pair, paired-end RNA-seq was obtained via laser capture microdissection from archival FFPE cross-sections. Systematic delineation of condition-specific alteration in transcriptional landscapes was achieved by combining pathway-centered analyses with methodologies derived from network science and integrating multiple bioinformatics resources.

Results: Compared to normal glomeruli, glomeruli from MCD displayed an inflammatory signature that appeared to be predominantly governed by the IL1 and IL7 systems. While enrichment of IL1 production and secretion was a shared feature of MCD and MN compared to normal tissue, responses involving IL7 pathway activation were unique to MCD. Indeed, IL7R expressed by glomeruli was the most up-regulated gene of the interleukin-family in MCD vs normal controls. IL7 pathway activation was paralleled by significant enrichment in adaptive immune system processes and transcriptional regulation, and by depletion in pathways related to energy metabolism and transcription. Downregulation of these organ function-related themes again occurred predominantly in MDC and were significantly less pronounced in MN.

Conclusions: Our results demonstrate that archival renal biopsies can be used to generate glomeruli-specific gene expression profiles suitable for systematic delineation of kidney diseases. We provide a data-driven rationale to experimentally address the MCD-specific features as biomarkers and as novel drug targets. In this context, inhibiting the activation of IL7 pathway is particularly promising.

FR-PO822

Expression of Beta-3 Adrenergic Receptor (β3-AR) in Normal and Pathological Renal Tissue

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Background: The β3-adrenoreceptor (β3-AR) is a G-protein coupled receptor whose expression has been reported in multiple nephron segments of the murine kidney, including thin ascending limb (tAL), thick ascending limb (TAL), distal convoluted tubule (DCT) and cortical collecting duct (CCD). However, no information is available regarding β3-AR presence in human kidney. The aim of our study was to investigate the presence of β3-AR at the glomerular and tubular level in normal and pathological human renal tissue.

Methods: β3-AR has been detected by immunohistochemistry in 10% formalin-fixed and paraffin-embedded kidney tissue sections of 6 glomerular diseases (GD), 6 autosomal dominant polycystic kidney disease (ADPKD) and 6 normal kidney donors (KD). We used three different β3-AR antibodies: rabbit polyclonal antibody (Biomatik), mouse polyclonal antibody (Abnova) and mouse monoclonal antibody (R&D System). Fluorescence co-localization analysis in combination with specific tubular markers was performed to characterize β3-AR expression in different tubular segments: LPR2 for staining in proximal tubule, AVPR2 for TAL, SLC12A3 for DCT and AQP-2 for CCD.

Results: β3-AR protein detected by polyclonal antibodies was present at the glomerular and tubular level in all renal samples with more intense staining in tubules from GD patients. β3-AR staining was also present in normal tubules from ADPKD samples but it was reduced in cystic tubules. Immunofluorescence studies performed using monoclonal antibodies showed β3-AR colocalization with tubular markers in TAL, DCT and CCD.

Conclusions: This is the first report on β3-AR localization in human kidney. Our data demonstrate that β3-AR is present in glomeruli and in nephron segments involved in water and solute reabsorption. The presence of this receptor in tissue from normal and diseased kidney suggests that further studies elucidating the physiology of β3-AR could lead to the identification of a new potential therapeutic targets in the treatment of renal diseases.

FR-PO823

Elucidating the Effects of Complement Stress in Neutrophil Extracellular Traps (NETs) Formation in C3 Glomerulopathy

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Background: Neutrophil extracellular traps (NETs) have been recently implicated in several disease states, which is mostly attributed to their pro-inflammatory and prothrombotic properties. Neutrophils carry complement proteins, and when activated, release these complement proteins and contribute to their activation via NETs. By improving our understanding of the interaction of the complement system and neutrophils and their respective response to produce these NETs, we will be able to better understand how neutrophils and NETs play a role in complement-mediated diseases such as C3 glomerulopathy (C3G), in which both neutrophils and complement are expected to contribute to disease pathogenesis.

Methods: Neutrophils freshly isolated from healthy controls (HC) were used (male, ages 18-24 years old). Experiments were done at least threefold (N=3). We either applied our established protocol of complement activation via the use of a sensitizing antibody (monoclonal anti-human CD59 antibody) in combination with 50% NHS using healthy control (HC) neutrophils or investigated patient-derived neutrophils incubated in autologous serum or serum-free media. Complement deposition (C3b; C5b-9) on neutrophils was detected via IF and flow cytometry. NETosis was detected using SYTOXGreen assay and immunofluorescence (IF) imaging.

Results: We found that complement activation of neutrophils resulted in (i) surface deposition of C3b and C5b-9; (ii) appearance of citrullinated Histone 3 (cit-H3) and myeloperoxidase (MPO) release; (iii) the stepwise completion of NETosis after the transfer of neutrophils into serum-free media (SFM). In addition, we found that C3G patient-derived neutrophils (i) were positive for surface complement deposition; (ii) were positive for cit-H3; and (iii) completed NETosis after transfer from autologous serum into SFM. Finally, HC neutrophils (i) when incubated with C3G patient-derived serum showed cit-H3 formation, and (ii) NETosis when transferred into SFM.

Conclusions: Complement activation of neutrophils induces NETosis in a step-wise fashion with cit-H3 formation in serum ("priming") and full NETosis in SFM. These findings can be interpreted as resemblance of an intra- vs. an extra-vascular environment, suggesting that neutrophils are primed intra-vascularly and committed to full NETosis only extra-vascularly.

Funding: Government Support - Non-U.S.

FR-PO824

Minimal Residual Autoimmunity After Rituximab in ANCA-Associated Vasculitis Patients

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Background: B-cell depletion with rituximab (RTX) is an effective treatment for ANCA-associated vasculitis (AAV) patients. Repeated RTX upon B-cell repopulation or return of ANCAs improved therapeutic efficacy, which indicates the presence of minimal residual autoimmunity (MRA) after RTX. Therefore, this study aimed to perform in-depth phenotypic and functional analyses of B and plasma cells after RTX in AAV.

Methods: EuroFlow-based highly sensitive flow cytometry (HSFC) was used during longitudinal follow-up of RTX-treated AAV patients (n=12). To investigate MRA in the memory B-cell compartment after RTX, peripheral blood mononuclear cells (PBMCs) were stimulated with CpG, IL-2 and IL-21 *in vitro* to induce plasma cells (PCs) and ANCA-IgG and -IgM were measured in these supernatants and in paired serum samples by ELISA.

Results: By employing HSFC we demonstrated that 12 weeks after RTX, low but significant numbers of circulating $CD19^+$ B cells (0.21^*10^6 cells/L) could still be detected (reduction of -99.7%). While naïve B-cells, memory B-cells and $CD20^+$ plasmablasts (PB) were rapidly depleted, $CD20^-$ PCs were reduced slower and depleted incompletely. Residual $CD20^-$ PCs were 0.05^*10^6 cells/L (-95.8% from baseline), whereof 57% were mature $CD138^+$ PCs. Early repopulation at 12 weeks was dominated by $CD20^-$ $CD138^-$ PCs, followed by $CD20^+$ PBs at 24 weeks while memory and naïve B cells remained suppressed. Simultaneously, serum ANCA IgG, IgM and IgA, produced by autoreactive PCs, decreased but did not disappear after RTX. Interestingly, 24 weeks after RTX, serum anti-MPO IgM increased in 3/4 patients, which associated with repopulating $CD20^+$ PBs. This suggested remaining autoreactive B cells despite RTX treatment, which was further studied by *in vitro* PBMC cultures. In these supernatants both anti-MPO-IgG and -IgM were detected at baseline, whereas anti-MPO IgG disappeared after RTX, in contrast to anti-MPO IgM, which was detected 24 weeks after RTX.

Conclusions: RTX results in a strong but not complete B cell depletion. In-depth analysis demonstrated that both ANCA-producing PCs and ANCA-memory B cells can be detected after RTX, indicating residual B-cell autoimmunity in AAV patients. Further identification of MRA could be worthwhile for guiding personalized treatment in AAV patients.

FR-PO825

Nonspecific Inflammatory Markers Can Be Predictors of Disease Activity in ANCA-Associated Vasculitis

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Background: The purpose of the study was to compare non-specific inflammatory markers such as high sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR) and procalcitonin level (PCT) in clinically active ANCA associated vasculitis (AAV) before and after the induction therapy.

Methods: 28 patients with AAV diagnosed in the Nephrology Clinic between 2014 and 2017 were included. sCRP was measured using nephelometry assay (BNII Siemens) with a cutoff point 0.8 mg/dl and procalcitonin level using electrochemiluminescence method (*Elecsys BRAHMS PCT Cobas*, Roche) with the upper reference range of 0.046 ng/ml. Statistical analysis was performed using Mann-Whitney, Wilcoxon signed-rank and Kruskal-Wallis tests (SPSSv18).

Results: 28 patients with a median age 58 years (67.9% female) were included. Granulomatosis with polyangitis (GPA) was diagnosed in 16 (57%) patients, microscopic polyangitis (MPA) in 13 (43%). The most frequently affected organs were: lungs (83%), joints (83%) and kidneys (75%). Before the treatment the median BVAS/WG score was 7 points, the median hsCRP was 2 mg/dl, median ESR 56 mm and the median PCT was 0.17 ng/ml. Severe, systemic disease (EULAR) was diagnosed in 12 patients (42.8%). The these cases median hsCRP (10.3mg/dl), ESR (81.6 mm) and PCT (3.4 ng/ml) were significantly higher in comparison to the rest of the study group (p=0.006,0.007, <0.001 respectively). The mean serum creatinine concentration (SCr) was 3.4 ±2.2 mg/dl, eGFR 33.2 ±30,4 ml/min/1.7 m^2, 12 patients were treated with hemodialysis. The median ANCA level was 51 IU/ml. In all patients concomitant infections were excluded. After 6 months of treatment the whole group reached clinical remission. Median hsCRP was 0.2 mg/dl, ESR 17 mm, PCT 0.05 ng/ml and were significantly lower (p<0.001) in comparison to the levels before the treatment. The mean ANCA level was 4.5 IU/ml and were significantly lower after the induction treatment (p<0.001).

Conclusions: Non-specific inflammatory markers such as CRP, ESR, procalcitonin levels are associated with AAV activity and decreases after immunosuppressive, induction therapy.

FR-PO826

Difference Between Urinary Vesicle Fibroblast Specific Protein 1 and Urinary-Soluble CD163 as a Marker of Crescent Formation

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Background: Extracellular vesicles (EVs) are present in urine. We previously reported that fibroblast-specific protein 1 (FSP1) levels in urinary EVs (U-EVs) reflect active and ongoing glomerular injury, such as cellular crescent formation. However, it is unknown whether FSP1 in U-EVs is superior to urinary soluble CD163 (U-sCD163) which was established as a biomarker of crescentic glomerulonephritis.

Methods: To address that issue, we collected urine samples from 37 patients with various types of glomerular disease (6 with ANCA-associated nephritis, 11 with IgA nephropathy, 11 with membranous nephropathy, 6 with minimal-change disease and 3 with lupus nephritis), and purified U-EVs using total exosome isolation regent. We measured FSP1 levels in U-EVs and sCD163 levels in total urine using ELISAs and analyzed correlation between FSP1 or sCD163 levels and rates of biopsy-proven crescent formation. To determine whether FSP1 and sCD163 levels were associated with crescentic formation, we used receiver operating characteristic (ROC) curve analysis.

Results: FSP1 levels in U-EVs correlated positively with U-sCD163 levels (r=0.367, P<0.05). FSP1 levels in U-EVs also correlated positively with rates of biopsy-proven cellular crescent formation (r=0.562, P<0.001). Meanwhile, U-sCD163 levels correlated positively with rates of biopsy-proven cellular (r=0.595, P<0.001), fibrocellular (r=0.511, P<0.001), and fibrous (r=0.501, P<0.001) crescent formation. FSP1 levels in U-EVs and U-sCD163 levels for predicting cellular crescent formation affecting more than 20% of total glomeruli was 2.4 μg/gCr and 14.5 ng/mgCr, respectively, with an area under the ROC curve were 0.88 (95%CI, 0.693 to 1.070) and 0.82 (95%CI, 0.673 to 0.961) (P=0.58). Both U-sCD163 levels and FSP1 levels in U-EVs were significantly reduced after treatment (median: 4.90 to 0.35 ng/mgCr, mean: 2.72 to 0.14 μg/gCr).

Conclusions: These data suggest that both FSP1 in U-EVs and U-sCD163 are available biomarkers of active and ongoing glomerular injury, such as crescent formation. However, it was FSP1 level in U-EVs that specifically reflected cellular crescent formation requiring urgent treatment.

Funding: Government Support - Non-U.S.

FR-PO827

Patients with ANCA-Associated Vasculitis (AAV) Display Major Phenotypic Signs of T-Cell Dysfunction

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Background: In chronic infection and tumors, persistent T cell stimulation results in functional T cell exhaustion and anergy but limited data are available on the association between chronic inflammation in AAV and T cell dysfunction.

Methods: We performed a comprehensive flow-cytometric analyses of major T cell markers of T cells dysfunction, including exhaustion ($KLRG1^+$ $PD1^+$ $CD57^-$), and anergy ($KLRG1^+$ $PD1^-$ $CD57^+$) in 20 patients with AAV with renal involvement (at clinical onset, before immunosuppressive therapy initiation) and 12 healthy controls (HC). We also measured $CD4^+$ $CD25^+$ $CD127^{low}$ regulatory T cells (Treg) and intracellular IFN-g, IL-4, and IL-17 production in the same study groups.

Results: We found a remarkable and statistically significant increase in $CD4^+$ and $C8^+$ T cells with exhausted and anergic phenotype in AAV patients compared to HC (**Fig. 1A-D**). AAV patients also displayed significantly higher levels of circulating Treg (**Fig. 1E**). Despite Treg increase, we did not record a significant difference in intracellular cytokine production.

Conclusions: Patients with AAV display a unique immune phenotype characterized by extensive T cell dysfunction, associated with increased Treg, suggesting the existence of chronic inflammation before clinical onset of the disease.

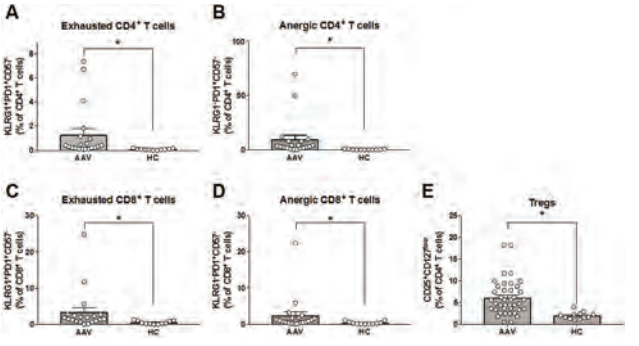

Fig. 1. Percentages of $CD4^+$ (**A-B**) and $CD8^+$ T (**C-D**) cells with exhausted or anergic phenotype and regulatory T cells (Treg) (**E**) according to disease group and in healty controls (HC). *P⟨0.05.

FR-PO828

Antibodies to Plasminogen and a Pathogenic Myeloperoxidase (MPO) Epitope Precede MPO- and Proteinase 3-ANCA in Patients with ANCA Vasculitis

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Background: The preclinical immunopathogenesis of anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis has not been elucidated. Antibodies to plasminogen (anti-PLG) and a specific epitope of myeloperoxidase ($MPO^{447-459}$, anti-KIV) are associated with active disease. The presence of these antibodies has not been examined prior to diagnosis. We hypothesized that anti-PLG and anti-KIV precede detectable MPO-ANCA and proteinase 3 (PR3)-ANCA.

Methods: Up to 4 serum samples collected before clinical diagnosis were available from 64 patients with ANCA vasculitis (50 PR3, 12 MPO, 2 unknown) and 63 healthy controls (HC) matched for age, gender, ethnicity, and timing of sample through the Department of Defense Biorepository. Anti-PLG, anti-KIV, MPO- and PR3-ANCA were measured by ELISA. Analyses accounted for matched pairs using McNemar tests and odds ratios and 95% confidence intervals from stratified exact conditional logistic regression.

Results: Anti-PLG was detected in 17/64 (27%) of cases prior to diagnosis (median = -8.8 years [IQR -13.1, -2.0]). Anti-PLG was positive before ANCA in 76% (13/17) of cases where both were positive. Anti-KIV was detected in 21/64 (33%) of cases prior to diagnosis (-6.6 years [-15.0, -4.1]), was elevated before ANCA in 71% (15/21) cases, and elevated when MPO-ANCA was negative in 33% (4/12) of MPO-ANCA patients. ANCA patients were more likely to have elevated anti-PLG and anti-KIV than matched controls (Table). Limiting analysis to PR3-ANCA patients, the odds ratio for anti-PLG remained statistically significant; the odds ratio for anti-KIV was the same albeit not statistically significant.

Conclusions: Anti-KIV and anti-PLG antibodies are present years before diagnosis and prediagnostic ANCA seropositivity. Thus, anti-KIV and anti-PLG may participate in the initial genesis of the ANCA autoimmune response and be part of a multi-hit immunopathogenic mechanism. The views expressed are those of the author and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.

Funding: NIDDK Support, Other U.S. Government Support

Paired Group	Variables	Exact odds ratio (CI)	P
All ANCA with matched-pair controls (n=63)	Anti-PLG	6.5 (1.47,59.33)	0.007
	Anti-KIV	3.0 (1.14,9.23)	0.023
Limited to PR3-ANCA with matched-pair controls (n=50)	Anti-PLG	5.0 (1.07,46.93)	0.039
	Anti-KIV	3.0 (0.91,12.76)	0.077

FR-PO829

CD4⁺ T Cell Abnormalities in the Myeloperoxidase-ANCA Associated Vasculitis

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Background: In ANCA-associated vasculitis, MPO-specific CD4 +T cells have been reported to involve in renal injury. Although in Granulomatosis with Polyangiitis (GPA), it has been found that lymphopenia is a common clinical feature, and the effect of treatment was excluded. However the pathogenesis of T cell recruitment is not fully elucidated. Thus, we dissect whether the microscopic polyangiitis patients have the similar symptoms and the underlying pathogenesis.

Methods: Clinical data from 143 newly diagnosed microscopic polyangiitis' patients (Collection time prior to use of Glucocorticoid and immunosuppressants) and 176 healthy controls was collected and analyzed. The phenotypic characterization of peripheral blood lymphocyte in 33 of MPA patients was measured by Flow cytometry. Meanwhile, disease activity of these patients according to the Birmingham Vasculitis Activity Score was marked. The cytokine produced by relevant CD4+T cells was detected. Chemokine and chemokine receptors axis concerning T cell recruitment was observed by immunohistochemistry in formaldehyde-fixed kidney nephridial tissue.

Results: MPA patients' lymphocyte count existing in peripheral blood was significantly decreased compared with healthy control. Besides, abnormal CD4+T cell subsets was found in MPA patients. Specifically, the proportion of Th1, Th9, Th17, Th22 was increased in these patients (BVAS≥15 points). In accordance with this, The concentration of IFN-γ, IL-9, IL-17A, IL-22 was observed to elevate. Moreover, both CXCL10+, CCL20+ cells and CCL27+cells, were adjacent to CXCR3+ cells, CCR6+cells, CCR10+ cells respectively in Paraffin section of kidney.

Conclusions: The activity of microscopic polyangiitis could lead to abnormalitis of absolute count and subsets in CD4⁺ T cells. CD4⁺ T cell is obviously activated and recruited to kidney to induce immunopathologic injury.

FR-PO830

Single-Cell RNA Sequencing Uncovers Distinct Clusters of T Helper 17 Cells In Renal Autoimmune Disease

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Background: T cells play a pivotal role in the pathogenesis in various autoimmune diseases by their ability to differentiate into pathogenic effector Th1 and Th17 cells, this includes human and experimental glomerulonephritis. CD4⁺ T cells and Th17 cells in particular can have a high degree of plasticity in the brain and intestine but show limited spontaneous plasticity in the kidney. However, the mechanisms that control stability and transdifferentiation of Th17 cells into alternate subsets and the impact of T cell plasticity on autoimmunity are incompletely understood.

Methods: To address the heterogeneity and plasticity of renal Th17 cells in experimental glomerulonephritis in more detail in an unbiased approach, we established single cell RNA-sequencing of FACS-sorted T cells from the kidney in experimental crescentic glomerulonephritis (cGN, NTN).

Results: Here, we report data from 6,841 eYFP positive renal Th17 cells from IL-17A fate reporter mice (Il17aCre x R26reYFP). Our analysis unveiled a pronounced variety within this population. We discovered 10 clusters based on transcriptional similarities. Overall, in 25% of all cells we could detect IL-17A mRNA. These actively IL-17A-expressing cells are enriched in 3 clusters, which underscores the heterogeneity of our dataset. Interestingly, 25% of IL-17A negative cells (exTh17) display expression profiles of inactive states. Moreover, one cluster of cells with a Th1 profile emerged from Th17 cells and one cluster displays high Foxp3 expression indicating transdifferentiation of Th17 cells into Th1 cells and regulatory T cells, respectively.

Conclusions: In summary, our single cell atlas of renal Th17 cells shows a high degree of heterogeneity and expression profiles of the different clusters could build the basis for the analysis of potential cell-cell crosstalk that include resident kidney cells.

FR-PO831

Novel Assays to Distinguish Between Properdin-Dependent and Properdin-Independent C3 Nephritic Factors Provide Insight for Properdin-Inhibiting Therapy

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Background: C3 glomerulopathy (C3G) is a severe renal disorder caused by dysregulation of the alternative complement pathway and is characterized by depositions of C3 fragments in the glomeruli. C3 nephritic factors (C3NeFs) are found in the blood of more than half of C3G patients. These autoantibodies recognize the alternative pathway C3 convertase and prolong its activity. C3NeFs can be dependent or independent of the complement regulator properdin for their convertase-stabilizing function. However, studies to determine the properdin-dependency of C3NeFs are rare and not part of routine patient investigations. Until recently, only supportive treatments for C3G were available. Complement-directed therapies are now being investigated. We hypothesized that patients with properdin-dependent C3NeFs may benefit from properdin-inhibiting therapy to normalize convertase activity.

Methods: Therefore, we have validated two hemolytic assays to distinguish between properdin-dependent and properdin-independent C3NeFs by assessing the convertase activity and stability in absence of properdin. The first assay measures convertase stabilization by patient immunoglobulins in properdin-depleted serum. The second measures convertase stabilization directly in patient serum supplemented with the Salp20, a properdin-blocking agent.

Results: Blood samples from 13 pediatric C3G patients positive for C3NeF were tested for convertase stabilization in absence of properdin. Three patients presented with properdin-dependent C3NeFs as no C3NeF activity was observed in absence of properdin, whereas the C3NeF activity of the other 10 patients was independent of properdin. In the samples of the patients with properdin-dependent C3NeFs, addition of the properdin-blocking agent Salp20 normalized the convertase activity profile.

Conclusions: These results indicate that inhibition of properdin in patients with properdin-dependent C3NeFs can normalize alternative pathway convertase activity and could represent a novel therapy. Our assays provide a tool for identifying C3G patients who may benefit from properdin-inhibiting therapy and should be incorporated into standard C3G laboratory investigations.

FR-PO832

High Levels of Intestinal-Activated IgA⁺ B Lymphocytes Support the Pathogenic Role of Intestinal Mucosal Hyper-Responsiveness in IgA Nephropathy (IgAN) Patients

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Background: In the last years, the role of mucosal immunity in IgAN, together with that of the gut microbiota in the activation of innate and adaptive immune cells, has gained importance. Particularly interesting is the role of the microbiota and intestinal immunity in IgAN, due to the activity of secretory IgA in the intestinal mucosa. Here we studied the intestinal-renal axis connections analyzing levels of BAFF, April and intestinal-activated B cells in patients and healthy subjects (HS).

Methods: Serum and fecal samples were collected from 44 IgAN patients and 23 HS. BAFF and APRIL serum levels were measured by ELISA assay. Metabolomic analysis of fecal microbiome was performed by mass spectrometry. B cell subsets were identified by FACS. We used anti-IgA, anti-Integrin β7 and anti-CCR9 antibodies to identify B cell subsets producing IgA and B cells from intestinal mucosa.

Results: IgAN patients had increased levels of Baff correlating to higher amounts of 5 specific microbiota metabolites (p=.012). We found also high April levels in IgAN patients. BAFF and APRIL can be produced by the intestinal epithelium, in response to signals triggered by TLRs activated by the commensal bacteria in the intestinal lumen. In addition, we found that IgAN patients have a higher proportion of circulating Breg activated at the intestinal level (CCR9⁺/INTB7⁺) compared to HS (p=0.02). Moreover, IgAN patients had also high levels of CCR9⁺/INTB7⁺ memory Bcells (p=.006) and of intestinal IgA-producing memory Bcells (CCR9⁺/INTB7⁺/IgA⁺ p=.03). Interestingly, they were significantly increased in IgAN patients but not in non-IgA glomerulonephritis. Finally, we found that IgAN patients had high levels both of total plasmablasts (p=.001) and of intestinal-activated plasmablasts (p=.01).

Conclusions: The results of our study showed for the first time an important difference in the amount of intestinal-activated B lymphocytes among patients with IgAN and HS, confirming the hypothesis of the pathogenic role of intestinal mucosal hyperresponsiveness in the IgAN patients. Therefore, this represents an important area of research for new targeted therapies aiming to stop the evolution towards end stage renal disease.

FR-PO833

B Cell and Monocyte Phenotyping in IGA Nephropathy: A Quick Asset to Investigate the Immune Status in Patients with IGA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common glomerulonephritis. Naive and adaptive immune cells play a major role in the development and progression of disease, therefore unraveling a correlation between changes in the immune status of the patient and clinical outcomes is of great value. We aimed to investigate B cell and monocyte phenotype, comparing the IgAN patients with disease controls (patients with polycystic kidney disease) and healthy individuals.

Methods: IgAN patients (n = 13) were recruited from Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden. Patients (men 46%,) with median age of 45 years (IQR 38-60), median eGFR of 57 ml/min x1.73m^2 (IQR 42-84) and median urine albumin-to-creatinine ratio of 74 mg/mmol (IQR 18-116). Disease controls with polycystic kidney disease (n=13) were matched for eGFR, gender- and age (±10 years). Healthy controls (n = 13) were gender- and age-matched (±5 years) with patients. CD3+ cells were isolated from freshly separated peripheral blood mononuclear cells by positive selection using a magnetic cell sorting system. CD3+ and CD3- cells were then divided and stained for different subsets of B cells and analyzed by flowcytometry. Cytokines were analyzed by ELISA.

Results: We report an increase in the proportion of CD14+ CD16++ cells (non-classical monocytes) in patient with IgAN comparing to healthy individuals and disease controls. Decrease in the proportion of CD19+ CD27+ IgD+ cells (pre switched B), CD19+ CD27+ CD38+ cells (plasmablasts) in the peripheral circulation of IgAN patients. IgAN and disease control showed an increase in CD19- CD27hi CD38 hi (transitioned plasma cells). We report a higher proportion naïve/pre switched in IgAN patients compared to healthy- and disease controls. We report significantly higher IL-6 in IgAN compared to helathy controls.

Conclusions: The decrease in the number of circulatory pre-switched B cells and plasmablasts, but an increase of transitioned plasma cells in our study suggests trafficking of subsets of B cells in IgAN patients between peripheral blood and extravascular lymphoid tissues. The increase in the proportion of inflammatory monocytes in IgAN patients may play a role in the high inflammatory state and possible crosstalk between different sectors of the immune system through the IL-6 axis.

FR-PO834

Transglutaminase 2 (TGM2) and Lysozyme Significantly Upregulated in Staphylococcus Infection-Associated Glomerulonephritis (SAGN): A Mass Spectrometry Study

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Background: SAGN and primary IgA nephropathy (IgAN) are considered separate disease entities with different treatment approaches. However, overlapping histologic features and mesangial IgA deposits in both lead to diagnostic dilemma. A proteomic study on kidney biopsies was performed to identify potential distinguishing biomarkers.

Methods: Formalin fixed paraffin embedded (FFPE) tissue was used - SAGN (4), primary IgAN (8), baseline transplant biopsies (7), and acute tubular necrosis (ATN) (8) for laser capture and HPLC-MS/MS using the Oribtrap Elite instrument. Spectral counts were modeled as negative binomial distribution and compared. Immunohistochemistry (IHC) for lysozyme, S100 A9, CD68, TGM2 was performed (n=68).

Results: SAGN glomerular proteome showed remarkable similarities with IgAN, but significantly higher expression of monocyte/macrophage proteins - lysozyme and S1009 compared to primary IgAN (Oxford Classification E0 C0 and E1 C1), confirmed by IHC cell counts (Fig.1 p<0.0001, p<0.005 respectively). Tubulointerstitial proteomes differed widely. SAGN proteome resembled that of ATN, with marked downregulation of tubular metabolic pathways (including amino acid degradation, fatty acid oxidation, mitochondrial respiratory pathway) as compared to IgAN. Stress molecule TGM2 was highly expressed in SAGN (and ATN) along with other extracellular matrix proteins, and epithelial tight junction proteins.

Conclusions: SAGN may represent an inflammatory and rapidly progressive form of GN with marked tubular dysfunction, in contrast to primary IgAN. Prominent endocapillary proliferative glomerular lesions with significantly higher number of lysozyme positive cells, coupled with severe ATN and diffuse tubulointerstitial staining for TGM2 may favor SAGN over primary IgAN, in the appropriate clinical context.

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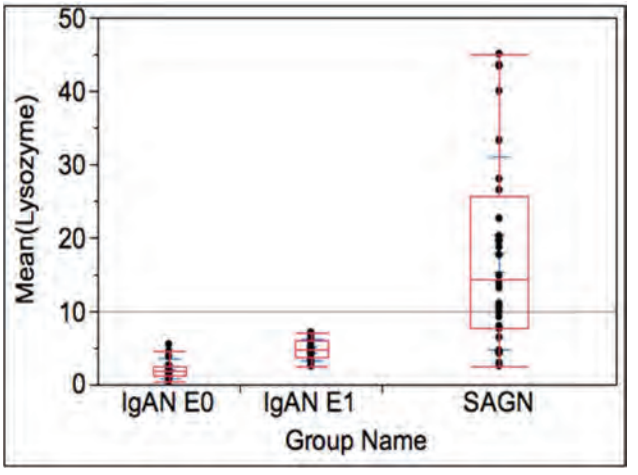

Mean Lysozyme positive cells /glomerulus.

FR-PO835

Genome-Wide Association Study for Serum Galactose-Deficient IgA1 in IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Galactose-deficient IgA1 (Gd-IgA1) plays a key role in the pathogenesis of IgAN. Although the heritability of serum Gd-IgA1 levels is high (ranging from 54% to 80%), the genetic association between Gd-IgA1 and IgAN has not yet been clearly determined. To further identify novel susceptibility loci, we carried out a genome wide association study (GWAS) for serum Gd-IgA1 levels in IgAN patients.

Methods: We performed a quantitative trait GWAS for serum Gd-IgA1 levels, with discovery and follow-up in 1,127 IgAN patients in a Chinese population. Gd-IgA1 levels were measured using a *Helix aspersa* lectin–based ELISA method. The mRNA levels of susceptibility genes in peripheral blood mononuclear cells (PBMCs) were evaluated by mRNA microarrays (Affymetrix PrimeView Human Gene Expression Array and Illumina HT-12 v4 Expression BeadChip).

Results: We identified two loci passing genome-wide significance, including *GALNT12* ($P = 1.67 \times 10^{-8}$, Beta = 0.68) and *C1GALT1* ($P = 3.10 \times 10^{-8}$, Beta = 0.24). Additionally, we confirmed reported association of *C1GALT1* with serum Gd-IgA1 levels, including rs1008897 ($P = 9.75 \times 10^{-3}$) and rs13226913 ($P = 3.89 \times 10^{-2}$), which are common variants in Europeans but rare in East Asians (MAF 34% vs. 5% and 58% vs. 7%). *C1GALT1* variant associated in our study is in partial linkage disequilibrium with rs1008897 (D' = 0.92, $r^2 = 0.07$) and rs13226913 (D' = 0.44, $r^2 = 0.02$). Compared with healthy controls (n = 61), *GALNT12* and *C1GALT1* showed lower mRNA expression in PBMCs from IgAN patients (n = 94) (0.86-fold change, $P = 1.00 \times 10^{-6}$ and 0.90-fold change, $P = 1.92 \times 10^{-4}$, respectively). Sub-phenotype analysis showed that the risk allele of *GALNT12* variant was associated with decreased serum C3 levels (P = 0.02, Beta = - 0.05).

Conclusions: Our study identifies two loci, which encode two enzymes (GALNT12 and C1GALT1) involved in O-linked glycosylation, are associated with serum levels of Gd-IgA1 in IgAN. Down-regulation of these two enzymes may contribute to the generation of aberrantly glycosylated IgA1 in IgAN.

FR-PO836

RNA Sequencing Identifies Novel Genes Implicated in the Pathogenesis of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is one of the most common form of glomerulonephritis throughout the world and also the leading cause of kidney failure among Asian populations. Previous genetic studies have identified several genetic factors predisposing to IgAN, however, the transcriptome changes of kidney tissue of IgAN are not thoroughly investigated yet, which was crucial for the exploration of the molecular pathogenesis of this disease.

Methods: We used RNA-sequencing to study the whole transcriptome of kidney biopsies of 8 IgAN patients and 5 control samples. Differentially expressed genes (DEG) were identified using DESeq2. GO and pathway enrichment analysis were applied to explore the biology relevance of these DEGs to IgAN.

Results: We identified 54 genes with differential expression between the IgAN patients and the healthy controls, with 41 genes were up-regulation and 13 were down-regulation in the IgAN patients (fold change >1.5 and FDR<0.1). Pathway enrichment analysis revealed that these DEGs were involved in cotranslational protein targeting to membrane, humoral and innate immune response and endothelium development. Among these, the top of six susceptible genes ($P<1\times10^{5}$) were MMP7, SERPINA3, SLPI, RPS27A, FLT1 and NES, which were related to renal fibrosis, innate mucosal defense,

angiotensin II production, and endothelial cell proliferation, indicating that they might participate in the pathogenesis of IgAN.

Conclusions: We found 54 genes were dysregulated in the kidney biopsies of IgAN patients, which provided new insights into the molecular pathogenesis of IgAN.

FR-PO837

Urine Biomarkers for Kidney Injury in IgA Nephropathy

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Background: IgA nephropathy is the most common primary glomerular disease leading to chronic kidney disease. Clinical management and prognosis rely heavily on renal pathology; reliable biomarkers are needed for non-invasive evaluation of the kidney. The aim of this study was to investigate potential urine biomarkers of kidney injury severity in IgAN.

Methods: Spot urines were collected from 45 IgAN patients at the time of diagnostic kidney biopsy and 29 healthy volunteers (control). Biopsies were classified by the Oxford system and the degree of activity and chronic damage was recorded blindly as none, mild, moderate or severe by the renal pathologist. The candidate biomarkers of kidney injury we assessed were adiponectin, CD163, EGF, NGAL, ICAM1, VCAM1 and complement component C5a. These were measured in urine using R&D DuoSet ELISAs. ANOVA, nonparametric Wilcoxon test and multiple linear regression were done using JMP14 pro for data analysis.

Results: Urine adiponectin, CD163, C5a and VCAM-1 were significantly different than healthy controls with fold-increases of 7, 399, 28 and 7 respectively (all $p<0.0001$), while EGF decreased about 1.4-fold compared to control ($p=0.0015$). Urine EGF was inversely correlated with interstitial fibrosis and tubular atrophy (IFTA, $R^2=0.35$, $p < 0.0001$) and overall chronicity ($R^2=0.49$, $p<0.0001$), while C5a positively correlated with IFTA ($R^2=0.21$, $p=0.0018$). Adiponectin and C5a were both positively correlated with overall activity (based on biopsy MEST score) ($R^2=0.51$, $p=0.0008$ and $R^2= 0.38$, $p=0.008$, respectively). Using receiver operating characteristic analysis, the area under the curve for EGF to differentiate between mild and moderate-severe chronic injury is 0.91 ($p<0.0001$), and for adiponectin to detect the presence of active lesions is 0.96 ($p=0.0011$).

Conclusions: Urine EGF could serve as a biomarker for chronic kidney lesions in IgAN while adiponectin and complement 5a may be biomarkers for active kidney lesions. These biomarkers could be helpful in non-invasively evaluating the efficacy of therapies for IgAN.

Funding: Clinical Revenue Support

FR-PO838

Aberrant Immune Response to Periodontopathic Microbiota in Patients with IgA Nephropathy

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Background: Aberrant mucosal immune response is implicated in terms of the multi-hit theory of IgA nephropathy (IgAN) development, however, microbiota responsible for pathogenic IgA production in IgAN remained obscure. We have focused until now on roles of microbiome in tonsillar crypts, considering efficacy of tonsillectomy for the treatment of IgAN. To reveal distinct immune responses in IgAN patients, we studied the binding ability of serum IgA against anaerobic bacteria in tonsillar crypts and its relationship with galactose-deficient IgA1 (Gd-IgA1).

Methods: We enrolled 30 biopsy-proven IgAN patients treated with tonsillectomy. Seven recurrent tonsillitis patients who had no urine abnormalities as control. Serum of enrolled patients were fractionated with high-performance liquid chromatography, and the levels of Gd-IgA1 in each fraction were determined by ELISA using KM55 monoclonal antibody. Then, we quantified the binding of each fractionated IgA against bacteria anaerobically cultured from tissues of tonsillar crypts of IgAN patients (*Porphyromonas gingivalis, Prevotella intermedia, and Fusobacterium intermedia,* well known as periodontopathic bacteria, *and Escherichia coli* as control) using flowcytometry.

Results: The serum levels of Gd-IgA1 in IgAN patients were significantly higher than RT patients ($P < 0.01$). In fractionated serum, Gd-IgA1 levels in polymeric IgA fraction of IgAN patients were significantly higher than those of RT patients ($P < 0.05$), but not in monomeric IgA fraction. Polymeric IgA of IgAN patients were more bound to both *Porphyromonas gingivalis* and *Prevotella intermedia* than those of RT patients. The amounts of polymeric IgA bound to *Porphyromonas gingivalis* were significantly correlated with the levels of Gd-IgA1 in polymeric IgA fraction of IgAN patients ($P < 0.01$).

Conclusions: Patients with IgAN exhibit perturbed immune response against periodontopathic microbiota.

FR-PO839

Validation Study of KM55 ELISA Kit in IgA Nephropathy (IgAN) Patients for the Detection of Galactose-Deficient IgA1 (Gd-IgA1) and Corticosteroid Therapy Monitoring

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Background: Serum levels of Gd-IgA1 may be considered the first biomarker of IgAN. In the past, Gd-IgA1 was detected by sophisticated methods such as mass spectrometry (MS) and lectin based assay. Recently, a monoclonal antibody KM55 that specifically binds Gd-IgA1 has become commercially available. Aim of our study has been i) to validate this tool, ii) to analyze relationships between serum Gd-IgA1 levels and the outcome of the disease and iii) to study the effect of corticosteroids (CS) on this non-invasive biomarker.

Methods: Serum levels of Gd-IgA1 were measured using ELISA Kit (Immune-Biological Lab. Co. LTD, Japan) in a cohort of 63 IgAN patients, 31 healthy blood donors (BD) and 31 primary non-IgAN (enrolled at the time of kidney biopsy in the Dept of Nephrology, Aristotle Univ of Thessaloniki, Greece). Fourteen IgAN patients were followed-up for a median time of 8.6±6.1 years. High resolution mass spectrometric (HRMS) analysis was used to study 2 IgAN patients with high serum level of Gd-IgA1, 2 IgAN patients with low serum Gd-IgA1 levels and 2 BD, to confirm the profile of IgA1 O-glycoforms.

Results: Patients with IgAN had higher values of Gd-IgA1 (1.53 ± 1.06 mg/dl) than controls (0.90 ± 0.65 mg/dl $p=0.002$) and patients with non-IgAN (0.89 ± 0.70 mg/dl $p=0.001$). HRMS analyses confirmed that less O-glycosylated glycoforms were predominantly presented in IgAN patients with high values of Gd-IgA1. A significant reduction of Gd-IgA1 serum levels was found during the follow-up compared to baseline values ($n=14$ $p<0.01$). This decline was more prominent in patients who received corticosteroids ($n=8$, $p=0.008$). The values of Gd-IgA1 did not influence the progression of renal damage (50% reduction of baseline eGFR).

Conclusions: High Gd-IgA1 serum levels characterize patients with IgAN at the time of kidney biopsy. During the clinical course of the disease Gd-IgA1 levels decline but this reduction is more prominent in patients receiving CS. This biomarker may be used for monitoring the effects of CS therapy

FR-PO840

Quantitative Determination of Human IgA Subclasses in Plasma and Their Fc-Glycosylation Patterns by Using Peptide Analogue Internal Standard and an UHPLC-Triple Quadrupole Mass Spectrometry

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Background: Glycosylation on the Fab and Fc regions of immunoglobulins is important for immune function. In this study, we developed and validated a method for the quantification of immunoglobulin A by using affinity purification and UHPLC (ultra-high-performance liquid chromatography)-MS/MS. Twenty-seven IgA-related Fc N-glycopeptides were also detected.

Methods: Peptide M was used to purify IgA, and a peptide analog was added as an internal standard. After on-bead digestion, samples were analyzed by UHPLC-MS/MS. After validation, the method was applied to plasma samples from 24 patients and 6 healthy controls, and the results were compared to those from ELISA assays.

Results: Correlation coefficients were greater than 0.999 for the IgA1 and IgA2 calibration curves and greater than 0.982 for glycopeptide regression curves. Intraday and interday precisions for IgA1 and IgA2 were <1.6% and <5.1% RSD, respectively. Intraday and interday accuracies ranged from 102.6-114.9% and 103.5-113.5% for IgA1 and IgA2, respectively. Recoveries for IgA1 and IgA2 in long-term and short-term stability ranged from 96.0-109.4%. Recoveries after three freeze-thaw cycles ranged from 93.2-113.2% for IgA1 and IgA2. The Pearson's correlation was 0.84 when comparing the quantification of the 30 clinical samples by ELISAs and the developed UHPLC-MS/MS method.

Conclusions: IgA1 and IgA2 were isolated by peptide M purification. An efficient on-bead digestion process was used prior to UHPLC-MS/MS analysis. The validated method was successfully applied to clinical samples which showed high correlation to the total IgA quantification ELISA results. This method has potential for investigating IgA profiles from human plasma.

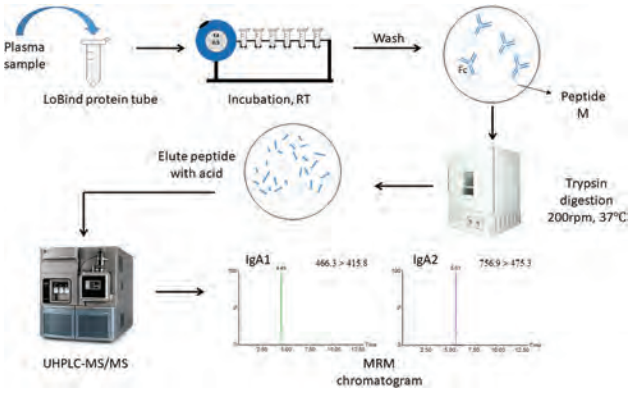

Figure 1. Workflow of IgA purification and UHPLC-MS/MS analysis.

FR-PO841

Prevalence of Periodontal Disease Bacteria in Tonsils of IgA Nephropathy Patients

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Background: IgA nephropathy (IgAN) is one of most common primary glomerulonephritis, whose pathogenesis had remained unclear. We had reported that *C.rectus* and *T.denticola,* kinds of major periodontal disease bacteria, in tonsils with IgA nephropathy patients were specific to IgAN patients compared with chronic tonsillitis (Nagasawa-Y et al, Plos One, 2014). We also reported *C.rectus* and S.mutans increased proteinuria synergistically (Misaki-T et al, Nephron, 2018). *P.gingivalis* had not been evaluated in IgAN patients, although *P.gingivalis* is well known as one of most common periodontal disease bacteria. In this study, we evaluated the periodontal disease bacteria including *P.gingivalis* in tonsils of IgAN patients, and the relationship between these periodontal bacteria clinical features in IgAN patietns.

Methods: Tonsils were obtained from 23 IgAN patients and 63 chronic tonsillitis patients when the tonsillectomy was operated. mRNAs were extracted from tonsils and the prevalences of *C.rectus* and *T.denticola*, and *P.gingivalis* were evaluated by RT-PCR using bacteria specific primers. All patients gave the written informed consent which was approved by Hyogo College of medicine.

Results: Average age was 33+-14 in IgAN patients, and the age in control patients was 27+-7. The average proteinuria in IgAN patietns was 0.9+-1.1g/gcre, and average hematuria was (2+). The prevalence of *C.rectus* in IgA patients was 76%, while the prevalence in control patients was 62%. The prevalence of *T.denticola* was very low in both groups (0%, 1.6%). The prevalence of *P.gingivalis* in IgA patients was significantly higher than that in control patients (33% vs 3.2%, respectively, P=0.0001), which had not been reported. IgAN patients with *C.rectus* had greater proteinuria than those without *C.rectus* (1.2+-0.4 vs 0.5 +-0.3, respectively). IgAN patients with or without *P.gingivalis* had same levels of proteinuria (1.1+-0.4 vs 1.1 +-0.3, respectively). The types of cilia of *P.gingivalis* (fim A types) were also evaluated. Obviously untypeable of fim A, which is usually minor type, was dominant in IgAN patients.

Conclusions: Periodontal disease bacteria including *P.gingivalis* in tonsils were related with IgAN. The type of cilia of *P.gingivalis* might have some relationship with pathogenesis of IgAN

FR-PO842

TLR7-GalNAcT2 Axis Modulated IgA1 O-Glycosylation in Patients with IgA Nephropathy

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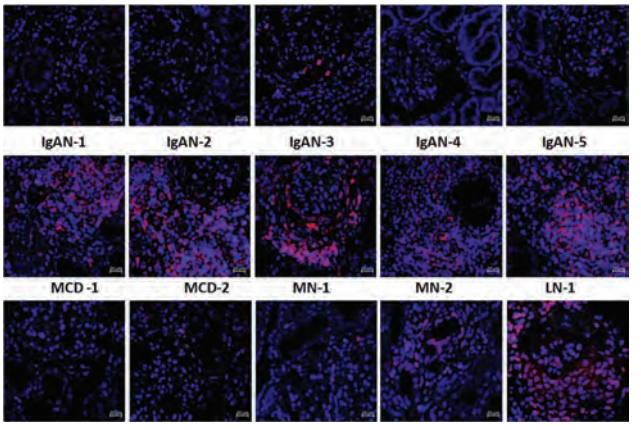
Background: IgA nephropathy (IgAN) was featured with galactose deficient-IgA1 (Gd-IgA1) complex deposit in kidney of patients. O-glycosyltransferases were responsible for O-glycan synthesis, which made them crucial for the production of Gd-IgA1. Toll-like receptors (TLRs) were shown to be related with pathogenesis of IgAN. The underlying mechanism between TLRs and the production of Gd-IgA1 was not known yet.

Methods: Biopsy proven IgAN patients with clinical features of primary IgAN, MCD, MN, LN were enrolled in this study. Paraffin-embedded sections of kidney biopsies were subjected to immunofluorescence staining for analysis of TLR7 expression. Peripheral blood mononuclear cells (PBMCs) were prepared and used for real-time PCR analysis or cell-culture experiments.

Results: Here we found that TLR7 proteins were abundantly presented in infiltrated leukocytes in kidney of IgA patients (n=90), as compared with healthy donors and patients with MCD or MN. The mean fluorescence intensity of TLR7 was associated with renal function deterioration. Renal expression of TLR7 protein was evidently presented in CD19+ B cells. Moreover, mRNA levels of TLR7 were significantly correlated with those of GalNAcT2 in PBMCs and they were both increased in B cells of IgAN patients. After activation with TLR7 ligand-R848, PBMCs from IgAN patients secret more Gd-IgA1 molecules than controls and expression GalNAcT2 was increased in sorted B cells from IgAN patients. Over-expression of TLR7 led to up-regulated expression of GalNAcT2, whereas knockdown-expression of TLR7 led to down-regulated expression of GalNAcT2. Over-expression of GalNAcT2 in B cells resulted in augmented synthesis of Gd-IgA1 molecules, but not total IgA1 molecules.

Conclusions: Taken together, the abundant presence of TLR7 play important roles in pathogenesis of IgA nephropathy, by promoting GalNAcT2 expression in B cells and later the synthesis of Gd-IgA1 molecules.

Funding: Government Support - Non-U.S.



FR-PO843

Novel Urine Metabolite in Human as a New Differential Diagnosis Biomarker for Lupus Nephritis

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Background: Lupus nephritis (LN) is one of the major causes of mortality and disability in patients with systemic lupus erythematosus (SLE). LN shows many phenotypes so diagnosis is not easy and takes time and labor. Non-invasive biomarkers are required to accelerate diagnosis. The present study aimed to identify urine metabolites as new biomarkers for screening for LN from another nephritis.

Methods: Using capillary electrophoresis and mass spectrometry (MS), we analyzed low molecular weight metabolites in a total of 394 urine samples obtained from Japanese patients with biopsy-proven LN (n=27, n=13), membranous nephropathy (n=78, n=43), diabetic nephropathy (n=29, n=14), MCNS (n=74, n=22), FSGS (n=29, n=10), IgA-nephropathy (n=18, n=10), and rheumatoid arthritis (n=19, n=8), in discovery (n=274) and validation (n=120) cohorts, respectively. All urine samples were collected at the time of diagnosis. Multivariate analyses were used for the identification of marker candidates and development of discriminative models. Identification of chemical structure was made on the basis of NMR and liquid chromatography and MS/MS.

Results: We found that an initially unknown metabolite (peak ID: CU040) was present in the urine of LN patients and that measurement of its concentration could distinguish LN from another nephritis. Logistic regression models facilitated the discrimination between LN and other nephritis and yielded high areas under receiver-operating characteristic curves. The area under the curve values, sensitivity, and specificity were 0.8218, 0.7037 and 0.9717 in the discovery cohort, and 0.8698, 0.8462 and 0.9346 in the validation cohort, respectively. Based on the result of chemical structure analysis, the CU040 was identified as 3',4'-didehydro-3'-deoxycytidine ($C_9H_{11}N_3O_4$, MW 225.07). To the authors' knowledge, this metabolite has not been detected in humans, but it has been reported in 2013 as a novel biomarker for infection of *Plasmodium berghei* in the urine of malaria model mice(PMID: 24067624).

Conclusions: The 3',4'-didehydro-3'-deoxycytidine in urine was a novel and excellent differential diagnosis biomarker for LN. Our results may suggest the existence of a common molecular mechanism between malaria and SLE, and it is also very interesting from the viewpoint of understanding the pharmacological effect of Hydroxychloroquine.

Funding: Government Support - Non-U.S.

FR-PO844

CTLA4-ICOS Intergenic Variants Associated with Lupus Nephritis in Chinese Populations

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Background: Lupus nephritis (LN) is one of the most prevalent and serious complications of systemic lupus erythematosus (SLE). *CTLA4* (cytotoxic T lymphocyte-associated protein 4) and *ICOS* (inducible T cell co-stimulator) are good candidate genes for SLE because of their role in regulating T cell activation. And the combination of CTLA-4Ig and cyclophosphamide therapy very effectively arrested the progression of murine lupus nephritis. Therefore, the aim of the present study was to identify susceptibility variants in *CTLA4-ICOS* intergenic region along with its functional significance.

Methods: In genetic association analysis, the discovery Beijing cohort (500 LN patients and 500 healthy controls) was adopted from previous reported GWAS data with the use of ImmunoChip arrays. The replication cohort was recruited from Henan population (508 LN patients and 812 healthy controls) and the genotyping was conducted by Sequenom Massarray. To identify functional significance, we analyzed publicly available Encyclopedia of DNA Elements data on transcription factor binding sites, blood expression quantitative trait locus data. The effect of SNP on expression was referred to GTEx2015_v6 and Westra2013 eQTL studies.

Results: In the discovery stage, a total of 136 single-nucleotide polymorphisms in a region spanning 113 kb encompassing *CTLA4-ICOS* were analyzed in 1000 individuals from Beijing cohort. Twenty four of them were significantly associated the susceptibility to LN ($p<0.05$). rs17268364 and rs13029135 were the top signals ($p = 1.41 \times 10^{-2}$, OR = 0.77, 95% CI 0.62 - 0.95) and were in high linkage disequilibrium (r-square = 0.99, D' = 1). This genetic association of rs17268364 was successfully replicated in an independent cohort with 508 LN patients and 812 healthy controls in Henan cohort ($p = 3.08 \times 10^{-4}$, OR 0.71, 95%CI 0.58 - 0.85). After combined analysis of Beijing cohort and Henan cohort, the association was further reinforced ($p = 1.31 \times 10^{-5}$, OR 0.73, 95%CI 0.64 - 0.84). Functional analysis predicted conservative and regulatory features of rs17268364. In eQTL analysis, rs17268364 was associated with the expression of CTLA4 ($p = 2.62\times10^{-6}$) and ICOS ($p = 3\times10^{-3}$).

Conclusions: Our results suggested genetic association between variants in the intergenic region of *CTLA4-ICOS* and LN risk in Chinese population.

Funding: Government Support - Non-U.S.

FR-PO845

Angiotensin II Type 1 Receptor Agonist Antibodies Are Prevalent in Lupus Nephritis Patients and May Be Associated with Vascular Damage

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Background: Angiotensin type II receptor antibodies (AT1R-Ab) have been linked to hypertension, vascular inflammation and atherosclerosis in human diseases. The aim of this study was to determine the association between AT1R-Ab and intima-media thickness (IMT), microvascular damage and lupus nephritis (LN) activity.

Methods: Plasma AT1R-Ab were evaluated in 107 patients with biopsy proven LN. Then 80 patients were prospectively followed for one-year. Plasma AT1R-Ab, double-strand DNA antibodies (dsDNA-Ab), complement C3 and C4 were assayed in plasma samples obtained at 3, 6 and 12-months from the start of treatment. Morphometric analysis of the kidney biopsy vessels was performed to determine intimal fibrosis and medial layer thickness. Carotid IMT was evaluated by USG at the time of biopsy and then at one-year in 22 AT1R-Ab patients. The comparisons between AT1R-Ab+ and AT1R-Ab- patients were performed by Chi-square and Mann-Whitney's U. Association between the AT1R-Ab course and other parameters was evaluated by linear mixed models.

Results: AT1R-Ab were positive in 58 (54%) patients and higher than in inactive LN patients and kidney donors. AT1R-Ab+ patients had higher dsDNA-Ab (287 UI/ml [97-814] Vs. 26 UI/ml [26-182], p<0.001), lower complement C3 (62mg/dl [43-80] Vs. 74mg/dl [50-101], p=0.016), higher histologic activity index (5 [3-11] Vs. 2 [1-7], p=0.020), more segmental lesions (67% Vs. 43%, p=0.013) and more class III LN (43% Vs. 20%, p=0.019) than AT1R-Ab- patients. The prevalence of subintimal fibrosis >10% was 47% and the percentage of subintimal fibrosis was higher in AT1R-Ab+ patients (12% [6-20] Vs. 7% [3-16%], p=0.025). The area of medial layer hyperplasia was greater in AT1R+ patients ($72um^2$ [61-88] Vs. $55um^2$ [42-66]). On multivariate analysis, AT1R-Ab titers were independently associated with the degree of medial hyperplasia. The course of AT1R-Ab on follow-up was associated with the course of dsDNA-Ab (r=+0.454, p<0.001), complement C3 (r=-0.185, p=0.049) and C4 (r=-0.281, p=0.013). There were no significant changes in IMT after 12 months of follow-up between AT1R-Ab+ and AT1R-Ab- patients.

Conclusions: AT1R-Ab are associated with vascular medial hyperplasia and segmental glomerular damage in LN patients and are associated with serological biomarkers.

FR-PO846

Increased CaMK4 Expression in Podocytes from Renal Biopsies of Patients with lupus Nephritis Is Mirrored by Its Levels in Cultured Podocytes Exposed to Serum IgG and in Urine Podocytes

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Background: Lupus nephritis (LN) is a devastating and potentially fatal disease that mainly affects women of child-bearing age. We previously demonstrated that Calcium/Calmodulin Kinase IV (CaMK4) inhibition in podocytes by cell targeted therapy prevents LN in mice. Here we explore the association of renal CAMK4 expression with the presence of LN in patients with SLE and describe novel noninvasive methods to identify patients prone to develop LN.

Methods: Expression of CaMK4 in frozen renal biopsy specimens from thirty individuals referred to rule out LN was evaluated by immunofluorescence. Logistic regression models were used to analyze the predictive value of CAMK4 in the development of LN. Immortalized human podocytes were examined for CaMK4 expression before and after exposure to IgG from ten SLE patients with and without LN and 5 healthy controls. We further devised a novel method to rapidly isolate urinary podocytes by using magnetic beads and successfully extract RNA.

Results: CaMK4 expression in podocytes is a strong predictor of active LN($p<.01$, β 2.36). Culture of podocytes in the presence of IgG from patients with active LN led to increased CaMK4 expression along with reduction in expression of nephrin while no changes were demonstrated in the presence of IgG from normal subjects or from individuals with SLE without nephritis. CaMK4 deficiency or pharmacologic inhibition preserved nephrin expression. CaMK4 inhibited GSK3beta by phosphorylating it at serine 9 which led to stabilization of transcription factor SNAIL and subsequent repression of nephrin transcription. Urinary podocytes from fresh urine were successfully and rapidly isolated by a novel magnetic bead method. Urinary podocytes from patients with active LN, but not from those without kidney disease, displayed increased expression of CaMK4 and CD80.

Conclusions: We conclude that CaMK4 expression in podocytes is a feature of patients with LN and more importantly, we present two novel assays to replace the need for kidney biopsy. We have shown that rapidly isolated urine podocytes from patients with LN, using a new protocol, and cultured podocytes exposed to IgG from patients with LN express CaMK4 which reflects the levels detected in the kidney biopsy material of patients with active LN.

Funding: NIDDK Support

FR-PO847

Self-Clustering of Tissue Gene Expression to Classify Patients with Lupus Nephritis

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Background: Histologic classification of kidney biopsy in lupus nephritis (LN), while used for treatment decisions, is not sufficiently robust to account LN's molecular heterogeneity that affects treatment response and outcomes. We tested whether unsupervised clustering of LN biopsies based on tissue gene expression was feasible to classify LN. We postulated that such a classification of LN would reflect disease pathobiology and would be more relevant to managing LN with drugs targeting specific pathogenic pathways.

Methods: Transcript levels of >500 genes involved in autoimmunity were measured using NanoString in microdissected glomeruli from 57 LN patient biopsies, and then used for unsupervised hierarchical clustering. For each gene, mRNA abundance was compared between each cluster group (CG) and the mean abundance of the other groups to determine genes that were differentially expressed. Differentially-expressed genes from each CG were used for pathway analysis. Demographic, clinical and histopathologic data were also compared between CGs using ANOVA and Fisher's exact test as appropriate.

Results: Clustering resulted in 4 CGs. There were no significant differences in baseline creatinine, proteinuria, NIH activity or chronicity indices, or ISN/RPS class between CGs. Canonical pathway and upstream regulator analysis differentiated CGs (Table).

Conclusions: Transcript expression in the glomerular compartment of LN kidney biopsies identifies 4 subsets of patients. Inflammatory pathways expression appears to be highest in CG2 followed by CG4, and relatively suppressed in CG1 & 3. We suggest it may be feasible to tailor treatment to patients based on their CG classification of injury pathways that are differentially expressed.

		Group 1	Group 2	Group 3	Group 4
Age, median (yrs)		32.7	28.0	27.5	26.7
% Female		20.0%	44.4%	10.0%	7.7%
Creatinine, mean (mg/dl)		1.00	0.72	0.97	0.71
uPCR, mean (mg/g)		3.42	2.36	3.27	3.95
Activity Index, Mean		7.3	7.3	8.3	4.7
Chronicity Index Mean		2.7	2.3	2.9	2.9
ISN class	Proliferative	66.7%	77.8%	75.0%	38.4%
	Mixed	26.7%	22.2%	25.0%	30.8%
	Pure membranous	6.6%	0.0%	0.0%	30.8%
Canonical pathway					
	Top 5 overexpressed	CCR5 Signaling in Macrophages	Dendritic Cell Maturation	LXR/RXR Activation	p38 MAPK Signaling
		STAT3 Pathway	TREM1 Signaling	STAT3 Pathway	Th1 Pathway
		IL-17A Signaling in	NF-κB Signaling	Phospholipase C Signaling	HMGB1 Signaling
		Signaling by Rho Family GTPases	Th17 Activation Pathway	Rac Signaling	IL-8 Signaling
		Rac Signaling	Th1 Pathway	FAT10 Signaling Pathway	Th2 Pathway
	Top 5 underexpressed				
		NF-κB Signaling	LXR/RXR Activation	Th2 Pathway	Rac Signaling
		Th1 Pathway	CCR5 Signaling in Macrophages	Th17 Activation Pathway	Signaling by Rho Family GTPases
		IL-8 Signaling	STAT3 Pathway	HMGB1 Signaling	Tec Kinase Signaling
		Th2 Pathway	IL-3 Signaling	Dendritic Cell Maturation	NF-κB Activation
		HMGB1 Signaling	IL-2 Signaling	TREM1 Signaling	STAT3 Pathway
Upstream regulator					
	Top 5 overexpressed	NCSTN	IL2	TNFAIP3	CD69
		NODAL	CD3	FOSL1	CD3
		miR-146a-5p	CD28	miR-155-5p	PIK3CD
		CIITA	TLR4	PPARD	IL17R
		INSIG1	TNF	TRAIP	IL2
	Top 5 underexpressed				
		MYD88	GFI1	KITLG	CIITA
		TLR9	miR-146a-5p	NFkB	NOTCH1
		TSLP	PTPN6	IL2	SP3
		IL2	CTLA4	IL1	RXRA
		CD28	TRAIP	CD3	RXRB

FR-PO848

Peripheral Blood RNA Signatures for Active Kidney Injury in Lupus Nephritis

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Background: Because lupus nephritis (LN) is a manifestation of a systemic process it is reasonable to ask whether circulating leukocytes can serve as a source of biomarkers of active kidney disease. To begin to examine this question we characterized the immune transcriptome of peripheral blood cells at the time of kidney biopsy and looked for associations with renal histology.

Methods: We studied 44 patients with SLE and kidney biopsies consistent with LN, 9 patients with IgAN as immune complex disease controls, and 5 healthy controls. Total RNA was extracted from buffy coats collected at the time of kidney biopsy and tested on a customized gene expression nCounter GX CodeSet. The Nano-String raw data were analyzed with nSolver™ 4.0 software and JMP 14 pro statistical program. Differential expression of significant transcripts was further confirmed by TaqMan gene expression real-time RT-PCR. The NIH activity (AI) and chronicity (CI) indices of the patients' kidney biopsies were scored by a renal pathologist.

Results: Compared to healthy and disease controls 57 out of 199 transcripts were overexpressed in LN patients. Of these, 25 genes were significantly increased 2-fold or more in active LN ($P<0.0001$). Over half of these 25 genes are involved in type I interferon signaling. Other differentially-activated pathways included cytokine-mediated responses, B-cell activation and apolipoprotein metabolism. The top overexpressed transcripts in LN were IFI27, CD169, LAMP3 and DNAPTP6 which were 49, 21, 18 and 12-fold higher than healthy and disease controls. PCR confirmed these RNA signatures with IFI 243-fold and CD169 24-fold higher than disease controls. AI correlated positively with APOEBC3A and IL-1A (both $R^2=0.19$) and negatively with TRADD ($R^2=0.31$), while MIP-1a ($R^2=0.2368$) positively correlated with CI (all, $P<0.01$).

Conclusions: Interferon-I signaling, cytokine response, B-cell activation and lipoprotein metabolism are the major differentially-activated in peripheral blood cells during LN flares. AI and CI correlates are mainly cytokines, mediators of innate immunity, and apoptosis.

Funding: Clinical Revenue Support

FR-PO849

Development of Novel Algorithms to Characterize Lupus Nephritis (LN) Renal Activity and Chronicity Using Urine Proteomics

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Background: We assessed the utilization of the widely available, high throughput platform for multiplex analysis of urine proteomics to define limited sets of baseline markers correlating with LN histopathology results assessed by the NIH Activity (NIH-AI) and Chronicity (NIH-CI) Indices. Novel algorithms were developed to characterize patients into high and low subgroups. Longitudinal urine sample were used as surrogates to monitor the disease indices over time.

Methods: Baseline urine samples were collected from 42 LN patients. Baseline LN biopsies were interpreted by an expert pathologist. Additional LN samples were collected over a year. Urine samples were tested on a large Luminex multiplex platform. Stepwise regression and single variable regression results were combined to limit the possible candidate urine biomarkers. A multivariate logistic regression model (MLRM) was applied to the remaining markers. Selection criteria for biomarkers were p values < 0.05, high area under the curve, and a low misclassification rate. Receiver operating characteristic curves based on cross-validations evaluated the predictiveness of selected biomarkers.

Results: Data from 288 markers were reduced to 177 by assessing assay robustness. Four markers (CD163, ferritin, KIM-1, and antileukoproteinase) were identified ($P<0.05$) in the MLRM, which predicted 93% of the NIH-AI high patients with a false positive rate (FPR) of 11%. The predicted probability of high activity patients decreased over time relative to baseline as serum albumin increased and proteinuria decreased, reflecting decreased activity. The markers identified for NIH-CI were hepatocyte growth factor, Eotaxin-2, IL-6R β, and ITAC. The model predicted 81% of patients with high NIH-CI with a FPR near 0%.

Conclusions: This study supports the continued evaluation of urine biomarkers with a multiplex immunoassay platform validated to clinical laboratory standards and could support wide distribution as a Luminex-based test. Novel combinations of markers were associated with renal histopathologic activity and chronicity (high and low categories) in LN. Treatment led to alterations in activity and chronicity longitudinally.

Funding: Commercial Support - Astra Zeneca

FR-PO850

Study of T-Regulatory Cells and B-Regulatory Cells in Lupus Nephritis: A Prospective Observational Study

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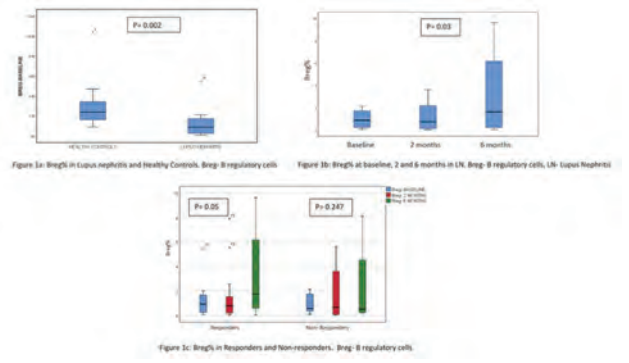
Background: Studies in lupus nephritis(LN) have shown impairment in both T regulatory(Treg) number and function. The data on B regulatory (Breg) is limited in LN. We conducted a prospective observational study of Treg and Breg populations in LN and their trend after initiation of immunosuppression.

Methods: Study included 20 patients of treatment-naïve LN of ISN/RPS Class III(±V), IV(±V), V and 10 healthy controls(HC). Immunophenotyping was performed for peripheral blood mononuclear cell samples using flurochrome labelled monoclonal antibodies for identification of Tregs ($CD3^+$ $CD4^+$ $CD25^{hi}$ $CD127^{lo}$ $FoxP3^+$), Bregs ($CD19^+$ $CD5^+$ $CD1d^{hi}$ $IL\text{-}10^+$), Immature cells ($CD19^+$ $CD24^{hi}$ 38^{hi}) and B 10 cells ($CD19^+$ $CD24^{hi}$ $CD27^+$), each expressed as percentage of T and B cells. Each lymphocyte population was analysed at baseline, 2 and 6 months after initiation of immunosuppression. Regulatory cells between groups was analysed by Mann Whitney U test and within groups by Wilcoxon signed rank test and Freidman's test, as applicable.

Results: Bregs were significantly decreased compared to HC at baseline ($p=0.002$). With immunosuppression, Bregs showed significant increase at 2 and 6 months ($p=0.03$). Bregs in responders showed an increasing trend at 2 and 6 months ($p=0.05$), while they did not in non-responders ($p=0.247$). The increase in Bregs did not significantly differ between different immunosuppressive regimens given. At baseline, Bregs in responders and non- responders were not significantly different. Immature cells and B10 cells were significantly higher compared to HC ($p<0.001$). Tregs did not differ significantly from HC and did not show significant increase at 2 and 6 months, in both responders and non-responders.

Conclusions: We observed that Breg populations in treatment-naïve LN were significantly reduced compared to HC and increased significantly with immunosuppression. Responders had a trend toward increase in Bregs over time, whereas non-responders did not.



Bregs in HC and LN

FR-PO851

C1q A08 Is a Half-Cryptic Epitope of Anti-C1qA08 Antibodies in Lupus Nephritis and Important for the Activation of Classical Complement Pathway

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Background: Anti-C1q antibody is one of the most important autoantibodies in lupus nephritis, while its role in pathogenesis of lupus nephritis is not so clear. Our previous study found that C1q A08 antibody correlated better with lupus nephritis relapse than antibody against intact C1q molecule in a large Chinese cohort, and could predict reanl prognosis in lupus nephritis. This study aims to verify the role of A08 by anti-C1q A08 antibodies in lupus nephritis

Methods: Anti-C1q A08 antibodies from ten patients with lupus nephritis were purified from plasmapheresis samples. Four monoclonal antibodies against C1q A08 is screened from mouse hybridoma cells to study the conformational change of C1q in different situation by ELISA and Biolayer Interferometry (BLI) method. The biofunction of anti-C1q A08 antibodies in activation of classical complement pathway was investigated by C3 activation assay.

Results: All C1qA08 antibodies isolated from ten lupus nephritis patients could not bind C1q coating on microtiter plate and the anti-C1q autoantibodies were not able to bind to resin coupled with C1q A08 peptide, which indicates that different epitopes of C1q were recognized by C1q antibodies and C1q A08 antibodies. One of the four C1q A08 mAb(32-4) binds to six amino acids of the N-terminal, while another C1q A08 mAb(17-9) could bind to eight or ten amino acids of the C-terminal. The third and fourth C1q A08 mAb(1A12 and 4B11) could bind to the whole sequence of C1qA08(Figure 1). 32-4 mAb could bind to C1q coating on ELISA plate, while 17-9 mAb, 1A12 mAb and 4B11 mAb could not. However, different result was shown by BLI method. That is, 17-9 mAb, 1A12 mAb and 4B11 mAb could bind to C1q but 32-4 mAb could not. 1A12 mAb and 4B11 mAb were able to prevent the activation of classical complement pathway, while 32-4 and 17-9 mAb could not.

Conclusions: C1q A08 is one important but half-cryptic epitope of C1q, only part of the six amino acids is cryptic. A08 is important in activation of classical complement pathway and some anti- A08 antibodies were able to prevent this process.

FR-PO852

Xenon Blunts NF-κB/NLRP3 Inflammasome Activation and Improves Acute Onset of Accelerated and Severe Lupus Nephritis in Mice

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Background: Accelerated and severe lupus nephritis (LN) might follow episodes of bacterial or viral infections as environmental triggers in patients with LN. Xenon (Xe), an anesthetic gas, is increasingly recognized to possess many desirable properties, including cytoprotective and anti-inflammatory effects.

Methods: The present study evaluated the effects of Xe on the progression of LN in a mouse model. A mixture of either 70% Xe or 70% N2 balanced with O2 was given daily to female NZB/W F1 mice with acute onset of progressive renal lesions and renal functional disturbance for 2 hrs for 5 weeks. Renal function and pathology and mechanistic studies were performed, including reactive oxygen species (ROS) production, activation of NF-κB/NLRP3 inflammasome and apoptosis-related pathway, proteomics-based NLRP3 inflammasome-mediated signaling.

Results: The mice that were induced of accelerated and severe LN were successfully treated with Xe in renal function and pathology, chemoattractants for neutrophils, and glomerular neutrophil infiltration, primarily through inhibiting ROS production, NF-κB/NLRP3 inflammasome activation, ICAM-1 expression, and apoptosis in the kidney. Moreover, Xe reduced the expression of p-NF-κB p65, ICAM-1 and p-p38 MAPK, and inhibited levels of total and mitochondrial ROS production as well as mitochondrial damage in activated primary mesangial cells. Proteomics analysis revealed that the Xe treatment downregulated renal NLRP3 inflammasome-mediated cellular signaling.

Conclusions: The results suggest that Xe may shed light of therapeutic value in treating such cases of LN although it might warrant further study.

Funding: Government Support - Non-U.S.

FR-PO853

Kidney Biopsy Proteome Reveals Novel Molecules and Pathways in Lupus Nephritis

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Background: Lupus nephritis (LN) is a major cause of morbidity and mortality. Pathogenesis of LN is largely unclear. Identification of molecules that are differentially expressed between LN classes and normal control kidneys may help in elucidating mechanisms of LN and to help to identify potential new targets of treatment. Our objective in this study was to identify differences in specific proteins and molecular pathways between LN classes and normal kidneys. We hypothesized that morphologic changes that define the pathology of each class of lupus nephritis are characterized by specific protein expression.

Methods: Forty-eight formalin-fixed, paraffin embedded kidney biopsy specimens were obtained from UCLA Pathology repository. Kidney specimens included 10 histologically normal kidneys and 38 biopsy-proven LN by the 2003 International Society of Nephrology/Renal Pathology Society classification. These tissues were subjected to proteomics analysis using nano-scale liquid chromatography tandem mass spectroscopy (nLCMSMS) and tandom mass tag method for protein labeling. Quantitative relative expression data is extracted using Proteome Discoverer 2.2 Software. Ingenuity software was used for pathway analysis. Clinical and histological data were collected

Results: A total of 2190 peptides were identified in all 48 kidney specimens. Of the 2,190 peptides, 655 were differentially expressed between LN and normal control kidneys (FDR <0.05). Some of the top upregulated proteins included alpha-1-antichymotrypsin, keratin family proteins, immunoglobumins, alpha-1-antitrypsin, vimentin, and complements. The top downregulated proteins included apoptosis-inducing factor 1, glutathione S-transferase, V-type proton ATPase catalytic subunit A, transforming acidic coiled-coil-containing protein 3, and dipeptidase 1. Pathway analysis of differentially expressed peptides revealed a set of upregulated molecular pathways including immune cell communication, acute phase response signaling, glucocorticoid receptor signaling, and complement system, while pathways linked to oxidative phosphorylation, fatty acid oxidation, and amino acid degradation were reduced in LN compared to controls.

Conclusions: Using a relatively large cohort of LN kidney biopsies, we report a novel LN proteome using nLCMSMS. These data pave the way for defining molecular pathogenesis of LN and for identifying novel treatment targets

FR-PO854

Serum Biomarkers of Histologic Activity in Lupus Nephritis Kidney Biopsies

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Background: The kidney biopsy is the gold standard for diagnosing and managing lupus nephritis (LN) but it is not practical to repeat biopsies frequently to follow disease status. Because LN is part of a systemic disease we interrogated the serum of LN patients for biopsies that could non-invasively reflect biopsy findings.

Methods: Serum was collected at the time of biopsy from 50 LN patients and from 9 healthy controls. Fifteen pro-inflammatory cytokines and immune mediators were measured using the Luminex multiplexing platform. Data were analyzed by Milliplex Analyst Version 5.1. NIH activity (AI) and chronicity (CI) indices of the LN biopsies were scored by a renal pathologist. Mild, moderate and severe acute injury were defined as AI scores of 1-4, 5-9, and >10, respectively.

Results: IL-2R, CXCL16, M-CSF, TNFR1 and VCAM-1 were increased 2.7, 1.9, 2.6, 3.4 and 2.1-fold respectively in LN compared to healthy controls (all $p < 0.01$). Adiponectin, NGAL and M-CSF were significantly elevated in Class IV LN compared to other classes (all $p < 0.01$). M-CSF and pentraxin 3 (PTX) positively correlated with AI (R^2=0.46, p<0.0001; R^2=0.27, p=0.0006, respectively), but none correlated with CI. With respect to the individual elements of the AI, M-CSF was elevated significantly in endocapillary proliferation (R^2=0.43, p< 0.0001), wireloop formation (R^2=0.29, p 0.0045), PMN infiltration (R^2=0.37, p 0.0002), fibrinoid necrosis (R^2=0.28, p 0.0022), and cellular crescents (R^2=0.2883, p 0.0052). PTX only correlated with the fibrinoid necrosis component of AI (R^2=0.22, p 0.008). The area under the receiver operating characteristic curve (AUC) for M-CSF to differentiate between mild and moderate-severe crescentic injury was 0.89 (p=0.003) and for M-CSF to differentiate mild from moderate-severe AI was 0.87 (p<0.0001). PTX differentiated between mild and moderate-severe necrosis with an AUC of 0.90 (p=0.01).

Conclusions: Serum M-CSF and PTX appear to reflect severe intra-renal injury in LN. These biomarkers may be useful in managing LN if they can be shown to decrease as crescents and necrosis resolve.

Funding: Other NIH Support - NIAMS

FR-PO855

Pediatric Patients with Membranous Glomerulopathy: A Single-Center Retrospective Study

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Background: Membranous nephropathy is a rare cause of pediatric nephrotic syndrome. The purpose of this study is to characterize the clinical presentation, treatment and outcomes of pediatric patients with membranous glomerulopathy in a single center over a 15 year period.

Methods: Patients with membranous nephropathy, age 18 years or less, were identified through an existing database of renal biopsy specimens at Indiana University and through billing records. Their charts were reviewed for clinical presentation, treatment and outcomes data.

Results: From 2002 to 2019, there were a total of 777 renal biopsy specimens interpreted at Indiana University with a diagnosis of membranous nephropathy. Of these, there were 14 patients, age 18 years or less, identified with primary membranous nephropathy and met inclusion criteria. An additional 4 patients were identified from billing data. Our cohort was primarily female (12/18) with a median age at presentation of 13 years (IQR 10.5--15.5). At presentation, nephrotic range proteinuria was present in 72%, hypoalbuminemia in 70%, edema in 62%, hematuria in 29%, and hypertension in 43% of patients. Renal function was normal in 17/18 patients at presentation. 3 patients had PLA2-R staining on biopsy and 2 were positive. 15 patients had treatment and/or outcomes data available. Median time to most recent follow-up was 20 months (IQR 7—35). 10/15 patients were treated with steroids; 12/15 had documented partial or complete remission at some point during their clinical course. Of the available data, 80%, 36%, and 15% had nephrotic range proteinuria at 3, 6, and 12 months, respectively. 27% and 38.5% of patients had entered complete remission at 6 and 12 months, respectively. One patient was steroid-dependent and relapsed when steroids were stopped. 14/15 patients were treated with an ACEi and/or ARB. One patient was treated with a steroid-sparing agent, mycophenolic acid, and did not enter remission. 14/15 patients had a creatinine less than 1.0 mg/dL at last follow-up. There were no documented complications of nephrotic syndrome such has thrombosis.

Conclusions: In our cohort, pediatric patients with membranous nephropathy presented with similar clinical characteristics as adult patients. Our patients had a good clinical response to steroids and/or ACEi/ARB with few documented adverse effects.

FR-PO856

Long-Term Exposure to Air Pollution and Increased Risk of Membranous Nephrology in China

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Background: We have previously shown that long-term exposure to $PM_{2.5}$ was associated with an increased risk of membranous nephrology(MN) in a large renal biopsy series in China, which partly accounted for the doubling of MN in patients with renal biopsy during the last decade. Due to limitation of the data, we were not able to assess the effect of the components of air pollution and to distinguish MN by presence and absence of PLA2R antigen in the tissue.

Methods: In the current study, we analyzed 94,388 renal biopsies conducted at 1,205 hospitals spanning 262 cities in China from 2015 to 2018, of which 31,481(33.35%) were diagnosed as primary MN. We obtained the daily air pollution data of each participating city from the Ministry of Ecology and Environment of China. We examined the association between the year-average exposure of each component of air pollution and the risk of MN in the biopsy series using a generalized additive model adjusting for age, gender, and biopsy indication.

Results: Higher exposure to each component was associated with increased risk of MN, thought the relationship appeared to be non-linear for $PM_{2.5}$ and linear for CO, NO_2, O_3, PM_{10}, and SO_2(Figure 1). Among the cases with primary MN, 7,947 had PLA2R test in the biopsy tissue, and the city-specific rate varied greatly, ranging from 73.68% to 88.26%.The overall PLA2R positive rate was 80.29%. Similarly, higher exposure to each component was associated with increased risk of PLA2R-related MN, thought the relationship appeared to be non-linear for CO, NO_2 and linear for PM_{10}, $PM_{2.5}$, O_3, and SO_2(Figure 2).

Conclusions: In conclusion, long-term exposure to $PM_{2.5}$,PM_{10},NO_2,SO_2,CO,O_3 in ambient air was associated with an increased risk of MN in patients with renal biopsy as well as with an increased presence of PLA2R antigen in patients with MN.

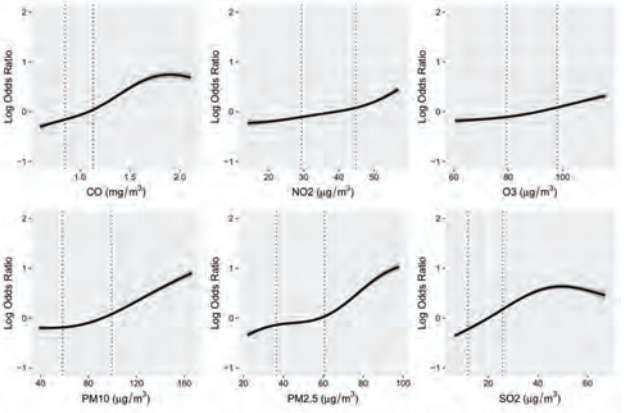

Figure 1. Smooth curves of the odds for MN along CO, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2 with adjustment for age, gender, and clinical indication.

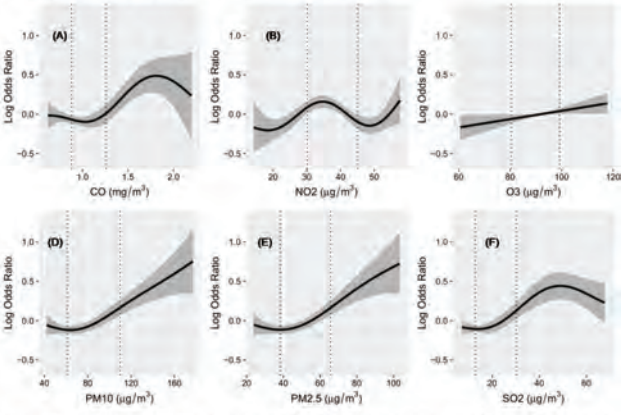

Figure 2. Smooth curves of the odds for PLA2R-related MN along CO, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2 with adjustment for age, gender, and clinical indication.

FR-PO857

Adoptive Transfer of Human Gingiva-Derived Mesenchymal Stem Cells Ameliorates Lupus Nephritis Depending upon CD39/CD73 Signals and the Induction of CD4+Helios-Foxp3+ Treg

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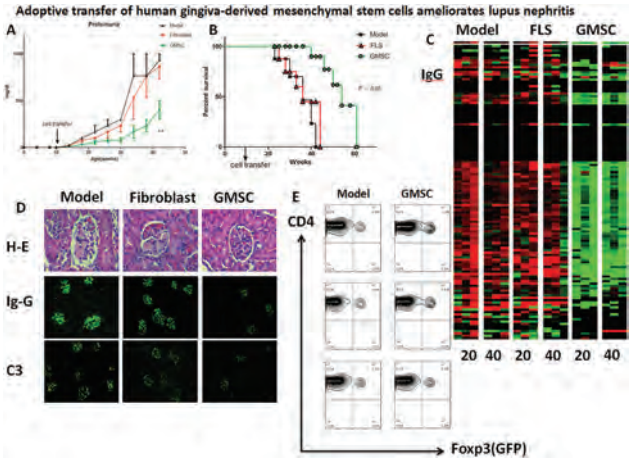
Background: Current approaches offer no cures for systemic lupus erythematosus (SLE)and lupus nephritis. Accumulating evidence has revealed that manipulation of bone-marrow mesenchymal stem cells (BMSCs) may have the potential to treat SLE. While BMSC-based therapy faces many challenges such as limited cell availability, BMSCs from patients with autoimmune diseases are dysfunctional, use of BMSCs with long term has a potential risk on tumorigenesis and reduced clinical feasibility, we herein demonstrate that substitution of gingival-derived mesenchymal stem cells (GMSCs) results in significantly improved therapeutic effects on lupus-like disease model.

Methods: Lupus-like disease has been induced with NZM2328 mice. In the study of prevention of lupus-like disease, GMSCs were injected i.v. into mice on age of 10 weeks. In some experiments, mice were injected with pre-treatment of GMSCs with CD39 or CD73 inhibitor. In the study of treatment of lupus-like disease, GMSCs were injected i.v. into mice on age of 20 weeks.

Results: In the study of prevention of lupus-like disease, infusion of GMSCs in NZM2328 mice significantly decreased the severity of lupus and kidney pathology scores, and down-regulated Th2, Tfh and Th17 cells. GMSCs significantly suppress activation and differentiation of B cells in vivo. Promotion of CD4+Helios-Foxp3+ Treg cells following treatment with GMSCs, these increased Tregs were noted in spleen, lymph nodes and kidney tissues. Pre-treatment of GMSCs with CD39 or CD73 inhibitor significantly reversed the protective effect of GMSCs on lupus-like disease model. In the study of treatment of lupus-like disease, GMSCs can also treat the established disease.

Conclusions: The role of GMSCs in controlling lupus-like disease mostly depends upon CD39/CD73 signals and upon the induction of CD4+Helios-Foxp3+ Treg cells. GMSCs provide a promising approach for the treatment of SLE and lupus nephritis.

Funding: Other NIH Support - National natural science foundation of China(81870481)



FR-PO858

Clinical Predictors of Acute Tubular Necrosis in Membranous Nephropathy

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Background: Acute tubular necrosis (ATN) is a common and important complication associated with membranous nephropathy (MN). Proteinuria magnitude is suggested as a cause for ATN in MN however clinical contributors to ATN in MN have not been previously evaluated. We queried the OSUWMC kidney biopsy repository to investigate predictors associated with ATN, and specifically explored the relationship between proteinuria magnitude and ATN in MN.

Methods: Ninety-five patients who underwent kidney biopsy from 2004 to 2017 were found to have MN. Pathology reports were reviewed for histologic findings including ATN. Patient demographics and clinical metrics collected at the time of biopsy were analyzed to determine their ability to predict ATN using univariate and multivariate testing. Metrics considered included age, gender, race, serum albumin, cholesterol, and proteinuria magnitude at diagnosis.

Results: A histologic diagnosis of ATN was identified in forty-three patients (45%) with MN. Serum creatinine at time of biopsy was higher in patients with ATN (1.39 mg/dL, IQR 1.06-2.3) compared to those without ATN (1.18 mg/dL, IQR 0.89-1.63), p=0.04. Proteinuria magnitude was the only clinical variable associated with ATN on multivariate testing (p=0.05). Proteinuria magnitude was then stratified into quartiles and ATN frequency was compared (Table 1). Overall, patients with > 4g/d proteinuria had a significantly higher rate of ATN on biopsy compared to those with 0-4g/d proteinuria (52.1% vs 22.3% respectively; OR: 3.7, 95% CI 1.23-11.07, p=0.03). The ATN rate did not differ at higher degrees of proteinuria above 4 g/d.

Conclusions: ATN commonly accompanies MN and is associated with a higher degree of renal impairment. Patients with MN and > 4 g/d proteinuria are at higher risk for ATN which may have both therapeutic and prognostic implications. Interestingly higher degrees of proteinuria did not further increase ATN rate suggesting additional factors may be involved and requires further study.

ATN Frequency According to Proteinuria Level

Magnitude of Proteinuria	Frequency of ATN
0-4 g/d	22.73%
4-6 g/d	50.00%
6-11 g/d	52.17%
> 11 g/d	53.57%

FR-PO859

Substitution of Oral for Intravenous Cyclophosphamide in Membranous Nephropathy

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Background: Optimal treatment for idiopathic membranous nephropathy (MN) is s till a matter of controversy. Current guidelines recommend oral cyclophosphamide combined with steroids, but concerns about the cumulative toxicity of oral cyclophosphamide persist. During the last 30 years, MN has been treated with steroids plus a low-dose intravenous (IV) cyclophosphamide-based regimen in Uruguay. The aim of the study was to assess the efficacy of this regimen to induce remission in MN.

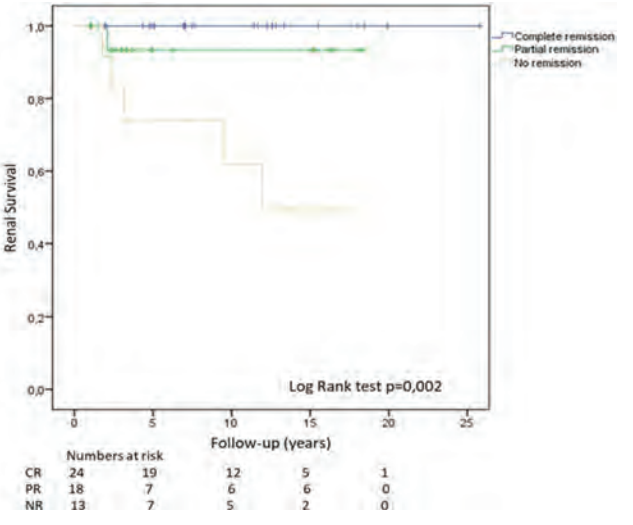
Methods: We performed a retrospective analysis of patients with membranous nephropathy, treated with a 6-month course of alternating monthly steroids (months 1, 3 and 5) plus IV cyclophosphamide (a single dose of 15 mg/kg IV the first day of months 2, 4, and 6).

Results: 55 patients treated between 1990 and 2017 were included; the median age was 53 years (IQR=38–64) and 69% of the patients were men. The follow-up was 7.1 years (3.2–13.9). Forty two (76.4%) patients achieved remission, 24 (43.6%) complete and 18 (32.7%) partial, respectively. Thirteen patients (23.6%) remained nephrotic. Time to achieve partial remission after treatment was 5.9 (4.6–16.0) and 11.5 (5.9–15.0) months to achieve complete remission (Table 1). During the follow up, six (10.9%) patients (one with partial and five with no remission) required chronic renal replacement treatment (Figure 1). The latency between diagnosis and end stage renal disease was 3.5 years (2.3–10.1).

Conclusions: Monthly IV cyclophosphamide plus steroids is an effective and safe treatment for membranous nephropathy and is worthwhile to be considered in prospective clinical trials.

Variable	All	Remission			p
		Complete	Partial	No	
Number, *n (%)*	55	24 (43.6)	18 (32.7)	13 (23.6)	
Men, *n (%)*	38 (69.1)	15 (62.5)	12 (66.7)	11 (84.6)	0.37
Age, *y*	53.0 (38-64)	52.5 (33.3-66.8)	49.5 (32.0-59.5)	57 (39-65)	0.43
Proteinuria, *g/d*	7.6 (4.5-11.2)	6.3 (3.7-8.6)	7.9 (4.4-13.3)	8.8 (6.8-12.5)	0.16
Creatinine, *mg/dl*	1.0 (0.79-1.28)	0.93 (0.76-1.19)	0.94 (0.78-1.35)	1.18 (1.04-2.14)	0.14
SBP, mm Hg	130 (111-140)	130 (110-142)	125 (116-148)	120 (100-143)	0.59
DBP, mm Hg	80 (70-90)	80 (70-90)	80 (70-90)	75 (60-83)	0.52

Values are median (IQR) or numbers of subjects (%).
SBP = systolic blood pressure. DBP = diastolic blood pressure.



FR-PO860

The Significance of Glomerular C1q Deposits in Primary Membranous Nephropathy

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Background: Unlike a previous report of no C1q deposition in idiopathic membranous nephropathy (iMN), recent studies have shown trace C1q deposition even in iMN due to improvements in the sensitivity of detection methods. The aim of study was to examine the clinical and pathological significance of glomerular C1q deposits in iMN.

Methods: 1) This single center retrospective study included 54 patients with MN who underwent renal biopsy from January 2005 to December 2017 (mean follow-up of 3.6±2.4 years). We evaluated remission of proteinuria (<1g/gCr) and other clinical examinations. 2) Next, after excluding patients with secondary MN (including hepatitis C virus infection, systemic lupus erythematosus, MCTD, malignancy and medication) (n=16), and those without immunofluorescence study (n=3), we selected 35 patients for further study. A variety of clinical parameters, outcomes and other serum and urine factors was compared in patients with and without significant glomerular capillary C1q deposits.

Results: 1) In 54 patients, 16 patients (29.6%) were diagnosed with secondary MN due to the detection of secondary causes including drugs, malignant tumors, autoimmune diseases and infectious diseases. A total of 40 patients (74.1%) achieved remission of proteinuria: 26 (48.2%) complete and 14 (25.9%) partial remission. 2) Glomerular C1q deposition was detected on capillary walls by immunofluorescence in 21/35 (60.0%) patients with iMN. In the group with glomerular C1q deposits, the remission of urinary protein was significantly delayed using a log rank test (log rank=0.019). In iMN, glomerular C1q deposition was an unfavorable predictor for remission of proteinuria (hazard ratio (HR) 2.41, 95%CI=1.13-5.14, P=0.022) in Cox proportional hazards analysis.

Conclusions: These results suggest that glomerular capillary C1q deposition was associated with poor renal outcome.

FR-PO861

Estimation of Nephron Number and Related Single Nephron Parameters in Patients with Idiopathic Membranous Nephropathy

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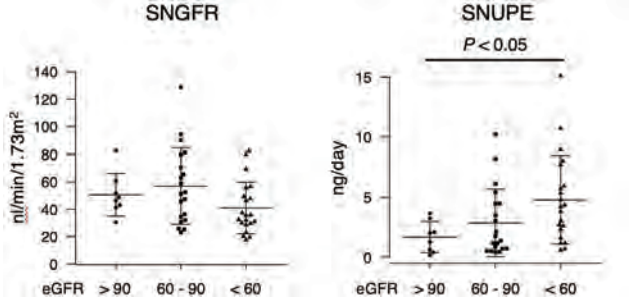
Background: Studies using animal models suggested that glomerular hyperfiltration as well as impaired hydraulic permeability play a crucial role in the progression of membranous nephropathy. To date, total nephron number and the related single nephron parameters have not been evaluated in patients with idiopathic membranous nephropathy (IMN) due to technical difficulties in counting nephrons in a clinical setting.

Methods: The total nephron number was calculated using a simplified method based on combined use of unenhanced computed tomography and stereology-based estimation of non-sclerotic glomerular density in biopsy specimens (Sasaki T et al. 2018, ASN). Single-nephron glomerular filtration rate (SNGFR) and single-nephron urinary protein excretion (SNUPE) were calculated by dividing eGFR or UPE by total nephron number, respectively.

Results: A total 49 IMN patients was included (age, 60 ± 14 years; 49 % male; UPE 4.1 ± 3.1 g/day). The total nephron number ranged from 197,561 to 1,824,272 per kidney. Compared to patients with CKD stage 1 or 2, the SNGFR showed a tendency to be low in patients with CKD stage 3 or higher. Patients with CKD stage 3 or higher were characterized by elevated SNUPE level (**Figure**). Nephron number and the related single nephron parameters were not associated with Ehrenreich-Churg stage of the glomerular basement membrane (GBM) lesions.

Conclusions: This study for the first time estimated total nephron number and the related single nephron parameters in IMN patients. Impaired single nephron functions may be involved in IMN patients with advanced-stage CKD regardless of severity of GBM lesions.



FR-PO862

Levels of Anti-Phospholipase A2 Receptor Antibodies (PLA2R) in Patients with Membranous Nephropathy in Argentina

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Background: Primary membranous glomerulopathy (NM) is the most common histological and immunohistochemical phenotype in adult non-diabetic nephrotic patients. 70% of untreated patients are positive for anti-PLA2R and this proportion is fairly constant We analyzed the experience of a single Center of the levels of AntiPLA2R in patients with MN or with a nephrotic syndrome without a renal biopsy and correlated with the histological and immunohistochemical phenotype and the clinical status at the time of the assay

Methods: We identified 169 adult patients who had anti-PLA2R antibody levels determined using ELISA between July 2015 and November 2018 in Argentina. We obtained relevant data on 101 patients

Results: The median time between the dosing and the biopsy was 12.1 (2.8-45) months. Levels were positive in 30.6%, doubtful in 4.7% and negative in 64.7%, with no significant differences between positive or negative groups in terms of age, sex, initial presentation, albuminemia, proteinuria and renal function. In patients whose first dosage was performed within 6 months of the biopsy (some had already started immunosuppressive treatment), the assay was positive in 45.5% and negative 54.3%. In the primary forms it was positive in 25, negative in 45 and doubtful in 4 patients. In secondary cases it was positive in only 1 patient and negative in 10 All patients with lupus MN were negative as were patients with other Glomerulopathies. Of four patients with a transplant who had a recurrence of MN in the graft 1 was positive, 1 had a doubtful result and 2 were negative All three pregnant women with a nephrotic syndrome were negative. In 12 patients the anti-PLA2 antibody titre decreased in response to immunosuppressive treatment (11) or spontaneous remission (1). Two patients who were negative in the course of a complete remission turned positive during a relapse

Conclusions: Our data show less positivity for anti-PLA2R than that reported in the literature in untreated patients with MN This is likely due to the fact that many patients were in complete or partial remission, and that treatments mostly consisted of Ponticelli regimens which induce a quicker reduction of antibody levels than other therapeutic options Our results are probably indicative of the wide spectrum of our sample in terms of clinical status and previous treatments

FR-PO863

Determination of Serum Anti-PLA2R and Anti-THSD7A Antibodies and Tissue Anti-PLA2R in Brazilian Patients with Primary and Lupus Membranous Nephropathy

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Background: Membranous Nephropathy (MN) is a common cause of nephrotic syndrome in adults. In Brazil, it is the second most frequent cause of glomerulopathies in biopsies registries. Incidence variations among the various studies may reflect patterns of biopsy indication in different countries, but it may also be related to socioeconomic, ethnic or environmental characteristics. In the past years, the role of anti-phospholipase A2 (anti-PLA2R) receptor autoantibodies and the antibody against THSD7A (thrombospondin type 1 domain-containing protein 7A) in the pathogenesis of idiopathic MN were described. The determination of these serum antibodies and renal tissue anti-PLA2R antibodies have not yet been performed in the Brazilian population.

Methods: Blood samples were collected from 28 patients diagnosed with MN, 17 patients with Lupus Membranous Nephropathy (LMN) and 8 patients with Focal and Segmental Glomerulosclerosis (FSGS), confirmed by renal tissue biopsy (OM and IF). The serum anti - PLA2R antibody was measured by the ELISA and IIFT techniques and antibodies against THSD7A by IIFT. In addition, immunohistochemistry was performed in paraffin blocks to identify the anti - PLA2R antibody in these patients.

Results: All 17 patients with LMN and the 8 patients with FSGS were negative for anti - PLA2R and anti - THSD7. A total of 28 patients with MN tested negative for anti - THSD7A. Among the patients with MN at admission, there was a positivity of 54% by IIFT and 39% by ELISA, considering VR of 20 RU/ml. When we reduced the ELISA reference value to 14 RU/ ml the sensitivity of the test equals the IIFT test. The specificity of both methods was 100% in this sample. Immunohistochemistry was performed in 24 of the 28 patients with NM, 15 (63%) presented positive labeling for the antibody in renal tissue. Of the 15 patients with tissue positivity, 13 tested positive for the antibody in the serum.

Conclusions: In this Brazilian population of MN patients, there was 54% positivity for anti - PLA2R. The IIFT and ELISA technique has the same sensitivity when considering the RV of 14 RU/ml for the ELISA. The sensitivity of immunohistochemistry in the tissue was greater than the serum antibody anti – PLA2R dosage.

Funding: Government Support - Non-U.S.

FR-PO864

Circulating Antibodies to Recombinant Exostosin 1 Are Detected in Patients with Primary and Secondary Membranous Nephropathy

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Background: Antibodies to phospholipase A2 receptor (PLA2R), a transmembrane podocyte protein, account for approximately 70% of cases of primary membranous nephropathy (MN). Antibodies to thrombospondin type-1 domain-containing 7A (THSD7A) account for approximately 10% of anti-PLA2R negative patients. Anti-PLA2R

and anti-THSD7A are rarely found in secondary MN, including class V lupus nephritis (LN). A recent report by Sethi and colleagues demonstrated glomerular deposition of exostosin 1/exostosin 2 (EXT1/EXT2) in about 10% of patients with anti-PLA2R negative MN, including 8 of 18 patients with pure class V LN. However, anti-exostosin antibodies were not detected in the 7 patients tested. This study tested the hypothesis that patients with class V LN have circulating antibodies to exostosin 1 (EXT1).

Methods: Recombinant full length human EXT1 (Abnova) was separated by SDS-PAGE and transferred onto a nitrocellulose membrane. Membranes were incubated overnight at 4°C with sera from patients (1:50-1:100) or rabbit polyclonal antibody to EXT1 (ABclonal; dilution 1:1000) followed by appropriate HRP conjugated secondary antibodies. 5 patients with class V LN (4 pure class V, 1 with class III/V) and 4 patients with primary MN (3 anti-PLA2R+) were evaluated. Secondary antibody controls were negative. All blots were run twice for validation.

Results: We found 3 of 5 patients with class V LN (including 1 patient with class III/V LN) had circulating antibodies to EXT1. We found 2 of 4 patients with primary MN (both anti-PLA2R+) had circulating antibodies to EXT1.

Conclusions: We conclude that circulating antibodies to EXT1 are found in patients with primary and secondary membranous nephropathy, including patients with circulating anti-PLA2R.

Funding: NIDDK Support

FR-PO865

Anti PLA2R Antibody Titers and Disease Course in Primary Membranous Nephropathy

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Background: The natural course of primary membranous nephropathy (pMN) is highly variable. Up to half of the patients presenting with nephrotic syndrome will show progressive kidney function decrease. The remaining patients will show a spontaneous remission of proteinuria. Early prediction of prognosis is needed to personalize treatment.

Methods: We included 216 pMN patients referred to our hospital for urine analysis and followed these patients until renal progression, defined as an increase in serum creatinine of >50% from baseline, >25% to a level >1.5 mg/dl, or start of therapy due to severe nephrotic syndrome, or sponteaneous partial remission, defined as a reduction in proteinuria of >50% from baseline to a level <3.5 g/g creatinine with a stable serum creatinine. Anti-PLA2R antibody titers were determined using a EuroImmun ELISA assay. We created a multivariate prognostic model using cause-specific Cox regression that included baseline values for serum creatinine, urine protein creatinine ratio, anti-PLA2R antibody titer, α-1-microglobulin excretion rate.

Results: The table shows baseline characteristics for the study population. The prediction model showed good prognostic performance with a C-statistic of 0.78 (95%CI 0.71 to 0.84) for progression and 0.78 (0.70 to 0.85) for spontaneous remission at 24 months. The table shows baseline characteristics for the study population. The hazard ratio for progression was 1.07 (0.88 to 1.30) per doubling of aPLA2R titer. Conversely, the hazard ratio for partial remission was 0.68 (0.54 to 0.85). Discrimination was good with a C-statistic of 0.80 (95%CI 0.74 to 0.86) for progression and 0.76 (0.68 to 0.83) for spontaneous remission at 24 months. Predicted and observed risk of respectively progression and spontaneous remission were well calibrated.

Conclusions: Anti-PLA2R antibody titers appear to be predictive of spontaneous partial remission but not progression in primary MN.

Funding: Private Foundation Support

Baseline characteristics

	Persistent NS	Progression	Partial Remission	p
n	1	136	79	
Age (yrs)	61	53.6 (13.6)	51.1 (14.9)	NA
Females (%)	0	38 (28)	28 (35)	0.41
Serum creatinine (µmol/l)	105	94.7 (19.5)	84.7 (15.2)	NA
Protein Creatinine Ratio (g / 10 mmol)	3.95	8.7 [6.2, 11.4]	5.9 [4.5, 8.1]	<0.001
A-1-microglobulin (ug/min)	12.1	59.7 [34.5, 95.0]	29.5 [19.4, 42.5]	<0.001
Anti-PLA2R antibody titer	829	100 [33, 249]	35 [1, 95]	<0.001

FR-PO866

Waiting for Spontaneous Remission in Primary Membranous Nephropathy: Is It Safe?

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Background: We advocate a restrictive treatment strategy in patients with primary membranous nephropathy (pMN): immunosuppressive therapy(IS) is started late, while awaiting spontaneous remission. Many patients thus have persistent nephrotic syndrome for >12 months. Since proteinuria is associated with podocyte loss, delaying treatment might increase the risk of podocte depletion and secondary FSGS. We evaluated the outcome in patients with persistent proteinuria not receiving IS within 12 months after onset of disease.

Methods: We included patients with pMN, normal eGFR and nephrotic range proteinuria (urinary protein/creatinine ratio(uPCR) >3.0 g/10mmol) at presentation and followed for >2 years. We assume that in patients with podocyte loss and secondary FSGS, a complete remission(CR) will not occur. Therefore we selected patients with early and late spontaneous partial remission(SRem) and compared CR rate as outcome parameter. Partial remission(PR) was defined as uPCR <3.0g/10mmol and >50% decrease from baseline and stable kidney function. CR was defined als uPCR <0.2g/10mmol with stable kidney function.

Results: We included 254 patients. 12 months(m) after first presentation, 64(25%) patients were treated with IS and 47(19%) patients were in SRem. 94(37%) achieved SRem after 12 months, 33(13%) were eventually treated with IS, and 16(6%) had no IS nor remission. Baseline characteristics of the patients with SRem <12 months vs. SRem >12 months were comparable, except for number of aPLA2r positive patients. CR rate was comparable (47 vs. 40%). In patients who started with IS >12 months after diagnosis, PR was achieved in 27(82%) and CR in 17(51%).

Conclusions: Waiting for SRem in pMN is safe. Most patients with persisting proteinuria for more than 12 months develop a remission, even if immunosuppressive therapy is needed.

Comparison of early vs. late spontaneous remission in pMN

Group (N)	Spontaneous remission <12m (N=47)	Spontaneous remission >12m (N=94)
Females N(%)	16 (34%)	34 (36%)
Age at onset*	52 [38-61]	51 [39-58]
Baseline serum creatinine (mmol/L)* Baseline serum albumin (g/L)* Baseline uPCR (g/10mmol)* Baseline aPLA2r positive IFT N(%)∫	82 [69-91] 24 [20-28] 6.1 [4.7-7.7] 18/34 (53%)	81.5 [70-90.25] 24 [20-27.5] 6.7 [4.5-9.4] 38/49 (78%)
Complete remission N(%) Time to complete remission (months) *	22 (47%) 30.5 [22.75-53]	38 (40%) 40 [25-72]
Relapse N(%)	11 (23%)	23 (24%)
Follow-up duration (months)*	76 [46-118]	75.5 [43.5-138.25]
Increase in serum creatinine at the end of follow-up*	6.9% [-5.4-16.4]	12.3% [-2.1-25.5]

*Median[IQR]

∫p=0.02

FR-PO867

Early vs. Late Start of Immunosuppressive Therapy in Membranous Nephropathy

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Background: Alkylating agents improve outcome in membranous nephropathy (MN). Guidelines advise restrictive treatment. Some centers wait beyond 6-12 months before start of immunosuppressive therapy. The risk of persisting proteinuria is podocyte loss, which may cause secondary focal glomerulosclerosis. This should reduce the likelihood of complete remissions. We evaluated the safety of delayed treatment.

Methods: We used data of two centers that participated in the MN registry (mnregistry.eu). In one center (Czech Republic (CZ)) treatment is started early after kidney biopsy, whereas in the Netherlands (NL) a restrictive treatment strategy is used[1]. For the current analysis we included incident patients, with proteinurie of > 2 grams/24 hours, treated with immunosuppressive therapy (ISRx) and available follow-up. To allow evaluation of late treatment, we included only patients from NL with an interval of more than six months from kidney biopsy. Partial and complete remissions were defined according to KDIGO criteria.

Results: In total 155 patients were included in the analysis. Baseline information and outcomes are presented in Table 1. Alkylating agents were mainly used, cyclophosphamide in NL (81 %) and chlorambucil in CZ (60 %). Overall remission rates (partial- and complete remission) calculated from start of therapy, were not different. Most importantly, also with delayed therapy complete remissions were observed frequently (Table 1).

Conclusions: The MN registry allows comparison of treatment protocols between centers. Our data support the safety of a delayed treatment strategy.

Funding: Government Support - Non-U.S.

Baseline characteristics and outcome

	NL N=90	CZ N=65
Mean age (years)	54 ± 13	56 ± 15
Gender (% males)	68 (76 %)	43 (66 %)
Screatinine (µmol/l)	90 [75-106]	93 [74-133]
UPCR (g/10 mmol)	7.9 [5.9-10.9]	6.6 [4.7-10.8]
Salbumine (g/l)	22 [18-26]	20 [16-24]
Interval biopsy till start of ISRx (months)	10.9 [8.1-19.5]	0.0 [0.0-0.0]
Follow-up duration (years)	7.3 [3.8-11.5]	2.2 [1.0-3.6]
N (%) PR after 1 year	67 (74 %)	48 (74 %)
N (%) CR after 1 years	34 (38 %)	15 (23 %)
N (%) PR after 2 years	85 (94 %)	48 (74 %)
N (%) CR after 2 years	45 (50 %)	15 (23 %)

Mean±SD, Median [IQR]

FR-PO868

Clinical Analysis of Short-Term Therapeutic Response Factors in Membranous Nephropathy

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Background: Membranous nephropathy (MN) is known to affect frequently in elderly patients. Since the duration of MN treatment is likely to be prolonged, it is desirable that the treatment duration would be shortened by the concomitant use of immunosuppressant and prednisolone (PSL). Here, we examined clinical and histological parameters related to the rapid response to the therapy by the retrospective analysis.

Methods: Biopsy-proven 82 cases with MN, hospitalized between April 2009 and December 2017, were enrolled in this study. All cases were divided into three groups, 1st (high responder), 2nd (middle responder) and 3rd (low responder) quantiles, based on the proteinuria-reduction ratio at a month after the beginning of therapy including sole administration of PSL and concomitant use of immunosuppressants such as Cyclosporin or Mizoribine. Cases in 1st and 3rd quantile were comparatively studied. All biopsy specimens were stained by anti-phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain containing 7A (THSD7A) antibodies by standard protocol.

Results: Age of 1st (n=23) and 3rd (n=24) quantile groups were 66.7±2.16 vs 66.6±3.11, showing no difference. Estimated glomerular filtration rate (eGFR) and baseline urine protein-to-Cr ratio (PCR) in 1st quantile group were significantly higher than those in 3rd quantile group; eGFR: 72.7±2.78 vs 59.7±4.64 ml/min (p = 0.018), baseline PCR: 8.39±1.37 vs 5.09±1.11 (p = 0.039). There was no difference in intensity of immunofluorescent staining of IgG, A, M, C3 between 1st and 3rd quantile groups. We also studied the difference in immunofluorescent intensity of PLA2R, THSD7A and IgG subclass, however, we could not find out significant difference in the both groups.

Conclusions: Obtained results showed that higher eGFR and baseline PCR might be related to the rapid therapeutical response. Contrary to our expectation, staining intensity of PLA2R, THSD7A and IgG subclass might not be related the rapid response to the therapy.

FR-PO869

Calcineurin Inhibitors Treatment and Renal Function Decline in Patients with Idiopathic Membranous Nephropathy

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Background: Calcineurin inhibitors (CNIs), including cyclosporine A(CSA) and tacrolimus, is an established therapeutic option suggested for treatment in IMN patients. The major concern with CNIs remains its propensity to induce renal function impairment. This study was designed to assess the influence of CNIs on renal function compared with cyclophosphamide(CTX), and seek factors that can predict renal function impairment in patients receiving CSA.

Methods: In this study, we included 555 IMN patients treated with CTX or CNIs, with or without glucocorticoids and other immunosuppressant. Data on age, sex, body mass index, presence of hypertension and diabetes, laboratory tests, and therapeutic regimens were retrospectively retrieved from medical record. Cox regression was employed to analyze risk factors indicating a 30% decline in estimate glomerular filtration rate(eGFR) or end-stage renal disease (ESRD) in total patients or those treated with CSA.

Results: During a median follow up of 2.9(1.0-4.6) years, 59(10.6%) patients developed a 30% eGFR decline or ESRD, of whom over 90% had been treated with CNIs before. CNIs treatment was an independent risk factors associated with developing 30% decline in eGFR or ESRD (*HR*=5.7, *95%CI* 2.2-14.8, *P*<0.001), independently of age, sex, hypertension, baseline serum albumin, urine protein, and eGFR, and the dose of glucocorticoids. Further analysis restricted in patients receiving CSA showed age over 50 years old (*HR*=3.7, *95%CI* 1.8-7.3, *P*<0.001) and mean CSA dose over 2.2mg/kg/d (*HR*=1.8, *95%CI* 1.0-3.1, *P*=0.035) might indicate 30% decline in eGFR or ESRD.

Conclusions: CNIs treatment may associate with renal function decline independently in IMN patients, especially in patients over 50 years old or receiving CSA over 2.2mg/kg/d.

FR-PO870

Efficacy of Cyclophosphamide in Association with Low-Dose Cyclosporine for the Treatment of High-Risk Primary Membranous Nephropathy

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Background: Ponticelli regimen is associated with the highest remission rate in the treatment of primary membranous nephropathy (pMN), but corticosteroids are associated important side effects. As such, we tested the efficacy of the combination of cyclophosphamide and low-dose cyclosporine in the management of high-risk pMN.

Methods: We prospectively followed 8 patients with high-risk pMN, treated with cyclophosphamide (iv, 15 mg/kg/month, for 6 consecutive months) and cyclosporine 100 mg/d (for proteinuria control) (CF/Cyc regimen). We compared this cohort to 8 consecutive, prospectively followed patients with pMN treated with the Ponticelli regimen, with a similar risk. Clinical and laboratory data were collected at baseline and at 1, 3, 6, 12- and 15-months thereafter.

Results: The two cohorts had similar baseline characteristics, except for higher antibody titer and proteinuria for patients treated with CF/Cyc regimen. The Ponticelli cohort of patients had a mean age, serum albumin and eGFR of 50 ± 10 years, 2.7 ± 0.8 g/dl and 55 ± 26 ml/min/1.73m^2, respectively, while the median proteinuria and anti-PLA2R-ab titer were 6.25 (5.25-11) g/day and 122.5 (71.5-211) UI/ml, respectively. By comparison, the CF/Cyc cohort had a mean age, serum albumin and eGFR of 50 ± 9 years, 2.5 ± 0.5 g/dl and 69 ± 30 ml/min/1.73m^2, respectively (p=0.9, 0.4 and 0.3), while the median 24-hour proteinuria and anti-PLA2R-ab titer were 9.85 (7.15-13.15) g/day and 291.5 (100-571.75) UI/ml, respectively (p=0.1 and 0.06). CF/Cyc regimen was associated with a 70% and 90% decrease from baseline in mean proteinuria and anti-PLA2R-ab titer, as opposed to a 58% and 97% decrease from baseline following Ponticelli regimen (p=0.7 and 0.8, respectively). There was a 41% and 31% increase from baseline in mean serum albumin following CF/Cyc and Ponticelli regimen, respectively (p=0.9). Overall, the remission rate (CR and PR) was 62% and 50% in the CF/Cyc and Ponticelli cohort, respectively, while 50% of patients in both cohorts showed complete immunological remission by 6 months.

Conclusions: In our cohort of patients with high-risk pMN, treatment with cyclophosphamide and low-dose cyclosporine was as effective as the Ponticelli regimen in inducing disease remission and could represent an alternative to steroid-based regimens.

FR-PO871

Membranous Nephropathy: Efficacy of Low or Standard Rituximab-Based Protocols and Comparison to the Ponticelli Regimen

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Background: About 80% of patients (pts) with primary Membranous nephropathy (PMN) have an autoimmune disease caused by autoantibodies and 75% of them have antibodies direct against the M-type phospholipase A2 receptor (PLA2R) present in podocytes. Immunosuppressive treatment is recommended in high-medium risk pts. Recently the use of rituximab (RTX), has emerged as an important therapeutic option in pts with PMN. The appropriate dose, the number of doses of RTX in MN pts is still uncertain. Few investigators have reported conflicting outcomes with low-dose of RTX. No randomized clinical trials have been performed so far to compare the efficacy and safety profiles of low-dose RTX (Protocol 1, one dose of RTX 375 mg/m^2) with standard dose RTX (Protocol 2, four weekly doses of Rituximab 375 mg/m^2) and Ponticelli regimen (PR). Waiting for the results of controlled trials that compare the efficacy of RTX with other therapeutic approaches in primary MN or different RTX regimens, we report our experience comparing 3 different treatment protocols. Our working hypothesis was that the efficacy of RTX was comparable to that of PR even at low dose.

Methods: 32 consecutive pts with PMN and nephrotic syndrome were included and received RTX (14 pts treated with Protocol 1; 17 with Protocol 2). All patients were followed for 24 months after RTX. 17 pts treated with PR were included as controls and matched with cases for age and baseline proteinuria. No statistical differences were observed among groups in baseline sCr and Proteinuria

Results: At 24 months, we observed a statistical significant improvement in terms of proteinuria levels in pts treated with Protocol 1 (7.5 +/- 4.8 at T0; 0.21 +/- 0.15 at T24, p<0.01) protocol 2 (5.1+/-1.41 g/24 at T0; 0.35 +/- 0.39 at T24 p<0.01) and in the controls (8.27 +/- 4.78 T0; 2.2 +/- 1.9 g/24h at T24, p<0.01). When comparing the 3 groups, we observed no differences in clinical response (p=0.53). No statistical significant change in sCr levels was observed, at baseline and during the follow-up.

Conclusions: Our data suggest that the RTX is a promising alternative to Ponticelli's protocol even at low-doses. RTX has the potential to be a cost-effective treatment in the short and medium terms despite the high single dose cost. The use of low dose can provide a further significant reduction in treatment.

FR-PO872

Remission and Relapse Rates for Primary Membranous Nephropathy Treated with Combination Rituximab, Cyclophosphamide, and Prednisone

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Background: We evaluated the efficacy of combination therapy with rituximab-induced continuous B cell depletion, a short course of low-dose, oral cyclophosphamide, and an accelerated prednisone taper (RCP) for the treatment of primary membranous nephropathy.

Methods: A retrospective analysis was conducted on 49 consecutive patients with primary membranous nephropathy treated with RCP at Massachusetts General Hospital. The co-primary outcomes were attainment of partial (PR) and complete remission (CR). PR was defined as a urinary protein to creatinine ratio (UPCR) < 3 g/g and a 50% reduction from baseline. CR was defined as a UPCR < 0.3 g/g. Secondary outcomes were SAEs and change in proteinuria, serum creatinine and albumin after 1 year of treatment. Relapse was defined as a UPCR > 3 g/g after having achieved CR or PR.

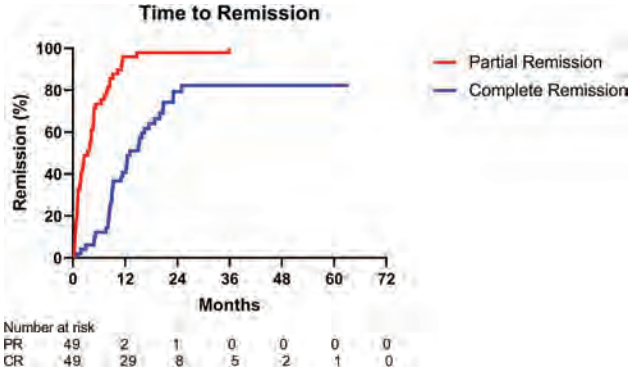
Results: Over a median follow-up of 36 (IQR 24 - 56) months, 100% of patients achieved PR and 82% of patients achieved CR at a median time of 3.4 and 13.1 months, respectively. After 1 year of treatment, median (IQR) UPCR declined from 8.2 (5.2 - 10.7) to 0.3 (0.2 - 0.7) g/g (P < 0.001). Fourteen SAEs occurred over 166 patient-years. One patient (2%) progressed to ESRD, and no patients died. Of those patients followed after B cell return (n = 25), only 1 patient relapsed over a median follow-up of 18 (IQR 6.2 - 37) months.

Conclusions: Treatment of primary membranous nephropathy with RCP resulted in high rates of complete remission and relapse-free survival.

Funding: NIDDK Support

Variable	Overall (n = 49)	Initial therapy (n = 27)	Second-line therapy (n = 22)	P-value
Age (years)	58 (51-66)	55 (51-62)	61.5 (49-68)	0.49
Female	22 (44.9)	14 (52)	8 (22)	0.28
Systolic BP (mmHg)	141 (124-150)	140 (124-152)	141 (126-148)	0.94
Diastolic BP (mmHg)	80 (70-85)	78 (69-85)	81 (72-86)	0.46
Serum creatinine (mg/dL)	1.2 (0.9-1.5)	0.99 (0.76-1.8)	1.2 (1.1-1.4)	0.25
eGFR group				0.73
> 60	29 (59)	15 (56)	14 (64)	
30-60	11 (23)	6 (22)	5 (23)	
< 30	9 (18)	6 (22)	3 (13)	
UPCR (g/g)	8.2 (5.2-10.7)	9.5 (5.2-11.6)	6.5 (4.8-9.5)	0.14
UPCR group				0.06
< 4	8 (16)	5 (19)	3 (14)	
4-8	14 (29)	4 (15)	10 (45)	
> 8	27 (55)	18 (66)	9 (41)	
Nephrotic Syndrome	40 (82)	24 (89)	16 (73)	0.15
Albumin (g/dL)	2.7 (2.3-3.1)	2.5 (2.2-2.9)	2.9 (2.5-3.3)	0.047
Total cholesterol (g/dL)	315 (235-389)	315 (248-385)	306 (230-427)	0.86
Triglycerides (mg/dL)	192 (144-270)	192 (145-265)	204 (137-468)	0.51
On ACE-I or ARB	45 (92)	25 (93)	20 (91)	0.83
On statin	34 (69)	17 (63)	17 (77)	0.28
Treatment Indication				
Failure of ACE-I or ARB	23 (47)	14 (52)	9 (41)	0.45
Declining of renal function	15 (31)	10 (37)	5 (23)	0.28
Debilitating symptoms from nephrotic syndrome	20 (41)	13 (48)	7 (32)	0.25
Relapsing disease	15 (31)	NA	15 (68)	NA
Refractory disease	8 (16)	NA	8 (36)	NA
Anti-PLA2R antibody status				0.003
Positive	36 (74)	25 (92)	11 (50)	
Negative	5 (10)	1 (4)	4 (18)	
Unknown	8 (16)	1 (4)	7 (32)	

Baseline characteristics



FR-PO873

Long-Term Outcomes of Rituximab Treatment in Membranous Nephropathy

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Background: Rituximab is increasingly used for the treatment of membranous nephropathy (MN), both as first line & for relapsing disease, but there are few published data on long term outcomes.

Methods: In this retrospective, observational cohort study we report outcomes of 38 adult patients with biopsy proven MN treated with rituximab between Jan 2008 & Jan 2018. Follow up was for a mean of 4 years (range 1-10). Rituximab, 2 x 1 g doses, was administered at days 0 & 14.

Results: We identified 38 patients, 25 male, median age 57.5yrs (range 23-77). At administration of rituximab, patients were heavily nephrotic with median urinary protein creatinine ratio (uPCR) 851 mg/mmol (range 574-1420) & median eGFR 33 ml/min/1.73m^2 (23-59). B cell depletion occurred within 2 weeks of administration; however, 73% of patients were B cell replete at 3 months. By latest f/up, 27 (71%) patients achieved remission (CR & PR). Median time to PR was 12 mths but CR took longer to achieve, up to 36 mths in some cases. Relapses occurred in 5 (18.5%) responders, of whom 1 died & 1 progressed to ESRD. There were 11 (29%) non-responders of whom 7 progressed to ESKD. The eGFR was less than 30ml/min/1.73m^2 in 17 patients (44.7%) at the time of rituximab treatment. Whilst 7 of these patients progressed to ESKD, in 10 cases renal function improved or stabilised. 3 patients died during the follow up period one from intracerebral haemorrhage, one from lung malignancy & one from a cardiac event.

Conclusions: Rituximab is effective in treating MN though the time to remission can be prolonged. B cell repletion occurs early in MN however this is not necessarily associated with relapse. Importantly, response to rituximab can lead to preservation or improvement of renal function even when severely impaired. Such patients may benefit from treatment and should not necessarily be excluded from controlled trials.

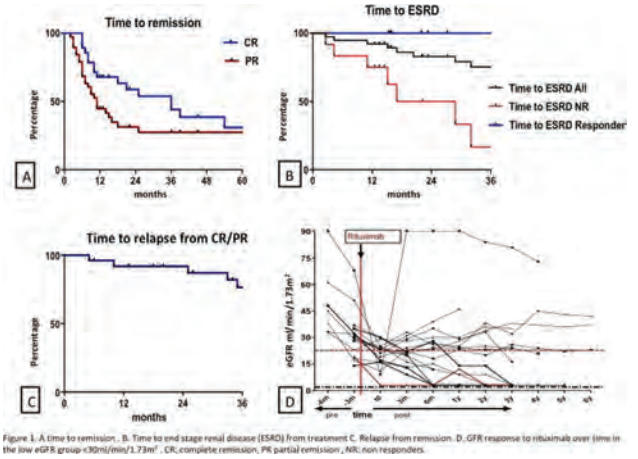

Figure 1. A time to remission , B. Time to end stage renal disease (ESRD) from treatment C. Relapse from remission. D. GFR response to rituximab over time in the low eGFR group <30ml/min/1.73m² . CR; complete remission, PR partial remission , NR; non responders.

FR-PO874

Long-Term Outcome of Treatment of Relapsing Primary Membranous Nephropathy with Rituximab

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Background: Primary membranous nephropathy is often susceptible to relapse after treatment with usual immunosuppresive therapy constisting of cyclophosphamide and glucocorticoids, or a calcineurin-inhibitor with glucocorticoids. Patients with relapse may be treated with rituximab. However its dose, frequency of administration and effect on long-term outcome have been incompletely evaluated.

Methods: Fourteen patients from our hospital were included in this study. The data were retrospectively extracted. Primary membranous nephropathy was diagnosed after exclusion of secondary causes, with finding of subepithelial deposits on electron-microscopy ± anti PLA2R antibodies. The inclusion criterion was relapse of a primary membranous nephropathy following a calcineurin inhibitor- or cyclophosphamide-based treatment. Patients recieved a single dose of intravenous rituximab (500 or 1000 mg), with target B-cell count < 5/μL. Subsequent courses of rituximab were administered following a repeat relapse.

Results: Ten patients were male and 4 female. The median age at time of diagnosis was 49 years (IQR 39-57 months). Median time from diagnosis to rituximab treatment was 17 months (IQR 10-41). During the median follow-up period of 47 months (IQR 32-68 months) 8 patients recieved one course of rituximab, 4 patients two courses and 2 patients three courses. Median time between two courses of rituximab was 16 months (IQR 6-26). Relapses following rituximab treatment responded to a repeat course of rituximab. There was a significant reduction in proteinuria from date of first rituximab treatment to date last seen (4±2.2 vs 1.1±1.1 grams, p<0.001), while there was no significant difference in serum creatinine (124±45 vs 102±21 μmol/L). Two patients had severe infective complications after rituximab treatment.

Conclusions: Rituximab is a safe and effective option in long-term treatment of relapsing primary membranous nephropathy.

FR-PO875

Low-Dose Rituximab Monotherapy Alone or in Combination with Tacrolimus Is Effective in Primary Membranous Nephropathy

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Background: Previous therapies though effective had more adverse events. Rituximab has been used to induce remission in doses of 2gms. It was therefore used in our patients with lower doses alone or in combination with Tacrolimus to achieve remmission. This is a retrospective study to evaluate the role of this treatment.

Methods: 15 patients aged 28 -72 years underwent treatment between since 2014 till 2018. Patients whose GFR was <40ml/min/1/73m2 were excluded from the study. Rituximab was given as a fixed dose of 500mg each. It was repeated if there was no response at 3 months. Rituximab was given as a monotherapy for 9 patients. Tacrolimus was added in 4/9 patients at the end of 3 months because of poor response. Rituximab and Tacrolimus were started together in 6 patients and out of these 2 were treated outside with modified Ponticelli regimen and had failed to show a response. Tacrolimus was given for 18 months. Complete remmission was defined as reduction in proteinuria of lessthan 0.3gms and partial remmission as less than 3gms or more than 50% reduction.

Results: Rituximab caused complete remmission in 4/ 9 patients and 1 patient attained partial remmission in the mean time of 8 months.2 patients attained remmission with the single dose of 500mg while another 2 required 2 doses of 500mg each. There was one relapse in this group who responded to one more dose of 500mg. Tacrolimus was added in 4 remaining patients at the end of 3 months.2 went into complete remmission after 3 months and one went into partial remmmission and one failed to respond. Tacrolimus was started along with first dose of Rituximab in 6 patients.2 patients received a single dose of 500mg, 2 received 500mg 2 doses and 1 received 3 doses of 500mg and 1 received 4 doses of 500mg. All went into complete remmission by mean time of 9 months.2 patients had relapses and both were sucessfully treated with 500mg of Rituximab. There was no fatal event in any group. There was only 1 patient who failed to respond to Rituximab and Tacrolimus combined therapy and subsequently responded to steroid and cyclophosphamide therapy.

Conclusions: Complete remmission was attained with a single dose of 500mg Rituximab monotherapy in 2 patients. This study showed complete or partial remmission in 14 /15 patients with this novel regimen with reduced side effects and cost by avoiding higher doses of Rituximab used in previous studies.

FR-PO876

Clinical Advantage of Mizoribine in Elderly Patients with Primary Membranous Nephropathy

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Background: Membranous nephropathy (MN) is usually managed in Japan by sole administration of Prednisolone (PSL) of 1 mg/kg for 4 weeks, and concomitant use of immunosuppressant would be thereafter considered. Here, we show the clinical efficacy of concomitant use of lower doses of Mizoribine (MZB) and PSL in elderly patients with MN.

Methods: Thirty-six elderly patients (age≥65) diagnosed primary MN showing nephrotic syndrome were enrolled from 24 independent facilities. The patients were randomly assigned to two groups, solely administered PSL 30 mg (P group, n=18), or concomitantly administered MZB 150 mg (MP group, n=18), and observed for 12 months. In some cases, anti-phospholipase A2 receptor antibody (PLA2R-Ab) titer was measured.

Results: Percent-urine protein-to-Cr ratio (PCR) comparing to baseline of MP was better than P (50.0% vs 55.6% at 3 M, 31.4% vs 39.9% at 6 M). Logistic analysis showed that the odds ratio of high responder (PCR<1.0 g/gCr at 3 M) in MP group was 1.50 (1.00 in P group), suggesting that the concomitant use of MZB might accelerate the remission. Total amount of administered PSL in MP group seemed to be less than that in P group. Kaplan-Meier analysis showed that time-course of complete-remission (PCR<0.3 g/gCr) ratio in MP group was significantly higher than P group studied by log-rank test (p=0.01) and generalized Wilcoxon test (p<0.01). In additional logistic analysis, the odds ratio of the high responder was 2.67 (MP) and 1.00 (P) in cases showing negative PLA2R-Ab whereas the odds ratio was 0.33 (MP) and 0.40 (P) in cases showing positive PLA2R Ab, suggesting that concomitant use of MZB might be more effective in PLA2R-Ab negative cases. Kaplan-Meier analysis also showed that time-course of remission (PCR<1.0 g/gCr) ratio in PLA2R negative group was higher than PLA2R positive group.

Conclusions: Concomitant use of low dose MZB and PSL at the start-up might be beneficial for elderly patients with MN. Qualitative measurement of PLA2R-Ab might be useful for the prediction of therapeutical response.

FR-PO877

Characterization of Lupus Nephritis in a Predominantly Hispanic Population in the Western United States

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Background: Lupus Nephritis (LN) is a serious complication of systemic lupus erythematous (SLE). Both genetic and environmental factors play a role in disease manifestation and outcomes. Our study aims to characterize LN and its treatment in a predominantly Hispanic population residing in the Western US.

Methods: A retrospective chart review was conducted on all native kidney biopsies performed at Los Angeles County + USC Medical Center between 2008-2018. 124 patients with biopsy proven LN were identified.

Results: Among the total 124 patients, median age of diagnosis was 32 (26-42.5) years and the majority were female (87.8%) and self-reported as Hispanic (72.9%). The median serum creatinine and urine protein to creatinine ratio at baseline were 0.98 (0.71-1.92) mg/dl and 3.89 (1.47-6.32) mg/g, respectively. 72.6% had biopsies compatible with proliferative LN. Degree of tubular atrophy was significantly associated with remission status at 1-year (p=0.004). Subgroup analysis demonstrated better 1-year post induction partial (PR) and complete remission (CR) rates in patients who received mycophenolate (MMF) and steroid (29.7% PR, 51.4% CR) as compared to cyclophosphamide (CYC) and steroid (18.8% PR, 40.6% CR). Higher rate of relapse was observed in patients who received MMF and steroid compared to CYC and steroid (24.3% vs. 9.4%, respectively). A lower percentage of patients on MMF and steroid developed ESRD compared to patients treated with CYC and steroid (2.7% vs. 18.8%). A significantly higher proportion of patients who were not on hydroxychloroquine were diagnosed with ESRD compared with patients who were taking hydroxychloroquine (22.5% vs 6.5%, p=0.03).

Conclusions: Our study showed that this Hispanic cohort residing in the Western US presented early, with mildly elevated serum creatinine, minimal to no tubular atrophy, and primarily with proliferative LN. Of these treated patients, although it did not reach statistical significance, a noticeable trend was observed in achieving better remission rates at 1-year endpoint with MMF and steroid as induction therapy compared to CYC and steroid. Additionally, the use of hydroxychloroquine in this cohort is significantly associated with lower ESRD rate.

FR-PO878

Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus with or Without Lupus Nephritis

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Background: Systemic lupus erythematosus (SLE) affects the pregnancy. Previous paper showed an increased risk of premature birth in patients who had a history of lupus nephritis. In the present study, we examined the outcomes of pregnancy in SLE patients with lupus nephritis (renal SLE) or without lupus nephritis (non-renal SLE).

Methods: We retrospectively examined 94 pregnancies in 53 SLE patients who treated in our department from January 1996 to March 2018.

Results: Mean patient age and serum creatinine at the beginning of pregnancy were not significantly different between renal and non-renal SLE patients: 29.4±5.8 vs 30.4±3.2 (years) and 0.48±0.11 vs 0.51±0.12 (mg/dL). Outcomes of pregnancy were shown in Table 1. Percentage of premature birth and low birth weight were more frequent in SLE patients in total, compared to the reported data of general population in Japan (19% vs 6% and 36% vs 10%, respectively). However, there were no significant differences between renal and non-renal SLE. Frequency of fetal loss was also not different between 2 groups, although natural abortion + stillbirth tended to be more in renal SLE than non-renal SLE (19% vs 4%, p=0.135). Among 43 renal SLE patients, 9 patients already had proteinuria at the beginning of pregnancy. Renal flare was observed in 5 patients (15%) out of 34 renal SLE patients without proteinuria at the beginning. In addition, pregnancy-induced hypertension was observed in 2 renal SLE patients (5%) and 3 non-renal SLE patients (6%).

Conclusions: In our study, frequencies of premature birth and fetal loss were not different between renal and non-renal SLE patients. However, both renal and non-renal SLE patients had higher rate of premature birth and low weight birth, compared to general population.

Table 1. Outcomes of pregnancy in SLE patients with or without lupus nephritis

	renal (n=43)	non-renal (n=51)	p-value
Delivery	30 (70%)	40 (78%)	0.354
Premature	9 (21%)	9 (18%)	0.794
Normal	18 (42%)	28 (55%)	0.222
Gestational week, unknown	3 (7%)	3 (6%)	1.000
Low birth weight	12 (40%*)	13 (33%*)	0.616
Fetal loss	13 (30%)	11 (22%)	0.354
Natural abortion	7 (16%)	4 (8%)	0.334
Artifical abortion	5 (12%)	7 (13%)	1.000
Stillbirth	1 (2%)	0 (0%)	0.457

* Percentage in total delivery.

FR-PO879

Venous Thromboembolism in Lupus Nephritis by ISN/RPS Biopsy Classification

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Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can be associated with venous thromboembolism (VTE). Lupus nephritis (LN) has been shown to be an independent risk factor for VTE. To our knowledge the risk of VTE has not been studied by International Society of Nephrology/Renal Pathology Society (ISN/RPS) LN class.

Methods: A cross-sectional analysis was performed using data from the Glomerular Disease Collaborative Network (GDCN). Patients with class V LN were compared to those with class III or IV (but not associated class V) LN. Classes I, II and VI were excluded from analysis due to their low prevalence. The outcome of interest was image-confirmed VTE. Logistic regression was used to calculate odds ratios and 95% confidence intervals (OR, 95% CI), adjusted for age, sex, race, hormonal contraception use, serum albumin and use of hydroxychloroquine. Effect modification was assessed between the main effect and other covariates and considered if p<0.05.

Results: Our cohort consisted of 533 patients; mean±SD age of 30.9±15.0 years (range 6-79 years), with an overall incidence of image-confirmed VTE of 54/533 (10.1%). In adjusted analyses, the odds of VTE were not significantly different for those with class III/IV compared to class V LN (OR, 95% CI: 1.00, 0.54-1.84). There was evidence of effect modification of LN class on VTE by age at biopsy. Among patients with an average age at biopsy of 15 (-1SD), class III/IV was associated with higher odds of VTE (5.38, 1.42-20.34) while among patients with an average age at biopsy of 45 (+1SD), class III/IV was associated with lower odds of VTE (0.26, 0.09-0.78).

Conclusions: VTE was common in LN patients in the GDCN, occurring in ~10%, and was similar among patients with class III/IV LN and those with class V LN. These findings suggest that the association between LN and VTE is not limited to class V-related nephrotic syndrome. Interestingly, however, age-specific analysis demonstrated increased odds of VTE with class III/IV LN diagnosed at a younger age and decreased odds of VTE with class III/IV LN diagnosed at an older age. This may suggest the presence of an age-sensitive modulation of LN class-specific VTE risk.

FR-PO880

Wide Fluctuation in Serum Creatinine Is Observed in Patient with Lupus Nephritis in Remission

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Background: Clinical trials in lupus nephritis (LN) typically base remission on proteinuria and the relative change in serum creatinine (sCr) compared to baseline. These sCr cutoffs have been arbitrary, however we observe considerable fluctuation of sCr levels in clinical practice. This study was undertaken to assess the variability of sCr in stable, non-flaring LN patients.

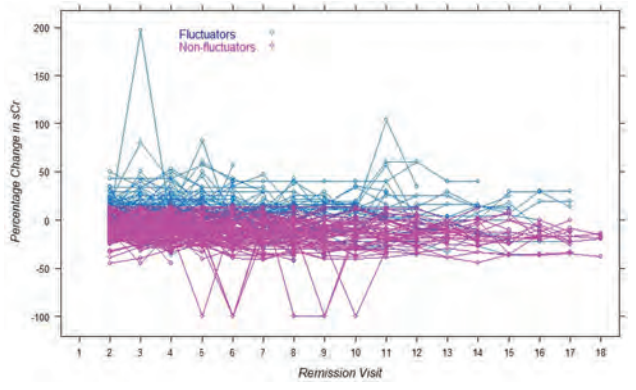
Methods: Patient-level clinical data from patients enrolled in the ALMS, MAINTAIN, and ELNT trials who had ≥3 consecutive sCr measurements while in remission (uPCR ≤0.5g/mg) were used. Patients were split into a group having at least 1 sCr measurement >115% of baseline (fluctuators) and a group with no sCr measurements >115% of baseline (non-fluctuators). Disease characteristics and demographics were compared using ANOVA and logistic regression as appropriate.

Results: Changes in sCr over time are depicted in the figure. Group characteristics are described in the table. In the fluctuator group, 33%, 20%, and 12% of each patient's creatinine measurements were >115%, 120%, and 125% above their baseline respectively. There was no significance difference between the two groups according to sex, race, C3 levels, hematuria, or ISN/RPS class. Univariate analysis revealed that older age and lower sCr levels were associated with fluctuation (p=0.007 and <0.001 respectively). In a multivariable model only sCr remained significant (p<0.001).

Conclusions: Wide fluctuation in sCr is observed in non-flaring patients with LN. The typically used 115% cutoff is too restrictive, and a 125% cutoff might be more reasonable. The fluctuation tends to occur more in patients with low sCr, where small absolute changes in sCr represent large percentage point changes.

Group	Patients, n	Samples per patient, Median	Age, mean ±SD (yrs)	% Female	Race White, Black, Asian, Other (%)	ISN class III/IV, III + V/IV+V, V (%)	Baseline creatinine, mean ±SD (mg/dl)	Induction Drug* CYC, MMF, AZA (%)
Fluctuators	84	8	29.7±9.9	94%	30%, 11%, 25%, 12%	76%, 11%, 13%	0.74 ±0.24	50%, 47%, 3%
Non-fluctuators	207	7	33.44±10.5	87%	50%, 10%, 34%, 6%	80%, 9%, 11%	0.94 ±0.41	59%, 39%, 2%

*data from MAINTAIN excluded



FR-PO881

Lupus Patients with Low-Level Proteinuria: Time to Revisit the Guidelines

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Background: Kidney biopsy is an important diagnostic tool in lupus nephritis. ACR guidelines recommend biopsy for proteinuria (>1000 mg), or proteinuria (≥500 mg) with hematuria, cellular casts or high creatinine. The presence of low level proteinuria (<1000 mg) alone doesn't qualify for a kidney biopsy.

Methods: We evaluated 150 SLE patients with low level proteinuria who underwent kidney biopsies between June 2003 to September 2018. 84 patients had only low level proteinuria.18 patients had low level proteinuria & hematuria. 48 patients had low level proteinuria & AKI

Results: Patients only with low level proteinuria: 67 of 84 patients (79.7%) had LN on kidney biopsy. 21 (25%) had proliferative LN; 16 (19%) had class III and 5 (6%) had class IV. 11(13.2%) had mixed classes (III or IV & V).17(20.2%) had LN class V. The remaining 17 (20.3%) had non-lupus diagnosis. When hematuria was present, 17 of 18 (94.4%) had LN: 9 (50%) had proliferative LN; 5 (27.8%) had class III & 4 (22.2%) had class IV. 3 (16.6%) had mixed classes. 4 (22.2%) had LN class V. Only one patient (5.6%) had non-lupus diagnosis. Adding AKI to low level proteinuria: 37 of 48 (77.1%) had LN on kidney biopsy. 11 (22.9%) had proliferative LN, 6(12.5%) had LN class III and 5 (10.4%) had LN class IV. 7(14.6%) had mixed classes. 8 (16.7%) had LN class V. The remaining 11(22.9%) had non-lupus diagnoses. Patients with AKI & low level proteinuria had a higher chronicity index (p-value 0.002) compared to patients with low level proteinuria alone.

Conclusions: SLE patients with low level proteinuria frequently have significant renal involvement on kidney biopsy including class III, IV, V and mixed class. This study, contrary to ACR guidelines, supports performance of kidney biopsy in those with isolated low level proteinuria

	Proteinuria <1 gm combined
Number	84
Male	9 (10.7%)
Female	75 (89.3%)
AA	48 (57.1%)
Others	36 (42.9%)
Use of steroids	42 (50%)
Use of IS	42 (50%)
Use of Ace/arb	46 (54.8%)
Lupus class I	3 (3.5%)
Lupus class II	12 (14.3%)
Proliferative LN	21 (25%)
Lupus class III	16 (19%)
Lupus class IV	5 (6%)
Lupus class V	17 (20.2%)
III or IV + V	11 (13.2%)
Advanced LN	3 (3.5%)
Other diagnosis (total)	17 (20.3%)
Activity index	4.9 (0-11). SD 2.8
Chronicity index	3 (0-7). SD 2.6
Low C3	38 (45.2%)
Low C4	31 (36.9%)
Positive Anti-DS DNA	41 (48.8%)

FR-PO882

Proteinuric Lupus-Related Kidney Disease: A Comparative Study of Pure Class V Lupus Nephritis vs. Lupus Podocytopathy

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Background: Lupus-related kidney disease research has focused on proliferative forms of lupus nephritis, and membranous (MLN) lupus nephritis is less studied. A newer clinical entity associated primarily with proteinuria is lupus podocytopathy (LP) which is

minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) in patients with lupus without proliferative forms of lupus nephritis. The prognosis of patients with primarily proteinuric lupus-related kidney disease (pure class V lupus nephritis and lupus podocytopathy) isn't well studied and especially in a predominantly African-American patient population. This is the first comparative study of outcomes between pure class V lupus nephritis and lupus podocytopathy.

Methods: Retrospective chart review from single academic medical system with statistical analysis using single tail t-test.

Results: Average age 34 years (MLN) and 35 years (LP). The initial serum albumin (sAlb) 2.6 g/dL (MLN) vs. 2.01 g/dL (LP) p<.01, initial serum creatinine (sCr) 1.19 mg/dL (MLN) vs. 3.01 mg/dL (LP) p<.005, and initial urine protein-creatinine ratio (UPC) 4.23 g/g (MLN) vs. 5.73 g/g (LP) p<.09. Mean follow-up 3.3 years (MLN) vs. 5 years (LP), p <.05. Final sAlb 3.4 g/dL (MLN) vs. 3.35 g/dL (LP) p<.41, final sCr 1.16 mg/dL (MLN) vs. 1.20 mg/dL (LP) p<.44, final UPC 1.11 g/g (MLN) vs. 1.11 g/g (LP) p<0.50.

Conclusions: Both groups at initial presentation with similar age and nephrotic range proteinuria but statistically significant differences with a lower sAlb and higher sCr in lupus podocytopathy. Prognosis similar with no statistically significant differences at final presentation in final sAlb, sCr, or UPC despite lupus podocytopathy having a more severe initial presentation. A strength of this study is length of follow-up with 3.3-5 years in our patient population. Both groups at final presentation with acceptable renal function with final sCr of 1.2 mg/dL and non-nephrotic range proteinuria.

FR-PO883

Wire-Loop Lesion Is Associated with Serological Immune Abnormality but Not Renal Prognosis in Lupus Nephritis

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Background: Revised ISN/RPS 2018 Classification of Lupus Nephritis (LN) includes wire-loop lesion (WL) as one of the activity indexes (AI). LN patients with WL are classified as class III or IV, both of which are associated with a poor prognosis and recommended to be treated by intense immunosuppressive therapy. However, few reports have focused on the clinicopathological impact of WL on serological immune abnormality and renal prognosis. We aimed to identify clinicopathological characteristics associated with WL, and to clarify whether WL predicts renal prognosis of LN.

Methods: We enrolled 126 Japanese LN patients subjected to renal biopsy in 11 hospitals from 2000 to 2018. We measured clinical findings at the time of renal biopsy, and determined the presence of comorbidities. We also measured Cr and eGFR at the last patient visit, and recorded medications prescribed for LN. Glomerular and tubulointerstitial lesions were expressed as the rate involved of all observed glomeruli or cortex, respectively. Chronic kidney disease (CKD) was defined as eGFR <60 ml/min/1.73m^2. In class III or IV patients, we retrospectively compared these clinicopathological findings between those with WL (WL+ group) and without WL (WL- group).

Results: Of 126 patients, 100 (79.4%) were classified as class III or IV (78 females; mean age 42.7 years; observational period 59.6 months). WL was found in 36 of them (36.0%). Although the renal function did not differ (eGFR; 83.1±33.7 vs 78.0±33.2 ml/min/1.73m^2, p=0.56), WL+ group had higher titer of serum anti-dsDNA Abs (median values; 184 vs 50 IU/ml, p=0.026) and lower level of C3 (42.6±19.4 vs 51.7±24.7 mg/dl, p=0.06) than WL- group. There were no significant differences in any other clinical findings. Linear regression analysis revealed associations between anti-dsDNA Abs and WL (β=0.36, p=0.01). There was no difference in the latest eGFR (78.1±24.5 vs 74.9±27.1 ml/min/1.73m^2, p=0.62) between the two groups. Cox regression analysis revealed significant associations of CKD at the last visit with age and hypertension, but not with WL.

Conclusions: WL was associated with serum anti-dsDNA Abs, but not with renal prognosis, suggesting that WL reflects immune abnormality, but is not an independent factor predictive of renal prognosis in LN.

FR-PO884

Renal Thrombotic Microangiopathy in Lupus Nephritis (LN)

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Background: Renal thrombotic microangiopathy (rTMA) is one out of many vascular findings in LN. However, the influence of rTMA on prognosis and its related factors has not been well established. Therefore, the objective of this study was to evaluate the clinical and pathological aspects of patients with rTMA in kidney biopsy.

Methods: Analysis of medical reports database and kidney biopsy of 253 patients who had biopsy-proven LN, between January 2012 and December 2018 in our Hospital. We performed comparative analyses between groups with and without rTMA in kidney biopsy.

Results: Forty-three (17%) of 253 patients showed rTMA on kidney histology. This group had a significantly lower glomerular filtration rate (GFR) estimated by CKD-EPI formula (ml/min/1.73m2) at the time of biopsy (40.5±38.2 vs. 71.6±40.6, p<0.001), at 1 year of follow-up (50.7±48.7 vs. 83.5±40.4, p<0.001), and at the end of follow-up (47.7±50.5 vs. 80.3±38.3, p< 0.001). Significantly more patients in the rTMA group reached the composite end-point of hemodialysis, death or GFR < 15 (79.5% vs.31.8%, p < 0.001). Patients with histological findings of microangiopathy had a lower mean of Hb, platelets and haptoglobin (10.3± 1.6 vs.11.1±1.5 p=0.0018, 194±88 vs. 253±92 p=0.0001 and 119±86 vs 160±104 p=0.02 respectively) and a higher LDH (391± 209 vs 303±147 p=0.008). However, if the classical diagnostic criteria for microangiopathic anemia (Hb <12, hapto <10 high DHL and platelet <150) were applied, no patient fulfilled the entire criterion. As expected, TMA group showed higher blood pressure (SBP 131±10.5 vs 124±17.3 p=0.01). There was no difference between groups concerning C3, C4, ANA, anti-Ro, and anti-La. Concerning histopathological features, rTMA group had significantly higher activity (9.0±4.8 vs. 6.0±4.5, p=0.001) and chronicity (4.4±2.9 vs. 2.7±2.2, p =0.001) scores. On the other hand, there was no difference in immunofluorescence.

Conclusions: The classical criterion of microangiopathic hemolytic anemia was not able to predict rTMA. For NL patients, these criteria could be more flexible. Serological data were also not predictors. Renal biopsy remains the critical method for diagnosis and rTMA was a frequent and serious finding. RTMA was an important risk factor for renal outcome, as demonstrated by lower GFR and higher hemodialysis rates in this group.

FR-PO885

A Urine Biomarker of Renal Prognosis in Lupus Nephritis

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Background: Urine epidermal growth factor (uEGF) has been described as a biomarker of progressive kidney failure in adults with glomerular diseases. Through an agnostic proteomic approach, we found decreased urinary pro-epidermal growth factor (EGF) levels in LN patients. Here we verified and evaluated uEGF as a biomarker of chronic kidney damage in lupus nephritis (LN).

Methods: Pro-uEGF was detected by urine proteomics in LN patients from the Ohio SLE Study. Then uEGF was measured by ELISA in two independent cohorts (US [n=29] and Mexican [n=120]) of LN patients. Serial uEGF measurements and renal outcomes were available from 92 patients of the Mexican cohort with long-term (>12 months) follow-up, and their association assessed by linear mixed modeling.

Results: The LC-MS/MS showed decreased pro-EGF peptides in active LN patients compared to normal controls. Western blot analysis corroborated decreased pro-EGF urine levels in LN. Measurement of urinary pro-EGF by ELISA closely correlated with mature uEGF levels. uEGF were decreased in active LN patients compared to LN in remission and healthy kidney donors from both cohorts. uEGF levels correlated with the percentage of glomerular sclerosis (r=-0.539, p<0.001), interstitial fibrosis (r=-0.665, p<0.001), tubular atrophy (r=-0.665, p<0.001) and overall histologic chronicity index (r=-0.669, p<0.001) of the kidney biopsies. uEGF levels at LN flare were independently associated with the combined outcome of doubling of serum creatinine/ progression to ESRD (HR=0.58, 95% CI 0.34-0.98, p=0.043). The slope of uEGF over time correlated with eGFR slope. Patients who developed the combined outcome had significant and progressive decreases in uEGF compared to those who did not (Figure).

Conclusions: uEGF correlates with LN kidney biopsy findings of chronic damage. uEGF at flare and during follow-up is associated with progressive kidney disease.

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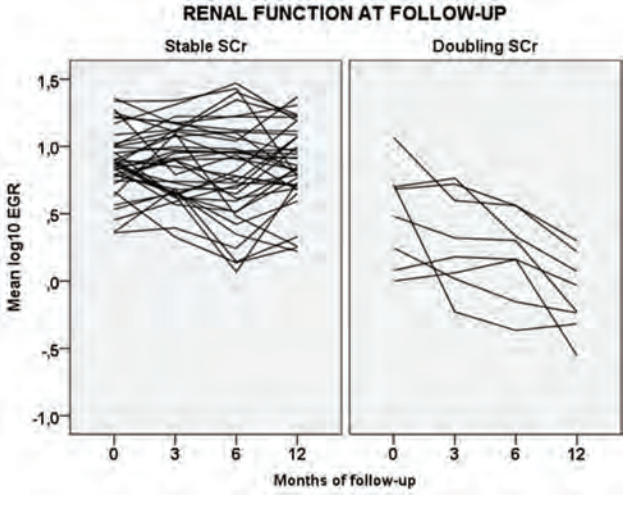

FR-PO886

The Value of Repeated Kidney Biopsies in Patients with Lupus Nephritis

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Background: The indication to repeat renal biopsy in lupus nephritis (LN) flare is controversial. Studies with protocol biopsies had shown a mismatch between clinical and pathological remission, giving even more importance to repeated biopsies. The aim of our study was to evaluate the pathological changes in patients with LN with a repeated biopsy

Methods: We analyzed 107 patients with LN biopsied between 1990-2018, we selected 26 patients who had had 2 renal biopsies

Results: Mean age at the diagnosis of LN was 29.6±3 years, 73.1% female and 73.1% caucasic. At 1 biopsy 30.7% of the patients were class II, 7.7% class III, 38.5% class IV, 11.5% class V and 11.5% mixed class. Cyclophosphamide was the induction treatment in 53.8% of patients and mycophenolate in 23.1%. Time between biopsies was 71.5±10.7 months. Proteinuria was the most common reason to repeat biopsy (73.1%). At 2 biopsy, patients had lower SLEDAI (12 vs 16, p 0.00) and less number of patients had anti-dsDNA antibodies (46.2 vs 73.1%, p 0.03). There were no differences in creatinine (SCr), proteinuria or complement. 73.1% of patients change of class at 2 biopsy; 38.4% to a higher and 34.6% to a lower class. There were no differences in analytical data between patients who changed class and those who didn't. Most patients 75% with class II changed to a proliferative class, while only 16.6% of patients with proliferative classes change to non-proliferative and 16.6% to a mixed class. There was an increased in chronicity index (CI) between biopsies (1 vs 3, p<0.001) and no difference in activity index. At the end of follow up (163.6 months), 38.5% patients had chronic kidney disease (CKD) and 19.2% end stage renal disease. Patients with CKD had more percentage of glomerulosclerosis (%GE) at first biopsy (8.7% vs 1.2%, p 0.02) and higher CI at second(4 vs 2, p 0.006). They also had less rate of complete remission (CR) at 12 months (0% vs 37.5%, p 0.02) and higher SCr (1.7 vs 0.9 mg/dl, p 0.004) and proteinuria (3.1 vs 4.5g/24h, p 0.02) at second biopsy

Conclusions: Our study suggests the utility of repeated renal biopsies as 38.4% of patients changed to a higher class without relevant clinical expression. The percentage of CR at 12 month, %GE and CI were the main prognosis factors for CKD

FR-PO887

A Fingerprint of Response to Treatment in Lupus Nephritis: Identification of a Panel of Eight Proteins from Baseline Renal Biopsies That Predict Response

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Background: Lupus nephritis (LN) carries significant morbidity & mortality risk. Only ~50% of patients respond satisfactorily to current standard of care. Likelihood of response & long term prognosis are unclear at the outset with no reliable predictors identified. We set out to establish if proteomic analysis of baseline kidney biopsies by relative quantification SWATH mass spectrometry (MS) could reveal biomarkers associated with subsequent response to treatment or mechanisms of disease in non-responders.

Methods: 32 FFPE renal biopsy tissue blocks were identified for analysis: LN class IV: 8 complete responders (CR) & 8 non responders (NR); class V: 5 CR & 4 NR; Controls: 7 thin basement membrane disease. Protein was extracted & trypsin digested using pressure-cycling technology. SWATH-MS analysis was performed using a 6600 TripleTOF mass spectrometer coupled to a Dionex Ultimate 3000 HPLC. Data analysis was performed using openSWATH plus, pyProphet & MSproteomicstools. The false discovery rate was 1%. Proteomic data was submitted for machine learning (1000 iterations) using the RandomForest R package (version 4.6-14) in which the dataset was split randomly 70:30 into a training & testing set.

Results: Of the 5139 proteins identified, 57 were significantly up-regulated in CR compared to NR and included Th17 cell differentiation, metabolic & RNA degradation pathways. Downregulation in CR compared to NR was noted in 106 proteins which included HIF-1 & MAPK signalling & melanogenesis. Further analysis revealed that a panel of 8 proteins separated CR from NR including moesin, a key protein in immunity, & eukaryotic translation elongation factor 1 epsilon-1, a negative regulator of cell proliferation, each downregulated in CR compared to NR. A validation study in a separate set of biopsies is underway.

Conclusions: Whilst the protein yields from FFPE blocks are extremely small (4-8ug protein), we demonstrate these can be successfully analysed by SWATH MS. Importantly, this approach allows us to use baseline biopsies to identify CR from NR using a panel of just 8 proteins and provides novel insights into the intra-cellular mechanisms governing response to treatment in LN, biomarkers of response to therapy as well as potential targets for new therapeutics.

Funding: Private Foundation Support

FR-PO888

Histologic Findings from Paired Renal Biopsies: Single-Site Results from the ALLURE Study of Abatacept for Lupus Nephritis

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Background: The optimal method for determining length of therapy for proliferative lupus nephritis (LN) is challenging. Discrepancies between clinical parameters and renal biopsies (Bx) remain. This is a *post hoc* analysis of repeat Bx and clinical outcomes from a single site in a study comparing abatacept (ABA) with placebo (PBO).

Methods: ALLURE (NCT01714817) is a PBO-controlled study in patients (pts) with active Class III or IV LN on mycophenolate mofetil/corticosteroids. We evaluated pts from a single site with repeat kidney Bx, which were classified by ISN/RPS and scored using National Institutes of Health activity index (AI) and chronicity index (CI). Findings were correlated with clinical outcomes.

Results: 20/25 pts at the site had pre- and post-treatment (tx) Bx. Clinical characteristics and AI/CI scores were similar at baseline (Table). Four pts discontinued tx due to lack of efficacy (ABA n=1; PBO n=3). Most pts achieved urine protein to creatinine ratio (UPCR) ≤0.5 at least once during therapy (ABA 6/8; PBO 8/12); mean UPCR at Year 1 was lower in ABA arm (0.56 vs PBO 1.53). ABA group had lower 2nd Bx mean AI score (0.8 vs PBO 2.9). 6/8 from ABA group had an AI of 0 in 2nd Bx vs 5/12 in PBO group (Figure). Two PBO pts had UPCR ≤0.5 but had activity on 2nd Bx; two ABA pts without activity on 2nd Bx had UPCR >0.5 (0.6 and 0.8).

Conclusions: Repeat Bx in pts with LN after therapy can reveal tx-dependent discrepancies between clinical and histologic responses. Most patients treated with abatacept showed lack of activity. Better methodologies are needed to assess LN activity and improve clinical tx in pts with LN. Writing assistance: Caudex.

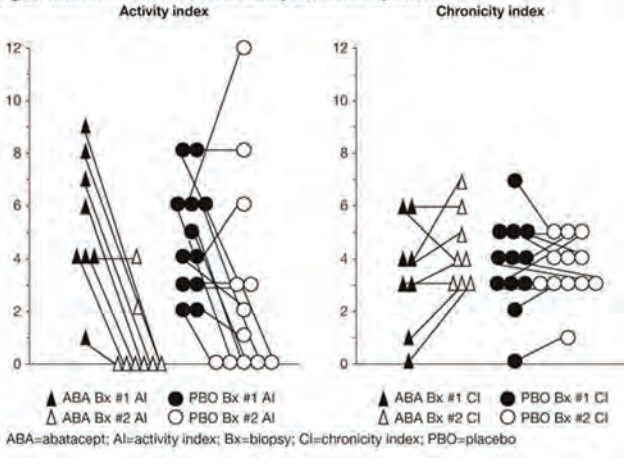
Funding: Commercial Support - Bristol-Myers Squibb

Baseline demographics, disease characteristics, duration of therapy and mean time between Bx

	Abatacept (n=8)	Placebo (n=12)
Age, years, mean	29.6	33.5
UPCR, baseline/at Year 1, mean (g/g)	4.12/0.56	4.18/1.53
Duration of therapy, days, mean	795	750
Time between Bx #1 and first study treatment, days, mean	92	102
Time between Bx, months, mean	39	32
Bx #1, AI/CI, mean	5.4/3.4	4.8/3.8
Bx #2, AI/CI, mean	0.8/4.4	2.9/3.6

AI=activity index; Bx=biopsy; CI=chronicity index

Figure. National Institutes of Health Activity and Chronicity Indices



ABA=abatacept; AI=activity index; Bx=biopsy; CI=chronicity index; PBO=placebo

FR-PO889

Characteristics and Treatment Patterns of a Real-World Lupus Nephritis Cohort Based on Primary Physician Specialty

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Background: Real-world data describing clinical characteristics and treatments of patients with lupus nephritis (LN) are limited. We describe characteristics and treatment patterns of patients with LN managed by rheumatologists and nephrologists.

Methods: This secondary analysis (GSK study 208683) used survey data of physicians and their patients with LN, enrolled in the 2015 Adelphi Real World Disease Specific Programme (GSK study 205086). Patients (≥18 years) with an LN diagnosis and their treating rheumatologists/nephrologists completed survey forms. Data relating to

characteristics, treatment patterns, and disease burden were extracted and compared using Mann-Whitney, Pearson's chi-squared and Fisher's exact tests.

Results: Overall, 38 rheumatologists and 113 nephrologists provided data for 819 patients with LN; 26.9% were provided by a rheumatologist and 73.1% by a nephrologist. Most patients were primarily managed by the responding physician (85.2%), although input was obtained from a range of healthcare practitioners (HCPs). Care for nephrologist-managed patients was shared by more HCPs from other specialties compared with rheumatologist-managed patients. Nephrologists saw significantly more patients with moderate to severe LN than rheumatologists ($p<0.01$) although LN histological class distribution was similar. Significant differences ($p<0.001$) were observed between rheumatologist- and nephrologist-managed patients respectively, for current kidney dysfunction (48.2% vs 69.9%), mean (standard deviation [SD]) time since diagnosis (364.6 [347.0] vs 296.8 [345.9] weeks), mean (SD) number of prior treatment lines (2.6 [1.1] vs 2.3 [1.1]), and associated systemic lupus erythematosus systemic features (93.2% vs 46.1%). Patient-reported activity impairment and fatigue were similar regardless of treating physician.

Conclusions: In a real-world setting, patients with LN managed primarily by nephrologists had more severe disease and involvement from more specialties than those managed by rheumatologists. Patient-reported experience was similar, reflecting a high overall disease burden regardless of treating physician specialty. Editorial assistance (GSK-funded): Gosia Carless, PhD, Fishawack Indicia Ltd, UK. **Funding:** Commercial support – GSK.

Funding: Commercial Support - GlaxoSmithKline

FR-PO890

Efficacy of Cyclophosphamide and Mycophenolate Mofetil as Induction Immunosuppression in Proliferative Lupus Nephritis in Ethnic Minorities

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Background: Among patient with lupus nephritis, proliferative glomerulonephritis has the worst prognosis. Cyclophosphamide (CTX) and Mycophenolate mofetil (MMF) remain the preferred agents for induction immunosuppression in these patients. Some studies have suggested that MMF may be a superior induction agent among African American and Hispanics. We reviewed our experience in a predominant minority population.

Methods: A retrospective review of renal biopsy database from Jan 2011-March 2018 identified 50 patients with biopsy-proven class 3 or class 4 (±class 5) lupus nephritis with at least 6 months of follow-up. Baseline characteristics between the 2 treatment groups were compared using independent sample t-test for continuous variables, and Chi-square test for categorical variables. The KDIGO 2012 definition of remission criteria in lupus nephritis was used in assessing treatment response.

Results: The overall remission rate was similar between CTX and MMF group (64.2% vs 68.2%, p=0.773). There was a trend to use CTX in patients with class 4 lupus nephritis. African American patients were more likely to have crescents on kidney biopsy (65% vs 41%) and a lower response rate (52% vs 78%, P=NS). Tubular atrophy and interstitial fibrosis >25% was significantly associated with a lower response rate (OR= 3.01). Although 8 patients had positive antiphospholipid antibodies, thrombotic microangiopathy on kidney biopsy was noted in only one case. The response rate was lower in patients with positive antiphospholipid antibodies (37.5% vs 68.8%, P=NS). Table 1: Demographic and clinical characteristics:

Conclusions: CTX and MMF are equally effective in inducing clinical remission in ethnic minorities with proliferative lupus nephritis. African American ethnicity, presence of crescents and higher tubular atrophy and interstitial fibrosis on renal biopsy was associated with lower response rate.

Table 1: Demographic and clinical characteristics:

		CTX	MMF	P-value
Age (years): 36.2 ±12.5	Class 3	N=8	N=16	
M:F 7:43	Class 4	N=20	N=6	
Ethnicity: African American: 23, Hispanic: 15, Others:12	S. Cr mg/dL (baseline)	1.7±1.3	1.1±0.7	0.046
	S. Cr (6 mo)	1.4±1.3	1.1±0.6	0.268
	Proteinuria g/g Cr (baseline)	4.6±3.3	2.8±3.0	0.571
	Proteinuria g/g Cr (6 mo)	2.4±2.9	1.3±2.0	0.158

FR-PO891

Ten-Year Outcome Differences in Lupus Nephritis Patients Treated with Cyclophosphamide and Mycophenolate-Based Treatment Regimen

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Background: Lupus nephritis(LN) poses a considerable impact on the morbidity and mortality of SLE patients. Long term comparative outcome data with cyclophosphamide (CP) and mycophenolate mofetil (MMF) based regimen from the Indian subcontinent is sparse.

Methods: In the study, between July 2008 to June 2018, We analyzed outcomes of 100 LN patients (26 class III, 25 class IV, 6 class III+V, and 10 class IV+V)) treated with CYP (euro lupus-40 and NIH-27) and MMF-33 based regimen with the steroid. Class distribution of the patients in the two groups was similar. The renal survival and patients survival at the end of follow-up between two groups were compared.

Results: The clinical characteristics were similar in both groups, except activity index was high in CP patients (6.13 ±4.48 Vs 4.61 ± 2.80), however, chronicity index was similar. The overall remission was 70% at end of induction, CR, PR, and NR in the CP group was 46.2%, 23.9 %, 29.9% respectively; and in MMF group was 57.6%, 12.1%, and 30.3% respectively. In CP 14.9% and in MMF 9.1 % of patients died. The 1-, 2-, 3-, 4-, 5- and 10-years patient survival in the CP induction was 89.5%, 86.2%, 86.2%,83.8%, 83.8% and 83.8%; and in MMF was 93.9%, 93.9%, 89%, 89%, 89% and 89% respectively. The most common cause of death was sepsis 9/13(69.2%) followed by uremia. The high serum creatinine, low Hb, male, thrombocytopenia, microscopic haematuria, leucocyturia, nephrotic proteinuria, lack of remission at 12 months, dialysis, doubling of creatinine on follow-up were significant predictors of mortality. The 1-, 2- 3-, 4-, 5- and 10- years renal survival(event death-censored, but dialysis dependency) in CP group was 98.5%, 96.7%, 94.7%, 92.4%, 92.4% and 84 % respectively; and in the MMF was 96.8 %, 96.8%, 91.9%, 91.9%, 91.9%, and 78.8% respectively. At the end of the study, dialysis dependency in the MMF group and CYP group was 7.5% and 12.1 % respectively(NS). In the maintenance therapy, 3/56(5.3%) had doubling of creatinine in MMF, and 7/34 (20.5%) in the AZA group(p=0.03).

Conclusions: Long term outcomes in terms of patient and renal survival of LN patients treated with CP and MMF based induction is similar. Serum creatinine doubling was more with MMF than AZA based maintenance. Majority of death occurred during induction and sepsis was the most common cause of death.

Funding: Government Support - Non-U.S.

FR-PO892

Calcineurin Inhibitors May Prevent Diffuse Membranous Lesions In Lupus Nephritis

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Background: Lupus nephritis (LN) is a relapsing disease. The pathologic features of LN may change with relapse, and such changes cannot definitely be predicted clinically. Current guidelines recommend selecting treatment for LN according to the 2003 ISN/RPS classification, which states that glucocorticoids (GC) are the key drugs. Little is known about whether or not other immunosuppressants are effective for LN, including cyclophosphamide, mycophenolate mofetil, azathioprine, and calcineurin inhibitors (CNI). In class V LN, accumulation of subepithelial immune complexes leads to glomerular inflammation. CNI have been reported to show a podocyte-protecting effect that is independent of their immunosuppressive activity. Accordingly, we examined the effect of CNI on class V lesions in patients with relapsing LN.

Methods: Forty-six Japanese patients with LN, who underwent one or more repeat renal biopsies at our hospital between May 1995 and May 2017, were analyzed retrospectively. Patients who received continuous administration of CNI were assigned to the CNI group and other patients were assigned to the non-CNI group.

Results: There were 25 patients in the CNI group and 21 patients in the non-CNI group. No significant differences of baseline characteristics were noted between the two groups. In the CNI group, the number of patients with class V lesions decreased from 13/25 (52%) at baseline to 9/25 (36%) at the time of re-biopsy. On the other hand, the number of patients with class V lesions increased from 6/19 (31.6%) at baseline to 14/21 (66.7%) at re-biopsy in the non-CNI group. We investigated risk factors for relapse of LN with class V lesions by performing multiple logistic regression analysis, and found that CNI use was a negative risk factor with an odds ratio (95% confidence interval) of 0.211 (0.0531-0.839).

Conclusions: CNI may prevent the relapse of LN with class V lesions.

FR-PO893

Tacrolimus Combined with Short-Term Corticosteroids for Inducing Remission in Membranous Lupus Nephritis: A Retrospective Study

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Background: We retrospectively analyzed the efficacy of Tacrolimus combined with short-term corticosteroids for inducing remission in membranous lupus nephritis.

Methods: We retrospectively reviewed purely class V LN patients that were followed up in our center between January 2012 and December 2017. They were divided into 2 groups: IVC group received intravenous cyclophosphamide (0.75g/m2,once monthly) combining with prednisone (0.6-0.8mg/kg/d) and the dose of prednisone was gradually tapered after 8 weeks. Tacrolimus group received tacrolimus (trough serum concentration 6-8ng/ml) combining with a course of methylprednisolone impulse (8-10mg/kg/d, maximum 500mg/d, for 3 days), with or without following methylprednisolone 40mg/d; the total duration of corticosteroids was less than 2 weeks.

Results: Totally 65 patients with class V LN were analyzed, including 26 patients in IVC group and 39 patients in tacrolimus group. There were no significant differences on serum albumin, proteinuria, blood cells and immunological index at baseline between IVC and Tacrolimus group. Also, there were no significant differences on the severity of pathological changes such as glomerular sclerosis, crescent formation, mesangial proliferation, segmental necrosis and interstitial infiltrates between two groups. At 6 months, there were no significant differences on the remission rates between IVC group and tacrolimus group (80.8% vs 64.1%). The median follow-up time was 15.0 (10.5, 36.0) months in IVC group and 12.0 (6.0, 24.0) months in tacrolimus group (P=0.119). At the end of follow up, the remission rate (CR and PR) was significantly higher in IVC group than that in Tacrolimus group (92.3% vs 66.7%, P=0.045). There were 10 relapses including 3 (11.5%) relapses in IVC group and 7 (17.9%) relapses in tacrolimus group

(P=0.369) at the end of follow up. Patients experienced less acne vulgaris in Tacrolimus group (10,25.6%) than IVC group (15,57.7%, P=0.010) and less Cushing syndrome in Tacrolimus group (5, 12.8%) than IVC group (13,50%, P=0.001).

Conclusions: Tacrolimus combined with short-term corticosteroids was as effective in short term but not as good in long term as intravenous cyclophosphamide combining with prednisone for inducing remission in membranous lupus nephritis, but with a tendency of fewer adverse effects.

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The Level of Proteinuria After 6 and 12 Months of Treatment Predicts Long-Term Renal Outcomes in Lupus Nephritis: Data from a Nationwide Cohort Study in Japan

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Background: Recent studies of lupus nephritis in European countries (the Euro-Lupus Nephritis Trial and the MAINTAIN study) showed the level of proteinuria at 12 months is the best predictor for long-term renal outcome. The aim of this study is to evaluate urinary protein levels after treatment as a predictor of long-term renal outcomes, by analyzing data of a recent nationwide cohort study of lupus nephritis in Japan.

Methods: Among 498 lupus nephritis patients who received renal biopsy between 2007 and 2012 at 27 institutions and were registered in Japan Renal Biopsy Registry, data of 282 patients were analyzed who were treated with immunosuppressive therapies after renal biopsy and were observed more than 5 years. Poor renal outcome was defined as doubling serum creatinine (S-Cr) or end-stage renal disease (ESRD). Deterioration of renal function was defined as 1.5 times increase in S-Cr from baseline. Clinical data at the time of biopsy, 6 and 12 months after treatment were analyzed.

Results: During the median observation period of 5.3 years, 32 patient reached poor renal outcome and 68 patients showed deterioration of renal function. ROC analysis revealed that levels of urinary protein/Cr (UP/U-Cr) predicting poor renal outcomes were as follows: 1.64 g/gCr at 6 months (sensitivity 83.0%, specificity 72.7%, AUC 0.828) and 0.87 g/gCr at 12 months (sensitivity 80.0%, specificity 81.8%, AUC 0.862). Levels of UP/U-Cr predicting deterioration of renal function were as follows: 1.10 g/gCr at 6 months (sensitivity 79.5%, specificity 63.3%, AUC 0.753) and 0.49 g/gCr at 12 months (sensitivity 73.4%, specificity 71.0%, AUC 0.745).

Conclusions: Levels of proteinuria at 6 months and 12 months after the treatment are good predictors for long-term renal outcomes in a recent nationwide cohort study of lupus nephritis in Japan.

FR-PO895

Relapse Risk of Lupus Nephritis After Discontinuing Maintenance Mycophenolate

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Background: Patients who achieved remission of lupus nephritis (LN) after induction immunosuppressive therapy are recommended to continue maintenance mycophenolate or azathioprine for at least three years.

Methods: In this study, we assessed the relapse risk of discontinuing mycophenolate after remission in 59 biopsy-proven LN patients on maintenance mycophenolate. Partial remission was defined as decreased urine protein/creatinine ratio (UPCR) <3 with prior nephrotic proteinuria or decreased UPCR ≤ 50% with sub-nephrotic proteinuria accompanied by improvement in or stabilization of creatinine (±25%). Complete remission was defined as UPCR <0.3 with creatinine <1.3 (in women) or <1.4 mg/dl (in men) and improved in the urine sediment. Relapse was defined as doubling of proteinuria (proteinuric) to UPCR > 1 from complete remission or > 2 from partial remission) or ≥50% increased creatinine.

Results: Patients who discontinued maintenance mycophenolate in <3 years compared with ≥3 years had similar baseline characteristics except for lower hematocrit (34 vs. 36%, p=0.026) and higher biopsy chronicity index (4 vs. 1 points, p=0.001). Discontinuing mycophenolate in <3 years compared with ≥3 years was significantly associated with relapse (adjusted hazard ratio of 3.56 [95% CL 1.33-9.54]) and shorter relapse free half-live of 3 years compared with 12 years.

Conclusions: Discontinuing maintenance mycophenolate prior to 3 years after remission of LN is significantly associated with relapse risk.

FR-PO896

Risk Factors for Poor Long-Term Renal Outcome and Death in Lupus Nephritis: Analysis on a Nationwide Cohort Study in Japan

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Background: We previously reported the outcomes of adult lupus nephritis (LN) in a recent nationwide retrospective cohort study in Japan (ASN 2018). Here we aimed to determine risk factors for poor long-term renal outcome and death.

Methods: Adult patients who received renal biopsy between 2007 and 2012 at 27 institutions and were registered in the Japan Renal Biopsy Registry as LN were analyzed. Poor renal outcome was defined as doubling serum creatinine (S-Cr) or end-stage renal disease (ESRD).

Results: 498 patients (88 male), median age 39 (IQR, 30-52) years-old were evaluated. Clinical data at the renal biopsy and the frequency of ISN/RPS Class were as follows: median eGFR 78.3 (IQR, 56.3-100.8) ml/min/1.73m^2, median urinary protein 2.04 (IQR, 0.87-4.30) g/gCr, Class I, 1.6%; II, 5.8%; III, 26.9%; IV, 46.6%; V, 18.5%; VI, 0.6%. Among 498 patients, 36 patients (7.0%) reached doubling S-Cr or ESRD, during the median observation period of 63 months (IQR, 49-82). Death was observed in 28 patients (infection, 14 pts; cardiovascular disease, 6 pts; malignant tumor, 4 pts; others, 4 pts). Univariate analysis revealed age, body mass index (BMI), systolic BP, serum albumin, urinary protein, eGFR and Class IV LN were significant risk factors for poor renal outcome (P <0.05). Multivariate analysis revealed BMI (HR, 1.11; 95%CI, 1.02-1.21; P=0.012) and eGFR (HR, 0.98; 95%CI 0.96-1.00; P=0.019) were independent risk factors. As risk factors for death, age, systolic blood pressure, serum albumin, eGFR and urinary protein were identified by univariate analysis (P <0.05). Multivariate analysis revealed age (HR, 1.04; 95%CI, 1.01-1.07; P=0.008) and eGFR (HR, 0.97; 95%CI, 0.95-0.99, P<0.001). Among 348 patients who received renal biopsy for the first time, 22 patients reached doubling S-Cr or ESRD and 28 patients died. Multivariate analysis also identified BMI (HR, 1.13; 95%CI 1.01-1.27; P=0.032) and eGFR (HR, 0.98; 95%CI 0.96-1.00; P=0.028) for poor renal outcome and age (HR, 1.04; 95%CI 1.01-1.07; P<0.010) and eGFR (HR, 0.97; 95%CI 0.95-0.99; P=0.003) for death.

Conclusions: Using recent data of the real-world clinical practice of LN in Japan, we identified BMI and eGFR at the time of renal biopsy as risk factors for poor long-term renal outcome and age and eGFR as risk factors for death.

FR-PO897

Influence of Therapeutic Drugs on Different Manifestations of Renal Involvement in 907 Chinese Patients with Ankylosing Spondylitis

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Background: Studies on renal involvement in AS are at the initial stage, and hardly we see systematic and large-scale study on the relationship between therapeutic drugs and renal involvement in AS patients. Moreover, the drug sensitivity of kidney varies significantly from races and regions. Therefore, the aim of this study is to investigate the impacts of therapeutic drugs on renal involvement in Chinese AS patients.

Methods: The clinical characteristics and biochemical data of the patients were collected and analyzed. The differences in clinical and laboratory characteristics between the drug and drug-free patients were calculated by Inter-group comparison to screen out confounding factors. Then the multivariate logistic regression analysis with correcting confounding factors was carried out to explore the impacts of the drugs on the renal involvement according to clinical manifestations.

Results: A total of 907 patients were enrolled in the study, 232(26%) patients suffered from renal involvement. Among them, there were 149/232(64%) hematuria, 55/232 (24%) proteinuria, and 27/232 (12%) patients with multiple clinical manifestations. 21/232 underwent a renal biopsy to determine renal pathology. 363/907 (40%) of the patients received therapy: 92(25%) NSAIDs monotherapy, 88(24%) csDMARDs monotherapy, 27(8%) TNF-α inhibitor monotherapy, and 156(43%) combination of the drugs. The probability of renal involvement in Chinese AS patients increased significantly in NSAIDS or csDMARDs monotherapy, and combination therapy of NSAIDs, csDMARDs and TNF-α inhibitor. For AS patients, NSAIDs monotherapy increased the probability of hematuria by 2.4 times, and the probability of mixed manifestations of renal involvement by 3.0 times; csDMARDs monotherapy increased the probability of proteinuria by 2.4 times; combination therapy of NSAIDs, csDMARDs and TNF-α inhibitor increased the probability of hematuria by 4.1 times. In addition, the study found that TNF-α inhibitor monotherapy and its combination therapy with NSAIDs or csDMARDs had no obvious impact on renal involvement in AS patients.

Conclusions: NSAIDs or csDMARDs monotherapy may significantly increase renal involvement in AS patients. The combination therapy of TNF-α inhibitor with NSAIDS and csDMARDs should be used prudently. Renal involvement should be closely observed during the treatment.

Funding: Clinical Revenue Support

FR-PO898

Clinical Value of Complement Biomarkers in Autoimmune Glomerulonephritis

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Background: Complement activation plays a central role in the mechanisms of injury of autoimmune glomerular diseases. Urinary excretion of different complement biomarkers could indicate relevant activated pathogenic pathways (classical, lectin, alternate), parallel disease activity and add clinical value beyond proteinuria.

Methods: We performed a prospective observational cohort study of 81 patients including focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), IgA nephropathy (IgAN), lupus nephritis (LN) and ANCA-associated vasculitis (AAV). Urinary samples were collected at different time points. We measured proteinuria, C4a (classical and lectin pathway), Bb (alternative pathway), and sC5b-9 (terminal cascade), expressed as creatinine ratios. We assessed remission status (partial or complete) as currently defined for each disease. For AAV, we assessed the renal BVAS score after 6 months of treatment.

Results: At baseline, urinary excretion of sC5b-9 was present in each individual (4.28, IQR 0.84-21.96 µg/mmol creatinine) and correlated with the initial proteinuria ($p<0.05$ for each disease). Urinary C4a and Bb were mostly absent. In those who obtained clinical remission, we observed a 92% reduction in urinary sC5b-9 levels, which was greater than the 69% reduction observed in proteinuria (p=0.02 by Wilcoxon signed-rank test), suggesting earlier and more precise variations in urinary sC5b-9. This same pattern occurred with each disease group (table), and reached statistical significance for MN (p=0.05) and AAV (p=0.03). When no clinical remission was obtained, there was a greater increase in sC5b-9 levels (43%) than for proteinuria (21%), although not statistically significant (n=12, p=0.68).

Conclusions: In active autoimmune glomerular diseases, urinary sC5b-9 is measurable in all individuals. In those who obtained a clinical remission, the urinary sC5b-9 reduction was greater than the decline observed with proteinuria. This pattern was seen in each disease suggesting that C5b9 is a more sensitive marker of remission.

Funding: Government Support - Non-U.S.

	n	initial urinary sC5b-9* (µg/mmol creatinine)	initial proteinuria* (g/mmol creatinine)	% Remission	Reduction of proteinuria at remission (%)*	Reduction of urinary sC5b-9 at remission (%)*
FSGS	16	5.36	0.46	56	76.2	86.5
IgAN	19	1.18	0.14	62	60.3	78.9
LN	16	5.80	0.33	100	71.4	93.0
MN	14	22.93	0.67	70	79.8	95.1
AAV	16	0.80	0.09	100	68.4	89.3

* median

FR-PO899

Outcome of Membranoproliferative Glomerulonephritis and Postinfectious Glomerulonephritis Stratified by New Classification

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Background: The new classification of membranoproliferative glomerulonephritis (MPGN) has been suggested based on the immunofluorescence (IF) staining: Immune complex (IC)-MPGN and C3 glomerulopathy. In addition, the possibility of overlap between C3 glomerulopathy and postinfectious glomerulonephritis (PIGN) has been raised because of high proportion of C3 dominancy and poor renal outcome in PIGN. However, little is known about clinical features and outcomes of C3 glomerulopathy compared to IC mediated GN (IC-GN).

Methods: A total of 4,431 patients who underwent kidney biopsy and had IF data were identified in six university hospitals during 1980-2018. We included 280 subjects with MPGN and 69 with PIGN. C3 dominant glomerulonephritis (C3DG) was defined as C3 staining stronger than immunoglobulins in patients with MPGN or PIGN.

Results: Among patients with MPGN and PIGN, 39 (14%) and 36 (52%) were classified as C3DG. C3DG had higher proportion of women, lower C3, nephrotic range proteinuria and serum cholesterol, and higher serum albumin although renal function was not different at the time of biopsy ($P<0.05$). In addition, C3DG had almost no association with viral hepatitis B (3.1 vs. 29.2%, $P<0.001$), and lower tendency of ANA ($P=0.085$). After 6 months of biopsy, C3DG had significantly lower proteinuria and high rate for remission of proteinuria ($P<0.05$). The incidence of 40% decline in eGFR was significantly lower in C3DG compared than IC-mediated GN (16.3% vs. 31.5%, $P=0.031$). The incidence of end stage renal disease (ESRD) was the highest in IC-MPGN and the lowest in C3-PIGN during 107 [28-247] months of median follow up (IC-MPGN, 37.4%; C3-MPGN; 26.3%, IC-PIGN; 22.2%, C3-PIGN, 9.1%; P=0.036). Together with MPGN and PIGN, C3DG was associated with better renal survival (P=0.016). Multivariate analysis showed that C3DG demonstrated 0.396-fold increase of ESRD (95% CI, 0.192-0.814) compared than IC-GN. Mortality was not significant between groups.

Conclusions: C3DG had lower rate of moderate proteinuria and less likely to be associated with chronic infection and autoimmune disease at presentation. The 13.7% of C3DG progressed to ESRD in although it showed favorable renal survival compared to IC-MPGN.

FR-PO900

Clinicopathological Study of Mixed Cryoglobulinemic Glomerulonephritis Caused by Non-Hepatitis C Virus Infection

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Background: To describe the clinical features, renal pathology findings and renal prognosis in patients with mixed cryoglobulinemic glomerulonephritis caused by non-hepatitis C virus infection.

Methods: This was a retrospective study including seven Chinese patients with non-HCV infection associated mixed cryoglobulinemic glomerulonephritis in a tertiary referral hospital from 2015 to 2018. The demographic, clinical, pathological characteristics, treatment and follow-up data were analyzed.

Results: Age at renal biopsy was 51±13 years, including five females and two males. 24hUP was 5.0±3.5g/d and three cases presented with nephrotic syndrome. The median baseline eGFR(CKD-EPI) was 40.5±15.8ml/min per 1.73m^2. The extrarenal manifestations were: purpura (n=6), arthralgia (n=2, 28.6%), peripheral neuropathy (n=1), cardiomyopathy (n=1). The etiologies of cryoglobulinemia were: HBV infection (n=4), Sjögren syndrome(n=2), essential(n=1). The median cryocrit was 4.9% (range4.0-5.0), rheumatoid factor was 567±153 IU/ml, C3 was 0.47g/L(range0.32-0.57), C4 was 0.003g/L(range0.001-0.013). Renal pathologic findings on light microscopy: endocapillary proliferative glomerulonephritis(n=4), membranoproliferative glomerulonephritis(n=3). Ultrastructural studies showed granular subendothelial electron-dense deposits in all patients and organized microtubules or fibrils were seen in three cases. Four patients with HBsAg positive receive antiviral medication. All patients were given corticosteroid, alone or combined with cyclophosphamide(n=5) or mycophenolate mofetil(n=1). One patient received plasmapheresis. The median follow-up time was 16 months (range 6-41). All patients survived, and no one progressed to ESRD. At endpoint of follow-up, 24hUP was 0.89g/d (range 0.17-2.0), and eGFR(CKD-EPI) was 72.6±21.2 ml/min per 1.73m^2.

Conclusions: Mixed cryoglobulinemic glomerulonephritis should be screened for non-HCV etiologies, especially in HBV-endemic country. Endocapillary proliferative glomerulonephritis was the common pathologic feature, as well as membranoproliferative glomerulonephritis. Early diagnosis and management of mixed cryoglobulinemic glomerulonephritis could benefit patients'renal outcome. Long-term prognosis should be investigated in further studies.

FR-PO901

DNAJB9 Protein Accumulation in Fibrillary GN Is Not due to Local RNA Upregulation

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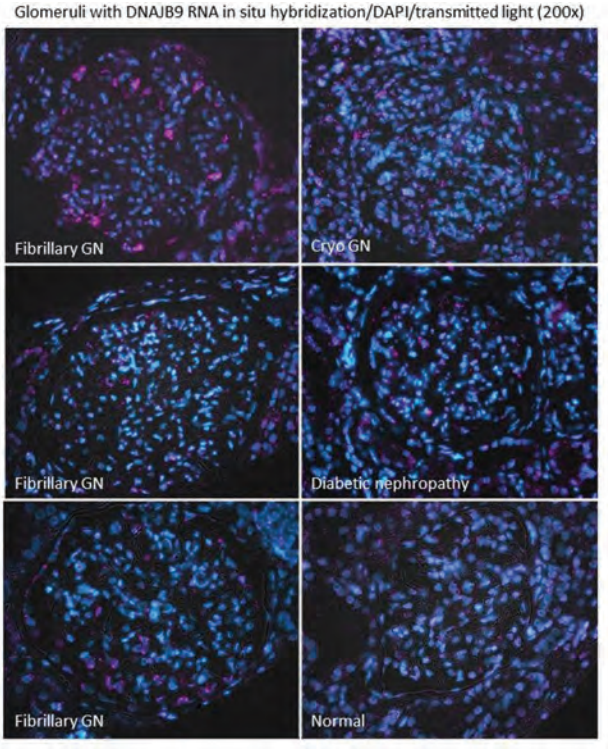
Background: Fibrillary glomerulonephritis (FGN) is characterized by glomerular accumulations of haphazardly arranged fibrils and deposition of IgG with DNAJB9, a protein in the ER stress/unfolded protein response pathway (UPR). In this study, we sought to determine source of glomerular abundance of DNAJB9.

Methods: We evaluated formalin-fixed paraffin embedded kidney biopsies from patients with FGN (n=6), non-fibrillary glomerular disease (n=2 amyloidosis, n=3 cryoglobululinemic gn, n=3 diabetic nephropathy) and normal controls (n=2). Confocal microscopy was performed on slides stained with a DNAJB9 RNA in situ hybridization probe and DAPI. Automated image analysis was performed and corroborated with DNAJB9 immunohistochemistry.

Results: By immunohistochemistry, FGN cases were DNAJB9-positive and non-FGN cases were DNAJB9-negative. DNAJB9 RNA signals were present in FGN, non-FGN glomerular disease, and normal controls; signals were identified in podocytes and mesangial regions as well as tubular, interstitial, and vascular tissue. There were no significant differences in glomerular DNAJB9 RNA signals (313 vs. 379, p=0.3), DNAJB9/DAPI ratios (2.25 vs. 3.3, p=0.3), or DNAJB9 signal intensity between FGN and non-FGN cases.

Conclusions: DNAJB9 RNA expression does not predict protein accumulation in FGN, suggesting that the pathogenesis of FGN is not dependent on local activation of the UPR. Our findings corroborate prior proteomic studies in which other components of the UPR pathway were not locally upregulated (PMID: 29097624), and provide contextual data to studies which identified increased levels of DNAJB9 protein in serum from patients with FGN (PMID: 31010480). This supports an alternate mechanism or circulating source for DNAJB9 accumulation in fibrillary GN.



FR-PO902

Proliferative Glomerulonephritis with Non-Organised Monoclonal Immunoglobulin Deposits (PGNMID): A Single-Centre Retrospective Study

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Background: PGNMID is a rare glomerular disease, most often seen in the context of MGRS. At present, optimal treatment is not established.

Methods: All native renal biopsies performed at the Hammersmith Hospital between 2006 and 2017 were analysed. 15 cases of PGNMID were identified. Baseline characteristics and clinical outcomes during follow-up to January 2019 are summarised in the Table.

Results: Mean age was 61, 31% were men, mean eGFR was 49 mL/min/1.73m2 and mean uPCR 384 mmol/mol. A circulating paraprotein was detectable in 5 (33%) of 15 patients. Most (73%) underwent bone marrow aspiration and trephine (BMAT), with a clone identified in two of 11. One had a plasma cell clone and was not immunosuppressed, having presented at end stage with an eGFR of 7mL/min/1.73m2 and 50% IFTA. The second patient had a B cell clone, with an eGFR of 83 mL/min/1.73m2 and 0% IFTA, and achieved remission of proteinuria and stabilisation of eGFR with prednisolone and rituximab. Three (20%) patients had a detectable paraprotein but no clone on BMAT, and all received treatment. Two progressed to ESRD despite steroids, rituximab and cyclophosphamide. One patient initially responded to steroids, MMF, rituximab and bortezomib, but relapsed following cessation of bortezomib due to peripheral neuropathy. 10 of 15 (67%) patients had no detectable paraprotein at diagnosis. Of these, 89% had partial or complete renal remission. Treatment of this group was variable; none had clone-directed therapy. One case was lost to follow-up post renal biopsy.

Conclusions: Our cohort of PGNMID patients corroborates the previously-described low rate of detection of circulating paraprotein and pathogenic clones on BMAT. Further collaborative studies are required to establish the safety and efficacy of clone-directed therapy, and to guide optimal management in patients with PGNMID.

	Details at diagnosis				Renal biopsy findings			Haematological findings		Treatment		Details at follow-up			
Patient	Age	Year	eGFR	uPCR	%GS	%IFTA	Bx IF	Paraprotein	Clone on BMAT	RASi	Immunosuppression	Months	eGFR	uPCR	Renal response
1	61	2007	7	210	10	10	IgG λ	IgG λ (SPEP; UPEP, SFLC)	Plasma cell, λ light chain restriction	Uninpsim	Uninpsim	37	RRT - HD	Not tested	NR
2	75	2015	83	358	0	0	IgG λ	IgM κ (SPEP)	B cell, λ light chain restriction	N	Pred, RTX	97	75	Undetectable	CR
3	57	2009	54	100	30	20	IgG κ	IgG λ (SPEP; SFLC)	N	Y	Pred, MMF, RTX, CYC	200	RRT - Tx	163	NR
4	78	2013	30	95	10	5	IgM κ	IgM κ (SPEP, UPEP; SFLC)	N	Y	PEX, Pred, RTX, CYC	88	RRT - HD	Not tested	NR
5	68	2017	59	713	30	25	IgG λ	IgG λ (SPEP)	N	Y	Pred, MMF, RTX, BOR	41	45	121	NR
6	25	2012	35	296	27	20	IgG λ	N	Not tested	Y	Pred, MMF, RTX	82	54	78	PR
7	60	2013	35	1099	16	10	IgG λ	N	Not tested	Y	Pred, MMF, RTX	7	38	141	PR
8	70	2014	72	771	29	10	IgG κ	N	Not tested	Y	Pred, MMF, RTX	142	73	59	PR
9	70	2015	7	221	14	15	IgG λ	N	N	Y	Pred	105	28	Undetectable	CR
10	57	2016	30	600	32	25	IgM κ	N	N	Y	Pred, RTX, CYC	90	43	251	NR
11	47	2016	75	36	0	0	IgG λ	N	N	Y	No immunosuppression	66	87	41	CR
12	72	2016	42	80	5	<5	IgG λ	N	N	N	No immunosuppression	64	58	Undetectable	CR
13	63	2017	26	768	0	20	IgG κ	N	N	N	Pred, RTX, CYC	19	34	293	PR
14	52	2017	29	502	17	30	IgG κ	N	N	N	No immunosuppression	48	32	Undetectable	CR
15	64	2017	80	997	0	0	IgG κ	N	Not tested	Y	Unknown	-	Unknown	Unknown	Unknown

Table: baseline characteristics and treatment outcomes for each patient with PGNMID

%GS, percentage glomerulosclerosis on renal biopsy at diagnosis; **%IFTA**, percentage interstitial fibrosis and tubular atrophy on renal biopsy at diagnosis; **anti-VEGF**, anti-vascular endothelial growth factor; **BMAT**, bone marrow aspiration and trephine; **BOR**, bortezomib; **Bx**, renal biopsy; **CR**, complete response, defined as stable (± 10%) or improved eGFR and uPCR <50; **CYC**, cyclophosphamide; **eGFR**, estimated glomerular filtration rate (expressed as mL/min/1.73m^2, calculated by MDRD); **HD**, haemodialysis; **Ig**, immunoglobulin; **IF**, immunofluorescence; **MMF**, mycophenolate mofetil; **NR**, no response, defined as stable (± 10%) or worsening eGFR and stable (± 10%) or worsening uPCR, or need for RRT; **PEX**, plasma exchange; **PR**, partial response, defined as stable (± 10%) eGFR and >50% reduction in uPCR; **Pred**, steroids; **RASi**, treatment with renin-angiotensin-aldosterone system inhibition; **RRT**, renal replacement therapy; **RTX**, rituximab; **SFLC**, serum free light chains; **SPEP**, serum protein electrophoresis; **Tx**, transplantation; **uPCR**, urine protein to creatinine rato (mg/mmol); **UPEP**, urine protein electrophoresis.

FR-PO903

Study of Anti-Complement Factor H Mediated Disease at a Tertiary Care Centre

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Background: Complement dysregulation is an important aetiology for glomerular diseases. Antibody against complement factor H which regulates the alternate complement pathway can cause atypical HUS and C3 glomerulopathy[1]. **Aim of the study :** To study the clinical profile and outcome of patients with anti complement factor H mediated disease at our centre.

Methods: Materials and methods : We studied the clinical profile and outcome of patients with anti complement factor H mediated disease at a tertiary care centre over 24 months (August 2016 to July 2018). We had a total of 18 cases during the study period. All patients were followed up to assess their response to therapy.

Results: A total of 28 cases of atypical HUS were seen during the study period of which anti factor H antibody was elevated in 18 (64.2%). Mean age of the patients was 26.6 +/- 3.2 yrs with 10 patients in the paediatric age group. There were 13 males (72.2%). 10 patients had a febrile prodrome (55.5%). All patients presented with hypertension with active urinary sediments and rapidly progressive renal failure. Mean serum creatinine at presentation was 6.8 +/- 1.2 mg/dl and all patients were oliguric at presentation and required haemodialysis. Serum C3 was low in all patients with a mean of 68 +/- 12.2 mg/dl with normal C4 levels. LDH was elevated in all patients with a mean of 2878 +/- 211.4 IU/ml. All patients had schistocytes in peripheral smear. Anti complement factor H antibody was elevated in all patients with a mean of 549 +/- 90 AU/ml. (normal - 0 to 100 AU/ml). Renal biopsy showed thrombotic microangiopathy in 12 patients (66.6%) while features were suggestive of C3 glomerulopathy in 6 patients (33.3%).

Conclusions: Our study shows that anti complement factor H mediated disease shows good response to plasmapheresis followed by immunosuppression with B cell targeted therapy. Anti CFH mediated disease should be ruled out in all patients with atypical HUS. It is more common in the paediatric age group with excellent response to plasmapheresis and immunosuppression in the form of oral steroids and cyclophosphamide. Also patients presenting with TMA have better prognosis compared to C3 glomerulopathy. Identification of the pathological clone of cells producing the anti factor H antibody would provide more insight into the nature of the disease. We also hypothesise that the clones producing antibody to the N and C terminals might be different.

FR-PO904

Outcome of First Relapse After Eculizumab Withdrawal in Atypical Hemolytic Uremic Syndrome: The CUREiHUS Study

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Background: Eculizumab was introduced as lifelong therapy for patients with aHUS. However, the costs of therapy and potential side effects have stimulated early drug withdrawal. The safety of an early withdrawal strategy is debated, since relapses may cause chronic kidney injury. In the Netherlands eculizumab is used according a restrictive treatment regime, with a preference to withdraw or taper the drug three months after start of therapy. Here, we present an interim analysis of the outcome of patients with a first relapse.

Methods: We evaluated outcome in all aHUS patients in whom eculizumab was tapered or withdrawn, and developed a (suspected) relapse necessitating renewed eculizumab therapy. Serum creatinine, eGFR (CKD-epi) and protein-creatinine ratio's at 6 and 9 months after relapse and last follow-up were compared with baseline.

Results: We evaluated 34 patients (20 F, 14 M; median age 35 years, IQR 34) with aHUS, in whom eculizumab was tapered or withdrawn. Fourteen patients (41%), including 3 children, had a relapse. Of these, 93% were known with a genetic variant in complement genes. Eight patients had a kidney transplant. Restart of eculizumab was effective in most patients, with no significant difference between eGFR at baseline (median 42.6 ml/min/1.73m^2, IQR 40) at 6 months (40.5 ml/min/1.73m^2, IQR 48), 9 months (36.6 ml/min/1.73m^2, IQR 42) after relapse, and at the end of follow-up (35.6 ml/min/1.73m^2, IQR 53). At the end of follow-up (18 months, range 2-31), one patient with multiple relapses had developed ESRD, with notable and unexplained cystic malformation in both kidneys. In four other patients eGFR had decreased ≥20% compared to baseline. All

four had received a kidney transplant, had moderate-severe CKD at baseline, with eGFR affected by viral infections and rejection episodes.

Conclusions: Eculizumab withdrawal was successful in 53% (18/34) of the patients. In 41% of the patients a relapse occurred. Overall, there was no safety signal. Still, the number of patients is limited. Patients with a kidney transplant, and/or moderate-severe CKD may be at risk for sustained kidney injury.

Funding: Government Support - Non-U.S.

FR-PO905

Mechanistic and Potency Evaluation of Complement Factor D and Factor B Inhibitors

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Background: Complement factor D (FD) and complement factor B (FB) are serine proteases essential for complement alternative pathway (AP) activity. FD and FB are present in normal human serum (NHS) at approximately 0.07 μM and 2 μM, respectively. Small molecule inhibitors of FD and FB have been discovered and a few, including ACH-4471 (FD inhibitor) and LPN023 (FB inhibitor), are in clinical development for multiple indications of AP dysregulation including the rare renal disease C3 glomerulopathy (C3G). In this study, we evaluated FD and FB inhibitors for potency and mechanism of action. We also examined their effect on ex vivo C3 consumption in serum from C3G patients.

Methods: FD and FB inhibitor potencies were profiled by AP hemolysis with rabbit erythrocytes and NHS. Mechanism of action (MOA) and potency of inhibitors were assessed in soluble and bound C3 convertase studies with purified components, including FB titrations and order-of-addition tests; convertase activity was assessed from C3 cleavage product generation measured by ELISA. Compound inhibition in C3G patient sera mixed equally with NHS was assessed in fluid phase, with convertase activity assessed by monitoring C3 cleavage products.

Results: ACH-4471 and next generation FD inhibitors were more potent than LNP023 in AP hemolysis with 4.0-fold to 32-fold lower IC_{50} values. A reference FD inhibitor (Schubart et al, PNAS 2019) was less potent, with a 1.2-fold lower IC_{50} than LNP023. LNP023 potency was comparable to input serum FB concentration, suggesting a stoichiometric limit for FB inhibition and a relative advantage for FD inhibitors. MOA studies with C3 convertase revealed that LNP023 binds free intact FB, and that it inhibits AP convertase activity but not proconvertase assembly or its activation to convertase. Inhibitor assessments in C3G patient sera also showed a potency advantage for FD inhibitors over LNP023; ACH-4471 and next-generation inhibitors showed comparable inhibition to LNP023 at 1 μM but all FD inhibitors were more inhibitory than LNP023 at 0.1 μM.

Conclusions: ACH-4471 and next generation FD inhibitors demonstrated greater achievable potencies than the FB inhibitor LNP023 in serum from healthy donors and C3G patients, likely due to the molar difference in systemic FD and FB concentrations.

Funding: Commercial Support - Achillion Pharmaceuticals

FR-PO906

C3 Inhibition with APL-2 Targets the Underlying Disease Process of C3G Complement Hyperactivity and Improves Proteinuria

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Background: C3G is a rare disease of complement dysregulation in which inappropriate C3 activation leads to excessive production of C3 breakdown products. The prognosis is poor with 30 – 50% of patients reaching end-stage renal disease within 10 years of diagnosis. APL-2, a cyclic peptide that inhibits C3 activation, has the potential to address the underlying pathophysiology of C3G. The study aims to assess whether APL-2 inhibits C3 activation, and improves proteinuria, in patients with C3G.

Methods: Adult and adolescent patients with primary C3G, proteinuria > 0.75 mg protein/mg creatinine and eGFR ≥ 30 ml/min/1.73 m^2, were eligible for this Phase 2 open-label study to assess the safety and biological activity of APL-2 over 48 weeks. Eight C3G patients were recruited. Biological activity was assessed by changes from baseline in serum C3 and proteinuria. Proteinuria was quantitated by urine protein-to-creatinine ratio (uPCR) from a 24-hour urine, or as the mean from triplicate first-morning urine samples. Data are reported through Study Day 84 (12 weeks) for the first three patients. Data for all eight patients through Study Day 84 are planned for November, 2019.

Results: Patient 1 was non-compliant with APL-2 dosing, and so data from this patient is not presented. In Patients 2 and 3, baseline serum C3 was low (≤ 13 mg/dL; normal range 90 – 180 mg/dL) and increased to > 130 mg/dL by Day 14 of APL-2 treatment. Both patients also had substantial improvements in proteinuria by Day 84, as evidenced by improvements in uPCR and serum albumin. In Patient 2, uPCR decreased from a baseline of 6.6 to 0.36 mg/mg on Day 84, with an increase in serum albumin from 2.4 to 4.4 g/dL. Patient 3 had a decrease in uPCR from a baseline of 3.2 to 1.6 mg/mg on Day 84, with a corresponding increase in serum albumin from 2.3 to 3.1 g/dL. APL-2 appears well-tolerated with no serious adverse events reported in C3G patients.

Conclusions: These data provide strong preliminary evidence that APL-2 targets the complement dysregulation of C3G with an increase in serum C3 levels and a reduction in proteinuria.

Funding: Commercial Support - Apellis Pharmaceuticals, Inc.

FR-PO907

Accelerated suPAR-Mediated Kidney Disease in the Solitary Functioning Kidney

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Background: Kidney mass and number of functioning nephrons are determinants of renal long-term health. Single functioning kidney (SFK) is a rare disease (1:1500 at birth) resulting in early onset chronic kidney disease (CKD) in over 50% of those affected. Similarly, kidney donors may have an increased risk for future CKD. The underlying mechanisms are not clear. The soluble urokinase receptor (suPAR) is an immune-derived circulating factor implicated in pathogenesis and prediction of CKD incidence and progression. We hypothesized that SFK condition could be more sensitive to increased suPAR levels and examined 3 different rodent models of SFK.

Methods: Uninephrectomy and sham surgeries were performed on C57B/6 mice, suPAR transgenic/knockout models or littermate controls. The minipumps with different concentrations of LPS were implanted subcutaneously. Proteinuria and suPAR were followed for 4 weeks. In congenital SKF rat model (HSRA), the recombinant human suPAR protein was injected intravenously into HSRA single kidney rats (HSRA-S) and two-kidney controls (HSRA-C). Proteinuria and beta3 integrin activity were assessed.

Results: Urinary protein slowly increased in nephrectomized suPAR transgenic mice, while the littermate controls with nephrectomy showed no change. LPS infusion resulted in increased level of serum and urine suPAR in C57B/6 mice. Interestingly, SFK models had a higher serum suPAR and substantially higher proteinuria, compared to the sham two-kidney groups. In contrast, uPAR deficient SFK mice were protected from LPS induced proteinuria. HSRA-S rats revealed an increase of proteinuria compared to HSRA-C after the recombinant human suPAR injection. The activity of the suPAR receptor beta3 integrin was increased in the kidney of HSRA-S rats following administration of suPAR.

Conclusions: Increased circulating suPAR levels, either induced by LPS, or from suPAR transgenic models or extrinsically injected, induce proteinuria in uninephrectomized mice or congenital SFK rats, when compared to their two-kidney controls. These findings suggest the importance of suPAR in SFK, possibly in kidney donors and support findings that suPAR cause declined renal function. Monitoring circulating suPAR levels might be important in understanding the pathogenesis and risk-control for patients who are born with or remain having only one functional kidney.

Funding: Clinical Revenue Support

FR-PO908

Mechanism of CLIC5A Action in Podocytes

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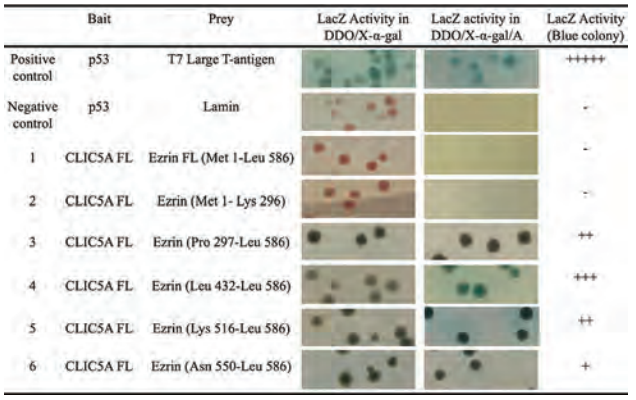
Background: CLIC5A is a major podocyte protein essential for assembly of the Ezrin/NHERF2/Podocalyxin complex that shapes the apical domain of foot processes. CLIC5A *does not* function as an ion channel, but it stimulates apical plasma membrane phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) generation by PI4P5 kinases (PI4P5Ks) through localized Rac1 activation. Docking on PI(4,5)P2 then changes the Ezrin conformation causing Ezrin to link Podocalyxin to actin. CLIC5A deletion in vivo abrogates podocyte Ezrin activation and heightens hypertension-induced glomerular injury.

Methods: We defined the relationship between CLIC5A, Rac1 and Ezrin by pull-down of Rac-GTP with Pak Binding Domain (PBD) beads, GST-CLIC5A pull-down, and Yeast-two-Hybrid (Y2H) assay, in which direct protein-protein interactions generate blue colonies by α-gal LacZ activity and growth on "DDO media" (Figure).

Results: CLIC5A overexpression in cultured podocytes and HEK293 cells increased Rac1-GTP levels 5-10 fold, and CLIC5A, Ezrin and PI4P5Kiα, PI5P4Kα, and PI4P5Kγ isoforms were all co-precipitated from cell lysates with GTP-Rac1 by PBD beads. Notably, Pak-PBD pulled the PI4P5Kα3 isoform from kidney cortex lysates of $CLIC5A^{+/+}$ but not $CLIC5A^{-/-}$ mice. GST-CLIC5A pulled Rac1-GTP and -GDP from cell lysates, but failed to interact directly with purified, recombinant Rac1-GDP or -GTP. Domain-based Y2H screening and mapping showed that CLIC5A interacts directly with the ezrin C-terminus (lys516-leu586; Figure) and the βPix/ARHGEF7 interacting protein Shank2. The CLIC5A/Ezrin interaction required the active conformation of Ezrin, and siRNA knockdown of Ezrin reduced CLIC5A-induced Rac1 activation in cultured podocytes.

Conclusions: Thus, CLIC5A, Rac1-GTP, Ezrin and PI4P5K exist in a protein complex. In which CLIC5A interacts directly with Ezrin. CLIC5A-dependent Rac1 activation requires the direct interaction with Ezrin, and probably Shank2, leading to the formation of the CLIC5A/Ezrin/ Rac1-GTP/PI4P5Kα3 complex that generates PI(4,5)P2 clusters at the apical plasma membrane.

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



	Bait	Prey	LacZ Activity in DDO/X-α-gal	LacZ activity in DDO/X-α-gal/A	LacZ Activity (Blue colony)
Positive control	p53	T7 Large T-antigen			+++++
Negative control	p53	Lamin			-
1	CLIC5A FL	Ezrin FL (Met 1-Leu 586)			-
2	CLIC5A FL	Ezrin (Met 1- Lys 296)			-
3	CLIC5A FL	Ezrin (Pro 297-Leu 586)			++
4	CLIC5A FL	Ezrin (Leu 432-Leu 586)			+++
5	CLIC5A FL	Ezrin (Lys 516-Leu 586)			++
6	CLIC5A FL	Ezrin (Asn 550-Leu 586)			+

FR-PO909

Anti-Apoptotic Role of Phosphatidylinositol-3 Kinase (PI3-Kinase) in Angiotensin II-Induced Podocyte Injury

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Background: PI3-kinase has distinct roles in cellular processes spanning from metabolism to cell motility and survival. Angiotensin II (Ang II) promotes the development and progression of proteinuria and renal diseases and induces podocyte apoptosis. Phosphatidylinositol-3 kinase (PI3-K), connected to CD2-associated protein (CD2AP) in podocytes, is known to send signaling through nephrin-CD2AP-PI3-kinase/Akt pathway and promote cell survival. Autophagy and apoptosis constitute the two processes through which injured/aged cells or organelles are eliminated. We investigated the role of PI3-kinase in angiotensin II-induced podocyte injury.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and at different incubation times. Cell survival/death-modifying reagents and siRNA targeting SHIP2, a negative regulator of the PI3-kinase/Akt signaling pathway, and Atg5 were applied. The changes of podocyte autophagy and apoptosis were observed by confocal imaging, western blotting, realtime PCR, FACS and TUNEL assay according to the presence of Ang II.

Results: Ang II-treated podocytes showed an increase in autophagosomes compared with control cells at early phase in a dose-dependent manner. This pro-autophagic effect of Ang II was inhibited by pretreatment with 3-methyladenine (3-MA), an inhibitor of PI3-kinase class III. Atg5 siRNA reduced LC3 puncta levels and increased the number of apoptotic podocytes over that observed with Ang II treatment at 12 hours. Thereafter, Ang II reduced the expression of autophagy-related genes, such as, *Atg3*, *Atg5*, *Atg7*, and *bcl-2* at 24 hours and induced podocyte apoptosis at later stages, 12 and 24 hours in concentration- and time-dependent manners in FACS and TUNEL assays. Thereafter, Ang II induced podocyte apoptosis significantly in concentration- and time-dependent manners in FACS and TUNEL assays. PI3-kinase inhibitors, 3-MA and LY294002, and Atg5 siRNA further increased Ang II-induced podocyte apoptosis. On the other hand, SHIP2 siRNA suppressed Ang II-induced podocyte apoptosis and the expression of apoptotic proteins. Therefore, PI3-kinase protect podocyte from apoptosis in angiotensin II-induced podocyte injury.

Conclusions: Our findings suggest that Ang II induces podocyte apoptosis, which could be prevented by PI3-kinase activation through the inhibition of SHIP2 and promoting autophagy.

Funding: Government Support - Non-U.S.

FR-PO910

Synaptopodin Deficiency Exacerbates Renal Disease in a Mouse Model of Alport Syndrome

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Background: Synaptopodin (Synpo) is a proline-rich actin-associated protein found in podocyte foot processes and dendritic spines. It has been reported (Asanuma et al., J Clin Invest 2005) that *Synpo*$^{-/-}$ mice lack Synpo-short and Synpo-long isoforms but show an upregulation of Synpo-T (truncated) in podocytes. *Synpo*$^{-/-}$ mice show an overtly abnormal phenotype in the brain but not in the kidney, demonstrating that Synpo-T may serve as a backup for Synpo-long in *Synpo*$^{-/-}$ podocytes. X-linked Alport syndrome is caused by mutations in *COL4A5*, which encodes the collagen IV α5 chain, resulting in structural and functional abnormalities of the glomerular basement membrane and leading to ESRD. It has been reported that expression of synaptopodin was decreased in Alport syndrome patients. We predicted that the deletion of *Synpo* in mice would exacerbate the effects of a *Col4a5* mutation.

Methods: To directly investigate the role that Synpo plays in Alport syndrome, we crossed mutant mice carrying null mutations in *Synpo* and *Col4a5* to produce mice deficient in one, both, or neither of these genes. Urine and tissues were taken at select time points to evaluate albuminuria, histopathology, and glomerular capillary wall ultrastructure.

Results: We generated novel *Synpo*$^{-/-}$ mice that should completely lack all known Synpo isoforms, but we did not observe obvious abnormalities in the kidneys. We found that the ablation of *Synpo* in *Col4a5*$^{-/-}$ or *Col4a5*$^{-/Y}$ mice led to shortened life span and acceleration of disease progression, such as more severe proteinuria and glomerulosclerosis. We obtained the same results except for decreased life span in *Col4a5*$^{+/-}$ females; surprisingly, most *Col4a5*$^{+/-}$ mice could live 5 months regardless of the presence or absence of Synpo. Immunostaining showed that the expression of COL4A345 was upregulated in these mosaic female mice in the absence of Synpo.

Conclusions: We conclude that *Synpo* deletion exacerbates the Alport syndrome disease phenotype in Alport mice, revealing the podocyte actin cytoskeleton as a target for therapy.

Funding: NIDDK Support

FR-PO911

β2-Adrenergic (β2-AR) Agonist Protects Mice from Glomerular Injury Through the Activation of β2-AR Receptor in Podocytes

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Background: Podocytes have a remarkable ability to recover from injury, however, little is known about the recovery mechanisms involved in this process. In this report, we demonstrate that pharmacological activation of β_2-AR dependent MB (mitochondrial biogenesis) is involved in the recovery of podocytes from injury in a PGC-1α dependent manner. We further demonstrate that the drug-induced podocyte recovery was significantly attenuated in podocyte-specific β_2-AR knockout mice.

Methods: The β_2-AR knockdown human podocytes were generated using specific shRNA, and the podocyte specific β_2-AR knockout mice were generated by crossing β_2-AR flox mice with podocin cre (B6.Cg-Tg(NPHS2-cre)295Lbh/J) mice to remove β_2-AR protein specifically in podocytes. The effect of a potent, specific, and long-acting β_2-AR agonist formoterol on MB was analyzed in control and β_2-AR knockdown podocytes by evaluating mtDNA (mitochondrial-DNA) copy number. Formoterol-induced (1mg/kg body weight/day) recovery of renal function was analyzed in wild-type and β_2-AR knockout mice by analyzing UACR, histological, ultrastructural and immunostaining analyses.

Results: β_2-AR knockdown in cultured human podocytes reduced mtDNA copy number indicating β_2-AR role in MB. While the podocyte-specific β_2-AR knockout mice developed normally, interestingly, when these mice were injured by treatment with adriamycin or nephrotoxic serum, unlike their WT (wild type) littermates, they failed to recover in response to treatment with formoterol and showed diseased glomerular morphology with consistent albuminuria.

Conclusions: Overall, these results confirmed that β_2-AR plays a critical role in podocytes recovery from injury and genetic deletion of β_2-AR affects the ability of mice to recover from injury. Overall these results suggest β_2-AR as a novel therapeutic target for treating podocytopathies.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO912

Melanocortin 5 Receptor (MC5R) Signaling Protects Against Podocyte Injury and Proteinuria

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Background: Melanocortin therapeutics represented by ACTH has a demonstrable steroidogenic-independent antiproteinuric and glomerular protective effect. It remains unclear which melanocortin receptors (MCR) mediate this renoprotective activity. MC5R was the last MCR to be characterized and has been involved in both biophysiology and pathology. However, the role of MC5R in glomerular disease is unknown and was examined here.

Methods: Adriamycin(ADR) nephropathy was induced in MC5R knockout (KO) and wild-type (WT) mice. Proteinuria and glomerular injury were evaluated. *In vitro*, ADR-insulted murine podocytes were treated with a highly selective MC5R agonist and cellular injury assessed.

Results: Under physiological condition, KO were no different from WT mice and had normal kidney physiology and histology. Upon ADR injury, KO mice demonstrated an exacerbated glomerular injury, featured by heavier albuminuria and worsened glomerular pathology, including glomerulosclerosis, podocyte apoptosis, loss of podocyte markers and ultrastructural lesions in podocytes like foot process effacement and microvillous transformation. Mechanistically, GSK3β, a transducer downstream of MC5R signaling and key regulator of podocyte injury, was more active in glomeruli of KO mice after ADR injury. This was concomitant with a potentiated activation of NFκB RelA/p65, a cognate substrate of GSK3β, in glomeruli in KO mice, and reinforced *de novo* expression of NFκB-dependent podocytopathic mediators, including B7-1, cathepsin L and MCP-1, in podocytes. Moreover, paxillin, a focal adhesion-associated adaptor protein and GSK3β substrate, was more activated in glomeruli of KO mice after ADR injury, associated with more disruption of podocyte cytoskeleton, shown by filamentous actin staining. In consistency, *in vitro* in ADR-insulted podocytes, treatment with a MC5R agonist rectified GSK3β overactivity, suppressed NFκB activation and the consequent *de novo* expression of B7-1, cathepsin L and MCP-1, and inhibited paxillin phosphorylation, resulting in a protection against podocyte injury, marked by cell shrinkage, hypermotility, cytoskeleton disorganization and apoptosis. This protective activity was blunted by ectopic expression of a constitutively active GSK3β mutant, signifying the mediating role of GSK3β.

Conclusions: MC5R-mediated melanocortinergic signaling protects against podocyte injury and proteinuria.

Funding: NIDDK Support

FR-PO913

Proteasomal Dysfunction Enhances the Glomerular Accumulation of the Membranous Nephropathy Antigen THSD7A Following Autoantibody Binding

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Background: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in Caucasian adults. In MN, podocyte membrane antigens such as the thrombospondin domain-like containing 7A (THSD7A) serve as targets to immunity. Diagnostic for MN is an enhanced antigen reactivity and antigen/antibody deposition in the subepithelial podocyte space and podocyte cytoplasm, for which the underlying mechanisms are unknown. The aim of this project is to investigate the mode of THSD7A degradation under homeostatic conditions and upon autoantibody binding, and whether alterations of THSD7A degradation relate to the pathological glomerular THSD7A accumulation in MN.

Methods: THSD7A half-life and homeostatic THSD7A degradation pathways were investigated in kidney slice cultures, cultured podocytes, and naïve Balb/C mice treated with either vehicle, proteasomal or lysosomal inhibitors. Furthermore, mice with genetic lysosomal dysfunction were used. To assess the involvement of protein turnover for the subepithelial accumulation of THSD7A following autoantibody binding, cultured podocytes were treated with rabbit anti-THSD7A IgG, and the model of rabbit anti-THSD7A MN was induced in Balb/C mice in the absence or presence of proteasomal or lysosomal inhibitors. Cells and mice were analyzed by Western blot, qPCR and high-resolution confocal microscopy.

Results: Under homeostatic conditions THSD7A has a long half-life in vitro and in vivo, and its protein content is regulated by the lysosomal system in naïve cultured podocytes and mice. Upon autoantibody binding, THSD7A is cross-linked at the plasma membrane and internalized through the endosomal system into multivesicular bodies. Internalized autoantibody-THSD7A complexes are degraded by both the lysosomal and proteasomal system. Impairment of the proteasomal system results in the (for MN typical) glomerular deposition of THSD7A in the subepithelial space and podocyte cytoplasm.

Conclusions: Homeostatic THSD7A levels are regulated by lysosomal degradation. Upon autoantibody binding, pathological glomerular THSD7A accumulation additionally strongly depends on the proteasomal system.

FR-PO914

ApoL1-DNA Cross-Talk with Cytosolic DNA Sensing Pathways in Podocytes

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Background: Viruses such as HIV are known to release double stranded DNA in cytosol and also known to induce activation of inflammasome Nod-like receptor (NLR) protein (P) 3 in podocytes. APOL1 renal risk variants have also been shown to activate NLRP3 pathway. The NLR family protein NLRC3 is a negative regulator of cytosolic DNA sensing pathway mediated innate immune response. We hypothesize that sensors of the NLR family, including NLRP3 inflammasomes, detect a variety of cytosolic nucleotides and trigger signaling that leads to pyroptosis and the maturation of interleukins.

Methods: Human podocyte stably expressing vector, APOL1G0/G1/G2 were activated with HIV (NL4-3) and evaluated for protein and mRNA expression of NLRP3, IL-1β, and Caspase-1. DNA binding site on ApoL1 variants was identified using DNABIND tool and by analyzing different DNA binding motifs on ApoL1 protein. Helix-turn-Helix motif and Leucine Zipper motif were analyzed using Prabi, iDNA-Prot, GYM2.0, 2Zip tools, and DNABINDPROT for the identification of DNA binding residues on ApoL1 variants protein. Models of ApoL1G0 and its variants ApoL1G1, ApoL1G2, NLRC3, and STING were generated using ITasser and protein-DNA and protein-protein complexes (docking approach); additionally, protein-protein interaction (PPI) interfaces and the thermodynamic properties of the protein-protein complexes were analyzed.

Results: HIV accelerated NLRP3 inflammasomes activation in APOL1RRVs milieu. ApoL1 variants displayed DNA binding sites, and the DNA binding residues provide ensemble for DNA-protein interactions. The ApoL1 and its variants showed potential to form protein-protein interaction (PPI) complexes individually with NLRC3 and STING, and also with the NLRC3-STING complex. Additionally, ApoL1G1 and ApoL1G2 could form thermodynamically favorable complexes with NLRC3 and stable complexes with STING individually. Since the interaction of ApoL1 and its variants seem to be weaker and transient with the NLRC3-STING complex, it indicates that ApoL1 variants and double-stranded cytosolic DNA could sequester NLRC3 and diminish NLRC3 interaction with STING and prevent inhibitory interaction of NLRC3 with STING.

Conclusions: ApoL1 variants provide a feed-forward response to STING pathway mediated inflammasome activation through cross-talk with cytosolic DNA sensing pathway.

Funding: NIDDK Support

FR-PO915

Alterations in Plasma Membrane Ion Channel Structures Stimulate NLRP3 Inflammasome Activation in APOL1 Risk Milieu

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Background: APOL1 has been demonstrated to act as ion transporter in cellular lipid membranes. APOL1 risk proteins have been shown to enhance K^+ -efflux and inflammasome activation. However, the involved mechanism is not clear. We evaluated the role of basic configurations of APOL1 pores on K^+-efflux and the activation of NLRP3 inflammasomes in APOL1 risk milieu.

Methods: Immortalized human podocytes were transduced with vector (V-PD) APOL1G0 (G0-PD), APOL1G1 (G1-PD), and APOL1G2 (G2-PD) employing lentivirus expression system and incubated with either vehicle or Glyburide (100 μM, a K^+- efflux inhibitor) for 48 hours (n=4). Protein blots and cDNAs were probed for NLRP3, IL-1β, and cleaved Caspase-1. Bioinformatics studies were conducted to evaluate alterations in plasma membrane ion channel structures in G0-, G1-, and G2-podocytes, including pore domain and structures, membrane integration and orientation, electrostatic properties and pKa calculation, binding with phosphatidic acid, and grid formation and docking of Glyburide in podocytes expressing APOL1G0 and variants.

Results: G1- and G2-podocytes enhanced the transcription of NLRP3. However, Glyburide inhibited this effect of APOL1G1 and APOL1G2. Superimposition of bioinformatic reconstructions of APOL1G0, G1, and G2 showed several aligned regions. The analysis of pore-lining residues revealed that Ser342 and Tyr389 are involved in APOL1G0 pore formation, however, conformations resulting from the Ser 384Met mutation in the case of G1 and deletion of the Tyr389 residue in the case of G2 are expected to alter pore characteristics, including K+ ion selectivity. Analysis of multiple membrane (lipid bilayer) models of interaction with the peripheral protein, integral membrane protein, and multimer protein revealed that for an APOL1 multimer model, G0 is not energetically favorable while the APOL1G1 and APOL1G2 moieties favor the insertion of multiple ion channels into the lipid bilayer. Protein-substrate/ligand interaction between Glyburide (a K^+- efflux inhibitor) and APOL1G0/APOL1G1/APOL1G2 revealed that a relatively lower concentration of Glyburide could bind to APOL1G1 and APOL1G2 multimer.

Conclusions: The altered pore configurations carry the potential to facilitate K^+ ion transport in APOL1 risk milieu.

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FR-PO916

Disruption of APOL1-mIR193a Axis (AMA) Facilitates the Development of Collapsing Phenotype in HIV-Associated Nephropathy

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Background: A recent discovery of APOL1-mIR193a axis (AMA) highlighted the role of parietal epithelial cells (PECs) in podocytes' (PDs) renewal both under normal physiological and pathological states. APOL1 and miR193a inversely regulate the expression of each other. PECs do not express APOL1. However, APOL1's induction stimulates PECs transition to podocyte molecular phenotype. We hypothesize that disruption of AMA in HIV-induced proliferating PECs expressing either APOL1G1/G2 or lacking APOL1G0 compromises PECs transition result in their accumulation in the Bowman's space (collapsing phenotype). We have validated this hypothesis in HIV transgenic mice experssing APOL1G0/G1/G2.

Methods: To aim transition (differentiation) to PDs, immortalized human PECs were incubated in special media for 14 days. PECs- transduced with either vector or HIV (NL4-3) were assayed for APOL1 expression. Differentiated PECs were transduced with vector, APOL1G0, APOL1G1, or APOL1G2 lentivirus. After 48 hours, cellular lysates were probed for PEC (PAX2 and Claudin 1) and PD (CD2AP, WT1, and podocalyxin) markers. Cellular lysates of above-mentioned transduced cells were assayed for miR193a expression and PEC, and PD markers. PECs' accumulation in Bowman's space was scored in renal cortical sections of 4-week and 8-week old HIV transgenic mice (Tg26) expressing APOL1G0, APOL1G1, and APOL1G2. Three-week old TG26 mice expressing APOL1G0 were administered Adriamycin (10 mg/Kg, IV) to induce APOL1G0 deficit.

Results: HIV induced APOL1 and PD markers, however downregulated miR193a expression in PECs. Differentiated- PECs and PDs expressing APOL1G1 and APOL1G2 displayed an attenuated expression of PD markers (protein as well as mRNA) but enhanced levels of miR193a expression. Renal cortical sections of Tg26 mice expressing APOL1G1 and G2 showed higher miR193a levels and abundance of PECs in Bowman's space. Tg26 mice expressing APOL1G0 displayed attenuated miR193a levels as well as minimal PECs accumulation in Bowman's space; in contrast, Adriamycin-treated Tg26 mice expressing APOL1G0 showed attenuated APOL1, increased miR193a expression, and abundance of PECs in Bowman's space.

Conclusions: Loss of APOL1's potential modulates miR193a expression and induces the collapsing phenotype in HIVAN.

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FR-PO917

Podocytes Expressing APOL1 Non-Risk and Renal Risk Variants Carry Potential to Secrete APOL1 Through Exosomal Pathway

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Background: Recent reports indicate a vital role of APOL1-miR193a axis in the development of focal segmental glomerulosclerosis. Circulatory APOL1 is bound to HDL complex and unlikely to pass through glomerular filtration barrier. Although APOL1 has been considered to be a secretory protein but its secretion by podocytes remains controversial. However, the realese of APOL1 from podocytes throuhg the exosomal pathway has not been studied to date. We asked whether cultured podocytes have potential to release APOL1 in exosomes. To confirm exosomal secretion, we validated this hypothesis in human embryonic kidney cells (HEKs) expressing vector, APOL1G0, APOL1G1, and APOL1G2. Additionally, we evaluated exosomal contents in the urine of the APOL1G0, APOLG1, and APOL1G2 transgenic mice.

Methods: Immortalized human podocytes and HEKs stably expressing vector (V), APOL1G0 (G0), APOL1G1 (G1), APOL1G2 (G2) were incubated with exosome-free media for 48 hours (n=6). Subsequently, media were collected and ultra-centrifuged for exosome isolation; Western blotting and FACS analysis were carried out for the expression of exosomal markers (CD81, HSP70), and cytosolic marker (Calnexin). The isolated exosomes were analyzed for their size by using Nano site system. To determine the presence of other relevant proteins, the single exo RNAseq and proteomic analysis was carried out. To validate these findings in vivo, the exosomes were harvested from the urine of the APOL1G0, APOLG1, and APOL1G2 transgenic mice.

Results: Exosomes harvested from both podocytes and HEKs expressing APOL1G0 and G1/G2 displayed the presence of APOL1. Nano Site analysis characterized the isolated exosomes in the range from 90-125 nM in size. Western blotting and FACS analysis displayed the exosomal expression of CD81 and HSP70 but Calnexin was not expressed. Release of exosome amounts differed in incubation med harvested from G0-, G1-, and G2-podocytes and HEKs. However, exosomes harvested from podocytes and HEKs expressing APOL1 risk variants showed a decrease in APOL1 expression. Data from urinary exosomes from APOL1 transgenic mice were consistent with *in vitro* findings.

Conclusions: Podocytes expressing APOL1G0, APOL1G1, and APOL1G2 carry potential to secrete APOL1 through the exosomal pathway.

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FR-PO918

APOL1 Renal Risk Variants (RRVs)-Induced Translocation of miR193a and Podocyte mRNAs to P-Bodies Prevents Their Degradation and Facilitates Translation

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Background: A disruption of APOL1-miR193a axis (AMA) has been reported in podocytes expressing APOL1 renal risk variants (RRVs, G1, and G2). However, the involved mechanism of disruption of AMA is not understood. We hypothesize that miR193a binding with APOL1G0 mRNA directs it for degradation, whereas, non-complementary binding with APOL1RRV mRNAs would facilitate their translocation to P-bodies to prevent their degradation as well as facilitate translation. To validate this hypothesis, we have evaluated the binding of APOL1G0 and APOL1RRVs mRNAs with miR193a and PKR in cultured podocytes. Additionally, we have examined the role of miR193a and involved mechanism of PKR activation in dual transgenic mice expressing miR193a and APOL1G0/APOL1RRVs.

Methods: RNAs of podocytes stably expressing G0s, G1s, and G2s were immunoprecipitated with anti-PKR antibody, and IP fractions were evaluated for PKR and downstream signaling (total and phospho--PKR, total and phospho-eIF2a, and GAPDH) and assayed for miR193a (n=6). Co-labeling of PKR and LSM14A/HEDLs (to localize PKR in P-bodies) were conducted. Protein blots of renal tissues of 10-weeks old control, single and dual transgenic (APOL1G0/G1/G2 and miR193a transgenic) mice (n=6; started on doxycycline [to induce miR193a and APOL1] feed at age 4 weeks) were probed for total and phospho--PKR, total and phospho-eIF2a and GAPDH. RNAs from renal tissues of single and dual transgenics were immunoprecipitated with anti-PKR antibody, and IP fractions were evaluated for PKR activation.

Results: PKR IP fractions from G1- and G2-podocytes displayed enhanced binding of APOL1mRNA; similarly, PKR IP fractions of renal tissues of dual G1- and G2 as well as single G1- and G2 transgenic mice displayed enhanced expression of miR193a. Immunolabeling studies showed enhanced translocation of PKR into P-bodies in G1- and G2-podocytes vs. G0 podocytes. Cellular lysates of G1- and G2-podocytes, renal tissues of both single and dual G1- and G2- transgenic mice, and miR193a mice displayed activation of PKR and associated downstream signaling.

Conclusions: APOL1RRVs facilitates translocation of miR193a and other podocyte mRNAs to P-bodies. It prevents their degradation and facilitates their translation.

Funding: NIDDK Support

FR-PO919

APOL1 Kidney Disease-Associated Variants Induce Differential Glomerular Expression of Immune Sensory Proteins in FSGS

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Background: Variants in *APOL1* (G1 and G2) associate with increased risk of CKD including hypertension-related CKD and focal segmental glomerulosclerosis (FSGS) in individuals with West African ancestry. Mechanisms by which the APOL1 variants contribute to the pathogenesis of CKD is not well understood. We hypothesized that variant APOL1 proteins mediate kidney disease through pathways independent from reference APOL1 protein. We aimed at characterizing differentially regulated protein networks in glomeruli of FSGS patients in presence of APOL1 variants.

Methods: Formalin-fixed paraffin-embedded kidney biopsies with a diagnosis of primary FSGS with (n=3) and without (n=3) homozygous *APOL1* risk variants and normal donor kidney biopsies (n=5) were identified. Glomeruli were isolated from the biopsies using laser capture microdissection followed by protein recovery, trypsin digestion and HPLC MS/MS using an Orbitrap fusion mass spectrometer. Label-free quantification in combination with global normalization of spectral count data was performed to determine changes in protein expression. Comparison of protein expression levels and upstream regulatory pathways were performed using Ingenuity Pathway Analysis software.

Results: In patients with FSGS, HLA-DQB1, HLA-DQA1 and ICAM-1 were significantly upregulated in the glomeruli in the presence of homozygous *APOL1* variants. Interferon-gamma regulated pathways were upregulated in glomeruli of FSGS patients in the presence of homozygous *APOL1* variants compared to FSGS with no *APOL1* variants and normal donor kidney.

Conclusions: Upregulation of immune sensory proteins in glomeruli in presence of APOL1 variants suggests that a differential cellular immune response mediated by the variants could contribute to the pathogenesis of FSGS. A larger cohort of patient samples needs to be interrogated to validate the observation.

FR-PO920

Nuclear Magnetic Resonance Studies Reveal Structural Differences Between APOL1 G0 and G1 C-Terminus

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Background: Common variants (G1: S342G and I384M, G2: N388del and Y389del) located in the C-terminus of APOL1 associate with high risk of progression to end stage kidney disease. Our previous studies using molecular modeling suggested that APOL1 C-terminus adopts an alpha-helical structure and G1 and G2 variants disrupt the structural integrity of the C-terminus leading to impaired intracellular protein interactions. We used nuclear magnetic resonance (NMR) spectroscopy to experimentally characterize the structural consequence of kidney disease-associated variants.

Methods: ^{15}N and ^{13}C isotope labeled C-terminus of APOL1-G0 and -G1 (aa 305-398) recombinant protein was generated using bacterial expression followed by metal affinity and size exclusion chromatography. The chemical shifts of backbone atoms in dodecylphosphocholine (DPC) micelles were determined by solution nuclear magnetic resonance (NMR).

Results: Two-dimensional solution NMR studies (^{1}H-^{15}N-HSQC spectra) demonstrated significant differences between reference protein G0 and G1 variant chemical shits suggesting variation in protein structure. The secondary structure determined using chemical shifts of backbone atoms demonstrated helical properties of APOL1 G0 and G1 C-terminus. G1 variant interrupted the alpha-helix of APOL1 C-terminus.

Conclusions: The changes in the structure of APOL1 C-terminus induced by kidney disease associated variants could disrupt protein interactions and underlie the intracellular mechanisms that mediate the pathogenesis of chronic kidney disease. Further characterization of the three-dimensional protein structure and dynamics using NMR and Molecular Dynamics simulations will refine the time-dependent behavior of APOL1 variants.

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FR-PO921

Mitochondrial Programming of Metabolic Signaling in Glomerular Podocytes

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Background: Metabolic signaling events are critical regulators of podocyte function. We have recently established a metabolic link between mitochondrial dysfunction and enhanced insulin signaling in podocytes. In this study, we interfered with OPA1 cleavage, a central regulatory hub that determines mitochondrial morphology under stress and in disease by conditional ablation of *Oma1* gene expression.

Methods: Conventional Oma1 KO animals and conditional Phb2$^{fl/fl}$;pod-cre mice were held in a pure C57/Bl6 background. Mice were characterized by observing survival and proteinuria while insulin-signaling activation was measured using histology and MS/MS. Oma 1 KO podocytes and Phb2 knockdown cells were utilized to further delineate the down-stream effects on MAPK, mTOR and GSK activation as well as MS/MS and seahorse measurements to assess glycolytic function and the metabolic status of the cells.

Results: An impaired OPA1 degradation by depletion of either Oma1 or Phb2, both, led to an increased insulin sensitivity as evidenced by increased Akt and mTOR-activation in vitro and in vivo. However, only loss of Phb2 resulted in a disrupted slit-membrane, proteinuria and premature death as previously published while Oma1 KO animals presented with normal glomerular function. Oma1/Phb2 double KO podocytes presented with an improved mitochrondrial cristae formation and prolonged animal survival. On a functional level, aerobic glycolysis was disrupted in both cases. Proteome analysis of Oma1 knockout mice glomeruli revealed elevated translation of proteins associated with fatty-acid metabolism and Acetyl-CoA synthesis and an increase in ribosomal protein s6 phosphorylation.

Conclusions: Here, we identified OMA1 as a critical regulator of podocyte metabolism in vitro and in vivo and demonstrate that a stress-induced OPA1 processing by OMA1 promotes a metabolic switch in glomerular podocytes. However, this metabolic switch alone was not sufficient to cause podocyte injury. Using mice lacking prohibitin membrane scaffols as a model of mitochondrial dysfunction, we demonstrate that additional ablation of OMA1 protects mitochondrial cristae formation from degradation leading to a significantly prolonged survival as compared to prohibitin deficient mice.

FR-PO922

Role of IRE1α in Podocyte Proteostasis

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Background: Podocyte (glomerular epithelial cell; GEC) proteostasis is disrupted in glomerular diseases. To maintain proteostasis, the endoplasmic reticulum (ER) orchestrates the unfolded protein response (UPR), which includes upregulation of chaperones. Proteostasis also involves clearance of misfolded proteins via autophagy. Inositol requiring enzyme-1α (IRE1α) resides in the ER membrane and is a transducer of the UPR. In mice, podocyte-specific deletion of IRE1α leads to age-related podocyte injury, autophagy impairment, and disruption of glomerular permselectivity. This study characterizes mechanisms by which IRE1α regulates proteostasis in GECs.

Methods: GECs were isolated from transgenic mice with loxP sites flanking the ribonuclease domain of the IRE1α gene. IRE1α was deleted by transduction of Cre recombinase (IRE1α KO). GECs expressing full-length IRE1α served as control (IRE1α WT). GECs were exposed to tunicamycin (TM), rapamycin (R), and glutamine starvation (GS) during 24 h. ER chaperones and LC3 were monitored by immunoblotting. Mitochondria were visualized using MitoTracker Red CMXRos.

Results: IRE1α KO and WT GECs exhibited comparable proliferation rates and protein content, implying that IRE1α is not involved in cell cycle progression. Stimulation of GECs with the ER stressor TM upregulated total IRE1α in WT, but not IRE1α KO GECs. After TM treatment, the chaperones BiP, GRP94, and mesencephalic astrocyte-derived neurotrophic factor increased in WT GECs. Deletion of IRE1α, or chemical inhibition of the IRE1α RNase with 4μ8C, significantly attenuated upregulation of chaperones and enhanced ER stress-induced apoptosis (evidenced by caspase-3 cleavage). Neither R nor GS enhanced expression of ER chaperones. Compared with WT GECs, IRE1α KO and 4μ8C-treated WT GECs showed similar basal autophagy, but reduced LC3 lipidation after stimulation with TM, R, and GS, indicating deficient autophagosome formation. Under basal conditions and after exposure to TM, the percentage of cell area occupied by active mitochondria in IRE1α KO and 4μ8C-treated GECs was significantly lower than in WT GECs, suggesting collapse of the mitochondrial network.

Conclusions: Stress-induced chaperone production, autophagy and mitochondrial distribution are compromised by deletion of IRE1α. The IRE1α pathway may play an important protective role in glomerular diseases associated with podocyte ER stress.

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FR-PO923

Angiotensin II Receptor Blocker Blocks Spreading Podocyte Damage in a Partial Podocytectomy Model

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Background: We established a new mosaic mouse model in which approximately 50% of podocytes express hCD25 and tdTomato whereas the other podocytes express EGFP but not hCD25. After the injection with hCD25-targeting immunotoxin, LMB2, not only hCD25-positive but also hCD25-negative podocytes were injured, and the mice developed global sclerosis. These indicated that injury incurred in a fraction of podocyte population causes secondary damage in other initially intact podocytes. This phenomenon may underlie progressive deterioration of chronic kidney diseases. In the present study, we tested whether this new mosaic 'partial podocytectomy' model can be used to evaluate renal protective effects of candidate drugs. As a proof of concept, we investigated the effect of angiotensin II receptor blocker (ARB), a well-established reno-protector, in this model.

Methods: Twelve female mosaic mice from 28 to 35 weeks of age were injected with LMB2. One day later, they were treated with losartan (0.5g/L in drinking water) (ARB group, n=6) or with 5% sucrose (Control, n=6). Fourteen days after LMB2 injection, kidneys were harvested and analyzed.

Results: Control mosaic mice developed severe glomerular damage with early sclerosis, adhesion, and hyalinosis, and dilated tubules with protein casts. These were markedly ameliorated in the ARB group. Glomerular injury index (in 0 (normal)-4 scales) was 3.3±0.30 (SE) in the Control group, which was improved to 0.13±0.083 in the ARB group ($p<0.01$). In addition, nephrin staining was more preserved (7.7±0.2 vs 3.0±1.0 in 0-8 (normal) scales, $p<0.01$) and desmin-positive podocytes were less observed (29±7% vs 74±11%, $p=0.026$) in the ARB group than the Control group. Importantly, EGFP-labeled podocytes, which do not carry hCD25 gene therefore are not directly injured by LMB2, were also secondarily injured, and the number decreased from 3.8±0.14 to 1.4±0.23 per a glomerulus after LMB2 injection in the Control group. The EGFP-positive podocytes were significantly more preserved in the ARB group (from 3.9±0.3 to 2.9±0.2, $p<0.01$).

Conclusions: Thus, our mosaic mouse model can visualize and evaluate secondary podocyte injury, and we have herein demonstrated that ARB attenuates the secondary podocyte injury.

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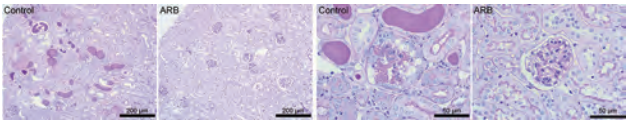

FR-PO924

Angiotensin II Impairs Podocyte Motility via Sirtuin-Mediated Zyxin Deacetylation and Cytoskeleton Rearrangement

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Background: Zyxin, as an adaptor protein primarily located at the adhesion plaque complex, has been implicated in the regulation of cytoskeletal dynamics and nuclear-cytoplasmic communication. However, the particular role of zyxin in regulating podocyte cytoskeleton assembly in kidney diseases remains obscure. In this study, we aimed to explore the role and mechanism of zyxin in SHR rats and AngII-treated podocytes.

Methods: The expression of zyxin and SIRT2, a mammalian homologue of NAD^+-dependent deacetylase sirtuin family, were detected by western blotting, immunohistochemistry, and immunofluorescence in glomeruli of SHR rats and AngII-treated conditional immortalized human podocytes (HPCs). Co-IP was performed to assess the level of acetylated-zyxin in AngII-treated HPCs and explore the interaction between zyxin and SIRT2. AGK2, the chemical inhibitor of SIRT2, was utilized to inhibit the activity of deacetylation. Finally, the podocyte motility was assessed by migration assay.

Results: Zyxin was widely expressed in kidney tissues and HPCs. Compared with the control group, the expression of zyxin in SHR rats was unchanged, which was in line with the results in vitro. Intriguingly, podocytes exposed to AngII showed a redistribution of zyxin, which was characterized by accumulation at adhesion plaques rather than along with actins in the cytoplasm, accompanied by F-actin disarrangement. Meanwhile, we found that zyxin was deacetylated in AngII-treated podocytes. On the other hand, SIRT2 level was upregulated in glomeruli of SHR rats and dual immunofluorescence staining revealed co-localization of zyxin and SIRT2. Co-IP also suggested that SIRT2 could interact with zyxin and modulate its function through deacetylation. Finally, we found that inhibition of SIRT2 activity ameliorated podocyte motility.

Conclusions: Zyxin participated in the actin rearrangement and podocyte injury induced by AngII exposure. Our results raise the possibility that SIRT2 regulates podocyte cytoskeleton dynamics and cell motility by modulating the function of zyxin via deacetylation.

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FR-PO925

Injured Podocytes Show an Increased Responsiveness to Angiotensin II-Mediated Calcium Transients

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Background: Angiotensin II (AngII) signaling has been shown to play a role in regulating glomerular perfusion and progression in kidney disease. The treatment of patients with ACE inhibitors is well established. Furthermore, AngII has shown to be able to trigger calcium signals podocytes *ex vivo*. In this study we aimed at unravelling AngII induced calcium signaling in healthy and diseased podocytes *in vivo*.

Methods: Kidney disease was induced in 4 week old mice expressing the calcium indicator GCaMP3 in podocytes (Pod:cre) by injecting 25 mg/kg Adriamycin. 4 days after injection the mice underwent 2-photon in vivo imaging. Mice were anaesthetized, a vascular access generated and the left kidney exteriorized. The vasculature was labelled with a 70 kDa dextrane (Texas Red). Untreated GCaMP3 Pod:cre animals were used as controls. AngII was infused with 100 ng/g/min. As inhibitors Losartan (10 mg/kg) and PD123319 (10 mg/kg) were used. The induced calcium transients were recorded as time lapse videos with 1 frame/second. The percentage of podocyte area showing an increase in calcium levels was calculated using ImageJ.

Results: The data shows that in 21 % of healthy glomeruli and in a mean of 2 podocytes a calcium signal can be triggered by AngII. The probability of inducing a calcium transient in a glomerulus by AngII stimulation increased by two-fold (41 %) in diseased (ADR) podocytes. Furthermore, the number of podocytes showing calcium transients is significantly increased. These findings correlate with a rise in the percentage of podocyte area showing a calcium signal from 12 to 26 %. The AngII induced calcium transient can be completely blocked by using Losartan, but not by PD123319.

Conclusions: Our study shows that calcium signaling in podocytes is highly regulated and the response to AngII increases upon injury. Additionally, we observed that not all podocytes react to AngII which points to heterogeneity in the podocyte population during health and disease. We can show that AngII mediates its calcium effects through the AT1R since Losartan completely blocked the calcium signal in podoyctes. Therefore our results

strongly support the need of a RAAS blockade in glomerular disease to protect podocytes from high calcium levels induced by AngII.

FR-PO926

Genetic Ablation of Calcium-Independent Phospholipase $A_2\gamma$ Exacerbates Glomerular Injury in Adriamycin Nephrosis in Mice

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Background: Genetic ablation of calcium-independent phospholipase $A_2\gamma$ (iPLA$_2\gamma$) in mice resulted in marked damage of mitochondria and enhanced autophagy in glomerular visceral epithelial cells (GECs) or podocytes. iPLA$_2\gamma$ knockout (KO) GECs in culture show mitochondrial dysfunction and enhanced autophagy. The present study addresses the role of iPLA$_2\gamma$ in glomerular injury, focusing on mitochondrial function and autophagy.

Methods: Adriamycin nephrosis was induced in wild type (WT) or iPLA$_2\gamma$ KO mice (age 3.5-4.5 months) by a single intravenous injection of adriamycin (12 mg/kg). Cultured WT or iPLA$_2\gamma$ KO GECs were transfected with mito-YFP (to label mitochondria), RFP-LC3 (to label autophagosomes) and RFP-LAMP1 (to label lysosomes). Colocalization of fluorescent signals was measured by the Pearson correlation coefficient.

Results: In adriamycin nephrosis, deletion of iPLA$_2\gamma$ exacerbated albuminuria and reduced podocyte number (WT1 counts). Glomerular LC3-II increased and p62 decreased in adriamycin-treated iPLA$_2\gamma$ KO mice, compared with treated control. In cultured iPLA$_2\gamma$ KO GECs, LC3-II was increased, compared with WT cells (by immunoblotting). After transfection of WT and KO GECs with RFP-LC3, RFP-LC3-II puncta and puncta area were enhanced in KO cells, consistent with greater autophagy. iPLA$_2\gamma$ KO GECs showed increased phosphorylation of AMP kinase (pAMPK), in keeping with mitochondrial dysfunction and lower cell ATP levels. Adriamycin further stimulated pAMPK and LC3-II. For comparison, induction of mitochondrial dysfunction with carbonyl cyanide m-chlorophenylhydrazone (CCCP) also increased pAMPK and LC3-II. There was greater colocalization of mito-YFP with RFP-LC3 and with RFP-LAMP1 in iPLA$_2\gamma$ KO GECs, compared with WT, indicating enhanced mitophagy in KO. Adriamycin and CCCP increased colocalization of mito-YFP with RFP-LC3 and with RFP-LAMP1.

Conclusions: iPLA$_2\gamma$ has a cytoprotective function in the normal glomerulus and in glomerulopathy, as deletion of iPLA$_2\gamma$ leads to mitochondrial damage and impaired ATP production. Deletion of iPLA$_2\gamma$ induces autophagy and mitophagy. Understanding how iPLA$_2\gamma$ maintains mitochondrial integrity and attenuates mitochondrial damage in glomerular diseases is essential for development of novel therapeutic approaches to glomerular injury and proteinuria.

FR-PO927

A Role for the Developmental Gene Pax2 in the Adult Kidney After Glomerular Injury

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Background: Pax2 is a member of the Pax family of highly conserved transcription factors that play important roles during development. Pax2 is essential for mammalian kidney organogenesis, without which the kidneys fail to form. We have previously reported that heterozygous missense mutations in Pax2 lead to focal and segmental glomerulosclerosis (FSGS) in ~5% of adults with the disorder. FSGS is a clinico-pathologic entity characterized by proteinuria and podocyte foot process effacement. We have obtained a mouse model with a Pax2 missense mutation to further investigate the mechanism by which the glomerular defect occurs.

Methods: We employed immunohistochemistry, electron microscopy, and Western blotting to examine kidneys from wild type and Pax2 mutant mice that were subjected to Adriamycin (ADR) administered through tail vein injections.

Results: Mice homozygous for Pax2 A220G (Pax2$^{A220G/A220G}$) develop dysplastic kidneys and are not viable though they survive to late gestation (E18.5). As expected, heterozygous Pax2$^{A220G/+}$ mice display smaller kidneys and reduced nephron number with no other obvious glomerular defects. Surprisingly, we find that Pax2 expression still persists widely in the adult kidney, both in the glomerular and tubular compartments. Challenging Pax2$^{A220G/+}$ mice with Adriamycin (ADR) recapitulated human FSGS with mutant mice more susceptible to injury compared to wildtype. Ki-67 staining revealed increased glomerular cell proliferation, that was not due to infiltrating immune cells, and caspase-3 staining demonstrated increased parietal epithelial cell (PEC) apoptosis that was observed in mutant but not wildtype mice.

Conclusions: We have demonstrated that a Pax2 heterozygous missense mutation renders the adult mouse kidney more susceptible to podocyte injury, approximating FSGS observed in humans. We postulate a role for Pax2 in the repair of injured glomeruli that may involve parietal epithelial cells.

Funding: Private Foundation Support

FR-PO928

Osteocrin Ameliorates Adriamycin-Induced Glomerular Injury

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Background: Natriuretic peptides including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) have cardioprotective effects through binding to natriuretic peptide (NP) receptors: Npr1 and Npr2. ANP or BNP exhibits potent renal effects in patients and animal models with heart failure. Recently a peptide, OSTN (osteocrin) is reported to bind to Npr3 which is a clearance receptor for NPs, and to prevent the worsening of congestive heart failure by increasing NPs with inhibition of degradation. However, the effect of OSTN on kidney function has not been elucidated yet. We hypothesized that OSTN has a renoprotective role by binding Npr3 to suppress clearance of NPs. We examined the role of OSTN in adriamycin (ADR) nephropathy, since podocytes are reported to express Npr3 in single-cell transcriptomics of the mouse kidney.

Methods: ADR was administered to wild-type and serum amyloid P (SAP) promoter-driven OSTN-transgenic (Tg) mice which showed plasma OSTN elevation, at dose of 8 mg/kg body weight via tail-vein injection. Mice were sacrificed at 4 weeks after ADR injection.

Results: There were no significant differences between wild-type mice and OSTN-Tg mice in systemic blood pressure, urinary volume, serum creatinine nor BUN. The body weight and body length of wild-type mice were significantly lower than those of OSTN-Tg mice (26.0 ± 1.0 g vs. 29.7 ± 0.6 g, $p < 0.01$; 9.5 ± 0.1 cm vs. 10.4 ± 0.1 cm, $p < 0.0001$, respectively). Increase of urinary albumin creatinine ratio of wild-type mice induced by ADR administration peaked at 2 weeks (165.6 ± 41.4μg/mgCr vs. 86.7 ± 7.6μg/mgCr, $p < 0.05$) and was significantly suppressed in that of OSTN-Tg mice at 4 weeks (91.5 ± 11.9μg/mgCr vs. 61.9 ± 3.0μg/mgCr, $p < 0.05$). Footprocess effacement observed in ADR-injected wild-type mice was ameliorated in ADR-administered OSTN-Tg mice, and thickness of glomerular basement membrane were significantly mitigated in OSTN-Tg mice in electron microscope (wild-type mice, 209 ± 12 nm vs. OSTN-Tg mice, 141 ± 3 nm, $p < 0.0001$).

Conclusions: These findings indicate that circulating OSTN has a reno- and podocyte-protective role in ADR nephropathy, probably through increase of natriuretic peptides on podocytes, and suggest that administration of OSTN could be a therapeutic option against podocyte injury.

FR-PO929

Shroom3-Fyn Interaction Regulates Podometrics via Activation of AMP-Kinase (AMPK)

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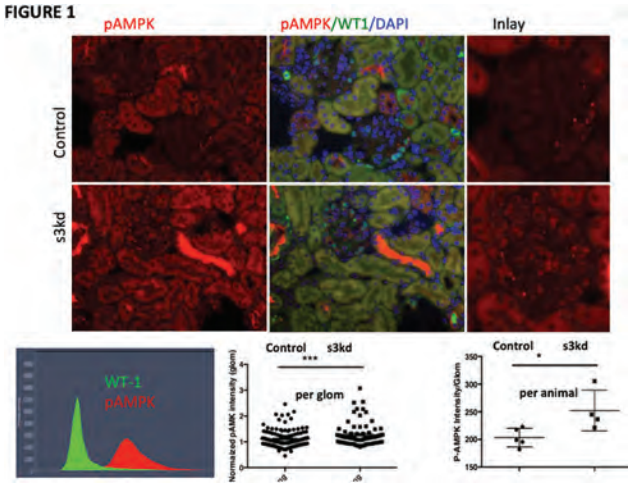
Background: We recently showed that Shroom3 interacts with Fyn, an Src kinase in podocytes, regulating Fyn activation. Intriguingly Shroom3 knockdown reduced podocyte and glomerular volume (Vglom).

Methods: To investigate mechanism of this phenotype, we examined Shroom3-(S3KD) & Fyn-knockdown (FynKD) human podocytes, and inducible Shroom3 knockdown mice (s3kd).

Results: FynKD podocytes also had reduced cell volume vs controls, suggesting that Fyn mediated the effect of S3KD on podocyte morphology. To investigate whether glomerular Shroom3 regulated Vglom hypertrophy, we performed unilateral nephrectomy in control and s3kd mice and examined Vglom in remnant kidneys. At day 7, s3kd mice showed restricted Vglom hypertrophy vs controls, (n=5; 8% vs 19%; $P<0.05$) and reduced expansion of podocyte fraction of Vglom. To investigate whether reductions of cell size were due to reduced protein content we measured protein:DNA ratio. S3KD & FynKD podocytes had reduced Protein:DNA ratios (n=5; $P<0.01$). Since MTOR is a key pathway regulating protein biosynthesis, we examined MTOR signaling. Phospho AMPK, a negative regulator of MTORC1 was significantly increased with S3KD/FynKD cells as well as in glomeruli of s3kd (Fig 1- immunofluoresence). Ribosomal biogenesis (18S RNA), downstream of MTORC1, was inhibited by qPCR in S3KD/FynKD cells (n=3) and s3kd kidney lysates. Since Fyn activation causes nuclear retention of LKB1, an AMPK-kinase, we examined ratio of cytoplasmic:nuclear LKB1, which was increased in S3KD and FynKD cells explaining AMPK activation.

Conclusions: In summary we show regulation of Vglom and podometrics by Shroom3-Fyn interaction that regulates protective AMPK-signaling. These findings have implications to loss of nephron mass and minimal change disease where podocyte Fyn-inactivation has been specifically observed.

Funding: NIDDK Support, Private Foundation Support



s3kd mice have activation of glomerular p-AMPK

FR-PO930

Regulation of Cytoskeletal Assembly by YAP (Yes-Associated-Protein) Mediates Podocyte Repair During the Response to Glomerular Injury

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Background: The HIPPO signaling pathway regulates the YAP/TAZ-Tead transcription factor complex involved in cell growth to determine organ size. Published studies have suggested that YAP is required for podocyte survival.

Methods: *Yap* was conditionally inactivated in podocytes of adult mice using an inducible Cre recombinase. *In vitro*, immortalized differentiated mouse podocytes were treated with *Yap* siRNAs. Podocyte injury was induced by treatment with adriamycin or trypsinization, *in vivo* or *in vitro* respectively. Electron microscopy, histology, molecular and cellular biology studies were conducted to characterize the phenotype of either *Yap* knockout mice or *Yap* knockdown cells.

Results: Electron microscopy analysis eight weeks after *Yap* inactivation in mouse revealed that *Yap* knockout led to mild foot process effacement. However, there was no evidence of proteinuria or glomerulosclerosis in *Yap* knockout mice, suggesting that there may be a redundant function of TAZ in uninjured podocytes. Treatment of *Yap* mutant mice with Adriamycin led to microalbuminuria and an increased frequency of histological lesions resembling Focal Segmental Glomerulosclerosis. *Yap* knockdown in immortalized differentiated mouse podocytes led to a reduction in focal adhesion area per cell and decreased area per cell. *Yap* siRNA treatment also led to a dramatic inability to spread and to organize actin stress fibers after trypsinization and reseeding. Consistent with the inability to spread, levels of pY397 FAK and phospho-cofilin, a downstream target of RhoA GTPase, were reduced in *Yap* knockdown podocytes. *Yap* knockdown also led to decreased inactivation of Rac1, a member of the Rho GTPAse family.

Conclusions: Our studies demonstrate that YAP has a crucial role in the assembly of the actin cytoskeleton during recovery from injury, affecting the polymerization of actin mediated by Rho family GTPases. In vivo, YAP appears to have a greater role in recovery from injury than in maintaining the cytoskeleton in uninjured podocytes.

Funding: NIDDK Support, Private Foundation Support

FR-PO931

Insights from Genome-Wide MicroRNA Target Identification In Podocytes Using Argonaute PAR-CLIP

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Background: MicroRNAs (miRNA) are a class of small non-coding RNAs that regulate gene expression through inhibition of translation or stability of target mRNAs. While several studies have shown the crucial role played by miRNAs in podocyte development and homeostasis, the specific miRNA and miRNA targets remain under-explored. Quantitative miRNA profiling is essential, but has a limitation: the inhibitory activity of a miRNA depends not only on its absolute expression level in the cell, but also on its loading onto the RISC complex and the availability of its target binding sites.

Methods: We have therefore applied argonaute-2 (AGO2) PAR-CLIP (Photoactivatable Ribonucleoside-Enhanced Crosslinking and Immunoprecipitation) to provide us with the miRNA target principles in podocytes. We searched for enriched miRNA seed-complimentary regions within PAR-CLIP output clusters using an in-house algorithm as well as Sylamer.

Results: The most enriched 6-8-mer sequences complimentary to the seed of miRNA that are expressed in podocytes, show extensive overlap between human and mouse. Surprisingly, the top enriched sequences were complementary to the seed of miR-27a and miR-27b, which are not among the most abundant miRNAs in podocytes, and thus might have been overlooked based on miRNA profiling alone. Subsequently, knocking down miR-27 expression in podocytes resulted in their reduced survival as well as an altered actin cytoskeleton pattern.

Conclusions: These results suggest a central role for miR-27 in podocyte maintenance. Furthermore our work implies that researchers interested in miRNA research may apply similar methods when choosing miRNA and miRNA targets suitable for their research.

Funding: Government Support - Non-U.S.

FR-PO932

Studying the Role of MiRNA in Podocyte Maintenance, Inspired by a Nephrotic Syndrome-Related Point Mutation in XPO5

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Background: MicroRNA (miRNA) are small noncoding RNA molecules that regulate gene expression, and are crucial for the development and homeostasis of podocytes. Biogenesis of miRNA requires a multistage process of which Exportin5 (*XPO5*) plays a rate limiting step by exporting miRNA precursors from the nucleus to the cytoplasm. Recently, steroid-resistant nephrotic syndrome (SRNS) in a child was attributed to a point mutation in *XPO5* (Braun DA 2016). However, whether or not the mutation affects the miRNA related function of Exportin-5 is not known. We hypothesized that the V552I mutation impedes miRNA maturation and that the association with SRNS may shed light on the roles of specific miRNA in podocytes.

Methods: We have successfully generated the p.V552I Exportin-5 ($XPO5^{V552I}$) homozygous mutation in HEK293 cells via CRISPR-Cas9. In addition we have generated human podocyte clones with a heterozygous mutation.

Results: Small RNA sequencing of our HEK293 cells shows a significant decrease in global miRNA content in $XPO5^{V552I}$ compared to parental cells. Principal component analysis (Figure) also revealed population separation between wildtype HEK293 and $XPO5^{V552I}$ cells, indicating miRNA expression segregated by genotype. Moreover, Small RNA sequencing of the podocyte clones revealed distinct changes in miRNA profiles.

Conclusions: These results strongly suggest the involvement of the $XPO5^{V552I}$ mutation in the dysregulation seen in the miRNA. Further investigation will lead us to the discovery of the specific miRNA involved in maturation and maintenance of podocytes.

Funding: Government Support - Non-U.S.

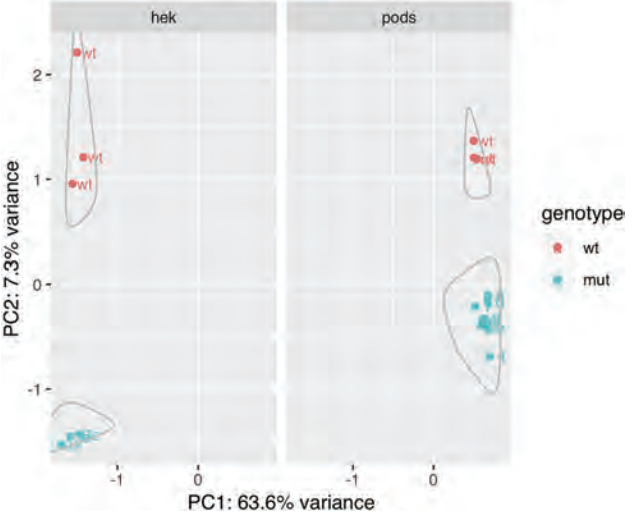

Figure: Principal component analysis plot by microRNA profiles showing samples arranging by cell type and genotype. hek, HEK293 cells; pods, podocytes; wt, control cells; mut, cells with mutated XPO5.

FR-PO933

Podocyte-Specific Deletion of Early B Cell Factor 1 Minimizes Sclerotic Damage After Glomerular Injury

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Background: It is now understood that podocyte loss, through sloughing and/or apoptosis, is the precipitating factor driving glomerulosclerosis. We also had previously reported that podocytes express the transcription factor Early B Cell Factor 1 (EBF1), although the function of this protein in these cells was unclear.

Methods: Utilizing a floxed version of *Ebf1* and podocin-cre we eliminated EBF1 specifically from podocytes, and injured glomeruli directly with either hypertensive

L-NAME injury or glomerular nephritis induced by anti-GBM serum. To identify the signaling pathways altered by EBF1 following its deletion alterations in RNA levels were compared to the chromosomal occupancy of EBF1 through ChIP-Seq.

Results: In both models of injury, EBF1 deletion from the podocytes was reno-protective. Fibrosis was reduced folowing anti-GBM serum at the at 7 and 10 days post injection. GFR decline and glomerular injury were found to be equivalent during the 20-week L-NAME hypertensive duration, however, recovery of the kidney for an additional ten-week period was dramatically accelerated when EBF1 was absent. This was reflected in the histologically as well as functionally through GFR measurement with the conditional knockout mice recovering almost half of their lost GFR within 3 weeks (no change in WT mice) and fully restoring kidney function by 10 weeks. Controls, by contrast, were not improved at the three-week mark, and only partially recovered by ten weeks. Less fibrotic injury was reflected in the RNA analysis of both models where markers of collagen formation, inflammation, and compliment and coagulation are all increased in controls. Conversely, pathway analysis performed with Metascape revealed EBF1 loss protects the integrity of the slit diaphragm components and that this is partially mediated by blunted calcium signaling, NFAT activation in the absence of EBF1. These changes were vified though clacineuin activity assay, reporter assays and western blots.

Conclusions: These results indicate that EBF1 normally promotes injury signals detrimental to the health of the podocyte through cell-intrinsic gene regulation. Deletion of this transcription factor from podocytes protects from glomerular injury at the initial stages of podocyte injury and these beneficial actions are mediated in part through minimizing NFAT signaling early in the injury process.

Funding: NIDDK Support

FR-PO934

Calcineurin Inhibitors Activate WNK1 Kinase to Preserve Glomerular and Podocyte Structure and Mechanics

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Background: Tacrolimus (FK-506) and cyclosporin A (CsA), both calcineurin inhibitors (CNIs), are immunosuppressants used to treat organ transplant rejection and auto-immune diseases. Although use of these drugs can be limited by side effects including hypertension, hyperkalemia, and vasculopathy with glomerulopathy, they can also protect podocytes and glomerular capillaries from injury by preserving podocyte cytoskeletal structure. Activation of WNK kinases by CNIs causes volume-dependent hypertension and hyperkalemia, but the mechanism of CNIs' vascular and glomerular effects is not understood.

Methods: Fresh, isolated mouse glomeruli were used for measurement of WNK1 activity (measured as pOSR1), glomerular elasticity using microindentation, F/G actin ratios, and confocal imaging for glomerular structure and pOSR1. Conditionally-immortalized podocytes were used for WNK1 activity measurements (pOSR1), confocal microscopy imaging, F/G-actin ratios, pOSR1, collagen gel contraction, and migration.

Results: We found that CNIs activate WNK1 in renal glomeruli and cultured podocytes increasing pOSR1 and F-actin. Treatment of glomeruli with CNIs increases the elastic modulus (E) of glomeruli (2.4 kPa vs control 2 kPa), an effect blocked by WNK463. FK-506 increases pOSR1, F/G Actin ratios and traction by podocytes in 3-dimensional collagen gels, increases lamellipodium formation, pOSR1 localization in leading edges, and migration of cultured podocytes, effects blocked by WNK463. In glomerular capillaries, CNIs increase pOSR1, while WNK463 reduces pOSR1and disrupts capillary structure.

Conclusions: The CNI-induced increase in glomerular F-actin and E, and modifications in podocyte cytoskeletal structure, provide mechanisms by which CNIs can protect glomeruli and podocytes against injury, and illustrate a novel mechanism involving WNK1 kinase and vascular tissue. This is the first report of a function for WNK1 in glomeruli.

Funding: NIDDK Support, Private Foundation Support

FR-PO935

TLR4-Myd88-NF-κβ and Calcineurin/NFAT Signaling Pathway Cooperatively Regulate Lipopolysaccharide-Induced Angptl4 in Podocyte

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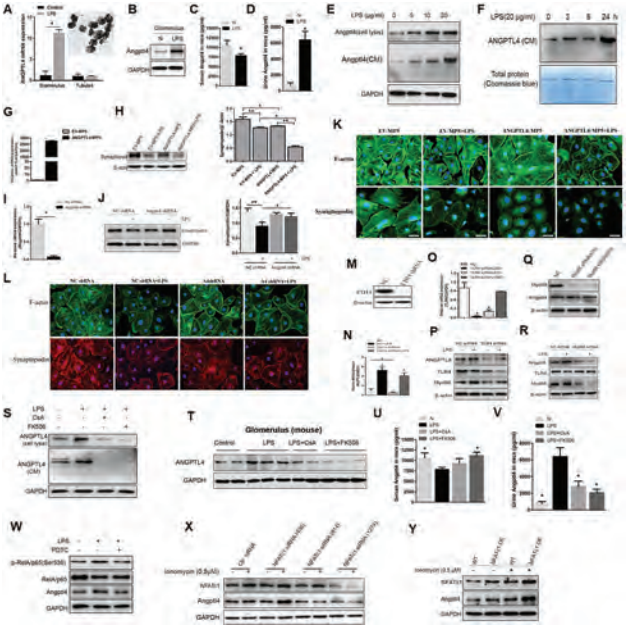
Background: Inflammation and immunological abnormalities damage podocytes and induce proteinuria. Angptl4 is a member of the angiopoietin-like protein family, which is involved in lipid metabolism, wound repair, tumor metastasis. Podocyte Angptl4 is involved in proteinuria formation, but its upstream regulation mechanism is still unclear. This study aims to clarify the molecular mechanisms involved in Angptl4 expression

Methods: LPS induced podocyte injury model was used to clarify the effect of LPS on Angptl4 in podocytes. Then, the effect of TLR4-Myd88- NF-κβ signaling pathway on Angptl4 expression was detected. In addition, Calcineurin inhibitors were used to detect Angptl4 expression in LPS-induced MCD model. Podocytes was transfected with Angptl4 to investigate the role of Angptl4 on podocyte injury.

Results: Angptl4 was promoted after LPS induction. Angptl4 overexpression disordered podocyte cytoskeleton, reduced synaptopodin, which was further decreased by LPS induction, while Angptl4 knockdown partially restored synaptoodin and podocyte cytoskeleton in LPS induced podocytes. In addition, TLR4, Myd88 siRNA and NF-κβ inhibitor PDTC effectively inhibited Angptl4 after LPS induction, while CD14 siRNA had no effect on Angptl4 expression, implying that Angptl4 was regulated by TLR4-Myd88-NF-κβ pathway. Furthermore, Calcineurin inhibitors significantly inhibited Angptl4, reduced the nuclear translocation of NFATc1, and restored podocyte cytoskeleton, which suggested that CaN inhibitors affected the expression of Angptl4 also through Calcineurin-NFAT signaling pathway.

Conclusions: LPS induced Angptl4 was regulated by Calcineurin-NFAT and TLR4-Myd88-NF-KB signaling pathway in podocytes

Funding: Government Support - Non-U.S.



TLR4-Myd88-NF-κβ and Calcineurin/NFAT signaling pathway cooperatively regulate LPS induced Angptl4 in podocyte

FR-PO936

NHERF2 Interacts with Ephrin-B1 at the Slit Diaphragm: NHERF2 Bridges Podocalyxin and Slit Diaphragm Components

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Background: We have reported ephrin-B1 is a novel component of the slit diaphragm (SD). Ephrin-B1 interacts with nephrin via their extracellular domains and plays an essential role in maintaining the barrier function of SD (JASN 29, 2018). We reported NHERF2, a scaffold protein possessing two PDZ domains, was downregulated in the glomeruli of the podocyte-specific ephrin-B1 KO mice, which suggesting NHERF2 is associated with ephrin-B1 (ASN 2018). It is reported that NHERF2 binds to podocalyxin at the second PDZ domain and plays the pivotal role in maintaining actin cytoskeleton by phosphorylating ezrin in podocytes. However, the precise localization of NHERF2 and its interaction with ephrin-B1 are unclear.

Methods: The interaction of NHERF2 with ephrin-B1 and nephrin was analyzed by the immunoprecipitation (IP) analyses with glomerular lysates and HEK293 transfected cells. The expressions of these molecules in glomeruli of normal rat and rat with nephropathy induced by the anti-nephrin antibody were analyzed by immunofluorescence.

Results: NHERF2 band was detected in the precipitates with anti-nephrin antibody by IP assay with normal rat glomerular lysate, which indicating NHERF2 is a member of the SD complex. The IP assay with the HEK cell expression system showed NHERF2 directly interacted with ephrin-B1 at the first PDZ domain and did not interacted with nephrin. The analyses with the HEK cells triple transfected with NHERF2, ephrin-B1 and nephrin showed that the anti-nephrin antibody binding phosphorylated not only nephrin but also ephrin-B1, and that the phosphorylated ephrin-B1 did not interacted with NHERF2. Dual-labeling analyses showed NHERF2 was detected not only apical area but also SD area, and a portion of NHERF2 was colocalized with ephrin-B1 in normal glomeruli. Ephrin-B1 was phosphorylated and dissociated from NHERF2 in the nephrotic state caused by the anti-nephrin antibody injection. The immunostaining of NHERF2 and ezrin as well as ephrin-B1 and nephrin were clearly decreased.

Conclusions: NHERF2 interacts with ephrin-B1 via its first PDZ domain and with podocalyxin via its second PDZ domain, and bridges podocalyxin, an apical surface protein and ephrin-B1, an SD component. The bridging structure was disrupted by the nephrin-mediated signal. The disruption is one of the critical mechanisms of podocyte injury.

Funding: Government Support - Non-U.S.

FR-PO937

Membrane-Associated Guanylate Kinase Inverted 2 Stabilizes Glomerular Filtration Barrier via the PDZ Domain

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Background: Slit-diaphragm (SD) of podocytes plays a crucial role as a final barrier of glomerular filtration. The main components of SD, such as Nephrin and Neph1, are indispensable in preventing progression of glomerulosclerosis. However, it remains unknown what is important for protecting these main components. Here, we demonstrate that Membrane-associated guanylate kinase inverted 2 (MAGI-2) functions as a critical scaffold protein for maintaining the SD components.

Methods: We examined the immunofluorescence intensity of MAGI-2 in human biopsy sample. We analyzed the phenotype of podocyte specific MAGI-2 knock out (KO) mice. Additionally, using *piggy-Bac* transposon and CRISPR-Cas9 system, we analyzed the function of MAGI-2 in cultured MAGI-2 overexpression podocytes and ZO-1 KO podocytes. Next, using biochemical assay, we investigated which domain of MAGI-2 is necessary for the binding among these molecules.

Results: In the immunofluorescence of human biopsy sample, MAGI-2 is downregulated in glomerular diseases such as focal segmental global sclerosis or IgA nephropathy. Actually, podocyte specific MAGI-2 KO mice also significantly exhibited glomerulosclerosis and the reduced expression of Nephrin and Neph1. Cultured MAGI-2 overexpression podocytes showed the colocalization of MAGI-2 and Nephrin in cell-cell contact, while Nephrin was not expressed in cellular edge of cultured control podocytes. Additionally, although ZO-1 deletion undermines the Neph1 expression in cultured podocytes, the transfection of MAGI-2 in the ZO-1 deleted cells could retrieve the reduced Neph1 expression. Biochemical assay demonstrated that MAGI-2 binds to Nephrin and Neph1 through different PDZ binding domains.

Conclusions: These results showed that MAGI-2 is crucial for maintaining the key components of SD such as Nephrin and Neph1. Moreover, they also showed that MAGI-2 could localize these main components to intracellular compartments through different PDZ domains. Therefore, the MAGI-2 protection strategy could be a new route to the new drug development against glomerular diseases.

FR-PO938

Fabry Disease and Renal Transplant

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Introduction: Fabry disease is a rare, X linked, multisystemic, multiorgan disorder in wich globotriaosylceramide (GL3) and other glycosphingolipids accumulate within lysosomes due to deficient activity of alpha-galactosidase A. The accumulation of GL3 in multiple cell types is associated with severe complications including cardiac events, stroke and renal failure. Fabry Nephropathy can lead to end stage renal disease requiring renal transplantation. Little is know about this outcomes and the overall patient survival after kidney transplantation.

Case Description: Here we report two Fabry patients (1 male and 1 female) who received kidney transplant and their treatment and follow-up with kidney biopsy at 5 and 10 years. Patients are 42 and 43 years old and received kidneys from deceased donors. We performed renal biopsies in both cases and GL3 levels in each patient.

Discussion: Over 874 kidney transplants perfomed at our Center, 3 patients had pre-transplant, Fabry Disease diagnosis. One patient died, 10 years post transplantation. Two more patients had excellent outcome with serum creatinine between 1,23 and 1,57 md/dl and Lyso GL3 between 14,9 and 52. In spite of good renal function, we decide to performed renal biopsies. Both patients show abnormalities: podocytes deposits of GLB3, in arteries and also found deposits in mesangial cells. Electron-dense lamellar inclusions were found in podocytes, and vascular endothelial cells.

FR-PO939

The Role of SOAT1 in Renal Disease Associated with Alport Syndrome

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Background: Defective cholesterol metabolism is closely associated with the progression of renal disease in Alport syndrome(AS), an inherited disease associated with progressive kidney failure, hearing loss and eye abnormalities. We recently demonstrated that accumulation of cholesterol esters occurs in experimental models of AS. SOAT1 is an enzyme that converts free cholesterol to cholesteryl esters at the endoplasmic reticulum, and plays an important role in cellular cholesterol homeostasis. Recent studies indicate that inhibition of SOAT1 may have beneficial effects in Alzheimer's disease and in cancer where SOAT1 inhibition reduced cancer proliferation and suppressed tumor growth. However, whether the accumulation of free or of esterified cholesterol contributes to progression of renal disease in AS remains unclear. With this study, we aimed at investigating the role of SOAT1 in the progression of renal disease in AS.

Methods: Normal human podocytes were treated with SOAT1 inhibitor (SI) or DMSO for 48h. Podocytes were stained with Bodipy and Cell Mask Blue. The Opera High Content screening system and Image Analysis software were used to quantify the density of lipid droplets. Cholesterol and triglyceride content was assessed using the Amplex Red Cholesterol kit and Triglyceride Colorimetric kit. Urinary albumin-to creatinine ratios were determined by mouse albumin ELISA and creatinine Companion kits.

Results: We observed a significant reduction of cholesterol esters in SI-treated human podocytes when compared to vehicle-treated podocytes in association with a decrease in lipid droplet density and triglyceride content. To assess the effect of SOAT1 deficiency in the kidney, the renal phenotype of *Soat1* knockout (SKO) mice was investigated. SKO mice did not develop albuminuria or mesangial expansion at 10 months of age. Analysis of SOAT1 expression in kidney cortexes of AS mice demonstrated increased SOAT1 mRNA when compared to WT mice, while expression levels of several other genes important in cholesterol homeostasis remained unchanged.

Conclusions: Our data suggest that increased SOAT1 expression in the kidney cortex of AS mice contributes to progression of renal disease in AS. We conclude that preventing cholesterol ester accumulation in kidney cortex of AS mice by SOAT1 inhibition may represent a new therapeutic strategy to treat renal disease in AS patient.

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FR-PO940

Plasma Circulating Factors in Recurrent Nephrotic Syndrome Increases Podocyte Motility via Signalling Pathways That Mimic PAR-1 Activation

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Background: Post-transplantation recurrence steroid resistant nephrotic syndrome (SRNS) is thought to be due to the presence of an unknown "circulating factor" the identity of which has so far remained elusive. Our previous work suggests that an unknown circulating protease in recurrent SRNS plasma signals to podocytes through protease activated receptor-1 (PAR-1), a G-protein-coupled-receptor and alters the actin cytoskeleton leading to increased podocyte motility via phosphorylation of vasodilator-stimulated phosphoprotein (VASP) a known actin cytoskeleton regulator. We have now further elaborated this signalling pathway in podocytes with the hypothesis that the circulating factor(s) in FSGS relapse plasma will initiate specific signalling pathways via PAR-1 receptor to the podocyte cytoskeleton and this consequently leads to increased podocyte motility and proteinuria.

Methods: Conditionally immortalised human podocytes (ciPods) were treated with 1) PAR-1 agonist; 2) Relapse and paired-remission plasma from FSGS patients, along with three different PAR-1 inhibitors, Vorapaxar, SCH 79797, and FR17113. A scratch assay was performed to determine the motility of ciPods after treatment with FSGS plasma. A mouse model of podocyte specific constitutively active PAR-1 was generated.

Results: We found that PAR-1 agonist and patient relapse disease plasma but not remission plasma from the same patient induced phosphorylation of VASP and JNK, a member of the mitogen-activated protein kinases (MAPK) superfamily in human podocytes, and increased motility compared to relevant controls. These changes were blocked by co-incubation of cells with certain PAR-1 inhibitors. These three PAR-1 inhibitors demonstrate distinct antagonistic properties and among 3 inhibitors, only FR17113 was effective, suggesting a non-canonical agonism of PAR-1 by disease plasma. The $PAR1_{active}$ mouse developed FSGS and upregulation of VASP, MAPK and JNK in podocytes by D8.

Conclusions: We reveal a consistent signalling pathway in 'circulating factor' SRNS that leads to increased podocyte motility and proteinuria and suggests direct therapeutic targets.

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FR-PO941

Towards Clinical Assays for Evaluating Circulating Permeability Factors in Nephrotic Syndrome

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Background: Circulating permeability factors (CPFs) have been implicated as one of the causes of nephrotic syndrome (NS). Evidence for CPFs comes mainly from clinical observations and animal studies, since reliable *in vitro* assays are lacking. Therefore, we aim to study the presence and pathogenic relevance of CPFs in plasma of NS patients during active disease and remission using conditionally immortalized human podocytes (ciHPOD) and primary human glomerular microvascular endothelial cells (GMVECs) *in vitro*.

Methods: Podocytes (ciHPOD) and primary endothelial cells (GMVECs) were incubated with plasma from NS patients in relapse and remission as well as from a non-renal control patient. Cell viability, podocyte motility, podocyte actin cytoskeleton architecture, and reactive oxygen species (ROS) formation at the presence or absence of ROS scavenger, dimethylthiourea, were investigated by CCK-8 assay, scratch-assay, immunofluorescence stainings, and CM-H2DCFDA probing, respectively.

Results: Plasma from active NS patients, but not from remission or control patients, caused excessive ROS formation in podocytes, but not in endothelial cells. Immunofluorescence microscopy revealed severe derangement of the podocyte's actin cystoskeleton in response to active NS plasma. Moreover, the motility of podocytes seemed to be reduced in the presence of active NS plasma, but not in the presence of remission or control plasma. Prolonged incubation of podocytes, but not endothelial cells,

led to cell death only when active NS plasma was present. Furthermore, the ROS scavenger dimethylthiourea abolished the ROS formation and the podocyte's actin cytoskeleton dearangement and cell death in response to active NS plasma, suggesting that ROS plays an important role in podocyte injury in NS.

Conclusions: We provide a high-throughput and sensitive assay to measure ROS in response to NS plasma, providing a new framework for monitoring *in vivo* CPF activity that could be used for diagnostics or disease monitoring purposes. Moreover, our findings suggest that the inhibition of ROS formation or facilitating rapid ROS scavenging might exert beneficial effects in patients with NS.

FR-PO942

Analysis of Urinary Extracellular Vesicle Autofluorescence by Imaging Flow Cytometry and Spectral Flow Cytometry

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Background: Urinary extracellular vesicles (uEVs) provide a source of valuable biomarkers for kidney and urogenital diseases. Analysis of uEVs in imaging flow cytometry is challenging for its intrinsic auto fluorescence emission across the whole electromagnetic spectrum. To date it is not known what the rate of the autofluorescence interference is with respect to the detection of specific uEVs markers

Methods: First morning void urine and citrate blood from the same donor were centrifuged at relative centrifugation force RCF of 4,600 g for 30 and 15 minutes respectively. The supernatant was further centrifuge at relative centrifugation force of 20,000g to collect urinary (uEVs) and plasma (pEVs) which were stained with the same commercial clone antibody (3D3) anti podocalyxin (PODXL) conjugated with 3 different fluorescent dyes: Alexa Fluor® 405 (AF405), Alexa Fluor® 488 (AF488) and Alexa Fluor® 647 (AF647). Stained EVs were acquired with both imaging flow cytometry and spectral flow cytometry. Gate strategy was based on the low scatter of the unstained uEVs and the negative control was the fluorescent probe alone in buffer.

Results: Acquisition of uEVs alone showed auto-fluorescence emission in channel 2 (λ_{ex} 488 nm; λ_{em} 480-560 nm) camera 1 and channel 11 (λ_{ex}658 nm; λ_{em} 660-740 nm) but not channel 7 (λ_{ex}405 nm; λ_{em} 420-505 nm) for camera 2 for the imaging flow cytometry meanwhile the spectral flow cytometry revealed a spectral fingerprint spanning from the violet to the red emission. Autofluorescence was detected for uEVs but not pEVs. Podocalyxin-AF405 conjugated stained both uEVs and pEVs with a double staining for the autofluorescence and PODXL on the same uEV. While PODXL-AF488 and AF647 stained better pEVs than uEVs as per PODXL-AF405. Same results were obtained for both flow cytometry instruments.

Conclusions: Our results showed an unexpected additional complication of the analysis of uEVs in flow cytometry originated from the auto-fluorescence of the uEVs fraction. In fact, the autofluorescence quenched the emission of PODXL-AF488 and AF647 but not AF405. Moreover, uEVs auto-fluorescence needs to be taken into account especially when simultaneous co-detection of uEVs markers of podocyte origin is planned with particular emphasis on the critical selection of the antibody conjugated fluorescent dye.

FR-PO943

C-Type Lectin-Like Receptor (CLEC)-2, the Ligand of Podoplanin, Facilitates Motility of Podocytes

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Background: Podoplanin is strongly expressed on podocyte membrane in an evolutionally conserved manner. Podoplanin binds to phosphorylated (p)ezrin, which binds and maintains filamentous (F-) actin. The endogenous ligand of podoplanin is C-type lectin-like receptor (CLEC)-2, which is highly expressed in platelets. Normally, podocytes are sequestered from platelets, but when the GBM barrier is injured, podocytes may have access to platelets or CLEC-2. In addition, soluble CLEC-2 was reported to exist in human serum. In the present study, we aimed to investigate the impact of CLEC-2 on podocytes.

Methods: Recombinant Fc-CLEC-2, a fusion of human Fc and CLEC-2 (51-229) proteins, which was reported to bind to mouse podoplanin, was generated in HEK293 cells and purified by Protein A affinity chromatography. Primary mouse cultured podocytes were incubated with the Fc-CLEC-2 or Fc protein (each 10 ug/mL) for 1 hour. Cell morphology, F-actin (Phalloidin staining), p-ezrin (immunostaining), cell adhesion to collagen-1 coated dish, and migration (Wound scratch test) were evaluated. To assess whether Fc-CLEC-2 has an impact on reversal from injury, podocytes were pretreated with protamine sulfate (PS) followed by heparin sulfate (HS), and then the effect of Fc-CLEC-2 or Fc on cell form, F-actin and p-ezrin were evaluated.

Results: No obvious change was observed in cell form and F-actin after the stimulation with Fc-CLEC-2. However, podocytes treated with Fc-CLEC-2 showed less adhesion to collagen-1 coated plate within 1 hour than the Fc control (86.7% vs. 100%). In migration assay, podocytes with Fc-CLEC-2 showed faster movement than control (11.1 vs. 9.2 mm/24hr) and faster wound closure (18.6 vs. 21.0 hours). After incubation with PS and HS, Fc-CLEC-2 retarded recovery of F-Actin formation compared to control (54.4% vs. 77.0%). Treatment with PS and HS increased p-ezrin, which was further enhanced by Fc. In contrast, Fc-CLEC-2 reduced cytosolic p-ezrin, suggesting that CLEC-2 inhibits F-actin formation by decreasing p-ezrin which binds to podoplanin.

Conclusions: These results indicate that CLEC-2 facilitates motility of podocytes and retards the reconstruction of F-actin during recovery from injury. Activation of motility of podocytes may be beneficial to wound healing, but the biological significance of these phenomena needs to be clarified in in vivo studies.

FR-PO944

Studying the Role of Fibronectin in Mechanically Stressed Podocytes

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Background: Glomerular hypertension induces mechanical load to podocytes *in situ*, often resulting in podocyte detachment and the development of glomerulosclerosis. Although it is well known that podocytes are mechanosensitive, the mechanosensor and mechanotransducer, respectively, are still unknown. Extracellular matrix proteins could function as such a mechanosensor. The objective was to clarify the potential significance of the extracellular matrix protein fibronectin which became up-regulated in cultured podocytes 2-fold after the exposure to mechanical strain. Furthermore, biopsies of patients suffering from diabetic nephropathy were used to study the expression of fibronectin.

Methods: Mouse podocytes were cultured on silicone membranes that were connected to the stretch apparatus for three days (0.5 Hz and 5% extension). To study the role of fibronectin in cultured podocytes under mechanical stretch, fibronectin was knocked down (Fn1 KD) by specific siRNAs. Additionally, we established a fibronectin knockout podocyte cell line (Fn1 KO) by CRISPR/Cas9. LC-MS as well as qRT-PCR were performed from mechanically stretched podocytes.

Results: Here, we demonstrate that the extracellular matrix protein fibronectin is essential for the attachment of podocytes during mechanical stress. By qRT-PCR as well as by LC-MS, we found a significant up-regulation of fibronectin in cultured podocytes after three days of mechanical stretch. Additionally, we observed a significant loss of Fn1 KD as well as Fn1 KO podocytes (> 80%) compared to controls in the presence of mechanical strain. Beside this, a significant down-regulation of the focal adhesion proteins talin, vinculin and paxillin and a reduced cell spreading was observed in Fn1 KO podocytes indicating an important role of fibronectin for the adhesion of cultured podocytes. Analyzing kidney biopsies of patients suffering from diabetic nephropathy, we found a significant up-regulation of fibronectin especially in podocytes in contrast to control biopsies.

Conclusions: Fibronectin plays an important role in the adaptation and adhesion of cultured podocytes in the presence of mechanical stretch and could serve as a mechanosensor in podocytes.

FR-PO945

Targetable Biomarker in Glomerular Disease: Determining the Role of Plasminogen in Podocyte Injury

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Background: Recent studies have shown significant quantities of plasminogen/plasmin, or plasmin(ogen)uria, in the urine of proteinuric patients and that exposure of cultured podocytes to plasminogen can result in injury via up-regulation of endothelin-1 (ET1) and oxidative stress pathways. However, a causative role for plasminogen as a "second hit" in disease progression has yet to be demonstrated *in vivo*, and the associations between plasmin(ogen)uria and kidney function in glomerular diseases remains unclear.

Methods: We performed comparative studies in a puromycin aminonucleoside (PAN) nephropathy rat model treated with amiloride, which has off-target effects inhibiting plasminogen activation, and measured changes in plasmin(ogen)uria and urinary ET1 by ELISA. Western blotting, proteomics, and IF were conducted to investigate changes in ET1 and plasmin(ogen) in isolated glomeruli as well as markers of oxidative stress and podocyte homeostasis. We used a biorepository at Mount Sinai hospital to identify patients with glomerular diseases (n=128). Urine samples were measured for time-of-biopsy albuminuria and plasmin(ogen)uria to assess for correlations with kidney function outcomes by logistic and linear regression.

Results: Plasmin(ogen) was found—for the first time to our knowledge—to be strongly bound within glomeruli in PAN rats, which was later confirmed in FSGS patients. PAN-treatment was associated with increases in plasmin(ogen)uria and urinary ET1, which was rescued by amiloride. Similarly, amiloride was protective against PAN-induced glomerular injury and oxidative stress. In the patient cohort, associations were shown between plasmin(ogen)uria and edema status as well as with eGFR, independent of age and gender.

Conclusions: Here, we (i) present strong supportive evidence for a causative role of the plasmin(ogen)-system in podocyte injury, with amiloride having reno-protective properties *in vivo*, and (ii) advance clinical correlations of plasmin(ogen)uria as a biomarker of glomerular injury in proteinuric patients. Plasmin(ogen) may thus aggravate renal disease through direct injury to podocytes during its trans-glomerular passage in the setting of proteinuria. Given such a function, plasmin(ogen) represents an attractive target for the development of mechanistically-based novel therapeutic interventions.

FR-PO946

Upregulated LRRC55 Aggravates Podocyte Injury Through Activating the BK Channel

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Background: Focal segmental glomerulosclerosis (FSGS) is a common podocytopathy, accounting for 40% of cases of nephrotic syndrome in adults, andits pathogenesis has not been fully elucidated. LRRC55 is a γ subunit of the BK channel, and the role of LRRC55 in podocyte injury has not been studied.

Methods: Glomerular tissues of FSGS patients and controls were isolated and subjected to transcriptome analysis. Cell biology techniques were used to analyze LRRC55 expression, BK channel current, intracellular potassium level, caspase-3 activation, DNA fragmentation and podocyte apoptosis in human podocytes and Ang II-treated mice.

Results: Based on transcriptome analysis and confirmation study, the level of LRRC55 was significantly increased in glomerular podocytes in FSGS patients. *In vitro*, treatment with Ang II induced NFATc nuclear translocation and promoted LRRC55 upregulation in podocytes. The upregulated LRRC55 and increased intracellular calcium led to BK channel activation and the loss of intracellular potassium, which caused caspase-3 activation and DNA fragmentation in Ang II-treated podocytes. In contrast, silencing of LRRC55 reversed the intracellular potassium loss, caspase-3 activation and DNA fragmentation in the Ang II-treated podocytes. *In vivo*, Ang II-infusion caused an obvious increase in LRRC55 expression, BK channel activation, intracellular potassium decrease, podocyte apoptosis and focal segmental sclerosisin mice. Knockout of BK channel or silencing of LRRC55 prevented intracellular potassium decrease and ameliorated podocyte injury and focal segmental sclerosis in Ang II-treated mice.

Conclusions: The results suggest that the upregulated LRRC55 aggravates podocyte injury through activating BK channel. Inhibition of LRRC55 attenuates podocyte injury, may representing a new therapeutic approach for FSGS patients.

FR-PO947

Loss of Robo2 in Mature Podocytes Is Protective from Injury by Enhancing Podocyte Adhesion That Helps Maintain Foot Process Structure

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Background: Repulsive guidance cue receptor ROBO2 plays an important role during early kidney development. ROBO2 is expressed in podocytes, inhibits nephrin-induced actin polymerization, down-regulates nonmuscle myosin IIA activity, and destabilizes kidney podocyte adhesion. However, the role of ROBO2 during kidney injury, particularly in mature podocytes, is not known.

Methods: In this study, we compared phenotypes between adult *Robo*2 podocyte specific knockout mice (*Robo2* cKO) and wildtype controls under two different glomerular injury conditions induced by protamine sulfate (PS) perfusion or nephrotoxic serum (NTS) injection. We also analyzed ROBO2 expressions in the glomeruli of NTS injured mice, passive Heymann nephritis (PHN) rat, and membranous nephropathy patients.

Results: Ultrastructural analysis reveals that *Robo2* cKO mice display less foot process effacement and better preserved slit-diaphragm density compared to wild-type littermates injured by either protamine sulfate (PS) or nephrotoxic serum (NTS). The *Robo2* cKO mice also develop less proteinuria after NTS injury. Further studies reveal that ROBO2 expression in podocytes is upregulated after glomerular injury since its expression levels are higher in the glomeruli of NTS injured mice and passive Heymann membranous nephropathy rats. Moreover, the amount of ROBO2 in the glomeruli is also elevated in patients with membranous nephropathy. Finally, overexpression of ROBO2 in cultured mouse podocytes compromises cell adhesion.

Conclusions: These findings suggest that kidney injury increases glomerular ROBO2 expression that might compromise podocyte adhesion and thus loss of *Robo2* in podocytes could be protective from glomerular injury by enhancing podocyte adhesion that helps maintain foot process structure. Our findings also suggest that ROBO2 is a therapeutic target for podocyte injury and podocytopathy.

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FR-PO948

Role of Sphingomyelin Phosphodiesterase Acid-Like 3B (SMPDL3b) in Fatty Acid Uptake and in Progression of Podocyte Damage

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Background: LD play an important role in many biological processes and LD size and number have been linked to several diseases such obesity, insulin resistance and type 2 diabetes, heart disease, and non-alcoholic fatty liver disease. LD are mainly composed of triglycerides and cholesterol. We previously demonstrated that the accumulation of LDs occurs in glomeruli of experimental models of focal segmental glomerulosclerosis (FSGS) and Alport syndrome and that lipid accumulation in podocytes is one of the factors contributing to the pathogenesis of kidney disease. We furthermore demonstrated that glomerular expression of sphingomyelinase phosphodiesterase like 3b (SMPDL3b), a glycosylphosphatidylinositol (GPI) anchored protein primarily localized at plasma membrane (PM), affects the function of podocytes in FSGS and diabetic kidney disease (DKD). With this study, we aimed at exploring a possible role of SMPDL3b in fatty acid uptake and in the formation of LDs ultimately contributing to podocyte damage.

Methods: Fatty acid uptake in podocytes was determined using the fatty acid uptake kit from Sigma (#MAK156). LDs were isolated using a kit from Cell Biolabs (#MET-5011) and proteins present in LDs were analyzed by Western blotting. Triglyceride (TAG) and esterified cholesterol (CE) content were measured using enzymatic and mass spectrometric methods. Lipolysis was measured using a lipolysis colorimetric assay kit from Sigma (#MAK211).

Results: Decreased SMPDL3b expression (siSMPDL3b) was associated with an increase in fatty acid uptake and an increased number of LDs, the number of LD was decreased in podocytes with increased SMPDL3b expression (SMPDL3b OE). Similarly, triglyceride and cholesterol ester content were increased in siSMPDL3b when compared to control podocytes. Finally, we demonstrate for the first time that SMPDL3b is present in isolated LDs suggesting a possible role for SMPDL3b in the formation of LDs.

Conclusions: Our results identify a new role of SMPDL3b in the uptake of fatty acids, the accumulation of TAG and the formation of LDs. Further experiments to understand the exact mechanism by which SMPDL3b controls the uptake of fatty acids thus contributing to podocyte damage are underway.

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FR-PO949

Podocyte Cell Cycle Manipulation as a Potential Tool in Treating Glomerular Disease

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Background: Loss of podocytes is a hallmark of most progressive kidney disease. Podocytes do not replicate in situ; hence, hypertrophy is the only mechanism they have to compensate for cell loss by allowing a smaller number of podocytes to effectively cover the glomerular tuft. To undergo hypertrophy, podocytes re-enter the cell cycle, moving from quiescent G0 to G1. Regulation of the G1/S checkpoint is critical. If podocytes exit G1 and continue toward mitosis, they detach from the GBM during cytokinesis and are lost in the urine. Understanding cell cycle regulation may be pivotal in developing novel therapies to prevent podocyte loss.

Methods: To the study the podocyte cell cycle, we established colonies of FUCCI2aR mice. These mice have ubiquitylation-mediated fluorescent protein expression, which reflects the cell cycle in vivo: red in G1/S, green in S/G2, yellow for S phase, no fluorescence in G0. These FUCCI mice were bred with our model of glomerular injury (Alport Syndrome, AS) and with a podocyte-specific Cre-mouse, yielding a model that allows real-time studies of the cell cycle specifically in podocytes.

Results: Podocytes isolated from glomeruli of wild type FUCCI2aR mice were 23% of total glomerular cells: 93% were in G0, 6% in G1 and none in S/G2. In late-stage proteinuric AS FUCCI2aR mice, 95% of the podocytes were in G1. We found that rapamycin (an mTOR inhibitor) was protective by supporting podocyte survival in vitro. Podocytes isolated from cultured glomeruli exposed to rapamycin for 3 days had increased survival (16%-20%) compared to podocytes not exposed to rapamycin (7%-9%). Furthermore, in PAN-exposed podocytes in vitro rapamycin increased the number of podocytes in G1 [from 4% to 13.5%]. The G1 podocytes were also larger by 41.5% ($p<0.05$) than those in G0 as assessed by flow cytometry forward scatter, confirming that the G1 podocytes are in a hypertrophic state.

Conclusions: Interventions that support podocyte hypertrophy, while limiting progression to mitosis or cytokinesis, may stabilize glomeruli against sclerosis following a loss of podocytes. Rapamycin presents a potential novel therapy in glomerular diseases such as AS by enhancing stable hypertrophy of podocytes in G1, while preventing progression through the cell cycle to S and mitosis.

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FR-PO950

ZNF277-Induced Podocyte Injury by Regulating the Expression of ITGAV and ITGB5

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Background: ZNF277, a newly discovered zinc finger protein, is highly conserved in evolution. Previously, by single-cell RNA sequencing, we found that ZNF277 was specifically expressed in mouse glomerular podocyte. Then, by searching Nephroseq database, the expression level of ZNF277 in glomerular of FSGS patients was significantly down-regulated. Therefore, we speculated that ZNF277 might be involved in podocyte injury.

Methods: Firstly, we detected the mRNA level of ZNF277 in human podocyte lines (HPCs) by Q-PCR. Then, ZNF277 was specifically knocked down by siRNA in HPCs, and the changes of podocyte-specific genes were detected by Q-PCR. Finally, by bioinformatics analysis of podocyte-specific genes down-regulated when ZNF277 was knocked down, we speculated the possible mechanism of ZNF277 involved in podocyte injury.

Results: In vitro, the expression level of ZNF277 in PAN-induced podocyte injury model was down-regulated (0.50 ±0.13). 92 podocyte-specific genes were detected in HPCs in which ZNF277 was knocked down by siRNA. Among them, 18 genes were down-regulated, including ITGB5, ITGAV, IFT80, MYOM2, HAUS8, RAB3B, CDKN1C, DTNB, CYB5R4, SDC4, ARPC1A, WT1, PODXL, ILDR2, SYNPO, ALCAM, SEPT10, TMOD3. Then, the 18 genes were analyzed by Bioinformatics analysis, including GO and KEGG analysis, The results suggested that they were mainly involved in biological processes such as cytoskeleton and cell adhesion,and ITGB5 and ITGAV were the main genes involved in the biological process.

Conclusions: the mechanism of ZNF277 participates in podocyte injury may be regulating the expression of ITGAV and ITGB5.

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FR-PO951

Protective Effect of Hydroxychloroquine on Cultured Mouse Podocytes Expressing the HIV Accessory Protein Vpr

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Background: Studies in HIV-transgenic mice have implicated the HIV accessory protein R (Vpr) in podocyte injury, culminating in HIV-associated nephropathy. Clinical studies indicate that hydroxychloroquine reduces kidney damage in lupus. In this study, we tested protective effects of hydroxychloroquine on cultured mouse podocytes expressing Vpr.

Methods: Stably-transfected mouse podocytes bearing three transgenes, expressing Vpr (thermosensitive SV40 T antigen, podocin-promoter-rtTA and tet-responsive element-Vpr) or control AI podocytes expressing two transgenes (thermosensitive SV40 T and podocin-promoter-rtTA) were grown at 33°C and differentiated at 37°C. Differentiated podocytes were plated on day 1, hydroxychloroquine at concentrations ranging from 0.63 to 80 μg/mL was added to podocyte cultures on day 3, and 1 μg/mL doxycycline (DOX) was added day 4). Cell death was observed by phase-contrast microscopy on day 6 and 9, and total cell number and dead cell number were counted in each condition to obtain the percentage of dead cells.

Results: AI control and Vpr-expressing podocytes tolerated hydroxychloroquine concentrations of 10 μg/mL of hydroxychloroquine or less but died at higher concentrations. Vpr podocytes died 48 h after 1 μg/mL DOX was added, likely due to induced expression of Vpr. DOX-treated Vpr podocytes were protected from cell death with 24 h pretreatment of 0.63, 1.25, 2.5, 5 and 10 μg/mL hydroxychloroquine (H), in a dose-dependent manner (H0: 30.2%, H0.63: 25.0%, H1.25: 20.8%, H2.5: 4.3%, H5: 0%, H10: 0%). DOX-untreated Vpr podocytes without hydroxychloroquine also underwent cell death on day 9 of 37°C culture due to leaky expression of Vpr, which was partly inhibited by 5 and 10 μg/mL of hydroxychloroquine pretreatment (H0: 56.3%, H5: 32.0%, H10: 2.6%).

Conclusions: In cultured mouse podocytes expressing Vpr, hydroxychloroquine showed protective effects at up to 10 μg/mL. Hydroxychloroquine has diverse effects on mammalian cells, including increasing lysosomal pH, which in turn alters protein processing such as glycosylation. Hydroxychloroquine also alters Toll-like receptor signaling. The effects of hydroxychloroquine on Vpr-induced podocyte injury deserve further study.

FR-PO952

Regulation of Podocyte Senescence by GSK3β: A Novel Senostatic Target for Delaying Glomerular Aging

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Background: Along with worldwide population aging, nephrology practice is challenged by renal aging, which is associated with progression of age-related glomerulosclerosis centrally involving podocyte senescence. Compelling evidence suggests that microdoses of lithium, an inhibitor of GSK3β, alleviated aging in *Drosophila* and *C. elegans*. As a multitasking kinase, GSK3β has also lately been implicated in podocyte pathobiology. However, it remains unknown if GSK3β regulates renal aging.

Methods: Renal aging was examined in mice with doxycycline-induced podocyte-specific ablation of GSK3β (KO) or in control littermates at 2, 12 or 24 months. Cultured podocytes were tested for senescence.

Results: Accompanying aging, control mice exhibited evident renal aging, featured by a decline in renal function, persistent albuminuria and typical pathologic changes, including glomerular hypertrophy, focal global glomerulosclerosis, hyaline arteriolosclerosis and renal fibrosis on light microscopy, associated with ultrastructural lesions in podocytes like foot process effacement and deposits of protein aggregates, podocytopenia, and loss of podocyte markers like synaptopodin and podocin. In parallel, senescence-associated β-galactosidase activity and expression of senescence-related $p16^{INK4A}$, p53 and p21 were progressively increased in glomeruli, correlated with concomitant GSK3β overactivity, as evidenced by linear regression analysis. In the aged KO mice, GSK3β was selectively ablated in podocytes, resulting in a blunted induction of $p16^{INK4A}$, p53, p21 and β-galactosidase activity in glomeruli, and alleviation of glomerulosclerosis and other signs of glomerular aging. Mechanistically, *in silico* analysis revealed that $p16^{INK4A}$, p53 and p21 are cognate substrates of GSK3β and contain the GSK3β consensus motifs. *In vitro*, ectopic expression of a constitutively active GSK3β mutant in podocytes promoted phosphorylation of $p16^{INK4A}$, p53 and p21, incurring a potentiated cellular senescence, marked by an elevated β-galactosidase activity and loss of podocyte differentiation markers like synaptopodin. Conversely, GSK3β knockdown attenuated phosphorylation of $p16^{INK4A}$, p53 and p21, leading to a diminished cellular senescence.

Conclusions: GSK3β plays a key role in glomerular aging by regulating podocyte senescence, and thus is likely an actionable senostatic target for delaying glomerular aging.

FR-PO953

APOL1 Renal Risk Variants Induce Disruption in APOL1-miR193a Axis Through Downregulation of Vitamin D Receptor

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Background: APOL1-miR193a Axis has been demonstrated to play a vital role in the maintenance of podocyte molecular phenotype. Both APOL1G0 (wild-type) and miR193a inversely regulate each other. However, APOL1 renal risk variants ([RRVs], G1 and G2) upregulated instead of downregulation of miR193a expression in podocytes. Recent reports indicate that Vitamin D Receptor agonist (VDA) downregulates miR193a expression in podocytes. We hypothesize that APOL1RRVs enhance degradation of Vitamin D Receptor (VDR) and that would enhance the expression of miR193a in podocytes. VDR heterodimerizes with RXR and VDR-RXR binds on the gene promoter.

Methods: Immortalized human podocytes stably expressing vector (V-podocytes), APOL1G0 (G0-podocytes), APOL1G1 (G1-podocytes), and APOL1G2 (G2-podocytes) were differentiated. Proteins and RNAs were extracted. Protein blots of V-podocytes, G0-, G1-, G2-podocytes were probed for APOL1, VDR, and GAPDH (n=6); cDNAs were amplified for VDR; RNAs were assayed for miR193a. Bioinformatics studies suggested that VDR binds at miR193a gene. To validate the binding of VDR and RXR on miR193 promoter, ChiP assay was carried out. To determine the role of proteasomal degradation, V-, G0-, G1-, and G2-podocytes were incubated in media containing either vehicle or MG132 (10 nM) for 48 hours (n=4); protein blots were probed for APOL1, VDR, and GAPDH. Podocytes were transfected with either scrambled or VDR siRNA; protein blots were probed for VDR and GAPDH; RNAs were assayed for miR193a.

Results: G0-podocytes displayed enhanced ($P<0.05$) APOL1 and VDR but attenuated ($P<0.05$) expression of miR193 when compared to V-podocytes. In contrasts, G1- and G2-podocytes showed decreased ($P<0.05$) VDR but enhanced ($P<0.01$) expression of miR193a when compared to V- and G0 podocytes. MG132-treated G1- and G2-podocytes showed an increased expression of VDR vs. only vehicle treated G1-and G2-podocytes. Podocytes silenced for VDR displayed enhanced miR193a expression. ChiP assay revealed binding of VDR and RXR at miR193a promoter.

Conclusions: APOL1RRVs enhance miR193a expression in podocytes through downregulation VDR.

Funding: NIDDK Support

FR-PO954

Molecular Mechanisms Underlying the GRK4 65L-Mediated Hypertension in Mice

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Background: The genetic causes of salt sensitivity and hypertension in humans are not completely understood. The kidney plays a preeminent regulatory role in water and electrolyte balance and blood pressure (BP) homeostasis. The renal dopamine receptors, D_1R and D_3R, engender natriuresis via the inhibition of renal Na^+ transport, whereas the angiotensin II type 1 receptor (AT_1R) does the opposite. The renal paracrine inhibition of Na^+ transport by dopamine is impaired in salt-sensitive rats, mice, and humans. Agonist activation promotes the phosphorylation of D_1R and D_3R by the G protein-coupled receptor kinase type 4 (GRK4), whose gene variants impair D_1R and D_3R activity.

Methods: To demonstrate the specific renal causal mechanisms in GRK4 65R>L-mediated hypertension, we heterologously expressed the *GRK4 65R>L vs. GRK4 wild-type* (WT) transgenes in the kidneys of *Grk4* knockout mice on normal salt diet. The transgenes were delivered selectively into the renal tubules by the bilateral retrograde ureteral infusion of AAV-9 vectors.

Results: The renal tubule-restricted expression of *GRK4 65R>L* increased the BP (117±4 *vs*. 93±1 mm Hg, P<0.05, n=4), while that of the *GRK4 WT* only tended to increase the BP (105±6 *vs*. 96±2 mm Hg, n=5), indicating that the presence of the GRK4 variant in the kidney caused the increase in BP. We next evaluated the renal expression profiles of select genes. We found that the expressions of the pro-natriuretic D_1R (0.81±0.01 *vs*. 1.28±0.04, P<0.01) and D_3R (0.44±0.02 *vs*. 1.27±0.07, P<0.01) were decreased. By contrast the expressions of the anti-natriuretic Na^+/K^+-ATPase (1.14±0.024 *vs*. 1.0 ±0.007, P<0.05) and a-ENaC (1.4±0.14 *vs*. 1.0±0.11, P<0.05) were increased, demonstrating the mechanistic changes that underlie the hypertension in these mice. Interestingly, we also observed that the expressions the AT_1R (0.82±0.02 vs. 1.02±0.02) and the proximal tubule Na^+ transporters NaPi2 (0.81±0.02 *vs*. 1.04±0.02), SGLT2 (0.89±0.03 *vs*. 1.07±0.05), and NBCe2 (0.50±0.07 *vs*. 1.15±0.03), were decreased, which may represent insufficient compensatory mechanisms against the increase in BP

Conclusions: Our results highlight the underlying and compensatory renal mechanisms for the hypertension that developed in mice with either kidney-restricted or globally expressed *GRK4 65R>L*.

Funding: NIDDK Support

FR-PO955

The Differential Expression Research of Circular RNAs in Exosomes from Serum and Urine in Systemic Lupus Erythematosus Patients

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Background: To further explore the pathogenesis of SLE, the technique of gene-sequencing was used to analyze the differentially expressed circular RNAs (circRNAs) in exosomes both from serum and urine of patients with SLE, which may lay the foundation for the research of circRNAs as a new class of exosome-based SLE diagnosis biomarkers.

Methods: Ten patients with SLE (SLE group) and ten normal controls (NC group) were recruited as experimental subjects in our research. The serum and urine were separated from each participant's peripheral venous blood and early morning urine, which the exosomes were extracted from the collected serum and urine by the ExoQuick Exosome Precipitation Solution and ultracentrifugation. Then the pure circRNAs were extracted from the exosomes with a series of enzymatic reactions. And then, the significantly differentially expressed circRNAs were picked out by the method of gene-sequencing to analyze the function of corresponding target genes.

Results: Compared with normal controls, the species of circRNAs were reduced in the exosomes from serum of patients with SLE, which were mostly originated from intron gene regions; Meanwhile, a total of 121 circRNAs were significantly differentially expressed, which were also mostly derived from intron gene regions, including 54 up-regulated and 67 down-regulaed. But the species were increased in the exosomes from urine of patients with SLE compared with normal controls, and which were mainly originated from intron gene regions; Simultaneously, a total of 14 circRNAs were significantly differentially expressed, which were primarily belonged to intron gene regions, including 7 up-regulated and 7 down-regulaed. Compared with the circRNAs detected from urinary exosomes, a total of 52 circRNAs were significantly differentially expressed in the exosomes from serum of patients with SLE, which were also mostly originated from intron gene regions, including 45 up-regulated and 7 down-regulaed.

Conclusions: The significantly differential and specific expression of circRNAs in the exosomes from serum and urine of patients with SLE were found. Such as gene snoU13, SNORA31 and SNORA51 could be regarded as potential diagnostic biomarkers of SLE. Furthermore,these figures suggested that the significantly differentially expressed circRNAs can be used as a reference or a supplement in the research of the pathogenesis of SLE.

FR-PO956

Proteomics of Human Glomerulonephritis by Laser Microdissection and Liquid Chromatograph-Tandem Mass Spectrometry (LMD-LC MS/MS)

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Background: Laser microdissection and liquid chromatograph tandem mass spectrometry (LMD-LC MS/MS) methods enable us to analyze the proteins from the tissue sections. In nephrology, they are preferentially applied in the diagnosis of abnormal protein deposition diseases, such as amyloidosis. In this study, we applied this method to the renal biopsy specimens obtained from the patients with IgA nephropathy(IgAN) and idiopatic membranous nephropathy(MN) to investigate its usefulness for the diagnosis and pathophysiological understanding of human glomerular diseases.

Methods: The 0.3mm^2 of glomerular tissue were dissected by LMD from 10μm-thick sections of renal biopsy specimens obtained from five patients with IgA nephropathy, membranous nephropathy and kidney transplant donor, respectively. The samples were analyzed by LC-MS/MS and the results were investigated to clinical and histological findings.

Results: From the control glomeruli, more than 300 types of proteins such as cytoskeleton proteins, nuclear related proteins, Extracellular Matrix(ECM) related proteins and enzymes were identified. In addition to IgA1 and C3, IgAN showed significant increases in the factors related to oxidative stress and cell proliferation, such as heat shock protein 70/71/90, peroxiredoxin, and elongation factor 1α, as compared to controls. In MN, the proteins such as IgG1, IgG4, C3, C4a, and phospholipase-A2-Receptor(PLA2R) were significantly elevated compared to controls.

Conclusions: By applying LMD-LC MS/MS method to renal biopsy specimens, it was possible to identify the pathognomonic proteins for the diagnosis of IgAN and MN as well as immunohistochemistry. Furthermore, we identified the several factors involved in the pathogenesis of glomerular diseases. Although further investigation is necessary, it seems that the proteomics of glomerular proteins analyzed by LMD-LC MS/MS is a promising method for the diagnosis and pathophysiological understanding of human glomerulonephritis.

FR-PO957

JNK-Associated Leucine Zipper Protein (Jlp) Protects Against Renal Fibrosis by Counteracting TGF-Beta1-Induced Profibrotic Effects and Autophagy on Renal Tubular Epithelial Cells

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Background: Renal fibrosis is a process involving a wide range of cells and molecules and is controlled by both profibrotic and antifibrotic forces. TGF-β1 has been identified as the primary driver of renal fibrosis, but direct targeting TGF-β1 in clinical trials has yielded no promising therapeutic effects. In this study, we identified the JNK-associated leucine zipper protein (Jlp) as a novel endogenous antifibrotic factor.

Methods: We studied the role of JLP in regulating the progress of renal fibrosis in vivo using the UUO mice model with jlp wildtype, jlp deficient, as well as jlp overexpression genotype, and explore the molecular mechanism in vitro on the tubular epithelial cells.

Results: We found that Jlp was predominantly expressed in renal tubular epithelial cells (TECs) in human or mouse kidneys in normal conditions, whereas Jlp was downregulated in fibrotic kidneys, including in kidneys of unilateral ureteral obstruction (UUO) mouse model and in kidneys of advanced CKD patients. In UUO mouse model, global or TECs-specific deletion of Jlp resulted in more severe lesion of kidney fibrosis, whereas TECs-specific transgenic expression of Jlp brought about the beneficial effects of fibrosis resistance. The protective role of Jlp in renal fibrosis could be ascribed to its potentials of overall counteracting the profibrotic effects induced by TGF-β1 through negatively regulating TGF-β1 expression, counteracting TGF-β1 induced ECM production, epithelial-to-mesenchymal transition (EMT), apoptosis, cell cycle arrest, and autophagy in TECs. The protective effects of Jlp could be compromised by its downregulation mediated by TGF-β1 and FGF-2 but not the inflammatory factor TNFα, implying that kidney fibrosis is a consequence of unbalanced forces of profibrotic factor TGF-β1 and FGF-2 and antifibrotic factor Jlp.

Conclusions: JLP is a novel endogenous antifibrotic molecule in renal fibrosis.

FR-PO958

A Novel Conductive Polymer-Based Biosensor for Ultrasensitive Detection of Biomarkers in Lupus Nephritis

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Background: Lupus is a systemic autoimmune disease that immune system can attack the organs and tissues, partiuclarly kidney causing highly mortality and co-morbidity. Unfortunately there is not a non-invasive diagnostic tool for lupus nephritis (LN). Recent studies have shown that urinary biomarkers are promising in LN diagnosis. However, since the concentration of biomarkers in urine sample is low, most the current assays are not optimial in detecting specific urinary biomarkers for LN due to their low sensitivity.

Methods: In this study, we developed a novel biosensor based on human thrombin aptamer-functionalized conductive gel-nanoparticle with poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) nanowires which could capture and concentrate low-abudant biomarkers, causing a binding-induced shrinkage of the gel nanoparticles, which could lead to a conductance change of the biosensor and subsequent signal amplification.

Results: By using Atomic-force microscopy (AFM), the topography and height profiles of the polymeric sensor were recorded and to analyze polymeric network shrinkage in response to PBS or Thrombin. Urinary thrombin levels were quantitatively analyzed through monitoring the conductance change caused by polymeric network shrinkage upon the aptamer-thrombin binding. A significant shrinkage of 18.14% of the biosensor was observed after biomarker recognition. The limit of detection (LOD) of the conductive gel-nanoparticle biosensor for human urine thrombin sample could reach 4.82×10^{-16} M. This thrombin-specific biosensor and a commercial human thrombin enzyme linked immunosorbent assay (ELISA) kit were used to perform side-by-side measurement of urinary thrombin in LN samples. The result obtained from the same patient using sensor or ELISA were used for pair test of correlation, and a strong correlation with a R^2 value of 0.97 was found between the sensor and ELISA. The results indicate that this conductive gel-nanoparticle biosensor is highly sensitive and selective in accurately differentiate LN from healthy controls using urinary thrombin as a biomarker ($P < 0.001$).

Conclusions: Collectively, this novel ultrasensitive conductive gel-nanoparticle biosensor may hold promise in biomarker detection and diagnosis of LN.

Funding: Other NIH Support - NIA support

FR-PO959

Deficiency of the Atypical Chemokine Receptor 2 (ACKR2) Accelerates Progression of Nephrocalcinosis-Related CKD

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Background: Primary and secondary hyperoxaluria lead to deposition of calcium oxalate crystals in the kidney, i.e. nephrocalcinosis. Calcium oxalate-induced necroinflammation is an important mechanism of kidney injury in nephrocalcinosis. The atypical chemokine receptor 2 (ACKR2) is a chemokine decoy receptor expressed in the tubulointerstitium, which scavenges inflammatory CC-chemokines and reduces renal inflammation in chronic kidney disease models. We therefore hypothesized that ACKR2 limits renal inflammation and fibrotic tissue remodeling in nephrocalcinosis-related chronic kidney disease and slows progression to end-stage renal failure.

Methods: Chronic oxalate nephropathy was induced in wild-type and Ackr2-deficient (Ackr2-/-) mice by feeding an oxalate-rich and calcium-depleted diet. Renal functional decline was monitored by measurement of glomerular filtration rates in weekly intervals until day 14. Renal injury, inflammation and fibrosis were assessed at day 14.

Results: Compared to wild-type, Ackr2-/- mice showed increased mortality following induction of oxalate nephropathy. Renal function declined more rapidly in Ackr2-/- mice, leading to end-stage renal failure until day 14. Tubular injury was worse in Ackr2-/- mice. Tubulointerstitial infiltrates of granulocytes and mononuclear phagocytes, but not T cells increased in Ackr2-/- kidneys. Moreover, Ackr2 deficiency aggravated renal inflammation, with increased expression of the inflammatory chemokine CCL2 and enhanced accumulation of CCR2+ inflammatory macrophages. Renal expression of annexin II and CD44, which mediate adhesion of calcium oxalate crystals to tubular epithelial cells, was increased in Ackr2-/- mice. This may contribute to more extensive crystal deposition present in Ackr2-/- kidneys despite comparable calciuria and oxalate levels to wild-type. More severe renal injury and inflammation in Ackr2-/- mice was paralleled by aggravated renal fibrosis, as revealed by increased expression of extracellular matrix molecules, renal accumulation of myofibroblasts and enhanced infiltration of bone marrow-derived fibrocytes.

Conclusions: This data suggest that ACKR2 limits renal inflammation, calcium oxalate deposition, tubular injury and renal fibrosis in nephrocalcinosis, and thus slows progression to end-stage kidney disease.

Funding: Government Support - Non-U.S.

FR-PO960

Assessment of Urinary Microparticles in Aristolochic Acid-Induced Nephropathy in Wild-Type and GPR40 Receptor Knockout Mice

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Background: Urinary microparticles (MP) are novel non-invasive biomarkers of renal injury. However, the dynamics of MP release in AKI/CKD are not well understood. We questioned whether urine MPs are generated early in disease and how their levels change as disease progresses. Lastly, we determined whether urine MP levels are altered in mice with deletion of the protective, anti-fibrotic Gpr40 receptor.

Methods: 8 week-old male [wild type (WT) or Gpr40$^{-/-}$] mice were subjected to aristolochic acid nephropathy (AAN) via four consecutive daily injections (3.5mg/kg, ip). Renal function was assessed by plasma creatinine measured (HPLC) at days -4, 4, 11 and 28 days post-AAN. At endpoint, tubulointerstitial injury was assessed histologically. Total urine MPs were measured using nanoparticle tracking analysis (NTA) and nanoscale flow cytometry. Podocyte derived MPs (Annexin V^{+}/Podoplanin^{+}) were quantified by flow cytometry. Finally, mouse proximal tubule epithelial cells (PTECs) were treated with aristolochic acid (50 μM) and formation of MPs was quantified by NTA.

Results: AAN was associated with albuminuria, decline in renal function and anemia. NTA and flow cytometry revealed that both total and podocyte-derived MPs were increased at day 4 and progressively decreased until day 28. The drop in MP levels were associated with tubular interstitial fibrosis, tubular dilatation and inflammatory cell infiltration. At endpoint, plasma creatinine was significantly increased in Gpr40$^{-/-}$ vs. WT mice and this was associated with higher levels of total MPs (P<0.05 at day 4). Finally, PTECs treated with AA exhibited a ~3-fold increase in MP formation at 24h (P=0.01).

Conclusions: Taken together, our data suggest that the dynamics of MP release by glomerular and tubular cells changes according to the progression of kidney disease. Gpr40 deletion is associated with increased early MP levels and impaired function at endpoint. The increased early MP levels may be indicative of greater injury compared with WT leading to increased functional decline.

Funding: Government Support - Non-U.S.

FR-PO961

RNA Sequencing in Proximal Tubule Cells Reveals Lack of Expression of Proximal Tubule Markers

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Background: There are close to 12 different immortalized cell lines available commercially or from other sources that are being used as models of renal proximal tubule cells. There is strong need to characterize these cells so as to establish their lineage and help the scientific community at large to make decisions regarding their suitability in experiments. Our goal is to characterize the cell lines using RNA-Seq.

Methods: To accomplish this goal, we grew 5 different human cell lines, one mouse, three rat, and 2 opossum kidney cell lines on Transwell filters using the recommended culture media. RNA-Seq was performed using Illumina kits following the manufacturer's protocol. The RNA-Seq was compared to a mouse S1 proximal tubule data. The data are presented as expression rank with the rank above 8000 as negative expression. To validate the data a native S1 proximal tubule cell line was used as a positive control.

Results: Results are shown in the Table.

Conclusions: Our data suggest that the available human and rat kidney tubule cells are epithelial cells (express occludin and claudins) but not of proximal tubule origin (lack sodium-dependent transporters, megalin and PTH receptor). Although, LLC-PK1 cells express the proximal tubule specific proteins, they also express markers of cortical tubule cells. These are therefore a mixed population and not specific proximal tubule cells. The opossum kidney cells express all the markers of proximal tubule cells and thus are the only cell of proximal tubule origin.

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Expression of proximal tubule markers

Gene Symbol	Slc5a1	Slc5a2	Slc9a3	Slc9a3r1	Slc34a1	Slc34a3	LRP2	Cldn1	Ocln	Pth1r	Avpr2
Common Name	SGLT-1	SGLT-2	NHE-3	NHERF1	NpT2a	NpT2c	Megalin	Claudin-1	Occludin	PTH Receptor	ADH Receptor
HKC-8	23754	12420	11915	915	23101	21580	21088	7427	5404	10798	21540
HKC-11	23754	14916	11222	1132	20077	23361	23028	7111	5166	10876	13060
HPTC-05-LTR	26753	11907	11703	997	26394	22534	25448	2696	9864	14722	25600
HPTC-05-CLA	27910	16403	11539	1124	22617	25157	25060	3526	11059	16557	25237
HK-2	21749	13130	12915	2924	19159	21019	21016	1473	15373	13575	26872
LLC-PK1	6036	7352	12612	455	3799	8342	2051	291	1371	14205	5507
Rat-SHR	16226	12143	15823	532	15830	14207	27648	2087	2424	13350	12977
OK-WT	683	6624	9106	743	1088	5677	2188	1209	12708	783	No Expression
OK-H	13464	3727	9886	2145	6831	13461	4829	1279	12135	2064	No Expression

FR-PO962

Tacrolimus Ameliorates Podocyte Injury by Restoring FK506 Binding Protein 12 (FKBP12) at Actin Cytoskeleton in Injured Podocyte

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Background: FKBP12 was identified as a binding protein of Tacrolimus (Tac). Tac binds to FKBP12 and exhibits immunosuppressive effect through inhibition of calcineurin (CN) activity in T cells. It is reported that Tac treatment directly ameliorates the dysfunction of podocyte by inhibiting the activation of NFAT, a substrate of CN in nephrotic syndrome. We reported that FKBP12 is expressed in glomerular podocyte and the altered expression of FKBP12 is involved in the development of podocyte injury. However, the precise pharmacological mechanism of Tac in podocyte injury was not well understood yet.

Methods: The protein expression of FKBP12 was investigated with western blot and the localization was analyzed with dual label immunostaining in human cultured podocytes. The localization of NFATC3 was also investigated.

Results: FKBP12 was detected both in cytoplasm and along actin cytoskeleton in normal human cultured podocytes. These FKBP12 stainings were decreased in the cultured podocytes treated with Adriamycin (ADR). Tac treatment restored the FKBP12 at actin cytoskeleton. The expression of FKBP12 at the actin cytoskeleton was increased by the Tac treatment to normal cultured podocytes. The western blot analysis showed the protein expression of FKBP12 was decreased in the podocytes with ADR (43.9% to normal, P<0.005). Tac treatment suppressed the decrease (80.5%). The FKBP12 expression of the cells treated with Tac only was 78.7%. NFATC3 staining in nucleus was increased in the podocytes with ADR. Tac treatment partially reduced the nuclear accumulation of NFATC3 in the ADR-treated cells. 27.5% of the cells showed multiple processes with positive actin staining in normal cultured podocytes. The proportion of the cells forming the processes to total cells was decreased in the podocytes treated with ADR (17.5%, P<0.05 vs. normal). Tac treatment suppressed the decrease in ADR (38.1%, P<0.05 vs. no treatment). Tac treatment to normal cells increased the proportion of the cells forming processes (55.7%, P<0.005 vs. normal).

Conclusions: The proper localization of FKBP12 at the actin cytoskeleton participates in the maintenance of process formation. Tac treatment ameliorates podocyte injury by restoring FKBP12 at actin cytoskeleton in injured podocyte.

Funding: Government Support - Non-U.S.

FR-PO963

Expression of Acsm2, a Kidney Specific Gene, Parallels the Structural and Functional Maturity of Proximal Tubular Cells

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Background: Acyl-CoA synthetase medium-chain family member 2 (Acsm2) gene was first identified and cloned by our group as a kidney specific "KS" gene. Acms2 may participate in fatty acid metabolism and glycine conjugation pathways. However, little has been reported on *Acsm2*, and the expression pattern and function of it remain to be clarified.

Methods: The expression pattern of *Acsm2* was investigated with RT-PCR using RNA extracted from multiple organs of adult C57BL/6 mice and kidneys at multiple age. Immunohistochemistry for Acsm2 was performed in kidney or liver tissue sections. *In situ* hybridization was performed using digoxigenin-labeled RNA probes for mRNA of *Acsm2*. We also investigated the kidneys from mice subjected to partial unilateral ureteral obstructions (pUUO) and chronic kidney disease (CKD) with total renin gene knockout or conditional knockout of integrin beta 1 gene in cells from the renin progeny using aforementioned methods. Data from the Encyclopedia of DNA Elements (ENCODE) project was analyzed to examine the epigenetic state at *Acsm2* locus in each organ of mice.

Results: We found that *Acsm2* was expressed in the kidney samples at high level. The expression of *Acsm2* in the liver was less than 1/10,000 of the expression in the kidney. No other organs tested expressed *Acsm2*. Immunohistochemistry and *in situ* hybridization revealed that *Acsm2* was highly expressed in the proximal tubular cells in normal adult mice. In contrast, Acsm2 was not detected in liver. The expression level of *Acsm2* in kidneys was at a low level in newborn mice, increased with development, and reached a plateau by 2 months of age. With pUUO and CKD, the expression of *Acsm2* in the proximal tubules was significantly decreased according to the severity of the renal impairment. Analysis using ENCODE database revealed that *Acsm2* locus in mice has specific histone modifications that are related to the active enhancer and promoter and transcription only in kidney cells.

Conclusions: The Acsm2 gene is specifically expressed in proximal tubules, and not in other tissues. The expression of *Acsm2* parallels the structural and functional maturation of proximal tubular cells. Downregulation of its expression in several models of kidney disease suggests that *Acms2* may serve as a novel marker of proximal tubular injury and/or dysfunction.

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FR-PO964

Total Extracts of Single Chinese Medicine Herb Attenuates Renal Tubule Injury via Suppression of ERK1/2-Mediated NLRP3 Inflammasome Activation

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Background: *Abelmoschus Manihot* (Linnaeus) Medik. is an herb used in traditional Chinese medicine to treat some kidney diseases. The chemical constituents in the plant are mainly flavonoids, organic acids, steroids and volatile compounds. Five flavonoids, hyperoside, myricetin, quercetin, isoquercitrin, and rutin, have been determined to be the major pharmacologically bioactive components via high-performance liquid chromatography (HPLC) that simultaneously quantifies the flavonoid compounds of *Abelmoschus Manihot* L. flower. To date, the detailed mechanisms by which *Abelmoschus Manihot* L. improves some kinds of renal disease are not fully understood. Our previous study showed that *Abelmoschus Manihot* L protects podocyte and reduce proteinuria *in vivo*.

Methods: In this study, we established Adriamycin-induced NRK-52E cells, the normal rat kidney epithelial cell line, and Sprague-Dawley rats with Adriamycin-induced nephropathy to evaluate the role and mechanisms of total extracts of *Abelmoschus Manihot* L. flower (TEA) on tubular cell both *in vitro* and *in vivo*.

Results: In Adriamycin-induced nephropathy rat model, TEA decreased proteinuria and attenuated renal tubule lesions. Interestingly, NLRP3 was increased mostly in tubule not in glomeruli and TEA inhibited the expression of NLRP3 in tubules. In vitro study, TEA ameliorated Adriamycin-induced cellular morphological changes, cell viability, and apoptosis through the suppression of protein oxidation and ERK1/2 signaling. However, this anti-oxidative stress role of TEA was independent of ROS inhibition. Adriamycin activated ERK1/2 signaling followed by activation of NLRP3 inflammasomes. TEA suppressed NLRP3 inflammasomes via inhibition of ERK1/2 signal transduction.

Conclusions: TEA protects renal tubular cells against toxity of Adriamycin via inhibition of ERK1/2-NLRP3 inflammasomes.

Funding: Government Support - Non-U.S.

FR-PO965

High-Throughput Determination of Aminoglycoside Antimicrobials in Human Plasma by Hydrophilic Interaction Liquid Chromatography Mass Spectrometry

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Background: Aminoglycoside antibiotics can cause acute kidney injury (AKI) due to tubular necrosis in a dose-dependent manner. Therefore, a qualitative and quantitative method for determining AG antibiotics in blood must be useful in prevention of AKI.

Methods: We developed a simple and rapid method for the analysis of six AG antibiotics, such as streptomycin, ribostamycin, kanamycin, amikacin, dibekacin, and arbekacin, in human plasma samples by hydrophilic interaction liquid chromatography (HILIC)-tandem mass spectrometry (MS/MS). Each sample was 50μl of plasma.

Results: All drugs showed base peaks due to [M+H]+ ions by HILIC-MS with positive ion electrospray ionization, and the product ions were produced from each [M+H]+ ion by HILIC-MS/MS. Quantitation was performed by selective reaction monitoring using each base peak of product ions of HILIC-MS/MS. Good peak shapes of the six drugs were achieved within an analysis time of 1.4 min. All drugs spiked into plasma showed recoveries of 23-77% and extraction efficiencies of 72-105%. The regression equations for the antibiotics showed excellent linearity with the limits of quantitation of 3.9-16 μg/ml. The intra- and inter-day relative standard deviations for all drugs were not greater than 19%. The accuracies of quantitation were 80-114%. Streptomycin and kanamycin in human plasma after intramuscular administration of the drugs could actually be determined.

Conclusions: A simple and rapid method was developed for the analysis of six AG antibiotics in human plasma by HILIC-MS/MS. This method seem to be useful for determining AG antibiotic residues in the edible tissues of livestock in addition to human plasma. therefore, it will be widely used in patients with kidney dysfunction *who need administration of AG.*

FR-PO966

A Modified Ellipsoid Formula for Estimating Total Kidney Volume

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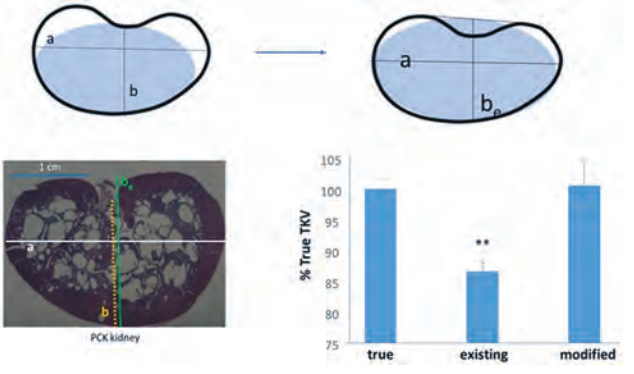
Background: Total kidney volume (TKV) informs progression of polycystic kidney disease, enables matching of donor organ to recipient, and surgical management of kidney tumors. The existing ellipse-based formula underestimates TKV by as much as 30%. We have reported (https://doi.org/10.1371/journal.pone.0190815) a modified ellipse-based formula to better estimate renal parenchymal area by extending the minor axis to the renal hilum. We sought to determine whether this modified formula better informs TKV.

Methods: PKC and Sprague-Dawley rats were used as kidney donors. True TKV was determined by the formalin displacement method. Renal thickness (t) was measured by a pair of Vernier calipers. Kidneys were then cut coronally and photographed. Treating the coronal section as an ellipse, the major axis (a), the minor axis (b) and the extender minor axis (b_e) were measured. TKV was calculated by entering t, a and b or b_e into an ellipsoid formula.

Results: Compared to true TKV, use of the existing formula underestimated calculated TKV by 14% (n=6, **, p<0.01). By contrast, there was no difference between true TKV and TKV calculated using the modified formula.

Conclusions: Use of a modified ellipsoid formula more accurately estimates TKV and has important ramifications for clinical management of polycystic kidney disease, kidney transplant, and surgical resection of renal tumors.

Funding: Private Foundation Support



Treating the kidney as an ellipse and extending the minor axis into the hilum provides a better estimate of renal dimensions. The existing formula underestimated TKV significantly in healthy and PKC rats whereas use of the modified formula provided an estimate of TKV no different than true or measured TKV.

FR-PO967

Kidney Injury Enhances Renal Granulocyte-Colony Stimulating Factor Expression, Granulopoiesis, and Human Neutrophilic Granulocyte Proteinase 3 Receptor CD177 Expression

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Background: Acute kidney injury causes significant systemic adverse events beyond retention of uremic waste and volume expansion, mechanisms of which are incompletely understood. Neutrophilic granulocytes, the most abundant human blood leukocytes, are characterized by a high turnover rate. They are chiefly controlled by granulocyte colony stimulating factor (G-CSF), which can be produced by diverse cell types. The impact of kidney injury on G-CSF production and granulopoiesis has not been determined.

Methods: Renal G-CSF expression in murine experimental kidney injury and after human kidney transplantation was assessed by immunostaining and qPCR. Neutrophils were characterized by flow cytometry in mice with experimental kidney injury, patients with chronic kidney disease, before and after kidney transplantation and in healthy controls. Human cell culture was employed for mechanistic experiments.

Results: In murine experimental ischemia reperfusion injury and unilateral ureteral obstruction, renal G-CSF mRNA and protein increased and characteristics of emergency granulopoiesis developed in bone marrow and blood. In humans, G-CSF and kidney transplantation similarly transiently elevated human neutrophil expression of CD177, a highly G-CSF responsive neutrophil gene. In kidney graft recipients, the rise in CD177 correlated with renal tubular G-CSF expression. In contrast, CD177 was unaltered in patients with chronic renal impairment independent of renal replacement therapy. As possible underlying mechanisms, hypoxia and proinflammatory cytokine interleukin 17A enhanced G-CSF expression in human renal tubular epithelial cells, while complement activation promoted G-CSF in endothelium.

Conclusions: Our data demonstrate induction of renal G-CSF and modulation of granulopoiesis after kidney injury. They delineate differential G-CSF regulation in renal epithelium and endothelium. Altered granulopoiesis may contribute to the distant effects and possibly prognostic role of kidney injury.

Funding: Government Support - Non-U.S.

FR-PO968

Integration of Spatial Metabolomics to Single-Nucleus Droplet-Based Sequencing Data Identifies New Glomerulus-Specific Gene Markers

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Background: The current study is a part of the NIDDK Kidney Precision Medicine Project (KPMP). We recently cross-validated that a sphingomyelin (SM(d18:1/16:0)) was a glomerulus-enriched marker, as visualized by two independent sites using matrix-assisted laser desorption/ionization-mass spectrometry imaging (MALDI-MSI). To establish integration of data with other Tissue Interrogation Sites (TIS) and technologies, we provided a tabulated list of 48 SM/ceramide metabolism-related gene/enzymes (from KEGG Ontology Database) to results from other TIS sites.

Methods: Two MALDI-MSI platforms (QE-HFX at UTHSA and FTICR at PNNL) were employed to spatially characterize the lipid profile in normal human kidney tissues (n = 6; U. Michigan) at 20-30 μm spatial resolution. 30 different cell types were identified using the single-nucleus droplet-based sequencing (snDrop-Seq) analysis developed by the UCSD-WashU TIS and the SM/ceramide genes were queried across the database. Enrichr software and the Database of Genotypes and Phenotypes (dbGaP) were used for enrichment analysis.

Results: *PLPP3*was identified as one of the few glomerular endothelial cell specific genes and can be added as a gene marker to KPMP Atlas. Furthermore, *PLPP1*was found to be localized to the glomerular endothelial cells and to endothelial cells of AEA and descending vasa recta. Fluorescence microscopy analysis showed that PLPP3 protein is localized within glomeruli but separated from synaptopodin (a podocyte marker). Further enrichment analysis using Enrichr and dbGaP showed that the identified glomerular specific genes are associated with carotid stenosis, diabetic nephropathies, and other phenotypes.

Conclusions: This highlights the value of the untargeted mass spectrometry imaging for linking the spatial metabolomic data to different kidney cells types, and an avenue connect metabolic information to gene expression. Integrated MALDI-MSI and snDrop-Seq data could help identify novel glomerular-specific gene markers.

Funding: NIDDK Support

FR-PO969

Protein Phosphatase Mg^{2+}/Mn^{2+}-Dependent 1A (PPM1A) and PTEN Deregulation in Kidney Fibrosis: Novel Mechanisms and Co-Dependency of Expression

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Background: PPM1A and PTEN emerged as novel suppressors of the TGF-β1 pathway during renal disease. Loss of PPM1A and PTEN, following obstructive renal injury, promoted tubular dysfunction as evident by fibrotic factor deposition, epithelial dedifferentiation and cell cycle arrest. However, the molecular mechanism of PPM1A deregulation in renal fibrosis is unknown. We hypothesize that TGF-β1 orchestrates PPM1A loss of expression and that there is functional collaboration between PPM1A and PTEN during progressive fibrosis.

Methods: A double transgenic mouse model of conditional TGF-β1 renal tubular upregulation (created by crossing Pax8-rtTA with Tet-O-TGF-β1 mice and subsequent doxycycline administration) and the TGF-β1-driven aristolochic acid nephropathy (AAN)-induced renal fibrosis system were employed to determine the role of TGF-β1 in PPM1A deregulation. Human renal epithelial cells (HK-2) and primary kidney fibroblasts (HKFs) with stable PPM1A and PTEN expression or depletion were created to investigate the potential functional interplay among TGF-β1, PPM1A and PTEN.

Results: Renal tubular-specific upregulation of TGF-β1 resulted in tubulointerstitial loss of PPM1A expression 2-3 days post-doxycycline administration in mice. TGF-β1 dramatically attenuated PPM1A and PTEN expression in both HK-2 cells and HKFs via mechanisms involving protein degradation. TGF-β1 promotes ubiquitination of PTEN and PPM1A. A proteasomal inhibitor, MG132 rescued PTEN and PPM1A expression, even in the presence of TGF-β1, along with decreased fibrogenesis. Concurrent loss of PPM1A and PTEN expression in a mouse model of AAN further suggests crosstalk between these repressors. PPM1A stable silencing in HKFs, in fact, resulted in PTEN loss, while PTEN stable depletion decreased PPM1A expression, resulting in a fibro-proliferative response in each case. Transient expression of PPM1A, conversely, increased PTEN protein levels, while PTEN transient induction led to elevated PPM1A expression.

Conclusions: TGF-β1 promotes loss of PPM1A and PTEN expression *in vitro* and *in vivo*. We are the first to uncover the pathological functional cooperation between PPM1A and PTEN as they co-regulate each other's relative abundance, identifying previously unknown links between TGF-β1-repressors in progressive renal injury and CKD.

Funding: Other NIH Support - NIH-GMS, Private Foundation Support

FR-PO970

The Spectrum of Renal Involvement in Four Murine Models of Multiple Myeloma

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Background: Approximately 20-50% of multiple myeloma involves kidneys, and additional ~38% of monoclonal gammopathy involves kidney (MGRS). The renal manifestations range from tubulopathies to a spectrum of glomerular diseases that can present with varying degrees of proteinuria and renal dysfunction, to amyloidosis and myeloma cast nephropathy. Although several mouse models of multiple myeloma have been reported, the studies of murine models of myeloma-associated kidney diseases are rather limited.

Methods: We examined renal pathology of four murine models of multiple myeloma (MM): First, mice carrying a human IL-6 Tg driven by the major histocompatibility complex H2-Ld promoter (IL-6), Second, IL6-Tg with concomitant Tg of i-Myc with deregulated expression of the Myc oncogene and enhancers in the IgH locus (designated i-Myc/IL6), Third, IL6-Tg with concomitant Tg of pro-survival oncoprotein Bcl2 (designated Bcl2/IL6), Fourth, xenograft model with mouse myeloma cells injected into KaLwRij strain mice.

Results: All four models of MM demonstrated M-spike paraproteinemia. The presence of second transgene in the IL6-Tg background significantly accelerated and aggravated the tumor burden and progression of MM, which developed at 3-6 months, characterized by paraproteinemia, marked splenomegaly and bone involvement. Light-chain restricted casts with variable acute tubular injury resembling cast nephropathy was present in 50-75% of IL6, i-Myc/IL6 and in Bcl2/IL6 mice. Features suggestive of light chain tubulopathy were present in ~25-50% of these three models. Various glomerular deposits were identified in ~50% of Bcl2/IL6 and ~80% of i-Myc/IL6, but not in the IL6 mice. The spectrum of glomerular involvement ranged from light chain deposition disease to intracapillary paraprotein plugs resembling cryoglobulin or crystalglobulin glomerulopathy. Surprisingly, the xenograft model did not show any significant paraprotein nephropathy, however, myeloma cells infiltration of renal tissue was observed in ~30% of xenograft model. Amyloidosis is not identified in any of the mouse models.

Conclusions: Transgenic IL6 mice develop various paraprotein-associated nephropathies and may serve as good preclinical models of myeloma-associated kidney diseases, to study the molecular pathogenesis and to develop nephroprotective strategies for myeloma-associated kidney diseases.

Funding: Other NIH Support - K08

FR-PO971

The Mechanisms of Gadolinium-Based Contrast Agent-Induced Nephrotoxicity

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Background: *All classes of gadolinium-based contrast agent* (GBCA) *are nephrotoxic*. This is well accepted from case reports, prospective studies, and prescriber information sheets.

Methods: Generation of chimeric transgenic mice provided a means of tracing myeloid-derived cellularity in the target organs. Groups were randomized to GBCA treatment versus none. Kidney sections were examined with a Hitachi HT7700 with an AMT 16 megapixel camera *and* a Jeol JEM 2010F field emission electron microscope at 200 kV with a GATAN Orius camera and Oxford Analytical ISIS energy-dispersive spectrometer (EDS).

Results: GBCA exposure caused significant renal fibrosis and podocyte injury associated with elevations in plasma creatinine *and* metabolic disorders as evidenced by dyslipidemia. Metabolomic analysis of flash-frozen renal cortex demonstrated that GBCA treatment—*far from being inert*—resulted in glycolytic switching—the Warburg effect—where glycolysis and lactate accumulation *increased* with suppression of the tricarboxylic acid cycle. In the treated group, the electron-dense deposits riddled the glomeruli and vacuoles of proximal tubular cells. By EDS, these contained high quantities of gadolinium ($P < 0.01$), calcium ($P < 0.01$), and phosphate ($P < 0.05$).

Conclusions: We provide the first evidence that GBCAs cause significant metabolic disorders and kidney injury in mice without pre-existent renal insufficiency. Accumulation of non-physiologic lanthanide heavy metals may be leaching phosphorous from lysosomal membranes, catalyzing the formation of calcium phosphates, and thwarting cellular energetics in this manner.

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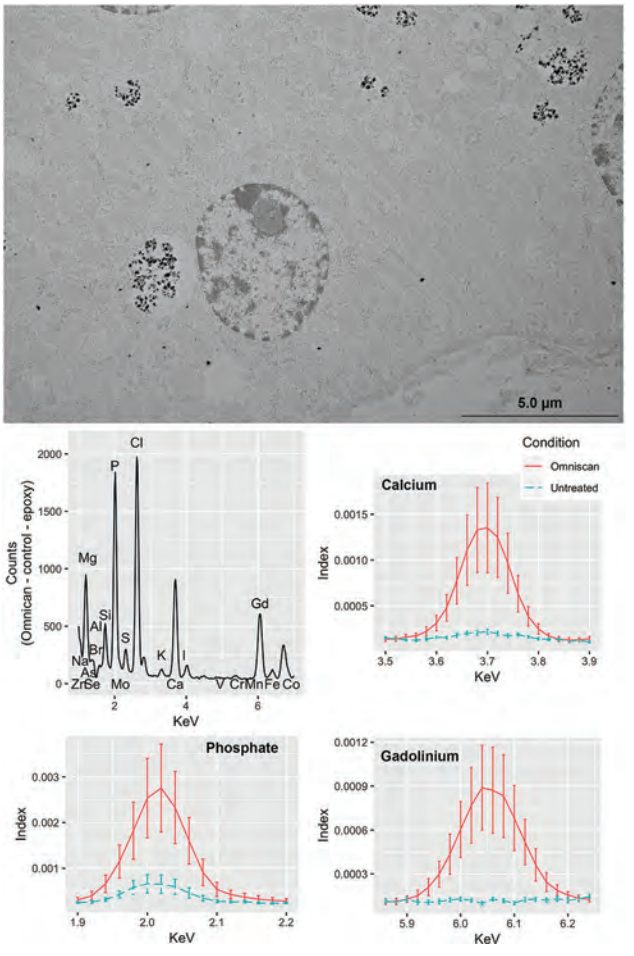

Transmission electron microscopy of proximal tubule (top) laden with electron-dense material. Energy-dispersive x-ray spectroscopy of the electron densities minus control and normalized counts in regions for gadolinium, calcium, and phosphate.

FR-PO972

CTGF/CCN2 Knockdown Prevents AKI-Induced Cellular Senescence and Subsequent Fibrosis

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Background: Acute kidney injury (AKI) involves damage to the tubular epithelium with subsequent accumulation of senescent cells and can progress to fibrosis and chronic kidney disease (CKD). Cellular senescence is characterized by anti-apoptotic and DNA Damage Response (DDR) features, and expression of a Senescence Associated Secretory Phenotype (SASP). Connective Tissue Growth Factor (CTGF/CCN2) is a constituent of the SASP and has been implicated in fibrosis as well as in (paracrine) senescence induction. Therefore we explored the involvement of CTGF and cellular senescence in two models of AKI and subsequent CKD development.

Methods: We subjected wild type (WT) and conditional tamoxifen inducible CTGF-KO mice (CTGF-cKO) to bilateral ischemia reperfusion injury (IRI) and to folic acid (FA) renal injury and studied damage parameters in relation to anti-apoptotic signaling and cellular senescence in the acute and chronic phase of both models.

Results: In WT mice, both IRI and FA induced AKI resulted in upregulation of DDR and anti-apoptosis markers, including yH2Ax, $p21^{CIP1}$ (p21) and the BCL-2 family members BCL-xL and MCL-1. This effect persisted largely in the chronic phase, during which also the expression of $p16^{INK4a}$ together with CTGF and other SASP factors like PAI-1, IL-1β, and IL-6 became markedly upregulated. Furthermore, CTGF expression levels correlated with senescence phenotype, including anti-apoptotic BCL-xL and MCL-1 in the acute phase, SASP factors like PAI-1, IL-1β and IL-6 in the chronic phase, and p21 in both phases. CTGF knockdown protected against acute tubular injury and functional decline in the initial phase of both injury models. Furthermore, DDR- and anti-apoptotic marker expression (p21 and MCL-1) were lower in CTGF cKO than in WT mice. Likewise, in both models tubular atrophy, interstitial fibrosis and functional decline in the chronic phase were less severe in CTGF cKO mice, together with reduced expression of senescence (p21 and MCL-1) and SASP markers (PAI-1, IL-1β and IL-6).

Conclusions: CTGF/CCN2, beyond its known profibrotic role in CKD, is also involved in AKI, possibly by modulating apoptotic and cellular senescence associated pathways. We propose that inhibition of CTGF might be beneficial in AKI and diminish AKI to CKD progression.

FR-PO973

Detection of Urinary MicroRNA Biomarkers Using Diazo Sulfonamide-Modified Screen Printed Carbon Electrodes

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Background: We have established RT-qPCR-based protocols for urinary microRNA (miRNA) quantification to determine expression profiles for diabetic kidney disease (DKD) and predict graft function following renal transplantation. In parallel we are developing electrochemical quantification methods, and have demonstrated that urinary miRNA detection by glassy carbon electrode-based biosensors is more sensitive than RT-qPCR. Here we describe development of disposable screen printed carbon electrode (SPCE)-based miRNA sensors that can discriminate between urine samples from DKD patients and controls with similar sensitivity.

Methods: Screen-printed SPCEs were modified by deposition of a diazotised naphthalene sulfonic acid derivative, 4-amino-3-hydroxy-1-napthalene sulfonic acid (ANSA). The ANSA was then transformed into a sulfonyl chloride, before a 5'-amine-tagged DNA oligonucleotide with complementary sequence to the target miRNA was attached via a sulfonamide linkage to complete the biosensor. Analysis of biosensor output was carried out via reductive and oxidative chronocoulometry, obtained by measuring negative and positive potential sweeps using a ferri/ferrocyanide electrolyte, respectively. Selected miRNA readings were compared before and after hybridization in exogenous control miRNA dilution series, and between urine samples from DKD patients and controls.

Results: We demonstrated a linear response for our SPCE sensors across physiologically relevant concentrations of exogenous miR-21, replicating the femtomolar limit of detection from our previous glassy carbon electrode-biosensor studies. Subsequently, our SPCE sensors successfully detected a DKD-associated decrease in miR-192 that we reported previously following RT-qPCR analysis. Using histochemistry and atomic force microscopy analyses throughout the biosensor fabrication process, we observed sequential deposition of sensor components at the electrode surface which demonstrated the desired biosensor composition.

Conclusions: Our disposable electrode-based biosensors have strong potential for use in rapid, highly sensitive miRNA biomarker quantification in urine and other body fluids. In parallel studies we have identified urinary miRNA expression profiles associated with renal pathologies, and are now adapting our technology for clinical testing purposes.

Funding: Government Support - Non-U.S.

FR-PO974

Automated Podocyte Foot Process Width Measurement Using Deep Learning

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Background: Increased foot processes (FP) width (FPW) is an important measure of podocyte injury. There is no consensus on how to estimate average FPW. The current gold standard (unbiased stereology) is time consuming and not widely available. We aimed to automate average FPW estimation using deep learning (DL).

Methods: A custom multi-layered deep learning model was trained on a normalized electron-microscopy (EM) dataset of 800 images (augmented 10000+) obtained at ~40,000X. Images were captured using systematic uniform random sampling. Testing was done on 29 new kidney biopsies (30-157 images per biopsy) from patients with Fabry disease and variable proteinuria and pathology severity and a compiles set of images from kidney donors as normal controls. DL FPW measurements were compared with measurements done by an experienced technician using unbiased stereology. Measurements were correlated with available clinical and structural parameters.

Results: The automated report utility substantially reduced the time needed for average FPW measurement per biopsy (<1 min DL vs. 6-8 hours human). The DL model accuracy based on human segmentation as the ground truth on a scale of 0-1 (1=perfect) accuracy was 0.8 for glomerular basement membrane and 0.6 for slits. DL measurements (737±151nm) were ~6.5% smaller (p=0.03) than human measurements (788±194nm), but these two were correlated (r=0.77; p<0.0001). Bland-Altman plot showed that ~94% of DL vs. human differences fell within mean ± 1.96 SD of the differences. Both human and DL showed increased FPW in Fabry patients compared with controls and similar correlations between age and FPW in Fabry patients. Globotriaosylceramide inclusion density in podocytes correlated with DL-measured FPW (r=0.33, p=0.04), but human measurements did not. DL-measured FPW showed a trend with urine protein excretion rate (r=0.31, p=0.058), but human measurements did not. DL showed substantial variability in individual FPW in Fabry patients but not in controls.

Conclusions: DL algorithms while substantially reduced time needed for FPW measurement, provided reasonably accurate data correlating with human stereology measurements and with relevant clinical correlations. In addition, DL readily provided additional information on individual FPW variability which may be useful in podocyte injury assessment in secondary podocytopathies.

Funding: Other NIH Support - NCATS

FR-PO975

Loss of Glomerular Thrombomodulin Precedes Diabetic Nephropathy in Diabetic Patients

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Background: Thrombomodulin (TM) is an endothelial transmembrane protein which regulates vascular homeostasis. Previously, it was demonstrated that TM-mediated protein C activation ameliorates glomerular apoptosis and inflammation in a DN mouse model (Nat Med 2007), indicating that diminished TM levels may contribute to DN. Cleavage of TM is a well-established feature of endothelial cell dysfunction, and serum levels of cleaved TM are increased in DN. Here, we investigate TM expression in glomeruli of patients with DN and in a DN mouse model.

Methods: We measured staining of glomerular TM in an autopsy cohort, including 94 DN patients, 57 diabetic patients without DN and 38 healthy controls. Additionally, TM mRNA expression was measured in microdissected glomeruli from renal biopsies of 24 patients with DN and 13 controls. Furthermore, we studied glomerular TM expression in a STZ-induced DN mouse model, including 20 STZ and 10 WT mice, at 5 and 15 weeks after diabetes induction – reflecting acute and chronic DN.

Results: TM expression was 1.7x lower in patients with diabetes compared to non-diabetic controls (p=0.004), but no differences were observed between diabetic patients with and without DN. TM mRNA levels of DN cases were 2.3x higher compared to control cases (p=0.017). In STZ mice, TM expression was 1.2x lower than in WT mice (p<0.001), but no difference in TM expression was observed between acute and chronic DN mice. TM expression correlated negatively with glomerular number of macrophages and TNF-α protein in these mice.

Conclusions: Glomerular TM expression is decreased on protein level, but increased on mRNA level in patients with DN. TM may be cleaved under diabetic conditions, which is compensated by increased production. Furthermore, a loss of TM is associated with increased glomerular inflammation in DN. Interestingly, no differences in TM levels were observed between diabetic patients with and without DN, nor between mice with acute and chronic DN. We speculate that TM loss is an early feature of the diabetic glomerulus, and contributes to glomerular inflammation and DN development. Restoration of TM levels may be a promising treatment to prevent DN in diabetic patients.

FR-PO976

Exploring Origins of Autoimmune Nephritis Using HLA DR+ CD34+ Humanized Immune System Mice

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Background: Autoimmunity causes most glomerulonephritis (GN) and must be controlled to limit nephron destruction. Understanding the origins of the autoimmune response can guide development of targeted intervention. We generated a human immune system (HIS) model to examine interactions of two potent disease susceptibility factors: autoimmune-linked HLA Class II receptor DR4 and inhalation of crystalline silica (Si), an environmental exposure linked to lupus and ANCA vasculitis.

Methods: NOD-scid-gamma mice lacking mouse MHC Class II and transgenic (Tg) for HLA DR4 were infused with T-depleted DR4+ CD34+ human hematopoietic stem cells (HSC) from 1 of 4 cord blood donors. The Tg DR4 is expressed in host thymus to educate human CD4+ T cells, and DR4 is expressed on HSC-derived B cells. 3 mon later mice were exposed by aspiration to Si, vehicle (V), or neither, followed in 0 to 10 wks by adjuvant±PR3 or foreign antigen injection. Organs were harvested 4-8.5 mon post-engraftment.

Results: Among 19 surviving engrafted DR4+/moCIIKO/CD34+HIS mice, mean spleen chimerism was 72.2±27%. Low levels of human anti-PR3 Ig were detected in bronchoalveolar lavage fluid (BALF) from 69% (9 of 13) of immunized HIS mice, representing all 4 HSC donors and each exposure group. Low levels of human anti-DNA Ig were detected in BALF of 3 immunized (1 Si/2V) HIS mice, derived from the same HSC donor; 2 had lung perivascular infiltrates. Among Si-exposed mice, 5 deteriorated clinically 5-9 wks post-exposure, precluding immunization. All 5 had severe lung injury, including findings typical of chronic silicosis with extensive fibrosis and/or alveolar proteinosis in 4 mice. These 5 Si-exposed HIS mice (derived from 3 HSC donors) with 77%-85% spleen chimerism had no detectable serum or BALF anti-DNA & anti-PR3 Ig.

Conclusions: DR+ CD34+ HIS mice provide a useful translational platform to study susceptibility factors and gene-environment interactions that promote human nephritogenic autoimmunity. Our findings suggest that immunization and/or adjuvant, but not silicosis alone, facilitates induction of humoral autoimmunity in the context of HLA DR4. Future models can test the impact on autoimmune control of alternative risk alleles, modifiable host factors, and environmental co-exposures.

Funding: Other NIH Support - NIDDK, Veterans Affairs Support, Private Foundation Support

FR-PO977

Sex-Dependent Modulation of Systolic Blood Pressure and Glucosuria in Tubule-Specific Heterogeneous Nuclear Ribonucleoprotein F Knockout Mice

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Background: We previously reported that mice with selective tubular deficiency of heterogeneous nuclear ribonucleoprotein F (hnRNP F) exhibit elevated systolic blood pressure (SBP) and glucosuria associated with up-regulation of renal angiotensinogen (Agt) and down-regulation of sodium-glucose co-transporter-2 (Sglt2) (2018 ASN TH-OR073). Here, we compared the impact of sex hormones on glucosuria and expression of Agt and Sglt2 in hnRNP F knockout (KO) mice and control littermates (Ctrls).

Methods: HnRNP F KO mice were generated by crossbreeding Pax8-Cre mice with floxed hnRNP F mice on a C57BL/6 background. Male KO mice and Ctrls were subjected to either sham-operation or bilateral castration at 12 weeks (wks) of age and followed until 20 wks of age. Female KO mice and Ctrls underwent either sham-operation or bilateral ovariectomy at the age of 8 wks and then followed until the age of 24 wks. Testosterone were implanted in female KO and Ctrls mice at the age of 8 wks and followed an extra 4 wks. Body weight (BW), SBP, blood glucose (BG), urinary glucose (UG) were monitored. Western blotting and real-time qPCR were used to quantify Agt and Sglt2 expression in renal proximal tubules (RPTs). Human RPTCs (HK-2) ± KO of HNRNP F by CRISPR/Cas9 method were also studied.

Results: Both male and female KO mice exhibited elevated SBP and glucosuria with up-regulation of Agt and down-regulation of Sglt2 expression in RPTs as compared to Ctrls. However, glucosuria disappeared in male KO mice at 12 wks of age whereas female KO mice had persistent glucosuria. Castration restored glucosuria in male KO mice; no change was seen in ovariectomized female mice. Gonadectomy had no effect on UG in Ctrls. Testosterone treatment prevented glucosuria in female KO mice. In vitro, HK-2 cells with HNRNP F KO displayed up- and down-regulation of AGT and SGLT2 expression, respectively. Finally, testosterone but not estrogen stimulated SGLT2 promoter activity in HK-2 cells but not in HK-2 with HNRNPF KO.

Conclusions: Our results indicate that hnRNP F may play an important role in the development of hypertension and glucosuria in mice in a sex-dependent manner through modulation of renal Agt and Sglt2 expression, respectively.

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FR-PO978

Role of ApoL1-miR193a Axis in Sox2-Mediated Reprogramming of Differentiated Podocytes

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Background: Enhanced autophagy maintains molecular phenotype in differentiated podocytes. The Sox2 is known to initiate autophagy by repressing Mammalin Target of Rapamycin (mTOR) expression; however, Sox2-induced autophagy induction carries negative feedback on reprogramming of differentiation. Since miR193a suppresses Sox2 expression, it would modulate the Sox2-induced transient autophagy during an early step in reprogramming to pluripotency/differentiation. Because APOL1 inversely regulates miR193a, it would de-repress Sox2 and accelerate autophagy in differentiated podocytes

Methods: Human podocytes expressing vector, APOL1G0/G1/G2 were differentiated; protein blots were probed for Sox2, APOL1, nephrin, CD2AP, and GAPDH. RNAs were assayed for miR193a and cDNA amplified for APOL1, and Sox2. The silico method was used to analyze motifs on ApoL1 and its variants mRNA. MEME suite for motif identification, JASPARv2010 and STAMP tool for alignment, and database matching for identified motifs were used. 3D models of ApoL1 and its variants mRNA segments (with mutations and deletions) were generated. Structural model of Sox2 (template-based method Itasser) docking approach was used to form the ApoL1 and its variants RNA and Sox2 complexes. The thermodynamic properties of ApoL1G0, G1, and G2 mRNAs and Sox2 were analyzed.

Results: Differentiated G0-podocytes displayed enhanced Sox2 but decreased expression of miR193a; in contrast, G1- and G2-podocytes showed the opposite outcome. The MEME suite identified motifs on ApoL1, and its variants and the JASPARv2010 and STAMP database for motif matching suggested that Sox2 can bind on ApoL1G2 mRNA. The thermodynamic properties of RNA-protein interaction interface suggested that the ApoL1G2 mRNA and Sox2 form a very strong and stable complex with surface area 4443.8 Å2, solvation free energy gain upon the formation of the interface (ΔiG) -93.8 kcal/mol and free energy of assembly dissociation (ΔGdiss) 95.6 kcal/mol. The ApoL1G2 mRNA-Sox2 complex has 38 hydrogen bonding interactions.

Conclusions: The Sox2 binding with ApoL1 and its variants mRNA suggests that Sox2 has an RNA binding property. This interaction carries the potential to modulate Apol1-miR193a-induced downstream signaling.

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FR-PO979

Intracellular Trafficking Pathway of Albumin in Glomerular Epithelial Cells

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Background: Recently, intracellular trafficking pathway of albumin through caveolae in glomerular epithelial cells (podocytes) has been suspected to new etiological hypothesis of albuminuria in addition to pathway through gap between foot processes. In this analysis, we analyzed albumin endocytosis, subsequent transcytosis in cytoplasm and exocytosis.

Methods: Alexa flour 488 labeled bovine serum albumin (AF488-BSA) were incubated with Podocytes for 30, 60, and 120 minutes, and analyzed co-localization with caveolin-1(which was main structural component of caveolae), clathrin, and FC receptors (FcRn) as endocytosis, with several organelles, such as early endosome, Golgi apparatus (GA), endoplasmic reticulum (ER), lysosome, and proteasome, and with cytoskeletons such as microtubules and actins as transcytosis by immunofluorescence analysis (IF). In western blotting (WB) and IF, methyl beta cyclodextrin (MBCD) were preincubated with podocytes, then incubated with AF488-BSA or human serum albumin (HSA), and the amount of intracellular albumin through caveolae was analyzed. HAS were incubated with full confluent podocytes on transwells plate with or without MBCD, and concentration of HAS in inside and outside medium between transwells plate were evaluated to analyze exocytosis.

Results: At first, AF488-BSA were colocalized with Cav-1 and FcRn, but not with clathrin. Then AF488-BSA were colocalized with actin cytoskeleton, but not with microtubules, and colocalized with early endosome, lysosome, and proteasome, but not with ER and GA. MBCD treatment significantly decrease the Cav-1 and decreased the 488-BSA in IF and HAS in WB. The amount of HAS were gradually decreased in inside medium over podocytes on transwells plate and gradually increased in outside medium under transwells plate, and MBCD interfered that phenomenon. All these results indicated that albumin entered into Podocytes through Caveolae or FcRn but not clathrin, moved along with actin but not with microtunules, and reached to early endosome. At endosome, some of them were sorted to be degraded in lysosome or proteasome, and others were bypassed GA and ER and transported to the other side of cells as exocytosis.

Conclusions: In this study, we have shown intracellular trafficking pathway of albumin, and this pathway may be a new etiological hypotheis of urinay albumin excretion.

FR-PO980

Defective ATP Synthase Mediates Renal Fibrosis and Tubular Epithelial-Mesenchymal Transition

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Background: Reduced mitochondrial function is a feature of chronic kidney disease (CKD). However, there is limited understanding of various aspect of mitochondrial biology in the renal injury.

Methods: This study aims to explore the role of mitochondrion dysfunction on TGFβ1–induced tubular cell epithelio-mesenchyamal transition (EMT) in vitro and renal fibrosis in vivo and clinical renal biopsy samples from patients with various stage of CKD.

Results: We observed TGFβ1-induced EMT in cultured renal tubular HK2 cells, and found that TGFβ1-treated cells have a decrease of oxygen consumption and an increase in use of non-oxidative phosphorylation glycolysis pathway as their energy source (by seahorse assay) while undergoing EMT, which was accompanied by increased mitochondrial membrane potential (MMP) and lower complex V activity (The activities of complex 1-IV were normal). Adding a mitochondrial complex V inhibitors (oligomycin) may induce EMT and further enhances TGF-β1-induced EMT. Blue native (BN)-PAGE studies showed a defective assembly of complex V (ATP synthase) in the mitochondria of EMT cells, which was possibly attributed by attenuation of its assembly factor ATPAF1. In HK2 cells, ATPAF1 knockdown caused EMT, and restoration of ATPAF1 protects renal tubule cells from TGFβ-induced mitochondrial dysfunction and EMT. Consistently, the animal model of tubulointerstitial fibrosis caused by unilateral ureteral obstruction (UUO) demonstrated attenuations in ATPAF1 level and complex V formation, accompanied by increased MMP. Overexpression of Atpaf1 in vivo attenuated mitochondrial dysfunction of tubular cells and interstitial fibrosis in UUO animal model. Thus, restoration of ATPAF1 in the kidney is protective against injury during the progression of renal fibrosis. In clinical renal biopsy samples, we performed immunostaining for ATPAF1, MMP and α-smooth muscle actin(α-SMA, a marker of fibrosis) and found that the severity of interstitial fibrosis (α-SMA staining intensity) negatively correlated with tubular ATPAF1 and positively with MMP. In addition, tubular ATPAF1 intensity also negatively correlated with MMP staining.

Conclusions: Our study underscores ATPAF1 is an important factor in maintaining mitochondrial energy capacity in tubule cells, and is vulnerability to injury and mediates the development of renal fibrosis.

FR-PO981

Loss of Endothelial Klf4 Leads to Severe Glomerular Endothelial Injury in Aged Mice

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Background: Renal-specific thrombotic microangiopathy (TMA) represents the most severe form of renal microvascular injury, and is associated with activation of complement and dysregulation of key endothelial genes. To investigate transcriptional mediators involved in renal-TMA, we reviewed expression arrays of global and single cell RNA-seq from human kidney biopsies with complement mediated renal microvascular injury and observed that Krüppel-Like Factor 4 (KLF4), a zinc finger transcription factor, is both differentially expressed in endothelial cells (ECs) and predicted to regulate other differentially expressed genes. Although previous reports show that *KLF4* coordinates an anti-thrombotic, anti-inflammatory phenotype in systemic vascular beds, its role in renal microvascular injury remains to be investigated.

Methods: Endothelial-specific *Klf4* knockout mice ($Klf4^{\Delta EC}$) were generated by crossing $Klf4^{fl/fl}$ with *Cdh5-Cre* mice. Mice were aged to 1 year as a model of endothelial dysfunction. Periodic acid-Schiff, electron microscopy, immunofluorescence (IF), ELISA and RT-PCR were performed to investigate the effects of endothelial *Klf4* in the renal microvasculature. Renal histology and ultrastructure were evaluated, blinded, by renal pathology (MPR).

Results: We demonstrated 80% knockdown of endothelial KLF4 by RT-PCR and IF. At 12 weeks of age, while we did not observe any histologic changes, $Klf4^{\Delta EC}$ mice exhibited increased glomerular *Pai-1, Vcam-1* and decreased *Nos3*, as compared with $Klf4^{fl/fl}$. Increased complement activation in glomerular capillaries was also noted in $Klf4^{\Delta EC}$ mice (complement factor 3 and C5b-9 fragments by IF). In addition to an exacerbation of these findings, at 1 year, $Klf4^{\Delta EC}$ mice exhibited histologic and ultrastructural changes observed across many TMA subtypes, including glomerular capillary dilation and congestion, EC swelling with loss of fenestrations, subendothelial expansion and mesangiolysis, as compared with aged matched controls. Furthermore, in line with this pathologic TMA signature, 1 year $Klf4^{\Delta EC}$ mice also demonstrated increased glomerular von Willebrand factor and albuminuria, compared with age-matched controls.

Conclusions: Loss of endothelial *Klf4* in aged mice recapitulates many pathologic features of renal-TMA, including complement activation and dysregulation of thrombotic and inflammatory genes.

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FR-PO982

Fibrillin 1-Enriched Tissue Microenvironment Plays a Key Role in Mediating Vascular Rarefaction in CKD

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Background: Vascular rarefaction, characterized by reduced capillary density due to the loss of endothelial cells, is a common pathologic feature in a wide variety of CKD. However, how endothelial cells are lost in CKD remains elusive. In this study, we report that Fibrillin-1, an extracellular matrix glycoprotein, plays a critical role for mediating vascular rarefaction after kidney injury.

Methods: Unilateral ureteral obstruction (UUO) and unilateral ischemic-reperfusion (UIRI) were used as models of kidney fibrosis. Decellularized kidney tissue scaffold (KTS) was prepared. The differential expression of KTS proteins was analyzed by mass spectrometry proteomics. The role of fibrillin-1 in endothelial cell survival and proliferation was investigated in vitro. The expression of fibrillin-1 was knocked down by shRNA approach in vivo.

Results: Compared to sham controls, KTS from fibrotic kidney induced human umbilical vein endothelial cells (HUVEC) to undergo apoptosis, characterized by an increased expression of cleaved caspase-3, PARP-1, Fas and p53. KTS from fibrotic kidney also promoted endothelin-1 expression, and inhibited c-fos and cyclin D1 expression in response to mitogen stimulation. Mass spectrometry proteomics analyses identified 414 proteins that were differentially expressed in the KTS of control and fibrotic kidney. Fibrillin-1 was one of the most upregulated. In vitro, recombinant fibrillin-1 protein inhibited HUVEC proliferation and the expression of proliferation-related genes. Fibrillin-1 also induced the expression of Fas, FADD and p53 in HUVEC. Fibrillin-1 expression was markedly upregulated in multiple models of kidney fibrosis. Knockdown of renal fibrillin-1 expression by shRNA approach ameliorated kidney vascular rarefaction and reduced renal fibrosis after UIRI.

Conclusions: These studies demonstrate that fibrillin-1-enriched KTS is a hostile environment for endothelial cells, leading to vascular rarefaction in CKD. Targeted inhibition of fibrillin-1 could be a novel therapeutic strategy for protecting kidney integrity against vascular rarefaction in CKD.

FR-PO983

Spironolactone Ameliorates Endothelial Dysfunction Through Inhibition of the AGE/RAGE Axis in a Chronic Renal Failure Mouse Model

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Background: Spironolactone can improve endothelial dysfunction in the setting of heart failure and diabetes models. However, its beneficial effect in the cardiovascular system is not clear in the setting of non-diabetic renal failure. We conducted this study to investigate whether spironolactone can ameliorate endothelial dysfunction in a 5/6 nephrectomy model, and to determine the underlying mechanism.

Methods: Twenty-four Sprague-Dawley rats were divided into four groups. A renal failure model was created using the 5/6 nephrectomy method. The four groups included: Sham-operation group (Group1), chronic kidney disease (CKD; Group2), CKD + ALT-711 (advanced glycation end products [AGEs] breaker; Group 3), and CKD + spironolactone group (Group4). Acetylcholine (Ach)-mediated vasodilatation responses were compared between the four groups. To investigate the underlying mechanism, we cultured human aortic endothelial cells (HAECs) for in-vitro assays. Differences between two groups were determined with the student's t test. Differences between three or more groups were determined through one-way analysis of variance (ANOVA) with post-hoc analysis with LSD method.

Results: Compared with Group 1, Group 2 has a significantly impaired Ach-mediated vasodilatation response. Group 3 and 4 exhibited improved vasoreactivity responses. To determine the underlying mechanism, we performed an in-vitro study using cultured HAECs. We noted significant sirtuin-3 (SIRT3) protein downregulation, reduced phosphorylation of endothelial nitric oxide synthase at serine 1177 (p-eNOS), and increased intracellular oxidative stress in cultured HAECs treated with AGEs (200μg/mL). These effects were counter-regulated when cultured HAECs were pretreated with spironolactone (10μM). Furthermore, the increased p-eNOS production by spironolactone was abrogated when the HAECs were pretreated with tenolvin (1μM), a SIRT3 inhibitor.

Conclusions: Spironolactone could ameliorate endothelial dysfunction in a 5/6 nephrectomy renal failure model through AGEs/Receptor for AGEs (RAGEs) axis inhibition, SIRT3 upregulation, and nicotinamide adenine dinucleotide phosphate oxidase-2 (NOX-2) and its associated intracellular oxidative stress attenuation.

FR-PO984

Fibroblast p90RSK Induces Epithelial-to-Mesenchymal Transition Through Oxidative Stress-Mediated β-Catenin Pathway

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Background: Healthy kidney structure and environment rely on epithelial integrity and interactions between epithelial cells and other kidney cells. p90RSK, a serine/threonine kinase, is recently shown to promote obstruction-induced kidney fibrosis, however, the underlying mechanism remains largely unknown.

Methods: We generated a novel fibroblast-specific p90RSK transgenic mouse (RSK-Tg) and established a fibroblast-epithelial coculture system using primary kidney fibroblasts from RSK-Tg and RSK-wt mice and human proximal tubular epithelial cells (HKC-8) to investigate the role of p90RSK in fibroblast-epithelial interactions and kidney fibrosis.

Results: It was found that RSK-Tg mouse has similar phenotype as the littermate control (RSK-wt). However, after UUO injury, RSK-Tg mice display significantly increased fibrosis, as demonstrated by renal collagen content and FSP-1 abundance, in comparison with their littermates. We further found that RSK-Tg mice display decreased E-cadherin, increased MMP-9, and de novo activation of alpha-SMA, indicating enhanced epithelial-to-mesenchymal transition (EMT), which was also visualized by double fluorescence staining of FSP-1 and lectin. Moreover, it was found, in our in vitro fibroblast-epithelial coculture system, that RSK-Tg fibroblasts consistently produce excessive H2O2 causing epithelial oxidative stress and inducing β-catenin nuclear translocation. Of note, blockade of reactive oxygen species (ROS) or β-catenin abolished fibroblast p90RSK-mediated EMT.

Conclusions: Thus, it is clear that fibroblast p90RSK induces EMT through oxidative stress-mediated β-catenin pathway.

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FR-PO985

Evaluation of CB1 Receptor Expression in Human Diabetic Kidney Disease and Rodent CKD Models

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Background: Published data suggest that cannabinoid receptor 1 (CB1R) is an attractive target for metabolic complications, including renal fibrosis and diabetic kidney disease (DKD). CB1R protein, detected by immunohistochemistry, was reported to be expressed at low level in normal kidneys from human and rodents, and increased in renal biopsy samples from patients with DKD and fibrotic kidneys in rodents. Elevated expression of CB1R is postulated to be implicated in DKD leading to metabolic derangement, inflammation and fibrosis. We aimed to characterize CB1R protein expression in human DKD and three rodent chronic kidney disease (CKD) models.

Methods: Histological sections of renal biopsies from DKD patients and autopsy samples from normal human subjects were analyzed by immunohistochemistry to assess CB1R protein expression. Rodent CKD models included subtotal nephrectomy (STNx, on 129/Sv), unilateral ureteral obstruction (UUO, on C57BL/6) and folic acid nephropathy (FAN, on C57BL/6). Paraffin sections of kidney from normal control and diseased groups from each model (12 weeks after surgery for STNx, 10 days after surgery for UUO, 6 weeks after folic acid injection for FAN) were evaluated. Anti-CB1R polyclonal antibody from ImmunoGenes (Hungary) was used for all immunohistochemistry. Sections from human brain and mouse tissues (brain, kidney) from CB1R wild type (WT) and knockout (KO) were used as positive or negative control.

Results: Specific CB1R protein expression was observed in the presynaptic axons in the human and mouse brains without non-specific background. CB1R labeling was absent in the CB1R KO brain and kidneys. No specific CB1R positive labeling was observed in the normal mouse kidneys, normal human kidneys, or renal biopsy samples from human DKD. Only minimal and focal (less than 5% of total kidney area) CB1R protein expression was observed in tubular epithelial cells in the kidneys from STNx, UUO, and FAN models.

Conclusions: CB1R protein expression was absent from normal and human DKD, and very low and only minimally and focally increased in diseased kidneys from rodent CKD models. These observations suggest challenges for validation of this target in renal fibrosis and diabetic kidney disease.

Funding: Commercial Support - Janssen R&D, Johnson & Johnson

FR-PO986

Melanocortin 1 Receptor (MC1R) Deficiency Exacerbates Glomerular Injury and Proteinuria in the Autologous Phase of Nephrotoxic Serum (NTS) Nephritis

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Background: The clinical effectiveness of melanocortin therapy with adrenocorticotropin in inducing remission of steroid-resistant nephrotic syndrome points to a steroidogenic-independent anti-proteinuric activity of melanocortins. However, which melanocortin receptor conveys this beneficial effect is controversial. A growing body of evidence suggests that activation of podocytic MC1R may convey a podocyte protective and anti-proteinuric effect. However, this paradigm seems inconclusive because MC1R agonist was seemingly ineffective in such nephrotoxic glomerulopathies as Adriamycin nephropathy. Moreover, how MC1R signaling is involved in immune-mediated glomerular diseases is unknown.

Methods: NTS nephritis was induced in mice with nonfunctional mutation of MC1R(e/e) and in wild-type (WT) mice by injection of rabbit NTS. Kidney function and renal injury were evaluated.

Results: Seven or 14 days after NTS injection during the autologous phase, e/e as compared with WT mice demonstrated an exacerbated kidney dysfunction and injury, as evidenced by higher serum creatinine levels, heavier proteinuria, and aggravated renal pathology, featured by glomerular hypercellularity, crescent formation, mesangial expansion, protein casts, and renal inflammation and fibrosis. Consistent with the worsened proteinuria, e/e mice displayed more severe podocyte injury, characterized by podocytopenia, marked by diminished WT-1 staining, and loss of podocyte markers like synaptopodin and podocin. Mechanistically, the aggravated renal disease in e/e mice was unlikely due to a sensitized response of the e/e kidney to injury, because 1 day after NTS insult during the heterologous phase, e/e mice developed albuminuria, podocytopathy and glomerular damage to a comparable extent as WT mice. Rather, deficiency of an MC1R-mediated non-kidney-autonomous or extra-renal mechanism may contribute. In support of this, e/e mice exhibited much more glomerular deposition of autologous anti-rabbit IgG together with the terminal complement complex C5b-9 along glomerular capillary loops than WT mice, despite the same degree of deposition of glomerular basement membrane-reactive rabbit IgG.

Conclusions: MC1R signaling protects against glomerular injury and proteinuria in immune-mediated glomerular disease *via*, at least in part, an immune modulatory effect.

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FR-PO987

Deletion of the Non-Canonical NOTCH Ligand DLK1 Promotes an Overactivation of the NOTCH Signaling Pathway and the Th17 Immune Response in the Unilateral Ureteral Obstruction Model

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Background: The NOTCH signaling pathway is activated in embryonic development, silenced in adult tissues, and reactivated in human kidney diseases. The non-canonical ligand DLK1 has been described as a Notch inhibitor in Drosophila and in mammal cells, but there are no data in renal injury. In renal pathologies, Th17 response has been involved in immune and nonimmune diseases, including diabetic nephropathy.

Methods: 129/SvJ mice with an embrionary deletion in the *Dlk1* gene were used. The Unilateral Ureteral Obstruction (UUO) model was performed in both the transgenic and the WT mice, and data studied at 2, 5, 10 and 14 days after the injury. C57BL/6 mice were treated daily with 0.1 mg/day of the γ-secretase inhibitor DAPT, starting one day before the UUO procedure and sacrificing the animals 5 days after.

Results: Non-canonical ligands DLK1 and DLK2 were studied at each point, showing increased gene expression levels from day 5 to 14 in the WT animals. The inflammatory infiltrate was scored by PAS staining in the obstructed kidneys and it was significantly increased in the *Dlk1*-null mice vs WT from 5 days and continued at 10 and 14 days. Remarkably, at 14 days these knockout obstructed kidneys showed a huge inflammatory infiltrate as aggregates, not found in the WT animals. These inflammatory aggregates were positive for the NICD, as well as some tubules, demonstrating that the *Dlk1*-null mice have an overactivation of the NOTCH pathway in the obstructed kidneys. They were also associated to a significant increase of CD3+, CD4+, F4/80+ infiltrating cells and neutrophils. At 14 days, the increase of the Th17 response in the *Dlk1*-null obstructed kidneys was very remarkable, as shown by the elevation of the transcription factors RORγt and STAT3 and the effector cytokine, IL17A. These factors were also increased at 5 days in the C57BL/6 mice and clearly diminished with the tratment of the γ-secretase inhibitor DAPT.

Conclusions: Deletion of DLK1 overactivates the Notch pathway in the UUO model, and this triggers an increase in the inflammation of the tissue as well as an induction of the Th17 response. Therefore, DLK1 can be suggested as a Notch inhibitor in this context.

Funding: Government Support - Non-U.S.

FR-PO988

A Novel Klotho-Derived Peptide KP1 Attenuates Renal Fibrosis by Blocking TGF-Beta Signaling

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Background: Renal fibrosis, characterized by excessive extracellular matrix (ECM) deposition, is a common feature of a variety of CKD. Klotho is an antiaging protein with remarkable reno-protective potential. Because Klotho is a large transmembrane protein, making it difficult to be used clinically, we hypothesized that a small Klotho-derived peptide may mimic the reno-protective action of Klotho.

Methods: A peptide mini-library was established, which encompassed the extracellular region of Klotho. The anti-fibrotic activity of the Klotho-derived peptide was screened in normal kidney fibroblast cells (NRK-49F) stimulated with TGF-β1. The effect of the identified peptide on renal fibrosis was tested in mouse models of fibrosis including unilateral ureteral obstruction (UUO) and unilateral ischemia reperfusion injury (UIRI).

Results: After screening the klotho peptide mini-library, one peptide with potent anti-fibrotic potential, designated as klotho-derived peptide 1 (KP-1), was identified. KP-1 was effective in blocking the upregulation of fibronectin and α-smooth muscle actin (α-SMA) in NRK-49F cells induced by TGF-β1. Mechanistically, we found that KP-1 bound to the TGF-β receptor type II (TβR-II), which competitively inhibited TGF-β1/TβR-II engagement. As such, KP1 was able to block Smad2/3 phosphorylation and activation induced by TGF-β1. KP-1 also inhibited TGF-β1-mediated mitogen-activated protein kinase (MAPK) activation in NRK-49F cells. In vivo, KP-1 blocked renal Smad2/3 and MAPK activation, inhibited myofibroblast activation and matrix production, ameliorated renal interstitial fibrosis and restored the expression of endogenous klotho protein in two models of renal fibrosis induced UUO and IRI.

Conclusions: We have identified KP-1 is a novel Klotho-derived peptide that specifically inhibits TGF-β signaling via binding to TβR-II. KP-1 could be used as a therapeutic agent for treating fibrotic kidney disease.

FR-PO989

A Deep Learning-Based Approach for Glomeruli Object Extraction from Multistained Renal Biopsy Pathologic Images

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Background: Glomeruli extraction from pathologic images is a key step in automatic analysis of renal biopsy. We present a deep learning-based approach for the object extraction of three types of glomeruli with various pathological lesions in multi-stained images.

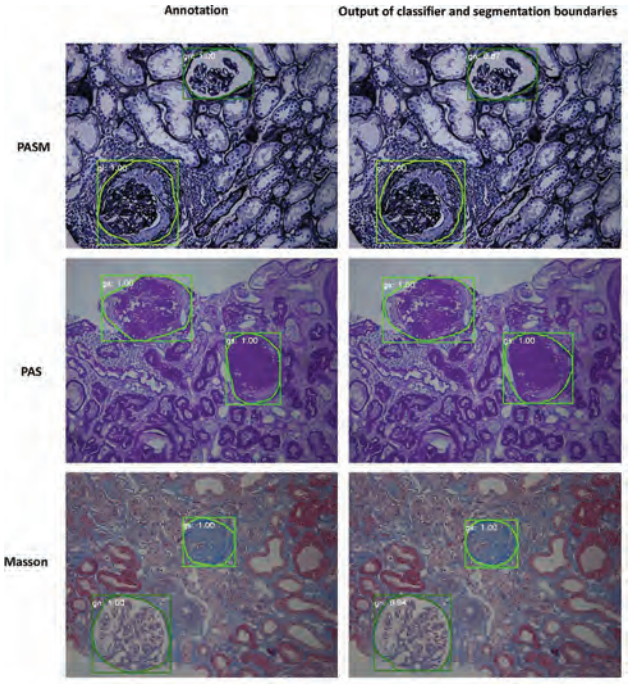
Methods: Sources of images: 1.1947 glomeruli from images captured at 10x, 20x, and 40x, including 33 pathological types of kidney diseases; 2. 601 glomeruli from 44 whole slide images (WSI) scanned at 40x using Precice 500B scanner (UNIC Technologies Inc, China). Slides were stained with Periodic acid-Schiff (PAS), Periodic Acid-silver Methenamine (PASM), and Masson's trichrome stains. Glomeruli were divided into training and testing sets. Mask R-CNN architecture based on convolutional neural networks (CNN) was trained by using glomeruli training set. The adopted mask R-CNN, which is built by extending Faster R-CNN by adding a branch for predicting an object mask, can detect, classify, and segment three types of glomeruli: 1. glomerulus with basically normal structure (gn), 2.global sclerosis (gs), and 3.glomerulus with other abnormal structure (gl) at the same time.

Results: The detection and pixel level segmentation results was graded via average precision, average recall, and F-score (true positives were defined by >50% overlap of the predicted region).

Conclusions: We present a robust network using relatively limited sample size, which can detect normal and abnormal glomeruli stained with PAS, Masson and PASM.

Funding: Clinical Revenue Support

Type	Average precision	Average recall	F-score
gn	0.903	0.862	0.882
gs	0.746	0.676	0.709
gl	0.750	0.689	0.718
All	0.796	0.742	0.768
Detection of total glomeruli	0.898	0.952	0.924



FR-PO990

Deep Learning-Based Segmentation of Normal Histologic Kidney Primitives on Whole Slide Images from NEPTUNE Digital Renal Biopsies

Catherine P. Jayapandian,[6] Yijiang Chen,[6] Andrew Janowczyk,[6] Matthew Palmer,[1] Jarcy Zee,[2] Clarissa A. Cassol,[7] Miroslav Sekulic,[6,3] Jeffrey B. Hodgin,[8] Stephen M. Hewitt,[9] John F. O'Toole,[4,6] John R. Sedor,[4,6] Laura Barisoni,[5] Anant Madabhushi.[6,10] *[1]University of Pennsylvania, Philadelphia, PA; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]UH Cleveland Medical Center, Cleveland, OH; [4]Cleveland Clinic, Cleveland, OH; [5]Duke University, Durham, NC; [6]Case Western Reserve University, Cleveland, OH; [7]The Ohio State University, Columbus, OH; [8]The University of Michigan, Ann Arbor, MI; [9]National Cancer Institute, Bethesda, MD; [10]Louis Stokes Cleveland Veterans Affair Medical Center, Cleveland, OH.*

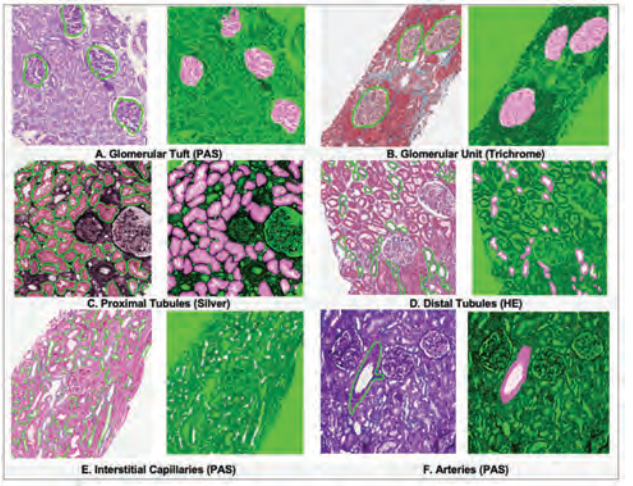
Background: The establishment of digital pathology repositories, such as Nephrotic Syndrome Study Network (NEPTUNE), enables large scale analyses of renal biopsies by sophisticated computational imaging approaches and machine-human interactive protocols. Here we evaluate the performance of U-Net deep learning algorithm for identification of normal histologic primitives in whole slide images (WSIs) across multiple stains.

Methods: Eighteen U-Nets were trained to segment: (i) normal glomerular tufts, (ii) normal glomerular unit (tuft + Bowman's space and capsule), (iii) normal proximal tubular segments (PT), (iv) normal distal tubular segments (DT), (v) interstitial capillaries, and (vi) arteries. Regions were extracted from 419 WSIs, including 103 H&E, 112 PAS, 100 Silver, 103 Trichrome) from 125 NEPTUNE digital renal biopsies with a diagnosis of Minimal Change Disease. The renal biopsies were randomly sampled into training, validation and testing sets in the ratio 6:1:3. Five pathologists provided the manual segmentation (ground truth). Detection and segmentation results were evaluated using F-Score, True Positive Rate (TPR), Positive Predictive Value (PPV) and Dice Similarity Coefficient (DSC), respectively.

Results: PAS stained WSIs yielded the best performance for all primitives with F-Score (i) 0.93, (ii) 0.94, (iii) 0.91, (iv) 0.93, (v) 0.93 and (vi) 0.85.

Conclusions: This work represents a solid foundation towards enlisting machine learning classifiers to aid large scale tissue quantification efforts. Ongoing effort is devoted to segment abnormal histologic primitives for the development of image-based predictors of disease prognosis.

Funding: NIDDK Support



Stain	Mag	Normal Histologic Primitive	F-Score	TPR	PPV	DSC
PAS	5X	Glomerular Tuft	0.9358	0.9354	0.9313	0.9700
	5X	Glomerular Unit	0.9297	0.9506	0.9370	0.9583
	10X	Proximal Tubular Segments	0.9106	0.9814	0.9177	0.9044
	10X	Distal Tubular Segments	0.9276	0.9597	0.9336	0.9224
	40X	Interstitial Capillaries	0.9179	0.9380	0.8934	0.9300
	10X	Arteries	0.8750	0.8461	0.8496	0.9149
HE	5X	Glomerular Tuft	0.9239	0.8921	0.9294	0.9328
	5X	Glomerular Unit	0.9137	0.8839	0.9313	0.9023
	10X	Proximal Tubular Segments	0.8817	0.9301	0.8403	0.9479
	10X	Distal Tubular Segments	0.7606	0.8262	0.8005	0.7840
Silver	5X	Glomerular Tuft	0.8961	0.9134	0.8685	0.9611
	5X	Glomerular Unit	0.9200	0.8882	0.8964	0.9792
	10X	Proximal Tubular Segments	0.9018	0.9572	0.8032	0.8781
	10X	Distal Tubular Segments	0.9054	0.8882	0.8964	0.9792
Trichrome	5X	Glomerular Tuft	0.8870	0.9099	0.8929	0.9369
	5X	Glomerular Unit	0.8876	0.9283	0.9242	0.9086
	10X	Proximal Tubular Segments	0.9010	0.9636	0.9148	0.8905
	10X	Distal Tubular Segments	0.8116	0.8217	0.8038	0.8443

Figure 1: Segmentation results of Normal histologic primitives from multi-stained Neptune Asset – glomerular tuft (A), glomerular unit (B), proximal (C) and distal tubules (D), interstitial capillaries (E), and arteries (F) stained with PAS, HE, Silver and Trichrome *(left: ground truth marked in green and manually annotated by an expert pathologist, and right: U-Net output in fuchsia overlaid on the original image).*

Table shows the stain, optimal magnification and UNet segmentation results (F-Score, TPR, PPV and DSC) for the primitives

FR-PO991

Deep Learning-Based Histopathological Assessment of Renal Tissue

Meyke Hermsen,[1] Marjolijn Den boer,[1] Thomas de Bel,[1] Jesper Kers,[2] Joris J. Roelofs,[2] Mark D. Stegall,[3] Mariam P. Alexander,[3] Byron H. Smith,[3] Bart Smeets,[1] Luuk Hilbrands,[1] Jeroen A. van der Laak.[1,4] *[1]Radboudumc, Nijmegen, Netherlands; [2]Academic Medical Center, Amsterdam, Netherlands; [3]Mayo Clinic, Rochester, MN; [4]Center for Medical Image Science and Visualization, Linköping University, Linköping, Sweden.*

Background: Quantitative measures are often used for histopathological assessment of renal tissue. We trained a convolutional neural network (CNN) for multi-class segmentation of digitized periodic acid-Schiff(PAS)-stained renal tissue sections.

Methods: The CNN was trained using annotations of 40 whole-slide images of PAS-stained renal transplant biopsies. Multi-class segmentation performance was assessed by calculating Dice coefficients (DCs) for 10 tissue classes on 10 transplant biopsies from Radboudumc and on 10 transplant biopsies from the Mayo clinic. Additionally, we fully segmented 15 nephrectomy samples and assessed the CNN's glomerular detection rates. Lastly, CNN-based measures were compared with visually scored histological (Banff) components in 82 transplant biopsies.

Results: The weighted mean DCs were 0.80 and 0.84 in 10 transplant biopsies from Radboudumc and the Mayo Clinic, respectively. The 'glomeruli' class was best segmented in both data sets (DC 0.95 and 0.94), followed by 'tubuli combined' and 'interstitium'. An example of the CNN's visual output is shown in Figure 1. The CNN detected 92.7% of all glomeruli in nephrectomy samples, with 10.4% false positives. In whole transplant biopsies, the mean intraclass correlation coefficient for glomerular counting performed by pathologists and the CNN was 0.94. Moderate to strong correlations were observed between components of the Banff scoring system and CNN-based measures (Table 1).

Conclusions: This study presents the first CNN for multi-class segmentation of PAS-stained nephrectomy samples and transplant biopsies. Our CNN can be of aid for quantitative studies concerning renal histopathology across centers and provides opportunities for deep learning applications in routine diagnostics.

Funding: Government Support - Non-U.S.

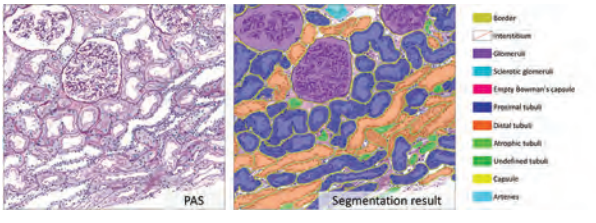


Figure 1. CNN segmentation result of a PAS-stained renal transplant biopsy.

Spearman's ρ		Visual scoring pathologists			
CNN	Intertubular area (% total cortical area)	ci score	ti score	IFTA grade	ct score
Interstitium (% total cortical area)	0.81	0.55	0.71	0.33	
Atrophic tubuli (% of total *n* tubuli)		0.62		0.58	0.58

Table 1. Mean Spearman's ρ for visually scored (Banff) components and CNN-based measures in 82 transplant biopsies.

FR-PO992

Deep Learning-Based Segmentation Enables an Efficient Assessment of Glomerulosclerosis That Is Predictive of Progressive Kidney Disease

Matthew Palmer,[1] Catherine P. Jayapandian,[2] Jarcy Zee,[3] Miroslav Sekulic,[5] Clarissa A. Cassol,[6] Andrew D. Rule,[4] Andrew Janowczyk,[2] Yijiang Chen,[2] John R. Sedor,[8] Stephen M. Hewitt,[9] Anant Madabhushi,[2] Laura Barisoni.[7] *[1]University of Pennsylvania, Philadelphia, PA; [2]Case Western Reserve University, Cleveland, OH; [3]Arbor Research Collaborative for Health, Ann Arbor, MI; [4]Mayo Clinic, Rochester, MN; [5]UH Cleveland Medical Center, Cleveland, OH; [6]The Ohio State University, Columbus, OH; [7]Duke University, Durham, NC; [8]Cleveland Clinic, Cleveland, OH; [9]National Cancer Institute, Bethesda, MD.*

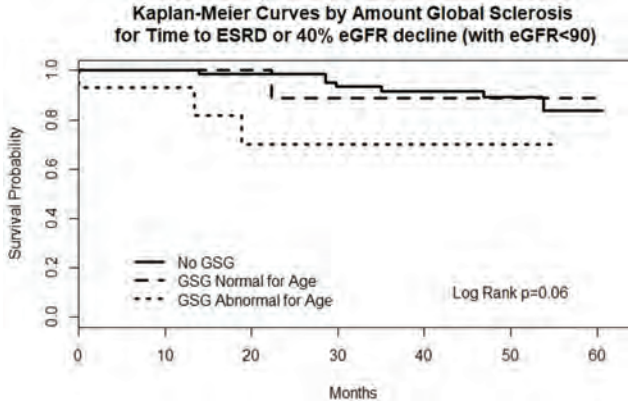
Background: The percentage of globally sclerotic glomeruli (GSG) adjusted by age is a clinically relevant parameter that has been shown to be associated with outcome across diseases. While annotation of glomeruli on whole slide images (WSI) using the NEPTUNE Digital Pathology Protocol has improved overall accuracy, manual counting remains time consuming. The aim of this study is to develop deep learning (DL) networks for automated annotation of GSG and test whether the DL-generated % GSG associates with clinical outcome.

Methods: 126 WSI (PAS) from 107 minimal change and 19 FSGS patients from the NEPTUNE dataset were used to train and test a DL network to identify normal glomeruli and GSG. The %GSG was calculated on 1 level and compared with %GSG visually assessed on the same level by 1 of 4 pathologists. Outcome data (ESRD or 40% eGFR decline) were available in 125 cases. Cases were divided into 3 groups: no GSG (95), GSG appropriate for age (14), and GSG excessive for age (16). Hazard ratios for clinical outcomes were compared across the 3 groups.

Results: The DL classifier's sensitivity as compared with visual assessment for detecting non-GSG was 0.85 and for GSG was 0.75. Compared with no GSG, GSG normal for age was associated with 1.06 (0.13-8.62) times the hazards of composite progression outcome and GSG abnormal for age was associated with 4.43 (1.14-17.26) times the hazards of composite progression outcome.

Conclusions: Our DL classifier is able to detect normal glomeruli and GSG with high sensitivity. The DL-generated %GSG correlates with clinical outcome in a manner similar to previously reported manual assessments. This work represents a foundation towards enlisting robust machine learning classifiers for evaluating clinically relevant pathologic parameters.

Funding: Private Foundation Support



FR-PO993

The Use of Quantitative Morphometrics in Nephrectomy Specimens to Understand Focal Segmental Glomerulosclerosis

Christopher L. O'Connor,[1] Jennifer A. Schaub,[1] Jeffrey B. Hodgin,[2] Roger C. Wiggins,[3] Markus Bitzer.[1] *[1]University of Michigan, Ann Arbor, MI; [2]The University of Michigan, Ann Arbor, MI; [3]University of Michigan Health System, Ann Arbor, MI.*

Background: Detection of a single segmentally sclerosed glomerulus is sufficient to establish the diagnosis of focal segmental glomerulosclerosis (FSGS), which guides management and prognosis of kidney function decline. Because 10-15 glomeruli are available for examination of standard kidney biopsies, glomerular lesions present in low frequency such as segmental glomerulosclerosis (SGS) may be missed. To determine the probability of detection of SGS and whether morphometric parameters in normal appearing glomeruli are associated with SGS, we evaluated larger kidney tissue samples from nephrectomy specimens.

Methods: We obtained specimens from 79 patients who underwent nephrectomy and abstracted clinical data from the patient's electronic medical records. We analyzed PAS-stained kidney sections for global and segmental glomerulosclerosis, and quantified glomerular morphometrics using chemical and immunohistochemical stains. We estimated the probability that a biopsy would identify FSGS using the geometric distribution with varying frequencies of SGS lesions and number of glomeruli obtained in a kidney biopsy.

Results: The median number of glomeruli per specimen was 227. 44% of patients were classified as having FSGS as defined by the presence of at least one glomerulus with SGS. Of those, 18 (39.1%) had less than 1% of their glomeruli with an SGS lesion. Patients with FSGS were more likely to be diabetic (37.5% vs. 8.1%, p=0.003), hypertensive (48.3% vs. 29.7%, p=0.006) and have a lower baseline eGFR prior to nephrectomy (69.6 vs. 86.7 - ml/min/1.73m^2, p=0.002). Patients with FSGS had increased glomerular volume (4.1 vs. 3.6 - 10^{6}μm^3, p=0.04), decreased podocyte density (106.4 vs.129.3 - podocytes/10^{6}μm^3, p=0.001), and increased podocyte volume (4885 vs 4100 - μm^3, p=0.005). For low frequency SGS lesions (<1% of glomeruli), a kidney biopsy could miss a FSGS diagnosis more than 74% of the time.

Conclusions: Qualitative and quantitative morphometric analysis of nephrectomy specimens identify low frequency SGS lesions. Kidney biopsy can frequently miss an FSGS diagnosis if there is a low frequency of SGS lesions. Future directions involve examining the possibility of using computer aided quantitative morphometry in order to impute the existence of rare glomerular features unlikely to be captured during routine biopsy.

Funding: NIDDK Support

FR-PO994

Classification of Cell Types with Neural Networks in Reference and Diseased Human and Mouse Kidney Tissue Using Nuclear Morphology

Andre Woloshuk,[2] Dawson F. Dean,[3] Andrew Mcnutt,[1] Michael T. Eadon,[3] Pierre C. Dagher,[1] Seth Winfree,[2] Tarek M. El-Achkar.[1] *[1]Indiana University, Indianapolis, IN; [2]Indiana University School of Medicine, Indianapolis, IN; [3]Indiana University Division of Nephrology, Indianapolis, IN.*

Background: Despite improvements in non-invasive analysis of kidney function, kidney biopsy remains the gold standard for diagnosing renal pathology. This field relies heavily on subjective interpretation and semi-quantitative image analysis of 2-dimentional (2D) images of stained tissue thin-sections. Advances in 3D confocal fluorescence imaging and machine learning approaches such as neural networks provide the opportunity for an automated and quantitative approach, and the potential for extracting new data from the 3-dimentional (3D) space. Neural networks have wide applications in image classification of natural images and medical imaging. Recent applications of neural networks in pathology are starting to explore segmentation and classification of histologically stained samples. The same approach has not been fully exploited in kidney tissue labeled with multiple fluorescent probes and imaged in 3D.

Methods: We identify individual cells in human and mouse kidney tissue and assigning each cell a ground truth classification based on validated cell markers. Images of the nuclei as 2D projections and 3D volumes from tissue are extracted and classified based on these markers using volumetric tissue exploration and analysis cytometry. Different neural network architectures are trained and evaluated using this image database. The efficacy of different architectures is assessed by their ability to distinguish different cell types within the biopsy.

Results: In this work, we create an image database of fluorescently stained nuclei collected from human and mouse renal tissue that can be used to identify and classify different cell types solely on their nuclear features. Furthermore, we begin to demonstrate the efficacy of identifying pathologies in either a mouse model of acute kidney injury or in human diabetes.

Conclusions: This work lays the groundwork for quantifying the types of cells present in biopsies, and the automatic classification of pathological cell states in a biopsy that may have otherwise gone unnoticed. Ultimately, machine learning-augmented image analysis has the potential not only to describe novel and distinct disease features, but also define a standardized approach to quantifying pathology in a kidney biopsy.

Funding: NIDDK Support

FR-PO995

Unsupervised Machine-Learning Cytometry of High-Dimensional Image Data from Fluorescently Labeled Mesoscale Kidney Tissue Automates Quantitation and Uncovers Unique Cellular Populations

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Background: The cytometric analysis of fluorescent mesoscale kidney imaging datasets presents unique challenges in segmentation, measurement and analysis. To address these challenges, we developed the tissue cytometry tool, Volumetric Tissue Exploration and Analysis (VTEA). VTEA streamlines nuclei segmentation, measurements and enables flow cytometry-like analysis in mesoscale 3D images of kidney tissue. However, as we add 1) additional fluorescent markers with novel imaging modalities and 2) imaging metrics, including texture and spatial characteristics, flow cytometry-like approaches become inadequate under the strain of these higher dimensional data. Here our goal was to implement and demonstrate the need and utility of unsupervised analysis of higher dimensional tissue cytometry data.

Methods: Imaging datasets were collected from fluorescently labeled mouse and human kidney tissue with confocal fluorescence microscopy and up to 8 independent

fluorophores. Image processing and analysis was performed with the recent version of VTEA that incorporates Java based libraries for clustering of datasets (e.g. K-mean, Gaussian-mixtures) and dimensionality reduction tools (e.g. PCA and tSNEs).

Results: We extended our cytometry tool, VTEA, incorporating unsupervised machine learning approaches with publicly available Java libraries. Using clustering, we identify cellular population of cells not readily identified with manual gating. The mapping of high dimensional cytometry data to lower dimensions facilitates rapid visual identification of cell sub-population not readily apparent. Lastly, we demonstrate the advantage of looking at our imaging data with both dimensionality reduction and clustering-an approach that has been exploited by the omics fields.

Conclusions: Our work demonstrates the need and utility for high dimensional analysis of mesoscale kidney imaging data and suggests we gain insight with the application of unsupervised machine learning approaches to image analytics, especially in the framework of the interactive exploratory platform VTEA. Lastly, our work underlines the importance of reusable software and the power of an open software community found in the NIH supported ImageJ community.

Funding: NIDDK Support

FR-PO996

Gene-Environment Interactions Modulate Anti-DNA and Anti-Myeloperoxidase. Autoimmunity in Lupus

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Background: Autoantibody (autoAb)-mediated glomerulonephritis develops in 60-85% of patients with lupus and ANCA vasculitis. Nephron preservation requires control of the systemic autoimmune response. To better understand factors driving autoimmunity, we used a mouse model system to study interaction of lupus genetic susceptibility and inhalation of crystalline silica (Si), an environmental exposure linked to human lupus. We previously showed that Si induces lung injury, lymphoid aggregates, and autoAbs in mice of genetically diverse backgrounds. Herein we report strain differences in Si-induced autoAb specificity, production site, and co-exposure requirements.

Methods: Wildtype (WT) and autoAb transgenic (Tg) B6, BXSB, MRL, and NZB mice were exposed to Si (Si+) or vehicle (V+) by aspiration; tissues were harvested for immunophenotyping 1 to 3 months later.

Results: Among WT lupus mice exposed to Si, anti-DNA IgG levels are significantly higher in bronchoalveolar lavage fluid (BALF) from Si+ MRL compared to other Si+ strains (mean OD405 1.35 vs 0.07, 0.49, & 0.36 for B6, BXSB & NZB, $p<0.05$). TLR7/TLR9 ligands induce significantly more anti-DNA IgG from cultured lung cells of Si+ vs V+ MRL (OD405 0.49±0.43 vs 0.11±0.21, n=6-9/grp, $p<0.05$), and vs lung cells of Si+ B6 and Si+ NZB (OD405 0.02±0.02 & 0.01±0.01). Anti-myeloperoxidase (MPO) Ig are detected only in BALF of Si+ BXSB, and are not found in BALF from V+ BXSB ($p<0.05$, n=7/grp) or from Si+ B6, MRL, & NZB. To probe the in vivo fate of autoAb-producing lymphocytes after Si exposure, we studied mice of each strain expressing an autoAb Tg. Results suggest that central deletion and anergy are intact: mean spleen B cell numbers (5.7±3.4 mil, n=25) are markedly lower than that for non-Tg counterparts (35±2 mil, n=53) and do not differ for Si+ vs V+ mice in any of the 4 Tg strains; and, the residual autoAb Tg B cells produce little Tg autoAb. However, TLR7/TLR9 stimulation induces Tg autoAb production by splenocytes from Si+ Tg B6 mice.

Conclusions: These results suggest that silica exposure can disrupt local and systemic autoimmune control in a strain-dependent manner, consistent with gene-environment interaction in modulation of the autoimmune response. The results further suggest that Si-induced subtle alterations in autoreactive lymphocyte regulation are unmasked by environmental co-exposure.

Funding: Other NIH Support - NIEHS, Veterans Affairs Support

FR-PO997

Imaging Renal Inflammation and Fibrosis After Ischemia-Reperfusion Injury by Novel Diffusion MRI

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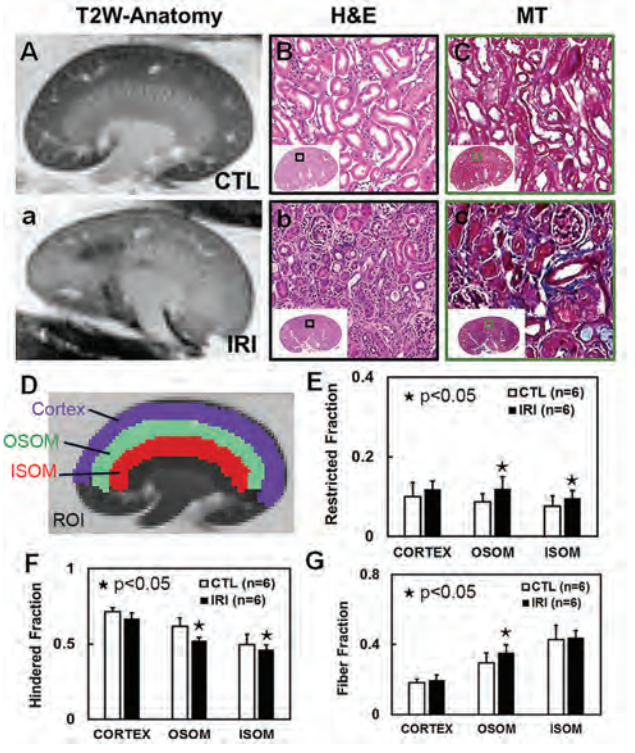
Background: Conventional MRI provides noninvasive assessment for disease progression but lacks the pathological specificity. Previously, we successfully developed diffusion basis spectrum imaging (DBSI) to assess coexisting axonal injury, demyelination, and inflammation. This study aims to test whether DBSI can noninvasively detect kidney pathologies after ischemia reperfusion injury (IRI).

Methods: Six 10-week-old female C57BL/6 mice received unilateral left kidney IRI for 30 minutes. Mice were euthanized and perfusion fixed with 4% PFA at 4-7 days after surgery. IRI and contralateral control (CTL) kidneys were harvested for *ex vivo* DBSI scans. The DBSI scan was performed on a 4.7-T scanner: TR = 1.5 s, TE = 33 ms, maximal b-value = 1,500 s/mm^2, image slice thickness = 0.5 mm, in-plane resolution = 156 × 156 μm^2. DBSI-assessed restricted (putative cellularity), hindered (putative cytotoxic edema) and fiber (putative interstitial fibrosis) were derived using a novel lab-developed software. H&E and Masson's trichrome (MT) stains were performed to validate DBSI findings.

Results: Representative H&E and MT images of IRI kidneys demonstrated obvious tubular injury, interstitial edema, inflammation (b) and fibrosis (c). The region of interest (ROI)s were defined on T2W anatomy image (D). The corresponding DBSI metrics suggested significant increased cellularity (higher restricted fraction, E) and reduced interstitial space (reduced hindered fraction, F) in outer medulla. Higher anisotropic fiber fraction in outer stripes of outer medulla of IRI group (G) indicated increased fibrosis at that region.

Conclusions: DBSI MRI could detect coexisting pathologies in kidneys after injury. It has potential to noninvasively follow kidney disease progress, monitor treatment efficacy, and translate to clinical application.

Funding: Other NIH Support - National Institute of Health R01-NS047592, P01-NS059560, U01- EY025500, Other U.S. Government Support, Private Foundation Support



FR-PO998

The Solute Carrier SLC16A12 Is Critical for Creatine and Guanidinoacetate Handling in the Kidney

Sofia N. Verouti,[1,2] Delphine Lambert,[1,2] Escher Geneviève,[1,2] Bruno Vogt,[1,2] Daniel G. Fuster.[1,2] *[1]Department of Biomedical Research, University of Bern, Bern, Switzerland; [2]Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, Bern, Switzerland.*

Background: A heterozygous mutation (c.643C.A; p.Q215X) in the creatine transporter *SLC16A12* was proposed to cause a syndrome with juvenile cataracts, microcornea and glucosuria in one Swiss family. However, we previously discovered a digenic syndrome in the index family and demonstrated that the glucosuria was due to a concomitant *SCL5A2* mutation. In localization studies, we found SLC16A12 expression at the basolateral membrane of proximal tubular cells (PCT), and patients with the heterozygous *SLC16A12* mutation displayed significantly reduced plasma levels and increased fractional excretion rates of guanidinoacetate (GAA).

Methods: To further explore the role of SLC16A12 in renal physiology and decipher the mechanism underlying the heterozygous *SLC16A12* mutation in humans, we studied SLC16A12 deficient rats.

Results: SLC16A12 KO rats had lower plasma levels and increased 24 h urinary excretion rates of creatine and GAA compared to WT littermates. SLC16A12 KO rats also displayed lower plasma creatinine levels, but urinary creatinine excretion rates were reduced in parallel compared to WT rats. The phenotype of heterozygous rats was indistinguishable from WT rats. Metabolic cage experiments revealed no additional signs of tubular dysfunction in SLC16A12 KO rats. In addition, glomerular filtration rate, measured by FITC-sinistrin, was unaltered in SLC16A12 KO rats. Selective renal artery and vein sampling showed similar A-V differences in GAA concentrations between WT and SLC16A12 KO rats, indicating incomplete compensation of urinary GAA losses by renal synthesis in SLC16A12 KO rats. In support of this finding, mRNA expression of L-arginine:glycine amidinotransferase (AGAT), the rate limiting enzyme in GAA synthesis, was significantly reduced in kidneys of SLC16A12 KO rats.

Conclusions: Our results reveal that SLC16A12 is critical for tubular reabsorption of creatine and its precursor GAA from the glomerular filtrate. In the absence of SLC16A12, ongoing urinary losses of GAA are not adequately compensated by increased intrarenal synthesis, possibly caused by AGAT feedback inhibition due to impaired basolateral exit of creatine from the PCT. Furthermore, the lack of a phenotype in SLC16A12 heterozygous rats suggests a dominant-negative mechanism underlying the phenotype observed in humans with heterozygous c.643C.A; p.Q215X *SLC16A12* mutation.

FR-PO999

Tubular Epithelial Cell-Derived Exosomal MiRNA-19b-3p Promotes M1 Macrophage Activation in Kidney Injury

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Background: Tubulointerstitial inflammation is a common characteristic for acute and chronic kidney injury. However, the mechanism by which the initial injury on tubular epithelial cells (TECs) drives interstitial inflammation remains unclear. Here we set out to characterize the miRNA profile of kidney exosomes and aim to explore the role of exosomal miRNAs derived from TECs in the development of tubulointerstitial inflammation.

Methods: Exosomes were isolated from kidney and characterized via electron microscopy (EM) and nanoparticle analysis(NTA). We examined profiles of miRNAs in kidney exosomes from LPS-induced kidney injury model by Exiqon microarray. Putative targets of miRNA were predicted by TargetScan. Chronic proteinuric kidney disease model was induced by adriamycin(ADR) injection. Exosomes purified from TECs were added to macrophages or intrarenal injected to mice to determine its effects both in vitro and in vivo.

Results: Serum creatinine and urine albumin to creatinine ratios were significantly increased in LPS treated mice compared with controls. Histologically, the tubular epithelial cell injury, protein cast and CD68+ macrophage infiltration was found in LPS injected mice. EM and NTA confirmed the typical characteristic of exosomes. Global miRNA expression profiling on renal exosomes was examined in LPS-induced AKI model and miR-19b-3p was identified as the most remarkable miRNA increased in TEC-derived exosomes compared with controls. Similar results were found in ADR-induced chronic proteinuric kidney disease model in which exosomal miR-19b-3p was markedly released. Interestingly, once released, TEC-derived exosomal miR-19b-3p was internalized by macrophages, leading to M1 phenotype polarization through targeting NF-κB/SOCS-1. Importantly, the pathogenic role of exosomal miR-19b-3p in initiating renal inflammation was revealed by the ability of adoptive transfer of purified TEC-derived exosomes to cause tubulointerstitial inflammation in mice, which was reversed by inhibition of miR-19b-3p. Clinically, high levels of miR-19b-3p were found in urinary exosomes and correlated with the severity of tubulointerstitial inflammation in patients with diabetic nephropathy.

Conclusions: Exosome/miR-19b-3p/SOCS1 axis played a critical pathologic role in tubulointerstitial inflammation that might represent a new therapeutic target for kidney disease.

FR-PO1000

Impact of Nephron Number on Renal Uric Acid Excretion in Patients with IgA Nephropathy

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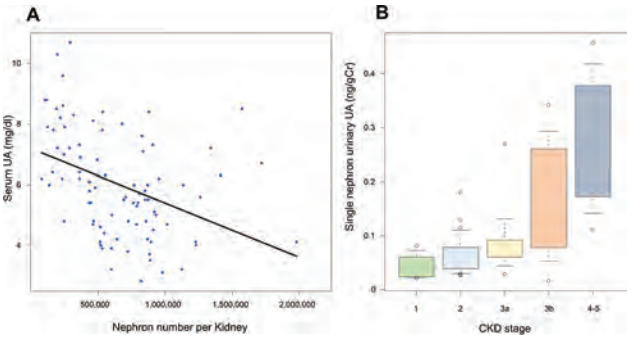
Background: Hyperuricemia is a risk factor for the progression of chronic kidney disease (CKD), which is characterized by a progressive loss of functioning nephrons. Uric acid (UA) induces renal tubular cell injury. To date, renal UA handling has not been examined in relation to nephron number in patients with CKD due to technical difficulties in counting nephrons in a clinical setting.

Methods: The relationships between parameters related to UA handling and clinically relevant factors, including total nephron number, were examined in patients with biopsy-proven IgA nephropathy (IgAN). The total nephron number was estimated by the combined use of unenhanced computed tomography and stereology-based estimation of non-sclerotic glomerular density in biopsy specimens (Sasaki T et al. 2018 ASN).

Results: A total 87 patients were included in the study (mean age, 39.7 years; 47.1% male; estimated glomerular filtration rate [eGFR], 67.1 ± 22.1 ml/min/1.73 m^2). The total nephron number in the patients ranged from 78,000 to 1,989,000 per kidney. The serum UA level and total nephron number showed a significant inverse correlation ($r = –0.395$, $p < 0.01$) (**Figure A**). Multivariate analysis showed that the association between the serum UA and nephron number was independent of gender, BMI, and renal function. The single-nephron excretion of urinary UA (urinary UA/urinary creatinine per total nephron number) was markedly increased in patients with advanced CKD at stage 3b or higher (**Figure B**).

Conclusions: The results of this study suggest that the total number of nephrons is an important determinant of the serum UA level in patients with IgAN. Abnormally concentrated UA in renal tubules due to compensatory failure may play additional roles in the progression of renal injury in patients with advanced-stage CKD.



FR-PO1001

Total Nephron Number and Renal Histopathological Lesions in IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most frequently occurring primary glomerulonephritis. It is histopathologically characterized by various degrees of glomerulosclerosis together with a series of active proliferative lesions, which represent a process of progressive loss of functional nephrons. To date, total nephron number has not been evaluated in relation to the histopathological findings of IgAN due to the technical difficulties in counting nephrons in a clinical setting.

Methods: The histopathological findings in diagnostic biopsies of IgAN patients were evaluated based on the Oxford international classification and the Japanese histological grade. The latter is a lamped scoring system of glomerular lesions exhibiting cellular or fibrocellular crescents, segmental sclerosis, and global sclerosis. Total nephron number was calculated using a simplified method based on the combined use of unenhanced computed tomography and stereology-based estimation of non-sclerotic glomerular density on renal biopsy (Sasaki T et al. 2018, ASN).

Results: A total of 107 cases (age 43, male 54%, estimated glomerular filtration rate 61.5 ± 24.2 ml/min/1.73 m^2, urinary protein excretion 1.4 ± 1.6 g/day) were included. The frequencies of the Oxford classifications were as follows: M (0, 51%; 1, 49%), E (0, 88%; 1, 12%), S (0, 10%; 1, 90%), T (0, 74%; 1, 20%; 2, 6%) and C (0, 64%; 1, 36%), respectively. The frequencies of the Japanese histological grades were as follows: H-I, 56.1%; H-II, 28.0%; H-III, 13.1%; and H-IV, 2.8%. Among all patients, the total nephron number ranged from 78,000 to 1,989,000. Total nephron number was significantly associated with the S score ($p < 0.042$) and the T score ($p < 0.001$), but was not associated with the M, E and C scores of the Oxford classification. Moreover, total nephron number significantly decreased in parallel with increasing Japanese histological grade ($p < 0.001$). Multivariate analyses showed that the associations between total nephron number and the T score or H-grade were independent of age, amount of urinary protein excretion, and renal function at the time of biopsy.

Conclusions: These results suggest that the total nephron number may be associated with certain histopathological lesions and thus may be involved in the progression of renal injuries in IgAN.

FR-PO1002

ChromA-ExM: A New Application of Expansion Microscopy for Optical Imaging of Chromatin Architecture in Renal Tubular Epithelial Cells with Nanoscale Resolution

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Background: In the eukaryotic cell nucleus, chromatin is physically organized into euchromatin and heterochromatin domains. Those domains regulate transcriptional accessibility to DNA, ultimately determining cell phenotype and function. Currently, high-resolution visualization of chromatin domain architecture can be achieved only with either electron microscopy or super-resolution microscopy. Both techniques have practical limitations, a major one being that they are not easily accessible to most laboratories. Here we introduced a modification to the original Expansion Microscopy (ExM) protocol developed at MIT that allows nanoscale resolution for visualization of high-order chromatin structures using regular confocal microscopes. The new procedure is called Chromatin Architecture Expansion Microscopy (ChromA-ExM)

Methods: Using conventional immunofluorescence techniques we labeled histone decorations in either cell or tissue specimens. The immunostained tissue specimens are subsequently embedded in a swellable polymer network, and digested with protease K. The combination of both treatments allows for ~4.5 isotropic expansion of the sample, which constitutes a magnification factor multiplied by the magnification of the microscope objective used. In ChromA-ExM we introduced steps of selective enzymatic digestion with DNAses allowing further expansion of chromatin domains

Results: Analysis of H3K9me3 chromatin domains in kidney PTECs indicated that, compared to regular ExM, the ChromA-ExM protocol results in increased resolution for visualization of high-order chromatin domains, including chromocenters associated with active cell phenotype, and senescence associated heterochromatin foci. Further, we can interrogate spatial interactions between $H3K9me3^{+}$ (silent chromatin) and $H3K4me3^{+}$ (open chromatin) domains in kidney tubular epithelial cells with exquisite detail, to detect architectural chromatin arrangements associated with kidney disease

Conclusions: ChromA-ExM is a new tool to study chromatin spatial configuration and chromatin status. The technique is useful for ultrastructural analysis of chromatin changes in PTEC senescence and tubular pathologies

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FR-PO1003

Deletion of Proximal Tubular Cell VEGF Production Promotes Renal Fibrosis: Implications for VEGF-Based Cancer Therapy

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Background: Targeting tumor angiogenesis by blocking VEGF (vascular endothelial growth factor) inhibits tumor development and growth, and is a common strategy in cancer therapeutics. Human and animal observations have shown that subtle changes in VEGF levels can result in hypertension, proteinuria, and glomerulopathies. VEGF deletion in all renal tubular epithelial cells has been reported to disrupt peritubular microvascularization. Since proximal tubular (PT) cells are arguably the primary target cells during kidney injury we hypothesized that loss of PT-VEGF production might provoke the development of renal fibrosis following injury.

Methods: We crossed GGT-$Cre^{+/-}$ mice with $VEGF^{f/f}$ mice to generate PT-specific VEGF knockout (GGT^{Cre+};$VEGF^{f/f}$) and control (GGT^{Cre-};$VEGF^{f/f}$) mice. Mice were challenged with unilateral ureteral obstruction (UUO) kidney injury model.

Results: PT-VEGF is dispensable for kidney development and health. No obvious histological differences including peritubular capillary assessment using CD31, an endothelial cell marker, was observed. To determine whether PT-secreted VEGF might contribute to the development of injury-induced interstitial fibrosis, both groups underwent UUO x Day 7. Increased tubular damage and interstitial fibrosis was observed in the PT-VEGF KO group compared to the control group. While there were no differences in peritubular capillary distribution in non-injured animals, segmental loss of peritubular capillaries with increased hypoxic areas was detected by carbonic anhydrase IX (hypoxia marker) staining in the PT-VEGF KO group. Furthermore, increased myofibroblasts was also observed in these animals.

Conclusions: PT-VEGF is necessary for the maintenance of the peritubular capillary network following kidney injury; preventing hypoxia, subsequent myofibroblast recruitment, and indirectly limiting renal fibrosis. Cancer patients are at high risk for developing acute kidney injury, and those on pharmacological inhibition of VEGF are even more vulnerable. These two factors alone warrant increased attention and diligence to our cancer patients who are at highest risk for progressive kidney disease and emphasize the growing importance of onco-nephrology.

FR-PO1004

Jade-1 in Double-Strand Break Repair in Kidney Cancer

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Background: Like many solid tumors, kidney cancer is characterized by chromosomal breaks and instability, which arise from defects in DNA double-strand break (DSB) repair. We have established that Jade-1 is a renal tumor suppressor that induces apoptosis, inhibits proliferation, and inhibits oncoproteins Akt and β-catenin. Jade-1 also functions on DNA, through gene transcription, histone acetylation and DNA replication. As an unbiased approach to identify new Jade-1 tumor suppressor functions, Jade-1 was immunoprecipitated with Flag antibody in kidney cells to discover novel interactors via mass spectrometry. Surprisingly, many DNA repair proteins were found associated with Jade-1, including those involved in DSB repair, such as DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and Ku70 and Ku80.

Methods: Kidney and kidney cancer cells were treated with a variety of agents that induce DSBs, including neocarzinostatin (NCS), a radiomimetic agent that induces DSBs. Immunofluorescence (IF) studies were done to visualize Jade-1 and DNA damage indicator γH2AX. Additionally, sensitivity assays were performed to assess for *Jade-1* dose-dependent survival differences in kidney proximal tubule-derived HK-2 cells, which serve as a model of renal cancer precursor cells.

Results: Interaction of endogenous Jade-1 and DNA-PKcs was confirmed in coimmunoprecipitations. Jade-1 was found to be inducible in kidney and kidney cancer cells in response to DSBs. IF studies demonstrated colocalization of Jade-1, γH2AX, and phospho-DNA-PKcs following DNA damage. Moreover, silencing of *Jade-1* in HK-2 cells offered protection against DNA damage in cell survival assays, supporting a direct role for Jade-1 in the DNA repair process.

Conclusions: We hypothesize that Jade-1 directly promotes DSB repair in part by binding and regulating DNA-PKcs, thereby favoring homologous recombination over error-prone repair through non-homologous end-joining. Our findings indicate that Jade-1 helps maintain genomic stability and further underscore its importance as a renal tumor suppressor. In short, understanding the molecular underpinnings of DNA repair may be critical for developing strategies for deterring progression of renal cancer and other solid tumors as well.

FR-PO1005

The Role of the Inflammatory Chemokine CCL20 in Renal Injury in Multiple Myeloma

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Background: The pathogenesis of the occurrence and development of renal injury in myeloma is unclear. In this study to investigate the role of inflammatory chemokine CCL20 in multiple myeloma with kidney injury.

Methods: To detect the expression of CCL20 in renal tissue and bone marrow of multiple myeloma patients with kidney damage by Immunohistochemical technique. Using flow cytometry to analysis proliferation of myeloma cells with overexpression or lowexpression of CCL20. By qRT PCR and flow cytometry method to detect expression of myeloma cells infiltrating organize related receptor CXCR4 and ROBO4 with overexpression or knockdown CCL20. Establish myeloma cells transplantation model. Vitro imaging techniques were used to observe myeloma cells implanted into the bone marrow and kidney tissue. By flow cytometry, to analysis the graft rate(%) of myeloma cells and expression of CXCR4 and ROBO4 in bone marrow cell population and renal tissue on mice with overexpression or knockdown CCL20. Morbidity and survival situation were dynamically observed for mice with overexpression or knockdown CCL20.

Results: The expression of CCL20 in myeloma and renal tissue was obviously higher than control group, and found that the myeloma cells with strong invasion ability had higher expression of CCL20 that suggested CCL20 were related with myeloma invasion ability. Showed that there was a difference in the ratio of immature cells in myeloma cells at different expression levels. The overexpression of CCL20 myeloma cell had significantly proliferated compared with the low expression of CCL20 myeloma cell. The CCL20 promoted the expression of CXCR4 and ROBO4 of myeloma cell. We had successfully established myeloma transplanted model. Animal experiments showed: After transplanting myeloma cells with knockdown CCL20 to immunodeficiency mice, myeloma cells badly survived and slightly damaged kidney. After transplanting overexpression of CCL20 myeloma cells to immunodeficiency mice, myeloma cell could survival well and damage kidney. The above thought that CCL20 in maintaining the survival of myeloma cells in bone marrow and renal tissue was necessary.

Conclusions: CCL20 plays an important role in the occurrence and development of renal injury in myeloma. Antagonistic CCL20 might be a new target for the prevention and treatment of renal injury in myeloma.

Funding: Government Support - Non-U.S.

FR-PO1006

AKI Promotes the Development of Papillary Renal Carcinoma from Tubular Progenitors

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Background: Renal cell carcinoma (RCC) accounts for about 2% of all cancers. Risk factors for RCC include obesity, diabetes, hypertension and genetic factors, but the majority of cancers occur in apparent absence of clear risk factors. As tissue injury is an important cofactor for many types of cancers, we propose to verify if acute kidney injury (AKI) plays a role in RCC development, and to identify the cellular origin of RCC.

Methods: We used the following techniques: 1. Experimental AKI induction in wild-type mice to study tumor development over 36 weeks. 2. Analysis of TCGA Research Network dataset on human papillary RCC (pRCC) molecular characterization, focusing on AKI-driven pathways. 3. Development of mouse models in which the intracellular domain of Notch 1 (NICD1) a molecule modulated during AKI, is expressed constitutively by all Pax8+ tubular epithelial cells (Pax8/NICD1) or only by Pax2+ renal progenitors (Pax2/NICD1) upon induction in adult mice. The mice were sacrificed at 36 weeks or 4 weeks after AKI. 4. Clonal analysis of tumoral lesions with Confetti reporter. 5. Examination of single cell RNA sequencing (RNAseq) data from pRCC patients.

Results: Wild-type mice subjected to AKI developed type 2 papillary adenomas and pRCCs over time. Among AKI-related pathways, Notch1 overexpression in human pRCC associated with worse outcome, prompting us to generate NICD1-overexpressing mice. At 36 weeks or at 4 weeks following AKI, Pax8/NICD1 mice presented a significant decline of renal function as well as type 2 pRCCs. Confetti lineage tracing showed that most of the pRCCs were mono- or biclonal, suggesting a local stem cell/progenitor cell origin. Pax2/NICD1 mice presented type 2 pRCCs, and lineage tracing identified single Pax2+ tubular progenitors as the source of pRCCs. RNAseq analysis confirmed that PT1 signature of pRCC cell of origin matched human tubular progenitor molecular characteristics.

Conclusions: AKI promotes long-term development of type 2 papillary tumors in mice by activating AKI-associated pathway Notch1. This study establishes Pax2+ renal progenitors as the cellular origin of the tumor in mice, and identifies renal progenitors as pRCC PT1 signature cells in humans.

Funding: Government Support - Non-U.S.

FR-PO1007

Light Chain Endocytosis in Renal Proximal Tubular Cells Lead to Impaired Autophagy and Mitophagy

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Background: AL amyloidosis is the result of clonal production of amyloidogenic immunoglobulin light chain (LC) proteins, often resulting in renal failure. Although amyloid fibril deposition of LC proteins is a major cause of renal damage in AL amyloidosis, amyloid precursor proteins might also directly impair renal tubular function at the cellular level, independent of fibril formation. Light chains are actively reabsorbed in the proximal tubular epithelial cells (PTECs) by endocytosis and degraded in lysosomes. Lysosomes are also essential for functional autophagy, a process responsible for the removal of damaged mitochondria (mitophagy) and denatured proteins. We hypothesize that LC endocytosis causes PTEC injury by inhibiting autophagy, including mitophagy, resulting in accumulation of dysfunctional mitochondria, that mediates PTEC injury.

Methods: Cultured primary PTECs extracted from kidneys of Balb/C mice were exposed *in vitro* to 6 different LCs purified from patients' urine. Light chains were derived either from AL amyloid patients with associated nephropathy or from a non-amyloid myeloma patient, as control. Autophagic flux was estimated by immunoblot using the autophagy marker LC3-II, in both bafilomycin treated and untreated cells. Autophagosomes were quantified in live cells using fluorescent microscopy as well as a microplate reader. Mitochondrial respiration and reactive oxygen species production were measured in live cells. Mitochondrial morphology was also assessed using confocal microscopy.

Results: Patient derived LCs caused autophagy inhibition at various levels. Amyloid LC exposed cells accumulated damaged mitochondria with altered mitochondrial function and morphology resulting in increased ROS production.

Conclusions: Dysfunctional autophagy and mitophagy caused by direct cellular toxicity of LCs likely contribute to tubular cell toxicity in AL amyloidosis.

Funding: NIDDK Support, Private Foundation Support

FR-PO1008

Repurposing Tolvaptan, a Drug for Polycystic Kidney Disease, for Renal Cell Carcinoma Therapy

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Background: The vasopressin type-2 receptor (V2R) plays an essential role in the regulation of salt and water homeostasis by the kidneys. Based on a serendipitous finding that V2R is ectopically expressed in human clear cell renal cell carcinoma (ccRCC) tumors, the current studies examined if V2R plays a pathogenic role in ccRCC tumor growth. The effect of Tolvaptan, an FDA approved drug for hyponatremia and polycystic kidney disease was also tested.

Methods: V2R expression was examined using the cancer genome atlas database, and analysis of human RCC tumor tissue microarrays, cDNA arrays and tumor biopsy samples. *In vitro* and *in vivo* mouse tumor xenograft studies were performed to determine V2R's role in ccRCC tumor growth and test therapeutic interventions.

Results: V2R expression and activity, suggested by high intracellular cAMP and phosphorylated ERK1/2 (pERK1/2), levels were detected in human ccRCC tumors. The V2R antagonists OPC31260 and Tolvaptan, as well as V2R gene silencing reduced *in vitro* clonogenicity, wound closure and cell viability of 786-O and Caki-1 human ccRCC cell lines. V2R antagonists reduced pERK1/2 levels, while V2R agonist increased cAMP and pERK1/2 levels. Tolvaptan and OPC31260 also decreased RCC tumor growth in mouse xenograft models by reducing cell proliferation and angiogenesis, while increasing apoptosis. In contrast, the V2R agonist dDAVP significantly increased tumor growth.

Conclusions: These results provide novel evidence for the pathogenic role of V2R signaling in ccRCC and suggest that V2R antagonists, including the FDA approved drug Tolvaptan, could be utilized as novel therapeutics for ccRCC.

Funding: NIDDK Support

FR-PO1009

TIMAP Drives Tumor Angiogenesis

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Background: TIMAP (TGFβ inhibited membrane associated protein) is an endothelial cell (EC)-predominant inhibitor of myosin phosphatase, which we first identified in glomerular EC. It is abundant in EC of developing, but not mature kidneys. Glomerular EC proliferation and sprouting angiogenesis *in vitro* require TIMAP. This study utilized the murine breast cancer model to determine whether *in vivo* angiogenesis also requires TIMAP.

Methods: Mouse mammary adenocarcinoma cells (E0771, syngeneic for C57BL/6 mice) were injected into mammary glands of 5 pairs of 8-week-old female TIMAP$^{+/+}$ and TIMAP$^{-/-}$ mice (C57BL/6 background). Each pair was euthanized on the day the tumor diameter, determined by externally applied calipers, in one mouse of the pair exceeded 1.5 cm. The tumors were excised, their weight and mean diameter measured. Vascular density was quantified using fluorescence microscopy for the EC marker PECAM1.

Results: Tumor size was similar in TIMAP$^{+/+}$ and TIMAP$^{-/-}$ mice through day 8-10. In 4 of 5 TIMAP$^{-/-}$, but not TIMAP$^{+/+}$ mice, the tumors then began to erode through the skin, bleed spontaneously and then regressed gradually. At the time of euthanasia (day 20-34 after injection) tumor size, weight and blood vessel density were significantly lower in TIMAP$^{-/-}$ compared to TIMAP$^{+/+}$ mice (Table).

Conclusions: The data are interpreted to indicate that mammary tumors in TIMAP$^{-/-}$ become necrotic and then involute due to insufficient hypoxia-driven angiogenesis. The data furthermore indicate that TIMAP provides a critical pro-angiogenic signal in EC, at least during tumor angiogenesis. Further work is required to determine whether TIMAP could be targeted in the treatment of highly vascular tumors, including renal cell carcinoma.

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

Tumor Parameters

	TIMAP+/+ (n=5)	TIMAP-/-(n=5)	p (Student t-test)
Mean Diameter (mm ± SD)	18.24 ± 3.56	10.85 ± 2.73	0.006
Mean Weight (g ± SD)	2.59 ± 0.92	0.55 ± 0.43	0.002
Vascular Density (arbitrary units ± SD)	32.05 ± 6.82	20.65 ± 8.52	0.048

FR-PO1010

Molecular Analysis of Urothelial Carcinoma After Kidney Transplantation

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Background: In Taiwan, urothelial carcinoma(UC) is the most common de novo cancer after kidney transplantation(KT). UC has high degree of molecular heterogeneity compared with other solid tumor. Mutational profiles as revealed by whole exome sequencing (WES) could help in identifying disease-specific genes and also novel genes for therapeutic target and outcomes. In this study, we perform WES of UC developed after KT in an effort to discover the molecular genetics of UC post KT.

Methods: Formalin-fixed paraffin-embedded tumor samples of UC and blood samples from 6 KT patients from our medical center were obtained. KT patients with UC diagnosed before the transplant surgery were excluded. All of the patients were sporadic, without any family history of UC. 5 hemodialysis patients with UC diagnosed after dialysis treatment were selected as control. DNA from tumor sample was extracted for WES analysis. Genomic DNA from blood sample was confirmed by Sanger sequencing as mutation validation.

Results: Our WES data was matched with the Catalogue of Somatic Mutations In Cancer (Cosmic), Intogen, and The Cancer Genome Atlas (TCGA) database for onco-driver genes. 8 genes were identified, including *GNAQ, MLLT10, SEPT6, SLC34A2, NTRK3, IKZF1, SH3GL1,* and *HOXD13.* After validation from genomic DNA, 6 genes were identified as uniquely found in tumor sample: *MLLT10, SH3GL1, SEPT6, IKZF1, GNAQ and NTRK3*.

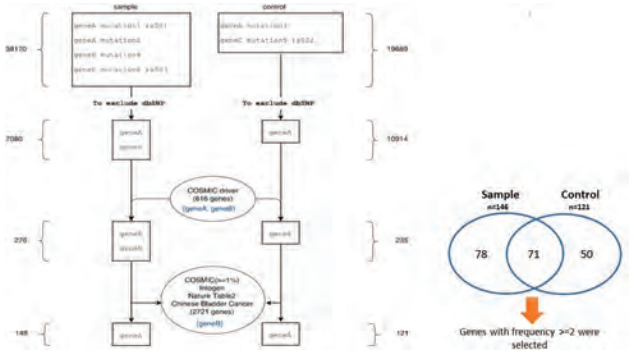
Conclusions: This preliminary data provides clues for understanding the mutational landscape of UC developed after KT. In future, functional study regarding these 6 genes will be developed in an effort to investigate the mutational environment of UC after KT.

Funding: Private Foundation Support

Patient ID	Age at diagnosis	Sex	Smoking	HBV/ HCV	Chinese Herb history	Occupation	Kidney transplant	Induction	Maintenance	Acute rejection	Tumor Location	Pathology	Treatment
KT17	48	F	No	No	Unknown	Bio-engineer	Yes	Steroid + IL2RA	Tac+MMF+Pred	Yes	Bladder	Infiltrating UC, high grade, pT3bxNx	Partial cystectomy
KT79	61	F	No	No	Yes	Housewife	Yes	Steroid + IL2RA	Tac+MMF+Pred	Yes	Bladder, ureter	Non-invasive UC, high grade, pTa	Left nephrectomy
KT80	51	F	No	HCV	Unknown	Housewife	Yes*	Steroid + IL2RA	Tac+MMF+Pred+ MTOR	No	Ureter(L2)	Infiltrating UC, high grade, pT2Nx	Bilateral nephrectomy
KT91	63	F	No	HBV	Unknown	Housewife	Yes*	Steroid + IL2RA	Tac+MMF+Pred+ MTORi	No	Renal Pelvis	Infiltrating UC, high grade, pT2Nx	Left Nephrectomy
KT720	49	F	No	No	unknown	Medical	Yes	Steroid + IL2RA	Tac+MMF+Pred+ MTORi	No	Renal Pelvis	Infiltrating UC, high grade, pT3	Right nephrectomy
KT721	55	F	No	HCV	Unknown	Housewife	Yes*	Steroid+ IL2RA	Tac+MMF+Pred+ MTOR	No	Bladder	Non-invasive papillary UC, high grade, pTa	TURBT
KT722	61	F	No	No	Unknown	Housewife	Yes	Steroid + IL2RA	Tac+MMF+Pred	No	Renal Pelvis	Infiltrating UC, high grade, pT2aNx	Left nephrectomy
KT25	52	F	No	No	Unknown	Housewife	No	No	No	No	Bladder, ureter	Non-invasive papillary UC, low grade	Right Nephrectomy and cystectomy
KT77	56	F	No	HCV	Yes	Housewife	No	No	No	No	Bladder	Infiltrating UC, high grade, pT1Nx	Radical cystectomy and bilateral nephrectomy
KT78	70	F	No	No	Unknown	Sales person	No	No	No	No	Bladder + ureter	Infiltrating UC, high grade, pT3aNx	Radical cystectomy
KT595	64	F	No	No	Yes	Worker	No	No	No	No	Renal Pelvis	Infiltrating UC, low grade, pT1cNxMx	Left Nephrectomy
KT596	66	F	No	No	Unknown	Housewife	No	No	No	No	Bladder	Non-invasive papillary UC, high grade	Left Nephrectomy

Abbreviation: UC, Urothelial carcinoma; IL2RA, IL2 receptor antagonist; Tac, Tacrolimus; MMF, Mycophenolate mofetil; Pred, prednisolone; MTORi, mammalian target of rapamycin inhibitors.
*Transplant Tourism in Mainland China
#KT80 and KT 721 sample are from the same patient at different time of surgery

Baseline characteristic of KT and dialysis patients with UC.



Bioinformatic analysis for WES result regarding UC post KT.

FR-PO1011

Kidney Involvement in Primary Myelofibrosis and Possible Role of the JAK-STAT Pathway

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Background: Isolated case reports have described a connection between primary myelofibrosis (PMF) and kidney disease. Activation of JAK-STAT pathways, commonly seen in PMF, leads to worsening kidney function in rodent models. Hence, we hypothesized that JAK-STAT activation in PMF may be associated with kidney disease.

Methods: We used the integrated data repository to identify all adult patients with PMF evaluated at an academic hospital between 1/1/2007 and 11/20/2017. We recruited a control group matched for age, sex, and presence or absence of diabetes mellitus. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2. Paired t-test was used to compare continuous variables and McNemar's test for categorical variables. Change in renal function over time was compared using mixed-effects model. A p-value < 0.05 was considered significant.

Results: Most patients with PMF(n=46) were Caucasian (93%), male (57%) and older (mean age of 66 ± 11 years). 70% had hypertension and 18% diabetes. Cytogenetic analysis showed more than half had a Jak2 mutation (67%). There were no differences in baseline renal function or prevalence of CKD between patients with PMF and matched controls. Proteinuria on dipstick was more common in PMF than controls (50 % vs. 18%, p=0.03). Patients with PMF and Jak 2 mutation were more likely to have proteinuria at baseline (73%) compared without Jak 2 mutations (22%) or controls (18%) Overall p<0.005. A mixed effects model showed no changes in eGFR over time. However, patients with PMF had higher blood urea nitrogen (BUN) levels at follow-up than matched controls (22±9 vs. 18±12 mg/dl, p=0.001) and a significant increase in BUN (3.3±9.8 vs. 0.5±8.2 mg/dl, p=0.03) from baseline.

Conclusions: Patients with PMF were more likely to have proteinuria, higher BUN at follow-up and a significant increase in BUN compared to controls matched for age, gender, and diabetes. Proteinuria was more likely in those with Jak2 mutations. Our results suggest that PMF is associated with kidney dysfunction and highlights the need for more thorough assessment of renal function in these patients. Identifying the molecular basis of these clinical observations could help improve outcomes in PMF and give us novel insights into the pathogenesis of kidney disease.

FR-PO1012

Urinary mRNA Signature of Graft vs. Kidney Disease in Hematopoietic Stem Cell Transplant Recipients Mirror Acute Rejection of Kidney Allograft

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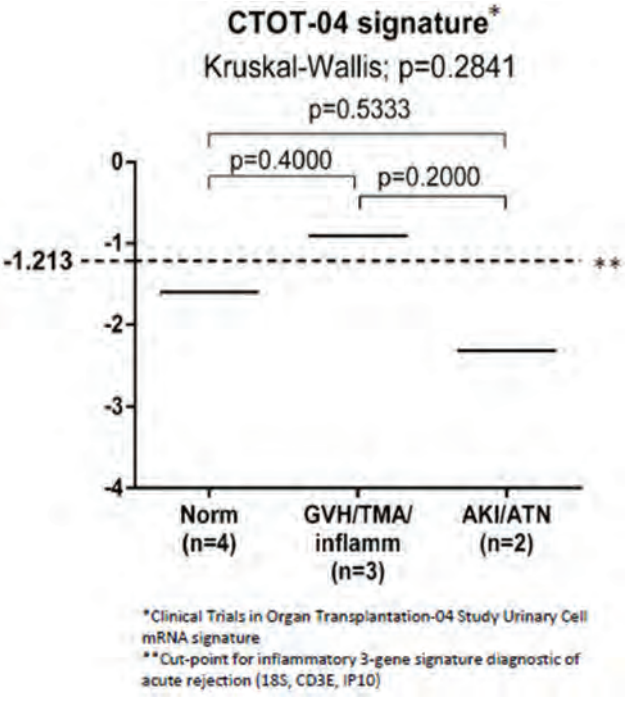
Background: Acute kidney injury (AKI) is a complication of hematopoietic stem cell transplants (HSCT). GVKD can resemble acute rejection (AR) of kidney allograft, with inflammation in the intersititium and tubules. In GVKD, the graft inflammatory cells attack the host kidney (compared to host versus graft disease in AR). HSCT recipients have multiple comorbid conditions and performing kidney biopsies in patients with AKI can be challenging. Development of urinary mRNA profiles as noninvasive biomarkers has been validated as a robust tool for the noninvasive assessment of kidney allograft status. We hypothesized that urinary mRNA cells in patients with GVKD would mirror AR in kidney allograft and could serve as a tool for the noninvasive diagnosis of AKI.

Methods: We obtained urine specimens from 9 HSCT recipients; 3 with AKI and biopsy diagnosis of GVKD; 2 with AKI that resolved spontaneously; and 4 with normal kidney function. We isolated RNA from urinary cells and quantified the CTOT-04 three-gene molecular signature for AR (urinary cell mRNA levels of 18S, CD3e and IP10, Suthanthiran et al, N Engl J Med 2013) by RT-qPCR assay.

Results: Of the 3 patients with AKI who received kidney biopsy, 2 had significant interstitial inflammation that stained positive for CD3 and/or Granzyme B in the interstitium and tubules. Figure 1 demonstrates the mRNA levels and 3 gene signature of the 3 patients with GVKD as compared to 2 HSCT patients with AKI that resolved and 4 HSCT patients with normal kidney function. The cell signature of GVKD most clearly resembles that found in AR.

Conclusions: Our results demonstrate an immune inflammatory signature in the urine of patients with HSCT who have GVKD. Our pilot study further advances urinary cell mRNA profiling as a noninvasive tool for the differential diagnosis of AKI in HSCT recipients.



FR-PO1013

Mesoscale Nanoparticles Treat Cisplatin-Induced AKI and Avoid Tumor Accumulation

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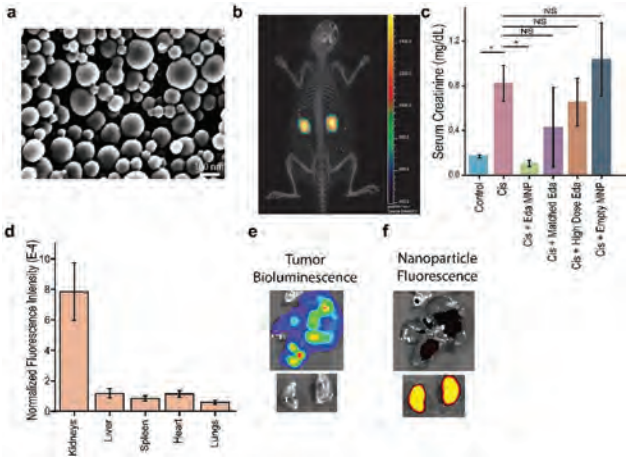
Background: Acute kidney injury (AKI) develops in ~ 30% of patients who receive cisplatin-based chemotherapy. In this setting, AKI can result in delays in completion of treatment or the need to switch to other therapeutic regimens. Despite its high incidence there is no effective pharmacologic intervention for AKI. In cisplatin-induced AKI, it is imperative that any intervention effective for AKI will not interfere with the chemotherapeutic effects of cisplatin. In prior work (Nano Letters 2015) we developed mesoscale nanoparticles (MNPs) that localize to the kidneys with high affinity, primarily to the proximal tubules.

Methods: We synthesized nanoparticles from PLGA-PEG and encapsulated the small molecule reactive oxygen species scavenger edaravone. Experiments were performed in C57 mice with cisplatin-induced AKI (25 mg/kg IP). To assess therapeutic efficacy, IV injections of 50 mg/kg edaravone-containing MNPs, control MNPs, or 30 mg/kg free edaravone were performed 24 hours after cisplatin. Mice were euthanized at 72 hours post-cisplatin. In a separate group of mice bearing metastatic small cell lung cancer, fluorescent MNPs were injected to determine whether MNPs localization.

Results: Compared to mice receiving cisplatin alone, mice receiving edaravone-containing MNPs had normal sCr and normal renal histology. Neither free edaravone nor empty MNPs improved sCr or histology. In mice with metastatic lung tumors, we determined that MNPs maintain their specific renal distribution and do not localize to tumors as has been described with smaller nanoparticle systems.

Conclusions: These studies confirm the likelihood of successful AKI therapy in the context of cisplatin-induced AKI, while avoiding the possible therapeutic abatement associated with tumor deposition of ROS scavengers. We anticipate that these studies will constitute the basis for the development of novel strategies for the treatment and prevention of cisplatin induced AKI in humans.

Funding: NIDDK Support



FR-PO1014

Association of Systolic Blood Pressure with Cardiovascular and Renal Outcomes in CKD: A Nationwide Cohort Study

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Background: Blood pressure (BP) is associated with a linearly incremental risk for cardiovascular disease and death in the general population. However, the ideal BP to decrease cardiovascular and renal risk in patients with non-dialysis-dependent chronic kidney disease (CKD) is unclear.

Methods: We studied the associations of baseline systolic BP (SBP) with the risk of composite outcomes (all-cause death, acute myocardial infarction, heart failure, stroke, and end-stage renal disease) in 1.5 million adults who participated in the NHIS National Health Checkup Program between 2009 and 2012 and had an estimated glomerular filtration rate (eGFR) 15–59 mL/min/1.73m^2 at study entry using Cox proportional hazard models.

Results: During 8,223,922 person-years of follow-up, the composite outcomes occurred in 305,851 (20.5%) subjects with a crude event rate of 37.2 (95% CI, 37.1-37.3) per 1,000 person-years. In fully-adjusted Cox models, there was a U-shaped association between SBP and composite outcomes, such that SBP <120 mmHg and SBP ≥130 mmHg were each associated with higher risk of cardiovascular and renal outcomes (reference: 120-129 mmHg): the HRs (95% CIs) were 1.20 (1.18-1.22), 1.08 (1.07-1.09), 1.03 (1.02-1.04), and 1.10 (1.09-1.11) for SBP <110, 110-119, 130-139, and ≥140 mmHg, respectively. These associations remained consistent and significant across all eGFR strata.

Conclusions: In a large national cohort of Korean adult population with CKD, the association of SBP levels with cardiovascular and renal risks was U-shaped, with both lower and higher SBP levels showing a substantial and significant increase in death, major cardiovascular events, and end-stage renal disease.

FR-PO1015

The Influence of Baseline Diastolic Blood Pressure on the Effects of Intensive Blood Pressure Lowering on Cardiovascular Outcomes in Type 2 Diabetes Mellitus

Olesya Ilkun,[1] Tom Greene,[1] Guo Wei,[1] Robert E. Boucher,[1] Alfred K. Cheung,[1] Glenn M. Chertow,[3,4] Walter T. Ambrosius,[5] Paul K. Whelton,[2] Srinivasan Beddhu.[1,4] *[1]University of Utah School of Medicine, Salt Lake City, UT; [2]Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; [3]Stanford University School of Medicine, Palo Alto, CA; [4]VA SLC Healthcare System, Salt Lake City, UT; [5]Wake Forest School of Medicine, Winston-Salem, NC.*

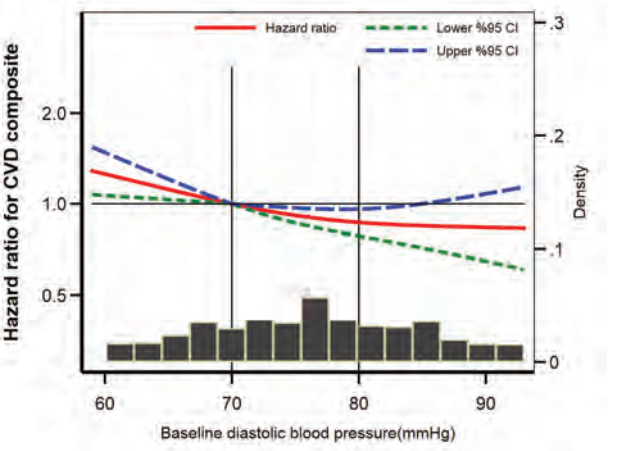
Background: Intensive (INT) compared to standard (STD) systolic blood pressure (SBP) control might be harmful in persons with low baseline diastolic blood pressure (DBP) and type 2 diabetes mellitus (T2DM).

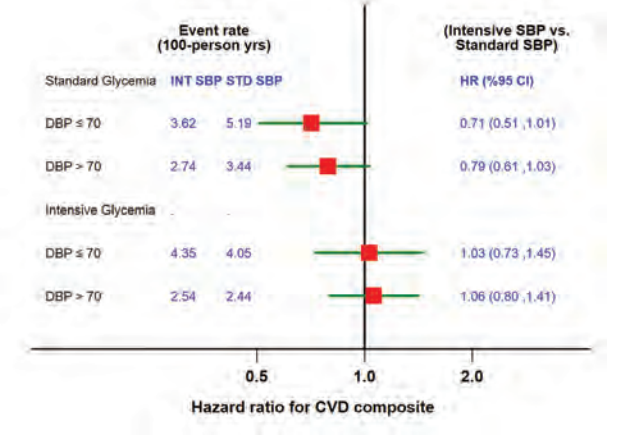
Methods: ACCORD BP was a 2X2 factorial design RCT that examined the effects of SBP control (<120mmHg vs. <140 mmHg) and glycemia (GLY) control (HbA1C goal < 6% vs. 7.0–7.9%) on a primary cardiovascular disease (CVD) composite outcome in T2DM (N = 4714). We examined whether the effects of INT SBP lowering on CVD was modified by baseline DBP stratified by the GLY arm.

Results: There were 689 CVD events/ 21,389 years of follow-up. Lower baseline DBP was associated with increased risk of CVD composite (Fig 1). INT SBP lowering decreased the risk of the CVD composite in the STD GLY arm (HR 0.76, 95% CI 0.62 to 0.93) but not in INT GLY arm (HR 1.05, 95% CI 0.85 to 1.31). Linear interaction p-values for SBP intervention and baseline DBP were not significant in the STD (p = 0.58) or INT (p=0.78) GLY arms. The effects of INT SBP lowering on CVD composite in those with DBP ≤70 mmHg compared to those with DBP > 70 mmHg were similar within the STD or INT GLY arms (Fig 2).

Conclusions: Low baseline DBP was associated with increased risk of CVD composite in T2DM. However, there was no evidence that the beneficial effects of INT SBP lowering on CVD events in STD GLY arm was modified by low baseline DBP.

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





FR-PO1016

Association of Pulse Pressure and Double Product with Cardiovascular and All-Cause Mortality in the LURIC Study

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Background: Systolic (SBP) and diastolic blood pressure (DBP) as well as mean arterial pressure (MAP) are already known as important predictors respectively risk factors for cardiovascular mortality. Pulse pressure (PP) is considered as an easily available marker of vascular stiffness and the double product (DP; SBP x heart rate (HR)) as a marker of cardiac workload. Therefore, we extended our analysis of outcome parameters by use of PP and DP.

Methods: We retrospectively analysed data from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, in which 3316 patients underwent coronary angiography.

Results: Long-term data from 3316 patients undergoing coronary angiography showed that by increasing SBP by 1mmHg the risk of both cardiovascular and all-cause mortality rose by 0.9 %. However, there was no significant relationship between DBP and mortality. A higher PP of 1 mmHg resulted in a higher cardiovascular mortality risk of 1.6 % and an all-cause mortality risk of 1.7 %. Increasing DP by 100 mmHg/min was associated with a 1.0 % higher risk of cardiovascular mortality and 0.9 % higher risk of all-cause mortality.

Conclusions: We provide evidence that not only the classic standard blood pressure parameters SPB and MAP predict cardiovascular mortality, but also that PP and DP are powerful predictors of cardiovascular and all-cause mortality in a cardiovascular risk population. PP and DP are superior predictors of a higher cardiovascular mortality in heart failure patients.

FR-PO1017

Systolic Blood Pressure and Risk of Incident CKD: A Nationwide Cohort Study of 10 Million Adults in South Korea

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Background: In the general population, guidelines recommend a target blood pressure (BP) <120/80 mmHg in order to reduce cardiovascular risk. However, the optimal BP to prevent chronic kidney disease (CKD) is unknown.

Methods: In a national population-based cohort of 10.5 million adults who underwent National Health Insurance Service health examination between 2009 and 2015 and had an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2 at baseline, we studied the association of time-updated and baseline systolic BP (SBP) with risk of incident CKD using marginal structural models (MSMs) and Cox models. Incident CKD was defined as *de novo* development of eGFR <60 mL/min per 1.73m^2 for at least two consecutive measurements.

Results: During 49,169,311 person-years of follow-up, incident CKD developed in 172,423 (1.64%) subjects with a crude event rate of 3.51 (95% CI, 3.49-3.52) per 1,000 person-years. Using MSMs, we found a graded association between incrementally higher time-updated SBP levels ≥130 mmHg and risk of incident CKD, whereas SBP levels <120 mmHg were associated with lower risk (reference: 120-129 mmHg): HRs (95% CIs) were 0.57 (0.55-0.58), 0.81 (0.80-0.82), 1.41 (1.39-1.43), and 2.16 (2.12-2.19) for SBP <110, 110-119, 130-139, and ≥140 mmHg, respectively. Using Cox models, the corresponding HRs for the noted SBP range were 0.84 (0.82-0.85), 0.92 (0.91-0.94), 1.11 (1.09-1.12), and 1.30 (1.28-1.32), respectively. Among subjects receiving antihypertensive medications, time-updated SBP of <110 mmHg was associated with higher risk of CKD: HR (95% CI) 1.07 (1.00-1.15).

Conclusions: In healthy people without kidney disease, higher SBP ≥130 mmHg was associated with higher risk of incident CKD. However, among those receiving antihypertensive therapy, low SBP <110 mmHg was also associated with incident CKD risk, suggesting that excessive BP control may contribute to adverse renal outcomes.

FR-PO1018

The Influence of Blood Pressure Patterns on Renal Outcomes in Patients with CKD: The Long-Term Follow-Up Result of the APrODiTe-2 Study

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Background: Blood pressure (BP) control is the most established practice for preventing the progression and complications of chronic kidney disease (CKD). We examined the influence of BP patterns on target organ damage in hypertensive patients with CKD by using long-term follow-up data of the APrODiTe-2 study.

Methods: We collected 5 years of data of APrODiTe-2 study participants (n=378).

Results: Initially, the BP control and the dipping states were as follows: true controlled (16.5%), white-coat (2.9%), masked (50.0%), and sustained uncontrolled (30.6%); extreme-dipping (11.4%), dipping (22.2%), nondipping (31.3%), and reverse-dipping (35.0%). Only 18.8% and 20.8% of participants showed a better change in BP control patterns (to true controlled and white-coat) and a dipping pattern change to dippers over 1 year, respectively. Twenty-two patients (5.8%) died. Composite of new cerebro-cardiovascular (CCV) accidents occurred in 43 patients (11.4%), and no BP patterns were associated with the occurrence of new CCV accidents. A worse change in BP control categories over 1 year was associated with increased occurrence of composite of doubling of serum creatinine, a 50% decrease in the estimated glomerular filtration rate (eGFR), the initiation of dialysis, and kidney transplantation after adjustment for age, sex, and the cause of CKD. Patients with a worse initial BP control category, a worse change in BP control categories over 1 year, and higher clinic systolic BP and pulse pressure (PP) (> median level) were more likely to have faster eGFR progression (absolute eGFR and eGFR ratio).

Conclusions: Higher BP burden (a worse change in BP control categories, higher initial clinic systolic BP and PP) was associated with faster eGFR progression and increased occurrence of renal outcomes.

FR-PO1019

Outcomes in Adults with Systolic Blood Pressure Between 130 and 139 mm Hg in ACCORD BP and SPRINT

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Background: Patients with stage 1 systolic hypertension (130-139 mmHg) have increased risk of cardiovascular disease (CVD) events compared to those with normal blood pressure.

Methods: In this post-hoc analysis, we assess the effect of targeting an intensive systolic blood pressure (SBP) goal of less than 120 mmHg compared with standard SBP goal of less than 140 mmHg on the risk of CVD events in adults with stage 1 systolic hypertension enrolled in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure (BP) Trial (n=1,901) and the Systolic Blood Pressure Intervention Trial (SPRINT) (n=3,484) using adjusted Cox models. In ACCORD, the primary composite CVD outcome was the first occurrence of myocardial infarction (MI), stroke or CVD mortality. In SPRINT, the primary composite CVD outcome was the first occurrence of MI, other acute coronary syndrome, stroke, heart failure or CVD mortality.

Results: In SPRINT, targeting an intensive SBP goal significantly reduced the risk of the primary CVD outcome (hazard ratio [HR] 0.75, 95% confidence interval [95% CI] 0.57-0.98; 1.78 vs. 2.37 % per year). In ACCORD BP, the relationships of SBP goal with the primary CVD outcome was modified by the glycemia goal intervention (interaction P = 0.039). In the standard glycemia subgroup (A1c target 7-7.9%), intensive SBP goal significantly reduced the risk of the primary CVD outcome (HR 0.61 [0.40-0.94]; event rates 1.63 vs. 2.56 % per year). In the intensive glycemia subgroup (A1c target <6%), the risk of the primary CVD outcome was not significantly different between SBP goal groups (HR 1.20 [0.76-1.89]; event rates 1.91 vs. 1.60 % per year).

Conclusions: Targeting a SBP goal of less than 120 mmHg significantly reduced the risk of CVD events in patients with stage 1 systolic hypertension without diabetes and with diabetes on standard glycemia goal.

Funding: NIDDK Support, Other NIH Support - ACCORD BP and SPRINT were supported by the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Disease, the National Institute on Aging, the National Institute of Neurological Disorders and Stroke, and the Department of Veterans Affairs. The study was approved by the SPRINT research group. Authors analyzed and interpreted the data for this abstract, with support from the Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC. All aspects of the abstract writing and revision were initially carried out by the authors, with subsequent revisions made according to the SPRINT research group recommendations. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the U.S. Department of Veterans Affairs, or the United States Government.

FR-PO1020

The Influence of Baseline Diastolic Blood Pressure on the Effects of Intensive Blood Pressure Lowering on All-Cause Mortality in Type 2 Diabetes Mellitus

Olesya Ilkun,[1] Tom Greene,[1] Guo Wei,[1] Robert E. Boucher,[1] Alfred K. Cheung,[1,4] Glenn M. Chertow,[2] Walter T. Ambrosius,[5] Paul K. Whelton,[3] Srinivasan Beddhu.[1,4] *[1]University of Utah School of Medicine, Salt Lake City, UT; [2]Stanford University School of Medicine, Palo Alto, CA; [3]Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; [4]VA SLC Healthcare System, Salt Lake City, UT; [5]Wake Forest School of Medicine, Winston-Salem, NC*.

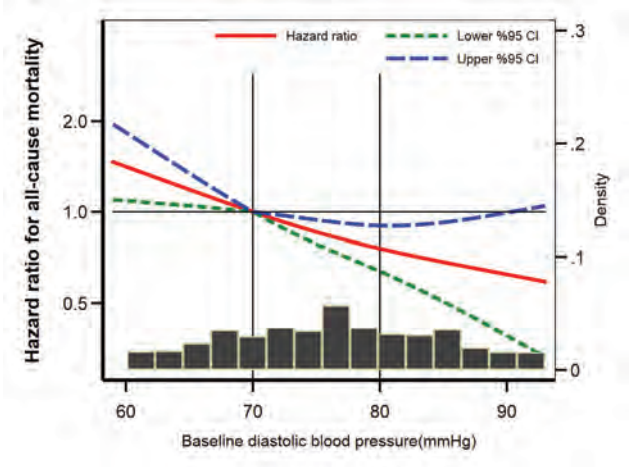
Background: Intensive (INT) compared to standard (STD) systolic blood pressure (SBP) control might be harmful in persons with low baseline diastolic blood pressure (DBP) and type 2 diabetes mellitus (T2DM).

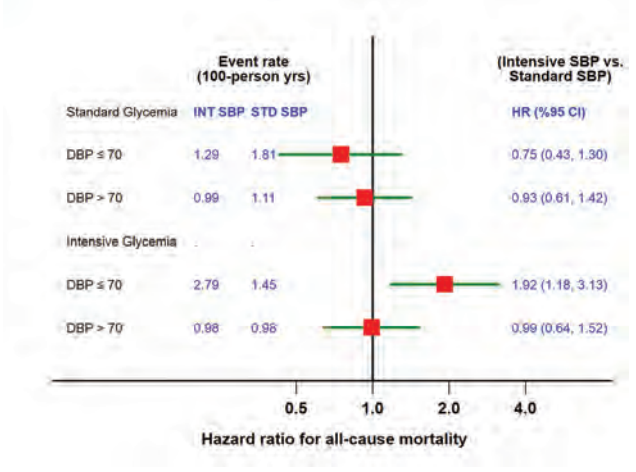
Methods: The Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD BP) was a 2X2 factorial design RCT that examined the effects of SBP control (<120mmHg vs. <140 mmHg) and glycemia (GLY) control (HbA1C goal < 6% vs. 7.0–7.9%) on cardiovascular events and all-cause mortality (ACM) in T2DM (N = 4714). We examined whether the effects of INT SBP lowering on ACM was modified by baseline DBP stratified by the GLY arm.

Results: There were 292 ACM events/ 23,326 years of follow-up. Lower baseline DBP was associated with increased risk of ACM (Fig 1). Hazard ratios for INT SBP lowering in the STD and INT GLY arms were 0.84 (95% CI 0.60 to 1.17) and 1.34 (95% CI 0.97 to 1.84), respectively. Linear interaction p-value for SBP intervention and baseline DBP was not significant in the STD GLY arm (p = 0.40) but significant in INT GLY arm (p=0.01). In those with DBP ≤70 mmHg, INT SBP lowering appeared not harmful in the STD GLY arm but deleterious in the INT GLY arm (Fig 2).

Conclusions: Low baseline DBP was associated with increased risk of ACM in T2DM. In persons with baseline DBP ≤70 mm Hg, INT SBP lowering increased ACM in the setting of INT GLY but not STD GLY.

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





FR-PO1021

Heart Failure Risk with Intensive Systolic Blood Pressure (SBP) Lowering Does Not Differ by Albuminuria Status in Diabetes

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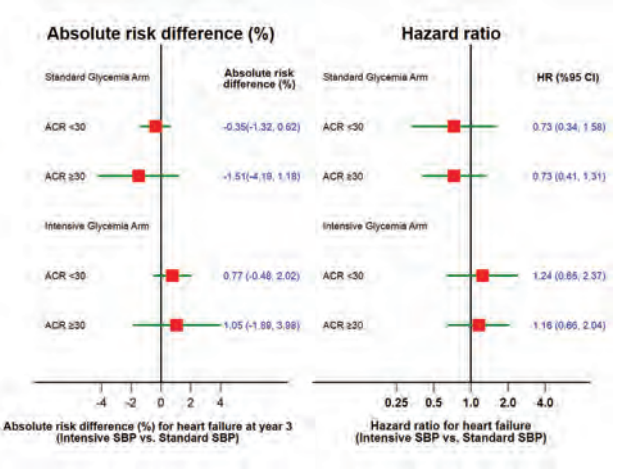
Background: Albuminuria is associated with heightened risk for heart failure (HF) in persons with diabetes mellitus (DM) but optimal SBP goals for reducing HF risk remain controversial. We examined the effects of intensive vs. standard SBP lowering on HF risk by baseline albuminuria status among adults with DM.

Methods: Using data from the Action to Control Cardiovascular Disease (ACCORD) trial. Kaplan Meier curves were used to examine time to acute decompensated HF events by intensive vs. standard SBP lowering and by baseline albuminuria status (albumin-to-creatinine ratio < 30 mg/g vs. ≥ 30 mg/g) after stratifying by intensive vs. standard glucose control. Interaction terms of albuminuria x intensive SBP lowering on HF risk were fitted into Cox proportional hazard models while adjusting for demographics, estimated glomerular filtration rate, blood pressure, and heart disease.

Results: A total of 4524 patients (2257 in standard SBP arm, mean age 62.5 (6.5) years and baseline SBP (142.9 (15.8) mmHg and 2267 in intensive SBP arm, mean age 63.2 years and baseline SBP 137.1 (14.6) mmHg), were followed for a mean of 4.78 years. Within the standard glycemia arm, the absolute risk difference of HF (intensive vs. standard SBP) was -0.35(-1.32, 0.62) in ACR<30 and -1.5(-4.19,1.18) in ACR >30, whereas in the intensive glycemia arm, it was 0.77 (-0.48,1.18) in ACR<30 and 1.05(-1.89,3.98) in ACR >30. Hazard Ratio(95% CI) in the standard arm was 0.73(0.34,1.58) and 0.73(0.41,1.31) in the ACR <30 and ACR>30 respectively, and in the intensive arm 1.24(0.65, 2.37) and 1.16(0.66, 2.04) in the ACR <30 and >30 respectively.

Conclusions: The effects of intensive SBP lowering on HF rates does not appear to be modified by albuminuria status in adults with DM.



Absolute risk difference and Hazard ratio in both the groups

FR-PO1022

Association Between eGFR Variability and Risk of Cardiovascular Events and Mortality: The SPRINT Trial

Rakesh Malhotra,[1] Ronit Katz,[2] Vasantha Jotwani,[15] Adhish Agarwal,[3] Debbie L. Cohen,[4] William C. Cushman,[5] Anthony A. Killeen,[14] Vasilios Papademetriou,[6] Chirag R. Parikh,[7] Kalani L. Raphael,[8] Michael V. Rocco,[9] Leonardo Tamariz,[10] Jackson T. Wright,[11] Michael Shlipak,[12] Joachim H. Ix.[13] *[1]University of California San Diego, San Diego, CA; [2]University of Washington, Seattle, WA; [3]University of Utah, Salt Lake City, UT; [4]University of Pennsylvania School of Medicine, Philadelphia, PA; [5]Memphis VA Medical Center, Memphis, TN; [6]Georgetown University, Potomac, MD; [7]Johns Hopkins University, Baltimore, MD; [8]VA Salt Lake City Health Care System, Salt Lake City, UT; [9]Wake Forest School of Medicine, Winston-Salem, NC; [10]University of Miami, Doral, FL; [11]Case Western Research University, Cleveland, OH; [12]San Francisco VA Medical Center, San Francisco, CA; [13]UCSD, San Diego, CA; [14]University of Minnesota, Minneapolis, MN; [15]UCSF, San Francisco, CA.*

Background: In clinical practice, there is considerable visit-to-visit variability in estimated glomerular filtration rate (eGFR). While low eGFR is an established cardiovascular disease (CVD) risk factor, less is known about the clinical significance of eGFR variability over time.

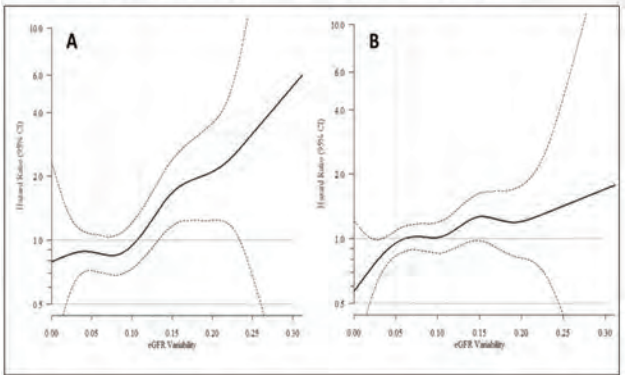
Methods: Among 7520 SPRINT participants, we used proportional hazards models to estimate associations between eGFR variability (measured by coefficient of variation, CV) and subsequent CVD events and all-cause mortality. The CV (SD/mean) was calculated from eGFR values measured at 6-, 12-, and 18-month study visits. CVD events were defined as the composite of MI, ACS, stroke, heart failure, or CVD death. The final model was adjusted for demographics, randomization, prior CVD, heart failure, current smoking, body mass index, serum lipids, baseline systolic BP, albuminuria, eGFR at month 6, medications (ACEI/ARB or diuretics at month 6) and fasting status.

Results: The mean age was 68±9 years, 65% were men, and 58% were white. The mean eGFR was 73±21 ml/min/1.73m^2 at 6 months. There were 370 CVD events and 154 deaths during a median follow-up of 2.4 years. In adjusted model, greater eGFR variability was associated with all-cause mortality (hazard ratio (HR) per SD increase in eGFR-CV (0.06), 1.28; 95% CI 1.14 - 1.44). Associations were somewhat weaker for CVD events (HR 1.06; 0.96 -1.17) (Figure 1). When variability was evaluated by quartiles, the highest compared with the lowest quartile was associated with both all-cause mortality (HR 1.57; 0.99 - 2.47) and CVD events (HR 1.35; 0.99 - 1.84). Associations were similar when stratified by treatment arm and baseline CKD status.

Conclusions: Greater eGFR variability was associated with higher risk for all-cause mortality in SPRINT trial participants, independent of baseline eGFR. Future studies should evaluate mechanisms underlying these associations.

Funding: NIDDK Support

Figure 1: Adjusted Spline curve for association of eGFR variability (Coefficient of variability) with A) all-cause mortality and B) cardiovascular events



FR-PO1023

Association of Pulse Wave Velocity with Renal Outcomes in Pre-Dialysis CKD: Results from the Korean Cohort Study for Outcomes in Patients with CKD (KNOW-CKD)

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Background: Vascular stiffness, a common complication of CKD, would inhibit the capacity of arteries to dampen systolic blood pressure, which would lead to increased barotrauma to glomerular capillary. Therefore, we assessed the effect of brachial-ankle pulse wave velocity (baPWV) on renal outcomes in pre-dialysis CKD.

Methods: KNOW-CKD is a currently on-going prospective cohort study of CKD in Korea in which nine major tertiary hospitals are participating (NCT01630486). A total of 1,903 subjects who performed baPWV test and have ankle-brachial index>0.9 was selected. Mean value of right and left baPWV (mbaPWV) was used for analysis. Renal event (RE) was defined by the doubling of serum creatinine or 50% decrease in CKD-EPI eGFR from the baseline values, or the initiation of renal replacement treatment. The subjects were grouped according to quartile value of mbaPWV. The values of mbaPWV in each quartile group were Q1: 857.5–1,292.5 cm/sec, Q2: 1,293.0–1,458.5 cm/sec, Q3: 1,459.0-1,701.5 cm/sec, Q4: 1,702.3-4,632.5 cm/sec respectively.

Results: Of 1,903 subjects, a total of 507 subjects (26.6%) developed RE during the mean follow up period of 3.6 years. Cox regression analysis adjusted by sex, age, CKD-EPI eGFR, urine albumin creatinine ratio (UACR), medical history of diabetes, hypertension, coronary diseases, hypercholesterolemia, smoking and alcohol revealed that each unit increase of ln (mbaPWV) was associated with 91.7% increase in risk for RE (HR=1.92 95% CI; 1.11-3.32, p=0.021). Time dependent Cox regression adjusted by the same variables revealed that RE increased along with mbaPWV quartile groups (Q1: reference, Q2: HR=2.13; 95% CI 1.07-4.23; p=0.032, Q3: HR=2.37; 95% CI 1.12-4.56; p=0.011, Q4: HR=3.43; 95% CI 1.77-6.65; p=0.000, respectively). While unfavorable effect of mbaPWV on RE was consistent in subject with UACR≤ 300 mg/g, this effect disappeared in subject with UACR> 300 mg/g. Unfavorable effect of mbaPWV on RE was more prominent in subjects with CKD-EPI eGFR≥ 45 ml/min/1.73m^2 than those with CKD-EPI eGFR< 45 ml/min/1.73m^2.

Conclusions: Vascular stiffness was associated the unfavorable renal outcomes in pre-dialysis CKD, particularly in non-proteinuric and early stage CKD.

FR-PO1024

Modification of Effect of Intensive Blood Pressure Lowering on Cardiovascular (CV) Outcomes by Baseline Body Mass Index (BMI)

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Background: It is unknown whether clinicians should consider body weight when determining the optimal blood pressure (BP) goal for a hypertensive patient. Obesity is independently associated with hypertension (HTN), CV outcomes and mortality; thus may modify the effects of BP control. We conducted a post hoc analysis of the SPRINT to assess whether baseline BMI modifies the effects of intensive (INT) systolic blood pressure (SBP) control.

Methods: SPRINT randomized 9361 high-risk non-diabetic participants with a SBP of 130 mm Hg or higher to either INT SBP target of < 120 mm Hg or standard SBP target of < 140 mm Hg. After excluding participants with a baseline BMI of <18.5 or > 50 Kg/m^2 (N= 9191) from SPRINT BioLINCC data, we evaluated the effects of INT SBP control on SPRINT composite outcome (composite of myocardial infarction (MI), acute coronary syndrome (ACS), stroke, acute decompensated heart failure, or CV death) and all-cause death during the mean 4.1 years follow-up in four strata defined by baseline BMI of < 25, 25 to <30, 30 to < 35, and >35 Kg/m^2 using Cox proportional hazards models. We also tested the interaction effect between treatment group and baseline BMI as a continuous variable.

Results: The mean age was 67.9 ± 9.4 years, 35.3 % were female, and mean baseline BMI was 29.8 ± 5.4 Kg/m^2. There were 1682, 3599, 2413, and 1497 participants respectively in the four baseline BMI strata. The effect of INT SBP control on CV outcome or all-cause mortality did not differ significantly between different baseline BMI levels (*P*- linear/categorical interactions 0.24/0.31 and 0.12/0.15 respectively).

Conclusions: In the majority of participants in the baseline BMI range of 22 to 35 Kg/m^2, INT SBP lowering was beneficial. However, in the extremes of BMI, there was not enough power to draw firm conclusions.

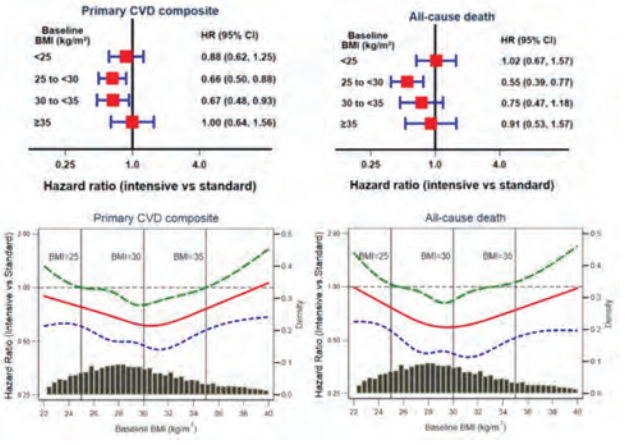

Figure: Forest Plots and Spline Curves with hazard ratios for risk of outcome with INT SBP control

FR-PO1025

Global Longitudinal Strain on Cardiac MRI Is Superior to Conventional Cardiac Parameters at Predicting Mortality in Patients with ESRD

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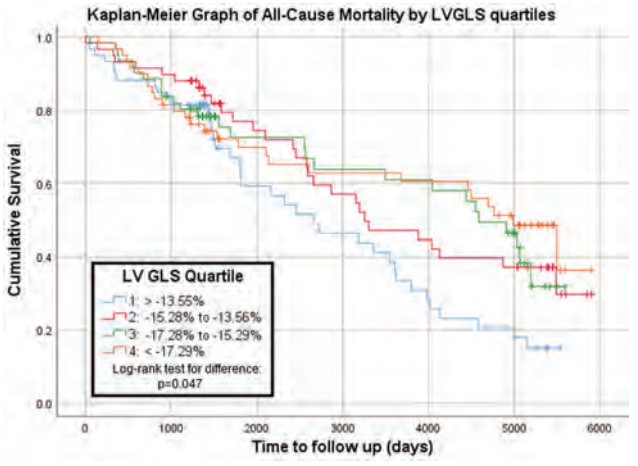
Background: Left Ventricular Global Longitudinal Strain (LV-GLS) by Feature Tracking Cardiac Magnetic Resonance (FT-CMR) is a non-contrast, post-processing technique that has shown promise as a sensitive predictor of cardiovascular mortality. We aim to assess the ability of LV-GLS to predict death in patients with end-stage renal disease (ESRD).

Methods: We retrospectively analysed research cardiac MRIs (CMR) performed at a major renal transplant centre between 2002-2016. Included patients were receiving, or within 6-months of receiving, renal replacement therapy for ESRD. CMR parameters were derived, including left ventricular mass index (LVMI), LV ejection fraction (LVEF), left atrial ejection fraction (LAEF), and LV-GLS. Cox proportional hazards regression analyses were used to identify potential predictors of all-cause death. Model fit was assessed using the C-statistic.

Results: Among 237 patients (mean age: 53.7, 61% male), mortality was 50.6% over 4.6-year median follow up. LV-GLS quartiles were significantly correlated with mortality (Figure 1). While 89.7% of patients had preserved LVEF (>55%), 24% of patients had abnormal LV-GLS. On multivariable Cox regression, age (HR: 1.04, 95% CI: 1.020-1.057), LAEF (HR: 0.98, 95% CI: 0.963-0.997) and LV-GLS (HR: 1.08, 95% CI: 1.011-1.044) were independent predictors of mortality. The C-statistic of this model for predicting ACM at 1-year was 0.955 (95% CI: 0.920-0.991). Traditional CMR parameters such as LVEF and LVMI were not correlated with mortality.

Conclusions: In this cohort of patients with ESRD, LV-GLS and LAEF as measured on FT-CMR demonstrate independent predictive utility for all-cause death, whilst conventional imaging biomarkers such as LVEF did not. The effect was present even with normal LVEF. LVGLS has a potential role in the prognostication and pre-transplant assessment of patients with ESRD.

Funding: Government Support - Non-U.S.



FR-PO1026

Magnetic Resonance Imaging Evaluation of Mineralocorticoid Receptor Antagonism in Diabetic Atherosclerosis (MAGMA) Trial: Baseline Characteristics

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Background: MAGMA is a multicenter double-blind, randomized controlled trial that aims to assess the effect of spironolactone on atherosclerosis progression and left ventricular (LV) mass regression in type 2 diabetic patients with CKD.

Methods: 46 adult diabetic patients with eGFR<90 ml/min/1.73m^2 and albuminuria>30 mg/g or eGFR<60 ml/min/1.73m^2 regardless of albuminuria, on ACEi/ARB were enrolled at 4 sites and randomly assigned to spironolactone (12.5mg with eventual escalation to 25mg daily) *vs.* placebo. 24hr ambulatory blood pressure monitoring (ABPM) and cardiac MRI and aortic plaque imaging were performed at baseline and will be repeated at 1 year. We examined baseline characteristics and achieved systolic blood pressure (SBP) at 6 weeks follow-up.

Results: The mean age(SD) was 63(8.3) years; 46% were women, and 52% were African-American. Baseline characteristics showed no significant differences between the groups(Table). Native myocardial T1 times, a marker of myocardial fibrosis, were high normal across groups. At 6 weeks, treatment A group had an increase in average 24hr overall and nocturnal SBP by 3.9(20.8) mmHg and 5.7(25.2) mmHg respectively. Treatment B group had an average decrease in 24hr overall and nocturnal SBP of –6.0(11.7) mmHg, and – 8.3(9.8) mmHg respectively.

Conclusions: MAGMA trial enrolled individuals with high atherosclerotic disease burden. Long-term follow-up will provide critical insights into the role of mineralocorticoid antagonism on LV mass and atherosclerosis reduction in high-risk patients.

Funding: Other NIH Support - NHLBI

History of atherosclerotic disease	Treatment A (n= 21)	Treatment B (n=25)
≥3 Antihypertensive medications	11 (52)	10 (40)
Statins	14 (66)	15 (60)
eGFR (mL/min/1.73m2)	20 (95)	23 (96)
eGFR (mL/min/1.73m2)	46.3 ± 19.9	50.5 ± 17.8
Urine Albumin/Creatinine (mg/g)	291.8 ± 461.9	139.8 ± 173.5
Hemoglobin A1C(%)	7.4 ±1.2	7.2 ±1.2
Potassium (mmol/L)	4.2 ± 0.5	4.1 ± 0.4
24hr ABPM SBP (mmHg)	136.8 ± 14.1	138.3 ± 15.0
Asleep SBP (mmHg)	129.8 ± 22.5	133.2 ± 17.8
Global native T1 myocardial time (ms)	1209.8 ± 41.9	1186.4 ± 40.9
LV mass index (g/m2)	64.54 ± 20.9	64.3 ± 11.0
LV ejection fraction (%)	57.3 ± 13.9	62.4 ± 10.4

Values represent mean±SD or number(%)

FR-PO1027

Association of Masked and Sustained Hypertension with Cardiac Magnetic Resonance Imaging Measures of Left Ventricular Structure and Function in Patients with Diabetes and CKD

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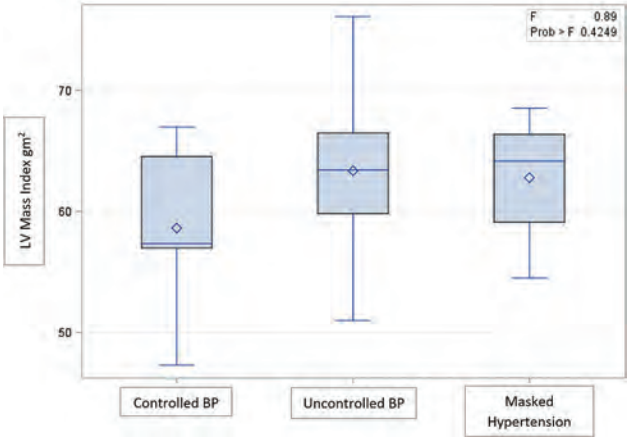
Background: Diabetes and chronic kidney disease (CKD) are risk factors for hypertension phenotypes, such as masked and sustained hypertension which lead to increased cardiovascular risk. We aimed to describe the association of masked and sustained hypertension with structural and functional left ventricular measurements as assessed by cardiac magnetic resonance imaging (MRI) in type 2 diabetic patients with CKD.

Methods: A total of 38 adult patients enrolled in a prospective randomized controlled trial of mineralocorticoid receptor antagonism in patients with CKD (MAGMA) who had 24hr ambulatory blood pressure monitoring (ABPM) and cardiac MRI performed at study baseline were included. Masked hypertension was defined as SBP<130 mmHg in the office, and >125 by mmHg 24hr ABPM and resistant hypertension was defined as SBP>130 mmHg in the office and >125 mmHg by 24hr ABPM. Analysis of Variance was performed to assess the difference in mean MRI measures of cardiac structure and function for various hypertension phenotypes.

Results: The mean age (SD) was 62.5(8.9) years; 61% were women, and mean eGFR was 48.6 (20.3)ml/min/1.73m^2. Compared to participants with controlled SBP (n=7), participants with masked (n=12) and sustained (n=17) hypertension had a higher left ventricular mass index (66.5±9 and 64.7±8.9 vs 58.6±7.7 g/m^2 respectively (Figure). In adjusted models we found no association between hypertension phenotypes and T1 times, cardiac output, LVEF, LVEDV and LVESV.

Conclusions: Masked and sustained hypertension are associated with a high left ventricular mass index in individuals with CKD and diabetes. Larger trials are needed to better characterize MRI cardiac structural abnormalities in individuals at high cardiovascular risk.

Funding: Other NIH Support - NHLBI



FR-PO1028

Reproducibility and Clinical Determinants of Stress T1-Mapping in Patients on Haemodialysis: A Feasibility Study

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Background: Identification of coronary artery disease (CAD) in patients with end stage renal disease (ESRD) is challenging. Adenosine stress non-contrast native T1 mapping on cardiac MRI has been proposed as a method to assess myocardial blood volume changes. It has been shown to accurately detect obstructive CAD and microvascular dysfunction in the general population. However, it has never been tested in patients with ESRD, who have higher resting native T1 times compared to control subjects. This study assesses the potential of stress T1 mapping to identify myocardial ischaemia in patients on haemodialysis (HD).

Methods: 124 patients underwent rest T1 mapping. 58 of them had stress scans. 10 patients had identical reproducibility scans within two weeks. Myocardial stress T1 reactivity was calculated as ΔT1=[(stress T1−rest T1)/rest T1]×100. Interstudy reproducibility, inter-observer and intra-observer variability were assessed using intraclass correlation coefficient (ICC), coefficient of variability (CoV) and Bland-Altman analyses.

Differences between groups and correlations between T1 and clinical variables were assessed. Independent predictors of ΔT1 were examined on multivariate linear regression.

Results: There were no clinically relevant differences between baseline characteristics of patients undergoing rest only or rest and stress scans. Of the 58 patients who had stress scans, only one had an inadequate haemodynamic response to adenosine. All patients tolerated and completed the scan, with no adverse effects. Inter- and intra-observer variability of rest T1, stress T1 and ΔT1 were excellent (ICC >0.9). Interstudy reproducibility for rest and stress T1 was good (CoV 1.2% and 1.5%; ICC 0.79 and 0.69, respectively), but average for ΔT1 (CoV 27.4%, ICC 0.55). On multivariate analysis, CAD, diabetes and rest native T1 time were independent predictors of ΔT1 (β= -0.244, p=0.038; β= -0.326, p=0.008; β= -0.458; p<0.001, respectively).

Conclusions: Stress T1 mapping is a feasible, reproducible and well-tolerated technique in patients on HD. It has the potential to evaluate myocardial ischaemia secondary to obstructive epicardial CAD or microvascular dysfunction despite the elevated resting native T1 values in this population. However, the reproducibility of ΔT1 is sub-optimal.

FR-PO1029

Comparability and Tolerability of Ambulatory and Home Blood Pressure Monitoring in Hemodialysis Patients

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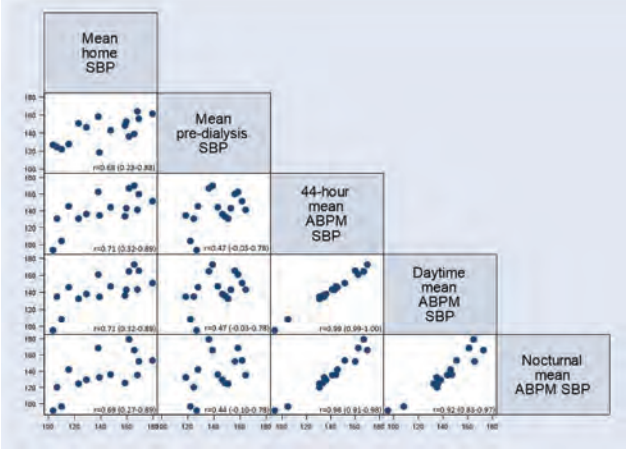
Background: 44-hour (hr) ambulatory blood pressure monitoring (ABPM) in hemodialysis (HD) patients provides valuable prognostic information, but is often impractical in clinical practice. Home BP monitoring (HBPM) may be better suited for longitudinal BP management. However, limited evidence exists regarding the comparability and tolerability of ABPM and HBPM in this high risk population.

Methods: In a post-hoc analysis, we studied pre-randomization data from participants who agreed to 44-hr ABPM in a randomized controlled trial targeting a home vs. pre-HD systolic BP (SBP) <140 mmHg (NCT03459807).

Results: Of the 50 in-center HD patients enrolled, 31 (62%) agreed to ABPM. The mean age was 56 (SD 14) years, 13 (42%) were black. Mean pre-HD SBP was 146 (19) mmHg, ABPM SBP 140 (21) mmHg, daytime SBP 141 (20) mmHg, and nighttime SBP 134 (25) mmHg; 24 (77%) participants were non-dippers, including 7 (23%) reverse dippers. Home SBP was correlated with ABPM SBP (Figure); the strongest correlation was with daytime SBP in the initial 24-hrs post-HD (r=0.76, 95% CI 0.43-0.91). Using ABPM instead of HBPM, 2 participants were reclassified from controlled to masked hypertension (HTN), 1 from white coat to uncontrolled HTN, and 1 from masked to controlled HTN. Most patients described their ABPM experience as neutral (e.g. “No problem”); however, some expressed substantial discomfort (e.g. “the pressure was way too high and unbearable”). Participants described HBPM more positively (“It was fun and gave me knowledge of my own BP’s”), with no reported discomfort.

Conclusions: Among HD patients, HBPM correlated with ABPM, particularly daytime post-HD ABPM readings. Given greater tolerability and feasibility for repeated measurements, HBPM seems to be a practical option for longitudinal monitoring and management of HTN among HD patients.

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



Correlation of HBPM, ABPM, and pre-HD BP

FR-PO1030

The Accuracy of Clinic and Home Blood Pressure Recordings in Diagnosing Hypertension Among Patients on Peritoneal Dialysis

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Background: Earlier studies testing the diagnostic accuracy of blood pressure (BP) measurement techniques among patients on peritoneal dialysis (PD) have shown that home BP recordings overestimate daytime ambulatory BP and are inferior to standardized automated clinic BP measurements in diagnosing hypertension. The aim of this study is to elucidate this paradoxical observation that contradicts evidence from the general hypertensive population and may be attributable to methodological limitations of earlier studies.

Methods: In a cohort of 81 stable PD patients with unmodified antihypertensive therapy or dialysis regimen for at least 2 weeks prior to study enrollment, BP was recorded using 3 different methodologies: (i) triplicate automated clinic BP recordings after a 5-min seated rest with the self-inflating monitor HEM 705 CP (Omron Healthcare); (ii) 1-week averaged morning and evening home BP recordings taken by the patients themselves with validated automated BP monitors; (iii) 24-hour ambulatory BP monitoring with the oscillometric device Mobil-O-Graph (IEM, Germany).

Results: In Bland-Altman analysis, clinic systolic BP (SBP) overestimated daytime ambulatory SBP by 5.02 mmHg with 95% limits of agreement ranging from -17.92 to 27.96 mmHg. Similarly, home SBP overestimated daytime ambulatory SBP by 4.23 mmHg, again with wide 95% limits of agreement (-16.05 to 24.51 mmHg). The area under the curve of receiver operating characteristic (ROC) curve for clinic and home SBP to detect a daytime ambulatory SBP ≥135 mmHg was 0.859 (95% CI: 0.776-0.941) and 0.895 (95% CI: 0.815-0.976), respectively. Home SBP of ≥138.5 mmHg had the best combination of sensitivity (80.6%) and specificity (84%) in diagnosing ambulatory systolic hypertension.

Conclusions: 1-week averaged home BP recordings are at least similar with a standardized BP measurement at clinic in detecting ambulatory hypertension among patients on PD.

FR-PO1031

Patterns of Nocturnal Blood Pressure Changes in Patients on Ambulatory Blood Pressure Monitoring (ABPM) in Patients with Complex Hypertension

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Background: Nocturnal blood pressure changes are associated with patient centered outcomes. We attempted to investigate the patterns of blood pressure changes in complex hypertensive patients with concomitant cardiovascular comorbidities.

Methods: We retrospectively reviewed 35 charts of patients who received ABPM from a single outpatient nephrology office. Of the 35, 3 were excluded due to incomplete data. We collected demographic information: Age, Gender, Ethnicity, Diabetic status, CKD stage, Indication for ABPM. ABPM data Including: Average daytime pressures, Average nighttime pressures, total average pressures, nocturnal dipping, hypertensive load. IBM SPSS® v22 was used for statistical analysis – t-tests.

Results: Of the 32 patients (22 Female, 10 Male), 20 were African American, 6 were diabetic, 17 had CKD stage 3 or greater, and mean age was 56±19 years. Among CKD patients, the mean nocturnal systolic dip was 3.4±9.8mmHg, mean diastolic nocturnal dip 8.2±8.3mmHg, mean MAP nocturnal dip 5.9±9.2mmHg. Among non-CKD patients, the mean systolic nocturnal dip was 6.9±5.8mmHg, mean diastolic nocturnal dip 11.9±6.5mmHg, mean MAP nocturnal dip 9.6±6.2mmHg. The mean difference between systolic nocturnal dip was 3.5±2.9 mmHg (p=0.2433), mean difference between diastolic nocturnal dip was 3.7±2.7mmHg (p=0.1708), mean difference between MAP nocturnal dip was 3.6±2.8 mmHg (p=0.2034). Among diabetic patients, the mean systolic nocturnal dip was 5.8±8.9mmHg, mean diastolic nocturnal dip 11.2±7.6mmHg, mean MAP nocturnal dip 8.8±8.2mmHg. The mean difference between systolic nocturnal dip was 3.8±3.7 mmHg (p=0.3148), mean difference between diastolic nocturnal dip was 7.1±3.3mmHg (p=0.0376), mean difference between MAP nocturnal dip was 6.2±3.5 mmHg (p=0.0864).

Conclusions: In our study, there was no difference in nocturnal blood pressure changes in patients with or without cardiovascular co-morbidities, except for nocturnal diastolic blood pressure in diabetic patients. Additional, larger scale trials are required to look for additional or synergistic risk of nocturnal blood pressure variability in patients with high cardiovascular risk.

FR-PO1032

A Pilot Trial Targeting Home vs. Pre-Dialysis BP in Hemodialysis (HD) Patients

Nisha Bansal,[4] David V. Glidden,[2] Rajnish Mehrotra,[4] Raymond R. Townsend,[5] Hanna L. Larson,[3] Lori Linke,[1] Farshad Palad,[2] Chi-yuan Hsu.[2] *[1]Kidney Research Institute, Seattle, WA; [2]UCSF, San Francisco, CA; [3]University of Washington, Seattle, WA; [4]UW, Seattle, WA; [5]UPenn, Philadelphia, PA.*

Background: Guidelines recommend treatment of pre-dialysis blood pressure (BP) among HD patients. However, there is a U-shaped association between pre-dialysis BP and death. We hypothesize that home BP may be a better target for treatment since there is a linear relationship between out-of-dialysis unit BP and death in observational studies. To test the feasibility of this approach, we conducted a trial of treating home vs. pre-dialysis BP in HD patients.

Methods: We conducted a 4-month randomized controlled trial of 50 HD patients at two centers, targeting home systolic BP (SBP) vs. pre-dialysis SBP 140-100 mmHg. Home and pre-dialysis SBPs were obtrained every 2 weeks and adjustments in dry weight and medications were made to reach the target SBP in each group. The primary outcomes were feasibility, adherence, tolerability and safety.

Results: One in four potentially eligible patients enrolled in the study. We had enthusiastic buy-in from 10 nephrologists from 8 different dialysis units (operated by 3 dialysis providers). The mean age of participants was 56 years, 40% were women, and 74% were non-white. All enrollees successfully completed the study except one who got a kidney transplant. Adherence to obtaining home BP was 97%. In the home BP group, there was no increased frequency of high or low pre-HD BP; lower frequency of intradialytic hypotension and falls; but more fatigue and syncope(**Table**).

Conclusions: This pilot study shows that HD patients can successfully participate in and adhere to home BP measurement. Given that there is a U-shaped association of pre-dialysis BP (but not out-of-dialysis-unit BP) with risk of death, targeting home BP may be a promising intervention to improve outcomes in this population and should be tested in larger clinical trials.

Funding: NIDDK Support, Private Foundation Support

Tolerability and safety over 4 months in HD participants randomized to home vs. pre-dialysis BP <140 mmHg

	Home BP treatment group	Pre-dialysis BP treatment group
Cramping*	19%	25%
Dizziness*	13%	12%
Lightheadedness*	18%	16%
Fatigue*	32%	16%
Duration of recovery from dialysis, mean (SD)	327 (42) min	268 (37) min
Intra-dialytic hypotension†	8.3%	13.4%
Pre-dialysis SBP<90 mmHg†	0.3%	0.2%
Pre-dialysis SBP>200 mmHg†	0.2%	0.0%
Post-dialysis SBP<90 mmHg†	1.8%	1.2%
Post-dialysis SBP>200 mmHg†	1.1%	0.3%
Syncope**	8%	0%
All-cause falls**	12%	28%

*denotes proportion of study visits; †denotes proportion of dialysis sessions; ** denotes proportion of study participants

FR-PO1033

Awareness and Monitoring Behavior of Home Blood Pressure Among Patients with CKD in Guangzhou, China

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Background: Home blood pressure monitoring (HBPM) has been proved superior to office measurements to predict cardiovascular outcomes and target organ damage in patients with chronic kidney disease(CKD). However, the awareness and monitoring behavior of home BP in CKD patients are still not explored in depth in China. The aim of this study was to investigate the awareness and monitoring behavior of home BP among patients with CKD and to compare the difference of control rate of BP between patients with and without HBPM.

Methods: This was a cross-sectional, descriptive study conducted in a hospital in Guangzhou, a city in southern China. The CKD patients complicated with hypertension (office systolic blood pressure(SBP)≥140mmHg and/or diastolic blood pressure(DBP)≥90mmHg) were recruited in 2019 by convenience sampling and were surveyed with the awareness and behavior model of HBPM questionnaire.

Results: A total of 114 patients with CKD stage 2-5, aged 52.8±14.2 years were enrolled. The mean values of office SBP and DBP were 145.8±20.2mmHg and 93.0±12.7mmHg respectively, while only 3.5%(4/114) patients correctly answered the upper limit of normal BP and 44.7% (51/114) of them reached the target of BP control (office BP<140/90mmHg). Although the BP monitors were owned by 91.2% (104/114) patients, in which 96.2% (100/104) were electronic device and 94% (94/100) were upper-arm BP monitors, 75% (78/104) of CKD patients didn't know that the monitor needed to be calibrated regularly. Regarding the monitoring frequency of home BP, 15.8% (18/114) didn't measure their BP at home, and 35.1% (40/114) measured only when they felt uncomfortable (e.g. headache, dizziness). 41.7% (40/96) never recorded the measurements, and 49% (47/96) never communicated the monitored data with their health professionals. The control rate of BP (office BP<140/90mmHg) in patients undergoing HBPM was 46.9%, which was higher than the one in patients without HBPM(33.3%, $p<0.05$).

Conclusions: CKD patients have poor BP control in Guangzhou, China. Although most of them have a HBPM device, the awareness of HBPM are still insufficient,and the utilizing rate of HBPM are undesirable. Given patients undergoing HBPM have a higher control rate of BP than those without HBPM, education and supervision should be strengthened to promote the application of HBPM on CKD patients.

Funding: Government Support - Non-U.S.

FR-PO1034

Survival of Patients with Percutaneous Coronary Intervention of Acute Coronary Syndrome in Left Main Coronary Artery Disease: The Role of Kidney Function

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Background: Chronic kidney disease (CKD) is associated with a high burden of stable coronary artery disease and an increased incidence of acute coronary syndromes (ACS). Left-main coronary artery disease (LMCAD) is the highest-risk lesion of ischemic heart disease, where revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is needed. Presence of CKD may increase the risk of complications and mortality connected with revascularization procedures. The aim of our study was to determine the role of CKD in the survival of patients after undergoing PCI for ACS in LMCAD.

Methods: In our retrospective study, 211 patients (142 male (67.3%)) were included. All patients underwent primary PCI because of LMCAD between January 1st, 2008 and December 31st, 2016. The patients were observed from PCI until their death or December 20st, 2018 (average time of observation was 5.3 years). Mean age of included patients was 69.2±11.3 years (minimum 38 years, maximum 91 years). CKD was defined as estimated glomerular filtration rate (eGFR)≤60 ml/min/1.73m^2 by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Comorbidities, such as arterial hypertension (AH), diabetes mellitus (DM), and dyslipidemia were recorded. Survival rates were analyzed using Kaplan-Meier survival curves. The Cox regression model was used to assess the influence of CKD, AH, DM and dyslipidemia.

Results: 82.5% of patients had AH, 28% had DM and 64.4% had dyslipidemia. 24.2% of patients had eGFR≤60 ml/min/1.73 m^2 (CKD group). Mean survival time of patients in the CKD group was 1294±1402 days and in the non-CKD group 2122±1246 days. 32 (62.73%) CKD and 53 (33.1%) non-CKD patients died. Kaplan-Meier survival analysis showed a higher risk of death for CKD patients (log-rank test; p<0.001). In Cox multivariable regression model, CKD remained a predictor of all-cause mortality in our patients (HR was 1.623 (95% CI 1.414-1.757; P=0.0001)). The impact of dyslipidemia on patient survival was statistically significant (p=0.0001), while AH (p=0.671) and DM (p=0.136) showed no impact on patient survival.

Conclusions: The results indicate an association between CKD and all-cause mortality in patients after undergoing PCI for ACS in LMCAD.

FR-PO1035

Number of Right Coronary Artery Lesions Increases as CKD Progresses

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Background: Chronic kidney disease is a risk factor for cardiovascular disease, and low glomerular filtration rate (GFR) is known to be associated with a higher risk of developing cardiovascular disease. However, there is currently no report on the association between the stage of chronic kidney disease and coronary artery lesion parameters such as site and number.

Methods: We examined variations in the site and number of coronary artery lesions in relation to the presence or absence of diabetes and dyslipidemia, and differences in laboratory parameter values such as serum blood urea nitrogen (BUN), creatinine (Cr), and estimated glomerular filtration rate (eGFR) in 2885 cases (average age: 68.96±10.32 years; 2140 men, 745 women) who underwent coronary angiography in our hospital from January 2009 to November 2011.

Results: Although there was no significant variation in coronary artery lesion sites in relation to differences in age or the presence or absence of diabetes or dyslipidemia, there was a significant increase in the number of right coronary artery lesions as the stage of chronic kidney disease progressed (P=0.001, Kruskal Wallis test).

Conclusions: Our results suggest that the progression of renal dysfunction may cause an increase in the number of right coronary artery lesions.

FR-PO1036

Association of Coronary Artery Calcification Density, Coronary Artery Calcification Score, and Cardiovascular Risk in Maintenance Hemodialysis Patients

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Background: Agatston's coronary artery calcification score (CACS) is a composite of coronary artery calcification (CAC) volume and CAC density (CACD). In general population, CAC volume is positively and CACD is inversely associated with cardiovascular disease (CVD) events. This study aimed to evaluate the association of CACD, CACS and cardiovascular disease (CVD) in MHD patients.

Methods: The subjects were Japanese MHD patients. CACD, CACS, laboratory parameters were assessed at baseline. The subjects were stratified into CACD and CACS level tertiles (T1–T3), respectively and assessed by Kruskal-Wallis test. Regression analyses for CACD were examined in MHD patients with and without CVD, respectively. Independent variables were age, sex, dialysis vintage, diabetes, current smoker, systolic blood pressure (SBP), serum magnesium, phosphate, uric acid, C-reactive protein (CRP), β2-microglobulin, albumin adjusted-serum calcium, and geriatric nutritional risk index (GNRI).

Results: Among all 291 patients (diabetes: 37.8%, past or present CVD: 39.9%), the mean age and dialysis vintage were 66±13 years, and 104±90 months. The CACD values for T1 (n=97), T2 (n=98), and T3 (n=96), were <3.67, 3.67-3.92, and >3.92. The CACS values for T1, T2, T3, were T1 (n=95), T2 (n=98), and T3 (n=98), were <380.0, 380.0-1931.0, and>1931.0. Multivariate regression analysis for CACD showed that age [β 0.30, 95% CI (0.02-0.03)], diabetes [β 0.31, 95% CI (0.39-0.80)], dialysis vintage [β 0.24, 95% CI (0.00-0.01)], β2-microglobulin [β 0.12, 95% CI (0.01-0.03)] and albumin adjusted-serum calcium [β 0.16, 95% CI (0.08-0.42)] were significantly related factors (P<0.001), but not CVD. Multivariate logistic regression for CVD showed that the highest CACS group [OR 1.9, 95% CI (0.94-3.98)], current smoker [OR2.19, 95% CI (1.22-3.99)], SBP [OR1.03, 95% CI (1.01-1.04)], and serum magnesium [OR 2.91, 95% CI (1.16-7.63)], CRP [OR0.73, 95% CI (0.53-0.95)], β2-microglobulin [OR0.97, 95% CI (0.93-1.02)] and GNRI [OR1.07, 95% CI (1.02-1.13)] were significantly related factors (P<0.05), but not CACD.

Conclusions: In MHD patients, presence of CVD is positively associated with CACS and hypomagnesemia, but not with CACD.

FR-PO1037

Blood Pressure and Renal Outcomes in Patients Undergoing Percutaneous Coronary Intervention

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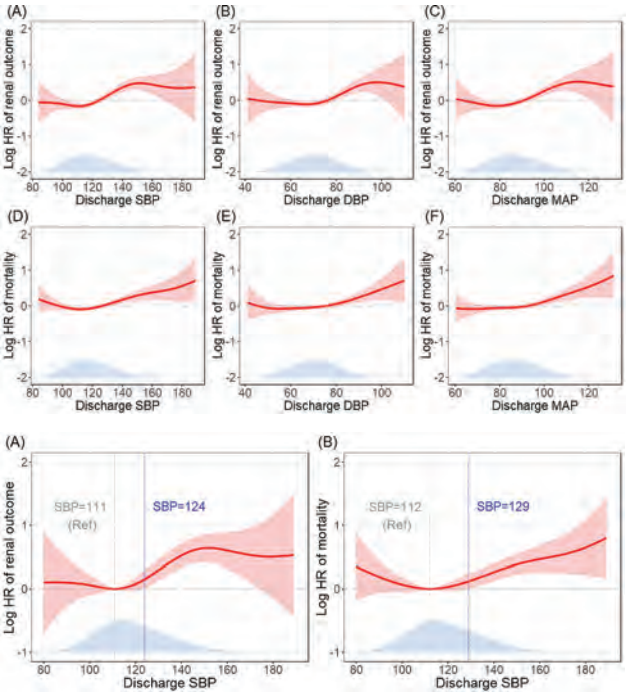
Background: Patients undergoing percutaneous coronary intervention (PCI) require strict control of blood pressure (BP) because abnormal control is related with worse cardiovascular and other organ outcomes. However, discharge BP-dependent renal outcome after PCI has not been thoroughly evaluated.

Methods: A total of 8204 adult patients undergoing PCI were reviewed at Seoul National University Hospital from 2006 to 2016. Renal outcome was defined when either a doubling of serum creatinine, ≥ 50% decrease of estimated glomerular filtration rate, or end-stage renal disease developed. The risks of renal outcome and all-cause mortality were evaluated according to BPs between 8:00 AM and 10:00 AM at discharge day using multivariable Cox proportional hazard regression and additive Cox regression with penalized splines.

Results: 9.5% (766 patients) of total patients reached renal outcomes during the median follow-up period of 6.5 years (maximum 13.0 years). Admission BP and discharge BP had poor correlation, and BP parameters at discharge including systolic BP (SBP), diastolic BP (DBP) and mean arterial pressure (MAP) mainly showed J-shaped relationship on renal outcome and all-cause mortality. Among BP parameters at admission and discharge, discharge SBP was the best predictor of both mortality and renal outcome. In additive Cox regression with reference BP which had minimal hazard ratios of study outcomes, there seemed to be threshold values for renal outcome (124 mmHg of SBP) and mortality (129 mmHg of SBP).

Conclusions: BP of patients undergoing PCI had J-shaped association on renal outcome and all-cause mortality. This non-linear relationship implies there could be a possible threshold of BP for renal outcome after PCI.



FR-PO1038

Cardiovascular and Renal Outcomes with Percutaneous Coronary Intervention Compared with Medical Therapy in Patients with CKD: A Meta-Analysis

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Background: The optimal management of coronary artery disease (CAD) in patients with chronic kidney disease (CKD) remains a matter of debate because these patients have been excluded from most randomized controlled trials (RCTs). The purpose of this meta-analysis was to examine whether percutaneous coronary intervention (PCI) among patients with CKD is associated with lower incidence of cardiovascular and renal outcomes compared with standard medical therapy.

Methods: A Medline literature research was conducted in PubMed for RCTs or cohort studies that compared different treatment strategies in adult patients with CAD and CKD. The primary outcome was the incidence of major adverse cardiovascular events. The secondary outcomes were progression of CKD and death from any cause. CKD was defined as an estimated glomerular filtration rate < 60ml/min/1.73m^2. The risk ratio (RR) was estimated using a random effects model.

Results: Four cohort studies and one RCT were included in this meta-analysis (839 CKD patients) for the primary outcome. Compared with optimal medical therapy, PCI was not associated with lower incidence of major adverse cardiovascular events: RR 0.91, 95% confidence interval (CI) 0.70-1.18 (**Figure**). In addition, PCI was not associated with lower incidence of CKD progression: RR 1.20, 95% CI (0.92-1.56). However, PCI was associated with lower all-cause mortality: RR 0.70, 95% CI (0.51-0.97), compared with medical therapy.

Conclusions: PCI may be superior to medical therapy in patients with CKD and CAD. Because of high inconsistency and risk of bias of the included studies, no definite conclusions can be drawn until ongoing RCTs report.

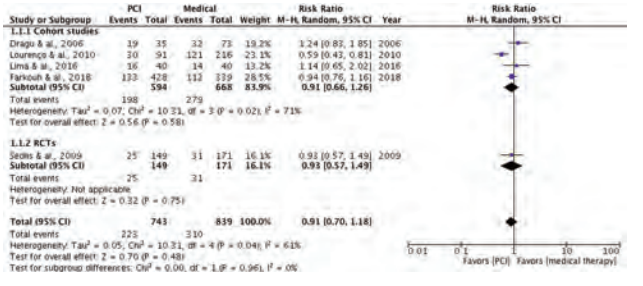

Figure Forest plot for major adverse cardiovascular events in patients with CAD and CKD

FR-PO1039

Prasugrel and Ticagrelor in Patients with Drug-Eluting Stents and ESRD

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Background: Prasugrel and ticagrelor have superior efficacy compared with clopidogrel in patients with preserved renal function. No randomized or cohort data exist with respect to their efficacy or safety in patients with end-stage renal disease (ESRD).

Methods: This retrospective cohort study used United States Renal Data System data from 2012 to 2015. We identified all dialysis patients who received a drug-eluting stent (DES) and were alive at 90 days after DES insertion. Prasugrel or ticagrelor users were matched 1:3 to patients treated with clopidogrel according to a propensity score. Outcomes were ascertained at 12 months. Competing risk survival models were used.

Results: Compared with clopidogrel, prasugrel or ticagrelor use was not associated with reduced risk of the composite outcome of cardiovascular mortality, myocardial infarction, or stroke: adjusted hazard ratio (HR) 0.91, 95% confidence interval (CI) 0.80-1.02 for prasugrel and HR 0.93, 95% CI 0.82-1.07 for ticagrelor. Ticagrelor use was associated with lower all-cause mortality and prasugrel use was associated with lower incidence of stroke, compared with clopidogrel. There was no difference in the incidence of fatal/intracranial or clinically-significant bleeding with either of the newer antiplatelet agents, compared with clopidogrel (**Table**). Shorter duration of the antiplatelet agent and acute coronary syndrome at presentation were independently associated with worse prognosis.

Conclusions: This is the first study examining clinical outcomes with prasugrel or ticagrelor in ESRD. Although no major efficacy benefit was detected, both prasugrel and ticagrelor were well-tolerated in patients with ESRD and may be considered in selected cases. Disclaimer The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

Clinical outcomes with prasugrel and ticagrelor, compared with clopidogrel in patients with DES and ESRD

Outcome	Prasugrel vs. clopidogrel		Ticagrelor vs. clopidogrel	
	HR (95% CI)	p	HR (95% CI)	p
CV death, MI, stroke	0.91 (0.80-1.02)	0.12	0.93 (0.82-1.07)	0.31
CV death	1.01 (0.81-1.27)	0.91	0.88 (0.69-1.12)	0.30
MI	0.98 (0.83-1.14)	0.75	1.03 (0.87-1.22)	0.74
Stroke	0.76 (0.64-0.91)	0.003	1.03 (0.86-1.23)	0.74
All-cause mortality	0.86 (0.72-1.03)	0.10	0.84 (0.70-0.99)	0.047
Fatal-intracranial bleeding	1.01 (0.59-1.72)	0.97	0.82 (0.43-1.57)	0.55
Clinically-significant bleeding	1.10 (0.94-1.28)	0.24	1.10 (0.93-1.30)	0.27

FR-PO1040

Thirty-Day Refill Gap in Prescription for P2Y12 Inhibitor Predicts Death in Dialysis Patients

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Background: It remains unclear whether gaps in refill of prescriptions for oral P2Y12 inhibitors (P2Y12-I) is associated with mortality in patients on chronic dialysis (ESRD).

Methods: USRDS registry from 2011 to 2015 was used to capture new P2Y12-I prescriptions for ESRD patients. The cohort was followed until death, kidney transplantation, switching between P2Y12-I, or lost to follow-up. After flagging and censoring key variables, all-cause death was counted and prescription refill pattern was ascertained for the first 6 months from the index date. Two major patterns were recognized: continuous users with no gaps in refills of 30 days and users with ≥30 days' gap in refills. Cox proportional regression (CPR) model analyzed association between all-cause death and ≥30 days' gap in prescription refills compared to continuous users with no such gaps in refill.

Results: Of the 32,886 patients in the cohort, median age of the cohort 64 years (IQR: 55 years, 72 years). 54% were male, 41% Caucasians, 36% African American and 18% Hispanic. 93% on hemodialysis, 7% on peritoneal dialysis, and average time on dialysis 3.8 years. Median modified Liu Index was 7 (IQR: 4, 10), and median number of baseline medications were 7 (IQR: 5, 10). During the first 6 months from the index date, there were 14,907 patients who filled prescriptions continuously without 30 days gap while 16,810 patients had ≥30 days' gap in refill. Compared to continuous refill pattern, ≥ 30 days' gap in refill of P2Y12-I prescription was associated with all-cause death, unadjusted hazard ratio (HR) 1.10 (95%CI: 1.06, 1.15) and adjusted HR 1.16 (95%CI: 1.11, 1.20).

Conclusions: Gaps in P2Y12-I prescription refills of ≥30 days among ESRD patients is independently associated with short term all-cause death.

Funding: Other NIH Support - American Heart Association grant # 16SDG31000045

FR-PO1041

All Types of Aortic Valve Replacement (AVR) May Not Be Equal in ESRD: Survival After Bioprosthetic, Mechanical, and Transcatheter AVR (bAVR, mAVR, and TAVR)

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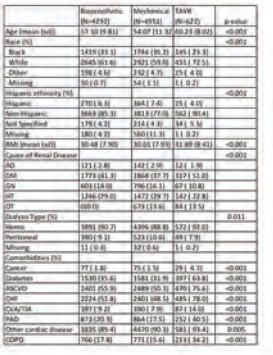
Background: Guidelines have no preference for bAVR or mAVR or TAVR in patients with ESRD. Their outcomes among those who subsequently get transplants is unclear.

Methods: All adult ESRD patients who were underwent AVR, between 1992 and 2015, were identified from the United States Renal Data System (USRDS) using ICD-9 codes. Baseline comorbidities were also identified using ICD-9 codes. Time to death was compared among the three groups (bAVR, mAVR, and TAVR) using Kaplan-Meier survival curves and with aHR (adjusted HR) using Cox proportional hazards model. These statistical procedures were performed separately for entire ESRD cohort and exclusively for those who subsequently underwent kidney transplant. TAVR group was excluded from latter analysis due to low numbers.

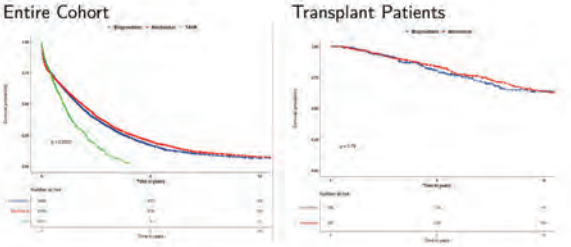
Results: There were a total of 9865 patients who underwent AVR (bAVR=4292, mAVR=4951, TAVR=622). Patients who underwent mAVR were the youngest and had the least comorbidity profile. Patients who underwent TAVR were the oldest and had the highest comorbidity profile (Fig 1). For the entire cohort, compared to bAVR, mAVR had better survival (aHR: $_{0.8}0.9_{0.96}$) but TAVR had worse survival (aHR: $_{1.14}1.27_{1.42}$). Among those who subsequently got kidney transplant, there was no difference in survival for the mAVR group compared to bAVR (aHR: $_{0.8}1.09_{1.53}$) (Fig 2).

Conclusions: Mechanical AVR is the preferred choice in ESRD. TAVR may be associated with worse survival but it may be due to higher baseline comorbidity.

BASELINE CHARACTERISTICS OF ESRD PATIENTS WHO HAD AORTIC VALVE REPLACEMENTS



KM SURVIVAL CURVES, BY TYPE OF AORTIC VALVE REPLACEMENT



FR-PO1042

Transcatheter vs. Surgical Aortic Valve Replacement in US Dialysis Patients

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Background: The benefits of transcatheter aortic valve replacement (TAVR) vs. surgical (SAVR) valve replacement are uncertain among patients receiving maintenance dialysis with aortic stenosis. We compared inpatient and 1-year mortality in dialysis patients with aortic stenosis receiving TAVR vs. SAVR.

Methods: We used the CMS 100% ESRD files from 2013-2015 to compare characteristics and outcomes among patients receiving TAVR or SAVR. The cohort comprised patients receiving an AVR between January 1, 2013 and December 31, 2014. Outcomes of interest were inpatient and 1-year mortality. We used the six-month period prior to the procedure to assess comorbidity using claims. We used Cox proportional hazards models to compare 1-year mortality, adjusting for patient characteristics and comorbidity.

Results: Of the 1867 patients who received an AVR, 66.1% received SAVR and 33.9% TAVR. TAVR patients were more likely to be older, female, white, and have a higher comorbidity burden. Although TAVR patients experienced less inpatient mortality (4.6% vs. 7.8% for SAVR), there was no difference in 1-year mortality among those discharged alive (HR 1.1, 95% CI 0.9-1.4).

Conclusions: Although TAVR is an increasingly attractive option compared to SAVR in the general population, there is less evidence supporting its use in dialysis patients. Short term outcomes appeared to be better among dialysis patients receiving TAVR despite their older age and greater comorbidity burden, and 1-year mortality was not significantly different than for SAVR.

TAVR vs. SAVR, Dialysis Patients
N = 1867

	SAVR (%)	TAVR (%)
Overall	66.1%	33.9%
Female	30.4%	37.6%
Cause of ESRD = DM	38.2%	37.9%
White	66.6%	80.6%
Hemodialysis	90.8%	91.6%
ASHD	79.3%	89.1%
CHF	72.4%	91.9%
PVD	45.1%	64.0%
COPD	25.6%	40.3%
GI	9.8%	15.3%
Liver disease	10.1%	8.4%
Dysrhythmia	69.8%	79.2%
Cancer	6.4%	11.9%
DM	62.2%	63.2%
Mean age	63.6	74.7
Inpatient death	7.8%	4.6%
Adjusted HR for 1-yr mortality (HR, 95% CI)	**1.0**	**1.1 (0.9-1.4)**

FR-PO1043

Health-Related Quality of Life After Ligation of Arteriovenous Fistula for Pulmonary Hypertension

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Background: AV fistulas (AVF) are the access method of choice in patients on long-term hemodialysis. Due to their high blood flow, AVFs are also a potentially reversible cause of secondary pulmonary hypertension. There are multiple small case series describing change in the hemodynamics and improvement in the symptoms after ligation of AVF for pulmonary hypertension. There is very little data regarding health related quality of life changes (HRQOL) after ligation AV fistula for Pulmonary HTN

Methods: Patients undergoing ligation of AVF for Pulmonary Hypertension (PHT) were identified from our AVF database from January 2017 to December2018. All patients were specifically referred from the PHT clinic with the diagnosis of moderate or severe PHT. Detailed demographics, postoperative clinical variables and recipient's outcomes were abstracted from electronic health records. We used ***emPHasis10***, a validated PHT HRQOL questionnaire developed by the Pulmonary Hypertension Association, United Kingdom and freely available over for use. Patients were asked to respond to the questionnaire before and after ligating the fistula. Statistical comparisons were made using the Wilcoxon signed-rank test.

Results: We identified 9 patients who underwent ligation of AV fistula for PHT. One patient died during the follow up period and one patient was lost to follow up hence 7 patients were included in the study. The mean age was 47.7 years (range 33-58), 5 patients were male and 2 females. All the patients presented with an upper arm arteriovenous fistula. **The mean pre-ligation emPH asis-10 score was 29.0±15.1 and post-ligation this significantly decreased to 6.1±5.2(p<0.01), indicating significant improvements in HRQOL surrounding PHT**

Conclusions: Ligation of AV fistula for secondary pulmonary HTN may potentially lead to significant improvement in pulmonary hypertension indices and health-related quality of life

Patient Number	Age	Sex	Race	Pre-Procedure emphasis 10 score	Post- Procedure emphasis 10 Score	Duration of follow Up in months
1	51	M	AA	18	4	21
2	39	M	AA	45	15	19
3	42	F	AA	24	1	16
4	58	M	AA	35	12	10
5	33	M	W	28	4	8
6	56	M	AA	48	4	7
7	55	F	AA	5	3	14

FR-PO1044

Impact of Electrocardiographic Finding on Cardiac Mortality in Hemodialysis Patients: Ten-Year Outcomes of the Q-Cohort Study

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Background: Electrocardiography is a noninvasive and inexpensive test and regularly performed in dialysis clinic. However, its clinical predictive value in hemodialysis patients is unclear. We investigated electrocardiographic finding associated cardiac-related mortality in Japanese hemodialysis patients.

Methods: A total of 1087 Japanese HD patients aged ≥18 years who underwent electrocardiography within 1 year from baseline were followed for 10 years. Multivariate-adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for electrocardiographic finding of cardiac death were calculated using logistic regression analysis. To assess the additional predictive value of electrocardiographic finding in risk assessment, we compared the c-statistics between clinical model included electrocardiographic finding and basic model.

Results: During the follow-up period, 492 patients died totally, and 119 patients died of cardiac disease. After adjusting for confounding risk factors, heart rate (odds ratio [OR] for all cause moratality.1.46, 95% CI 1.28-1.67 for every 10/min increase), QT prolongation (OR 2.23, 95% CI 1.46-3.42), and left ventricular hypertrophy by Sokolow-Lyon voltage criteria (OR 1.81, 95% CI 1.15-2.86) was an independent predictor of cardiac-related mortality. The c-statistics of the traditional risk factors with the elcectrocardiographic findings in cardiac mortality were significantly increased compared to those of the traditional risk factors without the elcectrocardiographic findings (0.713 vs.0.753, p = 0.02).

Conclusions: We demonstrated electrocardiographic finding associated with all-cause and cardiac-related mortality in hemodialysis patients. Moreover, addition of the electrocardiographic finding to models with standard risk factors significantly improves the predictive ability of cardiac-related mortality.

FR-PO1045

The Ankle-Brachial Index Is Linked to the Subendocardial Viability Ratio: A Correlation Between Peripheral and Myocardial Perfusion

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Background: Subendocardial viability ratio (SEVR), non-invasively calculated through pulse wave analysis (PWA), is an index of myocardial oxygen supply and demand. Lower SEVR values are linked with advanced coronary artery disease (CAD) and higher mortality, especially in patients with chronic kidney disease (CKD). Peripheral artery disease (PAD) can be assessed by the ankle-brachial index (ABI) and is also associated with increased cardiovascular mortality. Both PAD and CAD are the result of advanced athersclerosis and increased arterial stiffness, but the direct correlation between these two entities is still not fully understood. The aim of our study was to determine the correlation between PAD and CAD by using ABI and SEVR.

Methods: 86 clinically stable patients with ishemic CAD (56 male, 65.1%), who were hospitalized due to elective coronary angiography, were included in the study. Kidney function was determined by the estimation of glomerular filtration rate (eGFR) using the CKD-EPI Creatinine equation. SEVR was determined with PWA (SphygmocorÒ, Atcor Medical, Australia) and ABI index was measured using an automated, non-invasive, waveform analysis device (MESIÒ, Slovenia). All the data were obtained prior to coronary angiography.

Results: Mean age of patients was 64.6±9.6 years (minimum 27, maximum 82 years). 23 patients had diabetes mellitus (26.7%) and 52 patients were smokers (60.5%). Mean eGFR was 74.5±18.4 ml/min/1.73 m^2. Mean ABI values were 1.0±0.1 (0.76-1.31), mean SEVR values were 163.1±34.7% (92-260%). Pearson's correlation test showed a statistically significant correlation between ABI and SEVR (r=0.251, p=0.02). Multiple regression analysis with SEVR as dependent variable has shown statistically significant association with ABI (p=0.032, beta coefficient=0.245) as independent variable, but not with age, diabetes, smoking, eGFR and cholesterol.

Conclusions: ABI is independently associated with SEVR in patients with stable CAD, suggesting a direct connection between peripheral and myocardial perfusion, independent of traditional atherosclerosis risk factors and kidney function.

FR-PO1046

Lipid Metabolic Profiling of Primary Sjögren Syndrome with Kidney Function Deficiency

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Background: Primary Sjögren Syndrome (pSS) is characterized by lymphocytic infiltration of the exocrine glands occurs primarily from age 50 onward, with a female to male ratio of 9:1. In the clinic, a severely affected pSS patient not only has the salivary and lacrimal glands damages, but also manifests other extraglandular diseases. Earlier research reported that lipid metabolism disorder linked to pSS caused renal disease. However, the overall lipid metabolic profile of pSS remains unknown. The aim of this study is to analyze lipid metabolic signature of the pSS patients with declined estimation of glomerular filtration rate (eGFR) by which to provide a new angle to underlying the pathogenesis of pSS associated renal diseases.

Methods: Dionex UltiMate 300 Ultra-high performance liquid chromatography system coupled online via electrospray ionization source with an Q Extractive Orbitrap MS instrument was used to evaluate lipid metabolites in 210 female patients with pSS, compared with 396 healthy subjects. We conducted analysis of covariance with potential confounders as covariates. Receiver operating characteristic (ROC) curves were plotted to explore the significance of multiple biomarkers for renal function in pSS.

Results: We identified 1001 differentially expressed lipid metabolites between healthy adults and the pSS patients. Subtype comparisons also revealed significantly differentially expressed lipid metabolites between the pSS patients with eGFR<90ml/min/1.73m2 and eGFR>90ml/min/1.73m2. Changes in triacylglycerol (50:4/14:0-18:2) and Phosphatidyl cholines (40:8/20:4) were the most distinctive lipids between the pSS patients eGFR<90ml/min/1.73m2 and eGFR>90ml/min/1.73m2. Particularly, the diagnostic outcomes are shown *via* the ROC curves for comparison between healthy adults vs pSS (eGFR>90ml/min/1.73m2), healthy adults vs pSS (eGFR<90ml/min/1.73m2), and pSS patients eGFR>90ml/min/1.73m2 vs eGFR<90ml/min/1.73m2. Consistent with the eGFR levels, specific lipidomics-based biomarkers provided AUC of 0.975 to 0.986 in different stage of kidney disease, compared with the healthy controls. The AUC is 0.690 if directly compare the pSS patients with eGFR>90ml/min/1.73m2 or eGFR<90ml/min/1.73m2.

Conclusions: pSS patients are characterized by a distinct lipid metabolic profile providing new insights into the pathogenesis of pSS renal damages.

FR-PO1047

Risk of Ischemic Heart Disease Is Increased in Patients with ANCA-Associated Vasculitis

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Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a chronic autoimmune disease characterized by inflammation of the small to medium-sized blood vessels. A well-established long-term complication of many inflammatory diseases is the occurrence of cardiovascular events. In AAV, the results of experimental studies indicate the occurrence of accelerated atherosclerosis. However, the risk of ischemic heart disease (IHD) in patients with AAV remains poorly quantified. The aim of this study is to investigate the IHD risk in patients with AAV and to examine the effect of immunosuppressive therapy on the IHD risk.

Methods: The study included patients with AAV treated at the Vasculitis and Lupus Clinic in Addenbrooke's Hospital (Cambridge, United Kingdom) between 1990 and 2015. The occurrence of IHD (defined as angina pectoris or myocardial infarction) in these patients was compared with the incidence in the general population by calculating standardized incidence ratios (SIRs), adjusted for sex, age, and calendar year.

Results: Of the 529 included patients, 51 patients developed a total of 57 ischemic heart events during a mean follow-up of 6.3 years. This represented a 2.0-fold increased (95%CI 1.53-2.58, p<0.001) IHD risk in AAV patients compared to the sex-, age-, and calendar year matched general population. There was no significant difference in follow-up duration of patients with and without IHD (mean follow-up of 6.3 year and 5.4 year, respectively) IHD risk was higher in patients with MPO-ANCA (SIR 2.31; 95%CI 1.55-3.44; P <0.001) than in patients with PR3-ANCA (SIR 1.63; 95%CI 1.01-2.61; p=0.043). Moreover, IHD was increased in patients treated with cyclophosphamide (SIR 1.78; 95%1.22-2.60; p=0.003), but not in patients treated with rituximab (SIR 1.03; 95%CI 0.26-4.10; p=0.971).

Conclusions: The result of this large study demonstrate that patients with AAV have an increased IHD risk as compared to the sex-, age-, and calendar year matched general population. IHD risk was higher in patients with MPO-ANCA. Importantly, IHD risk was not increased in patients treated with rituximab but was increased in patients treated with cyclophosphamide. The results of this study demonstrate a need for the active monitoring and treatment of cardiovascular risk factors in patients with AAV.

FR-PO1048

Apabetalone Lowers Serum Alkaline Phosphatase in CVD Patients with and Without CKD and Improves Cardiovascular Risk

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Background: Patients with cardiovascular disease (CVD) with or without chronic kidney disease (CKD) have considerable residual risk despite optimal standard of care. Alkaline phosphatase (ALP) has been suggested as a modifiable CVD risk factor. Apabetalone, a bromodomain and extraterminal (BET) inhibitor selective for bromodomain 2 (BD2) lowers ALP in a dose-response fashion. In phase 2 studies apabetalone treatment was associate with a significant 44% reduction in CVD events. We sought to determine whether this CVD risk reduction by apabetalone is associated with the concomitant lowering of serum ALP.

Methods: In a pooled phase 2 post-hoc analysis of 795 CVD patients on standard of care treatment including statins, of which 11.8% had CKD as defined by eGFR <60 m/min/1.73m^2 (n=94; 71=apabetalone; 23=placebo) we assessed the effect of apabetalone vs. placebo treatment for up to 24 weeks on the incidence of CVD events and serum ALP.

Results: Apabetalone treatment decreased serum ALP in CKD and non-CKD CVD patients by 10.2% and 6.5%, respectively (12 weeks), and 7.7% and 7.2%, respectively (24 weeks) (all $p<0.01$). Further analysis on the whole population showed that baseline ALP (median 72 U/L) predicted MACE (death, non-fatal myocardial infarction, coronary revascularization, or hospitalization for cardiovascular causes), independent of high-sensitivity C-reactive protein (hsCRP), sex, age, study, established CVD risk factors, CKD, and treatment allocation (hazard ratio [HR] per standard deviation [SD] 1.6, 95% CI 1.2-2.1, $p<0.001$). In the apabetalone group, a 1 SD reduction in ALP was associated with a HR for MACE of 0.58 (95% CI 0.43-0.78, $p<0.001$).

Conclusions: Serum ALP predicts strongly the residual cardiovascular risk, independent of hsCRP, established cardiovascular risk factors and CKD, in patients with cardiovascular disease on statin treatment. Apabetalone lowers serum ALP and may prevent the incidence of new cardiovascular events. The phase 3 BETonMACE CVD outcomes study reporting H2 2019, will provide further insights about apabetalone's ALP reduction and potential causality for CVD events.

FR-PO1049

Use of Bisphosphonates in CKD Is Associated with Incident Cardiovascular Disease (CVD)

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Background: CKD-mineral bone disorder, including vascular calcification, is associated with increased CVD risk. Studies suggest that bisphosphonates, the preferred therapy for osteoporosis, are safe in CKD patients. In animal models, bisphosphonates inhibit vascular calcification. We hypothesized that use of bisphosphonates in CKD is associated with lower incident CVD, CVD mortality, and all-cause mortality.

Methods: 2593 Framingham OFFSPRING participants were included. We used propensity score-adjusted Cox regression models to determine the relationship between bisphosphonate use and the following outcomes: time to incident CVD, time to CVD mortality, and time to all-cause mortality. The data were stratified by presence or absence of CKD, defined as eGFR <60 mL/min/1.73m2. The propensity score model included age, sex, hypertension, smoking status, diabetes, total cholesterol, and HDL.

Results: Mean age was 70±9 years and 10% were male. Of the 371 participants using bisphosphonates, 31 had CKD. In the unadjusted analysis, those with CKD who used bisphosphonates had a significant increase in incident CVD [HR 2.061 (95% CI, 0.99-4.29; p=0.05)] compared to those with CKD who did not use bisphosphonates. After adjusting for the propensity score, the HR for incident CVD in participants with CKD who used bisphosphonates increased [HR 2.76 (95% CI, 1.24-6.18; p=0.01)]. There was no significant association between bisphosphonate use and mortality from CVD or all-causes in participants with CKD. In participants without CKD who used bisphosphonates, there was a trend showing a decrease in time to CVD mortality [HR 0.28 (95% CI, 0.07-1.14; p=0.08)] compared to those who did not use bisphosphonates. However, after propensity score adjustment, the HR was attenuated [HR 0.39 (95% CI 0.09-1.67; p=0.21)]. There was no significant association between bisphosphonate use and incident CVD or all-cause mortality in those without CKD.

Conclusions: Contrary to our hypothesis, we show, for the first time, that bisphosphonate use is associated with increased incident CVD in CKD patients. Our analysis was limited by a small sample size. However, future studies in larger cohorts are necessary to confirm these findings and to better understand the mechanisms underlying this association.

Funding: Veterans Affairs Support

FR-PO1050

Effects of Vitamin D on Cardiovascular and Renal Outcomes in Adults with CKD: A Systematic Review with Meta-Analysis of Randomized Controlled Trials

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Background: Cardiovascular disease is the leading cause of mortality in patients with chronic kidney disease (CKD). The excess risk has been attributed to increased vascular calcification and higher prevalence of left ventricular hypertrophy. Vitamin D therapy plays an important role in management of secondary hyperparathyroidism but may also have cardioprotective effects. This systematic review was performed to study the effects of vitamin D therapy on cardiovascular and renal outcomes.

Methods: MEDLINE, EMBASE and Cochrane databases were searched for randomised controlled trials involving CKD patients stages 3-5D with ≥3 months follow-up that compared a vitamin D compound (nutritional or active) with placebo, no study medication, or an active medication. For continuous variables, the change between the baseline value and end-of-treatment value was calculated. Summary estimates were obtained by a random-effects model and expressed as weighted mean differences (WMD) or relative risks (RR) with 95% confidence intervals (CI).

Results: One hundred and thirteen trials (9973 participants) were included (mean age 60.5 years, median follow-up 6 months). Of these, 71 trials were conducted in 6036 dialysis patients, and 42 trials were conducted in 3937 non-dialysis CKD patients. Trials were generally at high or unclear risk of bias. There was no significant difference in risk of major adverse cardiovascular outcomes when comparing vitamin D and placebo (11 trials, RR 0.98, 95%CI 0.65-1.48), or active and nutritional vitamin D (2 trials, RR 0.85, 95%CI 0.32-2.31). Compared to placebo, vitamin D did not significantly change systolic blood pressure (7 trials, WMD 0.43 mmHg, 95% CI -3.43 to 4.29), diastolic blood pressure (5 trials, WMD 0.58 mmHg, 95%CI -2.16 to 3.32), pulse wave velocity (4 trials, WMD -0.75 m/sec, 95%CI -1.56 to 0.07), left ventricular mass (4 trials, WMD 2.17 g/m^2, 95%CI -8.01 to 12.36) or glomerular filtration rate (11 trials, WMD -0.25 mL/min/1.73m^2, 95%CI -0.78 to 0.29). Data for B-natriuretic peptide levels and urine albumin/creatinine ratio were insufficient for meta-analysis.

Conclusions: The effects of vitamin D compounds on cardiovascular and renal outcomes in CKD are uncertain. Further research with adequately powered trials is required.

FR-PO1051

Effect of Renin-Angiotensin System Blockade on Stroke in Kidney Transplant Recipients: Retrospective Multicenter Study in Japan

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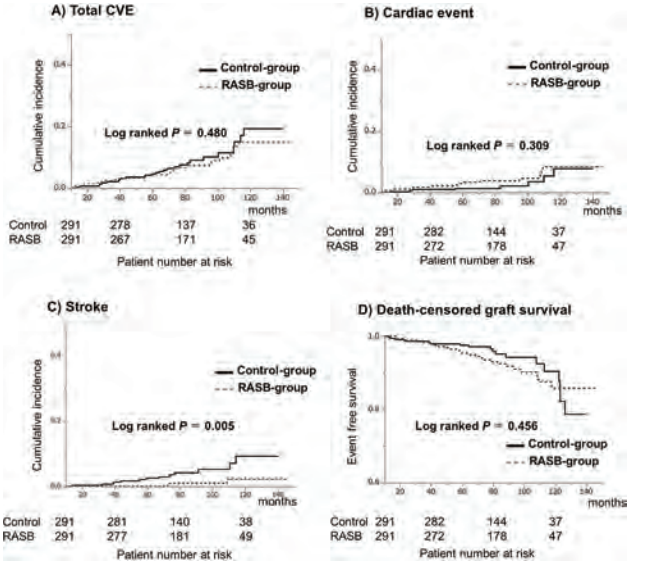
Background: Renin–angiotensin system blockers (RASBs) reduce end-stage kidney disease and cardiovascular event (CVE) development in chronic kidney disease. However, whether RASBs improve long-term prognosis in kidney transplant (KT) recipients remains unknown.

Methods: We investigated 900 kidney transplant patients in a multicenter retrospective cohort study in Japan and compared death-censored graft-survival and CVE (total, cardiac events, stroke) based on RASB use within 12 months after KT. The associations were examined using a Cox hazard model and propensity score-matching analysis.

Results: The cohort comprised 375 patients treated with RASBs (RASB group) and 525 patients without RASBs (control group). The median observational period was 82 months, with 68 patients reaching graft loss: 79 total CVE, 36 cardiac events, 26 stroke. In a matching cohort comprising 582 patients, graft survival, total CVE, and cardiac events were not different between the two groups. Only stroke incidence rate was significantly lower in the RASB group compared with the control group (1.4 vs. 6.4 per 1000 patients/year, log-ranked P=0.005). In a multivariable analysis, stroke events were also significantly lower in the RASB group compared with the control group (Hazard ratio and 95% confidence interval, 0.20 [0.04–0.62]).

Conclusions: RASBs potentially reduce stroke events in KT recipients.



The cumulative incidence for each endpoint was compared between the RASB and control groups: (A) Total CVE, consisting of cardiac event, stroke, and peripheral artery disease; (B) Cardiac event; (C) Stroke; (D) Death-censored graft-survival

FR-PO1052

Postural Blood Pressure Control Is Decreased in Diabetic Patients After Successful Renal Transplantation

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Background: The postural control of blood pressure (BP) under othostatic challenges, a measure of the robustness of the autonomic nervous system, is reduced in both renal insufficiency and diabetes mellitus (DM). The present study was undertaken to assess the effect of normalization of kidney function by renal transplantation (TX) on postural changes of BP and autonomic indices in uremic patients, without [DM(-)] and with [DM(+)].

Methods: Continuous interbeat interval (IBI), systolic (SBP) and diastolic (DBP) BP and their variabilities in the low (LF) and high (HF) frequency ranges were recorded during sitting and standing in 48 TX DM(-), in 14 TX DM(+) patients and in 37 control (C) individuals of similar age range. α index, a measure of baroreflex function was obtained from the square roots of the ratio of average IBI and SBP powers. LF IBI/HF IBI was considered a measure of the sympatho-vagal balance.

Results: Plasma creatinine was 116±31 and 113±43 μmol/l in TX DM(-) and TX DM(+) respectively (pNS). Differences (Δ) in BP and variability measures between sitting and standing positions (median and interquartile ranges) are shown in Table1. In C, moving from sitting to standing was associated with increased BP, decreased IBI, decreased α indices and increased sympatho-vagal balance. These changes were partly maintained in TX DM (-) but markedly suppressed in TX DM (+).

Conclusions: Our data show that in C, BP during postural changes is maintained by sympathetic activation, which is partialy attenuated in TX DM (-) and almost abolished in TX DM(+), despite the reversal of renal failure. These alterations, arguably the consequence of long standing DM autonomic neuropathy, may be responsible for frailty, gait instability and falls in these patients.

Table 1.

	C	TX DM (-)	p vs.C	TX DM (+)	p vs. C
Δ SBP (mmHg)	9.7 (16.2)	8.9 (18.1)	0.818	-1.6 (32.4)	0.045
Δ DBP (mmHg)	9.6 (11.3)	10.8 (11.0)	0.697	1.6 (9.1)	0.008
Δ IBI (ms)	-78 (82)	-58 (81)	0.111	-45 (67)	0.028
Δ LF SBP (mmHg^2/Hz)	103 (117)	47 (90)	0.002	19 (64)	0.002
Δ HF SBP (mmHg^2/Hz)	17.7 (35.1)	10.5 (22.9)	0.089	3.6 (20.2)	0.018
Δ LF IBI (ms^2/Hz)	597(2445)	-79 (1347)	0.018	-0.8 (139)	0.076
Δ HF IBI (ms^2/Hz)	-122 (928)	-57 (505)	0.484	-22 (61)	0.047
Δ LF α (ms/mmHg)	-1.68 (2.16)	-1.21 (2.10)	0.405	-0.52 (0.83)	0.002
Δ HF α (ms/mmHg)	-3.40 (4.54)	-2.07 (4.36)	0.072	-0.27 (1.53)	0.001
Δ (LF IBI/HF IBI)	1.51(3.92)	0.39 (2.53)	0.001	0.06 (2.01)	0.002

Δ: difference of standing- sitting measurements.

FR-PO1053

The Relationship Between Retinal Artery Wall-to-Lumen Ratio and Kidney Pathology Findings in Accelerated Hypertension

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Background: Accelerated hypertension is characterized by macrovascular and microvascular endothelial damage. In this study we analyze the relationship between retinal artery wall-to-lumen ratio (WLR) and renal histology.

Methods: All patients hospitalized into Kidney Intensive Care Unit for malignant hypertension with acute kidney injury had measurement of retinal wall-to-lumen ratio (WLR) using SPECTRALIS retina imaging. Renal clinical and pathology findings were collected as well as details pertaining to heart echography. Data were presented as median [25th-75th], correlation were calculated according to Spearman's test.

Results: Twenty-seven patients were hospitalized for accelerated hypertension in our center between September 2016 and April 2019. Median age was 39.4 years old [30.7-45.3]. Initial systolic, diastolic and mean arterial pressure were 218 [185-239], 128 [113-162] and 153 [137-187] mmHg, respectively. Ten (37.0%) patients underwent haemodialysis during their stay, 8 (29.6%) patients underwent chronic haemodialysis, 4 (14.8%) had myocardial microvasculature involvement, 4 (14.8%) had posterior-reversible encephalopathy syndrome. Seventeen patients (63.0%) had kidney biopsy. Retinal WLR was correlated with systolic and mean arterial pressure, respectively r=0.56 (p=0.003) and r=0.46 (p=0.02), but did not reach significance for tubulo-interstitial fibrosis (r=-0.45, p=0.09) or glomerulosclerosis (r=-0.38, p=0.15). Retinal WLR was not correlated with renal WLR (r=0.13, p=0.6). Retinal WLR did not correlate with left ventricular mass estimation (r=0.10, p=0.6)

Conclusions: Retinal WLR was found to be closely correlated to initial systolic and mean arterial pressure. Perhaps due to the cohort size, we failed to demonstrate an association between retinal WLR and kidney pathology findings.

FR-PO1054

Role of Endothelial Function Determined by Asymmetric Dimethylarginine in the Prediction of Resistant Hypertension: A Subanalysis of the ReHot Trial

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Background: Endothelial dysfunction has been conceived as the basis of cardiovascular disease. Brought in core of global epidemic of obesity and the increased life expectancy, resistant hypertension (ReHy) represents a growing public health issue. We conducted a subanalysis of the Resistant Hypertension Optimal Treatment (ReHOT) study to evaluate the association between endothelial dysfunction and resistant hypertension in a population of patients treated in a staged fashion for hypertension.

Methods: ReHOT was a prospective, multicenter, randomized trial comprising 26 sites in Brazil. One hundred and three hypertensive patients of one site were included for this 6 months study in 7 visits (V0-V6), 28 days apart. There was a first phase (V0-V3) of antihypertensive adjustment with 3 drugs to detect ReHy. A second randomized phase (V3-V6) of treatment with a fourth drug (clonidine or spironolactone) in the hypertensive patients characterized as resistant. Serum asymmetric dimethylarginine (ADMA) was determined by high performance liquid chromatography (HPLC) on Visits 1 and 7.

Results: Of the 103 patients included, 86 (83.5%) underwent the randomization visit (V3), 71 were characterized as non-resistant hypertensives (82.5%) and 15 as resistant hypertensives (17.5%). Patients from the upper tercile of serum ADMA had a higher V1 blood pressure, higher total cholesterol values as well as higher prevalence of cardiovascular disease. There was a parallel reduction in blood pressure levels and ADMA values during follow-up with a positive correlation in both groups and a greater reduction among those with ReHy. Serum ADMA was shown to be an independent predictor of resistant hypertension after adjustment for multiple variables (OR: 11.42, 95% CI: 1.02 - 127.71, p = 0.048).

Conclusions: We demonstrated that ADMA was an independent predictor of resistant hypertension, and we observed that the improvement in blood pressure levels obtained with the treatment was proportional to the reduction in ADMA values, suggesting a complementary role of ADMA not only as a stratification tool for the occurrence of resistant hypertension, but also as a potential therapeutic target in this population.

Funding: Government Support - Non-U.S.

FR-PO1055

Impedance Cardiography-Guided Individualized Hypertension Treatment

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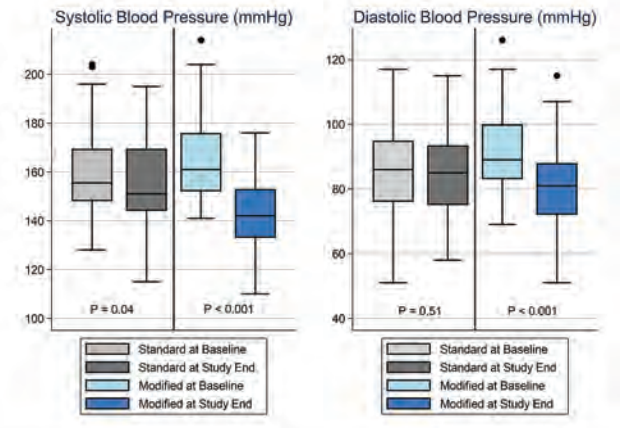
Background: Current guidelines for management of hypertension (HTN) allow considerable leeway in selection of antihypertensive medications to achieve new lower blood pressure (BP) targets. Success in achieving target BP remains suboptimal. We observed BP outcomes under standard (standard) and individualized (modified) HTN treatment protocols.

Methods: We instituted a practice improvement project comparing standard to modified treatment protocols for the management of patients referred for resistant HTN with or without chronic kidney disease. The modified protocol, managed by two nephrologists, was centered around hemodynamic status: vasconstricted, hyperdynamic, or mixed state. Hemodynamic status was defined by impedance cardiography (central BP and pulse wave velocity were measured in a subset of patients). Antihypertensive medications were adjusted to treat the hemodynamic state. During an initial 6-month run-in, patients not in target BP were assigned to study groups. We compared BP outcomes using paired and unpaired t-tests at the study end.

Results: Of 169 patients at baseline, 88 continued with standard care and 81 were managed with the modified protocol. Demographics were similar in both groups. The modified group had significant reductions in both systolic BP and diastolic BP baseline to study end but the standard care group had little to no change (see Figure 1). At study end, 45.7% and 11.4% were in target BP in the modified and standard groups, respectively (p<0.001). This correlated with increased use of calcium channel blockers and beta-blockers in the modified group compared to standard care.

Conclusions: Impedance cardiography is a simple, noninvasive method for evaluating underlying hemodynamic drivers of HTN. Hypertension management is more effective when guided by hemodynamic parameters.

Funding: Commercial Support - New NI Medical, AtCor Medical, Inc.



Box Plots of BP Outcomes by Study Group

FR-PO1056

Determination of Adherence to Antihypertensive Medications by Urine Testing In Patients with Advanced CKD

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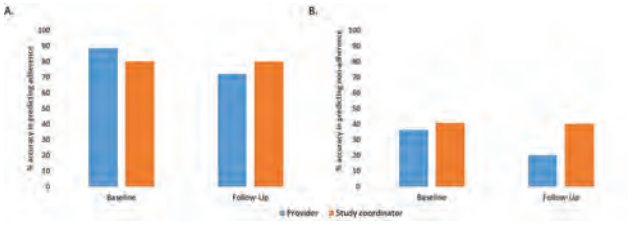
Background: Our objective was to assess blood pressure (BP) medication adherence and its predictors in adults with advanced CKD using KardiAssure, a commercially available urine test that detects a comprehensive battery of BP medications. We also aimed to compare assessments of medication adherence by providers and study coordinators compared to KardiAssure testing in the clinical and research setting.

Methods: Participants with advanced CKD (stage 4-5) in a randomized pilot trial were included. Urine specimens were collected at baseline and 4-month follow up visits. Adherence was defined as agreement between patient-reported BP medications and medications detected by KardiAssure. Providers and study coordinators were surveyed regarding their perceptions of patient BP medication adherence. Logistic models were used to examine predictors of adherence.

Results: We included 57 patients at baseline and 40 patients at the 4-month follow-up for study. Mean age was 54±17 years; 58% were male; mean baseline eGFR was 22 mL/min/1.73m^2. Diuretics and beta blockers were the the most common agents that patients were non-adherent to by KardiAssure testing (27% and 23%, respectively). Providers and coordinators identified adherence accurately but significantly under-estimated non-adherence (Figure). Factors predictive of adherence included provider perceptions of adherence and female sex.

Conclusions: Non-adherence is common in patients with advanced CKD, especially to diuretics and beta-blockers. Further studies are needed to understand how to best assess adherence in clinical practice and research studies and identify reasons for selective adherence to different classes of BP agents.

Funding: Other NIH Support - NHLBI, Commercial Support - Aegis Sciences Corporation



Predictors of adherence	OR (95% CI)
Sex	
Female (vs males)	7.6 (1.2-48.2)*
Race	
Non-Hispanic White	Reference
Non-Hispanic Black	0.3 (0.0-6.3)
Hispanic	0.6 (0.1-5.7)
Asian/Pacific Islander	1.2 (0.2-6.1)
Other	2.0 (0.1-46.9)
CKD stage	
5 (vs 4)	4.1 (0.4-37.8)
Number of patient-reported medications	
1	Reference
2	0.96 (0.1-12.4)
3	0.2 (0.0-2.7)
≥4	0.3 (0.0-2.8)
Provider AA	8.6 (1.0-71.6)*
Study coordinator AA	3.9 (0.7-21.9)

AA=adherence assessment, *p<0.05

FR-PO1057

Management of Resistant Hypertension due to Renal Artery Stenosis

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Introduction: Medical management of secondary hypertension caused by renal artery stenosis (RAS) remains mainstream especially after the publication of Coral Study. Coral Study suggested no difference in blood pressure (Bp) control between medical management alone and medical management plus percutaneous intervention. Some patients' clinical picture does not fit in the inclusion criteria of Coral Study, the management should be individualized.

Case Description: A 68-year-old white male with uncontrolled HTN on 5 antihypertensives, HLD, T2DM, CKD Stage 3-4. His antihypertensive medications include: amlodipine 10mg daily, Chlorthalidone 25mg daily, hydralazine 50mg 3 times a day, terazosin 5mg daily at bedtime, and clonidine 0.3mg twice a day. Patient was briefly on lisinopril which was stopped after patient developed acute renal failure with hyperkalemia. His Bp had been 180-210's/80-90's for most time. Our work-up was significant for renin activity 27.36 ng/ml/h, serum aldosterone 5.9 ng/DL. Renal US showed right kidney 10.2cm, left kidney 7.4cm. Angiography showed severe narrowing at the right renal artery orifice which has early bifurcation, involving the upper and lower branches. Left renal arteriogram: A small accessory lower pole left renal artery is visualized with complete occlusion of the main left renal artery. Renal vein sampling was done 3 days later. Renin activity of left renal vein was 30.62, whereas that of the right renal vein was 117.05, that of inferior vena cava was 41.85. Thus the decision was to re-vasculize the right renal artery in 1 week to avoid repeated iv contrast exposure in very short time. Placement of 6 mm x 18 mm balloon expandable stent in the dominant branch of the right renal artery was done. Patient's systolic Bp was 140-160's mmHg one month later on only lisinopril 2.5mg daily. His Bp were ~ 130/70 mmHg one year later on lisinopril 10mg daily.

Discussion: The management of resistent hypertension due to renal artery stenosis needs to be individualized.

FR-PO1058

Chronotherapy of Renin-Angiotensin System (RAS) Inhibitor Ameliorates Renal Damage via Suppression of Intrarenal RAS Activity

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Background: We have shown that intrarenal RAS with chronic kidney disease (CKD) patients is activated and that intrarenal RAS activity contributes to blood pressure (BP) elevation, abnormal circadian rhythm of BP and renal damage. Moreover, changing the administration time of RAS inhibitors from morning to evening, namely chronotherapy, decreases BP and ameliorates renal damage during nighttime. However, it has not been clarified whether chronotherapy changes intrarenal RAS activity and the change of intrarenal RAS activity by chronotherapy reflects the change of BP and renal damage.

Methods: We recruited 34 CKD patients who took RAS inhibitors in the morning (sex: 22 males / 12 females, age: 60.2±19.4 years, estimated glomerular filtration rate (eGFR): 34.8±30.8 ml/min/1.73 m^2). We collected urine during daytime and nighttime, respectively, and evaluated urinary albumin (U–Alb) and urinary angiotensinogen (U–AGT), a surrogate marker for intrarenal RAS activity. Ambulatory BP monitoring was conducted at 30–min intervals during the daytime and nighttime. Thereafter, the same experiments were made after 4.1±0.5 days from change of the administration time. The ratios of clinical parameters morning dosing against evening dosing were defined as M/E ratio.

Results: The excretion levels of U–Alb and U–AGT during daytime and nighttime were significantly decreased by chronotherapy in all CKD patients. M/E ratio of U–Alb had significant and positive relationships with M/E ratio of U–AGT. Moreover, there were significant and positive relationships between M/E ratio of U–Alb and U–AGT during nighttime (β=0.73 and p=0.005), but not daytime (β=0.39 and p=0.098) in the CKD patients whose eGFR is less than 45 ml/min/1.73m^2. In addition, significant and positive relationships were found between M/E ratio of U–Alb and U–AGT during nighttime (β=1.04 and p <0.001), but not daytime (β=0.52 and p=0.074) in the CKD patients who have nondipper or riser patterns when the night–to–day ratio of systolic BP is 0.90–1.00 or >1.00, respectively.

Conclusions: The present study indicated that chronotherapy of RAS inhibitor improved renal damage via intrarenal RAS suppression in CKD patients. This effect was more remarkable in patients with highly impaired renal function and nocturnal hypertension.

FR-PO1059

RNF213 p.Arg4810Lys Variant Screening in Renovascular Hypertension in Korean Children

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Background: Moyamoya disease (MMD) -a steno-occlussive disease of the distal cerebral arteries- is often accompanied by renovascular hypertension (RVH), and a variant of *RNF213* p.Arg4810Lys is known as a susceptibility gene of MMD. There is a report for a *RNF213* variant-associated vasculopathy with peripheral pulmonary arterial stenosis and homozygous variant for *RNF213* p.Arg4810Lys without the presence of MMD. The purpose of this study was to evaluate clinical manifestations and gene test for the *RNF213* variant in Korean pediatric patients with initially presenting with isolated RVH.

Methods: A retrospective analysis of medical records in pediatric patients with isolated RVH from January 2001 to October 2017 were performed. The presence of renovascular hypertension was confirmed by computer tomography (CT) angiography or renal doppler ultrasonography. The genetic test for *RNF213* variant was performed in the pediatric patients with RVH.

Results: The gene test for *RNF213* was performed in 11 patients with isolated RVH. The molecular testing revealed homozygosity of *RNF213* p.Arg4810Lys in 5 patients, and heterozygosity in 2 patients. Among 7 patients with *RNF213* variant, on CT angiography, it revealed bilateral renal artery stenosis of ostial lesions in 3 of the patients and unilateral stenosis of ostial to proximal lesions in 4 of the patients. Among 7 patients with *RNF213* variant, MMD developed in 4 patients during follow-up. In one patient with homozygosity of *RNF213* p.Arg4810Lys, he showed the isolated RVH, and his mother with heterozygosity of *RNF213* p.Arg4810Lys presented with MMD and no evidence of RVH.

Conclusions: Our study suggests that *RNF213* may be the causative gene in RVH in Korean children. The screening for MMD and other organ involvement might be helpful in children and family members with RVH and *RNF213* variant.

Case	sex	RNF213	Brain image	Time interval RVHT →MMD	Family History
1	F	Homo	MMD	2 months	Sibling: case 2, MMD (+), RVHT (+)
2	F	Homo	MMD	1 week	Sibling: case 1, MMD (+), RVHT (+)
3	M	Homo	normal	-	NA
4	M	Hetero	normal	-	Twin Brother (hetero), MMD (-), RVHT (-)
5	F	Hetero	MMD	6 years	Mother(hetero), MMD (+), RVHT (-)
6	M	Homo	normal	-	Father (hetero), MMD (-), RVHT (-) Mother (hetero), MMD (+), RVHT (-) Elder brother (Hetero), MMD (-), RVHT (-) Elder sister (Homo), MMD (-), RVHT (+)
7	M	Homo	MMD	10 years	Father (hetero), MMD (+), RVHT (-) Mother (hetero), MMD (-), RVHT (-) Younger sister (Hetero), MMD (-), RVHT (-)

FR-PO1060

Dual Renin-Angiotensin System Blockade: A Meta-Analysis of Cardiovascular and Renal Outcomes

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Background: Dual renin-angiotensin (RAS) blockade has shown to decrease blood pressure, proteinuria and hospitalization due to heart failure (HF). We intended to evaluate its efficacy and safety in HF, diabetes mellitus (DM), hypertension (HTN), and chronic kidney disease (CKD).

Methods: All randomized trials comparing dual RAS blockade with monotherapy in HF, CKD, DM, and HTN as of January 31, 2019, were identified after searching the PubMed, EMBASE, and CENTRAL databases. Those which compared the dual RAS blockade [Angiotensin converting enzyme inhibitor+ Angiotensin receptor blocker] (ACEI + ARB) or [Direct Renin inhibitor (DRI), aliskiren combined with ACEI or ARB] with monotherapy (ACEI or ARB) were selected. Major outcomes were all-cause and cardiovascular mortality, progression to end-stage renal disease (ESRD), and

hospitalization due to HF. Minor outcomes were proteinuria, BP change, renal failure, hyperkalemia, hypotension, and withdrawal due to adverse events.

Results: Eighty-one studies fulfilled the inclusion criteria, yielding 76,866 patients. When compared to monotherapy, the dual RAS blockade reduced blood pressure and proteinuria. In HF subgroup, dual RAS blockade reduced hospitalizations due to HF [relative risk (RR)=0.82, 95% CI0.71-0.94; P=0.004], [number needed to treat (NNT=15)], but had no effect on all-cause mortality (RR=0.98, 95% CI=0.88-1.09; P=0.72) and cardiovascular mortality (RR=0.92, 95% CI=0.79-1.06; P=0.25). Despite a decrease in blood pressure of 11.7 / 7.5 mm Hg in the HTN subgroup and a decrease in proteinuria, dual RAS blockade failed to slow progression to ESRD and was associated with increased rates of renal failure, hyperkalemia, hypotension, and withdrawal due to adverse effects. Neither in DM or CKD were there any outcome benefits.

Conclusions: When compared to monotherapy, dual RAS blockade failed to improve morbidity and mortality in HF, CKD, DM, and hypertension but reduced hospitalizations due to HF. Dual RAS blockade failed to slow progression to ESRD and led to higher withdrawal rates because of adverse effects.

Outcome	Dual RAS blockade Events	Dual RAS blockade Patients	Mono RAS blockade Events	Mono RAS blockade Patients	RR (95% CI)	RR (95% CI)
All-cause mortality	453	5203	434	5220	1.05 (0.92 - 1.19)	
Progression to ESRD	76	999	83	996	0.92 (0.70 - 1.22)	
HF hospitalizations	220	4505	238	4523	0.93 (0.77 - 1.11)	
Renal failure	357	5601	315	5616	1.07 (0.78 - 1.48)	
Hyperkalemia	1537	5485	1123	5447	1.45 (1.08 - 1.94)	
Withdrawal due to adverse events	651	4894	509	4887	1.28 (1.15 - 1.43)	

Summary forest plot of outcomes in CKD subgroup

FR-PO1061

Uremic Pericarditis in CKD: National Estimates of Hospitalizations, Procedures, and Outcomes (2006-2015)

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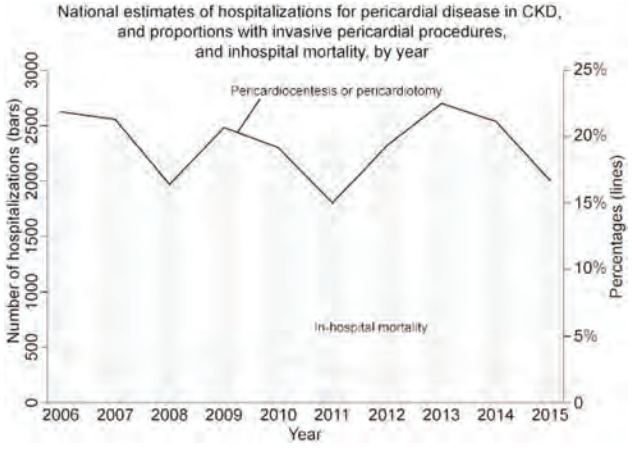
Background: Uremic pericarditis and pericardial effusions are well-known and potentially deadly complications of chronic kidney disease (CKD). These complications can often be managed with intensive hemodialysis, but sometimes invasive procedures are indicated, for cardiac tamponade, diagnosis, or definitive management. We investigated national trends in uremic pericardial disease hospitalizations, procedures, and mortality.

Methods: We used the National Inpatient Sample, a 20% sample of US hospital discharges, from 2006-2015. We applied appropriate survey methods to obtain national estimates. We identified any CKD using ICD discharge codes, and pericarditis or pericardial effusion using the first 10 discharge codes. We excluded patients with possible non-uremic causes of pericardial disease (e.g., malignancy, myocardial infarction, myocarditis, non-pericardial cardiac surgery). We identified pericardiocentesis and pericardial window procedures using procedure codes.

Results: There were an estimated 24,508 (95%CI 23,647-25,369) hospitalizations for pericarditis in CKD that met the inclusion criteria. Age was 61±18 years. 43% of patients were female. An estimated 9.1% underwent pericardiocentesis alone, 8.8% underwent pericardiotomy alone, and 1.5% underwent both procedures. In-hospital mortality was 2.8% (2.5%, 6.4%, 2.7% and 2.8%, respectively, among those who underwent neither procedure, pericardiocentesis alone, pericardiotomy alone, and both procedures; p>0.05). Median (IQR) length of stay was 5 (3-8) days.

Conclusions: Uremic pericarditis and pericardial effusions remain an important complications of CKD, with approximately 1 in 5 hospitalizations involving an invasive pericardial intervention. In-hospital mortality is relatively low, but we were not able to assess post-hospital outcomes. Further investigations can target improved causal understanding and management.

Funding: Veterans Affairs Support



FR-PO1062

Relationship Between 24-Hour Blood Pressure (BP) Load and Renal or Cardiac Outcomes in Children with CKD

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Background: Blood pressure (BP) load, the proportion of elevated BPs detected by 24h ambulatory blood pressure monitoring (ABPM), is not a uniform criteria for diagnosing hypertension in all BP guidelines. We aimed to determine whether systolic BP load on ABPM was associated with adverse renal or cardiac outcomes in children with chronic kidney disease (CKD).

Methods: We analyzed data from 533 children with CKD. We categorized the BP status of participants as normotensive (normal mean awake/sleep BP and normal BPL), isolated BPL elevation (normal mean awake/sleep BP, elevated BPL >25%), or hypertensive (elevated mean awake/sleep BP, regardless of BP load). We examined the association between BP status and left ventricular hypertrophy (LVH) in logistic models and ESRD in Cox models. We also examined the value of considering BPL (as a continuous variable) independently and in conjunction with mean BP in predicting outcomes. We tested for differences in risk discrimination in our models (using c-statistics).

Results: One-third of the cohort met criteria for ambulatory hypertension and an additional 25% of participants had isolated BPL elevation. In both unadjusted and adjusted analyses, isolated BPL elevation was not statistically significantly associated with LVH or ESRD compared to those with normotension, whereas hypertension was (figure). Although BPL was independently associated with risk of ESRD, when used in conjunction with mean BPs, BPL was no longer associated with outcomes [table]. BPL also provided poor risk discrimination for LVH and ESRD [table].

Conclusions: BPL may not provide additive prognostic information over and beyond mean BP, and isolated BPL elevations were not associated with risk of LVH or ESRD in children with CKD.

Funding: NIDDK Support

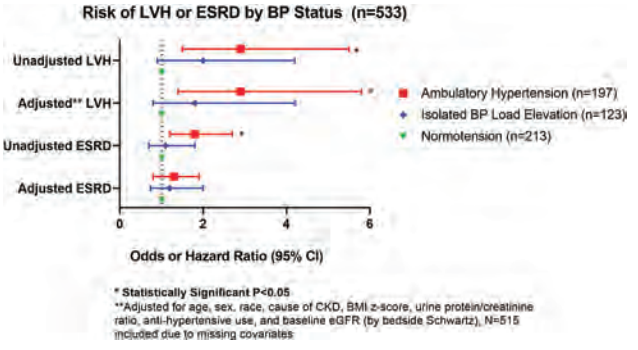

Table. N=533	LVH Unadjusted OR‡ (95% CI)	LVH C-statistic (95% CI)	ESRD Unadjusted HR‡ (95% CI)	ESRD C-statistic (95% CI)
Awake SBP load (every 10% increase)	1.2 (1.0-1.3)	0.61 (0.53-0.68)	1.2 (1.1-1.2)	0.60 (0.55-0.67)
Awake mean SBP* (per 0.1 increase)	1.7 (1.2-2.3)	0.62 (0.55-0.69)	1.6 (1.3-1.9)	0.60 (0.56-0.68
Awake SBP load + Awake mean SBP*	0.9 (0.7-1.2) 2.4 (1.0-5.6)	0.63 (0.55-0.69)	1.1 (1.0-1.3) 1.2 (0.7-1.9)	0.60 (0.56-0.68)

*Mean SBP is represented as an index (ratio of the patient's mean BP to the 95th percentile for age/height, such that a ratio of 1 represents a 95th percentile BP)
OR = odds ratio; HR = hazard ratio; LVH = left ventricular hypertrophy

FR-PO1063

Ambulatory Hypertension Disproportionately Affects African American Children with Non-Glomerular CKD Independent of Socioeconomic Factors

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Background: Although hypertension is common in children with chronic kidney disease (CKD), particularly among African Americans (AA), the extent to which that association is explained by socioeconomic factors (SES) is not well known. The objective of this study was to contrast racial differences in ambulatory hypertension among children with CKD before and after adjustment for putative confounding SES factors.

Methods: This cross-sectional analysis comprised 1021 repeated measures from 475 children enrolled in the CKiD study, stratified by glomerular and non-glomerular diagnosis. Children (1-16 years, eGFR 30-90 ml/min/1.73m^2 at study entry) with at least 1 ambulatory blood pressure monitor (ABPM) measurement were included. Logistic regression models were used to estimate odds ratios (OR) of ABPM hypertension (systolic

or diastolic wake/sleep blood pressure ≥95th or load>25th percentile) associated with AA race. Inverse probability weighting was used to account for potential confounding of SES (public insurance, food insecurity, household income, maternal education), abnormal birth history, demographics (age, sex), obesity (BMI>95th percentile) and disease severity (eGFR<45 mL/min|1.73m²) at study entry.

Results: Overall prevalence of ambulatory hypertension was 54%. AA children with both glomerular and non-glomerular CKD were disproportionately affected by SES variables by univariate analysis. In unadjusted models, AA children with non-glomerular disease had higher odds of ambulatory hypertension (OR=2.93; 95%CI:1.57, 5.47, p=0.001). Multivariable analysis adjusted for demographics, SES, birth history, obesity, and disease severity showed that among the non-glomerular group, AA children had 3.08-fold odds (95%CI:1.58, 6.00, p=0.001) of ambulatory hypertension. However, there was no difference in ambulatory hypertension between AA and Caucasian children with glomerular CKD, either unadjusted (OR=1.54; 95%CI:0.73, 3.26, p=0.262) or adjusted (OR=1.26; 95%CI:0.40, 4.00, p=0.694).

Conclusions: AA children with non-glomerular CKD are disproportionately affected by ambulatory hypertension, independent of SES. Glomerular injury is a driving force of hypertension, thus minimizing racial differences in ambulatory hypertension after adjustment for SES in children with glomerular CKD.

Funding: NIDDK Support, Other NIH Support - Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01-DK-66143, U01-DK-66174, U24-DK-082194, U24-DK-66116).

FR-PO1064

Discordances Between Pediatric and Adult Thresholds in the Diagnosis of Ambulatory Hypertension in Adolescents with CKD

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Background: The diagnostic threshold for hypertension (HTN) by 24-hour ambulatory blood pressure (ABP) monitoring in adults was changed in the updated American Heart Association (AHA) 2017 guidelines. Our objective was to compare the prevalence, sensitivity/specificity, and predictive value of a diagnosis of HTN by pediatric versus adult ambulatory thresholds in children with CKD.

Methods: We included 371 children with CKD ages 13 or older. We used normative pediatric cutoffs (sex/height-based), prior adult cutoffs (awake SBP>135 mmHg, sleep>120), and updated AHA 2017 cutoffs (awake>130mmHg, sleep>110) to define HTN and determine its prevalence. We then compared the sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of each threshold for development of left ventricular hypertrophy (LVH) and progression to end-stage renal disease (ESRD).

Results: 27% of the cohort met criteria for HTN using pediatric ABP normative thresholds, versus 44% by the updated AHA 2017 adult threshold and 16% by prior adult guidelines (Table). For LVH, the sensitivity of all thresholds was poor with the prior adult criteria being the least sensitive but most specific (Figure). For ESRD, the updated AHA 2017 adult threshold had the greatest sensitivity but lowest specificity (Figure). Overall, the PPV and NPV were similar across all thresholds for LVH and ESRD.

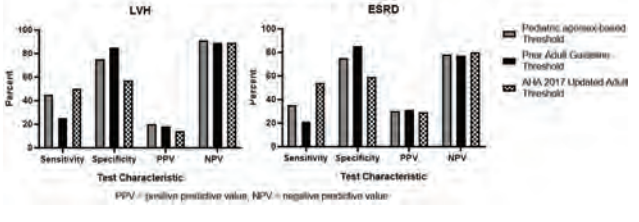
Conclusions: In adolescents with CKD, the updated AHA 2017 adult threshold leads to the highest prevalence of ambulatory HTN and has variable sensitivity and specificity for LVH versus ESRD. The pediatric thresholds had lower sensitivity but higher specificity vs. the AHA 2017 criteria. Further research is needed to optimally define ambulatory HTN as adolescents transition to adulthood.

Funding: NIDDK Support

Table: Prevalence of HTN by different SBP cutoffs from 24-hour ABP monitoring (n=371)

	Pediatric Age/Sex-based Threshold	Prior Adult Guideline Threshold	AHA 2017 Updated Adult Threshold
Ambulatory Hypertension by SBP N (%)	102 (27)	61 (17)	163 (44)
Awake Hypertension N (%)	72 (19)	37 (10)	81 (22)
Sleep Hypertension N (%)	77 (21)	48 (13)	152 (41)

Figure: Test Characteristics for LVH (n=44) and ESRD (n=89)



FR-PO1065

Hypertension and Obesity in High School Students: Genetic and Environmental Factors in the HYGEF Study

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Background: The clinical outcomes associated to hypertension and obesity in the young population are major risk factors for renal and cardiovascular events in the adult age. Objectives of the study are: to assess the associations among genetic and environmental factors and blood pressure (BP) in a high school population before developing hypertension and to study the transition from normotension to hypertension.

Methods: This observational cohort study obtained data from 3057 high school students in three different regions of Italy. Participants underwent anthropometric, BP measurement and saliva and urine sample collection. Selected genetic variants were determined.

Results: Our results confirmed the link between body weight, salt intake and BP in adolescents (p<0.005; R square 30%). Analysis of BP values (adjusted for BMI, waist circumference, age, sex, region) and genetic polymorphisms evidenced associations with Lanosterol Synthase (LSS), an enzyme involved in Endogenous Ouabain synthesis. The A allele of a missense variant in LSS gene was associated to higher diastolic and systolic BP levels (DBP: LSS AA+AC 69.7±0.32 mmHg, LSS CC 68.8±0.3, p=0.004; SBP: LSS AA+AC 120.3±0.5, CC 119.3±0.4, p=0.008). Furthermore, a Klotho (KL) missense genetic variant resulted strongly associated to 24h-urinary Na excretion (p=0.017, recessive model). The urinary proteomic study showed an augmented excretion of IL1 in both ADD1 T subjects and LSS C subjects, suggesting an increased inflammatory activity.

Conclusions: In this young Italian population we detected specific environmental factors (such as high salt intake) and gene polymorphisms linked to higher BP values. This help to create the basis for future interventions in educational, clinical and/or pharmacological studies

FR-PO1066

Persistence of Hypertension from 5-7 Years After Pediatric Cardiac Surgery

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Background: We have determined that children who require surgery for congenital heart disease (CHD) are at an increased risk for hypertension 5 years after cardiac surgery. The goal of this study is to assess the long-term risk of hypertension after cardiac surgery and if hypertension improves or is sustained.

Methods: We prospectively enrolled children from 1 month to 18 years old, undergoing cardiopulmonary bypass. Children who survived their surgical hospitalization had blood pressure measured at two in-person follow-up visits (median 5.4 years and 7.4 years after surgery). Elevated blood pressure and hypertension was defined using the American Academy of Pediatrics 2017 Hypertension guidelines. We compared the risk of hypertension status at the 5 and 7-year visits using the McNemar test.

Results: Of the 131 children with a follow-up visit 5 years after cardiac surgery, 88 (67%) children participated in the 7-year follow-up visit. Baseline characteristics were not significantly different between children that participated in both the 5 and 7-year visit vs those who only participated in the 5-year visit. The median age of the cohort at the 7-year follow-up was 10.6 [IQR: 7.6 – 15.2] years and 47% were female. 32 children had previously had a septal defect repair, 15 an inflow/outflow tract or valve procedure, 34 had a combined procedure, and 7 were not defined. Elevated BP was present in 16 (18%) and 13 (15%) children at the 5-year and 7-year visit, respectively. Hypertension was present in 13 (15%) and 15 (17%) children at the 5-year and 7-year visit, respectively, with no statistically significant change in risk at the two visits (p=0.56). Between the 5-year and 7-year visits, hypertension was sustained in 8 (62%) patients.

Conclusions: The long-term risk of elevated blood pressure and hypertension was common at both the 5 and 7-year visits and hypertension was sustained in the majority of children after cardiac surgery. The risk factors for sustained hypertension should be studied in children with congenital heart disease.

Funding: NIDDK Support

FR-PO1067

Hypertension as a Modifiable Risk Factor in Children with Immune Complex MPGN and C3 Glomerulopathy

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Background: Hypertension is a known complication of complement-mediated renal disease and carries prognostic significance. Hypertension is associated with reduced GFR in children with immune-complex membranoproliferative glomerulonephritis (IC-MPGN). Similarly, hypertension has been associated with poor renal function and

long-term outcome in patients with C3 glomerulopathy (C3G). This study explored the prevalence of hypertension in a IC-MPGN/C3G cohort.

Methods: Renal biopsy reports of 45 patients <18 years of age (originally diagnosed as MPGN between 2003 and 2012) across three centers were reviewed. Patients were re-classified as either IC-MPGN or C3G in 2019 based on consensus criteria. Demographic, clinical, and biochemical results were collected at enrollment and retrospectively at disease onset. Data were analyzed using Fisher's exact test. Hypertension was defined as blood pressure > 95th percentile for age, sex, and height.

Results: 19 of 45 (42%) of patients were diagnosed with hypertension at disease onset; only 2 of 19 (10%) resolved by the time of enrollment (mean 4 years later). 27 of 45 (60%) required antihypertensive medication at disease onset (mean 2.3 medications per patient); the same number (60%) required ongoing antihypertensive support at enrollment (mean 1.7 medications per patient). 9 of 27 (33%) required multiple antihypertensive medications. Baseline demographics, clinical and biochemical parameters, incidence of hypertension, and antihypertensive use were similar between C3G and IC-MPGN patients (P>0.05). Specifically, the use of angiotensin-converting enzyme inhibitors (86% vs. 76%, P=0.66) was the same in both groups, and though proteinuria improved significantly from disease onset to the time of study enrollment, hypertension continued to require treatment.

Conclusions: The incidence of hypertension in both pediatric C3G and IC-MPGN is similar to previously reported data. Interestingly, resolution of hypertension was low in this cohort (10%), and many patients (33%) required multiple antihypertensive medications. These data suggest that more aggressive hypertension management may be required and may potentially help to improve the long-term outcomes of children with C3G and IC-MPGN. The prognostic relevance of persistent hypertension in these diseases should be further studied.

FR-PO1068

Recategorization of Adolescent Hypertension (HTN) by Ambulatory Blood Pressure (ABPM) Using Adult Norms Compared with Pediatric Norms

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Background: 2017 guidelines for pediatric blood pressure (BP) applied adult BP norms to define clinic HTN in patients (pts) ≥ 13 yrs. The 2014 pediatric ABPM guidelines recommend age and sex specific percentile norms for pts < 18 yrs. Data applying adult ABPM norms to define ABPM HTN in adolescents is scarce. We aimed to evaluate the re-categorization of HTN by ABPM alone when applying adult ABPM norms in pts ≥ 13 yrs. We then assessed the association of left ventricular hypertrophy (LVH) with HTN.

Methods: Retrospectively, pts 13-17 yrs who wore an ABPM between 9/2018 and 5/2019 were reviewed to collect gender, age, BP med status, ABPM systolic and diastolic BP mean and load for 24hr, day, and night, and left ventricular mass index (LVMI). The ABPM adult norms applied were based on American Heart Association (AHA) 2005 (AHA2005), AHA 2017 (AHA2017), and European Society of Hypertension 2018 (ESH) guidelines and were compared to 2014 AHA pediatric norms (pABPM). HTN was defined according to the respective guidelines using only ABPM. LVH was defined as LVMI > 51 g/m$^{2.7}$.

Results: 357 pts (243 male) had ABPM data. 172 had LVMI data; 33 pts on BP meds with controlled HTN were excluded (final n=139). LVMI correlated significantly with systolic BP (24h, day, night mean and load) but not diastolic BP. All adult norms resulted in significant differences in the re-categorization of HTN (Table). The odds of a pt with HTN having LVH was significant only when defined by AHA2005 and ESH norms [OR 3.86 (1.55, 9.61), p=0.004 and OR 2.63 (1.05, 6.57), p=0.04 respectively].

Conclusions: There is significant difference in the categorization of HTN depending on the norms applied. HTN is significantly associated with LVH when AHA2005 and ESH norms are applied. Application of adult norms to define ABPM HTN in adolescents should take into account these differences with thoughtful evaluation of outcomes.

Categorization of HTN by adult norms (%)

		AHA2005		AHA2017		ESH	
		no HTN	HTN	no HTN	HTN	no HTN	HTN
pABPM	no HTN	44	2	31	15	43	3
	HTN	35	19	7	47	20	35
p by X^2		<0.001		<0.001		<0.001	

FR-PO1069

Relationship of Blood Pressure to Sleep in High School Students

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Background: Childhood hypertension is a risk factor for adult hypertension and target organ damage. Emerging data suggests a role of inadequate sleep in hypertension. In our previous study, newly diagnosed primary hypertensive children had less weekend catch up sleep than age and sex matched normotensives. The usual sleep pattern of adolescents shows less sleep on school days with catch up sleep on the weekends, but it is not known if blood pressure (BP) tracks the changes in sleep over the course of the week. The aim of this study is to compare the BP of high school students at the beginning of the week with that at the end of the week. We also studied the relationship of self-reported weekday and weekend sleep duration to the BP.

Methods: Students from a public high school (11 and 12th grade) were asked to participate. Interested students completed a questionnaire. BP, height and weight were measured on Monday and Thursday morning of the same week. Average of 3 consecutive BP was taken using automated Omron BP 786 monitor. Weekday and weekend total sleep time (WDTST and WETST) was estimated from the questionnaire responses for usual getting in and getting out of bed time. T-test and multivariate linear regression were used for analysis.

Results: Of the 32 students recruited, 24 were female. Systolic BP on Monday and Thursday was 114.8 ± 16.5 and 110.9 ± 13.1 mm Hg respectively. Diastolic BP on Monday and Thursday was 72.7 ± 7.4 and 70.9 ± 13.7 mm Hg respectively. BMI was 25.7 ± 5.5 Kg/M^2. WDTST was 418.6 ± 80.1 and WETST was 566.9 ± 132.3 minutes. Paired T-test showed no significant difference between SBP and DBP for Monday and Thursday. However, multiple regression analysis showed significant inverse relationship of SBP-Monday (adjusting for BMI) with WDTST (p= 0.016) and WETST (p=0.017). Similar results were seen for DBP-Monday (adjusting for BMI) with WDTST (p= 0.049) and WETST (p=0.038).

Conclusions: Our results show that shorter sleep time is associated with higher BP in high school students. Previous studies in children and adults have also shown higher BP in subjects with short sleep durations. Beneficial effect of sleep extension has also been observed in prior studies. In our subjects, weekend sleep duration was about 2.5 hours longer, but BP-Monday was not different from that on Thursday. Lack of information on Sunday night sleep time and a small sample size are main limitations.

FR-PO1070

Clinical Features of Pediatric Patients with Severe Hypertension (HTN) Requiring Infusions in the Pediatric Intensive Care Unit (PICU)

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Background: Data regarding PICU management of severe HTN, defined as receiving continuous antihypertensive infusions (antiHTN), are scarce. We aimed to describe the clinical characteristics of this population.

Methods: A medication order report from January 2017-July 2018 identified pts 2-22 years receiving antiHTN infusions in the PICU. Vasopressors 6 hrs prior to antiHTN, cardiac surgery, neurosurgery, or ECMO were reasons for exclusion. For comparison among age groups, we defined systolic and diastolic blood pressure index (sBPI,dBPI) as the ratio of absolute BP to the threshold for stage 2 HTN [95th percentile +12 mmHg for age, sex, and height (< 13 yrs) or 140/90 mmHg (≥ 13 yrs)] based on 2017 guidelines. Acute kidney injury (AKI) was defined by KDIGO guidelines. Left ventricular hypertrophy (LVH) was defined as left ventricular mass index (LVMI) > 51 g/m$^{2.7}$.

Results: All 78 pts (11.7 +/- 5.3 yrs, 56% male) had sBPI ≥ 1 and 85% had dBPI ≥ 1 at antiHTN initiation. Nicardipine was the most common antiHTN (90%). The most common symptoms (64.1%) were neurologic (headache, altered mental status, seizure); 22% were asymptomatic. Neuroimaging was performed in 49 pts of which 68% (33/49) were abnormal. 45% (35/78) had AKI. Only 21 pts had eye exams; 19% (4/21) had retinopathy. 68% (53/78) had echocardiograms of which 53% (28/53) had LVH. There was no association between LVH and sBPI (95% CI 0.7 to 565.3, p=0.08) or dBPI (95% CI 0.2 to 100.9, p=0.3). Pts with chronic HTN had a higher odds of having LVH (OR 3.98, 95% CI 1.1-15.0, p 0.04).

Conclusions: A significant number of children who present with severe HTN have evidence of end organ damage on assessment. Neurologic findings are most common and frequently accompanied by abnormal neuroimaging. LVH is common and more likely present in patients with chronic HTN.

Baseline Characteristics, reported as mean +/- SD or median (IQR)

BMI centile (%)	87.5 (40.6-98.4)
ICU LOS (days)	10.5 (5-27)
Length of antiHTN (hr)	57.7 (32.6-105.9)
eGFR at antiHTN start (ml/min/1.73m2)	84.5 (31.7-98.4)
LVMI2.7 (g/m)	52.1 +17.5
LV Mass (g/m2)	81.7 +31.3
sBPI	1.32 +0.17
dBPI	1.16 +0.19

FR-PO1071

Family History as a Risk Factor for Blood Pressure Control in Pediatric Hypertension

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Background: Hypertension (HTN) in adults is aa leading cause of death worldwide. Pediatirc HTN often persists into adulthood. We investigated whether a family history of HTN influences blood pressure (BP) control in hypertensive children.

Methods: A retrospective chart review was done on patients aged 0-18 at a HTN clinic between 2002-2014. HTN was defined as a systolic or diastolic BP greater than the 95th % for age and gender. Patients with chronic kidney disease and those without HTN were excluded. We included children with both primary and secondary HTN. Linear mixed effects regression models were used to compare BP z scores over time. Cox proportional hazards regression was used to assess time to achieve BP control, defined as a systolic and diastolic BP less than the 90th %. Models were adjusted for age, gender and presence of antihypertensive medications.

Results: 410 patients were included in the analysis. Mean age at diagnosis was 9.17 years and 268 (65%) were male. 233 (57%) had a positive family history of HTN. There was no significant difference in systolic BP Z scores over time between the two groups

(*p>0.5*). Diastolic Z scores were significantly lower in those with family history compared to those without (*p<0.01*) [Figure]. There was no significant difference in achieving BP control between both groups (*p>0.5*).

Conclusions: There was a known family history of HTN in over 50% of children with HTN. Family history did not significantly affect longitudinal BP control nor the time it took to achieve good BP control. Future research should be directed at evaluating short and long-term outcomes in these children.

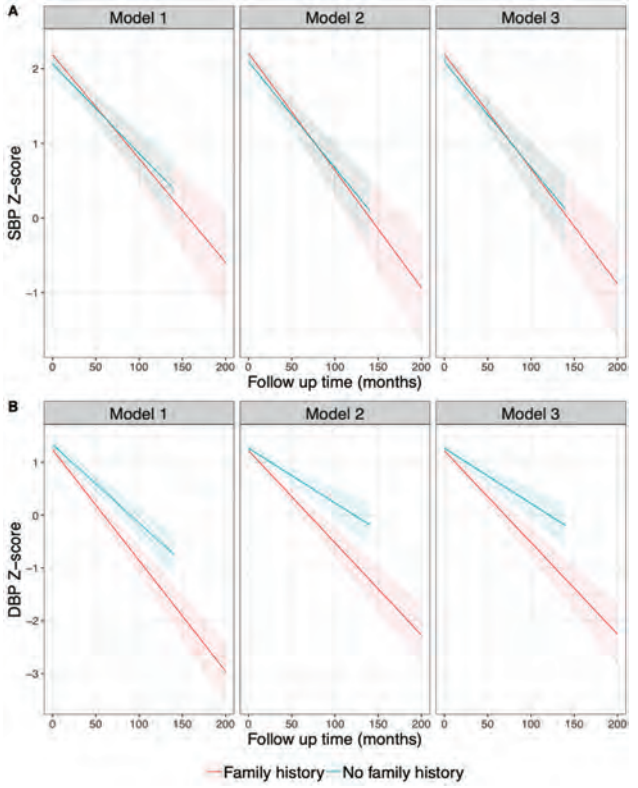

Figure 1 SBP and DBP z-scores over time. Model 1 unadjusted; Model 2 adjusted for age and gender; Model 3 adjusted for age, gender, number of antihypertensives

FR-PO1072

Abnormal Blood Pressure Patterns on Ambulatory Blood Pressure Monitoring Prior to Pediatric Hematopoietic Cell Transplantation (HCT): False Alarm or Cause for Concern?

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Background: Hypertension (HTN) influences morbidity and predicts renal and cardiovascular (CV) outcomes following HCT. Systematic misclassification of HTN may occur with the use of casual blood pressure (BP) measurements; therefore, ambulatory blood pressure monitoring (ABPM) is recommended in children and adolescents with high-risk conditions. Diagnosis of HTN by ABPM strongly correlates with risk of target organ damage. We conducted a pilot prospective observational study using ABPM to determine BP risk profile of patients (pts) undergoing first allogeneic HCT.

Methods: Pts age 5-21 yrs at Texas Children's Hospital were recruited prior to HCT from November 2018 to May 2019. Of 22 pts recruited, 16 had APBMs placed and 14 were adequate for analysis.

Results: Mean age was 14.3 yrs (6.7-19), 7 pts were male. Mean baseline GFR was 113 ml/min/1.73m2, (SD 19.1) mean baseline LVMI [2.7] was 42.4 g/m (SD 7.8) and spot urine protein/creatinine ratio (UPC) was 0.3 (SD 0.28). Two pts had severe ambulatory HTN based on elevated daytime, nighttime, and 24hr mean recordings and elevated BP load in all categories. Of the 12 remaining pts, 25% had elevated nighttime load, and 33% had attenuated nocturnal dipping despite normal office BP and normal average BP. There was no association with baseline LVMI[2.7] or UPC for pts with HTN by casual BP or ABPM, elevated daytime/nocturnal load, or attenuated dipping when univariate analysis was performed.

Conclusions: Elevated BP load and abnormal nocturnal dipping were seen in our pts prior to HCT despite normal mean ABPM and office BP. According to the 2017 guidelines for pediatric HTN, this group is termed 'unclassified', but may have increased risk for end organ effects and may require closer supervision. Screening with APBM can be beneficial in this high risk population.

ABPM Results

Prior HTN	Yes 2 (14.3) No 12 (85.7)
Office BP	N 10 (71.4) Ab 4 (28.6)
24 hr mean 24 hr load	N 13 (92.8) Ab 1(7.1) N 12 (85.7) Ab 2 (14.3)
Daytime mean Daytime load	N 12 (85.7) Ab 2 (14.3) N 12 (85.7) Ab 2 (14.3)
Nighttime mean Nighttime load	N 12 (85.7) Ab 2 (14.3) N 9 (64.3) Ab 5 (35.7)
Nocturnal Dipping	N 8 (57.1) Attenuated 6 (42.9)

N=normal, Ab= Abnormal;

Values reported as n value (%)

FR-PO1073

Adverse Childhood Experiences in Adolescents with Hypertension in an Inner-City Population in the Bronx, New York

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Background: Adverse Childhood Experiences (ACEs) are associated with hypertension (HTN) and increased risk of cardiovascular (CV) disease in adults, however less is known of risk factors in adolescence. The prevalence of HTN in adolescents is 3.5% and leads to increased CV risk in adulthood. We hypothesized: ACEs in adolescents are associated with increased CV risk factors, particularly HTN and end organ damage.

Methods: ACE survey was administered in both general pediatric and subspecialty clinics including 10 questions [max score 10 ACEs]. A retrospective study was used to assess whether ACE scores are associated with uncontrolled HTN and left ventricular hypertrophy (LVH) in adolescents. Using Clinical Looking Glass (a software to extract information from the electronic health record), data on ACE screenings at Montefiore Medical Center, latest blood pressures (BP) and echocardiograms were obtained. Adolescents ages >/=13 or <25 years old with a ICD10 diagnosis of HTN and a recorded ACE score were included. BP control was assessed with BP cutoff of 130/80mmHg and end organ damage was based on presence of LVH on echocardiograms.

Results: In 302 hypertensive patients, 38.7% were female and 61.3% male. 40.4% were African American, 10.9% Caucasian, 1.7% Asian, and 36.4% other/unknown race; 39.7% were Spanish/Hispanic/Latino. The median ACE score was 0 [IQR 0-1] adverse experiences. At least one ACE was reported in 44.4% of children and 20.8% had 2 or more ACEs. There was no difference in the age of completion of the ACE screen (16.6 ± 2.5 years with-ACE & 15.95 ± 2.3 years without-ACE), or in the average BP (128/76mmHg ± 13.6/8.8 with-ACE & 126/76mmHg ± 12.4/8.1 without-ACE). Using a cutoff of 130/80mmHg there was a trend toward worse BP control with ACE exposure: Uncontrolled BP was noted in 53% with an ACE vs. 43% without an ACE (p=0.09). Echocardiograms were present in 35.8% of patients and there was no difference in LVH (4.3% with-ACE and 4.8% without-ACE).

Conclusions: 20.8% of adolescents with HTN in the Bronx report an ACE score of 2 or more, comparable to national data. Our findings suggest that BP control may be worse with ACEs present, however the data was limited by a small sample size. Additional study is needed to assess the impact of ACEs and resilience factors on BP control and end-organ damage in adolescents with HTN.

FR-PO1074

Immune Cell Profiles in Children with Essential Hypertension (EH)

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Background: There is growing evidence that sodium is stored in a non-osmotic form in the interstitial compartment of skin and muscle. In these sites, sodium may contribute to the development of EH by altering the immune system. These effects may be reflected in peripheral blood (PB). We tested PB of children with EH to examine the diversity of immunophenotypes, and to test whether disease treatment changed circulating cells. We deployed high parameter flow cytometry, which allowed detailed characterization of T-cell subsets.

Methods: Eight pediatric patients with EH were enrolled. PB was collected at baseline for all patients, and after 4 and 16 weeks of anti-hypertensive treatment for 3 patients. We designed a 24-parameter flow cytometry panel to enumerate various T-cell subsets, including naïve, memory, dividing, exhausted, regulatory, and suppressive cells. We analyzed data using t-sne, a dimension reduction algorithm that provides a broad overview of the landscape of T-cell immunophenotypes, and applied bivariate difference gating to identify the cell populations uniquely altered with treatment.

Results: At baseline, 7 of 8 patients showed the expected diversity in T-cells subsets. There were dominant populations that differed by patient, suggesting heterogeneity that might be linked to clinical outcome. The 8th patient had a striking polarization in T-cell phenotype at baseline, with two major subpopulations and very few other cells. Her "skewed" T-cell landscape resolved with treatment, and we could precisely identify the cells lost. Cells were uniformly CD4+CD45RA+CD127+CD25-CD38+CCR4-Ki67-LAG3+CTLA4-CD39-IDO-HELIOS-FoxP3-CXCR3-GITR+. This phenotype represents

a class of naïve, non-classical regulatory (i.e., suppressive) T-cells. Subsets also expressed other suppressive markers like LAP, GARP, and CD73. Interestingly, the other two patients also showed loss of cells expressing LAG3, CD73, LAP, and/or GARP with treatment.

Conclusions: Children with EH have heterogeneous regulatory T-cell subsets. Successful control of blood pressure with anti-hypertensive drugs re-shapes the T-cell landscape in PB, reducing the number of suppressive T-cells. Our approach – to precisely identify specific cell types altered with disease – is well-suited to identifying biomarkers, and can provide detailed mechanistic information that informs treatment approaches.

Funding: NIDDK Support

FR-PO1075

An Evaluation of Renin-Angiotensin System Markers in Youth with Type 2 Diabetes and Associations with Renal Outcomes

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Background: Activation of the renin-angiotensin system (RAS) is associated with diabetic kidney disease in adults, and may also have prognostic significance in youth. We evaluated serum and urine RAS markers in youth with T2D and associations with albuminuria status, glycemic control, eGFR and blood pressure.

Methods: This is a cross sectional analysis of 183 youth with T2D and 100 controls from the iCARE cohort. Youth further stratified by albuminuria status (ACR < or ≥2mg/mmol (Alb)) and ACEi/ARB excluded. RAS levels measured with ELISA and enzyme activities measured by synthetic substrates. Differences in levels between groups were evaluated. For T2D group, levels log transformed and Tobit regressions evaluated for associations with ACR, HbA1c, eGFR and 24 BP loads (correcting for age, sex, BMIz-score and duration of diabetes).

Results: Mean age 14.7 yrs, duration of diabetes 1.7 years and 21.3% with Alb. Serum PRA (p=0.0006), aldosterone (p=0.004) and sACE activity (p=0.005) were higher in T2D than controls (C). uACE (0.1 (C), 1.2 (T2D) and 2.0 (Alb) ng/mgCr; p<0.001) and uACE2 activity (6.0 (C), 160.8 (T2D), 505.2 (Alb) ng/mgCr; p<0.001) also increased. In mulitvariable regressions, higher aldosterone (p=0.02), urinary AGT (p<0.0001), and ACE2 activity (p=0.009) associated with albuminuria. Higher AGT and urinary ACE2 protein and activity associated with higher HbA1c. No associations seen between RAS marker and eGFR or BP loads.

Conclusions: RAS activation is present in youth with T2D. The prognostic and therapeutic significance of the combined effect of glycemia and RAS activation on renal outcomes requires additional investigation.

Funding: Government Support - Non-U.S.

FR-PO1076

Improving Recognition and Reporting of AKI in the Neonatal Intensive Care Unit

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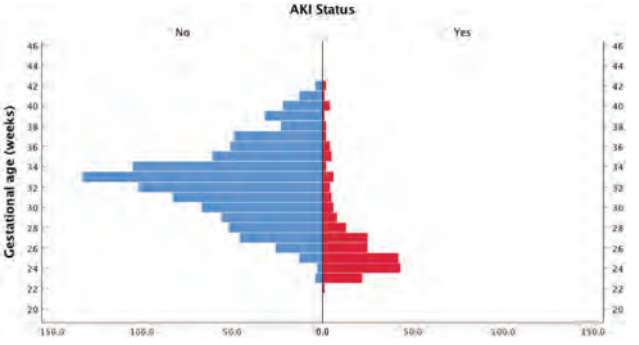
Background: Neonatal AKI leads to increased short and long-term morbidity and mortality. Recognition of AKI is essential as monitoring can lead to earlier detection of kidney dysfunction, particularly in neonates who are at high risk of CKD. This study determined prevalence of AKI among infants admitted to a NICU, and evaluated the frequency of AKI recognition/reporting over time.

Methods: Records of all infants admitted to a level 3 neonatal intensive care unit from 2012 to 2017 were reviewed. During this time period, several interventions were instituted including AKI education, a dedicated AKI followup clinic, and NICU nephrology rounds. AKI was classified using the Kidney Disease: Improving Global Outcomes definition modified to include only serum creatinine. Continuous variables were compared using t-test, and categorical variables with chi-square or Fisher exact test.

Results: AKI occurred in 19.1% of 1168 infants. AKI varied by gestational age, occurring in 171 (54.3%) of 315 of patients born at 22 weeks to <29 weeks, 36 (5.6%) of 643 patients born from 29 weeks to <36 weeks, and 16 (7.6%) of 210 patients born at 36 weeks or older (Figure 1). Infants with AKI were more likely to die than those without AKI (p<0.001). While AKI was recorded in the discharge summary for only 17.0% of AKI survivors, recognition improved during this study (p=0.03). No infants were referred to a nephrologist for AKI follow-up.

Conclusions: AKI occurred in 1 in 5 NICU patients and in over half of the most premature infants. While AKI was rarely noted in the discharge summary, recognition improved during this study. This may be in part due to dedicated AKI follow-up clinics, AKI specific education, and multidisciplinary rounding which began during this study. Nephrology AKI followup did not occur, highlighting areas for ongoing improvement.

Funding: NIDDK Support



AKI occurance by gestational age among infants; 77% of infants who experenced AKI were born at <29 weeks gestationa age; whereas 85% of infants who did not experience AKI were born at ≥29 weeks

FR-PO1077

Association of Pediatric Cardiac Surgery-Associated AKI with 1- and 5-Year Healthcare Utilization and Kidney Outcomes

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Background: AKI in children undergoing cardiac surgery (CS) is strongly associated with hospital morbidity. Post-discharge CS AKI outcomes are less clear. Hypotheses: Pediatric CS AKI is associated with a) increased hospitalizations, emergency room (ER) visits and physician visits within 1 and 5 yrs post-discharge and b) increased risk for chronic kidney disease (CKD), hypertension (HTN) or death within 5 yrs post-discharge.

Methods: Retrospective 2-centre cohort study (children surviving to hospital discharge after CS, 2003-2005). Exposure: post-CS AKI (KDIGO serum creatinine and urine output definition). Outcomes: Number of hospitalizations, ER visits, and physician visits within 1 and 5 yrs of CS discharge; composite of CKD, HTN or death within 5 yrs of discharge. Multivariable Poisson regression: evaluate association of AKI with health care utilization; multivariable Cox-proportional hazards analysis: evaluate association of AKI with composite patient outcomes. Models adjusted for age and RACHS-1 score (surgical severity) ≥3.

Results: N=350 (age 3.1 ± 4.5 years; 180 [49%] AKI; 60 [17%] ≥Stage 2 AKI). See Table for detailed results: In adjusted analyses, AKI was associated with increased risk for 1-yr physician visits and 5-yr hospitalizations, ER visits and physician visits. 12.03% and 11.54% of AKI *vs.* non-AKI developed the composite patient outcome within 5 yrs of discharge. In adjusted analyses, AKI was not associated with CKD, HTN or death by 5 yrs post-discharge (Table).

Conclusions: Post-CS AKI is associated with higher 5-yr healthcare utilization, but not the composite outcome of CKD, HTN or death. Studies should aim to better understand post-CS surgery healthcare utilization patterns and non-AKI risk factors for CKD and HTN, to develop cost-effective strategies to reduce long-term CKD and HTN after CS.

Funding: Government Support - Non-U.S.

Table. Association of post-cardiac surgery AKI with risk for A) hospitalizations, emergency room (ER) visits and physician visits and B) chronic kidney disease (CKD), hypertension (HTN) or death within 1 and 5 years after hospital discharge.

Outcome	1-yr post-discharge	5-yrs post-discharge
A) Healthcare utilization outcomes		
Stage 1 or worse AKI (*vs.* no AKI) association with outcomes Poisson regression-derived adjusted Relative Risk (aRR, 95% CI), adjusted for age and RACHS-1≥3		
Hospitalizations	1.16 [95% CI 0.93 - 1.44]	**1.17 [95% CI 1.01 - 1.35]**
ER visits	0.98 [95% CI 0.82 - 1.16]	**1.14 [95% CI 1.03 - 1.26]**
Physician visits	**1.13 [95% CI 1.06 - 1.20]**	**1.09 [95% CI 1.05 - 1.13]**
Stage 2 or worse AKI (*vs.* no AKI or Stage 1) association with outcomes Poisson regression-derived adjusted Relative Risk (aRR, 95% CI), adjusted for age and RACHS-1≥3		
Hospitalizations	1.04 [95% CI 0.80 - 1.35]	**1.12 [95%CI 0.95 - 1.33]**
ER visits	1.06 [95% CI 0.85 - 1.32]	**1.13 [95% CI 1.01 - 1.27]**
Physician visits	**1.19 [95% CI 1.11 - 1.29]**	**1.08 [95% CI 1.03 - 1.13]**
B) Patient outcomes		
Stage 1 or worse AKI (*vs.* no AKI) association with outcomes Cox regression-derived adjusted Hazard Ratio (aHR, 95% CI), adjusted for age and RACHS-1≥3		
CKD, HTN or death	*n/a* (low sample size)	0.82 (95% CI 0.42 - 1.58)
Stage 2 or worse AKI (*vs.* no AKI) association with outcomes Cox regression-derived adjusted Hazard Ratio (aHR, 95% CI), adjusted for age and RACHS-1≥3		
CKD, HTN or death	*n/a* (low sample size)	0.95 (95% CI 0.41 - 2.21)

BOLD = statistically significant association (p<0.05)

FR-PO1078

Point-of-Care Urinary Neutrophil Gelatinase-Associated Lipocalin Readings Are Highly Predictive of Formal Laboratory Levels

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Background: Since the discovery and validation of urinary neutrophil gelatinase-associated lipocalin (NGAL) as an early, non-invasive marker of kidney injury, clinicians are able to more rapidly, and reliably, predict the development of acute kidney injury (AKI.) Urinary NGAL has been validated on various clinical lab platforms, but has yet to be assessed using point of care (POC) techniques. A reliable POC urinary NGAL test would offer a rapid and inexpensive screening test for AKI that could be clinically valuable in both inpatient and outpatient settings.

Methods: Hospitalized patients from 2 different pediatric hospitals who were exposed to 3 or more nephrotoxic medications simultaneously or 3 or more consecutive days of either IV vancomycin or an IV aminoglycoside had a daily urine collection for 7 consecutive days. Discrete laboratory urinary NGAL results were obtained using The NGAL Test™ (Bioporto, Denmark) and stratified corresponding to a colorimetric NGAL test (Bioporto) with ranges of: 25ng/mL, 50ng/mL, 100ng/mL, 150ng/mL, 300ng/mL and 600ng/mL. Different urinary NGAL cutoffs were then used to determine sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), with the laboratory NGAL Test™ serving as the reference standard.

Results: In total, 86 individual patients (55% male, median age 13.2 years, range 4 months to 34 years) had 521 paired laboratory and POC urinary NGAL assessment. Of the 521 urine samples, 94 were analyzed using fresh urine and 427 using frozen urine samples. The POC performance data are depicted in the table.

Conclusions: A POC urinary NGAL assessment of <300ng/mL was highly predictive of an NGAL Test™ value <300ng/mL. We suggest this colorimetric POC assay is useful as a surrogate to the laboratory NGAL Test™ and to rule out risk for AKI. Patients with a POC test >300 ng/ml should have a confirmatory NGAL Test™ assessed.

Results

NGAL Test™ threshold	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
<50ng/mL	93.90% (89.01-97.04%)	66.11% (60.94-71.01%)	56.00% (52.28-59.66%)	95.93% (92.8-97.74%)
<150ng/mL	97.14% (85.08-99.93%)	81.48% (77.74-84.84%)	27.42% (23.71-31.46%)	99.75% (98.29-99.96%)
<300ng/mL	100.00% (85.75-100%)	89.34% (86.28-91.91%)	31.17% (25.99-36.87%)	100.00%

Sensitivity, specificity, PPV, NPV (95% confidence intervals)

FR-PO1079

Cell Cycle Arrest Biomarkers and Kidney Injury Molecule 1 (KIM-1) in Pediatric Aminoglycoside-Induced AKI

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Background: AKI is common in children treated with aminoglycosides (AG). We evaluated urine KIM1 and cell cycle arrest biomarkers (tissue inhibitor of metalloproteinase 2 [TIMP2]; insulin-like growth factor-binding protein 7 [IGFBP7]) for AG-AKI diagnosis.

Methods: Nested-case control study from a prospective 2-center (Montreal, Cincinnati) cohort (non-critically ill children starting AG's; 3 months-18 years old; no known kidney condition; AG treatment ≥3 days; recruited within 48 hours of AG start; ≥1 SCr's/5 AG days). Urine was collected daily, measured for KIM1 (pg/ml), TIMP2 (ng/ml) and IGFBP7 (ng/ml) (expressed as TIMP2*IGFBP7). AKI: KDIGO SCr definition. Non-AKI *vs.* AKI biomarkers were compared on a) AG treatment day 2 and 3, and b) 3, 2 and 1 day before and the day of AKI onset (Mann-Whitney). Area under the receiver operating characteristic curve (AUC, 95% CI) to detect AKI was calculated.

Results: 104 AG episodes (48% male, age 8.0 ± 4.9 years; AG treatment days 8.1 ± 7.7); 41% developed AKI. *Results in Table*: KIM1 ~3-fold higher in AKI *vs.* non-AKI, on day of AKI onset (AUC 0.87 [0.72-1.00]); no statistically significant AKI association on other days. TIMP2*IGFBP7 ~6-fold higher in AKI *vs.* non-AKI on AG treatment day 2 (AUC 0.72 [0.57-0.87]); on day of AKI onset (AUC 0.75 [0.54-0.97]) to detect AKI. *Results not in Table*: KIM1 combined with TIMP2*IGFBP7 on the day of AKI onset detected AKI with AUC 0.90 (0.78 – 1.00, p<0.05).

Conclusions: KIM1 and TIMP2*IGFBP7 are diagnostic of AG-AKI only the day of AKI onset. Future research should validate our findings and investigate these biomarkers to predict AKI severity and recovery.

Funding: Government Support - Non-U.S.

Biomarker	AG Treatment Day	Non-AKI (n=61)	AKI (n=43)
		Median [IQR]	
		AUC (95% CI)	
KIM1 (pg/ml)	2	121 [297]	442 [1100]
		0.66 (0.45-0.86)	
	3	178 [246]	112 [289.5]
		0.49(0.23-0.76)	
TIMP2*IGFBP7 ((ng/ml)²/1000)	2	0.0351 [0.291]	0.201 [0.784] *
		0.72 (0.57-0.87)	
	3	0.0809 [0.226]	0.132 [0.270]
		0.39 (0.17-0.62)	
	Day relative to AKI Onset		
KIM1 (pg/ml)	-2	178 [246]	260 [4023]
		0.67 (0.42-0.92)	
	-1	133 [279]	372 [511]
		0.62 (0.41-0.83)	
	0	88.3 [97.6]	286 [320] *
		0.87 (0.72-1.00)	
TIMP2*IGFBP7 ((ng/ml)²/1000)	-2	0.0809 [0.226]	0.134 [1.33]
		0.64 (0.45-0.83)	
	-1	0.0539 [0.217]	0.201 [0.265]
		0.35 (0.19-0.52)	
	0	0.0407 [0.070]	0.202 [0.385]
		0.75 (0.54-0.97)	

Table: Urinary KIM1 and TIMP2*IGFBP7 concentrations by AKI status, with AUC to detect AKI during AG treatment Bolded value: AUC Confidence Interval >0.5

***p-value <0.05 for comparison between AKI *vs.* Non-AKI**

FR-PO1080

Cell Cycle Arrest Biomarkers to Diagnose Pediatric AKI due to Cisplatin

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Background: Cisplatin (CisP) causes AKI and electrolyte abnormalities. Urine tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7) may be early AKI biomarkers.

Methods: 12-site, prospective cohort study of children treated for cancer with >=1 CisP cycle. Excluded: >18 years, kidney transplant, GFR<30ml/min/1.73m². Blood and urine collected at pre and 24-hrs post CisP during 1st or 2nd CisP cycle (Early Visit [EV]) and during 2nd to last or last CisP cycle (Late Visit[LV]). Urine measured for TIMP2(ng/ml), IGFBP7(ng/ml) (expressed as TIMP2*IGFBP7). AKI Outcomes: 1) **KDIGO SCr** definition; 2) Combined KDIGO SCr and electrolyte abnormality-based definition (from National Cancer Institute [NCI] criteria) - **KDIGO+NCI**. AKI *vs.* non-AKI TIMP2*IGFBP7 were compared pre and post CisP (Mann Whitney); within-subject pre *vs.* post CisP were compared (Wilcoxon signed-rank). Area under the curve (AUC, 95% CI) to detect AKI was calculated. Clinical model comparison for AKI prediction: neuroblastoma (yes/no) + age<3 years; assessed added benefit of TIMP2*IGFBP7 to increase AUC (DeLong).

Results: n=159, median [IQR] age 5.4 [9.4] years, 50% male. KDIGO AKI: EV 30%; LV 16%. KDIGO+NCI AKI: EV 20%; LV 11%. Table: AKI *vs.* non-AKI: EV Pre TIMP2*IGFBP7 is 5-7 fold lower in AKI, p<0.05; LV Post TIMP2*IGFBP7 is 4-6 fold higher in AKI, p<0.05. Non-AKI pre *vs.* post: TIMP2*IGFBP7 drops after CisP, p<0.05. Highest AUC: LV post (0.70-0.73). Clinical model: AUC 0.70 (0.58-0.81); addition of TIMP2*IGFBP7 increased LV Post AUC (0.77 [0.66-0.87]), p<0.05.

Conclusions: TIMP2*IGFBP7 is a modest predictor of CisP-AKI. Drop in TIMP2*IGFBP7 might be protective of CisP induced injury, but results must be validated in another cohort.

Funding: Government Support - Non-U.S.

Timepoint	KDIGO		KDIGO+NCI	
	Non-AKI (n=111)	AKI (n=48)	Non-AKI(n=127)	AKI(n=32)
	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
	AUC (95% CI)		AUC (95% CI)	
EV Pre	0.017 [0.048]	0.0032 [0.019] *	0.015 [0.048]	0.0021 [0.015] *
	0.62 (0.52-0.72)		**0.65** (0.54-0.76)	
EV Post	0.0016 [0.0027] #	0.0023 [0.0063] #	0.0017 [0.0028] #	0.0023 [0.0063]
	0.55 (0.44-0.66)		0.56 (0.43-0.69)	
LV Pre	0.014 (0.057)	0.0073 [0.027]	0.013 [0.055]	0.0092 [0.043]
	0.58 (0.45-0.71)		0.56 (0.41-0.71)	
LV Post	0.0014 [0.0039] #	0.0060 [0.017] *	0.0013 [0.0041] #	0.0078 [0.012] *
	0.70 (0.57-0.83)		**0.73** (0.59-0.86)	

Table: Urinary TIMP2*IGFBP7 ((ng/ml)²/1000) excretion pre and post Cisplatin with AUC's to diagnose post-Cisplatin AKIBolded values: AUC 95% CI >0.5

*Indicates p<0.05, comparing AKI *vs.* non-AKI (Mann-Whitney U)

#Indicates p<0.05, comparing pre- *vs.* post-biomarker concentrations (Wilcoxon signed-rank)

FR-PO1081

Outpatient Follow-Up After AKI in the Pediatric Intensive Care Unit (PICU)

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Background: Although KDIGO AKI guidelines recommend re-evaluation at 3 months, few studies have characterized pediatric AKI follow-up. This information is needed to target knowledge translation to enhance post-AKI care. Aims: 1) Describe outpatient follow-up of children with PICU-AKI; 2) Determine factors associated with nephrology follow-up in AKI patients.

Methods: Two-center retrospective cohort study (PICU admissions ≥2 days from 2003-2005; children 0-18 years old surviving hospitalization; non-cardiac surgery; no baseline kidney disease). Provincial administrative databases used to determine outcomes (until 2010). Exposure: AKI (KDIGO serum creatinine and urine output definition). Primary outcome: outpatient nephrology (Neph) visit by 1 yr post-discharge. Secondary outcomes: a) family physician (FP) or pediatrician (Ped), b) FP, Ped or non-Neph specialist (Spec) visits. Univariable analyses used to compare outcomes by AKI stage and evaluate patient factors associated with 1-yr Neph follow-up.

Results: Of n=2041, 355 (17%) had AKI: 64/355 (18%), 198 (56%) and 338 (95%) had Neph, FP or Ped and FP, Ped or Spec follow-up by 1 yr post-discharge. Figure: Children with AKI were more likely to have Neph follow-up (p<0.0001). There was no AKI *vs.* non-AKI difference in follow-up for other physicians (p>0.05). 44/142 (31%) stage 2-3 AKI patients had Neph follow-up by 1 yr. Factors associated with 1-yr Neph follow-up in AKI patients were: longer hospital stay; AKI stage 2-3; dialysis receipt; discharge SCr >1.5x baseline (all p<0.0001).

Conclusions: Children with PICU-AKI are more likely to receive Neph follow-up, though follow-up is suboptimal for severe AKI. Non-Neph physician follow-up is very high, suggesting AKI follow-up knowledge translation strategies for non-Neph providers should be a priority.

Funding: Private Foundation Support

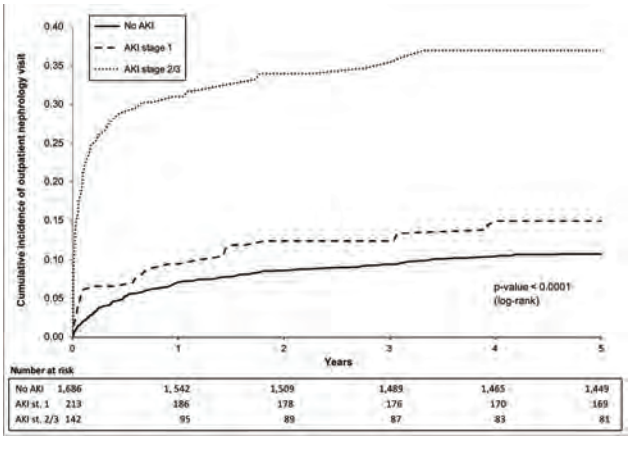

Figure. Time to outpatient nephrology (Neph) visit after PICU hospitalization, by AKI status

FR-PO1082

Efficacy of Rasburicase in Children with AKI from Diarrhea-Associated Hemolytic Uremic Syndrome

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Background: Diarrhea associated hemolytic uremic syndrome (D+HUS) is a common etiology of acute kidney injury (AKI) in children. Hyperuricemia during acute phase is a typical finding of D+HUS. Recently we have used rasburicase to manage hyperuricemia, thereby ameliorate AKI and accelerate their recovery. Here we assessed the efficacy of rasburicase in D+HUS.

Methods: We retrospectively analyzed the medical records of pediatric D+HUS patients who were admitted to Seoul National University Children's Hospital between January 2001 and July 2017. We compared the clinical outcomes between those treated with rasburicase (rasburicase group) and the rest (control group).

Results: A total of 72 patients were analyzed. Their median age was 3.2 years old. Median values of the lowest hemoglobin, the lowest platelet, and the highest uric acid were 6.3g/dL, 24,000/uL, and 12.6mg/dL, respectively. Twelve (16.7%) were treated with rasburicase. It was administered once at a median dose of 0.10 (range 0.05–0.20) mg/kg during the first day of admission. There was no difference in age, sex, the lowest hemoglobin, the lowest estimated glomerular filtration rate (eGFR), and the highest uric acid between the rasburicase group and the control group. The lowest platelet in rasburicase group was lower than that in the control group (14,000 vs. 25,000/uL; *P*=0.002). In the rasburicase group, hyperuricemia was rapidly reversed (2.4 vs. 6.5 days; *P*<0.001). There was no statistical difference in requirement of dialysis (66.7% vs. 55.0%; *P*= 0.456) and the duration of dialysis (5.5 vs. 8.6 days; *P*=0.262) between the two groups. However, median hospital length of stay was shorter in the rasburicase group than in the control group (12.9 vs. 18.2 days; *P*=0.043), and median eGFR at 1 year follow up was lower in the control group than in the rasburicase group (81.2 vs. 111.0 mL/min/1.73m², *P*=0.002).

Conclusions: Although rasburicase treatment in patients with D+HUS did not lower the requirement of dialysis, patients who were treated with rasburicase during the acute phase were discharged earlier from the hospital and had better renal function at 1 year follow-up. Since there are no known effective therapies for AKI induced by D+HUS, we may consider rasburicase to improve their long-term renal outcome.

FR-PO1083

HIP/PAP and BD-1 Indicate Successful Surgical Intervention in Pediatric Patients with Ureteropelvic Junction Obstruction

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Background: We have previously found a panel of antimicrobial peptides (AMPs) to be significantly elevated in ureteropelvic junction obstruction (UPJO). We sought to see if these same AMPs decreased after surgical correction of UPJO to further test their ability to identify obstruction.

Methods: Bladder urine was collected from pediatric patients (≤18 years old) immediately prior to surgical correction of an UPJO and then at least 6 months after surgery according to an IRB-approved protocol. Patients were included only if they did not have signs of active urinary tract infection at time of collection. Based on a prior study demonstrating that the AMPs beta defensin 1 (BD-1), hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein (HIP/PAP), LL-37, and neutrophil gelatinase-associated lipocalin (NGAL) were significantly elevated in patients with UPJO as compared to patients without, we performed enzyme-linked immunosorbent assays on these four AMPs to compare their expression before and after surgical intervention. AMP levels were normalized to urine creatinine. Results were analyzed with paired t test or Wilcoxon test using Graphpad software. A p-value of <0.05 was considered significant.

Results: Follow-up samples were obtained a median of 27.4 months (average 27.4; range 7.8-45.3 months) after surgery and removal of all drainage tubes on 13 patients on whom we also had urine samples collected immediately prior to pyeloplasty for their UPJO. Nine of the patients were male. Their age at urine collection at time of surgery was a median of 4.3 years (average 6.1; range 0.4-18.4 years). All 13 patients showed clinical improvement from before surgery and/or signs of improved hydronephrosis on post-operative imaging. We found that HIP/PAP and BD-1 were significantly decreased in post-surgical samples compared to pre-surgical samples (p=0.0215 and 0.0052, respectively); NGAL and LL-37 did not significantly change. The sensitivity/specificity of HIP/PAP to show correction of an obstruction was 77% and 85%, respectively, while for BD-1 it was 75% and 67%, respectively.

Conclusions: HIP/PAP and BD-1 are significantly elevated in upper urinary tract obstruction and significantly decrease with correction. These AMPs could serve as markers of successful surgical intervention.

FR-PO1085

Associations of Plasma Neutrophil Gelatinase-Associated Lipocalin, Anemia, and Renal Scarring in Children with Febrile Urinary Tract Infections

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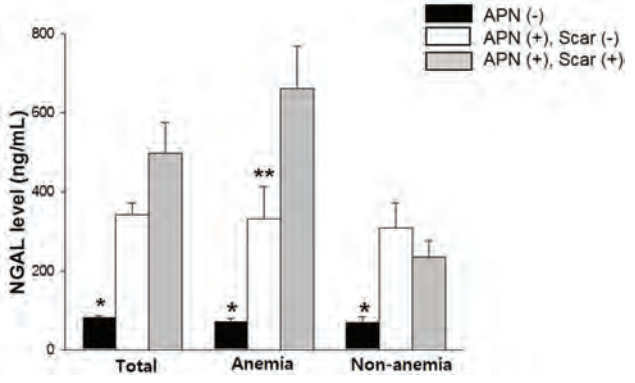
Background: Neutrophil gelatinase-associated lipocalin (NGAL), a bacteriostatic agent, is known to inhibit erythropoiesis leading to anemia. We aimed to investigate the relationships of NGAL, anemia, and renal scarring in children with febrile urinary tract infections (UTIs).

Methods: We retrospectively reviewed the medical records of 261 children with first febrile UTIs. The associations between plasma NGAL levels and indices of anemia were studied. NGAL performance in comparison with serum C-reactive protein (CRP) at admission and after 72 hours of antibiotic treatment was also evaluated for the prediction of renal scarring.

Results: Plasma NGAL levels were considerably elevated in patients with anemia compared with those without anemia ($P < 0.001$). NGAL concentrations were inversely correlated with levels of hemoglobin and hematocrit and red blood cell count (all $P < 0.001$). Increased NGAL, but not CRP, was independently associated with the presence of anemia in a multivariable logistic analysis [OR 2.37 (95% CI 1.07-5.27), $P < 0.05$]. Receiver operating curve analyses showed good diagnostic profiles of NGAL at admission and after treatment for identifying renal scarring (all $P < 0.05$). Plasma NGAL after treatment showed a higher area under the curve (AUC) (0.730; 95% CI 0.591–0.843) than that of CRP after treatment (AUC 0.520; 95% CI 0.395–0.643) ($P < 0.05$). In a multivariable analysis, elevated plasma NGAL level at admission and the presence of anemia were independently associated with the presence of renal scarring in children with febrile UTIs (all $P < 0.05$). In the presence of anemia, NGAL concentration increased consecutively in febrile UTI, APN, and renal scar ($P < 0.05$).

Conclusions: Increased plasma NGAL levels may be associated with the presence of anemia and renal scarring in children with febrile UTIs.



Plasma NGAL levels at admission in febrile UTI, APN, and renal scar (*$P < 0.05$, febrile UTI vs. APN & scar, **$P < 0.05$, APN vs. renal scar)

FR-PO1086

Long-Term Renal Outcomes in Children with AKI Post Cardiac Surgery

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Background: Acute Kidney Injury (AKI) is associated with poor short-term outcomes such as mortality, longer ICU and hospital length of stay and duration of mechanical ventilation as demonstrated by numerous studies. Our objective was to study the long-term renal outcomes and markers of kidney injury in pediatric patients with congenital heart disease who did and did not develop AKI following cardiac bypass surgery.

Methods: This was a prospective case-control observational study in which all infants and children who underwent cardiac bypass surgery from 2010-2017 and who had a long term follow up were included. Patients with CKD, Hypertension, AKI from primary kidney disease and previous history of AKI were excluded. 44 Patients who developed AKI were matched to 49 consecutive controls who did not develop AKI postoperatively. GFR was estimated by Schwartz formula and cystatin C. Kidney injury biomarkers that were used are NGAL, L-FABO, KIM-1, IL18.

Results: Age, Gender, weight, height, aortic cross-clamp (ACC) time and cardiopulmonary bypass (CPB) time were not statistically significant among cases and controls. Patients with AKI had a higher baseline serum creatinine (0.43±0.22, p<0.001) and longer ICU length of stay (days, 5.7±3.0, p<0.001) than the control group. On the long term follow up, patients with AKI had a higher serum creatinine level, the trend towards higher urinary KIM-1 levels and lower estimated GFR but were not statistically significant. When backward linear regression analysis was performed, CPB time (Odds Ratio: -0.550, p<0.05) and AKI (OR: 10.913, p>0.05) were the only risk factors associated with lower GFR at follow-up. CPB time (OR: 0.010, p<0.05), baseline serum creatinine (OR: -0.643, p>0.050) and AKI (OR: -0.381, p<0.05) were the only risk factors associated with higher KIM-1 at follow up.

Conclusions: Cardiopulmonary bypass time (CPB) is significantly associated with a decrease in GFR and a rise in kidney injury biomarker KIM-1 level several months post postoperatively independent of postoperative AKI.

FR-PO1087

Perioperative AKI in Pediatric Liver Transplant Patients

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Background: Acute kidney Injury (AKI) is a common complication in children in the post- orthotopic liver transplant (OLT) period. However, data regarding pre OLT AKI are scarce. We examined the incidence of perioperative AKI (7 days pre OLT- 7 days post OLR) in pediatric OLT population. AKI was defined using KDIGO criteria and HRS was defined using revised consensus recommendations of the International Club of Ascites, 2015 publication.

Methods: This is a single center retrospective chart review.

Results: A total hundred twenty-two pediatric patients (pts) underwent OLT between 11/2011- 3/2017. One patient who had known chronic kidney disease (CKD), was excluded. The median age was 2.5 years (IQR:0.83-10) and 71 were female (59%). Most common etiologies of liver disease were biliary atresia (BA) (68/121, 56%) and autoimmune idiopathic hepatitis (AIH) (25/121, 20%). Forty pts (33%) had perioperative AKI: 15% stage 1, 30% stage 2 and 55% stage 3. Of those, 15 (38%) pts had AKI pre-OLT, with hepatorenal syndrome (HRS) diagnosed in 11(73%). Twenty-five (62%) pts experienced post-OLT AKI. Most common etiologies for post OLT AKI were abdominal compartment syndrome (ACS), acute tubular necrosis (ATN) due to hypotension or bleeding, or nephrotoxin exposure. 29 pts (24%) received continuous renal replacement therapy (CRRT), 24 of those were started pre OLT due to AKI, fluid overload (FO) or hyperammonemia without AKI and 3 of those were discontinued after OLT. Five pts needed CRRT only post-OLT. Unfortunately, 7 AKI pts were never recognized by the clinical team.

Conclusions: AKI is common in perioperative period in children receiving OLT. HRS was the most common etiology for pre OLT. Post OLT, operative complications with ascites leading to ACS and hypotension leading ATN predominated. Majority of AKI pts were stage 3 and needed RRT. Unless monitored in a systemic fashion with structured diagnostic criteria, AKI can be missed by the clinical team. Short- and long-term outcomes of this population need to be elucidated through further studies.

FR-PO1088

The Long-Term Kidney Outcomes of Prune Belly Syndrome in Australia

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Background: Prune Belly Syndrome (PBS) a rare congenital disorder consisting of the triad of: absence or incomplete abdominal wall muscle development, bilateral cryptorchidism and urinary tract anomalies including hydronephrosis, kidney dysplasia and dilated ureters, urethra or bladder. PBS varies considerably in clinical severity, with prognosis primarily being influenced by the degree of chronic kidney disease. The aim of this study was to describe the long-term kidney outcomes of people with Prune Belly Syndrome in Australia.

Methods: We identified all Australians treated with renal replacement therapy (RRT) who had a diagnosis of PBS (as determined by the treating unit) from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). ANZDATA is a clinical quality registry containing information on all people receiving dialysis or a kidney transplant since 1977.

Results: We identified 37 males (no females) with a diagnosis of PBS who received RRT in Australia and were recorded in ANZDATA. Commencement of RRT was at a median age of 17yrs (mean 19yrs, range 1-45yrs) when median creatinine was 720umol/L. RRT at first treatment was haemodialysis in 54%, peritoneal dialysis 30% and pre-emptive kidney transplant in 16%. Twenty percent of patients were late referrals to the dialysis unit (referral <3 months prior to starting dialysis). Comorbidities of diabetes, heart disease or vascular disease were not present at commencement of RRT. One man had chronic lung disease. Forty-five kidney transplants (including 33 first, 10 second and 2 third grafts) occurred, of which 47% were from deceased donors. Mean age at first transplant was 21yrs (range 2-47yrs). Graft survival at 1, 5 & 10 years for first grafts was 94%, 67% and 48% respectively (range 6 days to 36 years). Parenthood was reported for 3 men at a median age of 35yrs. There were 10 deaths reported at a median age of 37yrs (range 17-49yrs) due to cardiac death (50%), malignancy (20%), dialysis cessation (10%) and uncertain cause (20%).

Conclusions: Prune Belly Syndrome has marked variation in the severity of kidney disease. For those who receive RRT, kidney transplant is the predominant treatment, but peritoneal dialysis has been used successfully. Infertility is not universal. There is early cardiovascular mortality associated with this syndrome.

FR-PO1089

Aptamer-Based Proteomics Analysis Reveals a Urine Protein Signature That Differentiates UTIs from Culture-Negative Pyuria and Normal Urine

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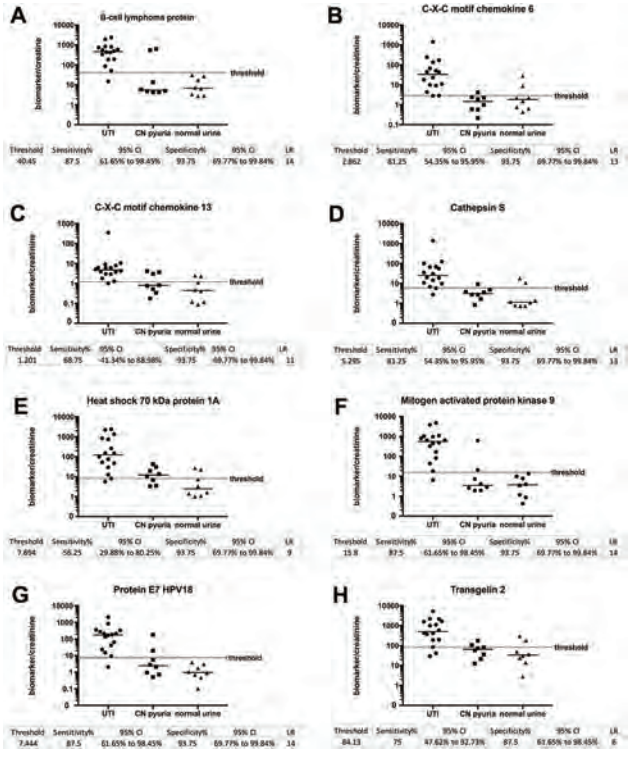
Background: UTIs account for 7% of pediatric emergency department antibiotic prescriptions. UTI diagnosis is typically made at the point-of-care by symptoms and the identification of nitrites and/or leukocyte esterase (LE) on urinalysis (UA). Growth of ≥ 50,000 colony forming bacterial units on culture is used to confirm a UTI. However accurate urine culture results can be dependent on collection methodology and take 24-72 hours to complete. UAs have limitations as well. The sensitivity/specificity for LE to detect childhood UTIs is 83%/78%.

Methods: An aliquot of urine was obtained from pediatric Emergency Department patients who had a sample collected for clinical urine culture. Included samples consisted of 16 with urinary tract infection (UTI), 8 culture negative (CN) pyuria, and 8 with normal UAs. The levels of 1,310 proteins were quantified as relative fluorescent units/ml using the SOMAscan platform (Somalogic Inc, Boulder, CO) and the normalized to urine creatinine (mg/dl). The results were filtered for proteins that were (a) significantly higher in the UTI vs CN pyuria samples and in the UTI vs normal urine samples with a p value of < 0.01 and that had an area under the curve (AUC) of > 0.9 which is used to define an "excellent" biomarker.

Results: Eight candidate biomarkers met this stringent filtering criteria and are presented along with the threshold urine biomarker to creatinine ratio with the highest likelihood ratio to differentiate UTI from non UTI samples in Figure 1.

Conclusions: A biomarker panel containing some of the candidates identified via this study has the potential to improve the timeliness and accuracy of UTI detection. Prospective studies evaluating levels measured by ELISA and conversion to a point of care testing modality are the next investigative steps.

Funding: Private Foundation Support



FR-PO1090

Incidence of Early Dysnatremia in the Assessment of Neonatal Acute Kidney and Epidemiology (AWAKEN) Cohort

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Background: Incidence of dysnatremia during the first postnatal week in the neonatal intensive care unit (NICU) and its association with mortality has not been well described. We hypothesized that incidence of dysnatremia would vary with gestational age (GA) and that early dysnatremia predicts mortality.

Methods: We studied neonates in the AWAKEN cohort, a 24-center retrospective study of NICU admissions on IV fluids ≥ 48 hrs, with ≥ 1 serum sodium (sNA) recording during postnatal days 2-7. sNA values were compared in 3 GA cohorts (24-<29 weeks(wk), ≥29-<36wk, ≥36wk). Hypernatremia was defined as sNa >145meq/L (moderate=146-155, severe=≥156); hyponatremia was defined as sNa <135meq/mL (mild=130-134; moderate=125-129; severe<125). Survival was considered reaching 36 wk post-GA or hospital discharge. Kruskal Wallis, Chi^2 tests, and multivariable logistic regression were used as appropriate.

Results: The cohort included 1,972 infants with 15,302 sNa values (Table 1). Of these, 23% developed hypernatremia and 35% developed hyponatremia. The incidence and severity of hypernatremia differed by GA (Figure 1). Infants <29 wk GA were most likely to develop severe hypernatremia (OR 8.8 95%CI 6.1-12.6, p<0.01). The incidence and severity of hyponatremia also differed across GA groups (Figure 2). Over 40% of infants in the 24-<29 wk and ≥36 wk cohorts developed hyponatremia, compared to 26.8% of the ≥29-<36 wk group (p< 0.001). Both hyponatremia (adjusted (a)OR 2.7 95%CI 1.6-4.5, p<0.001) and hypernatremia (aOR 2.2 95%CI 1.3-3.8, p=0.005) in models adjusted for GA predicted increased odds of mortality.

Conclusions: This is the largest and most inclusive cohort to describe the incidence and impact of dysnatremias in critically ill neonates. The incidence and severity of hypernatremia differed by GA category and was most substantial in very premature infants. However, infants 24-<29 wk and ≥36 wk GA developed hyponatremia at similar rates, which may reflect oliguria and/or fluid provision strategies. Further evaluations of this cohort will evaluate whether hyponatremia and hypernatremia are independently associated with mortality after adjusting for other important cofounders.

Funding: NIDDK Support, Other NIH Support - NIH/National Center for Advancing Translational Science (NCATS) Einstein-Montefiore CTSA Grant Number UL1TR001073

FR-PO1091

Delta Bilirubin: A Lesser-Known Bilirubin Fraction and Its Impact on Interpretation of Single-Pass Albumin Dialysis (SPAD) Efficacy

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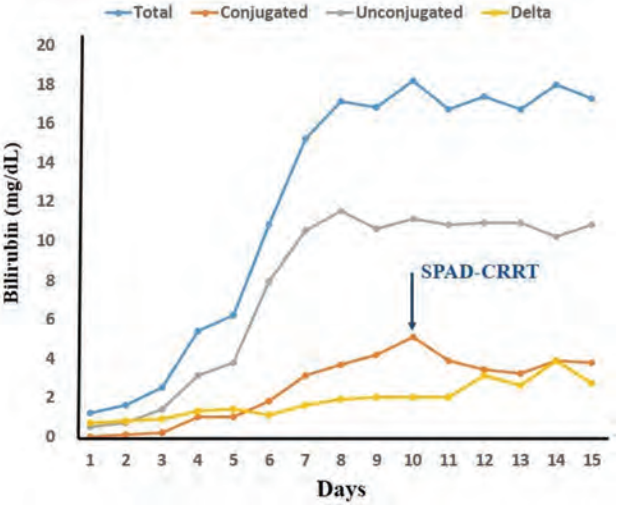
Background: Acute liver failure (ALF) is a rapidly progressive disease that leads to multiple organ failure with high mortality. Combination of supportive therapies are utilized to stabilize these patients until recovery, or as a bridge to liver transplant. As MARS is not readily available in all pediatric centers, modification of continuous renal replacement therapy (CRRT) with SPAD is an equally efficacious alternative. During SPAD, bilirubin clearance is used as a surrogate marker for clearance of protein bound-toxins. We have previously shown >10 fold increase in bilirubin clearance with SPAD as compared to CRRT alone. However, we failed to observe increased bilirubin clearance in a group of ALF patients who received SPAD.

Methods: We studied 3 patients with ALF who failed to show increased bilirubin clearance. These patients had significant unconjugated hyperbilirubinemia which is not cleared by SPAD as it is tightly albumin-bound. However, we also found significantly decreased clearance of conjugated-bilirubin in these patients. We thus studied the bilirubin fractions in the serum and the effluent by using Vitros 5600 chemistry analyzer, a unique method that uses two slides to measure total, unconjugated and conjugated-bilirubin fractions, and calculates delta bilirubin, a form of conjugated-bilirubin that is covalently bound to albumin.

Results: Review of our raw data showed that these 3 patients had significant proportion of their conjugated bilirubin in the form of delta-bilirubin (Figure), which is not cleared by SPAD due to its tight albumin binding. Delta bilirubin is known to accumulate in patients with prolonged liver failure and biliary atresia.

Conclusions: Decreased bilirubin clearance in this subset of ALF patients was found to be due to increased serum delta-bilirubin. Since most laboratories do not measure or report delta-bilirubin, increased delta-bilirubin may lead to the perception that SPAD is not working efficiently, and may lead to unnecessary and expensive work-up.



Bilirubin fractions

FR-PO1092

Undetected Sexual Transmitted Infection in Adolescents with Sterile Pyuria

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Background: The percentage of sexual transmitted infection(STI) in adolescents had been underestimated and misdiagnosed as urinary tract infection(UTI), which may lead to unnecessary treatment and public health issue. We aimed to distinguish STIs through symptoms, laboratory and urinary analysis. We emphasize on the correlation of STIs and child maltreatment.

Methods: We performed a retrospective study of adolescents aged from 15-18 years old, who visited a tertiary center from January 1, 2015 through July 30, 2018, with diagnosis of urinary tract infection, acute cystitis, acute pyelonephritis, dysuria, urinary frequency, or renal colic. We compared clinical characters, symptoms, serum laboratory data, urine analysis, percentage of been reported to Social Affair Bureau between STIs and UTIs groups.

Results: Of the 45 adolescents, there was a significant difference in pyuria count(p=0.036), with 44.7% of UTI group reached the highest pyuria level (WBC>100/HPF) and none in STI group had pyuria >100/HPF. 71.4% of STIs had only mild pyuria with 5~49/HPF. No significant difference in clinical symptoms, including fever, dysuria, hematuria, abdominal pain, flank pain, serum white cell count, or CRP level between UTIs and STIs groups. We found 71% of adolescents with STIs had been reported as in need of child protection.

Conclusions: The clinical features and serum laboratory data were overlapping in STIs and UTIs, and both of them cause pyuria, which may lead to over-diagnosis of UTIs. Adolescents with lower degree of pyuria had higher possibility of STIs. The incidence of family dysfunction in STI is extremely high.

FR-PO1093

Renal Abnormalities in HIV-Exposed Children: A Guatemalan Retrospective Cohort Study

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Background: Among the various organs involved with the progression of HIV infection, the kidneys have had a significant impact Studies have highlighted the importance of early detection of kidney disease in HIV-infected patients in order to reduce the progression of CKD We identify the renal abnormalities in HIVexposed children in a tertiary hospital in Guatemala

Methods: After ethics approval, we retrospectively evaluated a cohort of patients perinatally exposed to HIV during the period 2015-2016 Patients attending the outpatient clinic for at least 6 months were captured in the study. eGFR, pr/cr, ca/cr ratio were obtained at the time of inclusion and at least 6 months after enrollment. Renal abnormality was outlined if lasting more than 6 months Clinical and immunologic status, viral load, time in which the patient was without antiretroviral treatment since HIV perinatal exposure and time of antiretroviral exposure were determined

Results: From 102 patients enrolled, 52 were HIV positive and 50 were HIV negative. The mean age was 12.2yr(SD, 4.9) and 40% of the patients were male. 56%(29/52) of the infected patients had a C clinical status, 62%(32/52) had a severe immunosuppression status and 39%(20/52) had a viral load<50 thousand The mean pretreatment time was 2.82yr(SD, 2.5) and the mean time of antiretroviral exposure was 8yr(SD,3). Regarding renal function marker, 42%(22/52) of the infected patients had an eGFR abnormality (20 patients had eGFR>140 and 2 patients had eGFR<90ml/min/1.73m2), compared to 10%(5/50) of the uninfected patients (all the patients had eGFR>140ml/min/1.73m2). Infected patients had 4 times higher risk to present abnormalities in eGFR compared to uninfected patients. IC-95%(1.73-10.30) The mean eGFR values at 0-2, 2-4, 4-6 and >6yr of pretreatment time were 177.73(SD,91.12), 171.59(SD,91.12) and 171.27ml/min/1.73m2(SD,94.16). The 0-2yr of pretreatment time group had the highest frequency of abnormalities in eGFR and pr/cr ratio, compared to the rest of the groups. 48%(25/52) of the patients during the antiretroviral exposure, 50%(26/52) with C clinical status, 52%(27/52) with 3 immunologic status and 21%(11/52) with ≤50thousand load had at least 1 renal abnormality

Conclusions: Hyperfiltration was the predominant renal abnormality in HIV infected patients The early screening for renal function is mandatory in all HIV exposed patients

FR-PO1094

Use of an Artificial Neural Network for the Prediction of Urine Culture Positivity from Urine Dipstick in Children

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Background: Urine dipstick results are important for clinical decision making regarding the presence or absence of urinary tract infections. The aim of the study was to analyse the performance of artificial neural network (ANN) in the prediction of positive urine culture from an automated urine dipstick test.

Methods: We retrospectively analysed all available automated urine dipstick (UD) and urine cultures (UCULT) tests performed at our institution over 2-year period (2015-2017). The final dataset (after merging and cleaning) consisted of 5912 complete UD and UCULT performed on the same date and time. Predictors of UCULT included: age, gender, and all UD results: glucose, ketones, specific gravity, blood, pH, protein, nitrates and leukocytes. ANN model (sequential, feedforward with backpropagation) consisted of 30 neurons in 2 hidden layers (Tensorflow Keras). Data samples (n=5912) were randomly divided into training (70%) and validation set (30%). ANN prediction probabilities thresholds for positive UCULT results were set to 0.5 (ANN05) and 0.3 (ANN03). The performance of both ANN models was assessed by accuracy scores, sensitivity, specificity, positive and negative predictive value (PPV, NPV).

Results: Out of 1773 children (aged 4.3 ±5.3 years) in the validation set, 449 had a positive UCULT. ANN05 correctly predicted 1272 negative + 254 positive UCULT; with ANN03 the prediction was: 1229 negative + 289 positive UCULT. The mean accuracy of both ANN05 and ANN03 models was 86% (95% CI = 84-88%). Sensitivity and specificity of ANN05 was 0.57 and 0.96 with PPV of 0.83 and NPV of 0.87. The corresponding numbers for the ANN03 model were: 0.64, 0.93, 0.75, and 0.89. The four most important UD variables for prediction of UCULT were: leukocytes, blood, nitrates and protein.

Conclusions: ANN predicted positive urine cultures from a simple urine dipstick (without urine microscopy) with 84-88% accuracy, PPV of 75-83% and NPV of 87-89%. ANN-powered automated urine dipstick lab prediction of positive urine cultures can be considered to facilitate clinical decision making.

FR-PO1095

Which Grading System Is More Useful to Estimate the Time to Resolution of Isolated Hydronephrosis Between SFU and APPD Grades? A Single-Center Study

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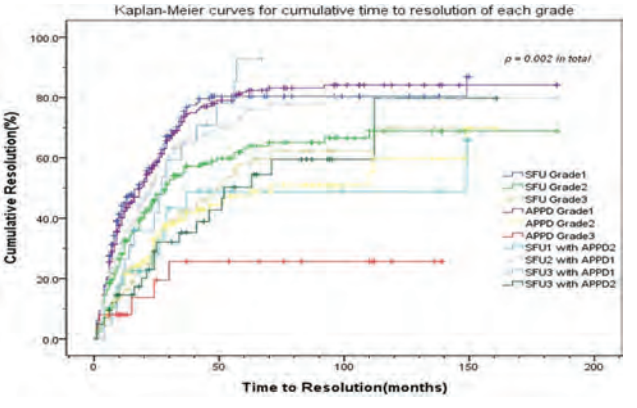
Background: Predicting the time to resolution of isolated hydronephrosis is an important topic for both clinicians and families. Because the Society for Fetal Urology(SFU) classification and Anterior-Posterior Pelvic Diameter(APPD) are the two most commonly used grading tools of hydronephrosis, we aimed to compare the ability of two systems in estimating resolution rate.

Methods: We retrospectively reviewed medical records of patients with isolated hydronephrosis prenatally detected and postnatally diagnosed between 1990-2018, and excluded patients with pyeloplasty, vesicoureteral reflux or other anomalies. SFU grade and APPD at first USG were collected and APPD ranges of 5–9mm, 10–14mm, 15–19mm, and above 20mm were classified as grade 1, 2, 3 and 4. Resolution was defined as APPD below 5mm with SFU grade 1. Log rank test and Kaplan-Meier curves were used to analyze time to resolution of each SFU and APPD grades.

Results: Of 432 patients(544 renal units), 382(88.4%) were male, and 398(73.2%) renal units were left sided. 217(39.9%) units reached resolution at a mean follow-up of 51±44 months. SFU grades 1 through 4 showed resolution rate of 80.0%, 60.2%, 48.0%, 20.0% respectively, and APPD grades showed resolution rate of 78.0%, 44.3%, 25.7%, 6.7% respectively at 48 months. There was discrepancy between SFU and APPD grades in 253(46.5%) units. In each disproportional case, resolution rate approximated to the rate of APPD grade without significant difference. In proportional cases, the cumulative resolution rate of each pair of grade 1 and 2(84.5%, 52.7%) approached the rate of each APPD grade(84.1%, 59.7%), while SFU grade 3 with APPD grade 3 showed a value of resolution rate(48.1%) between the resolution rate of each SFU(69.8%) and APPD(25.7%) grade.

Conclusions: APPD grade is more useful than SFU grade in predicting time to resolution when there is discrepancy between two grades. In the low grade concordant cases, prediction of time to resolution can be resonably based on APPD.



FR-PO1096

The Ribonuclease 6 Antimicrobial Peptide Limits Bacterial Burden During Experimental Pyelonephritis

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Background: Ribonuclease 6 (RNase 6) is an evolutionarily-conserved antimicrobial peptide that kills uropathogenic bacteria at low micromolar concentrations *in vitro*. Here, we investigated the hypothesis that RNase 6 limits urinary tract colonization by uropathogenic *Escherichia coli* (UPEC) *in vivo*.

Methods: We generated mice with a *Rnase6*^{EGFP} knock-in allele on a C57BL/6J genetic background. We identified cellular sources of RNase6 based on flow cytometry, epifluorescence, and immunofluorescence microscopy. We transurethrally inoculated *Rnase6*$^{EGFP/EGFP}$ and control female mice with UPEC strain CFT073 and enumerated bacterial burden in urinary tract tissues by homogenization and serial plating.

Results: Flow cytometry in *Rnase6*$^{EGFP/+}$ mice identified EGFP expression by circulating Ly6C^{hi} monocytes which were recruited to the infected bladder by 6 hours post inoculation (hpi). In addition, EGFP was expressed by two discrete resident macrophage populations within the kidney. We confirmed *Rnase6* deletion in *Rnase6*$^{EGFP/EGFP}$ mice, which displayed normal urinary tract development, fertility, and hematopoiesis. *Rnase6* deficiency led to increased renal and ureteral UPEC burden at 6 and 12 hpi, compared to control mice.

Conclusions: In the infected urinary tract, RNase6 is primarily expressed by resident macrophages and recruited monocytes. We have demonstrated a critical role for RNase 6 in UPEC clearance from the upper urinary tract during ascending UTI *in vivo.*

Funding: Other NIH Support - R03 DK118306-01

FR-PO1097

Urinary Klotho Abnormalities in Pediatric Sickle Cell Disease (SCD)

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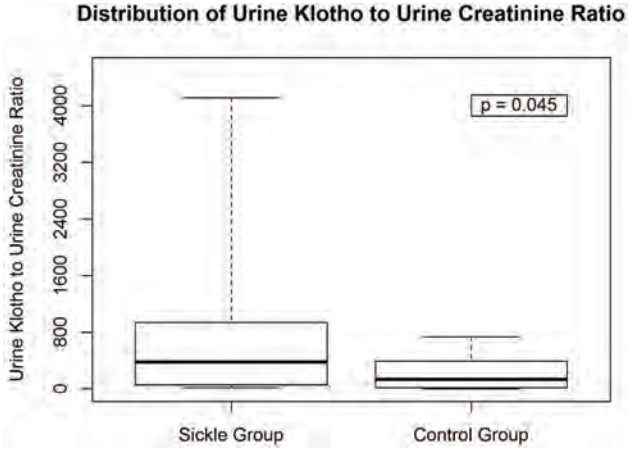
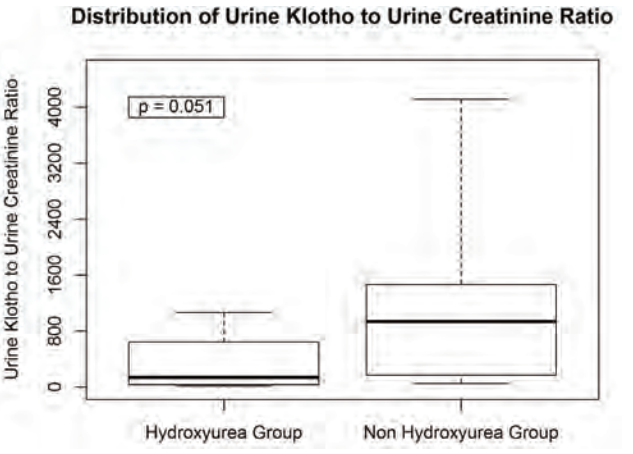
Background: Klotho is a transmembrane protein expressed in the renal tubules and serves as an obligatory co-receptor for FGF23 to aid in phosphorus excretion. Prior studies have shown FGF23 resistance in SCD. The purpose of the study is to investigate urinary klotho/creatinine (Ur Kl/Cr) in pediatric SCD and no markers of ongoing renal damage (eGFR > 90 ml/min and no microalbuminuria) and to compare it with healthy control population.

Methods: Cross sectional observational study to compare Ur Kl/Cr in pediatric SCD and controls. To do a sub group analysis among the study population to assess the effect of hydroxyurea(HU) on Ur Kl/Cr

Results: 20 control and 22 pediatric SCD were enrolled. In SCD group, 13 were on HU. The baseline characteristic of the study and control group were same. Wilcoxon rank-sum test was used to compare the levels of Ur Kl/Cr ratio between SCD and control. For P value of 0.05, the levels of Ur Kl/Cr were statistically significantly higher in the sickle cell group (752.7 ± 1101.0) over the control group (216.8 ± 225.3). Subgroup analysis in the SCD group showed high Urinary Kl excretion in the non HU group(1346.7 ± 1523.4) vs non HU group (341.4 ± 355.3) but not statistically significant.(Fig 1 & 2)

Conclusions: Children with SCD tend to have increased secretion of Ur Kl/Cr compared to control likely due to tubular receptor resistance. HU tends to reverse this phenomenon by it's effect on preventing tubular damage.





FR-PO1098

Genetic Background of Infants with Urinary Tract Infection and Transient Pseudohypoaldosteronism

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Background: Transient pseudohypoaldosteronism type 1 (PHA1) is a rare but severe complication of urinary tract infection (UTI) in infants. A detailed clinical and molecular analysis for this patient cohort is still lacking.

Methods: Transient pseudohypoaldosteronism type 1 (PHA1) is a rare but severe complication of urinary tract infection (UTI) in infants. A detailed clinical and molecular analysis for this patient cohort is still lacking.

Results: They included twelve infants (9 male) with an age of 1-8 months. All of them exhibited hypovolemic hyponatremia (125.3 ± 3.3 mmol/L), hyperkalemia (6.4 ± 0.2 mmol/L), metabolic acidosis (HCO_3^- 15.1 ± 1.5 mmol/L), low TTKG (3.3 ± 0.5), and relatively elevated FENa (2.4 ± 0.2 %), high plasma renin (476.2 ± 295.2 pg/ml) and aldosterone levels (869.8± 280.3 pg/ml). The time from onset of UTI to occurrence of PHA1 was 2.4 days. Vomiting and poor feeding were the most common symptoms. Seven had hyperkalemia-related arrhythmia and two of them developed life-threatening ventricular tachycardia. With prompt therapy for PHA1 and UTI, clinical manifestations and biochemical abnormalities were all resolved. Despite vesicoureteral reflux as the most common urinary tract anomalies, five patients had normal urinary tract and one of them harbored a novel mutation at phosphorylation site (heterozygous S544A) of *NR3C2*. During follow-up, none of them had recurrence of PHA1 and 4 of them developed renal scaring.

Conclusions: The development of PHAI from UTI is rapid and may exhibit severe features. Besides the well-known urinary tract anomalies, genetic mutation on *NR3C2* may contribute to PHA1 in UTI infants without identifiable risk factors.

FR-PO1099

Context-Specific Cellular Mechanisms of Urothelial Development and Repair in the Kidney

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Background: Congenital urinary tract obstruction (UTO) is a leading cause of pediatric chronic kidney disease and end stage renal disease. The renal urothelium is the kidney's anatomic front line of defense during UTO, and represents an understudied but novel therapeutic target. Renal urothelium contains two mutually exclusive, Krt5+ and Upk+ renal urothelial cell (RUC) populations. UTO triggers an iterative RUC remodeling sequence that culminates in the formation of bladder-like Upk+ apical plaque producing RUCs, which attenuate UTO injury. The ontology of Upk+ RUCs is unknown, stalling efforts to therapeutically promote protective renal urothelial remodeling.

Methods: In this study, we performed genetic fate mapping to determine whether Upk+ RUC arise through self-renewal or via differentiation from Krt5+ RUC. We mapped the fate of Upk+ and Krt5+ RUC lineages in *Upk2*$^{CreERT2/+}$*;R26*$^{tdT/+}$ and *Krt5*$^{CreERT2/+}$*;R26*$^{tdT/+}$ mice, and performed immunofluorescent assays to mark Krt5, Krt14, p63, foxa1, Upk, Krt20, tdT-expressing and proliferating cells across development. Unilateral ureteral obstruction was used to trigger UTO.

Results: Renal urothelium develops at embryonic day 17, and temporal waves of Upk and Krt5 expression are observed through adulthood. Krt5+ RUCs commonly express Krt14 and p63 and are the primary proliferative RUC. Adult Upk+ RUCs derive from

embryonic and neonatal Krt5+ RUCs. Paralleling a proliferative decline, Krt5+ RUCs lose progenitor capacity by postnatal day 14. In a temporally restricted manner, UTO triggers formerly lineage restricted Krt5+ RUCs to regain progenitor capacity and form bladder-like Upk+ RUCs. In addition, adult Upk+ RUCs possess the ability to lose Upk protein expression, proliferate, and give rise to daughter Upk+ RUCs that reacquire Upk protein synthesis.

Conclusions: This study is the first to establish the temporal manner in which the embryonic and postnatal renal urothelium is patterned, and demonstrates the contexts during which Upk+ RUCs arise via self-renewal versus differentiation from Krt5+ progenitors. Identification of the context-specific mechanisms governing progenitor plasticity or restriction have broad implications for urothelial development, repair and therapeutic manipulation.

Funding: NIDDK Support

FR-PO1100

Mercaptoacetyltriglycine Scan vs. Functional Magnetic Resonance Urography: A Comparison and Long-Term Follow-Up of Clinical Outcomes

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Background: Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are the leading cause of End Stage Renal Disease in children. Obstructive uropathy (OU) presenting with urinary tract dilation (UTD) is one of the most common forms of CAKUT. While there is no gold standard for OU evaluation or clear cutoffs for surgical intervention, functional imaging evaluation is recommended to help the decision making process. In children, functional Magnetic Resonance Urography (fMRU) is increasingly used because of its superior anatomic detail when compared to the most widely used MAG3 nuclear medicine renal scan (RS). However, there is not enough data to assure that fMRU-based differential renal function is equivalent to RS results. Here we compare the functional results of fMRU and RS in a pediatric cohort presenting with UTD.

Methods: This is an IRB-approved retrospective review of 37 out of 988 (3.75%) fMRUs performed in 735 children (0-21 yrs) at our institution between 2007 and 2017, which had an accompanying RS within 6-months and with no interval surgical intervention.

Results: The 37 unique patients (15 F, 25 M) had a median age: 6 months (range: 2mo-19y) and; 24% were caucasian. The majority (26/37, 70.3%) presented with UTD P3. Main diagnoses included uretero-pelvic junction obstruction (UPJO) in 21/37, megaureter (5/37) and duplex kidney (4/37). Differential renal function (DRF) was obtained from each test and 14 fMRU and 12 RS patients were grouped as normal but there was no significant agreement between tests in the dilated groups ($p = 0.135$). Only 7/33 (21%) patients had concordant (<5% DRF difference) DRF from fMRU and RS. Upon evaluating obstruction determinants fMRU was found to be 88.24% specific and 38.10% sensitive with 69.09% accuracy (95% CI 55.19-80.86). 2/19 patients who had follow up for a mean of 3 years (range 6mo-9 years) had elevated BP. eGFR was found to be >100mL/min/1.73m2 consistent with normal renal function at follow-up in 15 patients.

Conclusions: The differential renal function determined by RS and fMRU in children is discordant in a majority of cases with significant agreement limited to those deemed normal in both modalities. Using RS as the gold standard, fMRU was found to be 88.24% specific though average sensitivity in determining obstruction. Overall cohort did not present adverse outcomes after a mean 3 years follow up.

Funding: Other NIH Support - T32 Grant

FR-PO1101

Pre-Transplant Elevated Chemokines CXCL9, CXCL10, and CXCL11 Influence Kidney Graft Status in Mexican Mestizos

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Background: A high incidence of CKD in Mexico, affects a significant number of young patients. Chemokines CXCL9, CXCL10 and CXCL11 may be sensitive markers of rejection or infection. Variability in the genetic background of populations is relevant. The clinical implications of these differences suggest the need to study other traits, including the influence of inflammatory processes in CKD Mestizos. Here, we explore how pre-transplant serum levels of CXCL9, CXCL10 and CXCL11 influence kidney grafts at 3 months after transplantation.

Methods: Retrospective study; 57 kidney receptors and 19 donors. Serum base levels of CXCL9, CXCL10 and CXCL11 were measured (Luminex 200). Other data were obtained from clinical charts. Correlations and mean comparisons were used to identify possible associations of chemokine levels with several conditions at 3 months.

Results: All chemokine levels were different between receptors and donors (CXCL9: 992.04 pg/mL vs 301.78 pg mL; CXCL10: 37.83 pg/mL vs 30.54 pg/mL; CXCL11: 333.98 pg/ml vs 23.78 pg/mL, respectively; $p< 0.05$). A negative correlation was identified between base creatinine and CXCL11 (r=-0.268, p=0.043), CXCL10 (r=-0.257, p=0.054), as well as time on dyalisis (r=0.329, p=0.019). CXCL9 was different between sexes (969.22 pg/ml male vs 433.57 pg/ml female; p=0.045). Receptors younger than 25 years had higher CXCL9 values (1282.91 pg/ml <25 y, vs 660.36 pg/ml ≥25 y, p=0.044). Other differences included pre-transplant type of dialysis (CXCL9 1643.95 pg/ml PD, vs 563.16 pg/ml HD, p=0.048). Preemptive patients had lower CXCL10 (23.41 pg/ml no dialysis vs 37 pg/ml peritoneal vs 41.29 pg/ml hemodyalisis; p=0.009). No associations were found between chemokines and infections at 3 months, but were found with calcineurin inhibitor toxicity (CXCL9: 1842.79 pg/ml toxicity vs 892.45 pg/ml no toxicity; p=0.049).

Conclusions: CKD patients have elevated chemokine serum levels, which associate with age, are reduced after transplantation, and correlate with creatinine. Type and time on dialysis may contribute to high chemokine levels, which may influence graft dysfunctions. Young Mexicans had a predisposition for higher chemokine production.

FR-PO1102

Everolimus Suppresses the BK Virus Replication in Human Embryo Cells In Vitro

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Background: BK virus causes BKV-associated nephropathy in about 8% of kidney transplant patients and allograft loss occurs in 10-50% of the affected individuals. There is currently no effective treatment for BKV and it is mainly treated by reducing immunosuppression or changing the treatment regimen. Therefore, the search for effective treatments and mechanisms for BK virus infection is important. To date, various immunosuppressants were reported to suppress the replication of BKV *in vitro*. However, there are few reports that showed the effects of everolimus. We report the in vitro study of the effects of everolimus on BKV proliferation.

Methods: Confluent human embryo lung cells were infected with BKV isolated from a renal transplant recipient. We first determined the replication time and viral infectivity in this system. BKV DNA replication was evaluated by the increase in the DNA copy numbers in infected cells and the tissue culture infectious dose ($TCID_{50}$) and viral copy number were determined in three viral stocks. Effects of immunosuppressants on BKV replication were examined in this system. Cells were infected and treated with everolimus, cyclosporine, and tacrolimus at various concentrations attained in the recipients for 72 hours and the amounts of the replicated viral DNA were determined by a real-time quantitative PCR with primers targeting the large T-antigen.

Results: BKV growth curve showed that BKV DNA increased at 48 hours and further at 88 hours after infection, indicating one replication cycle was 48 hours. Viral infectivity was attained at 10^8 to 10^9 $TCID_{50}$/mL and particle per infectivity ratio was 2.12 $TCID_{50}$/1,000 DNA copies (n=3) in this system. BKV replication was not affected by treatment with tacrolimus and cyclosporine at concentrations from 1 to 30 ng/mL and from 0.01 to 1 μg/mL, respectively. Everolimus at concentrations from 0.1 to 300 ng/ml significantly suppressed BKV replication to 20 to 40% of untreated cells.

Conclusions: Everolimus has been reported to alleviate BKV infection in the TRANSFORM study. Everolimus suppressed BKV replication at the concentrations attained in the serum of renal transplant recipients and this results support the alleviation of BKV infection with everolimus.

FR-PO1103

B Cell and T Cell Subset Changes in a Rat Kidney Transplant Model of Chronic Antibody-Mediated Rejection

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Background: Chronic antibody mediated rejection (cAMR) is a leading cause of kidney graft loss. In many instances, mixed chronic AMR and cellular rejection are observed. We examined B and T cell populations in the lymphoid organs of a sensitized rat kidney transplant model. We hypothesized that sensitized recipients would have increased populations of memory and proinflammatory B and T cells in lymphoid tissues.

Methods: Minor mismatch kidney transplantation was performed to generate cAMR. The cAMR model had 3 groups: 1) syngeneic (Syn, Lewis donor to Lewis recipient), 2) allogeneic (Allo, Fisher donor to Lewis recipient), and 3) sensitized (Sens Allo, Fisher donor to Lewis recipient that received blood transfusion 21 days pre-transplant). Animals were harvested at 6 months post-transplant and lymphoid cells were analyzed by flow cytometry.

Results: Sensitized recipients demonstrated increased numbers of nonswitched and memory B cells in the bone marrow compared to allogeneic recipients (Figure 1). Sensitized recipients demonstrated increased numbers of splenic CD4+ T cells compared to allogeneic recipients. However, splenic CD8+ T cells and T regulatory cell numbers were similar between sensitized and allogeneic recipients. Additionally, splenic T follicular helper (Tfh) cells were elevated in sensitized recipients compared to allogeneic recipients.

Conclusions: We show sensitized kidney transplant recipients with cAMR develop increased populations of memory B cells and CD4+ T cells, including Tfh cells. The interactions of CD4+ T cells, including Tfh cells, with B cells promote the generation of memory B cells and antibody production and support a role for T and B cells in chronic rejection.

Funding: Other NIH Support - KL2 award

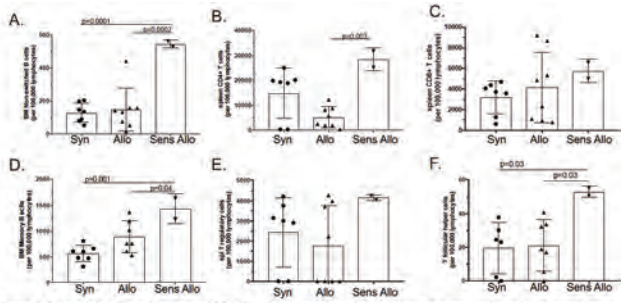

Figure 1. B cells in the Bone Marrow and CD4+ T cells in the spleen are increased by sensitization prior to transplant. Both early A) non-switched B cells and late D) Memory B cells in the bone marrow were expanded in sensitized animals B) CD4+ T cells in the spleen were elevated in sensitized animals. In contrast, C) splenic CD8+ T cells were not different between groups. E) Tregs were not significantly increased with sensitization, but F) T follicular helper cells were expanded in animals

FR-PO1104

Ex Vivo Exposure to IL-6 and TNFa Improves Proliferation of Regulatory T Cells Without Impairing Their Function and Lineage Stability

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Background: Clinical trials testing the efficacy of regulatory T cell (Treg) therapy in kidney and liver transplantation are underway. The survival and function of the infused Tregs in the inflammatory environment of the recipient are key determinants of the safety and efficiency of Treg therapy. We sought to investigate the impact of ex vivo exposure to IL-6 and TNFa on Treg proliferation, phenotype, and function.

Methods: First, we isolated $CD4^+$ $CD25^+$ $CD62L^+$ Tregs from C57BL/6J mice lymph nodes using fluorescence activated cell sorting (FACS). We stimulated the Tregs with anti-CD3/CD28 beads in the presence of IL-2, with or without IL-6 and TNFa and monitored Treg proliferation over a 10-day period. In addition, we adoptively transferred IL-6 and TNFa exposed NOD.BDC2.5 TCR transgenic Tregs into NOD.CD28KO mice. Similarly, we setup ex-vivo cultures of human $CD4+CD25^{hi}$ $CD127^{lo}$ Tregs isolated from peripheral blood mononuclear cells of healthy donors. Finally, we profiled both murine and human Tregs using flow cytometry, luminex, bisulfite conversion and pyrosequencing.

Results: We observed that C57BL/6J mouse Tregs exposed to IL-6 and TNFa have increased proliferation (136+/-28 versus 1106+/-505 fold; n=3; p=0.02), expressed Foxp3 and Helios and remained demethylated at the Treg specific demethylated region (TSDR). Adoptive transfer of IL-6 and TNFa exposed NOD.BDC2.5 TCR transgenic Tregs protected NOD.CD28KO recipients from diabetes. Similarly, ex-vivo exposure to IL-6 and TNFa increased proliferation of human $CD4^+$ $CD25^+$ $CD127^{lo/-}$ Tregs (24+/-13 versus 53+/-19 fold; n=4; p=0.04). IL-6 and TNFa exposed human Tregs remained $FOXP3^{hi}$ $HELIOS^{hi}$, did not produce pro-inflammatory cytokines such as IL-2, IL-4, IFNg or IL-17, and maintained demethylated TSDR. Finally, IL-6 and TNFa exposed human Tregs maintained their suppressive function against pre-activated $CD4^+$ Teff cells, similar to their non-exposed Treg counterparts.

Conclusions: Our results demonstrate that Treg exposure to IL-6 and TNFa enhances their proliferation without negatively impacting their lineage stability and suggests that Tregs positively respond to these cytokines by increasing their proliferation as a way to scale to inflammation. This property may be exploited to improve therapeutic Treg manufacturing for transplantation.

Funding: Other NIH Support - NIAID Support, Private Foundation Support

FR-PO1105

Association of the Insertion/Deletion Polymorphism of the ACE Gene with Acute Rejection and Chronic Dysfunction of Kidney Allografts

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Background: There are several factors influencing the outcomes of kidney trasnplantion. It should be noted, that several individual genes are suspected to have a role in the clinical outcome of rejection. One of these candidates, is the insertion/deletion polymorphism, of the angiotensin converting enzyme (*ACE*) gene.

Methods: This work focuses on the role of the insertion/deletion polymorphism of ACE, in the clinical rejection of kidney allografts. We performed an analysis of 166 patients, and looked for a possible association between alleles and genotypes of (I/D) polymorphisms of the *ACE* gene, with episodes of acute rejection and CAN, in patients with kidney transplantation.

Results: In the 166 patients included in the study, the genotype frequencies were heterogenous. We found that 35 patients (21%) were homozygous for the insertion genotype, 80 patients (48%) were heterozygous, and 51 patients (31%) had a homozygous genotype for deletion. Another statistical analysis was performed, in which the control group was considered independently from the four sub-groups of adverse events. We could observe statistically significant differences in the comparison amongst all of the groups (p 0.003) and in the analysis for the generalized additive models (I+ p <0.0001, D+ p 0.029).

Conclusions: No particular allele or genotype of the I/D polymorphism of the ACE can be associated with episodes of acute rejection, or with chronic allograft nephropathy, in patients with kidney allograft transplant. We can also conclude that the Homozygous Deletion allele of the I/D polymorphism, can be associated with toxicity by calcineurin inhibitors, at least in the population studied in this present work.

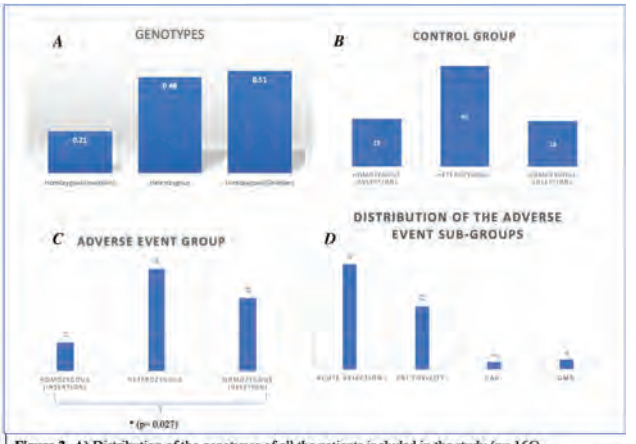

Figure 2- A) Distribution of the genotypes of all the patients included in the study (n= 166) **B)** Distribution of the genotypes of the patients in the control group **C)** Distribution of the genotypes of the patients in adverse event group **D)** Distribution of the sub-groups included in the adverse event group

FR-PO1106

Angiotensin-(1–7) Attenuates Tacrolimus-Induced Apoptosis in Human Renal Proximal Tubular Epithelial Cells

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Background: Tacrolimus (FK-506) is used clinically to reduce the rejection rate in patients with kidney transplantation; however, the nephrotoxicity induced by tacrolimus remains serious clinical problem. Although tacrolimus-induced nephrotoxicity might be involved renin-angiotensin system, but the role of angiotensin-(1–7) [Ang-(1–7)] has not been completely understood. The present study was aimed to investigate the renoprotective effects of Ang-(1–7) in tacrolimus-induced renal tubular injury.

Methods: To investigate the molecular mechanisms underlying tacrolimus-induced renal tubular cell injury, human proximal tubular epithelial (HK-2) cells were treated with tacrolimus (75 μM) in the presence or absence of Ang-(1–7) (1 μM) and Mas receptor antagonist A779 (1 μM). Cell viability was examined using WST-1 assay. Cell cycle arrest was assessed by the protein expression of cyclin B1, phospho-Cdc2 (Tyr 15) and phospho-Histone H3 (Ser 10).

Results: Treatment of tacrolimus decreased cell viability in a dose or time-dependent manner in HK-2 cells. In addition, treatment of tacrolimus decreased the protein expression of cyclin B1, phospho-cdc2 and phospho-Histone H3 in cytosol and nuclear fraction compared with control, indicating that cells arrested at G_0/G_1 phase. Moreover, tacrolimus induced the expression of nuclear factor-κB (NF-κB) signaling, pro-apoptotic markers Bax and cleaved caspase-3 and necrotic cell death marker cleaved PARP1, as well as attenuated the anti-apoptotic marker Bcl-2 in HK-2 cells. However, these changes were attenuated by pretreatment with Ang-(1–7), while co-treatment with A779 abolished the effect of Ang-(1–7). In addition, tacrolimus increased tumor necrosis factor-α converting enzyme (TACE) and decreased angiotensin-converting enzyme 2 (ACE2) expression in HK-2 cells, while pretreatment with Ang-(1–7) or A779 significantly inhibited or enhanced these effects, respectively.

Conclusions: NF-κB signaling and cell cycle arrest at G_0/G_1 phase might be mediated in tacrolimus-induced apoptosis. Also, tacrolimus increased TACE expression, which could mediate the vicious cycle of decreasing ACE2. However, Ang-(1–7) protects the cell viability by suppressing apoptosis and necrosis via Mas receptor in tacrolimus-induced HK-2 cells.

FR-PO1107

Whole Blood vs. Packed Red Blood Cell-Based Perfusate in Normothermic Machine Perfusion of Kidneys

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Background: With a rapidly growing gap between supply and demand for donor kidneys, transplant centres look to utilize extended criteria donors to meet the demand. Normothermic machine perfusion (NMP) is a novel preservation method that offers opportunities for graft evaluation and therapeutic interventions not possible with traditional

hypothermic methods. With higher metabolic demand, NMP requires an oxygen carrier for efficient tissue oxygenation, and the most common choice is packed red blood cells or leukocyte depleted blood. We aim to investigate the effects of whole blood compared to packed red blood cell-based NMP perfusate on graft perfusion and inflammation.

Methods: Porcine kidneys were recovered and perfused with our pressure controlled NMP system for 12 hours. The NMP system is primed with a modified plasmalyte (crystalloid) solution and either whole donor blood or washed donor packed red blood cell. Perfusate is supplemented with heparin, glucose, and insulin over time through infusions. Perfusate and urine samples are collected for analysis throughout perfusion.

Results: Both groups experienced comparable mean renal blood flow consistently over 12 hours of perfusion, with a trend showing increased renal blood flow in whole blood perfusates (whole blood: 719±27.5ml/min; packed red blood cell: 639±28.8ml/min). No significant differences in perfusate pH were detected. Pro-inflammatory cytokines TNF-alpha and IL-6 were significantly increased in whole blood compared against packed red blood cell-based perfusate. Anti-inflammatory cytokine IL-10 was also significantly increased in whole blood compared to packed red blood cell-based perfusate.

Conclusions: Both whole blood and packed red blood cell-based perfusates demonstrated equivalent perfusion resistance and perfusate biochemistry in a porcine model of kidney normothermic machine perfusion. With the presence of leukocytes in whole blood-based perfusates, there was a significant increase in perfusate cytokines, including both pro-inflammatory cytokines TNF-alpha and IL-6 and anti-inflammatory cytokine IL-10. However, the physiological significance of perfusate cytokine presence still requires further study through histological evaluation and a transplant model with long term follow up.

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

FR-PO1108

Downregulation of Allograft 25-Hydroxyvitamin D3 1 Alpha-Hydroxylase Is an Early Biomarker for Rejection in Kidney Transplantation

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Background: 1a, 25(OH)2 vitaminD3 (1a,25VitD3) results from both renal and extrarenal 25-Hydroxyvitamin D3 1 alpha-Hydroxylase (1a-HOase) activity. Renal 1a-HOase is classically associated with mineral metabolism whereas extrarenal 1a-HOase exhibits immunomodulatory effects. Vitamin D deficiency may also be prevalent in the immediate post-transplant period. In the present study, we investigated the relationship between cytokine secretion, graft 1a-HOase expression, renal cortical epithelial cell injury (RCEC), and allograft rejection in a pig model of kidney transplantation and in cultured human RCEC.

Methods: Outbred Yorkshire pigs underwent autotransplants or mismatched allogeneic kidney transplants as we described (Transplant Immunol 42:40). No immunosuppression was used. The vitamin D axis was assessed 72 hours post transplant. The effect of 1a,25VitD3 and 25VitD3 on T cell proliferation and epithelial-mesenchymal transformation (EMT) were investigated using cultured RCEC.

Results: Circulating levels of 1a,25VitD3 and 25VitD3VitD were increased and decreased, respectively, in 30 pigs following auto (n=5) or allotransplantation (n=25). Allograft 1a-HOase was decreased in rejection showing a negative correlation with the extent of rejection (Banff) (r=-0.712 ($p<0.01$), and renal function (BUN (r=-0.706 ($p<0.01$); creatinine (r=-0.673 ($p<0.05$)). Additionally, IL17 and FGF23 were upregulated, and 1, 25-hydroxyvitamin D3 24-hydroxylase was downregulated in rejecting grafts. 1a-HOase was mainly expressed in RCEC. Activating cultured RCEC with cytokines gave a rapid, 10x reduction of 1a-HOase, associated with dramatic decreases of protective E-cadherin (E-cad) and tight junction protein-1 (TJP1), whereas 1a,25VitD3 attenuated cytokine induction of EMT, as well as normalized expression of E-cad and TJP1. When compared to 25VitD3, 1a,25VitD3 exhibited a 50-fold greater suppression of T cell proliferation.

Conclusions: Allograft 1a-HOase expression may predict allograft rejection, not the circulating 1a,25VitD3. Allograft 1a-HOase may play a key role in the prevention of allograft rejection.

Funding: Private Foundation Support

FR-PO1109

Inhibition of Spleen Tyrosine Kinase Decreases Donor-Specific Antibody Levels in a Rat Model of Presensitization

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Background: Antibody mediated rejection (ABMR) is the leading cause of allograft failure post transplantation and there is currently no available effective treatment. Orthotopic kidney allographs from Fischer F344 DU (F344) to Lewis RT1[l] (LEW) rats is a model for chronic allograft nephropathy. The aim of this study was to determine if LEW pre-sensitized with F344 whole blood produced donor specific antibodies (DSA); and whether inhibition of SYK with Fostamatinib had efficacy in reduction of circulating DSA levels.

Methods: Male LEW rats were transfused with whole blood from male F344 rats. Transfused LEW rats were treated with 40mg/kg of Fostamatinib or vehicle by oral gavage twice daily for 14 days from 7 days (early treatment), or 11 days (late treatment) post transfusion. Serum MFI levels for IgG DSA levels were determined on a BD LSRFortessa™ X- 20.

Results: This is the first time F344 to LEW whole blood transfusion has been described as a pre-sensitization model. Transfused LEW rats developed IgG DSA. Early treatment was implemented at onset of IgG antibody production (day 7), and late treatment where IgG antibody production was established and nearing peak levels (day 11) (Fig1a). In our experiments, early treatment with Fostamatinib significantly decreased circulating IgG levels (Fig1b), late treatment, when antibody levels were established was not effective (Fig1c).

Conclusions: In conclusion, we have shown that treatment of pre-sensitized LEW rats with selective SYK inhibitor Fostamatinib at the start of IgG antibody production significantly reduced levels of circulating IgG DSA. Cytotoxic IgG antibodies have a well-established role in ABMR. This indicates a potential use of Fostamatinib as a treatment option for pre-sensitized patients requiring renal transplant or following development of a de novo DSA.

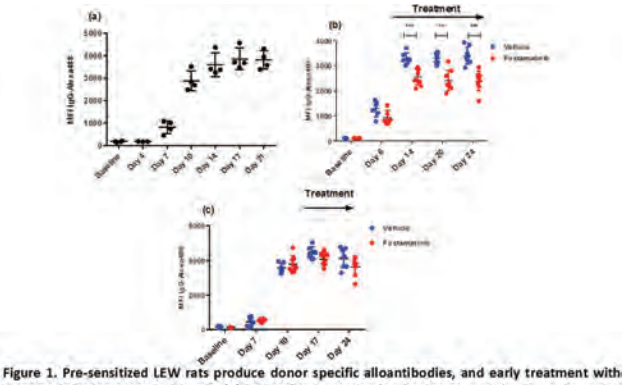

Figure 1. Pre-sensitized LEW rats produce donor specific alloantibodies, and early treatment with Fostamatinib decreases IgG levels. (a) IgG antibody production begins around day 7, peaks at day 17, remaining high at day 21 (n=4). Pre-sensitized LEW rats treated with 40mg/kg Fostamatinib twice daily for 14 days, commencing 7 days post transfusion (b) had significantly decreased IgG levels at days 14, 20 and 24. Late treatment, commencing 14 days post-transfusion did not affect IgG levels (c). Both (b,c) n=7 per group. Error bars represent SD. Results were analysed by the Mann-Whitney U test. (P ** ≤ 0.01, *** P ≤ 0.001).

FR-PO1110

Calcineurin Inhibitors Induce Endoplasmic Reticulum Stress in Kidney Epithelial Cells via PERK- and ATF6-Dependent Mechanisms

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Background: Calcineurin inhibitors such as cyclosporine A (CsA) or tacrolimus (Tac) form the core of immunosuppressive regimens in organ transplant recipients but may cause substantial nephrotoxicity with induction of endoplasmic reticulum (ER) stress and maladaptive unfolded protein response (UPR) in kidney epithelia. Calcineurin stimulates the activity of PKR-like ER kinase (PERK), which is an ER stress sensor suppressing protein translation. Calcineurin may also promote ATF6-induced autophagy to alleviate ER stress. We hypothesized that calcineurin inhibition interferes with functions of PERK and ATF6, thereby inducing ER stress and UPR.

Methods: To test this hypothesis, we generated PERK-deficient and ATF6-deficient human embryonic kidney (HEK293) cell lines using CRISPR/Cas9-mediated gene editing. Effects of CsA on expression and cellular distribution of two critical UPR transcription factors, CHOP and spliced XBP1, were monitored using quantitative PCR, immunoblotting and immunofluorescence.

Results: Treatment of control HEK293 cells with CsA (10 μM for 6h) induced a two-fold increase of CHOP abundance and a 70-fold increase of spliced XBP1 abundance in cell lysates. Parallel immunofluorescence analysis showed CsA-induced nuclear translocation of CHOP. In contrast, PERK-deficient and ATF6-deficient cells showed no significant CsA-induced increases of CHOP expression. Stimulation of spliced XBP1 was weaker in PERK-deficient (five-fold increase) and ATF6-deficient HEK293 cells (30-fold increase) compared to control cells. To extend these results, we evaluated effects of Tac in cultured murine distal convoluted tubule (DCT) cells. In this model, treatment with Tac (10 μM for 6h) increased CHOP expression by two-fold but did not affected spliced XBP1.

Conclusions: In sum, these results suggest that calcineurin inhibitors cause ER stress and UPR in kidney epithelial cells, which may in part depend on suppression of PERK or ATF6 functions.

Funding: Government Support - Non-U.S.

FR-PO1111

Blockade of PKCδ in Donor Kidneys Protects Against Cold Ischemia-Reperfusion Injury in Kidney Transplantation

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Background: Ischemia-reperfusion injury (IRI) is an inevitable consequence of kidney transplantation. PKCδ has been reported to contribute to mitochondrial pathway of apoptosis during cell stress, but role of PKCδ in kidney IRI remains unknown. This study aims to evaluate the role and regulation of PKCδ in cold storage with renal transplantation.

Methods: C57BL/6 mice kidneys were preserved in an ice bath for 0.5, 4, 8, 10 or 14 hours in University of Wisconsin solution (UWS) and transplanted into syngeneic recipients. Renal injury and regeneration were examined at 24 hours or day 6 after transplantation. The responses of kidneys from wild-type and PKCδ-null mice were examined and compared. Rat proximal tubular cells (RPTC) were exposed to hypothermia at 4°C with UWS incubation and then changed with complete medium in 37°C. Mitochondria morphology was examined under confocal microscopy and mitochondria dysfunction was evaluated by Cytochrome C release and Bax translocation. Active and kinase-dead PKCδ were transfected to determine the role of PKCδ in RPTC cells.

Results: Post-transplant injury in WT kidneys was mild when cold storage time was shorter than 4 hours, but the injury increased notably with 8 hours and longer cold storage. Ki-67+ tubules peaked at 8 hours of cold storage, while longer cold storage suppressed post-transplant tubular proliferation. PKCδ was activated during cold storage as indicated by its phosphorylation at Y-311 and proteolysis. WT kidneys with 10 hours cold preservation showed remarkable damage and tubular apoptosis at 24 hours after transplantation. In comparison, PKCδ-KO kidneys had significant less injury and better tubular proliferation. Furthermore, PKCδ-KO kidneys had improved kidney repair and function as life-supporting kidney at day 6 when native kidneys were removed from recipient. Consistently, pharmacological inhibitors of PKCδ also prevented early post-transplant injury at day 1. In RPTC cells, mitochondrial fragmentation and leakage were involved in cold storage injury. Mitochondrial injury and cell death were inhibited by PKCδ kinase-dead mutant but were aggravated by active PKCδ fragment.

Conclusions: PKCδ is activated during cold storage of donor kidneys and mediates subsequent renal IRI during kidney transplantation. Inhibition of PKCδ may alleviate kidney injury during cold storage and benefit subsequent renal transplantation.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO1112

Developing an Imaging Mass Cytometry-Based Injury Panel to Define the Pathogenesis of Delayed Graft Function

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Background: Delayed Graft Function (DGF) is a significant source of morbidity in transplant patients and is associated with decreased graft survival and increased mortality; however, treatment is restricted by limited mechanistic understanding of its pathogenesis. To better define the cellular architecture of the human kidney, we developed an imaging analysis pipeline using Imaging Mass Cytometry, a novel approach for simultaneous mass spectrometry-based analysis of up to 42 protein targets on formalin-fixed tissue. While antibodies to resident and infiltrating cell populations are in our panel, antibodies to identify cell injury are needed.

Methods: In vitro models were developed for inducing programmed cell death (apoptosis—TNFa, ATP depletion; necroptosis—TNFa, ATP depletion, zVAD) and cell stress (autophagy—serum starvation, TGFb; ER stress—serum starvation, tunicamycin) pathway activation in human proximal tubule HK-2 cells. Antibodies showing specificity by IF were conjugated to heavy metals to be used for IMC.

Results: HK-2 cells showed reduced viability under cell death conditions (control 95.0+/-0.9%; apoptosis 46.3 +/- 5.9%; necroptosis 66.6 +/- 5.9%). Validated antibodies showed significant differences under injury vs control conditions, including: apoptosis (anti-cPARP: 9.5 +/- 2.5% vs 0.8 +/- 0.3%); necroptosis (anti-pMLKL: 17.9 +/- 5.1% vs 2.8 +/- 0.7%); autophagy (anti-P62: 29.8 +/- 7.4% vs 7.1 +/- 1.9%); and ER stress (anti-GRP94: 21.0 +/- 0.6% vs 2.0 +/- 0.7%). All 4 antibodies retained staining by IMC in a tumor-associated interstitial nephritis kidney biopsy.

Conclusions: We now have 35 validated antibodies, including the 4 described above, to simultaneously quantify injured tubular and vascular cell populations and their frequency of interaction with immune subtypes. We will perform IMC with this expanded panel using our cohort of pre-implantation transplant biopsies from 16 deceased donors (7 with subsequent DGF) and 15 living donors as healthy controls.

Funding: NIDDK Support

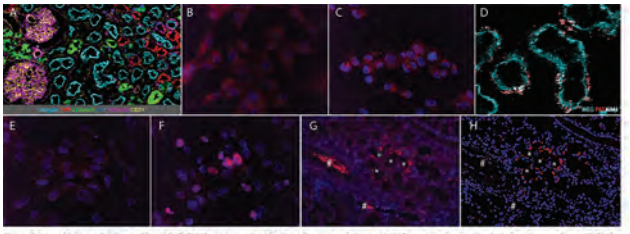

Figure 1. Injury Marker validation by IF and IMC. (A) Illustrative region of a Living Donor sample imaged in IMC, pseudocolored with selected markers as shown. (B-C) IF validation in HK-2 cells of anti-P62 antibody under control (B) and autophagy (C) conditions. (D) IMC image of kidney with tumor-associated interstitial nephritis showing proximal tubule cells co-expressing P62 (red) and KIM1 (white). P62 positive cells also co-expressed LC3B (not shown). (E-F) In vitro IF staining for pMLKL in control (E) and necroptosis-treated (F) cells. (G-H) Human kidney tissue with tumor-associated interstitial nephritis was stained by IF with anti-pMLKL-175Lu (G), followed by IMC ablation of the same region (H), pseudocolored for pMLKL (red) and DNA intercalator (blue). Note corresponding tubules show pMLKL positivity (*), with absence of RBC autofluorescence by IMC (#). Meg – Megalin; THP – Tamm Horsfall Protein.

FR-PO1113

Differential Control of COX-2 Expression in Macula Densa Cells Under Calcineurin Inhibition by Cyclosporine A

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Background: Calcineurin inhibitors such as cyclosporine A (CsA) are in use as immunosuppressive drugs to prevent rejection of transplanted organs. Despite positive outcomes, side effects such as decreased GFR and overall functional and structural deterioration may affect the kidney. Among the causes, interactions of vasoactive systems have been considered. We therefore studied how CsA may cause dysregulation of key juxtagomerular signaling components.

Methods: Wistar rats received vehicle or 25mg CsA/kg b.w./d for 14d. Organs were perfusion-fixed and embedded for morphology. Cultured macula densa (MD) cells were treated with CsA (5 μM) and angiotensin II (AngII; 1 μM) for 6 or 24h. Tissues or cells were immunohistochemically studied for renin, COX-2, NFAT subtypes 1 to 4, p38 MAPK, CREB, NF-kB, and activating p38 MAPK and CREB phosphorylation. Inhibitors to p38 MAPK (SB203580; 10 μM) and NF-kB (Bay 11-7082; 5 μM) were applied in cells. Cells were also analyzed by PCR and Western blot.

Results: CsA caused the known upregulation of renin and complete downregulation of COX-2. An assumed link between NFAT and COX-2 within MD could not be established. In MD cells, CsA caused a rise in COX-2 abundance at 6 and 24 h (2-fold each); p38 MAPK phosphorylation was increased in parallel (1.9-fold). Inhibition of p38 MAPK attenuated CsA-induced COX-2 upregulation by 50%. Under the same conditions, NF-kB showed nuclear translocation (+50%). Inhibitor to NF-kB (6h) blunted COX-2 stimulation by 35%. CREB phosphorylation was increased 2- to 4-fold with COX-2 stimulation (6h). AngII substantially decreased expression of baseline COX-2 by 40% (6h) and blunted CsA-induced COX-2 stimulation by 30% (6h). All data were significant (min. $p<0.05$).

Conclusions: In sum, calcineurin inhibition by CsA *in vivo* suppressed juxtaglomerular COX-2 independently of NFAT signaling. Contrastingly, cultured MD cells show substantial stimulation of COX-2 upon CsA, involving MAPK, NF-kB, and CREB. Dominant, antagonistic AngII is likely to act on the same signaling cascade. This novel, MD cell-specific regulatory synergism of calcineurin and angiotensin, governing COX-2 biosynthesis, may serve to address juxtaglomerular dysregulation under CsA treatment.

Funding: Government Support - Non-U.S.

FR-PO1114

Non-Cultured Adipose-Derived Regenerative Cells Limit Early Inflammation and Fibrosis in Renal Ischemia-Reperfusion Injury

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Background: Studies in our rat model of ischemic reperfusion injury (IRI) demonstrate improved kidney function post injection of adipose-derived regenerative cells (ADRC). The mechanism on how these cells induce reparative effects during IRI remains elusive. We investigated ADRC-derived effects within the injured kidney at early timepoints.

Methods: Inguinal rat ADRC or vehicle control were injected via the renal artery of the IRI rat model. At 48 hours and 1-week post-ischemia injury, kidney was evaluated for fibrotic and inflammatory markers through qPCR and western blotting of (n=6-8). Leukocyte quantity was assessed by flow cytometry (n=4-5). Histology was used to measure infiltrative lesions and Masson Trichrome stained collagen accumulation (n=8-20).

Results: ADRC-treated kidneys expressed lower levels of inflammatory gene CXCL12 and significantly lower protein levels of granulocyte macrophage colony-stimulating factor (both $p<0.05$). In addition, a consistent increase in cytotoxic T-lymphocyte-associated protein 4 transcript was characteristic of ADRC treated kidneys. At 48 hours post-IRI, half of vehicle controls contained higher levels of CD45+ leukocytes. Assessment of leukocyte infiltrate indicated a trend of higher infiltrate in vehicle control kidneys compared to ADRC kidneys at 48 hours with significant apparent differences by 1-week post IRI ($p<0.05$). Early accumulation of interstitial factors: tissue inhibitor of metalloproteinase-1 ($p<0.05$) and collagen type 1, alpha 2 ($p<0.001$) in vehicle control kidneys indicated early fibrotic development. This was mirrored by significantly high levels of collagen staining in control compared to ADRC treated kidneys at 1-week post IRI ($p<0.001$).

Conclusions: Collectively, gene, protein expression and histological evidence suggest that ADRC treated IRI kidneys experience early anti-inflammatory changes conducive to the inhibition of fibrogenesis.

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

FR-PO1115

Alternative M2 Macrophages Activation and TGF-β1 Production Are Induced by TNF-α Through the Adenosine A2A Receptor Pathway

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Background: Kidney transplants from deceased donors have a worse prognosis than those from living donors. Early and persistent inflammation may contribute to the development of fibrosis and impact transplant outcome. We showed previously that, in renal tissue from deceased donors, increased expression of A2A adenosine receptor, that could be involved in anti-inflammatory activity and M2 macrophage activation, correlated with inflammatory and anti-inflammatory mediators such as TNF-α and TGF-β1. The aim of this research is to study the association between TNF-α and A2A in macrophage phenotype differentiation.

Methods: THP-1 cells were seeded in the presence of TNF-α at different time-points (3, 6, 18 and 24 hours) and concentrations (5, 10 and 20 ng/ml). Cells were pretreated for 30 minutes with 1 μM of the A2AR antagonist ZM241385 before TNF-α was added and samples were analyzed by Real-time PCR.

Results: TNF-alpha significantly augmented the expression of A2A but not A2B at all points analyzed, reaching the maximum increase at a concentration of 10 ng/ml at 3 hours of treatment ($p<0.001$). TNF-α also induced the expression of TGF-β1 and the M2 marker CD163 at 18 and 24 hours (figure 1A). Interestingly, the expression the M1 macrophage marker CD86 decreased with TNF-α treatment. Pretreatment with ZM241385 abolished the effect of TNF-α over CD163 (figure 1B) and TGF-β1, providing evidence that A_{2A} receptor is involved in M2 macrophage activation by TNF-α. In fact, induction of CD163 expression by IL-10 ($p=0.0006$) was partially but significantly blocked by ZM241385 (31.4% increase blocked, $p=0.018$). We did not detect any effect of IL-10 on TGF-β. The decrease in CD86 does not seem to involve the A2A purinergic pathway.

Conclusions: Our results suggest TNF-alpha induces macrophage M2 switching and TGF-β1 expression through A2a receptor activation.

Funding: Government Support - Non-U.S.

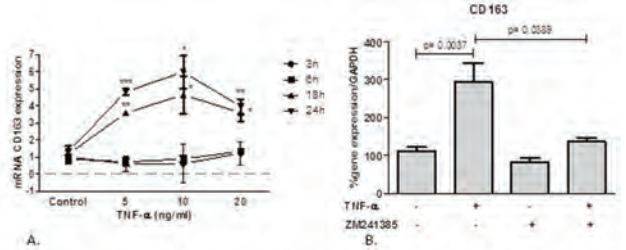

Figure 1. Expression of the M2 macrophage marker CD163 in THP-1 cells. (A) CD163 was increased by TNF-α at time-points and concentrations indicated. (B) Induction of CD163 by TNF-α was blocked by A2A receptor antagonist ZM 241385.

FR-PO1116

Dual Treatment of CD40 Silencing or Mesenchymal Stem Cells Infusion with Sub-Therapeutic Doses of Cyclosporine Effectively Prevents Acute Rejection in an Allogenic Model of Renal Transplantation

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Background: Previous studies in our group, showed partial protective effect of costimulatory silencing with a siRNA-CD40 or MSC infusion in life sustaining model of rat renal allograft transplant. This study was designed to investigate the combination of CD40 silencing or MSC infusion with suboptimal doses of Cyclosporine in this renal allograft model.

Methods: In this model, rats were randomly allocated into different groups: Non-Treated (n=10); Scrambled siRNA (n=10); Cyclosporine (control full dose, 5 mg/kg/day) (n=9); CsA1/2 (sub-therapeutic, 2.5 mg/kg), (n=5); MSC, group treated with two MSC doses at day -7 and day 0 (n=8); siRNA-CD40 (500 ug), (n=5); CsA1/2+siRNA-CD40 group (n=5) and CsA1/2+MSC group (n=8). Heterotopic renal transplantation was performed from Wistar to Lewis rats, with 21 days of follow up. Survival, renal function, conventional histology and immunohistochemistry (CD68 cells, CD3 cells, glomerular and peritubular capillary C4d) were analyzed in all groups.

Results: Monotherapy either with CsA1/2, siRNA-CD40 or MSC showed slight improvement in all the studied parameters compared with Non-treated or Scrambled groups. The combined therapy using CsA1/2+MSC or CsA1/2+siRNA-CD40 displayed significant amelioration of these parameters compared to monotherapy groups. Interestingly, the CsA1/2+siRNA-CD40 group presented a clear reduction of glomerular and peritubular C4d deposition and the degree of CD3 infiltrate, reaching similar values to Cyclosporine full dose group.

Conclusions: In conclusion, siRNA or MSC combined with sub-therapeutic doses of Cyclosporine offered better prevention in allograft rejection and survival than monotherapy groups. But was the CsA1/2+siRNA-CD40 group that gave the greatest prevention both in the cellular and humoral arms, perhaps by an additive effect.

Funding: Government Support - Non-U.S.

FR-PO1117

Contrasting Effects of Conventional Immunosuppressants in Establishing Murine Transplantation Tolerance

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Background: Tacrolimus (TAC) is one of the most commonly used calcineurin inhibitors (CNIs) for immunosuppression maintenance after kidney transplantation. It inhibits immune responses by suppressing T-cell receptor signaling and downstream expression of interleukin-2. An inhibitor of the mammalian target of rapamycin (mTOR-I) such as everolimus (EVL) shows immunosuppressive activity by inhibiting other pathways. Since, regulatory t cells (Treg) function depends on interleukin-2 signaling, CNIs could affect their suppressive potentials. However, mTOR-I has a weaker effect on Treg proliferation. We previously reported an approach to induce mixed chimerism by stimulating invariant natural killer T cells with liposomal formation of alpha-galactosylceramide (RGI-2001) and CD40 ligand (CD40L) blockade. We evaluated the impact of TAC or EVL on chimerism establishment and Treg in this regimen.

Methods: Recipient mice were treated with either TAC or EVL from day 1 to day 14 after bone marrow transplantation from donor mice, in addition to the regimen using sublethal irradiation, and a single injection of RGI-2001 and anti-CD40L antibodies. Then, we analyzed the proportion of donor cells and Treg in peripheral blood mononuclear cells. Isolated Treg were co-cultured with the mixture of host T cells and T-activator CD3/CD28 beads. After 4-day culture, the proliferation of responder cells was analyzed.

Results: In immunosuppressive drug-dosing phase, chimerism was comparably enhanced by TAC and EVL. Following drug discontinuation, TAC-treated mice exhibited a gradual decrease in the donor cell proportion. In contrast, EVL-treated mice sustained long-term robust chimerism. Treg of TAC-treated mice showed lower prolifration and low suppressive activity than EVL-treated mice.

Conclusions: TAC negatively impacted the regimen by interfering with Treg proliferation and activation.

Funding: Government Support - Non-U.S.

FR-PO1118

Anti-CD40 (Iscalimab) Treatment Results in Preserved Allograft Histology in Non-Human Kidney Transplantation Compared with Calcineurin Inhibitors

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Background: The CD40-CD154 costimulatory pathway has been implicated in the pathology of transplant rejection, and blockade of this interaction using anti-CD40 antibodies significantly prolongs renal allograft survival in non-human primates (NHPs). Further, recent clinical data indicated that the anti-CD40 mAb Iscalimab (CFZ533) demonstrated comparable efficacy and superior renal function versus tacrolimus in de novo calcineruin inhibitor (CNI)-free kidney transplantation. One possible explanation for superior renal function was that Iscalimab treatment may have resulted in improved graft quality compared to CNIs, a notion supported by data from a small number of patients from the aforementioned clinical study.

Methods: To further examine this notion, allograft histology from baseline and up to one hundred days post-transplanted NHP kidney allografts from transplanted animals treated with Iscalimab, anti-CD154 mAb, Cyclosporine A, PKC inhibitors or FTY720 were reviewed and scored in a blinded fashion by a pathologist according to the Banff classification.

Results: In addition, we performed molecular analyses of these samples. Our analyses indicated that the quality of allografts as defined using total, inflammatory and fibrotic BANFF scores, from Iscalimab treated animals were superior to that observed in animals dosed with all other immunomodulatory and immunosuppressive agents. This was also reflected in the molecular analyses of allograft biopsies showing that CFZ533 was more likely to preserve the gene expression profile of baseline tissue following transplantation compared to other drugs.

Conclusions: Collectively our data indicated that prevention of allograft rejection by Iscalimab appears to be associated with higher graft quality compared to other drugs, including CNIs.

Funding: Commercial Support - Novartis Pharmaceuticals AG

FR-PO1119

T Cell-Specific miR-17-92 Knockout Improved Skin Graft Tolerance by Modulating T Follicular Helper Cell Development and Regulatory T Cell Activity

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Background: T follicular helper (T_{FH}) cell provide crucial growth signals to germinal center (GC) B cells supporting antibody production. Tight control of T_{FH} numbers maintains self-tolerance. Regulatory T (Treg) cells play a critical role in maintaining self-tolerance and controlling the magnitude of physiologic immune response. The Treg transcription factor forkhead box P3 (Foxp3) works in concert with other co-regulator molecules to determine suppressive phenotype of Treg. MicroRNA-17-92 (MiR-17-92) has been shown in our previous study to regulate the suppressive effect of Treg on mice EAE models. The knockout of Mir-17-92 increase the immunosuppressive activity of Treg.

Methods: We generated T cell specific miR-17-92 knockout (miR-17-92-/-) mice, followed by skin transplantation. B6 miR-17-92 -/- and B6 wild type littermates were used as recipients of *BALB/c* skin grafts. By bioinformatics study, possible targets of mir-17-92, related to Treg function was evaluated. In addition, we performed a MLR (mixed lymphoid reaction) by co-culture donor APC with recipient derived T cells.

Results: The sirolimus-treated, miR-17-92 -/- mice showed less TFH cells, less GC B cells and the less plasma cells as compared with those in the sirolimus-treated, wild type mice. Consistent with the reduction germinal center response, skin histological analysis revealed a lower mean histopathology score. Moreover, miR17-92 knockout enhance the suppression function of Tregs. Th1 and Th17 are decreased in the miR-17-92 -/- mice.

Moreover, T cells from miR-17-92 -/- mice demonstrated a donor antigen-specific hyporesponsiveness in vitro MLR.

Conclusions: We found that the skin graft survival was significantly better in the sirolimus-treated, miR-17-92 -/- mice, unveiling the future therapeutic potential of microRNA manipulation in transplantation.

Funding: Government Support - Non-U.S.

FR-PO1120

Examination of a Novel Emerging Immune Checkpoint in Kidney Transplant Recipients

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Background: The balance between T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) and its co-receptor CD226 function as an 'immune checkpoint' with immunomodulatory functions in both T and NK cells. Immunomodulation is mediated through the balance of TIGIT/CD226 binding with the ligands CD155/CD112. Interaction of CD226 with the ligands CD155 and CD112 co-stimulates T cell, whereas TIGIT exerts the opposite effect and inhibits T cell response. This ligand/receptor network plays an important role in various autoimmune diseases and cancer, but its role in transplantation remains unclear. We examined the expression levels of TIGIT, CD226 and their ligands CD155 and CD112 in kidney transplant recipients (KTR) and healthy controls (HC) to understand the relevance of TIGIT/CD226 co-signaling in transplantation.

Methods: Blood samples were collected from 23 HC and 68 KTR and cell surface expression of CD226, TIGIT, CD155 and CD112 and other cell markers on peripheral T and NK cells were determined by flow cytometry.

Results: We observed that in the KTR group both T and NK cell populations showed a significant decrease in TIGIT and an increase in CD226 expression compared to HC. Interestingly, in the KTR $CD4^+$ T cells showed a significant increase in CD226 expression whereas $CD8^+$ T cells showed a significant decrease in TIGIT expression. Both these changes lead to an increase in IFN-γ production and a pro-inflammatory environment. The predominant peripheral $CD16^+$ NK cells also showed an inflammatory phenotype with both increased CD226 expression and decreased TIGIT expression and also showed a significant increase in the expression of both the ligands CD155 and CD112 in comparison to HC.

Conclusions: Increased expression of CD226 in both T and NK cells and increased expression of its ligands CD155 and CD112 on NK cell populations were observed in KTR, suggesting a pro-inflammatory phenotype and a pluasible NK-T cell-cell interaction in the periphery. The TIGIT/CD226 axis members are potential targets for reducing the alloimmune response mediated by T and NK cells.

FR-PO1121

Dissecting the Role of Adipocyte Na-K-ATPase Signaling in Attenuating Experimental Uremic Cardiomyopathy by Adipose Tissue Transplantation

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Background: Adipocytes contribution to systemic disease has become an important topic. We have recently demonstrated that administration of NaKtide, antagonist of Na/K-ATPase (NKA) signaling, coupled to adipocyte specific promoter adiponectin can improve adipocyte phenotype. In experimental uremic cardiomyopathy, uremic toxin exposure of adipocyte will generate ROS, subsequently activating adipocyte NKA signaling and causing adipocyte dysfunction, cytokine production, and systemic oxidative stress. Studies have shown that transplanting brown adipose tissue from C57BL6 mice reduced obesity and improved whole energy metabolism. Based on these observations, we hypothesize that the transplantation of NaKtide transfected subcutaneous fat tissues into mice with partial nephrectomy (PNx) will improve adipocyte phenotype and attenuate uremic cardiomyopathy.

Methods: Following 4 weeks of PNx or Sham surgery and lenti-adiponectin-Naktide treatment, 300mg of fat pads (Sham, Sham+NaKtide, and PNx+NaKtide groups) were subcutaneously transplanted into strain- and age- matched donor littermates in the dorsal interscapular region of PNx mice. Following 4 weeks after transplantation, tissues were harvested for morphological and molecular analyses.

Results: Histological analysis of cardiac tissue shows increased fibrosis with PNx, which was decreased with transplantation of adipose tissue from mice treated with NaKtide ($p \leq 0.01$). PNx mice developed cardiomyopathy characterized by increased heart weight and decreased cardiac function, assessed by echocardiography measurements, as compared to Sham operated mice ($p<0.01$). These alterations were reversed in PNx mice, by the transplantation of NaKtide transfected adipose tissues from PNx+NaKtide donor mice ($p<0.01$). Our results also showed that NaKtide transfected adipose tissue from PNx+NaKtide mice, transplanted to PNx recipient mice improved glucose tolerance, hematocrit levels and levels of plasma inflammatory cytokines, including TNFα, IL-6 and MCP-1.

Conclusions: Our study demonstrates that adipocytes contribute to the oxidant stress associated with uremic cardiomyopathy by activation of NKA signaling, which is improved by the subcutaneous fat transplantation transfected with NaKtide. These data suggest that the adipocyte NKA signaling may be a viable clinical target for the prevention or treatment of uremic cardiomyopathy.

Funding: Other NIH Support - National Institutes of Health Grants HL109015, Private Foundation Support

FR-PO1122

Human Donor-Specific Regulatory T-Cell Line Function Is Mediated Through the Adenosinergic Pathway

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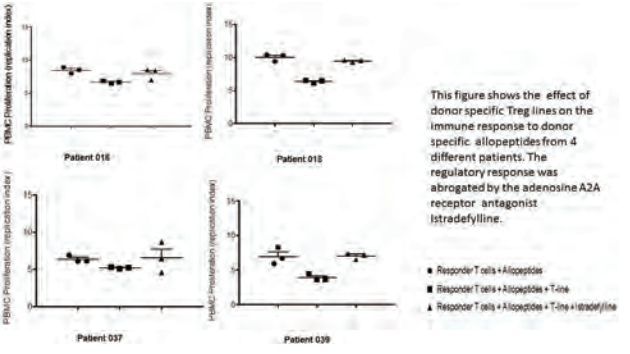
Background: We have previously shown that regulatory T cell lines generated and expanded from transplanted individuals have the capacity to induce longterm allograft survival in an animal model and suppress human donor specific effector T cell responses *in vitro*. In murine models targeting the CD39/73 adenosinergic pathway is associated with long-term graft function and reduced graft versus host disease severity. Little is known about the role of this pathway in human regulatory T cells.

Methods: 45 Kidney transplant recipients were included in the study and 19 T-cell lines were generated from 17 patients by stimulating PBMCs with mismatched donor-derived HLA-DR allopeptides. T-cell lines were immunophenotyped with fluorphore conjugated human anti-CD39 and anti-CD73 and analyzed using Flowjo. Involvement of the adenosinergic pathway by using Adenosine A2A receptor (A2Ar) antagonist.

Results: The functional characterization of the *ex vivo* expanded T-cell lines was determined by assessing their immunosuppressive function to inhibit antigen specific and non specific T cell proliferation. We observed that all *ex vivo* expanded T-cell lines were able to substantially inhibit donor antigen specific T cell proliferation. Expression of both CD39 and CD73 in our T-cell lines, both related to the adenosinergic pathway. Inhibition using the A2Ar antagonist Istradefylline resulted in abrogation of suppression and increase in antigen specific T cell proliferation (Figure).

Conclusions: Our results suggest that the CD39/CD73 adenosinergic pathway is important in the function of regulatory T cells and therapies targeting CD39 and CD73 may enhance human regulatory T cell function.



FR-PO1123

Increased Mitochondrial Metabolic Enzymes Are Associated with Superior Kidney Function After Normothermic Ex Vivo Kidney Perfusion: A Proteomics Study

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Background: Normothermic ex-vivo kidney perfusion (NEVKP) is associated with significantly improved graft function following transplantation in comparison to static cold storage (SCS). We hypothesized that NEVKP would induce key alterations in the kidney proteome compared to SCS, and provide insights into the molecular mechanisms central to superior graft function.

Methods: Porcine kidneys were removed following 30 minutes of warm ischemia, and then subjected to either SCS or NEVKP (n=5 each) for 8 hours prior to auto-transplantation. Kidney biopsies were collected at time zero, upon reperfusion, and at POD3. We conducted an unbiased proteomics analysis by LC-MS/MS on Q-Exactive-Plus mass spectrometer. Subsequent analyses were performed using MaxQuant, Perseus, R, pathDIP, mirDIP, and NaVIGATOR.

Results: Kidney function was significantly improved with NEVKP compared to SCS with higher creatinine clearance on POD3 (F-test, $p < 2.2 \times 10^{-15}$). We identified 6354 proteins in total (FDR<0.01), with 70 proteins significantly differentially expressed between experimental groups and time points (2-way ANOVA, $p<0.05$). Gene ontology and pathway enrichment analyses revealed that the proteins increased in NEVKP were significantly associated with the preservation of metabolic processes such as fatty acid ß-oxidation, the TCA cycle and oxidative phosphorylation (e.g. CPT2, MPC2, ETFB, COX4I1). Additionally, proteins associated with the maintenance of adherens junctions and the actin cytoskeleton (e.g. CGNL1, PDLIM4) were enhanced in NEVKP in contrast to SCS. Proteins increased in SCS were associated with RNA binding and protein translation.

Comparison with external datasets of ischemia reperfusion injury, and datasets relating to other models of acute and chronic kidney injury confirmed that many of the molecular changes observed in these datasets are expected to be reversed or attenuated by NEVKP.

Conclusions: The proteome-level changes associated with NEVKP demonstrate that the preservation of major metabolic pathways, and of cell polarity and integrity may be pivotal mechanisms by which NEVKP results in improved graft function.

FR-PO1124

Role of Interferon-γ Associated Chemokines and FOXP3+ T Cells in BK Virus Nephropathy

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Background: BKV reactivation has been associated with increased expression of interferon-γ (IFNγ) induced chemokines and increased levels of granzyme B, cytotoxic T cell molecule. Histological findings of BK virus nephropathy (BKVN) have been compared to those with acute cellular rejection (ACR) but the role of FOXP3 has not been studied. We hypothesized that heightened expression of IFNγ associated chemokines and lower expression of FOXP3 would be prognostic of 3-year outcomes in BKVN.

Methods: To address this hypothesis, we studied absolute mRNA copies of MIG, IP-10, CD3, granzyme B, FOXP3 and 18SrRNA in biopsy matched urine cell pellets of 53 BKVN and 33 ACR patients using a standard curve method in real-time quantitative PCR assay. Continuous variables were compared using Mann-Whitney test and logistic regression was used to determine if urine mRNAs were predictive of graft loss in BKVN patients.

Results: We found that urinary cell mRNA for interferon-γ inducible chemokines IP-10 was higher and mRNAs for CD3, GB and FOXP3 were lower in BKVN cohort compared to ACR cohort. Ratio of IP-10/CD3 mRNA in urinary cells was significantly higher in BKVN cohort versus ACR cohort. Urinary cell mRNA for IP-10, MIG and GB were associated with increased risk of 3 year graft loss.

Conclusions: We conclude that BKVN is associated with increased levels of IP-10 and lower levels of CD3 as compared to ACR and the ratio of IP10/CD3 mRNA can be used to distinguish inflammation associated with BKVN from that of ACR. Urinary cell mRNA levels of IFNγ associated chemokines are associated with 3-year graft loss.

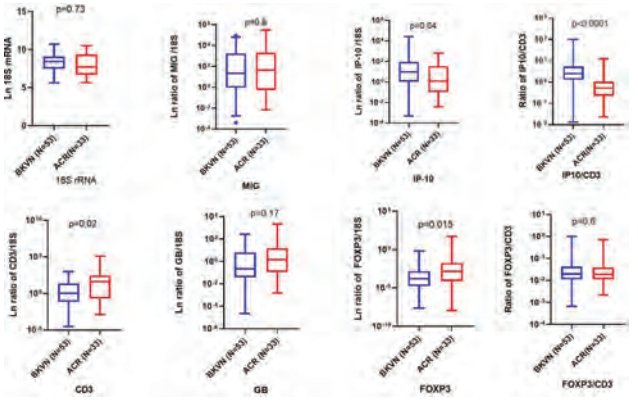

Table 1: Association of urine mRNA profiles with graft loss at 3 years following BKVN

	Odds Ratio	95% CI	P-value
Ln (IP10/18S)	1.55	1.0-2.43	0.04
Ln (MIG/18S)	1.32	1.0-1.81	0.05
Ln (CD3/18S)	1.21	0.84-1.76	0.28
Ln (GB/18S)	1.65	0.94-2.04	0.08
Ln (FOXP3/18S)	1.23	0.81-1.8	0.3

FR-PO1125

Proteomics of Laser-Captured Microdissected Glomeruli and Tubulointerstitium Reveals Extracellular Matrix Remodelling of Kidney Allografts with Antibody-Mediated Rejection

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Background: Kidney transplantation is the optimal treatment for end-stage kidney disease, but most grafts fail prematurely. Antibody-mediated rejection (AMR) accounts for >50% of graft loss. AMR is caused by antibodies against HLA and non-HLA antigens in two main renal compartments: glomeruli and tubulointerstitium. We hypothesized that compartment-specific proteome alterations may uncover the mechanisms of early antibody-mediated injury.

Methods: We performed laser-capture/microdissection to isolate glomeruli and tubulointerstitium from FFPE kidney biopsies, and subjected samples to proteome analysis. We compared 7 biopsies with AMR with 23 matched 'non-AMR' biopsies with T-cell rejection or acute tubular necrosis. Primary human glomerular microvascular endothelial cells (HGMEC) were studied *in vitro*.

Results: We identified 2026 proteins in glomeruli and 2399 in tubulointerstitium (FDR=0.01). 120 proteins were differentially expressed ($p<0.05$) in AMR vs. non-AMR glomeruli and 180 in the tubulointerstitium. Proteins involved in HLA-mediated antigen presentation were increased in AMR. Proteins decreased in AMR were basement membrane components, and belonged to processes such as extracellular matrix (ECM) and cytoskeleton. Reduced glomerular protein levels of LAMC1, NPHS1, and PTPRO in AMR was verified by immunostaining. Levels of ECM proteins correlated directly and significantly ($R>0.7$; $p<0.05$), suggesting co-regulation in AMR. Protein expression of CCT8 (cytoskeleton dynamics) and CALU (protein folding) significantly and directly correlated with histological features of AMR, namely glomerulitis and peritubular capillaritis ($q=0.017$). Protein-protein interaction and pathway analysis of our glomerular protein signature revealed enrichment of inflammatory pathways, such as IL-8 signaling. Stimulation of HGMECs with anti-HLA class I antibody increased the secretion of IL-8 and MCP-1 cytokines.

Conclusions: Basement membranes are often remodeled in late chronic AMR and are the targets of non-HLA antibodies, suggesting that our findings may represent early, important alterations in AMR. Targeting early ECM changes in AMR may represent a new therapeutic opportunity.

Funding: Government Support - Non-U.S.

FR-PO1126

A Proteomic Atlas Depicting the Changes in Small Urinary Extracellular Vesicles Throughout Kidney Transplantation

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Background: Extracellular vesicles (EVs) have come into the research focus of many life sciences. Urinary EVs, specifically since they can be collected noninvasively, hold the prospect of harboring valuable biomarkers to complement renal biopsies. We aimed to establish a concise atlas of the urinary EV protein content and its changes during living donor transplantation as a resource for the investigation of biological processes and biomarker identification.

Methods: We employed a protocol of differential highspeed- and ultracentrifugation for the separation of small urinary EVs (suEVs) of 22 recipient-donor pairs collected on day -1 (donor sample), 0, 1 as well as 3 and 12 months after transplantation (recipient samples). Quantitative mass spectrometry was used to detect the suEV proteome with subsequent GO analysis to define the involved and changing biological processes. We used linear regression models to correlate the proteomic data set with transplant function 6 and 12 months after transplantation. The resulting candidate proteins were validated in a targeted proteomic analysis of additional 22 recipient-donor pairs sets.

Results: More than 1700 unique proteins were identified in ≥50% of the initial sample set. The single samples depicted a clear clustering by time point of urine collection with specific proteomic time course patterns apparent over the course of transplantation when analyzing the mean protein intensities per time point. Specifically, we detected a decrease in membrane trafficking and increased complement components directly after transplantation. Linear regression models identified a list of 64 candidate proteins with a correlative potential for renal function (eGFR) 6 and 12 months after transplantation. The performed validation experiments showed the abundance of one protein - PEPCK – to be a potential predictor of allograft eGFR after 12 months.

Conclusions: We present the first concise atlas of the changes in the human suEV proteome throughout living donor kidney transplantation. This data set serves as a valuable resource for the investigation of both the biological processes affected by renal transplantation and the identification of potential biomarkers as indicated by our first correlation analyses.

Funding: Government Support - Non-U.S.

FR-PO1127

DNA Methylation Profiling Reveals Epigenetic Differences Before and After Acute Rejection-Induced Allograft Dysfunction

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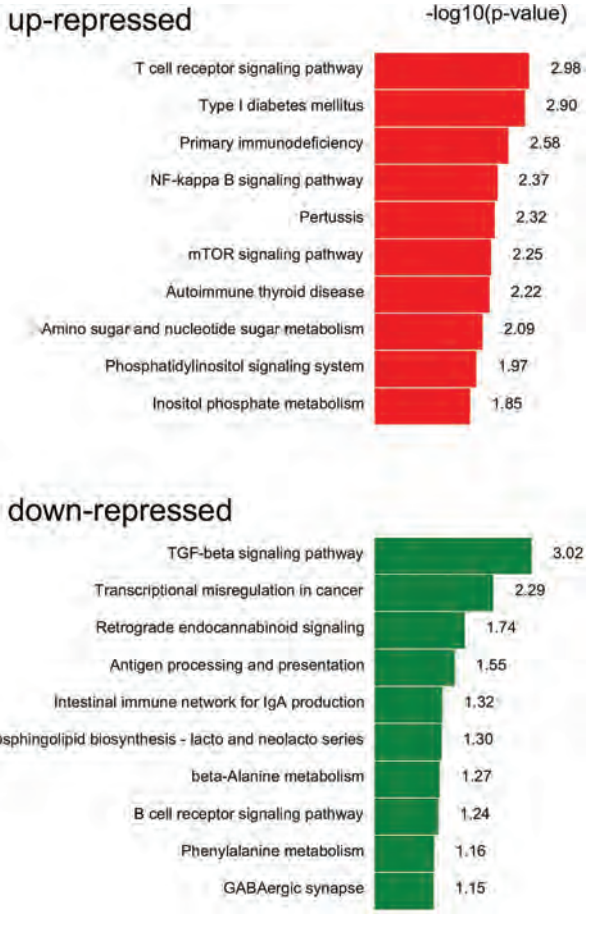
Background: The incidence of acute rejection (AR) has declined to <15% in the first year after renal transplantation but remains a risk factor for allograft nephropathy and determination of allograft fate. DNA methylation regulates gene expression and persists after removal of the stimulus. Here, we analyzed dynamic changes in the methylation landscapebefore and after AR-induced allograft dysfunction.

Methods: In this two-cohort study, we followed-up with identical patients who successively experienced end-stage renal disease, renal transplantation with allograft function or dysfunction, and final hemodialysis. Peripheral blood mononuclear cells from the same patients were collected at different time points and used for mircoarray analysis of changes in DNA-methylation status.

Results: In contrast to the allograft-stable cohort, AR accelerated changes in DNA-methylation patterns. Pathway analysis revealed that hypermethylated areas associated with genes were related to T cell receptor, nuclear factor-kappa B, and mammalian target of rapamycin signaling in the AR-induced allograft-dysfunction group, which differed from pathways associated with hypomethylated areas. Moreover, AR altered the methylation status of genes related to epigenetic modification, and in a mouse model of AR, the DNA-methyltransferase inhibitor decitabine ameliorated renal allograft-related inflammatory injuries by enhancing regulatory T cell activities through inhibiting DNMT1 and suppressing T helper 1/2/17.

Conclusions: These results revealed that AR after renal transplantation reshapes the DNA-methylation landscape, with hypermethylated genes associated with AR, and suggested inhibition of DNA methylation as a potential therapeutic approach for AR after organ transplantation to improve allograft survival.

Funding: Government Support - Non-U.S.



FR-PO1128

Calcium Release-Activated Calcium (CRAC) Channel Inhibitor BTP2 Blocks IL2 and CD25 Expression in Human Peripheral Blood Mononuclear Cells

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Background: CRAC channels are essential for the signaling of cells via calcineurin. BTP2, a tri-fluoro methyl pyrazole has been found to be a selective blocker of CRAC channels, prevents calcineurin activation and subsequent import of dephosphorylated NFAT into the nucleus in cell lines. In a search for a new type of calcineurin inhibitor, we investigated whether BTP2 inhibits calcineurin activation dependent expression of IL-2 and IL-2R alpha (CD25) by normal human peripheral blood mononuclear cells (PBMC).

Methods: PBMC isolated from healthy volunteers (N=4), were incubated alone, with 2ug/ml phytohemagglutinin (PHA) or with PHA + 1000nM BTP2 for 16 hours at 37C in 5% CO2. The cells were retrieved and analyzed by two methods: (i) Single cell Flow cytometry by labelling the cells with CD3-PE and CD25-FITC antibodies and (ii) Pre-amplification enhanced real time quantitative PCR (RT qPCR) to quantify the absolute copy numbers of mRNA encoding IL2 and CD25.

Results: BTP2 was a potent inhibitor of PHA induced expression of IL2 mRNA (Figure 1) and CD25 mRNA (Figure 2). In accord with its effect on CD25 mRNA, BTP2 inhibited the induced expression of CD25 protein as assessed at the single cell level by flow cytometry (Figure 3A & 3B).

Conclusions: To date, the effect of CRAC channel blockade with BTP2 has been studied in rat models and cell lines. We established normal human PBMC cell culture to investigate the effect of BTP2 and demonstrate that BTP2 reduced IL2 and CD25 expression in human PBMC. These inhibitory effects would effectively block T cell clonal expansion, a prerequisite for allograft rejection. CRAC channel blockade represents a novel strategy for immunosuppression.

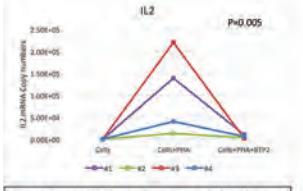

Figure 1: BTP2 inhibits PHA-induced expression of IL-2 mRNA. X-axis: Test conditions; Y-axis: mRNA copy number per microgram of RNA. P value calculated using Friedman test

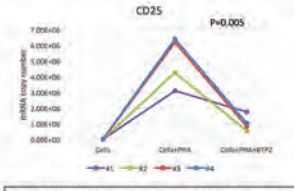

Figure 2: BTP2 inhibits PHA-induced expression of CD25 mRNA. X-axis: Test conditions; Y-axis: mRNA copy number per microgram of RNA. P value calculated using Friedman test

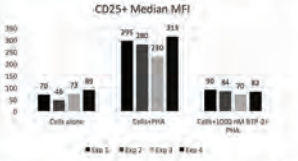

Figure 3A: BTP2 inhibits PHA-induced expression of CD25 protein. X-axis: Test conditions; Y-axis: Median fluorescence intensity (MFI) of CD25+ cells.

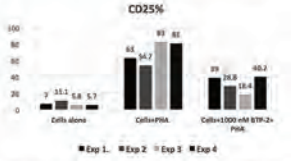

Figure 3B: BTP2 inhibits PHA-induced expression of CD25 protein. X-axis: Test conditions; Y-axis: Percentage of CD3+ cells positive for CD25 protein.

FR-PO1129

AKI in Renal Transplant Recipients Undergoing Cardiac Surgery

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Background: Acute kidney injury (AKI) is a key risk factor for chronic kidney disease in the general population, but few studies have assessed AKI among renal transplant recipients (RTRs). Moreover, most studies of AKI among RTRs focused on AKI occurring in the immediate peri-transplant period, included heterogenous (or unknown) causes of AKI, and relied on diagnostic/billing codes rather than granular patient-level data. We conducted a detailed investigation into the incidence, severity, and risk factors for AKI following cardiac surgery among RTRs.

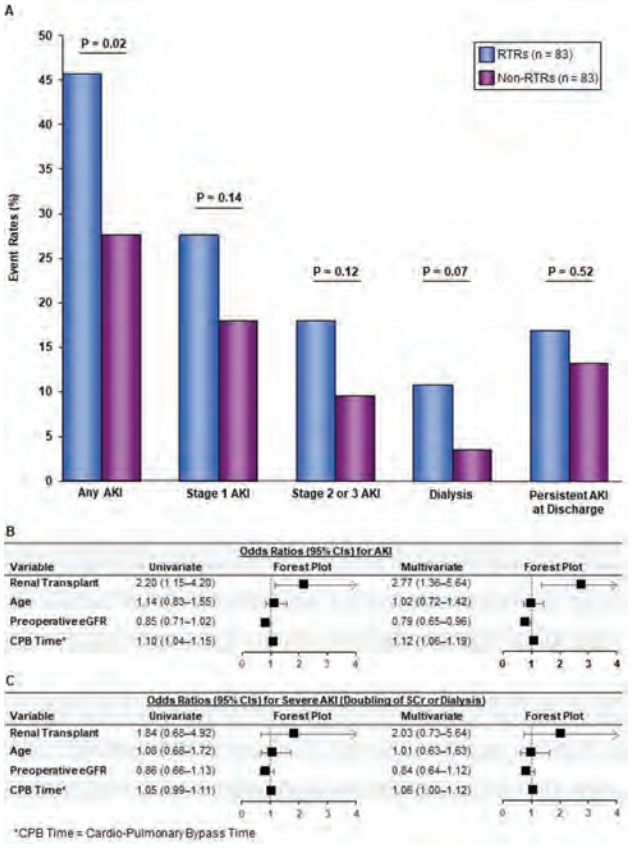
Methods: We queried electronic medical records of >20,000 cardiac surgeries at two major academic medical centers in Boston, MA, from 2005-2018. We identified 83 RTRs and matched them 1:1 to non-RTRs by age, preoperative eGFR, and type of surgery. We used multivariable logistic regression to adjust for potential confounders. AKI and its severity were defined according to KDIGO criteria.

Results: RTRs had a higher rate of AKI following cardiac surgery compared to non-RTRs (46% vs. 28%; adjusted OR 2.77 [95% CI, 1.36 to 5.64]). Among RTRs, deceased donor (DD) vs. living donor (LD) status, as well as higher vs. lower preoperative calcineurin inhibitor (CNI) trough levels, were associated with higher rates of AKI (57% vs. 33% for DD-RTRs vs. LD-RTRs, P=0.03; 73% vs. 36% for RTRs with higher vs. lower CNI trough levels, P=0.02). The combination of both risk factors (DD status and higher

CNI trough level) had an additive effect (88% AKI incidence among patients with both risk factors vs. 25% incidence among RTRs with neither risk factor, P=0.004).

Conclusions: RTRs have a higher risk of AKI following cardiac surgery compared with non-RTRs with otherwise similar characteristics. Among RTRs, DD-RTRs and those with higher preoperative CNI trough levels are at highest risk.

Funding: NIDDK Support



FR-PO1130

Transcatheter vs. Surgical Aortic Valve Replacement in US Renal Transplant Patients

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Background: Renal Transplant (RT) patients are a high risk group for surgical aortic valve replacement. Few data exist on the comparative outcome of renal transplant patients with aortic stenosis receiving transcatheter (TAVR) vs. surgical (SAVR) aortic valve replacement.

Methods: The CMS 100% ESRD files from 2013-2015 were used to find RT patients receiving TAVR or SAVR, and to compare inpatient death and adjusted 1-year mortality. The cohort comprised patients receiving TAVR or SAVR 1/1/2013-12/31/2014. Patients with endocarditis or multivalve SAVR were excluded. A six-month period prior to the valve replacement procedure was used to assess comorbidity from claims. Post-discharge mortality rates were estimated and Cox proportional hazards models were used to compare post-discharge 1-year mortality, adjusting for patient characteristics and comorbidity.

Results: (Table 1) Of the 303 RT patients receiving aortic valve replacement, 73.3% received SAVR and 26.7% TAVR. TAVR patients were more likely to be older, male, with a higher comorbidity burden. TAVR patients experienced lower inpatient mortality (3.7% vs. 5.4% for SAVR). The post-discharge one year mortality rate was 30.2/100 pt-yrs for TAVR and 12.4/100pt-yrs for SAVR. For those patients discharged alive, the adjusted hazard ratio for one year mortality (TAVR vs SAVR) was 1.1(95% CI, 0.5-2.2).

Conclusions: RT patients undergoing TAVR have lower in-hospital mortality compared to SAVR, but higher post-discharge mortality rate. After adjustment for comorbidity, the hazard ratio for one year mortality is similar for TAVR vs SAVR in RT patients undergoing TAVR and SAVR in 2013-2014. Future studies comparing TAVR to SAVR in the more recent treatment era are warranted.

Funding: Private Foundation Support

N = 303	SAVR (%)	TAVR (%)
Overall	73.3%	26.7%
Female	36.5%	29.6%
Cause of ESRD = DM	25.2%	37.0%
White	80.6%	81.5%
Black	15.3%	16.1%
ASHD	76.1%	92.6%
CHF	53.2%	86.4%
PVD	35.6%	67.9%
COPD	17.1%	34.6%
GI	7.7%	7.4%
Liver disease	5.4%	9.9%
Dysrhythmia	68.0%	75.3%
Cancer	6.8%	4.9%
DM	55.0%	75.3%
Mean age	66.7	72.9
Inpatient death	**5.4%**	**3.7%**
Adjusted HR for 1-yr mortality (HR, 95% CI)	**1.0**	**1.1 (0.5-2.2)**
Post-discharge 1-year mort rate per 100 PY	**12.4**	**30.2**

Table 1. TAVR vs. SAVR, Transplant Patients

FR-PO1131

Development and Validation of a Risk Score for the Prediction of Cardiovascular Disease in Kidney Transplant Recipients

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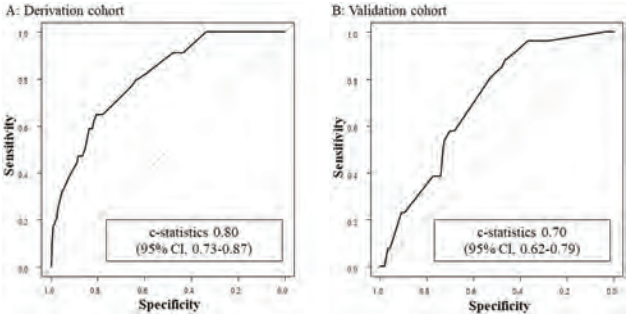
Background: Cardiovascular disease (CVD) is a major cause of death in kidney transplant (KT) recipients. It is clinically important to estimate the risk of CVD after a KT.

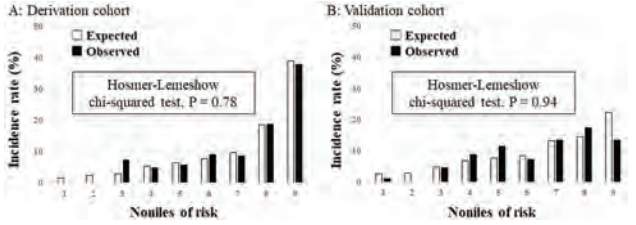
Methods: A derivation cohort contained 387 KT recipients underwent KT at Kyushu University Hospital from January 2006 to December 2012. A prediction model was retrospectively developed and risk scores for CVD were investigated via multivariable logistic regression. The internal validation of the prediction model was estimated via the c-static and the external validation was calibrated via the Hosmer-Lemeshow goodness of fit test using a validation cohort containing 332 KT recipients underwent KT at Tokyo Women's Medical University Hospital.

Results: In derivation cohort 34 patients (8.8%) had CVD events during the observation period. Age, CVD history, diabetic nephropathy, dialysis vintage, and serum albumin at 12 months after KT were significant predictors of CVD. A prediction model consisting of integer risk scores demonstrated good discrimination (c-statistic 0.80) and goodness of fit (Hosmer-Lemeshow test P = 0.78). In a validation cohort containing 332 KT recipients the model demonstrated moderate discrimination (c-statistic 0.70) and goodness of fit (Hosmer-Lemeshow test P = 0.94), suggesting external validity.

Conclusions: This simple model for predicting CVD after kidney transplantation was moderately accurate and useful in clinical situations. In also suggested that nutritional status was an influential risk factor for CVD in KT recipients.



The receiver operating characteristic curves plotted by the prediction model



The observed and expected incidence rates by the simple prediction risk score

FR-PO1132

Cardiovascular Disease After Kidney Transplantation: A Nationwide Study in South Korea

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Background: Cardiovascular disease (CVD) is the most common cause of death in end-stage renal disease (ESRD). Kidney transplantation (KT) is an effective treatment for ESRD, and is known as lowering risk for CVD compared to the ESRD patients on the transplantation waiting list. However, there is a lack of large-population studies especially for Asians.

Methods: We analyzed the nationwide health insurance database of South Korea and identified patients who received kidney transplantation from the year of 2007 to 2015. Patients who were under 20 years of age, had previous CVD identified, or had multiorgan transplantation were excluded from the study. As controls, ESRD and GP groups were extracted after same exclusion and matching with KT recipients by age, sex, and inclusion year. CVD was defined as major cardiovascular events (MACEs) consisted of myocardial infarction, ischemic stroke, and all-cause mortality.

Results: During the study period, a total of 13,179 patients received KT. After exclusion, 4,156 KT recipients were selected. The same number of ESRD and GP control were extracted after matching. Mean age was 41.3 ± 10.2 years and 55.2% were men in all 3 groups. KT recipients had similar proportions of diabetes and hypertension and a lower proportion of dyslipidemia compared with ESRD controls, although significantly higher co-morbidities than GP controls. The total number of MACEs was 76 (3.7 per 1000 person-year) in KT recipients, 377 (21.7 per 1000 person-year) in ESRD, 51 (2.5 per 1000 person-year) in GP, respectively. KT recipients showed a significantly lower MACE risk (adjusted HR 0.16, 95% CI 0.12-0.20, p <0.001) than ESRD controls. And the MACE risk were not significantly different between KT recipients and matched GP controls (adjusted HR 0.81, 95% CI 0.52-1.27, p=0.365). When subgroup analysis of age, sex, diabetes and hypertension was performed, similar trends were observed regardless of subgroups.

Conclusions: In this study, we found that the KT recipients had a lower risk of newly onset MACE after transplantation compared to patients maintaining dialysis in Korea, and showed a similar MACE risk compared to the general population.

FR-PO1133

Pre-Transplant Body Mass Index as a Risk for Late Post-Kidney Transplant Hypertension: A Propensity Score Weighting

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Background: Body mass index (BMI) at the time of kidney transplantation (KT) is associated with post-transplant hypertension (HTN). However, imbalance between comparison groups can distort the result.

Methods: Kidney transplant recipients from a single center were divided into obesity and non-obesity with BMI < or≥30 kg/m^2, respectively. Baseline pre-transplant characteristics of both groups were balanced by propensity scores (PS) with weighting method leading to new study populations. Association between BMI and post-transplant systolic (SHTN) and diastolic HTN (DHTN) defines as systolic (SBP) and diastolic blood pressure (DBP) of ≥130 and 80 mmHg, respectively at 1.5 year among this new study population was examined by multiple logistic regression.

Results: Of all 70 patients, mean age±SD was 52.7±11 years old, 58.6% were male, and 31% were obese. Mean BMI was significantly higher in obese than non-obese groups (34.1±3.8 vs 24.7±3.4, mean difference 9.4, 95% CI 7.5, 11.3). Several baseline characteristics between 2 groups are different. After using PS weights with generalized boosted modeling to balance covariates (Figure 1), obese group has 7.09 and 9.21 times higher the odds of having SHTN and DHTN, respectively compared to non-obese group (SHTN: OR 7.09; 95% CI 1.19, 42.17; DHTN: OR 9.21; 95% CI 2.13, 39.77). After adjusted for race, age, gender, type of induction immunosuppression, type of KTx, the association remains (SHTN: OR 5.53; 95% CI 4.12, 741.02; DHTN: OR 12.32; 95% CI 2.23, 68.15).

Conclusions: With PS as a balancing method to examine inference, pre-transplant obesity remains one of the risks for post-transplant HTN. Pre-transplant weight should be controlled to mitigate poorer transplant outcomes.

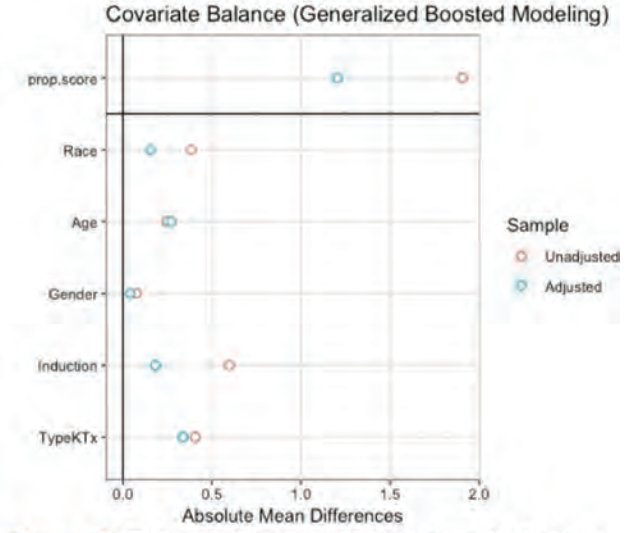

Figure 1: Estimated propensity score weights using generalized boosted modeling

FR-PO1134

Renal Graft Resistivity Index Utility in Cardiovascular Risk (CVR) Evaluation in Long-Term Kidney Transplant Recipients (KTR)

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Background: Intra-renal graft resistivity index (RI) is an echographic measure widely used as early dysfunction marker in renal transplant (RTs). Associated factors with this index as a prognostic, outcome and patient survival are controversial. Our aim is to analyse the relationship between the RI with renal outcomes, clinical variables and cardiovascular risk (CV).

Methods: This observational study enrolled 220 stable RTs were (134 M & 86 W; Mean age 56±13.1 yo, 34% DM, 15% previous CV events), CKD stages 1-4 & more than 12 months after transplantation. Immunosuppression (IS) included anticalcineurin/mTOR with Mycophenolate Mofetil, besides steroid therapy. Variables studied: Diabetes Mellitus (DM), CV diseases history, ankle-brachial index, 24h-ABPM, anthropometric & nutritional measurements (including handgrip); as well as biochemistry parameters: hemoglobin, albumin, transferrin, creatinine, GFR estimated by CKD-EPI formula, urinary albumin/creatinine ratio (UACR), calcium, phosphorus, PTHi, vitamin D & C reactive protein. Cardiovascular risk was assessed by REGICOR equation. RI was measured by Echo-Doppler US following the standard of care technique being RI ≥0.8 as pathologic

Results: 28% showed a pathologic RI. The univariable analysis showed a significant correlation IR with age (r=0.40, p<0.01) Higher in diabetic population (0.81±0.09 vs 0.73±0.10) without influenced by IS treatment. A significative negative correlation was evidenced with diastolic arterial pressure, as well as daytime (r=-0.35) as nocturnal (r=-0.23). A positive significant with a number of antihypertensive drugs (r=0.23). Also, GFR-EPI (r= -0.27) and UACR (r= 0.21) were significant as well. Bone mineral markers PTHi (r=0.18) & P (r=0.28) were positively related to RI, meanwhile Hb (r=-0.22), albumin (r=-0.16), transferrin (r=-0.15) and dynamometry (r=-0.21) shown negative correlation. Ankle-brachial index (ABI) and REGICOR equation (r=0.18) showed also significance. Multivariable adjustments, only age and DM hold a significant relationship with RI

Conclusions: Although RI is related to functional graft factors, factors depending on RTs as age and diabetic status appear more relevant. RI may express the subclinical atheromatosis status, related to CV risk in RTs, that with the renal function itself.

FR-PO1135

Detection of BK Virus in Renal Allograft Biopsies by RNA In Situ Hybridization RNAscope® Assay

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Background: BK polyomavirus associated nephropathy (BKpyVAN) remains a cause of graft loss in kidney transplant recipients on immunosuppressive therapy, and its diagnosis relies on identification of BK virus in the renal allograft biopsy based on positive immunohistochemical stain for the viral SV40 large-T antigen. Real time PCR (qPCR) and in situ hybridization (ISH) for BKv DNA can also be used to identify BKv in kidney tissue. Aim of this study was to evaluate RNAscope®, a novel-next generation technique for in situ hybridization with probes designed to increase the signal-to noise ratio to visualize RNA transcripts, for the detection of BKv RNA in allograft biopsies.

Methods: SV40 IHC stain (Santa Cruz, Ventana System) and RNAscope® ISH (following Advanced Cell Diagnostics manufacturer protocol), were performed on serial paraffin embedded tissue sections of kidney allograft biopsies. The number of tubules showing positive SV40 nuclear staining was compared to the number of tubules showing positive RNAscope® ISH signal in each biopsy (paired, 2 sides t-test, linear regression, Pearson).

Results: From 2010 to 2018, a diagnosis of BKpyVAN was made on 32 allograft biopsies from 30 renal transplant recipients (66% Caucasian, 58% male, average age at biopsy 54 ± 13 years). Median time of diagnosis post-transplant was 366 days (range 21-1577), median serum creatinine at diagnosis was 1.6 mg/dl (range 0.84-3.48 mg/dl), range BKv viremia levels: <201 – 1,270,000 DNA copies. We excluded 3 biopsies with equivocal SV40 stain, low BKv viremia (296 and 2830 DNA copies) and negative RNAscope® ISH. Three biopsies from 2 patients with high BKv viremia (>100,000 DNA copies), basophilic inclusion, negative SV40, showed positive staining by RNAscope® ISH in more than 50 tubules. In the remaining 26 biopsies with BKpyVAN there was no significant difference (P=0.207) in the average number of BKv-positive tubules detected by SV40 (26 ± 33) or RNAscope® ISH (21 ± 44), with good correlation between the two methods (r^2=0.798, P<0001). Weak correlation was seen between the level of BK viremia and the number of positive tubules detected by either SV40 (r^2=0.250, P=0.012) or RNAscope® ISH (r^2=0.255, P=0.014).

Conclusions: Our data suggest that RNAscope® ISH may be comparable to SV40 for detection of BKv in renal allograft biopsies.

FR-PO1136

Assessment of the Banff Working Group Classification of Definitive BK Polyomavirus Nephropathy

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Background: The Banff Working Group on Polyomavirus Nephropathy (PVN) proposed a classification of definitive PVN based on polyomavirus replication/load level and the extent of interstitial fibrosis. This study is to test the classification using independent cohorts of patients with PVN in renal allograft biopsies, and to analyze the significance of other variables that may play a role in the outcome of PVN, namely presence of tubular basement membrane deposits (TBMD) and peak level of plasma BK particles by PCR.

Methods: Four institutions participated in this study. Patients with kidney allograft biopsy-proven PVN with at least 24 months follow up were identified. Clinical data was captured and biopsies were scored according to the Banff PVN classification. Statistical analysis was performed using multivariable logistic regression and analysis of covariance (ANCOVA) to assess dichotomous and continuous outcomes, respectively.

Results: 145 patients met the criteria for the study. 25 (17%) biopsies were classified as Class 1; 97 (68%) as Class 2; and 20 (14%) as Class 3. Baseline serum creatinine (Scr) levels were elevated and similar regardless of class, with Class 1 mean 1.78 mg/dl, Class 2 1.62 mg/dL, and Class 3 1.78 mg/dL. At the time of diagnostic biopsy the median change in Scr was parallel across classes of PVN (increase in Scr 0.60, 0.52, and 0.60 respectively, p=0.57). At 24 months, median Scr change from baseline increased numerically, as also seen in previous reports (increases 0.45, 0.75 and 1.2, p=0.29). In this cohort overall graft failure was 22% (compared to 30% previously reported), and was equally distributed amongst classes (25%, 20% and 25%). TBMD were found in a subset of all PVN classes (10%, 10% and 20%), and were associated with a trend toward worse outcomes (p=0.15). The highest mean number of plasma BK particles was seen in PVN Class 3, but was not statistically different from other classes.

Conclusions: The proposed classification of PVN is promising for evaluation of allograft biopsies; however, the classes do not stratify and identify patients at increased risk of allograft loss. Additional parameters need to be identified to determine risk for adverse allograft outcome.

FR-PO1137

The Incidence of BK Viremia Among Recipients Who Received Kidney Transplants (KT) from Hepatitis C-Infected and Uninfected Donors

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Background: Our previous data showed KT from hepatitis C virus(HCV) infected donor to non-infected recipients might be associated with higher incidence of BK viremia.

Methods: One hundred and ninety-two deceased KT recipients (74 HCV infected(D+/R-) and 55 HCV negative (D-/R-) donor) to HCV negative recipients were included. Outcome was defined as time to incidence BK viremia which 1)was detectable in blood specimen by PCR (BK viremia;n=21), 2)was greater than 10,000 copies/mL (high BK viremia;n=9). We performed time to event analysis from KT to 120 days after KT with unadjusted and thymoglobulin dose adjusted Cox regression model.

Results: The mean age at KT was 52±11 years old and 80% were African-American. Table shows the baseline characteristics of HCV D+/R- and D-/R- groups. The median number of the highest viral copies was tended to be 5-fold higher in HCV D+/R- group (median:19,632; interquartile range (IQR):2,329-303,823 copies/mL) than D-/R- group (median:4,356; IQR:2,931-15,219 copies/mL,p=0.45). Figure shows the probability of the (high) BK viremia over the follow-up time. Compared to D-/R-, HCV D+/R- group reported similar probability of BK viremia in unadjusted (Hazard Ratio(HR):1.32, 95% Confidence Interval(CI):0.54-3.19) and adjusted (HR:1.28, 95%CI:0.52-3.13) model, a trend for higher risk for high BK viremia unadjusted (HR:2.87, 95%CI:0.60-13.8) and adjusted (HR:2.68, 95% CI:0.56-12.9) Cox regression model.

Conclusions: HCV D+/R- KT was not associated with higher incidence of BK viremia and showed trend for higher incidence of BK viremia.

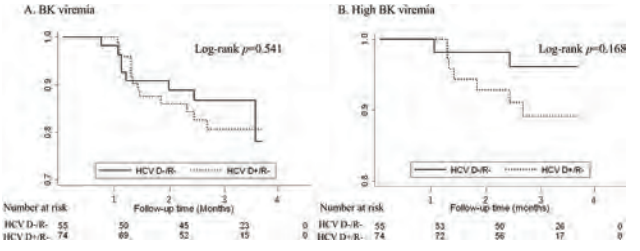

Figure 1

Table 1. Baseline characteristics of the entire cohort and comparison between HCV D+/R- and D-/R- groups

	Entire cohort N=129	HCV D+/R- group N=74	HCV D-/R- group N=55	p value
Recipient information				
Age, years, mean±SD	52.3±11.2	52.5±11.0	52.2±11.6	0.901
Sex, male, n (%)	73 (56.6)	46 (62.2)	27 (49.1)	0.139
BMI, kg/m^2, mean±SD	28.5±7.1	28.4±8.3	28.6±5.3	0.879
Race, n (%)				0.585
African American	103 (79.8)	60 (81.1)	43 (78.2)	
Caucasian	25 (19.4)	13 (17.6)	12 (21.8)	
Cause of ESKD, n (%)				0.123
Hypertension	55 (42.6)	32 (43.2)	23 (41.8)	
Diabetes	46 (35.7)	25 (33.8)	21 (38.2)	
Glomerular nephritis	16 (12.4)	13 (17.6)	3 (5.5)	
Comorbidity-Hypertension, n (%)	127 (98.4)	73 (98.6)	54 (98.2)	0.832
Comorbidity-Diabetes, n (%)	59 (45.7)	36 (48.6)	23 (41.8)	0.441
Dialysis duration before transplantation, months, median (IQR)	62.1 (41.5, 87.5)	53.8 (32.9, 74.8)	73.8 (51.4, 99.1)	0.004
cPRA, %, median (IQR)	1 (0, 70.0)	0 (0, 32.0)	23.0 (0, 98.0)	0.010
CIT, minutes, median (IQR)	1095 (775, 1312)	1168 (969, 1404)	918 (544, 1218)	<0.001
Delayed graft function, n (%)	14 (10.9)	8 (10.8)	6 (10.9)	0.986
Total dose of thymoglobulin, g, mean±SD	4.9±1.0	4.8±0.8	5.2±1.2	0.033
Donor information				
Age, years, mean±SD	33.5±9.2	32.0±5.4	35.5±12.4	0.030
Gender, male, n (%)	74 (57.4)	44 (59.5)	30 (54.5)	0.724
Donor Race, n (%)				0.804
Caucasian	106 (82.2)	70 (94.6)	36 (65.5)	<0.001
African American	19 (14.7)	0	19 (34.5)	
Donation after cardiac death, n (%)	17 (13.2)	7 (9.5)	10 (18.2)	0.148
KDPI, %, mean±SD	45.6±18.8	51.0±15.6	38.3±20.5	<0.001

Abbreviations: HCV: Hepatits C; D: Donor; R: Recipient; BMI: Body mass index; ESKD: End-stage kidney disease; cPRA: Calculated panel reactive antibody; CIT: Cold ischemic time; KDPI: Kidney Donor Risk Index

FR-PO1138

Nocardiosis in Renal Transplant Patients

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Background: Kidney transplant (Tx) patients are chronically immunosuppressed and are at increased risk for opportunistic infections, including the gram positive rod *Nocardia*. Nocardiosis is rare, with an incidence of 0.4%-3.6% in solid organ Tx recipients. The disease is difficult to diagnose, and targeted therapy is required for treatment. In kidney Tx patients specifically, information on the incidence and risk factors for *Nocardia* infection

is limited. To address this issue in a large at-risk population, we utilized the United States Renal Data System (USRDS) to investigate the incidence and risk factors for *Nocardia* in over 200,000 kidney Tx patients. Sequelae of allograft failure or rejection after infection was also examined.

Methods: Demographics, clinical risk factors, *Nocardia* diagnosis, and allograft failure following *Nocardia* infection were queried in kidney Tx patients from the USRDS using ICD-9 codes and CMS Form 2728. Generalized linear models incorporating the number of person years at risk were used to examine risk factors for *Nocardia* and the adjusted relative risks (aRR) and 95% confidence intervals were determined.

Results: We queried 203,233 kidney Tx patients and 657 (0.32%) were diagnosed with *Nocardia.* Pneumonia was the most frequent presentation (15.2%) followed by brain abscess (8.4%). Factors that increased the risk for *Nocardia* included granulomatous disease (aRR=7.65), history of allograft rejection (4.82), tacrolimus use (2.45), and age > 65 years (2.11). Azathioprine use (0.73), hepatitis C (0.56) and tobacco use (0.74) were associated with decreased risk. Patients with nocardiosis had associated high percentages of graft failure (67.28%) and kidney rejection (60.58%).

Conclusions: In this large kidney Tx population, nocardiosis affected 0.3% of patients and presented most often as pneumonia or brain abscess. A history of granulomatous disease, allograft rejection, and tacrolimus use increased the risk for infection, presumably due to higher rates of immunosuppression associated with these comorbid events. This study may improve early recognition of nocardiosis in kidney Tx patients.

FR-PO1139

Cytomegalovirus Prevention Strategies and the Risk of BK Polyomavirus Viremia and Nephropathy

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Background: Polyomavirus BK (BKV) is the cause of polyomavirus-associated nephropathy resulting in premature graft loss. There are limited data regarding the role of cytomegalovirus (CMV) infection and its prevention in developing BKV viremia and PVAN.

Methods: In a prospective study, we analyzed 207 consecutive renal transplant recipients previously enrolled to 2 randomized trials evaluating different CMV prevention regimens with routine screening for BKV and CMV. Of these, 59 received valganciclovir and 100 valacyclovir prophylaxis, 48 patients were managed by preemptive therapy.

Results: At 3 years, the incidence of BKV viremia and PVAN was 28% and 5%, respectively. CMV DNAemia developed in 55% and CMV disease in 6%. Both BKV viremia (42% vs. 23% vs. 21%, P=0.006) and PVAN (12% vs. 2% vs. 2%, P=0.011) were increased in patients treated with valganciclovir prophylaxis compared to valacyclovir and preemptive therapy. Using multivariate Cox proportional hazard regression, valganciclovir prophylaxis was independent predictor of BKV viremia (hazard ratio [HR]=2.38, P=0.002) and PVAN (HR=4.73, P=0.026). In contrast, the risk of subsequent BKV viremia was lower in patients with antecedent CMV DNAemia (HR=0.50, P=0.018).

Conclusions: These data suggest that valganciclovir prophylaxis is associated with increased risk of BKV viremia and PVAN. CMV DNAemia did not represent a risk for BKV.

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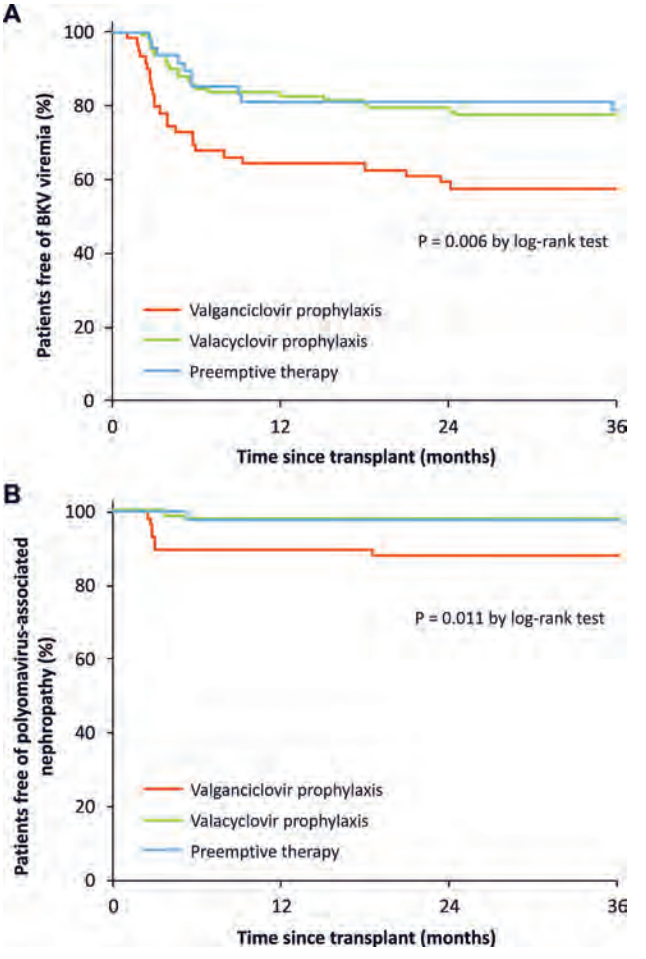

Kaplan-Meier curves for the cumulative probability of freedom from (A) polyoma BKV viremia, and (B) polyomavirus-associated nephropathy based on cytomegalovirus prevention strategy. BKV, polyomavirus BK.

FR-PO1140

Serum Albumin Levels Prior to Kidney Transplant Predicts Post-Transplant BK and Cytomegalovirus Infections

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Background: Post-transplant Infections are a common cause of morbidity and mortality in kidney transplant recipients (KTRs). Prior studies have shown that pre- and post-transplant hypoalbuminemia are associated with graft failure and all-cause mortality. Others suggested that low post-transplant albumin is linked to cytomegalovirus (CMV) infections. These studies suggest serum albumin levels could indicate post-transplant infection risks. Our study evaluated the association between pre-transplant serum albumin and post-transplant BK Virus (BKV) and Cytomegalovirus (CMV) infections in KTRs.

Methods: We used our university database to identify adult KTRs transplanted between 01/01/2005 and 12/31/2015. All subjects had serum albumin measured within 45 days before the transplant. We categorized all KTRs into three pre-transplant albumin levels: Group 1: normal serum albumin ≥ 4.0 g/dL, Group 2: moderate hypoalbuminemia 2.5-3.9 g/dL, and Group 3: severe hypoalbuminemia < 2.5 g/dL. We used incidence models per 100 person-years and Cox proportional hazards to compare outcomes between groups.

Results: 1717 patients were included in the study. Of those, 36.2% (n=622) were identified as group 1, 62.3% (n=1070) as group 2, and 1.4% (n=25) as group 3. Albumin groups differed by age, cause of end-stage renal disease, BMI, induction immunosuppression and maintenance immunosuppression with tacrolimus vs other, all with a p-value less than 0.001. Incidence of BK viremia for group 1 was 2.2 per 100 person-year which was lower, compared with group 2: 4.6/100 person-year and group 3: 9.9/100 person-year; as well as for CMV viremia, group 1: 1.75/100 person-year, group 2: 2.7/100 person-year and group 3: 3.6/100 person-year. The adjusted relative hazard for BK was also higher for group 2 (HR=1.25, 95% CI[0.95 -1.6]) and group 3 (HR=2.3, 95% CI[1.0-4.9]) compared to group 1. A similar trend was found for CMV for group 2 (HR=1.1, 95% CI[0.77-1.53]) and group 3 (HR=1.4, 95% CI (0.43-4.5])

Conclusions: Our results suggest that the degree of hypoalbuminemia pre-transplant is directly correlated with the risk of BKV and CMV post-transplant. Proper screening and management of hypoalbuminemia may be helpful in reducing the future risk of these infections.

FR-PO1141

BK Virus Surveillance and Outcomes

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Background: Polyoma virus associated nephropathy (PyVAN) caused by BK virus (BKV) occurs in 1-10% of kidney transplant recipients (KTR). Due to lack of effective treatment options, early screening for BKV replication is the most important tool to improve outcomes. Proposed screening strategies are based on consensus guidelines but protocols vary across centers. We report the outcomes in a single center with an intensive BKV screening protocol.

Methods: We performed a retrospective analysis of KTR between Jan 2014 and Nov 2017. We obtained monthly plasma BKV DNA PCR in the first year and every other month in the 2nd year after transplant. A BKV load of >1000 copies/mL was considered positive. Information regarding incidence, treatment and outcomes of patients with BKV, rejection episodes and graft and patient survival was collected.

Results: Among 144 KTR, data were available for 138. There were 34 (25%) patients who developed BKV during a median 2.6-year follow-up period. Baseline characteristics of patients with BKV and no BKV were similar except that more patients in BKV group were on maintenance steroids (62% vs 32%, P 0.004). Median time from transplant to detection of BK viremia was 139 days (range 34-743). Of those who developed viremia, 30 (88%) developed BKV in 1st year. Median initial and peak viral loads were 7762 copies/ml (Range, 1044-862,198) and 26200 copies/ml (Range 1145-5,000,000) respectively. Six patients developed biopsy proven PyVAN. Almost all patients (32/34) were managed with reduction in immunosuppression (IS). The initial IS reduction was MMF in 16 patients, CNI in 8 patients and 7 patients required reduction in both CNI and MMF. IVIG was used in 6 (18%) of patients in whom viremia persisted despite decrease in IS. Over our follow-up period, 27 (79%) patients had resolution of BK viremia (<1000 copies/ml), another 4 patients had >75% reduction in viral load and only one patient developed biopsy proven rejection. No grafts were lost as a result of BKV or rejection as result of reduction in IS for BKV.

Conclusions: Intensive BKV screening in the 1st year post kidney transplant allows for early detection to guide IS management with excellent graft outcomes. Few patients develop BK viremia in the 2nd year and a less intense monitoring can be considered in 2nd year. Larger trials are needed to determine the optimum frequency of BKV monitoring.

FR-PO1142

Efficacy and Safety According to Dose of Valganciclovir for Cytomegalovirus (CMV) Prophylaxis in Transplantation: Network Meta-Analysis Using Recent Data

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Background: Valgancivlovir is importantly used to prevent post-transplant CMV infection among kidney transplantation patients. However, the dose of such drug being used still remains controversial since the continuous use of such drug decrease kidney functions and induces leukopenia in some of the cases. Accordingly, the purpose is to measure the appropriate dose of the drug required for preventing CMV using network Meta analysis.

Methods: We searched the Cochrane Central Register, OVID MEDLINE and Pubmed until April 15, 2019. Studies evaluating among valganciclovir 900 mg, 450 mg and controls were evaluated. We performed direct and indirect network meta-analysis using Bayesian models and generated rankings of the different dose of valgaciclovir agents by generation mixed treatment comparison (GeMTC).

Results: Twenty-three studies involving 3,478 participants were eligible. As a result of analyzing among three groups, following completion of the research, the analysis revealed that the glomerular filtration rate, graft loss, tacrolimus level, antibody mediated rejection, fungal, and *Candida* infection rates were not different among groups. Compared with control, there was no difference between low dose 0.79 [95% Crl, 0.50-1.40] and standard dose 1.0 [95% Crl, 0.61-1.60] groups when CMV incidence was compared. In the Rank probabilities table, the best order for lowering the CMV event was as high as dose of 450mg (71.1%). Incidence of leukopenia showed a significant difference, but there was no statistical significance in the low dose group 1.5 [95% Crl, 0.99-2.20] compared with the control group, but 4.3 times higher in the high dose group [95% Crl, 2.69-7.10], which was 2.9 times higher in the high dose group compare with low dose group [95% Crl, 1.88 -4.67].

Conclusions: The use of valganciclovir did not show any difference in other side effects, but the use of low doses of leukopenia significantly reduced side effects. The incidence of CMV was not different among the three groups, but the tendency was also decreased at low dose.

FR-PO1143

Incident Cancer After Kidney Transplantation in South Korea: A Nationwide-Population Based Study

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Background: Cancer is one of the most common cause of death with functioning graft in kidney transplantation (KT) patients. In this study, we aimed to investigate post-KT cancer incidence using a nationwide data compared with end-stage renal disease (ESRD) control and general population (GP).

Methods: We included incident KT recipients aged over 20 years without previous cancer history using a Nationwide Health Insurance Database of South Korea from January 1, 2007, to December 31, 2015. We analyzed the incidence rate (IR) per 1000 patient-year of cancer in KT recipients compared with ESRD and GP cohorts which were extracted after matching by age, sex, and inclusion year.

Results: A total of 10,203 KT recipients were analyzed with matched ESRD and GP controls. Their mean age was 45.2±10.7 years and 60.3% were men. Economic status of KT recipients was lower than GP but better than ESRD control. Combined diabetes or hypertension of KT recipients was similar to ESRD control but higher than GP. Incident cancer IR in KT recipients (8.63/1000 patient-year) was higher than that of GP (5.28/1000 patient-year), but lower than ESRD controls (12.27/1000 patient-year). In overall, KT recipients had 65.3% higher risk of incident cancer, whereas ESRD patients were at 2.4-fold higher risk of cancer development than GP. Among various cancer types, KT recipients showed higher risk of urinary tract cancer (HR 3.01, 95% CI 1.45-6.22), non-Hodgkin lymphoma (HR 3.97, 95% CI 1.14-13.79), and skin cancer (HR 4.33, 95% CI 1.46-12.83), whereas ESRD patients revealed higher risk of urinary tract cancer, and leukemia compared with GP. We can show a similar trend of cancer IR according cancer type within 5 years after KT, but after then, only stomach cancer IR in KT patients (0.88/1000 patient-year), was higher than that of GP (0.25/1000 patient-year).

Conclusions: In this study, we found that KT recipients had higher risk of incident cancer than GP, although this did not exceed that of ESRD patients. It is suggested that KT recipients should be monitored on the occurrence of urinary tract cancer, skin cancer and non-Hodgkin lymphoma more meticulously than GP, especially, within 5 years after KT. Gastroscopy should be recommended for all KT recipients regardless of the post KT duration.

FR-PO1144

Graft Survival and Characteristics of Kidney Transplant Recipients with Renal Cell Carcinoma

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Background: The risk of acquiring renal cell carcinoma (RCC) is the greatest among all solid tumors in kidney transplant recipients (KTRs). While most RCCs are caught in the localized stage incidentally, leading to low cancer-specific mortality, there is limited information on how to properly screen for RCC in KTRs based on risk stratification, and how RCC impacts graft survival down the line.

Methods: We analyzed risk factors and determined patient and graft survival of all KTRs with RCC in both native and grafted kidneys compared to those without RCC in our institution between 01/01/1994 and 12/31/2014. Risk factors analyzed were race, age, mean time on dialysis prior to transplantation, causes of ESRD, re-transplant, type of graft, and type of induction agent.

Results: 48 cases of RCC were found among the 4,837 KTR's performed at our institution. The mean interval from transplant to RCC was 8.0±6.3 years. Glomerulonephritis was the most common cause of ESRD in KTRs with RCC at our institution (n=17), but this was not found to be a signficfant risk factor for acquiring RCC (p=0.54 in univariate analysis, p=0.42 in multivariate analysis). None of the risk factors analyzed were associated with a statistically significant higher risk for RCC. Graft survival at 10 years was significantly lower in KTRs with RCC compared to those without (Figure 1, p<0.001). However, the trend toward shorter 10 year patient survival did not reach statistical significance (p=0.13).

Conclusions: Although no factor was identified in our sample population that specifically was associated with increased risk for RCC in KTRs, KTRs with RCC were found to have significantly lower graft survival. Identifying specific risk factors in patients with graft failure following RCC can lead to better screening, treatment, and immunosuppression strategies to bolster graft survival in KTRs with RCC.

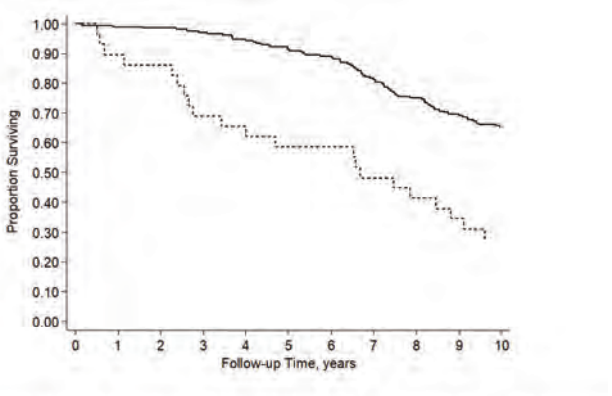

Figure 1: Mean graft survival in all post-transplant patients (solid line) vs patients with post-transplant RCC (dashed line). P<0.001.

FR-PO1145

Immunosuppression Management in Kidney Transplant Recipients with Malignancy/Mortality and Renal Graft Outcome

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Background: Kidney transplant recipients(KTR) are at high risk of cancer compared to general population. Prognosis is poor and the data of how to manage immunosuppression(IS) after cancer diagnosis is scarce. We aims to assess the impact of IS dose reduction on graft survival and mortality outcome in KTR diagnosed with cancer.

Methods: We retrospectively reviewed and collected the data of KTR with cancer diagnosis after kidney transplant. Early stage non-melanoma skin cancer was excluded. We divided our study population in 2 groups, IS reduction and no reduction. Study outcomes were mortality and graft failure. Follow-up time was 10 years. Data were calculated as percentages for categorical variables and mean or median for continuous variables. Patient survivals and graft survivals were analyzed using Kaplan-Meier survival curves with log-rank test. Competing risk analysis was used for graft failure outcome and Cox proportional hazards was used for mortality analysis.

Results: There were 110 patients in total. The mean age at cancer diagnosis was 60.2 years. IS was changed in 74%. Solid organ tumor was 79.1%. Mortality rate was 46.4 % with median survival time of 1.8 years after cancer diagnosis. Graft failure rate was 16.4%. Median graft survival was 2.97 years. Kaplan-Meier curves showed that IS reduction was associated with higher mortality risk and graft failure. However, from multivariable models, history of chemotherapy was the only factor associated with increased mortality(image1). Creatinine at cancer diagnosis and history of rejection were significant predictors of graft failure(image2).

Conclusions: Reduction of IS after cancer diagnosis was not significantly associated with patient mortality, nor with increased risk of kidney allograft failure.

	Univariable model		Multivariable Model	
Variables	Odds ratio (95%CI)	p-value	Odds ratio (95%CI)	p-value
Age at cancer diagnosis	1.04 (1.02-1.07)	< 0.01*	1.02 (0.99-1.05)	0.13
IS dose reduction	2.68 (1.21-6.00)	0.02*	1.94 (0.85-4.41)	0.12
Chemotherapy	3.08 (1.69-5.61)	< 0.01*	2.30 (1.21-4.35)	0.01*
Female	2.44 (1.24-4.77)	0.01*	1.97 (0.98-3.99)	0.06

Image 1

	Univariable model		Multivariable Model	
Variables	SHR (95%CI)	p-value	SHR (95%CI)	p-value
Age at cancer diagnosis	0.97 (0.93-1.01)	0.16	0.99 (0.94-1.03)	0.62
Cr at cancer diagnosis	1.83 (1.45-2.30)	< 0.01*	1.72 (1.28-2.30)	< 0.01*
History of rejection	3.63 (1.45-9.08)	0.01*	3.44 (1.25-9.49)	0.02*
IS dose reduction	6.19 (0.82-46.73)	0.08	4.46 (0.58-34.48)	0.15
Solid tumor	0.35 (0.13-0.95)	0.04*	0.48 (0.16-1.42)	0.18

Image2

FR-PO1146

Characteristics of Malignancy in Kidney Transplant Recipients at the Keck Hospital of USC in Year 2006 Through 2009 Compared to Year 2000 Through 2004

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Background: Recent national kidney transplant registry data reported that 17 % reported causes of death are due to malignancy after transplant, which suggests higher incidence of malignancy as a cause of death compared to 13% about a decade ago.

Methods: The study has been conducted by reviewing medical records of kidney transplant recipients who had been followed by the transplant team at Keck Hospital of USC in 2000 through 2019. The findings have been compared in 200 patients who had received a kidney transplant in two time periods; 100 patients each in 2000 through 2004 (group 1) and 2006 through 2009 (group 2) and had at least 10 years of follow-up.

Results: Subjects (83 female, 116 male) were 134 recipients of a kidney transplant from a deceased donor and 66 from a living donor. Mean age of patients at the time of the first kidney transplant was 48 (range 17-77) and 48 (range 23-75) in group 1 and group 2. Hispanic is the majority followed by Caucasian, Asian, African American; 56, 22, 13, 3% in group 1 and 52, 19, 21, 7%, respectively in group 2. In group 1, 14 patients developed malignancy after kidney transplant; 8 within 10 years post-transplant. In group 2, 12 patients were diagnosed with malignancy; 11 within 10 years. In group 1, 32 patients died and in group 2, 25 patients died. Seven died with functioning graft in group 1 (22% of mortality) and 5 died with functioning graft in group 2 (20% of mortality). Types of cancers were variable; adenocarcinoma of lung, GI and prostate, squamous cell carcinoma of the skin, lymphoma, and thyroid cancer. In group 2, HCC was in 4 among 12 reported malignancies. HCC was diagnosed in 3 recipients of combined liver and kidney transplant. In group 1, 15 patients received induction immunosuppression (OKT3, Thymoglobulin, Basiliximab/Daclizumab), while in group 2, 69 patients received Thymoglobulin or Basiliximab. Duration until the time of cancer diagnosis after transplant seems shortened considerably; median and mean time, 4 and 6.9 years in group 1 vs. 2.4 and 2.7 years in group 2, respectively.

Conclusions: In kidney transplant recipients who received a kidney transplant in 2006-2009, incidence of cancer seems increased during 10 year follow-up and duration until the time of cancer diagnosis seems shortened, compared to those in 2000 through 2004, in the patient population studied.

FR-PO1147

Plasma Citrulline and Mycophenolate Mofetil-Induced Enterocyte Toxicity in Renal Transplant Recipients

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Background: Citrulline is a non-protein amino acid mainly produced by enterocytes of the small intestine which can be used as a biomarker of functional enterocyte mass. Plasma citrulline is reduced in diseases characterized by enterocyte damage. Diarrhea is a well-known side effect of Mycophenolate Mofetil (MMF), as a consequence of MMF induced gastrointestinal mucosal injury. To prevent complications from severe diarrhea, clinicians often lower MMF dosages or change to other immunosuppressive regimens. We aimed to investigate whether citrulline levels are associated with MMF use in a large cohort of stable renal transplant recipients (RTR).

Methods: Plasma citrulline concentrations were measured in 567 stable RTR with a ≥ 1 year functioning graft, from the TransplantLines Biobank and Cohort study (Clinicaltrial.gov NCT03272841). Citrulline was measured using a validated UHPLC-MS/MS method. MMF through levels were available in 234 RTR and were natural log transformed to obtain a normal distribution. Associations between MMF use, MMF through levels and plasma citrulline concentrations were analyzed using linear regression analyses.

Results: Mean age was 55.5±13.2 years and 392 RTR (69.1%) used MMF. Mean plasma citrulline concentration was 42.1±14.2 μmol/L. In univariable linear regression analyses, MMF use was inversely associated with plasma citrulline (β: -6.8, P<0.001). After adjustment for age, sex and eGFR, MMF use remained significantly associated with lower citrulline levels (β: -4.6, P<0.001). Moreover, among MMF users, through

levels were inversely associated with citrulline levels, independent of age, sex and eGFR (β: -2.8, *P*=0.02).

Conclusions: This study demonstrates that MMF use is associated with lower citrulline levels in RTR potentially related to MMF induced enterocyte toxicity, which may lower systemic citrulline levels. More research is warranted to validate whether citrulline can be used as biomarker of MMF induced enterocyte toxicity in RTR.

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FR-PO1148

Diagnostic Yield of Multiplex Polymerase Chain Reaction for Diagnosis of Acute Gastroenteritis in Renal Transplant Recipient: A Single-Center Study from India

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Background: Acute gastroenteritis is an unwelcome and harmful yet unavoidable complication in the renal transplant patient. Standard methods of staining and culture have poor sensitivity as well as require significant time for the reports. Stool Polymerase Chain Reaction is a quick, sensitive and hassle-free method which diagnose more than 20 organisms within 1 hour.

Methods: We retrospectively analyzed all renal transplant patients admitted between 2015 to 2018 with diarrhea. The sample was tested for conventional microbiological methods including stool routine for microscopy and culture. A stool sample was also sent for Multiplex PCR which was analyzed by Bio Fire FilmArray GI Panel which identifies 22 enteropathogens.

Results: 110 diarrheal events were recorded in 82 patients with 181 organisms isolated in all samples. 85% sample yielded a positive result. The conventional method yielded a positive result in only 32.3% as compared to stool PCR. Coinfections were common as 71.2% events were associated with 2 or more organisms. Norovirus(20%) was the most common organism isolated from stool followed by Giardia (17%) and Enteropathogenic E.Coli (16%). Giardia Lambia with Norovirus was the most common co-infection in 19% of patients.

Conclusions: Stool PCR significantly improves the diagnostic yield in diagnosing enteric pathogens. Stool PCR is especially sensitive in detecting multiple organisms. Norovirus is the most common enteropathogen. Giardia with Norovirus was the most common co-infection among post-transplant patient.

Frequency of Enteropathogens diagnosed by stool PCR

Enteropathogens	No. of Positive cases (%)
Norovirus	37 (20%)
Giardia	30 (17%)
Enteropathogenic E.Coli	29 (16%)
Cryptosporidium	21(12%)
Shigella/Enteroinvasive E.Coli	20 (11%)
Others	44 (34%)

FR-PO1149

Incident Dementia in Kidney Transplantation Recipients: A Nationwide Population-Based Cohort Study in Korea

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Background: Recent studies have shown that patients with end stage renal disease (ESRD) are at elevated risk of dementia. However, whether kidney transplantation lower the risk of dementia development or not remains unclear. In this study, we aimed to estimate the risk of incident dementia in KT recipients compared with ESRD patients and healthy controls (HCs).

Methods: From the Korean National Health Insurance Service database, we identified KT recipients aged ≥ 20 years without any history of dementia between 2007 and 2015. We also established two control cohorts without a history of dementia: 1) incident ESRD cohort, 2) HC cohort of insured subjects without a history of kidney disease with frequency matched for age, sex, and inclusion year. All-cause dementia (F00-F03), Alzheimer' disease (AD, F00), and vascular dementia (VD, F01) were diagnosed on the code of the International Classification of Disease, 10th Revision.

Results: We followed 11,385 KT recipients, ESRD patients, HCs for 54,454, 46,260, and 56,020 patient-years, respectively (mean age: 45.7 years, 6754 male/4631 female). Over observation periods, 44, 231, and 44 dementias occurred in KT recipients, ESRD patients and HCs. AD/VD was found in 21/14 KT recipients, 144/58 ESRD patients, and 26/13 HCs. KT recipients showed lower risk of all types of dementia (hazard ratio [HR] 0.15, P<0.001), AD (HR 0.11, P<0.001), and VD (HR 0.20, P<0.001) compared with ESRD patients even after adjustment. These findings were reproduced even when KT recipients were compared with HCs. The strongest predictors for dementia in KT recipients were older recipient age, diabetes and numbers of Charlson's comorbidity index.

Conclusions: These findings suggest that KT recipients had a lower risk of incident dementia, AD, and VD than those of ESRD patients. Furthermore, their dementia development risk was lower than even HCs in spite of long-standing kidney disease and/or use of neurotoxic immunosuppressants.

FR-PO1150

Health-Related Quality of Life Among Kidney Transplant Patients Using the PROMIS Global Health Scale

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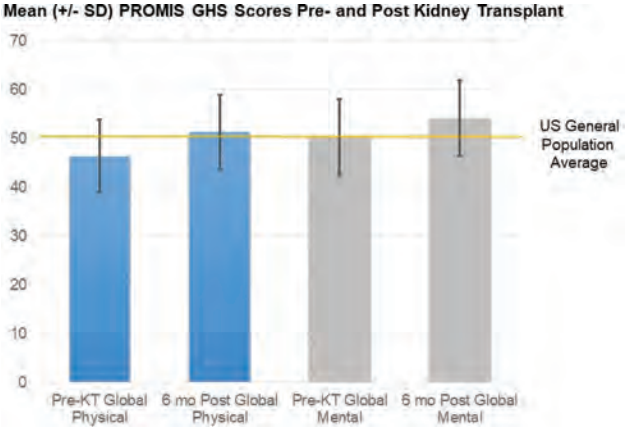
Background: Survival after kidney transplant (KT) is increasing, turning attention to health-related quality of life (HRQOL). Brief but valid measures are needed to screen HRQOL among KT patients. We examined the 10-item PROMIS Global Health Scale (GHS) pre- and post-transplant among KT patients. We also examined GHS scores among a cohort of liver transplant (LT) patients for comparison.

Methods: Data were from KT and LT patients at a transplant center in the United States. PROMIS GHS was assessed pre-transplant (KT, n=189; LT, n=88) and 6 months post-transplant (KT, n=43; LT, n=16). We estimated global physical health (GPH) and global mental health (GMH) summary scores from the GHS. We compared KT and LT to the US general population normative mean value of 50. We then estimated associations between PROMIS GPH and GMH scores with clinician-rated functional status sourced from the Scientific Registry for Transplant Recipients.

Results: Among KT patients, the mean GPH and GMH scores at pre-transplant were 46.3 and 50.2, respectively, which increased to 51.1 and 54.1 at 6 months post-transplant. As expected, LT patients had lower physical and mental HRQOL than KT patients. Among LT patients, mean GPH and GMH scores at pre-transplant were 42.1 and 46.3, respectively, which increased to 44.7 and 50.1 at 6 months post-transplant. Pre-transplant differences in functional status were not statistically significant for KT patients. However, in comparison to LT patients with normal function, LT recipients unable to carry-on normal activities had significantly lower mean GPH (39.9 vs. 47.4, p<0.001) and GMH (44.5 vs. 50.3, p=0.01) scores.

Conclusions: The PROMIS GHS is a brief, clinically-feasible, and patient-centered approach to tracking changes in patients' health over time for KT and LT patients. Inclusion of patient-reported outcomes like the GHS can enhance the standard health metrics collected for transplant patients.



FR-PO1151

A Modified Charlson Comorbidity Index (CCI) for Predicting Kidney Transplant Outcomes in the Elderly

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Background: Contemporary kidney transplant recipients are older and tend to have significant comorbidities. However, the impact of comorbidities in elderly kidney recipients is unclear. This study used a modified Charlson comorbidity index (CCI) to compare the clinical features of elderly patients surviving ≤ 3 years versus those with post-transplant survival > 3 years.

Methods: A prospective database was reviewed for patients aged ≥70 years undergoing deceased donor renal transplantation from 2007 – 2016. A modified CCI score was used designating 3 points for history of myocardial infarction and heart failure, traditional comorbidities as 1 point, and excluded renal disease. Multivariable analysis identified predictors of 3-year mortality.

Results: Among 114 elderly patients undergoing transplantation, 43 (38%) had 1 comorbidity and 39 (34%) had ≥2 comorbidities. The most common comorbidities were diabetes (45%), heart disease (39%), and peripheral vascular disease (18%). Patients were stratified based on 3-year post-transplant survival (Table). Male gender, heart disease, and an unweighted and modified CCI scores were significantly greater among patients surviving ≤3 years post-transplant. Multivariable analysis identified the unweighted CCI (OR= 1.47, CI: 1.02-2.13) and modified CCI (OR= 1.35, CI: 1.08-1.69) as significant predictors of 3-year mortality, but not age, gender or time on waitlist. However,

after adjusting for age and gender, only the modified CCI was predictive (OR= 1.30, CI: 1.03-1.64).

Conclusions: A modified CCI is a simple and effective tool for predicting 3-year mortality following transplantation in elderly patients. This scoring system should be considered as an adjunct in determining transplant candidacy in this population.

Elderly kidney recipients (N= 114)	Survival ≤ 3 years (N= 22)	Survival > 3 years (N= 92)	P value
Age, years (SD)	74 ± 4	75 ± 4	0.29
Male gender	19 (86%)	58 (63%)	0.04
Waitlist duration, months (SD)	28.5 ± 19.9	25.2 ± 20.0	0.50
Heart disease	14 (64%)	31 (35%)	0.015
CCI unweighted	1.82 ± 1.26	1.20 ± 1.18	0.03
CCI modified	3.00 ± 2.39	1.65 ± 1.80	0.004

FR-PO1152

A Cross-Sectional Prospective Study of High Serum Adipocyte Fatty Acid Binding Protein Level Associated with Low Handgrip Strength in Renal Transplant Recipients

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Background: Adipocyte fatty acid-binding protein (A-FABP) involved in lipid metabolism and metabolic and inflammatory responses and can accelerate cardiovascular disease. Low muscle strength is related to functional limitations and physical disability and is associated with all-cause mortality. The present study evaluated the relationship between fasting serum A-FABP level and handgrip strength (HGS) in renal transplant recipients.

Methods: Fasting blood samples were collected from 80 renal transplant recipients. HGS was measured using a Jamar Plus Digital Hand Dynamometer for assessment of muscle strength. Low muscle strength was defined as HGS less than 26 Kg for men and 18 Kg for women, according to the Asian Working Group for Sarcopenia (AWGS) criteria. Serum A-FABP levels were determined using a commercially available enzyme immunoassay.

Results: Thirty-one renal transplant recipients (38.8%) had low HGS, and they included a higher percentage of patients with diabetes (P = 0.025), serum triglyceride (P = 0.003), fasting glucose (P = 0.009), blood urea nitrogen (P = 0.003), creatinine (P = 0.005), and A-FABP level (P < 0.002), while lower estimated glomerular filtration rate (P = 0.008) compared with renal transplant recipients with normal HGS. After adjusting for factors significantly associated with low HGS in these patients by multivariate logistic regression analysis, serum A-FABP level (Odds ratio (OR): 1.037, 95% confidence interval (CI): 1.012–1.064, P = 0.004) was independently associated with low HGS in renal transplant recipients. The serum A-FABP level is also statistically significant in male renal transplant recipients (OR: 1.052, 95% CI: 1.000–1.107, P = 0.049) and female renal transplant recipients (OR: 1.132, 95% CI: 1.008–1.272, P = 0.037) after multivariate logistic regression analysis.

Conclusions: The serum fasting A-FABP level is positively associated with low HGS in renal transplant patients.

FR-PO1153

Impact of Delayed Graft Function (DGF) on Length of Stay After a Deceased Donor Kidney Transplant

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Background: The goal of the Medicare Diagnosis Related Group bundled payment system was to increase efficiency and decrease cost of hospital care. We examined trends over the past decade on the length of the index hospitalization (LOS) for deceased donor kidney transplant (DDKT) recipients and the impact of the increasing incidence of DGF.

Methods: We identified a cohort of 118,865 patients receiving a DDKT between 1/1/2009 and 12/31/2018, excluding those with LOS >180 days (0.3% of sample). We compared the LOS for patients with and without DGF (defined as the need for dialysis in the first 7 days post-transplant) and estimated the excess LOS attributable to DGF.

Results: From 2009-2018, the incidence of DGF for DDKT rose from 23.9% to 28.3%. Median(IQR) LOS decreased from 8(6-13) to 6(5-10) days for DDKT with DGF but remained significantly higher than LOS for DDKT without DGF, which was unchanged at 5(4-7) days (p<0.001). Despite decreasing LOS for DDKT DGF, patients with DGF accounted for an increasing share of the total LOS for all DDKT, from 32.9% in 2009 to 36.3% in 2018 and the excess LOS attributable to DGF rose by 13% from a total of 10,025 days in 2009 to 11,314 days in 2018. [Fig1]

Conclusions: Although the LOS in DDKT with DGF is decreasing, the increasing incidence of DGF is has led to an absolute increase in the number of hospital days that are attributable to DGF after DDKT.

Funding: Commercial Support - Angion Biomedica Corp.

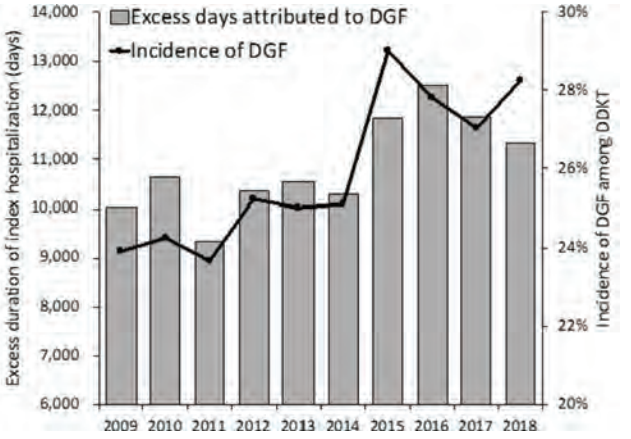

Fig.1

FR-PO1154

Histopathological Findings on Biopsy Among Kidney Transplant Recipients Needing Dialysis Within 2 Weeks Post-Transplant

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Background: The need for dialysis acutely after transplant is associated with an increased risk of graft loss. No studies have characterized post-transplant graft and mortality outcomes based on biopsy-proven causes of early need for dialysis, to our knowledge. Our study reports the incidence and outcomes of histopathological cause-specific need for dialysis within two weeks following kidney transplantation at our university.

Methods: We examined kidney transplant recipients transplanted at our center between 2000-2015 who required dialysis within the first two weeks of transplant and received a biopsy during this time. Subjects were categorized into one of five categories based on their biopsy results: acute rejection (AR), acute tubular necrosis (ATN), both acute rejection and ATN (Both), other findings including tubular injury (Other), and no findings on biopsy (None). Outcomes examined included baseline characteristics, graft failure, death-censored graft failure (DCGF), and death after biopsy.

Results: Of a total of 291 patients, 111(38.1%) had Other pathology, 86 (29.6%) had ATN, 67 (23%) had AR, 22 (7.6%) had Both, and 5 (1.7%) had None. Mean time to biopsy was 8 ± 2.83 days. Of those with a diagnosis of AR, the incidence of graft failure was 36.2 per 100 person-years within the first year post-biopsy, compared to 25.1 per 100 person-years for those with ATN, and 18.9 per 100 person-years for those with Other pathology. A similar trend was seen for DCGF within the first year (32.4 for AR, 18.1 for ATN, and 12.6 for Other pathology). AR was associated with greater risk for DCGF compared to other categories, as illustrated in the K-M curve in Figure 1.

Conclusions: AR is associated with a greater risk for graft failure and DCGF than other causes of dialysis within the first two weeks post-transplant. Identification of cause of graft failure may help inform prognostic information.

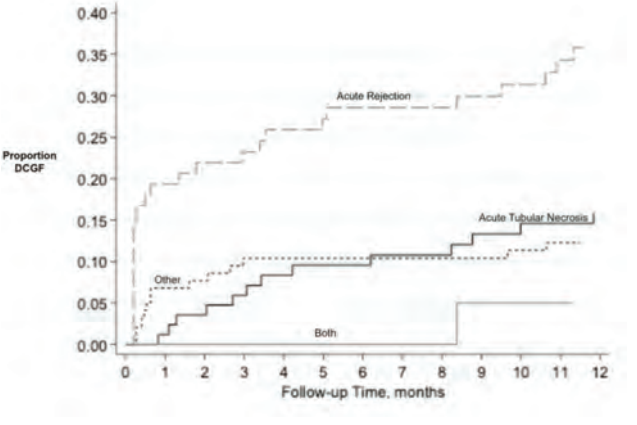

Figure 1. DCGF between study groups.

FR-PO1155

Delayed Graft Function (DGF) in Kidney Transplantation Patients: An Analysis of Disease Burden

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Background: Kidney transplantation patients with DGF are at greater risk of graft failure and mortality, as well as additional disease burden. Hospitals are sensitive to both short- and medium-term costs as they are reimbursed through a 90-day Diagnosis Related Group (DRG) code and must manage all related expenses within the bundled payment. This study aims to assess patient characteristics, Health Resource Use (HRU) and costs associated in post-transplant patients with and without DGF in the hospital setting.

Methods: A retrospective analysis of the Premier Hospital Database (PHD) was performed on adult kidney transplant patients from January 2014 to December 2018. Kidney transplant patients were identified via ICD9/10 procedure codes and charge codes. DGF status was defined as the presence of a dialysis charge code within 7 days following a transplant. Patient and admission characteristics, HRU and costs were calculated for patients with and without DGF.

Results: Of the 12,097 kidney transplant patients, 3,087 (25.5%) had DGF. The majority of transplants (79.2%) were performed at large 500+ bed facilities and in urban areas (95.5%); males represented 61.1% of all transplant patients with a slightly higher proportion (64.2%) in the DGF group. The primary insurer (67.9%) of all patients was Medicare. Black patients (36.5%) had a higher incidence DGF compared to other races. DGF patients were also older (median 55 vs 53 years). The incidence proportion of DGF increased from 22.6% to 26.7% from 2014 to 2018. Patients with DGF had longer mean and median hospital stays of 11.5 and 8 days, compared to 7.3 and 6 days ($p<0.01$) in non-DGF patients. A significantly higher proportion of DGF patients (59.1% vs 56.0%, $p<0.01$) were admitted to the ICU and had a longer length of stay (mean days: 4.8 vs 2.5, $p<0.01$. The mean total admission costs for the Medicare patients were higher in DGF patients ($113,628.9 vs $105,962.4, $p<0.01$). The same trend was observed for ICU costs during admission ($5,815.0 vs $3,901.4, $p<0.01$).

Conclusions: DGF leads to longer hospital stay, significantly higher admission costs and a higher percentage of patients being admitted to the ICU compared to patients without DGF.

Funding: Commercial Support - Angion Biomedica

FR-PO1156

Potential Prognostic Value of Immediate Postoperative Proteinuria Predicting Early Renal Outcome After Kidney Transplantation

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Background: Proteinuria in kidney transplant recipients (KTRs) is associated with poor patient and allograft survival. However, the relationship between urinary protein to creatinine ratio (uPCR) or urinary albumin to creatinine ratio (uACR) during the immediate postoperative period and renal outcome of KTRs is yet to be determined.

Methods: This single center retrospective cohort study included 474 KTRs who underwent kidney transplantation (KT) from January 2014 to December 2017 and followed up for ≥ 1 year. After excluding patients without urine PCR and ACR within 7 days after KT and those without serum creatinine at 1 year after KT, a total of 353 KTRs were finally analyzed: living donor KT in 186 KTRs and, deceased donor KT (DDKT) in 167 KTRs. Immediate postoperative uPCR and uACR were measured within postoperative day 7. The primary outcome was estimated glomerular filtration rate (eGFR) at 1 year after KT. The secondary outcome was the incidence of delayed graft function (DGF) in DDKT recipients.

Results: Patients with higher eGFR (≥ 60 mL/min/1.73 m^2) at 1 year after KT had lower uPCR (patients with ≥ 60 mL/min/1.73 m^2 vs. those with < 60 mL/min/1.73 m^2, median 810 ug/mgCr [IQR 500 - 1780] vs. median 1220 ug/mgCr [IQR 632 – 3905]; p = 0.007) and lower uACR (median 342 ug/mgCr [IQR 165 - 976] vs. median 613 ug/mgCr [IQR 284 - 2562]; p = 0.002) during the immediate postoperative period than those with lower eGFR. DDKT recipients with uPCR ≥ 3 mg/mgCr during the immediate postoperative period is associated with the higher incidence of DGF (DDKT recipients with uPCR ≥ 3 mg/mgCr vs. those with uPCR < 3 mg/mgCr, 30% vs. 13% [odds ratio 2.87]; p = 0.007), and lower eGFR before discharge (60 mL/min/1.73 m^2 [IQR 41 – 84] vs. 75 mL/min/1.73 m^2 [56 – 92]; p = 0.001) than those with uPCR < 3 mg/mgCr.

Conclusions: Our results suggest immediate postoperative uPCR as a potential predictor of early renal outcome in KTRs.

FR-PO1157

Preventable 30-Day Readmission After Kidney Transplantation: Classification System and Risk Association

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Background: Preventable readmissions post kidney transplantation (KT) may reflect cost inefficiencies and gaps in quality of care. There is no practical tool to identify preventable 30-day readmissions post KT, and it is not known whether socioeconomic status (SES) influences risk of preventable readmissions.

Methods: A single-center cohort of 756 adult first-time kidney-only transplant recipients from 2013-2017 was followed for 30 days post-discharge. We merged electronic health records with national databases to develop a classification system assignment of 30-day readmission (preventable vs. non-preventable) using All-Patient Refined Diagnosis Related Group and International Classification of Diseases, ninth and tenth revisions, Clinical Modification and assessed its performance and discrimination against clinical assignment (chart review). We used multivariable logistic regression to assess the independent association of patients' SES and preventable readmissions.

Results: Recipient median age was 57 years (IQR, 45-66); 51% were white, 45% black, and 4% Hispanic. The sensitivity and specificity of the classification system were 92% and 96%, respectively, with area under the receiver-operating-characteristic curve (AUC) 0.94 (95%CI 0.89-0.97). Residents within the lowest ZIP code level neighborhood household income had the highest odds of preventable readmissions (adjusted odds ratio [OR] 2.16; 95%CI: 1.25-3.72).

Conclusions: Our classification system had a comparable discriminating ability to the gold standard of chart review identifying preventable vs. non-preventable 30-day readmission; however, our new tool requires prospective validation. Low income recipients had greater risk of preventable readmission.

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Preventable Readmission	Clinically Observed	Clinically Observed	
Classification System	Yes	No	Total
+	67	4	71
-	6	99	105
Total	73	103	176

Sensitivity: 91.78%; Specificity: 96.12%. Area under ROC: 0.9395

FR-PO1158

Perioperative Antibiotics for Preventing Post-Surgical Site Infections in Solid Organ Transplant Recipients

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Background: No consensus exists on the role of antibiotics for preventing surgical site infections (SSIs) in solid organ transplant recipients (SOTRs). Objectives: To assess the benefits and harms of prophylactic antibiotics for preventing SSIs in SOTRs.

Methods: The Cochrane Kidney and Transplant Register was searched up to 8 Dec 2018. Studies were identified through searches of CENTRAL, MEDLINE, EMBASE, conference proceedings, International Clinical Trials Register (ICTRP) Search Portal, and ClinicalTrials.gov. All randomized controlled trials (RCTs) and quasi RCTs in any language assessing prophylactic antibiotics for preventing SSIs in SOTRs at any time point after transplantation. Two authors independently determined study eligibility, assessed quality and extracted data. The primary outcome was SSI incidence. Summary effect estimates were obtained using a random-effects model and results were expressed as risk ratios (RR) and 95% confidence intervals (CI) for categorical variables, and mean differences (MD) or standardized mean differences (SMD) and 95% CI for continuous variables.

Results: This review included 9 eligible studies (803 participants). Six studies (416 participants) compared antibiotics versus no antibiotics and 3 studies (387 participants) compared extended duration antibiotics versus short duration antibiotics. Risk of bias was assessed as high for performance (9 studies), detection (9 studies), attrition (2 studies) and selective outcome reporting (1 study). Antibiotics had an uncertain effect on SSI incidence (RR 0.63, 95%CI 0.37-1.06; 6 studies, 416 participants, I^2=61%, very low certainty evidence). Most RCTs occurred prior to 200 (RR 2.17, 95%CI 0.84-5.66; 1 study, 188 participants, very low certainty evidence) with only 1 RCT in the last 2 decades (RR 0.30, 95%CI 0.15-0.60; 5 studies, 228 participants, I^2=33%, very low certainty evidence).

Conclusions: There is very low certainty evidence to support perioperative antibiotics for preventing SSIs in SOTRs. Further high quality, adequately powered RCTs would better inform practice.

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FR-PO1159

Serum Phosphate Levels Modify the Impact of Intact PTH Levels on Renal Outcomes in Kidney Transplant Recipients

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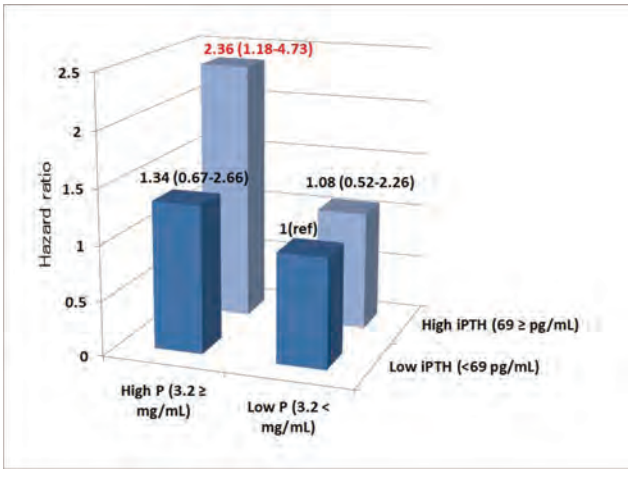
Background: Mineral bone disorder (MBD) parameters including parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), calcium, phosphate (P), 1,25-dihydroxyvitamin D (1,25D), and 25-hydroxyvitamin D predict renal outcomes, when assessed separately, in kidney transplant recipients (KTRs). However, data evaluating those parameters simultaneously and interwoven relationships on renal outcomes are scarce.

Methods: In this single-center prospective cohort study, we included 263 KTRs with grafts functioning at least 1 year after transplantation. The renal outcome was a composite of estimated GFR (eGFR) halving and graft loss. We performed Cox regression analyses to assess associations of MBD parameters with the renal outcome.

Results: Median eGFR was 38 ml/min/1.73m^2. The renal outcome occurred in 98 KTRs during a median follow-up of 10.7 years. In a multivariable Cox model, intact PTH (iPTH), P, and 1,25D, but not intact FGF23 levels, were associated with the renal outcome (HR 1.60 per log scale; 95%CI 1.19-2.14, 1.60 per mg/dL; 1.14-2.23, 0.98 per pg/mL; 0.96-1.00, and 0.99 per log scale; 0.74-1.34, respectively). A competing risk analysis with death as a competing event yielded a similar result. After stratification into 4 groups by the median values of iPTH and P (Pinteraction<0.1), however, high iPTH levels (69 ≥ pg/mL) were not associated with worse renal outcomes when serum P levels were less than median (3.2 mg/dL) (Figure). Only in KTRs not receiving oral active vitamin D, 1,25D levels predicted the renal outcome (Pinteraction<0.1).

Conclusions: High iPTH, P, and low 1,25D levels predicted poor renal outcomes in KTRs. Given that PTH promotes phosphaturesis and enhances 1α-hydroxylase activity in proximal tubules (PT), low P and high 1,25D levels may reflect viable PT function.



Hazard ratios for renal outcomes stratified by the median values of serum iPTH and phosphate levels

FR-PO1160

Bone Turnover Markers Are Associated with Hypocalcemia Immediately After Renal Transplantation

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Background: Bone and mineral disorders occur commonly after renal transplantation (RTX). Serum calcium levels decreased after RTX and gradually reach calcium homeostasis. Hypocalcemia immediately after RTX may influence QTc interval and myocardial contractility, thus it is a life-threatening phenomenon after RTX. Bone turnover markers (BTMs) are markers reflect the bone turnover stage and bone and mineral disorders. Whether BTMs can predict the occurrence of hypocalcemia after RTX has not been reported.

Methods: A total of 101 patients receiving ABO compatible living donor renal transplantation were assessed. General patient information, kidney function and calcium metabolism indexes were measured before transplantation. Calcium metabolism indexes included calcium, phosphorus, parathyroid hormone (PTH), 25-dihydroxyvitamin D (25(OH)D3) and BTMs. BTMs included procollagen type I N-terminal propeptide (PINP), N-terminal mid-molecule fragment osteocalcin (N-MID) and β-C-telopeptide of type I collagen (β-CTX). The patients were divided into two groups dependent on post-transplantation calcium levels, non-hypocalcemia group and hypocalcemia group. The prediction value for hypocalcemia were evaluated by concordance index (c-index), akaike information criterion (AIC) and cayesian information criterion (BIC) methods.

Results: General patient information, kidney function and calcium metabolism indexes were compared between non-hypocalcemia group and hypocalcemia group. Age, dialysis type, serum calcium levels, PTH, 25(OH)D3 and BTM levels showed differences between non-hypocalcemia group and hypocalcemia group. Then correlation analysis showed calcium levels after RTX showed positive correlations with serum PTH, 25(OH) D3, PINP, N-MID and β-CTX amounts. Further utilizing multi-regression selected risk factors to established basic model equation (AIC=126.85 and BIC=134.69; c-index 0.78). Then we added PTH, 25(OH)D3, N-MID and PINP to basic model respectively and found no influence on predictive ability. Final inclusion of β-CTX, one of BTMs, to basic model improved the predictive performance significantly (AIC=113.44 and BIC=123.9; c-index 0.83).

Conclusions: Low levels of BTMs were associated with hypercalcemia after RTX. To predict the occurrence of hypocalcemia, β-CTX, one of BTMs, could improve the predictive ability.

FR-PO1161

Vitamin D Status in a Cohort of Renal Transplanted Patients: Factors Related and Impact on Rejection Occurrence and Long-Term Graft Outcome

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Background: Immunomodulatory properties in renal transplant (RTx) have been hypothesized for vitamin D (VD). We evaluated retrospectively, in a cohort of renal transplanted patients (RTxp): a) VD status at 1 (T1) and 12 (T12) months after RTx; b) the factors related to VD status; c) the impact of VD status on rejection rate and long term graft outcome.

Methods: The study includes 438 (M=265;age 49[40-50]years), out of 670 patients (pts) transplanted between April 2004 and November 2017, where VD status parameters were available both at T1 and T12. Included and not included pts did not differ in general features. VD status, based on 25OH-VD levels, was categorized as: insufficient (iVD) or sufficient (sVD), if 25OH-VD was < or ≥30 ng/mL, respectively. Patients were followed-up for 65[33-97] months and evaluated for rejection rate, diagnosed on renal biopsy (RBx) performed for clinical indication, and for achieving combined major adverse clinical events (MACE: death or graft failure, considered as either return to dialysis or eGFR halving).

Results: A) 25OH-VD levels increased from 14[8-18] ng/mL at T1 to 17[10-23] ng/mL at T12 (p<0.0001), with iVD being present in 425 (97%) pts at T1 and in 380 (87%) pts at T12. VD status normalized spontaneously or after VD supplementation in 19 and 35 pts, respectively; 9 sVD pts at T1 were iVD at T12. b) 25OH-VD levels were negatively related with PTH both at T1 and T12, while they were positively related with Ca levels at T12. c) Rejection (REJ+) was diagnosed in 38 (36%) out of the 105 RTxp submitted to RBx. No difference was found in 25OH-VD levels between REJ+ and REJ- pts, both at T1 and T12. MACE occurred in 66 (15%) pts (MACE+). 25OH-VD levels at T12 were significantly lower in MACE+ pts and were the only variable significantly associated with MACE+ at multivariate analysis (OR=0.96, p= 0.01).

Conclusions: With the limitations of the retrospective design and the relatively low number of pts, we found that: a) iVD was highly prevalent in RTx patients both at T1 and T12; b) VD levels were inversely related with PTH levels; c) no association was found between VD status and REJ occurrence, while 25OH-VD levels at T12 were inversely and independently related to MACE+.

FR-PO1162

The Risk of Hypercalcemia After the Kidney Transplantation? Analysis of Cinacalcet Therapy with 10 Years of Follow-Up in a Single Center

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Background: The persistence of secondary hyperparathyroidism after kidney transplantation (KT) occasionally manifests itself by hypercalcemia and hypophosphatemia. In patients with KT, Cinacalcet is an off label treatment for hypercalcemia related to hyperparathyroidism. The aim of our study is to evaluate which factors are predictive of hypercalcemia that requires the use of Cinacalcet.

Methods: We retrospectively examined all the patients who received a KT from 2008 and 2018. In each patient we evaluated demographic characteristics and the following parameters: creatinine, hemoglobin, albumin, Calcium, Phosphate, PTH, vitD25OH, and the linked therapies. T Student, Kruskal Wallis, and Pearson's chi-square tests were used, as appropriate. The regression model was used to evaluate the predictive variables for the use of Cinacalcet.

Results: In a 10-year period 459 KT were performed. Only 9.2% of the patients needed Cinacalcet therapy. Table 1 shows the comparison of the characteristics of those

patients who needed Cinacalcet therapy and those who did not. Dead donor transplantation (OR 4.3 p = 0.023), number of KT received (OR 6.8 p <0.0001), PTH levels (OR 1.01 p <0.001), and phosphate levels (OR 0.44.6 p = 0.01) were all independent predictors for Cinacalcet use in multivariable analysis.

Conclusions: Our data show that dead donor transplantation, presence of previous KT, and both PTH and phosphate levels were able to predict Cinacalcet therapy. In these cases we suggest a more careful monitoring of the calcium levels.

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	No Cinacalcet	Cinacalcet	p value
Age (years)	55.8±12.9	55.2±12.4	0.753
Dead donor transplant (%)	78.2	92.3	0.025
Previous transplant (%)	4.1	26.2	<0.001
Calcium (mg/dl)	9.2±0.6	9.6	<0.001
Phosphate (mg/dl)	3 (2.6-3.4)	2.5 (2.2-2.9)	<0.001
PTH (pg/ml)	46 (33.2-70)	70 (59.5-112)	<0.001
Hemoglobin (g/dl)	12.9±1.8	13±1.6	0.55
Albumin (g/dl)	3.6±0.36	3.7±0.36	0.12
ICN therapy (%)	99.7	97.6	0.17
MMF therapy (%)	82.5	85.7	0.598
mTOR therapy (%)	9.8	9.5	0.949
AZA therapy (%)	7.9	4.7	0.463
Cholecalciferol therapy (%)	48.2	40.5	0.339
Calcitriol therapy (%)	16.7	2.3	0.422
Calcium binders therapy (%)	0.9	0	0.524

FR-PO1163

The Impact of Periodontitis on Recipient Outcomes After Kidney Transplantation

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Background: Periodontitis has a high prevalence in patients with chronic kidney disease and has been reported to increase systemic inflammations and cardiovascular risks. Although dental care is usually recommended prior to transplantation due to potential for serious infection, little is known about impact of periodontitis on transplant outcomes. The purpose of this study was to examine whether periodontitis before KT affects post-KT recipient outcomes.

Methods: This was a single center, retrospective study including KT recipients from April 2008 to October 2018. The panoramic radiographs at pre-KT work up were analyzed by a dentist with severity of periodontitis graded according to new classification system developed in 2017.

Results: One hundred and sixty-six recipients who received pre-KT dental examination were divided into 3 groups according to 1st, 2nd, 3rd and 4th-stage periodontitis; group1 (1st and 2nd stage, 28.9%), group2 (3rd stage, 35.8%), and group3 (4th-stage, 22.6%) respectively. Seventy-seven patients (46.4%) with periodontitis received treatments such as scaling or surgical extraction before KT. Advanced stage periodontitis patients were more likely to be older, obese, smoker and had higher prevalence of diabetes. However, pre-transplant immunological variables or immunosuppression were not different according to periodontitis grades. The mean follow-up period is 4.16 years. Advanced stage periodontitis without treatment was associated with significantly increased risk of CMV and BKV infection. However, rate of acute T cell mediated rejection was significantly lower in patients with advanced stage periodontitis. eGFR measured at 36 months after KT was significantly higher in patients with advanced periodontitis (p=0.016) and this association was evident only in younger (<50yrs), male and non-diabetic patients. Multivariate logistic regression analysis showed that low stage of periodontitis and the use of cyclosporine were independent predictors for lower eGFR at 36 months.

Conclusions: These results suggest that pre-transplant periodontitis could be a manifestation of systemic inflammation and altered immune function in patients with end-stage renal disease and may affect long-term post-transplant outcomes. Impact of periodontitis or its treatment on transplant outcomes needs to be further clarified.

FR-PO1164

Effect of a Good Oral and Dental Care on Inflammation and Oral Lesions in Renal Transplant Patients

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Background: Inflammation plays an important role in causing complications in CKD and transplant patients. C-reactive protein and pro-inflammatory cytokines could predict outcomes in transplant patient. Poor oral health results in inflammation and cytokine production. There is need to evaluate the benefit of good oral hygiene on renal transplant outcome.

Methods: A randomized controlled trial was carried out amongst CKD patients going for renal transplantation. All patients had dental and oral examination (Type III clinical examination as per American Dental Association specifications and WHO oral health proforma, 2013) Group I (Non interventional group) 50 patients. Group II (Intervention group) - 50 patients of chronic kidney disease going for transplantation. Group III (Control group) comprised of 50 healthy age, sex matched subjects. Intervention group followed regular tooth brushing, use of dental floss along with use of mouth wash twice every day and counseling sessions for good oral and dental care for a period of 3 months after transplant. Non-intervention group continued usual oral and dental care. The oral and dental findings specially the periodontitis score was compared between groups I and II and with the healthy controls. CRP (C- reactive protein) values were assayed at baseline and after 3 months.

Results: Comparison of CRP values between Interventional and non-interventional groups at baseline and at 3months showed that periodontitis score and CRP significantly came down at 3 months in intervention group as compared to non- intervention group. CRP values in the interventional and non-intervention groups were analyzed in relation to presence of donor specific antibodies (DSA) and HLA mismatch scores in the two groups. Our data shows that after aggressive dental and mouth hygiene routine, intervention group patients showed significant decline in CRP values as compared to the non intervention group. It almost reached close to values in normal controls.

Conclusions: The present study concludes that the oral hygiene of the patients with chronic kidney disease going for transplant is deteriorated. Good oral and dental care in transplant recipients can improve inflammation which could have beneficial effect on post transplant outcomes ”

FR-PO1165

Safety and Effectiveness of Ferric-Carboxymaltose in Kidney Transplant Patients

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Background: In kidney transplant patients (KTx), the post-transplant anemia (PTA) is associated with worst graft outcome and increased cardiovascular/all causes mortality. With common available iron treatments, iron deficiency (ID) in KTx is highly prevalent and represents one of the major causes of PTA. This prospective study evaluates the safety and effectiveness of ferric-carboxymaltose (FCM) in KTx patients with iron deficiency anemia (IDA) and no/low response to other previous iron treatment.

Methods: Consecutive, stable (tx age > 1-y), CKD-3/5 stages, anemic (Hb <11g/dl and/or ESA treatment), iron deficiency (TSAT <20% and/or ferritin <100 ng/ml), previous iron intolerance or low-responce, KTx were prospectively enrolled. Each patient was administered FCM, 500 mg, in standardized conditions at baseline, and eventually a second dose 500 mg dose one month later. Patients were evaluated for clinical conditions, iron status, anemia and renal function every month during a 6-months follow-up (irrespective of iron administration). Clinical and lab side-effects FCM related (nausea, vomiting, diarrhea, headache, fever, rush, erythema, itching, myalgia, bronchospasm, anaphylaxis) were monitored during the study.

Results: 32 KTx (M15-F17); Diabetes: 19%; Age: 55.8±11.7years; BMI: 26.3±4.5 kg/m^2; transplant age: 104±92 months; eGFR: 38.2±11.9 ml/min; SBP:135±21, DBP:81±12 mmHg; ACEi/ARB:28.1%; previous iron: naïve, n=7 (reported intolerance during dialysis), os, n=20 (16 ongoing), i.v., n=4 (0 ongoing). At 34±4 days after FMC infusion, ferritin increased from 44±53 to 149±136 ng/mL (p<0.001), TSAT from 10±6 to 18±10% (p<0.001), Hb from 10.2±1.0 to 11.3±1.4 g/dl (p<0.01); at 160±71 days, ferritin was 93±110 ng/mL, TSAT 19±9% and Hb 12.0±1.7 g/dl (all p<0.05 *vs* Baseline and NS *vs* 34days). At baseline, 81% of pts were on ESA at a mean dose of 9.960±6.620; during the follow-up, pts on ESA reduced to 75% and 44% and ESA dose to 10.480±9.670 and 6.760±11.220 IU/week, respectively. No changes of clinical parameters, renal function or electrolytes occurred; no side effect was detected.

Conclusions: In stable KTx patients with iron deficiency related anemia, the treatment with FCM is safe and effective, even in subjects resistant to previous iron treatment, allowing an optimal and stable correction of both iron deficiency or anemia, while reducing the ESA dose.

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FR-PO1166

Impact of Peritransplant Red Blood Cell Transfusion on Long-Term Renal Outcome After Kidney Transplantation

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Background: Patients undergoing kidney transplantation (KT) frequently receive red blood cell (RBC) transfusion perioperatively. Transfusion of blood products may induce allosensitization in KT recipients. The effects of peri-transplant transfusion on graft survival were investigated using a nationwide database.

Methods: Data were collected from the National Healthcare Insurance Service database in Korea. 13,872 patients who received KT in Korea between 2007 and 2015 were analyzed. The outcome measures were graft failure rate at 5 years from KT and overall patient survival depending on the amount of RBC transfusion. Diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, transplantation period, and Elixhauser comorbidity index were adjusted as covariates.

Results: The 5-year graft failure rates were 17% in the no transfusion group, 17% in 1-2 units group (OR 0.98 [95% CI 0.84–1.16]), 26% in 3-5 units group (OR 1.51 [95% CI 1.19–1.91]), and 38% in 6 units or more group (OR 2.13 [95% CI 1.39–3.27]) (P < .001, 3-5 units or 6 units or more vs. no transfusion group). The 10-year survival rates were 97% in no transfusion group, 96% in 1-2 units group (OR 1.44 [95% CI 1.19-1.75]),

92% in 3-5 units group (OR 2.38 [95% CI 1.86-3.05]), and 67% in 6 units or more group (OR 10.78 [95% CI 8.47-13.71]) (*P* <.001, 1-2 units, 3-5 units or 6 or more units group vs no transfusion group).

Conclusions: Peri-transplant RBC transfusions in KT recipients were independently associated with increased risk of renal allograft failure and death. Further studies are required to confirm the risk of allosensitization following blood transfusion and to search for alternative ways to reduce sensitization with blood products.

FR-PO1167

Changes in Blood Pressure, Graft Function, and Proteinuria After Dialysis Arteriovenous Fistula Closure in Kidney Transplant Recipients

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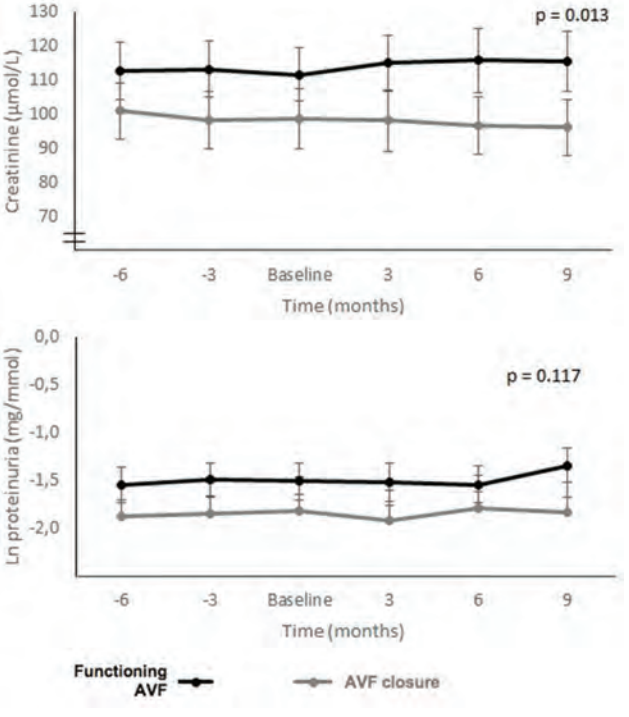
Background: The aim of our observational historic cohort study was to evaluate the impact of dialysis arteriovenous fistula (AVF) closure on systolic and diastolic blood pressure (SBP, DBP), graft function and proteinuria in kidney transplant recipients.

Methods: The study group included 111 kidney transplant recipients with an AVF closure after a median 34 months' post-transplant. Controls included 53 recipients with a functioning AVF after a median 33 months of follow-up. Graft function was assessed by serum creatinine and estimated glomerular filtration rate (eGFR) using CKD-EPI formula, and proteinuria was assessed by spot urine protein/creatinine ratio. SBP and DBP was measured at each visit. We used linear mixed models to calculate the slope of serum creatinine, eGFR and proteinuria change versus time.

Results: Baseline mean SBP and DBP were comparable between groups (134±16 *vs.* 138±16 mmHg; P=0.150, and 79±10 *vs.* 77±13 mmHg; P=0.472). Following AVF closure, SBP increased from 134±16 to 138±15 mmHg (P=0.001), and DBP increased from 79±10 to 84±10 mmHg (P<0.001). In the control group with functioning AVF SBP decreased (138±16 to 135±15 mmHg; P=0.038), while DBP did not change (77±13 to 76±11 mmHg; P=0.122). The course of serum creatinine and proteinuria and 95% confidence intervals are shown in Figure 1. The mean eGFR slope improved before (0.224 mL/min/1.73m^2 per month) and deteriorated after AVF closure (-0.023 mL/min/1.73m^2 per month) (P=0.044). The groups were significantly different with respect to serum creatinine slope (primary study end point; P=0.013) but not with respect to proteinuria slope (P=0.117).

Conclusions: The closure of a dialysis AVF may affect blood pressure and kidney graft function, but it does not impact proteinuria.



FR-PO1168

Kidney Recipients with Allograft Failure, Transition of Care (KRAFT): Practice Survey

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Background: Sensitization after failed allograft in the setting of withdrawal of immunouspression makes re-transplantation increasingly difficult. We sought to understand how different centers and clinical care providers approach withdrawal of immunosuppression in a failing kidney allograft through a survey of US kidney transplant centers.

Methods: After approval from IRB and the AST Education Committee, a survey about practices related to withdrawal of immunosupression was distributed electronically to members of the AST members between Nov 2018 and May 2019.

Results: There were 101 responders with a response rate of 31%. Most survey respondents were Transplant Nephrologists (80.4%) at academic medical centers (90.2%). The most common approach to withdrawal of immunosuppression was withdrawal of the anti-metabolite first; with 64.2 % respodning they would withdraw antimetabolite first, 24% with no unified protocol, and 9.4% responding they would stop CNI first. Most providers would stop immunosupression over a time frame of 2-6 months (38.9%), although 24.1% responded they would keep a low dose of prednisone, and 20.4% had no unified protocol. Approach to tapering of immunosuppression did differ based upon whether or not practitioners felt the patient would be re-transplanted shortly. While most practitioners, 96.6% felt development of sensitization was of intermediate or most importance in the decision to taper immunosuppression there were many concerns of risk of infections, malignancy and patient age which were factors in the decision to taper or continue immunosuppression. Overall, 57.4% providers felt there was a need for standardized approach to taper immunosuppression in the failing allograft.

Conclusions: In a sample of US Kidney Transplant centers, we found a wide range of approaches to withdrawal of immunosuppression in a failed kidney transplant with no unified protocols in quarter of the respondents. Efforts to standardize clinical practice are warranted to tailor immunosuppression withdrawal according to the availability of a second kidney transplant and patient comorbidities.

FR-PO1169

Safety and Efficacy of a Kidney Graft Biopsy Program by Nephrologists with Short Post-Biopsy Surveillance Times

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Background: Kidney graft biopsies (KGB) are the gold standard for diagnosis of kidney graft dysfunction. Since Jan/2015 we have increased the KGB, reducing wait times and costs, due to the implementation of a ambulatory program (intrahospital surveillance <6 hrs), in charge of the fellows of the transplant nephrology program, supervised and guided by an interventional nephrologist.

Methods: Prospective, observational and descriptive study.

Results: 1091 KGB were made (jan/15-dec/18). Indications: protocol 463 (43.8%), de *novo* or increase of DSA 231 (21.2%), post-rejection control 149 (13.7%), graft dysfunction 146 (13.4%) and others 87 (7.9%). A total of 33 (3.0%) complications were reported; 5 (0.5%) were serious (persistent hematuria and hospitalization requirement). 11 (1%) were hematuria; 21 (1.9%) peri-graft hematomas. No infections, graft loss, or other procedures were required. In 1070 KGB (98.1%) the sample was adequate. Protocolized KGB at 3 and 12 mo post-KT and surveillance KGB for new pts from other centers carried out in 463 cases; 236 at 3 mo, 187 at 12 mo and 40 of newly admitted pts. Spite of not having clinical/laboratories alterations, the result of the KGB was abnormal in 58% of the total; 50% at 3 mo, 63% at 12 mo and 67% in new pts. Findings were: borderline alterations 158 (34%), humoral rejection 44 (9.5%), cellular rejection 24 (5%) and other alterations 36 (7.7%). In 161 (14%) pts we evaluated the relationship between the angle of incidence of the needle on the renal graft and the quality of sample and complications. The firing angle was 33.1±8.8 degrees, with a median of 12 (8-16 glom). There were no relation between angle of incidence and the quality of sample, or in the probability of

complications. We observed a saving of 75% in each KGB ($680 before 2015 vs $172 after 2015); total savings of $553,855, and a reduction 1091 hospital beds in the 4 yrs.

Conclusions: The implementation of a KGB program by nephrologists reduced costs and hospital stay. It was effective (adequate sample in 98%) and safe (3% complications). In our study there were no serious complications that required invasive procedures, transfusions or graft loss. The angle of shot does not impact on the frequency of complications or the quality of the sample.

FR-PO1170

Renal Transplant Complications in Patients with and Without Gout

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Background: Graft-related complications are among the most serious issues solid-organ transplant recipients and their healthcare teams face post-operatively. Gout is a known frequent co-morbidity in transplant patients. Whether renal transplant patients with gout suffer from higher rates of transplant-related complications, as compared to transplant patients without gout, has not been investigated. We analyzed a large US population database to determine the overall transplant complication rate in patients having a renal transplant with and without gout.

Methods: A retrospective review of Humana Research Database claims (2007-2017) was undertaken to identify kidney transplant patients with ≥6 months in plan before and after transplant. Diagnostic gout codes (ICD9/10) were used to categorize patients into gout and non-gout groups. Additionally patients were classified as having gout pre- or post-transplant based on first gout code occurrance. Transplant complications were determined using codes for complications of transplanted kidney, unspecified and other complications of kidney transplant, kidney transplant rejection, failure, and infection.

Results: The database contained 6085 patients with a kidney transplant and ≥6 months in plan both pre and post-transplant. Of these, 1504 patients had ≥1 gout codes (the first code occurred in 909 patients pre-transplant and 595 post-transplant), and 4581 patients never had a gout code. The renal transplant complication rate in the overall cohort was 36.0%. Patients with gout had a higher complication rate (40.4%) than those without gout (34.6%, OR: 1.28, 95%CI: 1.136–1.443, p<0.001). The higher complication rate in gout patients was driven by those who developed gout post-transplant.(**Table 1**)

Conclusions: Our analysis indicates that patients with gout, especially those with gout arising post-transplant, suffered from higher rates of overall transplant-related complications. In addition to more research on this topic, an increased focus on awareness and screening of renal transplant patients for gout is warranted.

Funding: Commercial Support - Horizon Therapeutics plc

Table 1. Renal transplant-related complications

Group	Number of Patients	Number with Complications	% with Complications
Enrolled Patients	6085	2191	36.0%
Gout and Transplant	1504	607	40.4%
Gout Pre-Transplant	909	304	33.4%
Gout Post-Transplant	595	303	50.9%
No Gout	4581	1584	34.6%

FR-PO1171

Assessing the Relationship Between Gout and Return to Hemodialysis Among Renal Transplant Patients

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Background: Although gout has been shown to be associated with poor renal outcomes among chronic kidney disease populations, this relationship is not well understood among renal transplant recipients. This analysis compared rates of return to maintenance hemodialysis, a negative transplant outcome, across three primary renal transplant patient cohorts based on gout status: non-gout, pre-existing gout, and new-onset gout.

Methods: This retrospective study of the United States Renal Data System examined Medicare beneficiaries that received a primary renal transplant between 2008-2013. Patients' Medicare claims data were used to identify pre-existing gout in the 2 years prior to transplant and new-onset gout in the 3 years post-transplant. To mitigate the effect of complications associated with acute allograft rejection/ failure, recipients who died, returned to dialysis, or received re-transplantation within 3 years after primary renal transplantation were excluded. Patients' return to hemodialysis was observed in the period between 3-5 years post-transplantation. The association between gout status (non-gout, pre-existing, and new-onset) and 5-year return to dialysis was evaluated via chi-squared tests.

Results: 39,780 patients received a primary renal transplant between 2008-2013 with Medicare as their primary payer after exclusions. Of these patients, 33,105 (83.2%) were non-gout, 4,747 (11.9%) had pre-existing gout, and 1,928 (4.8%) developed new onset gout post-transplant. 2,211 (5.6%) primary renal transplant recipients returned to hemodialysis 3 to 5 years post-transplantation. The rate of return to hemodialysis 3 to 5 years after transplantation for non-gout, pre-existing gout, and new onset gout was 5.6, 4.6, and 7.5%, respectively (all pairwise comparisons yielded p<0.05).

Conclusions: Compared to non-gout and pre-existing gout patients who received a primary renal transplant, patients who developed new-onset gout after transplantation were more likely to require maintenance hemodialysis, a negative renal transplant outcome. Further investigation is needed to determine if the presence, timing, and duration of gout relative to renal transplantation are independent predictors for return to dialysis.

Funding: Commercial Support - Horizon Therapeutics plc

FR-PO1172

Can Uric Acid Blood Levels in Renal Transplant Recipients Predict Allograft Outcome?

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Background: Hyperuricemia is common after renal transplantation, especially in those receiving calcineurin inhibitors (CNI). Increased uric acid (UA) levels were found predictive of kidney disease and end-stage renal disease in those with normal renal function and disease progression in individuals with kidney disease. Little, however, is known about the relationship between UA levels and allograft outcome.

Methods: We conducted a retrospective single-center analysis (N=368) in order to assess UA blood levels posttransplant association with allograft outcome.

Results: Patients were divided into 2 groups based on the mean UA level measured between 1-12 months posttransplant. Those with mean UA level ≥ 7 and 6.5 mg/dL (N = 164) versus mean UA level< 7 and 6.5 mg/dL for men and women respectively (N=204) had lower GFR values at 1, 3 and 5 years posttransplant. In a multivariate analysis adjusted for age, gender, race, transplant type, mean CNI levels, presence of slow graft function (SGF) and baseline allograft function (GFR at 3 months posttransplant) the association of UA levels to allograft function were not significantly associated with differences in GFR at 1, 3 and 5 years posttransplant.

Conclusions: Hyperuricemia is a surrogate for a worse allograft function. After adjustment for baseline allograft function increased UA levels were not found to be an independent predictor of long-term allograft function despite the known association of hyperuricemia with progression of cardiovascular and renal disease.

Baseline Characteristics of the High versus low UA groups

	High UA (N=164)	Low UA (N=204)	P Value
Age (years)	52.24 (13.76)	51.38 (13.92)	0.553
Males	84 (51.2)	124 (60.8)	0.083
Whites	99 (60.4)	134 (65.7)	0.462
Blacks	40 (24.4)	38 (18.6)	
LD	70(42.7)	138(67.6)	<0.001
DCD-ECD	57(34.8)	35(17.2)	
SCD	37(22.6)	31(15.2)	
SGF	86 (52.4)	61 (29.9)	<0.001
GFR 3M (ml/min)	43.33 (15.06)	58.37 (17.84)	<0.001
GFR 1Y (ml/min)	45.92 (17.30)	60.77 (19.70)	<0.001
GFR 3Y (ml/min)	43.42 (20.64)	58.02 (19.87)	<0.001
GFR 5Y (ml/min)	41.81 (21.38)	53.59 (23.12)	0.009

Continuous variables are presented as means (and standard deviations), categorical variables are presented as number of patients (and % of the entire group).

FR-PO1173

Longitudinal Kidney Function After Liver Transplantation in Patients with Acute-on-Chronic Liver Failure

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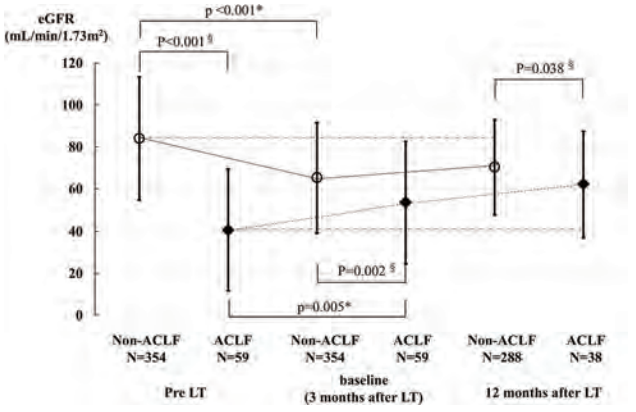
Background: Acute on Chronic Liver Failure (ACLF) is a syndrome defined as acute decompensation on pre-existing chronic liver disease (cirrhosis) caused by hepatic or extra-hepatic insights with several organ failures including acute kidney injury and associated with worse prognosis unless undergoing liver transplantation (LT). However, it has not been well known whether ACLF affects mid- and long-term kidney function after transplantation.

Methods: From 687 eligible LT recipients, 413 patients who had the data of serum creatinine at 3 months after LT (baseline) has been included, in this single-center, retrospective cohort study. Association of ACLF and estimated glomerular filtration rate (eGFR) at baseline and 12 months, also eGFR slope after baseline assessed by mixed effect model has been assessed.

Results: Fifty-nine patients (14.3%) was assigned to ACLF group. ACLF group was significantly younger, higher prevalence of alcoholic hepatitis, higher MELD score, and lower mean eGFR at the time of LT compared to non-ACLF group. The eGFR recovered toward to baseline then stabilized through 12 months after LT in ACLF group and eGFR decreased toward to baseline then stabilized through 12 months after LT in non-ACLF

group. However, eGFR at baseline and 12 months in ACLF group was still significantly lower than that in non-ACLF group (53.6±29.1 and 62.3±25.2 ml/min/1.73m^2 in ACLF group and 65.4±26.2 and 70.5±22.6 ml/min/1.73m^2 in non-ACLF group) (Figure). The eGFR slope in non-ACLF group was decreasing (-2.58 ml/min/1.73m^2/year, 95%CI: -4.79 to -0.38); however, the eGFR slope in ACLF group did not have significant trajectory (0.93 ml/min/1.73m^2/year, 95%CI: -6.08 to 7.94) during observational period. These slopes were not statistically different between two groups (p=0.431).

Conclusions: The mid- and long-term eGFR in ACLF group would be corresponded to deteriorated eGFR before LT and would not recover to the same level of non-ACLF group.



FR-PO1174

Sex Differences in Multimorbidity Clusters in Kidney Transplant Patients: Data from a Multicentre Trial

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Background: Multimorbidity is a complex phenomenon which is highly prevalent in patients with chronic kidney disease (CKD). Comorbidities can create a 'treatment burden' and specific combinations of conditions may have greater effects on functional status, quality of life, and mortality than others. Before determining the impact of multiple chronic conditions on kidney transplant recipients, the patterns of multimorbidity disease need to be identified.

Methods: Data was derived from a cross-sectional multicentre survey study. Principal Components Analysis (PCA) (orthogonal (varimax) rotation with a minimum factor loading of .40) was used to identify multimorbidity clusters for both sexes. The number of components ('clusters') was determined by the Eigenvalue of >1 or visual interpretation of the scree plot.

Results: Data from 2240 transplant patients [age: 52.6 (13.6) years; males: 1289 (58%); white: 1503 (67%); total number of additional (to CKD) comorbidities: 1.35 (1.1); cadaver donor grafts: 1077 (48%); months with transplant: 71.0 (85.2)] were collected from 17 geographically diverse transplant centres. Five multimorbidity clusters were identified for males, and three for females, which are displayed in Figure 1. For males, one cluster included cardiopulmonary diseases; in females this cluster also included musculoskeletal conditions. In females, hypertension clustered with diabetes, whereas in males it was a standalone condition.

Conclusions: Patterns of comorbidities are different between male and female transplant patients, and include concordant (i.e. sharing common pathophysiological pathway with CKD (e.g. diabetes)) and discordant conditions (i.e. not sharing common pathway with CKD (e.g. depression)). Recognition of multimorbidity clusters may help identify patients at risk of co-occurring diseases. This may favour a more patient-orientated management strategy to reduce treatment burden and improve quality of life. Further research is needed to enhance the understanding of the identified clusters to improve the management of multimorbid kidney transplant recipients.

Funding: Private Foundation Support

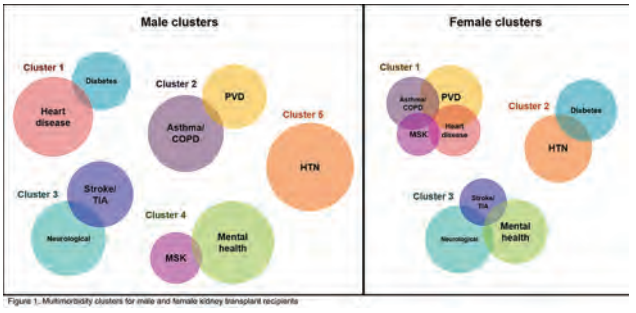

Figure 1. Multimorbidity clusters for male and female kidney transplant recipients

FR-PO1175

Long-Term Changes in Sleep Disordered Breathing in Renal Transplant Patients

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Background: Sleep Disordered Breathing (SDB) triggers sympathetic over-activity, hypertension and cardiovascular (CV) events in the dialysis population. SDB improves after renal transplantation but long term changes in SDB in renal transplant patients have not been studied.

Methods: We studied long term changes in SDB in a series of 221 renal transplant patients (age: 46.9±11 years; M: 70.1%). Over a median follow up of 52.1 months (Interquartile range: 36.8-67.3 months) we performed 404 polysomnographic recordings (on average 2 studies per patient). Data analysis was performed by Generalized Estimating Equations (GEE).

Results: At baseline, the median value of the apnea-hypopnea index (AHI) was 1.8 episodes/h [interquartile range (IQR): 0.6-5.0]. One-hundred and sixty-six patients (75%) had a normal AHI (<5). Thirty-seven patients (17%) had mild to moderate SDB (AHI 5 to 14.9) and a minority (18 patients, 8%) had severe SDB (AHI >15). At baseline, AHI was directly related with age (rho=0.24, P<0.001), BMI (rho=0.27, P<0.001), fibrinogen (rho=0.16, P=0.027) and glucose (rho=0.14, P=0.035). The median values of minimum ($MinSaO_2$) and average nocturnal O_2 saturation were 89% and 95.6%. On longitudinal observation, the median AHI rose from 1.8 (IQR: 0.6-5.0) to 2.9 (IQR: 1.0-6.6) and to 3.6 (IQR: 1.7-10.4) at the second and the third longitudinal visit, respectively (P for trend=0.009) and the proportion of patients with mild to moderate and severe SDB rose to 22.7% and 20.5%, respectively. Longitudinal changes in MinSaO2 paralleled those in the AHI. In adjusted analyses BMI (P<0.001) and C-reactive protein (P=0.001) emerged as the sole independent longitudinal correlates of AHI and $MinSaO_2$.

Conclusions: Sleep Disordered Breathing worsens over time in renal transplanted patients. The post-transplantation rise in BMI, a potentially modifiable risk factor, is an important factor underlying the risk for SDB worsening in this population.

FR-PO1176

Prevalence of Depression in Kidney Transplant Recipients: A Long-Term Population-Based Study

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Background: Depression is associated with impaired quality of life and increased morbidity and mortality in patients with end-stage renal disease (ESRD) and kidney transplant (KT) recipients. Few data is known about the prevalence of depression in KT recipients. In this study, we aimed to explore the prevalence of depression in KT recipients compared with ESRD patients and healthy controls (HCs) in a long-term population-based cohort.

Methods: We analyzed a Nationwide Health Insurance Database of South Korea and identified patients who received KT from the year of 2007 to 2015. KT recipients were selected and matched with ESRD patients and HCs considering age, sex, and inclusion year. KT and ESRD patients were further matched with diabetes and hypertension. The prevalence (prevalence ratio, PR per 1000) of depression in KT recipients was compared with ESRD patients and HCs, respectively.

Results: A total of 7,971 patients were analyzed in all three groups, respectively. Both KT recipients and ESRD patients were poorer, having more co-morbidities than matched HCs. KT recipients revealed markedly a lower prevalence of depression than in ESRD patients (IR, 66.1 vs 23.5 per 1000 patient-year; Hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.33-0.39), although they showed only slightly higher prevalence of depression than in HCs (IR, 19.4 vs 23.5; HR, 1.21; 95% CI, 1.09-1.35). Interestingly, after adjusting the comorbidity status with Charlson Comorbidity Index (CCI), KT recipients showed a lower risk of depression compared with HCs (adjusted HR 0.64; 95% CI, 0.54-0.75, P<0.001), whereas ESRD patients remained at higher risk of depression development than HCs (adjusted HR 1.80; 95% CI, 1.55-2.10, P<0.001). Among KT recipients, older age, female sex, lower socioeconomic status, and more co-morbidities represented by CCI score were associated with increased risk of depression.

Conclusions: KT recipients showed a markedly lower risk or depression than ESRD patients and even than matched HCs after adjustment of co-morbidities. Our data suggest a broader role of KT than previously appreciated in terms of improving quality of life by reducing the risk of depression.

FR-PO1177

The Potential for Improved Medication Adherence with a Complete Once Daily Immunosuppression Regimen in Kidney Transplant: Results of a Randomized Controlled Study

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Background: Medication non-adherence is common after transplant and a major contributor to rejection and graft loss. The objective of this study was to obtain preliminary

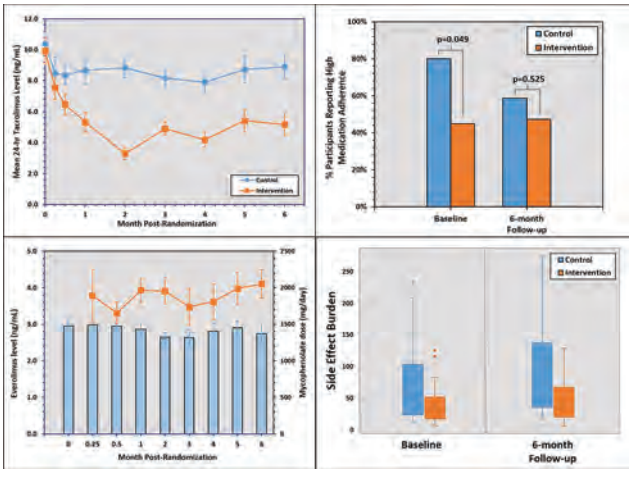
safety, tolerability and efficacy data of a complete once daily immunosuppression regimen of LCP-Tac (Envarsus XR), everolimus and pred, compared to LCP-Tac, mycophenolate BID and pred.

Methods: This was a randomized, controlled pilot study with the primary aim of assessing self-reported medication adherence and comparing this between a once and twice daily immunosuppressant regimen. At 3±2 months post-transplant, patients were randomized to receive LCP-Tac and everolimus once daily or LCP-Tacand mycophenolate BID (control arm) for 6-months.

Results: 354 were screened, 80 met eligibility, and 40 were randomized. The mean age was 51±14 years, 33% were female, 45% African-American, and 55% had a cPRA >20%. Baseline characteristics were similar between study arms. Tac exposure was lower in the intervention arm (left side of Figure). Self-reported high medication adherence was higher at baseline in the control group (80% vs. 45%, p=0.049), which equilibrated at study end (59% vs. 47%, p=0.525; right side of Figure). Medication side effect burden tended to be less severe in the intervention group, with both regimens being well tolerated. For QOL, role limitations improved in the entire study group similarly across arms while social functioning trended towards improving to a greater degree in the intervention arm (net change: +8.8 intervention arm, -4.1 control arm; p=0.0898). There were no acute rejections, graft loss or death in either arm during the study.

Conclusions: These results provide preliminary evidence of the safety, efficacy, tolerability and potential benefit of sustaining high medication adherence with a novel once daily immunosuppression regimen.

Funding: Commercial Support - Veloxis



FR-PO1178

Can Pretransplant Psychosocial Factors Predict Racial Difference in Post-Transplant Adherence?

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Background: The success of a kidney transplant (KT) relies on patients' ability to adhere to a complex medical regimen and routine follow up post-transplant. Non-adherence is common post-transplant and is a leading cause of allograft loss. In this study, we aimed to *identify non-medical factors at the time of initial KT evaluation that predicted racial difference in non-adherence post-transplant.*

Methods: We performed a prospective cohort study of patients who underwent initial KT evaluation, received a KT and were interviewed at 6 months post-transplant. We collected data on baseline demographics, medical, cultural, psychosocial and transplant related factors. We quantified adherence to each medication within the first 6 months post KT (immunosuppressants and anti-hypertensives) with a Likert scale ranging from never to daily missing of medications and used the average of the individual scores as a continuous outcome variable. We then built multiple linear regression models using variables with effect estimates ≥0.2 and p-values <0.1 in bivariate analyses to identify factors that predicted adherence.

Results: 1152 patients were enrolled in the initial study, 149 patients underwent KT and had ≥6 months follow up; 123(82.55%) were White, 84(56.38%) were male and 103(69.13%) were age >45; adherence scores ranged from 1-7 [mean(SD)=6.8(0.78)]. African American race predicted lower adherence, even after accounting for cultural, psychosocial and transplant factors. Age > 45 and having public insurance predicted greater adherence(Table 1).

Conclusions: African American race was a significant risk factor for post-transplant non-adherence. Data from this study showed that cultural and psychosocial factors did not affect this association.

Funding: Commercial Support - Dialysis Clinic Inc

Table 1. Linear regression models of baseline factors associated with non-adherence[1]

Variables	Simple Model			Multiple Model		
	Estimate	95% CI[2]	P-value (F-test)	Estimate	95% CI[2]	P-value (F-test)
Demographics Factors						
Race						
NH[3] white	*Reference*			*Reference*		
NH[3] black	-0.63	(-1.06; -0.20)	0.02	-0.62	(-1.05; -0.19)	0.02
Other	-0.07	(-0.53; 0.39)		0.02	(-0.43; 0.47)	
Age						
18-45				*Reference*		
> 45				0.30	(0.03; 0.56)	0.03
Insurance						
Private only				*Reference*		
Other				0.38	(0.13; 0.63)	< 0.01
Medical/Health Factors	*(none selected)*			*(none selected)*		
Culturally-Related Factors						
Experienced discrimination						
No				*Reference*		
Yes				-0.33	(-0.68; 0.03)	0.07
Psychosocial Characteristics						
Social support				0.02	(-0.01; 0.05)	0.22
Self-esteem				0.18	(-0.12; 0.48)	0.25
Transplant-Related Beliefs						
Number of learning activities				0.07	(-0.02; 0.16)	0.13

Note: [1]Interactions between race with cultural, psychosocial and transplant related factors were not significant; [2]CI = Confidence interval; [3]NH = Non-Hispanic

FR-PO1179

Noncompliance: A Significant Contributor for Renal Allograft Loss

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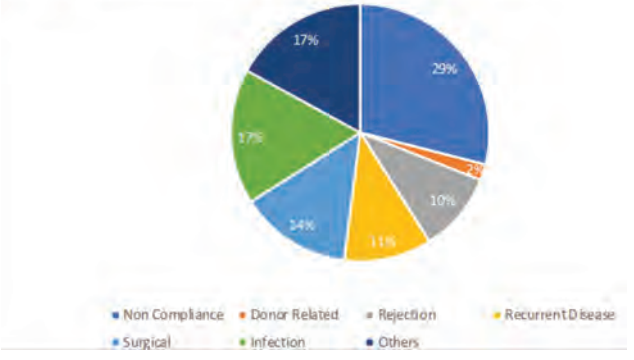
Background: United network for organ sharing (UNOS) implemented the new kidney allocation system (KAS) in 2014 to reduce inequity and improve life-years gained from kidney transplantation (KT). KAS allowed matching of high quality kidneys to younger recipients and allowed backdating of waitlist date to account for dialysis vintage. Additionally, transplant centers have aimed to increase access to KT by streamlining evaluation process and reducing barriers to wait listing. Potential unintended consequences of these policies may be selection of patients with higher disease burden and lower social support. We investigated this by examining causes of allograft loss within the first 5 years at our center.

Methods: Single center study of kidney transplant recipients between 2013- 2017. Causes of death-censored allograft loss was examined using the following 7 categories: 1. Non Compliance (medication, follow up, blood work), 2. Donor Related (High KDPI), 3. Rejection (Acute/Chronic T- Cell and Antibody Mediated Rejection), 4. Recurrence of primary kidney disease, 5. Surgical/Technical, 6. Infection Related (BK Virus, Pyelonephritis), 7. Others. Differences in baseline characteristics for patients with and without noncompliance were examined.

Results: 18 of 63 (29%) graft losses were attributed to noncompliance. Noncompliance group had younger patients (mean age 38 y vs 55 y; p=0.0001) and higher proportion of African American race (47% vs 22%;p=0.055)

Conclusions: Early allograft loss due to noncompliance is high and is more common among African Americans and young patients. This might offset the potential benefits arising from the new KAS. This data should be used to further investigate specific reasons for non-adherence that can be targeted for intervention.

Patient Demographics	Graft Loss N=63	p-value
Recipient		
Age	50.07 ± 16.22	<.0001
Male	39 (61.90%)	
Race		
White	44 (69.84%)	
African American	18 (28.57%)	
Other	1 (1.59%)	
BMI mean ± std	28.23 ± 4.95	
Dialysis days before transplant, mean ± std	1725.62 ±1354.29	
Cause of ESRD		<0.0012
Cystic	0 (0.00%)	
Diabetes	12 (19.05%)	
Glomerulonephritis	3 (4.76%)	
Hypertension	19 (30.16%)	
Other	29 (46.03%)	
Donor		0.0009
Age(years) mean± std	41.33 ± 12.96	
Deceased Donor %	48 (76.19%)	0.0071
KDPI, %, mean ± std	52.98 ± 24.24	
Transplant		
CMV- High Risk	13 (20.63%)	0.32
EBV-High Risk	3 (4.76%)	0.96
% cPRA >20	32 (50.79%)	0.11



Demographics and Results

FR-PO1180

Clinical Outcomes of HLA-Identical Transplants in the Tacrolimus Era

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Background: HLA identical living donor transplants (LDKT) have excellent graft survival. It remains unclear if causes of death/graft loss, histology or complications associated with tacrolimus-era immunosuppression are different when compared to non-HLA identical recipients.

Methods: We performed a nested case control study of HLA identical full sibling LDKT recipients (cases) and non-HLA identical LDKT recipients (controls) matched for age, sex and year of transplant from 1999 to 2018. Baseline characteristics, overall survival and death censored graft survival (DCGS), histology, and complications were compared.

Results: 184 recipients were in each cohort with similar baseline characteristics except for induction regimens: cases were more likely to receive anti-CD25 and alemtuzumab and less likely to receive thymoglobulin (p=<0.01). Cases had longer median follow-up [7.6 (3.7-11.9) vs 5.7 (2.8-10.1) years, p=0.01], better overall survival (81% vs. 71%, p<0.001) and better DCGS (94% vs. 77%, p<0.001). Protocol biopsies at 1, 2, 5, and 10 years showed more tubulitis, peritubular capillaritis and glomerulitis in controls. Acute cellular rejection, chronic antibody-mediated rejection, and BK nephropathy were more common in controls (Table 1). Causes of DCGS and death were similar between groups (Table 1). Time to DCGS from alloimmune injury was shorter in controls (p=0.01); all events in cases (n=3) occurred in the absence of immunosuppression (two were non-adherent and one had PTLD). Rates of leukopenia, proteinuria, and urinary tract infections were similar.

Conclusions: HLA identical LDKT recipients had better patient survival and DCGS when compared to a non-HLA identical cohort. Causes of DCGS and death were similar. Time to DCGS from alloimmune injury was shorter in controls. Controls had higher rates of both cellular and antibody-mediated injury and BK nephropathy. These results suggest a potential role for reducing immunosuppression in HLA identical sibling LDKT.

Outcomes	Cases	Controls	p-value
Complications at any time point – N (%)			
-Borderline acute cellular rejection (ACR)	8 (4.4%)	15 (8.2%)	0.13
-ACR Banff 1A	7 (3.8%)	18 (9.8%)	**0.04**
-ACR Banff 1B	6 (3.3%)	6 (3.3%)	1.0
-ACR Banff 2A	1 (0.5%)	3 (1.6%)	0.32
-ACR Banff 2B	0 (0%)	1 (0.5%)	0.32
-Acute (active) antibody mediated rejection	3 (1.6%)	8 (4.4%)	0.13
-Chronic antibody mediated rejection	4 (2.2%)	21 (11.4%)	**<0.0001**
-BK nephropathy	3 (1.6%)	11 (6.0%)	**0.03**
Causes of DCGS	**Cases (n=17)**	**Controls (n=41)**	0.69
-Alloimmune injury	3	14	0.37
-Glomerular disease	4	8	0.84
-Tubular Injury	5	9	0.81
-Structural or vascular	4	7	0.49
-Other	1	3	0.79
Causes of death	**Cases (n=32)**	**Controls (n=29)**	0.87
-Cardiovascular	5	6	
-Infection/sepsis	5	4	
-Malignancy/hematologic complications	8	9	
-Neurologic complications	2	2	
-Trauma or surgical complications	1	1	
-Unknown or natural causes	10	7	

Table 1. Complications, death censored graft loss and death in cases vs controls

FR-PO1181

Impact of 1-Year Post-Transplant Tacrolimus Trough Levels on Long-Term Renal and Cardiovascular Outcomes in Stable Kidney Transplant Recipients

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Background: This study aimed to investigate the impact of 1-year post-transplant tacrolimus (TAC) trough levels on renal and cardiovascular outcomes in stable kidney transplant recipients (KTRs).

Methods: KTRs receiving TAC and mycophenolate-based immunosuppression who have never experienced renal or cardiovascular events within 1-year post-transplant were included from a multicenter observational cohort study. Renal outcome was defined as a composite of biopsy-proven acute rejection, interstitial fibrosis and tubular atrophy, and death censored graft loss. Cardiovascular outcome was defined as a composite of de novo cardiomegaly, left ventricular hypertrophy, and cardiovascular events.

Results: A total of 603 eligible KTRs were divided into low-level (LL) and high-level (HL) TAC based on the median TAC level at 1-year post-transplant of 5.9 ng/mL (range 1.3-14.3). During the mean follow-up of 38.2 ± 13.0 months, 27 and 166 episodes of renal and cardiovascular outcomes occurred, respectively. In multivariate Cox regression analysis, LL-TAC and HL-TAC were not independent risk factors for renal and cardiovascular outcomes, respectively. Instead, deceased donor KT (adjusted hazard ratio [AHR], 2.52; 95% confidence interval [CI], 1.10–6.01; P = 0.037) and male (AHR, 1.62; 95% CI, 1.06–2.47; P = 0.025) were independent risk factors for renal and cardiovascular outcomes, respectively. No significant differences in estimated glomerular filtration rate at 2- and 3-year post-transplant were observed between two groups.

Conclusions: TAC trough levels after 1-year post-transplant were not directly related to long-term renal and cardiovascular events in stable KTRs. There might be no need to insist higher TAC trough levels after 1-year post-transplant in KTRs with stable post-transplant clinical course.

FR-PO1182

Induction Therapies in the Tacrolimus-Based Immunosuppression Era: A Meta-Analysis

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Background: Induction therapy with rabbit Anti-thymocyte Globulin (rATG) and IL-2 Receptor Antagonist (IL-2RA) resulted in marked reduction of acute allograft rejection rate. However, the relative value of these agents in the era tacrolimus-based maintenance immunosuppression remains uncertain.

Methods: A systematic review of Pubmed, Medline, Embase and Cochrane databases was conducted to identify outcomes in terms of graft and patient survival, rejection, infection and malignancy rates in renal transplant recipients (RTRs) (Figure 1). Based on received induction therapy, RTRs were divided into 2 groups (IL2-RA versus rATG). All subjects were on tacrolimus-based immunosuppression. The meta-analysis included 6 randomized case-control studies with total of 1017 subjects and follow-up period ranged from 12 months to 36 months. Random effects model (REM) was used to identify risk difference. Confidence interval excluding the value 1 was used as evidence for statistically significant risk difference. Heterogeneity was assessed using Der Simonian analysis (P value<0.1).

Results: The REM showed no significant differences in acute rejection rates, graft survival and patient survival between IL2-A and rATG induction therapies with confidence interval ranges (CIR) from 0.94 to 1.64, 0.57 to 1.42 [relative risk (RR): 0.9], and 0.6 to 2.35, RR:1.19 respectively (Figure 2, 3). REM for CMV infection showed a lesser tendency for CMV infection and higher rate of acute rejection in high-risk transplants of

the IL2-RA group compared to ATG group with CIR from 0.52 to 1.05 (RR: 0.73) and 1.05 to 2.51 (RR: 1.55) respectively. In standard risk transplants, there were no significant differences between acute rejection rates (CIR from 0.71 and 1.47, RR: 1.02).

Conclusions: This meta-analysis revealed no significant difference in patient and graft survival when using IL-2RA vs rATG with the tacrolimus-based maintenance immunosuppression. Subgroup analysis noted a trend for reduced rejection in high-risk recipients receiving rATG compared to IL-2RA.

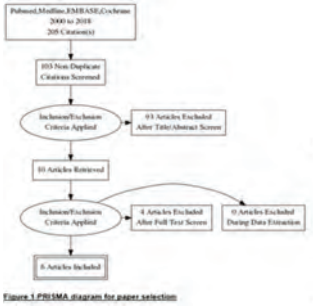

Figure 1 PRISMA diagram for paper selection

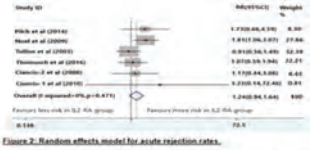

Figure 2: Random effects model for acute rejection rates.

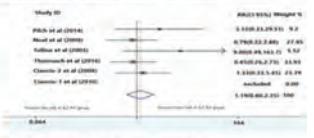

Figure 3: Random effects model for patient survival.

FR-PO1183

Renal Transplant Patients Under Calcineurin Inhibitor Therapy Rapidly Acquire an Aberrant Lysosomal Lesion in Proximal Tubular Cells

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Background: Calcineurin inhibitor therapy has changed the field of (renal) transplantation by considerably prolonging graft survival. Yet, all immunosuppressive calcineurin inhibitors are nephrotoxic that eventually contribute to complete scarring of the renal allograft. In renal biopsies, many histopathological features have been considered indicative of CNI nephrotoxicity, i.e. striped fibrosis, vascular hyalinosis, isometric tubular vacuolization, glomerulosclerosis, cellular infiltration and tubular atrophy, however, all are rather aspecific and can be secondary to many other causes. During the course of evaluating the specificity of a recently discovered proximal epithelial lysosomal lesion (i.e. multiple enlarged (>1,2µm) dysmorphic lysosomes containing electron dense non-membrane bound aggregates) in patients with Chronic Interstitial Nephropathy in Agricultural Communities (CINAC), we observed this lesion in renal transplant patients treated with cyclosporine or tacrolimus. Here, we test the hypothesis whether this lysosomal lesion is acquired during CNI therapy.

Methods: A retrospective transmission electron microscopic analysis was performed to evaluate the presence of the typical lysosomal lesion on the following biopsies from renal transplant patients: 20 deceased donor implantation biopsies; 5 living donor implantation biopsies. For another 10 additional deceased donor renal allograft recipients, we evaluated implantation as well as protocol biopsies taken after 6 and 12 months of CNI treatment that started immediately after transplantation. Also included were 24 indication biopsies of CNI treated renal transplants.

Results: Of the total set of implantation biopsies (n=35), 2 (6%) were positive for the aberrant lysosomal phenotype on EM, whereas in the protocol and indication biopsies prevalence of the lesion was considerably higher ranging between 56% (protocol) and 80% (indication) of cases.

Conclusions: CNI therapy is associated with the fairly rapid appearance of a particular proximal tubular lysosomal phenotype observable on EM, that was not (or rarely) present at implantation. Whether this lesion is related to CNI toxicity and indicative for the outcome for the graft and/or patient survival after renal transplantation has to be investigated in a prospective trial.

Funding: Government Support - Non-U.S.

FR-PO1184

Drug Formulation Associates with Patterns of Serum Trough Tacrolimus Levels: Experience at a Single Irish Centre

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Background: Consistently maintaining serum trough tacrolimus levels in the desired therapeutic range is critical to optimise outcomes in kidney transplant recipients. Patients are typically prescribed twice-daily (BD) or once-daily (OD) tacrolimus formulations (e.g. Prograf ® or Advagraf ®). Not uncommonly, patients switch formulation in the course of their follow-up. This study examines associations between BD and OD tacrolimus formulations and achieved serum trough levels (TL) in a cohort of kidney transplant recipients.

Methods: Data pertaining to tacrolimus prescription (date, dose, formulation) and serum TL in kidney transplant recipients was extracted from eMedRenal for a 3-year period (January 2016 to December 2018). Descriptive and inferential analyses were first performed on all TLs in the study population. Mean TL and standard deviations by formulation type were then calculated for each patient. Comparisons of mean TL and standard deviations within subjects who switched formulation during the study period were made by paired samples t-test. The potential for time post-transplant influencing observations was recognised and all analyses were performed in stratified datasets of TL within and after the first post-transplant year.

Results: 2870 serum TL were analysed for 142 patients; 67.6% male and 32.4% female with a mean age of 57 (±14) years. The mean allograft vintage in our study population was 8.1 (± 5.7) years. In the 47 patients who switched formulation during the study period, fluctuation in within-patient TL levels was reduced ($p<.001$), but overall mean serum TL per patient was 1.6ng/mL lower (95% CI,1.18 to 2.04, $p<0.001$), on OD versus BD tacrolimus.

Conclusions: The differences in serum TL noted by formulation beyond 1-year post-transplant in this cohort were very significant. Furthermore, switching to OD formulations while associated with less fluctuation in levels is associated with lower mean TL. The data emphasises the importance of attending to tacrolimus trough levels, and by implication drug dosing, beyond the first transplant year and especially after switches in formulation.

	<1 year post-transplant	>1 year post-transplant
BD Tacrolimus	n=540	n=1555
% Trough <4	1.7	6
% Trough 4-9	63.9	79.2
% Trough >9	34.4	14.8
OD Tacrolimus	n=284	n=491
% Trough <4	2.1	11.4
% Trough 4-9	69.7	79.2
% Trough >9	28.2	9.4

FR-PO1185

Prevalence of CYP3A Haplotype and Its Relation to Calcineurin Inhibitors Toxicity in Patients with Renal Transplantation Greater Than a Year in Western Mexico

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Background: ESRD is a public worldwide health problem and kidney transplantation is the RRT of choice. Immunosuppressive treatment with tacrolimus has significantly improved short-term graft survival. It has a narrow therapeutic index and a pharmacokinetic variability that may predispose to nephrotoxicity. Polymorphisms of cP450 (CYP3A4 and CYP3A5) have been related to variability in tacrolimus metabolism.

Methods: Retrospective study in 338 patients with renal transplant over a year being cared in our hospital, in treatment with tacrolimus, January 2017 - January 2018. Genotyping of the variants CYP3A5*3, CYP3A5*1, CYP3A4*1, and CYP3A4*1b was performed and frequency of nephrotoxicity and blood tacrolimus levels were associated with each of the genotypes.

Results: The most frequent polymorphisms were CYP3A5*3/*3 in 53% and CYP3A4*1/*1 in 84%. The most frequent haplotype was CYP3A5*3/*3 + CYP3A4*1/*1 in 50.59%, followed by CYP3A5*1/*3 + CYP3A4*1/*1. Figure 1 shows the behavior of the CYP3A polymorphisms. CYP3A4*1b/*1b and CYP3A5*1/*1 required the highest tacrolimus weight dose and had the lowest blood tacrolimus levels, statistically different from CYP3A*1/*1 and CYP3A5*3/*3, respectively. The comparison between different haplotypes showed a significant difference only in the weight dose, not in the tacrolimus blood levels. There was no significant statistical difference in CNI toxicity.

Conclusions: In the western Mexican population, CYP3A4*1/*1 and CYP3A5*3/*3 are the most prevalent polymorphisms, with a slow metabolizer profile. Recipients with CYP3A4*1b/*1b or CYP3A5*1/*1 polymorphisms require higher tacrolimus dosage and show a tendency to have higher rates of CNI toxicity despite having low tacrolimus blood levels.

Figure 1. CYP3A4, tacrolimus pharmacology and CNI toxicity

	CYP3A4			
Variable	CYP3A4*1/*1	CYP3A4*1/*1b	CYP3A4*1b/*1b	p
Tacrolimus daily dose (mg)*	4.0105	3.7021	4.2500	0.619
Blood Tacrolimus levels (ng/ml) *	7.3100	7.1050	3.4208	0.668
Tacrolimus weight dose (mg/kg/day)*	0.0619	0.0571	0.1485	0.000
CNI Toxicity**	34.84	46.81	50.00	0.270

*Results are shown as means, and its statistical analysis was carried out using ANOVA.
**Results are shown as percentafes and its statistical analysis was carried out using Kruskall-Wallis.

Figure 2. CYP3A5, tacrolimus pharmacology and CNI toxicity

	CYP3A5			
Variable	CYP3A5*1/*1	CYP3A5*1/*3	CYP3A5*3/*3	p
Tacrolimus daily dose (mg)*	5.6842	4.7674	3.2579	0.000
Blood Tacrolimus levels (ng/ml) *	4.7982	7.1253	7.5540	0.410
Tacrolimus weight dose (mg/kg/day)*	0.1039	0.0759	0.0488	0.000
CNI Toxicity**	26.32	35.66	38.42	0.506

*Results are shown as means, and its statistical analysis was carried out using ANOVA.
**Results are shown as percentafes and its statistical analysis was carried out using Kruskall-Wallis.

FR-PO1186

Safety and Efficacy of LCP-Tacrolimus (LCPT) in Hispanic De Novo Kidney Transplant Recipients (KTR)

Rafael Villicana,[3] Giselle Guerra,[4] Misbah A. Moten,[1] Samir J. Patel,[1] Daniel R. Stevens,[1] Ulf Meier-Kriesche,[1] Suphamai Bunnapradist.[2] *[1]Veloxis Pharmaceuticals, Cary, NC; [2]University of California Los Angeles, Los Angeles, CA; [3]Loma Linda University, Loma Linda, CA; [4]University of Miami/ Miller School of Medicine, Miami, FL.*

Background: Safety and efficacy of once daily, LCPT have been established among various subgroups of KTR, however outcomes in Hispanic patients have yet to be analyzed. The purpose of this analysis was to investigate treatment failure and safety outcomes in Hispanic de novo KTR on LCPT or twice daily, immediate-release tacrolimus (IR-TAC).

Methods: A post hoc, subgroup analysis of patients identifying as Hispanic/Latino from a phase III randomized controlled trial was conducted. Patients were dosed at 0.17 mg/kg/day LCPT and 0.1 mg/kg/day IR-TAC on day 1, with target tacrolimus trough concentrations of 6-11ng/mL for the first month, then 4-11ng/mL. Treatment failure was defined as a composite of biopsy-proven rejection (BPAR), graft loss, death, and loss-to-follow up. Concomitant immunosuppressants included basiliximab induction, mycophenolate, and steroids.

Results: Seventy-four LCPT and 79 IR-TAC patients were included in the analysis. Demographics were similar between the two groups. Overall, fewer treatment failures occurred in Hispanic LCPT recipients compared to those on IR-TAC at 12 months (12.2% vs. 25.3%, p=0.04). BPAR largely accounted for the difference in efficacy (Table 1). Mean tacrolimus trough levels were higher with LCPT during the first 2 weeks post-transplant and similar thereafter. Renal function remained stable from 1 month to 12 months for LCPT patients, however the incidence of NODAT at 12 months in at-risk patients was 18.8% in LCPT patients and 3.8% in IR-tac patients (p=0.057). Remaining adverse events and opportunistic infections were similar between groups.

Conclusions: Hispanic de novo KTR on LCPT experienced fewer treatment failures at 12 months, however a trend towards increased NODAT was noted. These findings may support the approved, lower recommended initial dose (0.14 mg/kg) in this population.

Funding: Commercial Support - Veloxis Pharmaceuticals

Efficacy and Renal Function

Outcome	LCPT (n=74)	IR-TAC (79)	p-value
Composite 12 Month Treatment Failure, n(%)	9 (12.16%)	20 (25.32%)	0.04
BPAR, n(%)	7 (9.46%)	16 (20.25%)	0.07
Death, n(%)	1 (1.35%)	3 (3.80%)	0.62
Graft Failure, n(%)	2 (2.70%)	4 (5.06%)	0.68
Lost to Follow Up, n(%)	0	2 (2.53%)	0.50
1 Month GFR, mean(SD)	61.8 (23.03) (n=69)	63.0 (23.07) (n=72)	0.75
6 Months GFR, mean(SD)	60.2 (19.89) (n=68)	65.9 (20.32) (n=68)	0.17
12 Months GFR, mean(SD)	60.8 (18.38) (n=68)	68.6 (19.38) (n=68)	0.03
General linear model fixed effect p-values for renal function over 12 months: Treatment, p=0.18; Day, p=0.20; Treatment*Day, p=0.06			

FR-PO1187

Weight-Based Dosing for Tacrolimus: A Single-Center Experience

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Background: Tacrolimus (FK) remains the mainstay of maintenance immunosuppression for kidney transplant (KT) recipients. A therapeutic trough (TT) is maintained by dose adjustments within an acceptable narrow range. Low TTs are associated with acute rejection (AR) episodes. In order to address a wide variability in the initial prescribed dose, as well as issues with delayed time to TT, we implemented weight-based dosing (WBD) for FK in our center. Herein we present the results following this change.

Methods: For WBD, patients received FK at 0.1mg/kg/day on first post operation day (POD), with dose adjustments thereafter per standard protocol, for target TTs of 8-11ng/mL. Patients who underwent KT in the 6 months pre and post implementation of WBD were included in the analysis. We looked at baseline demographics, as well as donor and recipient characteristics. Rates of AR (per Banff 2017 criteria) at 90 days, serum creatinine (SCr) at 30 days, time to TT, and delayed graft function (DGF) were reviewed. Multi-organ txps, except kidney-pancreas were excluded.

Results: Following KT, 70 patients in the WBD cohort, and 68 patients in the cohort prior to the implementation [non WBD (nWBD)] were included. AR was seen in 7/65 of the WBD group, and in 3/56 of the nWBD group; p=0.281. On POD 3, the median FK TT was 8.5ng/mL in the WBD, versus 5.9ng/mL in the nWBD (figure 1). To avoid confounding, 38 live donor KT recipients were excluded from DGF analysis. In patients with deceased donor KT (DDKT), DGF rate was significantly higher in nWBD versus WBD group (19/41 [46.3%] vs 9/42 [21.4%], respectively; p<0.05). No difference in median SCr was noted.

Conclusions: FK levels are expected to reach a steady state after 3-4 doses. The WBD group achieved TTs earlier than the nWBD group. Significantly higher DGF rate was noted in the nWBD group, with similar rates of rejection in both groups. Further large-scale studies are needed to examine the role of WBD on DGF, AR and its effect on graft function, as well as costs in the immediate post txp period.

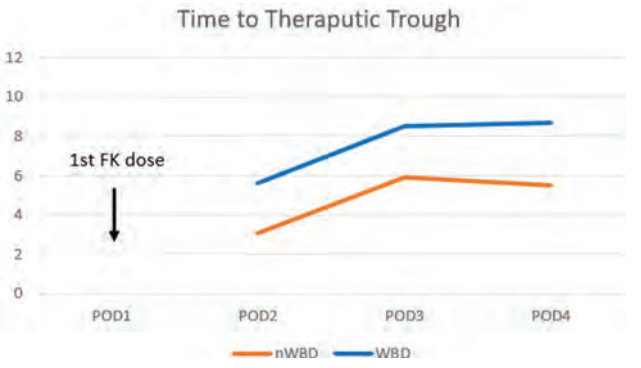

Figure 1

FR-PO1188

Safety and Efficacy of Conversion from Immediate-Release Tacrolimus (IR-TAC) to LCP-Tacrolimus (LCPT) in Hispanic Kidney Transplant Patients (KTR)

Suphamai Bunnapradist,[3] Giselle Guerra,[4] Samir J. Patel,[1] Misbah A. Moten,[1] Daniel R. Stevens,[1] Ulf Meier-Kriesche,[1] Rafael Villicana.[2] *[1]Veloxis Pharmaceuticals, Cary, NC; [2]Loma Linda University, Loma Linda, CA; [3]University of California Los Angeles, Los Angeles, CA; [4]University of Miami/ Miller School of Medicine, Miami, FL.*

Background: A large phase III study demonstrated safety and efficacy of once daily, LCPT in stable KTR converted from twice daily IR-TAC. Hispanic patients comprise a substantial proportion of KTR, however analyses within this cohort had yet to be conducted. The purpose of this subgroup analysis was to investigate treatment failure and safety outcomes of Hispanic KTR converted from IR-TAC to LCPT.

Methods: A post hoc, subgroup analysis from a phase III randomized controlled trial was conducted. Hispanic/Latino patients at least 3 months post-transplant on a stable IR-TAC dose were converted using a multiplier of 0.85 for non-Black recipients and 0.7 for Black recipients to maintain target tacrolimus trough concentrations of 4-15 ng/mL. Treatment failure was defined as a composite of for cause biopsy-proven acute rejection (BPAR), graft loss, death, and loss-to-follow up.

Results: 55 patients were included in this analysis. LCPT and IR-TAC groups were similar with respect to age, gender, donor type, and sensitization. Overall, treatment failure was low for both LCPT and IR-TAC groups at 12 months post-conversion (3.85% vs. 3.45%, p=1.00) (Table 1). Tacrolimus trough levels remained similar in between groups throughout the study renal function was stable at 12 months post-conversion. Adverse events related to study drug occurred in 27% of LCPT patients and 14% of IR-TAC patients (p=0.32), with no significant differences seen in any specific AE. Rates of new-onset diabetes and opportunistic infections were similar for both groups.

Conclusions: This analysis demonstrates safe and effective conversion from IR-TAC to LCPT in a subgroup of Hispanic KTR.

Funding: Commercial Support - Veloxis Pharmaceuticals

Table 1. Efficacy and Renal Function

Outcome	LCPT (n=26)	IR-TAC (n=29)	p-value
Composite 12 Month Treatment Failure, n (%)	1 (3.85%)	1 (3.45%)	1.00
BPAR, n (%)	1 (3.85%)	0	0.47
Death, n(%)	0	0	n/a
Graft Failure, n(%)	0	0	n/a
Lost to Follow Up, n(%)	0	1 (3.45%)	1.00
Baseline GFR, mean (SD)	66.5 (15.3) (n=26)	70.5 (20.7) (n=29)	0.39
1 Month GFR, mean(SD)	67.4 (15.3) (n=22)	70.2 (17.2) (n=25)	0.18
6 Months GFR, mean(SD)	65.0 (14.1) (n=18)	74.2 (23.1) (n=24)	0.05
12 Months GFR, mean(SD)	71.5 (14.6) (n=18)	74.0 (21.0) (n=24)	0.36
General linear model fixed effect p-values for renal function over 12 months: Treatment, p=0.14; Day, p=0.80; Treatment*Day, p=0.11			

FR-PO1189

Outcomes of Kidney Allograft Function in a Patient with Thrombotic Microangiopathy Switched to Co-Stimulation Blocking Agent (Belatacept)

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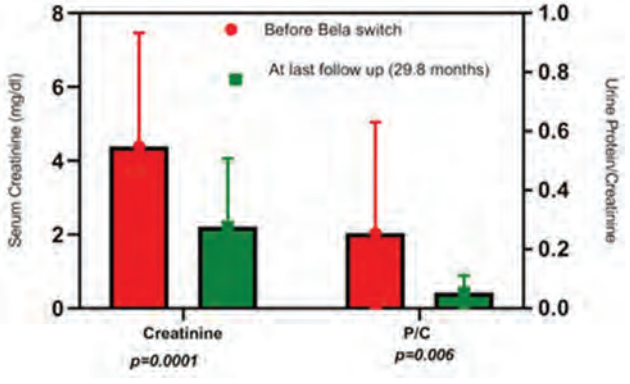
Background: Thrombotic microangiopathy (TMA) is a severe complication of kidney transplantation. TMA may occur de novo or as recurrent disease post transplantation. De novo disease is usually associated with immunosuppressive drugs [calcineurin inhibitors (CNI's) and sirolimus] or can be seen as a part of endothelial damage that accompanies antibody-mediated rejection (AMR). Treatment for de novo TMA is limited to plasma exchange and change in immunosuppression. Belatacept a co-stimulation blocking agent

is considered least nephrotoxic, and may provide an immunosuppression option in patients with TMA.

Methods: A retrospective review of prospectively collected data was conducted on kidney transplant from 2013 to 2019, 45 kidney transplant patients were switched from CNI's to a Belatacept due to concerns of TMA. Seventy percent of the patients had kidney biopsy proven changes of TMA. Continuous variables are being reported as mean with SD. A paired t-test was used and P value of <0.05 was considered to be significant.

Results: Majority of patients were Hispanic with age 54Y± 11.9, 55% were females. Post belatacept switch follow up on these patients was 29.8±15 months. Significant improvement in pre and post switch serum creatinine (p=0.0001) and urine protein/creatinine (0.006) was observed (Graph). Fourteen patients had detectable DSA at the time of switch, out of these 4 patients were still positive at last follow up, where as 2 new patients developed DSAs. Four (8%) patients developed acute cellular rejection, and one (2%) patient had AMR.

Conclusions: Belatacept appears to be useful alternative immunosuppressive agent in kidney transplant patients with TMA without increasing the risk of rejection. Switching maintenance immunosuppression to Belatacept will likely result in significant improvement in renal outcome.



FR-PO1190

Surveillance Biopsy-Driven Steroid Withdrawal

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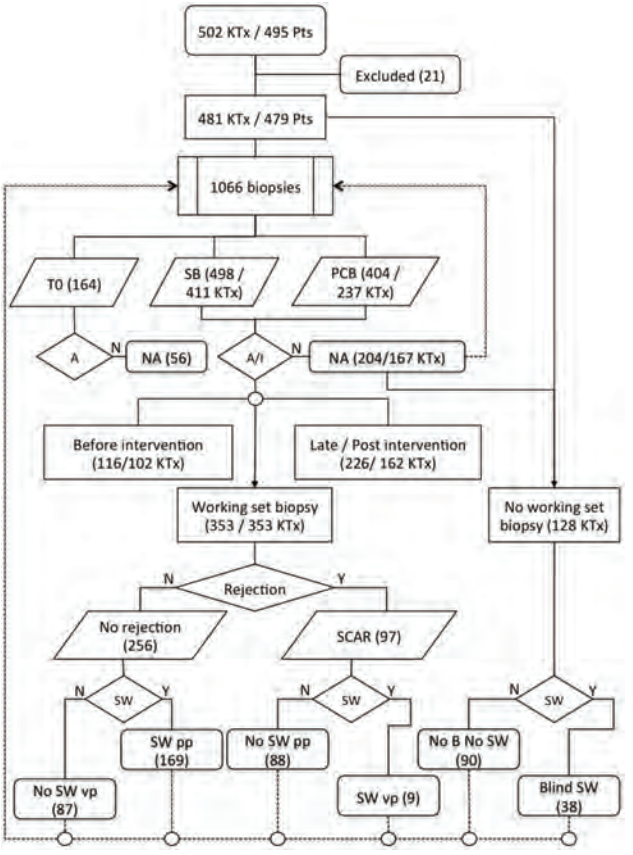
Background: Steroids withdrawal (SW) is the most frequently used IS minimizing-strategy, but it increases the risk of AR. We reasoned that surveillance biopsy (SB) could help individualized selection of patients with low risk of AR after SW. We implemented a systematic SB-driven SW protocol since 2007. We present a critical appraisal of the safety, efficiency and utility of this procedure.

Methods: Mono-centric analysis of all KTx performed from 2007 to 2015 and followed until March 2019. SB was performed at a prednisolone dose of 5 mg. SW was only allowed in kidney transplant (KT) with no sign of rejection (including borderline). Combining the two possible interventions (SB and SW) and adherence to the clinical protocol, we defined 6 groups as depicted in the study flow-chart. The safety and efficiency analysis are purely descriptive. The primary end-point for the utility analysis is the prevalence of late (occurring after the intervention) AR and the secondary is time-to-event analysis (Cox model) of a combination of graft lost or eGFR decline>30% from 1 to 3 years post-KTx.

Results: The complication rate after SB was 2,5%: 1,8 % requiring non- or minimally-invasive intervention and 0,3% necessitating an embolization. No graft lost or procedure-related death was encountered. Out of the 481 KTx analyzed, 169 (35%) were withdrawn from steroids after SB and 97 (20%) showed some degree of SCAR. Rate of late AR were distributed as follow: [SW pp] 6%, [No SW vp] 8%, [No SW pp] 14% and [SW vp] 22% (Chi-2 for trend 0.008). Breakdown of the population according to pre-specified groups was associated to the secondary end-point in both total (p=0.0002) and death-censored (p=0.019) in univariate analysis with [SW pp] being among the best survival groups.

Conclusions: SB-driven SW was safe and associated with good long term outcome.



FR-PO1191

Center-Level Variation in the Association of Clinical Factors with Use of an Early Steroid Withdrawal Regimen in Kidney Transplant Recipients

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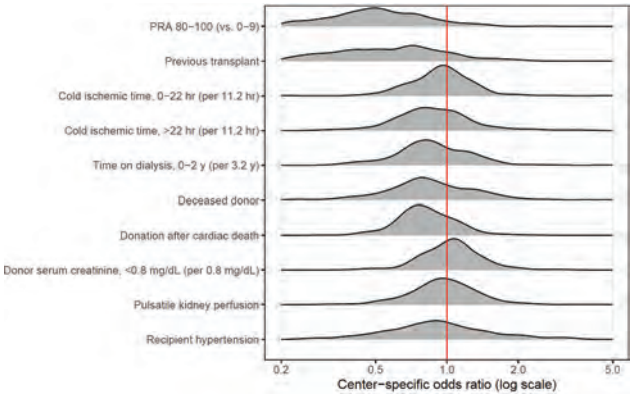
Background: Early steroid withdrawal (ESW) may confer net benefit to low-risk kidney transplant (KT) recipients. However, there is limited evidence on what clinical factors constitute the "low-risk" status that favors ESW, possibly resulting in heterogeneous, and even contradicting, practices across KT centers. Quantifying this heterogeneity using real-world data is also crucial for making unbiased inferences on ESW. We aimed to characterize the center-level variation in how clinical factors influence the selection of ESW.

Methods: Using SRTR data, we studied 210,133 KT recipients in 2002-2017, after excluding who did not receive tacrolimus and mycophenolate for maintenance immunosuppression (n=47,756). ESW was defined as withdrawal of steroid by the time of discharge from KT admission. We quantified the center-level variation in the associations of 74 variables with ESW, via the standard deviation (SD) of the random slope terms in multilevel logistic models.

Results: We identified 10 variables with greater variation (Figure). Factors such as recipient hypertension and pulsatile perfusion were associated with ESW in opposing directions at different centers. For example, the center-specific odds ratio (OR) of ESW for recipient hypertension was <0.8 at 110 (39.6%) centers, but >1.25 at 63 (22.7%) centers. On the other hand, factors such as increased PRA and longer cold ischemic time were associated with lower odds of ESW at most centers, but to substantially varying degrees. For example, while high PRA (80-100 vs 0-9) was associated with lower odds of ESW in the entire population ($OR=_{0.44}0.50_{0.58}$), this association was particularly stronger at some centers [eg, OR<0.2 at 29 (10.4%) centers].

Conclusions: Our findings suggest a substantial discordance among KT centers on what clinical factors indicate ESW and how important each factor is.

Funding: NIDDK Support, Private Foundation Support



Distribution of center-specific odds ratios of early steroid withdrawal

FR-PO1192

The Graft and Patient Survival Rate According to Ethnicity in US Kidney Transplant Recipients

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Background: African American(AA) kidney transplant recipients experience disproportionately high rates of graft loss. The aim of this analysis was to use a UNOS data set that contains detailed baseline and longitudinal clinical data to establish and quantify the impact of the current overall graft loss definition on suppressing the true disparity magnitude in US AA kidney transplant outcomes.

Methods: Longitudinal cohort study of kidney transplant recipients using a data set created by United Network for Organ Sharing (UNOS), including 266,128 (African American 70,215, Non-African American 195,913) transplant patient between 1987 and December 2016. Multivariable analysis was conducted using 2-stage joint modeling of random and fixed effects of longitudinal data (linear mixed model) with time to event outcomes (Cox regression).

Results: 195,913 non-African American (AA) (73.6%) were compared with 70,215 AA (26.4%) recipients. 10-year-graft survival of AA in all era is lower than that of non-AA (31% in deceased kidney transplants (DKT) AA recipient and 42% in living kidney transplantation (LKT) non-AA recipient). 10-year-patient survival of AA with functioning graft in all era is similar that of non-AA. Multivariate Cox regression of factors associated with patient survival with functioning graft are acute rejection within 6 months, DM, hypertension and etc. Pre-transplant recipient BMI in AA show the trend as a protective factor in patient survival with functioning graft although not significantly in statistics

Conclusions: African American kidney transplant recipients experience a substantial disparity in graft loss, but not patient death with functioning graft.

Characteristics	Year 1987-1999 (n = 69,749)			Year 2000-2016 (n = 197,986)		
	Living KT	Deceased KT	Total	Living KT	Deceased KT	Total
Recipient Age (years)	42.2 ± 12.7**	46.2 ± 12.7#	45.6 ± 12.7*	49.2 ± 13.8**	52.8 ± 13.0#	51.2 ± 13.4*
Body Mass Index (kg/m²)	25.4 ± 4.7	25.5 ± 4.6#	25.4 ± 4.6*	27.6 ± 5.1	27.8 ± 5.1#	27.7 ± 5.1*
Donor Age (years)	38.8 ± 11.0**	33.9 ± 17.0#	34.6 ± 16.4*	41.6 ± 11.6**	38.6 ± 16.7#	39.6 ± 15.2*
Cold ischemic time (hours)	1.9 ± 5.0	22.0 ± 9.7#	19.4 ± 11.5*	2.1 ± 5.0	18.1 ± 9.0#	13.5 ± 10.8*
Ethnicity (%)						
White people	65.5	58.1	59.2	64.2	43.6	50.5
African American	16.7	26.3	24.8	14.8	32.7	26.7
Hispanic people	12.1	10.0	10.3	14.6	15.2	15.0
Asian	3.6	3.8	3.8	4.8	6.3	5.8
Native American	0.9	0.9	0.9	0.7	1.1	1.0
Other	1.2	0.9	1.0	0.9	1.1	1.0
Donor type (%)						
Living	NA		14,9/10,393	NA		33.2/65,731
Deceased	NA		85.1/59,356	NA		66.8/132,255
Recipient gender (M/F %)	59.1/40.9**	61.5/38.5#	61.1/38.9	61.9/39.1**	60.8/39.2#	61.2/38.8
HLA full match (%)	13.4**	6.5#	7.4	7.4**	8.6#	8.1
Donor gener (M/F %)	42.6/57.4**	60.9/39.2#	58.1/41.9	39.2/60.8**	59.7/40.3#	52.9/47.1
AR within 6 months (%)	29.6**	35.5#	24.3*	6.3**	8.6#	6.5*
Recipeint Age > 65 years (%)	4.2**	7.4	6.9*	12.6**	20.0	17.5*
Delayed graft function (%)	5.6**	24.3	21.2*	3.9**	25.5	18.2*
Comorbidity, no. (%)						
Peripheral vascular disease	4.3	4.7#	4.6*	4.3	5.6#	5.1*
Diabetes Mellitus	26.5**	28.1#	13.7*	28.4**	35.7#	33.0*
Hypertension	15.4**	21.0#	11.5*	17.3**	26.1#	23.1*
Donor Age > 65 years (%)	1.2	3.4#	3.1	1.9	4.0#	3.3
High (> 50%) PRA (%)	4.5	8.2#	7.7*	5.6	10.9#	9.2*
Body Mass Index (kg/m²-%)						
< 18.5	3.2**	3.1#	3.1*	1.7**	1.4#	1.5*
18.5-24.9	49.4**	48.8#	48.9*	32.7**	30.7#	31.3*
25-29.9	31.2**	31.3#	31.3*	34.4**	34.0#	34.7*
30-34.9	11.5**	12.7#	12.5*	21.8**	22.8#	22.4*
> 35	4.8**	4.1#	4.2*	9.5**	10.2#	10.0*

FR-PO1193

Association of Race and Risk of Graft Loss Among Kidney Transplant Recipients in the Military Health System

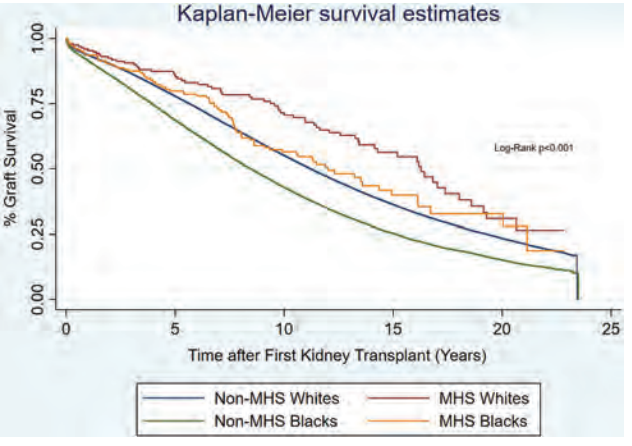
Crystal Forman,[4] Christina M. Yuan,[1,2] Rahul M. Jindal,[2] Lawrence Agodoa,[3] Kevin C. Abbott,[3] Robert Nee.[1,2] *[1]Walter Reed National Military Medical Center, Bethesda, MD; [2]Uniformed Services University of Health Sciences, Bethesda, MD; [3]The National Institutes of Health, NIDDK, Bethesda, MD; [4]San Antonio Uniformed Services Health Education Consortium, San Antonio, TX.*

Background: Racial disparities in transplant outcomes are well documented, attributed to both immunologic and non-immunologic risk factors that include social determinants of health. We assessed differences in graft survival between Black and White kidney transplant recipients in the Military Health System (MHS), a model of universal health care and free lifelong access to immunosuppressive medications.

Methods: Using the United States Renal Data System database, we identified 449 (0.16%) MHS patients first transplanted from January 1, 1995 to January 1, 2018, out of a total of 276,564 patients in the US. We examined the time to first graft loss using Kaplan-Meier and Cox regression analyses, adjusted for demographic, clinical and socioeconomic factors (health insurance, employment, education level, ZIP code-level median household income).

Results: In the MHS, 43% of Black recipients experienced graft loss compared with 35% of Whites (p=0.11). Death-censored graft loss for Blacks was 28% vs. 19% in Whites (p=0.05). MHS Blacks had an adjusted hazard ratio (aHR) of 0.88 (95% CI 0.39-1.98, p=0.75) for overall graft loss compared to their White counterparts. In the wider non-MHS cohort, Black recipients had an increased risk of overall graft loss compared to Whites (aHR 1.11, 95% CI 1.08-1.14, p<0.001). Estimated graft survival was similar between MHS Blacks and non-MHS Whites (Figure).

Conclusions: In the MHS, Black transplant recipients did not have a statistically significant higher risk of overall graft loss compared to their White counterparts, a finding that differs from the broader transplant population. {The views expressed in this abstract are those of the authors and do not reflect the official policy of the National Institutes of Health, the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government}.



First graft loss in kidney transplant recipients, stratified by racial/MHS groups

FR-PO1194

Impact of First Kidney Transplant Type on the Outcomes of a Subsequent Transplant

Kalathil K. Sureshkumar,[2] Rita L. McGill,[1] Pratik B. Shah,[1] Bhavna Chopra,[2] Patrick Cunningham,[1] Michelle A. Josephson.[1] *[1]University of Chicago, Chicago, IL; [2]Allegheny Health Network, Pittsburgh, PA.*

Background: Many patients with kidney failure will require more than one kidney transplant during their life time. It will be useful to know the impact of the type of (living vs. deceased donor) first transplant on the outcomes of a subsequent transplant as well as cumulative graft survivals between first (G1) and second (G2) espeically in patients with limited living donor options.

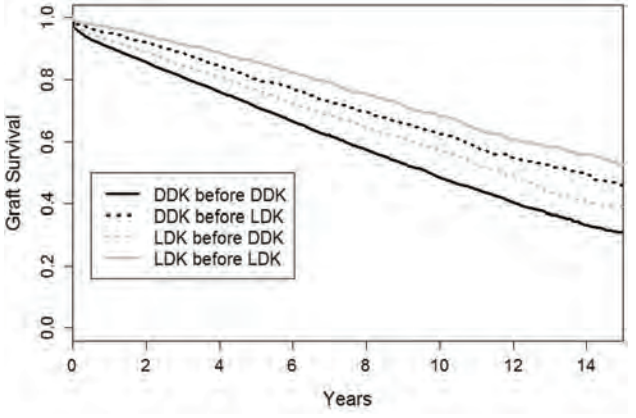
Methods: Using OPTN/UNOS database, we identified patients who underwent a second kidney transplantation between 1996 and 2016. Patients were then stratified into 4 groups based on the sequence of the transplant type as follows: living donor (LD) first, LD second (n=4402); deceased donor (DD) first, LD second (n=2460); LD first, DD second (n=5723); DD first, DD second (n=11411). Using a Cox model, graft outcomes were compared for the second transplant (G2) in all 4 transplant sequences. Subsequently a cumulative combined allograft failure risk (G1 + G2) was also calculated.

Results: Survival plots for G2 are shown in figure 1. Adjusted graft failure risks for G2 along with G1+G2 are shown in the table.

Conclusions: We observed reduced cumulative graft failure risk associated with DD followed by LD sequence compared to LD followed by DD sequence. This interesting observation could be related to the disproportionately negative impact of second DD transplant on overall outcomes.

Graft Failure by Donor Type Sequence

1st - 2nd	Graft 2 Failure	G1 + G2 Failure
LD - LD	Ref	Ref
DD - LD	1.25 (1.13, 1.38)	1.43 (1.30, 1.58)
LD - DD	1.64 (1.51, 1.78)	2.10 (1.94, 2.28)
DD - DD	1.91 (1.77, 2.05)	2.54 (2.36, 2.73)



FR-PO1195

Non-Preemptive vs. Preemptive "Second" Kidney Transplant with Graft Failure Risk Among Pediatric Kidney Transplant Recipients

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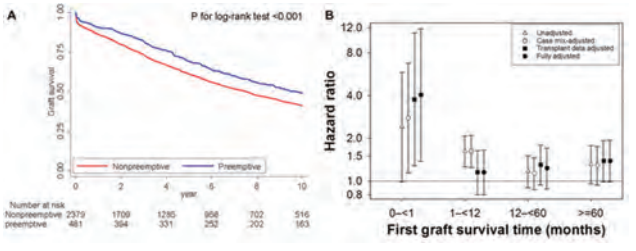
Background: Preemptive kidney transplant may have a graft survival benefit for the first kidney transplant among children. However, its benefit is less clear for subsequent transplantation after allograft failure. This study aimed to evaluate the graft failure risk associated with nonpreemptive (vs. preemptive) second kidney transplant among pediatric recipients.

Methods: In a cohort of pediatric kidney transplant recipients who underwent a second kidney transplant by the age of 21 years old between 1987 and 2016 from the United States Renal Data System, we examined the association of nonpreemptive (vs. preemptive) second transplant with risk for second graft failure, using a Cox proportional hazards regression in case mix, transplant data, and fully (transplant data plus preemptive first transplant, first graft survival time and total duration of receiving renal replacement therapy) adjusted models.

Results: Among 2,860 included patients, the median age at the second transplant was 16 (interquartile range: 12–19) years old, and 481 (17%) underwent a preemptive transplant. A total of 1,351 graft failures were observed during a total follow-up of 14,960 patient-years (median 4.8 years). Nonpreemptive had higher graft failure risk [Figure A]. In the fully adjusted Cox model, hazard ratio (HR) for the nonpreemptive group was 1.43 (95%CI, 1.18–1.72). In subgroup analysis by the first graft survival time, the fully adjusted HRs (95%CIs) for the nonpreemptive group were 4.04 (1.38–11.80), 1.15 (0.80–1.66), 1.23 (0.88–1.71), and 1.38 (0.99–1.94) in first graft survival time 0–<1, 1–<12, 12–<60, and ≥60 months, respectively [Figure B].

Conclusions: Nonpreemptive second transplant was associated with higher graft failure risk compared to preemptive transplant. Our results demonstrate the benefit of preemptive second transplant among pediatric kidney transplant recipients.

Funding: NIDDK Support



FR-PO1196

Pre-Transplant Dialysis Modality and Long-Term Patient and Kidney Allograft Outcome: A 15-Year Retrospective Cohort Study

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Background: Among factors determining long-term kidney allograft outcome, pre-transplant renal replacement therapy (RRT) is the most easily modifiable. Previous studies analyzing the impact of RRT modality on patient and graft survival are conflicting. Studies on allograft function are scarce and lack sufficient size, follow-up time or generalizability.

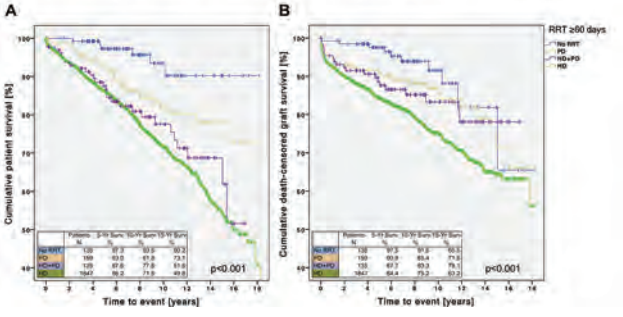
Methods: We retrospectively studied patient and allograft survival as well as allograft function and its decline in 2277 allograft recipients who received a kidney transplant at our tertiary care center during 2000-2014. Pre-transplant RRT modality ≥60 days as grouped into 'no RRT' (n=136), 'hemodialysis (HD)' (n=1847), peritoneal dialysis (PD)' (n=159), and 'HD+PD' (n=135) was evaluated.

Results: Unadjusted (Kaplan-Meier) primary outcomes demonstrated superior 5-, 10-, and 15-yr patient and death-censored graft survival in PD vs. HD patients (p<0.001 and p=0.016, respectively). Adjusted Cox regression revealed 35.6% lower hazards of death (p=0.038), whereas hazards for death-censored graft loss were similar (p=0.204). Secondary outcomes of allograft function showed significantly lower 1-, 3-, and 5-yr serum creatinine in 'PD' vs. 'HD' groups (p=0.007, p=0.048, and p=0.012, respectively). Living donation benefit for allograft function was most pronounced in groups 'no RRT' and 'PD'. Although not statistically significant, functional allograft decline measured by estimated glomerular filtration rate (eGFR) slope was lowest in PD patients. Recipients on pre-transplant PD with living donation grafts even demonstrated eGFR gain during post-transplant years 1-5.

Conclusions: Allograft recipients on pre-transplant PD vs. HD demonstrated superior all-cause and similar graft survival. Allograft function was better in PD vs. HD patients, although the trajectory of functional decline was similar.

Funding: Private Foundation Support

Figure 2. Unadjusted (Kaplan-Meier) primary outcomes comparing allograft recipients according to pre-transplant RRT modality. Shown are patient survival (A) and death-censored graft failure (B). Maximum follow-up was 18.3 years, log rank (Mantel-Cox) p<0.001 for (A) and (B); HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy.



FR-PO1197

CKD Progression Rate from Stage 4 to 5 Is Faster in Kidney Allograft Recipients

Sahin Eyupoglu,[1] Gizem Kumru,[1] Damla Örs Şendoğan,[1] Rezzan Eren Sadioglu,[1] Sim Kutlay,[1] Gokhan Nergizoglu,[1] Sehsuvar Erturk,[2] Kenan Keven.[1] *[1]Nephrology, Ankara University School of Medicine, Ankara, Turkey; [2]Ankara University School of Medicine, Ankara, Turkey*.

Background: In kidney transplant recipients (KTR), average glomerular filtration rate (GFR) is around 55-70 ml/min in early period after transplantation. Although, chronic kidney disease progression (CKD) rates have been extensively studied in non-transplanted CKD patients, there are limited comparative studies in KTR. In this study, we aimed to evaluate whether CKD progression from stage 4 to 5 is different in KTR than those of CKD patients.

Methods: The study included 76 stable CKD patients and 34 stable RTR (24 living donor, 10 deceased donor) with stage 4 CKD who reached stage 5 during their follow-up between May 2017 and December 2018 in our hospital. Patients with graft loss due to early acute rejection, early graft loss due to surgical complications, immunosupressive non-compliant patients were excluded in KTR. In control, patients with rapidly progressive glomerulonephritis, acute kidney injury on chronic were excluded. CKD stage was determined according to Kidney/Disease Outcomes Quality Initiative staging system. The progression rate from stage 4 CKD to 5 was calculated retrospectively and compared through Kaplan-Meier analysis between groups. Also, clinical features which could contribute to disease progression were assessed and Cox regression analysis was performed for adjustment.

Results: The KTR were under triple immunosuppressive treatment including prednisolone, mycophenolate mofetil (azathioprine) and tacrolimus (cyclosporine). The average follow-up were 89±77 months in KTR. Median progression time in RTR patients was significantly shorter than CKD patients 18 (95% CI: 13.5-22.6) vs 38 (95% CI: 33.25-42.75) months, p= 0.017. GFR levels were 28.2 ml/min and 29.5 ml/min in KTR and CKD patients on stage 4, respectively. At the end GFR levels were 7.43 ml/min and

7.4 ml/min in KTR and CKD groups on stage 5. Male patients had shorter progression time than women (25 [%95CI: 22.1-27.8] vs 42 [95% CI:37.2-46.7] months p=0.01). After Cox regression analysis gender (p=0.016) and transplant status (p=0.015) remained their significance.

Conclusions: Progression time from stage 4 to 5 is shorter in RTR than native CKD patients. Gender and age also can contribute disease progression.

FR-PO1198

Reporting and Handling of Missing Outcome Data in Systemic Reviews of Kidney Transplant Studies

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Background: Missing outcome data (MOD) can be absent not at random but due to side effects or in effectivity of interventions and can have implications on the validity, reproducibility and generalizability of the results. Hence, before concluding the effectiveness of the intervention in clinical setting it is important for the systematic reviews (SRs) to collect information about MOD and perform appropriate analysis to assess the robustness of the results.

Methods: We conducted a methodological survey of reporting and handling of MOD in SRs published in past 5 years. We included meta-analyses of randomized controlled trials performed in adult kidney transplant recipients that provided pooled estimate of an intervention on at least one dichotomous outcome. We used a standardized pilot tested forms with detailed instructions for each step of the review process. Title, abstract, full text screening and data abstraction all are done in duplicates. We studied how SRs collected, reported and handled MOD in the primary analysis.

Results: Seventy-one SRs (14 Cochrane and 57 Non-Cochrane reviews) met the inclusion criteria. Drugs were the most common intervention studied (84%) and average follow up was 12 months. Intention to Treat (ITT) or modified ITT was reported in 50% Cochrane and 9% non-Cochrane reviews. Ninety one percent of SRs did not collect information for number or reasons for participants with MOD. Only 5% handled and justified the analytical method(s) used to handle MOD. Furthermore, only 4% performed sensitivity analysis to account for MOD and considered the uncertainty associated with imputing outcomes in the analysis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for evaluation of the confidence in estimates of effect was used in 21% of the SRs.

Conclusions: Missing outcome data can introduce bias due to systematic differences between the observed and unobserved data, which can compromise the certainty in the evidence. SRs in kidney transplant recipients do not adequately report, handle or discuss the risk of bias associated with the MOD before concluding the results.

FR-PO1199

Clinical Trials in Nephrology: An Updated Systematic Review of ClinicalTrials.gov

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Background: Previously published reviews have highlighted low rates and poor quality of clinical trials in nephrology compared to other specialties. In this review, we assessed temporal trends in the quantity and quality of nephrology trials.

Methods: We conducted a systematic review among nephrology trials registered on ClinicalTrials.gov from inception to November 2018. Two independent reviewers assessed every trial and extracted data.

Results: A database of 288,515 registered interventional trials was restricted to studies that included one of 154 nephrology terms. We screened 5412 studies and included 4943 in the analysis. Figure 1 summarizes the number of registered nephrology trials over time. Trials were grouped into 3 Eras [Table 1]. Compared to Era 1, Era 3 had more randomized, blinded, and large trials. Fewer studies were NIH and industry-funded. Drug trials decreased while device and behavioral interventions increased. While there was a decrease in transplant trials, there was an increase in living donor recipient and in glomerular disease trials.

Conclusions: There has been an increase in the number of nephrology trials conducted over time with some improvement in quality and an increase in trials for devices, behavioral interventions, and rare kidney diseases.

Table 1	Era 1: 09/30/1982 - 08/31/2010	Era 2: 09/01/2010 - 08/31/2014	Era 3: 09/01/2014 - 11/31/2018
Randomization	77.4%	84.5%	82.6%
Blinding	30.3%	34.1%	34.7%
> 1000 Patient Enrollment	1.5%	2%	4.1%
NIH Funded	8%	4.5%	6.6%
Industry Funded	45.3%	42.8%	32.2%
Drug Intervention	73.5%	64.5%	57.2%
Device Intervention	6%	8.9%	10.7%
Behavioral Intervention	2.7%	4%	6.2%
Glomerular Disease	5.8%	6%	7.5%
Renal Transplant (living donor recipient out of all renal transplant trials	12.7% (11.4%)	11.6% (8.6%)	8.1% (23.4%)

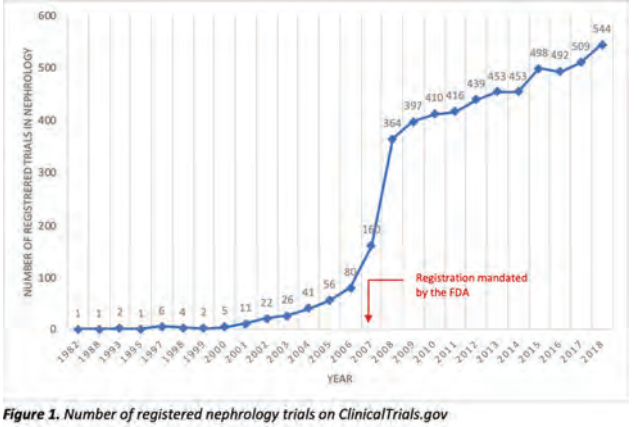

Figure 1. *Number of registered nephrology trials on ClinicalTrials.gov*

FR-PO1200

Plasmapheresis Reduces Mycophenolic Acid Concentration: A Study of Full AUC_{0-12}

Sudarat Piyasiridej,[1] Natavudh Townamchai,[2] Suwasin Udomkarnjananun,[1] Somchai Eiam-Ong,[1] Kriang Tungsanga,[3] Kearkiat Praditpornsilpa.[1] *[1]Chulalongkorn University, Bangkok, Thailand; [2]Division of Nephrology, Bangkok, Thailand; [3]King Chulalong Memorial lHospital, Bangkok, Thailand.*

Background: Mycophenolic acid (MPA), which is a crucial immunosuppressive drug, and plasmapheresis, which is an effective immune reduction method, are simultaneously used for the management of various immune-related diseases, including kidney transplantation. While plasmapheresis has been proven for removing many substances from the blood, its evidence on MPA levels remains unestablished.

Methods: A cross-sectional study was conducted in kidney transplantation recipients who were taking a twice-daily oral dose of mycophenolate mofetil (MMF, Cellcept®) and undergoing plasmapheresis at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, during January 2018 and January 2019. The MPA levels were measured by enzymatic method (Roche diagnostic®) at 0, 1/2, 1, 2, 3, 4, 6, 8 and, 12 hours for AUC_{0-12} calculation on the day with and the day without plasmapheresis sessions. Plasmapheresis was started within 4 hours after the oral morning dose of MMF. Our primary outcome was the difference of AUC_{0-12} between the day with and without plasmapheresis.

Results: Forty complete AUC measurements included 20 measurements on the plasmapheresis day and the other 20 measurements on the day without plasmapheresis of six kidney transplant patients. The mean age of patients was 56.2 ±20.7 years. All patients had received MMF 1,000 mg/day for at least 72 hours before undergoing 3.5±1.2 plasmapheresis sessions. Mean AUC on the day with plasmapheresis was lower than the day without plasmapheresis sessions (28.22 ±8.21 vs 36.79 ±10.29 mg x hour/L, p=0.001) and the percentage of AUC reduction was 19.49 ±24.83 %. This was mainly the result of a decrease in AUC_{0-4} of MPA (23.96 ±28.12% reduction).

Conclusions: Plasmapheresis significantly reduces the level of full AUC_{0-12} of MPA. The present study is the first to measure the full AUC_{0-12} in MPA-treated patients undergoing plasmapheresis. Our study suggests that a supplementary dose of MPA in patients undergoing plasmapheresis is necessary.

Funding: Private Foundation Support

AUC0-12 on PP and non-PP day

Parameters	Day without PP	PP day	p-value
AUC0-12	36.79 ±10.29	28.22 ±8.21	p=001
AUC0-12 reduction (%)	19.49 ±24.83		
AUC0-4	21.78 ±5.66	15.79 ±6.46	p<0.001
AUC0-4 reduction (%)	23.96 ±28.12		

FR-PO1201

Outcome Implications of Benzodiazepine and Opioid Co-Prescription in Kidney Transplant Recipients: A Pharmacoepidemiologic Analysis

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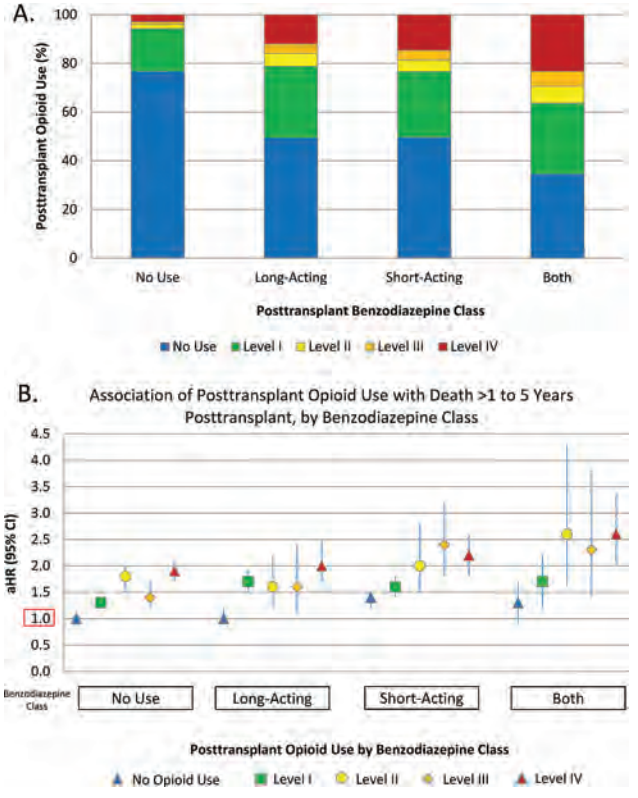
Background: Recent studies identify coprescription of benzodiazepines and opioids as a risk factor for adverse outcomes in the general population, but relationships have not been described among kidney transplant (KTx) recipients.

Methods: We examined a novel linkages of national registry data with records from a pharmaceutical claims warehouse (2008 to 2017) to characterize benzodiazepine and opioid use in the year after KTx and associations (adjusted hazard ratio, 95% $_{LCL}$aHR95%$_{UCL}$) with death >1 to 5 years post-KTx.

Results: Among 103,969 KTx recipients 15% filled benzodiazepines in the year after transplant: 6.3% long-acting, 7.5% short-acting, 1.8% both. Considered alone, benzodiazepine use in the first year posttransplant was associated with increased (P<0.05) mortality >1 to 5 yrs after KTx: aHR long-acting, $_{1.14}$1.25$_{1.36}$; aHR short-acting, $_{1.33}$1.44$_{1.56}$; aHR both, $_{1.41}$1.64$_{1.91}$. Opioid use was higher in those who also filled benzodiazepines, especially both long- and short-acting (**Fig A**). Use of both medications was more common among recipients who were white, unemployed, and received prior KTx. There was also graded association of higher level opioid use with mortality that appeared additive with benzodiazepine coprescription (**Fig. B**). Patients who filled both classes of benzodiazepines and high-level opioids had 2.6-times mortality risk, compared to no use.

Conclusions: Benzodiazepines use is correlated with opioid fills after KTx, and these agents have additive associations on post-KTx mortality. Future work is needed to examine mechanisms of these associations and impact of reducing coprescription on improving outcomes after KTx.

Funding: NIDDK Support



Opioid Use by Benzodiazepine Use, and Associated Outcomes

FR-PO1202

Correcting Anemia and Native Vitamin D Supplementation in Kidney Transplant Recipients: A Randomized Clinical Trial

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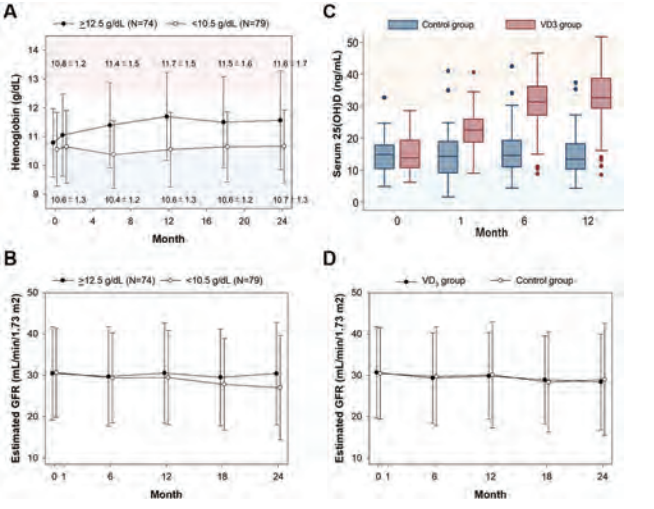
Background: Higher levels of hemoglobin (Hb) and serum 25(OH)D have been associated with better allograft survival among kidney transplant recipients (KTRs). Therefore, aggressive anemia correction and cholecalciferol (VD_3) supplementation may preserve allograft kidney function.

Methods: This is a multicenter, open-label, randomized clinical trial with a 2-by-2 factorial design. KTRs with anemia and >1-year history of transplantation from 23 facilities were randomly assigned to either the high or low Hb target group (>12.5 vs. <10.5 g/dL) and to either the VD_3 (1000 IU/day) or control group. The primary outcome was the 2-year change in eGFR from baseline.

Results: This trial was stopped early after a planned interim analyses using a Pocock type α-spending function (α=0.036). At that time, 153 patients had undergone randomization, and 133 were available for the intention-to-treat analysis. Mean Hb levels at Year 2 were 11.6±1.7 g/dL and 10.7±1.3 g/dL in the high and low Hb group, respectively (**Figure A**). The high Hb group showed a smaller decline in eGFR than the low Hb group (i.e., -1.9±5.4 vs. -4.2±6.9 ml/min/1.73 m^2; *P*=0.032) (**Figure B**), which was consistent in the per-protocol analysis. Mean serum 25(OH)D levels at Year 1 were 31.9±9.1 g/dL and 14.9±6.6 ng/mL in the VD_3 and control group, respectively (**Figure C**). The difference in 2-year change of eGFR did not reach statistical significance between the VD_3 and control groups (i.e., -4.0±6.1 vs. -2.2±6.3 ml/min/1.73 m^2, respectively; *P*=0.10) (**Figure D**), but the VD_3 group showed a greater decline in the per-protocol analysis (*P*=0.033). VD_3 supplementation did not modify the effect of the high Hb target strategy on eGFR ($P_{interaction}$=0.74).

Conclusions: Aggressive anemia correction preserves allograft kidney function while VD_3 supplementation may accelerate the decline rate among KTRs (ClinicalTrials.gov Identifier: NCT01817699).

Funding: Commercial Support - Chugai Pharmaceutical, Roche Diagnostics, Private Foundation Support, Government Support - Non-U.S.



FR-PO1203

Application of the IBox Clinical Trial Simulation Tool to Project Long-Term Kidney Allograft Outcome in the TRANSFORM Study

Gillian Divard,[1] Olivier Aubert,[1] Marc Raynaud,[1] Julio Pascual,[2] Peter Bernhardt,[4] Christophe M. Legendre,[1,3] Alexandre Loupy.[1] Paris Transplant Group *[1]Paris Transplant Group, INSERM U970, Paris, France; [2]Hospital del Mar, Parc de Salut Mar, Barcelona, Spain; [3]Hôpital Necker, Paris, France; [4]Novartis Pharma AG, Basel, Switzerland.*

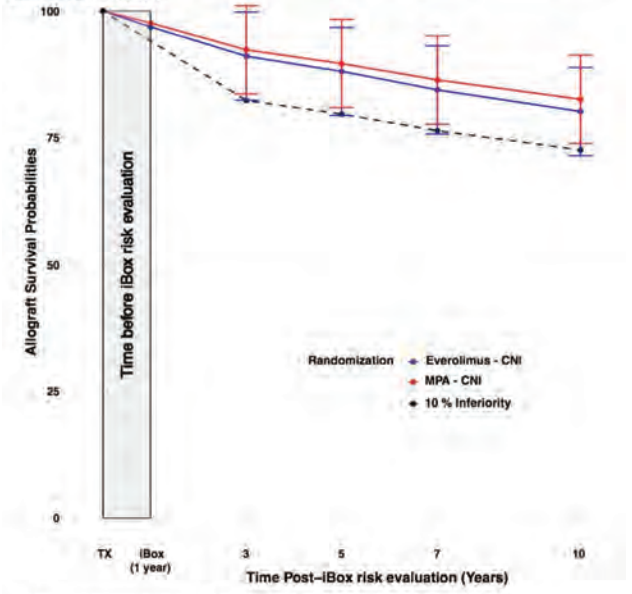
Background: Development of pharmaceutical agents in transplant is currently limited by long waits for hard endpoints. We sought to use a risk stratification system in a randomized control trial (RCT) and determine individual patient long-term graft survival.

Methods: We used validated data from TRANSFORM trial (NCT01950819), a RCT that compares KTR to receive everolimus with low-exposure CNI or mycophenolic acid (MPA) with standard-exposure CNI. We applied the iBox (NCT03474003), an integrative and validated risk score which used parameters measured at 1 year after randomization and projected patients individual long-term allograft survival.

Results: A total of 1855 patients (930 with everolimus and 925 with MPA) reached the 1 year after transplant primary endpoint. Mean eGFR was 55.9±19.7 mL/min/1.73m^2 with everolimus vs 56.1±19.1 with MPA. Mean protein/creatinin ratio was 0.32±0.67 g/g vs 0.26±0.63 with MPA. The incidence of BPAR was of 2.5% with everolimus *vs* 3.6% with MPA. The rate of DSA was 13.7% with everolimus *vs* 15.9% with MPA. These immunological, functional and histological parameters were entered into the iBox, which translated to an overall patient graft survival at 3, 5 and 10 years after randomization of 94.2% *vs* 94.7%, 91.2% *vs* 92.0% and 83.3% *vs* 84.9% in the everolimus and MPA arms respectively (95%CI -3.1% to 0.2% below the non-inferiority margin of 10%) **Figure.**

Conclusions: The iBox system confirms the non-inferiority of everolimus vs MPA 10 years after patient's randomization in the RCT. Given the unmet need for surrogate endpoint for clinical trials, this study shows the potential of a clinical trial simulation tool to fast track the development and approval of pharmaceutical agents.

Figure: Projected long term allograft graft survival between the everolimus and MPA groups using the iBox clinical trial simulation tool.



Mean projected allograft survival

Everolimus - CNI	94.2%	91.2%	87.6%	83.3%
MPA - CNI	94.7%	92.0%	88.7%	84.9%

FR-PO1204

Association Between Post-Transplant Opioid Use and Immunosuppressant Therapy Adherence Among Renal Transplant Recipients

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Background: Little is known about the effect of post-renal transplant opioid use on adherence to immunosuppressant therapy (IST).

Methods: Longitudinal data were analyzed from a retrospective cohort study examining US veterans undergoing renal transplant from October 1, 2007 through March 31, 2015. Opioid prescriptions dosages were collected and divided based on annual morphine milligram equivalent (AMME) within a year of transplant. Proportion of days covered of at least 80% indicated adherence to tacrolimus. We used logistic regression analyses to examine the association between posttransplant opioid use and adherence to IST.

Results: Compared to renal transplant recipients (RTRs) without opioid usage, RTRs with opioid usage had lower probability of being adherent to tacrolimus in unadjusted and multivariable adjusted models (model 2-5) [Figure]. In the adjusted Model 5, RTRs with AMME opioid dose of 1-30 [OR (95% CI): 0.17 (0.05-0.56)], 31-60 [OR (95% CI): 0.21 (0.06-0.74)], and >60 [OR (95% CI): 0.18 (0.05-0.61)] had lower probability of tacrolimus nonadherence compared to RTRs without opioid usage.

Conclusions: RTRs who use prescription opioids during the first year posttransplant are less likely to be adherent to tacrolimus. Future studies are needed to better understand underlying causes of the association between opioid use and tacrolimus nonadherence.

Funding: NIDDK Support

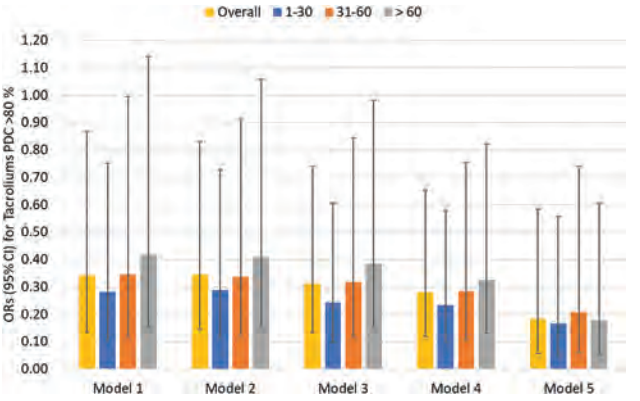

Figure: Association of one-year posttransplant opioid AMME dose with tacrolimus adherence in unadjusted models (Model 1) in 1,229 RTRs and adjusted models (Models 2-5) in 1,068 RTRs. Overall, Any opioid use; AMME dose categories, 1-30, 31-60, >60; Reference, No opioid use.

Model 1: unadjusted; Model 2: demographic characteristics; Model 3: model 2 variables plus comorbidities and smoking status; Model 4: model 3 variables plus medications; Model 5: model 4 variables and systolic/diastolic blood pressure and body mass index.

FR-PO1205

Trends in Causes of Death in Australian and New Zealand Kidney Transplant Recipients: A Registry Analysis by Era and Time Post Transplant

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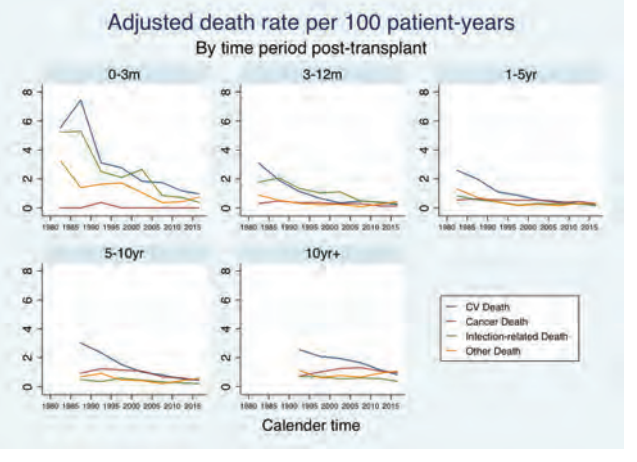
Background: Donor and recipient characteristics in kidney transplantation (KT) have changed dramatically since the 1980s. Along with an increase in marginal donors and older recipients, incremental improvements have ensued in immunosuppression, surgical techniques and cardiovascular (CV) disease management. A contemporary assessment of the risks and determinants of deaths in KT recipients is required to better inform our patients.

Methods: Using the ANZDATA registry, we included all kidney-only transplant recipients between 1980 to 2017. We censored patients at graft loss or date of last follow-up. We calculated crude death rates by dividing the number of deaths by the total patient-years at risk. Adjusted death rates per 5-year intervals were compared using a piecewise exponential model, stratified by time period post-transplant.

Results: 22,078 incident KT recipients accumulated 183,964 person-years of follow-up. The adjusted all-cause death rate was 2% per annum, remaining stable since 2005. Compared with 1995-1999, KT recipients in 2015-2017 were older (mean age 47 vs. 41) and had more comorbidities (CVD 25% vs. 13%, diabetes 24% vs. 10%). Since 1980, there has been a significant reduction in CV and infection-related deaths at all periods post-transplant (Figure-1). Recipients in the current era had a 56% reduction in CV deaths (adjusted HR=0.44, 95%CI 0.36-0.52) and 53% reduction in infection-related deaths (adjusted HR=0.47, 95%CI 0.36-0.61), compared with recipients in 2000-2004. Short-term cancer-deaths have remained stable over time, with a marginal fall in long-term cancer-deaths since 2005.

Conclusions: The risk of death after KT has reduced significantly since the 1980s, driven by a reduction in CV death at all time points and a decline in infection-related deaths. Contrary to previous studies, cancer-deaths have remained stable over time after adjusting for time post-transplant.



FR-PO1206

Improvement in Long-Term Graft Survival of Post-1-Year Survivor Kidney Transplant Recipients in the United States

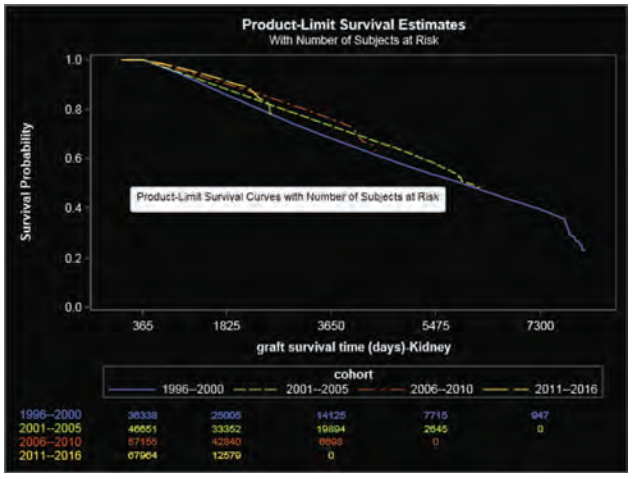
Catherine Wu, Abbas Rana, John A. Goss, Samaya J. Anumudu, Bhamidipati V. Murthy. *Baylor College of Medicine, Houston, TX.*

Background: Advances in prevention and treatment of acute rejection of kidney transplants significantly improved the short-term allograft survival. However, these successes have not been translated to long term outcomes of kidney transplants. We re-evaluated long-term graft survival for recipients whose survived one year after kidney transplantation such that the short-term adverse outcomes do not cloud the long term outcomes.

Methods: We retrospectively analyzed 219,645 recipients from 1995 to 2017 using data from the United Network for Organ Sharing. Patients undergoing re-transplants, multiorgan transplants, and recipients <18 years age at transplantation were excluded. Patients who died within 1 year of transplantation were excluded. Multivariable Cox regression was employed to estimate graft survival.

Results: Compared with patients transplanted during the period 1996-2000, on multivariate analysis, the hazard ratio (HR) for graft loss for 2001-2005 was 0.88, 2006-2010 was 0.73, and 2011-2016 was 0.63. The HR for graft loss for males was 1.12, age >60 years (vs 18-40) was 1.39, Blacks (vs Whites) was 1.34, BMI >30 (vs 18.6-25) was 1.13, dialysis prior to transplant (vs pre-emptive) was 1.40, diabetes was 1.52, and deceased donor (vs living donor) was 1.38. Compared to patients with PRA 0-79%, the HR for graft loss for PRA 80-89% was 1.15, and for 90-100% was 1.22. Compared to donor age 18-29 years, HR with donors 30-39 yrs was 1.10, 40-50 years was 1.26, and >50 years was 1.50. All these were statistically signicant with p<0.0001.

Conclusions: Long-term graft survival among kidney transplant recipients in the US has improved steadily over time. While advances in maintenance immunosuppression, and prevention and treatment of antibody-mediated rejection may have contributed, further research is needed to better understand other causes behind this improvement in kidney graft survival over the past 30 years.



FR-PO1207

Outcomes of Deceased Donor Kidney Transplant Recipients Based on Age and Kidney Donor Profile Index

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Background: The Kidney Donor Profile Index (KDPI) is a score used to estimate the overall quality of a deceased-donor kidney prior to transplant. This study sought to determine the outcomes of receiving KDPI >85% Kidneys relative to KDPI ≤85% kidneys based on graft survival and patient survival at two different age groups.

Methods: This was an observational study of all deceased-donor kidney transplant recipients >40 years of age at the time of transplant between 2011 and 2015 at our University hospital (n=837). Patients were divided into two groups, group 1 included patients between >40 and 59 years of age at the time of transplant (n=176) who received a KDPI >85% (n=15) or KDPI ≤85% (n=161). Group 2 included patients ≥60 years of age (n=121) who received a KDPI >85% (n=11) or KDPI ≤85% (n=110).

Results: Most of the baseline characteristics were similar across groups. Around 25-27% of ESRD was due to Diabetes (DM) in both groups, Recipients were on dialysis for a longer time in group 1 compared to group 2. In the univariate analysis, KDPI >85% or presence of delayed graft function (DGF) in either group were not associated with patient or graft survival. However, DM as a cause of ESRD was significantly associated with increased risk of graft failure and patient death in group 2 but not in group 1. Similarly, the use of depleting induction immunosuppressive compared to the non-depleting agent was significantly associated with increased risk of graft failure and patient death in both groups. After adjustment in multivariate analysis, in group 1, DM was associated with increased risk of graft failure [HR: 1.4, CI: 1.0-1.9, p=0.03] and death [HR: 1.44, CI: 1.1-1.9, p=0.03], along with in group 2 for graft failure [HR: 1.76, CI: 1.2-2.6, p=0.003] and death [HR: 1.75, CI: 1.2-2.5, p=0.002]. The similar, association was found for the use of depleting immunosuppressive medications in both groups for graft and patient survival.

Conclusions: In our observation, elevated KDPI >85% and delayed graft function were not associated with patient or graft survival regardless of age. The provider should consider these factors during transplant.

FR-PO1208

Reverse Epidemiology and the Obesity Paradox for Patients with CKD

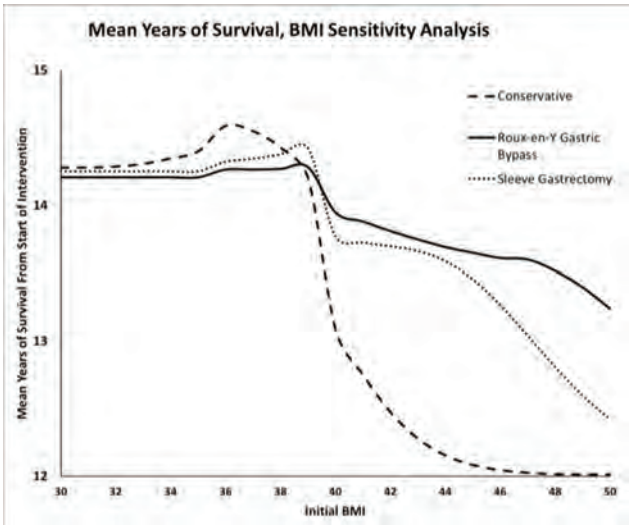
Rashikh A. Choudhury,[1] Dor Yoeli,[1] Hunter B. Moore,[1] Gerard Hoeltzel,[2] Kristoffel R. Dumon,[2] Peter L. Abt,[2] Kendra D. Conzen,[1] Trevor Nydam.[1] *[1]University of Colorado Hospital, Denver, CO; [2]University of Pennsylvania Hospital, Philadelphia, PA.*

Background: Obesity has been associated with both increased progression of chronic kidney disease as well as with a paradoxical improvement in survival among ESRD patients undergoing hemodialysis. As such, the optimal weight management strategy for obese CKD patients remains unclear.

Methods: A decision analytic Markov state transition model was created to simulate the life of 30,000 obese patients with CKD stage 3b, as they progressed to ESRD, transplantation, and death. Life expectancy following conservative medical weight management (observation), Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG) were estimated. Base case patients were defined as being 55 years old and having a pre-intervention BMI of 40 kg/m^2. Sensitivity analysis of initial BMI was performed. All Markov parameters were extracted from literature review.

Results: RYGB and SG were associated with improved survival for patients with pre-intervention BMI of > 39.6 kg/m^2. Compared to conservative weight management, base case patients who underwent RYGB gained 10.3 months of life, and gained 8.2 months of life following SG.

Conclusions: Balancing progression of CKD with improved survival on ESRD for obese patients requires selective use of weight management strategies. RYGB and SG improved survival for CKD patients with Class III obesity, but not for patients with Class I and Class II obesity. As such aggressive weight loss interventions should be reserved for patients with Class III obesity, while more conservative methods should be offered to those with Class I and II obesity.



FR-PO1209

One-Year Outcome of Deceased Donor Kidney Transplantation in the Elderly Using High Kidney Donor Profile Index Kidneys

Wei Xiang Wong, Nicole Low, Wina Yousman, Pablo Loarte, Angelo M. De Mattos, Lavanya Kodali. *University of Arizona, Banner Medical University Tucson, Tucson, AZ.*

Background: Elderly patients with end stage renal disease account for 22.5% of the adults on kidney transplant waiting list in 2016, a significant rise from 15.3% in 2006. At our institute, deceased donor kidney transplant (DDKT) rate for elderly patients (defined as ≥ 65 years of age) was 33.8% between 2016-2017, much higher than the national rate of 19.2%. The use of kidneys with Kidney Donor Profile Index (KDPI) higher than 85 has facilitated shorter waiting time for this target population. Our objective is to see the outcome of the elderly patients who received high KDPI>85% DDKT.

Methods: Retrospective chart review was done on patients who received deceased kidney transplants from July 2016 to August 2017 at Banner University Medical Center in Tucson, Arizona. Primary outcomes were glomerular filtration fraction (GFR) 1-year post transplant, rejection rate (RR) and delayed graft function (DGF) rate in the elderly who received high KDPI deceased donor kidneys. Data was analyzed using SPSS. GFR is calculated using MDRD.

Results: Among 154 patients who received kidney transplantation at our institute, 52 (33.8%) patients were elderly and 34.6% of them received high KDPI kidneys.

Characteristics of our cohort were represented in table 1. The elderly who received high KDPI kidneys have similar rate of DGF, RR, and GFR 1 year post transplant compared to the rest of the cohort (50.0% vs 48.6%, 11.1% vs 18.9%, 47 vs 58 ml/min/1.73m^2, all p>0.05). Elderly patients had significantly higher cold ischemic time (CIT) compared to the rest of the cohort (32.4±9.7 vs 27.2±12.5h).

Conclusions: Elderly patients at our institute who received high KDPI kidneys have similar rate of DGF, RR and GFR 1-year post transplant compared to the rest of the cohort. Compared to the national rate, elderly high KDPI recipients in our study have prolonged CIT (32.4±9.7 vs 17.0±8.7) and higher DGF (50% vs 23.8%) but comparable rejection rate (9.5% vs 11.1%) and GFR 1-year post transplant was 47 vs 58 ml/min/1.73m2.

Variables		Age ≥ 65 (n=52)	Age < 65 (n=102)	p value
KDPI, N (%)	> 85	18 (34.6%)	9 (8.8%)	<0.01*
	≤ 85	34 (65.4%)	93 (91.2%)	
EPTS, N (%)	> 70	37 (71.2%)	19 (18.6%)	<0.01*
	≤ 70	15 (28.8%)	83 (81.4%)	
PRA, N (%)	> 40	10 (19.2%)	26 (25.5%)	0.43
	≤ 40	42 (80.8%)	76 (74.5%)	
Induction, N (%)	Basiliximab	42 (80.8%)	69 (67.6%)	0.09
	rATG	10 (19.2%)	33 (32.4)	
DGF, N (%)	Yes	25 (48.1%)	50 (49%)	1
	No	27 (51.9%)	52 (51%)	
Rejection, N (%)	Yes	7 (13.5%)	18 (17.6%)	0.65
	No	45 (86.5%)	84 (82.4%)	
CIT, mean		31.9 ± 11.5	25.5 ± 12.1	0.01*
GFR 1-year post transplant, ml/min/1.73m^2		56	58	0.75

Table 1: Elderly vs non-elderly 1-year outcomes in our cohort

FR-PO1210

Single Cell RNA-Seq profiling of renal endothelial cells in experimental diabetic nephropathy model reveals transcriptomic changes in separate endothelial subpopulations

Alex X. Zhou,[1] Pernille B. Laerkegaard Hansen,[2] Christer Betsholtz,[3] Marie Jeansson,[4] Liqun He,[3] Martin Uhrbom,[5] Jianping Liu,[4] Anna Granqvist,[5] Pernilla Tonelius.[6] *[1]AstraZeneca Gothenburg, Mölndal, Sweden; [2]Imed CVMD, Mölndal, Sweden; [3]Uppsala University, Uppsala, Sweden; [4]Karolinska Institutet, Huddinge, Sweden; [5]AstraZeneca, Mölndal, Sweden; [6]AstraZeneca R&D Gothenburg, Sweden, Mölndal, Sweden.*

Background: Endothelial dysfunction and vascular rarefaction are hallmarks of chronic kidney disease, while little is known about the transcriptomic changes of renal endothelial cells (ECs) during disease progression. Moreover, kidney contains heterogenous EC subpopulations that are structurally and functionally distinguishable. This study aims to determine and compare transcriptome profiles in separate renal EC subpopulations between healthy mice and mice of diabetic nephropathy (DN) using single cell RNA-seq (scRNA-Seq).

Methods: Kidneys of BTBR lean and *ob/ob* mice at 6, 11 and 20 weeks of age were enzymatically dissociated with Liberase™. After incubation with Pecam1 antibody and Calcein-AM, Pecam1$^+$ and Calcein-AM$^+$ single live cells were FACS sorted into 384-well plates. Single EC cDNA library was generated by Smart-seq2 technique and the sequencing was performed on Illumina HiSeq 3000. Unsupervised clustering of EC subpopulations was performed with Pagoda2 analysis.

Results: BTBR *ob/ob* mice develop vascular rarefaction with age. Compared to the lean mice, the proportion of renal single live ECs in the *ob/ob* mice showed no difference at 6 weeks of age, a 25% reduction at 11 weeks of age, and a 32% reduction at 20 weeks of age (P=0.01). The current Pagoda2 analysis on the 11-week-old lean and *ob/ob* mice revealed twelve EC subpopulations and 142 genes with significantly altered expression in *ob/ob* mice. Among differentially expressed genes (DEGs), certain redox genes were ubiquitously regulated. However, majority of the DEGs were altered in distinct EC subpopulations, likely owing to either the different sample sizes or the heterogeneity on gene expression/regulation in various EC subpopulations. The data of 6- and 20-week-old BTBR mice is under analysis to explore the time course of the transcriptomic changes.

Conclusions: The full length scRNA-seq on FACS sorted renal ECs provides a feasible approach to a high-resolution transcriptomic profiling of heterogenous EC populations in kidney and importantly the heterogenous transcriptomic changes in an experimental DN model.

Funding: Commercial Support - AstraZeneca R&D Gothenburg

SA-PO001

ASN Communities: A Growing Thriving Online Educational Asset

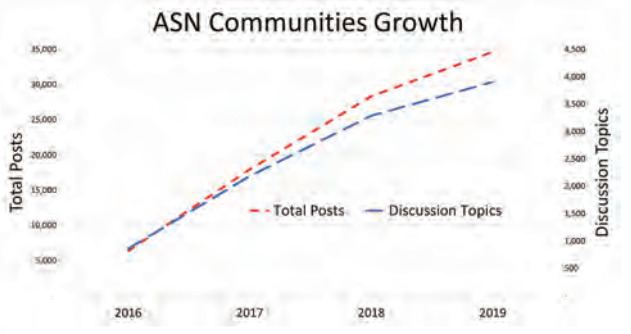
Roger A. Rodby,[1] Susan Willner.[2] *[1]Rush University Medical Center, Chicago, IL; [2]American Society of Nephrology, Washington, DC.*

Background: Doctors are turning to social media (SoMe) and internet-based venues to teach, improve patient care, and to bolster knowledge. In 2016**,** the American Society of Nephrology launched "ASN Communities" ("Comms") an online collaboration platform designed to provide ASN members with a dynamic international peer to peer venue to discuss challenging clinical cases, as well as other professional education activities. The clinically oriented Comms include: Open Forum, Patient Care Q&A, AKI, Kidney Transplantation, Onco-Nephrology and Nephrologists Transforming Dialysis Safety. Other Communities include Public Policy and Public Health, Renal Educators, Women's Health and Research, Basic Science Research, Career Advancement, Fellows Connect, and Renal Educators.

Methods: ASN members are automatically enrolled in the Open Forum Comm while the other Comms require a one-click join process. Members can opt to receive email alerts for each Comm in which they are a member. ASN Comms combines the best of all SoMe platforms into a professional, iterative, educational experience for the mundane to the most complex questions of health care workers around the world, and by design not limited to academia. Each Comm has "Community Leaders" (topic experts that help lead the discussions) who are chosen by the ASN's Media and Communication Committee which also oversees the activities of all Comms.

Results: ASN members from throughout the world regularly leverage the expertise and knowledge of the greater community as evidenced by 25% of logins and 30% of posts originating from outside of the U.S. To date there have been 3,902 Discussions generating 27,871 replies (see Figure) from 180 countries and over 4,800 cities, with 330,149 logins representing 13,300 ASN Members. Each month approximately 3,000 ASN members access Comms. Comms are accessible on any computer as well as smart phones via a dedicated Comms app and on Twitter at @ASNCommunities.

Conclusions: ASN Communities should serve as a template for other medical subspecialties interested in the education and growth of their members.



SA-PO002

Survey-Based Evaluation of Home Dialysis Education During Nephrology Fellowship in United States

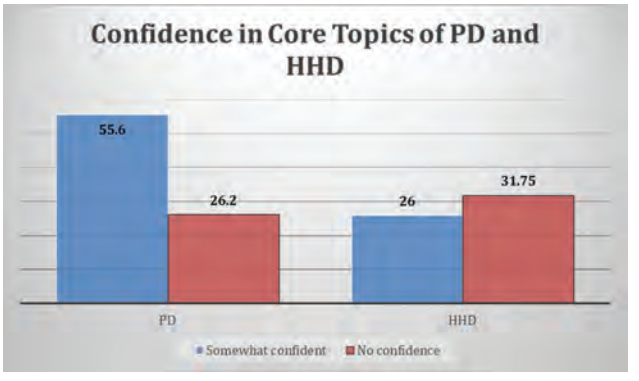
Nupur Gupta,[1] Elizabeth Taber-Hight,[1] Brent W. Miller.[2] *[1]Indiana University, Indianapolis, IN; [2]Indiana University School of Medicine, Carmel, IN.*

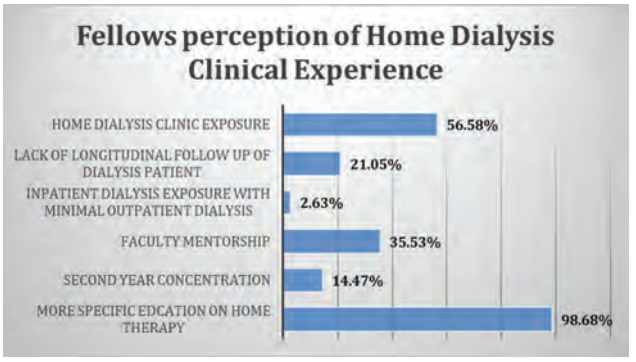
Background: Home Dialysis seems to be an underutilized modality for many reasons, one of which includes physician unfamiliarity with the practical aspects in both Peritoneal Dialysis (PD) and Home Hemodialysis (HHD). Previous surveys have suggested suboptimal exposure and confidence amongst fellows. The goal was to identify gaps in knowledge and evaluate possible areas of improvement in Home Dialysis

Methods: A 23 question survey on education during fellowship training was developed and distributed at 3 Home Dialysis University Symposia in 2019. Survey assessed core competencies, clinical experience and overall preparedness of Home based renal therapies amongst graduating fellows.

Results: 76 out of 250(30%) graduating fellows completed the survey. Nearly all the respondents (98.7%) desired more teaching focused on both Home Therapies. Assessing the core competencies of PD, majority (55.6%) of them were "somewhat confident" and 26.2 % selected "no confidence". A larger portion of respondents (31.8%) felt "Not at all confident" regarding HHD key competencies. Most of the participants believed fewer than national average (< 10%) patient population were on Home Therapies in their Academic practice. A large number of fellows (71.7%) reported that patients followed in Home Continuity clinic were on PD but fewer on HHD. Approximately half the fellows have opportunity of continuity clinic with Faculty mentorship.

Conclusions: Nephrology fellows felt significantly more prepared for PD than HHD but moderate overall preparedness. Implementation of well-structured curriculum integrated with robust clinical experience would improve utilization of Home Therapies with preparedness of fellows.





SA-PO003

Comparing Author Gender and Publications in Two Medical Subspecialties

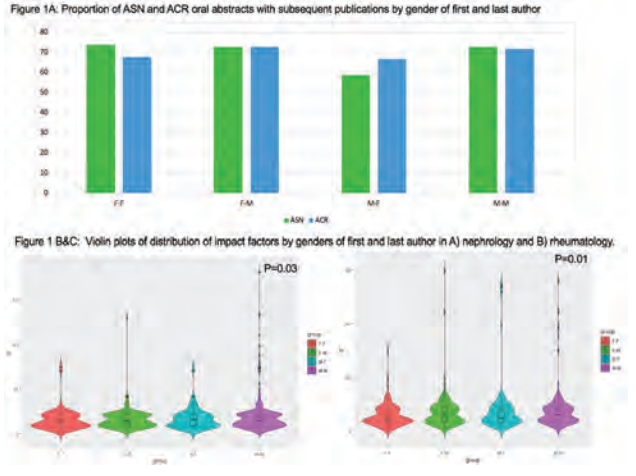
Niralee Patel, Yumeng Wen, Nidhi Naik, Benjamin O. Adegbite, Steven G. Coca, Girish N. Nadkarni, Lili Chan. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: A gender gap exists in scientific publications, with women being underrepresented. We assessed the proportion of oral presentations that are subsequently published in peer-reviewed journals and their impact factor (IF) by gender in nephrology (40% female fellow trainees) and rheumatology (60% female fellow trainees).

Methods: We reviewed oral abstracts presented at American Society of Nephrology (ASN) Kidney Weeks 2011-2013 and American College of Rheumatology (ACR) annual conferences 2011-2013. Proportions of gender combinations for first and last author (Female-Female (FF), Female-Male (FM), Male-Female (MF), and Male-Male (MM)) were compared utilizing Chi^2 and IFs using ANOVA.

Results: Of 1,262 ASN oral abstracts, 39% had female first authors and 21% had female last authors. MF had the lowest proportion (59%) of abstracts published compared to FF, FM, and MM authors (74 vs. 73 vs. 73%, P=0.005) (Figure 1A). MM papers were published in journals with higher IF (Figure 1B). In contrast, of 1,191 ACR oral abstracts, females comprised of 52% of first authors and 41% of last authors. There were no significant differences seen in the combinations of authorship (FF 68%, FM 73%, MF 67%, vs. MM 72% p=0.35) (Figure 1A). MM papers were published in journals with higher IF (Figure 1C).

Conclusions: Author gender differences seen in the proportion of oral abstracts that were later published were inconsistent between nephrology and rheumatology. However, MM abstracts were published in higher impact journals in both fields. Whether these findings hold true in other medical subspecialties with varying proportions of female trainees should be further explored.



SA-PO004

Kidney Disease Screening and Awareness Program Is an Effective Model to Expand the Recruitment Pipeline by Capturing Undergraduates for Nephrology

Rui Song,[4] Rebecca P. Chen,[2] Min Zhuo,[1] Sirine Bellou,[3] Andrew Cho,[6] Jiahua Li,[4] Li-Li Hsiao.[5] Kidney Disease Screening and Awareness Program (KDSAP) Clinical Research Team *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]University of California, Los Angeles, San Diego, CA; [3]Brigham & Women's Hospital, Brookline, MA; [4]Brigham and Women's Hospital, Chestnut Hill, MA; [5]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [6]Harvard University, Cambridge, MA.*

Background: Physician shortage in nephrology is causing an impending workforce crisis. The Kidney Disease Screening and Awareness Program (KDSAP) is a national student-led organization targeting college students via community health screening and mentorship. This longitudinal study aims to assess the impact of KDSAP on career choice of its alumni in nephrology.

Methods: KDSAP alumni were defined as college graduates from 2009 to April 2019, who have attended at least one KDSAP health screening or KDSAP academic event. There are 173 alumni who met the criteria and with valid contact information. An online survey evaluating demographics, career choice impact, perspectives on nephrology was sent by email. To gain in-depth knowledge of KDSAP's impact, one-on-one interviews were conducted with those who are currently practicing medicine; and focus group discussions were conducted with medical students and health-related graduate students. This study was conducted via a mixed-method study approach.

Results: Our study enrolled 112 alumni who completed the survey. Among them, 75 (67%) reported "very" or "extremely" invested in KDSAP activities. The community screening is the most meaningful (97%) and influential (69%) to their career choices. Out of 112 respondents, 94 (84%) are in the field of medicine in various stages, including 3 nephrologists. While 40 (36%) consider doing kidney-related research or patient care, impressively 8 (24%) of those attending medical school (n=34) consider Nephrology as their career choice. Our results also revealed favorable perceptions of Nephrology among KDSAP alumni: Nephrology is exciting compared to other specialties (79%), Nephrologists are important to community health (97%), Nephrology is a well-respected practice (91%), Nephrology is a rewarding field for a career option (88%) and considering a kidney-related profession for the further career (31%). Qualitative analysis (n=8) revealed four main categories in the impact of KDSAP on alumni: career choice, mentorship, career development, and community health services.

Conclusions: In fighting the Nephrology workforce crisis, KDSAP is an effective model to expand the recruitment pipeline by capturing undergraduates entering the field of Nephrology.

Funding: Other NIH Support - Sundry Fund

SA-PO005

What Do Internal Medicine Residents Consider When Choosing Careers? An Exploratory Q Sort Study with a Focus on Nephrology Interest

John K. Roberts, Charles Hargett, Myles Wolf. *Duke University, Durham, NC.*

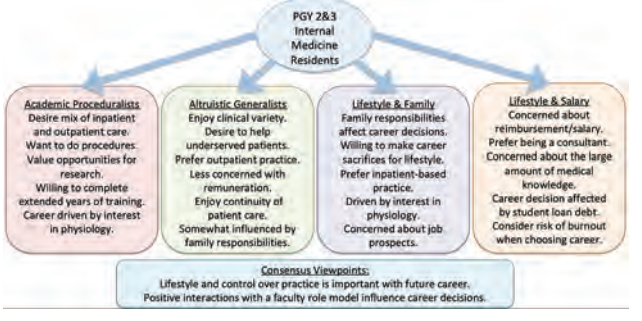
Background: Interest in nephrology among internal medicine (IM) residents has been low in recent years. A better understanding of contemporary attitudes about career choice decisions in IM residents could help nephrology recruiting efforts. Therefore, we used a Q sort survey to better understand IM resident attitudes surrounding career choice decisions in the modern era.

Methods: We invited IM residents (post-graduate year 2/3) at an academic medical center to take a Q sort survey in the late fall of the training year. Residents prioritized 50 statements that reflected issues affecting career choice: scope of practice, patient continuity, procedures, consultant care, general care, family responsibilities, debt, remuneration, length of training, interest in physiology, and lifestyle concerns. To find statistically significant perspectives, we performed by-person factor analysis using the Centroid method. At the conclusion of the Q sort, we collected the residents' top three career interests.

Results: Out of 47 sorts, we identified four viewpoints that accounted for 43% of the variance in the sample. Figure 1 shows the viewpoints. Across all four groups, all agreed that positive interactions with a faculty role model and control over future practice are important for career decisions. Among residents considering nephrology, two loaded onto the Academic Proceduralist viewpoint, five loaded onto the Lifestyle-Family viewpoint, and one loaded onto the Lifestyle-Salary group.

Conclusions: The Q-sort survey identified the dominant career choice viewpoints of contemporary IM residents. Two of the viewpoints were centered on lifestyle considerations: one focused on family responsibilities and the other focused on remuneration, educational debt, and burnout. To make nephrology more attractive to the current generation, changes to the profession are needed. Interventions that support an attractive lifestyle, control of practice, while accommodating to family responsibilities and educational debt may impact interest more than other factors.

Funding: Private Foundation Support



SA-PO006

A Unique Hybrid Nephrology Training-Hospitalist Medicine Track: The University of Kentucky Experience

Faris Khasawneh,[1] Jon C. Webb,[2] B. Peter E. Sawaya.[2] *[1]University of Kentucky, Lexington, KY; [2]University of Kentucky Medical Center, Lexington, KY.*

Background: There has been a declining interest in nephrology training as evidenced by a decline in the number of applicants and increased number of unfilled positions through the Match. On the other hand, hospitalists are a growing group of physicians with some gaining mature interest in nephrology. However, salary disparity has been an obstacle to translate this interest into pursuing nephrology training. The creation of a hybrid program combining nephrology training and hospitalist work is a possible pathway that would be of value to Nephrology programs and interested hospitalists.

Methods: In 2016, the nephrology program at the university of Kentucky embarked in a systematic creation of a hybrid program combining nephrology training and hospitalist practice. A curriculum expanding over 4 years with alternating 6-month blocks was developed. The salary of the candidates alternates between PGY-4 or 5 remuneration and those of a full time hospitalist faculty. The curriculum was approved by the university graduate medical education (GME) and by the ACGME. ABIM recognizes this fellowship under the "interrupted" training track. A major obstacle is the alignment of the offices of human resources, hospital administration and GME. An effective communication system is necessary to signal the switching between the different status. A geographic separation where the training is in one hospital, while the faculty hospitalist practice is in another proved to be a practical mechanism to circumvent potential confusion. Once the program is approved, advertisement in prominent hospitalists journals was necessary.

Results: After 1 month of advertisement in two hospitalists journals at a cost of $2500, we identified 9 interested candidates after the match. We offered the position to two. The average yearly salary for the hospitalist-fellow trainee is $138,250/year. Moonlighting is allowed as a supplementation to their salary, provided that it does not interfere with the duty hours regulation. Currently, the two hybrid trainees have completed two years in this program with 1 year of accredited training toward nephrology. Their feedback has been very positive.

Conclusions: Nephrology Fellowship-hospitalist track appears to be a valid approach to ameliorate the negative impact of declining interest in nephrology fellowship on the manpower and overall training programs.

SA-PO007

The Nephrology Immersion Classroom: Using Digital Videos to Boost Knowledge in Nephrology

John K. Roberts, Myles Wolf. *Duke University, Durham, NC.*

Background: Improving residents' nephrology knowledge is one way to stimulate interest and self-efficacy in nephrology. Newer methods of resident education should be sought to better personalize the learning process and meet resident needs. One way to foster self-directed, asynchronous learning is through digital chalk talk videos. We hypothesized that adding a nephrology video curriculum to a nephrology rotation would improve medical knowledge in internal medicine residents.

Methods: Internal medicine residents (post-graduate year 2/3+) on the nephrology consult rotation were invited to participate in the study. In both a control and intervention year (access to the videos), we surveyed and tested residents' knowledge using 15 case-based multiple-choice questions (MCQs) before and after their nephrology rotation. We created a library of 32 short, digital blackboard videos that covered high-yield topics in nephrology. We hosted the video curriculum on Google Classroom, so that access could be restricted to study participants and they could view content using the Google Classroom smartphone app. In the post-rotation survey, we measured satisfaction and usability of the nephrology classroom.

Results: 39 residents completed the nephrology rotation in the control group and 26 (66%) participated in the study. In the intervention group, 33 residents completed the nephrology rotation, 25 (75%) enrolled in the Google classroom, and 30 (90%) participated in the study. Performance on nephrology MCQs improved between the pre and post-tests in both years, but the difference was not statistically different. During the study period, videos were viewed on average 5.6 times and the classroom was considered very easy to use. Other usability metrics suggest high levels of satisfaction with the video curriculum.

Conclusions: Adding a digital chalk talk curriculum did not improve short-term medical knowledge, but hosting videos on a mobile classroom platform resulted in modest usage with high resident satisfaction. Efforts to boost video views may improve both short and long term learning outcomes.

Funding: Private Foundation Support

Nephrology Medical Knowledge in Control and Intervention Years

Study Condition	Control		Intervention	
	Pre-Test	Post-Test	Pre-Test	Post-Test
Number	18	21	29	22
Median time to complete (min)	30	33	38	40
Mean Number of Correct Questions (%)	8.7 (58%)	10 (68%)	8.3 (56%)	9.5 (63%)

Interim analysis, full data will be available by Oct 2019

SA-PO008

Internal Medicine Residents' Perception of the Nephrology Specialty

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Background: Interest in nephrology as a specialty has been declining among US medical graduates As a result, more than half of the fellowship programs remain unfilled. To better understand this phenomenon, we intended to qualitatively explore the nephrology perceptions among Internal Medicine (IM) residents and to identify factors influencing their choice of a subspecialty career.

Methods: A qualitative study was designed using the grounded theory methodology. Ten semi-structured interviews were conducted with randomly selected internal medicine residents (Postgraduate Year (PGY) 1 and 2). The interview questions were guided by the Professional Identity (PI) Formation Framework, which captures key elements of the socialization processes contributing to the development of the PI. Interviews were recorded and transcribed verbatim. Coding was performed by 2 independent reviewers who met to reach consensus on emerging themes. Data saturation was reached after the 8th interview. Decision to stop interviewing was made after the 10th interview.

Results: Several recurring themes emerged in our analysis (Table 1). The negative factor that recurred most commonly was the lack of exposure to nephrology rotations both in the clinical and pre-clinical years. This was mentioned by 9 out of 10 residents. Other frequently recurring themes were: patient population (mentioned by 5/10 residents), lack of innovation in the field (4/10) and inability to make a difference (4/10). Factors positively influencing residents' decision included: breadth (5/10) and complexity of pathology (7/10) and perception of nephrology as a highly intellectual specialty (7/10).

Conclusions: Lack of exposure to nephrology rotations in preclinical and clinical years appears to be the most important factor dissuading residents from pursuing a career in nephrology.

Funding: Private Foundation Support

	NUMBER OF TIMES CITED	
EDUCATIONALFACTORS	POSITIVE PERCEPTION	NEGATIVE PERCEPTION
PRECLINCAL EXPOSURE	0	9
CLINICAL EXPOSURE	0	9
QUALITY OF PRECLINICAL INSTRUCTION	2	3
QUALITY OF CLINICAL INSTRUCTION	0	3
LENGTH OF TRAINING	1	0
COMPLEXITY OF PATHOPHYIOLOGY	7	6
FIELD-RELATED FACTORS	POSITIVE PERCEPTION	NEGATIVE PERCEPTION
HIGHLY CEREBRAL	7	1
INNOVATION IN THE FIELD	1	4
PRESTIGE / INFLUENCE	0	2
JOB-RELATED FACTORS	POSITIVE PERCEPTION	NEGATIVE PERCEPTION
BREADTH OF PATHOLOGY	5	0
COMPENSATION	0	3
JOB MARKET	0	1
WORK-LIFE BALANCE	3	1
STRESS / ACUITY	1	1
ACADEMIC PROSPECTS	2	0
PROCEDURES	1	2
PRACTICE FOVUS (NARROW VS. WIDE)	0	2
SOCIAL FACTORS	POSITIVE PERCEPTION	NEGATIVE PERCEPTION
PATIENT POPULATION	0	5
ABILITY TO MAKE A DIFFERENCE	0	4
INPATIENT VS OUTPATIENT	0	1
SOCIAL ASPECT (TEAMWORK)	1	1

SA-PO009

Factors Influencing Residents Career Decision-Making

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Background: Interest in nephrology as a specialty has been declining among US medical graduates and more than half of the nephrology fellowship programs remain unfilled. To better understand this phenomenon, we aimed to identify factors influencing residents' choice of a "subspecialty career".

Methods: A qualitative study was designed using the grounded theory methodology., Ten semi-structured interviews were conducted with randomly selected internal medicine residents (Postgraduate Year (PGY) 1 and 2 PGY2). The questions were guided by the Professional Identity (PI) Formation Framework, which captures key elements of the socialization processes contributing to the development of the PI. The residents' answers were recorded and transcribed verbatim. Coding was performed by 2 independent reviewers who met to reach consensus on emerging themes. Data saturation was reached after the 8th interview. Decision to stop interviewing was made after the 10th interview.

Results: Several recurring themes emerged in our analysis and were classified into three general categories: personal attributes (personality, family tradition, experiences and values), social factors (Mentors, transformative events, exposure, quality of instruction, performance and autonomy) and specialty-specific factors (Field, lifestyle and job-related

factors) (Table 1). Among those themes, the role of role models/mentor stood out as the most important as it was mentioned by 100% of the residents. This adds new information to the factors that were previously identified by the ASN workforce.

Conclusions: We identified the factors influencing career decision-making in internal medicine residents and the key role of mentorship in this process. Understanding these factors could help the nephrology community understand the declining interest in the field and formulate interventions to potentially remedy the current situation.

Funding: Private Foundation Support

PERSONAL ATTRIBUTES	SOCIAL FACTORS	SUBSPECIALTY SPECIFIC FACTORS
Personality	**Role models / mentors**	**Field-related factors:** - Innovation in the field - Social aspect (teamwork) - Breadth of pathology
Family Tradition	**Transformative events**	**Lifestyle-related factors** - Work-life balance - Stress level / Acuity - Work load
Experiences	**Formal learning (pre-clinical)** - Exposure - Topic Difficulty - Intellectual challenge - Quality of instruction - Experience / performance on block	**Job-related factors** - Prestige / Influence - Compensation - Job Market - Academic prospects - Opportunity for procedures
Values	**Clinical years** - Exposure - Environment - Quality of instruction - Experience / performance on rotation - Autonomy on rotation	**Patient-related factors** - Patient population - Longitudinal care / continuity - Inpatient vs. outpatient focus - Practice focus: narrow vs. wide - Ability to make a difference

SA-PO010

An Innovative Night Float System in Nephrology: A Mixed-Methods Evaluation

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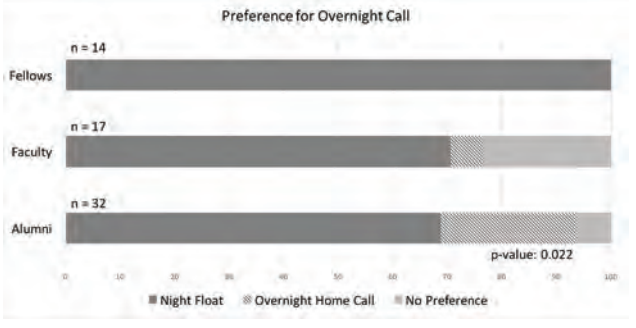
Background: Johns Hopkins was early to adopt an in-house nephrology fellowship night float to improve work-life balance. The aim of our study was to elucidate attitudes about night float to guide fellowship structuring.

Methods: We conducted a mixed-methods study. We surveyed current fellows, program alumni, and current faculty and conducted a focus group of current fellows. Surveys were developed through literature review, queried on a 5-point Likert scale, and analyzed with unpaired t and ANOVA tests. The focus group transcript was iteratively analyzed by two independent reviewers to identify major themes.

Results: Survey response rates were 14 (100%) fellows, 32 (91%) alumni and 17 (94%) faculty. All groups felt quality of patient care was good to excellent with no significant differences among groups (mean (SD) range 4.12 (0.70) - 4.57 (0.65), p=0.12), but we found a statistically significantly more positive view on autonomy rated by fellows compared to faculty (4.57 (0.51) vs. 4.12 (0.33), p=0.006). Exploring the impact on the day team experience, fellows indicated a statistically significant improvement across domains (range 4.21 (0.80) - 4.64 (0.63), p<0.001 compared to neutral effect). Focus group themes included wellness, professional development, patient care, continuity of care, and structural components. Says one fellow, "…my bias is that every program would switch to a night float system if they could." All groups were satisfied with night float with 4.71 (0.47), 4.18 (0.81) and 4.03 (0.86) for fellows, faculty, and alumni respectively; fellows were more enthusiastic (p=0.028). Overall, all three groups preferred night float; fellows did so unanimously.

Conclusions: Night float was well-liked by fellows and improved the experience of the daytime fellow. Alumni and faculty were also positive about night float; however, they were less enthusiastic than fellows possibly because alumni and faculty have concerns about career preparation. Implementation of night float at other nephrology programs should be considered.



SA-PO011

Non-Tunneled Hemodialysis Catheter Placement Experience and Perception of Graduating US Adult Nephrology Fellows

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Background: Nephrology fellows are required to acquire skills and demonstrate competency in the placement of non-tunneled hemodialysis catheter (NT-HDC) during fellowship. To gain a greater insight in the NT-HDC placement experience and perception of US adult nephrology fellows, we carried out a national survey.

Methods: An on-line survey was created and sent to US adult nephrology fellows in May 2018. Data was further analyzed for fellows graduating in 2018.

Results: 254 fellows responded to our survey (31.4% response rate). 128 (50.4%) were graduating in 2018. Most NT-HDCs were placed in the hospital and 17.3% reported having a dedicated rotation for NT-HDC placement. 33.9% received simulation based training, 14.2% received bedside training, 20.5% received both simulation and bedside training, while 29.1% did not receive any formal training in NT-HDC placement. 45.3% did not receive any formal didactic session on NT-HDC placement during fellowship. Of the 128 graduating nephrology fellows (G-NFs), 27.3% had not placed any femoral NT-HDC during fellowship while 25.8% had placed ≤3 and 27.3% had placed >10. While 35.1% of G-NFs had placed >10 internal jugular NT-HDCs during fellowship, 21% had placed ≤3 and 23.4% had placed none. 14.8% of G-NFs had not placed any NT-HDC. 41.4% of G-NFs needed to place at least 5 NT-HDCs before independently performing this procedure during fellowship, while 11.7% required ≥10. While 64.8% of the G-NFs reported having received adequate training in NT-HDC placement, only 37.5% planned to place NT-HDCs after graduation. Majority (57%) of G-NFs felt that nephrologists should not place NT-HDC in clinical practice. Reasons cited for those who had inadequate or no training in NT-HDC placement included: lack of opportunities to place NT-HDCs (53.9%), lack of formal training (41.4%), lack of nephrology faculty interest (42.97%) and expertise (32.8%).

Conclusions: While majority reported adequate training in NT-HDC placement, a significant percentage of graduating fellows had not placed either a femoral or internal jugular NT-HDC or both during fellowship. Majority received simulation based training, however a significant percentage did not receive any didactic session or formal training in NT-HDC placement during fellowship. Fellowship programs should take measures to ensure that all fellows receive adequate training in NT-HDC placement.

SA-PO012

A Program of Renal Biopsy Training Using Low-Cost Realistic Models

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Background: Renal biopsy is a necessary procedure in Nephrology practice, but adequate training is necessary to minimize its inherent risks.

Methods: We developed a method for the training of residents and professional nephrologists in percutaneous renal biopsy, utilizing homemade simulators that imitate a lumbar torso and contain a dummy kidney made of colored forensic gelatin. The "kidneys" exhibit realistic physical appearance, consistency and ultrasound properties, yielding equally real looking fragments when "biopsied". The models were manufactured locally with a cost of less than 20 USD.

Results: Two workshops were carried out involving 61 nephrologists and Nephrology residents. The procedure consisted of the presentation of archived glomerulopathy cases, followed by an explanation of the biopsy procedure, after which hands-on ultrasound guided obtainment of "kidney" fragments (Figure), available to all participants, was performed. Afterwards, the possible complications, and the measures to avoid or limit them, were discussed. As a final step, the "results" were presented and discussed in the form of digitized renal slides corresponding to each case studied, along with the response to treatment and outcomes. When invited to evaluate the course, 98% of the respondents declared that they would recommend the course to others, whereas 100% considered the workshop "excellent" or "very good", and 92% assigned these same attributes to the hands-on training procedure. This method is currently being applied in the training of Nephrology Residents in our Division.

Conclusions: The use of these inexpensive dummies is a useful and well-received tool that can improve the efficiency of training in renal biopsy and increase the safety of the procedure.

Funding: Government Support - Non-U.S.

SA-PO013

Exploring Nephrologists' Attitudes Towards Kidney Biopsies for Research

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Background: Recent interest in kidney biopsies for research purposes raises the question of safety versus benefit of the procedure. Physician perspectives on indications for kidney biopsy and perceived safety of the procedure have not been studied in detail

Methods: We sent an IRB-approved, anonymous, online survey to 98 nephrologists at three Boston academic hospitals. Participants were asked about their clinical experience, their perception of the risk of kidney biopsies, and the likelihood that they would support biopsies being obtained from their patients for research purposes. We scored responses using a Likert Scale (1 = "absolutely not"; 5 = "definitely yes"). We compared scores using independent sample t-test

Results: Response rate was 58%. The Table shows mean scores according to whether nephrologists were primarily clinicians (n=12) or clinician-researchers (n=43). There were no differences between the respondents' assessment of renal biopsy risk when comparing researchers vs. clinicians or stratifying by years of experience or number of biopsies performed. Overall, nephrologists who were primarily clinicians scored lower than researchers on the scale for willingness to allow research kidney biopsies

Conclusions: Substantial variability exists among nephrologists regarding the indications for kidney biopsy and their comfort with kidney biopsies for research purposes

Funding: Other NIH Support - T32

Willingness of nephrologists to allow patients to be approached for research kidney biopsies. Results are reported as mean (SD) on a 1 through 5 scale (higher number suggests higher likelihood

	Primarily clinical care (n=12)	Primarily research (n=43)	p-value
Reserve a portion of an existing core	4.7 (0.6)	4.7 (0.5)	0.74
Perform extra pass to obtain a research core	2.3 (1.3)	3.3 (1.2)	0.02
AKI with clinical equipoise			
Suspected AIN from nafcillin vs. ATN from hypotension	2.6 (1.2)	3.6 (1.1)	0.006
Suspected CIN vs. atheroemboli post cardiac catheterization	2.6 (1.2)	3.2 (1.0)	0.09
Suspected ATN vs. AIN post cardiac surgery	2.8 (1.3)	3.4 (1.0)	0.07
AKI without clinical equipoise			
Clinical diagnosis of AIN from nafcillin	2.1 (0.9)	3.1 (1.2)	0.007
Suspected CIN post cardiac catheterization	2.1 (1.0)	2.6 (1.1)	0.18
Suspected ATN post cardiac surgery	1.9 (0.9)	2.6 (1.2)	0.09
CKD			
Non-proteinuric CKD stage 3	2.4 (1.0)	3.2 (1.2)	0.04
CKD stage 3 suspected to be due to diabetes	2.3 (1.2)	3.3 (1.2)	0.01
Average score	2.6 (0.9)	3.3 (0.8)	0.008

SA-PO014

Association of Nephrology Inpatient Service Size on Medication Safety Recommendations

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Background: Providing quality and safety care are the highest goals for most medical institutions. Quality care is difficult to define but has been linked with adequate staff to patient rato, timely care, and medical error reduction. Emergency department and intensive care units have studies that have identified safe and optimal nurse-to-patient ratios and physician-to-patient ratios respectively. The nephrology field lacks data in this area.

Methods: Retrospective chart review of general nephrology consults placed from Jan 1st 2018 to Dec 31st 2018. Daily service size and physician work schedules were reviewed with distribution analyzed. High patient census defined as greater than 40 (top 10%), low patient census defied as less than 26 (bottom 10%). Four types of renal related medications were assessed: electrolyte related, antibiotics related, nephrotoxic agents and central nervous system related. Medication errors were exressed as percentage and coordinated with daily service size. Clinical adverse outcomes associated with medication erros were also reviewed.

Results: 11.2% of the medication errors were experienced by our patients during the high census days vs 19.4% during the low census days. P= 0.225 Potential confounders include: higher census days were more prevalent in the winter months, and more experienced fellows and house staff worked during the winter months. Also there was low awareness of nephrologists responsibility to commend of renal dosed medication as standard consult recommendations amongst nephrology fellows.

Conclusions: The number of overloaded medication errors did not differ based on renal service size. However, patients expereinced greater than 10% of the medication errors in 2018. A pharmacist might be needed in the nephrology consult service to reduce the errors of renally excreted medication experienced by our patients. Awareness of nephrologists' role in medication safety recommendation shall be heightened by nephrology training programs.

Baseline comparison	High	Low
Month	Jan 1st-August 1st	August 13-Dec 4th
Quantity of charts	83	39
Residents	28 (34)	9 (23)
Medical Students	6 (7)	5 (12)
Specialty Fellow	6 (7)	0 (0)
Average census	42	23

SA-PO015

Timing and Type of Nephrology Consults in an Academic Medical Center: A Springboard for Quality Improvement

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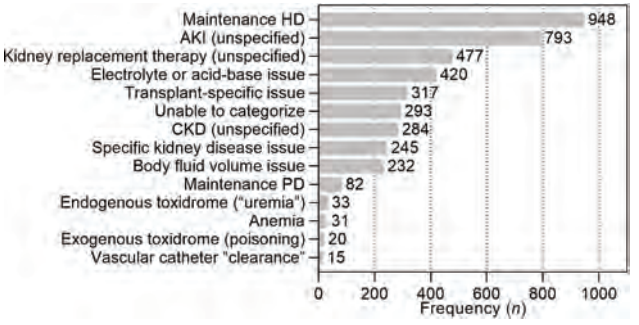
Background: Inpatient consultation is a common part of nephrology practice. Give our decreased work force and increasing clinical demand, knowing the type and timing of consult requests can improve the quality of care that we provide.

Methods: VCU Health is a large tertiary-care hospital with a clinical nephrology fellowship and 15 faculty members. An electronic consult request process was implemented in 2017. For nephrology, inpatient consult requests were submitted to 1 of 4 services: Floor (non-ICU), ICU, Chronic Dialysis, or Transplant. We used a health care informatics platform to abstract data for 3087 consults over a 12-mo period. Data included time of consult request and free-text reasons for consult (RFC); the latter were categorized using 1 or more of 16 prespecified categories.

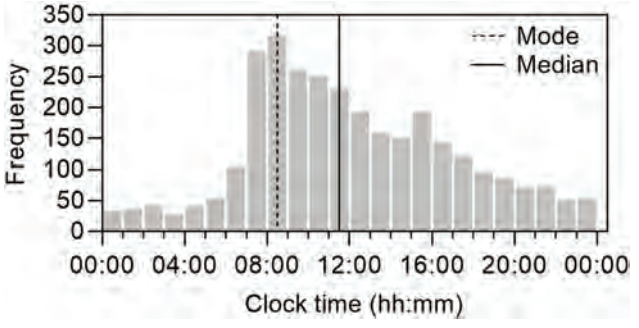
Results: The most common RFC was maintenance HD, followed by AKI (Figure 1). The maximum frequency (mode) of nephrology consultation occurred between 08:00 and

09:00, though a second mode arose between 15:00 and 16:00 (Figure 2). The frequency distribution of consultation was not different between the 4 consult services. Limitations include subjectivity and interrater variability in RFC categorization, and inability to capture consult requests that were not submitted electronically.

Conclusions: We identified the timing and type of consults requested over a 12-mo period. Our hope is to identify consultation patterns that place workload strain on the available nephrology staff. From that, we seek to undertake quality improvement initiatives to alter these patterns in order to maximize the quality of care rendered by our limited workforce.



Consult frequency by reason-for-consult.



Consult frequency by time of day

SA-PO016

The Impact of the Electronic Medical Record (EMR) on Nephrology Fellowship Training

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Background: A potential unintended consequence of EMR use is the impact on physician training. We surveyed U.S. Nephrology fellows to assess perceived burdens and benefits of the EMR on fellow education.

Methods: Using the ACGME 2018-2019 public list of nephrology programs, we contacted 148 program directors (PDs) by email requesting completion of an anonymous on-line survey on EMR impact on fellow education. PDs were asked to forward an anonymous survey link to their clinical fellows, and indicate to how many they forwarded the link. Surveys were open for 2 months, with reminders sent to PDs every 2 weeks.

Results: PD response rate was 34% (51/148 programs). 22% (33 PDs) forwarded the link to their fellows (n=216; 26% of U.S. nephrology fellows). Median fellows/program was 6 (range 2-20). 72 fellows (33%) responded. 39 were 1st year; 33 were 2nd/3rd year fellows. 42% indicated that their institution's EMR functionality was "slowed, disrupted, or completely lost" monthly or more. 51% of fellows agreed/strongly agreed that the EMR contributed positively to their education. The 3 most frequently cited positive effects were: access to EMR from home/mobile device (81%); efficient laboratory result trending (70%); and efficient determination of patient medications (47%). The 3 most frequently cited negative effects were: more time spent with the EMR than the patient (75%); excessive/irrelevant documentation (67%); and preventing fellows from learning the minimal essential evaluation for a given disease (42%). More than 50% of fellows agreed/strongly agreed they were "often reluctant" to do procedures (52%), participate in conferences (57%), prolong patient interactions (74%), and do independent case-directed literature review (55%), because of the competing time demands of EMR completion. 65% "sometimes" or "often" exceeded work hours limits because of time spent on EMR documentation. 54% "sometimes" or "often" made mistakes in the EMR due to the use of "copy forward".

Conclusions: Although the nephrology fellows surveyed indicated that the EMR had positive impacts on their education, the time demands of data entry appear to interfere with educational opportunities and may contribute to work hours violations. *The views expressed are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or the US Government.*

SA-PO017

Evaluation of an Online Conservative Care Curriculum for Nephrology Fellows

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Background: Older patients with advanced kidney disease experience increased mortality and morbidity despite life prolonging treatments such as dialysis. Conservative care (CC) without dialysis may provide better symptom management and quality of life. Yet nephrologists rarely offer CC, and most patients initiate dialysis without knowing about CC as a treatment option. We developed an online CC curriculum for nephrology fellows to increase knowledge and preparedness in CC skills.

Methods: ACGME accredited nephrology programs were invited to participate in the curriculum and designate a nephrology educator to serve as local champion of the curriculum. Participating programs received the multimodal curriculum including: 1) four online content modules; 2) online communication skills demonstrations; 3) worksheet activities; and 4) a post-curriculum session at each participating program facilitated by local champion to augment the online learning. Using RedCap data management, pre- and post- surveys measured fellow experience, preparedness, and knowledge in CC before and after undergoing the curriculum.

Results: Nineteen nephrology programs participated in the online CC curriculum. 150 of 176 participating fellows (85%) completed the CC pre-survey. Fifty-nine (49%) of fellows were female and almost all were first or second year fellows. Over 75% reported no or limited (1-2 times) teaching in how to define CC, identify who would benefit from CC, and use a values-based communication framework for treatment decisions for CC or time-limited trial (TLT). Using a 5-point Likert scale, most fellows felt 'not very' or 'somewhat' prepared to use a communication framework for treatment decisions for CC or TLT. Almost all fellows who completed the curriculum (46 at time of submission) felt 'very' and 'extremely' prepared to do the following: define conservative care; identify patients who will do poorly on dialysis; how to respond when a patient is emotional; and how to incorporate values-based communication framework for CC and TLT. Almost all fellows were 'very' to 'extremely' satisfied with the curriculum.

Conclusions: Fellows report little to no preparedness in CC or how to discuss CC with patients. An online conservative care curriculum led to increased perceived preparedness in core CC skills. Future research can track CC curriculum impact on patient outcomes and treatment decisions.

SA-PO018

Teaching Renal Physiology and Pathophysiology to Second- and Third-Year Medical Students by Combining Lecturing and Hands-on Computer Simulation

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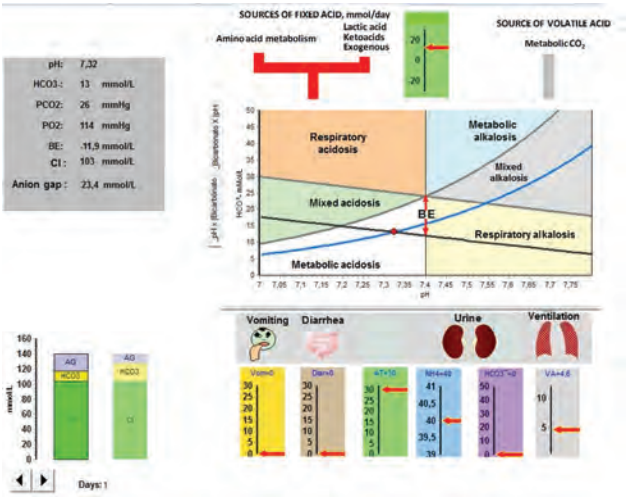
Background: Teaching of Renal Physiology and Pathophysiology (RPP) is one of the most challenging tasks in medical training, given the complexity of concepts and the number of interacting variables.

Methods: We devised a method to teach RPP to second and third-year medical students, consisting of one-hour lectures, followed by one-hour hands-on computer simulation during which students utilize mathematical models that we developed in Visual Basic® and Delphi®, presented through a friendly graphic interface (example in figure). Complex events such as glomerular ultrafiltration and acid-base disorders are simulated by changing variables through ordinary tools such as scrolling bars and sliding arrows. In a final step, students undergo a quick exam consisting of multiple-choice tests, which are discussed afterwards. At the end of each class, students are invited to fill in a self evaluation form about their perception as to whether preestablished learning outcomes were achieved.

Results: Evaluation made by third-year students in 2018/19 showed a high degree of perceived learning, with 79,1% reporting complete, and 18,5% partial, goal fulfillment in subjects such as Dehydration, Acute Kidney Injury, Chronic Kidney Disease and Acid-Base Disorders. In a more objective evaluation, 92 students who attended computer simulation scored 7.8±0.2 SE (on a 0-10 scale) in a test involving the pathophysiology of Edema and Hypertension, as compared to 7.1±0.1 obtained by 87 who just watched the presentation of a computer model ($p<0.05$).

Conclusions: These observations indicate that computer technology associated with classical methods can strongly improve the teaching of RPP, and confirm the concept that hands-on activity can be a more efficient learning method than passive transmission of knowledge.

Funding: Government Support - Non-U.S.



Acid-base equilibrium: dynamic Davenport nomogram.

SA-PO019

Application of a Virtual Patient (VP) Program in a Medical School Nephrology Curriculum

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Background: Immersive simulations have been shown to motivate students and promote learning in a fun and safe environment. Body Interact (BI) is among the most successful VP programs and has been used as a teaching adjunct by medical schools in the United States and Europe.

Methods: We identified 2 nephrology cases that would be appropriate for virtual simulation. We solicited the help of experts in order to build them in a VP platform. The VP cases were piloted then used during class in groups of 8 students accompanied by 1 teaching faculty. The VP allows direct interaction with the students including history gathering, physical examination, testing and live reaction to proposed treatments. At the end of each class, students were asked to fill a survey/feedback form that consisted of a 4-point Likert scale questionnaire rating student agreement [(SA) strongly agree, (A) agree, (D) Disagree and (SD) Strongly Disagree]. The questionnaire focused on 6 parameters: program interface, user engagement, perceived educational value, likability, need for improvement and interest in dissemination.

Results: All 32 CCLCM students used the VP platform for the 2 designed cases. The survey response rate was 73%. Ninety two percent of answers related to the program interface fell into positive categories (55% A and 37% SA), 90% of answers related to user engagement fell into positive categories (50% A and 40% SA), 85% of answers related to educational value fell into positive categories (55% A and 30% SA), 90% of answers related to the likability/need for improvement fell into positive categories (61% A and 29% SA) and 90% of answers related to the interest in dissemination fell into positive categories (60% A and 30% SA). Despite generally favorable feedback by the students, 68% thought that the program could be improved. Most of the desired improvements related to the speed of the program and to the presence of technical glitches on library computers.

Conclusions: We successfully incorporated a VP platform into the nephrology educational curriculum. The BI program was well received and was found to be a useful educational adjunct. Our experience taught us that the use of gaming engines may require considerable computer processing power and this will need to be taken into account in future virtual endeavors.

SA-PO020

The Renal Biopsy Trainer: A Cheaper and More Practical Approach to Procedure Simulation

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Background: Current kidney biopsy simulators are scarcely available, expensive and hard to maintain. We developed a Renal Biopsy Trainer (RBT) based on 3D printing technology. This RBT is a life size recreation of the abdominal cavity and the anatomy of the kidney and lumbar region with use of 3D volume visualization of CT images of the abdomen. From the CT the kidney was reconstructed and ported into a CAD program and to create a mold. Silicone molds of the various anatomical structures (e.g. cortex, medulla, calices) were printed so that these structures can be visually distinguished upon taking a biopsy core. The "Renal Biopsy Trainer (RBT)" intends to teach both the anatomy of the kidney as well as serve as an introductory tool to performing kidney biopsy, which can allow a learner to train on a more accurate model obtain immediate feedback on core sample that was taken.

Methods: The RBT is a life-size recreation of the abdominal cavity, kidney and lumbar region with the use of 3D volume visualization of CT images of the abdomen. The kidney was reconstructed into a 3D object which was exported into a computer assisted design (CAD) program. We created silicone molds of the various anatomical structures of the kidney (e.g. cortex, medulla, calices). Each structure was color coded and can be visually distinguished upon inspection.

Results: We created a life-size RBT at a cost of $20. It allows more than 20 passes. The replacement parts (lower pole of the kidney) cost less than $10. The RBT is ultrasound compatible and allows real-time performance of the kidney biopsy. The varied density of each layer allows the operator to "feel" when penetrating the cortex. The color coded sections of the kidney permits immediate feedback about the section from which the biopsy was obtained.

Conclusions: In contrast to commercially available simulators, which are prohibitively expensive, and their use is limited to only a few large medical education centers with a high cost of operation. The RBT is a practical and cheap introductory tool to teach both the anatomy of the kidney and the performance of a renal biopsy with all its intricacies. It can be easily located in the trainees' room for practicing frequently and gaining confidence in performing this critical procedure in Nephrology training.

SA-PO021

NephroPro v2: A New Smartphone App for Medical Students and Residents

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Background: There has been a marked decline in applicants to US Nephrology programs. According to some studies, one-third of the medical residents would have considered Nephrology as a career path if topics would have been explained in a manner that facilitated improved understanding.

Methods: We formed a committee of IM residents and Nephrology faculty at Saint Louis University and the University of Pittsburgh Medical Center with the aim to design an educational tool that would help trainees to engage in nephrology. A list of high yield topics was created and ranked. Selection criteria included relevance for medical education and complexity. We then generated short case-scenarios based on real-world problems. Questions were added to help solidify the educational points.

Results: We created *NephroPro*; an interactive app that includes medical scenarios designed around high yield knowledge useful for inpatient rounds, and shelf examinations. In the exploration of the case, students touch on relevant aspects of renal physiology/pathophysiology. An immediate feedback system helps to efficiently educate users on diagnostic tests/management. Each case has a set of 5 questions. Correct/incorrect alternatives are followed by a short explanation, summary tables/graphics. *NephroPro* was developed in partnership with professional developers and is available through Android/iPhone with no registration fee. The maintenance cost of the app is very low. New cases can be upload via our software (*Mobincube*). This app is not financially supported by any private or public institution.

Conclusions: *NephroPro* offers an innovative teaching tool to learn Nephrology. By expanding its use in the medical community, *NephroPro* could serve to generate a dynamic and fun environment to promote renal education.

SA-PO022

Role Play Simulation to Improve Empathy in Nephrology Trainees

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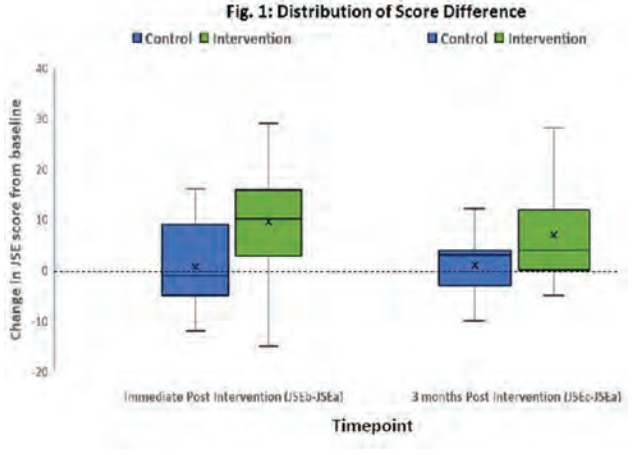
Background: Empathy enables one to identify with another's situation, thoughts, or condition. Empathizing with patients is believed to enhance patient satisfaction & treatment adherence. Simulation is increasingly used to teach empathy to health professionals. Using a randomized controlled trial design we assessed whether role play simulation improves empathy in nephrology trainees (NT).

Methods: All NT at the University of Toronto were eligible to participate. Participants were randomized to either Intervention or Control. The intervention comprised participation in medication intake (7-day dosette with QID placebo pills) & a clinical encounter (either ½ day outpatient clinic (MCKC) or a mock dialysis visit. Both involved clinical assessment by a physician, dietician, social worker & pharmacist. Control group was not exposed to any interventions. Empathy was assessed using the questionnaire for empathy (Jefferson Scale of Empathy for Health Professionals – JSE) at baseline (JSEa), within 24h of interventions (JSEb), & again at 3 months (JSEc). A difference in empathy scores was analyzed, between JSEa & JSEb, and JSEa & JSEc, using the paired T-test.

Results: All 36 NT were approached, 29 consented & randomized (Intervention n=16; Control n=13). Participants were mostly male (69%) & aged 31-40 yrs. In the Intervention group, 16 completed all JSE questionnaires & medication intake, 5 completed a dialysis session, & 5 completed MCKC session. Incomplete questionnaires were given by 2 Control group NT. At baseline, no differences were found between Intervention & Control groups (JSEa 108 ± 14 & 113 ± 8 respectively, NS). An increase in empathy was seen in the intervention group, but not the control group (JSEb 117 vs.113, P=0.03, Fig 1). A trend to persistent improved scores was seen (115 vs 113, P 0.09 at JSEc).

Conclusions: This small study suggests that role play simulation can increase empathy in NT at least over the short term. Larger studies, with longer time period follow up are required.



SA-PO023

NephSim: An Innovative, Mobile-Friendly Nephrology Education Tool

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Background: The evolving landscape of technology in medicine has created the need for new approaches to medical education in nephrology. Free open-access medical education (FOAMed) tools provide educational growth at no cost to the user. NephSim is a FOAMed tool that teaches pathophysiology and diagnostic approach to interactive nephrology cases through history and physical, diagnostic tests, and pathology. Cases provide real-time, iterative feedback and allow users to learn from mistakes. Tutorials and infographics illustrate nephrology concepts. NephSim, recipient of the 2018 ASN Innovation in Kidney Education Award, was created as an innovative tool for educators and trainees.

Methods: Built in WordPress, new content is published on NephSim.com every 2-4 weeks and can be accessed using mobile devices or computers. HIPAA compliant, peer reviewed content is distributed via social media and an email subscriber list. To evaluate the scope, effectiveness, and reach of NephSim, we assessed the website usage via WordPress analytics and administered an anonymous survey to evaluate user demographics and experience.

Results: To date, 31 cases have been published on NephSim (29% glomerular, 23% acid-base/electrolyte, 19% dialysis, 19% AKI/other, 6% transplant). 94,000 pageviews represent 100 countries. 17% (76/445) of email subscribers completed the survey. Most users were between 31-45 years (52%). 32% of users were nephrology fellows, 25% nephrology attendings, 9% internal medicine residents, and 1.4% medical students. The majority of users agreed or somewhat agreed that they use NephSim for individual learning (68%) or to teach others (75%). 96% agreed or somewhat agreed that NephSim was easy to use. Nearly all users either agreed or somewhat agreed that they enjoyed using NephSim (96%) and planned to continue using it in the future (99%). Anecdotally, NephSim has been used by educators to guide case-based lectures, teach medical students on nephrology electives, and foster independent learning for trainees at all levels.

Conclusions: NephSim has successfully deployed a mobile-friendly, cased-based approach to teaching nephrology. In just 1 year, usage continues to grow with global participation. Feedback has been positive. We aim to incorporate NephSim in medical school, internal medicine, and nephrology training program curricula while diversifying content and contributors.

SA-PO024

CME Effectively Improves the Clinical Performance of Nephrologists, Nurses, and Nurse Practitioners Related to Comprehensive, Chronic Hyperkalemia Management

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Background: Chronic hyperkalemia requires comprehensive management. We sought to determine if online continuing medical education (CME) could improve the clinical performance of nephrologists and nurses/nurse practitioners related to chronic management of hyperkalemia.

Methods: The CME activity was a 15-minute interactive case study with patient-physician vignettes featuring a patient with uncontrolled T2D, HF, and CKD for whom chronic hyperkalemia management was required. A repeated pairs pre-/post-assessment study design was used and chi-square test (P <.05 is considered significant) assessed educational effect for each activity. Cramer's V was used to calculate the effect size (0.06-0.15 is a noticeable effect, 0.16-0.26 considerable, and >0.26 extensive). The activity launched September 21, 2018 and data were collected through November 30, 2018.

Results: In total, 88 nephrologists and 1,504 nurses were included in the study. Upon patient presenting with increasing serum creatinine levels, proteinuria, and mild hyperkalemia, 52% (P <.001; V=.473) of nephrologists and 41% of nurses (P <.0001; V=.364) improved at recommending a low-potassium diet in addition to dose reduction of a potassium-lowering drug One month later, upon recognition of chronic potassium elevation, 36% of nephrologists (P <.001; V=.357) and 29% of nurses (P <.001; V=.214) improved at adding a potassium binding agent Three months post potassium binder initiation, patient returns with normal serum potassium levels, 42% of nephrologists (P <.001; V=.388) and 36% of nurses (P <.001; V=.370) improved at managing continued elevated blood pressure 32% of nephrologists and 44% of nurses reported increased confidence in adding a potassium binding agent in a patients taking multiple drugs that can induce hyperkalemia Continued educational gaps: 36% of nephrologists and 53% of nurses failed to effectively manage the patients' blood pressure 23% of nephrologists and 39% of nurses failed to initiate a potassium binding agent when indicated

Conclusions: This study demonstrates the success of online, CME-accredited, interactive case study with patient-physician vignettes on significantly improving clinical performance of nephrologists and nurses related to chronic management of hyperkalemia. Continued gaps were identified for future educational targets.

Funding: Commercial Support - independent educational grant from AstraZeneca

SA-PO025

Online Quizzes Based on Nephrology Social Media Coverage: A Novel Enduring Educational Material

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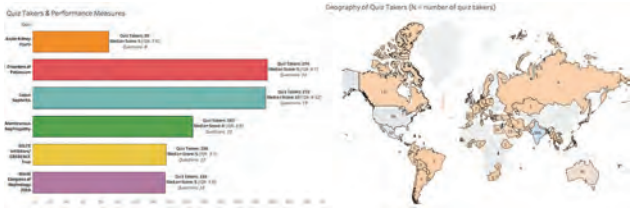
Background: The ACGME defines an **enduring educational material** as one that can be repeatedly utilized for learning purposes. Social media education, however, poses a challenge in creating enduring materials. Learning from tweets is difficult because of a large number of tweets posted rapidly and poor Twitter search engine. A quiz employs active learning which helps develop critical thinking and enhances interest in knowledge acquisition. The ISNeducation team created **online quizzes** to package **scientific tweets** into a readily useable enduring educational material. This is a pilot study to evaluate them as a tool to disseminate knowledge and **improve social media learning.**

Methods: Each monthly quiz is untimed **MCQ based learning activity**, consisting of 10-20 questions. Questions are derived from the **most informative tweets** on a concept covered in a **recent nephrology conference**. Answers, scores, and global ranking are revealed in real-time. Each question also has an explanation with a link to the original supportive evidence-based tweet. Learner details and scores are recorded. The quizzes can be freely shared via a link on Twitter, Facebook, WhatsApp and the top scorers for each quiz are acknowledged at the end of the month.

Results: 6 quizzes were analyzed on the following topics: Glomerular diseases, AKI, Potassium disorders, Advances in membranous nephropathy, SGLT2 inhibitors, and WCN 2019 twitter coverage. **2,237** users visited the quiz page and **1,133** completed the quiz. Maximum participation was seen from Asia (35%) followed by North America (15.5%). The median score was 5 (for 10 questions quiz) and 9.5 (for 19 questions quiz). https://twitter.com/i/moments/1132700081767890944 is the link for a running collection of quizzes URL.

Conclusions: Online quizzes highlight informative evidence-based tweets from which learning can occur at any time and location, fulfilling ACGME criteria as an enduring

educational material. They have the potential for augmenting **active learning** and also to improve the **reach of conferences** globally. With free access and minimum time required they also enhance the interest of medical graduates in the field of nephrology.



Quiz Analytics

SA-PO026

Online Anemia: An Online Educational Approach to the Management of Outpatient Renal Anemia

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Background: Nephrology trainees spend the majority of clinical training in the acute inpatient setting. Unfortunately, the lack of ambulatory experience results in the inexperience of new graduates to manage patients with chronic disease longitudinally. One area of weakness is the management of renal anemia, which is further exacerbated by the mainstream use of anemia protocols. We decided to address this educational gap by creating a comprehensive online module.

Methods: Using the Cleveland Clinic "MyLearning" platform, we constructed an interactive online module that focuses on renal anemia, and we focused particularly on the landmark trials. The module incorporated several tools such as infographics and embedded videos. The module also included problem-based case discussions that gave the opportunity for teacher feedback. Prior to its implementation, the module was piloted by faculty and students. Eight nephrology fellows received a 30-minute orientation course discussing the goals and objectives along with the expectations and assignments. They filled out an anonymous 10- question pre-test to assess their baseline renal anemia knowledge. The time allotted for completion of the module was 1 month. Upon module completion, fellows were required to complete a 10-question post-test and a 4 point Likert-scale questionnaire/feedback survey addressing six parameters: program interface, user engagement, education value, course feedback, interest in dissemination and need for improvement. Six months after module completion, fellows completed the same 10-question post-test in order to assess long-term retention.

Results: All 8 fellows completed all the surveys. Fellows scored an average of 49% on the 10-question pretest vs. an average of 79% on the 10-question post-test. At 6 months, the average post-test score was 65%. The overall impression of the online module was positive with 100% of fellows favoring the modules, finding them useful and asking to duplicate the approach in other topics. Fifty percent of the fellows preferred less content. Twenty-five percent of fellows found that the module could use technical improvement with the interface.

Conclusions: Online modules can be used with success in training programs as an adjunct to traditional education. Our experience shows improvement in both short-term and long-term retention.

SA-PO027

Gender Disparities in Social Media and Medical Education

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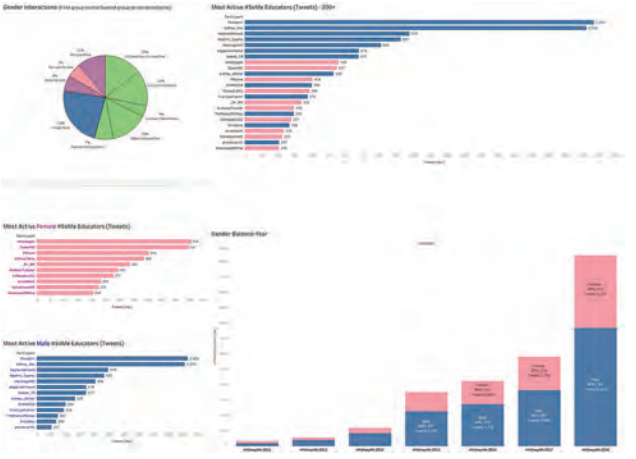
Background: Gender inequality is a pervasive societal issue and medicine is not immune. The American Society of Nephrology (ASN) has prioritized initiatives to promote diversity, including addressing gender equality. In order to understand gender disparities in nephrology social media (#SoMe) education, we report data that measures the magnitude of the imbalance.

Methods: We examined the official #KidneyWk, the social media education platform of the annual ASN Meeting from 2011-13 and 2015-18 using NOD Analytics (@nephondemand). We measured the differences in tweets authored by and the interactions between men and women.

Results: As of 2019, the ASN had 18,041 current members; 11,179 males, 5,386 females, and 1,476 no gender selected. Since 2012, the number of female and male #SoMe educators has been increasing but the proportion of each has remained unchanged since 2015. Additionally, we also found that 64% of the 48,852 tweets included invitations for #SoMe educators to opine and join the online discourse during #KidneyWk; however, only 6% of these invitations were male #SoMe educators inviting a female #SoMe educator to join the conversation.

Conclusions: The number of female #SoMe educators and their tweeting activity are increasing but continues to be under-represented; both are needed prerequisites to restore gender balance in the online medical education community. Unfortunately, there is a gender imbalance and the percentage of invitations that females receive from their male counterparts to join various online discussions, particularly during #KidneyWk remains low. Indeed cross-gender invitations (either M-F and F-M) are low and can promote "educational islands" where knowledge of female perspectives are not adequately represented. Having gender diversity in #SoMe would not only mean a high number of female educators tweeting, but an equal exchange of ideas between females and males.



SA-PO028

KIDNEYcon: An Innovative Conference for Nephrologists and Trainees

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Background: KIDNEYcon is an annual conference geared towards trainees and practicing nephrologists established in 2016 with a goal to fill important educational, career development, and practice gaps in nephrology. KIDNEYcon features unique interactive workshops, hands-on educational experiences, clinical sessions, and mentoring opportunities provide to provide rich opportunities for learning, fostering research careers, networking, and enhance collaboration. In addition, KIDNEYcon provides a venue to foster enthusiasm and interest in nephrology among medical students and residents.

Methods: KIDNEYcon is a 3-day conference held each April in Little Rock, AR. We evaluated the content of interactive workshops, assessed attendee demographics over the last 4 years, and sent an anonymous survey to trainee attendees to evaluate the experience and impact of KIDNEYcon.

Results: Attendance to KIDNEYcon grew from 35 in 2016 to 109 in 2019. In 2019, 38% (42/109) of the attendees were trainees (20% from the Northeast, 7% Midwest, 51% Southeast, 10% Southwest, 12% West). Of the 42 trainees, 59% were fellows (13 programs), 24% residents (9 IM residency programs), and 17% medical students (3 medical schools). 57% of trainee attendees responded to the survey. 100% rated their experience at KIDNEYcon as 4 or 5 out of 5, with 5 being the highest. 92% learned either "a great amount" or "quite a bit." 92% strongly agreed or agreed that KIDNEYcon contributed to their overall knowledge base. 50% reported increased interest in a research career. 88% and 92% strongly agreed or agreed that they would maintain relationships with nephrologists and other trainees, respectively. Topics for the interactive workshops (4 hrs) vary each year, though several high interest workshops have been repeated including the Kidney Biopsy Academy, Pathology Workshop, Acid-Base & Electrolytes workshop.

Conclusions: KIDNEYcon is a unique opportunity for trainees and practicing nephrologist to learn hands-on skills, network with colleagues, while increasing interest in nephrology and research careers. Response from trainees has been overwhelmingly positive. Goals for future conferences are to continue to expand workshop and didactic offerings, including direct solicitation of workshops from the community, and to further develop trainee engagement.

SA-PO029

Effect of Renal Replacement Therapy Options Education Class on Patient Outcomes

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Background: Transition from CKD into ESRD is a traumatic and often uncoordinated process. Many patients "crash landing" into hemodialysis with a central venous catheter. Structured CKD care can better prepare patients for transition to ESRD. Yet, it has not been systematically implemented nationally due to fragmented care outside of integrated health care systems, lack of patient awareness or engagement regarding CKD issues. Kaiser Permanente East Bay Nephrology Group implemented patient education program delivered by renal RN's to provide patients and family education on RRT modalities with the goal of providing smoother transition into ESRD.

Methods: KP East Bay implemented a standardized RRT option class for patients with CKD stage 4 and 5. It was highly recommended to be completed when a patient's

eGFR reaches 20ml/min or below. It was taught by a renal nurse. The class last average 1-2 hours. It was attended by a patient and family members. The nurse discussed different type of RRT options, including: conservative management without dialysis (CMWD), kidney transplant, in-center hemodialysis (HD) and home dialysis (PD and HHD).

Results: Since the initiation of new Options Class in 2016, 460 patients have attended it. The average creatinine at the time of referral was 3.58 mg/dl and average eGFR was 18.71 ml/min. After the option class, 43.3% patients chose home therapy: 37.3% chose PD and 5.4% chose HHD. 26.5% chose ICHD, 3% chose CMWD. 31% remained undecided on their care plan after attending option class. As of 2019, 86 (11.7%) patients who attended Options education initiated dialysis. Among them 53.2% on home dialysis (50% with PD; 2.3% with HHD); 47.6% with ICHD, 2.3% received a pre-emptive transplant. 29% expired before dialysis initiation and 59.3% remained dialysis independent.

Conclusions: A structured RRT option class resulted in a smoother transition into RRT with higher percentage of patients chose home modality. Further work needs to be done to improve targeted interventions to guide patients who have difficulties to formulate decision or ESKD Life Plan. Comparison of characteristics of patients who attended the classes versus those who did not, as well as details of outcomes of patients remaining with CKD and those who died before reaching RRT need to be studies to confirm and quantitate benefits of this educational program.

SA-PO030

Nephrology Fellow Performance on a Formative Peritoneal Dialysis Objective Structured Clinical Examination

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Background: Less than 10% of prevalent ESRD patients are treated with peritoneal dialysis (PD), and nephrology fellows may not have sufficient PD exposure to be comfortable with the procedure. We previously developed and initially validated a formative objective structured clinical examination (OSCE) assessing management of PD-associated peritonitis (based on the International Society for Peritoneal Dialysis practice guideline). We now report the preliminary results of fellow testing.

Methods: The OSCE test committee set the passing threshold at 16/22 points (Ebel's method), with median relevance essential/important for all questions (content validity index 91%). Validators (16 board-certified practicing nephrologists) had a mean score of 19 (SD 2) points, with 94% passing. Cronbach's alpha was 0.70. Score agreement between investigators was very good (Kappa =0.85). The OSCE is being prospectively administered by 19 U.S. nephrology fellowship programs. Fellows are anonymous, and have 1 hour to take the test (using local institutional order sets at the program director's discretion).

Results: 9 programs have submitted OSCE results. 48 fellows were tested (25 1st year and 23 2nd year). Mean time to take the test was 34 (SD 8) minutes. Mean score was 17 (SD 3), with 71% passing. 19% correctly indicated the 3 diagnostic criteria for peritonitis (vs. 44% of validators); 72% recognized peritonitis-associated ultrafiltration failure (vs. 100% of validators); and 22% correctly prescribed a 21 day course of antibiotics for gram negative peritonitis (vs. 63% of validators). Some programs used the OSCE to introduced a didactic session on PD-associated peritonitis management.

Conclusions: The OSCE is an opportunity for program directors to assess local curriculum effectiveness, and for fellows to ascertain their familiarity with PD-associated peritonitis management practice guidelines. *The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or the US Government.*

SA-PO031

A Novel Smartphone-Based Self-Management System for Hemodialysis Patients

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Background: Dialysis patients are commonly disengaged from hemodialysis their care. Evidence suggests that the care of patients with advanced CKD and ESRD does not optimize patient engagement. Lack of self-participation in dialysis care may worsen clinical cardiovascular outcomes and warrants the need to educate and engage patients. In particular, patient engagement is essential to achieve optimal fluid balance and avoid excessive fluid intake. Increasing patient active participation in their dialysis care through a digital health application can potentially improve the clinical outcomes and patient satisfaction. Mobile app use among healthcare professional is still limited. Smartphone apps are deemed "useful tools at the point of care and in mobile clinical communication, as well as in remote patient monitoring and self-management of disease." Utilization of digital health application in hemodialysis patients has not been explored yet. There is a lack of readily available and validated mobile apps for the HD population.

Methods: We performed 200 interviews with hemodialysis patients. Dedoose software was used for cording and conducting this qualitative research. Smartphone app (herein referred to as Kidney Tracker) was developed through feedback loops.

Results: The smartphone dialysis application proposed (Kidney Tracker) offers four main functions. The first function of the smartphone dialysis application is the dialysis tracking function. Data from the patient's dialysis treatments will automatically be migrated to the fluid tracking function. The second function of the smartphone dialysis application, the fluid, and activity-tracking page, features intuitive fluid tracking that streamlines the tracking process. The third function of the smartphone dialysis application, the game function, offers awards and challenges that use game-design concepts to keep the patient engaged. The fourth function of the dialysis application is the direct patient to care provider contact function.

Conclusions: This is an innovative project that specifically targets HD patients and resulted in developing a smartphone app for use in this patient population. This digital health technology can be a very helpful tool in the dialysis setting.

SA-PO032

Establishing Inpatient Dialysis Education Program Using an iPad

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Background: It is well known that providing chronic kidney disease education to patients will result in better planning for dialysis. However, there are patients who are admitted to hospitals with advanced kidney diease and require dialysis either during hospitalization or shortly after discharge. Many of these patients are started on hemodialysis (HD) rather than home dialysis despite dialysis modalities such as peritoneal dialysis (PD) and home hemodialysis (HHD) offering better quality of life. To address this gap, we established a quality improvement initiative to educate hospitalized patients near dialysis about kidney disease and dialysis modalities. The primary aim is to improve patient understanding of dialysis modalities and chronic kidney disease. Secondary aim is to refine educational material and determine what dialysis modality patients chose in long term and if there is an increase in number of peritoneal dialysis patients.

Methods: Enrollment criteria was patients admitted to UPMC Magee-Women's and Presbyterian-Montefiore hospitals who are advanced CKD (stage 4/5) and planning to start dialysis on their admission or within several weeks of discharge as identified by nephrologist. The dialysis education was provided on iPad by a physician. Patient response to dialysis education was recorded using a survey.

Results: The project was initiated in January 2019 with enrollment of 10 patients. The average age was 57.5 years and 70% female with 70% of patients having previously seen a nephrologist. The average time required for education was 45 minutes. Patient reported post education understanding of dialysis and kidney disease as 4.6 (scale of 1 to 5). Post education, 50% of patients were leaning towards home dialysis.

Conclusions: Our preliminary results show that providing education increases awareness of home dialysis modalities with 50% choosing to do so. Interestingly, majority of our patients had previously seen a nephrologist but had required re-education highlighting that CKD patients require significant re-enforcement of their disease process. The patient response is overall positive (rating 4.6 out of 5). Results of a follow up survey to patients who did and did not receive education are pending and will help in determining the secondary aim. For furture improvement, we aim to incorporate tele-health nurse and patient advocate as educators.

SA-PO033

Effect of an Audiovisual Educational Program on Nutritional Knowledge and Adherence to Dietary Treatment in CKD Patients Undergoing Hemodialysis

Ximena Atilano carsi,[1] Estefanía Veles mariscal,[1] Ricardo Velázquez garcía,[2] Celene V. Arce santander,[3] Paola V. Miranda,[1] Angeles Espinosa-Cuevas,[1] Ricardo Correa-Rotter.[1] *[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, Mexico; [2]Universidad Mexiquense del Bicentenario, Estado de Mexico, Mexico; [3]Lapi Unidad de Hemodiálisis, Ciudad de México, Mexico.*

Background: Multiple complications of advanced chronic kidney disease require specialized treatment and nutritional education. In Mexico, there are no formal education programs in hemodialysis (HD) units that allow improvement in the patient's self-care. The aim of this study was to assess the effect of an audiovisual nutritional education program on the nutriological knowledge and adherence to dietary treatment in patients of two different hemodialysis units

Methods: Three videos, with dietary phosphorus, potassium and sodium topics, were created and projected during the HD sessions of all shifts during 9 weeks. Nutritional knowledge was measured with a questionnaire and adherence to diet was evaluated with a 3-day food record, before and after the educational intervention. Level of knowledge was classified according to the percentage of correct answers, being bad with <60%, regular between 60 and 79.9% and good > 80%

Results: One hundred and thirty eight patients from both units were included. Average age was 38.9 ± 14.3 years. Nutritional knowledge changed significantly after the intervention: from 30.4% to 6.6% for the bad level, from 57.2% to 30.4% for the regular level, while the level of adequate knowledge increased from 12.4% to 63%. Increase of knowledge was greater in potassium topic followed by phosphorus. After the intervention, the percentage of correct answers for sodium, potassium and phosphorus knowledge

were significantly higher; 75.5 ± 17 vs 87.6 ± 9.0 (p <0.001), 57.3 ± 20.4 vs 78.3 ± 12.8 (p <0.001) and 64.4 ± 18.3 vs 81.9 ± 15.7 (p <0.001) respectively. A significant correlation was found between educational level, dialysis vintage and nutritional knowledge; r = 0.41, p <0.05 and r = 0.43, p <0.05, respectively. Regardless of the increase in nutritional knowledge, no improvement in adherence to the dietary plan was found

Conclusions: The audiovisual educational program had a positive impact on the nutritional knowledge of the patients, however nutritional education alone did not improve adherence to diet

SA-PO034

Respectful Engagement of Indigenous Peoples in a Pan-Canadian Kidney Research Network

Helen Robinson-Settee, Craig Settee, Kevin Settee, Catherine Turner, Cathy Woods. Can-SOLVE CKD Network *Can-SOLVE CKD Network, Vancouver, BC, Canada*.

Background: Kidney disease has a disproportionate impact on the health of Indigenous communities in Canada. A national strategy to improve kidney health must include meaningful, culturally appropriate engagement with Indigenous peoples. Can-SOLVE CKD Network is a pan-Canadian patient-oriented kidney research initiative that is working to improve the health of all Canadians and bring Indigenous ways of knowing into health research.

Methods: As part of the Can-SOLVE CKD Network, Indigenous patients, caregivers, researchers, and community leaders created an Indigenous Peoples' Engagement and Research Council (IPERC). IPERC supports collaboration grounded in traditional values and partnerships with Indigenous peoples and communities. IPERC guides Can-SOLVE CKD research projects in respectful engagement of Indigenous communities. The network has created a training pathway, *Wabishki Bizhiko Skaanj* ("White Horse" in Anishinaabe), helping researchers and patient partners build respectful partnerships with Indigenous peoples in health research. Participants are encouraged to look, listen, learn, and lead their way along the pathway by examining racial identities, privileges, and biases, as well as participating in interactive learning exercises, facilitated online modules and webinars. The *Wabishki Bizhiko Skaanj* learning pathway includes a focus on Indigenous Elders in research. This training aims to create a culturally safe space for researchers, patients, and Elders to come together to gain understanding of a holistic context for scientific observations.

Results: Can-SOLVE CKD and IPERC has created a culturally safe space for Indigenous individuals to participate in all aspects of patient-oriented kidney research. *Wabishki Bizhiko Skaanj* represents a novel learning platform for Indigenous cultural safety in Canadian health research. By enhancing knowledge, self-awareness and strengthening cultural competency, this learning pathway is enabling all partners in health research to close the gaps in kidney health outcomes between Indigenous and non-Indigenous communities.

Conclusions: The Can-SOLVE CKD Network offers a model for respectful engagement of Indigenous communities in health research. By adopting Indigenous ways and fostering cultural competency, kidney health outcomes and overall wellness for and with Indigenous peoples across Canada will be enhanced.

Funding: Government Support - Non-U.S.

SA-PO035

Patient and Caregiver Views on the Definitions and Impact of Terms Used to Describe Kidney Health

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Background: The terminology for kidney health is inconsistent, inaccessible, and may be conceptualized differently between patients and health professionals. These problems can impair the quality of communication, care and patient outcomes. As part of the Kidney Disease: Improving Global Outcomes (KDIGO) Nomenclature Initiative, we aimed to describe patient perspectives on the definitions and impact of terms for kidney health.

Methods: 54 patients and 13 caregivers from the United States, United Kingdom and Australia participated in 10 focus groups to discuss terms and concepts used for kidney health (e.g. kidney, renal, CKD, end-stage kidney disease, kidney failure, and descriptors and measures for kidney function i.e. CKD stages). Transcripts were analyzed thematically.

Results: We identified four themes: ***frustrated by ambiguity*** (with subthemes of: confused by medicalized language, lacking relevance to personal circumstances, baffled by imprecision in meaning, uncertainty of what can be controlled, opposed to obsolete terms); ***making sense of the prognostic enigma*** (conceptualizing level of kidney function, characterizing function based on symptoms and life impact, predicting progression and need for intervention); ***provoking and exacerbating undue trauma*** (fear of the unknown, denoting impending death, losing hope in having no treatment options, premature labeling and assumptions, judgment and failure of personhood); and ***mobilizing self-management*** (needing to accept the harsh reality, prompting and motivating behavior change, learning medical terms for self-advocacy). (Fig 1)

Conclusions: The obscurity and imprecision of terms in CKD can be unduly distressing and traumatic for patients. Consistent and meaningful patient-centered terminology may improve patient autonomy, satisfaction and outcomes.

Theme	Selections quotations
Frustrated by ambiguity	
Confused by medicalized language	*What is renal? Just say kidney and I'll understand that more. What's renal failure?* *I used to get confused about kidney failure and my nephrologist would say "you're not in kidney failure yet, you've got kidney disease." He was using it as the end point. I was thinking my kidneys are failing.*
Lacking relevance to personal circumstances	*Pre-kidney; replacement, it is not luxury that everybody has.* *Even when they're putting the GFR out there for you to read and understand they have in parenthesis that if you're African American it's a different number, but they didn't explain why it's a different number.*
Baffled by imprecision in meaning	*A disease is something you've caught or something that you have. I don't think that reflux is a disease. It's an abnormality.* *I never thought of myself as having end-stage renal failure because I was on renal replacement therapy.* *I feel end stage refers to palliative care. My husband was on dialysis for 20 years. That's hardly end stage.*
Uncertainty of what can be controlled	*The language doesn't give a sense, that's used, doesn't give a sense of control or that it's controllable.*
Opposed to obsolete terms	*The more technology develops, the less appropriate that word end becomes. For the majority of people there are life sustaining treatments: dialysis and transplant.*
Making sense of the prognostic enigma	
Conceptualizing level of kidney function	*The percentage, this is where I'm confused. If it has to be over an eGFR of 60 do you consider 60 100%? I mean what percentage is the hundred percent because it could up to 115?* *But when they say now you're at stage three, now you're at stage four kidney disease, you think, what is that? What is stage three, what is stage four?*
Characterizing function based on symptoms and life impact	*I was in stage five and I still didn't have any symptoms.* *My kids would say, "kidney disease means you're sick, tired, or vomiting." To them kidney disease impacts how I was rather than anything to do with what treatment or what was required to keep me well.*
Predicting progression and need for intervention	*Stage1 It's good in terms of qualifying where you're at in that. Is it one of those things that you put a time onto though? How long are you going to be stage one for, how long before stage two?* *Stage one is your kidneys are not working, full stop. Stage two is getting bad. stage three is getting to the fistula stage, stage four, dialysis, stage five is not working.*
Provoking and exacerbating undue trauma	
Fear of the unknown	*It was quite upsetting the first time it was mentioned. It's just basically, denial, what does it actually mean?* *It scared me because no one was telling me anything. All that you hear, the whispering going on about the GFR. I was lying there. I felt like a cattle being led into slaughter.*
Denoting impending death	*When they told me end-stage I thought I was dying. I accepted the fact that it was just a matter of weeks.* *The problem is that end stage in other areas is referred to as those last few months of life, you're at the end. Whereas with this it's really saying this is the end of my kidney. It could be the start of a transplant or dialysis.* *You're on the cliff, about to fall off. It was quite traumatic and scary.* *You're watching the creatinine go up and the kidney function come down and you're watching this guillotine, but terms don't help. This wicked term, end-stage.*
Losing hope in having no treatment options	*Once they say 'end-stage,' it's kind of like, why not let nature run its course?* *Chronic kidney disease. It's very terminal and final and nothing you can do about it.*
Premature labeling and assumptions	*I would rather you educate me as to what stage I'm at then using a word that doesn't apply to me such as pre-dialysis. Dialysis doesn't apply to me now, why do I need to even use the word?* *Pre-dialysis, that just alludes to you will be doing that, because some people don't ever have to have dialysis.*
Judgment and failure of personhood	*The connotation of end-stage, isn't helpful. Your kidneys fail and so will you. By association, your physical existence is failing. Separate it from the person.* *Other people said to me 'you've got kidney failure' and it was like I had done something wrong.* *Pre-dialysis is derogatory: if I'm in Stage 3 I don't want someone telling me I'm pre dialysis because I could change my lifestyle.*
Mobilizing self-management	
Needing to accept the harsh reality	*The words are kind of damaging and painful to the patient, but they're a necessary damage, because you have to understand it. End-stage is a really harsh term, but I feel it's a good term, because you have to drill it home that that really is the last stage of whatever you're going through. If you'd been told that you're a stage V, I would have been like, oh, it's just stage V, I can still reverse it.*
Prompting and motivating behavior change	*When people say you're prediabetic, okay that means that you're headed for diabetes, but if you make these changes then you, you can either not get the disease or control the effects of the disease on you? If you're saying pre dialysis in my mind that says I'm about to go on dialysis. I'm going to wonder is there something I can do to keep me from going on dialysis.*
Learning medical terms for self-advocacy	*Understanding the big words; although it can be intimidating, this is your life.* *That's the kind of things that you need to know. Every profession wants to use their language, you can't stop it. But we need to know what it is.*

SA-PO036

Computational Fluid Dynamics Modeling (CFD) of Wall Strain in a Murine Glomerular Capillary Segment

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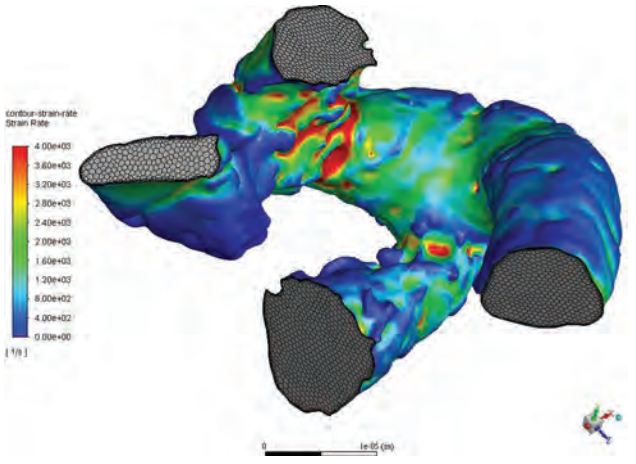
Background: Mechanical forces such as pressure and stress in the glomerular capillary tuft have been proposed to mediate hyperfiltration and podocyte injury and detachment, leading to irreversible glomerular disease. However, the actual forces imposed by blood flow in the tuft are incompletely defined. Simple tube models poorly capture the complex anatomy of the tuft. We undertook to model fluid flow through an actual capillary tuft to understand the feasibility of applying CFD to glomerukar physiology.

Methods: Mouse kidneys were cut into 1 mm cubes and fixed wiht glutaraldehyde and prepared for electron microscopy with osmium. Tissue was mounted onto an aluminim cryo pin using cyanoacrylate and all block surfaces trimmed. A gold coating was applied to the block to create a conductive surface. The block was placed in the Quanta 250 FEG/Gatan 3view system and a 41 x 41 field of view was imaged at an approximate pixel size of 10 nm and section thickness of 50 nm. MIMICS (Materialise, Ann Arbor, MI) image reconstruction software was used to create a 3D surface representation of the capillary segment. The flow through the capillary segment was then modeled using ANSYS-Fluent (ANSYS, Canonsburg, PA) CFD software. Steady-state, laminar flow conditions were modeled and a pressure differential across the section was applied to provide the desired velocities within the capillary lumen. Estimates of desired fluid velocity in the capillary were drawn from 2-photon intravital microscopy experiments.

Results: The CFD solution predicted values of fluid shear stress, fluid streamlines, and wall strain along the glomerular capillary segment.

Conclusions: End-to-end estimation of physical forces at the glomerular capillary wall is possible by computational modling of flow through structures imaged via serial block section EM. Further work is needed to capture unsteady flow and the influence of blood cells on local wall strain.

Funding: Clinical Revenue Support



SA-PO037

Prolonged In Vivo Perfusion of a Re-Endothelialized Human-Scale Tissue Engineered Kidney Graft

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Background: Advances are desperately needed to increase the supply of transplantable kidneys for the 100,000 patients on the waiting list. Whole organ engineering is one approach that holds tremendous promise and to date, the most successful approach utilizes perfusion decellularization to provide the ideal kidney extracellular matrix scaffold that maintains the organ's native vasculature and architecture, and allows recellularization with human cells. A critical component and the focus of the current study is to demonstrate the ability to functionally revascularize clinically relevant whole kidney matrix with human endothelial cells and provide sustained in vivo perfusion following orthotopic implantation.

Methods: Kidneys recovered from adult pigs were decellularized via detergent perfusion through the vasculature. The porcine matrix was seeded with human umbilical vein endothelial cells (HUVECs) and cultured using a custom perfusion recellularization bioreactor until sufficient cellular coverage of the vasculature was obtained. Functional testing of the renal vascular bed was performed using an ex vivo porcine blood flow model. Re-endothelialized kidney grafts were transplanted orthotopically in a pig model and evaluated with angiography at days 3, 7, 10, and 14 days before explantation.

Results: A minimum glucose consumption rate of 20 mg/hr was determined to represent sufficient endothelialization to sustain continuous blood flow (>100 mL/min) ex vivo, and was predictive of early patency in orthotopic transplants. At 7 days after transplantation in pigs, 83.3% (n=5/6 pigs) of grafts in surviving animals maintained renal perfusion during follow-up angiography. One kidney graft remained patent through post-operative day 14.

Conclusions: As 14 days is the longest reported continuous perfusion of a revascularized kidney graft to date, these results lay the foundation for the long-term success of human-scale recellularized kidney grafts and move the field closer to increasing the supply of transplantable kidneys.

Funding: Private Foundation Support

SA-PO038

Tunable Stiffness Polyacrylamide Hydrogels with Functionalized Matrigel for Renal Tissue Culture

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Background: Tunable stiffness polyacrylamide (PA) based hydrogels are commonly used for mechanotransduction studies. PA gels must be functionalized with protein for cell attachment. This is commonly accomplished using sulfo-SANPAH or acrylic acid NHS ester to bind protein to the gel surface. However, these methods do not produce reliably uniform surface protein concentrations. In order to produce PA gels with highly reproducible surfaces, we modified methods used for producing methacylated gelatin (GelMA), to produce methacrylated Matrigel. The "MatrigelMA" can be added into the polymerization mix prior to casting gels, where it is covalently linked to the gel network.

Methods: 5 ml of Matrigel (10 mg/ml) with phenol red, was mixed with 5 ml of ice cold 50mM HEPES pH 8.5 while stirring at 4° C. 25 ul of methacrylic anhydride was added dropwise. 1N Sodium hydroxide was added as needed to maintain an alkaline pH. After 30 minutes, this was repeated with an additional 25 ul of methacrylic anhydride. The reaction was continued overnight, then the mix was dialyzed against sterile deionized water for 5 days at 4° C, with daily changes of water. The resulting solution was aliquoted and stored at -20° C. MatrigelMA was added to PA mixes designed to produce gels with expected stiffnesses of 4.5 kPa or 40 kPa. The elastic modulus was measured using an Electroforce 3100 mechanical analyzer.

Results: Gel stiffnesses were not significantly altered by the addition of up to 100 ug/ml of MatrigelMA. Immunohistochemical staining for laminin was highly uniform wihtin and between gels. RPTEC/TERT1 cells were found to attach exceptionally well when seeded on both soft and stiff gels containing 100 ug/ml MatrigelMA. However, the cells tended to become round and detach from the soft gels after 6-8 days in culture, but persisted for several weeks on stiffer gels.

Conclusions: Extracellular basement membrane (Matrigel) was functionalized with methacrylate groups to facilitate crosslinking to polyacrylamide. The addition of 100 ug/ml to PA gels resulted in surfaces with the expected stiffnesses that promoted excellent attachment of RPTEC/TERT1 cells. However, cells tend to detach from the softer gels. We are continuing to determine if this results from degradation of matrix or if this is due to a cellular response to soft matrices.

Funding: Other NIH Support - NIBIB, Private Foundation Support

SA-PO039

A High-Throughput Oxygen Biosensing Platform for a Microfluidic In Vitro Kidney Models

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Background: Oxygen concentration and dynamics directly influence renal cell function *in vivo.* For example, low oxygen tension plays a significant role in both acute and chronic kidney disease. In addition, decreased cellular oxygen consumption in the kidney has been linked to mitochondrial and metabolic dysfunction. Therefore, monitoring oxygen levels within *in vitro* kidney models will enable physiologically accurate oxygen conditions for the models and allow assessment of metabolic function for normal tissue or metabolic changes due to toxic insults, disease states, or therapy administration. Current microfluidic *in vitro* kidney models control flow to generate tissue with kidney-specific functionality, however, such systems lack high-throughput oxygen sensing capabilities.

Methods: We integrated optical luminescence based oxygen sensors into a high-throughput microfluidic *in vitro* kidney model platform (PREDICT-96), previously developed at Draper, for real-time and non-destructive monitoring of dissolved oxygen in the tissue microenvironment. PREDICT-96 supports renal co-cultures under flow in a 96 tissue replicate device. The oxygen sensor probes, deposited in each microfluidic channel, are excited by red-light transmitted via a fiber optic cable resulting in near infrared emission with an oxygen dependent phase-shift. The O_2 measurement system was adapted to fit a standard microscope stage. High-throughput readings are accomplished by programming the stage to align the optic fiber with each sensor probe and to cycle through all 96 devices.

Results: Oxygen consumption rates for co-cultured human renal proximal tubule epithelial and human microvascular endothelial cells under flow and static conditions were quantified. A COMSOL-based computational model indicates the ability to regulate oxygen concentration via controlling flow of the PREDICT-96 pumps. In this way, oxygen levels will be characterized for varying *in vitro* model parameters, resulting in both physiologically accurate renal co-culture conditions of normal tissue and hypoxic or ischemic injury tissue.

Conclusions: The PREDICT-96 oxygen biosensing platform will enhance *in vitro* renal tissue function and provide a high-throughput respirometric platform for studying renal metabolic dynamics in response to nephrotoxic drugs or disease progression.

Funding: Other U.S. Government Support, Commercial Support - Draper Laboratory, Boston University

SA-PO040

Screening of Drugs for Nephrotoxicity Using a Microfluidic Proximal Tubule on-a-Chip

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Background: Off target effects of pharmaceutical drugs account for approximately 20% of all patients diagnosed with acute renal failure. To avoid such scenarios and prevent drugs that have nephrotoxic effects from advancing past pre-clinical testing to late-stage clinical trials, it may be necessary to evaluate drug induced nephrotoxicity early during the drug discovery cycle to ensure safety and minimize costs associated with drug failure in late-stage clinical trials.

Methods: We engineered a scaffold that enables co-culture of human proximal tubule epithelial cells (RPTEC) with renal microvascular endothelial cells (MVEC) on either side of a porous polycarbonate membrane which enables cell-cell and soluble factor communication and facilitate reabsorption. The surface was coated with Collagen IV for cell attachment and approximately $1x10^6$ cells of each RPTECs and MVECs were seeded on each side of the membrane. The device was then integrated into a microfluidic flow loop assembly to match physiological and biomechanical conditions associated with tubular flow and resorption to accurately recreate the proximal tubule.

Results: We evaluated the cells integrated within a flow loop to determine the effects of fluid shear associated with tubular flow. Our results indicate that the cells can be grown to confluence and can be maintained in culture under fluid flow at physiological levels of shear (approximately 0.1 dynes/cm^2). We used immunofluorescence to determine confluency using phalloidin for actin skeleton, LIVE/DEAD® for cell viability, and occuldin for the establishment of barrier function. These stains provided insight of cell-cell tight junction formation, monolayer integrity, and paracellular permeability in polarized and transporting RPTECs.

Conclusions: In this project, we were able to recreate the architecture of the proximal tubule using the bilayer scaffold within the microfluidic flow loop to reproduce the fluid flow associated with both tubular flow and resorption ensuring a physiologically accurate model of the tubule. This model was evaluated for cell viability, resorption and establishment of barrier function to further validate the physiological function. Finally, we expect to be able to reproduce effects of drugs known to have low, intermediate and high levels of toxicity using our model and will confirm that this model can be used for pre-clinical evaluation of new drugs.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO041

Culturing of Murine Podocytes via a 3D Suspension Culture System Using the Microcarrier

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Background: Cell culture in two dimensions has been well established in the worldwide for the past decades. However, the culture of cells in two dimensions is unable to representative of real cell environments, lack of predictively to anatomy or physiology *in vivo*. Creating a third dimension for cell culture is clearly a better way of representing physiological relevant then 2D culture.

Methods: Murine poodcytes were determined that stirred suspension bioreactors utilizing Cytodex-3 microcarrier beads represent a viable platform for the differentiation of podocytes. 1 gram microcarrier beads were loaded, an inoculation ratio of 2 x 10^7 cells per 1 gram beads, and discontinuous agitation in a medium with 10% serum resulted in high cell attachment efficiencies.

Results: At the end of incubation, the expression levels of nephrin and synaptopodin were examined after various microcarriers beads culture time periods. Compared to static tissue culture dishes, a bioreactor-based bioprocess requires fewer handling steps, lower operating cost of culture consumable, less differentiation time needed when compared to 2D culture.

Conclusions: stirred suspension bioreactors incorporating microcarrier technology represent a viable and more efficient platform than tissue culture flasks for the generation of differentiated podocytes in culture.

Funding: Government Support - Non-U.S.

SA-PO042

Protocol to Make Renal Tubuloids from Human Kidneys

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Background: Kidney organoids derived from human induced pluripotent stem (hiPS) cells can be used to simulate a response to drugs in human kidneys. We have developed an alternative way to make more homogeneous epithelial-like structures from kidney tissue derived from multiple patients in a short period of time.

Methods: Human primary epithelial cell cultures were obtained from the non-tumor kidney tissue removed from patients with renal cell carcinoma. Human renal cortex was diced and then digested with collagenase. Tubules were seeded on matrigel-coated plates with serum-free media containing epidermal growth factor. After passage, primary cells and immortalized LLC-PK1 cells, for comparison, were cultured on ultra-low attachment plates for several days. Then cells were transferred into media containing matrigel, hepatocyte growth factor, fibroblast growth factor-2 and 5% fetal bovine serum.

Results: Primary human renal tubular epithelial cells (hRTECs) tubuloids were generated from dissected patients' kidneys using epidermal growth factor, serum-free media and matrigel. We have generated a library of hRTECs derived from 15 patients. hRTECs showed phenotypes reflecting age and renal function of each original patient, especially in growth rate and in γH2AX expression, a marker for DNA damage response. We also generated tubuloids using a 3D culture technique both with hRTECs and with LLC-PK1 cells. Tubuloids had polarized expression of cell surface markers, LTL, KIM-1 (apical) and Na-K-ATPase (basolateral). The tubuloids endocytosed labeled oxidized LDL, which is observed in 2D KIM-1-expressing epithelial cell culture. It took only a week to establish hRTECs from patient kidneys and four weeks to form tubuloids from hRTECs.

Conclusions: We succeeded in making renal tubuloids using hRTECs derived from multiple patients. This strategy is potentially an excellent way to simulate pathological conditions and response of epithelial cells to toxins and therapeutic agents in a personalized fashion.

Funding: NIDDK Support

SA-PO043

Activation of AMPK and Inhibition of TGFß Stimulate In Vitro Transport in Human Renal Epithelial Cells

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Background: Qualitative and quantitative fidelity of a cultured cell to its *in vivo* counterpart is critical to a wide variety of organs-on-a-chip applications including drug discovery, physiology-based pharmacokinetics, toxicity screens, as well as therapeutic applications for *ex vivo* or implanted engineered organs. Investigators have shown several differentiated functions of renal tubule cells *in vitro* including Vitamin D hydroxylation, ammoniagenesis, and specific drug uptake and excretion, but the tubule cells' primary role in the kidney, electrolyte and water transport, has been elusive.

Methods: Primary human renal tubule epithelial cells (RPTEC) harvested from transplant discards were seeded at passage 1-3 onto Costar permeable supports and cultured at 37 on an orbital shaker. 3 weeks post-confluence a TGF-b inhibitor, SB431542, and metformin were added to hormonally-defined media. Apicobasal transport was measured by weighing apical volumes before and after culture, and by measuring the change in apical inulin concentration.

Results: RPTEC in hormonally defined media showed negligible transport (14 μL/cm^2/day), but addition of SB431542 increased transport 5.2-fold; addition of metformin increased transport 5.6-fold; addition of both increased transport 10-fold. Addition of 10nM ouabain reduced transport by about 45% in all groups. Inulin leak rate did not increase.

Conclusions: Using simple modifications to cell culture protocols, we were able to attain inhibitable apicobasal transport, a key attribute of differentiated RPTEC.

Funding: Other NIH Support - NIBIB, Private Foundation Support

SA-PO044

Whole-Slide Podocyte Quantification in Renal Tissue via p57 Immunohistochemistry

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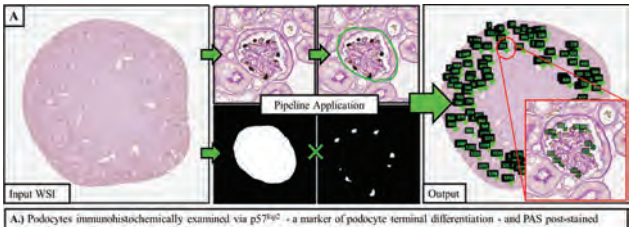
Background: Podocyte injury and podocytopathy drive the progression of Diabetic Nephropathy (DN). Histologic examination of podocytes in disease sections is challenging due to the lack of podocyte specific markers, as well as the limited resolution of podocytes, from all glomerular cells, in traditional stains. Based on our unique podocyte staining protocol, we have developed a whole slide podocyte computational pipeline.

Methods: Murine kidney sections (n = 66) were IHC stained for p57^{kip2}, and PAS post-stained. Whole slide images (WSIs) were acquired, and a neural network segmented glomeruli. WSIs entered our MATLAB pipeline, which applies color deconvolution and morphological processing to segment and quantify podocytes (Fig A). We derived 28 features from segmented podocytes and glomeruli. Pathologist estimated podocyte count per glomerulus was compared with computational results for pipeline evaluation.

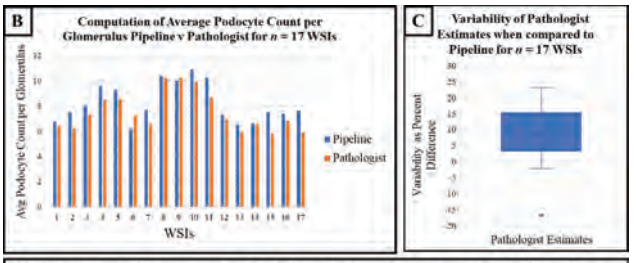
Results: For a subset of WSIs, pathologist and pipeline counts were comparable (Fig B). In practice, pathologist estimates are based on small, random samples of glomeruli from WSIs. Our computational pipeline analyzes all glomeruli, thus producing more accurate results. Pathologist assessments were found to be highly variable with estimates ranging ±23% (Fig C). Our pipeline averages 0.04 seconds per glomerulus, while the pathologist averages 36. Therefore, our computational approach achieves higher precision at a conservative estimate of 900x faster rate than a pathologist.

Conclusions: Our unique staining protocol and pipeline enable rapid quantification of podocyte populations in renal tissue specimens, which will expedite disease-specific evaluation of podocytes, and inform on the contribution of podocyte structural and functional integrity to disease progression.

Funding: NIDDK Support



A.) Podocytes immunohistochemically examined via p57^{kip2} - a marker of podocyte terminal differentiation - and PAS post-stained without hematoxylin counterstain. Pipeline output includes podocyte and glomerular segmentation, as well as 28 derived features. Podocyte quantification viewed here in Aperio Imagescope.



B.) Comparing pipeline computed and pathologist estimated podocyte count per glomerulus on WSI basis for $n = 17$ WSIs. **C.)** Variability of pathologist's estimates when compared to pipeline results, expressed as percent difference. When compared to pipeline results, pathologist assessments were highly variable. . The pathologist overestimated up to 23%, depicted as positive percent difference, and underestimated down to 18%, depicted as negative percent difference.

SA-PO045

Machine Learning and Glomerular Remodeling

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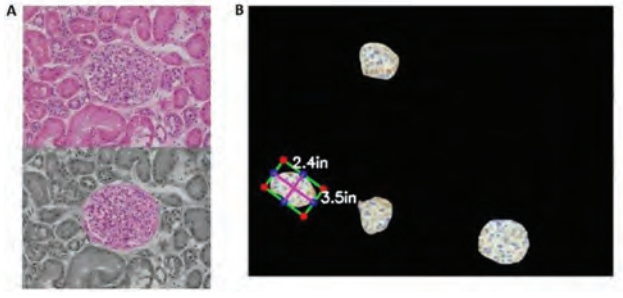
Background: Glomerular hypertrophy is an early biomarker of ongoing renal disease and informs glomerulosclerosis and proteinuria. Using machine learning we trained a computer to first identify glomeruli and then measure glomerular dimensions.

Methods: The training set comprised ~100 images (varying magnification) of hematoxylin-eosin (H-E) or periodic acid Schiff (PAS)-stained kidney tissue sourced from published literature. An open-source git-hub implementation of the mask region-convolutional neural network was used to generate a model and Keras HDF5 data used to identify, count, and measure areas of glomeruli present in the renal tissue on a Raspberry Pi 3 server. The test set comprised images (40X and 10X, n=16) of stained kidney tissue from rats sacrificed 14 days after puromycin aminonucleoside (167 mg/kg, intraperitoneal, n=3) administration, and a sham cohort of animals (n=3). Kidney sections comprising the test set had been stained with H-E or hematoxylin alone.

Results: The Raspberry Pi 3 machine was able to correctly identify glomeruli (A) while excluding non-glomerular structures in all test cases. Having correctly identified glomeruli, the machine was able to measure (B) glomerular area using a precalibrated tool.

Conclusions: Machine learning has enabled both recognition of glomeruli within renal sections and measurement of their dimensions, reducing time and labor while eliminating operator bias. This technology can be used in images from renal biopsies to diagnose ongoing glomerular kidney disease.

Funding: Private Foundation Support



A glomerulus (A) amidist in a renal section was identified by the machine, greying out the surrounding nephrons. The machine was able to isolate several glomeruli and start quantifying their area (B).

SA-PO046

Unsupervised Modeling of Glomeruli for Diabetic Nephropathy Staging in Renal Biopsies

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Background: As biological science pushes for computational analysis, the success of deep learning has obliged its adoption. However, biological datasets are different from the well-annotated standardized data used to develop such algorithms. Due to availability of unlabeled biological data, we have tested a variational autoencoder (VAE) for unsupervised modeling of glomeruli images (without labels). We show that encoded features allow interpolation between image states and are predictive of biopsy-level Tervaert classing of diabetic nephropathy (DN).

Methods: A VAE was trained using 87K 256x256 PAS and H&E stained glomeruli images, segmented from whole-slide kidney biopsies. The VAE encodes the images into a code of 200 numbers able to be decoded back to the input image. This technique automatically clusters similar images together in the code space. To show the relevance of our trained VAE, we model Tervaert DN class for expert staged human biopsies using the image codes as sequential input for a recurrent neural network (RNN). Namely a network model which predicts DN class from sequencial reading of glomeruli codes, similar to how experts read biopsies.

Results: While our decoded (simulated) glomeruli images lack detail, exploration of the image code space shows smooth interpolation between holdout images, verifying the continuity of the encoded data distribution. Figure 1 shows simulated samples between class I and IV DN glomeruli generated by our VAE. Despite having only 54 staged biopsies, an RNN model using our image codes for biopsy level DN class prediction predicts <1 class off with a mean square error of 0.971 and linear weighted Cohen's kappa of 0.402 with 10-fold cross validation.

Conclusions: Further refinement of the VAE architecture is needed to produce sharp images, but current image codes are predictive of Tervaert DN class using supervised regression modeling. In the future, this promises powerful ways to incorporate unlabeled biological data to augment machine learning training sets of medical images.

Funding: NIDDK Support

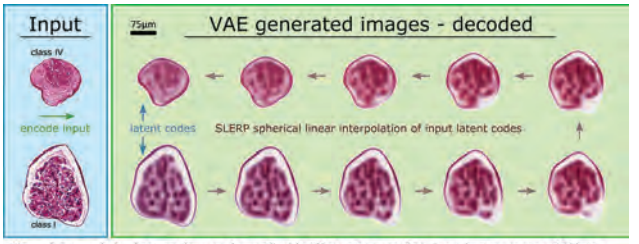

Figure 1. Interpolation between human glomeruli with different Tervaert class. Input images are encoded into a code of 200 numbers which is representative of the input image. These codes are interpolated and decoded back into intermediate images. The VAE network was trained using the input images alone - without data labels.

SA-PO047

Analyzing the Influence of Glomerulus Structural Features Using Minimum Spanning Trees

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Background: Patients with Type 1 or Type 2 Diabetes mellitus are at an increased risk for extensive vascular dysfunction which leads to Diabetic Nephropathy (DN) in close to 40% of cases. Structural changes within the glomerulus resulting from the diabetic phenotype are used to classify glomeruli into different stages of DN. Using Minimum Spanning Trees (MST's) we are able to quantitatively define these structural abnormalities and assess their contribution to DN stage of that glomerulus. We employed Bayesian Networks (BN) to visualize and assess the relationships between different MST features and the glomerulus's DN stage.

Methods: We used stain deconvolution to isolate nuclear regions in 799 H&E stained glomerulus images. The centroids of glomerular nuclei were used as nodes to create a MST in Matlab. Features calculated from these MST's quantified spread, connectedness, and fraction of terminal "leaf" nodes present as a representation of degree of glomerular expansion, cellularity, and sclerosis. Using these features, a BN was generated in R using the Hill-Climbing structure learning method. The resulting network was thresholded so that only the most significant relationships were included.

Results: Graph features calculated from the glomerular MST had a significant influence on the DN Stage. From this network, we are able to generate conditional probability distributions for each of the feature values that can be used to predict the DN classification.

Conclusions: By analyzing glomeruli using MST's we can impose repeatable, robust measures of nuclei distribution and derive further information as to what biological factors contribute to DN progression. Incorporation of BN and other probabilistic graphical models in medicine allows for more informed diagnosis and research.

Funding: NIDDK Support

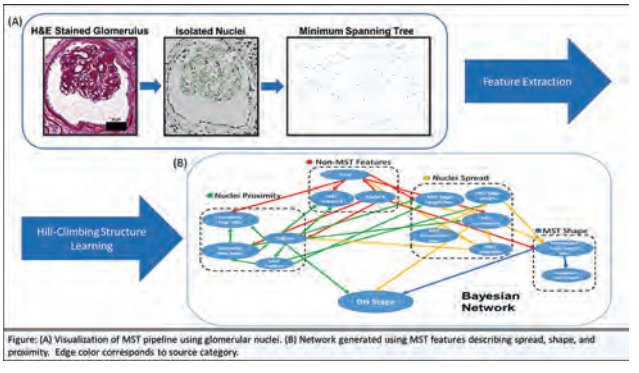

Figure: (A) Visualization of MST pipeline using glomerular nuclei. (B) Network generated using MST features describing spread, shape, and proximity. Edge color corresponds to source category.

SA-PO048

Contribution of Glomerular Phenotype to Digital Classification of Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is a leading cause of kidney disease; renal pathologists assess its pathology via visual interpretation of biopsied tissue in the form of a digitized whole slide image (WSI). Inter-rater agreement increases with consensus classifications like the Tervaert approach, but reproducibility could still be improved. Computation can unify interpretation of image structure. We engineered a complete start-to-finish glomerular detection and classification pipeline for digitized biopsies of DN. Further, we investigated the glomerular phenotypes and features that it relies on to make decisions.

Methods: We studied 54 patients. Glomeruli were detected from WSIs using our previously published method for WSI segmentation. Glomerular structure was condensed to a three-component system that facilitates detection in widely varying phenotypes. Handcrafted features (n = 232) were used to quantify glomerular structures. Glomerular features from a single biopsy were fed as a sequence to a recurrent neural network (RNN) which yields a continuous number representing Tervaert class. Glomeruli and features were dropped from the network one-by-one; the resultant shift in predicted class was used as a proxy to investigate how much each glomerulus and feature contributed to the overall output. We trained our method by taking one renal pathologist as ground truth, and compared its performance against two other renal pathologists.

Results: Digital classification agreed with the ground truth renal pathologist with linear weighted Cohen kappa κ = 0.55, 95% confidence interval (CI) [0.5, 0.6]. The other two other renal pathologists agreed with the first with κ_1 = 0.48, 95% CI [0.32, 0.64], and κ_2 = 0.68, [0.5, 0.86]. The features that hurt network performance the most when dropped out included features quantifying color of glomerular structures as well as those quantifying mesangial width. The network was most sensitive to dropped glomeruli when there were fewer total glomeruli contained in the biopsy.

Conclusions: Our digital classification reaches agreement similar to renal pathologists and makes decisions intuitively. Digital quantification of renal tissue can enhance clinical workflow by improving precision used to describe disease state.

Funding: NIDDK Support

SA-PO049

Neutrophil Extracellular Trap (NET) Quantification in Lupus Nephritis Potentiates NETs as a Prognostic Biomarker

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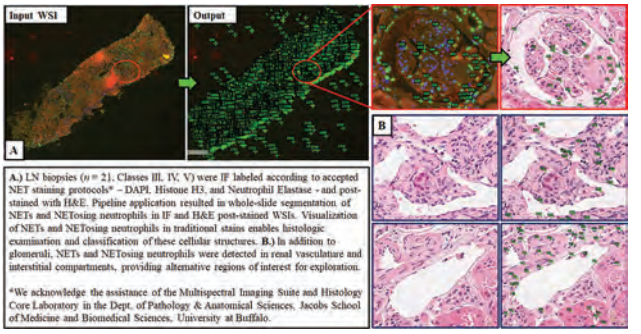
Background: Lupus Nephritis (LN) is a major risk factor for morbidity and mortality in Systemic Lupus Erythematosus (SLE), with 10% of patients developing ESRD. LN classification, which involves pathologist visual scoring of active and chronic lesions in renal biopsies, is limited due to lesion complexity. NETs have been implicated in SLE as immunogenic structures which contribute to lesion manifestation. Glomerular NET density may function as a predictive biomarker in LN, defining active to chronic lesion transition. We have developed a whole slide image (WSI) NET segmentation pipeline which enables computation of NET glomerular density in renal biopsies.

Methods: LN biopsies (n = 21) were labeled according to accepted immunofluorescence (IF) NET staining protocols, post-stained with H&E, and imaged. Our WSI NET segmentation pipeline, as well as a convolutional neural network for glomerular boundary segmentation, were applied. NET+ regions were identified and lesions were hand annotated in glomerulus images.

Results: A two-sampled t-test confirmed that glomerular NET density, for all active and chronic lesion affected glomeruli, is significantly different with p = 0.0002. Therefore, NET glomerular density co-occurrence with active lesion manifestation is statistically significant. NETs may serve as a prognostic biomarker in LN, and may functionally contribute to glomerular injury.

Conclusions: Our pipeline enables evaluation of glomerular NET density as a prognostic biomarker of LN progression, which could improve the clinical interpretation and treatment of LN in SLE. This pipeline may be used to compute NET density in other diseases featuring NET effected tissues, thus potentiating NET density as a universal prognostic biomarker. In addition, NET quantification will enable implementation of supervised classification for classifying NET structures in histology WSIs.

Funding: NIDDK Support



SA-PO050

Measuring Nephron Endowment by Positron Emission Tomography

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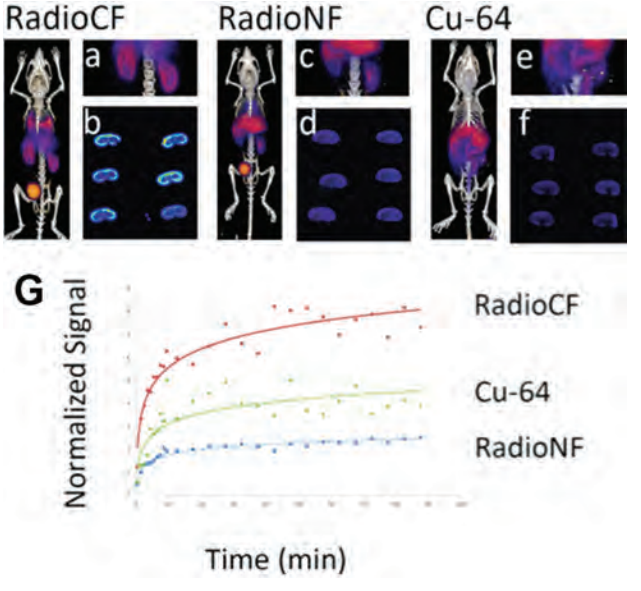
Background: Nephron loss is a primary feature of kidney disease. Recent MRI tools using cationic ferritin (CF) offer a unique view of nephron mass in the intact kidney *in vivo*. We propose a novel contrast agent (RadioCF) based on CF for positron emission tomography (PET). Because RadioCF is detected in trace (<100 ug) doses in humans, RadioCF-PET may enable rapid translation of nephron endowment as a clinical marker.

Methods: Cationic ferritin was filled with Cu-64 created by cyclotron. Radiochemical purity was assessed by radioTLC. 24 mice were anesthetized and administered intravenous injections of radioCF (n = 8), radioNF (uncationized native ferritin, n = 8), or Cu-64 alone (n=8). Mice were injected with 50-80 μCi of radioCF. In four animals of each cohort, a single 3D image series was acquired post-injection.

Results: RadioCF accumulated specifically in the cortical glomeruli, while radioNF and Cu-64 did not. Binding of radioCF was confirmed by phosphorimaging. RadioNF and Cu-64 did not bind. Dynamic imaging and timecourse from renal cortex showed continuous radioCF accumulation in cortex over 90 minutes compared to radioNF or CU-64. Selective accumulation of RadioCF in cortex was confirmed by biodistribution.

Conclusions: RadioCF is a new, translatable molecular imaging tool. Because it binds selectively to the glomerulus, RadioCF accumulation should directly reflect the number of perfused nephrons.



PET imaging in mice after RadioCF injection. RadioCF accumulated in the renal cortex (a, RadioCF in red), while radioNF and Cu-64 do not (c,e). Binding of radioCF, blue, was confirmed by phosphorimaging (b). radioNF and Cu-64 were absent (d,f). Dynamic whole body imaging and timecourse from the renal cortex (G) showed continuous radioCF accumulation in cortex over 90 minutes compared to radioNF or CU-64.

SA-PO051

Renal PET/CT-Rubidium-82 (Rb-82) Is a Precise and Reliable Method for Determination of Renal Blood Flow (RBF)

Stine Langaa,[1] Thomas G. Lauridsen,[1] Claire A. Fynbo,[2] Jorn Theil,[2] Jesper N. Bech.[1] *[1]University Clinic of Nephrology and Hypertension, Holstebro Hospital, Holstebro, Denmark; [2]Department of Nuclear Medicine, Herning Hospital, Herning, Denmark.*

Background: Changes in RBF may play a pathophysiological role in hypertension and kidney disease; however, RBF determination in humans has proven difficult. In a previous study, we demonstrated that RBF estimation based on PET/CT and Rb-82 is feasible and established that RBF can be determined based on a single PET/CT-Rb-82 scan, hereby minimizing radiation exposure associated with the method. We also found an intra-assay coefficient of variation of approximately 5.5% for both kidneys which indicates that the method is precise. The aim of this study is to test the reliability of renal PET/CT-Rb-82 for RBF estimation.

Methods: Ten healthy subjects underwent three dynamic PET/CT-Rb-82 scans spread over two days. Rb-82 was given as bolus injections. On day 1, a single 8 min dynamic scan was performed. On day 2, an 8 min dynamic scan was performed before and after RBF was stimulated by a two-hour long infusion of an amino acid-solution. Time activity curves of arterial activity and renal uptake were recorded, and a 1-tissue compartment model was used for Rb-82 renal clearance estimation using PMOD® software. The clearance constant K1 in the model represents RBF. The day-to-day variation was calculated as the difference between the unstimulated K1-values on day 1 and day 2. K1-values determined before and after RBF stimulation on day 2 were compared.

Results: The mean unstimulated K1 value was 1.80 ± 0.17 ml/min/g for the right kidney and 1.78 ± 0.19 ml/min/g for the left kidney. The mean stimulated K1 value was 1.97 ± 0.17 ml/min/g for the right kidney and 1.95 ± 0.19 ml/min/g for the left kidney. There was no significant difference between the right and the left kidney for either the unstimulated or the stimulated K1 values. The day-to-day variation was 5.2% for the right kidney and 5.3% for the left kidney. For both kidneys, K1-values determined after RBF stimulation were significantly higher than K1-values determined before stimulation.

Conclusions: The approximate 5% day-to-day variation was acceptably low. For both kidneys, a significant increase in RBF was detected after application of a well-documented RBF stimulus. In conclusion, our preliminary results indicate that renal PET/CT-Rb-82 is a precise and reliable method for RBF determination.

Funding: Government Support - Non-U.S.

SA-PO052

Diffusion-Weighted Magnetic Resonance Imaging (DWI) Correlates with Renal Injury in Patients with Renovascular Disease (RVD)

Christopher M. Ferguson,[2] Alfonso Eirin,[2] Abdelrhman Abumoawad,[2] Kai Jiang,[2] Ahmad F. Hedayat,[3] Amir Lerman,[2] Stephen C. Textor,[2] Lilach O. Lerman.[1] *[1]Mayo Clinic College of Medicine, Rochester, MN; [2]Mayo Clinic, Rochester, MN; [3]University of Mississipi Medical Center, Ridgeland, MS.*

Background: There is pressing need to identify novel markers that can predict response to therapy in patients with RVD. DWI is a useful tool for the assessment of renal microstructure and DWI-derived apparent diffusion coefficient (ADC) reflects unobstructed water diffusion. We hypothesized that lower values of ADC (index of fibrosis) can be used as an index of renal injury and response to therapy.

Methods: ADC and renal hypoxia (R2*; blood oxygen level dependent-MRI) were studied before and 3 months after treatment in 20 patients (23 stenotic kidneys) with hemodynamically significant RVD under constant sodium intake. Patients were treated with medical therapy (n=9) or medical therapy plus renal revascularization (n=11, n=14 kidneys). Serum creatinine (Scr), eGFR (CKD-EPI), blood pressure (BP), and systemic levels of pro-inflammatory marker tumor necrosis factor (TNF)-α, were measured at each time-point. Baseline ADC values were correlated with change in renal hypoxia and systolic BP (SBP), as well as TNF-α levels at 3 months.

Results: BP and Scr decreased and eGFR increased 3 months after therapy (Table), but renal hypoxia and TNF-α levels remained unchanged. Overall, ADC values increased 3 months after therapy (Fig. A), although not in medical therapy or renal revascularization considered separately. Baseline ADC values modestly and inversely correlated with changes in hypoxia and SBP, and with TNF-α levels at 3 months (Fig. B), but not with levels of or changes in renal function.

Conclusions: Lower levels of ADC may potentially reflect kidney injury, but do not predict changes in renal function after therapy over 3 months in patients with RVD. Future studies need to identify indices of renal recovery potential.

Funding: NIDDK Support, Other NIH Support - NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI): HL123160

Patients	Baseline	3 months
Age (years)	69.7±8.3	------
Gender (M/F)	10/10	------
BMI	28.1±4.0	28.2±4.4
SBP (mmHg)	141.4±17.89	132.8±14.0*
DBP (mmHg)	67.6±9.4	63.4±9.4*
Serum Creatinine (mg/dL)	1.4±0.4	1.2±0.3*
eGFR (mL/min/1.73m2)	54.1±22.5	58.9±23.0*
BOLD-MRI R2* (1/s)	23.6±4.7	22.2±3.8
TNF-α (pg/ml)	12.9±8.5	11.9±6.2

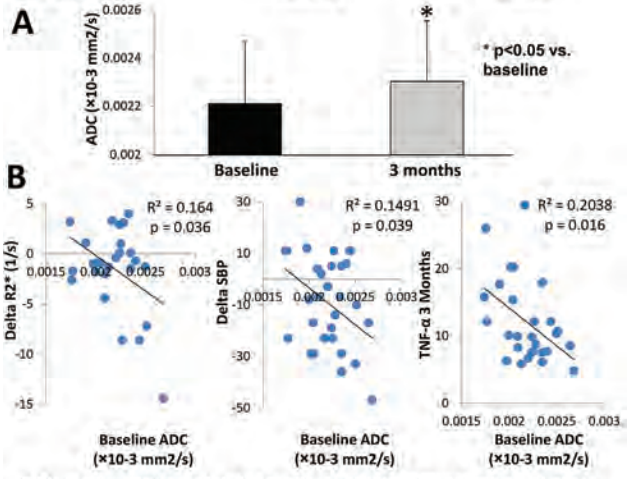


Table 1: Characteristics of study patients. A: ADC (monoexponential analysis) in patients with RVD at baseline and 3 months after therapy. B: ADC values correlated inversely with delta R2*, delta SBP, and TNF-α levels at 3 months.

SA-PO053

Detection of Acute Change in Renal Perfusion Using Arterial Spin Labeling MRI

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Background: Magnetic resonance imaging(MRI) with arterial spin labeling(ASL) is a noninvasive promising approach to measure renal blow flow without the use of contrast dye. The purpose of this study was to evaluate change in renal perfusion following a physiological stress(Experiment 1), by ASL kidney perfusion measurements. We also compared the renal perfusion in 3 different study populations(healthy controls(C), patients with hypertension(HT) and chronic renal failure(CRF)- Experiment 2).

Methods: MRI with ASL was performed with a 1.5 Tesla MRI(Magnetom Aera, Siemens Healthineers, Erlangen, Germany) using a FAIR True-FISP sequence. Cortical, medullary, and whole kidney parenchymal perfusion were determined separately. After initial MRI measurement in C and HT, the measurement was repeated after both feet were covered with 1 degree C ice packs, which trigger a systemic sympathetic activation leading to vasoconstriction(cold pressor test).

Results: The group of C subjects(11 males, aged 35.2 ± 12 years) was compared to HT(11 males, aged 39.2 ± 10.3 years) and CRF patients(8 males, 2 females, aged 68.3 ± 7.8 years). The renal perfusion of both kidneys in HT(309.5 ± 17.3 mL/100 g/min) and CRF patients(260.4 ± 29.0 mL/100 g/min) were significantly lower compared to C subjects(338.7 ± 30.0 mL/100 g/min)(C vs. HT- age adjusted p=0.014, C vs. CRF- age- and gender adjusted p=0.004). Renal perfusion was also significantly different between patients with HT and patients with CRF (age- and gender-adjusted p=0.047). In the first experiment blood pressure and heart rate increased significantly in response to the sympathetic trigger. Significant reduction in renal cortical perfusion also has been found. A trend has been noticed in the whole renal perfusion.

Conclusions: With Experiment 1, we could demonstrate that acute changes in renal blood flow could be detected using ASL-MRI. Experiment 2 documented that this technology is able to detect differences in renal perfusion between heathy subjects and diseased subjects by needing only few subjects per group. This offers an advantage in conducting clinical trials in humans compared to other technologies.

Renal perfusion (mL/100 g/min)	before cold stimulus (n=22)	during cold stimulus (n=22)	p-value
Whole renal perfusion	324.1 ± 28.2	318.7 ± 27.8	0.053
Cortical perfusion	368.3 ± 41.5	357.6 ± 38.5	0.042
Medullary perfusion	301.7 ± 32.4	297.5 ± 32.6	0.592

SA-PO054

Fluid Dynamics Analysis by CT Imaging Technique of Hollow Fiber Dialyzer with Medium Cut-Off Membrane

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Background: Inadequate removal of molecules between 5and50KDa, due to their restriction in diffusibility, may cause long-term complication in chronic hemodialysis patients. Medium Cut-off(MCO) is a new class of membranes with enhanced sieving properties and negligible albumin loss, thanks to its high molecular weight(MW) retention onset and MW cut-off value lower than albumin MW. MCO membrane used in HD allows to perform expanded hemodialysis (HDx), a technique based on high internal filtration(IF). Our previous study quantified the IF of Theranova dialyzer leveraging a nuclear imaging technique. In order to characterize the local distribution of the IF, an *in vitro* study assessing the fluid dynamics inside Theranova dialyzer was conducted through CT imaging technique.

Methods: Dialyzer Theranova400(Baxter, Deerfield, USA) was placed in vertical position in the CT gantry. Blood and dialysate compartments were analyzed separately. Dye solution was circulated through blood compartment at 300ml/min and through dialysate one at 500ml/min. Longitudinal sections, 0.5cm thick, were recorded for 60seconds.

Results: In blood compartment, dye solution immediately after its entrance in the dialyzer demonstrates homogeneous progression, while different velocity profiles were observed among the fibers proceeding to the outlet port (Fig b). In dialysate compartment, dye solution is distributed in the periphery first (Fig d), then seeps in the fibers bundle and reaches the complete compartment filling.

Conclusions: The homogeneous dye profile immediately after its entrance in blood compartment demonstrated a good design of the inlet port; the optimal dye distribution reached in both blood and dialysate compartments ensure that IF phenomenon is equally achieved in both central and peripheral regions of the dialyzer.

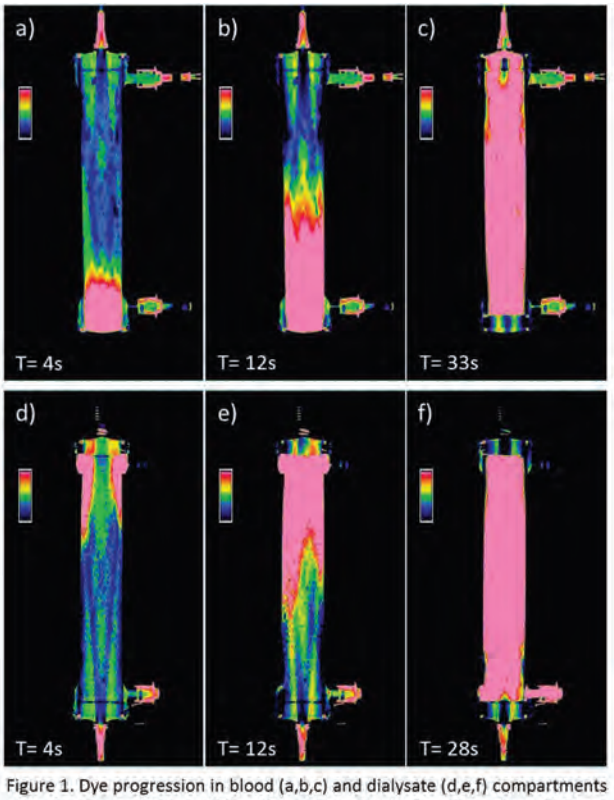

Figure 1. Dye progression in blood (a,b,c) and dialysate (d,e,f) compartments after 4s, 12s, and at total filling. Central longitudinal sections show different profiles in the two compartments: in blood, initial progression is homogeneous, at 12s different velocity profiles emerge along the fiber bundle; in dialysate, dye solution proceeds faster along the dialyzer wall than within the fiber bundle, at the end the whole compartment is reached by the dye solution.

SA-PO055

Feasibility and Effectiveness of 6-Week Plantar Electrical Stimulation Therapy During Routine Hemodialysis Sessions to Improve Gait and Balance: A Randomized Controlled Trial

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Background: Poor gait and balance are serious problems for people with diabetes undergoing hemodialysis (HD). These patients visit their clinic three times weekly to receive HD which provides an optimal opportunity for intervention. This study aims to examine the feasibility and effectiveness of plantar electrical stimulation therapy (PEST) during routine HD sessions to improve gait and balance.

Methods: Twenty-six participants with diabetes receiving HD were recruited and randomized into an intervention group (IG: n=13, age=59.5±10.4years, BMI=29.7±6.0kg/m^2, female=39%) or a control group (CG: n=13, age=63.2±6.1years, BMI=30.9±6.0kg/m^2, female=54%). The IG received 1-hour PEST during routine HD process (3 sessions/week) for 12 weeks. The CG was provided with an identical but non-functional device for the same period. Participants were blinded to the group allocation. Gait and balance were examined at baseline, midline (6-week), and conclusion of the program. This study however focused on changes in gait and balance at 6-week.

Results: All participants in the IG tolerated the PEST and completed all sessions of the therapy indicating the feasibility. None of the gait or balance parameter showed noticeable differences in the CG group (p>0.050). However, improvement trends were observed in the IG with the largest effect observed in double support for gait parameters (13% improvement, Cohen's effect size d=0.66) and eyes-open center of mass sway for balance parameters (27% improvement, d=0.31).

Conclusions: This pilot study provides earlier results on the feasibility and effectiveness of PEST during routine hemodialysis. The study is still ongoing and is expected to recruit 100 eligible participants for sufficient power. If results can hold in a larger sample size, it may recommend the use of routine plantar electrical stimulation therapy to improve mobility and potentially prevent falls in this highly vulnerable population, who are highly prevalent with frailty, depression, and falls caused by decline in motor function associated with hemodialysis.

Funding: Government Support - Non-U.S.

SA-PO056

Size and Charge Effects of Nanoparticles for Renal Targeting in Polycystic Kidney Disease

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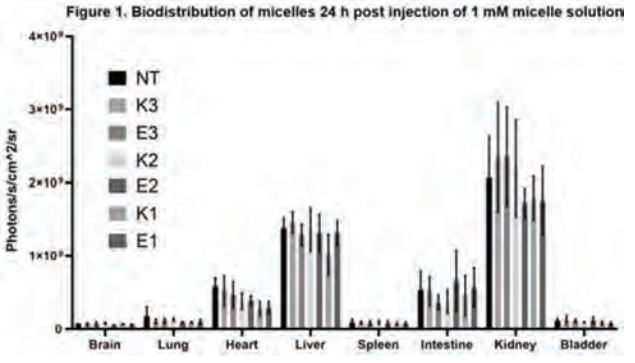
Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by renal cyst formation and leads to ESRD. Tolvaptan, the only FDA approved treatment for ADPKD, has low bioavailability and results in non-specific uptake and liver toxicity. Our group has recently developed a novel nanoparticle system based on peptide amphiphile micelles (PAM) with the kidney-targeting peptide, $(KKEEE)_2K$ (K3) (Wischnjow, 2016 and Wang, 2018). To improve the nanoparticle targeting efficiency, we incorporated and tested a variety of peptide sequences: $(EEKKK)_2E$ (E3), $(KKEEE)_2K$ (K2), $(EEKKK)_2E$ (E2), (KKEEE)K (K1), and (EEKKK)E (E1). K2, E2, K1, and E1 are shorter amino acid sequences that result in smaller nanoparticles to cross the filtration barrier easily and E3, E2, and E1 are positively-charged sequences to allow for binding to the negatively-charged glomerular basement membrane.

Methods: All peptides were synthesized on an automated peptide synthesizer, conjugated to DSPE-PEG2000, and purified and characterized by HPLC and mass spectrometry. Size and charge of nanoparticles were measured by dynamic light scattering and zeta potential. The *in vivo* renal targeting ability of Cy7-labeled nanoparticles was assessed by tail vein injection of kidney-targeting PAMs, non-targeting PAMs, or PBS in C57BL/6 mice models. Organs were excised and imaged for Cy7 and the fluorescence signal was quantified using the AMI imaging system.

Results: K3 micelles had the largest diameter of 15.4 nm with a negative charge of -17.04 mV, while E1 had the smallest size of 10.6 nm with a near-neutral charge of 0.1 mV. *Ex vivo* imaging results demonstrated all micelles accumulated in the kidneys to a greater extent than other organs, and K3 and E3 demonstrated the highest uptake although not statistically significant (Figure 1).

Conclusions: Our approach demonstrated that our library of kidney-targeting PAMs can accumulate in the kidney. Future studies will further optimize charge and size to understand nanoparticle structure-function relationships in the context of kidney uptake.

Funding: Other NIH Support - NIH New Innovator Award (DP2)



SA-PO057

Next-Generation Renal Replacement Therapies (RRT): How Do Patients Weigh the Risks and Benefits?

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Background: Device developers are increasingly asking patients for input on product developments, and the FDA now uses patients' risk-benefit preferences in approving new devices. Implantable/wearable devices under development may revolutionize patient lives by providing more frequent/prolonged RRT, releasing them from in-center/home dialysis (ICHD). Our objective was to determine key risks/benefit considerations that would drive ESRD patient choices.

Methods: We developed a choice-based conjoint discrete choice instrument (CBCDCI) and surveyed by computer 498 ESRD patients. The CBCDCI consists of 9 attributes of risk and benefit derived from literature reviews, patient/clinician interviews, and pilot testing. Attributes include risk of: serious infection, death within 5 years, permanent rejection, surgical requirements, diet restrictions, flexibility in mobility (no ICHD), follow-up requirements, pill burden, and fatigue reduction. We used a random, full profile, balanced overlap design from Sawtooth Software with 12 choice pairs and 2 fixed tasks to test validity. We used a mixed effects regression with attribute levels as independent predictor variables and choice decisions as dependent variables.

Results: In univariate and multivariate analyses, all variables were significantly important to choice preferences except follow-up requirements. For each 1% increase in risk of death within 5 years, preference utility across factors decreased by 2.2, while for each 1% increase in infection, utility decreased by 1.4. Avoiding a 1% risk of infection or death was 1 and 1.5 times preferred over no ICHD, respectively. Pill burden and diet restrictions were less important.

Conclusions: ESRD patients had a strong aversion to even a 1% increase in death within 5 years, infection risk or permanent device rejection, but were willing to trade-off these risks for the benefit of moving to complete mobility. These results will inform device developers on acceptable benefit-risk thresholds for next generation RRT.

Funding: Other NIH Support - NIBIB, Private Foundation Support

Attributes	Beta (preference utilities)	p value
avoiding death in 5 yrs	-2.217	<0.01
no ICHD	1.520	<0.01
avoiding infection	-1.384	<0.01
risk of rejection	-1.066	<0.01
70% fatigue decrease	0.977	<0.01
only 1 implant surgery	0.844	<0.01

SA-PO058

Diagnosticator: A Time-Sparing Web-Based Tool for Easy Clinical Annotation of Genetic Data

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Background: Genetic testing is increasingly used in clinical medicine and has been shown to impact clinical care in Nephrology. The American College of Medical Genetics and Genomics (ACMG) has provided standardized guidelines for clinical interpretation of variants, but the large quantity of data generated from genome-wide testing pose a challenge for seamless clinical interpretation of results. We developed a web-based tool that allows users to upload genetic data, analyze them with customizable filters and easily navigate results.

Methods: The analysis algorithm prioritizes results based on customizable parameters: allele frequency from several publicly available databases (GnomAD, ExAC, EVS and 1000Genome), prior reports of disease association (Clinvar and HGMD) and proximity with hot-spot regions, functional and pathogenicity prediction (VEP, pLI, SIFT, PolyPhen, REVEL, dbNSFP, dbscSNV), and ACMG interpretation. Both Dominant and Recessive models are analyzed based on the OMIM-known (or selected) disease inheritance mode for each gene. The final results are presented as an easily interacting and customizable patient-, genelist- or gene-centered interface. Aggregated variant information is presented on a single page, facilitating decision-making about its pathogenicity. Once accepted/rejected, the variant is flagged, to avoid needless re-interpretation of the same variant on other patients or by other users. Moreover, the platform offers a feature that will alert users about a change in status of variants based on interpretation from available databases or other users in the group.

Results: We tested our algorithm on a cohort of 3315 patients with nephropathy with known and validated genetic results (Groopman et al. NEJM, 2019) and we could replicate all of the significant findings (n: 343). The average time required for upload and generation of candidate genes was only 27'. Moreover, causative variants were proposed as the top 10 candidates in 97.8% of the time, significantly speed up annotation. Diagnosticator also flagged 87 new possibly pathogenic variants that we are currently validating.

Conclusions: In summary, we developed an easy to use interface for prioritization and annotation sequencing results, which facilitates clinical interpretation of results and keep users updated about their findings.

SA-PO059

Outcomes of Using Telemedicine to Provide Nephrology Care in Rural Hospitals

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Background: Telemedicine has recently permeated into the nephrology space allowing patients in rural underserved areas to be treated in their local hospitals without transfer to larger healthcare systems miles away. We report our two year experience providing telenephrology consult services to both ESRD and non- ESRD patients in rural hospitals.

Methods: A retrospective, descriptive study of patients receiving tele-nephrology consultation and chronic dialysis services between September 2017 and May 2019 in three South Georgia (GA) rural hospitals. Consultations were requested by the on-site physicians and were performed by Emory University Tele-nephrologists based in Atlanta, GA by reviewing the patient's hospital electronic medical record (EMR) and performing a real-time history and physical exam with audio-video technology and Littman electronic stethoscope. Nephrologists documented treatment plan in the hospital's EMR on each follow-up visit and provided orders for dialysis when indicated using portable dialysis machines that captured electronic data on each HD session.

Results: In three rural hospitals we provided care to 128 unique patients (pts) with a total of 525 patient encounters. Average age for ESRD pts - 59 and for non-ESRD-66. 60% of the consults were in dialysis patients with congestive heart failure being the major admitting diagnosis in 42%, while 88% of ESRD pts were discharged to home. For the non-ESRD consults: 24.6% were acute kidney injury who had 71% renal recovery at discharge; and 15.6% were electrolyte disorders- mainly hyponatremia. 34% of overall renal consult patients were treated in the ICU with 8.3% requiring pressor support. See Table for other outcomes including length of stay (LOS), mortality rate, and discharge status (DC) for both the ESRD and non-ESRD patients.

Conclusions: Both ESRD and non-ESRD patients in rural hospitals who received nephrology care via telemedicine were effectively managed in their local hospitals, had low mortality rates, and had similar LOS to larger healthcare systems. Telemedicine is an innovative and feasible option to provide specialty care in rural hospitals.

Clinical Outcomes of Rural Hospital Patients Managed by Telenephrology Sevices

	LOS (days)	Mortality	Transfer to higher level of care	DC to skilled nursing/LTAC
ESRD (n=76)	4.3	0	5.7%	3.8%
non-ESRD (n=52)	7.1	5.7%	11.4%	14.3%

SA-PO060

Identification of Very Early Response Genes and Sex-Dependent Response Genes for Ischemia-Reperfusion Injury in Human Transplant Patients

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Background: Ischemia-reperfusion injury (IRI) is highly implicated in various kidney conditions leading to acute (AKI) and chronic kidney disease (CKD). IRI during renal transplantation often initiates responses that can result in poor outcome and the loss of kidney graft viability. It is important to identify very early response programs that can be utilized to better characterize the pathobiology and identify therapeutic targets to minimize the injury. Furthermore, it has been shown that sex influences susceptibility to kidney IRI. However, such early response programs for IRI and sex-dependent response programs are poorly understood with most of our knowledge derived from animal studies or tissue analyses after longer times post-ischemia in the transplant population.

Methods: Twenty paired biopsies from the cortical region of the human kidney were obtained before and after ischemia-reperfusion during living donor transplantation, with minimal cold ischemia time (1-2 hours) compared to other studies. Glomeruli were

removed and the tubulointerstitial fraction was subjected to RNA sequencing (RNA-seq). Genes were identified that were differentially regulated early in response to IRI.

Results: There was a robust and novel early response program to IRI. When compared to published datasets of both human and rodents, there was a significant overlap of the post-ischemic transcriptional profiles. Interestingly, however, our results identified a unique set of highly upregulated early response genes that have not been identified previously for their roles in kidney IRI. Furthermore, we identified sex-dependent genes that were differentially upregulated in males and females.

Conclusions: Within 1-2 hr of cold ischemic time in transplanted human kidneys there is a unique set of genes which reflect a very early response. There was a different early response to IRI between males and females. Findings from this study can be utilized to further investigate mechanisms and potential therapeutic options for IRI and AKI.

Funding: NIDDK Support

SA-PO061

Circular RNA Expression Profiles in Cisplatin-Induced AKI in Mice

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Background: Cisplatin is an effective chemotherapeutic agent whose nephrotoxicity is a serious clinical problem. However, the molecular mechanisms underlying cisplatin-induced acute kidney injury (Cis-AKI) remain unknown. Circular RNAs (circRNAs), a novel class of noncoding RNAs, have been reported to be involved in a variety of diseases. However, the roles of circRNAs in AKI are poorly understood.

Methods: In this study, an AKI model was established in cisplatin-treated mice, and the expression of circRNAs was profiled by next-generation sequencing. The differential expression levels of selected circRNAs were determined by qRT-PCR. Bioinformatics analysis was conducted to predict the functions.

Results: In total, 368 circRNAs were detected to be differentially expressed in response to cisplatin treatment. The qRT-PCR analysis showed that the expression of six selected circRNAs was consistent with that determined by RNA sequencing. The GO and KEGG pathway analyses indicated that the parental genes of the differentially expressed circRNAs were predominantly implicated in the cell part and organelle, cellular process, metabolic process and cancer pathways.

Conclusions: Our study yielded a comprehensive expression profile of differentially expressed circRNAs associated with AKI, indicating the possible involvement of these dysregulated circRNAs in the pathophysiology of cisplatin-induced nephrotoxicity.

Funding: Government Support - Non-U.S.

SA-PO062

Mitochondrial Fission and Apoptosis-Related CircRNA Plays an Important Role in Ischemia-Reperfusion-Induced AKI by Sponging miR-652-3p

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Background: Circular RNAs (circRNAs) can serve as sponges of microRNAs (miRs) to participate in the pathogenesis of various diseases. A study reports that mitochondrial fission and apoptosis-related circRNA (*MFACR*) mediates cardiomyocyte apoptosis by sponging miR-652-3p to regulate mitochondrial fission process 1 (MTFP1) pathway. However, the role of *MFACR* in acute kidney injury (AKI) remains unclear. We aim to investigate whether *MFACR* is involved in ischemia and reperfusion (I/R)- induced AKI and its corresponding mechanisms.

Methods: Male Balb/c mice were subjected to 35 mins of bilateral renal ischemia and then reperfusion. We evaluated AKI by examining blood urea nitrogen (BUN), tubular necrosis with PAS and spoptosis by TUNEL staining, and renal inflammation by measuring interleukin-6 (*Il6*) and tumor necrosis factor-α (*Tnfα*) 48h after the reperfusion. Meanwhile, we examined the expression of mitochondria related mRNAs and proteins including optic atrophy 1 (OPA1), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a), and mitochondrial transcription factor A (TFAM). Finally, we measured the levels of *MFACR*, *miR-652-3p*, and *Mtfp1*. *We* analyzed the match seeds between *MFACR* and *miR-652-3p as well as miR-652-3p* and *Mtfp1* with TargetScan and miRanda.

Results: We found that kidney function declined with elevated BUN levels, increased renal tubular necrosis scores on PAS and positive apoptosis on TUNEL staining in kidneys 48h after I/R in mice compared to the shamed control mice. *Il6* elevated 14-folds and *Tnfα* elevated about 5-folds in I/R mice compared to shamed mice. Renal mitochondrial damage biomarkers including OPA1, PGC-1α, TFAM statistically decreased in I/R mice on the levels of their mRNAs and proteins. Importantly, renal *MFACR* was downregulated, *miR-652-3p was* upregulated, and *Mtfp1* was downregulated in I/R-induced mice compared to the shamed mice. Finally, we found perfect match seeds between *MFACR* and *miR-652-3p* as well as between *miR-652-3p* and *Mtfp1* on TargetScan and miRanda analysis.

Conclusions: Our findings suggested that MFACR played an important role in I/R induced AKI. The mechanism might be that MFACR regulates renal mitochondrial functions by sponging miR-652-3p and consequently increasing MTFP1. Regulating MFACR-miR-652-3p-MTFP1 pathway may open a novel therapeutic avenue for AKI.

Funding: Government Support - Non-U.S.

SA-PO063

Sex Transcriptomic Signatures in Pig Kidneys After Ischemia-Reperfusion Injury and Recovery

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Background: Renal ischemia/reperfusion injury (IRI) is a major cause of acute kidney injury (AKI). Men are more prone to AKI and to CKD than women and it is accepted that androgens have a role in these processes. The mechanisms involved in injury/regeneration and the impact of gender remain to be fully elucidated. We propose that the identification of differentially expressed genes in male and female pig kidneys in basal, after injury and upon renal function might unravel genes and pathways useful to understand the different outcomes observed in men and women.

Methods: IRI was performed in single-kidney female and male pigs by clamping the renal artery for 30 minutes. Pre-ischemic, ischemic and post-ischemic kidney tissues (one week later) were collected for microarray assays. Pathway enrichment analysis and visualization of -omics data was done by GSEA, cytoescape and enrichment map. Systems biology-based mathematical models were also conducted to identify injury/recovery pathways and networks modulated in a sex-dependent manner.

Results: The numbers of genes differentially expressed in males versus females (adj P value 0.25) were 100 in pre-ischemic conditions, 858 at 5 min post-ischemia and 2 at one week pos-ischemia, indicating that although males were exhibiting differences in gene expression in basal situation and after injury, the general pattern of expression was similar to that of the females after one-week post-injury. Enriched pathways containing different gene sets down-regulated in males after one-week post-injury, but activated in basal situation and injury included, among others, immnune cell regulation, ion transpost transmembrane, steroid hormone response, type inteferon interleukins and intrinsic and extrinsic apoptosis. Contrarily, males after one-week have activated responses to growth factors such as the TGF-beta family members and extracellular matrix organization and collagen formation. Anaxomics systems biology patented technology has also pointed to STAT-1 and STAT-3 as crucial effectors of androgen mediated injury in kidney.

Conclusions: The targets identified in female and male pig samples together with the extensive bioinformatic analyses we have performed shall provide with novel mechanistic insights into the role of sex hormones in the kidney injury and regeneration processes.

Funding: Government Support - Non-U.S.

SA-PO064

Drug Repurposing for the Prophylaxis of Renal Ischaemia Reperfusion Injury

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Background: Ischaemic Preconditioning applied to the kidney (direct IPC) or to distant sites (indirect IPC) confers protection from subsequent ischemic Acute Kidney Injury (AKI). However, IPC has not proven effective in clinical trials enrolling individuals at high AKI risk. The purpose of this study was to employ a drug repurposing approach, in an attempt to translate the experimental benefit of IPC into candidate agents for clinical testing.

Methods: IPC regimens were tested iteratively in a rat model of bilateral IRI. Optimised direct and indirect IPC approaches were transcriptomically profiled by RNA sequencing, and a shared protective signature identified. Computational prediction of drug repurposing candidates was performed by Ingenuity Pathway Analysis. Effects of predicted candidates were evaluated *in vivo*, by renal histology and serum creatinine.

Results: Optimum benefit was observed with direct and indirect pulsatile IPC employing two minutes of ischaemia followed by five minutes of reperfusion, repeated for 3 cycles. Whole kidney transcriptomic profiling performed across sham, IRI, and direct- and indirect-IPC/IRI groups (n=6 per group) mapped to 16,780 unique genes, of which 2,193 genes were differentially expressed between IRI and sham, which IPA attributed to a phenotype of Acute Renal Failure ($p = 1.32 \times 10^{-27}$) and Renal Proximal Tubular Toxicity ($p = 5.06 \times 10^{-15}$). A core set of master regulators and pathways were identified within inflammatory response, oxidative stress and cell cycle, that were diminished by direct and indirect IPC. Comparison with transcriptomic information available for 23,686 biological drugs and chemicals (compounds) contained within the IPA knowledge base was employed to identify repurposing candidates for benefit in IRI prophylaxis. Six compounds exhibiting favourable characteristics for progression to clinical testing were further evaluated *in vivo*, and all exhibited functional benefits when administered as a single dose prophylaxis pre-IRI.

Conclusions: Our data identify a common protective gene expression signature between direct and indirect IPC. These findings provide novel insights into the pathology of IRI injury and protection afforded by IPC. Computational transcriptional analysis using this dataset has identified candidate drugs for repurposing.

SA-PO065

Neuro-Immune Cross-Talk in Pathophysiology of AKI

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Background: Acute kidney injury is a heterogeneous syndrome characterized by inflammation, decrease in glomerular filtration rate, vascular modulation, oliguria and swing in nervous system. Its progression is mediated by cytokines production, neuro-molecules and infiltration of immune cells into kidneys and other organs including brain. Lead molecule, TNF-α aids in the recruitment & activation of immune response. The neuropeptide calcitonin gene-related peptide (CGRP) has been significantly observed in pain pathways, hemodynamic and nerve signal modulation in AKI. The interdependent mediation of immune molecules and neuropeptide during AKI further point to the progression of pain pathways that still remains unexplored in AKI.

Methods: A systems biology approach was used to find neuro-inflammatory molecules of AKI by employing *in-silico* retrieval of AKI genes and investigation of their role in mouse model. The neuro-inflammatory genes in AKI and the respective signalling pathways were searched by PANTHER, GENOMATIX and Target Explorer. Common interactors between TNF and CGRP were expedited by STRING and CYTOSCAPE. The AKI was induced in male Balb/c mice through an intraperitoneal injection of folic acid (250 mg/kg). Kidneys and brains were harvested and expression of CGRP and TNF-alpha, TRPV1, PTGER4 and CGRP receptor genes were analyzed by quantitative real-time PCR analysis. Immuno-histology of kidney and brain and Serum ELISA were employed to study the CGRP and TNFα protein expression. The changes in BBB were evaluated by Evan's blue estimation.

Results: The in-silico search retrieved a list of 49 genes which participate in neuro-immune axis of AKI. KEGG pathway analysis revealed that most of these communicators converse through the calcium signalling pathways. With progression of injury mRNA expression of CGRP, TNF- α and other genes was found modulated. The variation in expression was also reflected by immuno-histology in kidney and brain. The serum CGRP and TNF were also modulated in similar fashion as estimated by ELISA. The changes in the cell architecture of brain and the changes in BBB evidence the kidney cross talk with brain.

Conclusions: The study unveils the route of the communication between CGRP and TNF on neuro-immune axis. Most of the mediators signal through calcium mediated pathways leading to pain and pointing towards one of the pilot routes between them.

Funding: Government Support - Non-U.S.

SA-PO066

Kidney-Targeting Nanoplatform for the Specific Delivery of Triptolide to Treat Renal Ischemia-Reperfusion Injury

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Background: Triptolide (TP) has been proved with a therapeutic effect on a few kinds of kidney diseases. However, its clinical application is limited due to high toxicity and low specificity. Herein, we report a novel kidney-targeting, safe nanoplatform for the specific delivery of TP.

Methods: TP was wrapped in a kind of meso-scale nanoparticles (MNPs) with promising kidney-targeting ability to synthesize the nano-polymer MNPs-TP. TP and then it was administrated to mice through tail vein to evaluate its toxicity to organs and immune system. The targets of MNPs-TP and its mechanism were explored by organ imaging, Transwell and other experimental methods. Finally, a mouse model of renal ischemia/reperfusion injury (IRI) was applied to explore the protective effects and mechanism of different concentrations of TP and MNPs-TP on renal tubules.

Results: The toxicity test showed serious pathological changes in liver and the proportion of CD4+/cd8+ also decreased in TP group, suggesting immune function was damaged. However, MNPs-TP showed no obvious toxic effect on organs and immune system. The pharmacokinetic experiments showed that free TP had no specificity in the distribution in various organs, while the MNPs-TP showed longer metabolic cycle and clear kidney targeting. Transwell experiments showed that renal tubular epithelial cells could ingest MNPs-TP from the basal medium and transport it to the apical side, suggesting that the uptake of MNPs-TP is related to their endocytosis and exocytosis. After administration of TP at the dose of 0.1mg/kg body weight to the IRI mice, the renal function assessed by BUN and SCr was alleviated. The lower score of renal tubular injury, and the down-regulation of p-ERK and NGAL further verified the therapeutic effect of TP. However, free TP at the dose of 0.01mg/kg lacked these protective effects, and surprisingly, MNPs-TP still showed protection, which demonstrated that the effective therapeutic dose of MNPs-TP was significantly lower relative to free TP.

Conclusions: MNPs-TP showed superior therapeutic effect on renal ischemia-reperfusion injury (IRI) model in comparison with TP. Furthermore, MNPs-TP conjugate presented much lower hepatotoxicity and no adverse effect on the immune and genital system. The kidney-targeting MNPs may provide a promising drug delivery platform of hydrophobic drugs for treatment of renal diseases.

Funding: Government Support - Non-U.S.

SA-PO067

Transcriptomic Mapping of Early Cellular Responses to Renal Ischemia-Reperfusion at Single-Cell Resolution

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Background: Therapeutic options for treating acute kidney injury (AKI) and the subsequent development of chronic kidney disease (CKD) are limited. The lack of a clear molecular understanding of its pathogenesis and renal reparative pathways contributes to this scarcity of targeted therapeutics. Recent technological advancements in single-cell RNA sequencing have revolutionized our understanding of complex and dynamic tissues such as the kidney. However, optimization is still required to successfully apply this technology to rodent AKI models. Understanding cellular events in AKI at single-cell resolution will guide us to develop new therapeutic strategies.

Methods: We have optimized the kidney digestion protocol to achieve high viability (>95%) and very few doublet formations to avoid flow-cytometry-based cell isolation. We used our unilateral ischemia-reperfusion injury (uIRI) mouse model, which causes severe renal atrophy at 21 days after IRI. Droplet-based single-cell RNA-seq libraries were created and sequenced from a total of 10,000 cells from both injured (IRI) and contralateral kidneys (CLK) using a Drop-Seq platform. Single-cell transcriptome profiles were clustered and annotated based on the expression patterns of known marker genes.

Results: Our tSNE analyses identified at least 25 clusters in our combined dataset of IRI and CLK. We captured podocytes in 1.97% of total cells, which is close to the published single-nucleus RNA-seq dataset (2.4%; Wu et al., JASN 2019). There was clear separation among epithelial cells between IRI and CLK kidneys. We successfully mapped the known expression pattern of epithelial injury marker genes such as Havcr1 (encoding kidney injury molecule1), Lcn2 (encoding neutrophil gelatinase-associated lipocalin), and cytokeratins. Gene ontology analyses identified unique cell-type specific signaling such as oxidative stress responses in the KIM1-expressing proximal tubular segment.

Conclusions: We have developed an optimized platform for generating and analyzing the single-cell transcriptome of mouse kidneys which underwent IRI. Future studies using this platform will inform us as to how the cell-type specific and shared gene signatures change during the course of the disease and guide us to identify novel therapeutic approaches for AKI and its transition to CKD.

Funding: Commercial Support - Duke university

SA-PO068

Whole-Genome Chromatin Immunoprecipitation Sequencing Identifies a Role of CtBP2 in Renal Cell Dysfunction and AKI

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Background: Acute kidney injury (AKI) is a clinical syndrome characterized by rapid decline in renal function that results in 2 million deaths annually worldwide and pays for billions of dollars in US healthcare costs. In a pathophysiologic manner, renal tubular cell dysfunction and cell death is the hallmark and the underlying cause of AKI. However, the transcriptional regulators that control alteration in epithelial cell gene expression that triggers renal tubular cell dysfunction and death remain underexplored. The application of deep transcriptional sequencing has provided the new insights of AKI. Here we have examined the role of transcription regulator C-terminal binding protein 2 (CtBP2) in the pathogenesis of AKI through global profiling.

Methods: The mRNA and protein expression of CtBP2 were determined in multiple AKI-associated mouse models, namely rhabdomyolysis, ischemia reperfusion injury, and cisplatin nephrotoxicity. To define the role of CtBP2 in vivo, a pharmacological inhibitor (MTOB) and CtBP2-specific siRNA knockdown (hydrodynamic intravenous injection) were examined in ischemia- and cisplatin- associated AKI. Finally, to directly determine the molecular targets of CtBP2, we carried out chromatin immunoprecipitation followed by sequencing (ChIP-Seq) in rhabdomyolysis-induced AKI and associated changes of the target gene expression of CtBP2 in multiple AKI-associated mouse models with RNA-sequencing (RNA-Seq) data.

Results: During the early phase of rhabdomyolysis, ischemia, and cisplatin induced AKI, there is a remarkable increase in CtBP2 protein expression in renal epithelial cells. Functional *in vivo* studies showed that inhibition of CtBP2 function significantly improves renal impairment in ischemia and cisplatin-associated kidney injury. Global analysis of CtBP2 in rhabdomyolysis-induced AKI revealed that it drives DNA damage, cell cycle, cell proliferation/differentiation pathway, and carbohydrate/lipid metabolism. These target genes of CtBP2 were validated by RNA-Seq and qPCR analysis in all three AKI-associated murine kidneys.

Conclusions: Here we first have identified broad roles for CtBP2 as a transcriptional repressor during acute kidney injury. We propose that development of CtBP2 targeting small molecules could provide a therapeutic strategy for the treatment of AKI.

Funding: Private Foundation Support

SA-PO069

Erythropoietin-Derived HBSP Binding to Tubular Epithelia In Vitro Reduces Apoptosis and Synergistically Protects Kidneys with Caspase-3 siRNA Against 2-Week Ischemia-Reperfusion Injury in the Mouse

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Background: Ischemia-reperfusion injury (IRI) induced acute kidney injury has high morbidity and mortality, but no specific treatment. Renoprotection by caspase-3 siRNA (C3siRNA), erythropoietin (EPO) derived peptide HBSP, or cyclic HBSP ± C3siRNA, has been previously demonstrated against IRI at 24 or 48 h. HBSP only recognizes tissue protective heterodimer receptor (EPOR/βcR) and highly expresses in early IRI kidneys. This study further explored the synergistic long-term effect and mechanism of these agents administrated at the onset of injury.

Methods: Bilateral occlusion and sham operation of renal pedicles for 30 min were performed on adult male C57BL/6 mice, followed by reperfusion for 2 w, with or without the treatment of HBSP ± C3siRNA/negative control siRNA (NCsiRNA, n=5-9). Twenty-four nmol/kg BW of HBSP was administrated at the onset of occlusion and 15 min after reperfusion, while 30 μg/kg BW of C3siRNA or NCsiRNA was injected via tail vein 2 h before surgery. Moreover, the localization of fluorescent iridium labeled HBSP (HBSP-Ir) at 25 μM was detected at 1 h post incubation with TCMK-1 cells (mouse kidney tubular epithelial cell line, TECs) ± H_2O_2 at 200 μM post 24 h. Apoptosis was assessed when HBSP-Ir at 5, 10, 20 or 40 ng/ml was added together with H_2O_2 for 24 h.

Results: The typical impairment of renal structure and function was observed in the IRI kidneys, with increased apoptotic cells. However, this injury was reversed by HBSP or C3siRNA, which decreased serum creatinine, tubulointerstitial damage and apoptosis. Furthermore, co-treatment with both agents resulted in greater preservation of kidney structure and apoptosis compared with single administration. In addition, HBSP-Ir bound to TCMK-1 cells only treated by H_2O_2. HBSP-Ir also significantly reduced cell apoptosis at all dosages.

Conclusions: HBSP binds to TECs and induces anti-apoptosis. HBSP administrated at the early stage of injury has long-term and synergistic effects with C3siRNA on renal IRI. These data indicate a feasibility that HBSP might be a guide for cell-specific delivery of siRNA, if both are conjugated, targeting caspase-3 in specific cells highly-expressed EPOR/βcR in IRI kidneys.

SA-PO070

Phenotype of Ksp-Cadherin Deficient Mice: Enhanced Recovery from AKI

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Background: We have generated a mouse line that is deficient in Ksp-cadherin (Ksp-null), a member of the cadherin superfamily of cell adhesion molecules that is primarily expressed on the basolateral membrane of renal tubular epithelial cells (Thomson *et al.* ASN 2019). To further elucidate the phenotype of this null-mutation, we exposed Ksp-null and wild-type (WT) mice to an aristolochic acid (AA)-based model of AKI.

Methods: A single application of AA (2 mg/kg body weight) or vehicle alone was administered by i.p. injection to 10 week-old Ksp-null and WT male mice.

Results: At one week post AA exposure both cohorts showed similar levels of renal injury by histological evaluation. BUN values rose to 74 and 79 mg/dL for Ksp-null and WT animals respectively and serum creatinine values rose to 0.473 and 0.632 mg/dL respectively. Three weeks post AA treatment, WT animals had persistently elevated BUN and serum creatinine values of 80 and 0.462 mg/dL respectively and substantial evidence of unresolved tubular injury. In contrast, the Ksp-null animals had significantly lower BUN and serum creatinine values (35 and 0.206 mg/dL respectively) and histological evaluation revealed that their tubular injury had largely resolved. To gain insight into the nature of this accelerated recovery, we performed a comparative evaluation of kidneys from Ksp-null and WT animals specifically looking for differences in cell proliferation indices, inflammatory cytokine expression levels, immune cell response, and Klotho expression levels. No differences were observed between Ksp-null and WT animals at 1 week post AA injection. At 3 weeks post AA injection, however, Ksp-null animals exhibited significantly lower levels of expression of CD68, TGF-β, $p16^{INK4a}$, IL-6, and Arg1. Furthermore, Ksp-null kidneys demonstrated significantly higher levels of Ki67 staining and significantly enhanced recovery of Klotho expression.

Conclusions: In conclusion, despite sustaining similar levels of initial injury in response to AA exposure, Ksp-null animals exhibited an accelerated recovery relative to WT controls that was characterized by enhanced cell proliferation, elevated levels of Klotho, lack of persistent expression of immune cells, and decreased expression of inflammatory cytokines.

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SA-PO071

GSK3-Beta Inhibits Tubular Regeneration in AKI by a FoxM1-Dependent Mechanism

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Background: Acute kidney injury (AKI) is characterized by injury to the tubular epithelium. Although renal tubules are capable of regeneration, inadequate repair and fibrosis can lead to chronic kidney diease. FoxM1 is a forkhead box family member transcription factor which regulates cell division, survival and oxidative stress. FoxM1 is also a substrate for glycogen synthase kinase 3beta (GSK3-beta), a known inhibitor of renal tubular regeneration in AKI. The current study tested the hypothesis that GSK3-beta suppresses tubular repair after AKI by inhibiting FoxM1.

Methods: To determine the role of FoxM1 in tubular repair, the effect of FoxM1 inhibition was examined in renal ischemia/reperfusion (I/R) induced AKI in C57BL/6J mice and HK2 proximal tubular cells *in vitro*.

Results: Renal FoxM1 expression increased after I/R induced AKI in mice and was accompanied by increased cell proliferation. Treatment with Thiostrepton, a FoxM1 inhibitor reduced renal tubular cell proliferation and kidney tubular repair. To test if GSK3-beta regulates FoxM1, the effect of FoxM1 inhibitor on tubule-specific GSK3-beta knockout mouse was determined. In GSK3-beta knockout mice, FoxM1 expression, cell proliferation and tubular repair were significantly high, leading to improved renal function. Significant increase in p21, a cell cycle inhibitor and reduction in pro-proliferative factors were found in cells and kidneys where GSK3-beta was inhibited. Thiostrepton treatment abolished the improved tubular repair in GSK3-beta knockout mice.

Conclusions: These studies demonstrate that FoxM1 is an important factor for renal tubular regeneration following AKI, and that GSK3-beta suppresses tubular repair by inhibiting FoxM1

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SA-PO072

Loss of Gsα Impairs Renal Tubular Epithelial Cell Regeneration via the Raf-MEK-ERK Dependent Inhibition of CDK2/Cyclin E Mechanism

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Background: The alpha subunit of the heterotrimeric G stimulatory protein (Gsa), encoded by the guanine nucleotide binding protein, alpha stimulating gene (Gnas), is expressed ubiquitously and mediates receptor-stimulated production of cyclic adenosine monophosphate (cAMP) and activation of the protein kinase A signaling pathway. We investigated the roles of Gsa in renal tubular epithelial cell regeneration.

Methods: We generated a distal tubule epithelial-specific Gsa deletion ($Gsa^{flox/flox}$ Ksp-Cre) mouse to demonstrate the essential role of Gsa in renal tubular epithelial cell regeneration in two AKI models: acute aristolochic acid toxic nephropathy (AAN) and unilateral ischemia reperfusion injury (UIRI). To further explore the effect of Gsa on cell proliferation, we next knocked down Gsa in cultured human HK-2 cells using a specific small interfering RNA.

Results: $Gsa^{flox/flox}$ Ksp-Cre mouse developed more severe renal impairment including higher levels of serum creatinine and massive tubular necrosis after AAN and UIRI. Gsa inactivation dramatically impaired renal tubular epithelial cell regeneration and blocked proliferating tubular cells in G1/S transition due to the reduction in the number of BrdU+ cells and the depression of cyclin-dependent kinase2 (CDK2)/ cyclinE1 activities. In vitro, treatment of renal tubular epithelial cells with Gsa-targeting small interfering RNA inhibited tubular epithelial cells proliferation by preventing cell cycle progression from G1 to S phase. Down-regulation of Gsa inhibited the activity of CDK2/cyclinE1 and inhibited the Raf-MEK-ERK signaling pathway before and after aristolochic acid stimulates HK-2 cells.

Conclusions: Gsa is required for tubular epithelial cell regeneration in the kidney repair stage after AKI. Loss of Gsa could dramatically impair the regeneration of renal tubular epithelial cells by blocking Raf-MEK-ERK pathway.

SA-PO073

FGF9 Signaling Is a Crucial Regulator of AKI

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Background: Acute kidney injury (AKI), a clinical syndrome characterized by rapid loss of renal function, is associated with significant mortality and morbidity in hospitalized patients. Currently, there is no effective treatment or prophylactic approaches available for AKI. Our overarching goal is to dissect the molecular pathways underlying renal tubular cell dysfunction, and to identify drug-able targets that can be therapeutically exploited and translated into patients. Over the past decades, significant advances have been made in understanding the pathogenesis of AKI, mainly through the study of small animal models. Compelling evidence supports that renal cell death and dysfunction are the major hallmarks of AKI. However, clinical translation of these findings remains a significant barrier, in part due to the lack of drug-able targets.

Methods: An unbiased drug-able genome siRNA screen for regulators of renal epithelial cells was carried out in murine and human tubular epithelial cells. Primary screening and validation studies revealed fibroblast growth factor 9 (FGF9) as a novel regulator of renal cell death. To directly define the role of FGF9 in vivo, kidney tubule specific FGF9 knockout mice were generated. In addition, FGF9 targeted therapies

(anti-FGF9 antibody or FGFR kinase inhibitor) were evaluated in multiple mouse models, namely cisplatin-, ischemia-, and rhabdomyolysis-associated AKI. Proteomic approaches were used to identify the downstream targets.

Results: Genetic ablation of FGF9 in kidney tubules ameliorated the severity of AKI in multiple mouse models. Moreover, FGF9 targeted treatment, e.g. anti-FGF9 antibody or FGF9 receptor inhibitor, significantly reduced the kidney damage and improved renal function in these models. We also found that Glutathione peroxidase 4 (GPx4) is the downstream target of FGF9-FGFR signaling during AKI.

Conclusions: Together these studies have identified a previously unknown pathway responsible for AKI pathogenesis. More importantly, our data provides strong preclinical evidence to further evaluate the use of FGF9 targeted therapy in AKI treatment.

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SA-PO074

Epithelial STAT5 Confers Protection Against Glomerular and Tubular Injury

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Background: Recent data support Janus Kinase/signal transducers and activators of transcription (JAK/STAT) signaling, a pathway described in immune cells, as relevant to the kidney's tissue-specific response to injury. Studies have shown a deleterious role of podocyte STAT3 in glomerular diseases and the involvement of tubular STAT3 in renal fibrosis. Recently, we showed a protective role for the podocyte gamma chain, a potential activator of STAT5, during experimental glomerulonephritis. Here, we hypothesized that STAT5 may protect the kidney epithelium.

Methods: Mice with a podocyte-specific deletion of STAT5 and their littermate controls were challenged with nephrotoxic serum or with adriamycin. Mice with an inducible tubular-specific deletion of STAT5 and their littermate controls were challenged with a cisplatin nephrotoxicity model. All mice were derived on a C57BL6/J genetic background. We also investigated epithelial STAT5 activation by immunohistochemistry in different clinical nephropathies.

Results: Podocyte STAT5 deficiency exacerbated proteinuria in both nephrotoxic nephritis and adriamycin nephropathy. In addition, loss of STAT5 in podocytes associated with a loss of epithelial markers, such as nephrin, and exaggerated foot process effacement. Furthermore, podocytic STAT5 is activated in vitro by interleukin 15. Tubular STAT5 deficiency aggravated renal dysfunction and tubular injury in cisplatin nephropathy. In man, we observed STAT5 activation in injured podocytes in focal and segmental glomerulosclerosis, and in tubular cells in those with acute tubular injury.

Conclusions: Our results suggest a novel protective role of the STAT5 transcription factor in podocytes and tubular epithelium in experimental nephropathy. Our clinical data suggest a similar cellular activation of STAT5 as seen pre-clinically. Epithelial STAT5 activation could represent a potential therapeutic target in AKI.

SA-PO075

Regulation of Epidermal Growth Factor Induced Rac1 Activity by the Adapter Protein Dok-4

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Background: Following renal ischemia-reperfusion injury (IRI), locally produced or exogenously administered growth factors such as EGF promote tubular repair. To better understand the intracellular signaling events that may regulate this response, we explored the role of Dok-4, a highly conserved member of the Dok family of adapter proteins most abundantly expressed in epithelial cells and thought to mediate inhibitory signaling through largely undefined molecular interactions.

Methods: We screened a kidney cDNA library by yeast two-hybrid using Dok-4 as bait, with co-expression of the tyrosine kinase Lyn in order to detect phspho-Tyr (pY)-dependent interactions. Interactions were validated and their structural basis mapped by mutagenesis, co-IP and pull-down in transfected 293 cells. Expression of relevant proteins was confirmed in mouse kidneys subjected to 30 min. of unilateral ischemia and in sham controls. A novel bioluminescence resonance energy transfer (BRET)-based Rac1 assay was used to study the impact of Dok-4/Chn2 interaction in on EGF-induced Rac1 activity.

Results: The Rac1 GTPase activating protein (GAP) β2-chimerin (Chn2) was identified as a Dok-4 partner. This interaction involved binding of the Dok-4 PTB domain to phosphorylated Y153 of Chn2. Notably, Chn2 Y153 is contained within a canonical PTB-binding motif (NPXY) that is conserved in the highly homologous Rac-GAP α2-chimerin (Chn1), where pY143 can also mediate binding to Dok-4. While Dok-4 protein is expressed in kidney tissue and all cultured tubular cells examined to date, Chn2 protein was undetectable except in cerebellum. However, 24h after renal IRI, Chn2 was strongly expressed. BRET-based quantification of GTPase activity in 293 cells showed a rapid activation of Rac1 by EGF. Chn2 attenuated this activation in the presence of Dok-4 WT, but not mutant Dok-4 lacking the membrane-targeting PH domain. Retargeting of mutant Dok-4 to the membrane by a myristoylation signal rescued the cooperative inhibition of Rac1 by Dok-4 and Chn2.

Conclusions: The Rac-GAP Chn2 is a novel pY-dependent Dok-4 partner and effector expressed in the injured kidney. Dok-4 facilitates inhibition of Rac1 by promoting recruitment of Chn2 at the membrane. This cooperative inhibition of Rac1 may regulate key downstream events in renal IRI, including proliferation, migration and tubular repair.

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SA-PO076

Induction of Hnf-1β Transcription Factor Protects Against Epithelial Hypoxia During Renal Ischemia-Reperfusion Injury

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Background: Ischemia-reperfusion injury is the crucial cause of acute kidney injury (AKI) in clinical settings. Proximal tubular cells are highly sensitive to ischemic injury and the following repair capability. Hnf-1β transcription factor drives the normal nephrogenesis and epithelial homeostasis. In the present study, we investigated the role of Hnf-1β regulation against hypoxic damage of proximal tubular cells in renal ischemia-reperfusion injury.

Methods: Renal ischemia-reperfusion was induced by bilateral clamping renal pedicles, the clamps were released for reperfusion. Kidney function was measured by BUN and serum creatinine, pathological damage was evaluated by HE and TUNEL stain. In vitro, cells were treated with hypoxia (1% oxygen) to represent ischemic condition, to test the effect of Hnf-1β, the editing-proficient Cas9 cell line was generated before hypoxia. The expression of Hnf-1β was tested by western blot and IHC. Flow cytometry and Hoechst stain were used to detect apoptosis. To explore the further effect of GJB1, the down-regulated stable cell line was created, and the expression was tested by realtime PCR. ChIP analysis was used to confirm the binding of NF-κB and Hnf-1β.

Results: Using western blot, we identified expression of Hnf-1β are significantly increased in kidney after 30 minutes of bilateral renal ischemia and reperfusion 12h, while the IHC staining showed the signal mainly in cortex. In vitro, hypoxia can also induce Hnf-1β in rat kidney epithelial cells (RPTC) as early as 4h and lasted to 12h. Interestingly, CRISPR/Cas9-mediated Hnf-1β knockout cells exacerbated apoptosis induced by hypoxic condition and caspase activity, whereas overexpression of Hnf-1β revealed more resistant to apoptotic responses in hypoxic cells. We further indicated these protective effects of Hnf-1β were mediated by *NF-κB,* which were confirmed by ChIP analysis, and its specific inactivator TPCA-1. Moreover, we also show that gap junction gene GJB1 could serve as downstream target of Hnf-1β as evidenced inhibition of GJB1 rescued Hnf-1β anti-apoptotic effect.

Conclusions: The study indicates the protective role of Hnf-1β against ischemic/hypoxic conditions in kidney. Hnf-1β performs anti-apoptotic factor mediated by NF-κB, and the renal protective effect may carry out via regulating its downstream gene GJB1.

SA-PO077

Inhibition of Ataxia-Telangiectasia Mutated Exacerbates AKI by Activating p53 Signaling in Mice

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Background: The DNA damage response (DDR) after kidney injury induces cell cycle arrest in renal tubular epithelial cells. Cell cycle-arrested tubular epithelia secrete pro-fibrotic cytokines, thereby promoting interstitial fibrosis in a paracrine manner. Phosphorylation of ataxia-telangiectasia mutated (ATM) is the initial step in DDR and subsequent cell cycle arrest. ATM inhibitors are emerging cancer drug candidates; however, the effects of ATM inhibition on the injured kidney have not been explored.

Methods: We administered KU55933, a selective ATM inhibitor, to cisplatin-treated mice and UUO mouse model. In order to specifically investigate the underlying mechanism in tubular epithelia, we isolated the proximal tubular epithelia by FACS from bigenic SLC34a1-CreERt2; R26tdTomato proximal tubular-specific reporter mice.

Results: ATM inhibition did not ameliorate but rather exacerbated cisplatin-induced DNA damage and tubular injury, thereby increasing mortality. Numerous tubules with denuded tubular basement membrane where the tubular epithelia had completely detached were observed in the kidneys of mice that received KU55933 and cisplatin. Analysis of isolated tubular epithelia revealed that KU55933 upregulated p53 and subsequent pro-apoptotic signaling, such as PUMA and Bax expression, in tubular epithelia of cisplatin-treated mice, leading to marked mitochondrial injury and apoptosis. In addition, ATM inhibition did not increase the nuclear expression of MutL homologue 1 in tubular epithelia of cisplatin-treated mice, suggesting that DNA mismatch repair after tubular injury was not sufficient to prevent cisplatin-induced tubular injury. Lastly, we investigated the effect of ATM inhibition on UUO kidney and found that KU55933 did not ameliorate the kidney fibrosis.

Conclusions: Our study suggested that ATM inhibition does not increase DNA repair after cisplatin-induced DNA damage and exacerbates tubular injury through the upregulation of p53-dependent pro-apoptotic signaling. Acute kidney injury must be carefully monitored when ATM inhibitors become available in clinical practice in the future.

SA-PO078

PTIP Deletion in Renal Proximal Tubules May Cause Epigenetic Change and Prevent Recovery After AKI

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Background: Paxip1gene encodes a PTIP nuclear protein that is expressed in most cells and is implicated in a variety of nuclear processes, including DNA repair, and transcription activation. Consequent to acute kidney injury (AKI), surviving proximal tubule cells re-enter mitosis and will form cysts if disease associated genes are mutated. Thus, epigenetic information that maintain a stable phenotype must be reset during regeneration. PTIP is part of an Mll3/4 histone H3K4 methyltransferase complex that is essential for development. To test whether such epigenetic imprints are dependent on histone H3K4 methylation, we generated a mouse model with deletion of PTIP (PTIP-) in the terminally differentiated renal proximal tubular cells.

Methods: We used Cre-loxP system, standard genetic and biochemical techniques to generate and study the deletion of PTIP- specifically in renal proximal tubular cells. Also mice carried the mT/mG; Pepck-cre. Mice were age-matched and injected i.p with a single dose of folic acid.

Results: The kidneys of mice carrying the PTIP- appeared normal with little evidence of loss of kidney function or other abnormalities. Upon AKI, such mice failed to regenerate damaged tubules leading to scarring and interstitial fibrosis. The inability to repair damage was likely due to a failure to re-enter mitosis and reactivate regulatory genes such as Sox9. PTIP- reduced histone H3K4M3 in uninjured kidneys but had no effect on H3K4M2. A transient decrease in trimethylation was also observed in controls after AKI but returned to normal after repair. Strikingly, cell lineage tracing revealed that surviving PTIP mutant cells could alter their phenotype and lose epithelial markers. These data demonstrate that PTIP is needed for regenerating proximal tubules and to maintain or reestablish the cellular phenotype

Conclusions: The process of regeneration must require changes in gene expression of surviving epithelial cells, which may involve the reactivation of genes controlling development and proliferation. Despite PTIP-, mice had no gross morphological phenotypes, suggesting that PTIP- at this stage of differentiation had little apparent effect on kidney function. However, when such mice were subjected to AKI, the ability to repair and repopulate damaged tubules was severely compromised.

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SA-PO079

HDAC3 Contributes to Necrotic Tubular Damage in Ischemic AKI

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Background: Histone deacetylases (HDAC) are group of enzymes that remove acetyl groups from lysine residues of histone and nonhistone proteins. The action of histone deacetylation condenses chromatin and DNA structure, resulting in the repression of gene transcription and expression. We reported that HDAC inhibitors attenuate apoptosis of renal proximal tubular cells during cisplatin treatment. This study was designed to determine the specific role of HDAC3 in acute kidney injury (AKI).

Methods: In vivo, we generated proximal tubule-specific HDAC3 knockout (PT-HDAC3-ko) mice, which were subjected to 30mins of ischemia with 48hrs of reperfusion. We also tested the effect of RGFP966, a specific pharmacological inhibitor of HDAC3. Serum sample was collected to check blood urea nitrogen (BUN) and serum creatinine. Kidney tissue was collected for histology, immunohistochemistry and immunoblot analysis. In vitro, rat proximal tubular cells (RPTC) were treated with azide for 4.5hrs followed by 2hr reperfusion to induce necrotic cell death to examine the effects of RGFP966. Necrosis was indicated by propidium iodide staining and LDH release. In addition, the effect of HDAC3 knockdown was examined.

Results: HDAC3 was localized in the nucleus and cytoplasm of proximal tubular cells in kidneys. After ischemic AKI, HDAC3 was induced. Compared to wild-type mice, PT-HDAC3-ko mice showed less ischemic AKI as indicated by less necrotic damage in proximal tubules and improved renal function with lower levels of BUN and serum creatinine. Consistently, RGFP 966 protected against ischemic AKI in mice. In immunoblot analysis, acetylation of histone H3, H2B and H4 was better preserved in kidney tissues of PT-HDAC3-ko mice. In RPTC cells, HDAC3 was induced during azide treatment and significantly increased during subsequent recovery. Both RGFP966 and HDAC3 knockdown suppressed HDAC3 induction and preserved the acetylation of histone H3, H2B and H4. Notably, both RGFP966 and HDAC3 knockdown suppressed necrosis following azide treatment.

Conclusions: HDAC3 is induced during ischemic AKI and plays an important role in necrotic damage in proximal tubules. Specific blockade of HDAC3 may have therapeutic potential in AKI.

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SA-PO080

Hdac8 Knockout Results in Amelioration of AKI in Zebrafish

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Background: Despite the prevalence of AKI, the need for therapeutics is currently unmet. One candidate for a small molecule therapeutic is 4-(phenylthio) butanoic acid (PTBA), which had previously shown increased RTEC productive repair and functional recovery by enhancing dedifferentiation and decreasing injury in both murine and zebrafish models of AKI. Here, we show that histone deacetylase 8 (HDAC8) is potential target of PTBA. HDAC8 is known to interact with cell cycle regulators, such as SMC3 and p53, to acetylate and modulate cell cycle activity. We further investigate the role of Hdac8 in affecting the cell cycle using a larval zebrafish model of AKI.

Methods: Cellular thermal shift assay (CETSA) was used to evaluate the target engagement of PTBA with HDACs. *hdac8*$^{sa14948/-}$and *hdac8* $^{sa14948/+}$mutant zebrafish were injected with gentamicin to induce AKI and observed for post-injury survival from 1-7dpi. Cells harvested from whole larvae were stained with propidium iodide and analyzed with flow cytometry for variation in the cell cycle phase. Using cell cycle specific antibodies, EdU and pH3, larval pronephros were stained for S and G2/M phases at various timepoints following AKI.

Results: PTBA was shown to stabilize HDAC8 at higher temperatures compared to control, consistent with PTBA binding to HDAC8. *hdac8* $^{sa14948/-}$ fish showed significantly increased survival when compared with wildtype and *hdac8* $^{sa14948/+}$. Analysis of whole larvae cell cycle showed increased G1/S population with injury at 1dpi. Immunohistochemistry showed increased EdU during an early injury timepoint (1dpi) while showing delayed G2/M entrance in a later injury timepoint (4dpi).

Conclusions: Absence of Hdac8 in larval zebrafish model of AKI improved survival. The survival correlated with increased G1/S cell cycle phase during earlier timepoints of injury, as well as delayed entrance to G2/M. Here, we demonstrate the role of Hdac8 in increasing repair by delaying proliferation after injury. Furthermore, we have identified PTBA as an HDAC8 inhibitor. Taken together these data suggest a potential mechanism to induce productive repair after an AKI event.

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SA-PO081

Removal of Apoptotic Cells During AKI

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Background: The incidence of acute kidney injury (AKI) is increasing worldwide, however, effective treatment for AKI remains elusive and no approved pharmacological agents exist. Tubular cell apoptosis has been shown to be present in preclinical models and also in some clinical samples from patients with AKI. The human body removes over 200 billion dead cells every day. This process, i.e. clearance of apoptotic cells or 'efferocytosis', occurs in nearly every major organ (Morioka et al., Nature 2018). Clearance machinery can often become overwhelmed by massive induction of apoptosis such as occurs with ischemia reperfusion injury (IRI). While it has been shown that defective clearance leads to exacerbation of AKI, whether promoting efferocytosis leads to amelioration of AKI has not been explored.

Methods: In order to delinate whether apoptotic cell clearance could be boosted for beneficial effects during AKI, we established a way to boost apoptotic cell clearance by modulating the protein structure of a previously characterized phosphatidylserine (PtdSer) receptor, BAI1. Previous studies have shown that while BAI1 interacts PtdSer via its extracellular region, BAI1 also binds via its cytoplasmic tail to ELMO1 and in turn, a second protein Dock180, which together serve as a guanine nucleotide exchange factor complex for the GTPase Rac1. Activation of Rac1 induces a conformational change of the actin filament to initiate the uptake of target cells. We generated a chimeric version of BAI1 where we deleted the natural ELMO1 binding site and directly fused ELMO1 to the BAI1 cytoplasmic tail (denoted BELMO).

Results: Strikingly, we found that expression of this chimeric BELMO receptor strongly boosted apoptotic cell engulfment. This chimeric receptor still behaved faithfully as it was dependent on PtdSer recognition, and an intact ELMO1 that can engage the downstream Dock180 and Rac1 signaling machinery. We have also generated transgenic mouse expressing BELMO receptor. We demonstrate that BELMO expression in tubular epithelial cells significantly improved the survival rate of the mice underwent AKI induced by renal IRI surgery.

Conclusions: Here we open up new avenue for targeting cell clearance in AKI therapy. In addition, BELMO transgenic mice allow us to explore the effect of boosting apoptotic cell clearance on variety of other disease models involving accumulation of dead cells.

SA-PO082

Quantifying Autophagic Flux in Kidney Tissue with Super-Resolution Structured Illumination Microscopy Imaging

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Background: Autophagy, a key homeostatic catabolic pathway in eukaryotic cells, is linked to pathological conditions in most organs as well as cancer and aging. In the kidney, autophagy has been shown to modulate both acute and chronic injury. Despite the importance of autophagy, few methods are available to monitor autophagic flux, i.e. clearance of autophagosomes by the lysosome. Autophagy is usually evaluated by presence of autophagosomes, LC3 II levels or EM but not autophagic flux. We combined the RFP-GFP-LC3 reporter mice with super-resolution structured illumination microscopy (SIM) to measure autophagic flux at an individual autophagosome level in response to kidney ischemia.

Methods: Kidneys of RFP-GFP-LC3 reporter mice were injured by unilateral ischemic reperfusion injury. The GFP of the reporter is sensitive to low pH, quenching the fluorescent signal upon autophagosome/lysosome fusion, leaving only RFP signal. At 48 hours the kidneys were harvested, fixed and paraffin imbedded. The tissue was sectioned at 4-6μm and mounted on silanized coverslips. Immunofluorescence staining was done using

antibodies against GFP and RFP and stained with DAPI. The tissue was imaged using an N-SIM microscope to obtain Z stacks. These images were reconstructed using Bitplane's Imaris software. Colocalization of RFP and GFP was quantified using NIS elements.

Results: SIM imaging captured LC3 positive structures ranging in size from <0.3 μm to >4 μm. LC3 positive autophagosomes were present in larger numbers and size in injured kidneys compared to contralateral. Analysis of the colocalization of RFP with GFP, to quantify flux, in the control kidney showed the presence of many small RFP only positive organelles, indicating that these were autolysosomes, i.e. autophagosomes fused with lysosomes. In the injured kidney the organelles were larger and positive for both RFP and GFP, thus indicating more autophagosomes but a lower autophagic flux.

Conclusions: Combining the RFP-GFP-LC3 reporter mouse with SIM imaging allows for the quantification of individual autophagosomes in kidney tissue and measurement of the dynamic flux of the process. In unilateral IRI injury, we found the autophagic flux to be higher in the contralateral kidney than the injured kidney at 48 hours despite the presence of very large autophagosomes. These data suggest autophagic clearance is overwhelmed following ischemic injury.

SA-PO083

Mapping and Functional Characterization of Proteolytic Cleavage of Murine Kidney Injury Molecule 1

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Background: Kidney injury molecule-1 (KIM-1) is a type I transmembrane glycoprotein expressed apically on proximal tubule epithelial cells. KIM-1, absent in healthy kidneys, is upregulated transiently during acute kidney injury (AKI). KIM-1 as a phagocytic receptor plays a protective role during AKI facilitating the clearance of apoptotic cells (efferocytosis) from the tubular lumen, thereby reducing inflammation and promoting repair. Human KIM-1 undergoes spontaneous and accelerated ectodomain shedding (into urine and blood) via metalloproteases including TACE/ADAM17 and ADAM10. Both blood and urine KIM-1 are clinically relevant biomarkers for AKI, however, the biological role of KIM-1 shedding is not known. In order to study significance of KIM-1 shedding *in vivo* in mice, we first aimed to identify the murine KIM-1 cleavage site and study its functional relevance *in vitro*.

Methods: Based on common structural motifs involved in TACE and ADAM10 recognition of substrates, we mapped out a potential cleavage site between A201 and I202 within the predicted cleavage region T194 to I202. Site-directed mutagenesis was used to generate various substitution mutants (I202Q and I202A) at the P1' position of the potential cleavage site. We generated HEK293 cells stably expressing expression vectors encoding either *wild type* (WT), I202Q or I202A (murine) KIM-1. Expression of KIM-1 was verified by Western blot. Phorbol 12-myristate 13-acetate (PMA) and ionomycin were used to induce general metalloprotease- or ADAM10-mediated shedding, respectively, with or without GI254023X (ADAM10-specific inhibitor). Transfected cells were fed pHrodo stained apoptotic thymocytes and percent efferocytosis was quantified using flow cytometry. ADAM10 siRNA was used to study effect of ADAM10 silencing on KIM-1 shedding and efferocytosis.

Results: Both PMA and ionomycin accelerated shedding were drastically reduced in both (I202Q and I202A) mutants compared to WT. Efferocytosis was significantly reduced with the two mutants compared to WT KIM-1. Cells treated with ADAM10 inhibitor or ADAM10 siRNA exhibited significantly reduced efferocytosis compared to their respective controls.

Conclusions: ADAM10 is involved with both *baseline* and *accelerated* shedding of murine KIM-1. ADAM10-mediated KIM-1 shedding is required for efficient efferocytosis.

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SA-PO084

The Protective Effects of Novel HIF-Hydroxylase Inhibitors in Renal Tubules

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Background: Acute kidney injury (AKI) has an increasing incidence. To date there are no specific pharmacological treatment options for AKI. Results from multiple rodent models of AKI suggest that the pre-conditional stabilization of hypoxia-inducible factors (HIFs) in renal tubular epithelial cells leads to improved kidney function. However, so far it is unclear whether these effects can be translated into human disease, and the underlying molecular mechanisms are poorly understood. HIF protein stability is regulated by prolyl hydroxylases (PHD) and HIF transcriptional activity is regulated by the Factor Inhibiting HIF (FIH). Novel inhibitors of PHDs (PHDi) have been developed to treat the anemia in chronic kidney disease by increasing EPO levels. Here we evaluate the effects of some of the novel selective PHDi on the HIF-response in human primary renal tubular cells and contrast them with effects of pan-hydroxylase inhibition.

Methods: Human primary renal tubular cells (hPTC) were isolated from kidney of patients undergoing tumour nephrectomy. hPTC were exposed to different hydroxylase inhibitors and HIF levels, HIF DNA-interactions as well as target gene induction were measured by western blotting, ChIP experiments and RNA analyses, respectively. We employed an in vitro model of cisplatin induced apoptosis to screen for protective effects of HIF stabilization in hPTC.

Results: PHDi stabilize HIF-1α protein to levels comparable to pan-hydroxylase inhibition by dimethyl oxalylglycine (DMOG) in hPTC. ChIP analyses confirmed comparable HIF-binding to selected gene loci under PHDi and DMOG. In contrast to equal protein levels and DNA-binding, transcriptional activation of selected HIF targets (CA9, EGLN3) was more pronounced in cells treated with DMOG suggesting that the additional inhibition of FIH increases the HIF response. PHDi led to reduced apoptosis in the cisplatin AKI in vitro model. However, combined inhibition of PHDs and FIH either by siRNA mediated knock-down or with a selective FIH-inhibition further increased target gene expression and cell protection.

Conclusions: Novel PHDi lead to a remarkable HIF-response in hPTC and have protective effects upon toxic stimuli. Additional inhibition of FIH which regulates HIF activity further improves cell survival. Therefore, pan-HIF hydroxylase inhibition is protective in tubular cells and might open a novel route into AKI treatment.

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SA-PO085

Deciphering the Molecular Mechanisms Underlying Nephroprotection by Hypoxia-Signalling: A Comparative Analysis of Prolyl Hydroxylase Inhibition and Hypoxic Preconditioning

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Background: Acute kidney injury (AKI) is one of the most common kidney diseases leading to increased morbidity and mortality. However, preventive or therapeutic strategies in the clinical setting are still missing. In animal models, AKI can be effectively prevented by preconditioning strategies – e.g. activating hypoxia signalling – that increase cellular stress resistance. Since translation of this approach by exposure to hypoxia (HP) is not feasible in the clinical setting, pharmacological strategies would be a favourable alternative. Therefore, inhibition of prolyl-hydroxylases (PHDi) and consecutive activation of hypoxia inducible factors (HIF) is an attractive strategy. Our aim was to confirm the protection by HP and PHDi in renal ischemia-reperfusion injury (IRI) and to characterize shared molecular patterns to identify novel therapeutic targets.

Methods: Male 14-week-old C57Bl6 wildtype mice were either treated with a PHD-inhibitor or by incremental exposure to hypoxia on three following days aiming for a similar induction of the HIF-target gene EPO to increase the comparability of both approaches. Afterwards all mice underwent a right nephrectomy and 40 min of contralateral renal IRI. In the following they were characterized functionally (e.g. by creatinine), histologically and by a transcriptomic and proteomic analysis of the right and left kidneys to unravel the molecular key players.

Results: Hypoxia and PHD-inhibition significantly ameliorated AKI 24 h after reperfusion. Histological analysis confirmed the protective effect of both strategies. The omics-analyses of the right kidneys revealed only little influence of HP and PHDi before damage. After damage, kidneys from HP and PHDi treated animals differed strongly from controls. There was only a limited overlap between both approaches which will allow for narrowing down the pathways and genes causally involved in organ protection.

Conclusions: Here, we confirmed the protective effect of HP and PHDi and performed the first comparative molecular phenotyping of kidneys treated with these strategies. Future studies will answer the question whether the genes and pathways identified can be modulated to prevent AKI.

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SA-PO086

Identification of Small Molecule Inducers of Heme Oxygenase-1 (HO-1) in Renal Epithelial Cells

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Background: Acute kidney injury (AKI) is a major public health concern that is associated with increased morbidity and mortality in hospitalized patients. Furthermore, the rising cost of care for these patients presents an increasing economic burden. While several promising biomarkers are emerging to aid in the early identification of AKI, no new therapies have succeeded in clinical trials. Currently, the only FDA approved treatment for AKI is dialysis. Recent studies from our laboratory and others have demonstrated the beneficial effects of HO-1, an enzyme that catalyzes heme breakdown into biliverdin, carbon monoxide and iron, in animal models of AKI.

Methods: We designed an assay suitable for high throughput screening to assist in the identification of novel small molecule targets that both induce HO-1 and have desirable pharmacologic characteristics. We created a stable HEK293 cell line that contains portions of the human HO-1 promoter and a unique 220 bp enhancer sequence in a luciferase reporter vector to screen a library of >150,000 compounds.

Results: We identified 2240 candidate compounds in the initial screen. Based on chemical structure, we pared these down to 800. Compounds exhibiting $E_{max} \geq 70\%$ of 5uM hemin and $EC_{50} < 10mM$ were assayed for endogenous HO-1 expression in HEK293 cells. The screen was repeated on a library of >4,000 FDA approved compounds and several additional candidates were identified, including broxaldine, an antiprotozoal drug. At low micromolar concentrations (1-5uM), broxaldine induced markedly high expression of HO-1 mRNA, protein and enzyme activity. Using RNA seq, the transcription factor,

Nrf2 was identified as a target for broxaldine induced HO-1 expression, which was confirmed using siRNA experiments. We further assessed the potential for broxaldine to inhibit cisplatin-induced cytotoxicity in HEK293 cells. Pretreatment with broxaldine preserved cell viability and reduced cleaved caspase-3 expression.

Conclusions: These studies provide a methodology for the identification of compounds that are clinically relevant and efficacious in inducing HO-1, and therefore confer protection against a variety of pathologies, including AKI.

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SA-PO087

The Effects of PARP Inhibitor Treatment on Early Renal Injury in a Murine Ischemic AKI Model

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Background: Intrarenal robust inflammatory responses following ischemia-reperfusion injury are major factors in the pathogenesis of renal injury in ischemic AKI. Although numerous studies have investigated various agents to modulate immune responses in ischemic AKI, few have demonstrated reproducible effects in animals and humans. We hypothesized that poly(ADP-Ribose) polymerase(PARP) inhibitor may change the post-ischemic intrarenal immunologic micromilieu favorably by reducing DAMP signal and protect the kidneys from further damage after ischemic injury. The effects of JPI-289 (PARP inhibitor) on early renal injury in a murine ischemia-reperfusion injury model were investigated.

Methods: Bilateral ischemic-reperfusion injury (BIRI) was induced in three groups of 9-week male C57BL/6 mice (control, JPI-289 50mg/kg, and JPI-289 100mg/kg; n=9-10 in each group) by laparotomy approach. Intraperitoneal injection of saline or JPI-289 were performed immediately before reperfusion and at 24 hours after IRI. Serial changes in renal function were assessed up to day 3 following BIRI. The effects of JPI-289 on HK-2 cells after a hypoxic insult were investigated.

Results: Deterioration of renal function was significantly attenuated in the JPI-289 treatment groups in a dose-dependent manner. The expression of proinflammatory cytokines such as IFN-γ, IL-2, and MCP-1 was reduced by the JPI-289 treatment, while intrarenal VEGF expression was higher after IRI in the JPI-289 groups. Intrarenal T cell infiltration following IRI was comparable between control and JPI-289 groups, but intrarenal B cell infiltration was increased by JPI-289 treatment. Low dose (0.5 μg/mL) JPI-289 treatment facilitated proliferation of hypoxic HK-2 cells, but very low dose or high dose treatment did not show favorable effects on hypoxic HK-2 cells.

Conclusions: JPI-289 treatment attenuated early renal injury in a murine ischemic AKI model and facilitated proliferation of hypoxic HK-2 cells. Further studies are needed to identify optimal dosage and administration timing of JPI-289 treatment.

SA-PO088

JNK Signalling Mediates Oxidant-Induced Tubular Epithelial Cell Death

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Background: The reactive oxygen species-inducible JNK signaling pathway is activated in tubular cells within 20min of renal ischaemia/reperfusion (I/R) injury. Tubular cell death following I/R injury is reduced by systemic JNK inhibitor treatment, but whether this is a direct or indirect effect and the contribution of JNK1 versus JNK2 isoforms are unclear. We aimed to define the role of JNK1 versus JNK2 signaling in oxidant-induced tubular cell death and whether this mechanism also operates in diabetes.

Methods: Bilateral renal I/R injury was induced in groups (n=8 to 10) of male wild type (WT), Jnk1-/-, Jnk2-/-, and Jnk1f/f γGT-Cre mice (all C57BL/6J) which were killed 24hr later. Diabetes was induced in WT mice by 5 low dose streptozotocin (STZ) injections.

Results: Compared to renal I/R injury in WT mice, Jnk1-/- but not Jnk2-/- mice were significantly protected from tubular cell death (PAS and cleaved caspase 3 staining) and renal failure (serum creatinine) (both P<0.01). Furthermore, conditional deletion of Jnk1 in proximal tubular cells (Jnk1f/f γGT-Cre mice) also showed a significant reduction in tubular cell death and renal failure (both P<0.01 vs WT I/R). H2O2 (0.25 to 1mM) induced dose-dependent cell death in primary cultures of WT tubular epithelial cells (TEC); however, Jnk1-/- TEC showed 50%↓ cell death (P<0.001), whereas Jnk2-/- TEC showed no protection. A JNK inhibitor reduced H2O2-induced cell death in WT and Jnk2-/- TEC by 50%, but did not affect cell death in Jnk1-/- TEC. In a further study, renal I/R injury was induced in WT mice 8 weeks after STZ-induced diabetes. Compared to non-diabetic controls, I/R injury caused increased JNK signalling, greater tubular cell death and more severe renal failure (all P<0.01 vs non-diabetic I/R). Culture of WT TEC in high glucose for 48hr increased H2O2-induced cell death. However, a JNK inhibitor reduced H2O2-induced cell death under high glucose by 38 to 45% (P<0.001).

Conclusions: JNK1 but not JNK2 direct contributes to oxidant-induced tubular cell death in vivo and in vitro. JNK signalling may also promote the enhanced tubular cell death and renal failure seen in renal I/R injury in established diabetes.

SA-PO089

Greater High-Mobility Group Box 1 (HMGB1) in Male Spontaneously Hypertensive Rats (SHR) Enhances Renal Ischemia-Reperfusion (IR) Injury Compared with Females

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Background: Renal IR injury is a major cause of acute kidney injury, which carries a high mortality rate and increases the risk of later developing hypertension and CKD. There are sex differences in renal IR injury, with males exhibiting greater injury following an ischemic insult than females. The mechanisms that are responsible for observed sex differences in IR injury are unknown. Recent studies have reported that increased HMGB1 after renal IR in males contributes to renal damage. The contribution of HMGB1 to renal IR injury in females is unknown. We hypothesis that greater HMGB1 in males promotes enhanced renal IR injury compared to females.

Methods: 13wk old male and female SHR were subjected to sham or 45-min warm bilateral ischemia followed by 24hr reperfusion. A separate set of SHR were pre-treated with control (IgG) or neutralizing anti-HMGB1 antibody (300 μg/rat) 1hr prior to renal IR (n=4-6). Blood was collected for biochemical analysis; kidneys were harvested for histological and WB analysis.

Results: IR significantly increased renal HMGB1 levels in both sexes compared to sham (P_{IR}<0.001). Renal HMGB1 levels were greater in males vs. females, although the effect of IR to increase HMGB1 levels was comparable between the sexes (P_{sex}= 0.009, $P_{sex*IR=}$0.3). Treatment with anti-HMGB1 ab prior to IR attenuated IR-induced increases in plasma creatinine ($P_{anti-HMGB1}$=0.02), tubular damage ($P_{anti-HMGB1=}$0.04), and tubular cell death ($P_{anti-HMGB1=}$0.04) compared to rats receiving control IgG. However, effect of anti-HMGB1 ab was only observed in males; treatment with anti-HMGB1 did not alter plasma creatinine (P_{sex}=0.1; $P_{sex*anti-HMGB1}$=0.0039), tubular damage (P_{sex}=0.99; $P_{sex*anti-HMGB1}$<0.003) and tubular cell death (P_{sex}=0.07; $P_{sex*anti-HMGB1=}$0.05) following IR in females. In addition, HMGB1 neutralization attenuated IR-induced activation of pro-inflammatory signaling molecules downstream of HMGB1 only in male SHR, including decreased renal Toll-like receptor (TLR) 4 phosphorylation ($P_{anti-HMGB1}$=0.08; $P_{sex * anti-HMGB1}$=0.004), IL1β mRNA ($P_{anti-HMGB1}$=0.04; $P_{sex * anti-HMGB1}$=0.05) and plasma TNFα ($P_{anti-HMGB1}$=0.61; $P_{sex * anti-HMGB1}$=0.03).

Conclusions: In conclusion, greater levels of HMGB1 in males compared to females results in enhanced pro-inflammatory signaling and exacerbation of IR-induced injury.

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SA-PO090

Cyclo(His-Pro) Prevents Against Oxidative Stress-Induced Renal Apoptosis and Fibrosis Through Activating the Nrf2-Mediated Pathway

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Background: Apoptosis is a key feature of the pathogenicity associated with glomerular and tubulo-interstitial injury of acute kidney injury (AKI) and chronic kidney disease (CKD). Cyclo(His-Pro) (CHP) is an endogenous cyclic dipeptide that exerts cellular protective effects against oxidative damages. Here, we show that treatment with exogenous (recombinant) CHP prevented renal structural and functional injury triggered by experimental ischemia-reperfusion injury (IRI) model in mice as well as 5/6 nephrectomy (Nx) model in rat.

Methods: In this study, to investigate the effect of CHP on AKI, we used IRI mice model and hypoxia-induced in vitro models with cultured human tubular epithelial cells (TECs). In addition, 5/6 nephrectomy rat model and TGFβ- and hydrogen peroxide (H2O2)-induced apoptosis models with cultured human podocytes were employed.

Results: Exogenous CHP pre-treatment prevented kidney function and accompanied by a significant reduction in ischemia-induced tubular injury, apoptosis, and inflammatory cell infiltration on renal IRI model. In vitro stimulation of TECs with hypoxia, CHP-mediated renal protection was associated with reduced IL-11, IL-18, reactive oxygen species (ROS) and the proportion of dead cells. Compared with control-treated 5/6 Nx rat, CHP-treated 5/6 Nx rat also restored kidney function and decreased proteinuria and pathologically decreased glomerulosclerosis, tubule-interstitial fibrosis in the remnant kidney of 5/6 nephrectomized rat. The administration of exogenous CHP significantly reduced not only ROS production via Nrf2-dependent pathway, but also the resultant apoptosis induced by H2O2 in cultured human podocytes. Microarray analysis highlights a cascade of specific gene expression patterns related to kidney injury, repair, and innate immunity. Notably, tubular epithelial cell and podocytes cell cycle arrest in G2/M mediates oxidative stress after injury.

Conclusions: This study has uncovered a major protective role of CHP in renal IRI and 5/6 nephrectomy through TECs and podocytes regeneration that could be potentiated as a therapeutic strategy.

SA-PO091

Tonsil-Derived Mesenchymal Stem Cells Protect the Kidney from Nephrotoxin-Induced AKI by an Amelioration of Oxidative Stress via Incorporation into Damaged Renal Tubules

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Background: The therapeutic effect of mesenchymal stem cells (MSCs) in repairing damaged renal cells in AKI has been demonstrated. Tonsil-derived MSCs (T-MSCs) derived from tonsillar tissues are reported to be effective in acute liver injury. The aim of this study is to investigate the therapeutic potential of T-MSCs in gentamicin-induced AKI

Methods: Twenty male Sprague-Dawley rats were divided into four groups: Control, GM (140 mg/kg/day, intraperitoneal injection for 10 days for 10 days), GM+T-MSCs ($1x10^7$ cells, intravenous injection at 1 day after the 1st GM injection), and T-MSC group. To examine the intra-renal localization of T-MSCs, T-MSCs were labeled with PKH-26 red fluorescence before infusion. Measurement of BUN, Cr, proteinuria and histologic analysis including TUNEL staining were performed on 16 days of GM injection. Effect of T-MSC on renal tubular cells was also evaluated using a transwell co-culture system of NRK cells and T-MSC. Intracellular ROS was analyzed by measuring NOX activity, H_2O_2 generation, NOX mRNA expressions with DCF-DA staining

Results: The infusion of T-MSCs in animal model of GM-induced AKI preserved renal function with a decrease in proteinuria. T-MSCs also ameliorated renal tubular dilatation and reduced apoptosis of renal tubular cells, which was associated with decreased number of apoptotic cells, down-regulating apoptotic genes and up-regulating anti-apoptotic gene. In addition, T-MSCs resulted in suppression of oxidative stress as reflected by a decrease in the level of urinary 8-OHdG with an increase in antioxidant enzymes (GPx and catalase) in the renal tissue. PKH-26-labeled T-MSCs were identified within the renal cortex and localized primarily in the renal tubules. The in-vitro study revealed that T-MSC and/or T-MSC-conditioned media ameliorated GM-induced NOX-1 expression, H_2O_2 generation, and apoptosis of NRK cells.

Conclusions: Our study demonstrated that T-MSCs ameliorated GM-induced AKI by directly incorporating into the damaged renal tubules, exerting anti-apoptotic and anti-oxidative effects

SA-PO092

Overexpression of MIOX Accentuates Gentamycin-Induced Acute Tubular Injury via ALOX12-12HETE-GPR31 Signaling

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Background: Myo-inositiol oxygenase (MIOX), a renal tubular enzyme, has been implicated in the pathogenesis of high glucose and cisplatin induced tubular injury. Gentamycin is an aminoglycoside antibiotic used clinically, and it is known for its nephrotoxic effects. The mechanism(s) for its nephrotoxicity are somewhat elusive

Methods: In the present investigation, we identified a novel signaling pathway, i.e., arachidonate 12-lipoxygenase (ALOX12)–12-hydroxyeicosatetraenoic acid (12-HETE) G-protein-coupled receptor 31 (GPR31) axis, relevant to gentamycin induced tubular injury. Wild type (WT), MIOX overexpressing (MIOX-TG) and MIOX knockout (MIOX-KO) mice received daily intraperitoneal injections of gentamycin (100 mg/kg) for seven days. The following day animals were sacrificed, and their urine, blood and kidney samples were collected for various studies

Results: We observed that gentamycin-treated MIOX-TG mice had relatively high serum creatinine levels and increased albuminuria compared to WT mice, whereas MIOX-KO mice had minimal increase in serum creatinine and no detectable albuminuria. Interestingly, the increased ROS generation induced by gentamycin promoted the expression of MIOX via ROS modulation, leading to accentuated lipid peroxidation. Arachidonic acid, a fatty acid present abundantly in renal tubules, which is metabolized into 12-HETE by ALOX-12, leading to acute inflammatory response under various pathologic conditions. We observed significant increase in ALOX-12 expression and 12-HETE production in gentamycin-treated MIOX-TG and WT mice. These perturbations were minimally seen in gentamycin-treated MIOX-KO mice. MIOX gene disruption in HK-2 cells abolished gentamycin induced cascade of inflammatory signaling events (p-p44/42, p-pERK, p-p38, p-pJNK, p-Nf-kB). Of note, the gentamycin-induced up-regulated 12-HETE binds with GPR-31 to accentuate the inflammatory response in renal tubules, which was attenuated by ML-355 (inhibitor of ALOX-12).

Conclusions: Collectively, these studies highlight a novel mechanism, i.e., ALOX12-12-HETE-GPR31 signaling axis, in the pathogenesis of gentamycin-induced nephrotoxicity modulated by MIOX.

Funding: NIDDK Support

SA-PO093

3-Deazaneplanocin A Protects Against Cisplatin-Induced Tubular Cell Apoptosis and AKI by Restoration of E-Cadherin Expression

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Background: 3-deazaneplanocin A (DZNeP) has been used as an inhibitor of enhancer of zeste homolog 2 (EZH2). Here, we explore the role and underlying mechanisms of 3-DZNeP in cisplatin nephrotoxicity.

Methods: Cultured mouse renal proximal tubular epithelial cells (mTECs) were exposed to cisplatin in the presence or absence of EZH2 inhibitors (3-DZNeP, miRNA). A murine model of cisplatin-induced acute kidney injury was used to examine the effect of 3-DZNeP on cisplatin nephrotoxicity.

Results: Exposure of cultured mTECs to cisplatin resulted in dose and time-dependent cleavage of caspase-3, decrease of cell viability and increase of histone H3 lysine 27 trimethylation (H3K27me3), whereas expression levels of EZH2, a major methyltransferase of H3K27me3, were not affected. Treatment with 3-DZNeP significantly inhibited cisplatin-induced activation of caspase-3, apoptosis, loss of cell viability but did not alter EZH2 expression and H3K27me3 levels. Similarly, administration of 3-DZNeP also attenuated cisplatin-induced renal dysfunction, morphological damage and renal tubular cell death in a mouse model. Mechanistically, 3-DZNeP treatment did not affect activation of extracellular signal-regulated kinase 1/2, p38 or c-Jun N-terminal kinases 1/2, which contribute to renal epithelial cell death, but caused dose-dependent restoration of E-cadherin in mTECs exposed to cisplatin. Silencing of E-cadherin expression by siRNA abolished the cytoprotective effects 3-DZNeP. In contrast, 3-DZNeP treatment potentiated the cytotoxic effect of cisplatin in H1299, a non-small *cell* lung cancer cell line that expresses lower E-cadherin level.

Conclusions: These data indicate that 3-DZNeP can suppress cisplatin-induced tubular epithelial cell apoptosis and acute kidney injury via an E-cadherin dependent mechanism and suggest that combined application of 3-DZNeP with cisplatin is a novel chemotherapeutic strategy that enhances the anti-tumor effect of cisplatin and reduces its nephrotoxicity.

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SA-PO094

Renoprotective Effect of IL-34 Inhibition on Cisplatin-Induced Nephrotoxicity in Mouse

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Background: Interleukin (IL)-34 is reported to mediate macrophage (Mø) proliferation and to be associated with kidney disease progression. However, the physiological properties of IL-34 on tubular epithelial cell (TEC) injury remain unclear. Thus, we investigated the effect of IL-34 on TEC damage caused by cisplatin nephrotoxicity (CP-N).

Methods: 7-week-old male C57BL/6 (B6) mice (n=16) were fasted for 8 hours and then induced CP-N by intraperitoneal injection (IP) of CP (25 mg/kg) on day 0. Groups of animals were given either anti mouse IL-34 antibody (CP+anti-IL-34 Ab, 400 ng/kg, n=8) or vehicle (CP+V, n=8) daily by IP from day -1 to day 2. Three age-matched male B6 mice were used as normal control (NC). All mice were sacrificed on day 3. In addition, mouse renal proximal TECs (MRTEpiC) were cultured to analyze the inhibitory effects of IL-34 on CP-induced TEC apoptosis. Cells were stimulated with CP (2 μg/mL), then treated with or without anti-IL-34 Ab (1000 pg/mL).

Results: Compared to the NC, CP+V mice exhibited marked acute kidney injury (AKI) and upregulated expression of IL-34 and its receptors, C-FMS and PTP-ζ. Compared to the vehicle treatment, anti-IL-34 Ab treatment significantly suppressed the protein levels of IL-34 and its receptors in CP-N mice; it also significantly improved serum Cr levels, ameliorated the numbers of casts/HPF, and suppressed the increased numbers of F4/80+, TUNEL+, and caspase-3+ cells in CP-N mice. The renal transcript levels of Kim-1, MIP-1/CCL3, TNF-α, and Bax were significantly lower in the CP+anti-IL-34 Ab mice than in the CP+V mice. Furthermore, CP+anti-IL-34 Ab mice showed significantly less renal infiltration of CD11b+F4/80+TNF-α+ cells. *In vitro*, stimulation with CP induced the expression of IL-34 and its receptors in MRTEpiC. Treatment with anti-IL-34 Ab significantly suppressed CP-induced caspase-3 and Bax expression with degradation of ERK1/2 phosphorylation in the damaged MRTEpiC.

Conclusions: These results indicated that IL-34 secreted from damaged TEC binds to its receptors and aggravates CP-N. Treatment with anti-IL-34 Ab directly prevented CP-induced TEC apoptosis by inhibiting the phosphorylation of ERK1/2, and the blocking of IL-34 might have indirectly attenuated CP-N via the suppression of cytotoxic Mø proliferation. Thus, IL-34 may be a therapeutic target for AKI.

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SA-PO095

MeCP2 Promotes Cisplatin-Induced AKI Through Epigenetic Regulation of Irf8

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Background: Emerging evidence suggests that epigenetic regulation like DNA methylation plays an important part in the process of acute kidney injury (AKI), but the mechanism remains largely elusive. Methyl-CpG binding protein 2 (MeCP2) is an epigenetic regulator which binds to methylated cytosines and functions as gene transcriptional inhibitor or activator. The role of MeCP2 was examined most notably in brain development, while the involvement of MeCP2 in renal disease remains unknown.

Methods: Twenty male C57 mice were randomly grouped into control, cisplatin-1d, cisplatin-2d, and cisplatin-4d according to the time of execution after cisplatin intraperitoneal injection. HK-2 cells were exposed to cisplatin at 20uM for variable incubation time. HK-2 cells were transfected by siRNA to knockdown MeCP2 expression. Apoptosis was detected with the TUNEL method. Chromatin immunoprecipitation assay (CHIP) was used to analyze the binding of MeCP2 to the interferon regulatory factor 8 (Irf8) gene.

Results: We found consistent expression of MeCP2 in renal cortical tubules of SD rat, WKY rat, and C57 mouse. Compared with the sham group, cisplatin-treated mice kidney showed significant upregulation of MeCP2 in proximal tubules in both protein and mRNA level, accompanied by severe renal histology changes and the upregulation of NGAL and KIM-1. In vitro, MeCP2 was also induced in cultured proximal tubular cells by cisplatin treatment. Interestingly, knocking down MeCP2 alleviated caspase-3-dependent tubular cell apoptosis but enhanced cell autophagy induced by cisplatin. Furthermore, a pro-apoptotic gene interferon regulatory factor 8 (Irf8) was found upregulated in tubular cells by cisplatin in vivo and in vitro. Importantly, we demonstrated that MeCP2 upregulated Irf8 expression by directly binding to its gene.

Conclusions: Elevated expression of MeCP2 was found in cisplatin-treated renal proximal tubules in vivo and in vitro. MeCP2 promoted cisplatin-induced renal tubular damage by facilitating apoptotic process and inhibiting autophagy activity. The epigenetic regulation of pro-apoptotic gene Irf8 by MeCP2 may be the possible mechanism implicated in the pathophysiological process of cisplatin-induced AKI.

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SA-PO096

The mRNA Editing via Apobec-1 Is Necessary to Repair Kidneys from Cisplatin (CP)-Induced Renal Injury

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Background: Cisplatin (CP) induces AKI as the proximal tubules (PT) undergo regulated necrosis. Repair is almost complete following such a single dose. Repeated doses of CP, however, leads to unresolved injury and progresses to chronic kidney disease (CKD). Interrogation of the renal transcriptome throughout the process of AKI to CKD progression identified Apobec1 protein, a cytosine deaminase that binds to and edits mRNAs that regulate mitochondrial metabolism, cell fate and proliferation pathways, which in liver, small intestine and brain play a crucial role in recovery from stress. We therefore examined the role of apobec1 in kidney nephrotoxicity.

Methods: Apobec1 knockout (ko) mice were given CP 15 mg/kg i.p. and renal function, histology, mRNA and protein expression were analyzed and compared to wild type (WT) mice of similar genetic background. We also overexpressed Apobec-1 in PT cells, after CP treatment, and assessed cell viability histologically and by WST-1 assay.

Results: Apobec-1 gene knockout resulted in more severe AKI, plasma creatinine 2.069 mg/dL ± 0.591, n=13) versus 0.228 mg/dL ± 0.087, n=8) 3d ($p < 0.01$) in WT. Remarkably all apobec1 ko mice died after 6 days, while WT animals all survived. The kidney showed greater necrosis and neutrophil invasion, but no change was noted in TUNEL or ki67 staining. mRNA and protein levels of RIPK3, MLKL, TLR2, and TLR4 were 3.76-, 3.54-, 6.26-, and 40.07-fold higher, respectively (p,001), in Apobec-1 kos than WT kidneys. Overexpression of Apobec-1 in mouse PT cells protected cells from CP-induced cytotoxicity: the CP-induced cell death was 2.35-fold lower in cells transduced with Apobec-1 than in cells transduced with vector alone ($n = 4$, $p < 0.05$). Such overexpression of Apobec-1 increased the activities of kinases associated with survival (ERK, STAT3, and AKT) and inhibited those inducing cell death (TLR4, IRF4, and JNK).

Conclusions: We have identified Apobec1 as a crucial gene regulating the necrotic response to CP-induced nephrotoxicity. The studies show that mRNA editing is a key survival response to CP-induced AKI and that increasing Apobec-1 activity could be an effective strategy to reduce or prevent CP-induced AKI.

Funding: NIDDK Support

SA-PO097

Proteomic Studies of Cisplatinated DNA Binding Proteins Identifies RtcB, a Novel RNA Ligase, as an Essential Regulator of Epithelial Cell Death and DNA Damage Response

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Background: Cisplatin is one of the most widely used and effective anti-cancer drugs. The therapeutic efficacy and side-effects of cisplatin are largely dependent on its ability to cause DNA damage in both normal and cancer cells. However, the molecular mechanisms involved in cisplatin-mediated DNA damage response and repair remains incompletely understood. In order to uncover novel proteins involved in the cisplatin-associated DNA damage response, we carried out immunoprecipitation of cisplatin-DNA adducts followed by mass spectrometric analysis of associated proteins. These studies revealed that RNA ligase RtcB is associated with cisplatinated DNA under in vitro and in vivo conditions.

Methods: In order to identify novel proteins associated with cisplatin-mediated DNA damage response, we used a cisplatin-DNA adduct antibody to pull down chromatin-associated proteins in murine kidneys after cisplatin treatment. Mass spectrometric analysis was then carried out to identify the proteins associated with cisplatinated-DNA. In vivo and in vitro siRNA approaches were then used to decipher the functional relevance of identified proteins in cisplatin-mediated renal epithelial cell death and DNA damage signaling. Western blot and immunofluorescence experiments were carried out in epithelial cells and renal tissues to measure the extent of DNA damage as well as the activation of DNA damage response.

Results: Initial pulldown studies followed by mass spectrometric analysis identified RtcB as a previously unknown sensor of cisplatin-associated DNA damage. Functional studies in murine renal epithelial cels showed that RtcB knockdown impairs DNA repair, increases DNA damage response and sensitizes cells to cisplatin-mediated cell death. In vivo siRNA mediated RtcB knockdown resulted in augmented AKI and higher renal epithelial cell death. While RtcB is known to play a role in tRNA splicing and unfolded protein response, our work has identified RtcB as a novel player involved in the DNA damage response and repair.

Conclusions: Together, these results suggest an important role for RtcB in the therapeutic efficacy and toxicities associated with the anti-cancer drug cisplatin.

Funding: Other NIH Support - NCI

SA-PO098

Role of AMPK and KLF4 in Determining the Survival of Cisplatin-Treated Human Umbilical Vein Endothelial Cells

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Background: We have reported that preconditioning renal tubular cells with A-769662, a specific pharmacologic activator of AMPK, increased the survival of these cells when subjected to hypoxic stress. We have also shown that preconditioning mice A-769662 ameliorates the severity of ischemic AKI in mice *in vivo*. In these studies we examined the role of AMPK and the Kruppel-like transcription factor-4 (KLF4) in determining the fate of human umbilical epithelial cells (HUVECs) exposed to cisplatin

Methods: The phosphorylation (activity) of AMPK was determined by immunoblotting and expressed as % of total AMPK. The expression of KLF4 was knocked down (by >85%) using a specific siRNA ("KD cells"). "Control cells" were transfected with a scrambled siRNA. The response of HUVECVs to cisplatin induced-injury was determined by first pretreating the cells with either A-769662 (250uM) or its vehicle for 24 h., followed by incubation with either cisplatin (100uM) or its vehicle) for an additional 18h. Then cell survival was determined by flow cytometry and expressed as a % of vehicle-treated cells.

Results: A-769662 increased the phosphorylation (activity) of AMPK to a comparable extent in control and KD cells (by 6.3±.24 and by 5.9±2.2 fold respectively). In control cells, the activation of AMPK induced by A-76962 (250mM), increased the expression of KLF4 mRNA (by 4±2.3 fold), and of KLF4 protein (by 3.9±2.2 fold). As expected, A-769662 had no effect on the expression of KLF4 in KD cells. In the absence of preconditioning with A-769662, the survival after cisplatin treatment was substantially higher in control cells (55.4%±4.2) than in KD cells (15.5±3.4%). These data show that KLF4 has pro-survival effects that are independent of AMPK. Furthermore, preconditioning HUVECs with A-769662, increased the survival of both control cells to 84.4±6.5%, and of KD cells to 57.9±7.6%. These data demonstrate, that the pro-survival effect of KLF4 is increased by the activation of AMPK.

Conclusions: i) AMPK induces the expression of KLF4; ii) AMPK and KLF4 both promote the survival of cisplatin-treated cells; iii) the pro-survival effects of AMPK and KLF4 are mediated by different pathways; iv) the activation of AMPK augments the pro-survival effect of KLF4 by increasing its expression.

Funding: Private Foundation Support

SA-PO099

Activation of Renal AMP-Activated Protein Kinase (AMPK) Is an Adaptive Response to Sepsis/Inflammation That Can Be Pharmacologically Harnessed to Improve Survival

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Background: To determine the role of renal AMPK activation and inhibition in the renal tubular epithelial cells (TEC) metabolic response to sepsis, and to investigate the effects of AMPK signaling on sepsis-induced TEC injury, clinical status and survival

Methods: Animals: Ten-twelve week old C57BL/6 (n=6-10/group) mice were randomized to vehicle, 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) or compound C (CC), and underwent cecal ligation and puncture (CLP). Outcome: Survival at 7 days. Cells: Human kidney 2 (HK2) cells were cultured in serum-containing media at 21% O_2 and were assigned to control, AICAR and CC, and then exposed to inflammatory mix (IM=LPS+HMGB1). Using the Seahorse metabolic analyzer, we measured oxygen consumption rate (OCR) as a surrogate of OXPHOS (mitochondrial respiration) and extracellular acidification rate (ECAR) as a surrogate of glycolysis at 24 hours. Spare respiratory capacity defined as the capacity of the cell to increase ATP production in conditions of increased energetic demands was assessed by comparing OCR at baseline and after uncoupling mitochondria.

Results: Pharmacologic activation of AMPK with AICAR before or after sepsis improves mice survival at 7 days (AICAR+CLP vs CLP; 70% vs 19%; $p<0.05$), and inhibition with CC before sepsis increases mortality at 7 days (CC+CLP vs CLP; 100% vs 81%; $p<0.05$). Cells exposed to IM and CC showed a decrease in OCR and spare respiratory capacity at 24 hours by 26% and 90.3% respectively when compared to IM (Fig 1B, C), and limited the recruitment of glycolysis upon blockade of the mitochondrial electron transport chain (Fig 1D).

Conclusions: Enhancement of AMPK with AICAR increases survival, whereas inhibition with CC increases mortality. AMPK inhibition limited the capacity of tubular epithelial cells to recruit OXPHOS and glycolysis, thereby limiting metabolic flexibility. These findings suggest that TEC metabolic response to sepsis is an adaptive mechanism and that maintenance of metabolic flexibility may be key to survival from sepsis

Funding: Other NIH Support - 1K12HL109068-02, 1K08GM117310-01A1

Figure 1

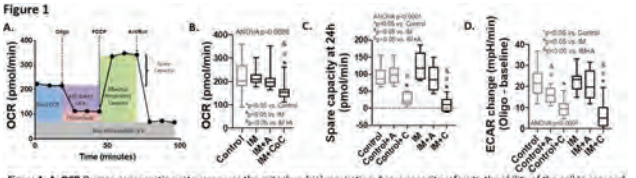

Figure 1: A: OCR Oxygen consumption rate measures the mitochondrial respiration. Spare capacity refers to the ability of the cell to respond to an energetic demand, and constitutes an indicator of how close the cell is respiring at its theoretical maximum respiration. **B: OCR 24h:** Inhibition of AMPK with compound C significantly decreases OCR at 24 hours when compared to control and IM. **C: Spare Respiratory Capacity:** Inhibition of AMPK during with compound C significantly decreases the spare respiratory capacity of the cell at 24 hours in the control and in the IM group. **D: ECAR change (Oligo-baseline):** Glycolytic metabolism recruitment is impaired in the compound C group after inhibition of OXPHOS with oligomycin.

SA-PO100

Alpha-7 Nicotinic Receptor Agonist GTS-21 Ameliorates Contrast-Induced Nephropathy in Rats

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Background: Despite the extensive use of contrasts in medicine, no proven pharmacological therapies exist to prevent contrast-induced nephropathy (CIN), which causes renal damage by renal vasoconstriction, medullary hypoxia, oxidative stress and direct tubular toxicity of the contrast agent. In an experimental CIN model, we aimed to evaluate the possible therapeutic effects of GTS-21, a selective alpha-7 nicotinic receptor agonist with anti-apoptotic, anti-inflammatory and anti-oxidative properties.

Methods: In male Sprague-Dawley rats, CIN was induced by intravenous injection of indomethacin (10 mg/kg), L-NAME (10 mg/kg) and a high-osmolar contrast agent (Urografin 76%, 6 ml/kg). Starting at 24 h before CIN induction, every 12 hours, rats were injected intraperitoneally with saline (contrast, n=14) or GTS-21 (GTS-21-contrast, 4 mg/kg, n=10), while the control groups with no CIN induction were treated with saline (control, n=8) or GTS-21 (GTS-21-control, n=8). At the 48th h of CIN, blood and kidney samples were obtained for the determination of cytokine expression (RT-PCR), oxidative stress parameters and histopathological analysis. Data were analyzed using ANOVA and Student's t-test.

Results: When compared to control and GTS-21-control groups, serum creatinine and BUN levels in the contrast group were elevated ($p<0.05$), while these measurements in GTS-21-contrast group were not different than controls. Increased histopathological damage score in contrast group ($p<0.01$) with respect to both control groups was significantly decreased in GTS-21-contrast group ($p<0.001$). Elevated malondialdehyde level in contrast group ($p<0.001$) was partially lowered by GTS-21 treatment, while antioxidant glutathione level was increased ($p<0.05$). In both contrast groups, an increase in IL-6 expression and a reduction in TGF-β expression were observed ($p<0.05$), but GTS-21 treatment increased TGF-β expression ($p<0.05$) and slightly depressed IL-6 expression.

Conclusions: GTS-21 improves renal dysfunction and provides a significant protection against contrast nephropathy via anti-oxidant and anti-inflammatory mechanisms.

SA-PO101

Molecular Pathways Driving Omeprazole Nephrotoxicity

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Background: Omeprazole, a proton pump inhibitor used to treat peptic ulcer and gastroesophageal reflux disease, has been associated to chronic kidney disease and acute interstitial nephritis. However, whether omeprazole is toxic to renal cells is unknown. Omeprazole has a lethal effect over some cancer cells, and cell death is a key process in kidney disease.

Methods: Thus, we evaluated the potential lethal effect of omeprazole over cultured tubular proximal cells.

Results: Omeprazole induces dose-dependent cell death in human and murine proximal tubular cell lines and in human primary proximal tubular cell cultures. Increased cell death was observed at the high doses used in cancer cell studies and also at lower concentrations similar to those in peptic ulcer patient serum. Cell death induced by omeprazole has features of necrosis such as annexinV/7-AAD staining and irregular chromatin condensation. Weak activation of caspase-3 was observed but inhibitors of caspases (carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone,zVAD), necroptosis (necrostatin-1) or ferroptosis (ferrostatin-1) did not prevent omeprazole-induced death. However, omeprazole induced a dose-dependent and early increase in ROS production as assessed by CM-H2DCFDA staining and flow cytometry. ROS production increased in mitochondria, as assessed by MitoSOX staining, and by NADPH activity role, determined by lucigenin assay. Moreover, the antioxidant molecule N-Acetylcysteine (NAC) partially prevented omeprazole-induced ROS production and cell death as assessed by the MTT assay and by annexin-V/7AAD staining. Omeprazole also induced lysosomal stress, evidenced by an increase in lysosomal pH and this was also prevented by NAC. Autophagy activation was also observed but blockade of autophagosome formation by 3-methyladenine did not decrease omeprazole-induced death. An adaptive increase in the expression of the antiapoptotic protein BclxL failed to protect the cells. In mice, parenteral omeprazole increased tubular cell death and the expression of NGAL, a marker of renal injury.

Conclusions: In conclusion, omeprazole nephrotoxicity may be related to induction of oxidative stress and renal tubular cell death, supporting the biological plausibility for the epidemiological association of chronic proton pump inhibitor use to kidney disease.

SA-PO102

Mechanistic Modelling of the Linkage Between Proximal Tubule Cell Sublethal Injury and Tubular Sodium Reabsorption Impairment

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Background: Renal epithelial cell injury, a prominent feature of drug-induced acute kidney injury (AKI), is characterized by loss of brush border and cellular polarity of proximal tubular cells (PTCs). The key alterations caused by sublethal injury involve impaired energetics and associated disruptions in cytoskeletal structure and sodium transporters activity. A mechanistic model relating AKI mediated cellular injury with renal tubular dysfunction is needed to address the complexity of renal physiology.

Methods: We developed a model of sublethal PTCs injury and sodium reabsorption impairment within the framework of RENAsym, a quantitative systems toxicology (QST) model of drug-induced AKI under development. The mathematical model represents major components of renal sublethal injury in a system of equations accounting for ATP decline, microfilament redistribution, and Na+/K+ ATPase activity reduction. The model equations were parametrized with an experimental study in which induced sublethal injury in rats, by selectively inhibiting cortical ATP production using maleic acid, was investigated and the effect of dose-dependent ATP decrement on apical F-actin networks and tubular sodium reabsorption was measured [1].

Results: Microfilament disruption was quantified with ATP decrement and then related to translocation-based loss of Na+/K+-ATPase, while a decline in the molecular activity of a sodium pump was directly related to ATP decrement. The model recapitulated the link between ATP decrement and sodium reabsorption impairment through the intermediate pathological pathways of microfilament redistribution and Na+/K+ ATPase activity reduction. Simulations of varying ATP decrement reveals a sharp decline in sodium reabsorption as the relative ATP decrement exceeds 40%, in accord with observations [1].

Conclusions: A mechanistic model of subcellular injury is developed to link cellular ATP decrement and tubular sodium reabsorption impairment. The model serves as a bridge between cellular toxicity and renal tubular functional impairment, allowing mechanistic prediction of AKI induced renal hemodynamics.

Funding: NIDDK Support

SA-PO103

Evaluating the Nephrotoxicity of Exemplar Compounds Using a Mechanistic Model of Drug-Induced AKI

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Background: Drug-induced nephrotoxicity is a common source of acute kidney injury (AKI) and brings clinical complexities. Drugs cause nephrotoxicity by various mechanisms, including mitochondrial dysfunction and oxidative stress. Predicting the AKI potential and toxicity mechanisms of drugs remains a challenge. We utilized a quantitative systems toxicology (QST) model to evaluate the nephrotoxicity and underlying mechanisms of two positive (cisplatin, gentamicin) and one negative (acetaminophen) control exemplar compounds.

Methods: We employed RENAsym, a QST model of drug-induced AKI that is currently under development, to evaluate the toxicity and injury mechanisms of the exemplar compounds. RENAsym represents aspects of renal proximal tubule cells (PTCs) including cell life cycle, bioenergetics, drug-induced cell death pathways, and biomarker (αGST) responses. *In vitro* data from literature were utilized to parameterize the oxidative stress production and clearance of the compounds. To determine the effects of drugs on mitochondrial dysfunction, electron transport chain (ETC) inhibition mechanism was parameterized using literature *in vitro* data.

Results: Drug nephrotoxicity was predicted by performing simulations using a virtual human model. In the simulations, a single dose of 533 mg/m^2 cisplatin resulted in 17% decline of PTC viability in 2 days. The simulations also showed a significant rise in urine aGST, a biomarker that marks PTC death. Similarly, a single dose of 3 mg/kg gentamicin showed 40% cell viability decline and high αGST elevations in 1 day. In contrast, no cell viability loss or aGST elevations were observed after multiple doses of 1 g QID (a maximum recommended dose for human) acetaminophen for over a week. In terms of injury mechanisms, simulations showed oxidative stress as the dominant mechanism for both cisplatin and gentamicin-induced toxicities.

Conclusions: Simulations predicted toxicity for two positive control compounds and no toxic response to the negative control compound, in qualitative agreement with the expected behaviors. RENAsym shows promise in providing a unique tool for drug-induced AKI prediction.

Funding: NIDDK Support

SA-PO104

Intravital Imaging of Single Collecting Ducts Micro-Perfused with Uropathogenic Escherichia coli Demonstrates Phagocytosis by Intercalated Cells

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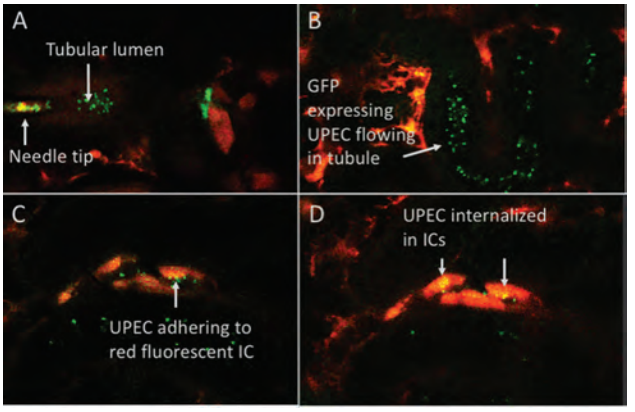
Background: Renal epithelial cells have a different lineage and historically were considered to have different functions than myeloid derived macrophages. However some epithelial cells, such as renal intercalated cells have been recently demonstrated to have distinct immune functions.

Methods: VATPaseB1-cre transgenic mice were crossed to tdTomato-loxp homozygous mice which results in red fluorescence of intercalated cells. Under isoflurane anesthesia a kidney was surgically exposed and a single collecting duct was cannulated with a 5 micron needle. The tubule was perfused with green fluorescent protein (GFP) expressing uropathogenic E.coli (UPEC) strain CFT 073 or E.coli coated bioparticles and imaged with Leica TCS SP8 (upright high-speed multiphoton and confocal imaging system).

Results: Single collecting ducts could be cannulated (Figure 1A). Micro-perfusion with UPEC could be confirmed by visualization GFP expressing bacteria flowing through a tubular structure (Figure 1B). Bacteria were internalized selectively in red fluorescent expressing intercalated cells (Figure 1C-D). Ecoli coated bioparticles were also selectively internalized by intercalated indicating an intercalated cell activated process not just bacterial invasion.

Conclusions: We demonstrate that micro-perfusion of single collecting ducts can be accomplished in vivo and imaged using intravital microscopy. Renal intercalated cells phagocytize bacteria similar to myeloid immune cells such as macrophages even though intercalated cells are renal epithelial cells.

Funding: NIDDK Support



SA-PO105

In Vitro and Ex Vivo Exploration of the Expression of MicroRNAs to Assess the Progression of AKI

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Background: MicroRNAs are endogenous short, non-protein coding RNAs that post-transcriptionally/translationally control protein expression by binding to target mRNA. There is increasing interest in miRNAs in disease research because of their ability to coordinate the regulation of protein expression by influencing multiple signalling pathways. Some miRNAs have previously been shown to be responsive to AKI, suggesting they may be mediators of the damage and repair processes and potential markers. To build on this work, we have sought to determine miRNA expression in AKI using a combination of *in vitro* and *ex vivo* models.

Methods: We first sought to categorise the urinary expression of selected miRNAs to determine their biological importance in AKI. Recognising the challenges of recovering low abundance transcripts in urine, we sought to firstly validate our experimental approach. We found that RNA recovery was similar in urine before centrifugation and after centrifugation. We further compared the RNA recovery rates between normal sample and exosome enriched samples, demonstrating that whilst exosome enrichment did not increase the overall yield of miRNAs, it did result in improved amplification profiles. Having demonstrated experimental validity, miRNA was assessed in urine samples obtained from patients with KDIGO Stage 2 and 3 and samples from non-AKI donors. Expression of miR-30a-e, miR-192, miR-101-3p was reduced in KDIGO 3 and KDIGO 2 compared to healthy control samples.

Results: Having shown that these miRNAs are differentially regulated in AKI *ex vivo*, we next sought to categorise *in vitro*. For these investigations, HK2 tubule epithelial cells were cultured with 10 µg/ml, 1 mg/ml and 0.1 mg/ml of LPS for 2, 4, 6, 12 and 24 hours. Following stimulation, RNA was extracted, cDNA prepared, and RT-PCR conducted to determine the expression of miR-30c, miR-101-3p and miR-192.

Conclusions: These investigations demonstrated LPS dysregulation of these target miRNAs in a time and concentration dependent manner. These data suggest these mediators respond to tubule injury and thus may be useful as early markers of AKI, as well as contributing to the changes in transcription which underpin the initiation, progression and outcome of AKI. Further investigations will focus on delineating the functional importance of MiRNAs as molecular drivers of AKI.

SA-PO106

Administration of miR-486-5p Protects Against Kidney Ischemic Injury and Alters the Transcriptome in Male and Female Mice

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Background: Ischemia-reperfusion is a common cause of acute kidney injury (AKI), and no treatments exist to restore function. We showed that cord blood endothelial colony forming cells (ECFCs) release exosomes (enriched in miR-486-5p) that are protective against ischemic AKI in male mice. This response involves inhibition of *phosphatase and tensin homolog* (PTEN, a target of miR-486-5p) and Akt activation. Here, we studied effects of direct administration of miR-486-5p to mice with AKI, and defined sex differences.

Methods: Kidney injury was induced in mice by 30-minute bilateral renal vascular clamping followed by reperfusion and sacrifice at 24 or 48 hrs. ECFC exosomes, miR-486-5p mimic (in cationic lipid), or scrambled miR were injected i.v. at the start of reperfusion. Kidney endothelial cells and proximal tubules were isolated for transcriptomic analyses.

Results: Male and female mice treated with miR-486-5p mimic at the time of reperfusion had increased miR-486-5p levels in kidney endothelial cells and proximal tubules, liver and spleen ($P<0.01$, n=8), but not in lung, heart or brain. In male or female mice with kidney ischemia-reperfusion, miR-486-5p mimic or exosomes significantly

decreased serum Cr and urea, histologic injury, apoptosis, and neutrophil infiltration (n=8). Delivery of miR-486-5p reduced kidney PTEN protein expression, and increased Akt phosphorylation (P<0.05, n=6). Female mice were resistant to kidney injury compared to males, by all parameters (P<0.05 vs male), showed fewer differentially expressed genes compared to males, and had less gene variation with treatments. Kidney ischemia induced higher numbers of differentially expressed genes in tubules compared to endothelial cells. In male mice treated with miR-486-5p mimic, the expression of most tubular genes that were significantly changed with ischemia-reperfusion alone returned to levels close to sham.

Conclusions: Systemic delivery of miR-486-5p to male and female mice with AKI increases miR-486-5p levels in kidney endothelial cells and proximal tubules, and prevents ischemic injury. Female mice are resistant to AKI compared to males, and exhibit fewer differentially expressed genes. Changes in the kidney transcriptome with miR-486-5p may define pathways relevant to prevention of AKI in humans.

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

SA-PO107

Association of Altered Urinary miR-141 and miR-192 Expression with AKI Outcome

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Background: Acute Kidney Injury (AKI) is characterised by a sudden decline in kidney function and affects over 20% of US hospitalisations, resulting in a greater than 4-fold increased mortality. The mechanisms underlying AKI recovery versus non-recovery remain poorly understood, and current biomarkers have limited capacity to predict outcome. These factors limit the development of new therapies. Here we evaluated the potential of urinary microRNAs (miRNAs) as biomarkers in patients with severe AKI.

Methods: Daily consecutive urine samples were collected from 30 patients with AKI stage III by KDIGO criteria. 377 miRNAs were profiled by RT-qPCR screening in pooled samples from recovery (n = 6) and non-recovery (n = 5) groups, with validation using individual assays. MiRNAs exhibiting altered expression in the urine of patients subsequently recovering vs. not recovering renal function were evaluated in *in vivo* (ischemia reperfusion injury (IRI) in the rat) and *in vitro* (proximal tubular epithelial cells (PTCs) exposed to hypoxia or oxidative stress) models by RNA sequencing and RT-qPCR. To identify miRNA targets, selected miRNAs were manipulated using transfection-based gain- and loss-of-function approaches *in vitro*.

Results: An extensive pattern of miRNA changes was observed, notably decreased miR-192 and increased miR-141 expression that predicted non-recovery. Alterations in miRNA expression were validated and linked to changes in our rat IRI model and in PTC miRNA expression *in vitro*. Network analysis of predicted miRNA targets converged on protein tyrosine phosphatase type G (PTPRG) and dysregulated PTPRG expression was confirmed.

Conclusions: These data identify quantifiable urinary miRNAs that predict outcome following AKI, and link these miRNAs to potential mechanisms of injury and recovery following AKI.

SA-PO108

miR-214 Promotes Mitochondrial Fragmentation and Cellular Apoptosis by Targeting MFN2 in ATP-Depleted Renal Proximal Tubular Cells

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Background: Mitochondria injury is a pathological factor for AKI by promoting cell apoptosis. microRNAs have been reported to play important regulatory roles in AKI. However, microRNA associated with mitochondrial injuries are poorly understood.

Methods: Azide-induced ATP-depletion model to study AKI in renal proximal tubular cells (RPTCs) in vitro. The mRNA expressions of miR-214 were detected by RT-qPCR. The protein levels of MFN2,β-actin and cleaved-caspase3 were determined by western blot, then analysis by image J. The mitochondria morphology was detected by confocal microscope.

Results: We found that miR-214 level was upregulated after azide treatment and reperfusion in RPTCs, while MFN2 protein level was reduced. Overexpression of miR-214 by transfection decreased MFN2 protein level. The inhibition of miR-214 by anti-miR-214 LNA reduced the decrease in MFN2 and induced by ATP depletion, and the percentage of RPTCs with fragmented mitochondria were decreased as well. The number of apoptotic cells and the increase in cleaved-caspase 3 expression induced by azide treatment in RPTCs were reduced by anti-miR-214 LNA transfection. On the contrary, overexpression of miR-214 increased apoptosis and cleaved-caspase 3 expression in ATP-depleted RPTCs.

Conclusions: These results suggest that miR-214 upregulation promotes mitochondrial fragmentation and cellular apoptosis by downregulating MFN2 expression and inhibition of miR-214 ameliorates mitochondrial fragmentation and reduces cellular apoptosis by upregulating MFN expression in ATP-depleted RPTCs. Targeting miR-214 could show potentially therapeutic effect in AKI.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO109

Endothelial-Derived miR-17~92 Protects Against Renal Ischemia-Reperfusion Injury

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Background: Acute kidney injury (AKI), resulting from renal ischemia reperfusion injury (IRI) among others, is an independent predictor of morbidity and mortality, and is identified in as many as 50% of ICU patients. Damage to the renal microvasculature is a hallmark of renal IRI. *miR-17~92* encodes 6 polycistronic microRNAs that show potent pro-angiogenic capacity by targeting anti-angiogenic factors. The function of miR-17~92 in renal microvasculature after renal IRI remains unknown. We hypothesized that endothelial-specific *miR-17~92* mediates endothelial repair and kidney recovery after renal IRI.

Methods: Endothelial-specific *miR-17~92* knockout (*miR-17~92$^{endo-/-}$*) transgenic mice were generated and a renal IRI model was performed. Mice were monitored for the development of AKI using serum chemistries, histology, and markers of renal tubular injury. The renal vasculature and infiltrating macrophages post-injury were evaluated using multiple markers.

Results: We demonstrate that miR-17, *miR-18a, miR-19b* and *miR-20a* in the *miR-17~92* cluster are up-regulated in CD31+ renal endothelial cells following renal IRI. Loss of *miR-17~92* in endothelial cells does not affect renal vascular development and renal function in adult mice. Following renal IRI, *miR-17~92$^{endo-/-}$* mice had worse renal dysfunction and epithelial damage, and exhibited up-regulation of the injury marker NGAL in proximal tubules compared to the controls. *miR-17~92$^{endo-/-}$* kidneys had decreased Endomucin-positive renal microvasculature post renal IRI. *miR-17~92$^{endo-/-}$* kidneys upregulated the potent anti-angiogenic factor Thrombospondin-1 (TSP1) in a subset of Endomucin-positive renal microvasculature. *miR-17~92$^{endo-/-}$* kidneys also had increased F4/80-positive infiltrating macrophages post renal IRI along with up-regulation of multiple macrophage markers in its kidneys.

Conclusions: These data suggest that *miR-17~92* in renal endothelial cells confers protection from damage in the renal microvasculature during renal IR mediated AKI by targeting an anti-angiogenic factor TSP1. This, in turn, mitigates hypoxic damage in tubular epithelial cells and down-regulates inflammatory activation following injury.

Funding: NIDDK Support, Private Foundation Support

SA-PO110

Proteomics Reveals the Principle of Transition from AKI to CKD

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Background: Chronic kidney disease (CKD) compromises renal function and occurs as a potential long-term outcome in response to acute kidney injury (AKI). Currently, lack of mechanistic understanding prevents the progression from AKI to CKD. As we enter the 'big data' era, multiple OMICS analyses provide a platform not only assist the field to further understand kidney disease transition, but also significantly enhance the possibility to translate novel findings from basic research into the clinic. The present study aims to systemically analyze the proteomes profiles from the onset of kidney injury to end stage renal disease and identify dynamic network biomarkers during disease progression.

Methods: We constructed renal ischemia reperfusion injury (IRI) mouse model for time series courses. Quantitative proteomics (isobaric peptide tags for relative and absolute quantification, iTRAQ) was applied in revealing the proteomes profiles in kidney tissues. Dynamic network biomarker (DNB) analysis was performed to clearly identify the critical state or tipping point during the transition of kidney disease.

Results: We identified 6146 proteins in the disease kidneys. Pearson correlation analysis indicated that the transitional process from AKI to CKD could be divided into 4 periods in mice, initiate phase (0-12h), switching phase (1d), repair phase (3-5d), and irreversible phase (after 5d). Impressively, protein signatures were completely different in the above 4 phases. Among these phases, two time points (4h and 3d) were critical in determining the prognosis of kidney disease. We then analyzed time-series protein expression data with the DNB method, and identified NCBP1 as a core DNB member. At a network level, the biological role of NCBP1 was prominent in kidney repair and regeneration.

Conclusions: Establishing disease monitoring system at appropriate time points will be greatly beneficial in understanding the pathogenesis of kidney disease transition.

Funding: NIDDK Support

SA-PO111

Proteomic Analysis of the Tubulointerstitium Characterizes Extracellular Matrix Changes in Acute Tubular Necrosis

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Background: Acute tubular necrosis (ATN) is the most common form of acute kidney injury (AKI) in the hospital setting. Urine proteomic analyses have been extensively performed in AKI, but the kidney proteome has largely been unexplored. Here, we performed unbiased proteomics on the tubuloniterstitium (TI) from kidney biopsies with ATN to identify kidney specific proteomic signatures that characterize ATN.

Methods: Laser microdissection was performed on FFPE kidney biopsy tissue from 8 ATN and 8 living transplant donor kidney biopsy controls (LTx). The TI was isolated and total protein was extracted and submitted for HPLC-MS/MS analysis using the Oribtrap Elite. Label free quantification followed by global normalization of spectral count data was performed. Proteomic expression of ATN was compared to LTx. Statistical significance was considered if 2-fold change and P<0.01.

Results: All patients had biopsy proven ATN. The average serum creatinine in ATN was 5.7mg/dl (SD: ± 2.7). Overall, 86 proteins were upregulated and 44 downregulated in ATN compared to LTx. The top upregulated markers included extracellular matrix (ECM) proteins implicated in AKI to CKD transition, ER stress proteins, and wound repair proteins (Figure 1). Meanwhile, transport, metabolism, and mitochondrial markers were suppressed. Pathway analysis revealed activation of remodeling of epithelial adheren junctions, acute phase response signaling, and coagulation and suppression of metabolic pathways.

Conclusions: Kidney proteomic evaluation demonstrates overexpression of ECM proteins in ATN that previously have been implicated in CKD progression and may reflect AKI to CKD transition. These markers could serve as novel therapeutic targets to arrest injury early and prevent progression to chronic kidney disease.

Funding: NIDDK Support

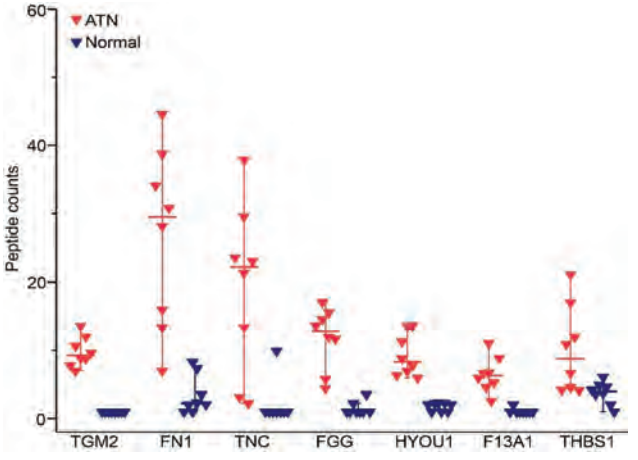

Figure 1. Markers overexpressed in ATN compared to controls

SA-PO112

Long-Term Outcomes in Mouse Models of Ischemia-Reperfusion-Induced AKI

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Background: AKI is a risk factor for CKD, but no therapies have improved outcomes. Therapies that are effective in models that mimic features in patients, and evaluate long-term outcomes, are more likely to be predictive of success in the clinic. Here, we evaluated susceptibility to CKD after unilateral ischemia reperfusion injury (uIRI) with a delayed contralateral nephrectomy (DN-IRI) in mice. We define the conditions to induce renal dysfunction and fibrosis without increased mortality, and evaluate effect of mouse strains, sexes, and pre-existing diabetes.

Methods: Studies were performed in different strains and sexes of mice, and in mice with streptozotocin (STZ)-induced diabetes mellitus (DM). DN-IRI with different renal pedicle clamp times was performed along with contralateral nephrectomy (Nx) 8 days after injury to identify conditions associated with reduced GFR 4 weeks after injury. After optimizing IRI clamp time, we evaluated renal function with serial BUN, creatinine and transdermal GFR. Renal fibrosis: QRT-PCR for fibrosis markers, picro-sirius red (PSR) quantification. Peritubular capillary density (PTCD) by quantifying CD31 immunostaining. Results expressed as means (SD).

Results: Male and female BALB/c mice had >90% survival after uIRI clamp times of 30 and 40 minutes, respectively. C57BL/6 mice from Charles River and Jackson labs had >90% survival with 28 and 21 mins uIRI, respectively, and male DBA2j mice with DM had >90% survival after 22 mins uIRI. These were all associated with reduced GFR and increased renal PSR staining 4 weeks after IRI. Long term studies in male BALB/c mice showed reduced GFR 6 weeks after ND IRI 229.1 (50.1) vs. 296.7 (44.1) microL/min in Nx only mice (p<0.05), but GFR recovered by 12 weeks. This was associated with increased PSR staining at 12 weeks, but PTCD, which was reduced at 4 weeks after IRI 0.67 (0.12) vs. 1 (0.21) FC (p<0.01), was the same as Nx control by 12 weeks.

Conclusions: These data define renal pedicle clamp times for the DN-IRI model in different mouse strains, sexes, and in the presence of DM. Long-term studies showed renal functional recovery at 12 weeks, and showed that peritubular capillary rarefaction is more closely associated with changes in GFR than fibrosis. This provides insight into the role of capillary rarefaction as the driver of AKI to CKD progression.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO113

Super-Resolution Ultrasound to Monitor Microvascular Rarefaction After AKI in Mice

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Background: Acute kidney injury is associated with an increased incidence of chronic kidney disease. One mechanism to explain this is the loss of vascular density in the kidney post-AKI, leading to chronic hypoxia. Current techniques to evaluate the vasculature are limited by a lack of resolution, technique causing harm to the subject, or inability to perform in live subjects. Super-resolution ultrasound (SRU) is an emerging technology to achieve high spatial resolution to identify microvessels in live animals.

Methods: C57BL/6 mice were subjected to unilateral ischemia-reperfusion injury (IRI) survival surgery. At 21 and 42 days after injury, mice were injected with clinical ultrasound contrast agent (Definity) and both the injured and contralateral control kidneys were evaluated *in vivo* under anesthesia. Using B-mode imaging the kidneys were imaged in the maximal longitudinal plane. Imaging data of 1000 effective frames were acquired using multi-angle ultrasound plane wave imaging at an effective frame rate of 250 Hz. Off-line signal processing was performed in MATLAB with radio-frequency data processed through beamforming, motion compensation, singular value decomposition filter, Richardson-Lucy deconvolution, and frame summation. After imaging, mice were euthanized, kidneys were recovered and subjected to immunohistochemistry to identify CD31 positive blood vessels. Fibrosis was assessed with trichrome and picrosirius red stains. Collagen and vascular endothelial growth factor (VEGF) levels were also assessed.

Results: SRU was capable of the accurate identification of microvessels with a resolution of 32 microns. Using SRU, a clear reduction in vascular density was identified in the IRI kidneys compared to control. SRU measurements correlated favorably with traditional CD31 immunohistochemical staining (R^2=0.8). This was accompanied by a reduction in renal blood volume and kidney size. As expected, there was an increase in renal fibrosis that appeared to peak at 21 days. VEGF levels were also decreased after IRI.

Conclusions: SRU was capable of identifying the decrease in microvascular density after IRI in mice at late timepoints after injury. This correlated favorably with traditional immunohistochemistry and could be a method to monitor the progression of kidney disease after AKI.

Funding: NIDDK Support, Private Foundation Support

SA-PO114

Capillary Rarefaction Is Associated with CKD Progression in Cisplatin and Rhabdomyolysis AKI

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Background: Incomplete recovery of renal function after AKI results in progressive CKD, but no therapies improve long-term outcomes in patients with AKI. For this reason there has been interest in pre-clinical models of AKI to CKD transition that mimic the pathophysiology of human AKI. One end point for pre-clinical interventions is renal fibrosis. However, reduced peritubular capillary density (PTCD) is also associated with CKD after ischemia-reperfusion AKI, and it is unknown whether PTCD is an independent predictor of CKD in models of AKI. Many studies have evaluated therapy in short term studies after cisplatin (CP), and glycerol-induced rhabdomyolysis (Rhabdo-AKI), but there are limited published data on long-term outcomes. In these studies we evaluated long-term renal outcomes, renal fibrosis and PTCD in mouse models repeat dose CP (RDCP) and Rhabdo-AKI.

Methods: RDCP was induced in male FVB/N mice with 7mg/kg CP weekly for four weeks, tissues harvested at 28 days. Rhabdo-AKI was induced by injecting 5.8ml/kg 50% glycerol IM in male BALB/c mice, tissues harvested at 36 and 66 days. Renal function: serial BUN, serum creatinine and transdermal GFR. Renal fibrosis: QRT-PCR for fibrosis markers, picro-sirius red (PSR) quantification. PTCD by quantifying CD31 immunostaining.

Results: There was a progressive decline in renal function with reduced GFR 110.69 (65.3) vs. 330.6 (36.8) microL/min (p<0.0001, T-test) and increased creatinine 28 days after RDCP-AKI. This was associated with increased expression of renal fibrosis markers, *LoxL2*, *Col1a1* and *Col1a3* mRNAs, but not PSR staining. In contrast, while mice treated with IM glycerol developed severe AKI, with peak BUN 161.6 (15.8) mg/dl at day 1, there was complete recovery of GFR at 36 and 66 days. This was associated with increased PSR staining, but unlike RDCP mice in which there was a reduction PTCD, PTCD was not reduced after Rhabdo-AKI.

Conclusions: These data demonstrate a dissociation between renal fibrosis and changes in GFR over time in different models of AKI to CKD transition, and that peritubular capillary rarefaction is more closely associated with changes in GFR than fibrosis. This provides insight into the potential role of capillary rarefaction as being the principal driver and candidate cellular target to prevent AKI to CKD progression, rather than renal fibrosis.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO115

Transplanted Senescent Renal Tubular-Like Cells Induce Renal Microvascular Injury

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Background: Cellular senescence is characterized by a senescence-associated secretory phenotype (SASP), which reinforces senescence and exerts noxious effects on adjacent cells. Recent studies suggest that transplanting small numbers of senescent cells suffices to provoke tissue inflammation. Several models of kidney disease show increased prevalence of senescent renal cells. We hypothesized that senescent cells can directly augment renal injury.

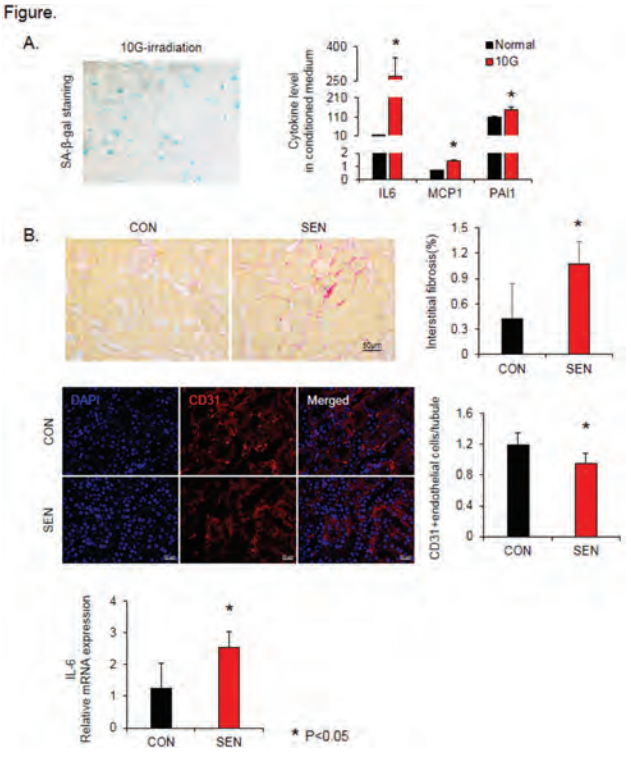
Methods: Cellular senescence was induced in primary tubular-like cells acquired from pig kidneys by 10Gy of cesium radiation, and 3 weeks later cells were characterized for senescence and SASP markers. Control (CON) or senescent (SEN) renal tubular-like cells were pre-labeled and injected intra-aorta to C57BL/6J mice. Four weeks later, renal oxygenation was studied using magnetic resonance imaging, and function by plasma creatinine level. Renal markers of SASP, fibrosis, and microvascular density were evaluated.

Results: Per flow cytometry, 80-99% renal tubular-like cells were senescent after irradiation. They showed increased mRNA of senescence and SASP markers, SA-ß-gal staining, and cytokines levels secreted in conditioned-medium. Four weeks after injection, cells were detected engrafted in the kidneys with no evidence for rejection. Plasma creatinine and renal tissue hypoxia tended to increase in SEN compared to CON. SEN kidneys were more fibrotic, with fewer CD31+ endothelial cells, and showed upregulation of IL-6 gene expression.

Conclusions: Senescent renal tubular-like cells directly induce renal inflammation, fibrosis, microvascular loss, and hypoxia. These observations suggest a role for cellular senescence in the pathogenesis of kidney injury, and support development of senolytic therapy.

Funding: NIDDK Support

Figure.



SA-PO116

IKKα Aggravates Renal Fibrosis by Positively Regulating the Wnt/β-Catenin Pathway

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Background: Acute kidney injury (AKI) with maladaptive repair is a major contribution to renal fibrosis characterized by tubulointerstitial fibrosis. Previously, we have revealed that IKKα was involved in inhibiting inflammation and kidney regeneration.

Methods: By mating IKKα-floxed mice with Kap-Cre transgenic mice, mice with IKKα gene specifically ablated in renal tubular cells were created. After dorsal incision, the left renal pedicle was clamped with a micro vascular clamp for 45 min, while the sham-operated mice underwent the same treatment except clamping renal pedicle. We added TGF-β1 to the culture medium to establish the cell fibrosis model in human tubular epithelial cells.

Results: The expression of IKKα was up-regulated in kidney tubular epithelium in mice models of unilateral ureteral obstruction and ischemic reperfusion injury. In addition, immunohistochemical staining showed IKKα renal expression positively correlated with the kidney fibrosis in chronic kidney diseases (CKD) patients. Futhermore, we generated a knockout mouse model with IKKα gene specifically deleted in renal tubules. These knockout mice were phenotypically normal at birth and had no significant defects in kidney morphology and function. Compared with controls, Kap-IKKα$^{-/-}$ mice decreased Wnt/β-catenin activation, serum creatinine and attenuated interstitial fibrosis at 14 days after ischemic reperfusion injury. In vitro, IKKα blocked the interaction of GSK-3β with β-catenin in TGF-β1-stimulated human tubular epithelial cells resulting in β-catenin nuclear translocation. Additionally, blocking IKKα by siRNA specifically suppressed β-catenin activation and profibrotic gene expression such as fibronectin and α-smooth muscle actin.

Conclusions: IKKα aggravates renal fibrogenesis by amplifying regulation of the Wnt/β-catenin signaling pathway which may provide a potential anti-fibrosis therapy target for chronic kidney diseases.

SA-PO117

β-Catenin/Foxo Promotes Epithelial Healing in Kidney Injury

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Background: Transforming growth factor (TGF-β) is known to promote healing after tissue injury, but also drives a maladaptive fibrotic response that leads to fibrosis and organ failure. β-catenin/TCF is central to TGF-β's profibrotic signaling pathways. β-catenin also binds to Foxo in competition with TCF and promote cell survival under oxidative stress. We propose that targeting TGF-β signaling by using an inhibitor of β-catenin/TCF will promote β-catenin/Foxo which results in physiological healing with epithelial rather than mesenchymal cells.

Methods: Scratch assay was used as an in vitro model of healing in murine proximal tubule-like epithelial C1.1 cells treated with TGF-β1 (3ng/ml) with or without β-catenin/TCF inhibitor ICG-001 (5μM). CRISPR/Cas9 was used to knockout Foxo1. Wound closure was measured as the percentage area of wound closure at 48 h (%). In vivo kidney injury healing was evaluated in murine unilateral ischemia reperfusion injury (UIR) by Gomori trichrome staining. Epithelial (E-cadherin) or mesenchymal (α-SMA) healing was examined by immunofluorescence staining and measured as percentage area of positive staining (%). β-catenin/Foxo or β-catenin/TCF interactions were examined by proximity ligation assay (PLA).

Results: The combined treatment of TGF-β1 and ICG-001 in C1.1 cells and UIR caused increased β-catenin/Foxo interaction as demonstrated by PLA. The combined treatment inhibited TGF-β-induced α-SMA expression and showed dominant E-cadherin expression to a greater extent than seen with TGF-β alone; α-SMA, 5±1% vs 40±3%, P<0.01 in vitro, and 18±1% vs 42±3%, P<0.01 in vivo; E-cadherin, 29±4% vs 2±3%, P<0.05 in vitro, and 22±5% vs 11±2%, P<0.05 in vivo. Foxo1 KO in C1.1 cells showed significant reduction in closure of the wound gap compared to WT cells (75±3% vs 95±3%; P<0.05). Foxo1 KO C1.1 cells slowed wound closure under combined treatment compared to that of WT cells (70±3% vs 98±2%, P<0.01) which could be explained by absence of β-catenin/Foxo in Foxo1 KO C1.1 cells. In UIR mice, combined treatment with rhTGF-β and ICG-001 significantly attenuated kidney fibrosis compared with TGF-β alone (42±5% vs 73±5%, P<0.01).

Conclusions: These results indicate that β-catenin/Foxo may serve as a therapeutic target to prevent pathological fibrotic healing and fibrosis in the treatment of kidney diseases.

SA-PO118

Endothelial Nitric Oxide Synthase/Nitric Oxide Pathway Underlies the Mechanisms of AKI to CKD Transition via Prolonged Activation of the Wnt/β-Catenin Pathway

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Background: Acute kidney injury (AKI) is not always reversible, but often promotes to chronic kidney disease (CKD), known as "AKI to CKD transition." Aging and disease conditions such as hypertension and diabetes are recognized as risk factors for AKI to CKD transition. These conditions are also closely associated with endothelial dysfunction (ED). Therefore, we hypothesized that AKI to CKD transition is promoted by ED characterized by deterioration in eNOS/Nitric Oxide (NO) /sGC/PKG pathway.

Methods: Wild-type mice (C57B6/J: WT) and eNOS deficient mice (eNOSKO) were used. WT and eNOSKO mice were divided into 4 groups: WT-sham, WT-IRI, eNOSKO-sham and eNOSKO-IRI. Mice were sacrificed on day 28 (D28) after ischemic reperfusion injury(IRI) (WT-IRI-D28 and eNOSKO-IRI-D28). To evaluate the therapeutic potential of sGC activation on the AKI to CKD transition, eNOSKO-IRI mice treated with PDE5 inhibitor (PDE5i, Sildenafil citrate, 5mg/kg/day, drinking water) from day 7 (D7) to day28 (D28) after IRI.

Results: Acute kidney damages of IRI were fully recovered in WT-IRI-D28 group. However, tubulointerstitial injuries, tubular cell damage, interstitial fibrosis and infiltration of inflammatory cells remained in eNOSKO-IRI-D28 group. These results indicate that deficient eNOS/NO/sGC/PKG signaling pathway promotes AKI to CKD transition after IRI. Next, the kidney damages in the early phase, day 1 and day 7, after IRI were examined in both groups. Histological examinations of kidney tissues failed to detect alterations in both groups at day 1 and day 7. However, RNA-seq analysis revealed significant increased expressions of Wnt/βcatenin-related genes and M2 macrophage (MΦ) related genes in eNOSKO-IRI-D7 group compared with WT-IRI-D7 group. In addition infiltration of M2 MΦ, evaluated by flow cytometric analysis, were increased in eNOSKO-IRI-D7 but not WT-IRI-D7. Furthermore, PDE5i treatment significantly ameliorated the kidney injuries compared with non-treated group.

Conclusions: Endothelial dysfunction, characterized by deterioration of eNOS/NO/sGC/PKG signaling pathway underlies prolonged activation of Wnt/βcatenin pathway and infiltration of M2 MΦ, thereby plays a pivotal role in AKI to CKD transition.

SA-PO119

Cyclin G1-Mediated Dedifferentiation of Proximal Tubular Cells Drives Fibrosis

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Background: Over 13% of the world's population have chronic kidney disease (CKD). Severe acute kidney injury can lead to chronic kidney disease (CKD) through maladaptive repair of proximal tubular cells (PTC) and cycle arrest in the G2/M transition. Recently, we identified an atypical cyclin, cyclin G1 (CG1), as a key mediator of G2/M arrest, maladaptive repair and fibrosis; however, the underlying mechanism how CG1 regulates G2/M arrest and fibrosis remains to be resolved. The aim of the current study is to ascertain whether CG1-induced dedifferentiation drives PTC profibrotic signaling and kidney fibrosis.

Methods: Protocol 1; 8-week-old male BL57Bl/6 (WT) and CG1 knockout mice (CG1KO) received unilateral ureteral obstruction (UUO). Kidneys were taken at day 9 and fibrosis was assessed by picrosirius red staining and polarized microscopy. PTC dedifferentiation was defined by upregulated kidney injury molecule1 (KIM-1) and staining and PCR for differentiation/dedifferentiation marker expression. Protocol 2; Primary PTCs isolated from WT and CG1KO mice were treated with aristolochic acid (AA) and gene expression was analyzed by PCR and western blot.

Results: In response to UUO, kidney fibrosis was dramatically reduced in CG1KO compared with WT. Upregulation of KIM-1 in WT-UUO was ameliorated in CG1KO and markers of differentiation were preserved at both protein and mRNA levels in CG1KO. Compatible with our animal data, connective tissue growth factor (CTGF) and fibronectin were upregulated by AA treatment in WT PTC and attenuated in CG1KO PTC. Further, AA-induced cell enlargement was restored by deletion of CG1. Na-K-ATPase and AQP1 mRNA were also maintained in CG1KO PTC. Importantly, inhibition of dedifferentiation reduced levels of G2/M arrested cells, marked by phosphorylated Histone 3 (pH3), in CG1KO-UUO kidneys compared to WT-UUO.

Conclusions: Cyclin G1 drives a maladaptive dedifferentiation of proximal tubular cells after kidney injury, resulting in increased secretion of profibrotic cytokines and progression of fibrosis. Cyclin G1-induced dedifferentiation facilitates G2/M arrest and subsequent maladaptive responses. As cyclin G1 is only expressed in chronically injured cells, it represents a potential therapeutic target for prevention of kidney fibrosis.

SA-PO120

The Role of Glycolysis in Progression of Renal Fibrosis

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Background: Fatty acid oxidation is reduced in renal fibrosis and drugs that increase it improve fibrosis. The role of glycolysis, however, is unclear. We mutated a key controller of glycolysis in mice to determine its effect on renal fibrosis.

Methods: 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB) is a key regulator of glycolysis. Mice with inactivating S466A and S483A mutations of the phosphorylation sites in PFKFB2 (PFKFB2 KI mice) were generated. The mutations are predicted to reduce the ability to increase the rate of glycolysis following stimulation. The unilateral ureteric obstruction (UUO) and folic acid nephropathy (FAN) models were used.

Results: In both UUO ($p<0.01$) and FAN ($p<0.05$) models, there was reduced expression of PFKFB2 in WT mice compared with controls. PFKFB2 KI mice showed no obvious phenotype and had normal plasma glucose. Serum creatinine and urea were similar to wild type (WT). Western blots confirmed unchanged levels of PFKFB2 expression in kidneys from PFKFB2 KI mice. In the UUO model, there were significant increases in renal fibrosis in PFKFB2 KI mice when assessed by picrosirius red staining ($p<0.001$), RT-PCR and Western blots for a-SMA ($p<0.05$) and fibronectin ($p<0.05$) compared to WT. Glycogen increased similarly in both KI and WT mice following UUO but lipid accumulation, measured by oil red O ($p<0.005$), was greater in PFKFB2 KI mice. In contrast, similar studies with the FAN model showed no significant increase in fibrosis, greater glycogen content in the PFKFB2 KI mice compared to WT ($p<0.05$) and no difference in lipid accumulation.

Conclusions: These data show that inhibition of the regulation of glycolysis by PFKFB2 increases fibrosis in the UUO but not the FAN model. Increased fibrosis in the UUO model may reflect a greater effect on distal tubules compared with the FAN model, with the well-known reliance of distal tubules on glycolysis leading to energy shortage and fibrosis.

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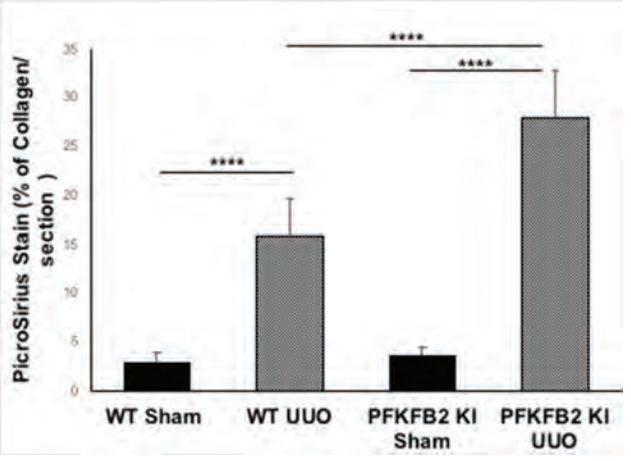

SA-PO121

Pyruvate Kinase M2 Mediates Fibroblasts Activation Alleviates AKI

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Background: Acute kidney injury (AKI) is a devastating condition with high morbidity and mortality. The pathologic features of AKI are characterized by tubular injury, infiltration of inflammation cells and vascular integrity impairment. Pyruvate kinase is the last rate-limiting enzyme in the glycolysis pathway, We have previously shown that Pyruvate kinase M2 (PKM2) plays an important role in regulating the glycolytic recombination of fibroblasts in chronic kidney disease. But the role of PKM2 in fibroblasts in the pathogenesis of AKI is unknown.

Methods: Lentivirus was used to down-regulate PKM2 expression in NRK-49F cells, and then analyzed the expression of the key enzymes of glycolysis and the ability of cell proliferation. *In vivo*, we generated fibroblast specific PKM2 knockout mice (Fibroblast-PKM2-/- mice) by crossbreeding PKM2-flox mice with S00A4-Cre mice. Then we compared renal function, expression of urinary KIM-1 and NGAL, pathological damage and renal tubular cell apoptosis between Fibroblast-PKM2-/- mice and control mice after ischemia-reperfusion injury(I/R) or folic acid (FA) injection. Reno-protective factors secreted by fibroblasts such as HGF and EPO were determined by RT-PCR and Elisa. Co-culture of NRK-52E cells and NRK-49F cells under oxygen deprivation condition was used to investigate the interaction between fibroblasts and renal tubular cells.

Results: Down-regulation of PKM2 can reduce glycolysis level and decrease the ability of proliferation of NRK-49F cells. Compared with control mice, Fibroblast-PKM2-/- mice had less fibroblast activation, more kidney injury indicated by increased BUN, KIM-1 and NGAL levels and more apoptosis of tubular epithelial cells after AKI induced by I/R or FA injury. Furthermore, Fibroblast-PKM2-/- mice secreted lower renal protective factors such as HGF and EPO. Additionally, Fibroblast-PKM2-/- mice showed suppressed of HGF-cmet signaling and decreased expression of p-ERK and p-bad. Co-culture experiment in oxygen deprivation condition revealed that down-regulation of PKM2 in NRK-49Fcells could decrease the expression of HGF and EPO in NRK-49F cells and inhibit fibroblast activation, and increase apoptosis in NRK-52E cells.

Conclusions: Collectively, these results suggest that PKM2 mediated fibroblasts activation plays a critical role in the pathogenesis of AKI.

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SA-PO122

Altered Citrate Metabolism Leads to Maladaptive Repair After Tubular Injury and Facilitates Kidney Fibrosis in Diabetic Nephropathy

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Background: Dysregulated lipid metabolism is a primary feature of DKD. Citrate is a tricarboxylic acid cycle metabolite and a regulator of lipid metabolism via ATP-citrate lyase (ACLY) and acetyl-CoA carboxylase (ACC). Citrate accumulates in the renal

parenchyma after AKI. We hypothesized that altered citrate metabolism contributes to maladaptive tubular repair after AKI and progression of diabetic nephropathy.

Methods: We generated C57B/6 Akita^{DTR} mice expressing the simian diphtheria toxin receptor (DTR) in the renal tubule in a non-obese diabetic background. Animals on a high-fat diet (HFD) were administered one dose of DT to induce tubular injury, and the kidney tissue damage was evaluated at four months. In a cisplatin toxicity model in vitro, LLC-PK$_1$ kidney epithelial cells were exposed to high glucose or high palmitic acid concentrations, and analyzed for cell cycle arrest, DNA damage response, and alteration in citrate metabolism.

Results: DT-treated Akita^{DTR} mice on HFD developed overt proteinuria, severe tubulointerstitial fibrosis, secondary glomerular sclerosis, interstitial inflammation, capillary rarefaction, and podocyte dropout, while the control littermates without tubular injury, or without diabetes, or without HFD did not. The Akita^{DTR} mice on HFD had increased inhibitory phosphorylation of ACC (p-ACC). In cisplatin-treated cells in high glucose, G2/M arrest was associated with increased citrate concentration, and compensatory decreased p-ACC and increased ACLY. Co-treatment with palmitic acid and cisplatin increased p-ACC and enhanced DNA damage and G2/M arrest. When compared with cisplatin treatment alone, co-treatment with a small molecule inhibitor of ACC and cisplatin also increased DNA damage, G2/M arrest, and the conditioned media from the kidney epithelial cells enhanced a-SMA production by 10T$^{1/2}$ pericyte-like cells.

Conclusions: Citrate-derived acetyl-CoA facilitates tubular repair. Inhibitory phosphorylation of ACC by exogenous lipid or pharmacological inhibition of ACC resulted in more DNA damage, G2/M arrest, and production of pro-fibrotic agents by renal epithelial cells after AKI.

Funding: NIDDK Support, Private Foundation Support

SA-PO123

COUP-TFII Enhances TGFβ-Induced Metabolic Reprogramming in Stromal Cells and Contributes to Kidney Fibrosis

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Background: Metabolic perturbation is implicated in the pathogenesis of kidney fibrosis, but the molecular mechanisms that couple myofibroblast metabolism and differentiation are unknown. COUP-TFII is an orphan nuclear receptor involved in metabolic regulation, but its role in the kidney has not been investigated. We hypothesized that TGFβ-induced metabolic reprogramming in stromal cells is regulated by COUP-TFII.

Methods: Unilateral ureter obstruction (UUO) surgery was used for *in vivo* modeling of kidney injury and fibrosis. *In vitro*, we used CRISPR and an inducible lentiviral construct to generate COUP-TFII loss- and gain-of-function models in C3H/10T1/2 cells. For metabolic assays, we used the Seahorse XF24 flux analyzer and JC-1 staining to estimate glycolysis and the mitochondrial membrane potential. We generated conditional COUP-TFII deficient (cKO) mice by crossing floxed alleles with an inducible Cre driver.

Results: We first examined gene expression in fibrotic kidneys and found that key glycolytic enzymes were upregulated while *PGC1α* was suppressed seven days after UUO. This expression pattern was conserved in TGFβ-treated C3H/10T1/2 cells. Accordingly, TGFβ treatment *in vitro* led to increased cellular lactate production and decreased mitochondrial membrane potential. Interestingly, we found that COUP-TFII was required for the TGFβ-induced shift toward glycolysis, and COUP-TFII KO cells exhibited an attenuated profibrotic phenotype. In contrast, overexpression of COUP-TFII was sufficient to enhance glycolysis and increase αSMA and collagen 1 levels. This pathway was further interrogated *in vivo*, where cKO mice were protected from kidney fibrosis.

Conclusions: TGFβ induces a shift in cellular metabolism from oxidative respiration to aerobic glycolysis, and this effect is dependent on COUP-TFII activation. Loss of COUP-TFII ameliorates fibrotic phenotypes both *in vitro* and *in vivo*. These findings provide new mechanistic insights into TGFβ-induced myofibroblast differentiation pathways, and targeting COUP-TFII may thus serve as a novel treatment approach for mitigating kidney fibrosis in chronic kidney disease.

Funding: NIDDK Support

SA-PO124

Cellular G2/M Arrest Induced by VPR in Kidney Promotes AKI or AKI-CKD Transition and Can Be Partially Rescued by Specific Small Molecule Inhibitors

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Background: HIV-1 encodes an accessory protein named vpr that will damage renal cells. Podocyte damage and tubular epithelial cell injury may lead to proteinuria, impaired renal function and acute kidney injury (AKI). AKI can contribute critically to chronic kidney disease (CKD). Studies show that vpr plays an important role in cell injury and leads to AKI or AKI-CKD transition. Developing the strategies for AKI-CKD transition is urgently needed. But the cellular and molecular basis of AKI-CKD transition by vpr is very complex and largely unclear.

Methods: Pax8-rtta; TRE-vpr double transgenic mice were fed with DOX to overexpress vpr in tubular cells. Similarly, podocin-rtta; TRE-vpr were generated to overexpress vpr in podocyte. DOX induction were started at the age of 4 weeks and the induction periods were 8wks, 18wks, 23wks and 28wks, respectively. To alleviate or reverse vpr related lesion,P53 inhibitor PFT- α or PLK 1 inhibitor BI 2536 was administrated by Peritoneal Injection for 4 weeks. Renal function and proteinuria were monitored. After sacrifice the mice, the renal cortex genes, proteins and histology are screened.

Results: Vpr in tubular cells led to proximal tubular cells injury, G2/M arrested cell, AKI and impaired renal function without proteinuria. Histopathological analysis indicated PTC injury and apoptosis, even interstitial fibrosis and secondary cyst formation and kidney enlargement in long-term induced mice, which indicated AKI-CKD transition. Vpr overexpression in podocyte led to massive podocyte injury, proteinuria and secondary reduced renal function. Dox withdrawal led to relative mild lesions and less AKI-CKD transition, which indicated vpr overexpression was responsible for those kidney lesions. P53 and PLK 1 activation were involved in vpr overexpression related G2/M arrest. Both inhibitors reduced P53 and PLK 1 level in vivo, and partially rescued tubular cell injury, proteinuria and renal function impairment, as well as AKI-CKD transition.

Conclusions: Our study demonstrates that vpr plays an important role in the pathogenesis of tubular epithelial cell and podocyte damage and subsequent AKI or AKI-CKD transition. P53 and PLK 1 inhibition are useful to relieve or rescue tubular cell injury, proteinuria and AKI-CKD transition in vpr induced damages.

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SA-PO125

ATG5-Mediated G2/M Arrest Through ATR-Chk1 Signaling Contributes to Renal Fibrosis After Injury Induced by Aristolochic Acid I

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Background: Recent studies have shown that autophagy is involved in the regulation of G2/M arrest and plays a renoprotective role after kidney injury. However, its role in aristolochic acid (AA)-induced AKI transition CKD remains largely unclarified.

Methods: Here, we investigated whether autophagy-related gene 5 (ATG5) modulation of Chk1 phosphate expression during AKI contributes to the progression to CKD. We tested this hypothesis by administration of aristolochic acid-I (AAI) in vitro.

Results: (1) CCK-8 showed that the viability of HK-2 cells treated with different concentrations of AAI (0, 2.5, 5, 10, 20, 40 μM) for 48 hours decrease in a concentration-dependent manner. The cell viability decreased in a time-dependent manner when HK-2 were stimulated with 5 μM AAI for different durations (0, 3, 6, 12, 24, 48 hours). (2) Western blot showed that the expression of LC3-II/I, DNA double-stranded damage marker γH2AX and FN in concentration-dependent, time-dependent increase after AAI stimulation. Phosphorylation level of Chk1(s345) and its upstream regulatory protein ATR(t1989) showed parabolic trends at 48 h after AAI stimulation. Chk1(345) and ATR(t1989) phosphorylation level increased in a time-dependent manner when AAI stimulation concentration was 5 μM. (3) Flow cytometry: After AAI treat of HK-2 cells for 48 h, the cell cycle G2/M arrest rate increased most at AA-I concentrations of 5 μM and 10 μM and the proportion of G2/M arrest was 39.12±9.1% and 40.88±10.1% respectively; the difference was statistically significant compared with 0μM (8.09±1.5%) ($p<0.05$, 0.05). While stimulation with AAI concentration of 5 μM for different times. The proportion of G2/M arrest gradually increased with time, and it was 41.57±16.6%at 48h; the difference was statistically significant compared with 0h (6.94±0.7%) ($p<0.05$). (3) ATG5 deletion led to enhanced G2/M cell-cycle arrest and increased expression of the Chk1 and of profibrotic factors (Fibronectin(FN), Connective Tissue Growth Factor (CTGF)). Autophagy activator (rapamycin) down-regulated phosphorylation level of chk1 and aggravated fibrosis (CTGF). Treatment with a Chk1 inhibitor reduced mRNA expression of fibrosis gene (FN).

Conclusions: Taken together,these findings indicated that ATG5 mediated G2/M arrest through Chk1 contributes to renal fibrosis after injury induced by AAI.

SA-PO126

The Progression of AKI to Chronic Tubulointerstitial Fibrosis Was Ameliorated in IL-18 Knockout Mice After Folic Acid Induction

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Background: Folic acid (FA)-induced acute kidney injury (AKI) can proceed to chronic tubulointerstitial fibrosis (TIF) in mice. This is clinical relevant animal model of AKI to latent TIF. The mechanisms of the progression still remain unclear. We aim to investigate the role of interleukin (IL)-18, a cytokine secreted by macrophages and T cells, in the progression from AKI to TIF induced by FA and its corresponding mechanisms.

Methods: We first explored time course of renal injury and IL-18 expression in *Il18*$^{+/+}$ mice at day 2, 14, and 30 after 250mg/ kg of FA intraperitoneal injection. Then we compared the acute necroptosis indicated by receptor-interacting serine/threonine-protein kinase1 (RIPK1), RIPK3, and phosphorylation of mixed lineage kinase domain like pseudokinase (p-MLKL); transdifferentiation marked by IL-11, transforming growth factor β1, vimentin, and connective tissue growth factor; renal fibrosis expressed with α-smooth muscle activating protein and collagen type I as well as inflammatory response including cytokines, M1 and M2 macrophages, and T lymphocytes infiltration in *Il18*$^{+/+}$ and *Il18*$^{-/-}$ mice after FA administration at each experimental time point.

Results: In *Il18*$^{+/+}$mice following FA injection, renal IL-18 and serum interferon-γ progressively increased accompanied with the progression from AKI to TIF. In addition, biomarkers of necroptosis on day 2, transdifferentiation on day 14, and tubulointerstitial fibrosis on day 30, M1 macrophages on day 14, and M2 macrophages on day 30 were peaked respectively at the different time points after FA injection. In *Il18*$^{-/-}$ mice, traditional acute and chronic renal damage, necroptosis, transdifferentiation, and renal fibrosis were all attenuated. Importantly, IL-18 deficiency decreased infiltration of M1 macrophages and its secreted cytokines on day 2 and day 14, reduced the infiltrated M2 macrophages and T cells as well as their related inflammatory responses at each time points from day 2 to 30 after FA.

Conclusions: IL-18 deficiency suppressed renal tubular damage, necroptosis, transdifferentiation, and fibrosis in FA-induced AKI to TIF. The renal protective role of IL-18 deletion in this progression might be mediated by inhibition of cytokines and the infiltrated M1, M2 macrophages, and T cells as well as the macrophage transformation from M1 to M2 types.

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SA-PO127

Soluble fms-Like Tyrosine Kinase-1 Promotes AKI and CKD After Renal Ischemia-Reperfusion Injury

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Background: Soluble fms-like tyrosine kinase-1 (sFlt-1), which is extracellular domains of Flt-1, acts as an antagonist of both placental growth factor (PlGF) and vascular endothelial growth factor A (VEGF-A). We previously reported that kidney is a main source of circulating sFlt-1 (about 50%). Generally, VEGF signaling is associated with angiogenesis and macrophage migration. Angiogenesis has a protective effect against renal ischemia, however macrophage migration contributes renal injury. The objective of this study is to examine the role of sFlt-1 in acute and chronic kidney injury after renal ischemia.

Methods: Unilateral or bilateral 30-minute renal ischemia were performed using sFlt-1 knockout (KO) and wild-type (WT) mice. For evaluation of acute kidney injury (AKI), plasma urea nitrogen levels and macrophage infiltration in the kidney were measured on day 1 and 7 after bilateral renal ischemia. Kidneys two weeks after unilateral renal ischemia were used for chronic kidney disease (CKD) model. Ischemic/non-ischemic kidney weight ratios (ischemic kidney weight divided by non-ischemic kidney weight) and renal fibrosis of the unilateral ischemic kidneys (Sirius red staining) were examined.

Results: After bilateral renal ischemia, plasma urea nitrogen levels from sFlt-1 KO mice were significantly lower than those from WT mice (130.5 ± 5.0 vs 164.0 ± 10.2 mg/dL, p=0.009 on day 1; 56.2 ± 2.9 vs 76.3 ± 4.1 mg/dL, p=0.001 on day 7). However, there was no difference in macrophage infiltration in the kidneys between sFlt-1 KO and WT mice on day 1 (49 ± 8 vs 59 ± 5/field, p=0.30). Two weeks after unilateral renal ischemia, ischemic/non-ischemic kidney weight ratios from sFlt-1 KO mice were significantly larger than those from WT mice (76.5 ± 7.6 vs 60.4 ± 1.9%; P=0.046). Finally, renal fibrosis from sFlt-1 KO mice was significantly reduced by 21.0% compared to WT mice (p=0.032).

Conclusions: sFlt-1, which is mainly secreted from kidneys, promotes AKI and following CKD after renal ischemia-reperfusion injury in a paracrine manner.

SA-PO128

Grhl2-Deficient Mice Are Protected from Renal Fibrosis After Ischemic AKI

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Background: Ischemic acute kidney injury disrupts epithelial tight junctions and induces a loss of epithelial cell polarity in the tubules of the nephron and collecting duct, leading to increased urine output and decreased urine osmolality. While the kidney can re-establish epithelial barrier integrity following injury, it is at an increased risk of developing fibrosis during recovery due to the activation of maladaptive repair mechanisms. Our group recently demonstrated that a transcription factor termed Grhl2 controls epithelial barrier formation of the collecting duct and is critical for renal osmoregulation. We showed that mice deficient for Grhl2 fail to properly concentrate urine and as a result exhibit reduced urine osmolality and develop diabetes insipidus. The relationship between the collecting duct barrier integrity and recovery post-injury is unclear.

Methods: To test this, we generated mice deficient for Grhl2 specifically in the collecting duct epithelium (Grhl2 $^{CD-/-}$). We subjected these mice, along with their control littermates, to kidney injury via unilateral ischemia of the left kidney for 25 minutes. Subsequently, we investigated renal injury and regeneration by allowing the mice to recover for reperfusion periods of 1, 3, 7, or 21 days.

Results: Semi-quantitative scoring of tubular damage in the initial phase of injury, at 1 and 3 days, did not reveal any significant differences between Grhl2$^{CD-/-}$ mice and controls. During the late recovery phase, 7 days post-ischemia, however, we observed a 38,52% decrease in tubular damage in Grhl2$^{CD-/-}$ mice (45.48% vs 27.96%, p<0.05). Additionally, we observed a 62.59% reduction in overall interstitial fibrosis 21 days post-ischemia in Grhl2$^{CD-/-}$ compared to control littermates (10.43% vs 6.53%, p<0.05). Further analysis of extracellular matrix components fibronectin and collagen IV, and the myofibroblast marker a-Smooth Muscle Actin, revealed marked reductions in Grhl2$^{CD-/-}$ mice. Additionally, we observed a significant reduction in mRNA expression of pro-inflammatory cytokines TNF-a (1.019 vs 0.4917, p<0.05) and IL-6 (1.027 vs 0.511, p<0.05) in Grhl2$^{CD-/-}$ mice 21 days post-ischemia.

Conclusions: Grhl2-deficient mice display an improved renal recovery following injury, raising the possibility that collecting duct epithelial barrier function and/or the intrarenal osmotic gradient contribute to renal recovery.

Funding: Private Foundation Support

SA-PO129

Ischemia-Reperfusion-Induced AKI (IR-AKI) Associated with Renal Fibrosis Is Attenuated Through Suppressing Indoxyl Sulfate Accumulation in Sulfotransferase (Sult) 1a1-Deficient Mice

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Background: IR-AKI is a high risk factor in the progression towards chronic kidney disease (CKD), which is featured by renal fibrosis. Indoxyl sulfate (IS), a typical uremic solute, is accumulated in the various organs of CKD patients, whereas the relationship of IS levels and AKI-to-CKD transition associated with renal fibrosis has not been clarified. IS is produced predominantly in the liver by CYP2A6/2E1-mediated oxidative metabolism of gut microflora-derived indole to indoxyl, followed by Sult1a1-mediated sulfate transfer to indoxyl. We established the Sult1a1 gene-deficient mice (Sult1a1$^{-/-}$), and explored the toxicological roles of IS in IR-induced AKI-to-CKD process associated with renal fibrosis.

Methods: C57BL/6 mice (WT) and Sult1a1$^{-/-}$ (9wks) were subjected to 30 min of renal IR, and sacrificed at 28 days after surgery. Serum creatinine (sCr) and BUN were evaluated as renal function markers. IS accumulation in serum and renal tissue was determined by LC-MS/MS. Renal fibrosis was assessed by Sirius red staining, and mRNA expression of fibrosis-related genes including Col1a1 and PAI-1 were determined by qRT-PCR.

Results: Sult1a1$^{-/-}$ mice subjected to IR showed partial prevention of renal damage compared to WT mice with IR treatment: sCr, 0.80 mg/dl in WT vs 0.33 mg/dl in Sult1a1$^{-/-}$, p<0.01; BUN, 75.0 mg/dl in WT vs 45.8 mg/dl in Sult1a1$^{-/-}$. Renal dysfunction was associated with the suppression of serum and renal tissue IS levels in Sult1a1$^{-/-}$ mice: serum, 23.1 μM in WT vs 1.8 μM in Sult1a1$^{-/-}$, p<0.01; renal tissue, 15.0 nmol/g tissue in WT vs 0.06 nmol/g tissue in Sult1a1$^{-/-}$, p<0.01). IR treatment caused marked renal interstitial fibrosis in both WT and Sult1a1$^{-/-}$ mice, whereas fibrosis formation in the cortex of the kidney showed a tendency to be reduced in Sult1a1$^{-/-}$ mice, compared to WT mice. mRNA expression of Col1a1 and PAI-1 in the kidney were markedly increased in both WT and Sult1a1$^{-/-}$ mice treated with IR, however, these gene levels were suppressed in Sult1a1$^{-/-}$ mice compared with WT mice.

Conclusions: Sult1a1 appeared to be the key hepatic enzyme responsible for deriving IS in IR-AKI. IS could be one of the exacerbation factors in IR-induced AKI-to-CKD transition by promoting renal fibrosis.

SA-PO130

Low-Dose Verteporfin Attenuates Tubule Interstitial Fibrosis from AKI via Inhibition of YAP-MCP1-Associated Inflammation

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Background: Incomplete recovery of AKI leads to an increased risk for CKD. Tubule-interstitial fibrosis (TIF) is the main pathological features of the AKI–CKD transition. Increasing evidence indicates that YAP, downstream of Hippo pathway, might be the key regulator of renal regeneration and fibrogenesis, but its role in the renal TIF after Ischemia-reperfusion (IR)-induced AKI remained unclear.

Methods: We established bilateral renal 30min-IR-induced AKI mice model and YAP expression was examined. Then different doses of Verteporfin (VP) were injected into AKI mice intraperitoneally (every other day) for 2 weeks. Hypoxia-reoxygenation (HR) was used to mimic IR in vitro.

Results: Renal interstitial inflammation and fibrosis were gradually aggravated from 1-to-12 weeks after IR. YAP was significantly activated in the epithelium of tubules, which usually surrounded by focal inflammation and fibrosis. Two weeks injection of VP into post-IR mice with a dose of 100 mg/kg caused 100% of death (n=10), 50 mg/kg caused 85% of death (n=10) and 25mg/kg only caused 25% of death (n=10). By using Low-dose of Verteporfin (LDVP, 25mg/kg) for 2 weeks, there was no significant change in levels of SCr and BUN, but the concentration of urine electrolytes including sodium, potassium and chlorine increased. Moreover, levels of serum IL-1β,TNF-α,and MCP1 and renal positive staining for CD3 or F4/80 were reduced, compared to vehicle treated post-IR mice. Masson trichrome and Sirius red staining showed a significant reduction of collagen deposition indicating inhibited fibrogenesis. Interestingly, we found LDVP down-regulated the expression of inflammatory factor MCP1 *in vitro*. And hyperactivate YAP via knocking down the Lats1 could up-regulated MCP1. While IR mice treated by bindarit, a MCP1 inhibitor, levels of serum IL-1β,TNF-α,and MCP1 and renal positive staining of CD3 and F4/80 decreased as well. In addition, LDVP did not attenuate oxidative stress *in vitro* and tubular damage *in vivo*.

Conclusions: This study indicates inhibition of YAP by low-dose of Verteporfin has an anti-fibrotic effects in the progression of IR-caused AKI, which might via inhibition

of YAP-MCP1 associated inflammation, whereas the higher-doses of Verteporfin has increased mortality.

Funding: Government Support - Non-U.S.

SA-PO131

15-Lipoxygenase Alters Inflammation, Metabolism, and Fibrosis in a Model of Renal Injury

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Background: 15-Lipoxygenase (15-LO, ALOX15) is implicated in the pathogenesis of a growing number of inflammatory and fibrotic diseases such as asthma, heart failure, and stroke but its role in renal injury is unexplored. We sought to examine if manipulating 15-LO would influence renal inflammation and fibrosis using a rodent model of unilateral ureteral obstruction (UUO).

Methods: Wild Type (WT) mice (N=18), mice lacking 15-LO (*Alox15-/-*) (N=11), and mice with transgenic overexpression of 15-LO (N=9) were subjected to UUO and kidneys were collected at 3 and 10 days postoperatively for histology, qRT-PCR, hydroxyproline assessment, and metabolomic and lipidomic analysis of over 200 unique compounds.

Results: At 3 days after UUO, as compared to WT controls, *Alox15-/-* kidneys had decreased mRNA levels of pro-inflammatory cytokines tumor necrosis factor alpha (TNFα) and fractalkine (CX3CL1) (0.84 vs 1.71 mean fold decrease, p<0.05; and 0.41 vs 1.04 mean fold decrease, p<0.01, respectively). Similar results were obtained 10 days after UUO (0.93 vs 1.39 mean fold decrease, p<0.01, and 2.79 vs 5.32 mean fold decrease, p<0.01, respectively). At 3 days after UUO, injured Alox15-/- mice had reduced levels of toxic reactive eicosanoids including 12(13)- and 9(10)-DiHOMEs, 9- and 13-OxoODEs, and 5(S)-HETE compared with WT specimens. At 10 days after UUO, *Alox15-/-* mice had evidence of marked oxidative phosphorylation vs. WT mice, which demonstrated a shift towards glycolysis. Also at 10 days after UUO, there was a trend towards reduced fibrosis in the Alox15-/- vs. WT by Picrosirius red staining (p=0.09), but not by mRNA for transforming growth factor beta (TGF-β) and smooth muscle alpha actin (αSMA). Next, we determined if overexpressing 15-LO would promote inflammation and fibrosis 10 days after UUO. As compared with WT mice, 15-LO transgenic mice had increase message for CX3CL1 (4.89 vs 1.69 mean fold increase, p<0.001), TGF-β (6.22 vs 2.35 mean fold increase, p<0.001), and αSMA (4.34 vs 2.52 mean fold increase, p<0.01). Fibrosis was significantly worse among the 15LOTG mice as compared to WT controls by Picrosirius red staining (7.52 vs 4.03 % fibrosis, p<0.05) and cortical hydroxyproline content (4.09 vs 1.99 mcg/mg total protein, p<0.01).

Conclusions: 15-Lipoxygenase contributes to inflammation, metabolic changes, and fibrosis in mice undergoing UUO.

Funding: Veterans Affairs Support

SA-PO132

Increased HIPK2 Expression in Tubular Epithelial Cells Aggravates Kidney Fibrosis

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Background: Irrespective of etiology, kidney fibrosis is a final common pathogenic process for the progression of chronic kidney disease (CKD) to end-stage renal disease. Therefore, there is an urgent need to develop effective anti-fibrosis therapy for CKD. We previously demonstrated that homeodomain interacting protein kinase 2 (HIPK2) is a critical protein kinase regulating multiple pro-fibrotic and pro-inflammatory pathways in the diseased kidney. The global knockout of HIPK2 attenuates kidney fibrosis in several animal models of kidney disease. However, the direct effects of HIPK2 in renal tubular cells have not been confirmed. Therefore, we used several conditional knockout or expressing mouse models to further investigate the role of HIPK2 in renal tubular epithelial cells in kidney fibrosis.

Methods: We generated tetracycline-inducible, tubule-specific HIPK2 knockout mice ($Hipk2^{fl/fl}$; pax8-rtTA; TRE-Cre). We also generated tetracycline-inducible tubule-specific HIPK2 wildtype overexpression mice ($Hipk2^{WT}$; pax8-rtTA), as well as kinase-dead HIPK2 mutant mice ($Hipk2^{MT}$; pax8-rtTA) as a control. Tetracycline analog doxycycline was administered for 3 weeks prior to unilateral ureter obstruction (UUO) and at the age of five-week-old Tg26 mice. Extent of fibrosis was assessed after 14 days of UUO and at the age of 10-week-old Tg26 mice by histopathological scoring and by assessment of fibrosis markers using quantitative PCR and western blot.

Results: We observed that the loss of tubular HIPK2 resulted in significant attenuation of kidney fibrosis, while tubular overexpression of wildtype HIPK2 resulted in marked augmentation of kidney fibrosis in UUO mice. Furthermore, the overexpression of kinase-dead HIPK2 mutant significantly diminished kidney fibrosis in UUO mice and Tg26 mice, suggesting that the kinase activity of HIPK2 is required for its pro-fibrosis effect.

Conclusions: Our results clearly demonstrate that increased HIPK2 expression in renal tubular cells aggravates kidney fibrosis progression. Therefore, the inhibitors of HIPK2 could be developed as a potential anti-fibrotic therapy for CKD.

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SA-PO133

Urinary EGF and ICAM-1 Predict Glomerular Number Using Cationic Ferritin Enhanced-MRI in a Murine Model Folic Acid Nephropathy

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Background: Chronic kidney disease (CKD) is difficult to detect in the earliest stages. Cationic ferritin enhanced-MRI (CFE-MRI) has been used to measure glomerular number (N_{glom}) in the entire kidney in 3D in animals and human kidneys. Although urinary biomarkers are used as early and sensitive predictors of acute kidney injury (AKI), there is little data correlating urinary biomarkers to nephron number following AKI. We hypothesize that urinary biomarkers can predict microstructural changes detected by CFE-MRI in the transition from AKI to CKD.

Methods: To induce CKD, male mice were injected with intraperitoneal folic acid (125 mg/kg, n=5); controls received $NaHCO_3$ (n=5). Urine was collected on day 4 after folic acid and at 12 wks following AKI. The mice received horse spleen cationic ferritin 12 wks after injury. Kidneys were imaged *ex vivo* using a 7T Bruker ClinScan MRI (3D T2*-weighted, TE:20, TR:80, 60 μm, 640x640). MRI-derived biomarkers included N_{glom} and cluster size (volume where glomeruli were detectable but lacked tubules). Forty urinary biomarkers (inflammation and growth factors) were analyzed using Mouse Cytokine Array Q1000 (RayBiotech).

Results: By CFE-MRI, the CKD group had 28% fewer glomeruli (8008 ± 2880) as compared to the controls (11105 ± 818, p=0.04). In the CKD cohort, nearly 9% of the kidney had labeled glomeruli with a lack of surrounding tubules designated as "clusters" (CKD: 8.8±2.4% vs. controls: 2.3±0.59%, p=0.03). Urinary EGF was higher 4 days after injury (AKI:11538 vs controls: 5087 pg/ml, 0.0004) and ICAM-1 was lower at 12 weeks (CKD: 2621 vs controls: 6629 pg/ml, p=0.007). Four days after injury urinary EGF correlated to N_{glom} at 12 weeks after injury (r=-0.71, 0.02) and cluster size (r=0.78, p=0.008). At 12 weeks after injury, urinary ICAM-1 correlated to N_{glom} (r=0.76, p=0.01) and cluster size (r=-0.80, p=0.005).

Conclusions: In this murine model of AKI transitioning to CKD, urinary EGF at the time of AKI correlate with both a lower N_{glom} and larger cluster size. At CKD, 12 weeks after injury, ICAM-1 strongly correlated with glomerular number and cluster size. Further work to define the pathophysiology of these biomarkers in AKI and CKD is needed, however this work highlights the utility of urinary biomarkers and CFE-MRI to noninvasively detect early nephron injury and track progression of CKD.

Funding: NIDDK Support

SA-PO134

MiR-874/ADAM19 Mediates Macrophage Activation and Renal Fibrosis After AKI

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Background: The pathogenesis of CKD following AKI is not fully investigated.

Methods: We established a mouse AC (AKI to CKD) model caused by ischemia/reperfusion(I/R), and identified miR-874 downregulated in fibrotic kidneys of both AC model and UUO model by RNA-Seq. Then we used human patient samples as well as animal and cell models to investigate how miR-874 regulates renal fibrosis after I/R injury.

Results: MiR-874 was reduced at different time point after I/R and UUO. In vitro, miR-874 was downregulated in HK2 cells treated with TGF-β1. Moreover, miR-874 level of peripheral mononuclear cells was lower in IgA nephropathy (IgAN) patients with proliferative sclerosing glomerulonephritis than those in pathological stage M0E0S0T0(p<0.01). In vitro, transient transfection of miR-874 inhibitor in HK2 cells induced the increase of mesenchymal makers, and transfection of miR-874 mimic in HK2 cells treated with TGF-β1 could alleviate EMT compared with negative control. Overexpression of human miR-874 into AC and UUO mice led to alleviated renal fibrosis with decreased expression level of Acta2, Col1a1, Fn1, chemokines including CCL2/CCL5, and ADAM19, a target gene of miR-874 verified by luciferase microRNA target reporter assay. F4/80 staining was also junior in miR-874 mice compared with negative control. In vitro, transfection of miR-874 mimic in mouse macrophage cell line Raw264.7 stimulated with LPS downregulated the expression of CCL2/CCL5. Then we focused on the biological function of ADAM19 expression towards renal fibrosis. ADAM19 was induced in both UUO mice and AC mice at different time point. Transfection of adenovirus carrying human ADAM19 into HK2 cells, ADAM19 could induce the increase of mesenchymal makers and inflammatory factors and decrease of epithelial markers. Overexpression of ADAM19 directly induced fibrotic changes in vivo. The expression of CCL2/CCL5 and F4/80 staining were also upregulated in ADAM19 mice compared with negative control. In vitro, transfection of adenovirus carrying human ADAM19 into Raw264.7 cells increased nitric oxide synthase 2 (NOS2), chemokines and proinflammatory cytokines such as interleukin-1β (IL-1β) at both mRNA and protein levels.

Conclusions: Our results suggest miR-874/ADAM19 could mediate renal fibrosis through regulating renal tubular epithelial cell injury and macrophage activation.

SA-PO135

A Selective USP30 Inhibitor Attenuates Progressive Fibrosis in Ischemia-Induced CKD

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Background: Much literature evidence points towards an essential role of mitochondrial quality control mechanisms in acute kidney injury progression. Ischemic-reperfusion injury (IRI) results in metabolic adaptation of Proximal Tubule Epithelial Cells (PTECs), a site of high mitochondrial turnover (1). Moreover, exacerbation of renal injury has been demonstrated following IRI in both PINK1 KO and PARK2 KO mice (2). USP30 is a mitochondrial associated deubiquitylating enzyme and represses PINK1/PARKIN-mediated mitophagy (3). Within the kidney, USP30 expression is predominantly tubular and accordingly, USP30 inhibition may provide a mechanism to protect against IR-induced tubular injury. Here we present data on MTX008, a selective small molecule inhibitor of USP30 in a mouse model of IRI induced kidney fibrosis.

Methods: MTX008 was administered to C57BL/6 mice 15 mg/kg (p.o.) and compared to vehicle treatment from Day -1 through to Day +21. On Day 0, mice were anaesthetized, and their left renal pedicle clamped for 45 min, then released to induce IRI. Mice were monitored and urinary kidney injury biomarkers (KIM-1 and NGAL) were measured on Day +1 and +7. On Day +14 and Day +21 kidneys were harvested. Morphology, fibrosis and immune cell infiltration were assessed.

Results: Body weight was similar between groups and remained constant throughout the observation periods. MTX008 appeared to limit urinary kidney injury biomarkers, KIM1 and NGAL on Day +1. There were large interindividual variations and the differences did not reach significance. Macrophage infiltration was significantly reduced on Day +21. Masson trichome stain revealed significantly less tubular atrophy in MTX008 treated animals on Day +14 and Day +21. Fibronectin expression in the cortex was significantly reduced in MTX008 treated mice on Day +14 and +21.

Conclusions: MTX008, a novel selective small molecule inhibitor of USP30 has shown efficacy in a model of IR-induced CKD. Daily treatment has shown significant benefits towards attenuated tubular atrophy and reduced cortical fibrosis. Mission Therapeutics is investigating MTX008 in a variety of preclinical renal injury models with a view to developing this novel molecule towards the clinic. 1 McWilliams, *et al.* 2017 2 Tang, *et al.* 2018 3 Bingol, *et al.* 2014

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SA-PO136

Tubulointerstitial Injury in Renal Congestion Was Suppressed by Inhibiting Platelet-Derived Growth Factor Pathway

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Background: Increased central venous pressure in congestive heart failure is responsible for renal dysfunction. We created a novel rat renal congestion model, resulting high renal interstitial hydrostatic pressure, tubulointerstitial injury and pericyte-myofibroblast transition (PMT). In this model, platelet-derived growth factor receptors (PDGFRs), PMT indicators, were also upregulated, especially in outer medulla. Thus we examined the effect of imatinib, a PDGFR inhibitor, for renal injury.

Methods: The inferior vena cava (IVC) between the renal veins was ligated by suture in male Sprague-Dawly rats to increase upstream IVC pressure and induce congestion in the left kidney only. Imatinib mesylate (20 mg/kg) or saline were injected intraperitoneally every day from one day of the operation. Both control right kidney and congesitve left kidney were obtained after 3 days of the surgery and were weighted. The expression of renal injury marker and PDGFRs were assessed by quantitative reverse transcription-polymerase chain reaction, western blot and immunohistochemistry.

Results: Kidney weight was significantly increased in left congestive kidney, and ameliorated by imatinib administration. Staining intensity and mRNA expression levels of Tagln, Pdgfra, Pdgfrb were higher in the control kidneys, especially in the cortex. Imatinib attenuated the intensity and mRNA expression levels. Fibronectin and Kim1 expression was higher in the control kidneys and were attenuated by imatinib.

Conclusions: Imatinib attenuates the elevation of kidney weight and PMT markers. These results suggest that imatinib has potentiality against renal fibrosis in renal congestion.

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SA-PO137

The Role of Akt1 in a Murine Model of AKI to CKD Progression

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Background: Acute kidney injury (AKI) is an underestimated, yet important risk factor for development of chronic kidney disease (CKD). However, underlying mechanism of AKI to CKD progression are poorly understood. Akt has been reported to be involved in renal ischemic reperfusion injury (IRI). In this study, we investigated the role of Akt1, one of the three Akt isoforms, in murine model of IRI-induced AKI to CKD progression

Methods: We subjected the wild type and *Akt1*$^{-/-}$ mice to renal IRI. Renal IRI was induced by clamping the left renal artery for 30 min followed by reperfusion. After 6 weeks of IRI, the renal fibrosis was assessed by histologic grading and Masson's-trichrome staining. Fibrosis/apoptosis markers and MAPKs were also assessed by western blot.

Results: After 6 weeks after IRI, IRI kidneys in wild type mice showed the typical features of progressive CKD: widespread interstitial fibrosis/tubular atrophy, as indicated by collagen deposition assessed by Masson's-trichrome staining. These fibrotic changes were significantly alleviated in *Akt1*$^{-/-}$ mice compared with the wild type mice. In addition, western blot analysis showed that *Akt1*$^{-/-}$ had attenuated expressions of fibrosis marker (vimentin and α-SMA) and phosphorylated-p44/42 MAPK (Erk1/2) compared with the wild type mice. Western blot analysis and TUNEL assay showed that the apoptosis was attenuated in *Akt1*$^{-/-}$ mice compared with wild type mice.

Conclusions: Our findings demonstrate that Akt1 contributes to IRI-induced AKI to CKD progression, suggesting that inhibition of this signaling pathway may provide a therapeutic approach of preventing IRI-induced AKI to CKD progression.

SA-PO138

Cholesterol Lipid Rafts When Blocked Prevent Epithelial-Mesenchymal Transition in Cisplatin-Induced Renal Injury

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Background: Cisplatin is a potent cytostatic, but its nephrotoxicity is a major complication and a dose limiting factor for anticancer therapy. Some evidences have shown that epithelial-mesenchymal transititon (EMT) contributes to the progression from acute renal failure to chronic renal failure. We have found that binding of cilastatin to renal dehydropeptidase-I inhibits transport and signalling of brush border lipid rafts in proximal tubule, thus providing protection.

Methods: In this study we investigated whether the protective effects of cilastatin are related to the prevention of the EMT-induced by cisplatin. Male Wistar rats were divided into 4 groups: control rats, cilastatin-control rats, cisplatin-injected rats, cilastatin-treated cisplatin-injected rats. Nephrotoxicity was assessed 5 days after cisplatin treatment, by measuring serum creatinine, blood urea nitrogen (BUN), glomerular filtration ratio (GFR), proteinuria and renal morphology. Some typical markers of EMT and cell-cell adhesion were measured by western blot and immunohistochemical studies.

Results: Cisplatin-treated rats showed significant elevations in BUN, creatinine, and proteinuria and decreased the GFR when compared with control rats. Cisplatin rats also exhibited severe morphological changes such as vacuolization and hyaline cast in the tubular lumen. Cilastatin significantly prevented partial or totally these changes in renal function and ameliorated histological damage in cisplatin-treated animals. On the other hand, cisplatin increased transforming growth factor beta, connective tissue growth factor (inducers of EMT and profibrotic markers), and vimentin (mesenchymal cell marker) levels while decreased significantly β-catenin and zonula occludens-1 levels, both proteins involved in cell adhesion. Cilastatin treatment reversed these changes.

Conclusions: This study provides evidence that the protection offered by cilastatin to acute renal failure-induced by cisplatin, is associated to the prevention of the EMT by decreasing the signaling pathways that cause it and avoiding the loss of cell junctions. EMT signals seem to be triggered during the renal injudy-induced by cisplatin.

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SA-PO139

A Furosemide Excretion Stress Test (FEST) Predicts Mortality After Sepsis Independent of Vasopressin Administration

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Background: The furosemide stress test (FST) has been shown to be a sensitive and specific predictor of progression to AKIN stage III in the ICU. FST measures the volume of urine produced after a furosemide bolus. Furosemide is actively excreted by the proximal tubules into the lumen where it inhibits NKCC2 in the thick ascending limb. Vasopressin is used as a vasopressor in some hypotensive sepsis patients and can markedly reduce urine production. We hypothesize that furosemide excretion (FEST) will be a more direct measure of tubule health than diuresis (FST) and may be insensitive to the effects of vasopressin on urine volume. We developed a protocol for FST and FEST in mice and tested this hypothesis in a murine model of septic-AKI.

Methods: Sepsis was induced in male and female CD-1 mice by cecal ligation and puncture (CLP). A subgroup of mice received 0.00114 U/(kg.min) vasopressin i.p. to simulate vasopressor support. The FST/FEST started at 42 hours post-CLP. 1 mg/kg furosemide s.c. was given and urine collected for 12 hours. The mice were monitored until 7 days post-CLP. Furosemide concentration was determined by a reverse phase HPLC assay.

Results: From 139 mice (79M/60F), 55 survived to 42 hours and underwent FST/FEST with 33 mice surviving to 7 days. Both FST and FEST predicted time of death (R^2 = 0.26 and 0.74) and mortality [AUC ROC values of 0.92 for FST in males, 0.95 for FST in females, 0.87 for FEST for males, and 1.00 for FEST in females]. Optimal performance was 91% sensitivity and 82% specificity for FST and 90%/79% for FEST

with cutoffs of 0.94 ml and 44%, respectively. In the subgroup receiving vasopressin, urine production was reduced by 0.6 ml (p = 0.03) without altering furosemide excretion (p = n.s.). Therefore, when we used the optimal cutoffs from septic mice not treated with vasopressin for vasopressin-treated septic mice, the specificity of FST was eliminated (0%, p < 0.01) but specificity of FEST was preserved.

Conclusions: The FST and FEST perform similarly in predicting mortality in untreated animals. Only the furosemide excretion stress test also predicted time to death and was insensitive to vasopressin treatment. In order to use FST in conjunction with vasopressin, cutoff values must be adjusted, but such adjustment is not needed for FEST.

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SA-PO140

Lysozyme-Induced AKI: A Case Series

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Background: Only rare case reports exist describing increased serum lysozyme with acute kidney injury. This study represents the first case series to describe the clinical and laboratory findings associated with this disease.

Methods: 17 kidney biopsy samples displaying lysozyme-induced acute kidney injury and associated clinical histories were prospectively collected from 2012-2019. 40 additional kidney biopsies were utilized as controls to compare morphologic findings. Light microscopy, immunofluorescence, electron microscopy, thioflavin T, Congo red, and lysozyme IHC were performed. Laser microdissection coupled with mass spectrometry was performed on our initial two patients.

Results: 82% of patients were male with an average age of 66 years. 94% presented with acute kidney injury and average serum creatinine of 2.95 mg/dL. All patients had proteinuria with an average protein:creatinine ratio of 2.2. Hematuria was present in 42%, however where available, all urine sediments were bland. Serum lysozyme results were available in 10 patients all showing elevated levels. Hematologic disease was present in 71% of patients with chronic myelomonocytic leukemia affecting 31%. Outcome data was limited but showed recovery to near baseline serum creatinine in 4/4 (13 months f/u) who were treated for their underlying disease. Progressive CKD/ESKD was seen in 3/3 (3 months f/u), who did not undergo treatment of their underlying disease. The most helpful histologic features in identifying this disease were the pattern and intensity of lysozyme staining, Congo red reactivity without birefringence, weak Thioflavin T staining, extent of proximal tubule protein resorption droplets, and refractile protein resorption droplets in proximal tubules. Laser microdissection of proximal tubules followed by mass spectrometry showed lysozyme as the most frequent protein hit identified and a >20 fold increase in lysozyme hits compared to controls.

Conclusions: Lysozyme-induced acute kidney injury occurs in the setting of increased serum lysozyme leading to increased lysozyme in the proximal tubules. It is most commonly seen in the context of hematologic malignancy. While subtle, a constellation of morphologic and immunohistochemical findings exist that allow for accurate diagnosis. In our limited outcome data, treatment of the patient's underlying disease is critical for recovery of kidney function and favorable prognosis.

SA-PO141

Assessment of Renal Angina Index for the Prediction of Severe AKI in Critically Ill Adults

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Background: Risk-stratification tools of incident AKI in critically ill adults are needed. The renal angina index (RAI) was developed and validated in the pediatric population. We evaluated the performance of the RAI for the prediction of severe AKI in critically ill adults.

Methods: A cohort of 12,084 patients admitted to the ICU at the University of Kentucky (2009-2017) was utilized. Inclusion criteria consisted of age ≥18, ICU stay ≥3 days, at least 2 serum creatinine (SCr) measures in the first 2 days of ICU stay and one measure at 3-7 days of stay. Exclusion criteria consisted of ESKD, kidney transplant or baseline eGFR <15. A modified RAI (mRAI) included risk level criteria 1) mechanical ventilation or vasoactive drug support, 2) sepsis, and 3) diabetes and injury level criteria of 1) SCr increments (<25%, 25-49%, 50-99%, ≥100) and 2) fluid overload (FO%, <5%, 5-10%, 11-19%, ≥20%). Performance metrics were used for evaluation of components of the mRAI in reference to isolated changes in SCr.

Results: Mean (SD) age was 57.3 (16.5), 42% were women and 90% white. Mean (SD) SOFA score was 5.2 (3.0). The incidence of AKI (KDIGO-SCr) stage ≥2 at 3-7 days of ICU stay was 15.7%. Median [IQR] mRAI (determined in the first 2 days of ICU stay) was 24 [8-40] vs 10 [5-40], p<0.001 for those with vs without AKI stage ≥2 at 3-7 days. Performance metrics are reported in **Table**. Similar performance was observed when the cohort was restricted to patients without AKI or AKI stage ≤1 in the first 2 days of ICU stay.

Conclusions: When compared with examination of isolated changes in SCr, components of the mRAI exhibited better performance for the prediction of severe AKI in critically ill adults, particularly when measured baseline SCr was not available. The mRAI is a feasible risk-stratification tool that needs validation in the adult population.

Performance metrics (95%CI) of components of the mRAI for the prediction of AKI stage ≥2 in critically ill adults

	ΔSCr first 2 days of ICU stay	mRAI using ΔSCr first 2 days of ICU stay	ΔSCr first 2 days of ICU stay (ref: measured baseline)	mRAI using ΔSCr first 2 days of ICU stay (ref: measured baseline)
AUC	0.59 (0.58, 0.60)	0.70 (0.69, 0.72)*	0.85 (0.84, 0.87)	0.87 (0.85, 0.88)*
Absolute IDI	ref	0.05 (0.04, 0.05)*	ref	0.01 (0.002, 0.01)*

*p<0.001 for performance comparison to corresponding reference; AUC = area under the receiving operating characteristic curve; IDI = integrated discrimination index; SCr = serum creatinine

SA-PO142

Clinical Characteristics and Prognosis of Patients with Community-Acquired AKI Compared with Hospital-Acquired AKI: A Meta-Analysis

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Background: The difference between hospital-acquired acute kidney injury (HA-AKI) and community-acquired AKI (CA-AKI) was inconclusive. We conducted a meta-analysis to summarize and quantify the meaningful diversities between CA-AKI and HA-AKI.

Methods: We identified observational studies reporting clinical characteristics and prognosis between HA-AKI and CA-AKI. Odds ratios (ORs) and mean differences (MD) were extracted for outcomes as mortality, oliguria, ICU risk, dialysis risk, hospital stay and renal recovery.

Results: Fourteen eligible studies were finally included, involving 43,949 patients: 21,418 CA-AKI patients and 22,531 HA-AKI patients. The mortality was significantly lower in CA-AKI patients than HA-AKI: 13.45%vs. 16.17% (OR 0.41, 95%CI 0.34-0.49). Oliguria incidence was lower in CA-AKI patients (OR 0.58, 95%CI 0.38-0.88). ICU was less required in CA-AKI patients (OR 0.24, 95%CI 0.14-0.40). CA-AKI patients were associated with a shorter hospital time (MD -10.08, 95%CI -15.44- -4.73). The renal recovery rate of the two groups' patients did not show a significant difference (OR 1.26, 95%CI 0.46-3.48). Dialysis need between the two groups was similar (OR 0.99, 95%CI 0.75-1.30).

Conclusions: CA-AKI showed better clinical manifestations with lower oliguria incidence, shorter hospital time and less risk of ICU treatment. The mortality of CA-AKI was lower compared to HA-AKI, indicating a better prognosis; whereas the renal recovery denoted no significant difference between the two groups. Further studies should be conducted to provide more evidence on the time, dose and prognosis for dialysis.

Funding: Government Support - Non-U.S.

Outcomes	No. of studies	No. of patients	Mean Difference [95%CI]	P value	I^2(%)
mortality	13	39,996	0.41[0.34,0.49]	<0.00001	83
renal recovery	8	20,409	1.26[0.46,3.48]	0.65	99
oliguria	3	630	0.58[0.38,0.88]	0.01	28
dialysis	10	27,480	0.99[0.75,1.30]	0.91	59
ICU	8	22,164	0.24[0.14,0.40]	<0.00001	96
length of hospital stay	8	27,005	-10.08 [-15.44,-4.73]	0.0002	98

SA-PO143

AKI Risk Stratification in Cardiac Surgery Patients: Is SPARK Index an Option?

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Background: The Simple Postoperative AKI Risk (SPARK) index has been proposed as a preoperative AKI risk score for patients undergoing "non" cardiac surgery, which is a summation of the integer scores of the following variables: age, sex, expected surgery duration, emergency operation, diabetes mellitus, use of renin-angiotensin-aldosterone inhibitors, baseline eGFR, albuminuria hypoalbuminemia, anemia, and hyponatremia. Based on the score, 4 SPARK classes were defined, A, B, C and D in the order of increasing score/AKI risk. Since the index incorporates many of the risk factors common to cardiac surgery (CS) patient, albeit with major differences, we investigated its usefulness in this cohort.

Methods: We utilized data from a previously published study where we reported that serum uric acid (SUA) is an independent risk factor for AKI in patients undergoing CS. SPARK scores were calculated for all patients (N=190). Odds ratio (OR) for AKI was calculated and AUC of SPARK scores, preoperative SUA, creatinine (SCR) and eGFR were compared.

Results: SPARK class A (score <20), B (≥20 to <40), C (≥40 to <60) and D (≥60) consisted of 18, 98, 45 and 9 patients, respectively. OR with $CI_{95\%}$ and p-value for AKI

were: raw SPARK score, 1.0 (1.0-1.0, 0.603); class A, 1.1 (0.8-1.4, 0.286); class B, 1.1 (2.0-1.2, 0.878); class C, 1.0 (0.9-1.1. 0.788); class D, unable to calculate due to small sample size. Pair-wise comparison of AUCs revealed significant differences between SUA and SCR (Z=3.6, <0.0003), GFR (Z=4.1, <0.0003) and SPARK score (Z=3.8, <0.0001). SPARK score did not demonstrate significant differences with GFR (Z=0.7=6, 0.552) or SCR (Z=1.2, 0.229). Receiver Operating Characteristics (ROC) curves shown in Figure 1.

Conclusions: Our data suggests that the SPARK Index is not a good predictor of AKI in CS where SCR, eGFR and SUA outperform its discriminatory capabilities and require only a single, cost-effective laboratory test.

SA-PO144

Impact of Clinical Variables at Dialysis Initiation for AKI in the ICU on In-Hospital Mortality

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Background: Current research on timing of dialysis in critically ill AKI has focused on analyzing survival outcome with arbitrary definitions of "early" or "late" start. However, the competing effects of other variables such as clinical comorbidities, dialysis indication, or acuity of illness at dialysis start are unknown.

Methods: We analyzed new adult AKI patients initiated on renal replacement therapy (RRT) while in our 5 intensive care units (ICU) from 1/1/2010 through 12/31/2015, to identify clinical variables associated with survival to hospital discharge.

Results: Of the 235 patients initiated on RRT in medical and surgical ICUs, the mean age was 61.8+/- 14.3 yrs; 60 % were male, 47 % were Afro-American with a Charlson Comorbidity Score (CCS) of 5.5 +/- 3.1 and acuity scores of 29.6 +/-7.6 (APACHE-II) and 12.0 +/- 4.4 (SOFA) at dialysis start. The most common modality of RRT was continuous (67.2%). Logistic regression identified independent association of survival with low serum lactate, low SOFA scores, elevated serum creatinine at RRT initiation and hyperkalemia but not with CCS and time from KDIGO Stage 3 AKI to dialysis initiation (as a surrogate for timing). Serum lactate{odd ratio (O.R.) 0.74- 0.91} at initiation also correlated inversely with survival beyond 48 hours. Stratifying patients by SOFA scores at RRT initiation (<10=low-risk, ≥10= high-risk) identified severity of volume overload or hyperkalemia (low-risk group) and RRT modality type or serum lactate (high-risk group), as being associated with survival. Receiver-Operator Characteristics (ROC) of biochemical variables at dialysis initiation showed that only serum lactate had a moderate c-statistic of 0.759 in discriminating survivors from non-survivors.

Conclusions: Data from critically ill AKI patients initiated on RRT in the ICU primarily showed acuity of illness at the start of RRT affecting survival. Since time from KDIGO Stage 3 AKI to dialysis initiation was not associated with survival, the validity of definitions such as "early" or "late" RRT initiation remains uncertain. Triaging clinical decision based on acuity scores may optimize clinical outcomes. Finally, the absence of any association between hospital survival and co-morbid scores has great implications for prognostication and palliative care.

SA-PO145

Simplified Acute Physiology Score II Predicts 4-Year Outcomes in Critically Ill Elderly Patients with AKI

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Background: Acute kidney injury (AKI) is a serious complication of critically ill elderlies. Several severity scoring systems have been used to predict the prognosis. However, which severity score has the better predictive efficiency in elderlies with AKI is unknown.

Methods: Data of AKI elderlies was extracted from Medical Information Mart for Intensive Care III database. Subjects were divided into three groups, according to 65-75 years, 75 - 85 years and ≥ 85 years. SAPS II, OASIS, MLODS, SIRS and SOFA were compared. The Kaplan-Meier and receiver operating characteristic (ROC) curves were performed to assess the prognostic values.

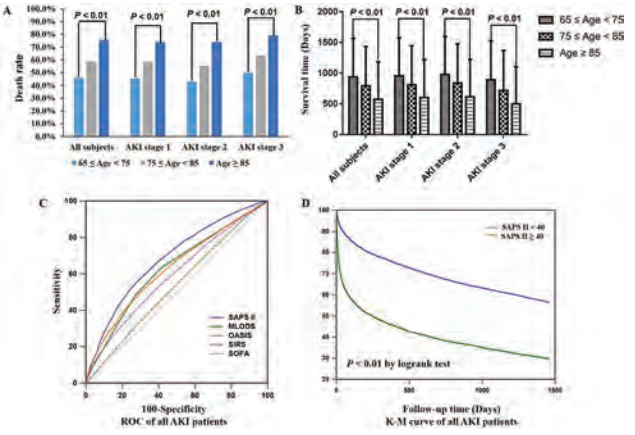
Results: Totally 10472 AKI elderlies were enrolled. Older patients had higher death rates (**Figure A**) and shorter survival time (**Figure B**). SAPS II had the best prognostic value ($P < 0.01$, **Figure C**). The AUC of SAPS II (95% CI, 0.676 to 0.694) was significantly the highest ($P < 0.01$, **Table**). The cut-off value of SAPS II was 40. Patients with SAPS II < 40 would have a better prognosis than those with SAPS II ≥ 40 (**Figure D**).

Conclusions: SAPS II could better predict the long-term prognosis of elderly patients with AKI.

Area under receiver operating curve (AUC) of mortality and different severity scores.

	All subjects (N = 10472)		AKI stage 1 (N = 3039)		AKI stage 2 (N = 4045)		AKI stage 3 (N = 3388)	
	AUC (95% CI)	P	AUC (95% CI)	P	AUC (95% CI)	P	AUC (95% CI)	P
SAPS II	0.685 (0.676, 0.694)		0.655 (0.637, 0.672)		0.662 (0.647, 0.676)		0.734 (0.719, 0.749)	
MLODS	0.630 (0.620, 0.639)	< 0.01	0.626 (0.608, 0.643)	< 0.01	0.585 (0.570, 0.600)	< 0.01	0.683 (0.667, 0.699)	< 0.01
OASIS	0.630 (0.620, 0.639)	< 0.01	0.584 (0.566, 0.601)	< 0.01	0.622 (0.607, 0.637)	< 0.01	0.679 (0.663, 0.694)	< 0.01
SIRS	0.533 (0.523, 0.542)	< 0.01	0.527 (0.509, 0.545)	< 0.01	0.519 (0.503, 0.534)	< 0.01	0.562 (0.546, 0.579)	< 0.01
SOFA	0.591 (0.582, 0.601)	< 0.01	0.582 (0.565, 0.600)	< 0.01	0.541 (0.525, 0.556)	< 0.01	0.655 (0.638, 0.671)	< 0.01

AKI, acute kidney injury; AUC, area under curve; CI, confidence interval; SE, standard error; RDW, red blood cell distribution width; SAPS II, simplified acute physiology and chronic health evaluation III; MLODS, modified logistic organ dysfunction system; SOFA, sequential organ failure assessment; OASIS, oxford acute severity of illness score; SIRS, systemic inflammatory response syndrome.



Comparisons of prognostic values among five severity scores.

SA-PO146

Atrial Fibrillation Chronicity in Patients with AKI on Continuous Renal Replacement Therapy

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Background: Atrial fibrillation (AF) has been reported in 44% of patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT), but the chronicity of AF remains unclear. We aim to assess the epidemiology and outcomes of AF among AKI patients receiving CRRT, including predictors of new-onset AF (NOAF) on CRRT.

Methods: This is a retrospective analysis of a cohort of patients admitted to the ICUs at a tertiary care hospital from 12/2006 through 11/2015 who had AKI and received CRRT. The primary outcome was mortality at three years, which was assessed using a Cox proportional hazard model. Secondary outcomes included in-hospital mortality. AF was ascertained by manually reviewing the chart. A random sample of 10% of cohort was independently reviewed by another investigator and agreement was reported using kappa coefficient.

Results: Out of 1,394 CRRT patients who had AKI, 582 patients did not have any arrhythmia. There were 419 (30%) patients who were known to have AF prior to starting CRRT. NOAF occurring while on CRRT developed in 193 (14%) patients. Another 160 patients (11.5%) developed NOAF during their index ICU admission prior to initiation of CRRT. Kappa was 0.95 (95% CI: 0.87-1, p<.001). A known history of AF (HR: 1.19, 95%CI: 1.01-1.41, p=0.04) and NOAF occurring on CRRT (HR: 1.27, 95% CI: 1.04-1.56, p=0.02) were independently associated with an increased hazard of death at 3 years, compared to the group who did not have any arrhythmia. There was no difference in in-hospital mortality between the AF groups. The models were adjusted for age, sex, BMI, SOFA score at CRRT initiation, baseline serum creatinine, Charlson comorbidity index, number of vasopressors used in the ICU, use of invasive ventilation. In multivariate analysis, using time-dependent covariates, higher potassium (HR 1.24, 95%CI: 1.01- 1.54, p=0.043) and bicarbonate (HR 0.95, 95%CI: 0.92-0.98, p=0.003) were associated with increased and decreased risk of NOAF on CRRT, respectively.

Conclusions: Incident NOAF in critically ill patients with AKI receiving CRRT is common and carries an unfavorable prognosis similar to patients with prevalent AF. Further studies are required to elucidate modifiable risk factors for NOAF occurring on CRRT and the mechanisms driving the observed association with adverse outcomes.

SA-PO147

Hypoalbuminemia Is Related with Short-Term and Long-Term Mortality in Patients Undergoing Continuous Renal Replacement Therapy

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Background: Hypoalbuminemia reflects several pathologic conditions such as nutritional deficiency and chronic inflammation. However, its relationship with short-term and long-term mortality in patients undergoing continuous renal replacement therapy (CRRT) remains unresolved.

Methods: A total of 1,581 patients who underwent CRRT due to acute kidney injury between 2010 and 2016 were retrospectively reviewed. Patients were categorized by the tertiles of albumin levels at the time of starting CRRT. Odds ratio (OR) and hazard ratio (HR) for the risk of all-cause mortality were calculated before and after adjustment of multiple covariates.

Results: Mean albumin level was 2.7 ± 0.6 g/dL. During the median follow-up period of 14 days (maximum 4 years), 1,040 patients (65.8%) died. The 1st tertile had a higher risk of mortality than the 3rd tertile with an HR of 1.9 (1.63–2.21). Although the mortality rate was stratified by the timeframe, the 1st tertile had a higher risk than the 3rd tertile as following ORs: 3.0 (2.34–3.87) in 2-week mortality; 2.7 (2.12–3.52) in 1-month mortality; 2.7 (2.08–3.53) in 6-month mortality; and 2.8 (2.11–3.62) in 1-year mortality. The 1st

tertile group had also higher rates of intensive care unit- and in-hospital mortalities than the 3rd tertile group.

Conclusions: Because hypoalbuminemia is associated with short-term and long-term mortality after CRRT, serum albumin levels should be monitored during the period of CRRT.

SA-PO148

Using Standardised Monitoring of Physiological Parameters (National Early Warning Score) to Predict AKI

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Background: Acute kidney injury (AKI) affects approximately 16% of inpatients, particularly the elderly and confers an increased length of hospital stay, medical intervention and mortality (Holmes et al, CJASN, 2016 and Kerr et al, NDT, 2014). Risk factors are well established and yet we cannot reliably identify susceptible patients before abnormal serum creatinine results, though this forms the basis of national AKI e-alert systems. In 2012, The Royal College of Physicians endorsed a National Early Warning Score (NEWS) to identify deteriorating and acutely unwell patients. The score is based on the physiological parameters of respiratory rate, oxygen saturation, systolic blood pressure, pulse rate, conscious level and temperature, with higher scores triggering urgent or immediate medical escalation. The utility of clinical early warning scores in predicting AKI severity and patient outcome has been variable (Kovacs et al, BJS, 2016; Potter et al, JICS, 2017 and Faisal et al, Clin Med, 2018). We predicted that those with high NEWS (>4) might correlate to AKI stage and form a useful pathway to highlight and appropriately escalate this patient group.

Methods: Retrospective data were collected on hospitalized patients (Jan-March 2019), identified by elevated serum creatinine results (as per national AKI reporting guidance). Highest NEWS within 5 days of AKI alert was recorded. Data sources were patient records and computerized reporting systems.

Results: 140 patients were identified (complete data for 138). NEWS is shown according to AKI stage in the table. Higher NEWS (>4) was unaffected by AKI stage (p= 0.75, 2-way ANOVA).

Conclusions: Those with stage 2 and 3 AKI did not trigger significantly higher NEWS. Whilst NEWS remains an important discriminator in escalating acutely unwell patients, it did not predict AKI or its severity. Biomarkers of AKI are in development, but clinically relevant discriminators remain elusive. Further parameters are urgently required to refine AKI alert algorithms for clinical use.

NEWS according to AKI stage

AKI stage (n=patients)	NEWS 0-4 (%)	NEWS 5-6 (%)	NEWS 7+ (%)
1 (63)	38 (60)	11 (17)	14 (22)
2 (52)	24 (46)	10 (19)	18 (35)
3 (23)	10 (43)	8 (35)	5 (22)

SA-PO149

The Development of AKI After Acute Nephrons Loss: An Unexpected Journey

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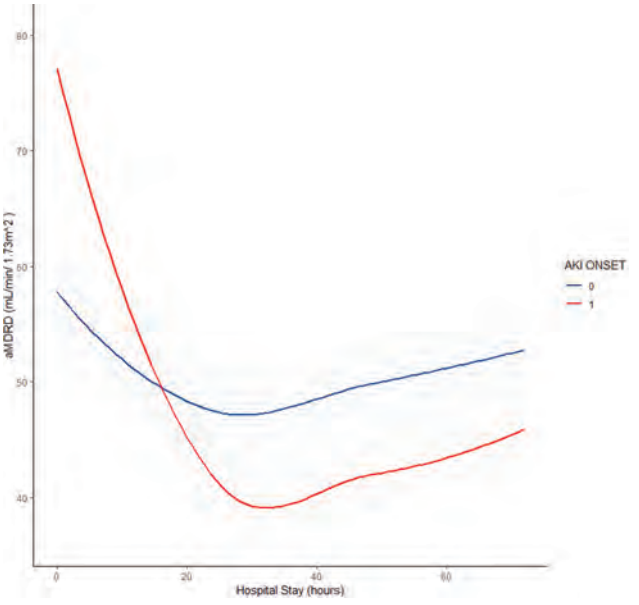
Background: Acute Kidney Injury (AKI) following radical nephrectomy (RN) is associated with an increased risk of morbidity and mortality. Up to know it is impossible to understand the major predictor for AKI developement.

Methods: We collected prospectively clinical data of a group of 195 patients who underwent RN for renal masses. To evaluate the risk of AKI after surgery, serum-creatinine (sCr) values were collected before surgery (t0), 24h and 48h after the operation (t1 and t2), and at dismissal (tf). We calculated eGFR with aMDRD formula. According to RIFLE criteria, we defined the AKI onset with a ratio of sCr/sCr(t0) higher than 1.5. A pathological evaluation using the Remuzzi Score was carried out on the healthy renal parenchima based on glomerular global sclerosis, tubular atrophy, interstitial fibrosis and arterial narrowing.

Results: In our study a strong significative correlation (p <0.001) was found with the basal eGFR at t0. In fact, the lower was the basal sCr, the higher was the risk of AKI development. A lower variation of eGFR from t0 to tf was related with the presence of tubular atrophy (p<0.01) or interstitial fibrosis (p<0.05)

Conclusions: An eGFR higher than 70 ml/min could represent an unexpected predictive cutoff of AKI development after RN. There are two possible explanation: a better medical treatment of the CKD patients; a "non adequate compensatory function mechanisms" after acute nephron loss. In fact, in healthy pts, the hyperfiltration mechanism is not yet well established (as in CKD pts) so that RN results in an unexpected trauma for the remnant kidney who will take time to restore the renal function.



Temporal pattern of renal function according AKI onset

SA-PO150

Factors Associated with AKI in Mexican Patients with Acute Coronary Syndromes

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Background: AKI is a leading cause of morbidity and mortality in hospitalized patients with ACS. The aim of this study was to identify potential risk factors and patient characteristics associated in patients with ACS.

Methods: We analyze a single center retrospective review of 77 patients with ACS. The sCr at hospital and daily during the coronary unit was available for analyzed patients to diagnose AKI. Demographics, clinical and biochemical profiles, risk factors for AKI and RRT prescription was assessed and reported during diagnosis and discharge. Outcome measures were renal recovery, mortality and causes of death. Statistical analysis was done with SPSS version 26.0. The categorical variables were analyzed using chi-square test or Fisher's exact probability test, as appropriate. The continuous variables were analyzed using the Student's t test. A value of $p < 0.05$ was regarded as statistically significant.

Results: Mean age was 65.45 ± 10.84 years and 70% were male. AKI was diagnosed in 50% of ACS cases. The mortality rate was 31% due to cardiovascular complications. Pre-existing comorbidities and other factors found to have increased association with AKI presence were: CKD (p < 0.0001), diabetes with complications (p=0.031), bacteremia (p=0.028), history of surgery complications (p<0.0001), nephrotoxic use (p=0.004) and biochemical alterations as anemia, hyperbilirubinemia, hyperglycemia, hyperlactatemia, metabolic acidosis, and elevated cardiac biomarkers (p<0.05).

Conclusions: This study shows that AKI is a frequent complication of ACS and its association with predictive factors. Further studies are needed to stablish early strategies aimed to preventing AKI or at reducing its severity might provide significant clinical benefit in patients with ACS.

Comparison of AKI presence in ACS patients

	AKI N = 39	Non AKI N = 38	p
Age (years)	67.41 ± 11.22	63.45 ± 10.19	0.818
Body mass index (kg/m2)	28.47 ± 3.97	27.98 ± 4.96	0.066
Procalcitonin (ng/ml)	26.36 ± 60.78	0.58 ± 0.93	0.001
Lactate dehydrogenase (U/L)	5522.47 ± 7329.03	742.58 ± 627.69	<0.001
Troponin I (mcg/L)	1719.92 ± 7038.70	15752.55 ± 16133.56	<0.001
B type natriuretic peptide (pg/ml)	1719.92 ± 7038.70	3039.23 ± 4928.30	<0.001
Serum creatinine (mg/dl)	15208.67 ± 9787.68	0.90 ± 0.31	<0.001
Uresis (ml)	0.50 ± 0.39	0.74 ± 0.23	0.018

SA-PO151

Predicting Major Adverse Kidney Events in the First Year After AKI

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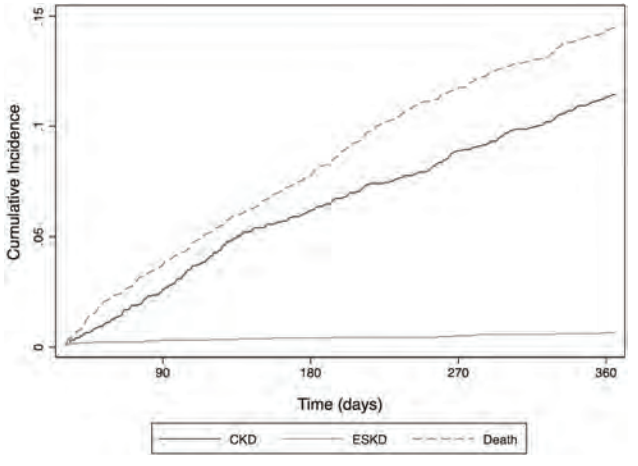
Background: Acute kidney injury (AKI) is a common complication of hospital admission, and survivors are at increased future risk of major adverse kidney events (MAKE), including chronic kidney disease (CKD), end-stage kidney disease (ESKD) and death. High-risk patients may benefit from specialist follow-up; however, the factors associated with increased risk have not been reported.

Methods: We conducted a retrospective study of all adult patients admitted with AKI to a single centre between 1 January 2012 and 31 December 2016. Cox regression models were performed to examine the primary outcome, which was the development of a MAKE in the first year following hospital discharge. The secondary outcomes (CKD, ESKD, and death) were studied using Cox and competing risk regression analyses. Candidate predictor variables included patient demographics, comorbidities, and laboratory values available at the time of hospital discharge.

Results: Of 2,101 patients included in the study, 767 patients (37%) developed a MAKE within the first year. MAKE occurred more frequently in patients who were older (HR 1.02 95% CI 1.01-1.02) and in those with a history of chronic heart failure (HR 1.41 95% CI 1.19-1.67), liver disease (HR 1.68 95% CI 1.39-2.03), and either non-metastatic (HR 1.44 95%CI 1.14-1.82) or metastatic (HR 2.26 95% CI 1.80-2.83) malignancy. They were also more common in patients with a greater severity of AKI (stage 2 HR 1.38 95% CI 1.16-1.64; stage 3 HR 1.62 95% CI 1.31-2.01) and in those with a higher serum creatinine level at discharge (HR 1.01 95% CI 1.00-1.01). Female sex (SHR 1.54 95% CI 1.27-1.88) and hypertension (SHR 1.28 95% CI 1.04-1.58) were additional risk factors for the development of CKD.

Conclusions: A significant number of patients with AKI will develop a MAKE within the first year. Clinical variables available at the time of discharge could be used to stratify risk and identify patients who may benefit from specialist follow up.



SA-PO152

AKI: A Risk Factor for Sepsis in Critically Ill Children

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Background: Acute kidney injury (AKI) affects up to 56% of pediatric patients admitted to pediatric intensive care units (ICUs) worldwide, and is now recognized as a systemic disease with numerous short and long-term complications that independently increase morbidity and mortality. Evolving evidence suggests that AKI alters innate immune function, which may place patients at increased risk for subsequent infection. We hypothesized that that critically ill children with AKI will be at higher risk of developing hospital-acquired infections compared to critically ill children without AKI. Our objective was to compare the rates of sepsis manifesting in critically ill children with and without AKI at ICU admission, while controlling for severity of illness.

Methods: Using a pediatric ICU database of 8,733 admissions, we included patients who had sufficient information to categorize AKI status, and excluded patients if they had sepsis prior to or within the first 48 hours of ICU admission. Using logistic regression analysis we evaluated the association between exposure to stage 2 or 3 AKI during the first 48 hours of ICU admission, on the development of sepsis during the 7 days following the 48 hour exposure window (days 3-9), adjusting for severity of illness and other known risk factors for sepsis. The covariates included in the final model were age, race, sex, Pediatric Index of Mortality 2 score, vasopressor use, mechanical ventilation, elective admission to the ICU, recovery from surgery and a history of heart failure, liver failure, chronic kidney disease or malignancy.

Results: A total of 5,590 patient admissions (male 58%, mean age 6.9 years) were included in the analysis. 5.2% of patients had stage 2 or 3 AKI during the first 48 hours of admission and 6.0% of patients developed sepsis on days 3 through 9 of ICU admission. The incidence of sepsis was 16.9% in patients with stage 2 or 3 AKI, as compared to 5.4% in patients without AKI. In the adjusted analysis, patients with AKI were more likely to develop sepsis (OR 2.04, P <0.001).

Conclusions: Stage 2 or 3 AKI is a significant risk factor for development of sepsis in critically ill children.

Funding: NIDDK Support

SA-PO153

The Association Between Kinetic Estimated Glomerular Filtration Rate and Clinical Outcomes: A Systematic Review

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Background: Accurate assessment of kidney function is an essential aspect of clinical care. In acute kidney injury or renal function recovery, serum creatinine lags behind true kidney function, and GFR estimation using conventional formulae is problematic when serum creatinine is not at steady state. The kinetic estimated glomerular filtration rate (KeGFR) was proposed an alternative as it takes into account changing creatinine over a period of time. The objective of this systematic review was to examine the association between KeGFR and clinical outcomes.

Methods: We conducted a systematic review of studies examining the association between KeGFR and clinical outcomes. The databases searched were PubMed, EMBASE, CINAHL, Scopus and Web of Science, searching for articles in French and English and published from 2013 until 2019. Quality of each study was assessed using the Newcastle-Ottawa scale.

Results: Of 488 articles identified, there were 19 that met inclusion criteria (12 full articles, 7 supplements/abstracts). Ten articles examined the association between KeGFR and acute kidney injury (AKI). KeGFR was not only associated with AKI, but all but one study found that that it better discriminated risk or injury in certain populations. KeGFR could also detect AKI earlier than other commonly used formulae. Four of the five studies that examined mortality found that KeGFR was associated with an increased risk of death and performed better than other biomarkers. KeGFR was also found to accurately predict delayed graft function (n=3) and discontinuation of renal replacement therapy (n=4). Two studies examining the use of KeGFR in therapeutic drug monitoring found it to be a poor predictor.

Conclusions: KeGFR has been shown to be an accurate method of predicting adverse outcomes including acute kidney injury, mortality and renal recovery, however, it appears to not be as effective when used for therapeutic drug monitoring. Prospective studies to validate its use in clinical practice are warranted.

SA-PO154

Severity of Sepsis-Associated Acute Kidney Disease and 90-Day Survival

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Background: Current evidence suggests that survival following sepsis with AKI (S-AKI) is strongly associated with recovery of renal function by hospital discharge. Acute Disease Quality Initiative (ADQI) consensus classifies persistent renal dysfunction for >7 days as acute kidney disease (AKD) with staging as per AKI using serum creatinine or dialysis. However, the relationship between AKD stage and the risks of death, chronic dialysis or persistent renal dysfunction over the following three months are unknown. Further, it is unknown if 14 or 28 day AKD status reflects 90 day status. Here, we examined the relationship between AKD at days 14, 28 and outcomes at 90 day in patients with sepsis.

Methods: We conducted a retrospective cohort study of patients admitted to any of 16 hospitals with in the University of Pittsburgh Medical Center between October 2008 and May 2014. We included critically ill adult patients who had s-AKI (stage 2-3 as per KDIGO criteria occurring after sepsis). Sepsis was identified using Sepsis-3 criteria plus an ICD9 code. We staged AKD at day 14 and 28 from first max AKI stage. Our primary outcome was survival at 90 day. We also assessed rates of dialysis and persistent renal dysfunction (>150% of baseline creatinine) as well as the composite of all three—major adverse kidney events (MAKE) at 90 day.

Results: Of 121,817 patients, 10,999 met our definition of s-AKI. Median age was 67 (IQR, 56-79) years., 50.2% were male, estimated baseline glomerular filtration rate was 70.12 (IQR, 47.19 – 93.44) mL/min/1.73m^2, APACHE III score was 61 (IQR, 46 – 78). Among the 2,402 (27.6%) patients known to have AKD on day 14, 1,897 (79%) met MAKE criteria by day 90. However, of the 2,354 (26.8%) patients known to have AKD on day 28, 2,031 (86.3%) met MAKE criteria by day 90. Overall, 182 patients (7.6%) recovered renal function between day 14 and day 28.

Conclusions: Permanent loss of renal function is more accurately assessed at day 28 compared to day 14 as well as risks for dialysis and persistent renal dysfunction in patients with s-AKI. However, day 14 evaluation may allow an early opportunity to focus attention on those patients who have not yet demonstrated evidence of renal function recovery.

Funding: Commercial Support - Atox Bio, Ness Ziona, Israel

SA-PO155

Fluid Overload Is a Major Predictor for Mortality in Critically Ill Patients with Cirrhosis and AKI

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Background: Fluid overload is associated with poor outcomes in critically ill patients with acute kidney injury (AKI), but data on whether this applies to patients with cirrhosis are limited. In the setting of portal hypertension, management of AKI can be challenging due to systemic vasodilatation and ineffective renal arterial blood flow. This study aims to determine whether fluid overload had a detrimental effect on critically ill patients with cirrhosis and AKI.

Methods: Clinical and demographic data from 81 hospitalized patients with cirrhosis transferred to the ICU with AKI were collected from a single academic medical center from 2012-2018. Fluid overload was defined as >10% weight gain after the first 3 days in ICU. The primary endpoint was 14-day survival after hospital admission. Kaplan-Meier survival and adjusted Cox hazards analyses were performed.

Results: There were no significant differences between the two groups in terms of age, sex, or etiology of cirrhosis. Non-survivors had a higher MELD-Na when compared to survivors (30 vs 22.5, p=0.001) at the time of transfer to ICU. Fluid overload in the first 3 days of ICU stay, oliguria, and the use of renal replacement therapy (RRT) were highly associated with mortality (p=0.04, 0.0004 and 0.01 respectively). Unadjusted Kaplan-Meier survival analysis demonstrated inferior 14-day survival for patients who developed fluid overload (36% vs 73%)while in ICU (log-rank p=0.006; Figure 1). A multivariable Cox Hazards model, adjusting for age, MELD-Na, and RRT, demonstrated that fluid overload after 3 days following ICU transfer was associated with a 2.45-fold increased risk of mortality (p=0.02).

Conclusions: Our data demonstrate that fluid overload in critically ill patients with cirrhosis and AKI is major predictor for short-term mortality. Prospective studies that focus on restrictive fluid management are warranted to improve care for this high-risk population.

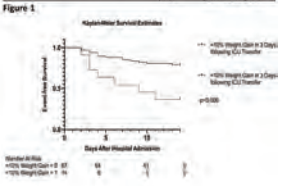
Table 1

Variables	Survivors (n=46)	Non-survivors (n=41)	p-value
Demographics			
Age (years)	64.5 (58.5 – 70)	64 (58 – 73)	0.52
Gender (male)	65%	83%	0.08
Race (AA)	30%	37%	0.36
Weight at Admission to ICU (kg)	74.7 (63.2-84.5)	82.45 (69-95.25)	0.19
Etiology of Cirrhosis			
Alcohol (%)	27.5	24.4	0.74
Hepatitis C (%)	27.5	41.4	0.19
Laboratory Values prior/at admission			
Baseline Creatinine (mg/dL)	0.98 (0.79-1.36)	0.98 (0.82-1.53)	0.31
Admission Creatinine (mg/dL)	1.65 (1.27-2.57)	1.745 (1.36-3.51)	0.07
Admission Sodium (meq/L)	137 (131-139)	132 (130-138.5)	0.52
Admission MELD-Na	22 (16-28)	26 (20-30.5)	0.07
Laboratory Values at ICU Transfer			
Sodium (meq/L)	137 (134-139)	135 (132-139)	0.19
Creatinine (mg/dL)	1.69 (1.23 – 2.93)	1.63 (1.07-4.2)	0.008
MELD-Na	22.5 (19.5-29.5)	30 (22-36)	0.001
Net Fluid Volume Balance after ICU Transfer			
Day 1 (Liters)	+0.66 (-0.24 – +3.51)	+0.83 (+0.06 – +2.24)	0.29
Days 1 and 2 (Liters)	+0.87 (-0.15 – +2.69)	+2.28 (+0.83 – +4.05)	0.10
Days 1,2 and 3 (Liters)	+0.84 (-0.43 – +2.90)	+3.43 (+0.62 – +6.51)	0.04
Average I/O change	+0.77 (-0.7 – +2.35)	+3.33 (+0.86 – +6.31)	0.02
% Weight Change	+1.8 (-0.4 – +4.8)	+3.5% (+0.8 – +8.9)	0.07
Oliguric Urine Output	74.4%	52.3%	0.0004
RRT			
Use of SLED	7.5%	29.2%	0.01
Days to RRT from ICU Transfer	1 (0 – 9)	2.5 (2 – 5.5)	0.62

Table 2

With RRT	Hazard Ratio	95% C.I.	p-Value
Weight Gain >10% in 3 Days Following ICU Transfer	2.45	1.18 – 5.45	0.02
Age	1.00	0.96 – 1.05	0.84
MELD-Na	1.04	0.99 – 1.10	0.09
RRT	1.87	0.53 – 2.26	0.84
Adjusted for RRT	**Hazard Ratio**	**95% C.I.**	**p-Value**
Weight Gain >10% in 3 Days Following ICU Transfer	2.42	1.19 – 5.56	0.01
Age	1.00	0.96 – 1.03	0.97
MELD-Na	1.04	0.99 – 1.10	0.09

Figure 1



SA-PO156

Similarity of Outcomes in Hepatorenal Syndrome and Other Forms of AKI in Cirrhosis

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Background: Recent data suggests that severe AKI from either hepatorenal syndrome type-1 (HRS-1) or acute tubular injury (ATI) may carry similar mortality, challenging the previous notion of a more ominous prognosis in HRS-1. However, those studies are confounded by uncertainties in adjudication of diagnosis imposed by retrospective designs and by the inherent limitations of the International Club of Ascites (ICA) criteria. Thus, we aimed to examine outcomes of AKI in cirrhosis via a prospective design.

Methods: We established prospective data collection in cirrhotics with AKI stage ≥ 2 (AKIN) over 1.5-years. To reduce uncertainty in diagnosis, we supplemented the standard ICA criteria for HRS-1 with supportive phenotypic criteria: urine Na <20 mEq/L, urine volume <500 ml, mean arterial pressure <80 mmHg, serum Na <135 mEq/L and absence of evidence of ATI by urine sediment microscopy (MicrExUrSed) using the Chawla score (CS). "Definite HRS-1" (Def-HRS) was assigned to those who met all ICA and supportive criteria. "No HRS-1" (No-HRS) was assigned to those with ≥1 unmet ICA criteria or CS for ATI. "Possible HRS-1" (Poss-HRS) was assigned to those who met the ICA criteria but either did not meet all supportive criteria, lacked MicrExUrSed or had a CS equivocal for ATI. Outcomes chosen: need for dialysis (RRT), discharge to hospice (Hosp), liver transplant (LT) and death at 1, 3- and 6-months post-AKI.

Results: We included 133 patients [40% women, age 58 (25-87)] in our cohort. MicrExUrSed was done in 88 (66%) patients. We categorized 29 (22%) patients as Def-HRS, 24 (18%) as Poss-HRS and 80 (60%) as No-HRS. Baseline serum creatinine [2.6 (2-4.1), 2.4 (2-3) and 2.8 (2.3-3.6) mg/dL] and bilirubin [5.6 (2.3-15.6), 5.4 (2.1-14.6) and 5.6 (2.3-14.5) mg/dL] were comparable for the 3 groups. At 30 days, need for RRT was 38%, 21% and 36% and for Hosp 41%, 33% and 28%, for Def-HRS, Poss-HRS and No-HRS, respectively. Mortality rates at 1, 3 and 6 months were: Def-HRS: 21%, 21% and 24%; Poss-HRS: 29%, 33% and 42%; and No-HRS: 35%, 43% and 44%, respectively. At 6 months, LT occurred in 15%, 17%, and 24% for each of the 3 groups, respectively.

Conclusions: Our prospective cohort with stringent adjudication of diagnosis indicates that HRS-1 is not associated with more ominous clinical outcomes compared to other forms of AKI in cirrhosis.

SA-PO157

A Decision Tree to Predict Renal Replacement Therapy Requirement in Rhabdomyolysis-Induced AKI

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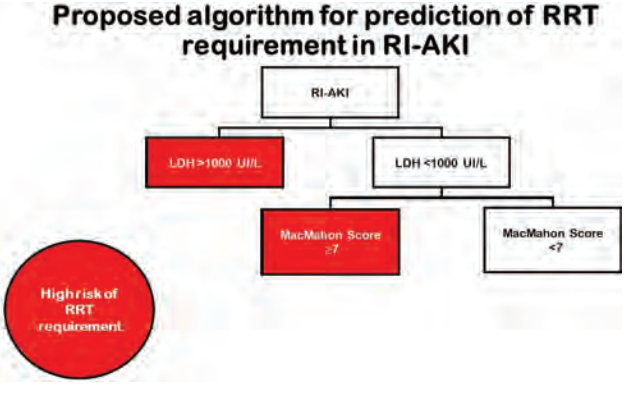
Background: Rhabdomyolysis Induced Acute Kidney Injury (RI-AKI) develops in 10-40% of patients who present rhabdomyolysis. When damage is severe enough to develop complications such as life-threatening hyperkalemia or anuria, up to 85% of patients will require renal replacement therapy (RRT). The aim of the present study was to study admission variables that predict RRT requirement.

Methods: Retrospective cohort study. All patients hospitalized for RI-AKI between 2007-2017 were included. Patients were divided according to RRT requirement and their admission parameters compared with Mann-Whitney's U test. Using ROC curves, we determined the best cut-off for lactate dehydrogenase (LDH), creatine kinase (CK) and the MacMahon score to predict RRT requirement and a decision tree was generated.

Results: We identified 42 RI-AKI hospitalizations. All patients had CK>5000 U/L. The main etiologies were drug-induced (41%) and excessive physical activity (21%). Nine patients (21%) developed stage 1 AKI, 5 (12%) stage 2 AKI and 28 (67%) stage 3 AKI. Twenty-two patients (52%) required RST. The most frequent indications for RRT initiation were anuria (64%) and hyperkalemia (32%). Intermittent hemodialysis was used in 52% of cases. The median time on RRT was 17.5 days (range 4-59). Five patients (12%) died during hospitalization due to infectious causes. On follow-up, 6 patients (14%) developed CKD. Patients with RRT requirement presented with higher serum phosphorus (6.2mg/dl [5.5-7.6] Vs. 3.3mg/dl [3.0-3.9], p<0.001), potassium (5.5mEq/l [4.8-6.3] Vs. 4.3mEq/l [3.6-4.8], p<0.001) and LDH (2124 U/l [1067-3193] Vs. 553 U/l [322-744], p<0.001). The AUC of LDH, MacMahon score and CK to predict RRT requirement were 0.873, 0.900 and 0.620 respectively. A decision tree was generated and shown in Figure 1.

Conclusions: A simple decision tree based on LDH levels and the MacMahon score at presentation can predict RRT requirement in RI-AKI



SA-PO158

Dyschloremia and Prognosis in Patients with AKI Requiring Continuous Renal Replacement Therapy

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Background: Dyschloremia is common in critically ill patients. There has been some interest in the low or high serum chloride levels as poor prognostic factor of them. However, litter is known about the impact of dyschloremia in patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT).

Methods: A total of 980 patients who received CRRT for AKI between 2009 and 2018 were collected and divided into 3 groups according to the serum chloride levels at the timing of CRRT. Thirty-day all-cause mortality and continued dialysis dependence after hospital discharge was compared among groups.

Results: The hypochloremia group (serum chloride < 98mEq/L, n = 190), normochloremia group (98 ≤ serum chloride ≤ 110 mEq/L, n = 647), and hyperchloremia groups (serum chloride > 110 mEq/L, n = 143) were divided based on the reference values of serum chloride. Compared to normochloremia group, simplified acute physiology III score were higher in hyperchloremia and hypochloremia group. On multivariate logistic regression, hypochloremia group (odd ratio, 1.38; 95% confidence interval, 1.12 - 1.69; p = 0.02) and hyperchloremia group (odd ratio, 1.57; 95% confidence interval, 1.32 - 2.54; p = 0.04) were significantly associated with mortality. In continued dialysis dependence after hospital discharge, similar trends were observed. Moreover, Kaplan-Meier analysis

revealed that mortality was significantly higher in hypochloremia and hyperchloremia groups than normochloremia group.

Conclusions: This study showed that dyschloremia was a predictor for poor prognosis in patients with acute kidney injury requiring CRRT.

SA-PO159

A Non-Steady State Adaptation of the CKD-EPI Equation

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Background: The CKD-EPI equation is one of the most widely used estimates of kidney function. It is commonly calculated whenever a plasma creatinine (pcr) is measured, although only valid when pcr is stable. Chen proposed a "kinetic eGFR" (JASN 24, 877-888 (2013)) for non-steady state conditions. Despite its name it essentially estimates a creatinine clearance (crcl). The goal of our calculations was to develop a true kinetic eGFR estimation and to improve the underlying kinetic clearance formula by explicitly including creatinine generation rate (cgr), the creatinine distribution volume (vd), and accounting for possible changes in distribution volume (deltavd).

Methods: The pharmacokinetics of creatinine are comprehensively described by equation A. To solve it for crcl requires an iterative process, so a simplified form has been used, which we modified to allow for corrections of deltavd (equation B). In steady state crcl is creatinine excretion rate (which equals cgr) divided by the pcr. To convert our kinetically determined crcl into CKD-EPI based eGFRs, we divided cgr by crcl and calculated a virtual steady state pcr. We then inserted this term into CKD-EPI. Cgr and vd were estimated with published formulas (incorporating age, gender, race, weight and height). We integrated all modifications into four final kinetic CKD-EPI formulations for female and male, as well as black and non-black, respectively.

Results: The comparison of crcl values obtained by equation B and the "gold standard" equation A demonstrated excellent agreement across physiologically plausible ranges of their variables pcr1, pcr2, vd, deltavd, time interval (t) and cgr. The final kinetic CKD-EPI equations were tested for sensitivity to deviations of cgr and vd from their estimated values. We show that differences within clinically meaningful ranges can have significant effects on the kinetic eGFR. Therefore, cgr and vd need to be checked for plausibility and adjusted (e.g. according to muscle mass, volume status) in individual patients.

Conclusions: We have developed a non-steady state adaptation of the CKD-EPI equation.

Funding: Private Foundation Support

Equation A:

$$pcr2 = pcr1\left(\frac{deltavd-vd}{vd}\right)^{-1\frac{crclt}{deltavd}} + \frac{cgr\left[1-\left(\frac{deltavd-vd}{vd}\right)^{-1\frac{crclt}{deltavd}}\right]}{crcl=\frac{deltavd}{t}}$$

Equation B:

$$crcl = -\frac{deltavd}{t} + \frac{2\left[cgr-\frac{(-pcr1-pcr2)\,vd}{t}\right]}{pcr1+pcr2}$$

SA-PO160

How to Estimate Kidney Function in AKI via the Basic Clearance: Role of the True Average (Creatinine)

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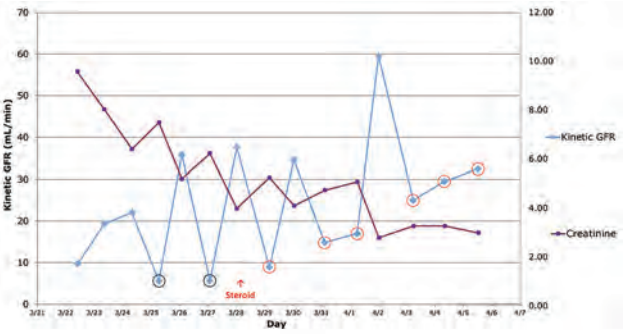
Background: The basic clearance formula U×V/**P** has a single **P**lasma creatinine ([Cr]), so it seems to apply only in the steady state. Can U×V/P be used in the non-steady state when there are multiple values of P? We postulate that if all the P's in a [Cr] trajectory are represented by a "true average" [Cr], then dividing by this one P will recreate the kinetic GFR.

Methods: Working from *any* differential equation that models creatinine kinetics, we can take the novel step of using the fundamental theorem of calculus at the start. This produces a definite integral that calculates the average (not the simple mean) of a [Cr] vs. time function, our candidate true average [Cr]. It ends up in the denominator after solving for kinetic GFR, fitting the template of U×V/P.

Results: To use the true average [Cr] to compute kinetic GFR, we present two techniques, a graphical one and a numerical one—Newton's method. Both yielded identical answers for kinetic GFR, verifiable by a gold standard technique. But the true average method arrived at the answer faster than the gold standard and without any false solutions. In analyzing a recent case, the kinetic GFR aided clinical decision-making on a 74-year-old man whose creatinine rose subacutely from 1.10 to 9.57 mg/dL. Intermittent dialysis was done, giving the [Cr] plot a sawtooth pattern (Fig., in purple). Despite an overall decline in [Cr] at first, the kinetic GFR (in blue) showed no improvement in his kidney function, since the "valleys" in between dialyses sank down to the same low level. Later, a renal biopsy (3/26) revealed acute interstitial nephritis, and prednisone was started (3/28). The next kinetic GFR valley (3/29) was slightly higher, hinting at an early renal recovery. The valleys kept increasing (3/31-4/5), telling us that the steroid was working and so dialysis was stopped.

Conclusions: The clearance paradigm applies to the non-steady state as well if the true average [Cr] is the divisor, providing a fundamental strategy to deduce the kinetic GFR from the plasma [Cr] trends occurring in real-life acute kidney injury or renal recovery.



SA-PO161

Kidney Recovery in Patients Discharged with AKI Requiring Hemodialysis to Outpatient Centers

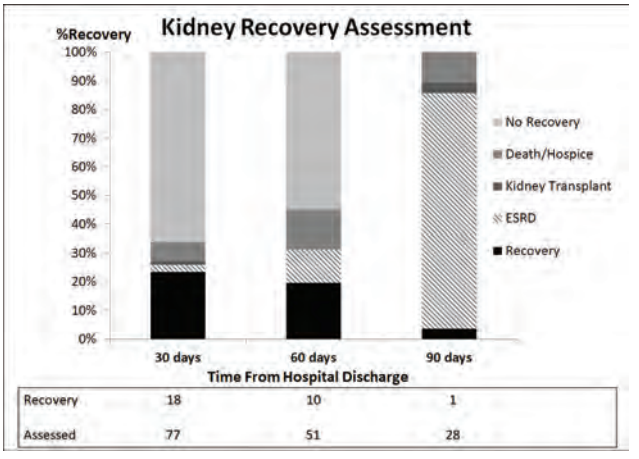
Melissa R. Jordan,[1] Victor M. Ortiz-Soriano,[1] Lauren Chism,[1] Aaron Pruitt,[1] B. Peter E. Sawaya,[2] Hartmut H. Malluche,[1] Javier A. Neyra.[2] [1]*University of Kentucky, Lexington, KY;* [2]*University of Kentucky Medical Center, Lexington, KY.*

Background: As of January 2017, patients with acute kidney injury requiring dialysis (AKI-D) can be discharged to outpatient centers for continued hemodialysis (HD) support. We aimed to examine kidney recovery and time-to-recovery in these patients.

Methods: Single-center, prospective cohort study of 118 adult patients who were admitted to the University of Kentucky Hospital (7/2017-2/2019), suffered from AKI-D and were discharged to non-academic affiliated outpatient HD centers. Kidney recovery was defined as the patient being alive and no longer requiring HD and was assessed at 30-day intervals up to 90 days post discharge.

Results: Of the 118 patients diagnosed with AKI-D during the index hospitalization, 15 patients were declared ESKD prior to discharge. We excluded patients that were prisoners (n=2) or were lost to follow-up (n=19). There were 5 patients that were misclassified as ESKD at their HD center despite being discharged as AKI-D. Among the remaining 77 patients, mean (SD) age was 54.4 (16.0) years; 61% were male and 88.3% white. Overall 29 (37.6%) patients recovered kidney function, about two-thirds of them within the first 30 days of hospital discharge [**Figure**].

Conclusions: At least 1 out of 3 AKI-D patients discharged to outpatient HD units with continued HD need recovered kidney function within 90 days of hospital discharge. The majority of patients recovered kidney function within 30 days of discharge, illustrating a critical window for surveillance and intervention. Future studies should focus on identifying best practices to promote recovery in this susceptible population.



Kidney recovery assessment in patients discharged with AKI requiring hemodialysis to outpatient centers

SA-PO162

The Value of Body Composition Analysis in Predicting the Prognosis of Patients with AKI Undergoing Continuous Renal Replacement Therapy

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Background: To investigate the value of nutritional and fluid status measured by bioelectrical impedance methods in predicting the prognosis of AKI patients undergoing continuous renal replacement therapy (CRRT).

Methods: Patients with severe AKI treated with CRRT in the first affiliated hospital of Nanjing medical university from Sep.2016 to Sep.2018 were prospectively enrolled, and divided into death group and survival group according to 28-day survival. Cox regression was used to analyze the association between 28-day survival and lean Tissue Index(LTI), fat Tissue Index(FTI), the ratio of extracellular water(ECW) and body cell mass (BCM) (ECW/BCM), and overhydration (OH), respectively.

Results: A total of 156 patients were included, including 101 males and 55 females. The average age was 62.7±15.4 years, with an average SOFA score of 9.9±3.9. The 28-day mortality rate was 46.2%. The pre-CRRT OH values and ECW/BCM values of the 28-day survival group and death group were 3.0(1.8, 5.5) L vs. 4.2(3.0, 5.7) L (P=0.016), 1.00(0.76, 1.18) vs. 1.07(0.88, 1.25) (P=0.033), respectively. Pre-CRRT high OH values (HR=0.83,95%CI=0.72-0.95,P=0.008) and high ECW/BCM values (HR=6.79,95%CI=1.72-26.82,P=0.006) were associated with 28-day death, while LTI and FTI were uncorrelated with 28-day death. The changes of OH values (HR=0.83,95% CI=0.72~0.95, P=0.008), ECW/BCM values (HR=6.79,95% CI=1.72~26.82, P=0.006) and FTI values (HR=1.12,95% CI=1.02~1.22, P=0.023) between pre-CRRT and the 7th day after CRRT initiation were significantly associated with 28-day mortality in patients survived 7 days after CRRT initiation. After adjusting for age, gender, and SOFA scores, the high OH value before CRRT, the changes of OH values, ECW/BCM values and FTI values between pre-CRRT and the 7th day after CRRT initiation, were independently associated with 28-day death.

Conclusions: In bioelectrical impedance analysis, the OH value and ECW/BCM value before CRRT is associated with 28-day mortality in patients with AKI, while the nutritional indicator LTI is not significantly related. The correction of fluid overload by CRRT within 7 days may reduce the 28-day risk of death.

SA-PO163

Preoperative Low Urine Specific Gravity Levels Predict AKI After Cardiac Surgery

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Background: Acute kidney injury (AKI) is a common and serious complication following cardiac surgery. However, strategies that could effectively stratify AKI risk before cardiac surgery are scarce. Recent investigations identified urinary osmolality to be associated with non-glomerular kidney damage in patients who are at higher risk for CKD progression. Patients with underlying kidney damage, although clinically insignificant, may be prone to cardiac surgery associated AKI. Hypothesizing that urine specific gravity (SG) could reflect kidney damage, the clinical implication of preoperative urine specific gravity on AKI occurrence after cardiac surgery was investigated in subjects with normal kidney function.

Methods: A total of 4135 patients who underwent coronary artery bypass or valve surgery at Yonsei University Health System from were enrolled. Patients whose eGFR was lower than 60mL/min/1.73m^2 were excluded. Fasting urinary specific gravity was measured from the morning first void a day before the surgery. The patients were divided into tertiles based on urine specific gravity. The primary outcome was the incidence of AKI within 48hours of cardiac surgery. AKI was defined according to Acute Kidney Injury Network criteria.

Results: The mean age of the patients was 60 years and 60% were male. Diabetes consisted of 25.6% of the patients and 54.5% were hypertensive. The mean eGFR and urine SG was 98.8mL/min/1.73m^2 and 1.020, respectively. AKI developed in 1,089 (26.3%) patients. The incidence of AKI was highest in the lowest urine SG tertile group (410, 29.0%) and lowest in the highest tertile group (304, 23.5%) (P < 0.001). Multivariable logistic regression analysis revealed that being included in the lowest preoperative urine SG tertile group was significantly related with higher post cardiac surgery AKI incidence risk (odd ratio (OR), 1.33; CI, 1.12-1.57; P =0.001). This association was significant even after adjustments were made for confounding factors.

Conclusions: Low urine SG was associated with increased risk of cardiac surgery associated AKI in patient with normal renal function. Evaluating preoperative urine SG may be useful in stratifying post cardiac surgery AKI risk.

SA-PO164

External Validation of an Electronic Health Record (EHR)-Based Machine Learning Risk Score for Hospital-Based AKI

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Background: We seek to externally validate our previously published EHR-based machine learning AKI risk score in data from a new hospital system.

Methods: All hospitalized patients who had SCr measured at Loyola University Medical Center (LUMC) from 2008 to 2016 were eligible. Patients with a first serum creatinine (SCr)>3.0mg/dl, those who had an ICD codes for CKD Stage 4 or higher, or received renal replacement therapy(RRT) within 48 hours(hrs) of admission were excluded. Demographics, vital signs, laboratory results, and nursing scores were utilized in the previously published gradient boosted machine learning algorithm based on data from the University of Chicago (UofC) to predict SCr-based KDIGO AKI. Areas under the curve (AUC) were calculated in the LUMC cohort, and subgroup analyses were conducted across admission SCr, AKI severity, and hospital location.

Results: Among the 194,930 included LUMC patients, 27,374 (14.0%) developed KDIGO AKI with 7,364 (3.8%) developing Stage 2 and 3,393 (1.7%) requiring RRT. These rates were similar compared to the UofC cohort (14.4% AKI, 3.5% Stage 2). The AUC (95%CI) of the model in the LUMC cohort was 0.80(0.80-0.80) for predicting Stage 2 AKI within 48 hrs compared to 0.86(0.86-0.86) in the UofC cohort. The AUC was 0.80(0.80-0.80) for Stage 3 in 48 hrs in the LUMC cohort. AUCs for subgroups (patient location and admitting SCr) at LUMC (24 and 48 hr predictions) can be found in the table.

Conclusions: We report the first externally validated machine learning EHR-based AKI risk algorithm. EHR data can be used to predict impending AKI prior to significant changes in SCr across different patient locations and baseline SCr values. We are using this validated EHR model in real-time in an active clinical trial seeking to improve AKI outcomes.

Funding: NIDDK Support

Validation of EHR Risk Score in Subgroups Based on Patient Location and Admission SCr

	AUC (95%CI) for Predicting Stage 2 AKI within 24 hrs in LUMC cohort	AUC (95%CI) for Predicting Stage 2 AKI within 48 hrs in LUMC
Patient Location		
Ward	0.80 (0.80 - 0.80)	0.75 (0.75 - 0.75)
ICU	0.77 (0.77 - 0.77)	0.74 (0.74 - 0.74)
Admission SCr (mg/dL)		
<1.0	0.81 (0.81 to 0.81)	0.78 (0.77 to 0.78)
1.0 to 1.9	0.84 (0.84 to 0.84)	0.80 (0.80 to 0.80)
2.0 to 2.9	0.87 (0.86 to 0.87)	0.83 (0.83 to 0.84)

LUMC- Loyola University Medical Center Validation Cohort

SA-PO165

Identification and Performance Evaluation of AKI Trajectory Subtypes Associated with Mortality and Kidney Recovery in Critically Ill Patients

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Background: Few risk-prediction models focus on outcomes specific to critically ill patients with AKI. We developed and evaluated the performance of a novel machine learning model called Trajectory of Acute Kidney Injury (TAKI) for the prediction of mortality and kidney recovery.

Methods: Independent cohorts from two academic institutions were used: UK (discovery, n=37,095) and UTSW (validation, n=10,590). Exclusion criteria consisted of age <18, eGFR <15 or ESKD, kidney transplant, absence of ≥2 serum creatinine (SCr) measures, absence of SCr-criteria of AKI in the first 7 ICU days or ICU stay <48 h. First, a trajectory based on KDIGO-AKI SCr-severity classification was composed for every patient using repeated SCr measures up to 7 days. Second, for trajectories with different length, population-based dynamic time-warping was developed for alignment. Third, the distance between any two aligned trajectories was computed and then adjusted using AKI severity. Fourth, hierarchical clustering was adopted with a dynamic merging process to determine the final trajectory subtypes, which were used as features for predicting hospital mortality and major adverse kidney events (MAKE) at 90 days following discharge (composite of death, RRT dependence or inability to recover 50% of baseline eGFR).

Results: The incidence of AKI was 33.4% (UK) and 27.0% (UTSW). Hospital mortality rates were 24.4% and 13.7% and MAKE rates 38.3% and 36.2% in UK and UTSW cohorts, respectively. TAKI identified improving, stationary and worsening AKI subtypes associated with outcomes beyond severity classification. TAKI improved prediction of mortality and MAKE when added to severity classification of AKI or multiorgan failure scores in both cohorts [**Table**].

Conclusions: TAKI is a feasible method of AKI subtyping that informs risk-stratification of mortality and kidney recovery in critically ill adults with AKI beyond current AKI severity classification. Further validation is needed.

Performance metrics (95%CI) of TAKI for the prediction of mortality and MAKE (UK cohort)

	SOFA Mortality	SOFA+TAKI Mortality	KDIGO Mortality	KDIGO+TAKI Mortality	KDIGO MAKE	KDIGO+TAKI MAKE
AUC	0.66 (0.65-0.68)	0.76 (0.74-0.77)*	0.63 (0.61-0.64)	0.73 (0.71-0.73)*	0.64 (0.62-0.65)	0.77 (0.76-0.78)*

*p<0.001 for performance comparison to corresponding reference; absolute IDI% (9.2-10.9) and continuous NRI% (46.5-61.4)

SA-PO166

Recovery Patterns After AKI Differentiate Risk of Long-Term Adverse Kidney Outcomes

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Background: Whether the trajectory of kidney function 72 hours after AKI informs long-term clinical outcomes, including CKD, dialysis and death, is unknown.

Methods: We prospectively enrolled patients who survived 90 days after hospitalization with or without AKI in ASSESS-AKI. Resolving AKI was defined as a decrease in SCr of 0.3 mg/dL or 25% from maximum in the first 72 hours after AKI diagnosis. Non-resolving AKI was defined as all AKI cases not meeting the 'resolving' definition. The primary outcome was a composite of major adverse kidney events (MAKE), defined as incident or progressive CKD, incident dialysis or death. Time to event analyses were completed conditioning on: demographics, comorbidites and KDIGO stage of AKI.

Results: We evaluated 772 participants with AKI and 831 participants without AKI over a median of 4.8 years. Among the AKI group, 479 (62%) had a resolving AKI pattern and 294 (38%) had a non-resolving pattern. The unadjusted incidence rate for MAKE was 5.5 events per 100 patient years in participants without AKI, 11.1 events in resolving AKI and 15.4 events in non-resolving AKI **(Figure 1)**. The adjusted hazard ratio (aHR) for MAKE was higher for both resolving (aHR, 1.76; 95% CI, 1.17 to 2.63; p=0.006) and non-resolving (aHR 2.54; 95% CI, 1.69 to 3.81; p<0.001) AKI compared to participants without AKI. Within the AKI population, non-resolving AKI was associated with a 45% greater risk of MAKE (95% CI, 17% to 78% greater; p<0.001) compared to resolving AKI. The higher risk of MAKE in non-resolving AKI was due to a higher risk of incident and progressive CKD.

Conclusions: The 72-hour time period post AKI diagnosis distinguishes the risk of MAKE. The identification of AKI recovery patterns may improve patient risk stratification, facilitate prognostic enrichment in AKI clinical trials, and recognize patients who may benefit from nephrology consultation.

Funding: NIDDK Support

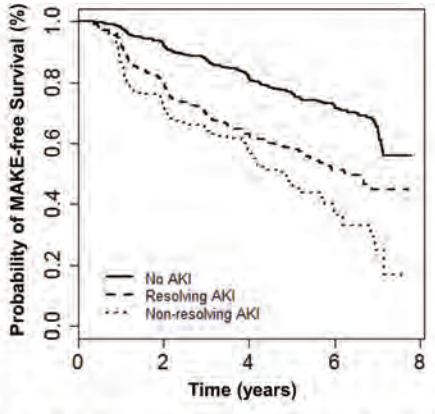

Figure 1. Kaplan-Meier plot demonstrates the highest risk for major adverse kidney events (MAKE) among participants in the non-resolving AKI recovery group with a step-wise decrease in risk for MAKE in the resolving AKI group and then in participants without AKI. MAKE is defined as the composite of death, dialysis, CKD incidence, or CKD progression during study follow-up.

SA-PO167

Crizotinib-Induced Pseudo-AKI: A Case Report

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Introduction: The appearance of treatment-related Acute Kidney Injury (AKI) or the worsening of a pre-existing Chronic Kidney Disease (CKD) often limit the correct administration of many potentially life prolonging Oncological treatments. Crizotinib is a multikinase inhibitor, used to treat ALK-traslocated non-small cell lung cancers (NSCLC). Chronic and acute (mainly due to competitive inhibition of creatinine at renal proximal tubule) kidney failure possibly related to Crizotinib treatment have been described

Case Description: A 59 year old male came to onconephrological evaluation with stage 5 CKD (creatinine 6.1 mg/dl, urea 76 mg/dl, no clinical signs of uremia); he had a solitary kidney after a previous right nephrectomy for urothelial carcinoma, and carried a left ureteral stent for concomitant nephrolithiasis. More importantly, he had a metastatic ALK-traslocated NSCLC previously treated with Cisplatin-based chemotherapy (CT), which lead to a first episode of AKI and then to CKD, presently treated with Crizotinib 250 mg b.i.d. with optimal disease control. Creatinine levels worsened from 1.6 mg/dl post nephrectomy, to 2.2 post CT, to 4 mg/dl after Crizotinib. The oncological treatment was thus stopped. When referred to us, a kidney sequential scintigraphy with Tc 99mDTPA was performed, which showed a glomerular clearance of 26 ml/min (vs a CKD-EPI of 9.2 ml/min and a Cockroft Gault of 13.2 ml/min). We thus postulated that CKD worsening could be due to the inhibition of creatinine tubular secretion by Crizotinib. We thus recommended to restart Crizotinib treatment at the reduced dose of 250 mg o.d., suggesting to perform more frequent urotelial stent changes. Two years after restarting Crizotinib, the patient is still on treatment, with stable oncological disease, as well as renal function

Discussion: Crizotinib may induce inhibition of creatinine tubular secretion together with creatinine increase, thus mimicking AKI on CKD. This case highlights the importance of renal scintigraphy in assessing these patients, as well as the role of Onco-Nephrologist

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De Novo Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits After Allogeneic Stem Cell Transplant

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Introduction: Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID) is a rare form of monoclonal gammopathy of renal significance (MGRS). Here we describe an unusual presentation of de novo PGNMID occurring in patient who underwent allogeneic stem cell transplant two years prior to the diagnosis.

Case Description: A 71-year-old male underwent matched related allogeneic stem cell transplant (SCT) for acute myelogenous leukemia (AML). The donor was the patient's brother. The patient's relevant medical problems at the time of transplant included enlarged prostate, status post prostatectomy, and previous acute kidney injury events attributed to sepsis and hypotension in the setting of chemotherapy administered for AML. At the time of transplant, serum creatinine was 1.5 mg/dL (eGFR 47 ml/min). Urinalysis was devoid of hematuria and proteinuria. Post SCT, he developed graft vs host disease involving the gastrointestinal tract which was treated with steroids. Subsequent restaging bone marrow biopsies showed no residual AML. Two years post SCT, he developed nephrotic syndrome associated with a rapid rise in serum creatinine to 4.5 mg/dL (eGFR 12 ml/min), and hematuria. Serum testing showed a new monoclonal IgG kappa, and kappa free light chain of 4.8 mg/dL (kappa/lambda ratio of 2). Kidney biopsy revealed a diffuse mesangial and endocapillary proliferative glomerulonephritis with immunofluorescence microscopy revealing capillary loop pseudolinear reactivity for IgG (2+), kappa (2+), and C3 (3+), with no reactivity for lambda. A subsequent bone marrow biopsy was negative for plasma cell neoplasm or lymphoma as was the flow cytometric analysis.

Discussion: To our knowledge, this is the first reported case of PGNMID following allogenic SCT. Similar to many other reported cases, a plasma cell clone was not identified via histologic examination of the bone marrow. Given the time of PGNMID diagnosis post SCT, transfer of plasma cell disorder from the donor is one consideration to explore by testing the donor for monoclonal dysproteinemia. This case illustrates the importance of considering MGRS in the differential diagnosis of kidney disease and proteinuria in patients with history of stem cell transplant.

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Ibrutinib-Induced Acute Tubular Injury: A Case Series and Review of the Literature

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Introduction: CLL is the most prevalent form of leukemia in adults. Treatment with Bruton tyrosine kinase pathway inhibitor, ibrutinib has revolutionized its treatment. HTN and tumor lysis syndrome (TLS) with ibrutinib are known but acute tubular injury (ATI)

has not been reported. Here, we describe 2 cases of biopsy proven ATI associated with ibrutinib and review its nephrotoxicity.

Case Description: Case 1: 63 year old man with CLL was started on ibrutinib with excellent disease control for the past 3.5 years. His baseline creatinine was 1.4 mg/dl but since starting therapy had slowly increased to 2.0 mg/dl. Non-invasive workup was unremarkable and hence underwent a kidney biopsy. This showed mild ATI on a background of mild chronicity. There was suspicion for low grade vascular injury on light microscopy but no endothelial injury was noted on electron microscopy. Clinically he had no HTN nor any lab evidence of microangiopathic hemolysis. Considering the unfavorable cytogenetics of his CLL and good disease control decision was made to continue ibrutinib and at 6 month follow up his creatinine continues to be stable. Case 2: 59 year old man with CLL was started on ibrutinib 6 months before nephrology consultation. His baseline creatinine was 1.1 mg/dL but with treatment slowly increased to a peak of 2.71 mg/dL. His BP was normal. Non-invasive workup was unremarkable and hence underwent a kidney biopsy which showed ATI alone. Based on absence of any other etiology of his kidney injury a diagnosis of ibrutinib associated ATI was made and ibrutinib was discontinued. One month later his serum creatinine had improved to 2.37mg/dL.

Discussion: We reviewed the FAERS quarterly legacy data file for ibrutinib associated adverse events (third quarter of 2014 to fourth quarter of 2018) and overall >600 events were reported of which >25% were for AKI. Conclusion: In addition to TLS and HTN, ATI can be seen with ibrutinib. Hematologists and nephrologists need to be aware of this rare but important toxicity of ibrutinib.

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Severe Placental Insufficiency 3 Years After Treatment with Bevacizumab: An Epigenetic Effect?

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Introduction: We report on a patient whose second pregnancy was complicated by severe intra uterine growth retardation and early preeclampsia with the HELLP syndrome, three years after she had been treated with Bevacizumab for breast cancer.

Case Description: A 26-year-old patient had had an uneventful first pregnancy in 1998. Ten years later, she was diagnosed with grade I intra ductal triple negative breast carcinoma, and treated with partial mastectomy, chemotherapy associated with Bevacizumab, and radiotherapy. Three years later, bilateral ovariectomy was about to be performed, when an unexpected pregnancy was found at echography. The patient elected to pursue this pregnancy. Severe intra uterine growth retardation occurred, and cesarean section had to be performed at 29 weeks of amenorrhea, because of preeclampsia with the HELLP syndrome. Four months later, blood pressure and renal function were normal, and there was no proteinuria. No congenital or acquired thrombophilia was found.

Discussion: Our patient had severe placental insufficiency during her second pregnancy, three years after treatment with conventional chemotherapy and Bevacizumab for breast cancer. Conventional chemotherapy, even if used during pregnancy, is not associated with an increased risk of preeclampsia (1). In non-pregnant patients, Bevacizumab may induce a preeclampsia-like syndrome, which disappears when treatment is stopped (2). In our patient, one may speculate that former bevacizumab treatment caused a long-lasting alteration of the balance of angiogenic and antiangiogenic factors, which was later revealed during pregnancy, a distinctly unusual event in that context. Antiangiogenic drugs can alter the transcription profile of acetylation genes in retinal cells (3). This very unusual observation supports the hypothesis that Bevacizumab may have long-lasting endothelial effects through epigenetic pathways. (1) Massey Skatulla L *et al.* Arch Gynecol Obstet 2012; 286 : 89-92 (2) Cross SN *et al.* Rev Obst Gynecol 2012; 5: 2-8 (3) Hamid MA *et al.* Ophtalmic Surg Lasers Imaging Retina 2018; 49 : S29-33

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Monoclonal Immunoglobulin Tubulointerstitial Deposits in Kidney in Sjogren Syndrome with MALT Lymphoma: Occam's Razor or Hickam's Dictum

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Introduction: Monoclonal gammopathy is a common phenomenon in patients with MALT (Mucosa Associated Lymphoid Tissue) lymphoma likely due to clonal production of paraproteins by lymphoplasmacytic cells, which responds to B cell directed therapy. We report a case of Sjogren's disease and MALT lymphoma with rearranged kappa light chain, serum monoclonal gammopathy, and monoclonal IgM-kappa tubulointerstitial deposits in the kidney, that presented with a challenging therapeutic dilemma

Case Description: 60 yo woman with Sjogren's disease presented with a subacute rise in creatinine from 1.4 to 1.8 mg/dl and 1 gm proteinuria. Work up was positive for low C3, undetectable C4, positive RF. SIFE showed weak IgM-kappa band, urine immunofixation showed kappa bence jones protein. Kappa/Lambda free light chain ratio was 23. She had a h/o parotid mass 2 years ago, diagnosed on excisional biopsy to be extra-nodal marginal zone lymphoma with IHC positive for CD20 and PCR showing rearranged kappa light chain. Repeat CT showed persistent low level + FDG activity in left eye and parotids that was decided to be monitored. A kidney biopsy was obtained that showed IgM kappa tubulointerstitial deposition disease with polytypic chronic active interstitial nephritis. Immunohistochemistry analysis revealed polytypic T cell predominant immunophenotype with no evidence of lymphoma. A subsequent work up included a bone marrow biopsy that showed a polytypic plasma cell population (0.6% of the cells) with a K/L ratio of 3:1. Immunohistochemistry showed polyclonal plasma cells. There was no evidence of myeloma or lymphoma. Considering the above, it was concluded that the low level lymphoma was likely the source of monoclonal protein and a decision was made to treat with B cell directed therapy only.

Discussion: Monoclonal gammopathy has been reported with MALT lymphomas but this is the first case in literature with associated monoclonal IgM-kappa tubulointerstitial deposition disease in the kidney. It is important to work up these patients for another clone producing site since it impacts decision making about immunosuppression. Close follow up is needed for monitoring renal and hematologic recovery.

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Rituximab Administration Unveils Monoclonal Gammopathy of Renal Significance (MGRS)

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Introduction: Cryoglobulinemic renal disease occurs in the presence or the absence of serological markers. In this case type I cryogobulinemia-associated MGRS was diagnosed after rituximab (Rx) administration.

Case Description: A 52 yr old man was evaluated for moderate proteinuria with no extrarenal manifestations. Laboratory evaluation disclosed low C3 and increased antistreptolysin titer. Ramipril treatment did not affect urinary protein excretion. On kidney biopsy, there were PAS positive proteinaceous thrombi obliterating capillary lumens in a focal segmental pattern. These findings were suggestive of cryoglobulinema. Immunofluorescence revealed intramembranous deposits positive for C3 and IgM κ chains (Figure1). Cryocrit increased from traces to 2% (Table 1). Anti HCV antibodies, rheumatoid factor, ANA, ANCA were negative. No paraprotein was detected. Treatment with Prednisone and subsequently with Rx had no effect. After Rx, the patient developed severe nephrotic syndrome and renal dysfunction. Cryocrit rose to 3% and IgM κ paraprotein appeared for the first time on immunofixation. A bone marrow biopsy showed 4-8% monoclonal plasma cells positive for IgM κ. Treatment with Bortezomib, Cyclophosphamide and Dexamethasone resulted in resolution of nephrotic syndrome and normalization of renal function.

Discussion: B cell suppression after Rx exposed the serum IgM/κ originating from a small clone of plasma cell and responsible for MGRS. A Bortezomib based protocol induced complete clinical and serological remission.

Table 1. Clinical course and response to treatment.

Year	2014	2015	2016	2017	2019
Urinary protein excretion (mg/24 hr)	945	1680	4600	11900	127
Serum creatinine (μmol/L)	70	79	79	203	88
Serum albumin (g/L)	42	39	36	23	43
Cryocrit	Trace	1%	2%	3%	Trace
Free kappa/lambda (κ/λ) light chains ratio*	NA	2.1	1.8	2.7	1.4
IgM κ**	NA	Negative	Negative	Positive	Negative
Treatment	ACE Inhibitors	Prednisone	Rituximab	Bortezomide, Cyclophosphamide. Dexamethasone	ACE Inhibitors

NA:not available; ACE: angiotensin converting enzyme

*Normal range: 0.26-1.65; ** Immunofixation.

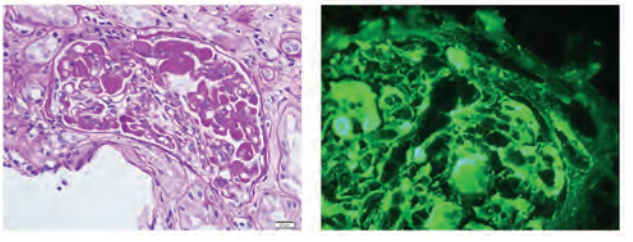

Figure 1.

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Amyloidosis Returns

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Introduction: AL Amyloidosis is the most common type of systemic amyloidosis and frequently involves the kidney. Renal outcomes in renal AL Amyloid post autologous stem cell transplant (ASCT) depend on hematologic remission, initial organ injury and depth of organ response. We describe a case of renal AL amyloid who developed worsening kidney function and nephrotic range proteinuria 3 years post ASCT and presented a challenging diagnostic and therapeutic dilemma.

Case Description: A 71 yo male presented with nephrotic syndrome with 5 gms proteinuria and had a renal biopsy revealing renal amyloidosis with lambda restriction. There was 50% interstitial fibrosis and tubular atrophy. Workup showed IgG Lambda monoclonal protein in serum and urine, normal troponin and mildly elevated NT-pro-BNP.

Skeletal survey was negative. ECHO showed EF of >70% with normal wall thickness. Bone marrow (BM) showed 70% cellularity with 15-25% plasma cells cytoplasmic lambda, and CD 38 and 138 were positive. Patient received cyclophosphamide, bortezomib and dexamethasone followed by ASCT. Following transplant, he developed acute kidney injury requiring short term dialysis with creatinine stabilizing at 1.6-1.8 g/dl and a proteinuria of 1-2 gms. BM biopsy post ASCT was negative. Serum immunofixation (SIFE) was negative. 3 years later, he presented with subacute rise in proteinuria to 8 gms and a serum creatinine of 2.5-3 mg/dl. He had a second kidney biopsy that showed lambda light chain restricted AL amyloidosis, with global sclerosis or obliteration by amyloid in 42% of glomeruli, tubular atrophy (70% of cortex), diffuse interstitial fibrosis and amyloid deposition. SIFE remained negative and Kappa/Lambda ratio was 1.3. A repeat BM biopsy was negative. Minimal residual disease testing on BM was also negative. There was no evidence of cardiac or hepatic amyloid. Considering the above, this was ascertained to be progression of the original amyloid disease and no further treatment was considered.

Discussion: We present a case of AL amyloidosis treated with chemotherapy and ASCT and remained in complete hematologic remission, but three years later presented with worsening renal failure and proteinuria with repeat kidney biopsy showing extensive amyloid deposits. This case highlights the importance of distinguishing between recurrence and progression of renal amyloidosis post ASCT by detailed hematologic work up and ruling out extra-renal disease.

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Autologous Stem Cell Transplant for the Treatment of Masked Crystalline Light Chain Tubulopathy and Podocytopathy Causing FSGS in the Context of Monoclonal Gammopathy of Renal Significance

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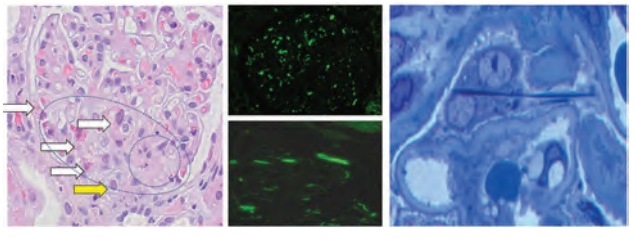
Introduction: MGRS encompasses a wide spectrum of renal histopathology. Light chain (LC) crystalline podocytopahty causing secondary FSGS has rarely been described. We present a case with masked crystalline tubulopathy and podocytopathy associated with MGRS which was treated with myeloma induction therapy followed by autologous stem cell transplantation (ASCT).

Case Description: A 47 year old male presented with nephrotic proteinuria (uPCR 760 mg/mmol), microscopic haematuria and renal impairment (Creatinine 146umol/l, eGFR 49ml/min). Autoimmune, virology screen, Complement were normal. Protein electrophoresis (SPEP) showed IgG kappa paraprotein 11g/l. Serum free light chain (SFLC) ratio was 9.5 (kappa level 91.3mg/l, lambda 9.6mg/l). No cryoglobulin was detected. Renal biopsy showed features of secondary FSGS. Immunofluorescence (IF) was negative for IgG, IgM, IgA, c3, c1q and equal kappa/lambda staining. We performed IF on paraffin sections after protease digestion unmasking crystalline inclusions in podocytes and tubules showing kappa LC restriction. Bone marrow biopsy (BMAT) showed 10-12% plasma cells. Normal skeletal survey. In conjunction, BMAT and renal biopsy results were in keeping with MGRS with an unusual histology of masked FLC-crystalline in tubules and podocytes causing FSGS. Treatment included VCD chemotherapy with partial response followed by melphalan conditioned ASCT. One month post ASCT renal function and proteinuria improved(Creatinine 120 umol/l, eGFR 60 ml/min).

Discussion: MGRS must be suspected in all patients with kidney disease and paraprotein regardless of the tumour burden. Protease digestion may be needed to unmask FLC restriction and should be considered in selected cases. Effective haematological treatment improved renal outcome.



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Minimal Change Nephropathy as a First Manifestation of Waldenstrom Macroglobulinemia

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Introduction: Waldenstrom's macroglobulinemia (WM) is an uncommon disease, with rare renal presentation. We report a case of nephrotic syndrome (NS) resulting from minimal change nephropathy (MCN) as a first presentation of WM.

Case Description: A 60-year-old woman presented with progressive generalized edema over 3 months. Her physical examination showed severe edema in both legs and mildly pale conjunctiva. Urinalysis revealed 3+ protein with bland sediment. Urine protein creatinine ratio (UPCR) was 7.28. Blood tests were hemoglobin (Hb) 9.3 g/dL, Cr 1.48 mg/dL and serum albumin 1.7 g/dL. Serum protein electrophoresis had no signs of monoclonal gammopathy. Serum kappa/lambda ratio was 5.51. Bence-Jones proteinuria was negative. Renal biopsy revealed unremarkable glomerular capillaries and mesangium on light microscopy. An immunofluorescent study unveiled trace kappa and IgM. Electron microscopy showed diffuse foot process effacement without electron-dense deposits. This patient was given a diagnosis of MCN, and prednisolone was started. After 6 weeks of corticosteroid treatment, her clinical outcomes did not improve, with her anemia worsening. The results of further investigations showed immunofixation: IgM kappa monoclonal gammopathy. The bone marrow biopsy had 85% dense atypical small lymphoid cell infiltration. The WM diagnosis was rendered, and treatment instituted with rituximab, cyclophosphamide, vincristine, prednisolone (R-CVP). WM went into partial remission, and MCN was in complete remission (UPCR 0.22, Cr 0.7 mg/dL) after 5 courses of R-CVP.

Discussion: MCN's good response to chemotherapy suggests a relationship between MCN and WM. However, the pathogenesis of MCN in WM remains unclear. It was suggested in cases of MCN associated with classic Hodgkin lymphoma that excessive production of inflammatory cytokines could alter the glomerular filtration barrier. An imbalance in T cell subpopulations, a significantly low ratio of CD4:CD8 and the decrease of T regulatory cells (Tregs), may be associated with the occurrence of MCN. More recently, clinical evidence of the effectiveness of B cell depletion via rituximab, an anti-CD20 monoclonal antibody, in different forms of NS has theorized a role for B cells as drivers of MCN. Moreover, targeting B cells may affect the cross-talk between T and B cells.

SA-PO176

Combination of Immune Checkpoint Inhibitor and Antiangiogenic Therapy for the First-Line Treatment of Advanced Renal Cell Carcinoma: A Combined Analysis of Three Phase 3 Randomized Controlled Trials

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Background: Management of advanced renal cell carcinoma (RCC) is an area in dire need of therapeutic innovation. Sunitinib, a tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF), has been the standard first-line treatment of advanced RCC for the past decade. Recently, combination of immune checkpoint inhibitor (ICI) and antiangiogenic agent has shown survival benefits. The purpose of our study is to stratify the efficacy of combination of ICI and antiangiogenic therapy for the first-line treatment of advanced RCC, according to international metastatic RCC database consortium (IMDC) risk groups and PD-L1 status.

Methods: PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through May 2019 were queried. RCTs utilizing upfront combination of ICI and antiangiogenic therapy in patients with advanced RCC were incorporated. A generic inverse variance method was used to calculate the estimated pooled hazard ratio (HR) for progression-free survival (PFS) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q -statistic.

Results: A total of 2662 patients from 3 phase III RCTs were included. The study arm used pembrolizumab+ axitinib, avelumab+ axitinib or atezolizumab+ bevacizumab while control arm utilized sunitinib. The randomization ratio was 1:1 in all studies. The I2 statistic for heterogeneity was 0%, suggesting homogeneity among RCTs. The PFS benefit was observed in all IMDC risk groups, including favorable group (HR, 0.70; 95% CI: 0.52- 0.96; P = 0.02), intermediate group (HR, 0.71; 95% CI: 0.60- 0.84; P < 0.0001) and poor group (HR, 0.58; 95% CI: 0.42- 0.80; P = 0.0009). The PFS benefit was only noted in PD-L1 positive (≥1%) cohort with HR of 0.66 (95% CI: 0.57- 0.77; P < 0.0001).

Conclusions: Our study showed that combination of immune checkpoint inhibitor and antiangiogenic therapy significantly improved PFS compared to standard sunitinib in patients with advanced RCC, regardless of IMDC risk categories. However, PFS benefit was only noted in PD-L1 positive cohort and further strategies are warranted in PD-L1 negative subset.

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Incidence of AKI in Melanoma Patients Treated with Immune Checkpoint Inhibitors

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Background: Immune checkpoint inhibition (ICI) had a major clinical success in clinical oncology. Immune related adverse events (irAEs) are well described toxicities. Unlike other common irAEs, the incidence of renal toxicity is reported 3.8% with varied definitions of AKI. In this study we sought to retrospectively review a single center 10 year experience of patients diagnosed with Melanoma and treated with CPI and evaluate incidence of AKI and overall survival.

Methods: We performed a retrospective chart review from 2008-2018 and extracted all patients treated with ICI. We identified 1691 unique melanoma patients and extracted

all available creatinine. We have defined AKI based on KDIGO guidelines. 1st definition: as an absolute increase in serum creatinine of 0.3 mg/dl within 48 hours and 2nd as 50% relative increase in serum creatinine within 7 days. Time to first AKI was defined as time from treatment initiation to time of AKI. Cumulative incidence rate of AKI after initiation of ICIs were calculated in the presence of death as a competing risk. The effects of covariates on the cumulative incidence function of AKI were evaluated in the univariate setting using Gray's test. Validity of the proportional cause-specific hazards and sub-distribution hazards assumptions were assessed using the proportionality test on time-varying covariates.

Results: Ipilimumab was the most commonly used ICI (27.63%). Incidence of AKI at median time of duration of treatment of 110 days using 1st definition was at 2.76% and using 2nd definition was at 3.25%. Patients older than 60 years of age (median) had a higher experiencing AKI than the younger patients. Compared to the patients treated with pembrolizumab, the patients treated with ipilimumab (HR3.68), ipilimumab /nivolumab (HR 5.271) Ipiliumab/Nivolumab/pembrolizumab (HR 4.284), ipiliumab/pembrolizumab (HR 7.285), nivolumab/pembrolizumab(HR 6.639) had significantly higher risk of experiencing AKI using both definitions.

Conclusions: With such a large population of melanoma patients treated with ICI we have the first accurate documentation of AKI in setting of ICI use and confirmation of incidence that has been reported. In addition, it's an expansive look at predictors of AKI and the use of ipiliumuab and combinations of ICI more associated with AKI. Impact of AKI on survival is underway.

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Incidence of Nephrotoxicity Secondary to PD-1/PD-L1 Inhibition: A Single Health Center Experience

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Background: Immuno-check point inhibitors (CPI) such as PD-1/PD-L1 inhibitors alone or in combination with other chemotherapeutic medications have been used to treat variety of metastatic neoplasms with amazing effects in recent years. However, cases of their associated nephrotoxicity become more often seen. Here we present a single health center experience of identifying CPI associated nephrotoxicities in renal biopsies and their follow-up data.

Methods: Over past 17 months (till April 2019), we have had approximately 620 cases of renal biopsies from our eight-hospital system (4000 beds in total) in Southeast Michigan. Seven indicated native renal biopsies were performed to evaluate renal pathology in patietns who were treated with CPI for various metastatic neoplasms, but developed acute kidney injury. Conventional light microscopy, immunofluorescent stains and electromicroscopy wrere used to assess renal pathology and clinical correlations were conducted.

Results: The cases are summarized in Table below. The identified cases represent 1.1 % of our renal biopsies. Typical acute interstitial nephritis (AIN) (composed of dominant CD3 positive T lymphocytes) was seen in five of seven patients (Table below) but remaining two patients' biopsies without AIN had either chromic thrombotic microangiopathy (TMA) or acute tubular injury (ATI). Three out the five patients with CPI induced AIN had significant recovery of renal function after steroid treatment, while other two AIN cases had limited renal functional recovery.

Conclusions: Since our first cases seen at the end of 2017, there have been increased incidence of nephrotoxcitiy cases due to CPI treatment, most characterized by T lymphocytes mediated AIN. Some patients had a good renal function recovery in response to steroid treatment.

Clinical and Pathologic Indices, and Follow-up Renal Function

Age/Gender/Tumors	CPI	Pre-sCr (mg/dl)	Biopsy diagnosis	Follow-up sCr (mg/dl)
68M, renal cell carcinoma	Opdivo	8.3	AIN, moderate	2.47
62M, lung cancer	Keytruda	2.0	AIN, moderate	1.93
66M, lung cancer	Keytruda	4.0	AIN, moderate	1.01
84F, lung adenocarcinoma	Opdivo	2.7	AIN, mild	0.95
82M, melanoma	Opdivo	2.9	TMA	1.77
38M, bladder cancer	Keytruda	2.0	AIN, mild	1.89
77M, lung cancer	Keytruda	1.9	ATI, mild	1.15

M - male; F - female

SA-PO179

A Single-Institution Study of Renal Outcomes in Patients Receiving Checkpoint Inhibitors

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Background: Checkpoint inhibitors (CPI) are becoming more widely used for various malignancies. The reported incidence of renal toxicities has varied, with a lower incidence reported in clinical trials but significantly higher in follow-up retrospective cohorts. Here, we present a single-institution retrospective study monitoring renal function in patients receiving CPI treatment.

Methods: An IRB-approved retrospective analysis was performed using patients seen at Moffitt Cancer Center between 1/1/2015 and 1/1/2016 who were receiving CPI therapy (ipilimumab, nivolumab, pembrolizumab or any combination). Selected patients had up to 12 months follow-up including laboratory analysis of renal function. If available, serum electrolytes and urine studies were also collected. Primary endpoint was acute kidney injury (AKI), defined as increase in serum creatinine by > 0.3 mg/dL or ≥ 50% from baseline.

Results: 206 patients were selected with most common diagnoses of melanoma (81%) or NSCLC (12%). Most patients (79%) also had stage 4 disease. There were 19 patients who had AKI, with a median age of 73 vs 68 in the non-AKI group (p = 0.057). There was no difference in HTN, DM, CKD stage, baseline creatinine, or baseline blood pressure between groups. There was no correlation between AKI and specific CPI therapy or combined CPI therapy. In the AKI group, there was a higher incidence of concomitant antihistamines (42% vs 15%, p = 0.003) and diuretics (37% vs 17%, p = 0.03). In the AKI group, 10 discontinued all CPI therapy due to disease status (progression or surveillance). 4 patients had AKI associated with autoimmune toxicity (2 colitis, 1 pancreatitis, 1 autoimmune nephritis) that resolved with steroids and stopping/changing CPI. 6 patients continued therapy without interruption, 4 had resolution of AKI. 5 patients had increasing SBP (>20 mmHg) at the time of AKI.

Conclusions: In our cohort, CPI therapy was well-tolerated from the standpoint of renal function. Of the 19 (9%) patients who experienced AKI, only 4 patients (1.9%) had AKI associated with autoimmune-related toxicity. Our data suggest the concomitant use of other potentially nephrotoxic drugs (e.g., antihistamines, diuretics) may be associated with increased risk of AKI.

SA-PO180

Incidence of Rash and Palmar-Plantar Erythrodysesthesia in Patients with Advanced Renal Cell Carcinoma Treated with First-Line Combination Therapy with Checkpoint Inhibitors

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Background: Renal cell carcinoma (RCC) is the most common form of kidney cancer and clear cell RCC, the most common histology, harbors genetic abnormalities involved in angiogenesis via production of vascular endothelial growth factor (VEGF). Sunitinib has been the standard first-line treatment of advanced RCC for the past decade with notable dermatologic toxicities. We performed a combined analysis of randomized controlled trials (RCT) to determine the risk of rash and palmar-plantar erythrodysesthesia (PPE) with newer first-line combination therapies with checkpoint inhibitors.

Methods: PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through May 2019 were queried. RCTs utilizing upfront checkpoint inhibitors combination therapy in patients with advanced RCC were incorporated. The primary meta- analytic approach was a random effects model using the Mantel-Haenszel (MH) method. It was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI).

Results: Four phase III RCTs including 3758 patients with advanced RCC were eligible. The study arm used nivolumab+ ipilimumab, pembrolizumab+ axitinib, avelumab+ axitinib or atezolizumab+ bevacizumab while control arm utilized sunitinib. The randomization ratio was 1:1 in all studies. The I2 statistic for heterogeneity was 98%, suggesting some heterogeneity among RCTs. Any-grade rash was reported in 295 (15.8%) vs 205 (11.0%) in control group with RR of 1.43 (95% CI: 1.21 –1.69, P < 0.001). High-grade rash was noted in 13 (0.7%) in study arm vs 6 (0.3%) in control arm (RR, 1.41; 95% CI: 0.36 –5.51, P = 0.62). Any-grade PPE was 289 (15.5%) in study arm vs 741 (39.8%) in control arm. The pooled RR was statistically significant at 0.21 (95% CI: 0.06 –0.71, P = 0.01). High-grade PPE was noted in 47 (2.5%) vs 124 (6.6%) in control group with RR of 0.20 (95% CI: 0.03 –1.59, P = 0.13).

Conclusions: Upfront checkpoint inhibitors combination therapy notably decreased the risk of any-grade PPE, a major cause of morbidity and one of the feared dermatological toxicities, with a RR of 0.21, despite increasing the risk of any-grade rash.

SA-PO181

Monoclonal Immunoglobulin Deposition Disease: Experience in a Single Institution

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Background: Recently described proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGNMID) has become of interest as it typically has clinically significant course, with a membranoproliferative (MPGN) pattern on light microscope, and selective glomerular deposition of an entire monoclonal immunoglobulin by IF. There is often no hematologic malignancy to explain the findings, leading to therapeutic difficulties.

Methods: We reviewed our MIDD cases (7/1/2017-5/1/2019).

Results: The prevalence of MIDD is 3% (28/860), including entire monoclonal immunoglobulin or light and heavy chain deposition disease (L&HCDD, n=12), renal light chain (AL) amyloidosis (n=13), κ light chain deposition disease (KCDD, n=1), and γ heavy chain deposition disease (HCDD, n=2). The L&HCDD group had 9 cases of monoclonal IgG deposition disease (PGNMID), with a predominant MPGN pattern, and 3 cases of monoclonal IgA DD, with a predominant mesangial glomerular involvement. Bone marrow (BM) was biopsied in 6/12 of the L&HCDD cases; 3 showed abnormalities. Serologically, 6/12 had no M-spike; 1 case with M-spike had negative BM workup; 1 case had an M-spike without BM biopsy; and 1 case had no serological workup. 7/9 PGNMID cases received bortezomib based treatment. Pre- and post-treatment proteinuria was 8.76±9.95 and 1.75±2.06; creatinine was 1.97±0.64 and 1.94±0.81mg/dL. Other MIDD cases had a clear connection with BM malignancy: multiple myeloma in 9/13 amyloid cases and all HCDD and KLCDD cases;1 case had a negative BM evaluation but a IgG-λ circulating paraprotein.

Conclusions: L&HCDD is almost as common as AL amyloidosis, and much more common than LCDD or HCDD. Despite not identifying a monoclonal disease in many of our PGNMID cases, bortezomib based treatment resulted in good renal outcomes.

Table: Clinical and histological characteristics of monoclonal immunoglobulin deposition disease

	Overall	L&HCDD	KCDD	HCDD	Amyloidosis
N of patients	28	12	1	2	13
Age (y)	63.0±20.7	54.4±26.8	50****	65±5.7	71.5±11.6
Male sex	12 (42.9%)	2 (16.7%)	1 (100%)	0	9 (69.2%)
Cr at renal biopsy (mg/dL)	2.19±1.38	1.68±0.72	NA*****	3.17±1.83	2.49±1.68
Urine Pro:Cr ratio at renal biopsy	5.89±7.40	5.97±8.63	NA*****	3.13±1.24	6.42±6.93
Cr at last follow-up (mg/dL) *	2.48±2.14	1.44±0.71	NA*****	2.2****	3.34±2.63
Urine Pro:Cr ratio at last follow-up	3.70±3.70	2.12±2.32	NA*****	NA	5.68±4.47
BM biopsy (%)	20 (71.4%)	6 (50%)	1 (100%)	2 (100%)	12 (92.3%)
Evidence of monoclonal Ig in circulation (%)**	21 (75%)	7 (58.3%)	1 (100%)	2 (100%)	11 (84.6%)
Follow-up time (months)***	7.2±9.0	6.5±5.7	0	5.7±7.4	8.8±12.0
ESRD or Death	4 (14.3%)	2 (16.7%)	1 (100%)	0	1 (7.7%)
Histological Parameters					
IF		IgG3-kappa: n=4 IgG1-kappa: n=3 IgG3-lambda: n=1 IgG-lambda: n=1 IgA-lambda: n=2 IgA-kappa: n=1	Kappa light chain	Gamma3 heavy chain: n=1 Gamma1 heavy chain: n=1	Lambda light chain: n=9 Kappa light chain: n=4
Global sclerosis (%)		22.58±22.63	0	5.5±3.5	24.13±18.60
Tubular atrophy and interstitial fibrosis (%)		24.58±18.40	10.0%	12.50±3.54	28.54±20.01

*only patients not progressed into ESRD are included in this calculation.

**evidence include bone marrow biopsy, serum/urine immunofixation, and/or serum protein electrophoresis.

***time from renal biopsy to the last follow-up or ESRD/death.

****only one data point available

*****on hemodialysis at the time of renal biopsy

SA-PO182

Outcomes of Renal Transplantation in Monoclonal Immunoglobulin Deposition Disease

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Background: Renal involvement in monoclonal immunoglobulin deposition disease (MIDD) is close to 100%. Therapies have dramatically improved in the last 2 decades leading to deeper hematologic responses and longer disease-free survival, however renal organ survival is lagging behind and progression to end stage renal disease (ESRD) is frequent. Data on overall survival (OS) and renal transplant outcome in this patient population are limited.

Methods: We report the outcomes of 23 patients with MIDD of whom 6 patients underwent renal transplantation. All patients were followed in the Amyloidosis Center at Boston University School of Medicine between January 1989 and December 2018.

Results: At the time of diagnosis median age was 51.7 years, median eGFR was 22 mL/min/1.73m^2 (range, 4-91) and median proteinuria was 3g (range, 0.8-12). At censor, 9 of the 23 patients (39%) were deceased. One, 5 and 10-year survival from diagnosis were 95%, 78% and 65%, respectively. Renal organ response was achieved only in 5 patients (22%) after a median time of 1 year (range, 0.9-1.2) from diagnosis. One, 5 and 10-year renal survival from diagnosis were 72%, 36% and 21%, respectively. Twelve patients (52%) reached ESRD. Fourteen of the 18 patients (78%) who received first line treatment with high dose melphalan/stem cell transplantation (HDM/SCT) or bortezomib achieved a very good partial response or complete response. In the renal transplant patient group (n=6), shortest survival from diagnosis was 13.7 and the longest was 27.7 years. Three patients were still alive with functioning grafts at censor: 1.7, 2.8 and 6.5 years after renal transplantation. Grafts were lost either due to disease recurrence after 0.3 and 3.8 years or as a result of patient's death 20.3 years from renal transplantation. Median OS from diagnosis of patients who progressed to ESRD was significantly better for those who underwent renal transplantation vs. those who did not (19.8 vs. 8.3 years, p= 0.016). Median OS from dialysis initiation was also better in this group of patients; however the difference was not statistically significant (p=0.06).

Conclusions: Renal transplantation is a viable option for some patients with MIDD and these selected patients have improved OS.

Funding: Private Foundation Support

SA-PO183

Impact of Autologous Stem Cell Transplantation on Renal Response in Multiple Myeloma Patients with Advanced Renal Failure

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Background: This study aimed to evaluate the impact of autologous stem cell transplantation (ASCT) on renal outcomes of multiple myeloma (MM) patients who had advanced renal failure with estimated glomerular filtration rates (eGFR) ≤60 ml/min/1.73m^2 at the time point of transplantation.

Methods: In our ASCT database from July 2009 to September 2018, 76 MM patients with median eGFR of 36.6 (range, 5.4-59.8) ml/min/1.73m^2 at ASCT were included: 47 (61.8%) with eGFR ≥30 and <60ml/min/1.73m^2; 16 (21.1%) with eGFR ≥15 and <30ml/min/1.73m^2; and 13 (16.9%) with eGFR <15ml/min/1.73m^2 and/or hemodialysis-dependent. Myeloma and renal response after ASCT were evaluated using the international myeloma working group response criteria.

Results: During median follow-up of 37.3 (range 0.9-108.3) months, transplant-related mortality occurred in seven patients (9.1%). Overall myeloma response was achieved in 70 patients (92.1%): 6 (7.9%) of partial response (PR), 12 (15.8%) of very good partial response (VGPR), and 52 (68.4%) of complete response (CR). Median year-probability of myeloma progression-free survival (PFS) and overall survival were 23.2 (95% CI, 16.9-32.1) and 61.5 (95% CI, 43.6-69.8) months, respectively. Among 20 patients (26.3%) who achieved renal response, including 19 (25.0%) of renal CR and 1 (1.3%) of renal PR, median time to achieve partial response was 267 days (range, 3-2022). In subgroup (n=29) with baseline eGFR <30 ml/min/1.73m^2, 21 patients (53.8%) achieved renal response after median 53 (3-1756) days post ASCT. In multivariate analysis, IgA type, advanced eGFR (<30 ml/min/1.73m^2), and shorter duration from diagnosis to ASCT (<6.6 months) were associated with higher cumulative rate for achieving renal response.

Conclusions: Clinical outcome of myeloma patients after ASCT was favorable. Patients with advanced renal failure may benefit from early ASCT.

SA-PO184

Monoclonal Gammopathy-Associated Thrombotic Microangiopathy

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Background: Thrombotic microangiopathy (TMA) is characterized by end-organ damage and classic histopathologic findings secondary to endothelial injury. Microangiopathic hemolytic anemia (MAHA) often accompanies the TMA. TMA in the setting of monoclonal gammopathy has been reported after hematopoietic stem cell transplant or with proteasome inhibitors in multiple myeloma (MM) but it is less clear if the monoclonal gammopathy itself may be involved in pathogenesis.

Methods: Cases were obtained from 6 institutions in the United States and Canada. TMA was confirmed histologically (kidney biopsy) or evidence of MAHA with thrombocytopenia (platelet count less than 150 x 10^9/L) and schistocytes, elevated lactate dehydrogenase (LDH), decreased haptoglobin, and indirect hyperbilirubinemia.

Results: Of the 9 patients, (33.3%) were female. The median age was 66 years. Five patients had MM (4 were treatment naive, 1 previously received melphalan and prednisone), one had Waldenstrom macroglobulinemia (WM), and 3 had monoclonal gammopathy of undetermined significance. The patient with WM had previously been treated with cyclophosphamide, rituximab and dexamethasone. No patient had otherwise received any medication associated with drug-induced TMA. All patients had renal involvement and a median creatinine of 3.3 mg/dl. Seven patients had a kidney biopsy and all demonstrated TMA. Median hemoglobin and platelet count were 108 g/L and 147 x 10^9/L, respectively. Six patients had thrombocytopenia but only 4 had evidence of MAHA. No patient had GI symptoms. ADAMTS13 level was only obtained in 1 patient and was non-deficient at 27%. Complement levels (C3, C4, total complement) were normal in 5 patients, and 1 patient had a low C4. Genetic testing for mutations in the alternative complement pathway were performed in 2 patients and were normal. Three patients were treated with plasma exchange, 1 patient initialy improved but died of multiorgan failure 6 days after presentation. One patient is awaiting treatment plan from hematology. The others have had resolution of TMA without recurrence after treatment of their disease. None of the patients received eculizumab

Conclusions: This study suggests that monoclonal gammopathies are assoicated with TMA. Disease-directed therapy should be considered first-line treatment of TMA, in addition to PLEX if there is ADAMTS13 deficiency.

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SA-PO185

Tubulointerstitial Lesions Associated with Monoclonal Gammopathies of Renal Significance

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Background: Monoclonal gammopathy of Renal Significance (MGRS) is not a benign monoclonal disorder, neither a determined disease; abridge many kidney pathologies related to low proliferative small B-cell clone, being associated with kidney-end-organ damage, therefore requiring treatment. Herein we present a series of 11 patients who had monoclonal gammopathy (MG) and performed kidney biopsy, showing tubulointerstitial MGRS.

Methods: A retrospective analysis was performed. Patients with systemic lupus erythematous, HIV infection or Hemolytic Uremic Syndrome (with TMA) were excluded. Demographic, clinical, pathological and treatment data were collected from the admission to last follow-up. MGRS were defined according to the last categorization by the International Kidney and Monoclonal Gammopathy Research Group. Proximal Tubulopathies (PT) were classified as (a) PT without cytoplasmic inclusions; (b) PT associated with interstitial inflammatory reactions; (c) LCPT with crystals, (d) Crystal storing histiocytosis and (e) miscellaneous.

Results: From a total of 329 patients who performed kidney biopsy, 29 patients were initially excluded. Were also excluded 258 biopsied patients who did not had confirmed MG diagnosis, leading to a total of 40 patients. Of them, 14 had MM, 4SMM, 1WM, 2SWM and 15 MGUS, 2 amyloidosis, 1CLL and 1NHL indolent. Of all of them, 26 had MGRS criteria (65%). In the MM group most patients presented cast nephropathy (71%, n=10). In MGRS group most patients had glomerular lesions (n=17, 65%), while 11 (42%) had tubular lesions (2 patient with both lesions). The majority of these had (b) lesions (n=7, 64%); one patient had Fanconi Syndrome with lambda deposit crystals (c); one with (a) and cell vacuolization; one with (d) and one patient had AL tubular amyloidosis (e). Patients with MGRS had 66±2,9yo, most admitted with AKI. Median SCr of 2,5 mg/dL(IQR 1,61–5,55); proteinuria 2,52 g/d (IQR 1,41-6,49); ACR 0,5 g/g (IQR 0,14-2,58) and mean hemoglobin 12,1±2,84g/dL at admission.

Conclusions: The histopathological features of monoclonal gammopathies are broad, reflected in the proposed MGRS spectrum of renal lesions. In our series with monoclonal gammopathy patients tubular lesions were diverse, but none patient had been found with crystal-storing histiocytosis, but tubular deposits were found in immunofluorescence and electronic microscopy.

SA-PO186

Effect of Bortezomib and Male Sex on the Risk for Developing Tumor Lysis Syndrome in Patients with Multiple Myeloma: A Retrospective Study

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Background: Tumor lysis syndrome (TLS) causes acute kidney injury and is a complication of cancer chemotherapy. TLS risk is classified by malignant disease type. Although multiple myeloma (MM) is a low-risk disease, treatment by novel therapies, including bortezomib, may increase TLS risk. This investigation was performed to obtain accurate information regarding TLS risk in MM patients.

Methods: We retrospectively investigated the incidences of laboratory and clinical TLS (LTLS and CTLS) in patients who received primary therapy for untreated symptomatic MM between May 2007 and December 2017. To identify potential TLS risk factors, we used univariate and multivariate logistic regression analyses to evaluate the associations between LTLS and several parameters hypothesized to be associated with an increased risk in prior reports.

Results: In total, 210 patients were included in this study. There were 17 (8.1%) and 7 (3.3%) patients with LTLS and CTLS, respectively; all CTLS patients were diagnosed due to elevated serum creatinine. Baseline characteristics were similar between patients with or without LTLS, although patients with LTLS tended to exhibit lower renal function. Multivariate analyses revealed that bortezomib-containing therapy (Bor-CT) was most strongly associated with LTLS (odds ratio (OR)=3.25, P=0.078) and male sex (OR=2.51, P=0.105). In subgroup analysis of patients treated with Bor-CT, male sex was significantly associated with increased risk of LTLS (OR=4.71, P=0.004, vs. other patients who received primary therapy) [Table].

Conclusions: Bor-CT may increase TLS risk, particularly among male patients with MM. Thus, TLS risk should be evaluated based on multifactorial.

Table. Odds ratios of laboratory TLS due to therapy regimen and sex in patients with multiple myeloma.

Therapy regimen	Sex	LTLS (+) n (%)	LTLS (-) n (%)	OR*	95% CI	OR*	95% CI
Bor-not containing	Female (n=42)	2 (4.8)	40 (95.2)	2.17	(0.19-25.50)		
	Male (n=38)	1 (2.6)	37 (97.4)	1.00	Referent	1.00	Referent
Bor-containing	Female (n=66)	3 (4.5)	63 (95.5)	2.04	(0.20-21.00)		
	Male (n=64)	11 (64.7)	53 (27.5)	8.33	(1.01-68.90)	4.71	(1.83-13.60)

TLS: tumor lysis syndrome, Bor: bortezomib, OR: odds ratio, CI: confidence interval.
*Adjusted for ISS stage 3, pretreatment serum creatinine level > upper normal limit.

SA-PO187

Assessment of Renal Impairment on the Prognosis of Newly Diagnosed Multiple Myeloma

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Background: The renal impairment (RI) at multiple myeloma (MM) ranged from 20 to 50% and RI is associated with reduced survival. The new criteria from the International Myeloma Working Group (IMWG) defined RI as serum creatinine (SCr) > 2.0 mg/dL or eGFR < 40 ml/min/1.73 m^2. If these definitions are associated to overall survival (OS) is still debatable.

Methods: All patients with newly diagnosed MM (up to three months) admitted for treatment at the Sao Paulo State Cancer Institute, between February 2012 and May 2016, were followed for a minimum of three years. Exclusion criteria were: age < 18 years; pts on dialysis; initiation of MM treatment before recruitment or exams; pts with follow up < 3 months. Chronic Kidney Disease (CKD) was diagnosed as eGFR < 60 ml/min/1.73 m^2. GFR was estimated by the CKD EPI formula. International Staging System (ISS) relyed on serum albumin (Alb) and $ß_2$ microglobulin (B2M).

Results: 255 pts were enrolled. Pts median age 61.70 ± 13.2 years (40.4% older than 65 yrs), 50.9% had hypertension and 20.4% diabetes. ECOG index was 0-2 in 61% of pts. Heavy chain IgG in 55.9% of pts and kappa light chain was in 65.8%. The Durie-Salmon stage III (DS-III) in 86.4% and ISS-III in 32.2% of pts. Exams associated with MM activity/prognosis were: 49% hemoglobin (Hb) < 10 g/dL; 13.3% total calcium (CaT) > 11 mg/dL; 45.9% Alb < 3.5 g/dL; 54.5% B2M > 3.5 mg/L; 30.6% elevated LDH. SCr was 1.06 (0.81 – 1.45) mg/dL and eGFR was 70.2 (44.5 – 91.7) ml/min/1.73 m^2. 14% of pts had RI with SCr > 2.0 mg/dL; CKD 3 was detected in 40.4% pts. Overall survival (OS) was 3.50 (1.74 – 4.95) years. No pts characteristics (age, performance, heavy of light chain type), CaT, Hb, Alb or DS-III were related to reduced OS. Neither was SCr > 2.0 mg/dL (P=0.730), eGFR < 40 ml/min/1.73 m^2(P=0.414). Variables related to low OS were CKD 3 (P=0.011), ISS-III (P=0.011) and B2M > 3.5 mg/L (P<0.0001). Elevated LDH value was marginally related to reduced OS (P=0.090). On Cox regression model, B2M > 3.5 mg/L (HR: 1.63 [1.02 – 2.63]) and abnormal LDH (HR: 1.61 [1.01 – 2.56]) were associated with lower OS.

Conclusions: KDIGO CKD definition seems to be superior to the IMWG criteria to assess the impact of RI on the prognosis of newly diagnosed MM pts. Markers of higher burden disease are strongly related to reduced survival.

Funding: Private Foundation Support

SA-PO188

Impact of Autologous Stem Cell Transplant in Myeloma Patients on Renal Function, Progression-Free Survival, and Overall Survival: A Longitudinal Analysis

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Background: Renal impairment has been negatively associated with progression free survival (PFS) and overall survival in patients diagnosed with multiple myeloma (MM). Autologous stem cell transplant (ASCT) has become a standard of care for treatment in MM. Most previous studies have assessed the safety of ASCT and the improvement in renal function in patients with MM. In our study we sought to understand how renal function was impacted over time, the predictors of renal function, progression free survival and overall survival after ASCT.

Methods: We performed a retrospective review of all MM patients who underwent ASCT at MDACC from January1, 2008 through December 31, 2013. A total of 885 none dialysis patients who received Melphalan alone as the conditioning regimen were identified. We collected demographic information, ISS stage, disease status at time of transplant (Day 0), and at last follow up. Creatinine, GFR (calculated using CKD Epi equation), calcium, and LDH were also collected at day 0, 100, 180, & 365. Given the longitudinal nature of the data, linear mixed effect models were used to study the change of GFR over time. A joint model approach for longitudinal, PFS and survival data was used to assess association of GFR with above variables. As sensitivity analyses, landmark analyses were conducted with day 0, 100, 180, and 365 days post-transplant as landmark time points.

Results: Patients' GFR at post-transplant time points were significantly higher ($p \leq 0.025$) compared to the day of ASCT. A higher ISS stage at diagnosis was significantly associated with a lower GFR ($p < .0001$) at all stages of chronic kidney disease. GFR value was not significantly associated with OS in any of the analyses described above. eGFR was not significantly associated with PFS when it was included in the models as a binary variable using median as the cutoff. However, disease status, ISS stage, response to induction prior to SCT were all associated with shorter OS.

Conclusions: The study demonstrates in a large cohort and in a longitudinal manner that MM patients who underwent ASCT did not have further decline in GFR over time. In addition, GFR was strongly associated with ISS stage. As far as OS, PFS, MM-related factors significantly impacted the survival while *GFR did not.*

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SA-PO189

Rate and Predictors of Developing Monoclonal Gammopathy of Renal Significance (MGRS) Lesion on Renal Biopsy in Patients with Positive Monoclonal Studies

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Background: Monoclonal gammopathy (MG) can cause renal damage in a subset of patients known as MGRS. However, the rate of finding an MGRS lesion on a biopsy in a patient with MG and the clinical factors that would predict the likelihood of finding such lesions remains unknown

Methods: We identified all patients that had a positive serum MG based on a positive serum electrophoresis or immunofixation between 2013 through 2018 at the Mayo Clinic Rochester. We then excluded those patients who had a diagnosis of multiple myeloma, amyloidosis, or those with a renal transplant.

Results: We identified 4257 patients who met the inclusion criteria, of which 105 had a renal biopsy (2.47%). Of the 105 patients, 25 (23.8%) had an MGRS lesions. The most common MGRS lesions included proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGNMID) (n=10, 40%) followed by cryoglobulinemic vasculitis (n=5, 20%). In the remaining 80 patients, the most common lesions included arteriosclerosis (n=19, 23.75%), diabetic nephropathy (n=14, 17.5%), ANCA associated vasculitis (n=8, 8.8%) and IgAN (n=8, 8.8%). At the time of renal biopsy, there were no differences in age, sex, serum creatinine, hemoglobin and type of light chain between 2 groups. Compared to non-MGRS patients, MGRS patients had a significantly higher systolic blood pressure (p= 0.03) and more likely to have IgG heavy chain (p =0.05). Hematuria at time of the renal biopsy was the most significant predictor of finding an MGRS lesion with an OR of 6.21 (2.1-18.3, p=0.0003), followed by proteinuria >3.5 g/d with OR of 2.61 (1.01-6.7, p=0.04), and an elevated ratio of affected/unaffected light chain (OR= 1.08, 1.0-1.16, p=0.0001). Having a combination of hematuria and proteinuria≥2 g/day was also highly predictive with an OR of 5.67 (2.0-16.1, P=0.001).

Conclusions: Among patient with a positive MG who had a renal biopsy in the absence of amyloidosis, 75% had a lesion unrelated to the MG with arteriosclerosis and DN being the most common findings. Hematuria, nephrotic range proteinuria or high risk features (hematuria+proteinuria≥2 g) were the strongest predictors of finding an MGRS lesion.

SA-PO190

Twenty-Eight Treatments of Acute Renal Failure Secondary to Multiple Myeloma (MM) with High Cutoff (HCO) Filters

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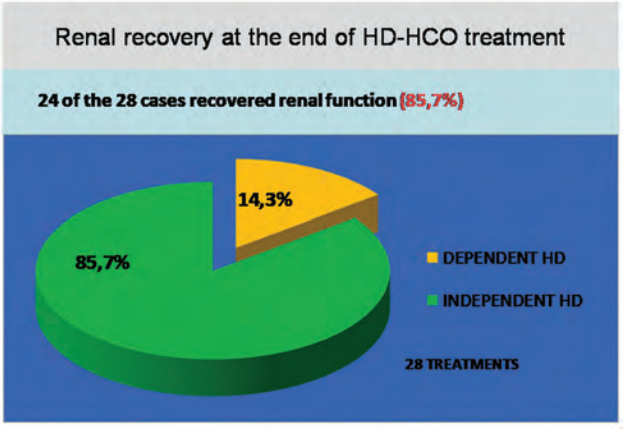
Background: Our hospital is a reference in Spain for the treatment of acute renal failure secondary to multiple myeloma with HCO filters. We present our experience with 28 treatments.

Methods: Treatment indication required the diagnosis of MM, the presence of AKI requiring dialysis, a free light chains (FLC) level greater than 500 mg/L. The patients were analytically monitored by blood sampling at the start and the end of the hemodialysis session. The dialysis protocol used was the following: daily dialysis for 6 sessions, ultrapure water, HCO filter of 2,1 meters. To pass then to dialyze every other day until reaching sFLC levels below 500 mg/L, or until the recovery of a renal function. The duration of the sessions was 6 hours. 2 vials of 20% human albumin, 50 mL, were infused in a protocolized manner during the last half hour of dialysis.

Results: 28 treatments were performed on 25 patients. The average age of the patients was 60.2 years; 17 men and 8 women. The chemotherapy regimen was based on Bortezomib and Dexamethasone as first line. 24 of the 28 cases (85.7%) recovered renal function to allow independent dialysis. At 3 months, the number of patients who remain independent of dialysis was 21 of the 28 cases treated (75%), 13 patients presented MM with Lambda chains and 12 were Kappa. The average reduction of FLC by dialysis session was 63%. The reduction in sFLC beginning and the end of the treatment reached an average of 91%. Reviewing our data in May 2019, after 8 years of treatment, we have found that 52% of patients live independently of hemodialysis, we have also compared our results with the studies that more patients have treated and we have proven that our results are beter.

Conclusions: Given our experience, we believe that prolonged hemodialysis with HCO filters is effective, safe and with a high rate of renal recovery, Thelefore its hould be the treatment option chosen, together with chemotherapy, in all patients with multiple myeloma, cylinder nephropathy and acute renal failure requiring dialysis



SA-PO191

Incidence of Hypertension and Hypothyroidism in Patients with Advanced Renal Cell Carcinoma Treated with First-Line Combination Therapy with Checkpoint Inhibitors

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Background: Utilizing immunotherapies and antiangiogenic agents has become a fundamental paradigm shift in the treatment of advanced renal cell carcinoma (RCC). Inhibition of vascular endothelial growth factor (VEGF) has antiangiogenic and immunomodulatory effects. Combination of these therapies has also shown to have synergistic antitumor activities and survival benefits. Yet, there are considerable safety concerns. We conducted a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of hypertension and hypothyroidism.

Methods: PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through May 2019 were queried. RCTs utilizing upfront checkpoint inhibitors combination therapy in patients with advanced RCC were incorporated. The primary meta- analytic approach was a random effects model using the Mantel-Haenszel (MH) method. It was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI).

Results: Four phase III RCTs including 3758 patients with advanced RCC were eligible. The study arm used nivolumab+ ipilimumab, pembrolizumab+ axitinib, avelumab+ axitinib or atezolizumab+ bevacizumab while control arm utilized sunitinib. The randomization ratio was 1:1 in all studies. The I2 statistic for heterogeneity was 98%, suggesting some heterogeneity among RCTs. Any-grade hypertension was reported in 567 (30.4%) vs 746 (40.1%) in control group with RR of 0.54 (95% CI: 0.27 –1.07, P = 0.08). High-grade hypertension was noted in 273 (14.6%) in study arm vs 317 (17.0%) in control arm (RR, 0.63; 95% CI: 0.30 –1.30, P = 0.21). Any-grade hypothyroidism was 450 (24.1%) in study arm vs 388 (20.8%) in control arm. The pooled RR was not statistically significant at 1.22 (95% CI: 0.76 –1.95, P = 0.41). High-grade hypothyroidism was noted in 5 (0.27%) vs 4 (0.22%) in control group with RR of 1.23 (95% CI: 0.33 –4.67, P = 0.76).

Conclusions: Our meta-analysis demonstrated that there was no significant increase in the risk of hypertension and hypothyroidism in upfront combination therapy group compared to standard sunitinib arm, despite achieving higher survival benefits.

SA-PO192

Graft vs. Kidney Disease in Recipients of Hematopoietic Stem Cell Transplantation: A Need for More Kidney Biopsies

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Background: Kidney biopsies are seldom done in patients with AKI after Hematopoietic Stem Cell transplant (HSCT). Graft versus kidney disease (GVKD) has not been well described. We aimed to assess the clinical and pathologic findings of patients with AKI after HSCT who received a kidney biopsy.

Methods: We conducted a chart review of 15 HSCT patients who underwent 17 kidney biopsies for AKI.

Results: Clinical characteristics and pathology results are listed in Table 1. Most patients who underwent kidney biopsy had both AKI and proteinuria. The most common biopsy finding was a mix of interstitial inflammatory cell infiltrate (GVKD) combined with acute or chronic endothelial injury, TMA (n=7, 41%). Other biopsy diagnoses included acute and chronic TMA, GVKD, acute tubular injury, and polyomavirus BK nephropathy. Immunohistochemical staining for C5b-9 was done on 7 biopsies with acute or chronic TMA and was positive in all 7. In 3 patients with GVKD and interstitial cell infiltrate, staining for granzyme B and CD3 was positive. Figure 1 demonstrates the pathology findings of a patient with AKI and biopsy diagnosis of GVKD with inflammatory cell infiltrate and chronic TMA. IHC was positive for both granzyme B in the interstitium and C5b-9 in the glomeruli and arterioles (Figure 1).

Conclusions: There is a range of pathologic findings in patients with AKI after HSCT. To understand the pathogenesis and explore therapies for AKI in HSCT we recommend a lower threshold for kidney biopsy in these patients.

Characteristic	HSCT patients (n=15)
Age (mean±SD)	58.1±9.6
Gender (% Women)	9/15 (60%)
Hematologic Malignancy AML (9) MDS (n=1) T-cell Lymphoma (n=1) MPD (n=1) ALL (n=1) Non Hodgkin's Lymphoma (n=1)	 10/15 (66.7%) 1/15 (6.7%) 1/15 (6.7%) 1/15 (6.7%) 1/15 (6.7%) 1/15 (6.7%)
Type of Transplant Matched Unrelated Donor Haplo-Cord Match Related Donor	 7/15 (46.7%) 5/15 (33.3%) 3/15 (20%)
Conditioning Regimen Fludarabine/Melphalan Fludarabine/Melphalan/TBI Fludarabine/Melphalan/Campath Azathioprine/Fludarabine/Melphalan	 7/15 (46.7%) 6/15 (40.0%) 1/15 (6.7%) 1/15 (6.7%)
Relapse after HSCT	3/15 (20%)
Graft Versus Host Disease	9/15 (60%)
Death	8/15 (53.3%)
Days from HSCT to Biopsy (median, range)	272 (115, 1000)
Mean Creatinine mg/dL at time of Biopsy (mean±SD)	2.8±1.2
Mean Proteinuria g/g	0.76±0.93
Biopsy Diagnosis (n=17) Acute TMA Chronic TMA Graft Versus Kidney Graft Versus Kidney with TMA Medication Toxicity Acute Tubular Injury/Interstitial Nephritis Polyoma Virus BK Nephropathy	 3/17 (17.6%) 2/17 (11.7%) 2/17 (11.7%) 7/17 (41.1%) 1/17 (5.9%) 1/17 (5.9%) 1/17 (5.9%)
Pathology Findings (IHC) C5b-9 staining (IHC on 8 biopsies, 7 of which had findings of endothelial injury/TMA) C4d staining (IHC on 8 biopsies)	 7/8 (87.5%, 100% of biopsies with endothelial injury/TMA) 5/8 (62.5% in small arteries where positive)
Most recent Creatinine mg/dL	3.6±2.4
ESRD or GFR <15	7/15 (46.7%)
Death with GFR<15 or ESRD	4/7 (57.1%)

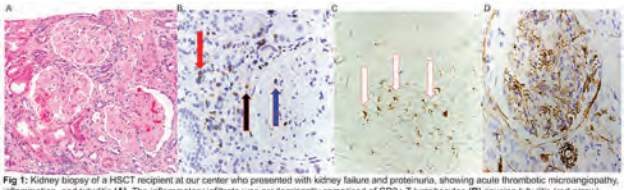

Fig 1: Kidney biopsy of a HSCT recipient at our center who presented with kidney failure and proteinuria, showing acute thrombotic microangiopathy, inflammation, and tubulitis (**A**). The inflammatory infiltrate was predominantly comprised of CD3+ T lymphocytes (**B**) causing tubulitis (red arrow), interstitial inflammation (black arrow), and glomerulitis (blue arrow). These cells were granzyme+ cytotoxic T-lymphocytes (white arrow in **C**). The glomeruli stained positive for terminal complement proteins C5b-9 (brown in **D**).

SA-PO193

Methotrexate-Induced AKI: A Retrospective Study

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Background: High Dose Methotrexate (HD MTX) defined as ≥ 1000 mg/m^2 is used to treat several tumors including lymphomas, leukemias and osteosarcoma. In a multicenter study in patients with osteosarcoma treated with HD MTX, Widemann et al reported a rate of AKI (defined as elevation in Cr 1.5-3 X ULN)of 1.8%. We aimed to look at the rate of AKI in patients receiving HD MTX across the range of primary tumors for which it is indicated.

Methods: Data was collected on all adult patients (>18 years) who received HD MTX for all diagnoses from 01/01/2003 – 12/31/2013 at a single academic medical center. We excluded patients who had received prior or concurrent cisplatin/ ifosphamide. AKI with HD MTX was defined as 1.5 fold increase in baseline serum creatinine within 4 days after HD MTX. Clinical and demographic data were collected. Data on cumulative dose (CD) of HD MTX and number of cycles was obtained in both groups.

Results: The observed rate of AKI was 32.1% (282/880). The most common malignancies treated with HD MTX were lymphoma (75.0%) and leukemia (13.6%). Table 1 shows that advanced age (64 vs 57, p<0.0001) was associated with a higher rate of AKI. CKD III was associated with a lower rate of AKI (19.5 vs 80.5, p=0.01). The (CD) of HD MTX in patients who developed AKI was lower in comparison to those without AKI (13884 ± 10135 mg vs 22820 ± 16538 mg, p=0.0001). The number of cycles for HD-MTX was lower in patients who developed AKI (2.5 vs 4.4, p=0.0001).

Conclusions: This study is the largest single center report on the rate of AKI following HD MTX treatment across all tumor types for which the drug has an indication in adults. Lower eGFR corresponding to CKD III and shorter duration of treatment with HD MTX were associated with a lower rate of AKI. A lower (CD) of HD MTX was associated with a higher risk of AKI. These findings suggest that clinicians are reducing the dose of HD MTX in patients with CKD or following an episode of AKI. Future studies on the impact of AKI on long-term renal function in patients receiving HD MTX would assess whether such dose modification is necessary and what the effect is on long-term survivorship.

Table 1

Demographic Variables	AKI (n=282)	No AKI (n=598)	p-Value
Age (years)	64 (54-73)	57 (44-68)	<0.0001
Female (%)	32.7	67.3	0.72
Male (%)	6.86	31.4	
White (%)	32.9	67.1	0.40
African American (%)	34.8	65.2	
Diagnosis for HD MTX Administration			
Lymphoma (%)	35.5	64.5	
Leukemia (%)	19.2	80.8	
Brain and Other Nervous System (%)	22.2	77.8	
Baseline eGFR			
% of patients with eGFR (<60 ml/min)	19.5	80.5	0.01
% of patients with eGFR (>60 ml/min)	33.3	66.8	
Cumulative Dose of HD MTX (mg)	13884 10135	22820 ± 16538	0.0001
Cycles of HD MTX	2.5 ± 2.2	4.4 ± 3.4	0.0001

SA-PO194

AKI in Allogeneic Hematopoietic Stem Cell Transplantation

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Background: The reported incidence of Acute Kidney Injury(AKI) after hematopoietic stem cell transplantation (HSCT) varies from 10 to 73%. The association between Graft vs Host Disease(GvHD), calcineurin inhibitors and risk for kidney injury remains controversial. We sought to describe the incidence of AKI and identify modifiable risk factors in patients undergoing allogeneic HSCT in our institution.

Methods: All patients undergoing allogeneic (non-cord) HSCT from 2014 to 2017 in our institution were included. Patient and graft characteristics associated with kidney injury were analyzed. AKI was defined using KDIGO criteria into grades 1, 2 and 3 including all serum creatinines obtained within the first 100 days after transplant. Differences across groups were assessed using either Wilcoxon rank-sum tests or Fisher's exact tests. AKI risk factors were estimated using cause-specific Cox proportional hazards regression.

Results: A total of 613 consecutive patients underwent allogeneic HSCT during the study period. Median age was 58(19-79) years, 59% male, 83% Caucasian. Indication for HSCT was leukemia in 49%, myelodysplastic syndrome in 16% and lymphoma in 17%. Median baseline creatinine was 0.8 (0.3-2.7) mg/dl. Median age-adjusted HCT-comorbidity index was 3(range 0-9). 97% patients engrafted with median time to engraftment of 12(8-33) days. Cumulative incidence of acute GVHD was 47%. By day100 postHSCT,143(23%) patients had grade 1 AKI, 153(25%) grade 2 AKI, and 78(13%) grade 3 AKI. Tcell depleted HSCT patients had a lower risk for AKI, hazard ratio 0.46 (0.35-0.62), p<0.001 (Table 1).

Conclusions: AKI in patients undergoing HSCT remains a major concern, affecting 61% of patients undergoing allogenic HSCT, with grade 2 and 3 AKI occurring in 25% and 13%, respectively. Patients undergoing T-cell depleted HSCT have lower incidence of AKI. Patients receiving GVHD prophylaxis with regimens including tacrolimus have a significantly higher risk for AKI, hazard ratio 2.63 (2.06-3.33). The effect of AKI after HSCT on long-term kidney function requires further prospective study.

Table 1: Risk factors for severe (grade 2-3) AKI

HSCT Regimen	N (%age)	Hazard Ratio (95% CI)	p-value
T-Cell Depleted	242 (39%)	0.46 (0.35, 0.62)	p<0.001
Conditioning			
Chemotherapy	461 (75%)	1	p=0.316
Total Body Irradiation	152 (25%)	0.86 (0.64, 1.16)	
GVHD Prophylaxis			
None	242 (39%)	1	p<0.001
Tacrolimus-based	263 (43%)	2.02 (1.62, 2.99)	
Tacrolimus/Sirolimus-based	37 (6.0%)	2.61 (1.58, 4.32)	
Cyclophosphamide-based	71 (12%)	1.84 (1.19, 2.84)	

SA-PO195

AKI in Critically Ill Patients After Oncological Surgery: Risk Factors and Mortality

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Background: Acute kidney injury (AKI) is a frequent complication in critically ill patients, major surgery is the second most important cause of AKI. In cancer patients AKI is associated with increased mortality, therefore it is necessary to identify modifiable risk factors for its prevention. Previous scores aimed to predict AKI in general surgery have shown poor predictive value in patients undergoing oncological surgery, possibly because these scores do not consider previously administered radiotherapy or chemotherapy. The aim of this study was to evaluate the incidence, mortality and risk factors for AKI development, defined by KDIGO criteria in patients admitted to the intensive care unit (ICU) in the first 24 hours after major oncological surgery.

Methods: We conducted a retrospective analysis using a logistic regression model to evaluate the association between preoperative and intraoperative variables with AKI, and a Cox regression model to evaluate factors associated with 12-month mortality.

Results: We included 434 patients, with a median follow-up of 432 days. We included 171 men (39%), with a median age of 53 years (IQR 41-63). All patients had solid tumors, most from gastrointestinal origin (124 patients, 29%) and female reproductive system (98 patients, 23%), and 294 (68%) underwent abdominal surgery. We diagnosed AKI in 264 (60.8%) patients: 135 (31.1%) stage-1, 66 (15.2%) stage-2 and 63 (14.5%) stage-3 AKI. In multivariate analysis, abdominal radiotherapy (OR 2.57, 95%CI 1.25-5.29, p=0.010), abdominal surgery (OR 2.46, 95%CI 1.31-4.62, p=0.005), surgical packing (OR 4.12, 95%CI 1.97-8.61, p=0.000) and sepsis (OR 2.39, 95%CI 1.31-4.37, p=0.005) were independent risk factors for AKI development, while pre-surgical albumin (OR 0.45 95%CI 0.32-0.63, p=0.000) and intraoperative urine output (OR 0.81, 95%CI 0.70-0-94, p=0.006) were protective factors. During the 12-month follow-up 108 died, and stage 2 (HR 2.90, 95%CI 1.47-5.73, p=0.002) and stage 3 AKI (HR 5.85, 95%CI 2.89-11.88, p=0.000) were associated with mortality.

Conclusions: Almost 30% of patients developed stage 2 and 3 AKI, and the associated risk factors were abdominal radiotherapy, abdominal surgery, surgical packing and sepsis. Stage 2 and 3 AKI were associated with 12-month mortality.

SA-PO196

AKI After Radical Nephrectomy as Risk Factor for CKD: Retrospective Analysis from an Italian Cancer Center

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Background: Radical nephrectomy is a significant risk factor for chronic kidney disease (CKD), and there are few reports on the renal outcome after radical nephrectomy for cancer. The aim of this study was to determine the incidence of AKI and whether postoperative AKI is associated with new-onset CKD after radical nephrectomy for renal cell cancer (RCC).

Methods: We conducted a retrospective study of 837 adult patients (>40 years old), from an Italian Cancer Centers with normal renal function who underwent unilateral radical nephrectomy for a solitary renal cortical tumor and were pathologically diagnosed with RCC between January 2010 and February 2019. Post-operative AKI was classed using risk, injury, failure, loss and end-stage kidney disease (RIFLE) criteria. CKD was defined as a decrease in estimated glomerular filtration rate (GFR) to <60 mL/min/1.73 m2.

Results: According with the RIFLE criteria, 250 of 278 patients fell into the AKI risk category 1, 21 patients fell into the AKI injury category and 6 patients fell into the AKI failure category. Multivariate analysis revealed as major result that higher preoperative GFR was an independent risk factor for postoperative AKI, although older age, male gender higher body mass index, smaller RCC size were independent risk factors too. New-onset CKD was more prevalent in the AKI risk group than in patients without AKI 1 year after surgery (56.1% versus 43.9%, respectively) and 3 years after surgery (52% versus 31%). Patients who experienced post-operative AKI had a 5.1-fold higher risk of new-onset CKD after multiple adjustments, that confirms other recent study.

Conclusions: AKI after radical nephrectomy in patients is a potent risk factor for new-onset CKD. Prevention of post-operative AKI, but also the assessment of kidney function pre-nephrectomy, is essential for reducing the incidence of CKD after nephrectomy.

SA-PO197

AKI in Patients with Haematological and Solid Organ Malignancy Receiving Chemotherapy

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Background: The aim of this study was to look at the incidence of acute kidney injury and its clinical correlates in patients with haematological and solid organ malignancies receiving chemotherapy.

Methods: All patients, more than 18 years of age receiving outpatient chemotherapy for solid organ and haematological malignancies at our hospital from Jan 2016 to Dec 2016. Incidence of acute kidney injury was computed and its causes and clinical correlates were analyzed using univariate analysis and multivariate analysis.

Results: 592 patients were included in the study. Acute kidney injury during the one-year course of chemotherapy was seen in 158 patients (27.24%). Pre-renal acute kidney injury was seen in 82 patients (51.8%) and intrinsic renal in 20 patients (12.65%) and post renal cause in 35 patients (22.15%). Sepsis was the most common cause of acute kidney injury, followed by hypovolumia. There were 13 patients where the acute kidney injury was attributed to drugs. The drugs were NSAIDS, Lenalidomide, Methotrexate, Ibrutinib, Pamidronate, Gemcitabine, Vemurafinib and Crizotinib. Patients with acute kidney injury attributed to above drugs had either a dose reduction or change in chemotherapy regimen. None of the patients had a renal biopsy to confirm drug-induced pathology. However all of the patients had resolution of AKI after stopping the drug or changing the regimen. Also of note, only one patient with Pamidronate induced acute kidney injury was referred to nephrology service. Looking at individual cancer types, 5 out of 10 patients (50%) with RCC developed acute kidney injury followed by lymphoma, prostate and myeloma. Factors associated with acute kidney injury, higher ECOG score, diabetes and hypertension were associated with higher risk of developing acute kidney injury. Contrast to other published papers, having metastatic disease and ACE inhibitors was not associated with higher risk of acute kidney injury. Acute kidney injury is associated with increased mortality. We observed the same trend in our study. Without adjusting for confounding factors, mortality in the acute kidney group at 6, 12 and 18 months was 15%, 31% and 46% compared to Non AKI group, which was 5%, 26% and 43%.

Conclusions: AKI is common in patients with malignancies and its associated with high mortality.

SA-PO198

AKI and Mortality in Umbilical Cord Transplant Recipients

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Background: Kidney injury occurs commonly after hematopoietic cell transplant (HCT) and negatively impacts outcomes. Umbilical cord blood transplantation (UCBT) is an established treatment for hematological malignancies. We sought to determine the incidence of, risk factors for, and outcomes in patients with AKI after UCBT.

Methods: Patients receiving a first UBCT at our Institution from 2006 to 2017 were included in this retrospective cohort study. AKI was defined by KDIGO stages 1-3 within the first 60 days post-transplant. Risk factors included age, gender, conditioning regimen, indication for transplant, graft vs. host disease (GVHD) prophylaxis, disease severity and clinical variables including acute GVHD, viral and bacterial infections. Cox regression models were used to identify risk factors for AKI and associations with non-relapse mortality.

Results: 276 patients were included in this study. 114 (41%) of patients developed Stage 1 AKI, 43 (16%) developed Stage 2 AKI, and 29 (11%) developed Stage 3 AKI. Risk factors prior to first episode of AKI stage 1 or higher included vancomycin use (HR=1.63; 95% CI 1.03-2.58), bilirubin rise of 1 mg/dL (HR=1.13; 95% CI 1.02-1.26), and cyclosporine level increase by 100 mg/dL (HR=1.23; 95% CI 1.13-1.34). Male gender and acute GVHD grade 2-4 were protective. Stage 2-3 and stage 3 AKI were associated with non-relapse mortality at 1 year (HR=3.26; 95%CI 1.65-6.45 and 42.41; 95%CI 16.18-111.18) respectively.

Conclusions: UCT recipients have a high frequency of stage 2 and 3 AKI. Risk factors for AKI appear to be different in the UCT population and further study is warranted to understand these differences.

Table 1. Multivariable cox regression models for more severe AKI and non-relapse mortality.

Variable	Hazard Ratio	95% Confidence interval	p-value
Age	1.03	1.01-1.04	0.0001
Gender			
Female	Reference		
Male	1.43	0.86-2.38	0.17
AKI Stage 2,3 (vs. 0,1)			
No	Reference		
Yes	3.26	1.65-6.45	0.001
AKI Stage 3 (vs. 0,1,2)			
No	Reference		
Yes	42.41	16.18-111.18	<0.0001

Model adjusted for age, gender, CMV status, and disease severity

SA-PO199

AKI Associated with Immune Checkpoint Inhibitor Therapy: Incidence, Risk Factors, and Outcomes

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Background: Immune checkpoint inhibitors (ICI) are a novel and promising anti-cancer therapy. There is limited data on the incidence, risk factors and outcomes of acute kidney injury (AKI) in patients receiving ICI.

Methods: We conducted a retrospective cohort study of patients receiving ICI at our center between 2010 and 2017 via electronic health record. The primary outcome was AKI [an increase of at least 50% from baseline serum creatinine (sCr)]. Risk factors for AKI were assessed using logistic regression. Survival among those with and without AKI was compared using time-to-event analysis.

Results: Among 309 patients on ICI, 52 (17%) developed AKI (KDIGO Stages 1: 9%, 2: 4%, 3: 4%). AKI was associated with other immune-related adverse events (IRAE) [odds ratio (OR) 3.2 (95%CI: 1.6-6.1), p <0.001], hypertension [4.3 (1.8-6.1), p<0.001] and cerebrovascular disease [9.2 (2.1-40.0), p<0.001]. Baseline sCr, cancer and ICI type were not associated with AKI. Use of ACEi/ARB [OR 2.9 (1.5-5.7), p =0.002], diuretic [OR 4.3 (1.9-9.8), p <0.001] and corticosteroid treatment [OR 1.9 (1.1-3.6), p =0.03] were associated with AKI. In the multivariable analysis, AKI was associated only with other IRAE [2.82 (1.45-5.48) p=0.002] and hypertension [2.96 (1.33-6.59), p=0.008]. AKI was not associated with increased risk of mortality [hazard ratio 1.1 (0.8-1.6, p =0.67). ICI nephrotoxicity was attributed via biopsy or nephrologist assesment in 12 patients (6 intersitial nephritis, 2 membranous nephropathy, 2 minimal change disease, 2 thrombotic microangiopathy). Re-challenge with ICI occurred in 12 patients with AKI, 1 (8.3%) had recurrent AKI.

Conclusions: AKI incidence during ICI therapy may be greater than previously reported and several etiologies must be considered. A minority of patients undergo kidney biopsy. The development of other IRAE is associated with AKI risk. AKI was not associated with worse cancer survival.

Table 1: Logistic regression for risk factors associated with AKI

Variable	Odds Ratio	P value	95% CI
Univariable Analysis			
Age	1.02	0.17	0.99 - 1.04
Female sex	0.58	0.1	0.31 - 1.10
Baseline serum creatinine (per 0.1 mg/dL)	1.02	0.72	0.90 - 1.16
Charlson score	1.16	0.042	1.01 - 1.33
Other IRAE	**3.19**	**< 0.001**	**1.68 - 6.05**
Cerebrovascular disease	**9.24**	**0.003**	**2.13 - 40.0**
CHF	1.27	0.83	0.14 - 11.6
Diabetes	1.78	0.19	0.75 - 4.20
Hypertension	**4.27**	**<0.001**	**2.28 - 8.01**
Myocardial infarction	1.91	0.29	0.58 - 6.26
ACE/ARBi	**2.90**	**0.002**	**1.47 - 5.69**
PPI	1.90	0.13	0.83 - 4.35
Diuretics	**4.34**	**<0.001**	**1.93 - 9.79**
NSAIDs	0.77	0.74	0.17 - 3.52
Steroids	**1.94**	**0.033**	**1.06 - 3.57**
Multivariate Analysis			
Other IRAE	**2.82**	**0.002**	**1.45 - 5.48**
Hypertension	**2.96**	**0.008**	**1.33 - 6.59**
ACE/ARBi	1.18	0.69	0.51 - 2.72
Diuretics	1.96	0.15	0.78 - 4.94

SA-PO200

Partial Nephrectomy Was Associated with Increased Risk of Long-Term CKD in Kidney Cancer Patients

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Background: Few prospective studies assessed the risk of late kidney function impairment in kidney cancer (KC) patients (pts) after partial nephrectomy (PN) and most of them are based on measurement of serum creatinine level (SCr). The aim of this study is to perform a serial evaluation of radioisotopic glomerular filtration rate (rGFR) in patients (pts) with KC submitted to PN

Methods: Prospective evaluation of 97 outpts with KC admitted at the Sao Paulo State Cancer Institute between September 2012 and May 2018. All patients were submitted to PN and renal function was evaluated through ^{51}Cr-EDTA rGFR at three different moments: before surgery (pre-rGFR), at three months after surgery (rGFR-3Mo) and twelve months after surgery (rGFR-12Mo). Acute kidney injury was defined as an increase ≥ 50% at the baseline serum SCr. GFR was expressed as ml/min/1.73m^2. Chronic kidney disease (CKD) was defined as rGFR < 60

Results: Patients were 60 ± 12 years, 50.5% male. Hypertension was observed in 66% of pts and diabetes in 25.8%. CKD was observed in 16.5% of patients. KM had 3.30 (2.55-4.55) cm at largest diameter. Pre-operative exams were serum creatinine (SCr) 0.86 (0.75 – 1.06) mg/d and pre-rGFR 80.9 ± 27.3. Trans and immediate post-surgery period (next seven days) developed without serious complications: time of surgery was 120 (90-160) min, blood loss was 200 (100-500) ml, only three patients requiring blood transfusion. AKI was observed in 20.6% of pts, none of them required renal replacement therapy. rGFR-3Mo and rGFR-12Mo were reduced compared to pre-rGFR: 74.37 ± 23.2 (P<0.0001), and 73.23 ± 22.5 (P<0.0001), respectively. CKD prevalence increased at three (23.7%, P= 0.04) and twelve months (21.6%, P= 0.03) compared to the pre-surgery period

Conclusions: Uncomplicated PN was related with reduced rGFR and higher risk of CKD development at the long term in this group of KC patients

SA-PO201

Kidney Dysfunction in Head and Neck Squamous Cell Carcinoma Patients After Cisplatin-Based Concurrent Chemoradiation in a Long-Term (LT) Follow-Up: A Cross-Sectional Study

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Background: Cisplatin-based concurrent chemoradiation (CRT) offers to head and neck squamous cell carcinoma (HNSCC) patients (pts) better overall survival, but is associated with significant acute and late toxicity. Here we aimed to study the frequency of kidney dysfunction in HNSCC pts treated with CRT with curative intent in a LT follow-up.

Methods: Cross-sectional study of pts treated at São Paulo State Cancer Institute under regular follow-up. Eligible pts had to be diagnosed with HNSCC and treated with CRT (adjuvant or definitive), with no evidence of disease (NED) for at least 2 years after CRT. Chronic kidney disease (CKD) was defined as glomerular filtration rate (eGFR) < 60ml/min/1.73m2. eGFR was estimated by the CKD-EPI equation.

Results: 120 pts were studied, median age 59 y.o. (21-78), being 88 (73%) male. The most common primary site was oropharynx (50 pts, 42%), followed by larynx (29 pts, 23%), oral cavity (23 pts, 19%), hypopharynx (9 pts, 8%) and nasopharynx (9 pts, 8%). Pts were staged as T3-T4 (87 pts, 75%) or N+ (86 pts, 72%). Comorbidities, such as hypertension or diabetes, were reported by 38 pts (32%). Most of the patients (107 pts, 97%) were ECOG-PS 0 or 1. CRT was administered either as adjuvant (59 pts) or definitive (61 pts) therapy, with a median RT dose of 70 Gy concurrently delivered with cisplatin (total median dose 300mg/m2, ranging from 100-300). Cisplatin-based induction chemotherapy was administered before CRT in 32 pts (total median cisplatin dose 225mg/m2, ranging from 75-300). In a median follow-up of 42 months (24-125) after CRT, we detected a significant increase of serum creatinine (1.01±0.35 mg/dL) in comparison with baseline values (0.84±0.18 mg/dL) (p < 0.001), and a decrease of eGFR (78±20 mL/min) versus baseline (93±19 mL/min) (p < 0.0001). Baseline (pre-treatment) eGFR was inferior to 60 mL/min in only 4 pts (3.4%). and in this analysis, eGFR was below 60 mL/min in 16 pts (14%) (p = 0.004). 44 pts (40%) had a decrease in eGFR above 5 ml/min/1,73m2/year. No clinically significant electrolyte abnormalities were detected and no pts were on dialysis at the end of follow up.

Conclusions: Chronic kidney disease features were frequently diagnosed in HNSCC pts with NED in a LT follow-up after CRT and may contribute to overall morbidity in these pts.

SA-PO202

Mortality Rates and Geographic Distribution of Kidney Cancer in Peru

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Background: Recent data showed decreasing prevalence rates of kidney cancer in the world. However, the epidemiology of kidney cancer in South America remains poorly explored. This study aims to illustrate the case of Peru.

Methods: Secondary data analysis from the Deceased Registry of the Peruvian Ministry of Health (PMH) database (2010 – 2015), which included reports from health care facilities located in 24 provinces, grouped into 3 regions: coast, highlands, and rainforest. Code 189 was used to identify deaths from kidney cancer based on ICD 9th Revision. Deaths were classified according to the birthplace. Calculations were made assuming an underreporting rate of 40%, as estimated by the PMH. We computed age-standardized mortality rates (ASMR, world population) per 100,000 person-year. Cluster map was developed to visualize data across regions.

Results: A total of 2074 kidney cancer deaths in Peru were identified. ASMR (per 100,000 individuals) due to kidney cancer increased in men by 15.3%: from 1.30 (2010-2012) to 1.50 (2013-2015). Similarly, ASMR (per 100,000 individuals) increased among women by 22.6%: from 0.70 (2010-2012) to 0.86 (2013-2015). When stratified by regions, people in the coast had the highest ASMR, in both men (1.83 - 1.99 per 100,000 individuals) and women (0.94 - 1.14 per 100,000 individuals); mainly in the provinces of Lima and Tacna. In contrast, people in the rainforest had the lowest ASMR.

Conclusions: Mortality rates due to kidney cancer have increased in Peru. People from the coast had the highest mortality rates, particularly in Lima and Tacna. The lack of healthcare access for early detection and limited coverage for treatment may play a role in the observed kidney cancer-related mortality rates in Peru. Further studies are warranted to identify modifiable epidemiological risk factors associated with kidney cancer in this country and region.

Provincial, regional and national age-standardized kidney cancer mortality rates per 100,000 in men and women in 2010–2012 and 2012–2015, and rate percentage change

Gender		Men			Women	
	2010-2012	2013-2015	%change	2010-2012	2013-2015	%change
Peru	1.30	1.50	15.3	0.70	0.86	22.6
Coast	1.83	1.99	8.80	0.94	1.14	21.2
Highlands	0.47	0.48	1.60	0.34	0.28	-18.2
Rainforest	0.20	0.28	39.3	0.23	0.15	-32.8

SA-PO203

AKI and CKD Prevalence in Pediatric Neuro-Oncology Survivors

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Background: In facing an oncologic diagnosis, the pediatric patient may face a host of concomitant diagnoses resultant of required treatments. These diagnoses will often influence life-long follow-up. The nephrologic impact of multimodal treatment regimens for childhood central nervous system (CNS) tumors is a topic of particular interest.

Methods: A pediatric CNS tumor survivor clinic follows patients who have been in remission for a minimum of 5 years. Medical records of 211 clinic patients were examined for renal sequelae of CNS tumor treatment. Patients were classified as having Acute Kidney Injury (AKI), using KDIGO definitions, if more than 2 serum creatinine (SCr) results were available over a 48hr period for trending. Patients were assessed for Chronic Kidney Disease (CKD) using nuclear or estimated GFR, positive proteinuria (PU) and/or microalbuminuria (MAU), and renal ultrasound. Stage I is defined as GFR>120, on 2+ measurements, with PU/MAU. Stage II is defined as GFR<90, and Stage III is defined as GFR<60. Patients with an abnormal renal ultrasound, or with PU/MAU but a normal or above normal GFR, were classified as having a marker of CKD.

Results: Survivors range in age from 7 to 53 years old, with the median age of 21. Eleven of the 211 patients could not be assessed for AKI due to inadequate SCr results. Of the remaining 200 patients, 11 (5.5%) experienced AKI. Evidence of CKD was observed in 62/211 patients (29.4%), six of whom previously had AKI. Of those with CKD, 15 (24.2%) had stage I, 27 (43.5%) had stage II, and 2 (3.2%) had stage III. The other 18 (29.0%) had either persistent PU/MAU with normal or above normal GFR and/or abnormal renal ultrasound.

Conclusions: Surveillance post AKI and mitigation of CKD after cancer remission helps to remove additional burden from pediatric cancer survivors. The high prevalence of CKD markers demonstrates that CNS tumor treatment regimens may cause significant subclinical renal damage during the acute treatment phase. Additional work should be done to assess the incidence of kidney disease in this population, and structure ideal follow-up.

	No CKD	Marker of CKD	CKD Stage I	CKD Stage II	CKD Stage III	Total
No AKI	144	17	14	24	1	200
Previous AKI	5	1	1	3	1	11
Total	149	18	15	27	2	211

SA-PO204

Cancer Risk and Mortality in Patients with CKD: A Population-Based Cohort Study

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Background: Patients with chronic kidney disease (CKD) may be at increased risk for cancer. CKD may also confer worse cancer outcomes. Existing data is limited and conflicting regarding the associations between kidney function and outcomes in specific malignancies.

Methods: We conducted a population-based cohort study of all Ontario residents 18 years of age or older with available serum creatinine data in the Ontario Laboratory Information System or inclusion in the Canadian Organ Replacement Register as chronic dialysis or kidney transplant patients between April 1, 2007 and October 31, 2016. We categorized patients according to CKD status [estimated glomerular filtration rate (eGFR) >60, 45-59, 30-44, 15-29, <15 mL/min/1.73m^2, dialysis and transplant recipients] and assessed overall and site-specific cancer incidence and mortality using multivariable Cox models, accounting for competing risks.

Results: Among 5,871,837 individuals with eGFR data, 29,809 on dialysis and 4,951 kidney transplant recipients there were 325,895 cancer diagnoses over 29,993,847 person-years of follow-up. Relative to patients with eGFR >60 mL/min/1.73m^2, total cancer incidence was increased in patients with CKD (stages 3a to 5), adjusted hazard ratios (aHR): 1.07, 95%CI: (1.05, 1.09), 1.04 (1.02, 1.07), 1.01 (0.98, 1.05), 1.13 (1.02, 1.25) on dialysis: 1.31 (1.25, 1.38), and transplant recipients: 1.22 (1.09, 1.36). The risks of bladder, kidney cancer and myeloma were particularly high in patients with CKD. Cancer-specific mortality was increased in CKD (stages 3a to 5), aHRs: 1.21 (1.17, 1.25), 1.30 (1.25, 1.35), 1.45 (1.37, 1.54), 1.41 (1.20, 1.67), dialysis: 1.36 (1.24, 1.49) and transplant: 1.46 (1.16, 1.84). Kidney cancer and myeloma mortality was observed to progressively increase with worsening baseline kidney function. Patients on dialysis had increased risk of mortality related to bladder, kidney cancer and myeloma.

Conclusions: Overall cancer incidence was increased in patients with CKD (stages 3a to 5) and end-stage kidney disease. CKD is associated with increased risks of bladder, kidney cancer and myeloma. Cancer-related mortality is also increased in patients with CKD, on dialysis and post-kidney transplant. Strategies to address the increased burden of cancer in the CKD population are needed.

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SA-PO205

Predictors of Mortality in Patients with CKD and Cancer

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Background: Cancer patients have a high prevalence of chronic kidney disease (CKD). The aim of this study was to assess prognostic factors for death in cancer patients with CKD.

Methods: Among 516 outpatients with cancer referred to nephrology evaluation (2009-13), 251 had CKD according KDIGO definitions and at least 3 months of follow up. Clinical and biochemical data were retrieved from patient medical records. The Cox regression was used to examine the predictors of mortality.

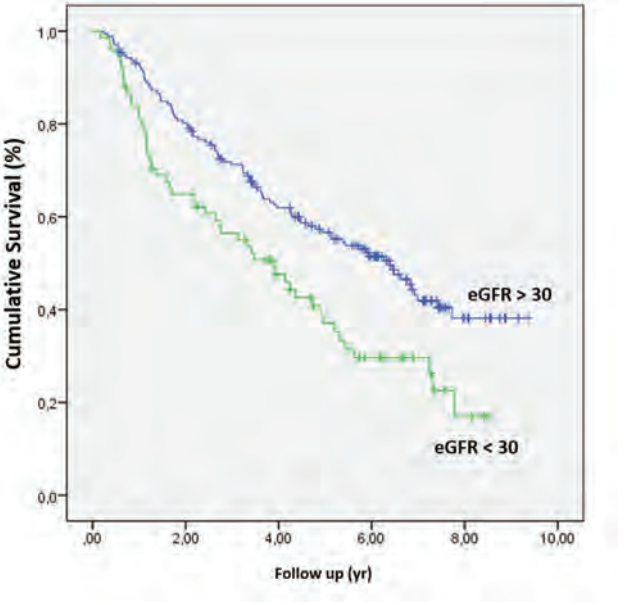
Results: After a mean follow-up of 4.2±2 years, the mortality rate observed was 57%. The patients features are shown in Table1. In the Cox regression analyses, ongoing chemotherapy [aHR=2.4; CI 1.3-4.5, p=0.004], Karnofsky index < 80 [aHR=2.1; CI 1.1-3.9, p=0.025], and eGFR < 30 ml/min/1.73m^2 [aHR: 1.9; CI 1.0-3.6, p<0.03) were the independent predictors of mortality in our population. Of note, kidney dysfunction remained a independet risk factor for mortality even after adjustments for age and the presence of metastasis.

Conclusions: Patients with cancer and CKD have a poor prognosis. Ongoing chemotherapy, Karnofsky index, and an eGFR lower than 30 ml/min/1.73m^2 were independent factors associated to mortality.

Table 1. Baseline Features

	Death (n=142)	Surviving (n=109)
Age (yr)	67±12	65±11
Female (%)	25	31
Metastasis (%)	37	16*
Ongoing Chemotherapy (%)	50	23*
Karnofsky index < 80 (%)	38	20*
eGFR < 30 (%)	36	22*
Serum Albumin > 4 g/dL (%)	64	75*
Solid tumors (%)	86	82

Results are expressed as mean±SD and percentage. * < 0.05 vs Death group.



Survival by eGFR

SA-PO206

Study of Relationship Between Etiology of ESRD and Cancer Incidence in Chronic Hemodialysis Patients

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Background: Previous research has shown that patients with end-stage renal disease (ESRD) treated with dialysis are at increased risk of cancer development. The aim of the present study was to examine a relationship between etiology of ESRD and cancer incidence in patients treated with chronic hemodialysis (HD).

Methods: We conducted a retrospective study of the cohort of hemodialysis patients over the age of 18 treated at teaching hospital between 2008 and 2017. Patients diagnosed with cancer prior to dialysis or with history of transplantation were excluded. Data on cancer diagnoses in the cohort population was collected from the National Cancer Registry. A multivariate analysis was conducted to examine the relationship between the various predictors and the incidence of cancer.

Results: The study included 333 patients, of whom 211 (63.4%) were males. The mean age at start of HD was 67.2±13.1 years. The etiology of ESRD was diabetes in 41%, hypertension in 31%, glomerulonephritis in 7%, cystic kidney disease in 5% and nephrolithiasis in 3% of cases. The median follow-up time was 4 (95%CI, 2.0-6.5) years. 28 patients (8.4%) developed 30 cases of primary malignancy during treatment with hemodialysis. The most common site of cancer was colon (33.3% of cases), followed by bladder (16.7%), kidney (10%) and prostate (10%). Higher patients' age was associated with cancer development: 72.3±7.7 years in patients that developed and 66.7±13.4 years in those that did not develop cancer (p=0.001). No statistically significant relationship was found between ESRD etiology and occurrence of malignancy.

Conclusions: We did not found association between ESRD etiology and cancer incidence in our cohort of hemodialysis patients.

SA-PO207

Dialysis Does Not Affect Outcomes in Stage IV Cancer Patients Admitted to the Intensive Care Unit with AKI at a Comprehensive Cancer Center

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Background: In advanced cancer patients, prolongation of life with treatment may incur substantial emotional and financial expense. Since acute kidney injury (AKI) in hospitalized cancer patients is known to be associated with poor survival, we investigated whether dialysis use in the intensive care unit (ICU) was a significant independent predictor of higher mortality or worse outcomes.

Methods: We retrospectively reviewed patients admitted in 2005-2014 who were diagnosed with stage IV solid tumors, had acute kidney injury and a nephrology consult. The main outcomes were survival from ICU admission, inpatient mortality and long-term survival after hospital discharge. Log-rank tests and Cox proportional regression were used to compare survival between dialysis and non-dialysis groups. Propensity score matched landmark survival analyses was performed with two landmark time-points chosen at day 2 and at day 7 from ICU admission.

Results: Of 465 patients, 176 needed renal replacement therapy. Landmark analyses at day 2 and day 7 indicated need for dialysis was not associated with worse mortality during ICU admission (HR, 0.926, p=0.6657), adjusting for age, baseline serum albumin, baseline creatinine, baseline, and baseline max SOFA. In the multivariate logistic regression model after adjusting for baseline serum albumin and baseline maximum SOFA, the patients who received dialysis were not less likely to be discharged alive than non-dialysis patients (p=0.9892). To evaluate the impact of dialysis on longer-term survival we evaluated 189 patients who were discharged alive. There was not a longer-term survival benefit after discharge for patients who received dialysis.

Conclusions: Our study found that receiving dialysis in the ICU did not adversely affect survival to discharge and longer-term survival after discharge for patients with stage IV cancer with AKI. Dialysis itself contributed little harm or benefit to survival after discharge of the patient. Prolongation of suffering with no meaningful longer-term survival should always be included in the shared decision-making discussion prior to reaching a decision about the initiation of dialysis in stage IV cancer patients with acute kidney injury.

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SA-PO208

Calendar Trends in Cancer Incidence Among US Kidney Transplant Recipients

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Background: Kidney transplant recipients (KTRs) are at 2-4 times greater risk of cancer compared with the general population, and older recipients are at highest risk. Kidney allograft survival is improving with newer immunosuppression and allocation policies. We assessed the changes in incidence of cancers after kidney transplant over time.

Methods: We compared the incidence of cancer in first time kidney-only transplant recipients within three ten-year calendar intervals (1987-1996, 1997-2006, 2007-2016) characterized through linkage of SRTR and cancer registry databases from 17 U.S. states and regions in the Transplant Cancer Match Study. KTRs were excluded for a cancer diagnosis before or within 90 days post-transplant, if transplanted before cancer registry coverage, or HIV infection. First cancers were identified from cancer registries if <5 years of transplant. We analyzed overall cancer and post-transplant cancers: colorectal, lung, melanoma, breast, prostate, kidney, and non-Hodgkin lymphoma (NHL). Non-melanoma skin cancer is not reported to cancer registries. Poisson regression was used to compare incidence rate ratios (IRR) across time intervals among KTRs with the earliest era as the reference, and adjusted for risk factors including age at transplant, gender, primary cause of ESRD, time on transplant waiting list, BMI, type of kidney donor, and maintenance immunosuppression.

Results: The KTR population increased in age over the three decades - mean age 44.3, 48.6, and 50.9 years, respectively. Unadjusted IRR of overall cancer in KTRs appeared to increase over this period, but IRRs decreased after adjusting for age and other variables; Differences across decades were not significant. Adjusted IRRs for most common post-transplant cancers decreased nonsignificantly over time, except for kidney cancer, which appeared to increase.

Conclusions: Overall cancer incidence has trended downward amidst an older KTR population in the last three decades. Kidney cancer incidence may have risen over time while all other common cancer IRRs were stable or lower. The reasons for the age-adjusted decline over time may include better cancer screening, tighter transplant listing criteria, and changes in immunosuppression.

Funding: Other NIH Support - NCI

	1987-1996	1997-2006			2007-2016			
Kidney Transplant Population	16,789	46,595			38,130			
	Cases	Cases	Unadjusted IRR	Adjusted IRR	Cases	Unadjusted IRR	Adjusted IRR	P-Value for Trend**
All Cancer	560	1848	1.13 (0.97, 1.32)	0.98 (0.76, 1.26)	970	1.13 (0.95, 1.33)	0.89 (0.67, 1.17)	0.39
Colorectal	41	97	0.81 (0.49, 1.36)	0.79 (0.37, 1.70)	38	0.60 (0.32, 1.13)	0.50 (0.20, 1.24)	0.14
Lung	75	216	0.99 (0.67, 1.46)	0.74 (0.43, 1.26)	93	0.81 (0.51, 1.27)	0.48 (0.29, 1.01)	0.05
Melanoma	29	85	1.00 (0.53, 1.92)	0.68 (0.25, 1.83)	53	1.19 (0.59, 2.39)	0.66 (0.22, 2.03)	0.48
Breast	37	105	0.98 (0.56, 1.73)	0.68 (0.29, 1.62)	53	0.89 (0.47, 1.68)	0.65 (0.23, 1.67)	0.32
Prostate	76	261	1.20 (0.82, 1.75)	0.78 (0.46, 1.31)	105	0.91 (0.58, 1.41)	0.48* (0.27, 0.86)	0.01
NHL	75	188	0.86 (0.52, 1.42)	0.79 (0.38, 1.90)	122	1.06 (0.62, 1.81)	1.01 (0.41, 2.50)	0.98
Kidney	39	205	1.81* (1.01, 3.22)	1.37 (0.57, 3.24)	148	2.47* (1.36, 4.49)	1.88 (0.74, 4.77)	0.18

*Statistically significant (p < 0.05); **Linear trend test for adjusted model

SA-PO209

Risk Factors for Advanced Colorectal Neoplasia in CKD

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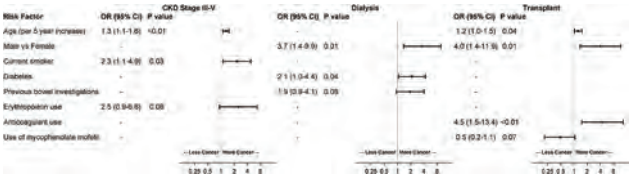
Background: Colorectal cancer is common in people with chronic kidney disease (CKD), but the risk factors are poorly understood. The aim of this study is to identify risk factors for advanced colorectal neoplasia in people with CKD (as a sub-study of DETECT).

Methods: People with CKD (stages III-V, dialysis and transplant) across eleven sites in Australia, New Zealand, Canada and Spain were screened for colorectal neoplasm using fecal immunochemical test (FIT). Advanced colorectal neoplasia was identified through a 2-step verification process with colonoscopy following a positive FIT and 2-year clinical follow-up for all patients. Potential risk factors for advanced colorectal neoplasia at different CKD stages were assessed using multivariable logistic regression.

Results: A total of 1706 patients received FIT screening (791 CKD III-V, 418 dialysis, 497 transplant). 323 (18.9%) had colonoscopy for positive FIT and 103 advanced colorectal neoplasia (44 CKD III-V, 31 dialysis, 28 transplant) were identified (overall detection rate 6%). At follow-up, 14 additional advanced neoplasia (10 CKD III-V, 3 dialysis, 1 transplant) were identified. Across CKD stages, older age and male sex were risk factors for advanced colorectal neoplasia (figure). Current smoking use was associated with advanced colorectal neoplasia among those with CKD III-V [odds ratio 2.3 (95% CI 1.1-4.9)]. For those on dialysis, patients with diabetes experienced 2.1 times greater odds of advanced colorectal neoplasia (95% CI 1.0-4.4). For kidney transplant recipients, daily anticoagulant use was associated with increased odds of advanced colorectal neoplasia [OR 4.5 (95% CI 1.5-13.4)].

Conclusions: Increasing age, smoking, male sex and having diabetes are associated with advanced colorectal neoplasia in patients with CKD. The observed increased risk associated with anticoagulation use in transplant recipients may be due to increased detection by FIT.

Funding: Government Support - Non-U.S.



SA-PO210

Increased Risk of Cutaneous Squamous Cell Carcinoma in Organ Transplant Recipients and Patients on Chronic Dialysis: A Cancer Registry-Based Study in Taiwan

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Background: Organ transplant recipients (OTRs), patients on chronic dialysis, and those with chronic kidney disease (CKD) have immune dysregulation and are at higher risk of skin cancers. However, the predominant histological skin cancer subtype in these populations has not been well-investigated among Asians. This study aimed to investigate the predominant histological skin cancer subtype among OTRs, patients on chronic dialysis, and those with CKD in Taiwan.

Methods: We obtained data between 2007 and 2014 from the Taiwan Cancer Registry Database and the National Health Insurance Research Database. The proportions of certain histological skin cancer subtypes in OTRs, patients on chronic dialysis, and those with

CKD were compared against those in the control group using a generalized estimating equation regression model.

Results: Among 23,644 patients with skin cancer, 53 were OTRs, 255 had chronic dialysis, 1,792 had CKD, and 21,544 were placed in the control group. The proportions of squamous cell carcinoma (SCC) were 52.8%, 47.8%, 40.1%, and 33.5%, respectively. Compared with the control group, OTRs (1.99-fold) and chronic dialysis patients (1.25-fold) were found to have higher risk of developing SCC than other skin cancers after adjustment for potential confounding factors. Other subgroups or covariates associated with increased SCC risk included CKD patients aged < 70 years (vs. control group; 1.3-fold), old age (vs. young age; 2.8-fold), male sex (vs. female sex; 1.1-fold), and south-Taiwan residency (vs. north-Taiwan residency; 1.1-fold).

Conclusions: OTRs and patients on chronic dialysis had a greater risk of developing SCCs than other skin cancer subtypes.

SA-PO211

Diversity of Nutritional Status in Patients with Cancer and CKD

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Background: Cancer patients (pts) constitute a population with heterogeneous range of nutritional status. There is scanty prospective data on nutrition aspects of cancer pts with chronic kidney disease (CKD).

Methods: A group of solid cancer pts with CKD (not in dialysis) admitted for treatment (AT) or already in follow-up (FU) at a cancer hospital in Brazil (São Paulo State Cancer Institute) was prospectively evaluated between April 2015 and October 2017. Patients underwent an evaluation including bioimpedance exam, weight, height and subjective nutritional assessment questionnaire (PG-SGA), assessment of the glomerular filtration rate through 51 Cr-EDTA (rGFR), serum creatinine (SCr) and albumin (Alb). Chronic Kidney Disease (CKD) was defined as rGFR <60 ml / min / 1.73 m2. Sarcopenia was defined when as Fat Free Mass Index ≤17.4kg/m2 for men and ≤15kg/m2 for women.

Results: One hundred sixty-one pts were enrolled. Pts characteristics were age 69.92 ± 10.46 years, 61.5% male, 72% AT. Most common tumor origins were: genitourinary tract 41%; gastrointestinal tract 12.4%, breast cancer 13.7%. ECOG was 0-1 in 89.5%, clinical stage III and IV comprised 53.4% of pts, with evidence of metastatic disease (MD) in 22.4%. Median rGFR was 49.9 (39.67 – 55.81) ml/min/1.73m2, SCr was 1.18 (0.96 – 1.44) mg/dL and Alb was 4.30 (4.10 – 4.60) g/dL. Nutrition evaluation revealed: weight 71 (62.6-80.35) Kg; body mass index (BMI) 25.71 (22.3 – 29.1); fase angle 5.20 (4.60 – 5.90); fat free mass 46.4 (39.4-56.25) Kg. BMI was < 23 in 29.8% and > 28 in 34.2% of pts. Sarcopenia was observed in 28.6% of pcts and 81.4% of pcts were considered well nourished by PG-SGA. AT and FU pcts presented no difference in either baseline variables (age, ECOG, MD, comorbidities, clinical stage, SCr, Alb) and in most of nutrition aspects (weight, sarcopenia, fase angle, fat free mass) (data not shown). FU pcts presented higher BMI (27.1 [24.2 – 30.20] vs 25.10 [22.2 – 28.7], P=0.330 and higher prevalence of well-nourished status by PG-SGA (93.3 vs 76.7%, P=0.015).

Conclusions: The nutritional status in cancer pts with CKD is diverse, ranging from significant malnutrition to expressive overweight both for AT and FU pts.

SA-PO212

Obesity and Renal Outcome in Patients with Renal Cell Carcinoma

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Background: Epidemiologic studies has been shown obesity is associated with renal cell carcinoma (RCC). Obesity causes dysregulation of adipokines, activation of inflammatory cytokines, angiogenesis, and may lead to development RCC and renal injury. We evaluate the relationship of obesity with the risk of RCC and renal outcomes in urologic cancers. In addition, we evaluate the effect of inflammation on the risk of RCC.

Methods: A total of 6,218 patients were enrolled in patients diagnosed with urological cancer at two University Hospital from 2001 to 2019. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2.

Results: The mean age of the patients was 65.5± 12.0 years and 87.3% was male. Out of 6,218 patients, 1011 were diagnosed with RCC, 2002 with urothelial cancer, 136 with genital cancers and 2979 with prostate cancers. RCC was significantly related to younger age, diabetes, higher BMI, CRP and monocyte count. RCC showed 1.584-fold increased risk of obesity than prostate cancer (95% CI, 1.097-2.288). Compared than non-obese patients, obesity was associated with risk of RCC in urologic cancers (RR, 1.901, 95% CI, 1.326-2.724). Serum monocyte count is a stronger risk factor for the risk of RCC (RR, 3.461; 95% CI, 1.079-11.095) in obese patients than non-obese patients (2.714, 95% CI, 1.648-2.867). Obese patients showed higher incidence of 30% and 40% eGFR decline in urologic cancers during 7.7±1.2 years of mean follow up (P<0.05). Obesity was related to increased risk of 40% eGFR decline in urologic cancers by multivariate analysis (1.596, 95% CI, 1.074-2.371).

Conclusions: Obesity was significantly associated with the prevalence of RCC than other urologic cancers. Serum monocyte count is a stronger risk factor for the RCC in obese patients. Obese patients had significant worse renal outcomes in urologic cancers.

SA-PO213

Comparing Glomerular Filtration Rate Equations with ^{51}Cr-EDTA in Patients with Renal Tumors

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Background: Assessment of glomerular filtration rate (GFR) is a crucial element to plan surgical strategies in patients with renal tumors. However, the estimate GFR (eGFR) trough equations was not validated in these patients. The aim of this study is to compare the performance of Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI), abbreviated Modification of Diet in Renal Disease (aMDRD) and Cockcroft-Gault (CG) equations with 51Cr-EDTA in patients with renal tumors eligible to surgical treatment.

Methods: Prospective evaluation of 142 outpatients with renal tumors and submitted to partial nephrectomy at Sao Paulo State Cancer Institute between April 2013 and November 2018. All patients were evaluated before surgery with ^{51}Cr-EDTA (rGFR) and serum creatinine (SCr), standardized to the isotope-dilution mass spectrometry reference method. rGFR and eGFR were expressed as ml/min/1.73 m^2.

Results: Patients were 59.4 ± 10.6 y, 50.2% male, 97.9% white. Renal tumor has 3.50 (2.70-4.72) cm at largest diameter and was malignant (histology confirmed post surgery) in 85% of cases. Comparing renal function before surgery, SCr was 0.86 (0.74 – 1.10) mg/d, rGFR was 81.1 ± 22.5 and rGFR < 60 was observed in 18% of pts. eGFRs using the CKD-EPI, aMDRD and CG equations were 80.6 ± 20, 77.3 ± 20.8, and 89.2 ± 30.6, respectively. CG and aMDRD showed significant differences in the means from the paired t-Test when compared to rGFR (P<0.05) (Figure 1 - Table 1). CKD-EPI equation demonstrated satisfactory precision and higher accuracy (Figure 1 - Table 2).

Conclusions: CG and aMDRD equations performed poorly compared with rGFR in this group of patients with renal tumors. CKD-EPI equation demonstrated adequate performance and should be considered when deciding upon surgical strategies in the setting of renal tumors.

Table 1: Mean bias rGFR vs eGFR

eGFR	Mean bias (entire group)	rGFR < 60	rGFR ≥ 60
CKD-EPI	+ 0.38	-7.91	+2.17
P value	*0.792*	*0.051*	*0.164*
aMDRD	+ 3.67	-6.21	+5.79
P value	*0.016*	*0.087*	*0.001*
CG	- 7.68	-5.86	-8.08
P value	*<0.0001*	*0.011*	*<0.0001*

If (-): eGFR overestimed rGFR. If (+): eGFR underestimated rGFR

Table 2: Percentage of studies with eGFR within 10 and 30% of the rGFR

	% within 10% of rGFR	% within 30% of rGFR
aMDRD	27.5	79.6
CKD-EPI	34.5	83.1
CG	29.6	71.8

SA-PO214

Dipstick Proteinuria and Cancer Incidence: A Nationwide Population-Based Study

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Background: Proteinuria is a representative indicator of chronic kidney disease (CKD) and an independent risk factor for both cardiovascular and non-cardiovascular mortality. Given that a major cause of non-cardiovascular mortality is malignancy, the association between proteinuria and malignancy has been discussed for several decades. We evaluated the clinical implication of dipstick proteinuria as a predictor for malignancy using nationwide population-based data.

Methods: We included subjects who had undergone a medical examination in 2009 (index year). Among 10,505,818 participants, we excluded subjects who did not satisfy the inclusion criteria. Finally, 9,714,387 subjects were included in this study and were followed from the index year to December 31, 2017. We categorized the results of dipstick proteinuria into three groups; negative (-), trace (±), overt proteinuria (more than 1+).

Results: The participants with overt proteinuria were more likely to be older, have hypertension, diabetes, and dyslipidemia. During the follow up period, we observed that overt proteinuria at baseline correlated with the risk of overall cancer incidence, even after it was adjusted by age, gender, smoking history, degree of exercise and diabetes (HR 1.151, 95% CI, 1.133 – 1.169, referenced to no proteinuria). In terms of site-specific cancer, the risks of colorectal, liver, lung, cervical, esophagus, kidney, bladder, and prostate cancer incidence gradually increased in proportion to the degree of proteinuria. In order to observe the risk of cancer incidence according to the change in proteinuria, we used the same participant's records from the 2005 NHID (National Health Insurance Database). We demonstrated that the risk of cancer incidence increased proportionally according to the changes in dipstick proteinuria over four years.

Conclusions: We elucidated the dose-response relationship between the degrees of dipstick proteinuria and the graded risk of overall and site-specific cancer development. We also observed that the long-term risk of cancer incidence increased proportionally according to the changes in dipstick proteinuria over four years.

SA-PO215

Combining a Digital Platform and Point-of-Care (POC) Testing to Extend Kidney Patient Participation in Cancer Trials: Technical Feasibility and Patient Acceptability Study (IDecide Program)

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Background: Recruitment to cancer clinical trials is an ongoing challenge and usually limited to patients with preserved kidney function. Eligibility often restricts recruitment to those with an eGFR of >50ml/min, this is arbitrary and not a risk-based approach driven by current clinical science in nephrology. Due to increased survival rates for both conditions, there is a significant population with both cancer and reduced kidney function. The aim of this body of research is to assess whether new technological advances in POC creatinine meters and digital science can be used to modernise eligibility criteria in oncology clinical trials through personalised risk-based monitoring. We created an approach that explored the potential and acceptability of using a POC device, data capture via a smartphone, and risk-categorisation through an Acute Kidney Injury (AKI) algorithm, to enable decision-making and the first step in addressing this unmet clinical need.

Methods: Three POC devices were evaluated for usability, size and complexity. A smart phone app was developed, which captures device data and sends securely to a Cloud environment. Creatinine testing, calibration and patient acceptability in the hospital was conducted over a 2 week period with 17 interactions (patient/carer/nurse), including 2 patient focus group with 8 participants from oncology and nephrology backgrounds.

Results: The Nova Biomedical Creatinine StatSensor® was the device chosen to enable home creatinine readings with good end user feedback and stable performance characteristics. The app user interface design was acceptable with patients based on patient acceptability testing.

Conclusions: This initial proof of concept successfully demonstrated that creatinine can be measured by a POC device, the data captured by an app and reported in near-real time. We have now developed a clinical rules engine based on the NHS/NICE published algorithm for AKI; and will be applying this to a clinical trial to detect AKI in patients receiving chemotherapy to quantify the potential clinical benefits. We aim that this will be the first step in a body of work to challenge traditional eligibility criteria for clinical trials and improve outcomes for this population of patients, through first improving their recruitment to cancer clinical trials.

SA-PO216

Effect on Renal Function of Repeated Administrations of Contrast Media in Cancer Patients Nephrectomized for a Metastatic Renal Cell Carcinoma: A Retrospective Italian Study

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Background: Patients with renal carcinoma (RCC) presents with concomitant chronic kidney disease (CKD) with a frequency which is about twice that of the general population; moreover, being often nephrectomised and therefore with a reduced renal functional reserve (RFR), they also present a higher incidence of acute kidney failure (AKI). Thus, we decided to evaluate the progression of renal impairment in metastatic RCC patients who underwent computed tomography (CT) scans every three months, being enrolled in experimental trials. The presence of risk factors for CKD and the possible correlation with the time elapsed between nephrectomy and the first CT scan showing the presence of metastatic disease was also evaluated

Methods: We analyzed a total of 76 patients, 59 males (78%) and 17 females (22%); 68 (89.5%) were nephrectomized for neoplasia (average age: 59.72, standard deviation (SD): 10.51; average Body Mass Index: 26.55, SD: 4.47). The trend of renal function was evaluated on the 40 mRCC patients for which all the data investigated at the following timepoints were available: T0 (i.e. baseline), T3, T6 and T9

Results: The eGFR trend (calculated by means of the CKD-EPI formula) was substantially stable, a drop of just 2 ml/min in 9 months having been observed. Intriguing, and statistically significant (p = 0.007), was the finding of a more marked worsening of eGFR (10 ml/min in 9 months) in hypertensive patients, worsening that is not observed in the other populations of patients considered, and that it could have been caused by the additional effect of the antiangiogenic drugs used. No correlations were found between renal function and the time elapsed between nephrectomy and the first CT scan

Conclusions: Even in nephrectomized patients, CT contrast medium appears to play a secondary role on the incidence of AKI, or on worsening of CKD. We should therefore be more liberal in the use of contrast medium, even in nephrectomized cancer patients

SA-PO217

Persistence of CKD and Hypertension at 12 Months After Cisplatin Therapy in Children

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Background: Cisplatin (CisP) commonly causes acute kidney injury (AKI). Late CisP-nephrotoxicity (chronic kidney disease (CKD); hypertension (HTN)) is poorly characterized in children. We determined prevalence and progression of CKD and HTN 3 and 12 months (m) post-CisP therapy, and if CisP-AKI is associated with these outcomes.

Methods: 12 Canadian-site prospective cohort study. Protocol: Children treated with CisP were followed during cancer therapy (labs, clinical data) and at 3 and 12m post-CisP therapy completion (blood pressure [BP], blood and urine collection). AKI during cancer therapy: defined per KDIGO serum creatinine criteria. Outcomes: a) CKD: eGFR <90ml/min/1.73m^2 or urine albumin/creatinine ratio ≥3mg/mmol; b) elevated BP and HTN, per 2017 child HTN guidelines. Paired t-tests and McNemar's test used to determine if outcome prevalence differed from 3 to 12 m. Logistic regression (odds ratio [OR], 95% CI) used to determine relation of AKI with 3 and 12m CKD and HTN.

Results: Of 159 patients (50.3% male; median age 5.5 [IQR 2.4–11.9] yrs), 37 % developed AKI. Figure (1): There was no significant change in 3 *vs.* 12m prevalence (McNemar p-values all >0.05) of any outcomes (CKD: 44% and 39%, respectively; HTN: both 17%). eGFR was significantly lower at 12 *vs.* 3m (Figure (2), median [IQR] 135.8 [52.1] vs. 120.6 [37.4], respectively, p-value <0.001). AKI during CisP therapy was associated with 3 and 12m CKD (OR 2.2 [95% CI 1.2-4.4] and 2.8 [95% 1.4-5.6], respectively) but not HTN (OR 1.6 [95% CI 0.7-3.9] and 2.1 [95% CI 0.9-5.1], respectively).

Conclusions: CKD and HTN were common and persisted from 3m to 12m after cancer therapy completion. AKI was associated with later CKD but not HTN. Research on interventions to prevent AKI and reduce post-CisP CKD and HTN is needed.

Funding: Government Support - Non-U.S.

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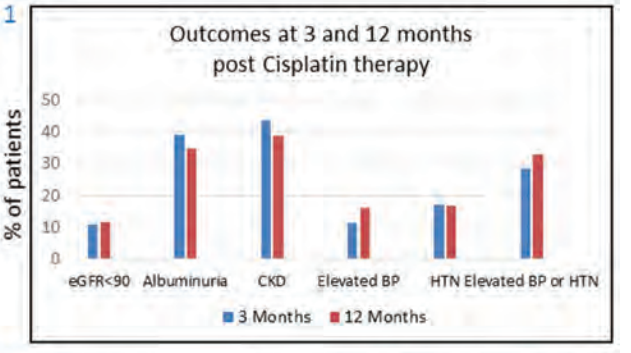

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Outcome	3 Months - median (IQR)	12 Months - median (IQR)	P-value
eGFR (SCr)	135.8 (52.1)	120.6 (37.4)	<0.001
Urine ACR	2.7 (4.4)	2.1 (3.3)	0.15
Systolic BP percentile	59 (54)	64 (45)	0.37
Diastolic BP percentile	64 (43)	70 (40)	0.24

ACR - albumin/creatinine ratio (mg/umol); BP - blood pressure; CKD - chronic kidney disease; eGFR - estimated glomerular filtration rate (ml/min/1.73m^2); HTN - hypertension; IQR - interquartile range; SCr - serum creatinine

SA-PO218

Anemia Management in Hemodialysis Patients: How Much Better Can We Do?

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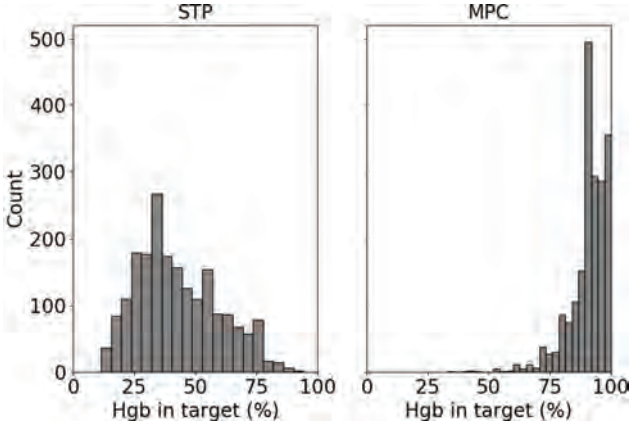
Background: The goal of anemia management with erythropoiesis-stimulating agents (ESA) is to achieve target hemoglobin (Hgb) levels while keeping drug doses low. Built on a physiology-based mathematical model of erythropoiesis (Fuertinger et al., PLoS ONE 2018), we developed an optimal control algorithm for individualized methoxy polyethylene glycol-epoetin beta (Mircera®) dose optimization.

Methods: The designed algorithm is a model predictive controller (MPC) that aims to stabilize Hgb levels at 10.5 g/dl. We compared the MPC administration regimen to a standard treatment protocol (STP) in an in-silico study for 6,659 chronic hemodialysis (HD) patients over a period of one year. Based on the Hgb levels obtained by the protocol, the in-silico population was divided into Hgb cyclers (cycles with amplitude >1.5 g/dl and duration >8 weeks, at least two cycles per year) and non-cyclers as defined by Fishbane & Berns (Kidney Int., 2015) yielding 1,987 cyclers.

Results: For non-cyclers, the MPC and STP regimens produced similar outcomes with respect to achieving Hgb targets and ESA usage. However, for cyclers, the MPC outperformed the STP. Cyclers' percentage of Hgb values within the target range of 10-11.5 g/dl for both treatment approaches are shown in Figure 1. The MPC lead to 91% of cyclers with at least 80% of Hgb values within the range and lowered the monthly Mircera® dose on average by 30%.

Conclusions: Our analysis shows a clear potential for better anemia management in Hgb cyclers as a subpopulation of HD patients: The MPC stabilized Hgb levels with a significantly reduced amount of Mircera® in this in-silico study. For non-cyclers, the STP could not be outperformed. Clinical studies are warranted to validate these findings.



Cyclers' percentage of Hgb values within the target range of 10-11.5 g/dl for the MPC and STP regimen.

SA-PO219

Anemia Disrupts Renal Compensatory Responses After Uninephrectomy in Mice

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Background: Kidneys with functional nephrons are essential for our life, but the numerous factors could reduce the numbers of nephron day by day. Kidney has ability to adapt its size and function against the nephron loss to maintain total renal function, for example, in both donor and recipient in renal transplantation. However, the factors that regulate this compensation have not been fully clarified yet. Hereby we examined the effects of erythropoietin (EPO)/anemia on the compensatory renal hypertrophy in mice model of renal anemia.

Methods: The mice lacking renal EPO production were used.

Results: The anemic mice showed renal compensatory responses, such as GFR more than half and cell hypertrophy, similar to normoxemic mice at week 1 after unilateral nephrectomy (UNX). However, the compensation was disrupted only in anemic mice at week 4 after UNX; the mice lacking EPO receptor in the kidney showed successful compensation. The disruption was accompanied by the increased oxidized glutathione and sustainable phosphorylation of ribosomal protein S6, a marker of mTOR activation, which had been decreased after successful compensation in the normal mice. In the renal interstitium of anemic mice at week 4 of UNX, the number of cells promoting epo gene transcription (but disable to produce EPO protein in the mice) was reduced even under the anemia, and the number of α-smooth muscle actin-positive cells was increased, suggesting the transdifferentiation of EPO-producing cells. These changes were restored by the supplementation of rEPO.

Conclusions: Anemia does not affect the onset of compensatory renal hypertrophy after UNX, but disrupts the persistent compensation process.

Funding: Government Support - Non-U.S.

SA-PO220

Patient-Specific Characteristics of Erythropoiesis and Their Influence on Hemoglobin Stability

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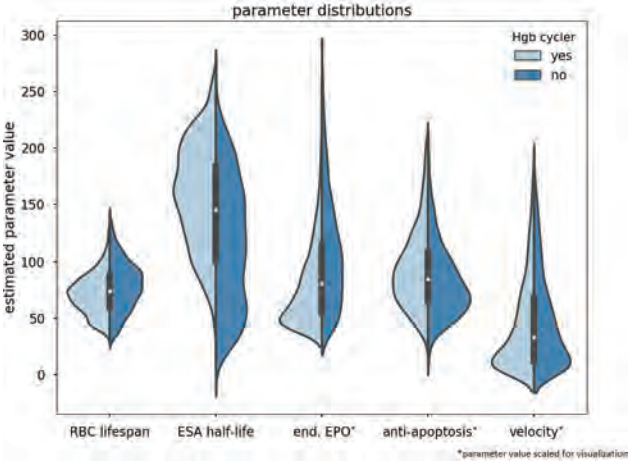
Background: In hemodialysis (HD) patients treated with erythropoiesis-stimulating agents (ESA) maintaining hemoglobin (Hgb) levels within recommended ranges is difficult. Many patients express Hgb excursions above and below the target range over the course of a year. This Hgb variability is associated with clinical events and ESA dose changes. This study investigates differences in biological key characteristics of erythropoiesis in HD patients and its influence on Hgb stability.

Methods: We adapted a comprehensive mathematical model of erythropoiesis to individual HD patients treated with methoxy polyethylene glycol-epoetin beta to estimate key characteristics of their red blood cell (RBC) reproduction cycles (Fuertinger, Plos One 2018), including RBC lifespan, endogenous EPO levels, ESA half-life and ESA influence on apoptosis and maturation velocity of RBC progenitors. In-silico tests were performed to distinguish Hgb "cyclers" from "non-cyclers" (criteria per Fishbane & Berns, Kidney Int. 2005). Estimated physiological parameters are depicted as violin plots, groups are compared by t-test.

Results: We estimated patient-specific characteristics of erythropoiesis in 6659 HD patients (♀: 46 %, Black: 43 %, mean ± SD: age 64 ± 14 years, BMI: 29.4 ± 7.6 kg/m^2). 29.8% were categorized as Hgb cyclers. Figure 1 compares erythropoiesis characteristics between cyclers and non-cyclers. We observed a statistically significant difference between Hgb cyclers and non-cyclers in RBC lifespan (mean±SD: 72±18 vs 78±21 days), endogenous EPO levels (13±6 vs 18±8 U/l), ESA half-life (159±46 vs 115±57 hours) and anti-apoptotic effects.

Conclusions: Patient-specific parameter estimates suggest that certain underlying biological characteristics may predispose patients to Hgb cycling. A better understanding of these effects could permit tailoring anemia algorithms to this subgroup to improve their Hgb variability and eventually clinical outcomes.



SA-PO221

The In Vitro Effect of Indoxyl Sulfate in Erythropoiesis of Human Hematopoietic Stem Cells: An Explanation of Anemia in CKD

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Background: The pathogenesis of anemia in chronic kidney disease (CKD) has been suggested to result from erythropoietin (EPO) insufficiency; however, several anemic CKD patients showed average to high plasma EPO levels. The presence of uremic toxins in patients with CKD has been suggested by several lines of evidence, including inhibition of erythroblast maturation. We suspected that EPO deficiency might not be the mainstay of anemia in CKD and then we focused on the effect of uremic toxins on the maturation of hematopoietic stem cells.

Methods: The effects of uremic toxin on red blood cell development was evaluated using hematopoietic stem cell (HSC) cultures. HSCs were isolated from umbilical cord blood using magnetic cell sorting to indicate CD34 positive cells. HSCs were then grown in differentiation medium combination with various concentrations of indoxyl sulfate (IS). Cell proliferation, viability, cell morphology, and erythrocyte specific markers were identified.

Results: The lower cell number in HSCs treated with IS was investigated in a dose-dependent manner. Proliferation and the percent viability of CD34 positive cells culture were observed with culture medium containing 0 (control), 25, 50, 100, and 200 ug/mL IS shown as Figure A. Erythrocyte differentiation tends to decline as demonstrated by lower numbers of CD235 and CD71 positive cells. Mature cells were counted using cell morphology assessments.

Conclusions: These findings conclude that uremic toxin (IS) appears to be a factor governing defective erythropoiesis. However, the pathogenesis of anemia involves multi-step processes that might be affected by the other types of uremic toxins and factors.

Funding: Government Support - Non-U.S.

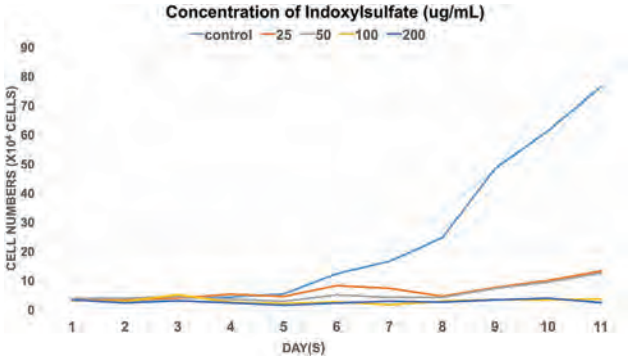

Figure A The proliferation of CD34 positive cells culture was observed for 11 days. Cells cultured with culture medium containing 0 (control), 25, 50, 100 and 200 ug/mL Indoxyl sulfate (IS)showed that all IS-treated cells decreased in cell number compared with control since day 6 of culture.

SA-PO222

LDL Lipidome and Erythropoiesis Stimulating Agent Response in Hemodialysis Patients

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Background: Anemia management in end-stage renal disease (ESRD) is difficult due to variable erythropoiesis stimulating agent (ESA) response. Hemodialysis alters lipoprotein composition. Additionally in-vitro erythropoietic burst assays respond to changes in lipoprotein supplementation; suggesting a role in RBC formation. We have previously shown HDL proteome differs with ESA response in maintenance hemodialysis (HD) patients. We hypothesized HD patients ESA response was associated with HDL/LDL composition.

Methods: HDL & LDL were isolated by dextran sulfate precipitation (n=105 patient samples). Purity was assessed by immunoblot and proteomics. Total cholesterol (Cho), phospholipid (PL) and triacylglycerol (TAG) were quantified by enzyme assay. Avanti SPLASH™ LipidoMix® standards were added before Bligh-Dyer LDL lipid extraction. LCMS analysis and informatics used Waters UPLC-Synapt G2-Si Q-Tof MSe (+/- ion modes) with Progenesis QI + LipidMAPS database. Data were normalized to internal spike-in and total Cho; results filtered based on mass accuracy (<15ppm), fragmentation score, and isotopic matching. Categorical differences (ESA naïve (38), ESA hyper (23)-, ESA normal (22)-, and ESA hypo-(22) responders) were compared by ANOVA, and continuous differences with Spearman correlation.

Results: LDL Cho but not HDL Cho was negatively correlated ($p<0.05$) with ESA utlization. Lipidomics identified 222 LDL-associated lipids including 36 different by ANOVA ($p<0.05$)- 22 increased and 3 decreased with EPO-dose response groupings; 11 lipids changed with EPO use relative to EPO naïve patients. Post-hoc ttest shows significant increase of four lipids (hyper-to-hypo-EPO response) including a cholesterol ester, ceramide, and a vitamin D3 analogue. Spearman analysis revealed LDL-lipid correlation to EPO dose (10), ESA response index (7), ferritin (12), hepcidin (3), and CRP (2); including polyunsaturated (PU)-ceramides, lysophosphatidylcholine, oxidized phosphoglycerolipid, Cho-esters and a statin.

Conclusions: In this study poor HD patient-ESA dose was associated with low LDL Cho levels suggesting ESA hypo-response is associated with LDL lipid composition including lipids associated cytotoxicity, proatherogenic pathways and a statin. Future/on-going work addresses anti-hyperlipidemic agents and ESA response.

Funding: NIDDK Support, Clinical Revenue Support

SA-PO223

ET-1-Dependent Impairment of Renal Iron Handling Leads to Iron Overload-Associated Tubular Injury in Sickle Cell Nephropathy

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Background: Iron overload, a major consequence of the sickle cell disease (SCD), promotes renal iron deposition that correlates with albuminuria in SCD patients. Also, elevated plasma endothelin-1 (ET-1) levels reported in SCD correlate with microalbuminuria. Excessive renal iron deposition in humanized sickle cell (HbSS) mice is attenuated by endothelin A receptor (ET_A) blockade.Thus, we hypothesize that elevated ET-1 via ET_A receptor activity leads to dysfunctional tubular iron handling, iron overload, and resultant tubular injury in SCD nephropathy.

Methods: C57BL/6 mouse primary tubule (PT) cells and 14 weeks old HbSS mice were utilized in this study.

Results: ET-1 directly increased the expression of iron trafficking mediators in mouse PT cells. This includes transferrin receptor 1 (TfR-1) for cellular uptake and H-ferritin for storage. ET-1 also, decreases the expression of the iron exporter, ferroportin-1 ((FPN-1) and increases the expression of FPN-1 regulator, hepcidin (HAMP). Exposure of PT cells to 50 nM ET-1 and 0.1 μM heme for 24h increased cellular heme uptake compared to untreated cells (19.31±2.51 vs. 1.85±0.26 μM/mg protein). The ET_A antagonist, BQ123, prevented ET-1-induced alterations in all iron trafficking mediators. Moreover, plasma ET-1 concentrations were positively correlated with renal iron deposition in HbSS mice (R^2=0.72, $p<0.0001$). HbSS mice showed altered PT iron transporter expressions consistent with promoting PT iron accumulation. 10-week in vivo treatment with an ET_A receptor antagonist prevented the induction of cellular iron uptake transporter, DMT-1, preserved FPN-1, and reduced HAMP expression in PT cells from HbSS mice. A potential mechanism(s) of ET-1-mediated iron overload-associated tubular damage may involve ROS and/or mitochondrial dysfunction. PT cells exposed to FeS (500 μg/mL) have increased ROS production (12.52±1.31 vs. 0.14±0.01 AUCx10^3/mg protein). PT cells from HbSS mice exhibit mitochondrial dysfunction indicated by doubled expression of markers of mitochondrial stress PTEN-induced kinase 1 (PINK1), heat-shock protein 40 (mtHSP40), and mitochondrial fission 1 protein (Fis1).

Conclusions: These results uncover a novel role for ET-1 in PT iron trafficking and provide rationale for use of selective ET_A receptor blockade as a potential therapeutic approach in SCD nephropathy.

Funding: NIDDK Support, Other NIH Support - NHLBI U01 HL117684 to DMP, Private Foundation Support

SA-PO224

Hemodialysis Augments Red Blood Cell Death and Intracellular Hypoxia

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Background: Previous studies have shown that uremia increases red blood cell (RBC) death (eryptosis) in hemodialysis (HD) patients, possibly aggravating their anemia. The present study tests the hypothesis that hemodialysis (HD) triggers eryptosis, as indicated by phosphatidylserine (PS) exposure, and calcium influx into RBC. In addition, we explored levels of RBC intracellular hypoxia.

Methods: RBC were obtained from healthy subjects (CON-RBC; n=8) and ESRD patients (HD-RBC; n=10) pre- and post-HD. Using flow cytometry, PS exposure (Annexin-V), calcium influx (Fluo 3-AM probe), and intracellular level of hypoxia (Hypoxia Green probe) were determined. Results are expressed in mean fluorescence units (MFI). We compared these parameters between healthy controls and pre- and post-HD, respectively.

Results: The age of the healthy subjects was 34.8±17.3 years, 20% were male. The patients were 73% males, the age was 58.1±18.1 years. Compared to CON-RBC, PS exposure, calcium influx, and levels of intracellular hypoxia were increased in HD-RBC pre- and post-HD, respectively. In addition, HD treatment was associated with significantly increased PS exposure and intracellular hypoxia (Table 1).

Conclusions: Taken together, our results suggest that HD increases RBC hypoxia, eryptosis, and RBC calcium influx. Lower oxygen levels in HD-RBC could be due to either an impaired uptake or enhanced release of oxygen. Oxygen-sensitive intracellular responses may regulate RBC lifespan.

Eryptosis and oxygen levels in RBC from healthy controls (CON-RBC) and hemodialysis patients (HD-RBC) pre- and post-HD.

Parameters [in MFI units]	CON-RBC (n=8)	HD-RBC Pre-HD (n=10)	HD-RBC Post-HD(n=10)
Ca2+ influx	31.9±14.6	60.9±17.4***	74±15.8***
PS exposure	2.6±1.6	12.5±6**	27.2±7.2*** (#)
Hypoxia level	9.7±2.3	14.63±3.3*	22.15±4.9***(#)

Data are shown as mean±SD of the Mean Fluorescence Intensity (MFI).

*p<0.05, **p<0.01, ***p<0.001 correspond to the difference between HD-RBC and CON-RBC. (#) p<0.01 corresponds to the difference between pre-HD-RBC and post-HD-RBC.

SA-PO225

Two Phase 3, Multicenter, Randomized Studies of Intermittent Oral Roxadustat in Anemic CKD Patients on (PYRENEES) and Not on (ALPS) Dialysis

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Background: Roxadustat is an oral HIF-PHI in late-stage development for treatment of CKD anemia.

Methods: Two phase 3 European studies enrolled non–dialysis-dependent (NDD; ALPS) and dialysis-dependent (DD; PYRENEES) patients with CKD anemia. In the double-blind NDD study, patients with hemoglobin (Hb) ≤10 g/dL not treated with erythropoiesis-stimulating agents (ESAs) were randomized (2:1) to oral roxadustat or placebo for 52-104 weeks. In the open-label DD study, stable hemodialysis or peritoneal dialysis patients with Hb 9.5-12 g/dL treated with ESAs were randomized (1:1) to oral roxadustat or ESAs for 52-104 weeks. Primary endpoints were change of average Hb levels at Weeks 28-52 from baseline. Secondary endpoints included change of average low-density lipoprotein cholesterol (LDL) at Weeks 12-28 from baseline, time to use of rescue therapy (ie, transfusion, ESA, IV iron; NDD study), and mean monthly IV iron use through Week 36 (DD study). Occurrence of adverse events (AEs) was also assessed.

Results: The NDD study randomized 594 patients to roxadustat (n=391) or placebo (n=203); the DD study randomized 836 patients to roxadustat (n=415) or ESA (n=421). Mean (SD) change of average Hb levels at Weeks 28-52 from baseline was 1.988 (0.953) for roxadustat and 0.406 (0.979) for placebo (P<0.001) in NDD patients and 0.396 (0.773) for roxadustat and 0.183 (0.860) for ESA in DD patients (P<0.001). The LS mean difference (95% CI) in LDL was -0.701 (-0.83, -0.57; P<0.001) mmol/L vs placebo in NDD patients and -0.377 (-0.451,-0.304; P<0.001) mmol/L vs ESA in DD patients. In NDD patients, roxadustat was superior to placebo in time to use of rescue therapy (hazard ratio [95% CI], 0.238 [0.17, 0.33]; P<0.001). In DD patients, roxadustat was superior to ESA in mean monthly IV iron use (LS mean difference [95% CI], -31.9 [-41.4, -22.4]; P<0.001). Common AEs in both treatment groups were ESRD, hypertension, peripheral edema, and decreased GFR in NDD patients, and hypertension, arteriovenous fistula thrombosis, headache, and diarrhea in DD patients. Roxadustat safety data will be integrated across all trials.

Conclusions: Roxadustat was effective in achieving and maintaining Hb levels compared with placebo and ESA in NDD- and DD-CKD patients.

Funding: Commercial Support - Astellas Pharma Inc

SA-PO226

Phase 3, Multicenter, Randomized, Open-Label, Non-Comparative Study of Intermittent Oral Roxadustat in ESA-Naive CKD Patients Not on Dialysis in Japan

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Background: Roxadustat, an oral HIF-PHI, is in late-stage development for treatment of chronic kidney disease (CKD) anemia. This phase 3 study evaluated efficacy and safety of oral roxadustat in erythropoiesis stimulating agent (ESA)-naïve non–dialysis-dependent (NDD)-CKD patients with anemia.

Methods: Multicenter, 24-week, Japanese study of NDD-CKD ESA-naïve anemic (hemoglobin [Hb] <10.5 g/dL) patients. Patients were randomized to roxadustat (initial dose of 50 mg or 70 mg) three times weekly; dose was adjusted to maintain Hb at 10-12 g/dL. Efficacy endpoints were response rate (Hb ≥10.0 g/dL and a Hb increase of ≥1.0 g/dL from baseline) at end of treatment; average Hb levels at Weeks 18-24; change of average Hb levels at Weeks 18-24 from baseline; maintenance rate of target Hb level (proportion of patients achieving average Hb level of 10-12 g/dL at Weeks 18-24); rate of rise in Hb (g/dL/week) from Week 0 to Week 4, time of discontinuation before Week 4, or time of dose adjustment before Week 4. Occurrence of adverse events (AEs) was assessed.

Results: Of 100 randomized patients, 99 started on 50 mg (n=49) or 70 mg (n=50) roxadustat. Response rate (95% CI) from baseline to end of treatment was 93.9 (83.1, 98.7) % and 100.0 (92.9, 100.0) % in the 50-mg and 70-mg groups, respectively. Mean (SD) of average Hb levels at Weeks 18-24 was 11.12 (0.57) g/dL and 11.23 (0.67) g/dL in the 50-mg and 70-mg groups, respectively. Mean (SD) change of average Hb levels at Weeks 18-24 from baseline was 1.39 (0.93) and 1.30 (0.80) g/dL in the 50-mg and 70-mg groups, respectively. Maintenance rate (95% CI) of target Hb level during Weeks 18-24 among patients with ≥1 Hb value at Weeks 18-24 was 88.6 (75.4, 96.2) % and 88.9 (75.9, 96.3) %, in the 50-mg and 70-mg groups, respectively. Mean (SD) rate of rise in Hb from Week 0-4 was 0.291 (0.197) g/dL/week and 0.373 (0.235) g/dL/week in the 50-mg and 70-mg groups, respectively. The most common AEs were nasopharyngitis (20.2%), hypertension (6.1%), diarrhea (5.1%), and hyperkalemia (5.1%).

Conclusions: Roxadustat was effective in achieving and maintaining Hb levels with the target range at both starting doses and in Japanese ESA-naïve NDD-CKD patients with a favorable safety profile. The rate of rise of Hb was dose dependent.

Funding: Commercial Support - Astellas Pharma Inc

SA-PO227

SIERRAS: A Phase 3, Open-Label, Randomized, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in Subjects with ESRD on Stable Dialysis

Chaim Charytan,[2] Roberto Manllo-Karim,[3] Edouard R. Martin,[4] Dylan Steer,[5] Marializa Bernardo,[6] Sohan L. Dua,[7] Moustafa A. Moustafa,[8] Gopal Saha,[1] Charles Bradley,[1] Meraf Eyassu,[1] Robert Leong,[1] Cameron S. Liu,[1] Lynda Szczech,[1] Kin-Hung P. Yu.[1] *[1]FibroGen, Inc., San Francisco, CA; [2]Nephrology Associates, PC, New Rochelle, NY; [3]South Texas Kidney Specialists, P.A., McAllen, TX; [4]South Florida Nephrology Associates, Lauderdale Lakes, FL; [5]Balboa Nephrology Medical Group, La Jolla, CA; [6]Southwest Nephrology Associates, Houston, TX; [7]Valley Renal Medical Group, Northridge, CA; [8]South Carolina Nephrology & Hypertension Center, Inc, Orangeburg, SC*.

Background: Roxadustat (FG-4592) is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and regulates iron metabolism.

Methods: Dialysis patients (pts) were randomized (1:1) to roxadustat (ROXA) or epoetin alfa (EPO). Oral iron was allowed; parenteral iron was restricted. ROXA was dosed thrice weekly. The initial ROXA dose was based on the pts' preceeding EPO dose. EPO was prescribed according to US Package Insert. An algorithm guided ROXA doses required to maintain Hb. The primary endpoint for US FDA was mean Hb change from baseline (BL) for Weeks (Wks) 28-52; the primary endpoint for the EU EMA submission was mean Hb change from BL to Wks 28-36. Safety and tolerability were assessed by adverse events, vital signs, electrocardiogram findings, and clinical laboratories.

Results: 741 pts (370=ROXA, 371=EPO) were randomized. The ROXA-treated pts were 44.6% Caucasian and 42.7% Black while the EPO-treated pts were 49.6% Caucasian and 42.0% Black. The percentage of pts with type-2 DM in the ROXA arm was 65.1% (n=241) and 65.8% (n=244) in the EPO arm. The mean Hb change from BL to the average over Wks 28-52 was 0.39 (ROXA) vs. -0.09 g/dL (EPO). The lower 95% CI for this difference was above the non-inferiority margin of 0.75 g/dL, and met the US criterion for superiority of ROXA over EPO (p<.0001). The mean Hb change from BL to the average over Wks 28-36 was 0.54 (ROXA) vs. -0.02 g/dL (EPO). ROXA met the non-inferiority criteria as the lower bound of 95% CI was above the non-inferiority margin of 0.75 g/dL compared with ESA. ROXA also achieved superiority, p<.0001. ROXA reduced RBC/blood transfusion risk by 33% compared with EPO (HR .67, p<.0037). The overall safety profile was consistent with results observed in prior ROXA trials and pooled safety findings will be submitted as a late breaker abstract.

Conclusions: ROXA was non-inferior and subsequently demonstrated superiority over EPO in the mean change in Hb from BL and in the rate of blood transfusions in dialysis pts.

Funding: Commercial Support - Fibrogen Inc.

SA-PO228

ANDES: A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in CKD Patients Not on Dialysis

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Background: Roxadustat (FG-4592; ASP1517; AZD9941) is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and regulates iron metabolism.

Methods: In this Ph3, randomized, double-blinded, placebo-controlled trial, the efficacy and safety of roxadustat vs. placebo was evaluated in patients (pt) with anemia and chronic kidney disease (stages 3-5) who were not dialysis-dependent (NDD-CKD). 922 pt were randomized (2:1) to receive oral roxadustat (n=616) or placebo (n=306) three-times weekly based on a tiered, weight-based scheme. Oral iron was allowed, IV iron was withheld except for rescue. Study drug dose was adjusted based on a dosing algorithm to correct and maintain hemoglobin (Hb). Primary efficacy endpoints were change in Hb from baseline (BL) to the average level during weeks (wk) 28-52 (for US [FDA]) and the proportion of subjects who achieve an Hb response at two consecutive visits during the first 24 wk of treatment without rescue therapy (for EU [EMA]). Safety and tolerability were assessed by adverse events, vital signs, ECG findings, and clinical laboratory values.

Results: Mean age was 64.9 years (yr) in the roxadustat arm and 64.8 in the placebo arm. Other BL characteristics were well balanced including BL Hb levels that averaged 9.1 g/dL in both arms. Treatment duration was up to 4.5 yr, with average duration of 1.7 yr. Mean change in Hb from BL to the average over wk 28-52 was 2.00 g/dL for roxadustat vs. 0.16 g/dL for placebo (p<0.0001). The proportion of pt who achieved an Hb response at two consecutive visits during the first 24 wk of treatment was 86.0% for roxadustat vs. 6.6% for placebo (p=0.0007). Roxadustat reduced the risk of rescue therapy by 81%

(HR=0.19) and the risk of blood transfusion by 74% (HR = 0.26), both p<0.0001. Pooled safety analysis will be submitted as a late breaking clinical trial abstract.

Conclusions: Roxadustat was superior to placebo in mean Hb change from BL to the average over wk 28-52 with a higher proportion of roxadustat-treated pt achieving an Hb response in the first 24 wk.

Funding: Commercial Support - Fibrogen Inc.

SA-PO229

Randomized, Open-Label, Active-Controlled (Darbepoetin Alfa), Phase 3 Study of Vadadustat for Treating Anemia in Non-Dialysis-Dependent CKD Patients in Japan

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Background: This open-label, active-controlled Phase 3 study (NCT03329196) evaluates the efficacy and safety of vadadustat (VDT), an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, in 304 nondialysis dependent (NDD) chronic kidney disease (CKD) subjects with anemia in Japan for 52 weeks. Prespecified primary analysis results at 24 weeks are presented here.

Methods: NDD-CKD subjects with anemia receiving (conversion) or not receiving erythropoiesis stimulating agents (correction) were randomized to VDT (n=151) or darbepoetin alfa (DA) group (n=153). After initial VDT dose of 300 mg daily, doses were adjusted within 150–600 mg to achieve and maintain target hemoglobin (Hb) of 11–13 g/dL. Primary endpoint was average Hb at weeks 20 and 24. Noninferiority of VDT to DA was tested using mixed model for repeated measures. Iron parameters were measured. Safety was assessed up to 24 weeks.

Results: LSMean of the average Hb at weeks 20 and 24 was 11.66 (VDT: 95% CI, 11.49 to 11.84) and 11.93 (DA: 11.76 to 12.10) g/dL; 95% CI of both groups were within the target Hb of 11–13 g/dL. Difference in LSMean between the groups was –0.26 g/dL (–0.50 to –0.02); the 95% CI lower limit was above the predefined noninferiority margin of –0.75 g/dL, demonstrating the noninferiority of VDT to DA. VDT improved mean Hb from baseline of 10.68 to 11.27 g/dL at week 24 (conversion, n = 80) and 10.17 to 11.85 g/dL (correction, n = 71). VDT regimen was associated with significant increases in total iron-binding capacity and decreases in hepcidin from baseline to week 24, not found in the DA group. At least one adverse event (AE) was seen in 72.2% (VDT) and 73.2% (DA) subjects. The most common AEs in the VDT group were nasopharyngitis (VDT: 14.6%, DA: 12.4%), diarrhea (VDT: 10.6%, DA: 3.3%), and constipation (VDT: 5.3%, DA: 3.9%). The incidence rates of serious AEs were 13.9% (VDT) and 14.4% (DA). No serious AE was considered related to the study drug.

Conclusions: VDT was effective as DA in controlling Hb within the target range in both conversion and correction without new safety concerns, indicating the usefulness of VDT for treating anemia in Japanese NDD-CKD patients.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation

SA-PO230

An Open-Label Extension Study to Evaluate the Efficacy and Safety of Roxadustat for the Long-Term Maintenance Treatment of Anemia in Dialysis and Non-Dialysis Patients with CKD

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Background: Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis via increasing endogenous erythropoietin, and regulates iron metabolism.

Methods: In this open-label, extension study, subjects with dialysis-dependent (DD-CKD) and non-dialysis-dependent chronic kidney disease (NDD-CKD) who have completed the treatment period of a phase 2 roxadustat anemia study in the U.S. were enrolled and treated with roxadustat. Subjects continued to receive roxadustat at the same dose and frequency unless a dose adjustment was required, followed by dose titration to Hb levels. Mean Hb values, total weekly roxadustat doses and dose frequencies over time were evaluated. Safety and tolerability were assessed by adverse events, vital signs, electrocardiogram findings, and clinical laboratory values.

Results: Fifteen subjects with NDD-CKD (n=14) and DD-CKD (n=1) were enrolled and treated. One subject with NDD-CKD who withdrew consent two weeks after enrollment and one other subject with DD-CKD were excluded from the analyses. Among the 13 NDD-CKD patients, mean age was 65.5 years; [range, 38 - 78 years], 61.5% (8/13) were female, and 100% (14/14) were white. Baseline Hb levels averaged 10.2 g/dL; [range, 8.7 - 11.2 g/dL], and eGFR averaged 26.1 mL/min; [range, 7.3 - 48.2 mL/min]. At the time of enrollment, 7.7% (1/13) of subjects were on TIW dosing regimen, 69.2% (9/13) on BIW, and 23.1% (3/13) on QW. Mean follow up was 3.7 years [range, 1.0 - 6.9 years]. Hb levels over time averaged 11.7 g/dL [range, 11.0 - 12.4 g/dL]. At patients' last dose, 7.7% (1/13) of subjects were on TIW dosing regimen, 69.2% (9/13) on BIW, 15.4% (2/13) on QW, and 7.7% (1/13) were on QOW dosing regimen. The mean total weekly dose of roxadustat was 241.2 mg; [range, 73.7 – 517.9 mg]. The safety and tolerability profiles observed were as expected for this patient population.

Conclusions: In this cohort of patients with NDD-CKD, long-term use of roxadustat for treatment of anemia resulted in continued efficacy in Hb maintenance in all patients with a safety profile consistent with the population of patients under study.

Funding: Commercial Support - Fibrogen Inc.

SA-PO231

Long-Acting Erythropoiesis-Stimulating Agent (ESA) Induced the Physiological Erythropoiesis via an Improvement of Iron Availability

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Background: Maintenance hemodialysis (MHD) patients with a dysutilization of iron for erythropoiesis exhibited significantly higher risks of cardiovascular disease and all-cause death compared to other groups. Thus, anemia treatment that improves iron availability for erythropoiesis might attenuate the risk of adverse events of these patients. Recently, basic studies or short-term clinical studies reported that the long-acting erythropoiesis-stimulating agent (ESA) significantly suppressed the expression of hepcidin, which regulates iron availability. In this study, we compared the iron availability for erythropoiesis between short- and long-acting ESA during a long-term period.

Methods: Sixty-nine MHD patients with renal anemia (mean age: 69 yo, % of male: 65%, mean duration of HD time: 122±98 months) were enrolled in this study. All patients were treated with a short-acting ESA (epoetinα or epoetinβ) for the first 30 months (short-acting ESA period). Then, all patients were switched to a longacting ESA (continuous erythropoietin receptor activator-methoxy polyethylene glycol-epoetin beta) for the next 30 months (long-acting ESA period).

Results: The mean dose of the short-acting ESA and longacting ESA was 2795±259 IU/week and 82.6±14.7 μg/month, respectively. Compared with the short-acting ESA period, the mean Hb (10.3±0.2 vs.10.6±0.2 g/dL) and TSAT (15±2.9 vs. 25.9±3.5%) levels were significantly (p<0.05) increased in the long-acting ESA period. Additionally, the mean serum ferritin level (72.0±22.2 vs. 56.3±14.0 ng/mL) and the dose of IV iron (108.0±63.7 vs. 53.4±26.9 mg/month) were significantly (p<0.05) decreased in the long-acting ESA period.

Conclusions: In this study, anemia treatment of MHD patients with a long-acting ESA attenuated iron utilization for erythropoiesis (decreased serum ferritin and increased TSAT) and maintained target Hb levels without a higher dose of IV iron and ESA. From these results, we hypothesize that anemia treatment with a longacting ESA might induce more physiological erythropoiesis in MHD patients via improvements in iron metabolism compared to treatment with a short-acting ESA. To evaluate the effect of the long-acting ESA on the adverse events or survival of MHD patients, further randomized control studies are needed.

SA-PO232

Understanding Patient Perspectives of the Impact, Awareness, and Treatment of CKD Anemia: A US Patient Survey

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Background: Anemia is a common complication of CKD that may reduce patients' (pts) quality of life (QoL) and/or require them to seek treatment. The objective of this study was to assess the perceptions of US CKD pts with anemia with respect to QoL, disease understanding, and management of their anemia.

Methods: In August–September 2018, a quantitative online survey was administered to 500 US pt volunteers aged ≥18 years with self-reported CKD with or without anemia; pts with cancer were excluded. Pts were recruited via open requests to online communities and support groups, pt associations, and pt referrals. This survey explored pt knowledge of anemia and its management, impact on symptoms, and QoL. Data were aggregated and anonymized to protect pt confidentiality.

Results: Respondents were 69% female, mean age 52.2 years, and 68% confirmed they had CKD stages 3–5, 24% had CKD stage 1 or 2; the remaining 8% did not know the stage. Of the entire cohort, 57% (n=255) of pts reported being told they had anemia by a healthcare professional (HCP). However, only 66% (n=168) of these 255 pts knew about the relationship between anemia and CKD. Of the entire cohort, only 38% (n=170) knew their hemoglobin levels, but most were aware of the key symptoms associated with anemia, identifying fatigue (89%) or weakness (70%). Pts with anemia reported lack of energy (82%), feeling sad and/or depressed (53%), noting pain (52%), difficulty sleeping (53%), and worrying about worsening anemia (63%). Most pts (67%) stated that their anemia was well managed mostly with iron supplements (55% of those treated) or erythropoiesis-stimulating agents (30%), while 11% had received transfusions. Less than half felt confident that they knew the adverse effects of their treatment.

Conclusions: US pts with CKD perceived that anemia had a negative impact on their physical symptoms and emotional wellbeing; their knowledge and understanding of CKD anemia and its management varied. These findings emphasize the challenges HCPs and pts face concerning the need for further education on the association between CKD and anemia, symptoms associated with anemia, and the available treatment options for anemia.

Funding: Commercial Support - AstraZeneca

SA-PO233

Understanding Patient Perspectives of the Impact and Treatment of CKD Anemia: A Patient Survey in China

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Background: Anemia is a common complication of CKD that may reduce patients' (pts) quality of life (QoL) and/or require treatment. The objective of this study was to assess the QoL burden, knowledge, and management of CKD anemia in a sample of Chinese pts.

Methods: In August–September 2018, a quantitative, online survey was administered to 500 Chinese pt volunteers aged ≥18 years with self-reported CKD with or without anemia; pts with cancer were excluded. Pts were recruited via online communities, pt associations, online support groups, and direct pt referrals. This 27-question survey explored pt knowledge of anemia, its management, impact on QoL, information sources for the condition, and effects on the healthcare practitioner–pt relationship. Data collected from the survey were aggregated and anonymized to protect pt confidentiality.

Results: Overall, data were evaluable for 456 pts, 44% female, mean age 41.0 years, and 23% reported receiving a CKD diagnosis stages 3–5, the remaining 77% had CKD stage 1 or 2, or did not know the stage. Of the entire cohort, 32% of pts reported being told they had anemia, 73% did not know their hemoglobin (Hb) level or had not had a blood test in the previous year. Of pts told they had anemia (n=148), most reported feeling ill (86%), lack of energy (75%), nausea (72%), pain (69%), and sadness and/or depression (61%). For these pts, a negative impact of CKD anemia on QoL was perceived: 66% reported less energy, 54% reported more sadness/depression, 50% felt they were more ill, 37% worried more that their condition was worsening, and 29% reported less ability to work. Awareness of the link between CKD and anemia was common (87%), and 71% thought that their anemia was well or very well managed: 64% reported taking iron supplements; 69% had received dietary advice; 26% were given erythropoiesis-stimulating agents; and 31% had received blood transfusions.

Conclusions: Chinese pts perceived that CKD anemia had a negative impact on their QoL. Although pt knowledge of anemia was varied, perceptions of its management were generally positive. There are opportunities for improving pt education on the association between CKD and anemia, improving Hb testing and monitoring, and increasing use of treatments to avoid blood transfusions.

Funding: Commercial Support - AstraZeneca

SA-PO234

Role of Nephrology Pharmacists in the Management of Anemia in Outpatient Dialysis Units: A Canadian Model

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Background: Hemodialysis patients frequently suffer from anemia. Proper utilization of therapies such as iron and erythropoiesis-stimulating agents (ESAs) are crucial to attain established hemoglobin targets. The purpose of this study was to evaluate the clinical and financial impact of nephrology trained pharmacists on anemia management in these patients

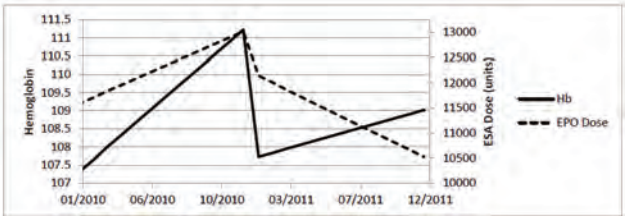
Methods: A retrospective study of patients who received hemodialysis between Jan 2010 and Dec 2011 in the outpatient hemodialysis units. In Dec 2010, pharmacists were tasked to manage anemia under medical directive. Primary endpoints were compared across years (2010 vs. 2011) using a mixed-effects model strategy An unstructured random effects correlation matrix was utilized to capture patient-level variation in 2010 and 2011 separately

Results: Of 202 patients, 163 contributed in both years, 57% were males, age 65.18± 16.3 years. Hemoglobin levels were 10.95±0.95 and 10.83±0.94 mg/dL in 2010 vs. 2011 respectively, p=0.158, while the transfusion rate was 1.3% and 1.8%, respectively, p=0.196. Ferritin levels 273.5±215 and 317.1±123, p=0.0019, iron saturation 0.30±0.11 and 0.30± 0.05, p=0.838, and Iron dose 215.4±100.2 and 317.1±123.7 mg, respectively, p= 0.996. Finally, the average weekly ESA use in 2010 was higher and trending up as compared to 2011 where it significantly trended down. Erythropoietin alfa dose 12315.6±7591 vs. 11364.1±5150, respectively, p=0.556 (figure1) with expenditure of 2.8 million CAD in 2010 vs. 2.3 million in 2011.

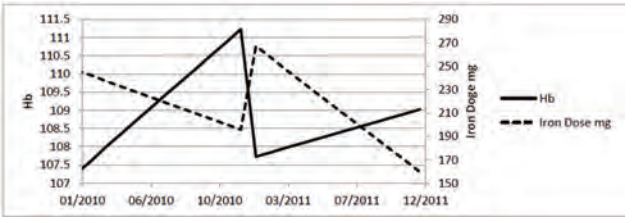
Conclusions: The participation of a nephrology trained pharmacist resulted in favourable outcomes in dose optimization (process), decreased expenditure (financial) and positive trends in therapeutic goal achievement coupled with reduced consumption (clinical)

Figure 1. Effect of ESA dosing (a) and Iron Dosing in mg (b) on Hemoglobin trend over the study period

a.



b.



SA-PO235

Anemia Nurse Manager in Peritoneal Dialysis: A Retrospective Study from Qatar

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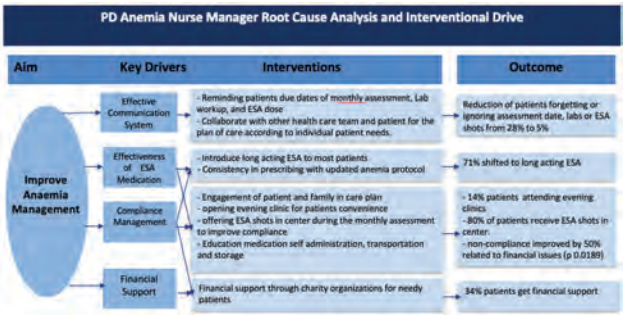
Background: Anemia management is challenging in peritoneal dialysis (PD) patients (home-based with dependence on patients' compliance). We implemented a special anemia nurse manager (ANM) model with nephrologist's supervision in PD to achieve better hemoglobin (Hg) targets. We performed a retrospective study to evaluate outcomes and cost effectiveness of the new model.

Methods: Our PD ANM is a PD nurse who was trained for 4 months (8-12/2017) by a nephrologist. The program expanded gradually to include all PD patients by 1/2018. Our PDANM role includes lab review, medications adjustments, patients' education and act as a focal point for anemia. We reviewed patients record for 1 year (1/2018-12/2018). We tracked laboratory values and medications. We performed root cause analysis (RCA) routinely to analyze and resolve challenges to achieve goals.

Results: PD census mean was 180 patients during study period (1/2018-12/2018). ANM model achieved a significant improvement in PD patients with Hg in target range (10-12g/dL) (54% in 1/2018 vs 75% in 12/2018 p=0.0004). Number of patients with extreme Hg (<9 g/dl or >13 g/dl) improved from 18% to 12% in the same period (p=0.03). Patients in ferritin target (200-800) improved (55% vs 69% p<0.005) without affecting iron saturation. Weekly Aranesp dose was reduced with the ANM model from 45mcg to 39mcg and monthly Mircera dose from 151mcg to 127mcg. Simple cost effectiveness analysis (saving in ESA consumption-nurse salary) showed estimated annual cost saving of 70000 dollars. Our RCA showed that the main cause of failure was compliance with visits and ESA shots. Based on our RCA we built a unique anemia management algorithm for PD (Figure 1).

Conclusions: Anemia management in PD was successfully shifted to our new ANM model. We were successful to achieve and maintain patients within anemia targets. The model was cost effective. We collaborated with a hematologist to address challenges. Similar models are applied throughout our dialysis service.



SA-PO236

Association Between Serum Total Bilirubin Levels and Mortality in Dialysis Patients

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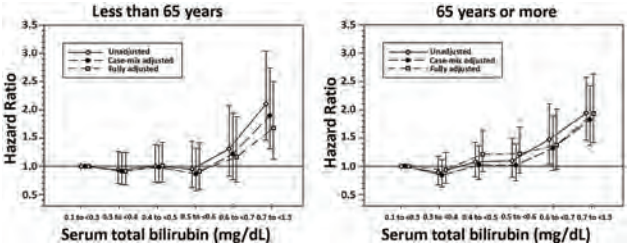
Background: Serum bilirubin may have a potent antioxidant effect and may be associated with protection from cardiovascular disease (CVD) in non-dialysis patients. It is unknown if serum bilirubin levels (sTB) can predict subsequent mortality risk following dialysis initiation in patients at high risk of developing CVD.

Methods: We identified 3,769 patients who transitioned to maintenance dialysis in a large US dialysis organization (2007-2011) and had available sTB data at baseline. Patients with abnormally high (>1.3 mg/dL) and low (<0.1 mg/dL) sTB or liver disease were excluded from the cohort. We divided patients into 12 groups based on their sTB levels (0.1-<0.3 [ref.], 0.3-<0.4, 0.4-<0.5, 0.5-<0.6, 0.6-<0.7, 0.7-<1.3 mg/dL) and age (<65 years, ≥65 years). All-cause mortality risk was examined using Cox models with adjustment for case-mix (age, gender, race/ethnicity, hypertension, diabetes and CVD) and a fully adjusted model (case-mix model plus body mass index and 11 laboratory variables).

Results: The mean age was 62 ± 15 (mean ± SD) years, 56% of patients were male, and 48% were non-white. There were significant differences in all clinically relevant factors used for adjusted models among the non-elderly and elderly groups. In both the non-elderly and elderly patient groups, those with high sTB levels had the highest hazard ratio (HR) after full adjustment vs. the 0.1-<0.3 mg/dL group (HRs:1.68 [95% CI, 1.13-2.50] and 1.93 [95% CI, 1.41-2.64], respectively). [figure]

Conclusions: In contrast to conventional studies, higher sTB levels within normal ranges are associated with higher mortality in incident dialysis patients. Aging and uremia under dialysis might attenuate an antioxidant effect of bilirubin. Whether bilirubin can be used as an independent risk factor for mortality in dialysis patients warrants additional studies.

Funding: NIDDK Support



SA-PO237

CKD Anemia Epidemiology and Associated Outcomes in Non-Dialysis-Dependent Patients

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Background: Anemia is a well-known CKD complication associated with increased risk of red cell transfusions (RBCs), low quality of life, and adverse outcomes such as cardiovascular events and mortality. Current treatments including erythropoietin-stimulating agents (ESAs) have not been shown to improve clinical outcomes in non-dialysis dependent (NDD) CKD patients. The aim of this study was to generate real-world evidence regarding the epidemiology and selected clinical outcomes of anemia and in NDD patients.

Methods: Data for this retrospective, observational study was extracted from Henry Ford Health System databases. Adults with NDD CKD (estimated GFR <60 ml/min/1.73m^2) between 01/01/13 to 12/31/17 were identified. Patients on renal replacement therapy or with active cancer were excluded. All patients were followed for ≥12 months and until 12/31/18. Outcomes included composites for CKD progression (end-stage CKD, 40% decrease in eGFR, CKD stage advancement, and doubling of serum creatinine) and major cardiovascular events (MACE). Logistic regression models, adjusted for baseline demographics and anemia, identified factors associated with MACE at 1 and 5 y.

Results: Study cohort (N = 55,447) demographics: median age 73 y (IQR 64, 82); 56% female; 63% White, 27% African American (AA), 2% Hispanic, 1% Asian, and 7% other/unknown race. Index CKD stages: 3A (60%), 3B (27%), 4 (10%), and 5 (3%). Baseline anemia prevalence, defined as Hb <10 g/dl, was 25%. Anemia treatments included iron (10%), RBCs (4%), and ESAs (1%). The 1- and 5-y cumulative incidences of CKD progression were 43% and 67%, respectively; for MACE, 8% and 37%, respectively. Baseline anemia (odds ratio (OR) 1.90) and AA race (OR 1.10) were associated with CKD progression risk at 1 y; both p <0.01. Both factors and strata of increasing age were modestly associated with CKD progression at 5 y. Increased risks of 1- and 5-y MACE were associated with baseline anemia (OR 3.22 and 3.02, respectively), male sex (OR 1.29 and 1.30, respectively), and increasing age (OR 1.32 and 1.50, respectively); all p <0.01, while AA race was slightly protective for 5-y MACE (OR 0.92, p <0.05).

Conclusions: Anemia is highly prevalent in NDD CKD patients, with a low frequency of treatment. Serum Hb <10 g/dL was associated with increased risk of CKD progression and MACE.

Funding: Commercial Support - AstraZeneca

SA-PO238

Anemia, Iron Status, and Anemia Development in Relation to Body Mass Index in Nondialysis CKD Patients: The Results from the KNOW-CKD Study

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Background: Anemia and iron deficiency are frequent findings in obese subjects. However, there were inconsistent results in adult studies. We aimed to investigate anemia, iron status, and anemia development in relation to body mass index (BMI) in chronic kidney disease patients

Methods: This prospective study included 2,214 patients from the KNOW-CKD study (KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease), after excluding 24 patients without data on BMI. Participants were classified by BMI categories as underweight (<18.5 kg/m^2), normal weight (18.5 to <23 kg/m^2), overweight (23 to <25 kg/m^2), and obese (≥25 kg/m^2) according to Asia-Pacific classification. Central obesity was defined as a waist circumference according to Asian-Pacific threshold (male ≥90cm, female ≥80cm). Hemoglobin levels were measured yearly during a mean follow-up period of 37.5±22.1 months. Anemia was defined as hemoglobin <13.0 g/dL in men and 12.0 g/dL in women. Iron deficiency was defined as serum ferritin <100 ng/mL or transferrin saturation <20%.

Results: The prevalence of underweight, normal weight, overweight, and obese was 2.4%, 29.4%, 26.5%, and 41.7%, respectively. Overall, 44.0% of patients were anemic and 55.0% of patients had iron deficiency. Obese patients had the highest hemoglobin concentration compared with other BMI groups (P< 0.001). The prevalence of anemia (P< 0.001) and iron deficiency (P< 0.001) and usage of iron supplement (P< 0.001) and erythropoietin stimulating agent (P=0.015) were significantly decreased in high BMI categories. BMI was positively associated with hemoglobin in multivariable linear regression analysis with adjustment (β, 0.16; 95% confidence interval [CI], 0.22-0.61; P< 0.001). Central obesity was also positively associated with hemoglobin (P< 0.001). Among 1,165 patients without anemia at baseline, 414 (35.5%) patients developed anemia during a follow-up period. In multivariable Cox regression analysis after adjustment, obese patients had a significantly lower risk of anemia development than those in the normal weight patients (HR, 0.76; 95% CI, 0.58-0.99; P = 0.046).

Conclusions: Obese patients had the highest hemoglobin concentration and had a significantly lower risk of anemia development than those in the normal weight patients.

SA-PO239

Prevalence, Correlates, and Outcomes of Absolute and Functional Iron Deficiency Anemia in Non-Dialysis-Dependent CKD

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Background: Anemia contributes to adverse outcomes in those with chronic kidney disease (CKD). We examined the association of absolute and functional iron deficiency anemia (IDA) with adverse outcomes (hospitalization, dialysis and mortality) in those with CKD.

Methods: Non-dialysis patients followed in the Veterans Administration with hemoglobin level measured within 90 days of the date of the second eGFR < 60 ml/min/1.73m2 were included. Logistic regression, multivariate Cox proportional hazard and poisson regression models adjusted for demographics and comorbidities were used to assess following outcomes: a) prevalence and correlates of absolute (TSAT < 20%, ferritin <100ng/ml), functional IDA (TSAT < 20%, ferritin 100-800 ng/ml) and b) association of absolute and functional IDA, those with Ferritin >800 ng/ml with mortality, dialysis and cardiovascular hospitalization.

Results: Out of 933,463 CKD patients included, 21.6% were anemic. Among patients with anemia with TSAT/Ferritin data, 50% did not have iron deficiency, 30% had absolute IDA, and 19% had functional IDA. Median follow-up was 3.9 years for mortality and 3.6 years for dialysis. Absolute IDA was not associated with an increased risk of mortality and dialysis but had higher risk of 1-year (RR 1.18, 95% CI: 1.11-1.26) and 2-year cardiovascular hospitalization (RR 1.10, 95% CI: 1.04-1.16) [FIGURE]. CKD patients with functional IDA had a higher risk of mortality along with a higher risk of 1-year and 2-year cardiovascular hospitalization. Ferritin > 800 ng/ml (treated as a separate category) was only associated with an increased risk of mortality.

Conclusions: In a large population of CKD patients with anemia, functional IDA was associated with higher risk of mortality and cardiovascular hospitalization while absolute IDA was associated with a higher risk of hospitalization.

Funding: Commercial Support - Keryx Biopharmaceuticals

Table 1. Associations of absolute and functional iron deficiency anemia with outcomes in those with CKD

Outcome	Variable	Cause-specific hazard	
		HR & 95% CI	p-value
Death	No iron deficiency	1.0 (ref)	
	Absolute	1.01 (0.98 - 1.04)	0.45
	Functional	1.12 (1.08 - 1.15)	<.0001
	Ferritin > 800	1.64 (1.41 - 1.90)	<.0001
Dialysis	No iron deficiency	1.0 (ref)	
	Absolute	0.95 (0.89 - 1.02)	0.13
	Functional	1.01 (0.94 - 1.08)	0.75
	Ferritin > 800	1.24 (0.92 - 1.67)	0.16

SA-PO240

Prevalence and Risk Factors of CKD Anemia in the United States

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Background: The most recent estimate to date of the prevalence of anemia in patients with chronic kidney disease (CKD) in the US is supported by data from US National Health and Nutrition Examination Survey (NHANES) in 2007-2010. We analyzed the NHANES database from 1999 to 2016 to update the prevalence of anemia among the US adult population with CKD and investigate risk factors.

Methods: CKD stage was assessed using the estimated glomerular filtration rate (eGFR) derived from serum creatinine using CKD-EPI equation. Anemia was defined as hemoglobin ≤13 g/dL in men and ≤12 g/dL in women, and severe anemia as hemoglobin (Hb) <10 g/dL (per KDIGO guidelines). Pregnant women were excluded. NHANES participants who had received dialysis treatment in the 12 months before the survey were considered as presenting CKD stage 5 but were excluded for estimation of prevalence of anemia. Associations between anemia and CKD stage, age, sex, race/ethnicity, smoking status, diabetes, hypertension, and body mass index were investigated. A logistic regression multivariate model was fit using a stepwise downward approach.

Results: Median age (yrs) of all the NHANES participants with CKD was 73.4 (interquartile range: 64.2-79.3); 59.4% (95% CI: 57.7-61.1) were female; 9.8% (95% CI: 8.4-11.1) were African-American; and 25.1% (95% CI: 23.3-26.8) reported diabetes mellitus. Prevalence estimates of anemia and severe anemia in 2015-2016 were 23.5% (95% CI: 19.4-27.7) and 1.2% (95% CI: 0.4-2.0), respectively. Association between CKD stage and anemia and severe anemia is shown in the Table.

Conclusions: Only a small fraction of CKD patients with anemia present with Hb <10 g/dL and are eligible for treatment. The risk of anemia and severe anemia is markedly increased in patients with lower eGFR.

Funding: Commercial Support - AstraZeneca

Table. Adjusted odds of anemia and severe anemia by CKD stage

CKD Stage	Prevalence of Anemia (%)	Prevalence of Severe Anemia (%)	Odds ratio [95% CI] of Anemia*	Odds ratio [95% CI] of Severe Anemia**
3A	12.6 [11.0;14.2]	0.59 [0.17;1.00]	Reference	Reference
3B	30.4 [27.0;33.8]	2.27 [1.21;3.32]	2.74 [2.19-3.44]	3.84 [1.60-9.21]
4	54.2 [47.6;60.9]	3.84 [1.22;6.46]	6.67 [4.87-9.12]	5.67 [2.04-15.77]
5	56.0 [41.7;70.3]	6.36 [0.96;11.76]	7.67 [4.11-14.33]	6.86 [2.07;22.71]

*After adjustment on age, sex, race/ethnicity, diabetes and body mass index.
**After adjustment on race/ethnicity.

SA-PO241

A Faster Decline of Residual Kidney Function and Erythropoiesis-Stimulating Agent (ESA) Hyporesponsiveness in Incident Hemodialysis Patients

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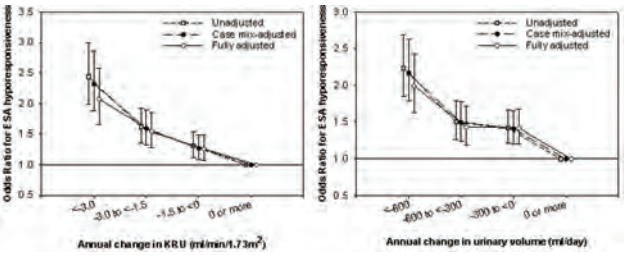
Background: In dialysis patients, resistance to ESA is associated with worse outcomes such as higher death risk. Prior studies have demonstrated that a slower loss of residual kidney function (RKF) in the first year of hemodialysis (HD) is associated with improved survival and potentially a healthier profile. However, little is known about the relationship between RKF decline and resistance to ESA.

Methods: The odds of ESA hyporesponsiveness with RKF decline in the first year were examined across four strata of annual changes in residual renal urea clearance ([KRU], <-3.0, -3.0 to <-1.5, -1.5 to <0, ≥0 mL/min/1.73m^2) and urinary volume (<-600, -600 to <-300, -300 to <0, ≥0 mL/day). Logistic regression models adjusted for demographic, clinical characteristics and laboratory variables were used in 5,239 incident HD patients from a large US dialysis organization (2007-2011).

Results: The median (interquartile range) baseline values of the annual changes in KRU and urinary volume were -1.2 (-2.8, 0.1) mL/min/1.73m^2 and -250 (-600, 100) mL/day, respectively. A faster RKF decline in the first year of HD initiation was associated with higher odds of ESA hyporesponsiveness (Figure). These associations remained robust across adjustment for laboratory variables and consistent in subgroup analyses across strata of baseline RKF, age, sex, race, diabetes, congestive heart failure, hemoglobin, and serum albumin. Similar results were found using urinary volume as another index of RKF (Figure).

Conclusions: A faster RKF decline during the first year of dialysis was associated with hyporesponsiveness to ESA among incident HD patients. Future studies are necessary to explain the underlying mechanisms of this association.

Funding: NIDDK Support



SA-PO242

Prevalence of CKD Anemia in Non-Dialysis-Dependent Patients Using Linked US Claims and Electronic Health Record Data

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Background: Novel strategies for the management of anemia, a complication of chronic kidney disease (CKD), are in development. Insights into CKD-related anemia burden, associated outcomes, and resource utilization are needed from representative non-dialysis dependent CKD populations receiving high-quality clinical care. The primary study objective was to describe baseline patient characteristics, comorbidities, and anemia prevalence in non-dialysis-dependent (NDD) CKD patients in US real-world practice.

Methods: This retrospective observational study evaluated the integrated Limited Claims and Electronic Health Record Data (IBM Health, Armonk, NY). The study cohort included patients aged ≥18 years with ≥2 eGFR measures <60 mL/min/1.73 m^2 at least 90 days apart. Anemia was defined as the first observed hemoglobin (Hb) <10 g/dl. The baseline period was defined as the date of the second confirmatory eGFR <6 months. Baseline anemia prevalence, demographics, comorbidities, laboratory measures, and selected medications were extracted and analyzed for the period from January 1, 2012 and September 30, 2017. Descriptive data were summarized, and no inferential statistics were performed.

Results: The study cohort (N = 33,088) was 57% female and mean (±SD) age was 70 (±13) years. The proportion of patients across CKD stages at baseline was: 3a (56%), 3b (23%), 4 (8%), and 5 (15%). Baseline comorbidities included type 2 diabetes mellitus (31%), cardiovascular disease (49%), heart failure (23%), and hyperlipidemia (62%). Median baseline (interquartile range) Hb was 12.4 (11, 13.6) g/dl, creatinine 1.3 (1.1, 1.7) mg/dl, ferritin 116 (53, 244) ng/ml, and total iron binding capacity 303 (254, 349). Baseline anemia prevalence was 30% (N = 9909/33,088). Erythropoiesis-stimulating agents (ESAs) were prescribed in 0.6% of all patients at baseline, and usage increased by worsening Hb strata (0.1% in Hb >12, 1.0% in Hb 10-11.9, 2.3% in Hb 8-9.9, and 2.6% in Hb <8 g/dl).

Conclusions: Anemia is a frequently observed complication of CKD in NDD patients and co-exists with other comorbidities. Baseline utilization of ESAs was very rare, and slightly increased use was associated with decreasing Hb in a large US cohort of NDD patients with anemia.

Funding: Commercial Support - AstraZeneca

SA-PO243

A Rapid Decline of Residual Kidney Function and Anemia in Hemodialysis Patients

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Background: Patients on dialysis commonly develop anemia due to the kidney's critical role in red blood cell production. Slower residual kidney function (RKF) decline on dialysis is associated with better outcomes. We hypothesized that a faster decline in RKF may be associated with a higher odds of developing anemia in the incident hemodialysis (HD) patients.

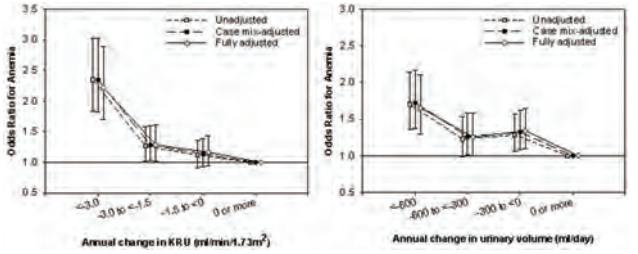
Methods: The associations of decline in RKF with anemia were examined retrospectively across four strata of annual change in RKF (residual renal urea clearance [KRU], <-3.0, -3.0 to <-1.5, -1.5 to <0, ≥0 mL/min/1.73m^2; urinary volume, <-600, -600 to <-300, -300 to <0, ≥0 mL/day) using logistic regression models adjusted for clinical characteristics and laboratory variables in 5,403 incident HD patients of a large US dialysis organization between January 1, 2007 and December 31, 2011.

Results: A total of 5,291 (98%) patients used erythropoiesis-stimulating agents (ESAs) during the first year of HD initiation. The median baseline values of the annual change in KRU and urinary volume were -1.2 (interquartile range [IQR]: -2.8 to 0.1) mL/min/1.73m^2 and -250 (IQR: -600 to 100) mL/day, respectively. Multivariate logistic regression models revealed that the fastest RKF decline in the first year of HD was associated with higher odds of anemia (Figure). These associations remained robust against adjustment for

laboratory variables and consistent across strata of baseline RKF, age, sex, race, diabetes, congestive heart failure, hemoglobin, and serum albumin. Analyses using urinary volume as another index of RKF showed consistent associations.

Conclusions: Rapid RKF decline during the first year of dialysis was associated with anemia among incident HD patients.

Funding: NIDDK Support



SA-PO244

Iron Deficiency Anemia in Clinical Practice: Can Virtual Patient Simulation Improve Management?

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Background: We sought to determine if an online, virtual patient simulation (VPS)-based continuing medical education (CME) intervention could improve performance of nephrologists and primary care physicians (PCPs) in diagnosising and managing iron deficiency anemia (IDA).

Methods: The intervention comprised two patient cases where learners ordered lab tests, made diagnoses, and prescribed treatments similar to practice. Tailored clinical guidance (CG), based on current evidence and expert recommendation, was provided following each decision, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user's baseline (pre-CG) decisions using a 2-tailed paired t-test to determine *P* values. The activity launched May 10, 2019; data were collected for initial abstract submission through May 22, 2019.

Results: To date, 11 nephrologists and 47 PCPs have participated (larger sample size expected by ASN conference). Case 1: IDA diagnosis: 22% absolute improvement among nephrologists (22% pre-CG vs 44% post-CG; P=.18), 5% improvement among PCPs (53% pre-CG vs 58% post-CG; P=.16) Diagnosis of chronic kidney disease stage 5: 33% absolute improvement among nephrologists (0% pre-CG vs 33% post-CG; P<.001), 34% improvement among PCPs (16% pre-CG vs 50% post-CG; P<.01) Dialysis referral: 22% absolute improvement among nephrologists (22% pre-CG vs 44% post-CG; P=.18), 21% improvement among PCPs (21% pre-CG vs 42% post-CG; P<.05) Initiate oral iron supplement: 22% absolute improvement among nephrologists (22% pre-CG vs 44% post-CG; P=.18), 32% improvement among PCPs (39% pre-CG vs 71% post-CG; P<.01) Case 2: IDA diagnosis: 27% absolute improvement among nephrologists (27% pre-CG vs 54% post-CG; P=.08), 21% improvement among PCPs (30% pre-CG vs 52% post-CG; P<.01) Diagnosis of chronic kidney disease stage 4: 36% absolute improvement among nephrologists (27% pre-CG vs 63% post-CG; P<.05), 32% improvement among PCPs (17% pre-CG vs 49% post-CG; P<.01) Initiate oral iron supplement: 36% absolute improvement among nephrologists (36% pre-CG vs 82% post-CG; P=.01), 21% improvement among PCPs (9% pre-CG vs 57% post-CG; P<.01)

Conclusions: VPS that immerses and engages specialists in an authentic and practical learning experience can improve evidence-based clinical decisions related to diagnosis and management of IDA.

SA-PO245

Ferric Citrate Hydrate on Anemia Management in Hyperphosphatemia Hemodialysis Patients with or Without Diabetes: ASTRIO Study Supplementary Analysis

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Background: It is reported that patients with diabetes in hemodialysis (HD) tend to be treated with higher ESA dose. The relationship is bi-directional, iron affects glucose metabolism and glucose metabolism affects iron metabolism pathway. In ASTRIO Study, Ferric Citrate Hydrate (FC) reduced dose of ESA. The effect of FC on anemia management in hemodialysis diabetes patients has not been extensively evaluated.

Methods: ASTRIO was a prospective, randomized, multicenter, 24-week study. 93 hyperphosphatemia HD patients who had been taking non-iron based phosphate binders (PBs) were randomized to FC group (n=48) or Control group (n=45). In Control, patients maintained treatment with their existing PBs. Serum P and Hb were controlled within 3.5 to 6.0 mg/dL and 10.0 to 12.0 g/dL, respectively. Oral iron was prohibited in Control group. Intravenous iron was permitted if iron replacement therapy was required, at the physician's discretion. The primary endpoint was change in ESA dose from baseline to the end of treatment (EOT); we evaluated a stratified analysis for diabetes patients whose main underlying disease is diabetic nephropathy.

Results: Serum P and Hb were maintained in both groups. Regardless of whether patients have diabetes or not, ESA doses decreased in FC group.

Conclusions: The effect of FC on anemia management in hyperphosphatemia HD was comparable between diabetic and non-diabetic patients.

FC (n=46)*							
	Diabetes (n=19)			Non-Diabetes (n=27)			P value [a]
Mean	Baseline	EOT	Change	Baseline	EOT	Change	
ESA dose (IU/week)	6104.4 (5560.6)	4909.1 (6999.5)	- 1195.3 (3113.1)	5475.7 (4532.8)	4252.3 (2552.2)	- 1223.4 (3979.9)	0.98
Control (n=45)							
	Diabetes (n=27)			Non-Diabetes (n=18)			
Mean (SD)	Baseline	EOT	Change	Baseline	EOT	Change	P value [a]
ESA dose (IU/week)	5717.1 (3921.6)	7107.7 (7687.8)	+ 1390.6 (6898.5)	6044.5 (4422.0)	6937.5 (5509.7)	893 -6477.4	0.81

*2 patients excluded who withdrew before receiving any FC

[a]:Within group comparisons of change (Diabetes and Non-Diabetes) by *t*-test

SA-PO246

Transferrin Saturation (TSAT) and Clinical Outcome in Patients with Advanced CKD

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Background: TSAT is frequently used in clinical practice as indicator of iron deficiency or overload, but its relationship with clinical outcomes in patients (pts) with advanced CKD is unclear. We investigated associations between TSAT and all-cause mortality in CKD5 non-dialysis (CKD5-ND) pts.

Methods: In 298 CKD5-ND pts (median age 56 years, 65% males, 38% cardiovascular disease, CVD, 31% diabetes, DM, median estimated glomerular filtration rate 6 (interquartile range, IQR, 5-8) ml/min/1.73^2), biomarkers of iron status (plasma iron, TSAT, transferrin and ferritin), presence of CVD and protein energy wasting (PEW; subjective global assessment), Framingham's CVD risk score (FRS; as a composite index of traditional CVD risk factors) and systemic inflammation (high-sensitivity C-reactive protein, hsCRP, and interleukin-6, IL-6) were assessed. During median follow-up of 23 months, 87 (29%) pts died and 129 (43%) pts underwent renal transplantation. Pts were stratified into high (n=74) and low (n=224) TSAT quartile groups. All-cause mortality risk was analyzed with competing risk regression with renal transplantation as competing risk.

Results: TSAT (median 21% (IQR 16-28%) was negatively associated with age, DM, CVD, FRS, white blood cell count, hsCRP, IL-6, use of erythropoietin stimulating agents and iron supplementation, and positively associated with hemoglobin (Hb), ferritin and s-albumin. In competing risk analysis, low TSAT (sHR 1.84, 95% CI 1.0-3.36) was associated with higher all-cause mortality, independent of FRS. However, after further adjustments for FRS, ferritin, Hb, hsCRP and PEW, the association was not significant (p=0.07; sHR 1.72, 95% CI 0.95-3.09).

Conclusions: TSAT was inversely associated with all-cause mortality in CKD5-ND pts, independent of traditional CVD risk factors represented by FRS, underlining the importance of iron status in CKD. Nevertheless, degree of anemia, inflammatory status and PEW should be considered when analyzing TSAT as risk factor for adverse clinical outcomes in non-dialyzed pts with advanced CKD.

Funding: Commercial Support - Baxter Healthcare

SA-PO247

Potential Safety Concern of Daprodustat Compared with Injectable Erythropoiesis-Stimulating Agents in Patients with Anemia on Hemodialysis and Not on Dialysis: A Pooled Analysis

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Background: Daprodustat is an oral hypoxia-inducible factor-prolyl hydroxylase inhibitor under development for treating anemia in hemodialysis (HD) and non-dialysis (ND) patients. Safety analyses were performed to evaluate potential safety concerns such as ocular, cardiovascular, and cancer related adverse events (AEs).

Methods: Post-hoc pooled analyses were conducted by using 2 open-label, randomized controlled trials (RCTs) compared to injectable erythropoiesis stimulating agent (ESA) in ND patients (ClinicalTrials.gov Identifier: NCT01977573, NCT02791763) and one open-label and one double-blind, RCTs compared to ESA in HD patients (NCT01977482, NCT02969655). The principal outcomes were frequencies of a subset of the predefined AEs of special interest (AESIs): ocular (proliferative retinopathy, macular edema, choroidal neovascularization), cardiovascular (all-cause death, myocardial infarction, stroke, heart failure, thromboembolic events, thrombosis of vascular access)

and cancer (cancer-related mortality and tumor progression and recurrence) related AEs, and ophthalmological findings by ophthalmologists during treatment.

Results: AEs in each AESI category were pooled from 549 patients (n=319; daprodustat, n=230; ESA) and 487 patients (n=313, n=174) in ND and HD patients, respectively. Median exposure (days, daprodustat vs. ESA) in ND and HD patients was 172 vs. 337 and 169 vs. 365, respectively. In ND patients, the incidence (daprodustat vs. ESA) of ocular, cardiovascular, and cancer related AEs were 3% vs. 3%, 3% vs. 6% and 1% vs. 1%, respectively. In HD patients, these were respectively 2% vs. 2%, 7% vs. 7% and <1% vs. <1%. The incidence of ophthalmological findings were 11% vs. 10% in ND patients and 6% vs. 8% in HD patients. There was no meaningful difference in the frequencies of these predefined AESIs and ophthalmological findings between the treatment groups in ND and HD patients.

Conclusions: Daprodustat showed no new safety concerns in these predefined AESIs in these clinical studies, but further investigation will be needed.

Funding: Commercial Support - GlaxoSmithKline

SA-PO248

Comparison Between a Novel Latex Immunoassay and LC-MS/MS for Hepcidin-25 Measurement

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Background: Hepcidin-25 is an iron regulatory factor in the in vivo evaluation of iron dynamics and plays an important role in determining the development and severity of anemia in patients with chronic kidney disease. Although the golden standard of measurement of hepcidin-25 is the LC-MS/MS method, results cannot be obtained immediately at the clinical site. However, the latex immunoassay (LIA) can be performed using general clinical laboratory equipment, and the results obtained quickly. Our aim was to measure hepcidin-25 by LIA and LC-MS/MS and compare the two methods.

Methods: Hepcidin-25 was measured by LIA and LC-MS/MS in 134 hemodialysis patients. We used a hepcidin-25 specific reagent (FUJIFILM Wako Pure Chemical Corporation) and the JCA-BM6050 automatic analyzer for LIA and the 4000 QTRAP LC-MS/MS system for LC-MS/MS. The results obtained by the two methods were compared by standard major axis regression.

Results: The standard major axis regression equation between the two methods was $y = 0.995x + 0.5$ ($r = 0.998$, $p < 0.001$). The correlation between the two methods was very strong and the measured values were almost identical.

Conclusions: The performance of LIA was equivalent to that of LC-MS/MS for hepcidin-25 measurement. LIA can be performed using general clinical examination apparatus and has a higher processing speed than LC-MS/MS. Therefore, measurement of hepcidin-25 by LIA may potentially be useful for routine laboratory testing.

SA-PO249

Hemoglobin Cycling Induced by Delayed Patient-Therapy Feedback During ESA Treatment

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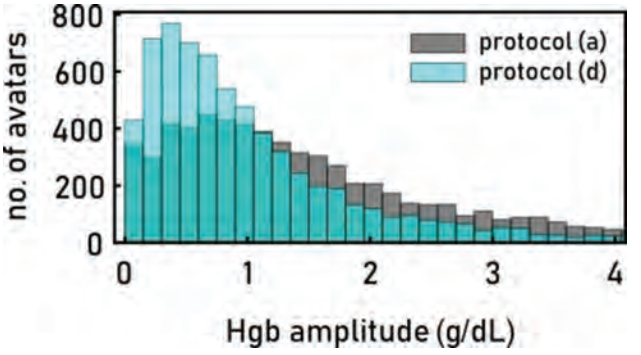
Background: Chronic kidney disease (CKD) commonly entails anemia, leading to poor patient outcomes. During treatment of anemia with erythropoiesis-stimulating agents (ESAs), patients frequently experience hemoglobin (Hgb) "cycling" periods during which the patient's Hgb levels periodically over- and undershoot a defined target range of 10–11.5 g/dL. Using a computational model of anemia treatment ("Virtual Anemia Trial"; Fuertinger et al., CPT Syst. Pharmacol. 7(4) 219, 2018), we aimed to detect treatment-related causes of this behavior.

Methods: We carried out Virtual Anemia Trials with 6659 virtual patients ("avatars") under 4 different anemia treatment protocols (a to d) for one simulated year of treatment. Avatars differed in endogenous EPO levels, total blood volume, and ESA half-life. Treatment protocols differed in ESA dosing charts (steps between doses and administration frequency) and the criteria that determine ESA dose recommendations based on the patient's Hgb history (i.e., critical Hgb levels and/or rates of change).

Results: The 4 treatment protocols yielded different distributions of Hgb amplitudes (difference between maximum and minimum Hgb in the second half of the simulated patient year), with mean ± s.d. given by (a) 1.7 ± 1.5 g/dL, (b) 1.7 ± 1.4 g/dL, (c) 1.6 ± 1.3 g/dL and (d) 1.1 ± 1.0 g/dL, respectively (see Figure). Except for (a) vs. (b), differences between the corresponding distributions were statistically significant when pairwise compared (Pearson chi-squared test; $p < 0.05$).

Conclusions: Our results suggest that certain treatment protocols can augment Hgb cycling instead of preventing it. Analysis of the differences between probed treatment protocols reveals two treatment-related causes for Hgb cycling: (i) too late ESA dose changes in response to falling/rising Hgb levels and (ii) too extreme dosing decisions (e.g., a complete ESA hold for a too long time) that prevent Hgb levels from remaining within target after transiently reaching it. Based on these insights, existing treatment protocols may be modified to reduce patients' Hgb cycling.

Funding: Commercial Support - Fresenius Medical Care Germany



SA-PO250

The Alteration of Non-Transferrin-Bound Iron (NTBI) and Malondialdehyde (MDA)-LDL After Single-Dose Oral Iron Administration (OIA) in Hemodialysis (HD) Patients

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Background: OIA is not considered to increase NTBI because of slow iron adsorption rate. Aim of this study is to assess the alteration of NTBI and an oxidative stress marker, MDA-LDL after single dose OIA.

Methods: 25 HD patients without any iron load within 4 weeks, whose Hb<12g/dl, ferritin<100ng/ml and CRP<1.0mg/dl and 13 healthy volunteers received oral ferrous sulfate 105mg. 21 HD patients without OIA were as HD control. We evaluated the following markers before and at 1, 2, 3, 4 and 48 hours(hrs) after OIA : MDA-LDL, NTBI, Hepcidin-25(HPC), serum iron(Fe), TSAT, ferritin, selenium(Se) and standard hematological parameters. Vitamin C(VC) were measured before and at 4 and 48hrs. MDA-LDL was measured by ELISA. NTBI was measured by recently described reliable method(Clin Chim Acta437:129-135, 2014).

Results: Fe, TSAT and NTBI increased after OIA and reached the peak at 4hrs, ferritin also increased at 48hrs in both HD patients and healthy control. In HD control without OIA, they did not change. NTBI and HPC basal levels were higher in healthy control than in HD patients. MDA-LDL before OIA was not different between the two groups. MDA-LDL increased from 1 to 4hrs during HD and returned to the basal level at 48 hrs irrespective of OIA, however, in healthy control, no significant alteration was observed. In HD patients, Se level before OIA was a negative predictor for Log(MDA-LDL) before OIA by stepwise analysis(β=-0.459, p=0.021, R^2=0.21). In healthy control, NTBI before OIA was a predictor for Log(MDA-LDL) before OIA(β=0.768, p=0.002, R^2=0.589). Percentage of hypo-hemoglobinised (HypoHe) in HD patients (β=-0.443, p=0.027, R^2=0.196) and HPC in healthy control (β=-0.637, p=0.019, R^2=0.406) before OIA were negative predictors for the maximum level of NTBI after OIA, respectively. Antioxydants, Se and VC basal levels were lower in HD patients. Se level did not change during HD. VC level decreased after HD and recovered at 48 hrs.

Conclusions: NTBI significantly increased after OIA. However, MDA-LDL significantly increased during HD session irrespective of OIA, whereas it did not change in healthy control after OIA. Although OIA increase NTBI, it had little influence on the MDA-LDL level. This may result of the exquisite balance of the oxydative stress and the antioxydant activity.

SA-PO251

Impact of a Novel Dose Calculation Method for Erythropoiesis Stimulating Agents on Renal Anemia Therapy in Hemodialysis Patients

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Background: Patients with end-stage renal disease requiring dialysis therapy have poor prognosis compared with normal population. Renal anemia is a common comorbidity and is a major cause of morbidity and mortality among hemodialysis patients. For treatment of renal anemia, empiric erythropoiesis stimulating agents (ESA) dosing method is generally used in hemodialysis patients and standardized method are shown by Fishbane et al. in 2005. However, hemoglobin (Hb) levels are not always within target range for favorable prognosis according to anemia guidelines. We developed a new method for ESA dose determination that uses individual increase value and individual decrease value calculated from Hb variability. Individual increase value and individual decrease value mean real response of Hb increase under maximum ESA dose and natural Hb decrease without ESA per week, respectively. There has never been a reliable and valid method to calculate individual increase and decrease values before the new method. The aim of this study was to estimate effectiveness of the new method for ESA dosing.

Methods: This was a 6-month randomized, controlled, parallel-group study in hemodialysis patients with renal anemia treatment. Patients were assigned to two groups receiving epoetin beta (EPO) dosing by new method and standardized method. The target range of Hb was set at 10.0 to 11.0 g/dL. EPO doses for two weeks were determined at every two-week Hb measurement. Iron was administered when ferritin was below 100 ng/mL or transferrin saturation below 20%.

Results: One-hundred and two patients were enrolled (61 men, 41 women; mean age 68.9 ± 12.5 years). There was no difference in baseline characteristics between the two groups. At end of study, mean Hb levels were not different between the new method group and standardized method group (10.5 ± 0.7 g/dL vs. 10.5 ± 0.7 g/dL, P = 0.936). The ratio of patients with Hb levels within target range were significantly different between the new and standardized method groups (75% vs. 50%, P = 0.021 by chi-square tests). Required EPO dose were not different between the new and standardized method groups (2578.1 ± 1851.2 IU/w vs 3046.9 ± 2627.3 IU/w, P = 0.359). There were no adverse events related to the new method.

Conclusions: The new method for EPO dosing is superior to existing standardized EPO dosing method.

SA-PO252

Modulation of Circulating Endothelial Progenitor Cells by Erythropoiesis-Stimulating Agent in Patients with Hemodialysis

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Background: Recent studies have suggested that erythropoiesis stimulating agent (ESA) may accelerate not only angiogenesis but also vasculogenesis, beyond erythropoiesis

Methods: We conducted a 12-week prospective study in 42 dialysis patients; 11 patients were treated with recombinant human erythropoietin (rhEPO) (EPO group, 5487.5 ± 735.1 IU/week), 11 patients with darbepoetin (DA) (DA group, 41.6 ± 4.7 μg/week), 10 patients with epoetin β pegol (CERA group, 49.5 ± 16.5 μg/week) and 10 patients with no ESAs (no-ESA group). Vascular mediators comprising EPCs, vascular endothelial growth factor, matrix metalloproteinase-2 (MMP-2), and high-sensitivity C-reactive protein were measured at 0 and 12 weeks. EPCs were measured by flow cytometry as $CD45^{low}$ $CD34^{+}$ $CD133^{+}$ cells.

Results: In the EPO and CERA group, EPC count increased significantly from 0 to 12 weeks in a dose-dependent manner (EPO; r = 0.77, p = 0.01, CERA; r = 0.72, p = 0.01). In the DA group, the EPC number did not change at 12 weeks. Furthermore, the serum levels of the above biomarkers except EPC were not affected by ESA in all groups.

Conclusions: We speculate that the pleiotropic effects of each ESA types beyond their hematopoietic effects may differ in ESKD patients.

Funding: Clinical Revenue Support

SA-PO253

Model Predictive Control (MPC) for Iron Dosing for the Management of Anemia

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Background: Recent studies have shown that anemia management can be improved using computer based tools to determine the dose of an erythropoietic stimulating agent (ESA). We tested the hypothesis that similar improvements can be acheived for iron dosing.

Methods: A ferrokinetic model was developed based on published data from iron studies. The model predicts monthly change in TSat and Ferritin in response to a dose adjustment of iron sucrose. Using this model, a dose adjustment algorithm was designed using principles of Model Predictive Control. The dosing objective was to drive TSat to a physician-specified target value of 35 without exceeding an upper Ferritin threshold, also specified by the physician user. Ten subjects were enrolled into a pilot study to test the safety and efficacy of the proposed approach. Subjects will be followed for 6 months and have completed 3 months follow up. Iron dose, Tsat, ferritin and epoetin beta methoxy polyethylene glycol (ESA) doses are recorded.

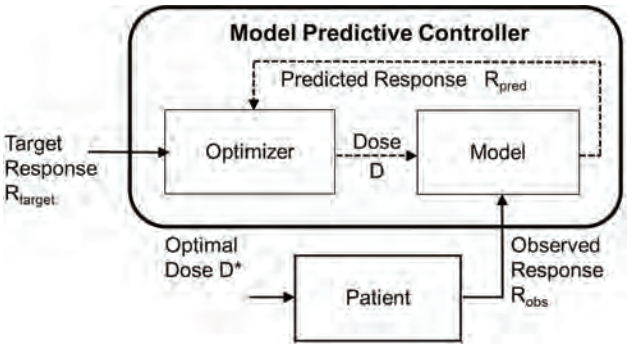
Results: Results for the control period (M-2,M-1) and treatment period (M1,M2,M3) are shown in the table by month. Tsat values increased following the implementation of the MPC reaching the mid-pint of the target range at 3 months. Hb values also increased and ESA dose decreased over the same period. No recommended doses were over-ridden by the physicians monitoring the project.

Conclusions: MPC control of iron dosing can compliment the use of similar decision support tools used to dose ESA's. Optiimal anemia management would maximize the dose of ESA and Iron to achieve individualized patient care. These results demonstrate the potential of simultaneously determing ESA and Iron dose in the management of patients with anemia of chronic kidney disease.

Funding: NIDDK Support, Veterans Affairs Support

	M-2	M-1	M1	M2	M3
Tsat (%)	26±6	28±12	30±13	29±9	33±12
Hb (mg/dL)	11.8±1.7	11.4±2.0	11.0±2.1	11.3±1.5	11.7±2.1
Iron Dose (mg/month)	500	325±189	478±370	507±265	375±228
ESA Dose (ug/month)	22±47	42±52	37±53	27±38	8±18

Month(M)



SA-PO254

Using a Predictive Algorithm to Provide Decision Support in Anemia Management

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Background: Anemia in hemodialysis is very common with most receiving erythropoietin stimulating agent (ESA) therapy. Most ESA dosing protocols are based on manufacturer recommendations and clinical experience. They are standardized across entire dialysis populations and do not account for individual response. To improve anemia management, we developed a predictive algorithm to forecast 1, 2 and 3 month hemoglobin (HGb) values as a way of providing decision support for monthly ESA dose adjustments.
Objectives: To determine if the addition of future HGb predictions to the information currently provided to anemia managers will result in a reduction in HGb variability, an increase in the number of HGb observations within the target range, and a decrease in the average per treatment ESA use.

Methods: We developed a predictive algorithm utilizing historic electronic medical record (EMR) data collected during the 2009-2017 time period. The data set included dialysis sessions, ESA administered, intravenous iron, HGb, ferritin, and transferrin saturation (Tsat %). Following algorithm development, we conducted a 10 month (July 2018 to April 2019) QI project with approximately 20 patients in an academic dialysis center. Each month, future hemoglobin predictions were provided for 1, 2, and 3 months based on the current monthly lab draw and patient's own historical data. These predictions were then provided to anemia managers along with interpretive guidance from the development team.

Results: Incorporation of this form of decision support into the anemia management process saw the number of HGb readings below 10 g/dL decrease from 23.7% pre intervention to 19.5% post intervention (p=0.44). There was an increase from 10.8 g/dL to 11.2 g/dL in the average patient mean HGb (p=0.09) and a 77.3% decrease in the average patient HGb variance (p<0.01). Overall, there was a 32.7% decrease in the average per treatment ESA dose (p<0.01).

Conclusions: Incorporating decision support from a predictive algorithm into an existing anemia management process resulted in a decrease in overall ESA use while decreasing patient HGb variability. Small study population was a limitation to this study.

SA-PO255

Contemporary Management of Anemia and Associated Risk Across the Spectrum of CKD: A Nationwide Analysis from the Swedish Renal Registry

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Background: The last decade has seen noteworthy changes in renal anemia guidelines. Here we explore the current management of renal anemia and associated cardiovascular (CV) risk in a contemporary nationwide cohort of chronic kidney disease (CKD) patients in Sweden.

Methods: Observational analysis from the Swedish Renal Registry, including nephrologist-referred adult CKD patients during 2015. The epidemiology and treatment of anemia across the spectrum of stage 3b-5 non–dialysis-dependent (NDD) and dialysis-dependent (DD) CKD were assessed. Logistic regression and Cox proportional hazard models were employed to explore the associations between anemia management, C-reactive protein (CRP), erythropoietin resistance index (ERI; [erythropoiesis-stimulating agent (ESA) dose/weight]/hemoglobin [Hb]), and subsequent risk of major adverse CV events.

Results: Data from 14,415 (NDD, 11,370; DD, 3,045) patients were included. Approximately 60% of NDD CKD patients had anemia (World Health Organization definition: Hb <12 g/dL for females; Hb <13 g/dL for males) compared with 93% of DD patients. The proportions of NDD patients who received iron (oral or intravenous) and/or ESA therapy were 21% and 24%, respectively; the proportions of DD patients were 62% and 82%, respectively. In both NDD and DD populations, about half of the patients receiving ESA had Hb levels between 10-12 g/dL; 27% had Hb >12 g/dL and 14% had

Hb <10 g/dL. Use of high-dose ESA (>6000 IU/week) was relatively common even among patients at earlier stages of CKD (~25%). The use of high versus low (<3000 IU/week)/medium (3000-6000 IU/week) dose ESA was associated with increased systemic inflammation in cross-section (CRP >5 mg/L) (odds ratio, 1.68 [95% CI: 1.45-1.94]), with a 40% higher risk of CV events (adjusted hazard ratio [HR], 1.40 [95% CI: 1.16-1.69]). Patients with high (0.81-12.0) versus low (0-0.4) ERI had a 2-fold higher risk of CV events (adjusted HR, 1.98 [95% CI: 1.61-2.43]). Treatment with iron was not associated with CRP levels or CV risk.

Conclusions: Anemia continues to be a highly prevalent complication among contemporary adults with CKD. Given the guideline recommendations, the use of iron was unexpectedly low. High doses of ESA and high ERI predicted increased CRP levels and subsequent CV risk.

Funding: Commercial Support - Astellas Pharma Inc

SA-PO256

Evaluating Anemia of CKD in Acutely Ill Patients

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Background: Anemia of chronic kidney disease (CKD) is one of the most common long-term complications as kidney failure progresses. The pathogenesis is multifactorial, but decreased erythropoietin production has a main role in later stages of CKD. The prevalence is approximately 33-67%. Treatment options include erythropoietin stimulant agents (ESA) once iron deficiency has been treated and contraindications have been evaluated. A decreased production of red blood cells is commonly seen in acutely-ill patients. We hypothesized that CKD/ESRD patients are at higher risk of worsening anemia even with adequate hemoglobin levels on admission.

Methods: We studied 53 patients with advanced CKD or ESRD admitted to our hospital between November 2017 and January 2018. Clinical data was obtained from chart review. Data incorporated in the analysis included: hemoglobin (Hb) on admission and upon discharge, outpatient treatment of anemia, and inpatient management of anemia such as transfusion, iron supplementation and ESA. Patients with acute bleeding during hospitalization were excluded.

Results: A total of 24 patients with Hb < 10 g/dl and 29 patients with Hb >10 g/dl on admission were included in our analysis. Patients with hemoglobin >10 g/dl on admission were noted to have significantly higher decrease in hemoglobin level upon discharge compared with patients with Hb < 10 g/dl (mean change from baseline Hb 0.9 vs -0.3, $p = 0.0014$). One third of patients with indication for ESA and no clinical contraindications for administration received EPO inpatient, while 33% of patients that were not treated with EPO received blood products.

Conclusions: Hospitalized patients with advanced CKD or ESRD are at high risk of worsening anemia despite adequate Hb levels on admission. We suggest considering a closer surveillance of hemoglobin for potential administration of ESA in order to prevent worsening anemia.

SA-PO257

Improving Rates of Epoetin Alpha Administration in ESRD Patients at Two Teaching Hospitals: A Quality Improvement Initiative

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Background: Adequate management of anemia in ESRD has important clinical implications for both patients and the healthcare system at large. It improves quality of life, prevents readmissions, decreases the need for transfusions while simultaneously improving efficiency of care. Subcutaneous (SQ) Epoetin Alpha (EPO) provides a dose-sparing advantage over Intravenous (IV) EPO. In hospitals A and B, following a switch in the process of EPO administration from IV during dialysis to SQ on the general floors, we noted rates of 19.5% and 14.5% of missed EPO doses at hospitals A and B respectively. Unrefrigerated, un-administered EPO doses are discarded leading to a significant waste and worsening hemoglobin levels. The aim of this QI initiative was to understand the roots and reduce missed EPO doses to <10% over 9 months.

Methods: We utilized the PDSA performance improvement model to manage this project. A multidisciplinary team including Nephrology, Nursing, Pharmacy and IT was created. We identified the most common cause of missed doses as an inpatient dialysis schedule switch (from Monday/Wednesday/Friday to Tuesday/Thursday/Saturday or vice versa) without a coinciding change in the EPO order. Our first intervention was the creation of an EMR alert notifying nurses to administer the dose as ordered regardless of patients' dialysis schedule and asking them to discuss with nephrology if they were to hold a dose. At month 5, we tested a second intervention: a collaborative nursing education about anemia management at Hospital B only, facilitated by a nephrologist and a nurse educator.

Results: The results of the study are summarized in Figure1. Following the creation of an EMR alert, there was only a mild and unsustained improvement in our rates at both hospitals. After nursing education at Hospital B, we noted a sustained improvement in our rates at Hospital B but not at Hospital A.

Conclusions: While technology is an important tool providing scale and efficiency in QI initiatives, the role of targeted Nursing Education remains an effective measure to prevent waste and sustain change.

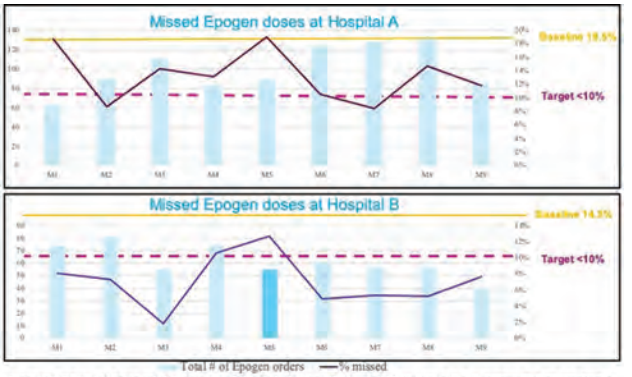

Figure1- Rates of missed doses at both Hospital A and B. M1 to M9 indicate the months 1 to 9 of the study. In addition to the EMR alert, Hospital B nurses underwent a series of **educational sessions** provided by a nephrologist focused on EPO administration and anemia management in ESRD patients starting at **Month 5**.

SA-PO258

24 Hydroxylase Deficiency: Comparison with Other Disorders of Vitamin D-Mediated Hypercalcemia

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Background: *CYP24A1* gene encodes 24-hydroxylase, an enzyme that converts $25(OH)D_3$ (25D) and $1,25(OH)_2D_3$ (1,25D) to inactive metabolites. Recent reports establish that loss of function mutations in *CYP24A1* are associated with 24 hydroxylase deficiency (24HD), characterized by hypercalcemia, nephrolithiasis, and/or nephrocalcinosis (NC). We retrospectively compared laboratory, imaging, and clinical characteristics of patients with suspected or confirmed 24HD to other disorders of vitamin D-mediated hypercalcemia: sarcoidosis (S), lymphoma (L), and exogenous vitamin D toxicity (EVT).

Methods: Patients seen at Mayo Clinic, Rochester between 1/1/08 and 12/31/16 were further evaluated if they met biochemical criteria: serum calcium ≥9.6 mg/dL, PTH <30 pg/mL, and 1,25D >40 pg/mL. Patients with 24HD were then identified if they met one of the following criteria: 1) positive genetic testing or 2) 25D:24,25D ratio ≥50. Patients with diagnosis of S, L, or EVT were identified by chart review. Patients with fungal infections were also identified but excluded from analysis due to lack of systemic involvement. Data were summarized and reported using median [IQR] for continuous variables and n(%) for categorical variables. Comparisons between disease groups were evaluated using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables.

Results: Comparison of 24HD (n=9) to all groups (n=28) revealed 24HD patients were younger at symptom onset (13.75 [1,35] vs 63 [56,79], p=0.001) and more likely to have family history (88.9% vs 20.8%, p<0.001), NC (88.9% vs 6.3%, p<0.001), lower lumbar spine Z-score (-0.50 [-0.80,0.70] vs 1.20 [0.80,2.10], p=0.011), and higher urine Ca:Cr ratio (0.24 [0.21,1.70] vs 0.17 [0.14,0.18], p=0.047).

Conclusions: Patients with 24HD have clinical and laboratory differences compared to other causes of vitamin D mediated hypercalcemia. 24HD should be suspected in hypercalcemic patients who present at a younger age, have a positive family history, and have nephrocalcinosis.

Funding: Private Foundation Support

SA-PO259

Severe Hypercalcemia Mitigated by Etelcalcetide in Continuous Renal Replacement Therapy

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Introduction: Secondary hyperparathyroidism (SHPT) is associated with increased bone turnover, risk of fractures, vascular calcifications, and cardiovascular and all-cause mortality. We describe a critically ill ESRD patient with SHPT who developed hypercalcemia with prolonged immobilization managed with continuous renal replacement therapy (CRRT) using regional citrate anticoagulation (RCA) without calcium supplementation and treatment with intravenous etelcalcetide.

Case Description: A 51 year old lady with ESRD on hemodialysis (HD) underwent aortic and mitral valve replacement. She received maintenance HD for 10 days after cardiac surgery. Post-surgical course was complicated by hypoxic respiratory failure, mesenteric ischemia, and septic shock warranting mechanical ventilation, colectomy and vasopressor use. In the setting of SHPT with high turnover bone disease and prolonged immobilization, she developed pathological bilateral subcapital femoral neck fractures with diffuse osteopenia 2 months after admission. She had elevated systemic ionized calcium (1.6 mmol/L), phosphorus (6.7 mg/dl), ALP (426 U/L), bone-specific ALP (90 mcg/L), and PTH (780 pg/ml) levels. The patient was started on citrate based CRRT without the use of a calcium infusion 10 days after cardiac surgery; and was treated with intravenous etelcalcetide 5 mg thrice weekly to mitigate severe hypercalcemia. After 3 weeks, she had a reduction in systemic ionized calcium (1.1 mmol/L), phosphorus (3.5 mg/dl), ALP (316 U/L), and PTH (310 pg/ml) levels. She eventually died from worsening septic shock.

Discussion: Etelcalcetide, a novel second-generation calcimimetic, has made significant advances in managing SHPT via improved control of PTH and FGF-23 levels. It can be used in critically ill patients with severe hypercalcemia and SPHT on CRRT as no renal dosing is required. RCA provides anticoagulation for CRRT by chelating calcium in the circuit and requires a systemic calcium infusion to replace calcium. Patients with severe hypercalcemia can be managed effectively with citrate-based CRRT without the need for systemic calcium replacement as long as systemic ionized calcium levels are monitored frequently.

SA-PO260

Effect of Transition from Vitamin D2 to Vitamin D3 Supplementation on Serum 25(OH)D Levels in Patients on Chronic In-Center Hemodialysis

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Background: Vitamin D deficiency (25(OH)D <12 ng/ml) can lead to osteomalacia in adults, and insufficiency (12 to 20 ng/ml) is associated with osteoporosis, increased falls, and possibly fractures. Clinical guidelines (KDIGO 2017) recommend correction of Vitamin D deficiency and insufficiency in all CKD 3-5D patients. Short-term pharmacokinetic studies in healthy adults have shown that Vitamin D2 (VitD2) is less effective at correcting 25(OH)D levels than Vitamin D3 (VitD3). We evaluated whether conversion from VitD2 therapy to VitD3 resulted in a meaningful change in 25(OH)D levels in hemodialysis (HD) patients.

Methods: Since 2006, we have directly administered 50,000 units of VitD2 monthly to all ~160 in-center dialysis patients. In June 2017, we converted to 50,000 units monthly of VitD3. We collected demographic and laboratory data from 2016 and 2017 (VitD2 dosing), and 2018-2019 (VitD3 dosing). 25(OH)D was measured each April at Quest laboratories. Assay detects both 25(OH)D2 and 25(OH)D3. Changes in 25(OH)D levels were analyzed, and relationships to demographic and other laboratory parameters were explored.

Results: 156 to 174 patients were included in each yearly analysis. Mean 25(OH) D levels (ng/ml) were 34.6 (2016) and 36.6 (2017) on VitD2. Levels increased to 52.9 (2018) and 53.7 (2019) on VitD3 (p<0.001). Use of VitD3 greatly reduced the proportion of patients with 25(OH)D 20-30ng/ml (29% pre; <1% post), but increased 25(OH)D levels >50 from 7% to 55%, and levels >80 from 0.3% to 4%. Among 96 patients present all 4 years, the results were similar (mean 35.2 on VitD2, and 55.0 on VitD3). There was no significant change in Calcium, PTH, or Alkaline Phosphatase

Conclusions: Consistent with short-term studies in healthy adults, at equal doses, VitD3 led to significantly higher 25(OH)D levels than VitD2. As 25(OH)D levels >20 ng/ml are sufficient to prevent osteomalacia, our data suggest use of either 50,000 units of VitD2 monthly, or a lower dose of VitD3 (likely 20-30,000 units monthly) is sufficient to prevent Vitamin D deficiency in HD patients.

Figure 1

	2016	2017	2018	2019	p-value
Vitamin D (ng/dL)	34.6	36.6	52.9	53.7	<0.001*
Calcium (mg/dL)	9.2	9.2	9.3	9.2	0.219
PTH (pg/mL)	450.2	517.2	471.1	575.5	0.217
Alk Phos (U/L)	94.3	97.6	89.2	96.4	0.542

SA-PO261

Serial Change of Serum Calcium and Management of Hypocalcemia After Denosumab Treatment in Hemodialysis Patients: A Single-Center Experience

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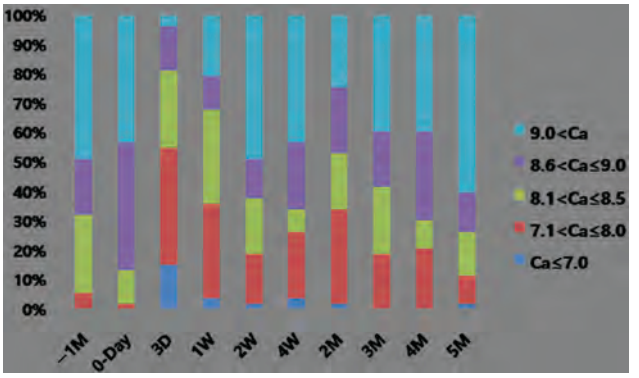
Background: Denosumab is a new drug of osteoporosis. It inhibits osteoclast formation and decreases bone resorption. Most common side effect is hypocalcemia. A prevalence of hypocalcemia after use of denosumab in HD patients is not clear.

Methods: We treated osteoporosis in HD patients with denosumab 60mg s.c. To prevent hypocalcemia, we gave Dicamax(cholecalciferol 1000 IU and calcium carbonate 1250mg) during a week before use of denosumab. After treatment, we checked serial serum calcium, every visit, during 2 weeks. When below 8mg/dL of serum calcium, patients was administrated with intravenous calcium gluconate(2g/20ml) according to our policy. We evaluated a serial change of serum calcium and prevalence of hypocalcemia after treatment. Also, We checked a percentage of patients who were replaced intravenous calcium.

Results: Total number of patients treated with denosumab was 53(female 43, 81.1%). Median age was 69 years old(45~83 years old). Median vintage of hemodialysis was 4.2 months(0.2~113.6months). Of 53 patients, there were 35(66%) diabetes and 19(35.8%) fractures. Basal calcium, phosphorus and iPTH were 9.1±0.53mg/dL, 4.1±1.34mg/dL, and 229.8±171.7pg/dL. Serial mean serum calcium was 8.4±0.80mg/dL, 8.8±0.82mg/dL, 8.9±1.14mg/dL, 8.6±1.11mg/dL, 8.9±1.03mg/dL, 9.1±1.13mg/dL and 9.2±1.01mg/dL, on the first day of 1st and 2nd week, 1st, 2nd, 3rd, 4st and 5st month later. Nadir calcium was detected during 2 weeks, 7.9±0.70mg/dL(6.5~9.2mg/dL). Patients who needed intravenous calcium, was increased during 2 weeks. 19patients(41.9%) was below 8mg/dL of serum calcium on the first day of 1st week after treatment. 21 patients(60.4%) were replaced intravenous calcium. One patient had hospitalization due to symptomatic severe hypocalcemia. After 2 months of using denosumab, serum calcium is stabilized to previous level.

Conclusions: Hypocalcemia is frequent in HD patients after use of denosumab. Intravenous calcium replacement is needed in patients with severe hypocalcemia.



SA-PO262

Assessment of the Confounding Factors to Affect Life Prognosis of Serum Magnesium in Hemodialysis Patients

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Background: Recently, some studies reported that hypomagnesemia was associated with mortality and cardiovascular events. However, optimal levels of serum magnesium (s-Mg) is unknown in hemodialysis (HD) patients. We have measured s-Mg levels once a month in HD patients. So, to identify the appropriate s-Mg levels, a 9-year survey was performed to investigate the relationships between s-Mg levels and a prognosis in HD patients. Moreover, the factors to affect s-Mg level were examined.

Methods: 148 HD-outpatients under seventy years old were followed from January 2009 to December 2018. Patients were divided to two groups according to the mean s-Mg levels during the first year period. Cutoff-point of s-Mg levels was used 2.5mg/dL, upper value of normal range in healthy subjects. The outcome was all-cause mortality/hospitalization due to be impossible of HD-outpatient. Statistical analyses were used Kaplan-Meier, log-rank tests and the Cox proportional hazards model. Then, multiple regression analysis was performed to examine factors related to s-Mg levels.

Results: The range of mean s-Mg levels for the first year was 1.9-3.8mg/dL. The survival rate in the s-Mg levels ≤2.5mg/dL group was significantly lower than that in the s-Mg levels >2.5mg/dL group (39.0% vs 72.0%; P < 0.001). The multivariate Cox proportional hazards model (stepwise method) showed that the risk of mortality/hospitalization were significantly higher in the s-Mg levels ≤2.5mg/dL group compared with the s-Mg levels >2.5mg/dL group (hazard ratio; 1.89; 95% confidence interval, 1.08–3.28, P = 0.025). Multiple regression analysis showed that s-Mg levels were associated with age, serum albumin and corrected calcium [serum calcium (mg/dL) + 4.0 - serum albumin (g/dL)]

Conclusions: This study indicated the s-Mg levels ≤2.5mg/dL was associated with high mortality/hospitalization in HD patients. The optimal s-Mg levels in HD patients may be higher level than that in healthy subject. Moreover, s-Mg levels may be affected by age, nutritional condition and calcium metabolism.

Multiple stepwise regression analysis for serum magnesium

	β	95% confidence interval	P value	R2
(Intercept)		(-0.233 - 2.672)	0.100	0.17
age (years)	-0.008	(-0.014 - -0.002)	0.009	
serum albumin (g/dL)	0.267	(0.069 - 0.464)	0.008	
corrected calcium (mg/dL)	0.100	(0.003 - 0.195)	0.044	

SA-PO263

Soluble Klotho Modifies the Mortality Risk Associated with Hypomagnesemia in Patients with Hemodialysis

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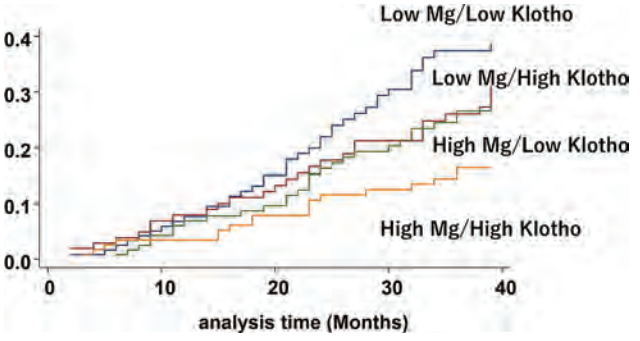
Background: Hypomagnesemia have been regarded as a risk factor of cardiovascular disease in patients with CKD. In vitro studies reported that hypomagnesemia induced downregulation of Klotho. We examined how soluble Klotho levels influence the association between serum magnesium levels and the risk of mortality in patients with hemodialysis.

Methods: This cohort study analyzed 1241 hemodialysis patients. We divided the study population into four groups based on serum soluble Klotho levels and magnesium levels. In this study, we defined the primary outcome was all-cause mortality. We used Cox proportional hazard model.

Results: Their mean age was 63.1 (±11,8) years, and median dialysis vintage was 84 (39 to 154) months. The distribution of Klotho levels was 325 (248 to 434) pg/ml. In addition, serum magnesium levels is 2.6 (± 0.46)mg/dl. During following period, 228 patients dead. Patients with lower magnesium (< 2.6mg/dl) and lower Klotho (325 pg/ml) were higher mortality than patients with higher magnesium and higher Klotho (HR 2.33,95%CI 1.37-3.97).

Conclusions: In this study, we found that lower magnesium and lower soluble Klotho is high risk of mortality in patients with hemodialysis.



SA-PO264

Circadian Rhythm of Plasma Magnesium in Patients with CKD Stage 3-4 and Healthy Controls

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Background: Chronic kidney disease (CKD) is associated with vascular calcification leading to cardiovascular morbidity and mortality. Decreasing levels of plasma magnesium (Mg) are associated with increased risk of cardiovascular disease in patients with CKD, which might be amendable to Mg supplementation. Several biochemical parameters follow a circadian rhythm, which may affect the way these parameters should be measured and may be of importance for their physiological effects and interaction. The aim of this study was to identify the circadian rhythm of plasma Mg in CKD.

Methods: This was an investigator-initiated observational clinical trial. Subjects included were patients with CKD 3-4 without diabetes (n=10 (9 males)) and healthy controls (n=10 (5 males)). Venous blood and urine samples were collected non-fasting at 8 a.m. and every third hour during a 24-hour admission with the final collection in fasting state at 8 a.m. the following day.

Results: The baseline mean (± SD) eGFR was 27 ± 8 mL/min/1.73m^2 in patients with CKD and 105 ± 10 mL/min/1.73m^2 in healthy controls. The overall mean (± SD) plasma Mg in patients with CKD was not significantly higher than in healthy controls (0.88 ± 0.04 mmol/L versus 0.84 ± 0.07 mmol/L (p = 0.220)). Cosinor analysis revealed no significant diurnal variation in plasma Mg in either subjects with CKD (p = 0.23) or healthy controls (p = 0.29). There was no significant difference between plasma Mg levels (mean ± SD) in fasting and non-fasting state in patients with CKD (fasting 0.90 ± 0.13 mmol/L and non-fasting 0.90 ± 0.06 mmol/L (p = 0.907)) or healthy controls (fasting 0.84 ± 0.07 mmol/L and non-fasting 0.83 ± 0.09 mmol/L (p = 0.598)).

Conclusions: Plasma Mg exhibits no diurnal variation and is not affected by fasting in patients with CKD 3-4. Evaluation of plasma magnesium levels in patients with CKD 3-4 requires no special precaution concerning the time of the day for sampling or whether the patient is in fasting state.

SA-PO265

Chemical Plausibility of the Tradeoff-in-the-Nephron Hypothesis

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Background: The tradeoff-in-the-nephron hypothesis attributes secondary hyperparathyroidism to events in the cortical distal nephron (CDN). The hypothesis suggests that high $[HPO_4^{=}]_{CDN}$ reduces $[Ca^{++}]_{CDN}$ and thus necessitates high [PTH] for normal Ca reabsorption (Nutrients 2017;9:427). We sought further evidence for the hypothesis with regressions of [PTH] on inferred values of $[HPO_4^{=}]_{CDN}$ and $1/[Ca^{++}]_{CDN}$.

Methods: Fasting data were obtained from 30 patients with CKD (mean eGFR 29.5) and 28 controls (mean eGFR 85.9). To estimate concentrations in the CDN, we assumed fractional delivery (k) of filtrate = 0.2 in controls and 0.35 in CKD; Ca delivery = 0.1(eGFR)$[Ca]_{uf}$, ($[Ca]_{uf}$ = plasma ultrafilterable Ca); and P delivery = urinary P excretion (E_p). We assumed pH in the CDN = 6.5 and pK of the $H_2PO_4^-$ Û $HPO_4^=$ equilibrium = 6.8. From the Henderson-Hasselbalch equation, we estimated delivery of HPO_4 to the CDN as 0.33(E_p). We calculated $[Ca]_{CDN}$ as (0.1)(eGFR$[Ca]_{uf}$)/k(eGFR) and $[HPO_4]_{CDN}$ as (0.33)(E_p/C_{cr})(eGFR)/k(eGFR), where E_p/C_{cr} = P excretion per volume of filtrate = $[P]_u[cr]_p/[cr]_u$. We assumed that $CaHPO_4$ Û Ca^{++} + $HPO_4^=$ in the CDN, with $K_{sp} = 10^{-7}$. Since equimolar amounts of Ca and P associate to form $CaHPO_4$, we let *complexed* [Ca] and $[HPO_4]$ = z. We calculated *ionized* $[Ca^{++}]_{CDN}$ as $([Ca]_{CDN} - z)$ and ionized $[HPO_4^=]_{CDN}$ as $([HPO_4]_{CDN} - z)$. Since $[Ca^{++}]_{CDN}$*$[HPO_4^=]_{CDN}$ = K_{sp}, we inferred that $([Ca]_{CDN} - z)([HPO_4]_{CDN} - z) = 10^{-7}$, and solved for z with the quadratic formula after algebraic manipulation. For CKD and controls, we examined linear regressions of [PTH] on $[HPO_4]_{CDN}$, $1/[Ca]_{CDN}$, $([HPO_4]_{CDN} - z)$, and $1/([Ca]_{CDN} - z)$.

Results: In CKD, regressions of [PTH] on $[HPO_4]_{CDN}$, $([HPO_4]_{CDN} - z)$, and $1/([Ca]_{CDN} - z)$ were significant; the regression of [PTH] on $1/[Ca]_{CDN}$ was not significant (see Table). In controls, only the regression of [PTH] on $1/[Ca]_{CDN}$ was significant.

Conclusions: In CKD (but not controls), [PTH] is related directly to ionized and total $[HPO_4]_{CDN}$, and inversely to ionized but not total $[Ca]_{CDN}$. The effect of $[HPO_4^=]_{CDN}$ on [PTH] appears to be mediated by $[Ca^{++}]_{CDN}$.

Funding: Veterans Affairs Support, Commercial Support - Genzyme

Regression of [PTH] on	CKD		controls	
	R2	p	R2	p
[HPO4]CDN	0.28	0.003	0.02	0.45
1/[Ca]CDN	0.004	0.73	0.27	0.005
([HPO4]CDN – z)	0.21	0.01	0.08	0.14
1/([Ca]CDN – z)	0.21	0.01	0.08	0.14

SA-PO266

The Importance of Biologically Active Vitamin D for Mineralization by Osteocytes After Parathyroidectomy for Renal Hyperparathyroidism

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Background: Hypomineralized matrix is a factor determing bone mineral density. Increased perilacunar hypomineralized bone area is caused by reduced mineralization by osteocytes. The importance of vitamin D in the mineralization by osteocytes was investigated in hemodialysis patients who underwent total parathyroidectomy (PTX) with immediate autotransplantation of diffuse hyperplastic parathyroid tissue. No previous reports on this subject exist.

Methods: The study was conducted in 19 patients with renal hyperparathyroidism treated with PTX. In 15 patients, the serum calcium levels were maintained by subsequent administration of alfacalcidol (2.0 μg/day), intravenous calcium gluconate, and oral calcium carbonate for four weeks after PTX (Group I). This was followed in a suset of for patients in Group I by a reduced dose of 0.5 μg/day until one year following PTX; this was defined as Group II. In the remaining four patients, who were not in Group I, the serum calcium levels were maintained without subsequent administration of alfacalcidol (Group III). Transiliac bone biopsy specimens were obtained in all groups before and 3 or 4 weeks after PTX to evaluate the change of hypomineralized bone area. In addition, patients from Group II underwent a third bone biopsy one year folllowing PTX. And we did Raman measurements ffrom the same sections as those used for histology.

Results: A significant derease of perillacunar hypomineralized bone area was obsered 3 or 4 weeks after PTX in all Group I and II patients. The area was increased in the Group II patients one year following PTX. In Group III patients, an increase of hypomineralized bone area was observed four weeks after PTX. Mineral maturity, defined by the bone's carbonate and shown as CO_3^2-v1/PO_4^3-v1, did not change following PTX in Group I and Group III. Crystallinity of the mineral did not change after PTX in either Group I and Group III.

Conclusions: The maintenance of a proper dose of vitamin D is necessary for mineralization by osteocytes, which is important to increase bone mineral density after PTX for renal hyperparathyroidism. Mineral maturity and crystallinity are not expected within 3-4 weeks after PTX.

SA-PO267

Abstract Withdrawn

SA-PO268

Vitamin D Status in CKD Patients Living in the Tropics: A Cohort in Thailand

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Background: Vitamin D deficiency is a key factor of secondary hyperparathyroidism in CKD and is recommended to be evaluated in the cases found persistently elevated PTH levels. Data survey during the last decade showed vitamin D deficiency among the general Thais for 6-30% compared to 60-70% in the Eastern Asians. Data of prevalent vitamin D deficiency in Thailand is scarce, but is seriously concerned in clinical practice to balance between standard of care and healthcare budget restraint. Therefore, the study is done to evaluate vitamin D status and predictors of vitamin D deficiency in CKD patients living in Thailand

Methods: 752 Stable CKD patients were included from CKD clinic and the outpatient section at Siriraj hospital. CKD is diagnosed based on KDIGO 2012 definition and GFR calculated with serum creatinine measured by using the enzymatic creatinine assay. Vitamin D levels were measured by using Elecsys® Vitamin D total (Roche Diagnostics, Germany). Albumin corrected serum calcium, phosphate, intact PTH, albuminuria were measured within 60 days of vitamin D levels, comorbidities and drugs related to vitamin D metabolism were collected.

Results: Mean age was 64.4±13.8 years old, 48% were female and 60.3% had diabetes mellitus. They were categorized to stage 1-2, 3a, 3b, 4 and 5 for 22.4, 18.7, 23.8, 24.1, and 11.0%, respectively. Prevalence of vitamin D deficiency (<20 ng/mL) and severe vitamin D deficiency (<10 ng/mL) were shown in Figure 1. Predicting factors of vitamin D deficiency in Thai CKD patients were stage 4-5 CKD 9.06 (3.64-22.58), albuminuria >1,500 mg/d 10.62 (3.97-28.41), calcium <9.0 mg/dL 3.99 (1.54-9.45), PTH >100 pg/mL 3.82 (1.54-9.49), diabetes 3.35 (1.33-8.46), and female 2.81 (1.19-6.62)

Conclusions: Vitamin D deficiency is highly prevalent in Thai stage 4-5 CKD patients. Considerations on GFR combined with serum calcium and PTH profiles and clinical characteristics would empower cost-effectiveness of 25-hydroxyvitamin D measurement in CKD population living in the tropic area.

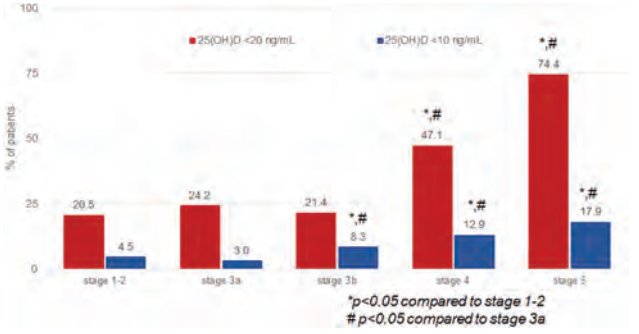

Figure 1 Prevalence of vitamin D deficiency in Thai stage 1-5 CKD patients

SA-PO269

1.25(OH)$_2$D Status in ESKD: Role of 25(OH)D and Residual Renal Function

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Background: Recent insights into vitamin D regulation suggest that CKD is a state of stagnant vitamin D metabolism characterized by reduced 1.25(OH)$_2$D production (mediated by CYP27B1) and catabolism. The present study aimed to clarify whether this is caused by insufficient delivery of substrate or low nephron mass. As a secondary aim we investigated seasonal variation and long term trends of vitamin D levels in patients with ESKD.

Methods: We analyzed serum levels of 1.25(OH)$_2$D (LC MS/MS), 25(OH)D (RIA), along with other parameters of mineral metabolism (including PTH, FGF23, sclerostin), markers of inflammation in 518 adult patients (age 54.7 ± 12.8 yrs, males 60.6%) with ESKD between April 23, 2006 and December 21, 2013. Data on residual renal function (RRF) were available in 330 patients: 115 patients were anuric (24h urine output < 100 ml) and 21 patients were anephric.

Results: Median 25(OH)D and 1.25(OH)$_2$D levels in the overall cohort were 35.9 [24.0 – 48.6] µg/L and 26.8 [18.2 – 36.9] ng/L, respectively. 25(OH)D levels showed seasonal variation and increased by 16% along the study period (2006-2013), most probably as a result of more intense supplementation. A parallel 31% increase of 1.25(OH)$_2$D levels was noted. In regression analysis, only high 25(OH)D and low phosphate and sclerostin independently associated with high 1.25(OH)$_2$D levels. 25(OH)D was the most important determinant of 1.25(OH)$_2$D levels, explaining 30% of its variability. RRF did not correlate with 1.25(OH)$_2$D levels. Remarkably, 1.25(OH)$_2$D levels were only slightly lower in anephric patients (20.3 vs 27.3 ng/L, median, p=0.02). This suggests that non-renal tissues may contribute substantially to circulating 1.25(OH)$_2$D levels. In anuric patients, 25(OH) D levels, but not mineral metabolism hormones or inflammation were associated with 1.25(OH)$_2$D levels.

Conclusions: 1.25(OH)$_2$D levels in patients with ESKD are manifestly dependent on the delivery of 25(OH)D. Extrarenal CYP27B1 activity may sustain normal 1.25(OH)$_2$D levels, even in anephric patients. Substrate delivery thus seems to be much more important than nephron mass in maintaining adequate 1.25(OH)$_2$D level. Seasonal fluctuations and long term kinetics illustrate that both vitamin D generation in the skin and nutritional vitamin D supplements contribute to 25(OH)D stores in ESKD.

SA-PO270

Expression of Vitamin D Receptor, CYP27B1 and CYP24A1 Hydroxylases, and 1,25-Dihydroxyvitamin D3 Levels In Stone Formers

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Background: The underlying pathophysiological mechanisms for hypercalciuria such as increased intestinal calcium absorption, reduced renal tubular reabsorption and increased bone resorption are influenced by calciotropic hormones. The levels of 1,25(OH)$_2$D$_3$ exceed the values of controls in some but not all hypercalciuric stone formers and the expression of vitamin D receptor (VDR) remains controversial in human studies. We aimed to evaluate the serum 1,25(OH)$_2$D$_3$ levels and the expression of VDR and the regulatory enzymes CYP27B1 (1α-hydroxylase) and CYP24A1, responsible for vitamin D degradation, in hypercalciuric stone formers (HSF) and compare to normocalciuric stone formers (NSF) and healthy subjects (HS).

Methods: Blood samples, 24-hour urine collection and a 3-day dietary record were obtained from 30 participants of each of the groups. The expression of VDR, CYP27B1 and CYP24A1 in monocytes were measured by flow cytometry.

Results: HSF presented a significantly higher mean urinary volume, sodium, magnesium, oxalate, uric acid, and phosphorus than NSF and HS. Mean daily calcium intake was lower in HSF versus NSF and HS (442±41 vs 594±42 and 559±41 mg, respectively, p=0.027). Ionized calcium was significantly lower in HSF than NSF (1.29±0.0 vs 1.31±0.0 mmol/L, p<0.01). Serum 1,25(OH)$_2$D$_3$ was significantly higher, even within normal ranges, in both HSF and NSF versus HS (22.5±1.2; 22.2±1.2 vs 17.4±1.2 pg/ml, p=0.007, respectively) but serum 25OHD$_3$, PTH, α-Klotho and plasma FGF-23 did not differ between groups. The VDR expression was higher in both HSF and NSF versus HS (80.8±3.2; 78.7±3.3 vs 68.6±3.2%, p=0.023). Although CYP27B1 and CYP24A1 expressions were similar among all groups, the ratio of 1,25(OH)$_2$D$_3$/CYP24A1 was higher in HSF and NSF than in HS (1.43±0.25 and 0.56±0.10 than 0.34±0.06, p=0.00).

Conclusions: Stone-formers, regardless of urinary calcium levels, had higher VDR expression and 1,25(OH)$_2$D$_3$ levels compared to HS. Higher 1,25(OH)$_2$D$_3$/CYP24A1 ratio suggested a lower degradation of 1,25(OH)$_2$D$_3$ by CYP24A1 in HSF and NSF.

SA-PO271

Stone Event Proximity Determines Health-Related Quality of Life (HRQoL) in Primary Hyperoxaluria (PH)

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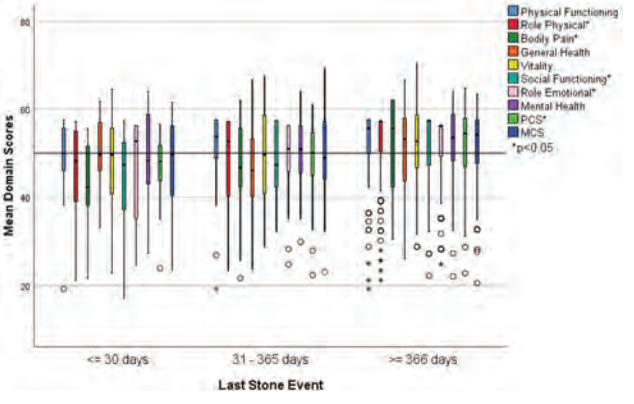
Background: We have shown previously that PH has better HRQoL compared to cystine stone formers and the US Standard Population. Now we show the first cross-sectional HRQoL profiles of PH patients.

Methods: PH participants were enrolled from the Rare Kidney Stone Consortium (RKSC) registry. The group of PH participants consist of PH 1, 2, 3, and PH-NMD (no mutation detected). PH-NMD met clinical criteria for PH. HRQoL was measured with the generic non-disease specific instrument (SF-36v2). Results were calculated as norm-based scores (NBS) based on US Standard Population (mean domain score = 50). We created three stone event groups (≤ 30 days, 31 – 365 days, ≥366 days). We compared HRQoL by last stone event for PH participants without a liver and/or kidney transplant. Group means < 47 indicate the presence of impaired functioning in associated dimensions.

Results: We used 184 surveys of adults with PH at different time points, adjusted for the last stone event, and compared SF-36 domain profiles. 56 participants were included with multiple surveys (PH1 26, PH2 8, PH3 13, PH-NMD 9; 30 males, 26 females; 42 years old, males 42 years, females 41 years). Lowest domain results were found in participants that experienced a stone event ≤ 30 days before the survey. Participants with no stone event within a year had the best HRQoL with domain scores above the US Standard Population. PH-NMD compared to PH1, PH2 and PH3 had the highest stone event rate within one year of the survey (58.1 vs 35 vs 3 vs 29.5%). All PH patients with a stone event within 30 days of the survey trended towards higher urine oxalate excretion and lower eGFR (underpowered, not significant). Figure 1 shows that time since the last stone significantly affected HRQoL.

Conclusions: PH participants as a group are not homogeneous and experience different HRQoL based on proximity to stone event. PH type is a covariate. Overall PH2 has fewer stone events compared to other PH participants, with an expected direct impact on HRQoL.

Funding: NIDDK Support



SA-PO272

Plasma Oxalate as a Predictor of Kidney Function Decline in Primary Hyperoxaluria

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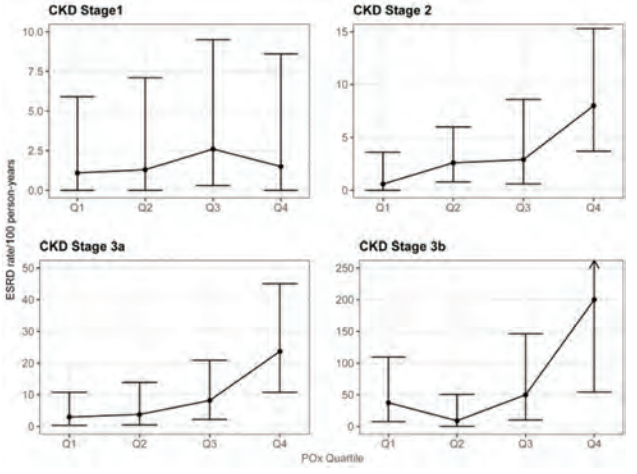
Background: This retrospective analysis investigated plasma oxalate (POx) as a potential predictor of end stage kidney disease (ESKD) among primary hyperoxaluria (PH) patients across varying stages of CKD.

Methods: PH patients with type 1, 2 and 3, age 2 or older, with estimated glomerular filtration rate (eGFR) and POx measures available during follow-up after PH diagnosis and prior to ESKD were identified in the RKSC PH Registry. Urinary oxalate (UOx) did not change across CKD stages 1-3, but POx increased with falling eGFR. Thus to maximize data for analysis of POx by eGFR stage, patients were further subdivided into CKD subgroups (stages 1, 2, 3a and 3b) such that a patient started in a given CKD stage subgroup on their first eGFR observed in that range, while also continuing to remain in any prior groups. ESKD was defined as an eGFR<15 ml/min per 1.73 m^2 or start of dialysis or renal transplantation. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for risk of ESKD were estimated using the Cox proportional hazards model with a time-dependent covariate.

Results: There were 118 patients in the CKD1 group (9 ESKD events during follow-up); 135 in CKD 2 (29 events); 72 in CKD3a (34 events); and 45 patients in CKD 3b (31 events). During follow-up, POx Q4 was a significant predictor of ESKD compared to Q1 across CKD2 (HR 14.2, 95% CI 1.8-115), 3a (HR 13.7, 95% CI 3.0-62) and 3b stages (HR 5.2, 95% CI 1.1-25), P<0.05for all. Within each POx quartile, ESKD rate was higher for more severe CKD stages, and within each CKD stage, ESKD rate was higher in Q4 compared to Q1-Q3, respectively.

Conclusions: Among patients with PH, higher POx concentration was a risk factor for ESKD, particularly in advanced CKD stages.

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



ESKD rate per 100 patient years by CKD stage and POx quartile.

SA-PO273

Proton Pump Inhibitors and Risk of Incident Nephrolithiasis: A Retrospective Cohort Study

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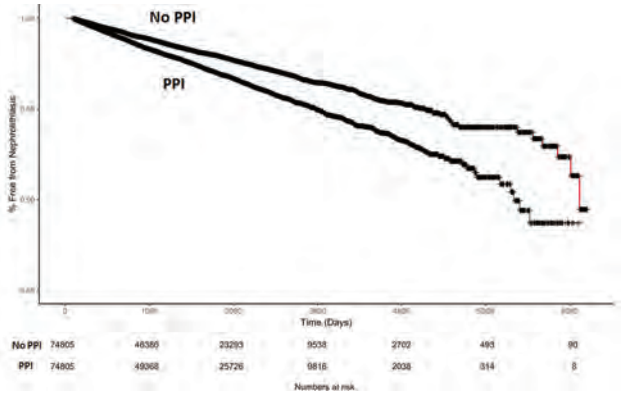
Background: Proton pump inhibitors (PPIs) have come under scrutiny given evidence of their association with various conditions including chronic kidney disease and fracture. Biochemically, the effect of PPIs and nephrolithiasis is unclear. PPIs decrease calcium gut absorption and decrease urine calcium and oxalate, which may be protective. However PPIs also decrease urine citrate which may increase stone formation. We studied the association of incident PPI use with nephrolithiasis in a large retrospective cohort.

Methods: Setting: Data were obtained from a large patient cohort from the Veteran's Health Administration (VHA). Data including demographics, encounters, comorbidities, medications, and laboratory values were obtained through querying the VHA system. Patients with prior nephrolithiasis or PPI usage were excluded. Matched Cohort: A cohort was developed with 1:1 fixed ratio matching for PPI users and non-users based on a propensity score developed from multivariate logistic regression of the patient's covariates. Kaplan-Meier survival analysis was used. Adjusted analysis was performed with Cox proportional hazards model from a robust set of covariates, including demographics, comorbidities, medications, and healthcare system interaction.

Results: Of 1,065,962 patients considered, 422,153 patients met eligibility criteria. 81,654 patients had exposure to PPIs at some point during observation. Of the 81,654 PPI users, 92% were matched based on propensity score to a non-PPI user. Over 660,426 patient-years of observation, PPI-exposed individuals developed nephrolithiasis at a higher rate compared to PPI-unexposed (62.3 versus 43.1 per 10,000 patient-years, relative risk ratio 1.43 (95% CI 1.33-1.54)). Under the Cox proportional hazards model PPI usage carried a hazard ratio of 1.32 (95% CI 1.23 - 1.42).

Conclusions: In our large retrospective cohort analysis, incident PPI usage was associated with a moderately increased risk of incident nephrolithiasis.

Funding: Veterans Affairs Support



SA-PO274

Nephropathic Cystinosis: A Distinct Model of CKD-MBD

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Background: Cystinosis is a rare autosomal recessive lysosomal storage disorder. Nephropathic cystinosis (NC) presents with Fanconi syndrome and CKD. Persistent phosphate wasting is a prominent feature; however, its impact on CKD-MBD has not been described. Thus, we compare CKD-MBD in NC (n=53) vs. non-NC (n=97).

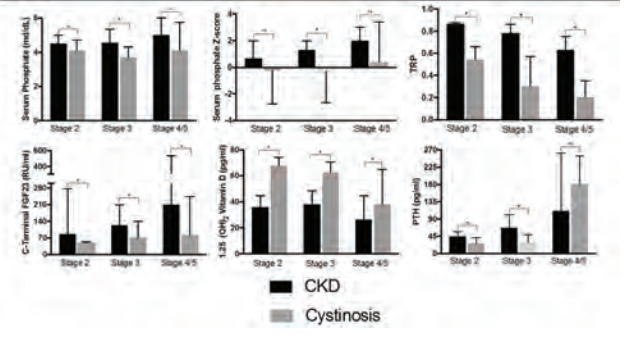
Methods: eGFR, Ca, P, PTH, 1,25D, FGF23, and TRP were assessed. C-terminal FGF23 was measured by ELISA (Quidel), S-PTH and 1,25D by immunoassay. Subjects were grouped according to CKD stage; CKD 4 and 5 were analyzed together. Dialysis pts. were excluded. All NC patients were treated with cysteamine, phosphate supplementation, and 1,25D; non-NC with 1,25D and binders as needed. Statistical analysis included Spearman correlations and the Mann-Whitney U test.

Results: Age and eGFR were similar between the groups (**Table**). In NC across all CKD stages, TRP and FGF23 were lower, and 1,25D higher (**Figure**). PTH and S-PO4 were lower in NC stage 3. In NC, FGF23 was inversely associated with eGFR (r=-0.30, p<0.05) and positively associated with S-PO4(r=0.53, p<0.001). All hypophosphatemic NC subjects had normal FGF23 levels, independent of eGFR.

Conclusions: NC is characterized by a distinct CKD-MBD, with lower FGF23 and higher 1,25D levels. Persistent phosphate wasting may lead to this phenotype. Such findings may: 1) explain the long-term musculoskeletal complications and 2) support the concept for induction of phosphate excretion in non-NC pts. to lower FGF23 and raise 1,25D levels.

Funding: NIDDK Support, Other NIH Support - NIDCR

	Non-NC CKD stage 2	NC CKD stage 2	Non-NC CKD stage 3	NC CKD stage 3	Non-NC CKD stage 4/5	NC CKD stage 4/5	P
N	11	15	34	20	52	18	ns
Age (years)	8 (5-14)	12 (8-18)	14 (12-17)	14 (8-20)	14 (9-17)	14 (12-20)	ns
eGFR (ml/min)	74 (64-88)	71 (65-76)	42 (37-46)	47 (41-51)	19 (15-23)	18 (14-24)	ns



SA-PO275

Prevalence of Kidney Stones in the United States over the Past 10 Years

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Background: Kidney stones (KS) are common in the US and cost billions of dollars on treatment. The overall prevalence of kidney stones rose from 3.2% in 1980 to 10.1% in 2014. We examined the prevalence trends of KS in subgroups of age, sex and race in the US and identify laboratory factors associated with a history of KS using National Health and Nutrition Examination Survey (NHANES) data

Methods: We conducted a cross-sectional study among 28,209 US adults aged >=10 years old in the NHANES from 2007 to 2016. We calculated the percent prevalence of a self-reported history of KS by using weights and standardized to the 2010 US Census population using age adjustment. We also analyzed relevant laboratory values and compared them according to history of KS.

Results: The prevalence of KS decreased from 8.8% in 2007-2008 to 8.6% in 2009-2010 and 7.2% in 2011-2012 but then increased to 9.0% in 2013-2014 and 10.2% in 2015-2016. Prevalence of KS was highest in 2015-2016 in every age range except in women aged 20-39 years. Among different races, non-Hispanic whites had the highest prevalence of KS at 12.1% for the last cycle of 2015-2016 and the trend was increasing from 2011-2016. Non-Hispanic Asians had the lowest prevalence of KS at 4.5% for the last cycle. The prevalence of KS among non-Hispanic blacks increased over the last 3 cycles from 4.2% in 2011-2012 to 5.0% in 2013-2014 and 5.7% in 2015-2016. We presented relevant laboratory values in Figure 1.

Conclusions: Overall prevalence of KS has been increasing for the last 6 years but this may be random variability as the prevalence decreased then increased since 2007-2008. Men had higher prevalence of KS and Asians had the lowest prevalence. Stone formers had lower urine flow rate, eGFR, bicarbonate, phosphate, serum estrogen and testosterone while they had higher serum osmolality, creatinine, chloride and uric acid compared with non-stone formers.

Figure 1: Relevant laboratory factors comparing non-stone formers with stone formers

Characteristics	Kidney Stone		P Value
	Non-stone formers (n = 25601)	Stone formers (n = 2608)	
Serum creatinine (mg/dl)	0.87 (0.003)	0.90 (0.01)	**0.006**
eGFR (mL/min/1.73 m^2)	96.42 (0.24)	95.17 (0.53)	**0.008**
albumin-creatinine ratio (mg/g)	31.67 (3.23)	30.72 (4.91)	0.87
Urine flow rate (ml/min)	1.12 (0.01)	1.02 (0.03)	**0.009**
Serum uric acid (mg/dl)	5.40 (0.01)	5.52 (0.04)	**0.004**
Serum calcium (mg/dl)	9.41 (0.007)	9.40 (0.02)	0.46
Serum phosphate (mg/dl)	3.77 (0.007)	3.68 (0.02)	**0.0001**
Serum sodium (mmol/L)	139.15 (0.06)	139.18 (0.08)	0.66
Serum potassium (mmol/L)	3.97 (0.006)	3.96 (0.010)	0.50
Serum chloride (mmol/L)	103.83 (0.08)	104.12 (0.11)	**0.001**
Serum bicarbonate (mmol/L)	25.02 (0.06)	24.64 (0.09)	**<0.0001**
Serum osmolality (mmol/kg)	277.86 (0.11)	278.24 (0.18)	**0.004**
Serum vitamin D (25OHD2+25OHD3) (nmol/l)	68.65 (0.78)	69.33 (1.18)	0.52
Serum estrogen among female (pg/ml)	108.52 (9.70)	74.51 (0.48)	**0.003**
Serum testosterone among male (ng/dl)	420.12 (3.24)	395.45 (6.93)	**0.001**

SA-PO276

Prevalence of Kidney Stones in Patients with Enteric Disorders

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Background: Hyperoxaluria (HOx) is a serious metabolic disorder and a risk factor for kidney stone disease (KSD) and chronic kidney disease (CKD). Enteric HOx (EH) develops as a complication of increased intestinal oxalate absorption due to an underlying GI disorder (e.g., bariatric surgery, inflammatory bowel disease (IBD). The prevalence of EH is not well described, due in part to infrequent testing for risk factors of KSD and the lack of a specific diagnostic code for EH. We sought to estimate the prevalence of EH and the distribution of underlying enteric causes.

Methods: We developed a state-transition Markov model to estimate the current US prevalence of malabsorptive enteric disorders and the total number of stone-forming patients using data from the published literature and from a four-year claims analysis (6/2012-6/2016) from the IBM Truven Health Analytics system. Patients with a malabsorptive enteric disorders (Roux-en-Y Gastric Bypass, Short Bowel Syndrome, Inflammatory Bowel Disease (IBD), Chronic Pancreatitis, and Celiac Disease) who had KSD or KSD and CKD were considered to have EH.

Results: The 2019 prevalence was determined to be 249,048 and the most frequent malabsorptive enteric conditions were Roux-en-Y gastric bypass at 62% and inflammatory bowel disease at 20%.

Conclusions: EH is associated with serious consequences, yet its prevalence is poorly understood. Based on this analysis of data across various sources, there are approximately 250,000 EH patients with kidney stone disease in the US, including those who develop CKD. Additional epidemiological research and a specific diagnostic code could further improve efforts to understand and improve the recognition of EH.

Funding: Commercial Support - Allena Pharmaceuticals

Prevalence of enteric hyperoxaluria with kidney stones	
Roux-en-Y gastric bypass	154,722 (62%)
IBD	48,614 (20%)
Celiac disease	29,118 (12%)
Chronic pancreatitis	13,647 (5%)
Short bowel syndrome	2,947 (1%)
Total	249,048

SA-PO277

NOSTONE Trial: Randomized Double-Blind Placebo-Controlled Trial Assessing the Efficacy of Standard and Low-Dose Hydrochlorothiazide Treatment in the Recurrence Prevention of Calcareous Nephrolithiasis

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Background: Nephrolithiasis is a global healthcare problem with a current lifetime risk of up to 18.8 % in men and 9.4 % in women. Without specific treatment, 5- and 20-year recurrence rates are 40 % and 75 %, respectively. Given the high cost of medical treatments and surgical interventions as well as the morbidity related to symptomatic stone disease, medical prophylaxis for stone recurrence is an attractive approach. Efficacy of thiazides for kidney stone prevention was tested in 11 trials in the past. However, all these trials had major methodological deficiencies. Nowadays, thiazides are widely used in the treatment of recurrent nephrolithiasis and arterial hypertension, but at significantly lower doses. In the case of recurrent nephrolithiasis, however, this practice is not supported by randomized evidence. Thus, evidence for benefits and harms of thiazides in the prevention of kidney stones remains unclear.

Methods: NOSTONE is a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial with the purpose to assess the dose-response relationship for three different dosages of hydrochlorothiazide (placebo, 12.5mg, 25.0mg, 50.0mg) in kidney stone prevention. The primary outcome is the incidence of stone recurrence (a composite of symptomatic or radiologic recurrence) at 3 years, a low-dose CT will be performed at the beginning and the end of the trial. A total of 416 patients from 12 hospitals throughout Switzerland will be included in the study.

Results: NOSTONE received all necessary approvals by the end of February 2017. Recruitment started in Bern on the 9th of March 2017, all study sites are operative since June 30th 2017. As of May 30th 2019, 270 patients were randomized in the trial (regular updates: www.nostone.ch). The end of recruitment is foreseen for August 2019. Baseline data concerning the study population will be available after the end of recruitment.

Conclusions: The NOSTONE study will provide critical information to physicians for the treatment of kidney stones. The impact of the results of this study will affect many patients currently treated with hydrochlorothiazide for the prevention of recurrent nephrolithiasis.

Funding: Government Support - Non-U.S.

SA-PO278

A Phase 3, Randomized, Placebo Controlled Trial of Reloxaliase in Enteric Hyperoxaluria (URIROX-1): Clinical Characteristics and Burden of Illness

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Background: Hyperoxaluria is a key risk factor for kidney stones (KS), and may lead to chronic kidney disease (CKD). Enteric hyperoxaluria (EH) results from excess gastrointestinal oxalate (Ox) absorption due to fat malabsorption. There are no approved therapies for EH; current recommendations are to reduce dietary Ox and increase calcium and fluid intake, calcium/citrate supplements, and thiazides. This phase 3 trial investigating reloxaliase, a first-in-class oral enzyme drug therapy that specifically degrades Ox within the gastrointestinal tract, for reducing urine Ox (UOx) excretion in patients with EH.

Methods: Adults with malabsorptive conditions, UOx ≥50 mg/d and eGFR >30 ml/min/1.73 m^2 were randomized to receive reloxaliase 7,500 U or placebo orally with food 3-5x/d for 28 d. The primary endpoint was percent change from baseline in 24-hour UOx during weeks 1-4, assessed from 24-hour urine collections obtained over 4 weeks. Clinical and 24-hour UOx data were summarized overall and by enteric condition.

Results: There were 88 subjects with available data, mean age 59 years, 48% female. The two most common enteric conditions were bariatric surgery (65%) and IBD (18%).

Recurrent kidney stones were reported by 70% (23% having more than 5 events in the past 5 yrs) while 23% had CKD stage ≥3. Mean baseline UOx was 91.5 mg/d, while 31% had UOx ≥100 mg/d. Patients with short bowel syndrome (SBS) had highest 24-hr UOx, whereas more patients with IBD had recurrent stones.

Conclusions: Patients with EH enrolled in the URIROX-1 trial from nephrologists and urologists had persistent and in some cases severe HOx and recurrent kidney stones, regardless of the type of underlying enteric condition. These clinical characteristics illustrate the limitations of existing therapeutic approaches, and the opportunity for a novel therapeutic approach to reduce oxalate burden on the kidney for patients with EH.

Funding: Commercial Support - Allena Pharmaceuticals, Inc

Enteric condition	N (%)	UOx (mg/d) – mean±SD	eGFR (mL/min/1.73m2) – Median (25th, 75th)	≥2 KS past 5 yrs
Bariatric surgery	57 (65%)	92.1±32.6	90 (73, 101.5)	63.2%
IBD	16 (18%)	90.6±32.4	59.5 (43.5, 81.8)	93.8%
Short bowel syndrome	9 (10%)	101.1±63.9	87 (56.5, 96)	66.7%
Pancreatic insufficiency	1 (1%)	92.5	67	100%
Other	5 (6%)	70.1±10.4	94 (63.5, 100)	80%

SA-PO279

Mediterranean Diet Adherence and the Risk of Kidney Stones

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Background: Diet plays an important role in kidney stone formation. Several individual components have been associated with an increased or decreased risk of kidney stones, but there is limited evidence about the role of healthful dietary patterns. The objective of this study is to examine prospectively the association of adherence to the Mediterranean diet and the risk of incident kidney stones.

Methods: We conducted a prospective study using three different cohorts: the Health Professionals Follow-up Study (n= 51,529 men), the Nurses' Health Study I (n= 121,700 women) and the Nurses' Health Study II (n=116,430 women). We assessed diet every four years using a food frequency questionnaire and calculated the adherence to a Mediterranean diet using the alternate Mediterranean Diet Score (aMED). The score considers: a high ratio of monounsaturated to saturated fatty acids; high intakes of: fruit, nuts, whole grains, vegetables, fish and legumes; low intake of red and processed meats; and a moderate alcohol consumption. The score ranges from 0 to 9, with higher scores for higher adherence to a Mediterranean diet. We used Cox proportional hazards regression to examine the independent association between the aMED and the incidence of kidney stones, adjusting for potential confounders.

Results: During more than 3 million person-years, 6,576 cases of incident kidney stones were identified. Participants with the highest aMED score (8/9) had lower BMI, lower percentage of hypertension, lower caffeine intake and higher intakes of supplements of vitamin C, calcium and total vitamin D. For participants in the highest aMED score category compared with participants in the lowest category, the risk of developing a kidney stone was between 20 and 43% lower in all the cohorts. The adjusted HR (95 % CI) for the highest category of the aMED score was 0.57 (0.38, 0.85) for HPFS (p-trend<0.001), 0.71 (0.45, 1.10) for NHS I (p-trend=0.001) and 0.80 (0.45, 1.10) for NHS II (p-trend= 0.003). When examining components of the score, high intake of fruits and whole grains, and moderate alcohol consumption, were associated with lower risk of kidney stone formation in all cohorts, while high intakes of legumes and nuts were associated with a lower risk in men, but not in women.

Conclusions: Adherence to a Mediterranean diet is associated with a lower risk of incident kidney stones.

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SA-PO280

Effect of Hydroxycitrate (HCA) on Urinary Risk Factors for Calcium-Based Kidney Stones

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Background: Potassium citrate is a mainstay of treatment to prevent calcium stones. However, it can increase urine pH and calcium phosphate (CaP) supersaturation (SS). HCA, extracted from garcinia cambogia, is a potent inhibitor of calcium oxalate (CaOx) crystal growth *in vitro* and may not yield HCO_3. It is "generally regarded as safe" and available over the counter. We studied how HCA supplementation affects urine chemistry.

Methods: We enrolled 2 groups: calcium stone formers (SF) and non-stone forming (NSF) controls. Thiazides and potassium citrate were held for 2 weeks prior to study. Participants recorded a self-selected diet for 2 days and performed 24-hour urine collection on day 2. HCA 300 mg 3 times daily was taken orally for 7 days, and 24-hour urine collected on day 7 while the patient replicated the initial, self-selected diet.

Results: 13 people, aged 26 - 76 years, participated. There were 6 SF and 7 NSF, combined into 1 group of 13. Patients replicated their diets well, as urine Na, volume, and creatinine were similar (data not shown). Results presented in Table. HCA increased urine K and citrate ($P < 0.001$ and 0.013 respectively). Mean urine pH was unchanged (6.25 to 6.47, P=0.14), while urinary NH_4 fell ($P = 0.017$). 24h excretion of Ca and Ox did not change. SS of CaOx and CaP did not change. Serum values did not change: baseline HCO_3 and K were 23.5 ± 2.5 and 4.0 ± 0.2 meq/L and 23.7 ± 1.8 and 4.4 ± 0.6 meq/L after HCA.

Conclusions: Urine K excretion rose by 29 meq/day compared with an expected increase based on the label of 14 meq, suggesting the label was not accurate. Increased citrate and lower NH_4 suggest some K is in the form of alkali salts or that some HCA is metabolized to bicarbonate. There was no change in CaP or CaOx SS. The lack of effect on SS may not reflect the potential ability of HCA to inhibit calcium crystallization, as it inhibits Ca crystal growth in vitro in supersaturated media.

Funding: Commercial Support - Litholink Corp

Effect of HCA Supplementation on 24h Urine Chemistry; n=13, mean (SD)

	Ca	Ox	K	Cit	pH	NH4	SS CaOx	SS CaP
Baseline	171.5 (68.5)	31.7 (8.1)	59.8 (16.6)	520.0 (191.1)	6.25 (0.58)	38.7 (12.8)	4.8 (1.7)	1.2 (0.8)
Hydroxycitrate	188.5 (77.9)	29.8 (8.1)	89.0 (22.1)*	660.8 (237.9)*	6.47 (0.58)	29.8 (8.6)*	5.2 (3.0)	1.6 (1.2)

SS CaOx and CaP: supersaturation of calcium oxalate and calcium phosphate. * = P<0.05

SA-PO281

Oxalate Degradation Rates of Oxalobacter formigenes

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Background: Kidney stones commonly affect US adults. In recent years, there has been increasing interest in the human anaerobic colonic bacterium *Oxalobacter formigenes* because of its ability to metabolize oxalate, and its potential to protect against calcium oxalate kidney stones. Currently, there are two known groups of *O. formigenes* (Group 1 and Group 2) with only a few isolates from each group characterized. In our experiments, we aimed to isolate *O. formigenes* from subjects with primary hyperoxaluria (PH), enteric hyperoxaluria (EH) and healthy controls (HC) to compare their metabolic activities. Understanding these differences will help expand our knowledge about this important organism and its effect on oxalate homeostasis in humans.

Methods: We collected fecal samples from 37 patients via clinical trials at New York University Langone Medical Center and Mayo Clinic with PH, EH and HC. We cultured fecal samples in 25mM oxalate-rich selective media, then isolated *O. formigenes* by picking characteristic colonies from calcium oxalate agar. We identified and grouped isolates using PCR and Sanger sequencing of the *oxc* gene. We then tested their oxalate consumption via Oxalate Degradation Assay to compute mean oxalate degradation rates (ODR) for each group of isolates.

Results: We isolated 25 *O. formigenes* colonies from 14 subjects, with all isolates belonging to either HC (n=11) or PH (n= 14) patients, and none from EH patients. Based on oxc sequences, we identified Group 1 (n=17) and Group 2 (n=5) strains, and potentially a new taxonomic group Group 3 (n=3). We were able to regrow 13 (76%) of 17, 1 (20%) of 5, and 1 (33%) of 3 Group 1, 2, and 3 strains, respectively. All 14 PH patient colonies were identified as Group 1, while HC had a mix of all three groups. Mean ODR was significantly higher in Group 1 vs Group 2 isolates (8.5 ± 3.3 vs 2.8 ± 1.9 micromole/hour, p=0.02). Group 3 isolates had intermediate ODR (5.7 ± 3.1) values. As expected, the ODRs of our Group 1 isolates were similar to the control group 1 strain OXCC13 (11.1±1.2). Mean ODR between PH, EH and HC did not differ significantly.

Conclusions: We were able to isolate and characterize 25 colonies of *O. formigenes*, including a potential new group of *O. formigenes*. Group 1 strains appear to be most metabolically active *in vitro*, and were exclusively present in PH patients.

Funding: Private Foundation Support

SA-PO282

Suboptimal Screening of Primary Hyperparathyroidism Among Veterans with Urinary Stone Disease

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Background: The American Association of Endocrine Surgeons recommends parathyroidectomy in stone formers with primary hyperparathyroidism to prevent osteopenia, osteoporosis, and recurrent urinary stones. However, rates of screening for primary hyperparathyroidism among stone formers remain unknown. To address this knowledge gap, we determined the rate of parathyroid hormone (PTH) testing in a national cohort of stone formers with hypercalcemia in the Veterans Health Administration (VHA).

Methods: We identified stone formers as Veterans with one or more inpatient or two or more outpatient encounters for urinary stone disease (USD), or one or more stone procedures between 2008 and 2013 using the national VHA database. We excluded patients who were previously screened for hyperparathyroidism and those with an eGFR < 45 to avoid identifying Veterans with secondary hyperparathyroidism. We first identified the highest serum calcium measurement within a 6 month period before and after initial

stone diagnosis. We then identified associated serum PTH concentrations within 9 months of initial stone diagnosis.

Results: We identified 140,181 stone formers who met criteria of whom 94.7% (132,787 individuals) were men. Within this cohort, 85% (119,197 individuals) had a serum calcium level measured; of these, 1.8% (2,142 individuals) were found to have at least one serum calcium concentration > 10.5 mg/dL. Among patients with hypercalcemia, 24.4% (523 individuals) had a serum PTH measurement, and 51.8% (271 individuals) of these had serum PTH concentrations above the population reference range, suggesting primary hyperparathyroidism

Conclusions: Among Veterans with USD, hypercalcemia, and normal or near normal kidney function, fewer than one in four undergo PTH testing, and among those who do, more than half have evidence of primary hyperparathyroidism. The majority of stone formers with hypercalcemia and normal or near normal kidney function are not screened for primary hyperparathyroidism, a treatable cause of USD. This information should raise clinical awareness about deficits in guideline-concordant care and inform future quality-improvement efforts in USD care.

Funding: Veterans Affairs Support, Private Foundation Support

SA-PO283

Variation in Radiation Dose of Computed Tomography Examinations Used for Renal Imaging

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Background: Computed tomography (CT) is the most commonly used imaging modality for the assessment of renal related problems (e.g. kidney stones or masses.) Patients may be exposed to higher than needed doses of ionizing radiation, a known carcinogen. The objective of this study is to examine current practice and quantify variation in radiation doses for urinary stone, renal mass, and urogram CT as a first step toward informing future quality-improvement efforts to reduce patient exposure to ionizing radiation.

Methods: We identified computed tomography examinations within the University of California San Francisco International Radiation Dose Registry which prospectively assembled CT examinations from 152 institutions in 6 countries between 2015 and 2018 for renal indications including kidney stones and renal masses. We examined variation in mean effective dose by facility and variation in the technical parameters used for these examinations.

Results: We identified 90,459 urinary stone CT exams, 12,489 renal mass CT exams and 45,391 CT urograms. We found radiation dose varied with a threefold range in mean effective dose for urinary stone exams (4.9-13.6 mSv) and renal mass exams (12.7-41.2 mSv) and a sixfold range in mean effective dose for urograms (8.4-46.0 mSv). Adjusting for patient characteristics including size, and machine, make and model did not change these results and substantial variation in dose persisted.

Conclusions: Radiation dose varied substantially for urinary stone CT exams, renal mass CT exams and CT urograms, and these differences were not attenuated by adjusting for patient or machine factors. Doses could be substantially reduced if facilities adopted the protocols of the facilities where low dose protocols are used. This study highlights the need to adopt lower radiation dose protocols and standardize technical parameters to prevent patients from receiving unnecessarily high doses of ionizing radiation in the assessment of renal disease.

Funding: Private Foundation Support

SA-PO284

The Study on Value of Bone Scan Technology in Early Diagnosis of Calciphylaxis

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Background: Current diagnostic criteria for calciphylaxis are based on ischemic necrosis and ulceration of skin and soft tissue. Nevertheless, once clinical diagnosis is confirmed, the disease progresses to the end stage with terrible prognosis. This study is aimed to investigate the early diagnostic role of bone scan technology in calciphylaxis patients undergoing dialysis, considering that this technology can reflect abnormal distribution of hydroxyapatite in eatra-osseous tissue.

Methods: Analyzed clinical data of 15 hemodialysis patients with calciphylaxis diagnosed by skin biopsy who had bone scan results in Zhongda Hospital Southeast University from Oct. 2017 to Dec. 2018. Meanwhile, non-calciphylaxis patients with the similar baseline values of clinical data were screened out (Ratio=1:2). Chi-square test was used to analyze the difference in positive rates of bone scan between two groups.

Results: General clinical data, including age, gender, dialysis time, history of diabetes and secondary hyperparathyroidism (SHPT), had no significant difference between two groups (P>0.05). In case group, 11 patients had positive result of bone scans and the positive rate was 73.3%. The positive results in calciphylaxis patients were mainly the increase in uptake or delay of clearance of radiotracer by soft tissue and the radiotracer under skin was linear or diffuse distributed. In control group, only 5 cases were positive with the rate being 16.7%, whereas the radiotracer was distributed in large patches, which was finally confirmed as SHPT-related metastatic calcification. The difference in the positive rate between two groups was significant (P<0.05). The sensitivity of bone scan for calciphylaxis was 73.3%, with the specificity being 83.3% and the Yoden index being 0.57, indicating bone scan had significant value in diagnosis of calciphylaxis. Moreover, its positive predictive value was 0.69, with the negative predictive value 0.86, suggesting that bone scan technology can be used in clinical work to screen high-risk patients in order to get clue for further examination such as skin biopsy to make early diagnosis of calciphylaxis.

Conclusions: Since bone scan has a high sensitivity and specificity in the diagnosis of calciphylaxis with a wide range of uptake for radiotracers by soft tissue, it has important application value in early diagnosis of calciphylaxis.

SA-PO285

The Specificity of Histology in Calciphylaxis

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Background: Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a devastating skin lesion that occurs most commonly in end-stage renal disease (ESRD). We previously showed that many of the histologic findings considered diagnostic of CUA can also be seen in normal skin from amputations in unaffected ESRD patients, raising questions about their specificity. To address this with more appropriate control tissue, we compared affected and unaffected skin from patients with a clinical diagnosis of CUA.

Methods: Hospitalized patients were recruited by the consulting dermatologist, who then performed skin biopsies of the lesion and of normal skin on the contralateral extremity. Skin tissue was obtained at autopsy in 2 cases. Hematoxylin and eosin and von Kossa stains were examined on each specimen. Histologic findings were evaluated by a single pathologist and included small vessel calcification, small vessel thrombosis, intimal hyperplasia, and extravascular calcification.

Results: Paired skin samples were obtained from 7 patients, of whom 4 were female, 5 were diabetic, 3 were receiving warfarin, 6 were receiving hemodialysis, and 1 was receiving peritoneal dialysis. Age range was 39-77. Lesions were located on the leg (4), thigh (2), and penis (1). In the latter case, control tissue was obtained from the mons pubis. The prevalence of findings in affected skin were: 5/7 (71%) small vessel calcification, 3/7 (43%) small vessel thrombosis, and 2/7 (30%) intimal hyperplasia, and 2/7 (30%) extravascular calcification. None of these findings were present in two biopsies. At least 2 findings were present in each of the other 5 specimens. Unaffected skin showed no abnormalities in the biopsies and only vascular calcification in the autopsy samples.

Conclusions: Based on this small study, histologic findings associated with CUA are absent in biopsies of unaffected skin from patients with suspected CUA. While small vessel calcification was noted in normal skin in the autopsy cases (possibly due to the larger sampling size), none of the other findings were present. Thus, the presence of at least 2 histologic findings appeared to be specific for CUA. Reconciling this with our previous results using amputation specimens as controls, we conclude that CUA is associated with specific histologic findings but only in patients without peripheral arterial disease. However, additional cases are needed to confirm this.

Funding: Clinical Revenue Support

SA-PO286

A Novel Approach to Treat Calciphylaxis, A Deadly Disease

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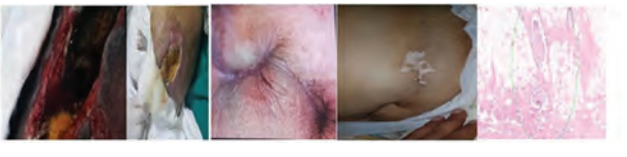
Introduction: Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a rare disease mostly occurring in patients with kidney disease (CKD). It is characterized by painful, indurated and ulcerative lesions often covered by dark eschar that is very tender and leads to necrosis following calcification and occlusion of small cutaneous arterioles. Lesions may be solitary or multiple, covering several body regions. The Prognosis is generally poor. Complications, septic episodes are common and explain the high mortality rate of about 45–80% particularly in patients with ulcerative disease [1]. We report a new therapeutic approach.

Case Description: A 66-years-old woman with known CKD stage 3 secondary to diabetic nephropathy, hypertension, coronary artery disease, hyperlipidemia and bronchial asthma. There was no history of any medication allergies. The patient presented to our hospital with urinary tract infection, which was complicated with acute deterioration of her renal function approaching ESRD. Her hospital stay was complicated with appearance of multiple red indurated skin lesions of variable sizes which were progressive. They were markedly painful and required strong Opiods for pain relief. These skin lesions were rapidly progressed to deep ulcers and were requiring multiple surgical debridement's. Skin biopsy was done and confirmed the diagnosis of calciphylaxis. She was supported with hemodialysis. Her labs showed. s PTH level of 30 pmol/l, scalcium was 2.4 u mol/l and s phos was 2.2 umol/l.

Discussion: The patient was Initially treated with intravenous sodium thiosulphate after each dialysis session, oral cinacalcet, oral sevelamer and low calcium dialysate. With These measures there was no relief of her lesions and pain. As a last resort Nitroderm patches (5 inches) and silver Alginate dressings were applied locally and she was given oral nifidepine 30 Mg LA once a day. Patient demonstrated a dramatic improvement over the subsequent months. Conclusions: This case illustrates that the local and systemic vasodilators including other general measures could be successfully used in managing resistant cases of calciphylaxis. This therapeutic approach should be evaluated in other such cases to revalidate.



1st 2 pics before ttt - After ttt -Skin biopsy

SA-PO287

Epidemiological Investigation of Calciphylaxis: Data from China

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Background: Calciphylaxis is a serious life-threatening vascular disease commonly occurred in dialysis patients. Chinese research on calciphylaxis is still in its infancy without epidemiological data. A regional epidemiological study of calciphylaxis was initiated at first time in China to find out its prevalence and clinical characteristics in Chinese hemodialysis patients.

Methods: The project was initiated in Aug. 2018. Stratified sampling method was used to select 28 dialysis centers in four regions of Jiangsu Province in China with an estimated sample size of 6000. Inclusion criteria: a. age≥18 years; b. duration of dialysis≥6 months; c. informed consent. The study used a questionnaire included general information and calciphylaxis-related symptoms.

Results: As of Apr. 30, 2019, 3799 hemodialysis patients had completed questionnaires. 77.0% of patients hadn't heard of calciphylaxis, and another 9.2% only knew the name. Among them, 27 patients were diagnosed with calciphylaxis and unadjusted prevalence rate in hemodialysis patients was 0.71%. Of the diagnosed patients, 70.4% were male with an average age and duration of dialysis of 55.8±15.3 years and 86.0 (36.0, 144.0) months respectively. 13 patients had diabetes and 19 had secondary hyperparathyroidism [the median iPTH was 561.8 (312.9, 817.8) pg/mL]. Only one used warfarin therapy. Surprisingly, 383 of 3799 (10.1%) had different types of skin lesions, including rough skin (48.3%), sensory sensitivity or loss (15.6%), diffuse rash (14.6%), calcified nodules (6.5%), painful papules (3.7%) and livedo or purpura (15.4%). Lesions were mainly in lower limbs, reaching 56.9%. 116 patients (30.3%) noticed a progressive deterioration of skin damage with potential calciphylaxis risks. Nevertheless, skin biopsy rate of these patients was only 6.3%, which affected further diagnosis.

Conclusions: This is the first epidemiological data about calciphylaxis from China. The preliminary analyses show that prevalence of calciphylaxis in Chinese hemodialysis patients is 0.71%, which seems to be lower than that from other countries due to differences in races and medication habits. In particular, we find some dialysis patients have atypical skin lesions which don't rule out early manifestations of calciphylaxis. It's urgent to improve clinical understanding of calciphylaxis, and multifaceted diagnostic methods will be applied for early screening.

SA-PO288

A Case-Control Study on Risk Factors of Calciphylaxis: Data from Chinese Hemodialysis Patients

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Background: Calciphylaxis (CUA) is a rare but potentially fatal disease that is commonly occurred in dialysis patients. Since there is no data based on Chinese population, the study is aimed to investigate risk factors of CUA in Chinese hemodialysis patients.

Methods: We retrospectively evaluated medical records of 20 hemodialysis patients who were newly diagnosed with CUA by skin biopsy admitted to Zhongda Hospital Southeast University from Oct.2017 to Dec.2018. Non-CUA dialysis patients with the same age and duration of dialysis were randomly selected as controls (Ratio=1:2).

Results: Most of CUA patients were male (80%) and elderly (55%), while 50% had a body mass index higher than 24. The mean time interval since start of dialysis to CUA diagnosis was 114.65±81.32 months, and the median time from appearance of skin lesion to diagnosis was 6 (2, 15) months. The incidence of hyperparathyroidism was higher in patients with CUA (80% vs 62.5%), but the differences of duration of elevated serum intact parathyroid hormone (iPTH) and its highest value were not significant compared with the controls. Warfarin therapy had no significant difference between two groups (15% vs 5%). Univariate logistic regression analysis indicated that male (OR 3.619, 95%CI 1.027-12.748), each 1 point increase in score of use of vitamin D and its analogues (OR 1.505, 1.029-2.201), each 1 mmol/L increase in corrected serum calcium level (OR 24.486, 1.570-381.873), each 1 mmol/L increase in serum phosphate level (OR 5.382, 1.767-16.389), each 1 pg/mL increase in iPTH level (OR 1.002, 1.000-1.003), each 1 g/L decline in serum albumin level (OR 1.181, 1.041-1.340), each 1 IU/L increase in serum alkaline phosphatase (ALP) level (OR 1.005, 1.000-1.009) and each 1 mg/L increase in hypersensitive c-reactive protein level (OR 1.029, 1.000-1.059) were significantly associated with CUA. Serum phosphate, albumin and ALP were still significant risk factors after multivariate analysis.

Conclusions: This is the first report of risk factors of CUA based on Chinese population. The results show that high levels of serum phosphate and ALP, low level of serum albumin are independent risk factors of CUA in Chinese hemodialysis patients. Unlike previous research from western countries, warfarin therapy didn't show an increased risk in this study, propably because of the low exposure rate of it in China.

SA-PO289

Outcomes Assessment in a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of SNF472 for Treating Calciphylaxis

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Background: Calciphylaxis (calcific uremic arteriolopathy, CUA) is a severe form of vascular calcification characterized by painful necrotic skin ulcers and very high mortality. No approved therapies are available. SNF472, an intravenous formulation of myo-inositol hexaphosphate, inhibits formation and growth of hydroxyapatite crystals, the final common step in the pathophysiology of vascular calcification. The objective of this Phase 3 randomized, double-blind, placebo-controlled trial is to evaluate efficacy and safety of SNF472 for CUA. Efficacy outcomes will include wound healing, pain, and wound-related quality of life (QoL). Standard safety assessments will be conducted.

Methods: Planned enrollment is approximately 66 adult patients on maintenance hemodialysis with a clinical diagnosis of CUA with wound ulceration and wound-related pain. Patients will be randomized 1:1 to SNF472 (7 mg/kg) or placebo 3x/week for 12 weeks via infusion through the dialysis circuit. In a subsequent 12-week open-label period all patients will receive SNF472. Patients will also receive background care for CUA in accordance with the practices of each site.

Results: Wound healing will be assessed with the Bates-Jensen Wound Assessment Tool (BWAT), BWAT-CUA, and qualitative review of wound images. All 13 items comprising the BWAT will be assessed: size, depth, edges, undermining, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin color surrounding the wound, peripheral tissue edema, peripheral tissue induration, granulation tissue, epithelialization. BWAT-CUA is an 8-item targeted modification of BWAT focused on prototypical features of CUA lesions including necrotic tissue type and amount, exudate type and amount, skin color surrounding the wound, peripheral tissue edema and induration, and granulation tissue. External, independent wound care experts blinded to treatment assignment will determine BWAT scores based on review of standardized images, measurements from imaging software, and assessments by site investigators. Pain will be assessed on a visual analog scale. QoL will be assessed with the Wound-QoL questionnaire.

Conclusions: Efficacy and safety of SNF472 for CUA will be evaluated.

Funding: Commercial Support - Sanifit

SA-PO290

Whole-Kidney and Single-Tubule RNA Sequencing Reveal Changes of Cell Types and Signaling for Nephrogenic Diabetes Insipidus After Ureteral Obstruction

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Background: Unilateral ureteral obstruction (UUO) models in rodents are commonly employed in the study of CKD. Early stages of UUO are marked by polyuria with impaired urinary concentrating ability, associated with loss of aquaporin-2 (AQP2) expression. Most mechanistic work in UUO models has been done at relatively late time points, making it difficult to discriminate 'first cause' events from secondary, tertiary, etc. changes in gene expression.

Methods: Preliminary whole-kidney RNA-Seq studies were performed after 0, 3, 6, and 12 hrs of UUO. Based on whole-kidney findings, cortical collecting ducts (CCDs) and cortical thick ascending limbs of Henle (cTALs) were microdissected from rats 3 hrs after UUO. Single-tubule RNA-Seq was carried out independently in 4 UUO rats versus 4 controls.

Results: Whole kidney RNA-Seq time course experiments revealed that Aqp2 and other collecting ducts markers started to decrease between 2 and 6 hrs. Decreases were seen in markers of connecting tubule (Calb1), distal convoluted tubule (Slc12a3) and thick ascending limb (Slc12a1) were also seen within 3 hrs. However, there were no effects on transcripts coding for classical markers of podocytes and proximal tubules within 12 hours. Expression of renal non-epithelial cell markers showed B lymphocytes (Cd19, Cd80) rapidly increased at 3 hrs and decreased at 12 hrs followed by increased abundance of markers of monocytes (Fcgr2b, Sell), macrophages (Gata6), and chemokines (Ccl2, Ccl6, Cxcl14) at 6 to 12 hrs. Several aldosterone-regulated genes showed increases in mRNA including Sgk1, Scnn1a, and Tsc22d3 at 3 hrs. Single-tubuleRNA-Seq data (both CCD and cTAL) showed a large number of transcripts coding for transporters and receptors that were decreased. It also revealedthat immediate early gene transcripts were increased significantly more frequently than expected from random sampling from the full pool of transcripts at 3 hrs.

Conclusions: Whole-kidney RNA-Seq results are consistent with very early effects on the distal nephron but not proximal tubule or glomerulus in terms of gene expression and provided evidence for invasion or activation of inflammatory cell types. Single-tubule RNA-Seq showed cellular signaling changes in CCD and cTAL, consistent with activation of the immediate early response.

Funding: Government Support - Non-U.S.

SA-PO291

Single-Cell Transcriptomics of Enriched Human Intercalated Cells Exposed to Uropathogen Reveal Differential Innate Immune Signature in Intercalated Cell Subsets

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Background: We have previously shown that intercalated cells (ICs) are important for innate immunity in murine model of urinary tract infection. Little is known about their role in human innate immune function. We explored the whole genome transcriptome after early 1 hour uropathogen vs saline exposure in enriched human intercalated cell at single cell level.

Methods: Human ICs were enriched from kidney biopsy samples using magnetic cell sorting with anti-human c-kit microbeads after removal of dead cells and $CD45^+$ immune cells. Enriched viable ICs were exposed to saline or UPEC for 1hr. Single cells were separated on 10x single cell instrument. Single cell gel beads containing barcoded oligonucleotides and reverse transcriptase reagents were generated with the v3 single cell reagent kit. Following cell capture and cell lysis, cDNA was synthesized and amplified. Illumina sequencing library was then prepared with the amplified cDNA. The resulting library was sequenced using Illumina NovaSeq 6000. 26 bp of cell barcode and UMI sequences and 91 bp RNA reads were generated. CellRanger 3.0.2 was utilized to process the raw sequence data generated. The R package Seurat development version 3.0.0.9 was used for the further gene expression analysis.

Results: Magnetically enriched $CKIT^+$ cells expressed higher levels of V-ATPase mRNA expression compared to $CKIT^-$ cells. 6 clusters of collecting duct cells identified including 4 alpha IC clusters with variable SLC4A1 (AE1) and innate gene including DEFB1 (anti-microbial peptide) expression, 1 beta IC cluster (showing no innate immune gene expression) and 2 PC vs transitional IC/PC clusters ($AQP2^{lo/hi}$ V-$ATPase^{lo}$) with distinct innate immune profile. Reactome pathway analysis predicted innate immune role for human ICs. Differential gene expression profiling found significantly upregulated gene with short UPEC exposure in IC clusters included Immunoglobulin lambda constant 3 (IGLC3) and adrenomedullin (ADM), an anti-microbial gene, integrin alpha E (ITGAE).

Conclusions: Innate immune function identified in murine models are conserved in human ICs. Enriched live human ICs can act as model system that can be used to determine human relevance of mouse findings. Single cell analysis reveals collecting cell types/subtypes are more diverse than previously recognized.

Funding: NIDDK Support

SA-PO292

Novel Transcriptional Regulators of Tight Junction Biogenesis in Renal Collecting Ducts

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Background: The renal collecting duct is comprised of a tight epithelial barrier resulting in a strict separation of intraluminal urine and the interstitium. Disruption of this barrier leads to impaired water reabsorption and loss of adequate urine concentration ability. However, the overall transcriptional network controlling this process is only incompletely characterized. Using an integrated bioinformatics approach, we identified two transcriptional regulators (TRs), Tfap2a and Ncor1, potentially involved in this network. The transcription factor Tfap2a is a trans-regulatory factor implicated in epithelial differentiation and Tfap2a mutations have been associated with renal malformations. Ncor1 is a nuclear corepressor that assists nuclear receptors (such as thyroid hormone receptor) in the downregulation of gene expression. We hypothesize that Tfap2a and Ncor1 play a role in tight junction biogenesis and epithelial barrier formation in the CD.

Methods: Inner medullary collecting duct (IMCD3) cells were engineered to harbour CRISPR/Cas9-induced knock outs (KO) of either Tfap2a or Ncor1. Deregulated genes were identified by mRNA sequencing and confirmed with qPCR.

Results: Tfap2a and Ncor1 show predicted binding to promotors of several critical tight junction components and are highly expressed in IMCD3 cells and CD in mice. Crispr/Cas9-induced KO of Tfap2a and Ncor1 were confirmed with allele-specific sequencing validating frameshift mutations in the targeted areas. mRNA sequencing revealed a strong impact of Tfap2a and Ncor1 KO on the expression of important tight junction components. For example, two claudins, Cldn4 and Cldn8, showed massive downregulation in comparison to WT clones. Interestingly, the TR grainyhead-like 2 (Grhl2), which we previously identified as a critical regulator of tight junction biogenesis, was also highly downregulated in Tfap2a and Ncor1 KO clones. These findings were confirmed by qPCR. A detailed characterization of the transcriptional network is still ongoing.

Conclusions: Our data support our hypothesis that the candidates Tfap2a and Ncor1 are involved in the transcriptional network regulating tight junction biogenesis and barrier formation in the renal CD. A detailed understanding of the underlying network mechanisms controlling tight junction biogenesis might provide important insights into their potential involvement in kidney disease.

SA-PO293

A Comprehensive Transcriptome Database for Mouse Renal Tubule Segments

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Background: The mammalian renal tubule is comprised of at least 14 segments, each with distinct cell types and unique sets of transcriptomes. Recent advances in RNA-seq techniques offer the ability to profile the transcripts at the level of single-microdissected tubules and single-cells. To better understand the mouse renal physiology and pathophysiology, a comprehensive transcriptome database for all the mouse renal segments/cells is needed.

Methods: Here, we microdissected all 14 mouse renal tubule segments and carried out single-tubule RNA-seq in each of them. These data were used to create an online database that allows for: 1) easy exploration of transcript expression; and 2) visualization of isoform distribution along the renal tubule through a genome browser, *JBrowse*. We also developed a flow-sorting procedure to enrich *Slc12a3*$^+$ distal convoluted tubule (DCT) cells and carried out single-cell RNA-seq (10X Chromium) to study their heterogeneity.

Results: We profiled at least 3 biological samples per segment and were able to detect more than 11,000 transcripts for each mouse renal tubule segment (mean TPM >1). We identified unique patterns of protein distribution along the renal tubule, including transcription factors, metabolic enzymes, and G protein-coupled receptors. Also, we incorporated JBrowse into the database, which allows for easy and intuitive visualization of exon usage for transcripts. Our data revealed distinct segment-specific isoforms of many genes including known isoforms of ROMK (*Kcnj1*), Wnk1, and SPAK (*Stk39*). This database allowed us to identify embigin (*Emb*) as a negative surface marker for proximal tubule cells, which was used to enrich non-proximal cell types by FACS sorting. We profiled ~2000 $embigin^+$ cells at a median depth of ~1000 genes. Single-cell RNA-seq analysis of Emb^+ $CD45^-$ $DAPI^-$ LTL^- PNA^- Kit^- cells indicated an enrichment of DCT cells (~1000 *Slc12a3*$^+$ cells). Initial results show evidence of heterogeneity of *Slc12a3*$^+$ cells separating into at least two independent clusters. Both clusters lacked AQP2 and 11β-hydroxysteroid dehydrogenase signals but a high percentage expressed ENaC subunits.

Conclusions: These data allowed us to create a resource in the form of a publicly accessible web page. They also expand our knowledge of the cell types that make up the DCT.

Funding: Government Support - Non-U.S.

SA-PO294

Identification of MAP Kinases-Regulated Proteins in Downstream Signaling Pathways of Vasopressin V2 Receptor in Kidney Collecting Duct

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Background: Vasopressin signaling mediated by G protein-coupled V2 receptor (V2R) is critical in water and electrolyte transport in the kidney collecting duct (CD) cells. Stimulation of V2R affects several downstream signaling pathways, including PKA, PI3K/AKT, Wnt, and Ca^{2+}/calmodulin. MAP kinases are also involved as an apparent downstream signaling pathway of V2R, however, the roles and their substrates of MAP kinases in the vasopressin signaling are unclear.

Methods: Comprehensive substrates of MAP kinases were identified using bioinformatic analyses: 1) expression of MAP kinases were studied using database based on high-throughput profiles of transcriptome and proteome (https://hpcwebapps.cit.nih.gov/ESBL/Database/index.html); 2) MAP kinase substrates expressed in the CD were identified using multiple protein phosphorylation databases. The identified substrates were mapped on the downstream signaling of V2R. Trim28-mediated AQP2 regulation was examined using immunoblotting and immunohistochemistry.

Results: Five MAP kinases (ERK1, ERK2, ERK3, JNK2, and MAPK p38 alpha) were identified as the MAP kinases expressed in kidney CD cells. From multiple protein kinase-substrates databases, 189 proteins were identified as the substrates of five MAP kinases. Among them, 51 transcription factors, 15 transcription co-regulators, 30 kinases, 4 E3 ligases and 1 deubiquitinating enzyme were classified. In particular, sequential data mining revealed that serine 595 in the tripartite motif-containing 28 (TRIM28), as the substrate of MAP kinases, was the only one phosphorylation site downregulated by vasopressin. Since TRIM28 is a transcription cofactor and also E3 ligase, we examined whether TRIM28 is a mediator of MAP kinases action on AQP2 expression. Immunofluorescent labeling of mouse and rat kidneys revealed that TRIM28 was exclusively localized in the nuclei of the tubular epithelial cells, including CD. dDAVP-induced AQP2 up-regulation was significantly attenuated in mpkCCD cells with TRIM28 knockdown.

Conclusions: We identified MAP kinase substrates of the kidney CD mapped on the downstream signaling pathways of V2R. TRIM28 was identified as a substrate of MAP kinases that involves in vasopressin-mediated signaling pathways, including regulation of AQP2.

Funding: Government Support - Non-U.S.

SA-PO295

Phosphorylation Profile of Human AQP2 in Urine Exosome Identified by LC-MS/MS Phosphoproteomic Analysis

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Background: AQP2 water channel is the key membrane protein which determines the water permeability of collecting ducts. Multiple phosphorylation sites at the C-terminal of AQP2 are identified including S256, S261 and S264. Interetingly, the amino acid at S269 of rodents AQP2 is Thr in human AQP2. The phosphorylation of S269 in rodents has been shown to be an important signal for the apical membrane accumulation. However, the phosphorylation of T269 in human is unknown. As AQP2 is excreted into the urine by the endocytosed exosomes, human AQP2 protein is easily obtained from the urine. The purpose of this study was to examine the phosphorylation status of human AQP2 from urine exosomes.

Methods: Human urine samples of volunteers were obtained from the morning first urine. Urine exosomes were isolated by differential centrifugations and digested with trypsin in solution. Tryptic peptides were purified by MonoSpin column (GL Sciences, Tokyo, Japan) and analyzed thrice by LC–MS/MS (Bruker Tims TOFpro). Western blots were used to detect the AQP2 phosphorylation with a usual and S256, S261, S264, and S269-phosphorylated AQP2-specific antibodies.

Results: Summation of thrice analysis identified total 185 PSMs (peptide spectrum match) of phosphorylated AQP2 at Ser and/or Thr. The most dominant form was S256 phosphorylated form (n=154), followed by S261 form (n=14). Small numbers of phosphorylation were observed at T244 (n=6), S264 (n=4), and T269 (n=2). Western blot of human urine exosomes detected dominant S256 and S261-phosphorylations and much lower S264 and T269-phosphrylations.

Conclusions: These results indicate that the all phosphorylation sites of human AQP2 including T269 are indeed phosphorylated and S256- and S261-phosphorylations play a dominant role in its urinary exosomal excretion. The newly identified T244 phosphorylation is intriguing and worth further studies.

Funding: Government Support - Non-U.S.

SA-PO296

Three-Dimensional Visualization of the Medullary Tubular-Vascular Relationship in Adult Mouse Kidneys

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Background: A close spatial relationship between renal tubules and blood vessels in the renal medulla forms the structural basis for urine concentration, but is also the site of acute and chronic kidney injury under certain pathological circumstances. Therefore, a comprehensive understanding of the structure of this area is indispensable for nephrologists.

Methods: The tubule-vessel arrangement through whole mouse medulla was investigated using serial sections with double immunofluorescent staining for CD34 and for either AQP-1 or AQP-2. Subsequently, 525 tubules and 333 vessels were traced with custom-made computer software, and ultrastructurally analyzed using EM.

Results: The main findings were: 1) Descending vasa recta (DVR) and ascending vasa recta (AVR) in the center of the vascular bundle (VB) of ISOM closely accompanied each other starting at the cortex-medulla transition towards the inner medulla and gradually draining into capillaries at papilla; 2) AVR arising from capillary nets of the different levels of the medulla always ran counter-currently in close contact with either descending thin limbs (DTL) or DVR in a VB or with collecting ducts (CD) in inter-bundle regions (IBR). AVR accompanying with type 3 short loop nephron-descending thin limbs (SLN-DTL) mainly drained into arcuate veins, while AVR in close contact with type 1 and 2 SLN-DTL often drained into the lobular veins in cortex; 3) Thick ascending limbs (TAL) from the longest long looped nephrons (LLN) entered into a VB, and ran mainly in proximity to and counter-current to the DVR that originated from same glomeruli; 4) The number of ascending and descending tubules and vessels were almost identical; and 5) In the inner medulla, DVR became thin-walled and fenestrated, closely related to the surrounding tubules or CD.

Conclusions: The present study shows a ubiquitous phenomenon that AVR is spatially arranged with DTL and DVR as well as CD in a counter-current way throughout the whole medulla. This contributes to an efficient reabsorption of water and electrolytes in the filtrate, and makes it sensitive to the damaging factors, such as hypoxia, hyperglycemia, cytotoxity, etc.

Funding: Government Support - Non-U.S.

SA-PO297

Molecular Dynamics Simulations Reveal the Residues Involved in NBCe1 Ion Coordination

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Background: We have recently solved by CryoEM the near atomic (3.9 Å) structure of NBCe1-A, an electrogenic Na^+-CO_3^{2-} cotransporter expressed on the basolateral membrane of the proximal tubule, which plays a key role in tubular bicarbonate absorption. Although our structure and functional mutagenesis data suggest that a set of residues from TMs 3, 8, 10 and their vicinity are likely involved in ion coordination, their exact roles cannot be determined given that 3.9 Å resolution was not sufficient to detect coordinated ions.

Methods: The NBCe1 membrane domain was placed in a cubic periodic box in a POPC bilayer using the CHARMM-GUI online server. MD simulations were performed with the CHARMM36 force field and the NAMD program, and ~600 ns long MD trajectories with 2-fs time steps were collected and used for analysis. Ion interactions with the NBCe1 residues were quantified as contact frequency (i.e. percentage of the MD trajectory steps, in which a given ion was found at 3.5 Å from a specific protein residue). Residues exhibiting high contact frequencies with respect to Na^+ and CO_3^{2-} were used for identification of the ion coordination sites.

Results: In the wild type NBCe1 protein, the Na^+ contact frequency was highest for residues D754 and T758 (TM8) and A799 (loop prior to TM10). The CO_3^{2-} contact frequency was highest for K924 (TM13), A800 (loop prior to TM10), T801 (TM10), with less interaction at T485 (loop prior to TM3), and G486 and P487 (TM3). Mutational data supported these results. The A799V mutation found in patients with proximal RTA affecting the Na^+ coordination site leads to significantly impaired protein-ion interactions for both Na^+ and CO_3^{2-}. Another proximal RTA causing mutation, G486R, affecting the CO_3^{2-} coordination site, demonstrates impaired Na^+ protein contacts and strong interaction between R486 and CO_3^{2-} with the arginine residue positioned away from the coordination site.

Conclusions: All-atom molecular dynamics simulations of the membrane domain of NBCe1 revealed that it binds stably Na^+ and CO_3^{2-}. Na^+ is coordinated by D754, T758, and A799. CO_3^{2-} is coordinated by K924, A800, A801, T485, G486, and P487. The proximal RTA patient mutations A779V and G486R drastically alter the coordination of Na^+ and CO_3^{2-}.

Funding: NIDDK Support

SA-PO298

Water Loading Increases Urinary Extracellular Vesicle Size but Not Excretion Rate

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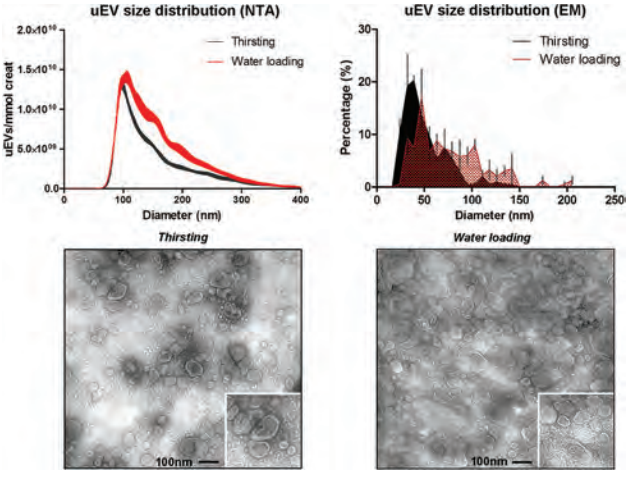
Background: Urinary extracellular vesicles (uEVs) are a promising source of kidney biomarkers, but the factors influencing uEV size and excretion rate are unknown. Here, we studied the effect of water loading on uEV size and excretion rate.

Methods: We performed a water loading test (20 ml/kg) in healthy men (n = 11) and isolated uEVs from whole urine at 6 time-points. uEVs were quantified using nanoparticle tracking analysis (NTA), a time-resolved fluorescence immunoassay that isolates CD9+ uEVs (CD9-TRFIA), and EVQuant, a novel technique that counts individual fluorescently labeled EVs after immobilization in a matrix.

Results: While EVQuant and CD9-TRFIA demonstrated that the excretion rate of uEVs was constant during water loading, NTA suggested a significant increase of 50% by the intervention ($p<0.0001$). Subsequently, we found on NTA that the size of uEVs generally increased ($p<0.0001$, Figure). This size increase was confirmed by EM (n= 4, $p<0.001$, Figure).

Conclusions: Water loading increases uEV size but not excretion rate. A lower urine osmolality may cause water to move into EVs. This phenomenon interferes with uEV quantification by NTA and is an important caveat in uEV studies.

Funding: Private Foundation Support



SA-PO299

Water Deprivation Shortens Primary Cilia Length in the Kidney Tubular Cells

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Background: The primary cilium, a microtubule-based cellular organelle, plays a key regulator for maintenance of cell homeostasis by sensing and transducing extracellular signals. In the kidney, the length of primary cilium links to the number of human kidney

diseases. Here, we investigated whether water deprivation affects the primary cilium homeostasis and its underlying mechanisms in the kidney tubule cells.

Methods: C57BL6 mice were dehydrated for 1 or 2 days. Some mice were administrated with tubastatin A (an inhibitor of histone deacetylase 6, HDAC6) or saline before restriction of drinking water supply.

Results: In this study, water deprivation significantly shortened primary cilia length in kidney tubular cells in mice along with increasing urine osmolality. The kidneys derived from water-restricted mice presented low levels of acetylated-α-tubulin, EXOC5, an exocyst complex, and α-tubulin transferase expression. In Madin-Darby canine kidney (MDCK) cells, high concentrations of NaCl or mannitol treatments shortened primary cilia length. This NaCl or mannitol treatment decreased the expression of acetylated-α-tubulin, EXOC5, and α-tubulin transferase. Treatment of tubastatin A prevented drinking water deprivation-induced shortening of primary cilia in the mice. In addition, this HDAC6 inhibitor treatment prevented the decrease of acetylated-α-tubulin, EXOC5, and α-tubulin transferase expression.

Conclusions: These findings demonstrate that the length of primary cilium in kidney tubule cells is associated with water supply and urine osmolality, suggesting that primary cilium may play an important role in body water homeostasis and regulation of urine osmolality.

SA-PO300

Inactivation of the Mitochondrial Structural Protein Opa1 in Distal Tubules and Collecting Ducts in the Mouse Causes Nephrogenic Diabetes Insipidus

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Background: Optic Atrophy-1 protein (OPA1) is a nuclear-encoded mitochondrial protein localizing in the inner mitochondrial membrane, where it participates to mitochondria fusion and supports cristae folding. Mitochondria in the kidney provide energy to the Na, K-ATPase that generates ion gradients for nutrient reabsorption, electrolyte and fluid balance (Bhargava 2017). Given their essential function in aerobic metabolism, mitochondria are of interest to the pathophysiology of diabetes. To study how mitochondria fitness contributes to kidney physiology, we inactivated *Opa1* gene expression in the kidney epithelium.

Methods: We generated a kidney-specific *Opa1$^{fl/fl}$* mouse model expressing the Cre recombinase under the kidney-specific cadherin 16 promoter (*Opa1* KO, for short). Mitochondria ultrastructure was analyzed by transmission electron microscopy (TEM), metabolomics analysis by NMR spectroscopy.

Results: *Opa1* KO mice die within the first three months of age. Mice were housed in metabolic cages and showed progressive polydipsia and polyuria, low urinary pH, decreased urinary electrolyte concentration but no gross alteration of total electrolyte excretion. We observed kidney enlargement from P30 onwards, which results from enhanced proliferation of *Opa1* KO epithelial cells of distal tubules and collecting ducts, where *Opa1* is inactivated, by Ki67 staining. Expression of markers of distal tubule subsegments is preserved indicating maintenance of cell identity, with the exception of aquaporin 2 that is reduced in *Opa1* KO collecting ducts, causing polyuria. We detected the expected alterations in mitochondria structure by TEM and decreased mitochondrial cytochrome *c* oxidase activity in *Opa1* KO epithelial cells. Metabolomics showed that these alterations result in a massive switch to glycolysis that sustains cell proliferation, ultimately resulting in renal dysfunction.

Conclusions: Inactivation of Opa1 induces kidney enlargement and a gross impairment of renal water reabsorption, thus recapitulating the key features of nephrogenic diabetes insipidus. Further investigations will clarify the molecular mechanisms that link mitochondria dysfunction to epithelial cell proliferation, a response that seems to be unique of the kidney.

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SA-PO301

Induction of the Intracellular Immunomodulator Toll-Interacting Protein (Tollip) Mediates Monophosphoryl Lipid A (MPLA)-Induced Protection Against Lipopolysaccharide in Medullary Thick Ascending Limb (MTAL)

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Background: LPS inhibits HCO_3^- absorption in the MTAL through activation of a basolateral TLR4-MyD88-IRAK-1-ERK pathway that is upregulated by sepsis. Recently we reported that pretreatment with the nontoxic immunomodulator MPLA prevents inhibition of HCO_3^- absorption by LPS through activation of a TLR4-TRIF-PI3K pathway that prevents LPS-induced activation of IRAK-1. Here, we examined the molecular mechanism by which MPLA pretreatment suppresses IRAK-1 activation. We investigated the role of Tollip, an inducible intracellular protein that negatively regulates LPS signaling by inhibiting activation of IRAK-1 downstream of TLR4. The expression and functional significance of Tollip in renal tubules are undefined.

Methods: .

Results: We found that treatment with MPLA in vitro increased Tollip protein level in mouse and rat MTALs and that the increase in Tollip expression occurs within a time frame (2 h) sufficient to account for the effect of MPLA pretreatment to inhibit LPS-induced IRAK-1 activation. The MPLA-induced increase in Tollip expression was prevented by PI3K inhibitors. In coimmunoprecipitation experiments in inner stripe of outer medulla, treatment with MPLA increased the amount of IRAK-1 stably bound to Tollip, an interaction shown to inhibit IRAK-1 activation after LPS stimulation. Treatment of mice with MPLA increased Tollip protein level in the MTAL and this increase was prevented by administration of a PI3K inhibitor. Thus, the ability of MPLA to upregulate Tollip expression in the MTAL in vitro translates to the MTAL in vivo.

Conclusions: We conclude that pretreatment with MPLA increases expression of Tollip in the MTAL through a PI3K-dependent pathway. Tollip, in turn, inhibits LPS-induced TLR4 signaling by suppressing activation of IRAK-1, thereby preventing downstream activation of ERK that inhibits HCO_3^- absorption. These results provide new evidence that MPLA induces immune reprogramming of MTAL cells that protects against LPS stimulation and that Tollip can function as an endogenous negative regulator of inflammatory TLR4-IRAK-1 signaling in renal tubule epithelial cells. Strategies targeted to manipulate Tollip expression may aid in protecting renal tubule function against infectious and inflammatory challenge.

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SA-PO302

AQP11 Deficiency Impairs Thymus Development Possibly Through Defective Fat Metabolism

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Background: Aquaporin11 (AQP11) is a superaquaporin permeable to both water and glycerol. AQP11 null mice suffer from polycystic kidneys and die within a month after birth due to uremia. Although AQP11 is expressed widely, it is most abundantly expressed in the thymus and testis. The purpose of this study is to clarify the role of AQP11 in the thymus.

Methods: Immunohistochemistry and microarray analysis with RT-qPCR.

Results: The immunohistochemical analysis revealed the AQP11 expression at the stromal-epithelial cells in the thymus medulla. Surprisingly, the size of the thymus from AQP11 null mice was much smaller than that of the wild mice by half and sometimes by 10%. The vacuolated medullary epithelial cells were observed in the thymus of AQP11 null mice with a normal cortico-medullary structure. The microarray analysis of the gene expression in the thymus was compared between AQP11 null mice and the wild mice by the annotation analysis based on the David Bioinformatics Resources 6.8(beta). We identified 1.5 or more up-regulated 66 genes which mainly participate in the PI3K/Akt signaling pathways to promote metabolism, proliferation, cell survival, growth and angiogenesis. We also found 0.5 or less down-regulated 55 genes, some of which are regulated by the peroxisome proliferator-activated receptor (PPAR) signaling pathway which is activated by fatty acids and their derivatives. RT-qPCR analysis confirmed the enhanced expression of Egfr (Epidermal Growth Factor Receptor), Itgb4 (Integrin beta-4) and Il2ra (interleukin 2 receptor alpha) and the diminished expression of AQP7, Pck1 (Phosphoenolpyruvate carboxykinase 1) and Ucp1 (Mitochondrial uncoupling protein 1). The up-regulated genes for growth signaling may support the survival of the regressed thymus while the down-regulated genes may cause deleterious effects on fat-glucose-energy metabolism in the thymus. The decreased aquaglyceroporin AQP7 in AQP11 null thymus may further compromise the glycerol accumulation leading to the thymus regression.

Conclusions: As the role of AQPs to support memory T cells through glycerol transport has been reported (Cui G et al. Cell. 161:750, 2015), such may also be working in the thymus development. AQP11 may also play an important role in the metabolic control of the thymus.

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SA-PO303

The CaSR Signals Through CDC42, MKK6, and p38 to Inhibit SP1, a Repressor of Claudin-14 Expression

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Background: Urinary calcium (Ca^{2+}) excretion increases in direct response to elevated plasma [Ca^{2+}], independent of hormonal signalling, by attenuating paracellular Ca^{2+} reabsorption from the thick ascending limb (TAL). This occurs via sensing plasma [Ca^{2+}] by the calcium sensing receptor (CaSR) expressed in the basolateral membrane of the TAL. This increases expression of the tight junction protein claudin-14, which blocks paracellular Ca^{2+} reabsorption. This pathway is inappropriately activated in some kidney stone formers, causing their disease. However, the signalling pathway between CaSR activation and increased claudin-14 transcription is unknown.

Methods: We identified the renal *CLDN14* transcript variant regulated by CaSR activation via quantitative PCR, using specific primers to the different variants on cDNA isolated from kidneys of mice treated with cinacalcet. We cloned the promoter region of this gene into a luciferase reported construct. This region also contained elements responsive to cinacalcet. We used this tool to delineate the signalling pathway downstream of CaSR activation.

Results: The region 1500 bp 5' to the 1st transcript variant when transfected in HEK293 cells contained promoter activity. Further, this region displayed more than double reporter activity in the presence of the CaSR and cinacalcet, but not in the absence of the CaSR. Increasing extracellular [Ca^{2+}] similarly increased reporter activity in the presence, but not the absence, of the CaSR. A prior microarray found increased renal MKK6 and *CLDN14* expression in mice treated with cinacalcet. However, expression of MKK6 reduced *CLDN14* reporter activity after cinacalcet treatment. MKK6 can signal through JNK or p38 MAPK. Inhibition of p38 but not JNK enhanced the cinacalcet

mediated increase in CLDN14 reporter activity. Sp1, a known downstream effecter of p38, was down regulated by CaSR activation, and co-expression attenuated the effect on the reporter construct. Upstream activation of MKK6 is through CDC42, as dominant-negative CDC42 attenuated reporter activity.

Conclusions: CaSR activation increases *CLDN14* transcription via signalling through CDC42, MKK6 and p38 to attenuate the expression of SP1 a repressor of *CLDN14*.

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SA-PO304

Is Claudin 16 Required for the Effect of Parathyroid Hormone (PTH) and Calcium Sensing-Receptor (CaSR) on Calcium and Magnesium Reabsorption in the Cortical Thick Ascending Limb?

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Background: The cortical thick ascending limb of the loop of Henle (CTAL) reabsorbs 25% of the filtered calcium (Ca) and 70% of the filtered magnesium (Mg), along the paracellular pathway. The expression of claudin 16 (Cldn16) at the tight junction is required for a normal paracellular permeability and selectivity to Ca and Mg. Loss-of-function mutations of Cldn16 in the CTAL cause familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC). No specific treatment has been developed so far. PTH increases Ca and Mg transport and CaSR decreases Ca transport across the CTAL but the mechanisms involved are imprecise. Recent studies suggested that both PTH and CaSR agonists act on Cldn14, which may control Cldn16 function and/or expression and, eventually, paracellular reabsorption of Ca and Mg. Our objective was to assess whether Cldn16 is actually involved in the effect of PTH and CaSR on Ca and Mg reabsorption in CTAL.

Methods: CTAL dissected from $Cldn16^{+/+}$ and $Cldn16^{-/-}$ male mice were microperfused *in vitro* to measure transepithelial ions absorption under symmetrical conditions. Measurements were made under control condition and after addition of PTH (10^{-10} M) or of the CaSR antagonist NPS2143 (10^{-6} M).

Results: PTH and NPS2143 increased Ca reabsorption in $Cldn16^{+/+}$ CTAL (+44 %, n= 5, p=0.06; and +23 %, n= 7, p=0.047, respectively) and $Cldn16^{-/-}$ CTAL (+37 %, n=8, p=0.02; and +59 %, n=7, p=0.02, respectively). PTH increased Mg reabsorption in $Cldn16^{+/+}$ CTAL (+57 %, n=7, p=0.03) and in $Cldn16^{-/-}$ CTAL (+27%, n=5, p=0.06). The effect of NPS2143 on Mg reabsorption is currently under study.

Conclusions: Cldn16 is not necessary for the effect of PTH and CaSR on Ca reabsorption by native CTAL. Cldn16 is not necessary for the effect of PTH on Mg reabsorption by native CTAL. Our results suggest that the current model describing the effect of PTH and CaSR on Cldn16 might not be accurate. Our results constitute a proof of concept to develop new therapeutic strategies based on CaSR inhibitor and/or PTH receptor agonist for FHHNC.

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SA-PO305

Colocalization of Claudin-10 with Other Transport Proteins in Basolateral Infoldings of the Thick Ascending Limb

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Background: The nephron is the structural and functional unit of the kidney and is composed of renal tubular segments. The thick ascending limb (TAL) of the loop of Henle is the essential segment for salt homeostasis and urinary concentration. The TAL originates from medullary and cortical nephron and share the basic transcellular transport mechanism that involve cotransport of sodium (Na^+), potassium (K^+) and chloride (Cl^-) and paracellular cation permeability. The selectivity of the paracellular pathway is determined by the combination of claudin protein expression in the tight junctions (TJ). In the TAL, TJs showed a mosaic expression of either claudin-10 or claudin-3/claudin-16/claudin-19 in a complex. TJ dominated by claudin-10 confer mainly paracellular Na^+ permeability. Interestingly, claudin-10 immunofluorescence showed also an extra-junctional localization in the basolateral region of the cells.

Methods: Freshly isolated single murine TAL segments of C57Bl6 and kidney specific (Ksp-Cre) Claudin-10 knockout mice were investigated by immunofluorescence and analyzed by *stimulated emission depletion* (STED) and Airyscan confocal microscopy.

Results: We performed triple staining with claudin-10, Na^+/K^+-ATPase (NKA) and the chloride channel subunit Barttin, which are both known to be prominent proteins in the basolateral TAL membrane. Antibody staining revealed the localization of all proteins in the infoldings of the basolateral membrane. Claudin-10 thereby showed a dotted pattern.

Conclusions: Claudin-10 shows extra-junctional expression and colocalization together with tramsmebrane transport proteins NKA and Barttin in the basolateral infoldings of TAL. This suggests a functional complex that facilitates or regulates ion transport function.

SA-PO306

Claudin 10b Is a Target for Parathyroid Hormone (PTH) in the Cortical Thick Ascending Limb (CTAL)

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Background: In the CTAL, 25% of the filtered calcium is reabsorbed, along the paracellular pathway; the reabsorption is driven by the lumen-positive transepithelial voltage (Vte). Vte depends on the back diffusion of sodium (Na) along the paracellular pathway. The expression of claudin 10b (Cldn10b) at tight junction makes the paracellular permeability to Na (P_{Na}) greater than that of chloride (P_{Cl}). PTH increases calcium reabsorption across the CTAL but the mechanisms involved are uncertain. We assessed whether the effect of PTH in the CTAL involves Cldn10b, which determines Vte and P_{Na}/P_{Cl}, and aimed at identifying the underlying mechanisms.

Methods: CTAL dissected from $Cldn10^{+/+}$ and $Cldn10^{-/-}$ male mice were microperfused *in vitro* to measure Vte and P_{Na}/P_{Cl} under asymmetrical conditions with 0.1 mM furosemide in the lumen. All measurements were made under control and/or after peritubular addition of PTH (10^{-10} M), phorbol 12-Myristate 13-Acetate (PMA, 10^{-6} M), dibutyryl cAMP (dbcAMP 5.10^{-4} M), ionomycin (10^{-7} M), PKI 14-22 amide (a protein kinase A inhibitor, 10^{-6} M), trifluoroperazine (TFP, a calcium-calmodulin kinase antagonist, 10^{-4} M), or Dyngo4a (a clathrin-mediated endocytosis inhibitor, 10^{-5} M). The ratio of permeabilities P_{Na}/P_{Cl} was calculated according to the Goldman-Hodgkin-Katz equation.

Results: PTH significantly increased P_{Na}/P_{Cl} in $Cldn10^{+/+}$ CTAL (p=0.0002) but not in $Cldn10^{-/-}$ CTAL. This effect was reproduced by dbcAMP (p=0.02) and ionomycin (p=0.047), but not by PMA. PKI, TFP and Dyngo4a inhibited the effect of PTH on P_{Na}/P_{Cl}.

Conclusions: We conclude that, in the mouse CTAL, PTH increases P_{Na}/P_{Cl} via a cAMP-, and calcium calmodulin kinase-dependent effect on Cldn10b. Inhibition of the clathrin-mediated endocytosis prevents this effect. Our results show that the properties of intercellular tight junctions can be directly and rapidly altered by intracellular signaling pathways and changes in intracellular protein trafficking.

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SA-PO307

Low Gut Microbiota Diversity and Dietary Magnesium Intake Are Associated with the Development of Proton Pump Inhibitor-Induced Hypomagnesemia

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Background: Proton pump inhibitors (PPIs) are used by millions of patients for the treatment of stomach acid-reflux diseases. Long-term PPI intake has been associated with serious adverse effects including enteric and respiratory infections, acute kidney injury (AKI) and chronic kidney disease (CKD). In addition, it has become increasingly evident that long-term PPI use induces hypomagnesemia (serum magnesium (Mg^{2+}) levels < 0.7 mmol/L). Despite rising attention for this issue, the underlying mechanism is still unknown. Recent studies have identified associations between PPI use and gut microbiota. Here, we examined whether the gut microbiome is involved in the development of PPI-induced hypomagnesemia.

Methods: To assess the effects of the PPI omeprazole on Mg^{2+} homeostasis and gut microbiota, C57BL/6J mice were treated daily with omeprazole (20 mg/kg bodyweight) or placebo for four weeks under normal (0.22 % w/w) or low (0.05 % w/w) dietary Mg^{2+} availability. Subsequently, Mg^{2+} homeostasis was assessed by means of serum, urine and faecal electrolyte measurements, RT-qPCR to evaluate renal and intestinal Mg^{2+}-related genes, and gut microbiota composition was investigated by 16S rRNA gene sequencing.

Results: After four weeks of treatment, omeprazole significantly reduced serum Mg^{2+} levels in mice on a low Mg^{2+} diet. Renal *Trpm6* expression was increased as compensation for the low Mg^{2+} diet in placebo-treated mice, but expression of this Mg^{2+} channel was not changed in the omeprazole-treated group. Moreover, these mice did not exhibit urinary Mg^{2+} wasting. Overall, 16S rRNA gene sequencing revealed a lower gut microbial diversity in omeprazole-treated mice. Omeprazole induced a shift in microbial composition that was associated with a 3- and 2-fold increase in the abundance of *Lactobacillus* and *Bifidobacterium*, respectively. To examine the metabolic consequences of these microbial alterations, the colonic composition of organic acids was evaluated. Low dietary Mg^{2+} intake, independent of omeprazole treatment, resulted in a 10-fold increase in formate levels.

Conclusions: Our results imply that both omeprazole treatment and low dietary Mg^{2+} intake disturb the gut internal milieu and may pose a risk for the malabsorption of Mg^{2+} in the colon.

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SA-PO308

Impaired Lymphatic Vessel Function Contributes to Edema in Nephrotic Syndrome

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Background: Edema is a cardinal feature of nephrotic syndrome (NS) although the underlying mechanisms are incompletely understood. Lymphatic vessels transfer fluids, solutes, and macromolecules from the interstitial space back into the circulation. We examined the structure and function of lymphatics in the puromycin aminonucleoside (PAN) model of NS.

Methods: PAN was induced in Sprague Dawley rats, while non-injected rats served as controls (Cont). Eight days later, blood, urine, renal and mesenteric lymph, kidney and ileum were analyzed. Renal lymphatic vessels were isolated, cannulated and mounted in a perfusion chamber to assess vasoactivity.

Results: PAN caused the expected proteinuria, hypoalbuminemia, hyperlipidemia and generalized edema including in the kidney and ileum. Compared to Cont, PAN increased lymphangiogenesis, reflected by significantly increased gene expression of podoplanin (1.7-fold), VEGFR3 (2.1-fold) and the number of lymphatic vessels. VEGF-C, the major growth factor for lymphangiogenesis was elevated (2.1-fold) and lymph contained significantly more VEGF-A (2.0-3.1-fold) in PAN vs Cont. Lymphatic endothelial cells (LEC) isolated from mesenteric collecting vessel showed significantly increased gene expression of VE-cadherin (2.2-fold) while ileal LECs had increased ZO-1 (2.7-fold) indicating intercellular junction transition from button to zipper type. Isolated renal collecting lymphatic vessels from PAN showed significantly increased vessel diameter (15%), deceased contraction frequency (30%), and reduced sensitivity to endothelial NO inhibitor (L-NAME), NO donor (sodium nitroprusside), and thromboxane A agonist (U46619).

Conclusions: Although edema-forming kidney injury increases the number of lymphatic vessels, this compensation is inadequate, and edema rather reflects impaired vessel function, e.g., reduced lymphatic vessel contractility and reabsorptive capacity that may be novel targets in edema-forming disorders.

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SA-PO309

Calcium Citrate Incorporated into Calcium Carbonate and Calcium Carbonate Nanoparticles Alleviate Cellular Injury from Acidosis

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Background: Metabolic acidosis is a common complication found in patients with chronic kidney disease (CKD), and causes cellular dysfunctions, protein degradation, inflammation, oxidative stress and cell death. Current medication to treat metabolic acidosis is the supplementation of alkalinizing agents such as sodium bicarbonate and sodium citrate. We proposed new nanoparticles as the adjuvant therapy to mitigate the consequences of metabolic acidosis in CKD patients.

Methods: Calcium citrate incorporated into calcium carbonate nanoparticles (CCNP) and calcium carbonate nanoparticles (CNP) were synthesized from calcium chloride and sodium citrate. A HK-2 cells cultured in DMEM with pH 7.4 (normal environment) and 4.0-5.0 (acidosis environment) were used to study the cellular toxicity by Resazurin oxidative-reduction assay, intracellular reactive oxygen species (ROS) production by 2,7-dichlofluorescein-diacetate (DCFH-DA) test, and cell death by flow cytometry. Fluorescence isothiocyanate (FITC) conjugated CCNP and CNP were used to study cellular uptake. Intracellular and extracellular bicarbonate concentration were measured by automated biochemical analyzer. Sodium citrate (Nacit) was used as a standard drug in these experiments.

Results: CNP and CCNP had very low cytotoxicity at the concentration up to 1 mg/ml. The results showed that CNP and CCNP did not alter the extracellular pH, or extracellular and intracellular bicarbonate concentration, and they were freely uptake into the cell in normal and acidic condition. Pharmacological tests revealed that both CNP and CCNP can suppress ROS production better than sodium citrate treatment. In addition, CNP and CCNP treatment ameliorated acidosis-induced cell death and apoptosis.

Conclusions: CNP and CCNP mitigates the consequences of metabolic acidosis, as they could reduce ROS production and cell death in acidic environment. Because they did not alter pH and bicarbonate concentration, they could be potentially used as the adjuvant therapy with alkalinizing agents to treat metabolic acidosis in CKD patients. A study of *in vivo* effects of these nanoparticles is ongoing.

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SA-PO310

Interdialytic Creatinine Rise as a Predictor of Hospital Length of Stay and Cause of Shortness of Breath in ESRD Patients

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Background: The Interdialytic Creatinine Rise (IDCR), calculated as the change in serum creatinine over time, in mg/dL/h, has been proposed as a novel marker of volume status and mortality in patients with end-stage-renal-disease (ESRD). We wanted to determine if IDCR was associated with the hospital length of stay (LOS), a metric reflecting the opposing factors of hospital efficiency and patient risks. We also studied a subgroup of patients in order to evaluate the relationship of IDCR to the cause of their shortness of breath (SOB).

Methods: This was a prospective cohort study of 142 ESRD patients on hemodialysis admitted to our institution who were followed from admission until discharge. IDCR was calculated as the difference in two serum creatinine values divided by the time between the samples. LOS and potential confounders of age, gender, race, cirrhosis, active cancer, left ventricular ejection fraction (LVEF) <40%, and insurance status were recorded. A sub-cohort of 53 patients admitted due to SOB as documented in emergency room records was divided into two groups according to the cause of SOB documented in the discharge summary, as SOB due to volume excess or not. The data was analyzed using univariate analyses, multiple regression, and multiple logistic regression.

Results: IDCR is negatively associated with LOS (Spearman correlation= –0.245; p=0.003). Adjusting for the significant covariates of age, gender, race, LVEF<40 and insurance, IDCR is negatively associated with LOS; so that for every 0.021 mg/dL/h increase in IDCR, LOS decreases by 1 day (95%CI -1.6,-0.4; p=0.002). In the subset of patients with SOB, 11 patients had SOB unrelated to volume excess and 42 patients had SOB due to volume excess, with significantly different respective IDCRs of 0.09 and 0.06 (Wilcoxon's Rank Sum Test; p=0.018). Adjusting for the significant covariate of age, when IDCR increases by 0.03 the odds ratio of SOB being unrelated to volume excess is 2.45 (95% CI 1.23, 5.80; p=0.02).

Conclusions: Our study showed that ESRD patients with lower IDCR values due to volume overload or decreased creatinine production have increased LOS, likely due to their higher risk. In ESRD patients admitted with SOB, higher IDCR values are more likely to exclude hypervolemia as the cause of SOB.

SA-PO311

The Role of the JAK2/STAT3 Pathway Activated by IL-22 in Angiotensin II-Induced Hypertensive Renal-Damage Mice

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Background: $CD4^+$ T cells and the secreted inflammatory cytokines contribute to the progress of hypertensive renal damage. Previously, we found that blood Th22 cells and its effect factor IL-22 increased significantly in hypertensive renal damage patients, and were positively correlated with renal pathological damage. It is reported that IL-22 binds to receptor IL-22R and activates JAK2/STAT3 pathway. Th22 cells and its secreted cytokine IL-22 may play a promoting role in hypertensive renal damage, however the effects and mechanisms remain unclear.

Methods: Angiotension II (Ang II) was infused subcutaneously at a rate of 1.5 mg/kg/d to C57BL/6 mice for 28 days. Hypertensive mice were treated with recombinant IL-22 (rIL-22), anti-IL-22 neutralizing antibody, IgG control and JAK2/STAT3 pathway blocker AG-490. Blood pressure (BP), serum creatinine (Scr), urinary albumin/creatinine ratio (UACR) and renal histopathology were measured; renal Th22 cells proportion were detected by flow cytometry; inflammatory factors were evaluated by ELISA, and JAK2/STAT3, fibrotic related factors were detected by western blot.

Results: 1. Expression of IL-22/IL-22R and infiltrated Th22 cells proportion in kidney were elevated in Ang II-induced hypertensive mice; 2. Treatment with rIL-22 resulted in further elevated BP, UACR, renal Th22 and IL-22, renal pathological damage and inflammatory responses, and increased renal fibrosis and JAK2/STAT3 pathway activation, compared to hypertensive mice treated by Ang II alone; 3. In contrast, treatment with the anti-IL-22 antibody decreased BP, UACR, renal Th22 and IL-22 and renal pathological damage, also attenuated renal inflammation, fibrosis and JAK2/STAT3 pathway activation.

Conclusions: 1. Recombinant IL-22 may activate JAK2/STAT3 pathway by binding to IL-22R in kidney, increase BP, aggravate immune inflammation and renal fibrosis in Ang II infused hypertensive mice; 2. Anti-IL-22 neutralizing antibody can reduce BP, inflammation and renal fibrosis in hypertensive kidney damage, which may be through inhibiting the activation of JAK2/STAT3 pathway.

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SA-PO312

Whole-Exome Sequencing and Monogenic Hypertension in a Multiethnic Cohort

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Background: A subset of hypertension (HTN) may be caused by monogenic mutations. We identified the prevalence of these mutations in a multiethnic cohort and determined their association with blood pressure, appropriate diagnosis, and adverse cardiovascular outcomes.

Methods: In 27,972 individuals from the Bio*Me* Biobank (8304 European, 6993 African, 9985 Hispanic, and 2690 Other ancestry), we identified ClinVar mutations pathogenic for secondary hypertension using exome sequencing. We conducted association analyses with mean arterial pressure and coronary artery disease (CAD)/congestive heart failure (CHF) and assessed whether individuals with mutations had appropriate diagnosis/evaluation.

Results: 3125 individuals (11.2%) had pathogenic mutations with a majority in genes associated with catecholamine excess (*SDHD, SDHB, TMEM127, RET*; n=1976) and sodium handling/hyperaldosteronism (*SCNN1G/ CYP11B1*; n=384). (Fig 1A,B). Individuals with mutations had elevated mean arterial pressure (b=0.7±0.6 mmHg;

p=0.03) and increased odds of CAD (adjusted OR=1.12, 95% CI 1.0 to 1.3, p=0.04) adjusting for sex, age, BMI, and 10 genetic principal components (PCs). Individuals with mutations in sodium handling/hyperaldosteronism genes had increased CHF (adjusted OR = 1.44, 95% CI 1.04 to 1.9; p=0.02) adjusted for age, sex, 10 PCs, and blood pressure. The majority of individuals with mutations were diagnosed with essential HTN (54.2%) and only 7.8% had appropriate diagnoses of secondary HTN or received appropriate biochemical evaluation. (Figure 1C)

Conclusions: Individuals with pathogenic mutations had higher blood pressures and elevated risk for CAD/CHF. The majority were not appropriately evaluated/diagnosed. These results suggest exome sequencing may have utility in hypertension diagnosis and management.

Funding: NIDDK Support

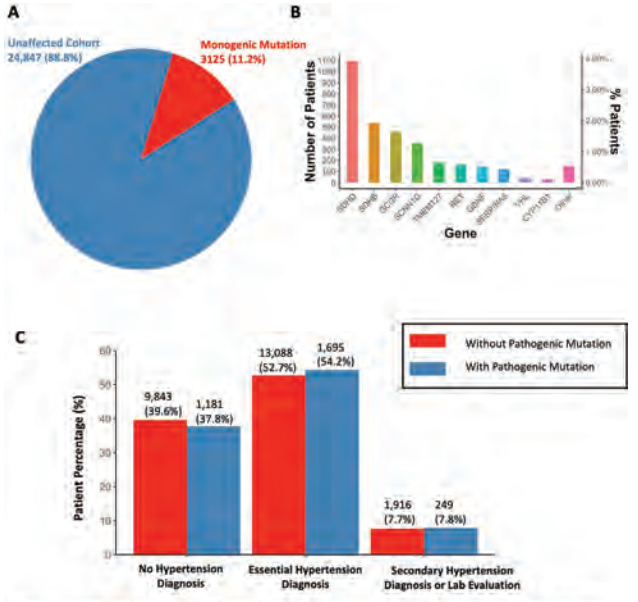

Figure 1 Prevalence of Pathogenic Mutations A. Proportion on individuals with mutation at least once loci cureated by ClinVar as pathogenic for secondary hypertension. **B.** Top 10 genes corresponding to mutations with greatest number of affected individuals. **C.** Percentage of individuals with no hypertension diagnosis, essential hypertension diagnosis, or secondary hypertension diagnosis/lab evaluation stratified by mutation status. Percentages indicate percent of individuals in each diagnosis group relative to the total number of people with or without pathogenic mutations.

SA-PO313

A Role for Toll-Like Receptors and Their Endogenous Ligands in CKD-Associated Cardiovascular Disease?

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Background: Cardiovascular disease (CVD) is greatly precipitated by chronic kidney disease (CKD). Overall, there is an approximately 20-fold increase in CVD mortality among CKD patients on dialysis compared with the general population. Traditional risk factors do not account for the high cardiovascular risk in CKD and standard clinical interventions are not always effective. CKD specific factors, such as anaemia, mineral metabolism disorders and the presence of uremic toxins are believed to be partially responsible. The inflammation associated with kidney tissue damage or the dialysis process has been suggested to play a substantial role in the onset and progression of CVD, however, it has yet to be demonstrated and the mechanisms elucidated. Kidney damage has been shown to lead to the local production of Damage Associated Molecular Patterns (DAMPs) that act as endogenous ligands of TLRs. We hypothesise that the TLR DAMPs being generated during CKD reach the circulation where they engage TLRs on the peripheral leukocytes and/or endothelial cells, inducing chronic vascular inflammation and dysfunction that promotes and/or accelerates CVD development.

Methods: Combination of ex vivo, in vitro and in vivo techniques

Results: A range of known TLR DAMPs were quantified in plasma from stage 5 CKD patients (n=40) at the start of PD and compared to the levels found in healthy individuals (n=30). Heat-shock protein (Hsp) 60, Hsp70, hyaluronic acid and calprotectin (S100A8/S100A9) were found significantly elevated in CKD patients. *In vitro* experiments were conducted to assess the ability of each of these TLR DAMPs to affect cellular responses related to initiation and progression of atherosclerosis. (expression of adhesion molecules by endothelial cells and monocytes, production of cytokines and chemokines, phagocytosis of oxidised LDL by macrophages). In preliminary *in vivo* experiments, chronic kidney injury was induced by repeated administration of the nephrotoxin aristolochic acid in mice prone to CVD development (LDL receptor deficient) to confirm the findings made *in vitro* and *ex vivo*.

Conclusions: Our preliminary results reveal significantly increased levels of several known TLR DAMPs in plasma from patients with late stage CKD. In ongoing work the role that these DAMPs and their interaction with TLRs may play in initiating or worsening atherosclerosis development is being investigated.

Funding: Government Support - Non-U.S.

SA-PO314

The Effect of the Sodium-Glucose Co-Transporter-2 Inhibitor in Angiogenesis of Diabetic Cardiovascular Disease

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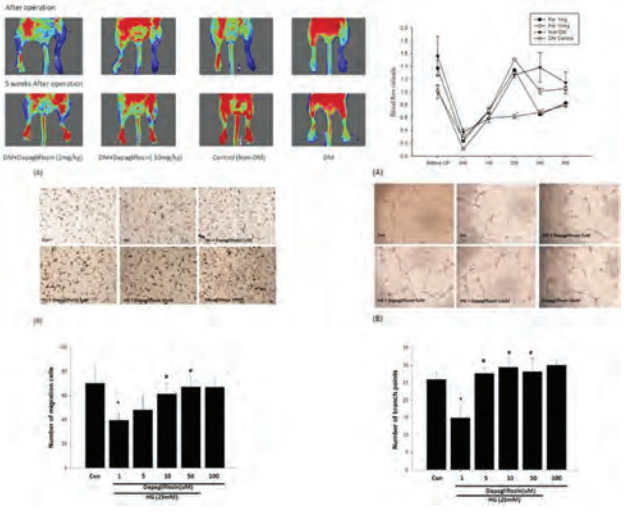
Background: Diabetic patients with peripheral arterial occlusive disease (PAOD) are at high risk from cardiovascular events, vascular death and ischemic ulceration. The most importantl induction of collateral vessels is essential to the initiation of angiogenesis. A sodium–glucose co-transporter-2 (SGLT-2) inhibitor (Dapagliflozin), is a novel class of antihyperglycaemic agent. In present study, we can evaluate the effects of SGLT2 inhibitors in diabetic mice with PAOD by cell and animal studies.

Methods: Chronic hind-limb ischaemia (15 mice) by ligating and transecting the left common femoral artery. **Laser Doppler measurement of tissue blood flow** to detect hind-limb blood flows **Human Endothelial progenitor cell culture** were cultured in 5% CO2 at 370C in cell growth medium. Cells from passages 4–8 were used for all experiments. **MTT assay** Cells were treated with variable concentration of dapagliflozin for 24 hours with hydrogen peroxide, washed with phosphate buffered solution, incubated in a conditioned medium for 1 hour with 2 μg/mL MTT, and then were lysed. Absorbance was measured at 570 nm using a spectrophotometric microplate reader (Multiskan EX, Labsystems; Helsinki, Finland). **EPC migration assay** was evaluated by a modified Boyden chamber assay. The magnitude of migration of late EPCs was evaluated by counting the migrated cells in six random high-power fields. **EPC tube formation assay** was performed with an In Vitro Angiogenesis Assay Kit(Chemicon). The average of the total area of complete tubes formed by cells was compared by using computer software, Image-Pro Plus.

Results: Dapagliflozin enhanced flow recovery in diabetic mice. Treatment of EPCs with dapagliflozin significantly increased tube formation and up-regulated impaired eNOS production and Akt action in hyperglycemic

Conclusions: SGLT-2 inhibitor improves blood flow recovery in diabetic mice with hind limb ischemia and promotes the functions of EPCs via NO-related pathways.

Funding: Government Support - Non-U.S.



SA-PO315

Myeloid PTEN Deficiency Exacerbates Renal Inflammation and Fibrosis in Angiotensin II-Induced Hypertension

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Background: Hypertension is a major cause of chronic kidney disease, which is characterized by inflammation, tubular atrophy, and fibrosis. However, the molecular mechanisms that are responsible for the induction of inflammation and fibrosis are not fully understood. In the present study, we examined the role of phosphatase and tensin homolog (PTEN) in the pathogenesis of renal inflammation and fibrosis in an experimental model of hypertension.

Methods: We generated myeloid cell-specific PTEN knockout mice by crossing floxed PTEN mice with LysM-driven Cre mice. Both LysM-Cre-/-PTENf/f mice and LysM-Cre+/+PTENf/f mice were infused with angiotensin II at 1.5ug/kg/min or vehicle for 28 days. To accelerate renal injury, all mice were subjected to unilateral nephrectomy and received 1% sodium chloride in drinking water. Blood pressure was monitored by BP-2000 system. Renal function was evaluated by measuring serum creatinine. Proteinuria was quantified by measuring albumin and creatinine in the urine. Kidney sections were stained for histological and immunological analysis. Western blot analysis and

immunostaining were performed to detect the levels of fibronectin, collagen type I, and alpha-SMA in the kidneys. Sirius red staining was performed to examine total collagen deposition in the kidney.

Results: Both LysM-Cre-/-PTENf/f mice and LysM-Cre+/+PTENf/f mice had comparable blood pressure at baseline. Angiotensin II treatment led to an increase in blood pressure that is similar between LysM-Cre-/-PTENf/f mice and LysM-Cre+/+PTENf/f mice. Compared with LysM-Cre-/-PTENf/f mice, LysM-Cre+/+PTENf/f mice developed significantly worse renal dysfunction, proteinuria, and fibrosis following angiotensin II treatment. PTEN deficiency in myeloid cells enhanced myeloid fibroblast accumulation and myofibroblast formation associated with a significant increase in total collagen deposition and extracellular matrix protein production in the kidneys in response to angiotensin II. Immunohistochemical analysis revealed that PTEN deficiency in myeloid cells augmented infiltration of F4/80$^+$ macrophages and CD3$^+$ T cells into the kidneys of angiotensin II-treated mice.

Conclusions: PTEN plays a crucial role in the development of hypertensive kidney inflammation and fibrosis trough regulation of macrophage and T cell infiltration and myeloid fibroblast accumulation.

Funding: NIDDK Support

SA-PO316

Grain vs. Casein-Based Diet Differentially Impact Angiotensin II Hypertension (AngII-HTN) Responses in Female vs. Male Sprague Dawley Rats

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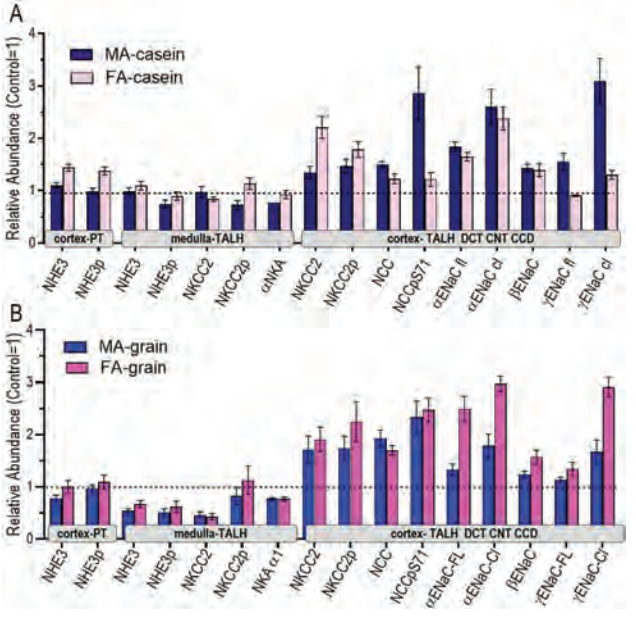
Background: We previously reported that the baseline renal transporter profile in females (F) is distinct from that in males (M), specifically: lower PT NHE3 activity, NaPi2, claudin 2 and AQP1, and higher DT NCC, SPAK, claudin 7 and cleaved γENaC abundance in F vs. M. We reported that F and M rats respond differentially to AngII-HTN (400 ng/kg/min for 14 days) when fed casein-based diet (Envigo TD 88239, 0.74% NaCl, 2% KCl). In F, abundance of cortical NHE3, NHE3p, NKCC2, and NKCC2p were increased, and NCC, NCCp, and cleaved γENaC were unchanged, while in M, abundance of cortical NHE3, NHE3p, NKCC2, NKCC2p were unchanged and NCC, NCCp and cleaved γENaC were increased (Fig A). Additionally, AngII-HTN increased proteinuria in M but not F despite similar HTN (~150 mmHg).

Methods: We aimed to determine if differential responses to AngII-HTN (as above) are also evident in SD rats fed grain based diet (LabDiet 5001), n=5 F and M.

Results: At baseline, in F fed casein (vs. grain) based diet, NHE3 and NHE3p are more abundant (1.27 ± 0.06 fold and 1.58 ± 0.15 fold) and NKCC2p and NCCp are less abundant (0.69 ± 0.04 and 0.7 ± 0.08), all p ≦ 0.01. M and F fed grain-based diet responded similarly to AngII-HTN (Fig B), with a pattern distinct from that in casein-fed rats: Cortical NHE3 decreased (M only), both M and F had significant decreases in abundance of medullary NHE3, NHE3p, NKCC2, NKA α1, and increases in cortical NKCC2, NKCC2p, NCC, NCCp and cleaved ENaC. Blood pressure and proteinuria were similarly increased in M and F on grain based diet.

Conclusions: In summary, diet impacts: 1) baseline Na transporter abundance, 2) Na transporters' regulation during AngII-HTN, and 3) AngII-HTN provoked proteinuria. Responses to AngII-HTN are similar in grain-based diet fed F and M.

Funding: NIDDK Support



SA-PO317

High Sodium Intake Impairs Afferent Renal Sympatho-Depressory Pathways in Rats

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Background: Afferent renal nerve pathways are likely involved in the development of salt sensitive hypertension. We recently reported that intrarenal NaCl elicited a long-lasting sympatho-depression via a neuro-humoral TRPV1 dependent and tachykinin mediated renal afferent nerve pathway. We now wanted to test the hypothesis that high sodium intake impairs this afferent sympatho-depressory mechanism.

Methods: Respective groups were put on tap water, 0.9 % saline for drinking or chow containing 8% NaCl. Cultured dorsal root ganglion neurons (DRG Th11-L2) of rats with renal afferents were investigated in current clamp mode to assess action potential generation during current injection. Rats with femoral catheters for blood pressure (BP) & heart rate (HR) assessment, drug application, a renal arterial catheter for intrarenal administration (IRA) of NaCl boli (10 % NaCl, 10 µl) or Capsaicin (CAP 3.3, 6.6, 10, 33*10-7 M, 10 µl) and a bipolar electrode for renal sympathetic nerve activity (RSNA) recordings; eventually an intravenous (iv) bolus of the NK1-receptor blocker RP67580 (10*10-3M, 15 µl) was administered. Results are mean±SEM.

Results: In neurons from rats on 8% NaCl, but not on 0.9 % saline or controls the relation of tonic highly active neurons to less active neurons shifted towards less active units. (62% tonic neurons in the control group and 63% tonic neurons in the saline group vs. 40%* tonic neurons in the high salt group, * p<0.05, z-test, mean +/-SEM). However, cultured renal neurons from rats on 0,9% saline or on 8% NaCl exhibited increased action potential production upon stimulation (controls 13,3+/11,03 APs/600ms vs. 0.9% saline 19,8+/-2,33* APs/600ms vs. high salt diet 22,2+/-4,54 APs/600ms, * p<0.05, t-test, mean+/-SEM). 10% NaCl boli IRA induced decreases of RSNA from baseline 4.1±0.6 µV*sec to 2.2±0.8 µV*sec impaired in rats on 8% NaCl. (Suppressed RSNA by an i.v. NK1-inhibitor).

Conclusions: In rats on a high salt diet the number of highly active tonic neurons with renal afferents in vitro decreased at the expense of less active phasic neurons in spite of tonic neurons producing more action potentials upon stimulation in the group on 8% NaCl. The sodium inducible long-lasting sympatho-depression via a neuro-humoral tachykinin mediated afferent renal nerve pathway was eventually impaired.

SA-PO318

Late-Onset Presentation of Severe Hypokalemic Hypertension Resistant to Mineralocorticoid Antagonism

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Introduction: We are presenting rare case of secondary hypertension who presented with muscle cramps and severe hypokalemia treated with ENaC (epithelium sodium channel) blocker

Case Description: A 45-year-old Caucasian lady was referred to clinic for management of refractory hypokalemia, uncontrolled blood pressure and metabolic alkalosis. She was complaining of intermittent muscle cramps. She was a healthy patient until 2017, when she was diagnosed with hypertension. Home medications were spironolactone 50 mg once daily, potassium chloride 20 mEq four times daily, clonidine 0.2 mg three times daily, lisinopril 20 mg once daily, amlodipine 10 mg, hydralazine 100 mg three times daily. There had been several emergency room visits for muscle cramps and uncontrolled blood pressure. Family history revealed mother died of heart attack at the age of 54 years. Father had problems of low potassium and a heart attack at a young age. Vitals revealed temperature of 98F, blood pressure 143/100 mmHg, heart rate 87 bpm, respiratory rate 16 per minute breathing on room air. Examination showed no edema and no abdominal bruits. Review of labs over the previous 2 months showed Na141-143, K 2.8-3.6, bicarbonate 23-27 mEq/L, BUN 6 mg/dL, creatinine 0.56 mg/dL, aldosterone 4.6 ng/dL and 5.4 ng/dL, plasma renin activity <0.6 ng/mL/h (checked twice), random cortisol was 0.6 – 4.6 ug/dL, urine potassium 13.5mEq/L. Renal ultrasound along with renal artery doppler, Echocardiogram, CT scan of head, MRI and MRA of the head and neck revealed with in normal findings. Stopped spironolactone and started amiloride 5 mg daily. Over the next few days, blood pressure dropped to ~100-120's/60-80's. Lisinopril, hydralazine, spironolactone and potassium supplements were stopped and clonidine was weaned off. Follow up labs in one week after starting amiloride showed potassium 4.2. Subsequently patient was advised to check blood pressure twice per day and closely followed

Discussion: Epithelial sodium channel blockade improved blood pressure and electrolyte abnormalities significantly suggesting either Liddle syndrome (autosomal dominant) or apparent mineralocorticoid excess (autosomal recessive) which typically present in childhood. Our case illustrates a rare cause of hypertension having at this age which is associated with hypokalemia and metabolic alkalosis that is not amenable to mineralocorticoid blockade

SA-PO319

Dietary Salt Modifies the Blood Pressure Response to Renin-Angiotensin Inhibition in Experimental CKD

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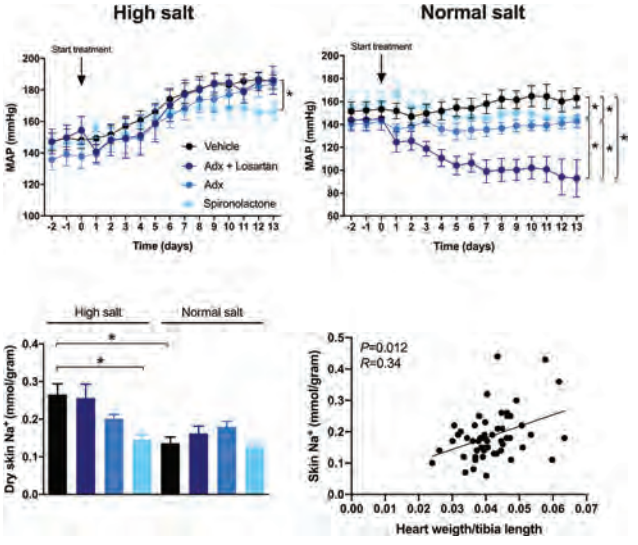
Background: Salt-sensitive hypertension is a hallmark of chronic kidney disease (CKD). The role of dietary salt and the renin-angiotensin system (RAS) in the pathogenesis of salt-sensitive hypertension in CKD is incompletely understood. Our aim was to dissect the role of dietary salt and the RAS in a rat model of hypertension and CKD.

Methods: Sprague Dawley rats were subjected to 5/6th nephrectomy, allowed to recover for four weeks, and subsequently subjected to one of four treatments: (1) vehicle, (2) adrenalectomy (Adx), (3) Adx + losartan (30 mg/kg/d), or (4) spironolactone (80 mg/kg/d). These interventions were performed either under normal dietary salt (0.4% NaCl) or high salt (4% NaCl) conditions. Mean arterial pressure (MAP) was measured by radiotelemetry, GFR by transcutaneous FITC-sinistrin clearance, and skin sodium (Na^+) by flame photometry after dissolving skins in nitric acid and hydrogen peroxide.

Results: 5/6th nephrectomy reduced GFR from 1.3 ± 0.4 to 0.4 ± 0.1 ml/min/100g. On a high salt diet, BP was resistant to RAS intervention, except for an attenuated BP rise in rats receiving spironolactone (Figure). On a normal salt diet, BP kept increasing with vehicle, but stabilized with Adx and spironolactone. Adx + losartan reduced BP remarkably. On a high salt diet, spironolactone prevented Na^+ accumulation in skin. For all groups, skin Na^+ correlated positively with heart weight.

Conclusions: High salt increases BP in CKD in part via direct effects on the mineralocorticoid receptor. Under normal salt conditions, however, hypertension in CKD depends on the combined effects of angiotensin II and aldosterone. Dietary salt modifies the BP response to RAS interventions in CKD, and accumulates in the skin. Our observations may have both therapeutic and prognostic implications for human CKD.



SA-PO320

The Effects of Sacubitril and/or Valsartan on Renal Disease Progression in Salt-Sensitive Hypertension

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Background: Available medications, such as diuretics and renin-angiotensin system (RAS) blockers, are often insufficient to control the blood pressure (BP) in the salt-sensitive (SS) hypertensive subjects. Abundant data support a pathogenic role for a low level of Atrial Natriuretic Peptide (ANP) in SS hypertension; ANP is known to promote salt excretion, vasodilation, and BP reduction. The goal of this project was to test if increasing the circulating ANP level using sacubitril in combination with a RAS blocker valsartan is beneficial for the alleviation of renal damage.

Methods: We performed chronic administration of sacubitril and/or valsartan at 75 ug/day to Dahl SS rats via an osmotic pump. All rats were fed a 0.4% NaCl (normal salt, NS) diet until 8 weeks of age, when they were challenged with a high salt (HS) 4% NaCl diet for 21 days. Vehicle, sacubitril (sacb), valsartan (val), or a 1:1 mix of both drugs (sacb/val) were administered together with HS diet; metabolic cage studies and GFR measurements were performed before the diet switch and at the end of the protocol.

Results: Upon a HS challenge, we observed renal hypertrophy reduction in the val group (p=0.047), and trend in the sac/val group (body weight was not affected). Urine flow was increased on HS diet compared to NS (p<0.01 for all groups), but not different between groups at the end of the protocol; we also observed a trend for lower water consumption in the sacb group. Upon a HS challenge, GFR was decreased in the control and elevated in the sacb/val and sacb groups; this increase was attenuated in the val treated animals. Interestingly, proteinuria was less pronounced in the sacb/val and val groups after 21 days on HS diet (vs control). In addition, we showed an increase in urinary KIM-1 in the control group, which was attenuated in the sacb/val and val animals.

Conclusions: Further mechanistic studies of the effects of sacubitril in the setting of SS hypertension are warranted in order to determine if pharmacological increase of circulating ANP level is a feasible therapeutic approach to interfere with the progression of the disease.

Funding: NIDDK Support

SA-PO321

Adrenal Hyperplasia, Hormonal Disturbance, and Salt-Sensitive Hypertension in a Novel Rat Model with Glucocorticoid Resistance Syndrome

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Background: Glucocorticoid resistance is often due to glucocorticoid receptor (GR) haploinsufficiency, and is characterized by partial target tissue resistance to glucocorticoids. In human, an elevation in circulating glucocorticoids may cause the development of hypertension and, in some cases, obesity and sterility.

Methods: So far, no animal model mimics all features observed in human generalized glucocorticoid resistance. To address the impact of GR haploinsufficiency on adrenal gland function, steroid expression and development of hypertension, we generated rats carrying a deletion within the second zinc finger of the GR, named $GR^{+/em2}$ (Ponce de León. V *et al*; Plos One, 2014).

Results: Heterozygous mutant $GR^{+/em2}$ rats showed a monolateral adrenal hyperplasia with hyperkalemia, an increase of plasmatic aldosterone (0,47 ± 0,018 nM vs 0,39 ± 0,019nM pm, p<0,01), plasmatic corticosterone (576 ± 88,96 nM vs 332 ± 75,45 nM am, p<0,05; 1000 ± 61,41 nM vs 615 ± 99,11 nM pm, p<0,05), plasmatic 11-deoxycorticosterone (76,6 ± 5,24 nM vs 50,3 ± 5,97 nM am, p<0,001; 101,8 ± 4,02 nM vs 74,6 ± 5,63 nM pm, p<0,01) despite a normal activity of the 11-β-hydroxysteroid-dehydrogenase II ($GR^{+/+}$= 15, $GR^{+/em2}$= 8). Furthermore, $GR^{+/em2}$ mutant rats develop salt-sensitive hypertension followed by an increase of adrenal and kidney weight. In addition, RNA-seq analysis reveals disturbances in **41 genes** (21 up, 20 down regulated) implicated in e.g, adrenal gland architecture and steroid biosynthesis. We currently focus on these identified candidate genes implicated in adrenal gland function and we perform electrophysiological measurements on primary adrenal cells upon stimulation with angiotensin II and potassium chloride to determine the cell depolarization capacity in these cells.

Conclusions: In summary, we demonstrated that $GR^{+/em2}$ mutant rats **are useful to study GR haploinsufficiency** and the underlying mechanism leading to adrenal gland hyperplasia. We confirm the role of the GR in the development of **salt-sensitive hypertension**. We are currently studying identified new candidate genes leading to salt-sensitive hypertension in this rat model.

Funding: Government Support - Non-U.S.

SA-PO322

Finerenone Improves Cardiovascular Benefits After Diet Normalization in a Mouse Model of High-Fat Diet-Induced Obesity

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Background: Patients with obesity exhibit high prevalence of Heart Failure with preserved Ejection Fraction (HFpEF). We hypothesized that the non-steroidal mineralocorticoid receptor (MR) antagonist Finerenone further improves cardiac function after normalisation of the diet in obese mice.

Methods: B6D2 male mice were fed a High Fat Diet (HFD) (60%) or maintained on normal diet (CTL). After 16 weeks, obese mice were divided in 3 groups for 8 more weeks with either: *i)* HFD; *ii)* normal diet (HFD-STOP); *iii)* normal diet plus Finerenone 1 $mg.kg^{-1}.day^{-1}$ in the food (HFD-STOP+FINE).

Results: After 16 weeks of HFD, mice showed an increased cardiac filling pressure (LV-End-Diastolic-Pressure, LVEDP: CTL 2.73±0.1, HFD 4.73±0.34 mmHg; P<0.001) and impaired LV compliance (LV-End-Diastolic-Pressure-Volume-Relation, LVEDPVR: CTL 1.19±0.26, HFD 4.77±0.31 mmHg/RVU; P<0.001) (without alteration of the LV Fractional Shortening) and reduced exercise ability in a stress-test on treadmill. These features are typical of HFpEF. Decreased LV Fractional Shortening developed if HFD is continued for 8 weeks more. Switching HFD to normal diet from weeks 16 to 24 improved LV compliance which was further improved by FINE (LVEDPVR: HFD-STOP 3.44±0.39, HFD-STOP+FINE 2.28±0.23 mmHg/RVU; P<0.05) as well as the reduction in LV fibrosis (% fibrosis: CTL 0.21±0.02, HFD 0.47±0.12, HFD-STOP 0.28±0.03, HFD-STOP+FINE 0.23±0.02 mmHg; P<0.05). Only the FINE treatment on top of diet normalisation improved LV filling pressure (LVEDP: CTL 2.73±0.16, HFD 4.73±0.34, HFD-STOP 4.53±0.33, HFD-STOP+FINE 3.18±0.26 mmHg; P<0.05), Fractional Shortening, Cardiac Output, Coronary Reserve (CR: CTL 3.76±0.72, HFD 1.00±0.33, HFD-STOP 1.19±0.25, HFD-STOP+FINE 2.78±0.67 $ml.mg^{-1}.min^{-1}$; P<0.05) and total runing distance. Renal function is not altered by HFD. Expression of some renal injury markers are increased by HFD and improved by HFD STOP without further additional effects of FINE.

Conclusions: When administered on top of diet normalisation after HFD-induced obesity, Finerenone improved LV compliance, LV filling pressure, Coronary Reserve and

exercise performance thereby indicating benefit of Finerenone in HFpEF associated to HFD in mice.

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

SA-PO323

Windkessel Modeling-Based Estimation of Intraglomerular Pressure Using Invasively Measured Renal Arterial Pressure and Flow Velocity in Humans

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Background: Glomerular hyperfiltration due to a combination of failed autoregulation and progressive glomerulosclerosis is important in the pathogenesis of chronic kidney disease (CKD). Although prevention is widely recommend in current guidelines, up to now it is only possible to measure intraglomerular pressure (Pglom) directly in animal models. We hypothesized that renal arterial compliance and Pglom can be estimated from proximal renal arterial measurements.

Methods: Pressure and flow velocity were recorded in patients with a clinical indication for either coronary or renal angiography. The data was acquired under baseline conditions and after hyperemia induced by dopamine 30 µg/kg intrarenal. This was further analyzed using an adapted 3-element Windkessel model, consisting of compliance, impedance, afferent resistance and Pglom.

Results: We included 33 subjects with a median age of 58 years (IQR 52-65), eGFR of 85.9 ml/min/1.73m^2, 31% had microalbuminuria. In 4 patients, a renal artery stenosis was found. The model showed a mean Pglom of 47.7 mmHg at baseline. After induction of hyperemia, flow increased by 90 (95%CI 66-133)%. This resulted in a 172 (95%CI 81-309)% increase in compliance and a decrease of Pglom of 12.6 (95%CI 9.5-15.7) mmHg. Patients with diabetes had a significantly higher Pglom of 10.8 (95%CI 5.3-15.5) mmHg, after correction for a significant positive association with BMI (0.81, 95%CI 0.37-1.59) and renal perfusion pressure (0.40, 95%CI 0.22-0.59).

Conclusions: The model enables determination of parameters for the renal macro- and microcirculation using proximal pressure and flow measurements, which could be useful to identify patients at risk for CKD.

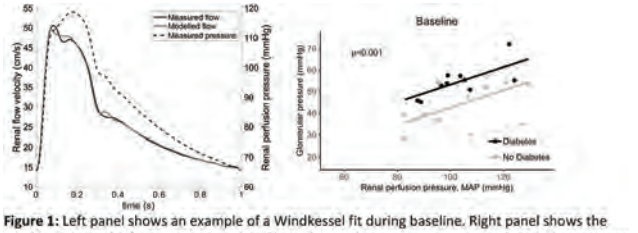

Figure 1: Left panel shows an example of a Windkessel fit during baseline. Right panel shows the results of the multiple regression model of intraglomerular pressure versus renal perfusion pressure under baseline, P value shows comparison of diabetes vs no diabetes.

SA-PO324

Indole-3-Methanol, a Dietary Constituent, Suppresses Uremic Toxicity of Indoxyl Sulfate

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Background: Indoxyl sulfate (IS), a bonafide uremic toxin, mediates its vasculotoxicity in chronic kidney disease (CKD) patients through activation of the Aryl hydrocarbon receptor (AHR)-tissue factor (TF) pathway in vessel walls. The management of patients with CKD focuses primarily on therapies to control the comorbidities associated with and contributing to CKD progression and recommends alterations in macronutrients. In essence, the current management of CKD patients completely lacks the strategies to directly target indolic toxins to prevent/retard the cardiovascular complications. The structural features of IS that impart toxicity and their therapeutic implications remain unknown.

Methods: A structure-activity analysis was conducted using an analog-by-catalogue approach, with the AHR-TF-thrombosis axis as a readout. A set of indolic compounds, including IS bioisosteres were analyzed in a three-tiered system along with validation in two human cohorts. This study employed three distinct animal models and two human cohorts to establish the role of the lead analog.

Results: Replacement of the sulfate moiety abrogated IS-mediated AHR-TF activation. Notably, of all the analogs, Indole-3-methanol (a.k.a. indole-3-carbinol or "I3M") showed a dose-dependent inhibition of the AHR-TF axis and suppressed IS-induced AHR activation and carotid artery thrombosis in discrete animal models. Mechanistically, I3M reduced TF protein without downregulating its mRNA. I3M suppressed TF in cells specifically in sera from CKD patients compared to the non-CKD controls, and the extent of TF suppression correlated with their levels of IS. I3Minhibited TF in vascular smooth muscle cells in response to pre-intervention sera from subjects who had developed post-angioplasty thrombosis from a sub cohort of a Thrombolysis in Myocardial Infarction-II trial.

Conclusions: This study demonstrates the importance of the IS sulfate group, and reveals I3M, as a suppressor of prothrombotic properties of IS. I3M is a naturally occurring phytochemical found in cruciferous vegetables that a rich source of indole-based glucobrassicin. These results can guide future campaigns to develop targeted therapies such as compounds against IS and plant-based diets that can be personalized to the blood IS levels in CKD patients.

Funding: Other NIH Support - NIH R01

SA-PO325

Precision Medicine: Lanosterol Synthase Gene Polymorphisms Affect Body Na^+ in Salt-Sensitive Hypertension

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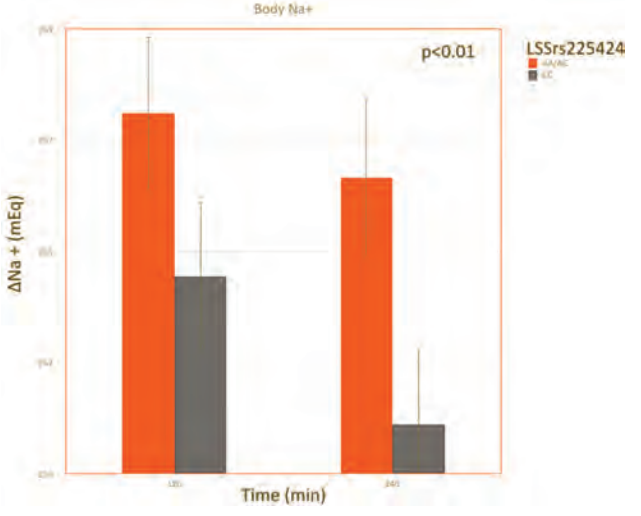
Background: For decades, it has been widely accepted that initiation of salt-induced hypertension involves a type of kidney dysfunction (natriuretic handicap) which causes salt-sensitive subjects to excrete less of a sodium load than normal subjects and to undergo abnormal increases in cardiac output, and therefore in blood pressure (BP). Our research group has reported that a Lanosterol Synthase (LSS) gene variant influences both the salt sensitivity of BP and changes in circulating Endogenous Ouabain (EO) in response to a low salt diet. Aim of the study is to explore the role of LSS genotypic variants comparing salt-sensitive (SSH) with salt-resistant (SRH) hypertensive patients for their impact on body Na+.

Methods: A large cohort (n=807) of naïve hypertensive patients (NHP) was phenotyped for salt sensitivity by giving NaCl 308 mEq/2h/iv. Total body Na^+ at the end of infusion (T120) and after recovery (T240) was assessed by calculating the differences between Na^+ infused and urinary excretion.

Results: 516 SRH display a decrease in systolic BP (-0.6±0.32 mmHg), while in 291 SSH, SBP increases of 11.8±0.42 mmHg. Meanwhile, there was no difference in total body Na^+ in both groups, 254.75±1.41 mEq in SRH patient and 254.02±2.03 mEq in SSH group. Moreover, LSS rs225424 AA+AC carriers retained more body Na^+ both at T120 and T240 (256.81±1.52 and 255.9±1.6 mEq) than LSS CC wild-type subjects (252.66±1.72 and 251.4±1.6 mEq; p<0.01).

Conclusions: LSS gene contributes to maintaining a positive Na^+ balance in SSH. In the precision medicine era, LSS gene may be considered as a "natriuretic handicap" gene.



SA-PO326

Different Forms of Afferent Nerve Input in Cardiac and Renal Disease in Rats?

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Background: Afferent nerve pathways form kidney and heart likely control sympathetic renal nerve activity. In renal disease (anti Thy1 nephtitis) the responsiveness of afferent renal nerve units was shifted from units with highly active primary neurons (tonic response pattern) to units with neurons of very low activity upon stimulation (phasic response pattern). Afferent renal nerve activity was likely decreased. Likewise, afferent vagal nerve activity in congestive heart failure (CHF) had a lower frequency at saturation than controls. Hence we wanted to test the hypothesis that in CHF the vagal afferent nerve pathway consists of a decreased number of highly active tonic sensory neurons in the nodose ganglion.

Methods: CHF was induced by coronary artery ligature, nephropathy by injections of an anti Thy1.1 antibody (OX7, 1.2mg/kg). After a respective time (CHF 21 days, nephropathy 7 days after induction) nodose ganglion neurons with cardiac vagal afferents from CHF rats or neurons form dorsal root ganglia with renal afferents from rats with nephropathy were cultured. Current clamp was used to characterize neurons as "tonic",

i.e. sustained action potential (AP) firing or "phasic", i.e. <5 APs upon current injection. Electrophysiological parameters and AP properties were determined in neurons from animals with CHF or nephropathy.

Results: In CHF rats, the number of neurons with a tonic, more active response pattern from CHF animals did not differ from controls (64% vs. 70 %, ns). However, tonic cardiac neurons from CHF rats exhibited an increased production of action potentials compared to controls (24.4+/-5.0 vs. 14.7+/-1.8 APs/10s; $p<0.05$; mean+/-SEM). In nephropathic rats, the number of neurons with a tonic response pattern decreased significantly (43% vs. 64 %, $p<0.05$), but there was no difference in action potential production as compared to controls.

Conclusions: In contrast to our hypothesis, in CHF the number of afferent neurons with a tonic response pattern was not altered, instead the action potential production of these neurons increased increased upon stimulation. Hence, in congestive heart failure vagal afferent neurons increase their sensitivity in the presence of impaired intracardiac receptors whereas in renal disease the responsiveness of the first part of the afferent pathway is impaired as a whole

SA-PO327

Afferent Peptidergic Nerve Fibers: Importance for the Salt Metabolism Beyond the Kidneys?

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Background: Sodium can be accumulated without commensurate water retention in the skin (non-osmotic sodium storage). Macrophages play a pivotal role in this context and their depletion can induce salt-sensitive hypertension. On the other hand renal afferent peptidergic nerves are involved. Since the skin is also densely innervated by afferent peptidergic nerves we hypothesized that high salt diet might enhance the release of neuropeptides from these nerve fibers

Methods: In a cross-over design, two groups of rats (n=4, each) were fed either low salt diet (LS; 0.2%) with free access to tab water for 14 days or high salt diet (HS; 8%) with free access to 0.9% saline as drinking water. After 14 days a skin sample (3x3mm) of the groin area was excised, and the diet was switched for another 14 days. Then a contralateral skin sample was taken. Tissue analyzed in an organ-bath and calcitonin gene related peptide (CGRP) content in the supernatant was measured with ELISA. After two baseline measurements within 5 min, the tissue was superfused with hypertonic saline (4.5%) for 5 min, and three further samples of the supernatant were taken every 5 min.

Results: Baseline CGRP release was similar with both diets (LS 11.9±1.5 vs HS 13.6±1.5ng/g skin). Maximum release was higher with HS diet (LS 17.5±1.8 5ng/g skin vs HS 29.8±1.3ng/g skin; *$p<0.05$). After diet switch the results were similar: baseline LS 9.4±1.2 ng/g skin vs HS 10.1± 1.1 ng/g skin, with HS diet the release was higher again (LS 19.7±2.1 vs HS 29.3±1.7*; *$p<0.05$).

Conclusions: High sodium diet sensitized neuropeptide release from peptidergic sensory nerves in the skin. Hence peptidergic afferent nerves might be an integrated body-wide system involved in sodium handling in very different target areas like skin and kidney. Putative peptidergic mechanisms (vasoregulation, chemotaxis) remain to be determined in this respect.

SA-PO328

Urinary Plasmin Plays Pathogenic Roles for the Development of Hypertension in Dahl Salt-Sensitive Rats

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Background: The epithelial sodium channel (ENaC) in the renal collecting duct plays pivotal roles in the regulation of sodium homeostasis and blood pressure. The proteolytic cleavage of γENaC by extracellular serine proteases is an important process for the full activation of this channel and is physiologically regulated by aldosterone. In the setting of proteinuria, proteases filtered through damaged glomeruli could activate ENaC leading to hypertension, independently of aldosterone. We reported that Dahl salt-sensitive (DS) rats with high-salt (HS) diet developed severe hypertension together with aberrant activation of γENaC by serine proteases. However, the role of plasmin in the hypertension of DS rats remain to be elucidated. In this study, we evaluated the relationship of proteinuria, urinary plasmin activity and hypertension, and the antihypertensive effect of a serine protease inhibitor camostat mesilate (CM) in DS rats.

Methods: Four-week-old DS rats were divided into normal-salt (NS) diet, HS and HS+CM (0.1% diet) groups. After systolic BP measurement and 24h urine collection were performed for 5 weeks, rats were sacrificed for biochemical examination. Urinary plasmin activities were evaluated by zymography and Western blotting.

Results: HS diet induced severe hypertension [SBP (mmHg): NS, 141.1±5.8; HS, 222.3±15.4; HS+CM, 199.5±5.0], marked proteinuria [U-TP (mg/day): NS, 23.8±12.1; HS 272.3±79.9; HS±CM, 135.1±27.4] and urinary plasmin activation, as well as the cleavage of urinary exosomal γENaC. The treatment with CM suppressed these changes, together with significantly reduced BP and proteinuria.

Conclusions: In conclusion, plasmin is associated with the pathogenesis of hypertension in DS rats, and serine protease inhibition could be a potential therapeutic strategy against salt-sensitive hypertension with proteinuria.

SA-PO329

Functional Impact of Proximal Tubule ATRAP in Blood Pressure Regulation

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Background: The angiotensin II (Ang II) receptor (AT1R)-associated protein (ATRAP) inhibits pathological activation of AT1R signaling in response to certain stimuli. We showed that systemic ATRAP knockout mice exhibits the exacerbation of Ang II-mediated hypertension via hyperactivation of distal tubule AT1R-ENaC pathway (Ohsawa Kid Int 2014; Kobayashi Kid Int 2017). Although ATRAP is also expressed abundantly in renal proximal tubules, little is known about a functional impact of proximal tubule ATRAP in blood pressure (BP) regulation in response to pathological stimuli.

Methods: We created proximal tubule-specific ATRAP knockout (PT-KO) mice using the Cre/loxP system with Pepck-Cre, and examined a functional role of proximal tubule ATRAP in angiotensin-mediated hypertension. For chronic Ang II stimulation experiments, Ang II (600 or 1000 ng/kg per minute) was infused subcutaneously in male WT and PT-KO mice (9–12 weeks old) for 14 days using an osmotic minipump (model 2002; ALZET).

Results: The ATRAP mRNA expression was decreased by ≈80% in renal proximal tubules of PT-KO mice compared with wild-type (WT) mice. The BP of PT-KO mice was comparable with that of WT mice at baseline. Moreover, in telemetry analysis, the 24-hour mean systolic BP was significantly and similarly increased in response to 2 weeks of Ang II infusion (1000 ng/kg per minute) in both PT-KO and WT mice (Ang II–infused PT-KO versus Ang II–infused WT mice, 2-way repeated measures ANOVA, F=0.04280, P=0.8407). Ang II infusion (1000 ng/kg per minute) for 2 weeks also significantly increased 24-hour mean systolic BP, not only in the light period but also in the dark period and to the same extent in both types of mice. The degrees of cardiac hypertrophy and albuminuria under Ang II -mediated hypertension were also similar in PT-KO and WT mice. In addition, the results of metabolic cage analysis showed that cumulative sodium balance during 2 weeks of Ang II infusion was comparable for PT-KO and WT mice.

Conclusions: Proximal tubule-specific down-regulation of ATRAP did not affect the Ang II-mediated hypertension *in vivo*. Since ATRAP is broadly expressed along renal tubules from proximal to distal tubules, proximal tubule ATRAP would be suggested to have a distinct function other than BP modulation in response to pathological stimuli.

SA-PO330

The Distal Convoluted Tubule Serves as a Potassium Switch in an Intracellular Chloride-Dependent Mechanism

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Background: The kidney plays a key role in the regulation of K^+ excretion and K^+ homeostasis. Previous studies have demonstrated that the thiazide-sensitive Na-Cl cotransporter (NCC) in the distal convoluted tubule (DCT) plays an important role in the regulation of renal K^+ excretion by controlling sodium and volume delivery to the distal nephron. It has been shown that NCC is inhibited when K^+ intake is high and activated when dietary K^+ intake is low. It is now generally accepted that WNKs (with-no-lysine kinases) plays a major role in NCC phosphorylation and activation. A large body of evidence has demonstrated that WNK1 and WNK4 are chloride-sensitive kinases, which are inhibited by high intracellular chloride concentration ($[Cl^-]_i$) and activated by low $[Cl^-]_i$. It has also been suggested that membrane voltage changes by extracellular K^+ concentrations are responsible for altering the $[Cl^-]_i$ thereby affecting WNK activity. The aim of our study is to test the hypothesis that changes in the basolateral cell voltage alter the $[Cl^-]_i$ in the DCT.

Methods: To determine the $[Cl^-]_i$ in the DCT, we have used isolated single DCT tubule of transgenic mice expressing *Cl-sensor*, a chloride-sensitive fluorescent protein modified from Chlomeleon. The *Cl-sensor* contains both a chloride-sensitive YFP moiety as well as a chloride-insensitive CFP moiety, allowing ratiometric estimation of $[Cl^-]_i$.

Results: We first measured the $[Cl^-]_i$ in the isolated DCT by establishing the calibration curve. Using this calibration curve, we estimated that basal DCT $[Cl^-]_i$ is 6.8 ± 2.3 mM (n=18). Changing the extracellular potassium concentration from 10 mM to 2 mM decreases the $[Cl^-]_i$. To test the role of the basolateral Kir4.1/Kir5.1 of the DCT in altering $[Cl^-]_i$, we examined whether inhibition of the basolateral K^+ channels with Ba^{2+} would increase the $[Cl^-]_i$ since Ba^{2+} has been shown to depolarize DCT membrane. Indeed, Inhibition of Kir4.1/Kir5.1 significantly increased the $[Cl^-]_i$ in the DCT bathed in a solution containing 2 mM K^+.

Conclusions: Our results indicate that the intracellular Cl^- concentrations of DCT cells are low at baseline and that the depolarization increases whereas hyperpolarization decreases the intracellular Cl^- concentrations. Thus, changes in DCT voltage are associated with alteration of intracellular Cl^- concentrations.

Funding: NIDDK Support, Private Foundation Support

SA-PO331

Assessment of Sublingual Microcirculation with the GlycoCheck System: Reproducibility and Examination Conditions

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Background: The glycocalyx is an extracellular layer lining the lumen of the vascular endothelium including the glomerular capillaries. It protects the endothelium from shear stress and atherosclerosis and contributes to coagulation, immune response and micro-vascular perfusion. Degradation of the glycocalyx is a part of several renal disease processes and ultimately results in proteinuria. The GlycoCheck system is a new method to estimate the glycocalyx' thickness in vivo from perfused boundary region (PBR) and microvascular perfusion (red blood cell (RBC)-filling) via a video camera coupled to a computer with integrated software. We evaluate reproducibility and influence of examination conditions on measurements with the GlycoCheck system.

Methods: Open-labelled randomised, controlled study including 42 healthy smokers investigating day-to-day, side-of-tongue and inter-investigator variance and influence of smoking, high calorie meal and coffee on PBR and RBC-filling at intervals from 0-180 minutes.

Results: The mean(SD) age was 24.9(6.1) years and 52% were male. There was no significant intra- or inter-investigator variance for PBR or RBC-filling and no for PBR for side-of-tongue. A small variance was found for day-to-day, PBR (0.012μm, p=0.007)/ RBC-filling (0.003%, p=0.005) and side-of-tongue, RBC-filling (0.025%, p=0.009). Significant influence of cigarette smoking (from 40-180 minutes), high calorie meal intake and coffee consumption was found, the latter two peaking immediately and tapering off but remained significant up to 180 minutes, highest PBR changes for the three being 0.042μm ($p<0.05$), 0.183μm ($p<0.001$) and 0.160μm ($p<0.05$), respectively.

Conclusions: Measurements with the GlycoCheck system have an acceptable reproducibility, even with day-to-day variability. Smoking, diet and coffee had influence on measurements of up to 180 minutes, thus abstinence is recommended at least 180 minutes before measurements. Future studies will address impact of renal disease and reno-protective intervention on glycocalyx but should standardise measurement conditions.

Funding: Private Foundation Support

SA-PO332

Impact of Oxidative Stress on Vascular Calcification in the Setting of Coexisting CKD and Diabetes Mellitus

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Background: Vascular calcification is a crucial complication in patients with chronic kidney disease (CKD). Particularly, CKD patients with diabetes mellitus (DM) manifest severe vascular calcification but its precise mechanisms are poorly understood. It has been reported that oxidative stress plays a key role for the progression of vascular calcification. In the present study, we investigated the pathophysiological mechanisms of vascular calcification in the setting of coexisting CKD and DM particularly from the perspective of oxidative stress.

Methods: Sprague-Dawley rats were randomly divided into six groups as follows; (i) control rats (control group), (ii) 5/6 nephrectomized rats (CKD group), (iii) streptozotocin (STZ) injected rats (DM group), (iv) 5/6 nephrectomized and STZ injected rats (DM+CKD group), (v) DM+CKD rats treated with insulin (DM+CKD+INS group), (vi) DM+CKD rats treated with apocynin, which is an inhibitor of NADPH oxidase (DM+CKD+APO group). All groups were fed a high phosphate diet from 11 weeks of age. At 18 weeks, the rats were sacrificed for blood and urine analysis, histopathological analysis and evaluating mRNA expressions of oxidative stress and osteoblast differentiation-related markers in the aorta.

Results: Von Kossa-positive mineralized area and calcium content of aorta were significantly increased in the DM+CKD group compared to the control, CKD and DM groups at 18 weeks. However, despite high serum glucose levels control, apocynin treatment prevented the progression of vascular calcification. The mRNA expressions of RUNX2 and ALP and the number of RUNX2-positive cells in the aorta were significantly increased in the DM+CKD group compared to the control, CKD and DM groups. Similarly, these expressions were significantly reduced by apocynin treatment. As for the assessment of oxidative stress, urinary excretion of 8-hydroxydeoxyguanosine (8-OHdG), the number of 8-OHdG positive cells in the aorta, and the mRNA expressions of NOX4 and NADPH p22 phox were significantly decreased in the DM+CKD+APO group compared to the DM+CKD group.

Conclusions: Our results suggest that coexisting CKD and DM accelerates vascular calcification mainly by increased oxidative stress.

SA-PO333

c-Src and Caveolin-1 in Na-K-ATPase Signaling Complex: A Cys-Cys Crosslinking Analysis

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Background: Activation of Na/K-ATPase signaling cascade regulates sodium handling in proximal tubule, systemic oxidative stress, and uremic cardiomyopathy. This study is to investigate the formation of the signaling complex, especially interactions amongst the α1 subunit, c-Src, and caveolin-1 (cav-1) under native condition in live cells.

Methods: Crosslinking studies were performed in resting live LLC-PK1 cells with Cys-Cys crosslinkers BMH (non-cleavable) and DTME (cleavable). Blue Native-PAGE was used to identify the molecular weight and protein components of the complexes under native condition. Capillary immunoblotting spectra analysis was used to determine the interactions amongst α1, c-Src, and cav-1, by comparisons between LLC-PK1 and cav-1-knockdown C2-9 cells (generated from LLC-PK1), as well as between triple Src kinase (c-Src, Yes, Fyn)-null mouse fibroblasts SYF cells and c-Src-rescued SYF cells, SYF+c-Src cells.

Results: (1) In Blue Native-PAGE, control samples showed a predominant complex around 480 kD (480-band), and crosslinked samples showed an additional complex around 720 kDa (720-band). Mass spectrometry analysis showed that, both the Na/K-ATPase α1 and β1 subunits were present in both 720-band and 480-band, in both control and BMH-crosslinked samples. Cav-1 was only present in the 720-band but not the 480-band. Moreover, in control samples, c-Src was detected in the 480-band, comparing with that c-Src was detected in the 720-band in BMH-crosslinked samples. (2) In spectra analysis of control and crosslinked samples, there were interactions between the α1 subunit and c-Src, and between the α1 subunit and cav-1. While depletion of c-Src or cav-1 clearly reduced the involvement of the α1 subunit in the crosslinked protein complexes, depletion of cav-1 did not affect the interaction of c-Src with other proteins including the α1 subunit. (3) Furthermore, there are multiple bands showing immuno-reactivity with the α1 subunit, c-Src, and cav-1, indicating the existence of different sizes of protein complexes that might contain different protein components with different functions.

Conclusions: In live cells, present study indicated that there are direct interactions between the α1 subunit and c-Src as well as between the α1 subunit and cav-1, but not likely between c-Src and cav-1. The α1 subunit functions as a bridge to link c-Src and cav-1.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO334

Prevalence, Level of Awareness, and Hypertension Control in Africans

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Background: Despite the availability of effective low-cost treatments, systemic hypertension continues to be a major cause of cardiovascular morbidity and premature death particularly in low resource countries where the overall prevalence of hypertension is increasing.

Methods: We estimated the prevalence, level of awareness and hypertension control in individuals the Human Hereditary and Health in Africa Kidney Disease Study (H3A-KDRN) in West Africa (n=8392). Using a standardized protocol, trained study staff measured three blood pressure in participants. We defined hypertension as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90mmHg and/or self-reported antihypertensive medication use. We defined awareness of hypertension was defined using self-report and hypertension control as blood pressure <140/90mmHg.

Results: The prevalence of hypertension in the entire cohort was 53.7%. Of those with hypertension, 70.4% were aware of their diagnosis of hypertension, 54% were on medication on medication while 32.3% had controlled blood pressure to <140/90mmHg. Older individuals, those with lower eGFR, Ghanaians compared to Nigerians, obese individuals and alcohol drinkers were more likely to be aware of their hypertension diagnosis. Older age individuals, those with lower eGFR, and Ghanaians were all less likely to have a controlled blood pressure.

Conclusions: Despite the moderate level of awareness of hypertension in this cohort, the rate of hypertension control was suboptimal. There is need for programs to ensure for reliable and affordable access to the treatment of hypertension in Africa.

Funding: NIDDK Support, Other NIH Support - NIH common fund, NHGRI

SA-PO335

The Circadian Clock Provides Beneficial Effects Against the Endothelial Dysfunction to Promote Atherogenesis by Regulating Angiotensin II Generation and Vascular Endothelial Growth Factor Expression

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Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial

structure and vascular stiffness. Chronic circadian clock disruption is also associated with dysfunction in endothelial signaling and responses. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence growth factors, such as Angiotensin II or Vascular Endothelial Growth Factor (VEGF) which play an important part in the progression of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of Angiotensin II and VEGF expression in the knocked down cells.

Results: Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was an increase in Angiotensin II and VEGF expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display premature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include Angiotensin II and VEGF, which are significantly elevated in Bmal1 KO mice. We also confirmed that PDGF levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating Angiotensin II and VEGF expression. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Government Support - Non-U.S.

SA-PO336

A Novel and Reproducible Model of CKD-Induced Vascular Calcification in Mice

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Background: Vascular calcification remains a frequent complication of advanced chronic kidney disease (CKD) and a leading cause of morbidity and mortality in this population. Various animal models have been introduced to induce CKD and study the pathomechanism of vascular calcification. The most commonly used such model in rodents is 5/6 nephrectomy followed by using high phosphate diet. However, the 5/6 nephrectomy in mice is markedly challenging and results are seldom consistent.

Methods: To address this challenge, we sought to examine a novel model of vascular calcification where ten-week-old mice with DBA2 background that are prone to vascular calcification, underwent unilateral ischemia reperfusion injury (UIRI) for 25 minutes followed by complete right nephrectomy after one week. The control group underwent sham surgery and both groups were fed high phosphate diet (0.6% Ca, 0.9% Pi) for twelve weeks at which point mice were sacrificed for analysis.

Results: While serum creatinine did not reveal significant changes (treatment group = 0.12 ± 0.01 mg/dL vs control group = 0.13 ± 0.03 mg/dL), glomerular filtration rate measurements (GFR) were lower in the treatment groups (treatment group = 187.68 ± 31.99 uL/min vs control group = 230.99 ±18.5 uL/min). Furthermore, protein analysis on aortae of the mice demonstrated significant upregulation of osteogenic markers including osteocalcin, alkaline phosphatase, and osteoblast specific transcription factor, cbfa-1.

Conclusions: Our findings suggest that UIRI followed by nephrectomy is a feasible and reproducible model of vascular calcification associated with CKD that would enable study of various transgenic mice to better understand the mechanistic pathways involved in mineralization of vascular tree and targeting novel therapeutics.

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SA-PO337

Bariatric Surgery Alters Fibroblast Growth Factor 21 and the Renin Angiotensin System in Patients with Obesity

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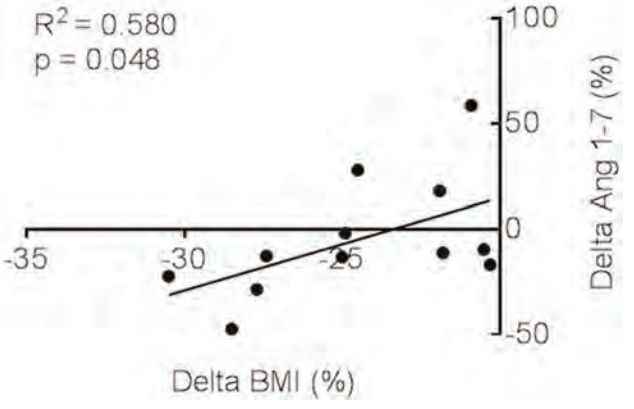
Background: Obesity is associated with overactivation of the renin-angiotensin system (RAS). Recent studies have shown that fibroblast growth factor 21 (FGF21) prevents angiotensin II (Ang II) induced hypertension and vascular dysfunction by activation of the angiotensin-converting enzyme 2 (ACE2)/Angiotensin 1-7 (Ang (1-7))/MAS axis in hypertension. However, it is not certain whether bariatric surgery changes FGF21/RAS in morbid obesity. In this study, we examined the relationship between circulating FGF21 and Ang II/ACE2/Ang (1-7) in patients with obesity after bariatric surgery.

Methods: We prospectively enrolled obese patient who underwent bariatric surgery and age-sex matched healthy volunteers (HVs) (n=12 each). Serum FGF-21, Ang II, ACE2, and Ang (1-7) levels were measured by enzyme-linked immunosorbent assay kits. We measured also FGF-21, Ang II, ACE2, and Ang (1-7) 6 months after bariatric surgery in obese patients (n=12).

Results: Ang II and ACE2 levels were significantly higher in obese patients compared with HVs (931.9 ± 189.2 vs 615.2 ± 79.9 pg/mL, $p < 0.001$, 273.8 ± 45.0 vs 240.8 ± 42.3 ng/mL, $p = 0.020$, respectively). Ang II and ACE2 levels were significantly decreased after bariatric surgery ($p = 0.005$, 0.023, respectively). In obese patients, FGF 21 levels was higher compared with HV ($p = 0.034$) and decreased after bariatric surgery ($p = 0.002$). There was no significant difference in Ang (1-7) levels between obese patients and HVs ($p = 0.887$). Although Ang (1-7) levels did not change after bariatric surgery ($p = 0.480$), changes in Ang (1-7) levels were positively correlated with changes in body mass index (BMI) ($R^2 = 0.580$, $p = 0.048$)(Fig 1).

Conclusions: Bariatric surgery reduced the elevated systemic Ang II, FGF21 and ACE2 levels in obese patients. A decrease in BMI after bariatric surgery was associated with a reduction in Ang (1-7) levels.



SA-PO338

Patrolling Monocyte Subsets in Patients with CKD and Coronary Heart Disease

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Background: Chronic low-grade inflammation is prevalent in Chronic Kidney Disease (CKD) patients and plays a role in the development and progression of cardiovascular diseases. Monocytes are key factors in atherosclerosis progression and can be classified into subtypes based on their profiles of LPS co-receptor CD14 and FCgIII CD16 expression. The aim of this work is to analyze circulating monocytes subsets in CKD patients with atherosclerotic coronary artery lesions undergoing coronary Artery Bypass Surgery (CABG).

Methods: A prospective Case-Control study was conducted in CABG patients. Controls were patients with non-coronary lesions undergoing valve repair heart surgery. The expression of CD14+ and CD16+ antigens were analyzed by flow cytometry in peripheral blood mononuclear cells. A sample of perivascular adipose tissue and a punch from aorta were also obtained from patients included in the study.

Results: A total of 72 CABG patients (56 males) from which 40 suffered CKD (stages 3 to 5) and 26 non-coronary heart surgery controls (17 males) from which 11 patient suffered CKD were included. Here, we show the flow cytometry analysis. The proportion of classical CD14+CD16- monocytes (78.5±11% in CABG vs 75.9±12.1% in controls; p=0.3), CD14++CD16+ (10.8±8% in CABG vs 12.9±9.7 in controls; p=0.2) and CD14+CD16++ (10.9±6.6 vs 11.1±5.2 %: p=0.9) was similar in CABG than in controls. CKD was associated with a depletion of the CD14+CD16++ subset (CD14+CD16-: 76.4±12.5% in patients without CKD; n=50, vs 78.6±10.1% in CKD, n=48; p=0.4; CD14++CD16+: 11.2±8.1% without CKD vs 11.7±8.8% in CKD; p=0.4; and CD14+CD16++:12.4±7.2 vs 9.7±4.5 %: p=0.026). The depletion of CD14+CD16++ monocytes showed a significant negative correlation with systolic arterial pressure (R=-0.374, p=0.0001).

Conclusions: CKD and systolic arterial pressure were associated with a depletion in CD14+CD16++ monocytes in peripheral blood of patients. Next, we plan to study the expression of adhesion molecules in the surface of the CD14+CD16++ monocytes to determine their ability to adhere to endothelial cells.

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SA-PO339

Deficiency of the Anaphylatoxin Receptors C5aR2 and C3aR Aggravates Hypertensive Renal Injury

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Background: Complement drives the host defense against microbes and mediates inflammatory responses. In addition, recent data also support a role for complement in arterial hypertension. During the activation and amplification of the complement cascade, the anaphylatoxins C3a and C5a are released and trigger pro inflammatory signaling

via their corresponding receptors. We recently described that C5a receptor 1 deficiency ameliorated hypertensive renal injury. However, the role of the second C5a receptor (C5aR2) and the C3a receptor (C3aR) in hypertension and hypertensive end organ damage remain unclear.

Methods: Expression of C5aR2 and C3aR on infiltrating and resident renal cells were determined using tandem tomato reporter mice for either C3aR or C5aR2 by flow cytometry and confocal microscopy. The hypertension model of angiotensin II infusion in combination with unilateral nephrectomy and high salt diet was induced in Balb/c wildtype, C5aR2- and C3aR-deficient mice. The glomerular filtration rate (measured with fitc sinistrin), albuminuria and glomerular damage were determined.

Results: Flow cytometric analysis of leukocytes isolated from the kidney of anaphylatoxin reporter mice showed C5aR2 expression on dendritic cells (34%), macrophages (30%) and neutrophils (14%) whereas dendritic cells are the major C3aR-expressing population (90%). C5aR2 and C3aR were also detected by confocal microscopy in the kidney only on infiltrating cells. Both anaphylatoxin receptor-deficient mice suffered from markedly increased renal injury after Ang II infusion with higher albuminuria, glomerular filtration rate and glomerular injury compared to hypertensive wildtype mice. The mortality in hypertensive C3aR-deficient mice was significantly higher than that observed in hypertensive wildtype or C5aR2-deficient mice and was associated with increased bleeding.

Conclusions: Our findings identify C5aR2 and C3aR expression on infiltrating (mainly dendritic cells, macrophages and neutrophils) but not on resident cells in the kidney. C5aR2 or C3aR deficiency was associated with strongly increased renal injury in response to arterial hypertension. Together, we propose that C5aR2 and C3aR mediate protective or homeostatic effects in hypertensive renal injury.

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SA-PO340

Indoleamine 2,3-Dioxygenase-1, a Novel Therapeutic Target in Thrombotic Uremic Toxicity

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Background: Metabolites associated with chronic kidney disease (CKD) are highly thrombogenic. Emerging evidence validated CKD-specific mediators and definined the uremic solute-aryl hydrocarbon receptor (AHR)-tissue factor (TF) axis resulting in increased thrombosis. Given the importance of tryptophan metabolites in inducing thrombosis in CKD, we examined the role of Indoleamine 2,3-dioxygenase-1 (IDO), the rate limiting enzyme of the kynurenine pathway in CKD-mediated thrombosis.

Methods: Global IDO knock-out and wild type mice treated with 1-methyltryptophan (1-MT), a specific inhibitor of IDO, were used in an adenine-induced model of CKD. Plasma uremic solutes were measured by LC/MS. IDO protein and mRNA were examined in vascular smooth muscle cells (vSMCs) and in flow-loops. Prothrombic effects of IDO were further confirmed in clinical, Dialysis Access consortium (DAC)-fistual and Thrombolysis in Myocardial Infacrction (TIMI)-II.

Results: Compared to $IDO^{+/+}$ mice, $IDO^{-/-}$ mice showed a significantly increased time to occlusion (TTO) in both non-CKD and CKD mice models ($p<0.05$). $IDO^{+/+}$ mice administered 1-MT in a CKD model had increased TTO compared to controls, supporting the role of IDO in thrombosis. ($p<0.05$). Indoxyl sulfate (IS), a prothrombotic uremic solute, increased IDO expression in a dose-dependent manner in vSMCs *in vitro*and 3D flow loops. IDO protein and mRNA was upregulated by IS at concentrations observed in CKD patients. Polyubiquitination and proteasomal degradation of IDO was substantially inhibited by IS. IDO activity of sera samples was significantly higher in those patients who subseqently developed AVF thrombosis (DAC-fistula trial, p=0.001) and post-angioplasty thrombois (TIMI-II trial, p=0.008) compared to subjects without a thrombotic event.

Conclusions: We demonstrate a novel role for IDO as a contributor to CKD-mediated thrombosis and as a potential therapeutic target in post-interventional thrombosis in CKD patients. The current study further underscores a complex interplay of unique mediators triggered in the uremic milieu that impart thrombotic risk to CKD patients.

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SA-PO341

Mechanisms for Increased Cardiovascular Risk in Patients with ANCA Vasculitis in Long-Term Remission

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Background: Current treatments have improved the short-term survival of patients with ANCA-associated vasculitis (AAV), an autoimmune disease that often involves the kidneys. Long-term outcomes remain poor due to an increased risk of cardiovascular disease (CVD). AAV is defined by systemic endothelial injury but few clinical studies have robustly explored endothelial dysfunction as a contributor to CVD risk in these patients. We assessed brachial artery vasodilation and release of tissue plasminogen activator (tPA, an endogenous thrombolytic) as measures of endothelial function that predict CVD.

Methods: We recruited 32 AAV patients in long-term remission and 32 age- and sex-matched healthy controls into a prospective cohort study. Those with renal impairment, proteinuria, diabetes and overt CVD were excluded. Vasodilation was assessed by gold standard forearm blood flow during randomized intra-arterial infusions of acetylcholine (ACh, endothelium-dependent vasodilator, 7.5/15/30μg/min) and sodium nitroprusside (SNP, endothelium-independent vasodilator, 2/4/8μg/min). tPA release was measured during intra-arterial bradykinin (100/300/1000pmol/min).

Results: AAV patients had a mean±SD age of 55±13 years and 23 (72%) were male. The median (range) time from diagnosis was 4 (1-13) years and 17 (53%) were PR3+. 22 (69%) patients were prescribed a renin-angiotensin system blocker, and 21 (66%) were receiving a statin or ezetimibe. Forearm blood flow increased dose-dependently during all infusions. AAV patients had reduced ACh-mediated vasodilation compared to controls ($p<0.01$ at peak dose, ~25% difference in area under the curve). Responses to SNP did not differ. Compared to controls, AAV patients had lower mean±SD tPA release (125±50 *vs* 65±52 ng/100ml/min at peak dose, $p<0.001$). tPA release was lower in PR3+ *vs* MPO+ patients (52±40 *vs* 90±70 ng/100ml/min, $p<0.05$), and in patients on maintenance immunosuppression compared to those on no immunosuppression (91±43 *vs* 54±50 ng/100ml/min, $p<0.01$), who had similar tPA release to controls.

Conclusions: AAV patients in long-term remission have significant endothelial dysfunction, comparable to that seen following myocardial infarction or in advanced CKD; this may partly explain their increased CVD risk. Targeting these with existing and novel therapies may improve long-term outcomes in AAV.

SA-PO342

Lanosterol Synthase (LSS) Gene as a Predictor of Kidney Dysfunction in Hypertensive Patients

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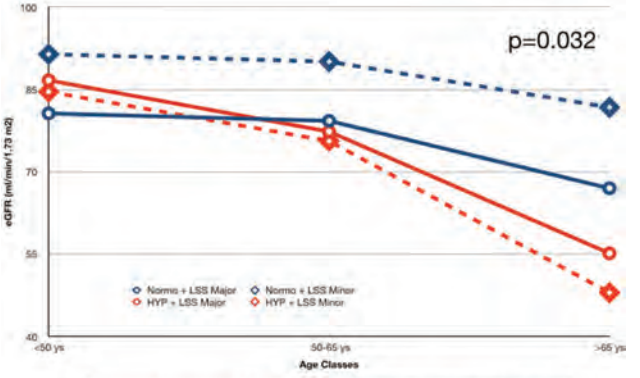
Background: Hypertension (HYP) is one of the main causes of chronic kidney disease (CKD). Recently we have proposed LSS as genotype-based risk stratification to predict accelerated eGFR decay in essential HYP patients. We tried to find a confirmation of this result in an observational study on general population.

Methods: We extracted clinical data of a general population from HYPERGENES Consortium. We also collected genetic data for LSS polymorphism that was already demonstrated as involved in kidney damage.

Results: A cohort of 3137 subjects was selected. Incidence of HYP and CKD was 49.8% and 9.1% respectively. Patients with well-known no-HYP / no-angiosclerosis related CKD (as diabetes, glomerulonephritis, ADPKD), were excluded. Population was divided into 3 classes according to age. At different age, HYP status have a deep impact on eGFR. Indeed in young (< 50ys) eGFR is higher in HYP vs control (86.2±19.3 vs 82.7±16.3 ml/min; p=0.04); vice-versa in elder (> 65ys) HYP have a reduction in eGFR (55.7±12.9 vs 71.0±12.9 ml/min; p<0.001). No direct influence of LSS polymorphism on eGFR was observed. When LSS is considered according to HYP status and age class it is possible to observe a preservation of age-associated eGFR reduction in normotensive patients (eGFR 91.4 vs 90.1 vs 81.8 ml/min for LSS risk allele); on the other side, LSS seems to enhance eGFR reduction associated with HYP status (eGFR 84.6 vs 75.6 vs 48.0 ml/min for LSS risk allele; p=0.032; fig. 1).

Conclusions: We confirmed on a large general population the involvement of LSS gene in enhanced eGFR loose in HYP patients. Indeed patients carrying the risk allele of this specific LSS polymorphism seem to express hyper-filtration if compared to their counterparts. When exposed to a specific pathological condition as HYP, with a further increase in eGFR in early phases, this could lead to an accelerated reduction in kidney function.



Age Class	Hypertension	LSS polymorphism	N	eGFR (ml/min/1.73m2)	
				Mean	S. D.
< 50 ys	Normo	Major	98	80.66	17.80
		Minor (risk)	8	91.43	12.85
	HYP	Major	767	86.69	19.08
		Minor (risk)	90	84.61	19.28
50-65 ys	Normo	Major	1051	79.31	16.55
		Minor (risk)	80	90.10	6.82
	HYP	Major	577	77.35	17.23
		Minor (risk)	74	75.64	19.17
>65 ys	Normo	Major	283	67.04	12.55
		Minor (risk)	13	81.77	5.21
	HYP	Major	79	55.19	13.83
		Minor (risk)	11	48.02	11.74

SA-PO343

Plasma Leucine-Rich Alpha-2-Glycoprotein 1 Predicts Cardiovascular Disease Risk in ESRD

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Background: Plasma Leucine-Rich alpha-2-Glycoprotein 1(LRG1) is an innovative biomarker for inflammation and angiogenetic diseases. End-stage renal disease (ESRD) is associated with adverse outcomes including inflammation, atherosclerosis, and premature mortality. However, whether levels of plasma LRG1 correlate with the co-morbidities of ESRD patients is unknown.

Methods: Plasma LRG-1 and high-sensitivity C-reactive protein were analyzed by ELISA in samples from 169 hemodialysis patients from the Immunity in ESRD study (iESRD study). Through history taking and detailed chart reviews, baseline co-morbidities were recorded. Peripheral blood monocyte and T cell subsets were assessed by multicolor flow cytometry.

Results: In the univariate analysis, LRG1 was found to be associated with the existence of cardiovascular disease (CVD) and peripheral arterial occlusive disease (PAOD). In multivariate-adjusted logistic regression models, higher LRG1 tertile was significantly associated with PAOD (odds ratio = 3.49), CVD (odds ratio = 1.65), but not with coronary artery disease, history of myocardial infarction, or stroke after adjusting for gender, hemoglobin, diabetes, hypertension, and level of C-reactive protein. In addition, the level of LRG-1 positively correlated with IL-6 and CRP and more advanced T cell differentiation, indicating the participation of LRG1 in the progression of atherosclerosis.

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SA-PO344

Potent Pro-Angiogenic Mediators Fail to Improve the Post-Ischemic Angiogenesis in the Uremic Milieu

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Background: Patients with chronic kidney disease (CKD) have been shown to have a 3-fold higher prevalence of peripheral arterial disease. Although CKD represents an independent risk factor for PAD, CKD-specific contributors remain unknown. The Wnt/beta catenin pathway is a potent pro-angiogenic pathway that increases endothelial cell proliferation and capillary permeability. Casitas b-cell lymphoma (c-Cbl) is a negative regulator of nuclear active beta catenin. We hypothesized that reduced activity of c-Cbl is likely to augment Wnt/beta catenin signaling in ischemia-induced angiogenesis in the uremic milieu.

Methods: Unilateral hindlimb ischemia (HLI) model was performed in 8-12 week old c-Cbl +/+ and c-Cbl +/- female mice under non-CKD and CKD conditions using the adenine-induced CKD model. Laser Doppler imaging was used to determine perfusion recovery over time. CD31 staining was used to determine capillary density. Capillary leakage was detected by dextran infusion. Both were quantitated as integrated density. Wnt/beta catenin activity was examined in primary human endothelial cells.

Results: On normal diet, c-Cbl$^{+/-}$ mice exhibited higher perfusion, capillary density, endothelial permeability and beta catenin expression in the ligated limb compared to c-Cbl$^{+/+}$ mice. Adenine diet significantly compromised all of these parameters in both c-Cbl$^{+/-}$ and c-Cbl$^{+/+}$ mice. Mechanistic probing revealed that the uremic milieu inhibited Wnt activity and the nuclear pool of active beta catenin in the endothelial cells, which was in part driven by P-cresyl sulfate.

Conclusions: This study demonstrates the detrimental effect of uremia on ischemia induced angiogenesis and suppression of Wnt/beta catenin signaling in endothelial cells by specific uremic solutes. These results provide the first potential link of uremic solutes with a potent pro-angiogenic Wnt/beta catenin pathway. This interaction warrants further exploration as a potential CKD-specific mediator of PAD.

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	Perfusion Index (Day 14)		Integrated density CD31 per micron surface area		Integrated density Dextran per micron surface area	
	c-Cbl+/+	c-Cbl+/-	c-Cbl+/+	c-Cbl+/-	c-Cbl+/+	c-Cbl+/-
Normal Diet	0.37 ±0.03	0.79 ±0.08 (p=0.01)*	337.9±49.43	849.2±125.4(p=0.01)*	87.44±9.71	147.9±24.97 (p=0.02)
0.2% Adenine Diet	0.26 + 0.07 (p = 0.05)#	0.23 ± 0.20	92.40±14.17 (p<0.001)#	117.6±10.46	51.81±4.99 (p=0.01)#	66.84±5.63

*compares both groups on normal diet, #compares c-Cbl+/+ mice on adenine and normal chow

SA-PO345

Factors Determining Timing of Onset of Hypertension in Premature Infants

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Background: We recently demonstrated that phthalate-exposed premature infants with unexplained hypertension (HTN) had evidence of inhibition of 11-BHSD2, and secondary activation of the mineralocorticoid receptor (MR). Neither HTN nor increased sodium transporter expression occurred until an adjusted age closer to term, despite phthalate exposure weeks earlier. We tested the hypothesis that other types of HTN in premature infants might also present with a similar timeframe.

Methods: We reviewed charts of all premature infants with HTN at two tertiary-care centers during the last 8 years, excluding infants with unknown phthalate exposures, and single case categories: neurology and renal vein thrombosis. Analyses included HTN incidence, time-course of HTN, and phthalate exposure.

Results: 106 infants with 107 episodes of HTN were found. In both AKI and thromboembolism groups, HTN developed at an early chronological and postmenstrual age. Their phthalate exposure was small. In all other categories HTN presented near 40 weeks postmenstrual age, usually with low renin. Phthalate exposures were large in the pulmonary and medications groups, and moderate in the CAKUT group.

Conclusions: The development of HTN in premature infants from AKI and thromboembolism is unrelated to phthalate exposure and to sodium transporter maturation. Onset of HTN for phthalate-exposed infant categories (pulmonary, medications, and CAKUT) occurs closer to an adjusted term age - more in line with activation and maturation of MR-dependent sodium transporter processes such as we reported for infants with unexplained hypertension. Phthalate exposure may be a major factor in influencing the onset of HTN amongst these categories of infant hypertension.

Diagnostic, time-course, and phthalate exposures by category for premature infants with hypertension

Categories	#	Plasma renin activity < 11.0 ng/ml/h #/n	Gestational age at birth weeks	DX of hypertension postmenstrual weeks	median IV fluid phthalate exposure ml (IQR)	Median respiratory phthalate exposure days (IQR)
Thrombolic	2	1/2	33.1 +/- 3.9	34.1 +/- 3.7	NR	4 (2)
CAKUT	8	NR	35.2+/- 0.8	41.8 +/- 6.7	235 (382)	18 (22)
AKI	4	NR	25.6 +/- 1.2	27.5 +/- 1.2	104 (160)	17 (4)
Pulmonary	84	73/74	27.6 +/- 2.7	39.5 +/- 2.7	21 (75)	68 (48)
Medications	9	5/5	29.9 +/- 4.6	43.7 +/- 5.9	181 (514)	71 (32)

NR, not reported; IQR, interquartile range; DX, diagnosis

SA-PO346

The Post-Stenotic Human Kidney Shows Microvascular Dropout and Remodeling

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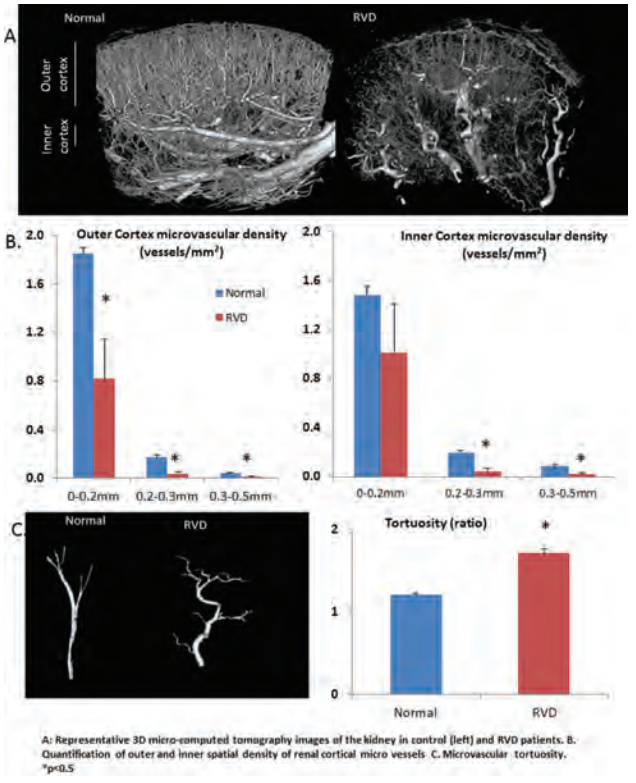
Background: In animal models, post-stenotic kidney shows microvascular rarefaction, with loss of small outer cortical vessels correlating with limited kidney recovery after revascularization. However, whether stenotic human kidney shows microvascular loss is incompletely understood. We tested the hypothesis that Renal srtery stenosis (RAS) leads to microvascular remodeling in human kidneys

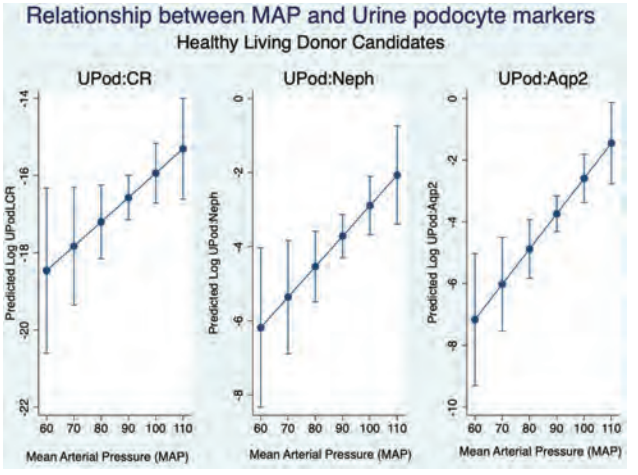
Methods: Nephrectomy samples from 4 patients with obstructive RAS, & 5 discard donor kidneys (Lifesource, MN) as controls were collected after IRB approval. The renal arteries were cannulated & perfused at physiological pressure with an intravascular radiopaque contrast agent. The kidney was segmented, scanned with micro-CT at 20μm resolution, & 3D images reconstructed. Microvascular diameter & spatial density were quantified (Analyze™). Cortical vessels were tomographically isolated to calculate tortuosity (ratio of path/linear length) as a measure of angiogenic activity & vascular immaturity.

Results: Age (55-65 yrs), sex, & body mass index were similar in both groups. Spatial density of medium & large cortical micro vessels (200-500μm in size) was significantly diminished in outer & inner cortex in Renovascular disease (RVD) compared with normal kidneys (Fig. 1A-B). RVD kidneys showed significant loss of small (<200μm) micro vessels in the outer cortex, as well as an increase in microvascular tortuosity compared with normal kidneys, suggesting remodeling & compensatory angiogenic activity

Conclusions: The post-stenotic human kidney shows cortical microvascular loss & remodeling. These alterations may magnify deterioration of renal function & interfere with renal ability to recover upon treatment, supporting development of pro-angiogenic strategies to preserve the kidney



A: Representative 3D micro-computed tomography images of the kidney in control (left) and RVD patients. B. Quantification of outer and inner spatial density of renal cortical micro vessels C. Microvascular tortuosity. *p<0.5



SA-PO347

Hypertension Is Associated with Podocyte Hypertrophic Stress and Detachment Among a Healthy Living Donor Cohort

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Background: HTN is a major cause of ESKD. Kidney donors are a highly selected cohort with normal renal function. Podocyte depletion is a major process by which kidney disease progression occurs. Therefore we tested the hypothesis that Mean Arterial Pressure (MAP) would be related to rate of podocyte detachment.

Methods: 87 living donors that eventually donated were utilized. Two podocyte markers (podocin,nephrin) and a distal tubular/collecting duct marker (aquaporin2) were measured from urine pellet in spot samples normalized to creatinine. UPod:CR is a marker of podocyte detachment, Podocin to Nephrin ratio (UPod:Neph) of podocyte hypertrophic stress and Podocin to Aquaporin ratio (UPod:Aqp2) to understand relation of glomerular to tubular injury. Linear regression was adjusted for donor age, BMI, eGFR before donation.

Results: No donors were on antiHTN therapy. Mean SBP was 124±13, DBP was 73±10. See table and figure.

Conclusions: MAP is linearly related to podocyte detachment, hypertrophic stress and preferential glomerular injury even among healthy controls cleared for donation.

Funding: NIDDK Support

UPod:CR (Podocyte Detachment) (Log Transformed)	Coef.	Std. Err.	P value	LCL	UCL
MAP (every 10 mm Hg)	0.63	0.32	0.055	-0.02	1.28
eGFR (per 10 ml/min)	0.05	0.21	0.83	-0.38	0.47
Donor Age (every 10 years)	0.13	0.28	0.64	-0.21	0.03
BMI (Kg/m2)	-0.09	0.06	0.15	-0.21	0.03
UPod:Neph (Podocyte Hypertrophic Stress) (Log Transformed)					
MAP (every 10 mm Hg)	0.82	0.33	0.01	0.17	1.48
eGFR (per 10 ml/min)	-0.79	0.21	0.71	-0.50	0.35
Donor Age (every 10 years)	0.03	0.29	0.91	-0.5	0.6
BMI (Kg/m2)	-0.09	0.06	0.16	-0.22	0.04
UPod:Aqp (Glomerular vs. Tubular Injury) (Log Transformed)					
MAP (every 10 mm Hg)	1.14	0.33	0.001	0.49	1.79
eGFR (per 10 ml/min)	-0.14	0.21	0.50	-0.57	0.28
Donor Age (every 10 years)	-0.21	0.28	0.46	-0.78	0.35
BMI (kg/m2)	-0.07	0.06	0.27	-0.19	0.05

SA-PO348

SNF472, a New Therapeutic Approach to Improve Outcomes in CKD Patients with Peripheral Artery Disease

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Background: Peripheral Artery disease (PAD) is a common vascular disease associated with functional impairment and increased risk of cardiovascular events in Chronic Kidney Disease (CKD) patients undergoing dialysis. Poor limb salvage outcomes and high post-amputation mortality in hemodialysis (HD) patients highlight the need for earlier medical therapies. Cilostazol (SOC) use stays limited and requires caution in this population. Clinical studies demonstrate associations between arterial calcification and adverse outcomes in PAD patients. SNF472, a selective calcification inhibitor that interferes in the formation and growth of hydroxyapatite, is under development for calciphylaxis. We evaluated the effects of SNF472 on limb functional recovery and blood perfusion in a rat model with Vitamin D3 (VitD)-induced arterial calcification.

Methods: Arterial calcification was induced in 32 SD rats using (VitD) by 3 consecutives daily s.c. dosing of 120 kIU/kg. Rats were divided into four groups and treated during 12 days by: vehicle s.c, vehicle p.o, SNF472 (20mg/kg/day, s.c.) or cilostazol (20mg/kg/day, p.o.). An additional group of 8 rats without VitD received vehicle only (sham). Efficacy was evaluated at day 12 and 5 days after treatment stop. Posterior limb blood perfusion was measured using Laser Doppler Imaging and limbs walking ability were evaluated by measuring Maximum Walking Distance (MWD) and Maximum Walking Time (MWT) using a treadmill. Rats were sacrificed 10 days after treatment stop, and aorta was collected for calcium analysis.

Results: VitD-induced arterial calcification was associated with decreased blood perfusion and impairment of limb walking ability (MWT and MWD) compared to sham. SNF472 reduced aorta calcification by 41% compared to vehicle. No effects of cilostazol on vascular calcification were observed. The inhibition of calcification in SNF472 treated animals was associated with significant higher limb blood perfusion compared to vehicle or Cilostazol (1.28 and 1.37-fold higher, respectively at D12: p< 0.001) and translated into significant improvement in limbs walking ability compared to vehicle (515±114 meters vs 334±187 meters, respectively: p<0.05).

Conclusions: Our results evidence that SNF472 may present a promising new therapeutic approach to treat PAD associated with high vascular calcification such as in CKD and HD patients

Funding: Commercial Support - Sanifit Therapeutics

SA-PO349

Carbamylated Homocitrulline Is Associated with Left Ventricular Hypertrophy in CKD: Results from the CAIN Study

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Background: Carbamylated proteins arise from post-translational modifications that accelerate with renal failure, can cause molecular and cellular dysfunction, and have been strongly associated to the presence of cardiovascular disease among patients with chronic kidney disease (CKD). To-date, it is unknown whether tissue levels of carbamylated proteins are linked to specific cardiac outcomes such as left ventricular hypertrophy (LVH). We hypothesized that carbamylated protein burden in cardiac tissue is associated with LVH in dialysis patients.

Methods: We analyzed 47 left ventricular (LV) human heart tissues collected in The CAIN (Cardiac Aging in CKD) Study Cohort. LV tissues from hemodialysis (HD; n=17), hypertensive (HTN; n=10) and healthy controls (n=20) were analyzed in a 3-arm cross-sectional controlled design. All tissues underwent gross pathologic exam. Tissue

carbamylation levels was assessed by western blotting using an antibody specific to homocitrulline as a marker (Cat. No. 22428, Cayman Chemical, MI, USA). Multiple regression analysis was performed to determine the association between carbamylated tissue levels and left ventricular free wall thickness (LVWT), an index of LVH.

Results: Across all 3 groups, there was no statistical difference in age (HD 46.2±11.2; HTN 55.9±5.0; control 49.2±15.3 yrs, p=0.2), gender (HD 59; HTN 60; control 50 % male, p=0.9) or BMI (HD 27.0±4.8; HTN 30.9±6.6; control 26.5±5.9 kg/m^2, p=0.1). HTN and HD patients had significantly greater LVWT standardized by body surface area on gross pathologic exam (p<0.0001). Basal homocitrulline was detected in LV tissues from control donors, however LV tissues from HTN patients exhibited increased homocitrulline levels (1.6-fold), while HD patients had even greater levels (2.3-fold) compared to control (P<0.0001). Multiple adjusted regression analysis showed that carbamylated homocitrulline levels was significantly associated with LVWT (p<0.05).

Conclusions: This present study is the first to assess carbamylated tissue levels in human hearts. We provide evidence that homocitrulline in LV tissues is associated with LVH as assessed by LVWT. Further studies are critically needed to determine the mechanisms involved.

SA-PO350

Higher Type VI Collagen Formation Is Independently Associated with Increased Risk of Cardiovascular Events and Mortality in the Canagliflozin Cardiovascular Assessment Study (CANVAS)

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Background: Patients with type 2 diabetes are at significantly higher risk of experiencing cardiovascular complications. It has been shown that type VI collagen (COL VI) is markedly upregulated during pathogenic processes of the heart and vasculature. The role of COL VI biomarkers has been sparsely investigated in relation to cardiovascular events. We evaluated a novel biomarker of COL VI formation as a prognostic marker for cardiovascular events and mortality in patients with type 2 diabetes from the Canagliflozin Cardiovascular Assessment Study (CANVAS).

Methods: COL VI formation was assessed with the PRO-C6 enzyme-linked immunosorbent assay (ELISA), detecting a specific fragment of COL VI released upon deposition in the extracellular matrix. PRO-C6 levels were measured in baseline plasma samples from 3531 patients from CANVAS. Results from Cox proportional hazard regression models were reported as unadjusted or adjusted for the traditional risk factors age, sex, BMI, systolic and diastolic blood pressure, duration of diabetes, LDL cholesterol, HbA1c, eGFR, and albumin/creatinine ratio.

Results: In the unadjusted analysis, levels of PRO-C6 were significantly associated with heart failure (HF), cardiovascular death (CVD), a composite of HF and CVD, and all-cause mortality (Table, all P<0.0001). To assess the independent association of PRO-C6 with these outcomes, the analysis was adjusted for traditional risk factors. In the adjusted analysis, PRO-C6 was significantly associated with the listed outcomes (Table, all P≤0.0001).

Conclusions: In conclusion, this study reveals an independent association of the COL VI biomarker PRO-C6 with cardiovascular events and mortality in the CANVAS study.

Funding: Commercial Support - Janssen Research & Development, LLC

Table. Association of PRO-C6 with heart failure (HF), cardiovascular death (CVD), HF+CVD, and all-cause mortality.

	Unadjusted			Adjusted		
	Sample size (n events)	HR [95% CI]	P-val	Sample size (n events)	HR [95% CI]	P-val
Heart failure (HF)	3531 (127)	1.06 [1.04-1.07]	<0.0001	3504 (126)	1.04 [1.02-1.06]	<0.0001
Cardiovascular death (CVD)	3531 (260)	1.05 [1.04-1.06]	<0.0001	3504 (257)	1.03 [1.01-1.05]	0.0001
HF+CVD	3531 (358)	1.05 [1.04-1.06]	<0.0001	3504 (355)	1.03 [1.02-1.05]	<0.0001
All-cause mortality	3531 (391)	1.05 [1.03-1.06]	<0.0001	3504 (388)	1.03 [1.02-1.04]	<0.0001

SA-PO351

Deletion of the Gene for Transient Receptor Potential Canonical 1 (TRPC1) Channel Induces Diabetes and Cardiovasculopathy but Paradoxically Prevents the Cardiomyopathy from a High-Fat Diet (HFD)

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Background: TRPC1 is key in transducing Ca signal in the hypertrophic response to aortic constriction, but its natural role is unknown. Since +/- & -/- mice are hyperglycemic & since untreated diabetes induces cardiomyopathy, we tested if TRPC1 deficiency creates cardiovascular phenotypes & if 45% HFD aggravates these abnormalities.

Methods: In age-matched wild type, +/- & -/- males, we measured body weights (BW), heart weights (HW) & did echocardiographic studiies at ages 3, 7, 17 & 23 mon. At 7 mon, we measured blood pressure (BP) by tail cuffs & direct intraarterial readings of systolic (S) & diastolic (D) to get mean arterial BP (MABP). We studied aortic relaxation in chamber.

Results: In null mice, HW was 12-13% lighter at 2 mon & 7 mon. At 23 mon, HW remained 19% & HW:BW 23% lower, documenting cardiac hypoplasia. At 7 mon, in null mice, left ventricular (LV) end-diastolic (ED) volume (29 vs 56 μl) was down by 48%, ES volume (3 vs 11 μl) by 73%, stroke volume (26 vs 45 μl) by 42%, & stroke index (SI) (0.8 vs 1.4 μl/g BW) by 44%. Cardiac output (CO)(14 vs 21 ml/min) was 33 % down, as were SBP (113 vs 121 torr), DBP (77 vs 86 torr) & MABP (89 vs 98 torr). Systemic arterial resistance [MABP/CO], was elevated (7 vs 5 torr/ml/min). Pulse pressure was similar. Arterial stiffness [pulse pressure/SI] was up 2 fold as arterial compliance was down by 49%. Aortic relaxation, normal at 2 mon, was reduced at 23 mon in null mice. At 17 mon, LV fractional shortening (FS) was down by 16% in null & by 13% in +/-. LVEF was down by 7% in null. In wild type, HFD x 3 mon reduced FS by 17%, LVEF by 8% & SI by 26%. In contrast, HFD did not alter FS, LVEF, or SI in null mice, as if without TRPC1, the reduced cytosolic Ca blunts the activation of cardiac myocytes by HFD via the signaling pathway of Ca-calcineurin (CN)-NFAT. Indeed, SI in +/- mice with less impaired Ca homeostasis tended to fall with HFD.

Conclusions: Given the blunted cell Ca response to activation in all cells we studied in null mice, these data support the thesis that TRPC1 deficiency attentuates the intracellular CN-NFAT signaling to normal proliferative stimuli, producing cardiac hypoplasia & low CO. The same blunted Ca signaling prevents the cardiomyopathy induced by HFD and seen in wild types.

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

SA-PO352

Normalization of Matrix Metalloproteinase Activity and Elastin Structure by Finerenone Reduces Arterial Stiffness in Mesenteric Resistance Arteries in a Rat Model of CKD

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Background: Both albuminuria and arterial stiffness are independent predictors of cardiovascular morbidity and mortality associated to the progression of chronic kidney disease (CKD). This association supports a potential generalized vascular dysfunction with similar pathophysiologic mechanisms linking the cardiovascular-renal axis in patients with albuminuria. We aim to explore the effect of the mineralocorticoid receptor antagonist, finerenone (FIN), on vascular mechanics and structure in 2nd branch mesenteric resistance arteries (MA) from Munich Wistar Fromter (MWF) rats, a genetic model of non-diabetic CKD.

Methods: Wistar (W) and MWF rats were randomly grouped (n=10 per group) to receive either 10 mg/kg/day FIN (W-FIN; MWF-FIN) or vehicle (W-C; MWF-C) for 4 weeks by oral gavage. Mechanical and structural properties of MA were determined by pressure myography. Elastin organization in the internal elastic lamina (IEL) was analysed by confocal microscopy based on elastin autofluorescence. Metalloproteinase activity was assessed by gelatin zymography.

Results: FIN led to a significant reduction (>40%) in albuminuria in MWF. The stress/strain relationship curve in MA from MWF-FIN exhibited a significant right-shift, indicative of lower intrinsic arterial stiffness. No changes were observed in structural parameters (external and internal diameter, wall-to-lumen ratio, cross-sectional area and adventitial, medial and wall thickness) of MA. IEL from MWF-C animals showed significantly smaller fenestrae than W-C, without changes in total number of fenestrae. FIN significantly reduced fenestrae number in both W-FIN and MWF-FIN, and increased fenestrae area in MWF-FIN. Pro-MMP-2 activity was significantly lower in plasma samples from MWF-C rats compared with W-C rats, paralleled by higher levels of active MMP-2 and MMP-9 activities. FIN restored pro-MMP-2, MMP-2 and MMP-9 activities in MWF to control levels.

Conclusions: This study demonstrates the efficacy of FIN to ameliorate albuminuria and normalize circulating MMP activities, elastin structure and intrinsic arterial stiffness in MA from MWF rats.

Funding: Commercial Support - Bayer AG (Germany)

SA-PO353

Cellular Remodeling of Cardiomyocytes: An Unappreciated Phenotype of Congenital Proximal Renal Tubular Acidosis?

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Background: Proximal renal tubular acidosis is caused by mutations in *SLC4A4* which encodes the electrogenic $Na^+/2HCO_3^-$ cotransporter variants NBCe1-A (predominantly renal and a major contributor to maintenance of plasma [HCO_3^-]) and NBCe1-B/C (predominantly non-renal and contributes to regulation of cardiomyocyte pH). Our laboratory has recently characterized a strain of Nbce1b/c-knockout (KO) mice that maintains Nbce1a in the kidney with widespread loss of Nbce1b/c elsewhere, allowing for the study of Nbce1 loss in non-renal organ systems in the setting of a normally maintained pH. To date no cardiac phenotype has been reported in pRTA patients (in fact Nbce1b/c blockade is considered to be cardioprotective under certain circumstances)

yet studies of cardiomyocytes isolated from spontaneously-hypertensive rats, in which Nbce1b/c activity is also impaired, reveal compensatory upregulation of the electroneutral Na^+/HCO_3^- co-transporter Nbcn1 and hypertrophy. Nbcn1 activity is predicted to impose a greater Na^+ load than Nbce1 activity. This is hypothesized to affect the activity of the Na^+-Ca^{2+} exchanger, decreasing Ca^{2+} extrusion, and ultimately activating Ca^{2+} dependent growth pathways. In the present study, we assess the hearts of Nbce1b/c-KO mice for signs of this pro-hypertrophic pathway.

Methods: Cardiac tissue from age and gender-matched C57 wild-type (WT) and KO littermates was weighed post-dissection and normalized to body weight for comparison. Cardiac tissue homogenates were prepared for RT-qPCR and western blot analysis of Nbcn1 expression.

Results: KO mice had 22 ± 8% larger heart-to-body weight ratios (n=5, p=0.03). Abundance of NBCn1 transcripts was 45 ± 10% greater in the KO compared to the WT (n=3, p=0.02). Abundance of NBCn1 protein was 85 ± 17% greater in the KO compared to WT mice (n=3, p<0.05).

Conclusions: Nbcn1 is upregulated both at the level of transcript and protein within cardiomyocytes of the enlarged hearts of Nbce1b/c-KO mice, consistent with the hypothesis that remodeling of acid/base transporter expression contributes to the enhanced growth of cardiac tissue.

SA-PO354

High PTH Levels Inhibit Biorhythm of Human Vascular Smooth Muscle Cells In Vitro

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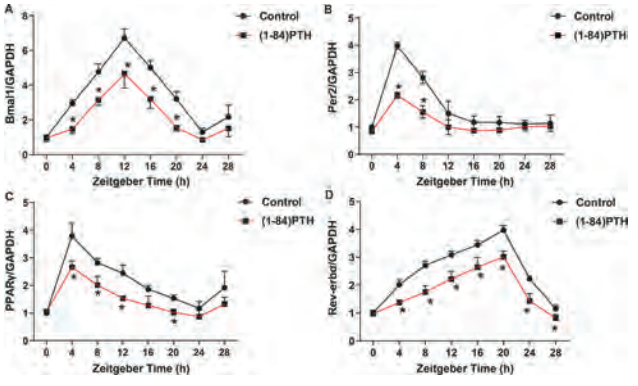
Background: In normal condition, vascular smooth muscle cells have self circadian rhythm. Here we observed the influences of high levels of parathyroid hormone (PTH) on circadian genes in human aortic vascular smooth muscle cells (hASMCs) *in vitro*.

Methods: Human ASMCs were divided into control and (1-84)PTH(10nmol/L) group. The timing of the beginning stimulated was counted as zeitgeber time 0 (ZT0). Thereafter, cells were collected every 4 hours for a total of 28 hours. The mRNA expressions of PPARγ, Bmal1, Per2 and Rev-erbα in different groups of cells at different time points were detected by quantitative polymerase chain reaction (qRT-PCR).

Results: mRNA expressions of PPARγ and clock genes Bmal1, Per2 and Rev-erbα showed circadian rhythms in the control group, and peaked at ZT4, ZT12, ZT4 and ZT20 respectively. High levels of PTH could inhibit the expression amplitudes of above genes, without affecting time phases of expressions.

Conclusions: High PTH levels could inhibit biorhythm of HASMCs, its relationships with vascular circadian rhythm abnormalities need further study.

Funding: Government Support - Non-U.S.



SA-PO355

G Protein-Coupled Receptor 37L1 Is Expressed on the Nuclear Envelope

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Background: G protein-coupled receptors (GPCRs), expressed on the plasma membrane, interact with various types of ligands, which trigger a cascade of signal transduction events leading to different intracellular responses that in turn manifest in physiological changes. Some GPCRs also reside and exert signals from intracellular organelles such as the nucleus, endoplasmic reticulum, and Golgi apparatus. Recently, we reported that G protein-coupled receptor 37L1 (GPR37L1) is expressed in the apical membrane of renal proximal tubule cells (RPTCs) and participates in luminal sodium transport and blood pressure regulation by regulating the renal expression of NHE3. However, the mechanism by which GPR37L1 regulates NHE3 expression and function in the RPTC has not been studied.

Methods: We employed Tandem affinity purification using GPR37L1 tagged with streptavidin and calmodulin binding peptides, followed by mass spectrophotometry (MS) analyses to identify the proteins interacts with GPR37L1. Subcellular location of GPR37L1 was determined by confocal fluorescence imaging and immunoblotting on the cells or the nucleus prepared from the RPTCs expressing GPR37L1 tagged with green fluorescence protein (GPR37L1-GFP).

Results: Tandem affinity purification of GPR37L1, combined with MS analyses, revealed the association of GPR37L1 with mediators of nuclear importing proteins, such as RAN-GTPase, importin-5, and importin-7. In silico analyses of GPR37L1 amino acid sequence revealed the presence of a potential nuclear localization signal at the N-terminus. Confocal fluorescence imaging of RPTCs expressing GPR37L1-GFP showed distinct nuclear membrane expression of GPR37L1. In addition, fluorescence imaging of nuclei isolated from the RPTCs expressing GPR37L1-GFP showed the expression on the nuclear envelope. Immunoblot analyses confirmed the presence of GPR37L1 in the nuclear protein prepared from the RPTCs expressing GPR37L1-GFP. The purity of the nuclear protein preparations was confirmed by the presence of histone deacetylase 2, a marker for nuclear protein, the absence of Na,K-ATPase, a marker for plasma membrane, and the absence of calnexin, a marker for endoplasmic reticulum.

Conclusions: Our results show that GPR37L1 also resides on the nuclear envelope and may play a critical role in the regulation of the expression of genes responsible for maintaining normal electrolyte balance and blood pressure.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO356

Identification of X-Linked Alport Syndrome by Genetic Testing in a Girl Who Had Remained Undiagnosed After Two Kidney Biopsies Within a 10-Year Period

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Introduction: Girls with X-linked Alport syndrome (XLAS) are reported to show slower disease progression than boy patients, and most of them are asymptomatic carriers. Previous reports suggest that proteinuria begins at a median age of 7 years, finally resulting in end-stage kidney disease at a median age of 65 years. However, it is well known that the rate of disease progression in girls with XLAS cannot be predicted accurately, and that the clinical phenotype shows considerable variation, even among affected girls in the same family.

Case Description: We describe a girl with XLAS who showed hematuria and proteinuria in a kindergarten urine test at the age of one year, and who was followed up regularly thereafter. Her father had undergone kidney transplantation due to an unknown primary kidney disease when he was in high school. At the age of 7 years, the patient underwent initial kidney biopsy. Light microscopy revealed mesangial proliferation but an immunofluorescence study revealed no IgA deposition, and electron microscopy demonstrated no basement membrane abnormalities. The patient was therefore diagnosed as having non-IgA mesangial proliferative glomerulonephritis. As her proteinuria persisted at about urine protein-creatinine ratio; 0.5 g/gCr, therapy with a cocktail of prednisolone, mizoribine, warfarin, and dipyridamole was started at the age of 8 years, and this led to a gradual decrease of the proteinuria to 0.2 g/gCr. However, from the age of 13 years, the proteinuria and creatinine increased gradually to 1.0 g/gCr and 1.0 mg/dL, respectively, so we performed a second kidney biopsy which yielded results similar to the first one. Finally, at the age of 17 years, we conducted genetic testing of both the patient and her parents. This revealed that the patient had a heterozygous missense mutation in intron 7 of the *COL4A5* gene, and that her father was homozygous for the mutation.

Discussion: This girl showed relatively rapid progression of XLAS. Most girls with XLAS have no problem with ocular lesions or hearing, and those with decreased kidney function are very rare. Therefore, even today many clinical issues remain unclear, and diagnosis of XLAS in girls is sometimes very difficult without genetic testing.

SA-PO357

Spontaneous Remission of Genetic, Apparently Primary FSGS Presenting with Nephrotic Syndrome Challenges Traditional Notions of Primary and Genetic FSGS

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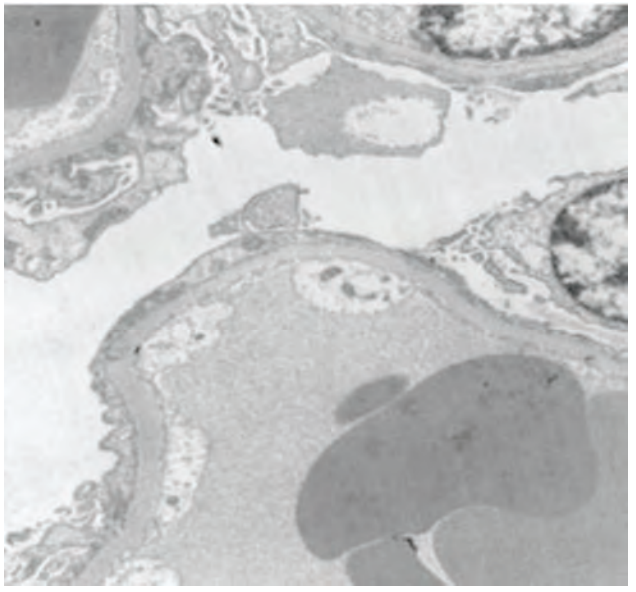
Introduction: Focal segmental glomerulosclerosis (FSGS) presenting with nephrotic syndrome (NS) with focal sclerosing lesions and diffuse foot process effacement (FPE) is considered diagnostic of primary FSGS. KDIGO guidelines advise against genetic testing in adult idiopathic FSGS. We report a case of genetic FSGS that presented with NS and biopsy features of primary FSGS which resolved spontaneously.

Case Description: A 26-year-old healthy Caucasian female was referred for new onset NS. She had peripheral edema, a BP of 157/110 a urine protein creatinine ratio (UPC) of 9.04, a serum albumin of 2.3 mg/dl and a serum creatinine of 1.2 (eGFR 62). Other serological tests were negative. A kidney biopsy showed focal, segmental sclerosis in 2 of 47 glomeruli with diffuse FPE on EM consistent with primary FSGS. She declined corticosteroid treatment. She was treated with lisinopril/furosemide. Genetic testing showed a missense variant (p.Asn125Ser) in TRPC6. This missense variant is ultrarare, is predicted pathogenic and was previously reported in two pedigrees with FSGS with demonstrated gain of function *in vitro*. We continued conservative therapy and 8 months after diagnosis she has had complete remission with her UPC declining to 0.67, serum albumin improving to 4.3 and serum creatinine to 0.9 (eGFR 88).

Discussion: Most authors differentiate primary FSGS from all other causes including genetic and adaptive forms of FSGS. Our case demonstrates that genetic FSGS cannot be

differentiated clinically from primary FSGS and can undergo spontaneous remission. Given prognostic and therapeutic implications, we suggest that genetic testing be performed in any young adult with FSGS prior to a therapeutic trial with high dose steroids.



SA-PO358

X-Linked Alport Syndrome Caused by Synonymous Mutation, p.Pro-786Pro Inducing Incomplete Aberrant Exon Skipping in COL4A5

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Introduction: X-linked Alport syndrome (XLAS) - a progressive hereditary kidney disease caused by mutations in COL4A5 gene coding type IV collagen α5 chain (α5(IV)), with the median age of developing end-stage renal failure in male XLAS patients of 25 years, and 70 or 90% of the patients had reached ESRD before the age 30 and 40 years, respectively. Additionally, patients with truncating mutations tend to show severe phenotypes.

Case Description: Two male siblings with mild phenotypes whose mother had hematuria, now 43, and 34 years old; both had hematuria since childhood. Their proteinuria appeared at 33, and 20 years, respectively. The elder recently developed ESRD, and the younger is still CKD-stage III b. The younger's kidney biopsy at 31 years of age, showed a thin glomerular basement membrane and normal α5(IV) expression. Gene analysis revealed both possessing only a novel hemizygous synonymous variant of c.2358A>G (p.Pro786Pro) in COL4A5 exon 29 among all 3 genes responsible for Alport syndrome. Further transcript analysis revealed this single base substitution caused aberrant splicing of exon 29 complete skipping which was shown both in peripheral lymphocytes and urinary sediments. Exon 29 is constituted by 151bp and the skipping of this exon leads to a frameshift mutation at the transcript level and supposed to be showing severe phenotypes. However, a small amount of normally spliced transcript was also detected in the transcript from urinary sediments which might be because of incomplete aberrant splicing by the variant.

Discussion: The synonymous mutation can cause aberrant splicing in COL4A5. However, relatively mild phenotypes were led by the presence of a small amount of normally spliced transcript along with aberrant splicing. By this normal transcript, α5(IV) expression was positive on glomerulus. In conclusion, synonymous mutations can have pathogenicity by causing aberrant splicing. Additionally, normal transcript production along with the aberrantly spliced transcript prevents the patients from presenting severe phenotype. Accurate genetic diagnosis would be required to elucidate the onset mechanism by synonymous variants or presentation of atypically milder phenotypes.

SA-PO359

A Novel Aquaporin 2 Insertion Mutation in a Chinese Family with Autosomal Dominant Nephrogenic Diabetes Insipidus and Chronic Renal Failure

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Introduction: Mutations in aquaporin 2 (AQP2) cause mostly autosomal recessive or rarely autosomal dominant nephrogenic diabetes insipidus (NDI). Patients with autosomal dominant NDI usually exhibit less phenotype and have mutations in the carboxyl-terminal tail important intracellular routing of the AQP2. We described a family of autosomal dominant NDI carried a novel AQP2 mutation but presented a severe phenotype, which led to early-onset renal failure.

Case Description: A 26-year-old Chinese female manifested polyuria, polydipsia, and nocturia after birth. Her family history was non-revealing. She did not have non-obstructive hydronephrosis and never received NSAID or thiazide to treat her polyuria. Pertinent laboratory investigations showed abnormal renal function with serum creatinine 3.4 mg/dL, and hyperchloremic metabolic acidosis (chloride 115, HCO_3^- 19 mmol/L), persistently low urine osmolality (around 50-100 mOsm/kg.H_2O) and markedly increased serum von Willebrand factor and coagulation factor VIII in response to desamino-8-D-arginine AVP (DDAVP) test. Direct sequencing of *AVPR2* and *AQP2* gene showed two nucleotide GC insertion at c.755 of AQP2, resulting in a frameshift mutation (p.R253Dfs*82, +52 AA) and altering the amino acid sequence between R254 to A271. Of note, her one-year-old son also exhibited severe polyuria two days after birth and was found carrying the same mutation.

Discussion: We presented the first autosomal dominant NDI family with a severe phenotype, including early-onset polyuria in the neonatal period and renal failure in early adulthood. The functional experiment focusing on autosomal dominant AQP2 mutations in the C-terminal end is warranted.

SA-PO360

A Case of Classical Fabry Disease due to De Novo GLA Genetic Mutation That Showed Characteristic Findings in Both Renal and Nerve Biopsy

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Introduction: Fabry's disease (FD) is an X-linked lysosomal storage disorder due to mutations in the alfa-galactosidase A(GLA). Most cases are related to GLA inherited mutations, cases of de novo onset occur rarely.

Case Description: A 53-year-old man has been pointed out proteinuria for 20 years, but the reason had been unclear. When he was 50 years old, he suffered from sick sinus syndrome and has been fitted pacemaker. 3 years later, his serum creatinine got worse to 1.5 mg/dl and urine protein 1.5 g/gCr. Kidney biopsy was done and diagnosed as FD due to de-novo GLA mutation (R112C). Enzyme replacement therapy (ERT) using agalsidase-alfa was started and the concentration of Lyso-Gb3 went down for 2 months. But his left leg's sensory neuropathy was obvious and nerve biopsy also showed peripheral neuropathy that could match to FD. Switching from agalsidase-alfa to agalsidase beta could lead to decrease the concentration of Lyso-Gb3.

Discussion: In Japanese FD's patient, genetic GLA de novo mutation is rare. After starting ERT, evaluation of organ damage is necessary, and if there were any problems, switching therapy may be suggested. There are few cases which both kidney and neuro biopsy were done. These findings emphasize the importance of early diagnosis, genetic analysis, and selecting appropriate enzyme replacement therapy to prevent irreversible organ damage that occurs during the course of the disease. In conclusion, early diagnosis, evaluating organ damage, and adequate ERT may be necessary for FD's patient to decrease Lyso-Gb3 that would be associated with good prognosis.

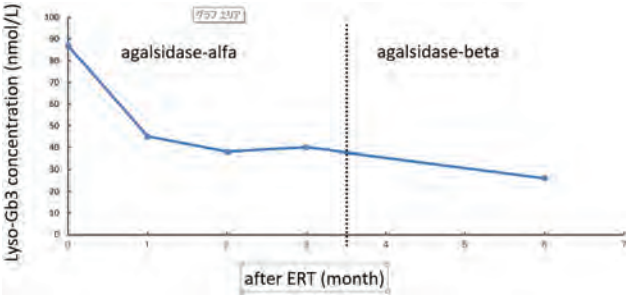

Figure 1 Lyso-Gb3 concentration after starting ERT

SA-PO361

An Unusual Case of Diffuse Proliferative Lupus Nephritis Presenting with Predominant C1q Deposition and No IgG Deposits That Is Responsive to Treatment

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Introduction: Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease, with nephritis as one of the most striking manifestations. Renal biopsy usually reveals glomerular deposits that stain predominantly for IgG and contain co-deposits of IgA, IgM, and C3. It is rare to have C1q as a dominant deposit with no IgG deposits on renal biopsy. We are presenting a case of lupus nephritis with predominant C1q deposits.

Case Description: 34-years-old female with history of idiopathic thrombocytopenia (10 years ago), SLE (1 year ago), antiphospholipid syndrome with history of stroke and one 2nd trimester miscarriage admitted with dyspnea, fever and AKI and suspicion of thrombotic thrombocytopenic purpura. Laboratory work up showed serum creatinine (SCr) of 2.13mg/dl, low complements C3/C4, positive cardiolipin IgM, anti-dsDNA and lupus anticoagulant. UA was positive for 2+ blood and 3+ protein with urine protein to

creatinine ratio of 3.2. Echocardiogram was suggestive of libman sachs endocarditis. Patient underwent kidney biopsy which revealed endocapillary proliferative GN (class IV lupus). It was negative for IgG but had 3+ C1q deposits, 2+ C3, 1+ IgA and trace IgM deposits. The patient was started on methylprednisone & mycophenolate and within a month her SCr returned to baseline with complete resolution of proteinuria and hematuria.

Discussion: C1q nephropathy is considered to be a variant of FSGS. It presents as mesangial proliferation with prominent C1q deposits on immunofluorescence microscopy and negative lupus serology. It typically has a poor response with immunosuppression. On the contrary, lupus nephritis presents as a 'full house pattern' with predominant IgG deposits. Our patient with predominant capillary and mesangial C1q deposits in lupus nephritis hasn't been described in the literature hence clinician needs to be aware that C1q deposits can be a variant of lupus nephritis and can be very responsive to immunosuppression.

SA-PO362

Tubulointerstitial Nephritis and Uveitis Unmasked by Decreasing Anti-TNF Alpha

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Introduction: Tubulo-interstitial nephritis and uveitis (TINU) is characterized by ocular and renal manifestations, and it could be associated with autoimmune, genetic, vascular, medication, and paraneoplastic etiologies. Here we present a case of TINU unmasked by decreasing anti-TNF alpha agent adalimumab.

Case Description: 55-year-old Caucasian male with history of hypertension on lisinopril and psoriatic arthritis on adalimumab admitted for acute renal failure. Four weeks prior to admission, patient presented to the ophthalmology clinic with sudden onset and progressively worsening bilateral blurring of his vision with symptomatic central vision loss. At that time, he was found to have a localized macular detachment with yellow choroidal lesions, and managed conservative with weekly follow up. Notable recent medication change was dose reduction of adalimumab from 40mg to 20mg every other week in the past year due to improvement of joint symptoms. On the day of admission at ophthalmology clinic, he was found to have an increase in retinal fluid and bilateral serous detachment with yellow/white choroidal lesions in the peripheral macula and fovea consistent with atypical uveitis. Routine labs showed sCr 12.3mg/dL (baseline 1.1 mg/dL 4 months ago), K 7.1mEq/L, HCO3- 14mEq/L, BUN 80mg/dL. Urinalysis showed 1+ leukocyte esterase, no blood or protein, urine microscopy showed WBC clumps. Despite medical management, and robust urine output, repeat K was 8.5 mEq/L required emergent hemodialysis. He was also initiated on prednisone for concerns of acute interstitial nephritis. Renal biopsy revealed acute interstitial nephritis with mononuclear cells and focal clusters of eosinophils. Other serologies showed CRP 23.7mg/L, ACE <5U/L, Lysozyme 9.9mcg/mL, ANA positive at 1:160, speckled, IgG4 negative. CT was negative for malignancy. His vision improved significantly after the first dose of prednisone. HD was discontinued on day 4 of admission, and prednisone was tapered over months. Discharge sCr was 6.76mg/dL and 2 weeks post discharge was 1.8mg/dL.

Discussion: In patient with TINU, uveitis can present as vision loss without apparent inflammation, and it often presents separately from interstitial nephritis. This patient has atypical posterior uveitis and biopsy-proven AIN consistent with TINU, likely unmasked by tapering of adalimumab.

SA-PO363

Syphilis-Associated Idiopathic Nodular Glomerulosclerosis

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Introduction: Idiopathic nodular glomerulosclerosis (ING) is a rare entity in non-diabetics with a similar appearance on biopsy to diabetic nephropathy. ING has been associated with hypertension, dyslipidemia, and cigarette smoking; however, there is no known association with syphilis. Here we present a case of possible latent syphilis associated ING.

Case Description: A 73-year-old non-diabetic male with history of urothelial carcinoma, chronic kidney disease stage III, and mild hypertension presented due to worsening lower extremity swelling. Initial creatinine was elevated at 2.2 mg/dL. Urinalysis was notable for large blood and protein. Workup revealed urine protein of 6939 mg. Serologic workup was negative including C3, C4, ANA, dsDNA, ANCA, Hep B/C, and monoclonal antibodies. Of note, rapid plasma reagin and fluorescent treponemal antibody were positive. The patient was without signs of syphilis with a diagnosis of latent syphilis made. Light microscopy noted interstitial fibrosis, tubular atrophy, and globally sclerotic glomeruli. Immunofluorescence staining highlighted linear IgG accentuation. Electron microscopy revealed foot process effacement, increased mesangial matrix, and swollen endothelial cells. He was diuresed and discharged with continued follow-up in clinic with control of symptoms.

Discussion: ING presents in non-diabetics likely due to the formation of advanced glycation end products, angiogenesis, and altered renal hemodynamics. ING has an association with cigarette smoking, hypertension, dyslipidemia, and obesity. Our patient did not have a history of diabetes or smoking and was found to have markers positive for syphilis. Manifestations of syphilitic renal disease include but are not limited to membranous glomerulonephritis, focal segmental glomerulosclerosis, minimal change disease, and interstitial nephritis. However, a review of the literature has not shown a case of syphilis associated ING. ING is most commonly seen with cigarette smoking with concurrent hypertension. However, other pathophysiologic factors cannot be excluded. Given the new diagnosis of syphilis, syphilitic involvement must be considered as an etiology in conjunction with underlying mild hypertension given lack of diabetes history. While it cannot be shown that syphilis is responsible, clinical awareness of the possibility may allow for further identification of cases in the future.

SA-PO364

Thrombotic Microangiopathy as the Presenting Feature of Newly Diagnosed HIV Infection Treated with Eculizumab

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Introduction: Thrombotic microangiopathy (TMA) is a known complication of HIV infection. HIV infection precipitates endothelial injury and has been associated with increased complement activation. It may also trigger the onset of atypical HUS in patients with genetic predisposition. We present a case of severe kidney failure due to TMA in the setting of newly diagnosed HIV infection which was successfully treated with eculizumab.

Case Description: 58-year-old Hispanic male with history of hypertension presented with 1 month of diarrhea, lower extremity edema and oliguria. Initial labs revealed a serum creatinine 9.0 mg/dL, albumin <2.0 g/dL, urine protein/creatinine 8 g/g, platelet count 103,000, hemoglobin 7.9 g/dL, LDH 619 U/L and schistocytes on peripheral smear. Workup revealed newly diagnosed HIV/AIDS with a CD4 count of 40 cells/uL, viral load of 124,000 copies and coinfection with hepatitis B. Kidney biopsy demonstrated chronic active TMA with focally positive c4d staining of the glomerular capillaries and acute tubular necrosis. ADAMTS13 was normal and stool Shiga toxin was negative. He was found to have CMV viremia but immunostaining for CMV on kidney biopsy was negative. Genetic testing for complement abnormalities revealed a complement factor H receptor 5 variant of unknown significance but was otherwise negative. The patient was dialysis dependent at presentation. He was initiated on antiretroviral therapy and started on eculizumab infusions every 2 weeks for treatment of HIV-associated TMA. Although his CD4 count remained low at 70, his HIV viral load became undetectable, his hematologic parameters improved and creatinine clearance improved to 25 mL/min leading to discontinuation of dialysis after 2 months.

Discussion: In the modern era of antiretroviral therapy, TMA is a rare complication of HIV infection. Because uncontrolled HIV infection has been associated with increased complement activation, we hypothesized that HIV infection triggered dysregulation of complement activity in our patient and that treatment with eculizumab would be beneficial. Although our patient did not have a common gene mutation associated with atypical HUS, treatment with eculizumab in conjunction with ART resulted in hematologic remission as well as improvement in kidney function and discontinuation of dialysis.

SA-PO365

Hypocupremia: Cause or Effect of Nephrotic Syndrome?

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Introduction: Nephrotic syndrome is well known to cause urinary loss of several factors including trace elements. Conversely, a rare association of copper deficiency with nephrotic syndrome (NS) has been reported in the literature with possible improvement in NS with correction of deficiency. Here we report an unusual presentation of Focal Segmental Glomerulosclerosis (FSGS) with worsening peripheral neuropathy and bicytopenia.

Case Description: A 57- year- old Caucasian female with history of hypertension, lower extremity edema and peripheral neuropathy of unknown etiology for several months admitted to the hospital for work up after outpatient testing revealed neutropenia and severe anemia. Hemoglobin on admission was 7.5g/dl (baseline hemoglobin of 12g/dl 6 months prior), WBC count of 1.5 x 109/L with absolute neutrophil count (ANC) of 0.4 x 10^9/L. Physical exam was unremarkable except for palor and sensory neuropathy lower extremities. Initial work up for bicytopenia was negative for evidence of hemolysis. Bone marrow biopsy showed megaloblastoid appearance. As part of megaloblastic anemia work up, levels of vitamin B12, folate, and zinc were within normal limits. However, serum Copper level was extremely low at 8 microgram/dl (72-166 microgm/dL). Urinalysis on admission with a bland urine and more than 300 mg/dl protinuria. Spot urine protein to creatinine ratio (UPC) of 14g/g, 24-hour urine protein excretion of 9 gram. Serum creatinine 0.5 mg/dl, serum albumin of 1.6 g/dl, and Triglyceride 232 mg/dl. Work up for NS included negative Hepatitis A, B and C panel, HIV, Syphilis T. Palladium antibodies, ANA, and Normal Complements levels. Copper gluconate supplement resulted in normalization of her anemia and leukopenia. Proteinuria improved from 9 grams to 6.8 grams after normalization of copper levels. A random kidney biopsy showed FSGS. Prednisone was started at 1 mg/kg daily with improvement in UPC ratio to 2.4g/g from 6.8g/g and serum albumin to 3.2 g/dl from 1.6g/dl at 12 weeks.

Discussion: FSGS is a diverse syndrome from several causes- some known and others unknown. There has been reports of urinary copper excretion correlated with urinary protein excretion in animal models. In our patient, severe copper deficiency likely explained sensory neuropathy and bicytopenia. It is open to debate weather NS started initially with urinary loss of copper leading to deficiency or copper deficiency exacerbated FSGS.

SA-PO366

Nephrocalcinosis Secondary to Excessive Oxalate Ingestion

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Introduction: Deposition of calcium oxalate or calcium phosphate within the renal medulla can lead to nephrocalcinosis. This most often occurs in the setting of hypercalciuria with or without hypercalcemia, but in rare instances, may occur due to hyperoxaluria. In the majority of cases, nephrocalcinosis is asymptomatic without progression to end stage renal disease, unless the underlying cause is left untreated. We present a case of renal failure secondary to nephrocalcinosis in the setting of prolonged secondary hyperoxaluria.

Case Description: A 68 year-old male with well-controlled hypertension presented to the emergency department after routine lab work at a yearly primary care visit revealed potassium 6.1 mEq/L, BUN 103 mg/dL, and creatinine 12.3 mg/dL. Corrected serum calcium was 8.2 mg/dL and 25-hydroxy vitamin D was 46.1 ng/mL. Two years prior to presentation, creatinine was 0.9 mg/dL, but had risen to 2.36 mg/dL one year prior to presentation. Four years prior to presentation, the patient had started a new diet consisting mainly of green beans, turnip greens, and broccoli. Review of previous urinalyses showed multiple instances of calcium oxalate crystals in his urine. Renal ultrasound showed decreased renal size bilaterally, as well as, bilateral non-obstructing renal calculi. CT abdomen and pelvis demonstrated bilateral nephrocalcinosis, likely secondary to hyperoxaluria in the setting of prolonged excessive dietary oxalate intake. Despite conservative medical management including initiation of a low oxalate diet, the patient did not recover renal function and became dialysis dependent.

Discussion: Once nephrocalcinosis is diagnosed, it is imperative to determine the underlying cause as to guide management. If standard laboratory testing does not reveal a cause, such as hypercalcemia or renal tubular acidosis, there should be increased suspicion for hyperoxaluria. Although secondary hyperoxaluria is most often due to fat malabsorption, a careful dietary history should also be taken to evaluate for chronic ingestion of excessive amounts of oxalate (e.g. rhubarb, spinach, green beans, etc.) or oxalate precursors (e.g. vitamin C), as highlighted by this case. In patients with secondary hyperoxaluria, dietary oxalate intake should be minimized, while calcium and fluid intake should be liberalized. If treated promptly, renal function often recovers.

SA-PO367

Fatal Hyperammonemia due to an Underlying Urea Cycle Disorder Unmasked by a High-Protein, Ketogenic Diet

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Introduction: Late-onset manifestations of urea cycle disorders may be difficult to recognize and if left untreated can lead to devastating, life threatening consequences. We present the tragic case of a young man who presented with acute hyperammonemic encephalopathy due to ornithine transcarbamylase (OTC) deficiency unmasked by a high protein, ketogenic diet.

Case Description: A 30-year-old male with no significant medical history presented with altered mental status. He was an avid hiker with recent tick exposure. Two months previously, he started a ketogenic diet and was taking high dose protein shakes and anabolic mimetics to build muscle. Initial workup including computed tomography (CT) of the head, magnetic resonance imaging of the brain, electroencephalography, urine toxicology screen, cerebrospinal fluid culture for bacterial meningitis and tick borne illness was negative. He was found to have an ammonia level of 215 umol/L with no evidence of liver failure and undetectable alcohol level. He received one hemodialysis session but quickly deteriorated, developing seizures requiring intubation and mechanical ventilation. Repeat ammonia level worsened to 430 umol/L and repeat CT head showed diffuse cerebral edema with impending herniation. He was treated with hypertonic saline, mannitol, an extraventricular drain was placed, and he was initiated on continuous-renal replacement therapy. Despite improvement in ammonia level to < 20 umol/L, the patient failed to make a meaningful neurologic recovery. Genetic testing for an underlying urea cycle disorder revealed OTC deficiency.

Discussion: Urea cycle defects result in the ability to breakdown protein and eliminate nitrogenous wastes, resulting in hyperammonemia. Symptoms vary from poor appetite, somnolence, and behavioral disturbances to rapid neurologic deterioration including seizures, coma, and death if not promptly recognized and treated. Although urea cycle disorders typically present shortly after birth, partial defects may manifest in adulthood in the context of increased catabolic stress. A high index of suspicion and rapid initiation of hemodialysis to remove ammonia is critical for a favorable outcome. We believe our patient's high protein diet and use of anabolic mimetics precipitated a hyperammonemic crisis in the setting of mild OTC deficiency which unfortunately proved fatal.

SA-PO368

Not All Severe Lactic Acidosis Implies an Ominous Prognosis

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Introduction: Glycogen Storage Disease (GSD) type 1, also knows as Von Gierke Disease is an inherited disorder caused by deficiencies of specific enzymes in the glycogen metabolism pathway. It comprises 2 major subtypes GSD 1a (deficiency of the enzyme Glucose 6 Phosphatase) and GSD 1b (deficiency of the transporter enzyme, Glucose 6 phosphatase translocase G6PT. GSD 1a results from mutation in G6PC gene on chromosome 17q21 that encodes G6Pase. GSD 1b results from mutations of SLC 37A4 gene on chromosome 11q23.3. Incidence is 1/100,000.

Case Description: This case is of 27 years old white female who was referred to clinic initially due to the following complaint metabolic acidosis and proteinuria of 3 gr/ 24 hr. Based on chart review, she has chronic lactic acidosis between 8-12 mmol/L and subsequent GAP metabolic acidosis. In addition, she has persistent hyperuricemia, hyperglycemia and hypertriglyceridemia. She used to have hypoglycemic episodes during childhood, however she has developed chronic pancreatitis and hyperglycemia due to glycogen deposition.

Discussion: GSD leads to accumulation of Glycogen and fat in the in Liver, kidney and intestinal mucosa is the final result. Initial laboratory findings include hypoglycemia, lactic acidosis, hyperuricemia, hypercholesterolemia and hypertriglyceridemia. Non-invasive molecular genetic testing that includes full gene sequencing of G6PC is preferred for making the diagnosis. Gene sequencing analysis has a detection rate of up to 100% however may miss certain mutations. Liver Biopsy has been also performed to demonstrate the glycogen deposition. Renal failure may occur from primary tubular or glomerular dysfunction. Glomerulosclerosis and podocytopaties have been described previously. The main targets for the management are the prevention of acute metabolic derangements, prevention of acute and long-term complications, attainment of normal psychological development and good quality of life. The main goal of this presented case that even though lactic acidosis is usually associated with poor short-term outcomes, the knowledge of metabolic pathways will help to approximate unusual etiologies of lactic acidosis in the adult population.

SA-PO369

Pharmacologic Management with Sodium Phenyl Acetate/Sodium Benzoate with or Without Dialysis for the Treatment of Hyperammonemia: A Case Study

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Introduction: Hyperammonemia is an underrecognized indication for emergent renal replacement therapy in patients with inborn errors of metabolism. Duration of hyperammonemia correlates with neurologic consequences: seizures, intracranial hypertension, cerebral edema, and herniation. Dialysis decreases ammonia levels acutely, but has associated risks. Additionally, sodium phenylacetate/sodium benzoate is an FDA approved ammonia scavenger for treatment of hyperammonemia in patients with inborn errors of metabolism. There is no current study comparing the effectiveness of ammonia scavengers and dialysis for the acute management of hyperammonemia in adult patients. We present a case in which both treatments were utilized.

Case Description: The patient is a 21-year-old man with a diagnosis of pyruvate decarboxylase deficiency type A on chronic tube feeds who presented with lethargy after one loose bowel movement. Initial workup revealed a lactic acid of 5mmol/L, ammonia level of 447mmol/L, and creatinine of 0.6mg/dL. On exam, the patient had no focal motor or sensory deficits but was agitated and combative. A central venous line was placed for dialysis access and he underwent 2.5 hours of hemodialysis followed by approximately 12 hours of central venovenous hemodiafiltration, in addition to IV dextrose-containing fluids. The ammonia level fell to 34mmol/L. In consultation with the Genetics service, intravenous sodium phenylacetate with sodium benzoate were started and maintained normal levels of ammonia while his home feeding regimen was adjusted. Two weeks later, the patient was readmitted to the ICU with a similar presentation and serum ammonia level of 338mmol/L. This time, sodium phenylacetate with sodium benzoate was initiated rapidly. Ammonia levels were decreased to 47mmol/L over 7 hours without requiring dialysis.

Discussion: This case highlights the potential effectiveness of sodium phenylacetate/sodium benzoate. These ammonia scavengers combine with amino acids to form alternative products for urinary nitrogen excretion. While therapy with hemodialysis should be pursued, patients with normal renal function may achieve rapid resolution of hyperammonemia with volume resuscitation, feeding, and administration of sodium phenylacetate/sodium benzoate as a low risk and cost-effective treatment strategy.

SA-PO370

A Rare Cause of Resistant Hypertension

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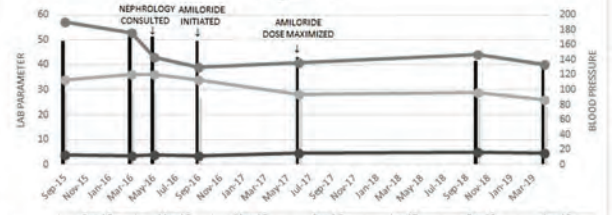
Introduction: Resistant hypertension is defined as suboptimally controlled blood pressure despite concurrent use of three antihypertensive agents of different classes, including a diuretic. A thorough evaluation for secondary causes of hypertension is crucial to allow timely institution of treatment to limit end-organ damage and associated morbidity and mortality.

Case Description: A 66-year-old African American gentleman was referred for evaluation of uncontrolled hypertension and declining renal function. His antihypertensive regimen consisted of maximal doses of Valsartan, Verapamil ER and Clonidine. Diuretics were being held due to persistent hypokalemia despite potassium supplementation. Family history was notable for his father succumbing to renal failure of unclear etiology at age 50, his sister passing from her ESRD, and his mother having well controlled hypertension. Physical exam was otherwise unremarkable, with the patient appearing euvolemic. Lab review suggested progressive decline in GFR, equating to CKD stage 3 with minimal proteinuria, with mild but persistent hypokalemia and metabolic alkalosis. An arterial blood gas confirmed chronic metabolic alkalosis. Both plasma renin activity and aldosterone were undetectable. Based on the above findings, a diagnosis of Liddle syndrome was made. Amiloride was started and gradually uptitrated. He had a reassuring response to treatment which translated into stability of his GFR (Figure 1).

Discussion: Liddle Syndrome is a rare autosomal dominant disorder associated with a gain-of-function mutation involving the epithelial sodium channels, which mimics the manifestations of hyperaldosteronism, without a demonstrable elevation in serum aldosterone. Our case illustrates the benefits of prompt diagnosis and treatment to arrest the progression of hypertension mediated end-organ damage.

Figure 1



	Sep-15	Mar-16	May-16	Sep-16	Jun-17	Oct-18	Apr-19
SBP	165	179	173	165	144	139	131
DBP	98	96	96	89	87	88	77
K	3.7	3.4	3.7	3.6	4.7	4.8	4.7
HCO3	34	36	36	34	28	29	26
eGFR	57	53	43	39	41	44	40

SA-PO371

Amphetamine Toxicity Mimicking Pheochromocytoma

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Introduction: Pheochromocytoma is a catecholamine-secreting tumor with about 95% of the tumors located in the abdomen. A typical patient will present with the classic triad of episodic headaches, sweating, and tachycardia. Interestingly, patients with amphetamine toxicity can also present with a comparable clinical picture and differentiating the two can be a challenging conundrum.

Case Description: A 50-year-old Caucasian female with a history of nonepileptic seizure disorder presented to the ER with chest pain, nausea, and vomiting. She was found to be markedly hypertension with associated supraventricular tachycardia (SVT) which did not respond to intravenous adenosine or to cardioversion. She was placed on esmolol infusion, with improvement in heart rate. However, the patient developed acute pulmonary edema resulting in respiratory failure needing intubation and mechanical ventilation. Despite esmolol infusion, she had persistent hypertension with the systolic blood pressure in the 200s and was started on nitroglycerin infusion concomitantly. The resistant nature of hypertension led to concern for pheochromocytoma, and on further evaluation, she was found to have elevated urinary catecholamines, metanephrines, and vanillylmandelic acid. However, urine drug screen was also positive for amphetamines. One week after presentation, repeat testing of urinary and serum catecholamines showed marked reduction in these values. MRI of the abdomen (adrenal protocol) showed no concerning solid lesions. She was eventually tapered off the infusions and started on low dose oral metoprolol, primarily with the intent of preventing recurrence of SVT. These findings led to the conclusion that the patient's symptoms and laboratory findings were secondary to amphetamine toxicity.

Discussion: This case illustrates the strikingly similar presentations of amphetamine toxicity and pheochromocytoma, and highlights the importance of a good history, along with work up, to be able differentiate between two conditions with remarkably different clinical implications.

SA-PO372

Invasive Primary Mucormycosis: Renal Rhizopus

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Introduction: Mucormycosis is a known entity among diabetics and immunosuppressed patients. There are cases where the mucormycosis spectrum can involve individual organs, and in this case, the renal system. Treatment is difficult as this fungus is angio-invasive and can cause tissue infarction, which limits antifungal penetration to the affected tissues. The choice of antifungal therapy has traditionally been set to amphotericin B in regards to mucormycosis, whether in systemic or focal disease. However, in this case, posaconazole was a successful alternative treatment option to amphotericin.

Case Description: A 49 year white male with chronic kidney disease, uncontrolled diabetes, and a history of IV drug use presented to urgent care with right flank pain, dysuria, and hematuria, sent home with a subsequent visit to the emergency department. Hydronephrosis was noted on the right kidney and a ureteral stent was placed by urology. 2 weeks later, the patient followed up with urology to undergo uretero-renoscopy. However, this was postponed 2 weeks due to severe hyperglycemia. The patient underwent the uretero-renoscopy, revealing amorphous material within the right renal pelvis. MRI revealed a fungus ball with 60 percent of the volume of the right renal parenchyma consistent with pyelonephritis, as well as poor blood flow consistent with renal infarction. Biopsy revealed Rhizopus species, with repeat renal biopsy demonstrating fungal colonization. Urine and blood cultures were negative. The patient was started on posaconazole, as opposed to amphotericin B, due to a relatively normal left kidney and overall clinical stability. Due to the vascular and parenchymal invasion, nephrectomy was performed with pathology demonstrating extensive fungal pyelonephritis with abscesses. The patient continued with oral posaconazole for any microscopic remnants of the fungus for six weeks and did well with monitoring of CKD and diabetes.

Discussion: In most cases of reported isolated renal Rhizopus, amphotericin and nephrectomy are standard of care with an azole anti-fungal used as step down therapy or therapy in which the patient does not respond to amphotericin. With utilization of both posaconazole and nephrectomy, alternative to amphotericin B, the patient was able to maintain stable residual kidney function in an infection associated with high mortality and was successfully treated for isolated mucormycosis of the rhizopus group.

SA-PO373

Monoclonal Gammopathy of Renal Significance: Not Just a Disease of the Old

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Introduction: Immunotactoid glomerulopathy is a rare finding on kidney biopsy, reported in 0.06-0.1% of biopsies. It is characterized by subepithelial and subendothelial microtubules made of immunoglobulin deposits. Without clinical findings suggestive of lupus or cryoglobulinemia, monoclonal gammopathy of renal significance (MGRS) should be considered. MGRS can be caused by any B cell or plasma cell clonal proliferative disorder. Less than 2% of those diagnosed with monoclonal gammopathy of undetermined significance (MGUS) are under the age of 40 years. Of all patients with MGUS, 1.5% have MGRS.

Case Description: This is a 26 year old man who presented for evaluation of proteinuria and hematuria, found incidentally during work-up for an acute episode of diarrhea that subsequently resolved. Initial UPCR and UACR were 977 mg/g and 740 mg/g, respectively. Past medical history was notable only for "ear problems" requiring Eustachian tubes as a child. He was not on any medications or supplements. Blood pressure was 143/89, but there were no other abnormalities on physical exam. Complements, anti-dsDNA Ab, and CBC were normal. eGFR was 125 ml/min/1.73m^2. SPEP and UPEP were not initially done as he was deemed low risk for harboring a plasma cell dyscrasia at his age. Kidney biopsy showed immunotactoid glomerulopathy with dominant IgG Kappa. SPEP and UPEP with IFE were then done and neither showed any monoclonal bands. Bone marrow biopsy showed rare polytypic plasma cells with a small kappa-restricted plasma cell population on flow cytometry. Given his young age and the natural history of MGRS, the plan is to treat with plasma cell directed chemotherapy.

Discussion: MGRS can occur in younger patients presenting with proteinuria. When evaluating young patients with proteinuria, a broad differential should be considered. The most common causes in adults are diabetes, amyloidosis, lupus, minimal change disease, membranous nephropathy, and FSGS. We also considered IgA nephropathy and Alport's syndrome. MGRS was low on our differential, yet kidney biopsy showed immunotactoid glomerulopathy due to MGRS despite negative SPEP and UPEP. Kidney biopsy was key in obtaining a diagnosis in our patient. It is important even in young patients not to rule out potentially treatable causes of kidney disease based on age.

SA-PO374

A Unique Case of Malakoplakia of the Kidney

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Introduction: Malakoplakia is a rare inflammatory condition that has a gross and microscopic appearance resembling xanthogranulomatous pyelonephritis but with distinctive Michaelis-Gutmann bodies on pathology. Malakoplakia can affect any organ system but genitourinary tract involvement is the most common, particularly in immunocompromised individuals. We are presenting a unique case of malakoplakia presenting with AKI requiring dialysis and our treatment approach.

Case Description: A 40yo Caucasian female presented to a local hospital with altered mental status. She had a history of tobacco, alcohol, and cocaine abuse. There was no history of IV drug abuse or prior urinary tract infections. She was found to be in septic shock due to Escherichia coli bacteremia from a UTI that progressed to multiorgan failure requiring ventilatory support and AKI (SCr=7.2) that required renal replacement therapy. UA demonstrated pyuria and proteinuria. Renal US showed bilaterally enlarged kidneys. Clinical status improved with antibiotic treatment although there was no recovery in kidney function and fevers persisted. Renal biopsy was performed revealing sheets of macrophages, eosinophils and Michaelis Guttman bodies on EM characteristic of malakoplakia. Antibiotics were changed to ciprofloxacin and she was transferred to a tertiary care facility for further care. A multidisciplinary approach involving nephrology, urology, infectious diseases and immunology was initiated. Patient was started on methylprednisolone and consideration of bilateral nephrectomy for source control was discussed. Five weeks into the hospital course daily fevers subsided and evidence of kidney recovery ensued. Ultimately, she was discharged off of dialysis with improving kidney function, prolonged course of antibiotics, and steroid taper. Six months later she is off both antibiotics and steroids with stable kidney function (SCr=1.4).

Discussion: Renal malakoplakia must be kept in mind for patients presenting with AKI and bilaterally enlarged kidneys especially in the setting of E. coli bacteremia from a urinary source. It was a challenging case given her age and nephrectomy as potential treatment options. We learned that in such cases suppressing the inflammatory process as an adjunct to antibiotic therapy can salvage kidney function. A multidisciplinary approach was very useful in avoiding surgery and coming up with treatment plan.

SA-PO375

Extramedullary Hematopoiesis Misdiagnosed as Interstitial Nephritis in a Patient with Renal Dysfunction: A Case Report

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Introduction: Extramedullary hematopoiesis is widely known to occur in patients with primary myelofibrosis (PMF). Autopsy studies on individuals with PMF revealed that extramedullary hematopoiesis occurred in the kidneys in 35% of the cases. However, there is little awareness regarding such lesions.

Case Description: A 63-year-old man was diagnosed with PMF (Dynamic International Prognostic Scoring System: intermediate-1-risk group) with a JAK2 V617F gene mutation based on a detailed examination of persistent white blood cells (white blood cell count, >10,000 /μL). An examination of the patient's medical records revealed a correlation between leukocytosis and deterioration of renal function and urinary protein. Thus, a kidney biopsy was performed. Advanced lymphocyte invasion was recognized in the interstitial tissue, and the uriniferous tubule extensively disappeared. Glomerular lesions were investigated, and only some were determined to have resulted from mesangial proliferative glomerulonephritis. Based on these findings, the pathologist diagnosed the patient with interstitial nephritis. However, because of the large number of cells with nuclear atypia in the stroma, additional immunohistochemical staining was also performed, such as Glycophorin A, Napthol AS-D, Myeloperoxidase and CD42b. As a result, invasion of three lineages of immature cells, erythroblasts, megakaryocytes, and granulocytes, was identified. Renal dysfunction resulting from interstitial cellular infiltration due to extramedullary hematopoiesis was therefore diagnosed. Treatment with ruxolitinib was initiated after a renal biopsy. The patient's decrease in estimated glomerular function rate stabilized, and urinary protein concentration decreased slowly.

Discussion: Although, in myeloproliferative disorders, proliferative glomerular lesions are widely considered to be renal disorders, there is little awareness regarding interstitial lesions. Extramedullary hematopoiesis of the kidney in PMF is not uncommon, but 40% of cases are reportedly misdiagnosed as interstitial nephritis. Because extramedullary hematopoiesis can be controlled by treatment with ruxolitinib, early detection is important.

SA-PO376

A Case of Membranous Nephropathy in a Child with Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked (IPEX) Syndrome

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Introduction: Classic IPEX syndrome is an autosomal recessive genetic disorder secondary to a mutation in the *FOXP3* gene. It is characterized by enteropathy, chronic dermatitis, type I diabetes mellitus (T1DM), hypoparathyroidism, antibody mediated cytopenias, and immune dysregulation. Up to 33% of patients with IPEX syndrome have renal complications, including tubulointerstitial nephritis, focal tubular atrophy, minimal change disease, membranous glomerulopathy and irregular granular immune deposits in glomeruli/tubular basement membranes. There are fewer than 10 reported cases in the literature.

Case Description: A 3-year-old female, with a history of IPEX (known gain of function mutation in *STAT3* gene), T1DM, hypothyroidism, nephrocalcinosis, and history of AKI presented with edema. Laboratory studies confirmed nephrotic syndrome: albumin of 1.6gm/dl, urine protein to creatinine ratio of 33. Renal function was normal. No abnormalities found on complement, ANA, or ANCA testing; renal biopsy demonstrated subepithelial electron dense deposits consistent with membranous glomerulopathy with autoantibodies to phospholipase A2 receptor (PLA2R-positive) on biopsy stain and negative serum PLA2R. She is currently treated symptomatically with twice weekly albumin infusions in addition to intermittent IVIG. Treatment with sirolimus was initiated based on successful outcomes reported in some case reports however it did not allow for remission of nephrotic syndrome after 9 weeks of treatment. Since non-autologous stem cell transplant allows for rapid clinical improvement, the aim is for this patient to receive a stem cell transplant from a sibling who will be born in a few weeks from the time of submission of this abstract.

Discussion: PLA2R-postive membranous nephropathy in the setting of IPEX syndrome is exceedingly rare and there is limited data in regards to treatment. Long-term immunosuppression and bone marrow transplantation are the current therapies utilized. IVIG and prophylactic antibiotics are often used adjunctively. Calcineurin inhibitors, mTOR inhibitors and/or steroids have been used to achieve long-term immunosuppression. As more cases are reported in the literature of PLA2R-positive membranous nephropathy in the context of IPEX syndrome better treatment options and outcomes may be established.

SA-PO377

Successful Pregnancies During Ongoing Complement Blockade in Two Patients with Complement Mediated Thrombotic Microangiopathy

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Introduction: In patients with pregnancy-associated complement gene variant mediated thrombotic microangiopathy (cTMA) terminal complement blockade is used for treatment of cTMA flares during pregnancy or following delivery. Data on pregnancies of cTMA patients during ongoing eculizumab (ECU) therapy, however, are scarce.

Case Description: We report pregnancy and delivery outcomes of two cTMA patients enrolled in the Vienna TMA cohort and measured complement related proteins and ECU concentrations at regular intervals during pregnancy, thereafter, and in cord blood. The first manifestation of cTMA occurred in both patients during childhood or young adulthood and was not related to pregnancy. One patient (genetic variants in *CFI, CD46, CFH, C3*) had a total history of 26 cTMA flares and of two uneventful pregnancies with prophylactic plasma infusions. She started ECU at her last cTMA flare, which was continued during her third pregnancy at the age of 27 yrs. The other patient (genetic variants in *CFH, CD46*), 29 yrs of age at her second pregnancy, had a history of recent early abortion during long-term ECU therapy following kidney transplantation, which was performed four years after her first manifestation of cTMA. ECU plasma concentrations were maintained in the therapeutic range during both successful pregnancies and were also detectable in the cord blood. Complement related tests did not indicate alternative pathway activation during pregnancies. Kidney function and blood pressure did not change substantially in both cases. However, proteinuria increased at the end of the third trimester in both patients. Both neonates were adequate for gestational age (weight: 3720 and 3082g; head circumference: 35 and 34 cm; length: 52 and 50 cm) with vaginal delivery in week 40+3 and 37+0 of gestation, respectively. Results of complement related tests in cord blood showed deficient complement activity, with low factor and regulator levels without overactivation, which most likely reflects the situation related to age and the presence of ECU in cord blood.

Discussion: Pregnancy and delivery outcomes with ongoing ECU therapy in two genetically high-risk cTMA patients with preserved native kidney and kidney transplant function were excellent.

SA-PO378

Hypokalemic Periodic Paralysis and Hypertension in Pregnancy: A Diagnostic Challenge

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Introduction: Geller syndrome is a rare autosomal dominant syndrome that causes new or worsening hypertension (HTN) during pregnancy associated with hypokalemia and metabolic alkalosis.

Case Description: We report the case of a 37-year-old Burmese female who presented at 24 weeks' gestation with a 3-day history of progressive lower extremity weakness leading to inability to walk. Her blood pressure (BP) was elevated at 180/90. Initial labs revealed serum potassium (K) 1.6 mMol/L with ECG changes of prolonged QT interval and U waves. Initial spot urine potassium was 5.7 mMol/L and sodium 54 mMol/L. A 24-hour urine potassium was 19.8 mMol/L. Following repletion of K both orally and intravenously, paralysis resolved. Initial diagnosis was hypokalemic periodic paralysis. She was started on nifedipine for HTN. Thyroid function was intact. Cortisol 3.4 mcg/dl (3.5-19.5 mcg/dl), renin <2.5 pg/ml (2.5-45.7 pg/ml), aldosterone <3.0ng/dl (4.0-31 ng/dl), and aldosterone/renin activity (A/RA) <3.8. Catecholamines were all normal. Moderate to severe hypokalemia recurred several times during the pregnancy, and urine K was not suppressed. BP remained high and she required addition of labetalol. She underwent cesarean delivery at 33 weeks' pregnancy due to severe pre-eclampsia. Amiloride was started postpartum. Hypokalemia and hypertension improved.

Discussion: Low renin and high aldosterone related HTN is mainly due to excess mineralocorticoid activity. Our patient experienced worsening HTN and severe hypokalemia during pregnancy, with low renin and low aldosterone levels. The improvement of HTN and hypokalemia postpartum suggests pregnancy-specific factors. Normally, activation of mineralocorticoid receptor (MR) causes renal salt reabsorption through the epithelial sodium channel (ENaC) activity. Progesterone binds to but does not normally activate the MR. Geller syndrome is caused by an activating mutation in the gene encoding the MR S810L. This allows progesterone (as well as spironolactone) to function as agonist, causing increases in BP, and hypokalemia during pregnancy. Liddle's syndrome was also considered as she responded well to amiloride. However, the age of the patient and the lack of family history argue against it. Geller syndrome is rare but should be considered in women with HTN and hypokalemia in pregnancy. Genetic testing is pending.

SA-PO379

Nutcracker Syndrome Treatment Complications

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Introduction: Nutcracker syndrome is the clinical manifestation caused by the situation that the left renal vein suffers from pressure when passing through the angle between the abdominal aorta and the superior mesenteric artery. The syndrome is characterized by hematuria, albuminuria, lumbar pain, and varicocele. Indications for surgical treatment include severe unrelenting pain, significant hematuria, renal functional impairment, and inefficacy of conservative treatment after one year.

Case Description: 29-year-old female with a past medical history of migraines presented to nephrology clinic for evaluation of fatigue, hematuria, and severe left flank pain. She previously was a healthy endurance athlete. Her left flank pain occurs daily and she describes that pain as 10/10 in severity, debilitating, and sharp. CT kidney/pelvis results with a mild narrowing of the left renal vein as it passes between the SMA and aorta and a 1.4 cm left renal cyst. Renal artery duplex subsequently performed revealed left renal vein proximal narrowing and midsegment dilatation suggestive of Nutcracker phenomenon. Venogram performed revealed a 6 mmHg difference between the IVC and the left renal vein confirming the diagnosis of nutcracker syndrome. Patient underwent a left renal vein to inferior vena cava bypass. Unfortunately, the bypass thrombosed and her pain returned. She is currently being considered for autotransplantation of her left kidney. Risks of autotransplantation include a high risk of left nephrectomy in this patient due to a short renal vein segment.

Discussion: Management of Nutcracker Syndrome is a challenging endeavor. Non-surgical approaches include observation, especially in patients younger than 18 years of age since increase in intra-abdominal and fibrous tissue at the SMA origin during growth releases the obstruction of the left renal vein. In addition, weight gain increases the retroperitoneal adipose tissue, which leads to change in the positioning of the left kidney with reduction of tension on the left renal vein. Surgery is definitive treatment, but does not come without risks as seen in our patient. Surgical complications include deep venous thrombosis, retroperitoneal hematoma, ileus, and renal vein thrombosis. Complications of surgery should be extensively reviewed with patients prior to surgery. In retrospect, weight gain should have been trialed in this endurance athlete prior to surgical bypass.

SA-PO380

In Vitro Fertilization (IVF): Early-Onset Preeclampsia Before 16 Weeks' Gestation

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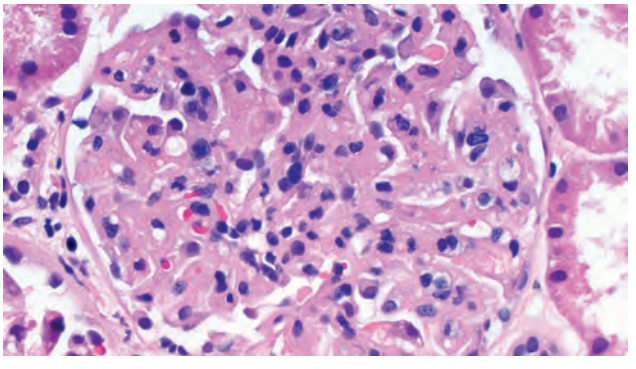
Introduction: Preeclampsia is a hypertensive pregnancy disorder diagnosed in women presenting with new onset hypertension and proteinuria > 20 weeks gestation. IVF has been suggested as a risk factor for preeclampsia. We describe a rare case of early onset preeclampsia < 20 weeks gestation conceived via IVF.

Case Description: A 38-year-old G2P0010 patient at 15w5d gestation conceived via IVF presented with headache and worsening bilateral lower extremity swelling. She was experiencing intermittent headaches and occasional foamy urine for a few weeks before presentation. No past or family history of renal disease. BP was 230/107mm Hg at presentation, UA showed >500 mg/dl protein with no hematuria, 24-hour urine protein was 18 gm/day, serum creatinine 0.76 mg/dl, ALT 88 IU/L, AST 55 IU/L, Platelets 165 K/μL. Transvaginal ultrasound(US) confirmed stated gestational age. Renal US was unremarkable. Relevant serologies were negative. Renal biopsy (see image) showed glomerular capillary endotheliosis and new subendothelial basement membrane (BM) formation creating BM double contours consistent with preeclampsia. The patient opted for termination of pregnancy at 17w2d. BP, transaminitis and proteinuria normalized after one week of pregnancy termination.

Discussion: Preeclampsia presenting before 20 weeks gestation is rare, and a case associated with IVF as a sole risk factor is unique. Other conditions like molar pregnancy, triploidy, lupus nephritis, antiphospholipid antibody syndrome, thrombotic thrombocytopenia, acute fatty liver of pregnancy, hemolytic uremic syndrome and fetal hydrops should be excluded. Common risk factors for preeclampsia are prior pre-eclampsia, chronic hypertension, pre-gestational diabetes, obesity and IVF. Embryo preservation, implantation techniques and placental development with IVF have been suggested as a cause for this serious systemic hypertensive disorder. This is the first reported case of early–onset preeclampsia before 16 weeks gestation with IVF.



SA-PO381

A 64-Year-Old Woman with Raccoon Eyes After Kidney Biopsy

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Introduction: Raccoon eyes is caused by blood tracking into periorbital tissues, which are easliy recognized as a symptom of basal skull fractures. However, it may be a sign of health threatening situations such as multiple myeloma, amyloidosis and so on. Here we discuss a patient with raccoon eyes after the kidney biospy who was finally diagnosed as immunoglobulin light chain (AL) amyloidosis.

Case Description: A 64-year old woman presented to our clinic with 1-year proteinuria. Laboratory study showed Scr was 382 umol/L and 24-hour urine protein quantification was 2.4 g. The testing for monoclonal protein by serum revealed an M-peak in the λ fraction of IgA (Fig1a). The concentrations of κ and λ were 44.95 and 173 mg/L, respectively. The bone marrow cytology test was negative. Ultrasound report indicated the size of right kidney was 9.1×4.4 cm and the left one was normal. But unexpectedly, the patient showed periorbital purpura 24 hours later after kidney biopsy (Fig1b). Congo red staining was positive and also showed strongly λ deposition. EM showing expansion of the mesangium by amyloid fibrils.

Discussion: AL amyloidosis is the most common type of systemic amyloidosis. Renal involvement accounts for almost 70% and most presents as clinically apparent nephrotic syndrome. Sometimes it only presented with proteinuria and slowly progressive deterioration of renal function. So it is necessary to perform tissue biospy once the patients with unknown renal failure accompany with monoclonal M protein. The vascular infiltration of amyloid fibrils in blood vessels in patients with amyloidosis can cause bilateral periorbital ecchymosis by a Valsalva maneuver or minor trauma. Here we firstly reported this rare symptom after kidney biospy in a patient who was finally diagnosed as AL amyloidosis. During the kidney biopsy, the patient was asked to hold breath after inhalation, which mimicked Valsalva maneuver, and thus contribute to the periorbital purpura. Therefore, periorbital ecchymosis warrant more attention as an early cue of amyloidosis.

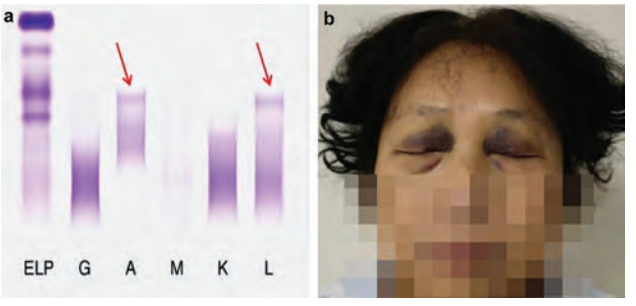

Fig1 (a) M-peak in the λ of IgA. (b) The patient showed bilateral periorbital ecchymosis.

SA-PO382

Hypervitaminosis D Secondary to Agaricus blazei Murrill Mushroom Supplementation: A Case Report

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Introduction: Hypercalcemia secondary to hypervitaminosis D is extremely rare. Vitamin D intoxication usually occurs as a result of inappropriate use of vitamin D preparations and can lead to life-threatening hypercalcemia.

Case Description: Here we present a case of a 45-year-old female diagnosed with colon adenocarcinoma stage IV with liver, lung and bone (ribs) metastases, s/p FOLFOX x 6 cycles, s/p FOLFIRI x 2 cycles. She was admitted for 3rd cycle chemotherapy but hospitalization was complicated by development of pneumonia with worsening of kidney function and initiation of hemodialysis. Despite being on regular hemodialysis, her calcium levels were noted to be increasing. She was also noted to be feeling weaker, with decrease in sensorium attributed to hepatic encephalopathy. Workup for hypercalcemia revealed low normal PTH (21.50 pg/mL, N: 14.0-72), with a normal phosphorus level and elevated Vitamin D (104.28 ng/mL, N: 30-50). It was later revealed upon review of the patient's medications that her mother was giving her various herbal supplements, the latest of which was one that contained an extract from *Agaricus blazei Murrill*, a mushroom native to Brazil that allegedly aids in the treatment of a variety of diseases such as cancer, chronic hepatitis, diabetes, atherosclerosis and hypercholesterolemia.

Discussion: Mushrooms are one of the main dietary sources of vitamin D. The probable offending agent was discontinued and the patient was given IV hydrocortisone. Other therapies such as calcitonin and denosumab were not given due to the patient's history of anaphylactic reactions. Serial monitoring showed that the calcium levels steadily decreased, as well as the Vitamin D levels, although at a slower rate. This case highlights the importance of assessing the intake of all substances, not only prescribed medications, and the potential danger of the ingestion of unlicensed herbal supplements.

SA-PO383

Looking Beyond Tenofovir Renal Toxicity as the Cause of Bone Disease in HIV

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Introduction: Chronic kidney disease (CKD) with tubular dysfunction from tenofovir therapy in HIV disease is frequently associated with bone disease. Here we present a patient referred for evaluation of osteoporosis.

Case Description: A 48-year-old African American phenotypic female with CKD stage 3a-A3 and sub-nephrotic proteinuria, was referred for osteopenia on bone densitometry in the setting of prior history of right hand fracture with minor trauma. Her past medical history was notable for HIV/AIDS diagnosed 24 years ago, for which she was on antiretroviral therapy (ART) including Tenofovir Disoproxil Fumarate (TDF) and protease inhibitors (PI). Upon evaluation, laboratory data showed serum creatinine of 1.5 mg/dL (eGFR 50 mL/min), low normal serum phosphorus with fractional excretion of phosphorus in the urine ~15% and glycosuria. There was mild elevation of serum alkaline phosphatase although bone alkaline phosphatase was normal. Other bone turnover markers (osteocalcin, C-Telopeptide and N-Telopeptide) were in the normal range. Patient underwent bone biopsy with double tetracycline labeling to evaluate turnover and mineralization; histological results showed high turnover osteoporosis with normal mineralization. Patient was started on anti-resorptive therapy with Alendronate. Patient was transitioned to combination ART (dolutegravir, abacavir, lamivudine) 2 years earlier, with improvements in renal parameters. Further review of medications revealed she was being treated with estradiol for gender dysphoria (male to female transition) and had levels below target; estradiol therapy was increased to better support hormone status and thereby mitigate bone loss.

Discussion: Although the impacts of HIV, ART with TDF and PI's, CKD, and tubular dysfunction contribute cumulatively to long-term consequences for bone health, in this patient, hypogonadism related to transgender status was likely a major contributing factor at the time of evaluation. This report highlights that bone disease in CKD patients with HIV is multifactorial and a potentially dynamic process over time in the context of evolving risk factors. Accurate diagnosis remains critical for optimal management.

SA-PO384

Dialysis for an Adult with Maple Syrup Urine Disease

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Introduction: Maple syrup urine disease (MSUD) is a rare genetic defect in branched chain amino acid (BCAA) metabolism which, if untreated, leads to accumulation of isoleucine accompanied by significant neurologic decompensation and even death. MSUD predominantly affects children and there is little data regarding the utility of renal replacement therapy (RRT) to correct metabolic derangements in adults with MSUD.

Case Description: We present the case of a 39-year-old man who was admitted to our facility with acute encephalopathy as a consequence of decompensated MSUD secondary to acute gastrointestinal bleed likely from prolonged high-dose NSAID use. He was transferred with cerebral edema attributed to an elevated leucine level of 2900 umol/L. The patient's baseline levels of leucine, at which he had minimal symptoms, was ~ 1000umol/L. Given the encephalopathy and cerebral edema, he was initially started on CVVHD with monitoring of mental status and leucine levels. Despite RRT, the patient remained symptomatic, raising the possibility his leucine levels were still elevated. He was therefore switched to intermittent hemodialysis for four hours to facilitate rapid removal of leucine, followed by resumption of CVVHD. CRRT was continued for a further 12 hours, with improvement in his leucine levels to <800 and in mental status. The patient made a full recovery and was discharged home 4 days later.

Discussion: Maple syrup urine disease is an inborn error of metabolism of BCAA, characterized by mutations in genes that result in a deficiency of the branched-chain alpha-keto acid dehydrogenase complex that is required to metabolize BCAAs. The disorder gets its name because the urine of affected infants has sweet odor. A specialized diet can prevent accumulation of BCAAs in these patients. However, any hypercatabolic state, including stressors such as infection, injury, and a failure to eat (as occurred in our patient due to his GI bleed), can lead to a metabolic derangement with a rapid increase in amino acid levels and accompanied clinical deterioration. Much of the experience in treating such patients nests in pediatric academic centers and literature, and physicians caring for adult patients have little experience with these complicated cases. Our case therefore illustrates a successful approach to managing metabolic crisis in the setting of an acute metabolic decompensation in an adult patient with MSUD.

SA-PO385

Hyperbilirubinemia and Acquired Fanconi Syndrome

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Introduction: Bile cast nephropathy is characterized by renal dysfunction in the setting of severe hyperbilirubinemia. It is a rare condition that occurs as a result of direct toxicity from bile acids and from tubular obstruction by bile casts. Diagnosis requires a high degree of clinical suspicion and it should be differentiated from hepatorenal syndrome.

Case Description: A 32-year-old man with past medical history of alcoholic liver cirrhosis was admitted for generalized jaundice and dark-colored urine. He reported taking 1.5 grams of acetaminophen daily for 4 days prior to admission. He endorsed stopping alcohol intake 19 months prior to admission. Physical exam was significant for tachypnea, tachycardia, and generalized jaundice. He did not have neurological deficits. Laboratory studies demonstrated severe hypophosphatemia (<1 mEq/L), hypokalemia (2.3 mEq/L), non-oliguric kidney (creatinine of 1.6 mg/dL, unknown baseline), elevated anion gap (14), and hypoalbuminemia of 3 g/dL. Total bilirubin level was elevated at 49.7 mg/dL with a direct bilirubin >30 mg/dL. Blood urea nitrogen (BUN) level was 11 mg/dL. A urine sample revealed glucosuria. The urine sediment demonstrated bile casts. The calculated fractional excretion of phosphate in urine was 40%. He was initially treated for suspected acetaminophen toxicity and for decompensated liver failure with octreotide, midodrine, and albumin. He required aggressive intravenous infusion of phosphate and potassium. The patient was medically stabilized and all his electrolyte imbalances corrected. After peaking at 1.8 mg/dL, his creatinine improved to 1.4 mg/dL with supportive care.

Discussion: In this presentation, we attributed the cause of severe hypophosphatemia and non-oliguric acute kidney injury to bile cast nephropathy. Risk of bile cast formation increases when total bilirubin levels rise above 20 mg/dL. As a majority of filtered phosphate is reabsorbed in the proximal tubules (>80%), severe hyperbilirubinemia can lead to hypophosphatemia by way of proximal tubulopathy, more classically known as acquired Fanconi's syndrome. Previous case reports have reported that the degree of hypophosphatemia is inversely correlated with bilirubinemia. As bile cast nephropathy is partially reversible, therapy should be focused on treating the cause of liver failure and correcting metabolic derangements.

SA-PO386

Euglycaemic Diabetic Ketoacidosis in Type 2 Diabetes: A Rare Complication of SGLT-2 Inhibitors

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Introduction: Diabetic ketoacidosis (DKA) is a commonly encountered condition worldwide, typically occurring in young patients with type 1 diabetes following a provoking illness. This case explores an atypical case of ketoacidosis in an elderly patient with type 2 diabetes, who was not on insulin treatment, providing a significant diagnostic challenge.

Case Description: An 81year old lady presented with a 48 hour history of poor oral intake, vomiting and dyspnea. Her past medical history was significant for schizophrenia and Type 2 Diabetes Mellitus. On examination she was dehydrated, but had an excellent urine output of over 100ml/hr. Investigations revealed a raised anion gap metabolic acidosis (pH 7.08, Anion gap = 23) and ketonaemia of 5.47 mmol/l. Blood glucose, lactate and renal function were within normal range and the patient denied ingestion of toxins. Chest X-ray showed evidence of pneumonia. Treatment with two litres of intravenous fluids and antibiotics did not correct the acidosis, the pH falling from an initial rise of 7.22 to 7.09 and blood glucose of 10.7 to 9.9 mmol/l (178 mg/dl). Dapagliflozin was identified in the drug history as a potential precipitant of euglycaemic diabetic ketoacidosis. Intravenous infusions of dextrose and insulin successfully corrected the blood pH to 7.36 with a resolution of ketonaemia over the course of twenty four hours.

Discussion: Euglycaemic diabetic ketoacidosis (euDKA) is defined as the clinical triad of a blood glucose <11.1mmol/l (< 200mg/dl), raised anion gap metabolic acidosis and the presence of ketones in blood or urine. Euglycaemic DKA has similar provoking factors to DKA, such as infection, fasting or surgery. This case is atypical as the patient was elderly and not on insulin treatment. The DECLARE (Dapagliflozin Effect on Cardiovascular Events) study with over 18,000 participants quoted an incidence of DKA in < 0.1% of patients on this treatment. The European Medicines Agency concluded in 2016 that life-threatening and fatal cases of diabetic ketoacidosis have been reported in patients treated with SGLT-2 inhibitors. SGLT-2 inhibitors act on the proximal convoluted tubule promoting urinary sodium and glucose excretion, inhibiting glucose reabsorption. Clinicians should be mindful of this potentially life-threatening complication and consider euDKA in challenging cases of acid-base disturbance.

SA-PO387

Ectopic Adrenocorticotropic Hormone Tumor Can Present as a Chloride-Depleted Metabolic Alkalosis

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Introduction: Metabolic alkalosis (MA) often presents with hypokalemia and is either Cl-depleted (CDMA, urine Cl<15 meq/L) or Cl-resistant (CRMA, urine Cl>15 meq/L). CDMA is due to sustained loss of Cl, most commonly from either renal or GI losses, leading to pendrin inhibition. CRMA is most often due to direct tubular stimulation from either apparent or actual hyperaldosteronism.

Case Description: A 67 year old man w/ PMH of HTN presents w/ lower extremity & scrotal swelling. No OTC, herbal, or dietary supplements. Meds: Lasix, Lisinopril-HCTZ, ASA and KCl. BP 186/100, 2+ LE & scrotal edema. Serum Na 140, K 1.8, Cl 82, HCO3 45, BUN 15, Cr 0.7. ABG pH 7.58/PCO2 52/HCO3 45. Urine pH 7.5, K 33 meq/L, Na<10meq/L, Cl<10meq/L, Cr 94mg/dL, Urine K:Cr 35.1meq/g. His CDMA and kaliuresis was attributed to remote use of HCTZ & Lasix. These were held, KCl & 0.9NS was initiated, but w/ only minimal improvement in his MA & hypokalemia. His edema & HTN was exacerbated by this therapy, & follow up labs revealed Plasma Renin 1.26 ng/ml, Aldosterone 2 ng/dl, Cortisol 114.2 mcg/dl and ACTH 231 pg/ml. Imaging revealed a lung mass with mets & biopsy confirmed metastatic small cell cancer. Spironolactone resolved his HTN, edema, hypokalemia, & MA, and he is currently undergoing chemotherapy for his malignancy.

Discussion: Though initially thought to be remote use of diuretic induced CDMA, our patient's lack of response to Cl repletion led us to search for an alternative diagnosis. After his aldosterone and renin levels returned low, we sent off ACTH & cortisol and found an ectopic ACTH producing tumor. His loop & thiazide diuretics had exacerbated his CMDA, but was not the sole underlying cause. At high concentrations, cortisol activates mineralocorticoid receptors (MR) in the cortical collecting duct, leading to epithelial Na channel (ENaC) & Na-K ATPase activation. This leads to Na reabsorption with K & H excretion through renal outer medullary K channels, thus causing HTN & hypokalemia. To maintain electrical neutrality, HCO3 is reabsorbed and Cl is secreted into the tubular lumen via pendrin. But contrary to expected, urine Cl was low in our case which makes it an unusual presentation of hypercortisolism. Treatment strategies in these patients should focus on eliminating the primary cause if possible (decreasing tumor burden) & using medications which inhibit MR (Spironolactone) or ENaC (Amiloride).

SA-PO388

SGLT2 Inhibitors Are a New String for Nephrologists' Bow: Time to Be Excited yet Exercise Caution

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Introduction: Diabetic ketoacidosis (DKA) is traditionally defined as a triad of hyperglycemia, anion gap metabolic acidosis, and ketosis. On the other hand, Euglycemic DKA (EDKA), associated with blood glucose levels of <200 mg/dL is a relatively rare variant that is being recognized more in the setting of sodium glucose cotransporter 2 (SGLT2) inhibitors use. With the recent CREDENCE trial showing that Canagliflozin (a SGLT2 inhibitor) portends better renal and cardiovascular outcomes in patients with type 2 diabetes mellitus, nephrologists need to be aware of EDKA, especially in the setting of acute kidney injury (AKI), which itself can contribute to metabolic acidosis and pose diagnostic challenge.

Case Description: A 69-year-old woman with a history of diabetes mellitus type 2, gastroparesis, hypertension and coronary artery disease presented with abdominal pain, nausea and vomiting for 3 days. She was on metformin 1000 mg twice a day and empagliflozin 25mg daily for her diabetes. She was found to have AKI with a serum creatinine of 4 mg/dL (baseline ~0.8). Other laboratory data was significant for hyperkalemia with a serum potassium level of 6 mmol/L and anion gap metabolic acidosis with a serum bicarbonate 10 mmol/L. There was no significant hyperglycemia and the blood glucose level was 150 mg/dL. Lactic acid level was near-normal. Her urinalysis was positive for ketones and plasma beta hydroxybutyrate level was found to be elevated at 3 mmol/L. She was diagnosed with EDKA and treated with intravenous insulin and fluids. Her ketosis and renal failure resolved subsequently.

Discussion: Despite euglycemia, EDKA remains a medical emergency and must be diagnosed in a timely manner. As the use of SGLT2 inhibitors is likely to increase considerably in near future, nephrologists should have high index of suspicion for their adverse effects including but not limited to EDKA, urinary tract infections, renal tubular acidosis, lower-limb ulcerations etc. Serum ketones should be obtained in any patient with nausea, vomiting, or malaise while taking SGLT2 inhibitors, and the drug should be discontinued if acidosis is confirmed. Moreover, other causes of metabolic acidosis such as acute kidney injury, metformin-associated lactic acidosis, superimposed Fanconi syndrome from SGLT2 inhibitors should be considered in the differential diagnosis.

SA-PO389

No Stone Unturned: A Case of Sjogren Syndrome Diagnosed by Recurrent Nephrolithiasis

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Introduction: The cause of nephrolithiasis is idiopathic in the majority of cases. Patients who are young, form stones recurrently, or have high stone burdens warrant more thorough investigation into an underlying cause.

Case Description: 59 year old female with past medical history of hypertension, Raynaud's, gastric reflux, and recently diagnosed nephrolithiasis who presented with malaise, dysuria, fever, and chills after a seven day course of antibiotics for a urinary tract infection. She was evaluated in emergency department one month prior for right sided flank pain and was found to have a 4 mm obstructing stone in the proximal right ureter. This stone passed with medical expulsive therapy after which she continued to pass sandy urine sediment. On the current admission, imaging demonstrated a new 6 mm obstructing stone in the distal right ureter and a non-obstructing stone in the left renal pelvis not present a month earlier. Routine laboratory evaluation revealed a creatinine of 1.8mg/dL, non-anion gap metabolic acidosis, hypokalemia with elevated urinary potassium, and a urine pH of 6. The urine anion gap was positive and a distal renal tubular acidosis (RTA) was suspected. Further serologic testing was notable for a positive ANA (1:80), negative double stranded DNA, strongly positive anti SS-A and anti SS-B antibodies, low C3 and very low C4. Anti-Scl-70 was normal. A diagnosis of Sjogrens with possible systemic lupus erythematosus overlap was made. She was treated with antibiotics and urology removed the stone cystoscopically. Her creatinine improved from 1.8 to 1.1mg/dL on discharge. As expected, the composition of her stone was 98% calcium phosphate, 2% calcium oxalate. She was started on potassium citrate which improved her hypokalemia and acidosis significantly.

Discussion: Distal RTA increases stone risk due to alkaline urine, hypocitraturia, and hypercalciuria related to bone buffering in chronic acidosis. General causes of distal RTA from defects in the tubular transporters in the alpha intercalated cell of the renal collecting duct include genetic mutations, autoimmune diseases, and medications. Systematic evaluation of this patient's nephrolithiasis led to a diagnosis of distal renal tubular acidosis and ultimately an underlying systemic disease, Sjogren's syndrome.

SA-PO390

Severe Hyponatremia Associated with Autoimmune LGI1 Encephalitis, an Underrecognized Cause of SIADH

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Introduction: SIADH is commonly caused by medications, malignancies, pain, and nausea, however autoummune encephalitis as a cause is often underrecognized. Here we present a case of severe SIADH secondary to autoimmune LGI-1 encephalitis.

Case Description: A 79-year-old male with hypertension on hydrochlorothiazide (HCTZ) presented to the ED 2 months prior for fatigue, and was found to have hyponatremia with serum Na (sNa) of 123mmol/L. It was attributed to HCTZ, and sNa improved to 127mmol/L after its discontinuation. A month later, patient was hospitalized for left arm twitching and recurrent hyponatremia with sNa 123mmol/L, sOsm 256mOsm/kg, uOsm 720mOsm/kg, serum Cr 0.81mg/dL. His twitches was associated with voluntary movements, occurred 3 times a day and each lasted for 10 seconds. Workups for SIADH were unrevealing. Given the concern for symptomatic hyponatremia with arm twitching, the patient was treated with ddavp and 3% saline for controlled sNa correction, and discharged with sNa 137mmol/L, on salt tablets, fluid restriction, and furosemide. Neurologic symptoms had improved. Patient returned to clinic 3 weeks after discharge, and reported recurrence of left arm and hand twitching with increased frequency and severity, and now with new onset facial clenching. Labs showed normal sNa of 135mmol/L, sOsm 280mOsm/kg, uOsm 681mOsm/kg, Ca 9.6mg/dL. Patient was referred to Neurology Dystonia Clinic, and the diagnosis of anti-LGI1 encephalitis was confirmed with positive Leucine-rich, glioma inactivated 1 protein IgG (LGI1) and positive Voltage gated potassium channel Ab (VGKC). He was promptly treated with pulse methylprednisolone with resolution of his neurologic symptoms and hyponatremia.

Discussion: It is estimated that 60% of the patient with autoimmune LGI-1 encephalitis presented first to health care providers with hyponatremia, and yet, it is an under-recognized cause of SIADH. LGI-1 is part of the voltage-gated potassium channel complex present in the hippocampus and temporal cortex, and LGI-1 encephalitis is characterized by hyponatremia, acute or subacute cognitive impairment, faciobrachial dystonic seizures, psychiatric disturbances and epileptic seizure. If left untreated, patient would progress rapidly to end stage dementia resulting in death. However, if treated early with steroids, it has low relapse rate and good clinical outcome.

SA-PO391

Unexplained Bromide Toxicity Presenting as Hyperchloremia and Negative Anion Gap

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Introduction: Brominev. is a deep red colored liquid primarily used in manufacture of chemical agents. Serum bromide concentration is difficult to quantify due to interference with other halogens, though when measured by x-ray fluorescence spectrometry is between 3.2 to 5.6 mg/L. Significant environmental exposure is mostly limited to industrial setting. Bromide toxicity was well recognized in early twentieth century when use of bromide containing drugs was widespread. Toxic effects of bromide include neuropsychiatric disturbances, tremors, gait imbalance, rash, and dermatitis.

Case Description: An 82-year-old male was seen in the emergency room with sudden cognitive decline, visual hallucinations, gait disturbance and multiple falls. His medical history was significant for squamous cell cancer of head and neck and Myasthenia Gravis. His medication list included scheduled infusion of IVIG every four weeks and ipratropium bromide 20 mcg inhaler two to three times daily. Notably, he was not on Pyridostigmine bromide. Physical examination was significant for blood pressure of 93/55 mm Hg, and fluctuating mental status. Serum chloride was found to be 163 mmol/L with anion gap of negative 65. Remaining serum chemistries, complete blood count, liver function tests, urinalysis, blood gas, TSH, Salicylate and Tylenol levels, B12 and cortisol levels were unremarkable. Multiple repeat labs continued to show high chloride concentration. Simultaneous chloride measurements were obtained employing indirect ion-selective and colorimetric method; serum values thus obtained were 135 mmol/L and 103 mmol/L respectively. Colorimetric method is less susceptible to interference from other halides. Concurrent serum bromide level was reported as 1100mg/L. Patient refused both saline diuresis and hemodialysis for bromide clearance, and expired at his home six weeks following discharge.

Discussion: Because of interference by other halogens in routine measurements, a high bromide level can masquerade as hyperchloremia with large negative anion gap. Thus when encountered, bromism should be kept in mind

SA-PO392

Fellow's Nocturnal "Natremic" Dilemma; True, Pseudo, or Both: Implications on Dialysate Sodium

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Introduction: Hyponatremia is the most common electrolyte disturbance in patients admitted to the hospital. We report a case of combined true- and pseudohyponatremia in a patient who was on continuous renal replacement therapy (CRRT).

Case Description: A 46-year-old female with a history of end stage renal disease (ESRD) secondary to lupus was admitted to intensive care unit with peritonitis and septic shock. The patient weighted 50 kg, with calculated Watson's volume of 26 L. She was started on CRRT due to hemodynamic instability. Her serum sodium (SNa) levels were stable around 129-130 mmol/L while on CRRT with a CRRT dialysate Na of 132 (to avoid over-correction). This was thought to be related to a hypotonic solution she was receiving (D20 for severe hypoglycemia). Overnight, the SNa was noted to drop to 122 mmol/L while she was receiving CRRT with no added hypotonic solutions administered. On call nephrology fellow was contacted urgently to establish the cause of this acute worsening of SNa. On medication review it was found that the patient received intravenous immunoglobulin (IVIG) for immune thrombocytopenia in the evening prior to the SNa of 122 mmol/L. That fact raised a suspicion of pseudohyponatremia. Further workup revealed serum Osmolality of 281 mOsm/kg and anion gap of 1. Whole blood electrolytes were obtained and showed sodium level of 129 mmol/L.

Discussion: IVIG can cause hyponatremia by multiple mechanisms. Pseudohyponatremia results from increased percentage of protein in plasma, with a normal plasma water Na concentration. IVIG therapy can also result in true hyponatremia, arising from sucrose-induced translocation of water from the intracellular compartment (ICF) to the extracellular compartment (ECF). Even in the presence of underlying true hyponatremia, nephrologist should be cognizant of possibility of additional pseudohyponatremia. Therapeutic strategies should target whole blood Na in these situations.

SA-PO393

Gitelman Syndrome in Pregnancy: A Therapeutic Challenge with Outcomes Repercussions

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Introduction: Gitelman Syndrome is an autosomal recessive disorder resulting in loss of function of the sodium chloride cotransporter (NCCT). Patient presents with metabolic alkalosis, hypokalemia and hypomagnesemia. It usually manifests in late childhood or adulthood; these symptoms can be exacerbated during pregnancy due to increased demand of potassium and magnesium. Here we present 2 difficult to manage cases of Gitelman syndrome with one manifesting and the other worsening during pregnancy.

Case Description: Case 1: 32-year old female with history of Gitelman syndrome on maintenance daily dose of 60 mEq KCl and 400 mg magnesium oxide oral supplementation. During the first trimester of her pregnancy, patient developed severe hypomagnesemia of 1.1 mg/dl and was subsequently started on amiloride 10 mg PO daily, increased dose of magnesium oxide to 800 mg PO twice daily and potassium 40 mg 3 times daily. Despite this intervention, she continue to have low magnesium of less than 1.3mg/dl requiring frequent hospitalization with intravenous and oral magnesium supplementation. Patient was eventually maintained on amiloride 10mg twice a day and maximum tolerable dose of 3200mg of magnesium oxide and 160meq of potassium chloride. Despite this she still gets admitted every week for intravenous magnesium supplementation to maintain levels more than 1.6 mg/dl. **Case 2:** 33-year old female with 32 weeks gestation presented with one day history of nausea, vomiting and severe leg cramping. She was found to have a potassium level of 2.7 mg/dL, calcium of 10.8 mg/dL and magnesium level of 1.3 mg/dL. She was started on oral Potassium chloride 40 mEq twice a day, Magnesium oxide 2400 mEq daily and Amiloride 10mg daily.

Discussion: Managing electrolyte abnormality in pregnant patients with Gitelman syndrome is very challenging. As we saw in our first case, patient remained hypomagnesemic despite maximum tolerable dose of 3200mg of magnesium, requiring multiple intravenous supplementations. The use of potassium sparing diuretics especially Amiloride (Class B in pregnancy) require close monitoring of amniotic fluid by obstetricians. To our knowledge, very few cases of pregnancy with Gitelman's syndrome are reported and these cases require a very close monitoring and managing by a multidisciplinary team of obstetricians and nephrologists

SA-PO394

Multiethnic GWAS for Idiopathic Nephrotic Syndrome in Adults and Children

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Background: Common *HLA* variants have been associated with steroid sensitive nephrotic syndrome (NS) in small cohort studies. We conducted a genome-wide association study (GWAS) for NS in different ethnicities, ages of onset and response to steroid therapy.

Methods: We genotyped 2,639 NS cases and 16,765 genetically-matched controls. After imputation, we performed ancestry-specific GWAS using an additive model corrected for population stratification, followed by meta-analysis across 11 populations. Subsequent meta-analyses were performed stratified by: age of onset (Pediatric and Adults), race (Caucasians and Africans) and steroid responsiveness (Sensitive and Resistant).

Results: In the combined meta-analysis (2,639 cases), we discovered significant associations for the *APOL1* (OR=2.87, P= 7.68x10^{-31}), which were driven solely by African individuals (520 cases; OR=2.82, P=1.45x10^{-37}), the *HLA-DQA*1 locus (OR=1.43, P= 3.2x10^{-22}), and a novel locus on chr.1q42.2 (OR=1.34, P=3.29x10^{-08}). After conditional analysis on the top two SNPs at *APOL1* and *HLA*, a second independent *HLA* genome-wide significant signal was discovered (OR=1.36, P=2.18x10^{-10}). Among adult onset patients (n=1,391), the strongest signals were for *APOL1* (OR=3.14, P=1.82x10^{-21}) and a novel locus on chr.14q21.3 (OR=1.54, P=1.62x10^{-8}). The *HLA-DQA1* was the strongest signal among pediatric cases (n=1,195; OR=2.01, P=4.06x10^{-32}). Interestingly, the *HLA* signal in Caucasians was significant also in adults (OR=1.33; P=1.20x10^{-8}). Additional signals were found in adult and pediatric cohorts stratified by race and response to therapy.

Conclusions: Our results reveal novel NS loci, pleiotropic risk predisposing alleles across different subphenotypes, and signals specific to race and age of onset. Specifically, we can now implicate variation in the *HLA* locus as a major contributor to NS also in adults. Fine-mapping of *HLA* in children and adults and integrating these GWAS alleles with other NS-associated genetic factors (Mendelian alleles, CNVs) holds promise in further elucidating the genetic architecture of NS.

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SA-PO395

Genetic Risk Factors in a United Kingdom Paediatric Nephrotic Syndrome Cohort

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Background: Up to 30% of steroid resistant nephrotic syndrome (NS) patients have a genetic cause while the cause of the remaining group remains unknown. A yet unidentified 'circulating factor' (CF) has been attributed to the subset of patients who fail to respond to immunosuppression and in whom disease recurs post-transplant. There are emerging reports that apart from disease causing mutations in 'nephrotic' genes there are also common genetic variations in 'susceptibility genes' that may play important role in the development and/or disease progression of NS. We aimed to validate and add to the published findings on genetic variations in 'susceptibility genes'. We stratified patients into groups based on their clinical course and hypothesised that they may have different genetic 'signatures' in the selected genes.

Methods: We searched literature for previously published risk factor/modifier genes for NS/FSGS. We then screened the genes in 133 exome sequenced Caucasian patients with paediatric onset of NS. Phenotypic data was collected through a National Registry of Rare Kidney diseases. The frequency of detected single nucleotide variations (SNVs) in the cohort was compared with the 'general population'. Chi-squared test with Yates correction (2x2 contingency tables) was used. Sub-group analyses were performed for genetic SRNS and the presumed CF patients.

Results: number of previously described SNVs were enriched in our cohort when compared to the general population. We have also found several other SNVs to be significantly over-represented, that were not described before and which may therefore, be involved in susceptibility to the disease in some way. The identification of these variants provides new avenues for further exploration. By stratifying NS patients in the

case of *HLA-DRB1* and *HLA-DQA1* for example, we found a sub-set of variants that are specifically enriched in likely CF disease.

Conclusions: These results support and add to the hypothesis that there are a number of genetic variants (residing outside of the known 'nephrotic' genes) working alone or in combination, to modify the pathogenesis of NS.

SA-PO396

Reverse Phenotyping After Whole-Exome Sequencing Reveals Frequent Podocytopathy Phenocopies in Steroid-Resistant Nephrotic Syndrome

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Background: Primary idiopathic nephrotic syndrome (NS) is a typical presentation of genetic or non-genetic podocytopathies but occasionally other genetic nephropathies can present as clinically indistinguishable phenocopies. We hypothesized that such phenocopies of steroid resistant NS (SRNS) represent a relevant percentage of patients with primary NS explaining frequent multi-drug resistance.

Methods: All patients affected by primary NS referred to our center between 2000 and 2018 were included in the study. Whole-exome sequencing and *in silico* filtering of 298 nephropathic genes were combined with reverse phenotyping performed right after genetic diagnosis in all the patients and families.

Results: A total of 111 patients (64 SRNS and 47 steroid sensitive NS, SSNS) were included in the final analysis. Not a single pathogenic variant was detected in the SSNS group. As expected, 20/64 (31.3%) SRNS patients had pathogenic variants in podocyte genes. However, 17/64 (26.6%) showed pathogenic variants in many other genes related to clinically unrecognized genetic nephropathies, i.e. in the absence of clinical signs of the underlying disorder at onset. Reverse phenotyping permitted the identification of minor clinical signs of the underlying genetic nephropathy in the patient or the family, confirming the diagnosis and explaining multi-drug resistance. Genetic patients did not experience recurrence of post-transplant NS (0/11), while NS relapsed in 40% of the others (4/10).

Conclusions: Our unique interdisciplinary workflow based on extended genetic analysis and reverse phenotyping can significantly increase the diagnostic accuracy in patients referred with the diagnosis of SRNS, avoiding mistreatment and predicting outcome in a large percentage of these patients.

SA-PO397

Genetic Identification of Two Novel Loci Associated with Steroid-Sensitive Nephrotic Syndrome

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Background: Steroid-sensitive nephrotic syndrome (SSNS), the most common form of nephrotic syndrome in childhood, is considered an autoimmune disease with an established classical HLA association. However, the precise etiology of the disease is unclear. In other autoimmune diseases, the identification of loci outside the classical HLA region by genome-wide association studies (GWAS) has provided critical insights into disease pathogenesis. Previously conducted GWAS of SSNS have not identified non-HLA loci achieving genome-wide significance.

Methods: In an attempt to identify additional loci associated with SSNS, we conducted a GWAS of a large cohort of European ancestry comprising 422 ethnically homogeneous pediatric cases and 5642 ethnically matched controls.

Results: The GWAS found three loci that achieved genome-wide significance, which explain approximately 14% of the genetic risk for SSNS. It confirmed the previously reported association with the HLA-DR/DQ region (lead single nucleotide polymorphism [SNP] rs9273542, P=1.59×10-43; odds ratio [OR], 3.39), and identified two additional loci outside the HLA region, on chromosomes 4q13.3 and 6q22.1. The latter contains the calcium homeostasis modulator family member six gene CALHM6 (previously called FAM26F). CALHM6 is implicated in immune response modulation; the lead SNP (rs2637678, P=1.27×10-17; OR, 0.51) exhibits strong expression quantitative trait loci effects, the risk allele being associated with lower lymphocytic expression of CALHM6.

Conclusions: As CALHM6 is implicated in regulating the immune response to infection, this may explain the typical triggering of SSNS onset by infections. Our results suggest a genetically conferred risk of immune dysregulation may be a key component in the pathogenesis of SSNS.

Funding: Private Foundation Support

SA-PO398

Genetic Variants in Basement Membrane Genes Are Enriched in Nephrotic Syndrome

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Background: Basement membranes (BM) are essential for tissue formation and function. Core components include laminins, collagens and heparin proteoglycans. Genetic defects in BM components cause a spectrum of rare human diseases, however, recent large-scale genetic studies have shown that variants in BM genes associate with more prevalent disease including diabetic nephropathy. Whilst the role of core BM components have been linked to human disease, there are more BM components and interactors that are likely to have key roles in BM assembly and regulation. We hypothesised that BM integrity is key to kidney survival and that genetic variants in a wide spectrum of BM genes associate with disease. We aimed to identify genetic differences in BM genes between patients with nephrotic syndrome (NS) and controls.

Methods: We assembled a list of 110 genes, likely to be important for BM function. The list was derived from Gene Ontology classification, proteomic analyses of extracellular matrix, and functional screens in *C. elegans*. We used this list to screen 133 exome sequenced Caucasian patients with paediatric onset of NS. The frequency of detected single nucleotide variations (SNVs) in the cohort was compared with the general population (gnomAD controls, European non-Finnish). Randomly selected genes were also examined and used as control genes. Chi-squared test with Yates correction (2x2 contingency tables) was used.

Results: 25 SNVs were found to be significantly over-represented in the NS patients when compared to controls. 16 of those had the minor allele frequency (MAF) over 2x higher than in the general population. The biggest MAF differences were found in *HMCN2*, *SMOC1*, *LAMA5*, *MATN1*, *LAMA2* and *ADAMTS16* genes. No SNVs were enriched in the control genes. Furthermore, we screened 50 genes (BM and other) known to cause NS and identified 5 candidates that caused a BM rupture phenotype in *C. elegans* and this frequency was approximately 20-fold higher than randomly selected genes.

Conclusions: Overall these findings support our hypothesis that BM integrity is key to long term kidney survival.

SA-PO399

Incidence of Single Heterozygous Variants in "Nephrotic" Genes in Non-Genetic Paediatric Steroid-Resistant Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) is a rare condition in childhood associated with considerable morbidity, particularly in those with early onset disease. Up to 30% of children have a monogenic cause, and research is focusing on stratifying patients at an early stage in order to 'personalise' their treatments. Over 70 genes have been associated with SRNS to date, most of them are autosomal recessive (AR). Exome analysis will not infrequently identify single rare heterozygous variants within AR genes that can cause uncertainty. It is often speculated that a second variant was either missed or lies within the non-coding part of the gene. There are pathogenic single heterozygous variants within recessive 'nephrotic' genes in the general population ('carriers' for the disease). This pilot project aims to compare the incidence of rare variants in randomly selected AR 'nephrotic' genes in paediatric SRNS patients with the 'general' population.

Methods: 133 exome sequenced Caucasian SRNS patients and the ethnically matched 'general' population data (gnomAD, exomes) were used for the analysis. Rare (MAF<0.01) single nucleotide variants (SNVs) from the coding and splice-site regions were selected from the AR genes and their incidence was compared between the two cohorts. The data was analysed in 3 consecutive stages: 1. Rare SNVs regardless of zygosity. 2. Rare heterozygous SNVs (not found as homozygotes in any cohort). 3. Rare heterozygous SNVs + small indels, predicted to be likely pathogenic. SRNS patients with confirmed monogenic disease were excluded from this analysis.

Results: In this preliminary work we have found no statistically significant difference in the frequency of rare variants in NS genes (seen as homozygous or heterozygous (48.4% cohort / 53.1% control) / only as heterozygous (27.5% cohort / 24.6% control) / heterozygous and likely pathogenic (7.7% cohort / 8.1% control)) between SRNS patients and the control population.

Conclusions: Our preliminary findings suggest, for the case of the likely pathogenic single heterozygous variants, that these may be incidental and not indicative of a missing 'second hit' within the gene.

SA-PO400

Development of a High-Throughput Screening System to Evaluate Nephrin Expression on Plasma Membrane

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Background: Nephrin is an important component of the podocyte slit diaphragm and its dysfunction leads to severe proteinuria and nephrotic syndrome. Most nephrin mutants possibly lack export to the plasma membrane as a result of abnormal folding and post-translational modification. Although normalization of nephrin trafficking is considered as a novel therapeutic target, promising agents have not yet been found, due in part to a lack of suitable screening system for drugs that target nephrin regulation. Here, we established a high-throughput screening (HTS) system for discovery of agents that improve plasma membrane expression of nephrin.

Methods: To establish a high sensitive HTS system, we utilized split Nano-luciferase. NanoLuc fragment (HiBiT)-fusion nephrin was transfected into HEK293T cells and cell surface expression was detected by luminescence upon addition of a nonlytic reagent containing LgBiT fragment and substrate. Treatment with glycosylation inhibitor (Tunicamycin) or chemical chaperone (4-PBA), as well as comparison of clinically reported mutants (15 missense mutants) evaluated the validity of this system.

Results: HiBiT-Nephrin showed remarkable RLU compared to mock (> 200-fold). In addition, the retention of nephrin phosphorylation was confirmed by western blotting. Under this condition, tunicamycin treatment significantly reduced HiBiT-nephrin RLU (< 40%). In contrast, 4-PBA treatment significantly increased RLU (>150%). Furthermore, each of the 15 mutants of HiBiT-Nephrin showed unchanged (5) or reduced (10) expression on plasma membrane, most of which were augmented or recovered by 4-PBA treatment.

Conclusions: In this study, we succeeded in establishing a HTS system that can easily and sensitively quantify the expression of nephrin on the plasma membrane. Although the cell-based assay has limitations, this system reflected the characteristics of nephrin consistent with previous reports. With further optimization, this system will be used to screen for compounds that target nephrin.

SA-PO401

A GWAS of Congenital Anomalies of the Kidney and Urinary Tract

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Background: Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are prevalent causes of pediatric renal failure. We investigated common risk variants that may be involved in the pathogenesis of diverse CAKUT.

Methods: A Genome-Wide Association Study (GWAS) was conducted on 2,894 ethnically and clinically heterogeneous CAKUT cases and 15,589 genetically matched controls. Association tests were performed on the imputed dosages of 10 subpopulations under the additive model with population stratification corrected and meta-analyzed.

Results: We identified a significant association on chr.21q.21.1 (P=1.91 x10^{-9}; OR=1.28) in *CHODL*, a gene that has been reported to be involved in motor axon differentiation in zebrafish models and has shown positive expression in the developing urogenital tract. We have found near genome-wide significant signals in 3 loci: *TMEM229B* (P=1.03 x10^{-7}; OR=1.25), previously reported as a suggestive locus associated to renal function measures and chronic kidney disease in a GWAS in children; *MARK1* (P=2.00 x10^{-7}; OR=1.21), a gene possibly implicated in autism and expressed in the pre and postnatal urinary tract; and chr.5p15.31 (P=1.07x10^{-7}; OR=1.43). Finally, we identified suggestive loci (P<1x10^{-5}) within or near essential renal development genes in human and mouse model, including *TWSG1*, *ROBO2*, *LAMA5*, and *GATA5*.

Conclusions: Our preliminary GWAS identified *CHODL* as a novel CAKUT candidate gene, and have shown suggestive associations of variants in critical renal development genes. Integration with a subphenotype analysis may allow us to refine these loci and prioritize candidate susceptibility genes in CAKUT.

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SA-PO402

Estimation of Adenine Phosphoribosyltransferase Deficiency Prevalence Using Public Whole-Exome Sequencing Data

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Background: Adenine phosphoribosyltransferase deficiency (APRTd) is a rare, hereditary cause of recurrent kidney stones and progressive chronic kidney disease (CKD). While treatment with allopurinol or febuxostat is effective, a delay in diagnosis frequently results in adverse outcomes. The small number of reported cases in countries other than France, Iceland and Japan suggests an extremely low prevalence, although missed diagnoses may significantly affect prevalence estimates. We assessed the prevalence of APRTd based on the frequency of mutated *APRT* alleles in public genomic databases.

Methods: Four databases containing genome sequencing data, the Genome Aggregation Database (gnomAD, n=141,353), the NHLBI GO Exome Sequencing Project (n=6503), the 100,000 Genomes Project (n=62,000) and the deCODE Genetics database (n=35,000) were searched for 64 reported *APRT* mutations and other potentially pathogenic variants. Minor allele frequencies (MAF) <0.01% were identified. The estimated prevalence of homozygous genotypes was calculated using the Hardy-Weinberg principle.

Results: A total of 30 disease-causing mutations with MAF <0.01% were detected in all databases. The variants with the highest allele counts are shown in Table 1. The p.Arg89Gln mutation was found to have a heterozygous frequency of 0.4087(%) in the South Asian population (n=1.3 billion), yielding an estimated 17.201 homozygotes, and a heterozygous frequency of 0.03714 (%) in the UK population (n=66 million) with an estimated 910 homozygotes. In the US, the p.Phe174 deletion had a heterozygous frequency of 0.3271 (%) in the European-American population (n=223 million), yielding an estimated 2408 homozygotes.

Conclusions: The data suggest a greater prevalence of APRTd in the Asian, UK and US populations than is reported in the literature. Based on these findings, APRTd appears to be a seriously underrecognized cause of kidney stones and CKD.

Funding: NIDDK Support

Table 1.

Database	Variant	Mutant Allele Frequency	Carrier frequency (1 in*)	Estimated prevalence (1 in*)
NHLBI, European-American	p.Phe174del	0.3271%	153	92,844
100.000 Genomes Project, UK	p.Arg89Gln	0.3714%	135	72,496
gnomAD, South Asia	p.Arg89Gln	0.4087%	123	59,864
gnomAD, East Asia	p.Ala116Thr	0.2307%	217	187,941
deCODE Genetics, Iceland	p.Asp65Val	1.2%	42	6874

SA-PO403

Designing a Return of Genetic Results Workflow in Nephrology: Lessons Learned from a Pilot Study

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Background: Genetic testing is an emerging tool in nephrology practice. Actionable genetic findings can be identified as part of research or clinical care. However, no best practice exists for return of results (ROR) and clinical implementation of results, for renal patients.

Methods: We developed a workflow for ROR of primary diagnostic and/or medically actionable (secondary) findings for adults with all-cause chronic kidney disease, who underwent exome sequencing, through participation in a biobank study.

Results: We attempted to re-contact a diverse group of 50 participants with potentially diagnostic findings. Among them, 36 were contacted and we returned actionable genetic findings to 23 individuals. We identified 6 major elements in the ROR workflow for research participants: subject identification; re-contact; pre-test counseling for clinical testing; retesting for secondary validation; return of results with post-test counseling; and clinical implementation. We identified over 20 major challenges to ROR, which were iteratively addressed to optimize the workflow. Some common challenges included changes of address, death, lack of insurance for clinical validation of genetic data, lack of interest in receiving actionable findings, unwillingness to contact at-risk relatives, access to genetic counseling, and lack of standardized tools for patients and physician education. Importantly, the genetic result meaningfully impacted the clinical care of all cases.

Conclusions: The lessons learned from this study provide valuable information for return of genetic result in the setting of clinical care and research for nephropathies.

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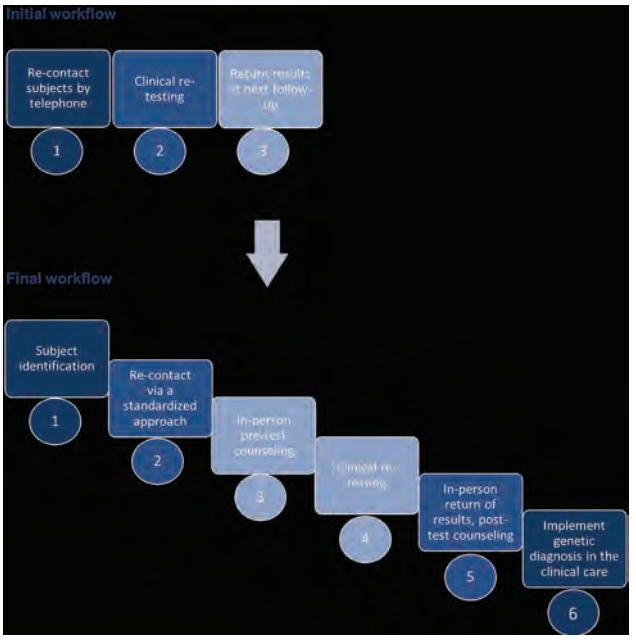

Figure 1: Iterative changes to workflow led to standardized approach for return of actionable genetic findings to nephrology research participants

SA-PO404

Diagnostic Utility of Next-Generation Sequencing in Patients Presenting for Percutaneous Renal Biopsy

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Background: Genetic testing is fast becoming a first line of investigation in many branches of medicine. Genetic causes of kidney disease may be under-recognised and exome sequencing has been shown to detect pathogenic mutations in up to 10% of patients with CKD. We aimed to genotype a cohort of patients undergoing renal biopsy.

Methods: We recruited adult patients attending for percutaneous kidney biopsy under investigation for acute or chronic kidney disease, over an eight-year period from 2010 to 2018. Patients undergoing post-transplant renal biopsy or patients whose renal biopsy showed diabetic nephropathy or pauci-immune vasculitis were excluded. Patients underwent next generation sequencing using a specially designed Roche NimbleGen HeatSeq panel, which sequenced for 227 genes associated with kidney disease. Data was analysed using an in-house bioinformatics pipeline and variants were classified using gold-standard American College of Medical Genetics and Genomics guidelines for variant pathogenicity.

Results: We sequenced 69 patients who had undergone native renal biopsy. These included 21 patients with a histological diagnosis of IgA nephropathy, 19 with other forms of glomerular disease, 14 with interstitial nephritis, and 15 with non-specific changes on histology. We identified a pathogenic variant for Alport Syndrome (*COL4A4*) in a single patient (1.5%). We also identified a variant of unknown significance in *CFH* in the same patient, which may be contributing to the patient's low complement levels. Additionally, we identified noteworthy variants of unknown significance in 39 patients including 12 loss-of-function variants and three truncating variants in genes previously established as contributing to renal disease.

Conclusions: Next generation sequencing may be a useful addition to renal biopsy in certain groups of patients. In an undifferentiated group of patients undergoing renal biopsy, we detected pathogenic mutations in 1.5%. This diagnostic yield may be improved when DNA is available from parents and other affected family members and with careful selection of patients sent for testing.

Funding: Private Foundation Support

SA-PO405

Diagnostic and Clinical Utility of Whole-Exome Sequencing in a Cohort with Clinically Suspected Genetic Kidney Disease

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Background: Genomic technologies enable rapid and cost-effective sequencing of DNA and have demonstrated a definitive diagnosis in several patient groups such as childhood syndromes and oncology. We sought to determine the diagnostic and clinical utility of WES in a cohort of adults and children with clinically suspected genetic kidney disease who were reviewed in multidisciplinary renal genetics clinic (RGC).

Methods: Sequential patients were prospectively recruited through five tertiary academic centres in Australia. Patients were referred by their treating nephrologist to a dedicated RGC. Following review by a multidisciplinary team consisting of a nephrologist, clinical geneticist and genetic counsellor, patients underwent genomic sequencing with analysis for a pre-determined phenotype specific list of genes of interest. We measured the diagnostic yield and the effect on short term clinical management. Full author list online at KidGen.org.au

Results: We performed WES in 204 patients (82 paediatric and 122 adults) with CKD. The median age at time of recruitment was 29 years (0-72). Preliminary results demonstrate a genetic diagnosis in 77 patients (38%). This includes (69) pathogenic variants and (25) likely pathogenic variants. When comparing the *a priori* clinical diagnosis at referral in patients with WES diagnoses, 48 (62%) had their suspected clinical diagnosis confirmed and 29 patients (38%) had a subsequent change in diagnosis. 42 patients (54%) with positive diagnoses had recommended changes to clinical management. This included the avoidance of immunosuppression, avoidance of renal biopsy, initiation of surveillance for extra-renal disease and facilitating transplant and reproductive decisions. In addition, at least 26 patients (13%) had a clinically relevant negative result with management implications.

Conclusions: To our knowledge this is the first study to report diagnostic and clinical utility of genomic sequencing in a pragmatic clinical setting. Our results confirm that in a clinically selected paediatric and adult cohort with kidney disease, WES is valuable for establishing a specific molecular diagnosis and demonstrates substantial quantifiable clinical utility.

Funding: Government Support - Non-U.S.

SA-PO406

Implementing Comprehensive Genetic Testing in Patients with Kidney Disease Improves Care by Identifying the Basis for a Wide Variety of Renal Phenotypes

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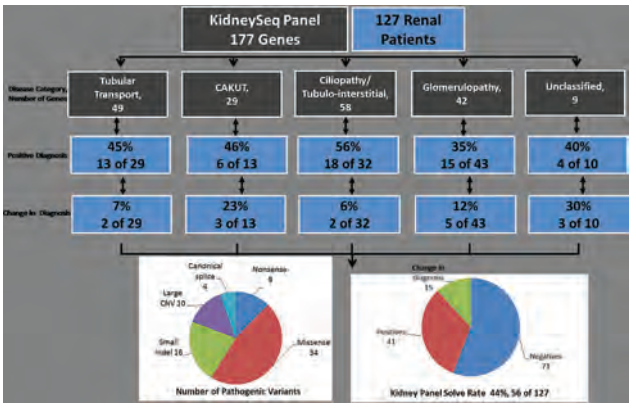
Background: The clinical diagnosis of genetic renal diseases may be limited by the overlapping spectrum of manifestations between diseases or by the advancement of disease where clues to the original process is absent. The objective of this study was to determine whether genetic testing informs diagnosis and facilitates management of kidney disease patients.

Methods: We developed a comprehensive genetic testing panel (KidneySeq) to evaluate patients with various phenotypes including cystic diseases, congenital anomalies of the kidney and urinary tract (CAKUT), tubulointerstitial diseases, transport disorders and glomerular diseases. We evaluated this panel in 127 consecutive patients ranging in age from newborns to 81 years who had samples sent in for genetic testing.

Results: The performance of the sequencing pipeline for single nucleotide variants was validated using CEPH controls and for indels using Genome-in-a-Bottle. To test the reliability of the copy number variant analysis, positive samples were re-sequenced and analyzed. For patient samples, a multidisciplinary review board interpreted genetic results in the context of clinical data. A genetic diagnosis was made in 56 (44%) patients and ranged from 56% for ciliopathies/tubulointerstitial diseases, 46% for CAKUT, 45% for transport disorders and 35% for glomerulopathies. Pathogenic and likely pathogenic variants included 46% missense, 13% nonsense, 5% splice site variants, 22% insertion-deletions and 13% copy number variants. In 15 cases, the genetic result changed the clinical diagnosis.

Conclusions: Comprehensive genetic testing should be considered in the evaluation of renal patients as it complements other tests and provides insight into the underlying disease and its management.



Outcome of comprehensive gene panel testing in 127 renal patients

SA-PO407

Identifying New CKD Drug Targets from Genetic Analysis

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Background: Identifying successful drug candidates to treat patients with Chronic Kidney Disease (CKD) is challenging due to the heterogenicity of the CKD population. As a result, no efficient treatment options to halt or reverse CKD development are today available. It's known that drug target genes associated with clinical phenotypes are more likely to succeed in pharmaceutical development. Thereby, in an unprecedent approach to identify CKD disease drivers we have performed whole exome sequence on 3315 CKD patients and 9563 controls to search for rare mutations in CKD patients.

Methods: Collapsing analysis generated a list with 417 enriched suggestive rare mutations in CKD patients. These genes where then prioritized through a comprehensive workflow aiming to validate the hits as potential drug targets. First the genes were filtered by bioinformatics analyses with genes being ranked and selected based on their gene expression correlating to renal function and CKD stage. In addition, integrative omics analyses were performed to give information on kidney enrichment and predict renal cell type expression.

Results: The analysis leveraged 93 genes with a strong CKD correlation. In the next step we ranked the genes based on literature data supporting a link to CKD relevant biology. The 31 genes with the highest scores went into experimental in vitro and in vivo validation. Loss of function phenotypes were investigated by siRNA KD in 2D and 3D human (organoid) renal cell systems. Gain of function phenotypes were investigated by overexpression or by studying KD protection in the presence of CKD stressors. In parallel, the importance of the genes on renal function was evaluated using CRISPR based gene knock-out of genes in zebrafish with the top ranked four genes being further processed using CRISPR knock-out mice.

Conclusions: This extensive workflow, that was processed within only one year, identified the first novel CKD target to have the potential to be first in class and as a result this gene entered our pipeline for drug discovery.

Funding: Commercial Support - AstraZeneca

SA-PO408

Unraveling the Genetic Contributions to Kidney Disease with the Kidney Genome Atlas

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Background: Focal segmental glomerulosclerosis (FSGS) is a progressive kidney disorder with limited treatment options. To discover novel drug targets for FSGS, we built the Kidney Genome Atlas (KGA), which currently contains whole-genome sequences (>30X) on 23000 individuals, including 3000 cases of FSGS, other proteinuric disorders, and diabetic nephropathy. Each patient genome is linked to longitudinal clinical records, and for a subset of 400 patients the KGA also includes matched transcriptomes from microdissected glomerular and tubulointerstitial samples. Our aim was to elucidate mechanisms of disease through genome-wide association studies (GWAS) of (1) disease severity in cases, (2) case-control status, and (3) gene expression in cases.

Methods: To measure disease severity, we calculated a combined Z-score based on age at presentation and eGFR slope, which was estimated using a Bayesian hierarchical linear model on 1797 patients with at least 3 eGFR measurements. Then we conducted an association study on this continuous phenotype with the burden of likely deleterious variants at the gene level. Additionally, we conducted a GWAS on case-control status and an expression quantitative trait loci (eQTL) analysis on a subset of 300 patients with transcriptomic data.

Results: As proof of principle, among all cases we found that two copies of APOL1 risk alleles were associated with earlier age at presentation (p=5e-6) and more rapid decline in eGFR slope (p=1e-2), and most strongly associated with the combined Z-score of age at presentation and eGFR slope (p=2e-8). A preliminary association test of the combined Z-score with variant burden in each of 15765 protein-coding genes showed one genome-wide significant association (FDR=0.01). A preliminary GWAS in AFR ancestry cases and controls (n=904) showed minimal impact of potential confounders, such as ancestry or sequencing batch differences (lambda=1.03). A preliminary eQTL analysis revealed 3562 genes had eQTLs in either microdissected glomeruli or tubules.

Conclusions: Integrating longitudinal clinical data, whole genome sequences, and transcriptomes from microdissected tissues is a promising approach to unraveling the molecular mechanisms of kidney diseases.

Funding: NIDDK Support, Commercial Support - Goldfinch Bio

SA-PO409

Single-Cell RNA Sequencing Identifies Candidate Renal Resident Macrophage Gene Expression Signatures Across Species

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Background: Resident macrophages are involved in homeostatic and disease processes in multiple tissues including the kidney. Despite the use of well-defined markers to identify these cells in mice, technical limitations have prevented the identification of a similar cell type across species.

Methods: As an entry point to determine novel markers that could identify resident macrophages across species, we performed single cell RNA sequencing (scRNAseq) analysis of $CD45^+$ innate immune cells in mouse, rat, pig and human kidney tissue.

Results: Using this approach, we identified multiple genes whose expression is enriched in mouse renal resident macrophages and in candidate resident macrophage populations across species. Further, we identified a novel set of possible cell-surface markers for these candidate kidney resident macrophages (Cd74, Cd81) and confirm using parabiosis and flow cytometry approaches that these proteins are indeed enriched in mouse resident macrophages. Our flow cytometry data also indicate there is a defined population of innate immune cells in rat and human kidney tissue that co-express CD74 and CD81, suggesting the presence of renal resident macrophages in multiple species. Finally, we show that we can use these novel resident macrophage markers to identify a population of cells that is independent of peripheral blood input in the rat.

Conclusions: Collectively, our data indicate that, based on transcriptional signatures, there is a conserved population of innate immune cells across multiple species that have been defined as resident macrophages in the mouse. In addition, we provide a proof of principle experiment showing that we can use our novel markers to identify a population of CD45+ innate immune cells that are independent of peripheral blood input in the rat.

Funding: NIDDK Support

SA-PO410

More Than Half of Patients Clinically Diagnosed as Gitelman Syndrome in Adulthood Do Not Have Causal Mutations in Known Pathogenic Genes

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Background: Gitelman syndrome (GS) is an autosomal recessive kidney disorder characterized by hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis. GS is caused by loss of function mutations in *SLC12A3* encoding Na-Cl cotransporters (NCC). Most of previous reports includes child-onset GS cases, and thus etiological profiles in adult GS have not been fully elucidated. The purpose of this study is to clarify mutation profiles of clinically diagnosed GS cases in adulthood, and to investigate the phenotypic difference between cases in which their genetic diagnoses were established or not.

Methods: A total of 84 genetically independent individuals who were referred to our institute with a clinical diagnosis of GS during 2012 to 2018 were retrospectively reviewed. Individuals who have any episodes of using loop or thiazide diuretics, or laxatives were not included. All of them received comprehensive genetic screening for known genes responsible for GS, Bartter syndrome, and hypomagnesemia (*SLC12A3, SLC12A1, KCNJ1, CLCNKB, BSND, CLCNKA, CASR, MAGED2, TRPM6, CLDN16, KCNJ10, etc.*). Twenty individuals were excluded because of the following reasons; 9 with insufficient clinical information, 5 under 18 years, 2 with only single heterozygous variant in *SLC12A3*, 3 with responsible mutations in *CLCNKB*, 1 with variants in *BSND*.

Results: Of the remaining 64 cases, 27 (42.1%) were genetically diagnosed as GS (solved cases). Thirty-seven (57.9%) did not have any responsible variants (unsolved cases). Unsolved cases were older (47.1 ± 15.2 vs. 37.3 ± 13.1 years, P = 0.01). Interestingly, most of unsolved cases were female (83.8% vs. 59.3%). Serum Mg was higher in unsolved cases (1.95 ± 0.47 vs. 1.67 ± 0.34, P = 0.02). There were no differences in serum K, HCO_3^-, FEK, urine Ca/Cr ratio between the groups. Regarding the causal mutations in *SLC12A3*, L858H (33.3%) and T180K (25.9%) were major, which are reported as hotspots in Japanese GS. In this study, R399C was also found in 11.1% cases.

Conclusions: More than half of the adult cases with GS phenotype were mutation-negative for known pathogenic genes. Phenotypic difference of the two was not evident other than age and serum Mg. Unsolved adult cases might have novel pathogenic genes responsible for their GS phenotype.

Funding: Government Support - Non-U.S.

SA-PO411

Metabolic Profiling of Urine from Patients with Cystinuria Provides New Insight into Disease Phenotype, Associated Microbiome Effects, and Treatment Efficacy

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Background: Cystinuria is a disease of impaired absorption of cystine and dibasic amino acids (DAA) from the intestine and renal tubule leading to formation of cystine kidney stones. However, the metabolic impact of reduced amino acid absorption and excessive loss in the urine is poorly understood. We measured endogenous, gut microbial, and xenobiotic metabolites, providing insight into consequences of the disease and its treatment.

Methods: Urinary biochemicals were assayed using LC-MS in 293 urine specimens from patients with cystinuria or control urinary phenotypes. Multivariate statistical analyses were conducted to reveal statistically significant biochemical signatures of the disease and products of cysteine-binding thiol drugs (CBTDs). 16s rRNA gene sequencing was performed on fecal samples from 12 wildtype (WT) and 12 cystinuric (*Slc3a1* knockout; KO) mice to evaluate their gut microbial composition.

Results: Cystinuric urine samples had elevated levels of cysteine-γ-glutamyl cystine disulfide (glutathione precursor), indole-3-acetic acid (microbial tryptophan metabolism), and novel conjugated forms of putrescine (microbial DAA decomposition). Conversely, taurine (sulfur metabolism), indole-3-acetic acid-glucuronide, and novel urinary metabolite N-methyl pipecolic acid (lysine metabolism) were reduced in cystinuric urine. Where cysteine-bound CBTDs were observed, substantial amounts of "wasted" drug were also detected as CBTD homodimers, non-cysteine disulfides, and mixed drug disulfides. The differentiation of gut microbially-derived metabolites led us to evaluate the gut microbiome diversity and composition in a mouse model of cystinuria revealing clear beta diversity and taxa differentiation between WT and KO mice.

Conclusions: Cystinuria is associated with unique urinary metabolic profiles beyond hyperexcretion of cystine and DAA, indicating perturbed metabolic processes and potential gut microbial effects. Study of the gut microbiome of WT and KO mice provides the first evidence for them having distinct taxa, perhaps due to poorly absorbed DAA present in the intestinal lumen. Urinary profiles allow us to characterize the excretion profiles of CBTDs, providing insight which may be helpful to tailor treatment.

Funding: Government Support - Non-U.S.

SA-PO412

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis: Expression Pattern of Urinary Exosomal MiRNAs

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Background: Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive tubulopathy caused by *CLDN16* or *CLDN19* genes mutations. FHHNC is characterized by urinary wasting of calcium and magnesium, nephrocalcinosis and progression to chronic kidney disease (CKD) and end-stage renal disease (ESRD). Also, some *CLDN19* patients develop ocular impairment. Patients homozygous for c.59G>A; p.G20D mutation in *CLDN19* gene, the most frequent in Spain, exhibit different progression to kidney failure, suggesting that other molecular events modulate disease evolution. In absence of biopsy availability, urinary exosome-like vesicles (uEVs) are a non-invasive source of information of the renal condition. In this work we analyzed the expression pattern of miRNAs obtained from uEVs of FHHNC patients.

Methods: uEVs isolation of non-transplanted FHHNC patients was performed by differential centrifugation and miRNA cargo was extracted with miRCURY RNA Isolation kit and analyzed through microarray assays. Statistical parameters were p-value<0,5 and an absolute logFC>1, except for renal progression comparison which was 0,5.

Results: Our cohort comprises 30 patients: 3 present mutations in *CLDN16* gene while 27 (90%) in *CLDN19*, of which, 63% (n=19) are p.G20D homozygous. Most patients (53%) exhibit a moderate renal phenotype whereas 17% and 30% are classified as severe and mild, respectively. In the ESRD group, 80% of patients were female, whilst in the non-ESRD group they represent only 40%. Comparisons revealed sets of deregulated miRNAs in FHHNC patients and specific miRNAs associated with the homozygous p.G20D mutation. Moreover, we identified two miRNAs differentially expressed in male patients and one related to renal disease progression.

Conclusions: The analysis of miRNAs defined a set of miRNAs commonly expressed in all FHHNC patients and other miRNAs exclusively associated with the homozygous p.G20D mutation in the *CLDN19* gene. Furthermore, gender of patients and renal disease progression were also associated with specific miRNAs each.

Funding: Government Support - Non-U.S.

SA-PO413

Phenotypic Expression of Primary Hyperoxaluria: Comparative Features of Types 1, 2, and 3

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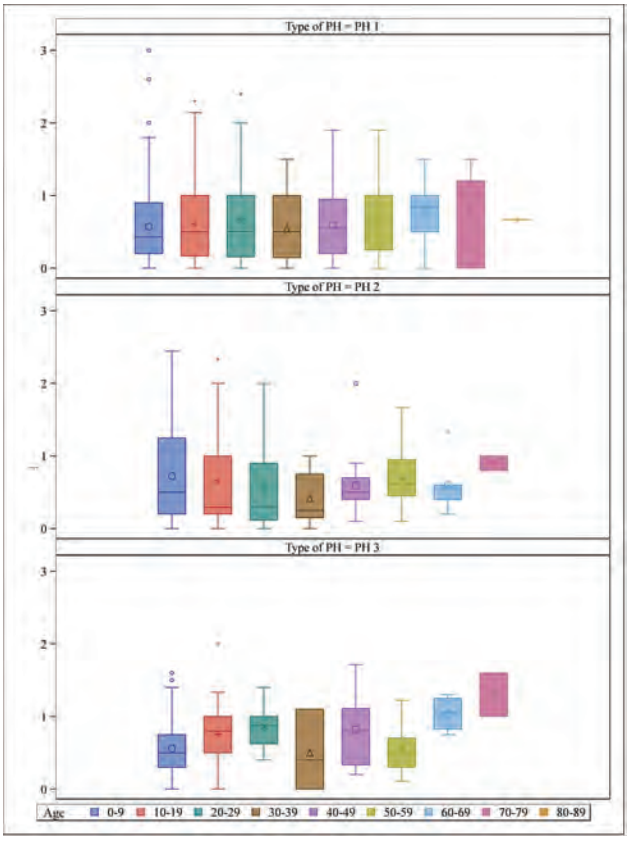
Background: Primary hyperoxalurias (PH) are inborn errors of metabolism that result from 3 specific hepatic enzyme deficiencies leading to hepatic overproduction of oxalate that must be excreted by the kidneys. Recurrent calcium oxalate kidney stones, nephrocalcinosis and decreased kidney function are common. PH type 3 (PH3) accounting for 10% of known PH cases was most recently described and hence the clinical expression is less defined due to small patient numbers and shorter follow-up.

Methods: Demographic and clinical data were obtained from patients enrolled in the Rare Kidney Stone Consortium PH registry. PH diagnosis was by molecular diagnostic testing of *AGXT* (PH1), *GRHPR* (PH2) and *HOGA1* (PH3) genes. Demographic, clinical, and laboratory features were compared by PH type using a Chi-square test (categorical variables) and Kruskal-Wallis test (continuous variables).

Results: Though they tended to be younger at onset of symptoms and diagnosis, PH3 patients were more likely to have had stones prior to diagnosis (p=0.025), a lower prevalence of nephrocalcinosis (p=0.002), and lower urine oxalate, and higher urine calcium and citrate excretions than PH1 patients.(p <0.001) PH3 patients continued to experience recurrent stones throughout all decades of life. See Figure 1

Conclusions: Though more likely to have stones at presentation and higher urine calcium, nephrocalcinosis is less prevalent and kidney function better preserved in PH3 compared to PH1 and PH2. The lower Uox and higher urine citrate may contribute to preserved renal function, although the higher urine calcium may contribute to frequent stone events throughout the lifespan. The data suggest persistent stone activity throughout life in PH3 patients.

Funding: NIDDK Support



Boxplot Stone events per patient per year

SA-PO414

Interim Results from the Ongoing Phase 2 Open-Label Extension Study of Lumasiran, an Investigational RNA Interference (RNAi) Therapeutic, in Patients with Primary Hyperoxaluria Type 1 (PH1)

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Background: PH1 is a rare genetic disorder characterized by persistent hepatic overproduction of oxalate. Oxalate crystalizes with calcium leading to recurrent kidney stones, nephrocalcinosis, progressive renal failure, and multiorgan damage from systemic oxalosis. Lumasiran is a subcutaneously-administered investigational RNAi therapeutic specifically designed to decrease oxalate production. In Phase 1/2, lumasiran demonstrated an acceptable safety profile and clinically significant urinary oxalate (UOx) lowering in patients with PH1. Emerging data from the ongoing Phase 2 open-label extension (OLE) study will be presented.

Methods: Phase 2 OLE includes patients who completed the Phase 1/2 randomized, placebo-controlled, multicenter trial, evaluating lumasiran in patients with PH1 ≥6 years old, UOx ≥0.7mmol/1.73m^2/day and eGFR >45mL/min/1.73m^2. Patients received 1 of 3 dosing regimens: 1mg/kg or 3mg/kg monthly x3 doses or 3mg/kg every 3 months x2 doses. After completing Phase 1/2, all patients enrolled in OLE, starting at their original dose unless a different dose was approved prior to dosing in OLE. Endpoints include safety and change in 24-hour UOx.

Results: The Phase 1/2 study enrolled 20 patients with PH1 at 9 sites in 5 countries; mean age 14.9 years (range: 6-43), mean baseline UOx 1.69mmol/1.73m^2/day (range: 0.83–2.97). As of February 2019, 18 patients were dosed in OLE for median of 4 months (range: 0.03–8.36). Continued dosing with lumasiran was well tolerated, with no discontinuations or drug-related serious adverse events. Adverse events were reported in 12/18 (66.7%) patients; majority were mild in severity and assessed as unrelated to study drug. Mean max reduction in UOx relative to Phase 1/2 baseline was 72% (N=9) and mean reduction at day 85 was 69% (N=7); all of these patients achieved normal or near normal levels of UOx.

Conclusions: To date, lumasiran has demonstrated an acceptable safety profile and clinically significant reduction in UOx in patients with PH1. A Phase 3 program evaluating efficacy and safety of lumasiran in patients with PH1 is ongoing.

Funding: Commercial Support - Alnylam Pharmaceuticals

SA-PO415

Alternative Promoter Type Influences the Expression of the GLA Gene in Human Kidney Cells

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Background: Diagnostic genetic methods for Fabry disease focus on molecular screening for mutations in *GLA* exons. Intriguingly, alternative promoters are greatly influencing differential gene expression in tissues and malfunctions in many disease-associated genes [Trends Genet (2008) 24(4):167-177; Genome Res (2011) 21(8):1260-1272]. *GLA* expression is one of more than 50% of human genes that are controlled by alternative promoters. We aimed to investigate the influence of alternative promoters on *GLA* expression in three types of human kidney cells (embryonic, epithelial and glomerular cells).

Methods: The *GLA* alternative promoters were searched in TRED, EPD, PrESSto/FANTOM5, and Ensembl databases. RNA extracted from embryonic, epithelial and glomerular kidney cells by RNAzol method. RT q-PCR was used for the analysis of *GLA* expression. Expression data of *GLA* alternative promoters were normalized to reference gene *HPRT*1, and the fold-change in the *GLA* expression was calculated by Livak and Schmittgen mathematical method [Methods (2001) 25(4):402-8.].

Results: Nine *GLA* alternative promoters were identified in the databases with overlapping sequences at 5-prime side of the *GLA* locus. EPD database showed 31 transcription starting sites (TSSs) along 150 bases (-99 to +50) from the main TSS at position 0. Three primers sets (G1, G2, and G3) were designed to cover several TSSs and were used in the *GLA* expression analysis by RT q-PCR. The expression data showed *GLA* expression differences over a wide range in kidney embryonic, epithelial and glomerular cells. For example, in the kidney embryonic cells, the *GLA*-G2 expression was decreased 12.5-fold, and *GLA*-G3 was increased 15.3-fold compared with *GLA*-G1 expression. Promoter efficiency depends upon regulatory sequences specific to transcription factors, mutations in the alternative promoters can alter the binding capacity of transcription factors.

Conclusions: RT q-PCR data showed the influence of alternative promoter type on the expression of the *GLA* gene in human kidney cells. Alternative promoters and their variants may serve as diagnostic biomarkers and potential therapeutic targets for Fabry disease.

Funding: Commercial Support - Sanofi Genzyme

SA-PO416

Variants in the Bidirectional Promoter of GLA and HNRNPH2 Associated with Fabry Disease

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Background: Heterogeneous clinical presentation of Fabry disease is not yet completely understood. Although, heterozygous Fabry females generally show an attenuated form of Fabry disease; in some cases, they show a severe phenotype. A severe case of heterozygous female (HF) was attributed to CpG Island (CGI) methylation specifically at mutation site c.36C>A in the *GLA* gene exon 1, the patient's non-mutated allele C, which is prone to methylation, remained unchanged [Mol Genet Metab (2017) 120(3):173-179]. Even though the status of the CGI methylation in silencing genes' expressions is divisive, the overall view is that methylation can repress transcription factor binding. Genomic databases show overlapping sequence at 5-prime sides of *GLA* and *HNRNPH2* divergently paired loci. Mutations at the upstream of *HNRNPH2* sequence can cause Fabry disease. We aimed to investigate the molecular features of *GLA* and *HNRNPH2* predicted bidirectional promoter that control the expression of the two divergently paired genes and their association with Fabry disease.

Methods: Genomic databases and prediction tools for promoters, transcription factor binding sites and CGI were used to identify and analyze the intervening sequence for *GLA* and *HNRNPH2* and the bidirectional promoter.

Results: Most bidirectional promoters are GC rich and exhibit CGIs prone to methylation, and characterized by five transcription factors binding sites (TFSBSs) (GABPA/NRF2, NRF1, NFY, YY1, and ZNF143). The predicted *GLA* and *HNRNHP2* bidirectional promoter sequence located at chrX: 101,407,191-101,409,040 on the reverse strand composed of 1850 bps. We identified 831 bps intervening sequence for *GLA* and *HNRNHP2*-reverse complement. The five specific TFBSs were identified and marked along the predicted bidirectional promoter sequence. The lengths of four identified CGIs were between 100 and 323 bases. The criteria used for identification of CGI were: CGI size > 100, %G+%C Percent > 50.0, Obs/Exp CpG ratio > 0.6). Intriguingly, the c.36C>A variant of HF patient was mapped at NRF1 motif identified by our bioinformatic analysis. Methylation reduced binding of NRF1 transcription factor to those sites [Cell Rep (2017) 19(11):2383-2395].

Conclusions: The molecular characteristics of identified *GLA* and *HNRNHP2* bidirectional promoter define the role of upstream variants of the divergently paired *GLA* and *HNRNPH2* genes in Fabry disease.

Funding: Commercial Support - Sanofi Genzyme

SA-PO417

Methyl-CG Erosion Define Core Pathways in the Progression of Diabetic Nephropathy

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Background: To apply systems level understanding of the role of DNA methylation, it is important to distinguish the essential sequence elements involved in regulating gene expression. This becomes a particularly challenging task for diabetic kidney disease (DKD) when reliable epigenetic markers such as DNA methylation are limited. While genome-wide methylation studies are typically performed using BeadChip array technology, this does not provide sufficient coverage to construct an integrated epigenetic regulatory network (ERN) important because diabetic nephropathy is considered a complex polygenic and multifactorial disorder. To address this knowledge gap, we examined DNA methylation using massive parallel sequencing to describe an ERN assessing methylation changes from multi-centre diabetes registries.

Methods: DNA methylation sequencing was used to define an epigenetic regulatory network in the Finnish Diabetic Nephropathy (FinnDiane) discovery cohort. DNA methylation changes were also assessed using independent replication cohorts from Hong Kong and Thailand. Methylation mediated gene regulation using primary human renal and vascular endothelial cells confirm functional methylation-dependent CTCF and Pol2B regulation of gene expression.

Results: Differential methylated regions (DMRs) in leukocytes are associated with DKD progression and integrative methylation analyses reveal 494 differentially methylated genes (DMGs) that intersect with CTCF binding sites (181 genes with increased- and 313 genes with reduced- methylation). Integration of DNA methylation and CTCF/Pol2B profiles confirm the major pathways associated with insulin receptor signalling, lipid metabolism and integrin cell interactions with the progression of DKD.

Conclusions: The progression of nephropathy in T1D remains unexplained, using multi-centre registries combined with functional studies using primary human renal cells we identify methylation indices and specifically erosion on core genes that functionally regulate pathways describing an epigenetic regulatory network.

Funding: Government Support - Non-U.S.

SA-PO418

Targeted Next-Generation Sequencing of Nephropathy Genes in Non-Diabetic and Diabetic Kidney Disease Patients Facilitates Clinical Diagnoses

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Background: For patients with concomitant diabetes and chronic kidney disease (CKD), diabetes is often assumed to be the underlying cause of their kidney disease. Without histopathological evidence, however, it's unclear if such patients have diabetic

kidney disease (DKD), nondiabetic kidney disease (NDKD), or concurrent DKD and NDKD. To examine the utility of targeted next-generation sequencing (NGS) in facilitating clinical diagnoses in CKD, we coupled this technology with a custom nephropathy gene panel to determine the genetic cause of CKD in NDKD and DKD patients from the Utah Kidney Study.

Methods: Targeted NGS of 345 nephropathy genes was performed in 186 patients (87 NDKD and 99 DKD). Identified variants were prioritized by predicted effect on protein function, frequency (minor allele frequency (MAF) < 0.1%), and a CADD-based mutation significance cutoff (MSC) at the 95% confidence interval for ClinVar.

Results: After applying a MAF filter and MSC impact score cutoff, retaining only variants marked as highly likely to be deleterious, we identified 563 rare, functional variants, 113 of which are novel. These included 509 nonsynonymous, 20 nonsense, 24 frameshift, and 10 splicing variants. No enrichment of these variants was observed in NDKD patients when compared to DKD patients (*P*=0.55); there was, however, a modest, non-significant excess of novel rare variants in the NDKD cohort (P=0.15). An excess of rare variants was identified in the NDKD cohort in several genes, including *COL4A5* and *PKD2*. Conversely, variants in *DYNC2H1, ATP7B, NEK8,* and *ACE* were enriched in the DKD cohort. Interestingly, variants *PKHD1* and *CUBN* were nearly equally distributed between the two cohorts.

Conclusions: We identified many rare and novel variants in known nephropathy genes in both NDKD and DKD patients. Our findings suggest that many DKD patients likely have concomitant diabetes and non-diabetic CKD that can be attributed to a genetic cause. Our study suggests that targeted NGS may prove useful as a diagnostic tool to enable an accurate molecular CKD diagnosis, particularly in patients whose underlying CKD cause is incorrectly attributed to their diabetes.

Funding: Private Foundation Support

SA-PO419

Effects of the GLUT1 A-2841T Polymorphism on Proteinuria in CKD Patients Prior to the Onset of ESRD

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Background: The potential role of selected Glucose transporter 1 (GLUT1) single nucleotide polymorphisms (SNP)s in the pathogenesis of diabetic kidney disease has previously been published in human studies, with certain polymorphisms conferring a higher risk of nephropathy. We studied the effects of the GLUT1 A-2841T SNP in the promoter region on proteinuria in chronic kidney disease (CKD) patients prior to onset of their end-stage renal disease (ESRD).

Methods: This was a prospective cohort study of 127 ESRD patients whose GLUT1 A-2841T genotype was determined from their blood specimen and classified as: AA, AT or TT with the T polymorphism present in none, one or both alleles, respectively. Proteinuria was assessed by the highest protein to creatinine ratio within the 6-month period prior to ESRD onset, provided there was no sign of acute kidney injury. Covariates collected were patient age, race/ethnicity, gender, ESRD cause and date of onset as documented by their chronic dialysis unit, left ventricular ejection fraction <40%, smoking status, and presence of coronary/peripheral arterial disease. The gene analysis was performed by the UF Center for Biotechnology. Protein to creatinine ratio results were available in 78 patients. ESRD causes were categorized as type 2 or 1 diabetes mellitus, hypertension, polycystic kidney disease, glomerulonephritis or primary nephrotic syndromes, and other. The data were analyzed using Fisher's exact tests and multiple regression.

Results: The distribution of genotypes does not vary among the ESRD causes (p=0.54), but differs among the race/ethnicities (p=0.0002), with the TT genotype present in 50%(4/8), 7.7% (8/104), 10%(1/10) and 40%(2/5) of Hispanic, black, white and American Indian/other patients, respectively. Adjusting for the ESRD cause, the TT genotype is associated with 5.73 g/g more proteinuria than AA (95%CI 2.9,8.5;p=0.0001). The AT genotype is associated with 0.71 g/g more proteinuria than AA, but the results are not significant.

Conclusions: Proteinuria in CKD patients tends to increase with a single A to T allele change at the -2841 position of the GLUT1 gene and becomes very significant with A to T changes in both alleles, with the results applicable to all ESRD causes.

Funding: Commercial Support - Dialysis Clinic, Inc.

SA-PO420

Contribution of SLC22A12 on Hypouricemia and Its Clinical Significance for Screening Purposes

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Background: Renal hypouricemia (RHUC) is a rare inherited disorder strongly associated with genetic mutations of renal transporters genes. Despite its adverse complications (e.g. acute kidney failure and nephrolithiasis), differentiating between inherited renal hypouricemia and transient hypouricemic status is challenging. Here, we aimed to identify genetic variants in hypouricemia patients using whole-exome sequencing (WES) and assess the feasibility for genetic diagnosis in primary screening.

Methods: We selected all cases (N=31) with extreme hypouricemia (<1.3 mg/dl) from Korean urban cohort of 179,381 subjects; selection criteria included 1) abstinence from alcohol or smoking and 2) an absence of underlying conditions (i.e., hypertension, diabetes and taking anti-hypertensive medication). WES and corresponding downstream analyses were performed for the discovery of coding variants causal for hypouricemia. Two known causal variants within *SLC22A12* (p.Trp258*, pArg90His) were identified, we then directly genotyped the 2 *SLC22A12* variants in independent 50 hypouricemia subjects to assess the diagnostic utility of these two causal variants.

Results: For the discovery cohort who had undergone WES, 27 of 31 (87.1%) individuals harbored missense or nonsense variants in either the homozygous or compound heterozygous state in *SLC22A12*. 24 of 31 (77.4%) subjects were shown to have at least 1 copy of the truncating p.Trp258* and/or p.Arg90His. Four novel variants in *SLC22A12*, p.Asn136Lys, p.Thr225Lys, p.Arg284Gln, and p.Glu429Lys were discovered and were predicted to cause uric acid transport defects by molecular dynamics. Individuals (n=50) from an independent cohort were directly genotyped for the p.Trp258* and p.Arg90His variants, 47 of 50 cases (94%) were explained by only these two variants.

Conclusions: This is the first study to show the value of genetic diagnostic screening for hypouricemia in the clinical setting. Screening of just two ethnic-specific variants (p.Trp258* and p.Arg90His) identified 87.7% (71/81) of Korean patients with hypouricemia. Early genetic identification of constitutive hypouricemia may prevent acute kidney injury by avoidance of dehydration and excessive exercise.

Funding: Government Support - Non-U.S.

SA-PO421

Long-Term Renal Outcomes with Migalastat in Patients with Fabry Disease: Results from Phase 3 Trials

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Background: Fabry disease is a multisystem disorder of which nephropathy is an important feature, with untreated male patients experiencing a decline in glomerular filtration rate (GFR) of up to 12.2 mL/min/1.73 m^2 per year. Here, we assessed long-term changes in renal function in patients with Fabry disease and amenable mutations who were treated with migalastat in the phase 3 FACETS (NCT00925301) and ATTRACT (NCT01218659) trials.

Methods: In FACETS, enzyme replacement therapy (ERT)-naive patients were randomly assigned to 6 mo of double-blind miglastat 150 mg every other day (QOD) or placebo, followed by an additional 18 mo of migalastat. In ATTRACT, patients receiving ERT were randomly assigned to 18 mo of miglastat 150 mg QOD or continued ERT, followed by an additional 12 mo of miglastat. Patients could continue migalastat in separate long-term extension trials. Renal outcomes were evaluated using the beginning of migalastat treatment as the baseline, and were analyzed by sex, baseline $eGFR_{CKD-EPI}$, and baseline 24-h urine protein.

Results: Overall, mean (range) duration of migalastat exposure was 4.4 (0.1-7.8) years. Mean (SD) baseline $eGFR_{CKD-EPI}$ (mL/min/1.73 m^2) was 93.1 (24.4) in FACETS and 89.0 (20.4) in ATTRACTS. Annualized rates of change in $eGFR_{CKD-EPI}$ by baseline variables are shown in the table.

Conclusions: Data suggest that patients who received long-term treatment with migalastat experienced a rate of eGFR decline comparable to published data with ERT. In addition, starting treatment early may prevent irreversible renal progression.

Funding: Commercial Support - Amicus Therapeutics

Annualized Rate of Change in $eGFR_{CKD-EPI}$		FACETS (n=48)		ATTRACT (n=49)	
	Analysis group	Mean (SD)	n	Mean (SD)	n
Overall	—	-1.7 (3.8)	47	-1.6 (6.5)	49
Sex	Male	-2.6 (4.1)	18	-3.8 (6.8)	19
	Female	-1.1 (3.5)	29	-0.2 (6.0)	30
Baseline $eGFR_{CKD-EPI}$	>90 mL/min/1.73 m^2	-2.1 (4.0)	26	-2.0 (5.1)	24
	60-90 mL/min/1.73 m^2	-0.6 (2.7)	16	0.0 (6.9)	22
	>30 to <60 mL/min/1.73 m^2	-2.7 (5.3)	5	-10.0 (9.3)[a]	3
Baseline urine protein	<100 mg/24 h	-0.9 (1.4)	7	-2.3 (7.6)	12
	100-1,000 mg/24 h	-1.4 (4.0)	33	-1.6 (4.3)	25
	>1,000 mg/24 h	-3.9 (3.7)	7	-8.0 (11.7)[a]	3

[a]Each subgroup included one patient with an annual eGR decline of 20 mL/min/1.73 m^2.

SA-PO422

Evaluation of Renal Biomarkers for Fabry Disease Patients with and Without Enzyme Replacement Therapy

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Background: Renal follow-up is an important part of clinical monitoring in patients with Fabry disease(FD)with the aim of avoiding renal failure. Despite its limitations, creatinine is still the most used biomarker. While new renal biomarkers are described, their effectiveness has not yet been fully evaluated for FD. This study aimed to compare renal biomarkers generally and rarely used in the evaluation of FD patients receiving or not enzyme replacement therapy(TRE).

Methods: The usual biomarkers for renal monitoring (microalbuminuria, proteinuria and creatinine) and the proposed biomarkers (cystatin C, beta-2-microglobulin (B2M), NGAL were quantified in blood and/or urine samples of 40 patients with FD, 39 controls without renal disease paired by age and sex and 38 controls with renal disease undergoing hemodialysis.

Results: In FD group, 32.5% are men with mean age of 41 years old and mean age of 37.8 years of FD diagnosis. There was a statistical difference($p<0.05$)for proteinuria and microalbuminuria in isolated urine samples and, in results for both serum and plasma samples for cystatin C,NGAL,B2M, creatinine and GFR. All analytical parameters evaluated, including ROC curve, sensitivity, specificity and accuracy indicated B2M as the best biomarker, followed by cystatin C, proteinuria and microalbuminuria. Results of NGAL and urinary creatinine do not indicate good predictors of renal impairment. Although 72.5% patients were receiving ERT, similar results were found when comparing individuals with and without ERT with controls, suggesting that the treatment does not seem to have influences on the evaluated parameters. When comparing the results of FD receiving or not TRE with the control volunteers without kidney disease, there was a significant statistical difference for the results of NGAL, microalbuminuria and proteinuria. Microalbuminuria and proteinuria are widely accepted as one of the evidences for starting TRE in FD patients. Since NGAL has already been described as a potential biomarker of inflammation, it might help to explain the higher results of this biomarker in FD patients when compared to control groups.

Conclusions: Considering the biomarkers proposed, serum B2M was the best renal biomarker for renal follow-up in FD patients, followed by cystatin C. Moreover, TRE does not seem to have influences on biomarkers results.

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Family Screening Among CKD Patients with Fabry Disease: A Very Important and Underrated Task

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Background: Introduction: Fabry disease is a chronic, progressive and multi-systemic hereditary condition, related to a Xq22 mutation in X chromosome, which results in deficiency of acid alpha-galactosidase, hence reduced capacity of globotriaosylceramide (Gb3) degradation. Gb3 accumulates in lysosomes throughout virtually every organ, thus carrying considerable morbidity and mortality. **Objective**: Evaluate the prevalence of Fabry disease, as well as its signs and symptoms, among relatives of chronic kidney disease (CKD) patients diagnosed with Fabry disease during a previously conducted study, entitled "Clinical and epidemiological analysis of Fabry disease in dialysis centers in Brazil – the Brazil Fabry Kidney project".

Methods: Transversal study, interviewing the relatives of patients and performed blood tests for both Gb3 dosage and genetic testing.

Results: Among 1214 interviewed relatives, 115 (9.47%) were given the diagnosis of Fabry disease, with a predominance of women (66.10%). The most prevalent comorbidities were rheumatologic conditions and systemic hypertension (1.7% each), followed by heart, neurological and cerebrovascular disease, and depression, in 0.9% of individuals. Intolerance to physical exercise and tiredness were observed in 1.7%, followed by periodic fever, intolerance to heat or cold, diffuse pain, burn sensation or numbness in hands and feet, reduced or absent sweating, as well as abdominal pain after meals, in 0.9%.

Conclusions: Family screening of Fabry disease is highly indicated, since we found a prevalence of 9.47% of relatives of CKD patients with this condition, remarkably with a 66.1% predominance of women, which contrasts with previous reports.

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Natural Killer Subsets in Patients with Fabry Disease

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Background: Fabry Disease (FD) is a storage disorder which affects mostly kidney, kardio and serebrovascular systems. The lysosome, whose function is impaired in FD and also is an important compartment for the innate immune responses. To date, invariant natural killer (NK) T cell functions was found be impaired in FD. Hovewer, there is no data regarding NK cell subsets in patients with FD. We aimed to analyze subtypes of NK cell in patients with FD and compared these results with healthy subjects.

Methods: 15 patients with FD and 10 healthy subjects were included in the study. Of these 15 patients 8 patients were receiving agalsidase alfa or beta. Blood samples obtained from the patients with FD and healthy subjects were taken into 2 ml EDTA tube to evaluate peripheral NK cell subgroups according to CD56 and CD16. These cells were evaluated by flow cytometry technique.

Results: The characteristic and demographic features of patients with FD and controls are depicted in Table 1. According to flow-cytometric analysis, total percentage of NK cells of FD patients are similar to healthy controls (11.6% vs 10.7%, p: >0.05, respectively). When we analyzed subgroups of NK cells, we determined that $CD56^{dim}$ $CD16^{dim}$ and $CD56^{bright}$ $CD16^{dim}$ NK cells were increased, however, $CD56^{dim}$ $CD16^{bright}$ NK cells were decreased when compared with healthy controls (59% vs 38%, p:, 13.4% vs 7.3%, p:, 18.9% vs 49.2% p:0.025, respectively).

Conclusions: $CD56^{bright}$ $CD16^{dim}$ subtype of NK cells which can secrete cytokines in normal population are increased in patients with FD. Additionaly $CD56^{dim}$ $CD16^{dim}$ subtype of NK cells are also decreased in these patients which is closely associated with cellular cytotoxity in normal population. Further studies are needed to clarify the roles of NK cells in patients with FD.

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Demographic and Laboratory Features of Patients with Fabry Disease and Healthy Controls

Parameters	Healthy subjects (n=7) Mean±SD or Median (IQR)	Patients with Fabry disease (n=15) Mean±SD or Median (IQR)	P value
Age (years)	30.86± 7.69	34.93± 15.06	0.511
Female/Male	5/5	7/8	0.666
Glucose (mg/dL)	95.71±15.88	91.46±9.64	0.443
eGFR (ml/min)	102 (36)	106 (54)	0.549
Creatinine (mg/dL)	0.78 ±0.24	0.82 ±0.38	0.827
Uric acid (mg/dL)	4.45 ±1.37	4.11 ± 1.51	0.643
Albumin (g/L)	4.41± 0.46	4.2± 0.40	0.538
Proteinuria	90 (61)	185 (218)	0.022
Crp (mg/L)	2 (5)	0.9 (3.4)	0.289

Table 1

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Tunneling Nanotubes Shuttle Lysosomes with Low-Level α-Galactosidase A from Non-Fabry to Fabry Podocytes In Vitro

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Background: Fabry disease is an X-linked disease; however, females can suffer from serious complications. Biopsy studies are suggestive of no efficient cross-correction between non-Fabry and Fabry podocytes. We aimed to examine if there is any level of cross-correction between these cells in-vitro.

Methods: A conditionally immortalized human podocyte cell line with complete knock out of GLA (GLA-ko) using CRISPR-Cas9 was developed. Wild type (WT) podocytes were co-cultured with GLA-ko cells for a week, after which, GLA-ko and WT cells were separated by FACS sorting based on GFP expression in GLA-ko cells. Purity of sorted cells was confirmed by genotyping. Sorted co-cultured (CC) WT and GLA-ko, no co-culture (no-CC) WT and GLA-ko cells and culture media were tested for GLA-mRNA (qPCR), α-Gal-A [western blot (WB) and immunofluorescence (IF)], and α-Gal-A activity.

Results: GLA-mRNA in CC-GLA-ko cells was 2.6 fold less than WT podocytes, but 2.7 fold greater than no-CC-GLA-ko podocytes. No GLA-mRNA was detected in culture media. By WB, while no α-Gal-A protein was detected in no-CC-GLA-ko cells, this was present in CC-GLA-ko cells, albeit being 6 fold less than in WT podocytes, confirmed by IF for α-Gal-A. There was very scant α-Gal-A in media from WT and co-cultured podocytes by WB (31 fold and 15 fold less than intracellular WT, respectively). While there was almost no α-Gal-A activity in no-CC-GLA-ko podocytes, this was present in CC-GLA-ko cells, albeit being 6 fold less than in WT podocytes. There was no detectable α-Gal-A mRNA or enzyme activity in the media. A survival assay showed similarly reduced cellular proliferation in both CC-GLA-ko and no-CC-GLA-ko podocytes compared to CC-WT or no-CC-WT podocytes. IF staining showed tunneling nanotubes (TNTs) containing lysosomes and α-Gal-A running between the cells.

Conclusions: Our data suggest that there is small transfer of GLA-mRNA and α-Gal-A protein from non-Fabry to Fabry podocytes through TNTs. This low level cross-correction led to small increase in α-Gal-A activity in Fabry podocytes but was not enough to improve survival of these cells. It will be important to demonstrate if this phenomenon exists in-vivo and between other cells. These studies may lead to novel treatment options for females with Fabry disease.

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SA-PO426

Think, Rethink, Diagnose: Dent Disease Type 1

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Background: Dent's disease type 1(Dent1) is a rare X-linked tubulopathy with no cure at the present time. It affects mainly males and is characterized by low-molecular-weight proteinuria(LMWP), hypercalciuria, nephrolithiasis, nephrocalcinosis and progressive renal failure. There's a broad phenotypic variability unrelated to the different mutations. LMWP is not routinely tested so that it may go unnoticed and lead to misdiagnosis. The prevalence of Dent1 is unknown. The geographic dispersion and the lack of common registries make epidemiologic studies difficult. We aim to evaluate the Spanish Dent1 cohort and assess its genetic and clinical characterization.

Methods: We identified 18 patients with genetic confirmation of Dent1 diagnosed in 9 different hospitals in Spain. Only two individuals belonged to the same family; the rest to different families.

Results: Genetic analysis revealed 17 different mutations in *CLCN5* gene in the 18 patients. The median age at diagnosis was 15 months [IQR,11-108] and the main sign leading to diagnosis was proteinuria (40%). All patients had proteinuria measured by protein/creatinine ratio(pCOR), median 1600mg/g [IQR.715-1665]) and LMWP. During follow-up, 40% of patients presented with nephrocalcinosis and 11% with lithiasis. Mean creatinine at diagnosis was 0,37±0,18mg/dl and estimated glomerular filtration rate(eGFR) 140±59 ml/min. After follow-up, (median 6 years [IQR,3-12.25]) creatinine was 1,2±0,9 mg/dl and eGFR 88±44 ml/min. No patients required renal replacement therapy (Table 1).

Conclusions: One should suspect Dent1 in males with a history of lithiasis, nephrocalcinosis or bone disease. Although LMWP is the hallmark of Dent1, many

patients show albuminuria. LMWP should be tested in young males with albuminuria and no other sign/symptom of nephrotic syndrome. Common registries are important.

Funding: Private Foundation Support

	Patients Dent1 (n=18)
Diagnosis	
Age at diagnosis, months (median, [IQR])	15 [11-108]
Symptoms/signs leading to diagnosis	
Proteinuria (%)	58,8%
Lithiasis (%)	11,1%
Rickets (%)	11,1%
Urinary tract infection (%)	5%
Acute kidney injury (%)	11,1%
Family history (%)	11,1%
Creatinine mg/dl (mean ± SD)	0,37 ± 0,18
eGFR Schwarts ml/min (mean ± SD)	140 ± 59
Low molecular weight proteinuria (µg/L) (median, [IQR])	89.900 [53.000-238.000]
Calciuria mg/kg/d (mean ± SD)	7,6 [2,07-9,4]
Proteinuria, protein/creatinine ratio (mg/g) (median, [IQR])	1600 [715-1665]
Aminoaciduria, yes (n,%)	2 (11%)
Uricosuria, yes (n,%)	3 (16,6%)
Glycosuria, yes (n,%)	2 (11%)
Evolution	
Follow-up time, years (median, [IQR])	6 [3,12,25]
Creatinine mg/dl (mean ± SD)	1,2 ± 0,9
eGFR CKD-EPI ml/min (mean ± SD)	88 ± 44
Calcium urine mg/24h (mean ± SD))	261±182,3
Phosphorus urine mg/24h (mean ± SD)	1407±580,7
Albuminuria pCOR (mg/g) (median, [IQR])	275(162,360)
Proteinuria, pCOR (mg/g) (median, IQR)	2744(2350,3024)
Low molecular weight proteinuria (µg/L) (median, [IQR])	63.000 [57950, 90940]
Nephrocalcinosis , yes (n,%)	8 (44,4%)
Lithiasis, yes (n,%)	2 (11,1%)
Rickets, yes (n,%)	3 (16,6%)
Fractures, yes (n,%)	3 (16,6%)
Renal replacement therapy, yes (n,%)	0 (0%)

SA-PO427

RNA Sequencing Profile of Circular RNAs in Mouse Kidney During Aging

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Background: Kidney aging is an important clinical problem, not only because normal aging reduces renal function but also because of the high frequency of ESRD, renal cancer, and renal failure in elderly people. At the present time, the molecular basis of renal aging is not clearly known. For example, the abundance and function of circular RNAs (circRNAs) in other disease have been reported, but their alterations in the biology of renal aging remain elusive.

Methods: Renal Specimens were collected from 3-month-old and 24-month-old C57BL/6 mice. Total RNA was extracted using Trizol reagent following the manufacturer's procedure. The circRNA expression was performed using secondary Sequencing. Quantitative real-time reverse-transcription polymerase chain reaction (qRT-PCR) was used to quantify the expression of circRNAs.

Results: A total of 134 distinct circRNA candidates were detected. Among them, we defined the statistical criteria for selecting aberrant-expressed circRNA using a p-value of < 0.05 with a fold change of > 2.0 or < 0.5. A total of 86 circRNA were upregulated and 48 circRNA were downregulated significantly in the 24-month-old tissues. Furthermore, an association of the circRNA-miRNA-mRNA was investigated, showing that 17 dysregulated circRNA successfully predicted an interaction with several age-related miRNAs-mRNAs. Finally, validation of down-regulation of circRNA6456 in 24-month-old compared to 3-month-old by qRT-PCR, indicating that circRNA6456 may delay renal senescence in mice.

Conclusions: This observational study demonstrated dysregulation of circRNA in age-related kidneys, which may have an impact on development of potential biomarkers in aging.

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SA-PO428

Amniotic Fluid Stem Cells Ameliorate Experimental Acute Renal Failure via Induction of Autophagy and Inhibition of Apoptosis

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Background: Amniotic fluid stem cells (AFSC) have been shown to contribute in renal repair after Acute Renal Failure (ARF), however, the mechanism responsible for its renoprotective effects still remains unclear. Therefore, in the present study we evaluated the therapeutic efficacy of AFSC and investigated the underlying mechanisms responsible for its renoprotective effect.

Methods: To study the therapeutic potential of AFSC, ARF was induced in rats by a single dose of cisplatin. Five days after cisplatin injection, AFSC or normal saline were injected intravenously. On day 3 and 7 post-therapy, blood biochemical parameters, histopathological changes, apoptosis and expression of pro-apoptotic, anti-apoptotic and autophagy-related proteins in renal tissues were studied in both groups of rats. Furthermore, to confirm whether the protective effects of AFSC on cisplatin-induced apoptosis are dependent on autophagy, chloroquine, an autophagy inhibitor, was administered intra-peritoneally.

Results: Administration of AFSC in rats with ARF, resulted in improvement of renal function and attenuation of renal damage as reflected by decreased blood urea nitrogen and serum creatinine levels and alleviation in tubular cell apoptosis as assessed by lower Bax/Bcl2 ratio and decreased levels of pro-apoptotic proteins viz. PUMA, Bax, cleaved caspase-3 and cleaved caspase-9 as compared to saline-treated group. Furthermore, in the AFSC-treated group as compared to saline-treated group there was increased activation of autophagy as evident by increased expression of LC3-II, ATG5, ATG7, Beclin1 and phospho-AMPK levels with a concomitant decrease in phospho-p70S6K and p62 expression levels. Chloroquine administration led to significant reduction in the anti-apoptotic effects of the AFSC therapy and further aggravated the deterioration in renal structure and function caused by cisplatin.

Conclusions: This study suggests that induction of autophagy is essential for the renoprotective effects of AFSC against cisplatin-induced apoptosis. Collectively, our results show that AFSC ameliorate cisplatin-induced ARF through induction of autophagy and inhibition of apoptosis.

Funding: Government Support - Non-U.S.

SA-PO429

Engineered Bone Marrow Stem Cell-Sheets Alleviate Renal Fibrosis in a Chronic Glomerulonephritic Rat Model

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Background: Although mesenchymal stem cell (MSC)-based regenerative therapy is currently being developed for treatment of kidney diseases, it is ineffective due to a few functional cells present at the target tissue. Thus, we developed an MSC-engineered cell sheet technology using the temperature-responsive cell culture surfaces to release cultured MSCs as confluent living cell-sheets. We hypothesized that this new technology would improve MSC transplantation efficiency and therapeutically reduce kidney disease.

Methods: . Three experimental groups included normal, untreated disease control but received sham surgery, and allogeneic bone marrow-derived MSC-sheets treated diseased rats. The chronic glomerulonephritis was induced by two injections of anti-Thy 1.1 antibody (OX-7) in rats. The MSC-sheets were prepared and transplanted as patches onto the surface of the two kidneys of each rat in the treated group at 24h after the first injection of OX-7.

Results: At 4 weeks, retention of the transplanted MSC-sheets was confirmed and animals with MSC-sheets showed significant reductions in proteinuria, glomerular staining for periodic acid-Schiff positive materials, collagen III and fibronectin, and in renal TGFß1, PAI-1, collagen I and fibronectin mRNA and protein levels. Treatment also altered renal overexpression of KIM-1 and NGAL mRNAs and reversed disease induced reduction of WT-1, podocin and nephrin mRNAs. Furthermore, treatment enhanced regenerative gene expression, and IL-10, Bcl-2, and HO-1 mRNA levels but reduced TSP-1 levels, NF-kB and NAPDH oxidase production in the kidney, which were consistent with the reduction of glomerular macrophage cell infiltration and glomerular and tubular cell apoptosis.

Conclusions: These observations strongly support our hypothesis that MSC-sheets facilitated MSC transplantation and effectively retarded progressive renal fibrosis through paracrine or autocrine signaling involved cellular inflammation, oxidative stress, apoptosis and regeneration.

SA-PO430

Gene-Modified Urine-Derived Stem Cells Home to the Ischemic Kidney

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Background: Acute kidney injury is a major cause of morbidity and mortality, with only half of those diagnosed surviving three months. The current therapies for acute kidney injury are supportive rather than regenerative. We sought to evaluate if human urine-derived stem cells were able to migrate to the kidney following ischemia/reperfusion injury in mice.

Methods: Urine is a practical and painless source of cells for gene and cell therapy applications. Urine-derived stem cells are adult human cells of renal origin that propagate in tissue culture in media containing growth factors on gelatin-coated plates. We have isolated, expanded, transfected, and tracked these cells following injection into live NSG immunocompromised mice order to assess their potential for regenerative gene and cell therapies.

Results: FACS characterization revealed that they expressed the characteristic marker panel (CD44, CD73, CD90, & CD146 + / CD31, CD34, & CD45 -). They differentiated into osteogenic and adipogenic lineages. Transfection was optimized to achieve 61% transfection. Five different *piggyBac* luciferase transposons were compared with the CMV and EF1-alpha giving the highest luciferase signals. When luciferase-modified urine-derived stem cells were injected directly into the renal pelvis of immunocompromised NSG mice they migrated to the surgical wound scar. To test the homing ability of the cells in the setting of ischemia reperfusion injury, we optimized the time of ischemia together with unilateral nephrectomy in immunocompromised NSG mice to be 22 minutes with 83% of mice having elevated creatinine. Urine-derived stem cells transfected with *piggyBac* transposons expressing luciferase were injected into the peritoneum of mice on Day 3 post-ischemia reperfusion injury. The cells were tracked via the InVivoPLOT

imaging gantry for quantitative tomographic optical live animal imaging. We found luciferase signal localized within 2 hours post-injection to the injured kidney with lower levels in the spleen.

Conclusions: Urine-derived stem cells represent an easily isolated, clinically relevant cell type that can be manipulated with non-viral genetic tools. We have found that the cells quickly migrate from their injection site to injured tissues. Next we will assess functional correction following injection of urine-derived stem cells into mouse models of acute kidney injury.

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SA-PO431

Bone Marrow Mesenchymal Stem Cells-Derived Exosomes Reduce Pericyte Transition by Inhibiting Core Fucosylation

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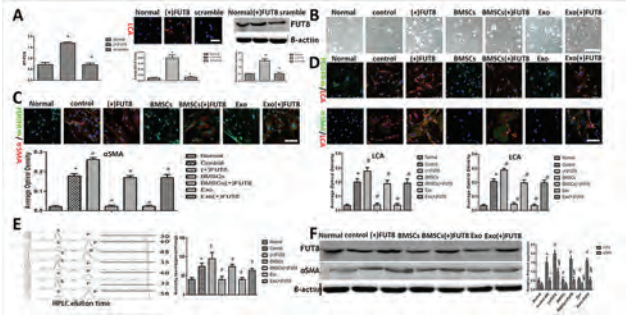
Background: Renal interstitial fibrosis is the last common pathway to progression to end-stage renal disease. Myofibroblasts are a key event in renal interstitial fibrosis, and pericyte transition is one of the major sources of myofibroblasts. Our previous study found that CF (core fucosylation) mediated by FUT8 (α1,6-fucosyltransferase) could regulate the "fibrotic signaling pathway" such as TGFβ/Smad and PDGF/ERK regulate the pericytes -myofibroblasts transition in renal interstitial fibrosis. MSCs (Mesenchymal stem cells) can alleviate renal interstitial fibrosis and are potential therapeutic targets, but the mechanism is still unclear. The exosomes are an extracellular vesicle secreted by MSCs, and can transmit functional substances such as microRNAs and proteins through membrane ligand-cell receptor interaction. It is found that exosomes could regulate damage repair, but the mechanism is also unclear.

Methods: Primary culture of pericytes to establish a TGFβ1-stimulated pericyte transition model. After cell modeling, they were co-cultured with transwell upper MSCs, exosomes, CM, and CM for exosomes removal. Morphological changes of pericytes were observed by light microscopy. The levels of αSMA and LCA were observed by immunofluorescence. The levels of αSMA and FUT8 were observed by Western blot. The level of FUT8 was observed by HPLC (High Performance Liquid Chromatography).

Results: TGF-β1 stimulated pericytes to form spindle-shaped myofibroblasts, and the expression of αSMA, LCA and FUT8 increased, TGF-β/Smad and PDGF/ERK pathway activity increased. MSCs have an inhibitory effect, CM and exosomes have similar inhibitory effects, while CM for exosomes removal is ineffective. RT-PCR, immunofluorescence and Western blot confirmed that FUT8 was successfully transfected into pericytes. After FUT8 transfection, the degree of spindle-shaped myofibroblasts increased, and the expression of αSMA, LCA and FUT8 increased, the inhibition by MSCs,exosomes and CM was significantly weakened.

Conclusions: MSCs-derived exosomes reduce pericyte transition by inhibiting CF

Funding: Clinical Revenue Support



SA-PO432

Human Mesenchymal Stem Cells Modulate High Glucose-Induced Inflammatory Responses of Renal Proximal Tubular Cell Monolayers and Their Cross-Talk with Macrophages

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Background: Renal proximal tubular epithelial cells (RPTEC) are dysfunctional in diabetic kidney disease (DKD). Mesenchymal stem cells (MSC) have been shown to modulate DKD pathogenesis. Having previously observed that soluble products of human MSC suppress high glucose (HG)-induced inflammatory responses of RPTEC/TERT1 stable monolayers, we aimed here to characterize the modulatory effect of MSC indirect co-culture on the transcriptional profile of RPTEC monolayers and to further explore the influence of MSC on RPTEC/Macrophage crosstalk.

Methods: Human RPTEC/TERT1 cells were cultured for 12 days to generate stable confluent monolayers. Normal medium or medium supplemented with 25mM D-Glucose (HG) or 25mM D-Mannitol (MAN) were applied for a further 5 days. Human bone marrow MSC were co-cultured 1:10 with RPTEC monolayers for the final 2 days in a trans-well system. RNA Sequencing, qRT-PCR and ELISA were performed on resulting samples. Conditioned Media from HG- and MAN-exposed RPTEC/MSC co-cultures were applied to monocyte-derived human macrophages under HG and MAN conditions.

Results: Bioinformatics analysis of RNA-sequencing data confirmed a predominant effect of HG on inflammation-related mediators and biological processes/KEGG pathways in RPTEC/TERT1 stable monolayers as well as the anti-inflammatory effect of MSC. KEGG pathway analysis showed HG-induced gene upregulation within the TNF-signalling, cytokine-cytokine receptor interaction and NOD-like receptor signalling. These gene expression signatures were modulated toward control expression by MSC co-culture. The HG-induced increase in RPTEC monolayer expression of transcripts for multiple cytokine (IL-1β, IL-6, IL-8, TNFα, MCP-1) and for NGAL as well as their counter-regulation by MSC were confirmed by qRT-PCR and ELISA. Conditioned medium from HG-exposed RPTEC/MSC transwell co-cultures attenuated secretion of inflammatory mediators (IL-8, TNFα, MCP-1) by macrophages compared to medium from HG-stimulated RPTEC alone.

Conclusions: Stable RPTEC monolayers demonstrate a delayed pro-inflammatory response to HG that is attenuated by close proximity to human MSC. In DKD, this MSC effect has potential to modulate hyperglycaemia-associated RPTEC/macrophage cross-talk - a key pathogenic mechanism of chronic interstitial inflammation.

SA-PO433

Mesenchymal Stem Cells Cultured in IFN-γ-Containing Medium Ameliorate Experimental Renal Fibrosis

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Background: Mesenchymal stem cells (MSCs) have been reported to promote regeneration of damaged tissues and suppress fibrosis. Recently, interferon-γ (IFN-γ) was reported to enhance the paracrine activities of MSCs. In this study, we investigated the effect of MSCs cultured in IFN-γ-containing medium on inflammation and fibrosis using unilateral ureter obstruction (UUO) and ischemia-reperfusion injury (IRI) models.

Methods: At 4 days after the UUO operation, we injected rat MSCs (3×10^6 cells/rat) cultured in 10% FBS-containing DMEM (rMSCs) or IFN-γ-containing medium (IFN-γ rMSCs), or PBS only (Control) through the rat tail vein. In addition, we injected rats after an IRI operation through the abdominal aorta with PBS, rMSCs, or IFN-γ rMSCs (5×10^5 cells/rat). Next, we investigated the effect of IFN-γ human MSC (hMSC)-conditioned medium (CM) on TGF-β1-induced fibrotic changes by western blotting. As an anti-inflammatory mediator, we analyzed CM from IFN-γ hMSCs by an enzyme-linked immunosorbent assay.

Results: Immunohistochemical staining revealed that IFN-γ-rMSCs strongly ameliorated interstitial fibrosis. IFN-γ rMSCs also attenuated renal fibrosis and inflammation more significantly than rMSCs in IRI models. IFN-γ hMSCs-CM decreased the expression of phosphorylated Smad2 and αSMA compared with hMSCs-CM without IFN-γ stimulation. We found that prostaglandin E2 (PGE2) expression was significantly increased in IFN-γ hMSCs-CM. Knockdown of prostaglandin E synthase (PTGES), which is a synthetic enzyme of PGE2, weakened the anti-fibrotic effect of IFN-γ MSCs in IRI models.

Conclusions: Our findings indicate that IFN-γ potentiates the anti-fibrosis and anti-inflammatory abilities of MSCs and administration of MSCs cultured in IFN-γ-containing medium has the potential to be a useful therapy to prevent the progression of renal fibrosis.

SA-PO434

Hypoxia Preconditioning Modifies Mesenchymal Stem Cell Senescence and Epigenetics Mechanisms in Experimental Atherosclerotic Renal Artery Stenosis

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Background: Atherosclerotic Renal Artery Stenosis(ARAS) is a contirbutor for hypertensive nephropathy(HN). Autologous mesenchymal stem cells(MSCs) is a promising therapy for ischemic nephropahty in patients with ARAS. However, MSCs from older ARAS patients are associated with impaired function, senescence, and DNA damage, possibly due to epigenetic mechanisms. Hypoxia preconditioning(HPC) exhibits beneficial effects on cellular proliferation, differentiation, as well as gene and protein expression. We hypothesized that HPC could influence MSC function, senescence and epigenetic mechanisms by modulating chromatin-modifying enzymes.

Methods: MSCs harvested from subcutaneous abdominal fat tissue of healthy(N=5) or ARAS(N=8)pigs were cultured under normoxia(20%O_2)or hypoxia(1%O_2) until 70-80% confluence. MSC function was measured by migration and proliferation assays, as well as cytokine levels in conditioned media. MSC senescence was evaluated by SA-β-gal activity and epigenetic markers, including HDAC activity and DNA hydroxymethylation using dot blot analysis.

Results: MSCs cultured under HPC had higher migratory and proliferative capacity as well as increased VEGF and IGF levels than normoxia-cultured MSCs(Figure). Under basal conditions, dot blot analysis showed lower DNA hydroxymethylation in ARAS. During HPC, MSC HDAC activity increased whereas DNA hydroxymethylation decreased, suggesting broad epigenetic changes. Furthermore, SA-β-gal activity fell, indicating lower senescence burden on HPC-MSCs.

Conclusions: HPC mitigates autologous MSC dysfunction, decreased MSC senescence and DNA hydroxymethylation in ARAS pigs. Future studies are needed to

determine the effect of HPC in MSCs of patients with other vascular nephropathies to optimize the potential use of autologous MSC therapy in this population.

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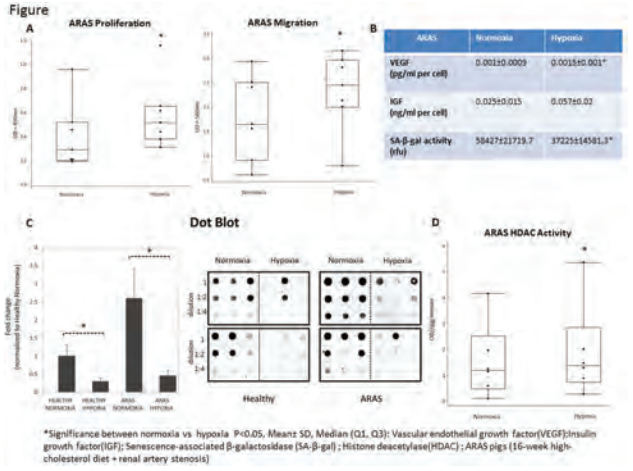
Figure



*Significance between normoxia vs hypoxia P<0.05, Mean± SD, Median (Q1, Q3): Vascular endothelial growth factor(VEGF);Insulin growth factor(IGF); Senescence-associated β-galactosidase (SA-β-gal) ; Histone deacetylase(HDAC) ; ARAS pigs (16-week high-cholesterol diet + renal artery stenosis)

SA-PO435

Hypoxia-Preconditioned Mesenchymal Stem Cells Prevent AKI to CKD Progression

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Background: Several studies have reported that mesenchymal stem cells (MSCs) promote regeneration of injured tissue via their paracrine activities, which are enhanced by hypoxic preconditioning. In this study, we examined the therapeutic efficacy of hypoxia-preconditioned MSCs for preventing acute kidney injury (AKI) to chronic kidney disease (CKD) progression using rat models of ischemia/reperfusion injury (IRI).

Methods: We injected rats through the abdominal aorta with hypoxia-preconditioned rat MSCs (1%O_2 rMSCs) or rat MSCs under normoxic conditions (21%O_2 rMSCs). We also administered hypoxia-preconditioned human MSCs (1%O_2 hMSCs) via the same procedure. In addition, we analyzed the conditioned medium from 1%O_2 hMSCs using ELISA kit and identified the humoral factor involved in anti-fibrotic abilities of MSCs.

Results: The administration of 1%O_2 rMSCs attenuated renal fibrosis induced by IRI more significantly than that of 21%O_2 rMSCs. 1%O_2 hMSCs also attenuated renal fibrosis and the anti-fibrotic effects of hypoxia-preconditioned MSCs were almost equivalent in bone marrow MSCs derived from rat and human. We also found that MSCs derived from rat and human were both observed in the kidney at day 21 post-IRI. Moreover, using flow cytometry, we confirmed that hypoxic preconditioning did not change the HLA expressions of MSCs. These results suggest that 1%O_2 hMSCs have low immunogenicity and may be a good candidate for allogeneic transplantation cell therapy. We also found that hypoxic preconditioning enhanced vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) secretion from MSCs. VEGF knockdown in 1% O_2 hMSCs by siRNA attenuated HGF secretion and the inhibition of TGF-β1 induced fibrotic changes in HK2 cells. It also weakened the suppression of renal fibrosis by 1%O_2 hMSCs in IRI models.

Conclusions: Our results indicate that hypoxia-preconditioned MSCs may be useful as an allogeneic transplantation cell therapy for preventing the progression of AKI to CKD.

SA-PO436

Metformin Improves Dysfunction of Mesenchymal Stem Cells Associated with CKD via Protection from Senescence

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Background: Mesenchymal stem cells (MSC) are promising source of cell-based regenerative therapy; however, adequate cell functionality is a critical factor for the success of autotransplantation. We previously reported a functional incompetence of CKD (chronic kidney disease) MSC.

Methods: In this study, we investigated the effects of metformin on CKD-associated cellular senescence using MSC isolated from sham operated and subtotal nephrectomized mice and further explored the protective role of metformin-treated CKD MSC in renal progression using unilateral ureteral obstruction (UUO) model and in vitro co-culture system.

Results: When compared to normal MSC, MSC isolated from CKD mice displayed reduced proliferation and early senescence as determined by enlarged cell morphology, increased oxidative stress, accumulation of DNA damage response marker p53 binding protein 1 (53BP1), phospho p53, $p16^{INK4a}$, and b-gal expression, and decreased cyclin-dependent kinase 4 (CDK4) and cyclin D. CKD MSC exhibited activation of NFκB resulting in expression of senescence-associated secretory phenotype (SASP) factors such as MCP-1, TNF-α, IL-6, and IL-1β compared to normal MSC. All of these changes were significantly prevented by metformin treatment. In vivo, metformin-treated CKD MSC attenuated inflammation and fibrosis in UUO kidney as compared to CKD MSC. Co-culture of LPS-treated HK2 cells with normal MSC almost completely rescued LPS-induced tubular expression of MCP-1 and TNF-α. Of note, metformin-treated CKD MSC markedly decreased tubular expression of MCP-1 and TNF-α when compared to CKD MSC suggesting paracrine action of CKD MSC enhanced by metformin treatment.

Conclusions: Taken together, our data suggest that metformin prevents cellular senescence of CKD MSC and improves their renoprotective effects.

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SA-PO437

Extracellular Vesicles from Human Bone Marrow Mesenchymal Stem Cells Repair Organ Damages Caused by Cadmium Poisoning in a Medaka Model

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Background: Treatment modalities for kidney disease caused by long-term exposure to heavy metals, such as cadmium (Cd), are limited. Often, chronic, long-term environmental exposure to heavy metal is not recognized in the early stages; therefore, chelation therapy is not an effective option. Extracellular vesicles (EVs) derived from stem cells have been demonstrated to reduce disease pathology in both acute and chronic kidney disease models.

Methods: To test the ability of EVs derived from human bone marrow mesenchymal stem cells (hBM-MSCs) to treat Cd damage, we generated a Cd-exposed medaka model that we treated with EVs.

Results: This model develops heavy metal-induced cell damage of various organs and tissues, and shows decreased survival. Intravenous injection of highly purified EVs from hBM-MSCs repaired the damage to kidney proximal tubules apical and basolateral membranes, and mitochondria, glomerulus podocytes, repaired bone deformation caused by Cd, and enhanced survival.

Conclusions: Our system serves as a model with which to study age- and sex-dependent cell injuries of organs caused by various agents and diseases. The effects of EVs on the tissue repair process, as shown in our Cd-exposed medaka model, may open new broad avenues for interventional strategies.

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SA-PO438

Extracellular Vesicles of Adipose-Derived Stem Cells from Obese Patients Drive ROS-Dependent Premature Senescence in Renal Tubular Cells

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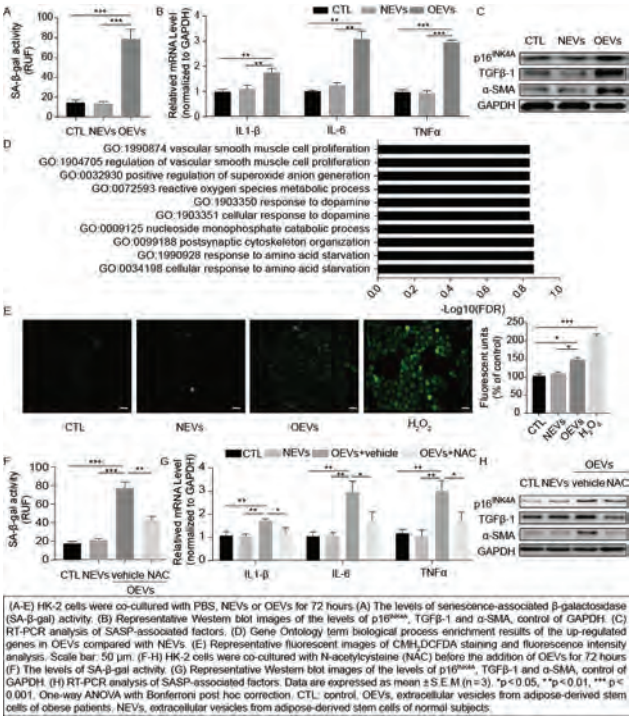
Background: Premature tubular cell senescence is characteristic of obesity-associated renal injury. Extracellular vesicles from adipose-derived stem cells (ADSC-EVs) are highly abundant, while their role in obesity-associated disorders remain unclear. We hypothesized that ADSC-EVs with obese patients were involved in renal tubular cell senescence, possibly via a ROS-dependent pathway.

Methods: ADSCs were isolated from the omental adopts from patients with morbid obesity and healthy volunteers (n=7 each). ADSC-EVs were co-cultured with HK-2 cells. The level of cellular senescence was assessed as senescence-associated β-galactosidase (SA-β-gal) activity using fluorescent quantitative detection, target gene expression using RT-PCR or western blot analysis, and reactive oxygen species (ROS) generation using CMH_2DCFDA staining. The next-generation mRNA sequencing was performed on ADSC-EVs to predict the enriched biological process (DAVID 6.8).

Results: Compared with the control, ADSC-EVs from obesity induced upregulation of SA-β-gal activity, $p16^{INK4A}$, TGFβ-1 and α-SMA in HK-2 cells. The mRNA levels of *IL-1β*, *IL-6*, and *TNF-α* also increased (Figure). Totally 56 up-regulated genes were found in ADSC-EVs from the obese compare to the control, and enriched the ROS-related biological processes (Figure). ADSC-EVs from obese patients could induce ROS formation in HK-2 cells. Conversely, ROS inhibitor N-acetylcysteine prevented the premature tubular cell senescence induced by ADSC-EVs from obese patients (Figure).

Conclusions: These findings suggest that EVs from the *ex vivo* ADSCs of obese patients induce premature tubular cell senescence through a ROS-mediated mechanism. Targeting ADSC-EV shedding may provide opportunities to limit the dysfunction of renal tubular cell post-obesity.

Funding: Government Support - Non-U.S.



(A-E) HK-2 cells were co-cultured with PBS, NEVs or OEVs for 72 hours.(A) The levels of senescence-associated β-galactosidase (SA-β-gal) activity. (B) Representative Western blot images of the levels of $p16^{INK4A}$, TGFβ-1 and α-SMA, control of GAPDH. (C) RT-PCR analysis of SASP-associated factors. (D) Gene Ontology term biological process enrichment results of the up-regulated genes in OEVs compared with NEVs. (E) Representative fluorescent images of $CM-H_2DCFDA$ staining and fluorescence intensity analysis. Scale bar: 50 μm. (F-H) HK-2 cells were co-cultured with N-acetylcysteine (NAC) before the addition of OEVs for 72 hours (F) The levels of SA-β-gal activity. (G) Representative Western blot images of the levels of $p16^{INK4A}$, TGFβ-1 and α-SMA, control of GAPDH. (H) RT-PCR analysis of SASP-associated factors. Data are expressed as mean ± S.E.M (n = 3). *p < 0.05, **p < 0.01, *** p < 0.001. One-way ANOVA with Bonferroni post hoc correction. CTL: control, OEVs, extracellular vesicles from adipose-derived stem cells of obese patients. NEVs, extracellular vesicles from adipose-derived stem cells of normal subjects.

Figure

SA-PO439

Systematic Implantation of Dedifferentiated Fat Cells (DFAT) Ameliorated the Monoclonal Antibody 1-22-3-Induced Glomerulonephritis with Stimulation of TSG-6

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Background: Implantation of mesenchymal stem cells has recently been reported to repair tissue injuries through anti-inflammatory and immunosuppressive effects. We established dedifferentiated fat cells that show identical characteristics to MSCs.

Methods: We examined the effects of 10^6 of DFAT cells infused through renal artery or tail vein on monoclonal antibody 1-22-3-induced glomerulonephritis and adriamycin-induced nephropathy in rats. The mAb 1-22-3-injected rats were also implanted with 10^6 of DFAT cells transfected with TSG-6 siRNA through tail vein.

Results: Although DFAT cells transfused into blood circulation through the tail vein were trapped mainly in lungs without reaching the kidneys, implantation of DFAT cells reduced proteinuria and improved glomerulosclerosis and interstitial fibrosis. Implantation of DFAT cells through the tail vein significantly decreased expression of kidney injury molecule-1, collagen IV and fibronectin mRNAs, whereas nephrin mRNA expression was increased. Implantation of DFAT cells did not improve adriamycin-induced nephropathy, but significantly decreased the glomerular influx of macrophages, common leukocytes and pan T cells. However, the glomerular influx of helper T cells, was increased. Implantation of DFAT cells decreased expression of interleukin-6 and IL-12β mRNAs and increased expression of TNF-stimulated gene-6 mRNA in renal cortex from mAb 1-22-3-injected rats. The basal level of TSG-6 protein was significantly higher in DFAT cells than in fibroblasts. Expression of TSG-6 mRNA in MCs cocultured with DFAT cells was significantly higher than in mesangial cells or DFAT cells alone. Systematic implantation of DFAT cells with TSG-6 siRNA through tail vein did not improve proteinuria, renal dysfunction and renal degeneration in the mAb 1-22-3-injected rats.

Conclusions: Systematic implantation of DFAT cells effectively ameliorated mAb 1-22-3-induced glomerulonephritis through immunosuppressive effects accompanied by the suppression of macrophage infiltration and expression of IL-6, IL-10 and IL-12β, and increased production of serum and renal TSG-6 that improved the mAb 1-22-3-induced renal degeneration by the immunosuppressive effects of TSG-6. Thus DFAT cells will be suitable cell source for the treatment of immunological progressive renal diseases.

SA-PO440

The Extracellular Vesicles from Adipose Tissue-Derived Mesenchymal Stem Cells Attenuate the Renal Senescence via SP1/Klotho Pathway in Obesity

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Background: Patients with obesity have a high risk of chronic renal disease and premature aging of the kidney has been proved as a major contributor. The extracellular vesicles from adipose tissue-derived mesenchymal stem cells (ADSCs-EVs) have therapeutic potential in many diseases. We aimed to investigate whether ADSCs-EVs could rejuvenate the senescent renal tubular cells in Obesity

Methods: ADSCs-EVs were isolated from the subcutaneous adipose tissues from healthy volunteers (n=6). The murine model with obesity was obtained after 8 weeks of the obese diet. ADSCs-EVs were injected to the obese mice in *vivo* and co-cultured with primary renal tubular cells from the obese mice *in vitro*. The level of senescence was assessed as P16, P21 with histological analysis and western blot. Next-generation mRNA sequencing (RNAseq) was performed to predict the key transcription factor. The expression of SP1 and Klotho were analyzed by PCR in cells.

Results: ADSCs-EVs treatment could rescue the obesity-induced senescence of renal tubular cells in *vivo* and in *vitro*. The expression of Klotho restored and the P16 was significantly ameliorated. Further study revealed the levels of SP1 and the Klotho were synergistically elevated after ADSCs-EVs treatment (Figure). RNA-seq identified five aging-associated genes upregulated after EVs treatment (fold change >2, p<0.05). The pathway analysis showed TGF- ß or ERK pathway could play a crucial role in ADSCs-EVs mediated rejuvenation through up-regulating transcription factor SP1 (Figure).

Conclusions: ADSCs-EVs ameliorate obesity-induced renal tubular injury by activating SP1 /Klotho and rescue senescence, thereby prevent the renal premature aging in obesity. ADSCs-EVs might be a natural nano-biomaterial for senescence-related diseases therapy.

Funding: Government Support - Non-U.S.

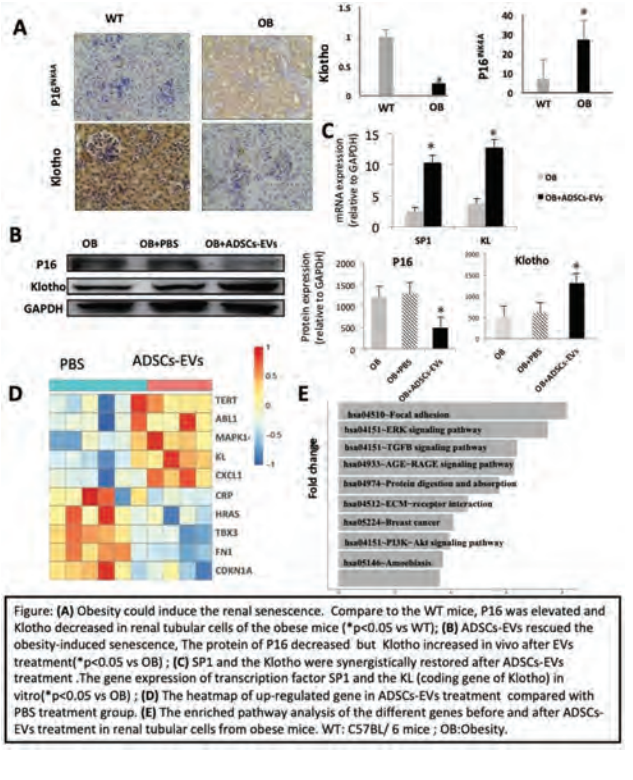

Figure: **(A)** Obesity could induce the renal senescence. Compare to the WT mice, P16 was elevated and Klotho decreased in renal tubular cells of the obese mice (*p<0.05 vs WT); **(B)** ADSCs-EVs rescued the obesity-induced senescence, The protein of P16 decreased but Klotho increased in vivo after EVs treatment(*p<0.05 vs OB) ; **(C)** SP1 and the Klotho were synergistically restored after ADSCs-EVs treatment .The gene expression of transcription factor SP1 and the KL (coding gene of Klotho) in vitro(*p<0.05 vs OB) ; **(D)** The heatmap of up-regulated gene in ADSCs-EVs treatment compared with PBS treatment group. **(E)** The enriched pathway analysis of the different genes before and after ADSCs-EVs treatment in renal tubular cells from obese mice. WT: C57BL/ 6 mice ; OB:Obesity.

SA-PO441

Spleen Is the Key Organ for the Renoprotective Potential of Adipose-Derived Mesenchymal Stromal Cells

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Background: Administration of mesenchymal stromal cells (MSCs), which exert immunomodulatory function, is considerable therapeutic agents for inflammatory disorders. However, it remains unknown where MSCs are distributed and act after administration. In this study, we evaluated the therapeutic efficacy of human adipose derived stromal cells (ASCs) on anti-GBM nephritis rats and where they exert therapeutic effects.

Methods: Anti-GBM nephritis was induced by monoclonal anti-glomerular basement membrane antibody, to female WKY/NCrj rats. We administrated human ASCs or bone marrow derived MSCs (BMMSCs) to them intravenously on day 0, 2, 4 and sacrificed on day 7. Therapeutic efficacy was evaluated by serum Cre, BUN, histological renal damage on day 7. To track MSCs, we also administrated MSCs labeled with DiD to the diseased rats and observed their distribution by flow cytometry and fluorescence microscope. Next, we inhibited MSCs accumulation in organs to reveal where they act.

Results: Human ASC-treatment decreased serum Cre and BUN in anti GBM antibody-induced renal dysfunction compared with BMMSCs. Histologically, crescent formation and accumulations of total macrophages in inflamed glomeruli were significantly decreased in ASC-treated groups. DiD positive cells are observed in lungs, kidneys, spleens and livers. The therapeutic efficacy was preserved even after reduction of

ASCs accumulation in lungs. Interestingly, splenectomy counteracted the effectiveness of ASCs completely, while sham operation did not affect their therapeutic effects.

Conclusions: Human ASCs have therapeutic potential for anti-GBM nephritis compared with BMMSCs. Spleen is a key organ for the therapeutic effect of MSCs. The elucidation of this mechanism would lead to the efficacy and safety of MSC based therapy.

SA-PO442

Cell Sheet Therapy to Suppress Renal Vascular Injury and Fibrosis in Rat Unilateral Ureteral Obstruction and Ischemia-Reperfusion Injury Models

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Background: CKD is a growing and unsolved problem and a new strategy to suppress renal fibrosis is required. In CKD, lack of vasoprotective factors such as VEGF and HGF causes renal vascular injury and subsequent progressive fibrosis. Recently, many researchers reported that administration of vasoprotective factors or the cells producing those factors suppressed vascular injury and fibrosis in preclinical studies. However, the therapeutic effects were limited due to their short half-life in circulation or low retention of the transplanted cells in the kidneys. To solve this problem, we applied cell sheet technology for kidney diseases. We aimed to suppress renal vascular injury and fibrosis by long-term and direct supply of vasoprotective factors secreted form cell sheets.

Methods: Using a temperature responsive culture dish, HGF transgenic mesothelial cell sheet (HGF-tg MC sheet) and rat bone marrow derived mesenchymal stromal cell sheets (MSC sheet) were prepared. In rat UUO or IRI models, the renal capsule was removed and cell sheets were transplanted onto the kidney surface. We analyzed the behavior of the transplanted cells (immunostaining, in vivo imaging system), morphology of the kidney/renal microvascular density/ renal artery blood flow rate (US, CT), and renal fibrosis. The effects were compared between those in receiving intravenous administration of rHGF protein or MSCs.

Results: Transplantation of HGF-tg MC sheets significantly protected microvascular density, maintained renal artery blood flow, and suppressed renal fibrosis compared with intravenous administration of rHGF protein. Transplantation of MSC sheets showed superior survival of the donor cells in the kidney compared with intravenous administration of MSCs, resulted in strong suppression of renal fibrosis and protection of microvascular density in the whole kidney.

Conclusions: Transplantation of cell sheets onto the kidney surface ameliorated renal vascular injury and suppressed renal fibrosis in UUO and IRI by long-term and direct supply of vasoprotective factors secreted from grafted cells. Renal treatment with cell sheets would be a promising strategy.

Funding: Commercial Support - CellSeed, Inc., Government Support - Non-U.S.

SA-PO443

Kidney Podocytes Generate Autonomous Calcium Transients That Regulate Glomerular Capillary Tuft Formation

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Background: Podocytes are critical to maintaining the glomerular filtration barrier; mutations in nephrotic syndrome genes lead to defects in barrier function and can affect podocyte calcium signaling. The role of calcium signaling during podocyte development *in vivo* remains unknown however.

Methods: Using the genetically encoded biosensor GCaMP6s expressed in zebrafish podocytes we quantified intracellular calcium dynamics in differentiating podocytes *in vivo*.

Results: Immature podocytes (2.5 days post fertilization (dpf)) generate calcium transients that correlate with cell motility and podocyte interactions with forming glomerular capillaries. Calcium transients persist until 4 dpf and are absent when glomerular barrier formation is complete. Calcium transients are not affected by deficiencies in heartbeat (*tnnt2* morphant), endothelium (*cloche* mutant) or endoderm (*sox32* morphant), suggesting they may be generated cell autonomously. Dissociated, intact GCaMP6s-expressing glomeruli in short term *in vitro* culture continue to exhibit calcium transients similar to *in vivo* podocytes, indicating the transients are autonomously generated. Inhibitors of SERCA or IP3 receptor calcium-release channels block calcium transients, while lanthanum and medium EGTA are ineffective, indicating the source of calcium is podocyte ER stores. Blocking calcium release impacts glomerular shape and cell organization, suggesting further that calcium signaling guides glomerular morphogenesis.

Conclusions: Our results establish cell autonomous calcium signaling as a prominent feature of podocyte differentiation and present a model to decipher mechanisms leading to proper glomerular morphogenesis.

Funding: NIDDK Support

SA-PO444

Whole-Genome Bisulfite Sequencing Identifies Key Roles for Dnmt3a and Dnmt3b in Renal Tubular Cell Development

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Background: Cytosine methylation is an epigenetic mark that can stably repress gene expression. *De novo* DNA methyltransferases 3a (*Dnmt3a*) and 3b (*Dnmt3b*) play key roles in establishing cell type specific methylation patterns. However, their roles in kidney development are poorly understood.

Methods: We generated mice with genetic deletion *Dnmt3a* and *Dnmt3b* in nephron progenitor cells using $Six2^{Cre}$ and tubule cell specific cells using the Ksp^{Cre} ($Six2^{Cre}$ *Dnmt3a/3b* and Ksp^{Cre} *Dnmt3a/3b*, DKO). Next generation sequencing techniques, such as reduced representation bisulfite sequencing (RRBS), whole genome bisulfite sequencing (WGBS) and RNA sequencing (RNA-seq) were performed on whole kidney samples and on isolated and sorted renal tubule cells from 3-week-old mice. We induced kidney disease by folic acid injection at 8 weeks of age.

Results: Compared with littermate controls, no obvious developmental defect was identified in Ksp^{Cre} and $Six2^{Cre}$ *Dnmt3a*$^{f/f}$ and *Dnmt3b*$^{f/f}$ double knock-out mice. RRBS data showed significant methylation changes in both DKO mice consistent with Dnmt3a/b role in establishing *de novo* methylation pattern. More hypo-methylated regions (Hypo-DMR) were identified in $Six2^{Cre}$ DKO mice, suggesting the key role of Dnmt3a/b in establishing cell type specific methylation in development. To explore the genome wide effect of *Dnmt3a* and *Dnmt3b*, WGBS was performed on isolated Ksp positive renal tubule epithelial cells. Remarkable decreased in cytosine methylation was observed at genome wide level, especially affecting fetal enhancers which gain methylation in normal development. Motif enrichment analysis showed the significant enrichment of hypo-methylated regions in binding sites of kidney developmental transcription factors including *Six2*. Despite the broad changes in cytosine methylation, the effect of *Dnmt3a* and *Dnmt3b* loss on gene expression was less pronounced. DKO mice showed no differences when compared to control following kidney injury.

Conclusions: Our results indicate *Dnmt3a* and *Dnmt3b* are necessary for *de novo* methylation of enhancers which are active in fetal kidney and closed in adult kidney. Despite the significant methylation changes on enhancer regions, the effect of *de novo* methylation on gene expression regulation and phenotype was less pronounced.

SA-PO445

Essential Roles of Testosterone in Male Kidney Maturation and Repair After Injury

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Background: The newborn kidneys are structurally and functionally immature. They mature after birth to adapt to extra-uterine life, yet the comprehensive changes of the kidney have not been defined. We investigated the structural and functional changes in the kidney after weaning and examined the effect of testosterone in this maturation process in male mice.

Methods: We performed phenotypic analysis of mouse kidneys utilizing a combination of histological analysis, bulk transcriptome analysis, charged metabolite analysis by CE-TOFMS and brush border membrane vesicles LC-MS/MS analysis.

Results: Bulk transcriptome analysis of postnatal 3 and 8 week male kidneys showed the gene sets enriched in 8w included those associated with metabolic process and transport in proximal tubule, and structural analysis revealed proximal tubule elongation and hypertrophy in 8 weeks. Most differentially expressed genes (DEGs) identified above were induced between postnatal day 28 and 40, a period of testosterone surge, and were closely correlated with DEGs between adult male and female kidneys. These structural and gene expression changes during maturation were mostly canceled by castration before testosterone surge. Proximal tubules expressed androgen receptor, and some gene expression changes were confirmed in cultured proximal tubules stimulated with testosterone. Consistent results with DEGs were also confirmed at protein levels and related metabolites in vivo. For instance, induction of cystine transporter SLC7A13 expression as well as the increase in cysteine and cysteine-glutathione disulphide-Divalent in the kidney were confirmed in this period. Fatty acid b-oxidation enzymes were also increased during this period. Some of the down-regulated genes across puberty were reactivated after injury and returned back with repair.

Conclusions: Proximal tubules are the main site of maturation after weaning and acquire the ability to absorb and metabolize a variety of filtered substances and increase energy metabolism, which were mainly driven by testosterone.

Funding: Government Support - Non-U.S.

SA-PO446

Ureteric Bud (UB) Prorenin Receptor (PRR) Directs UB Branching Morphogenesis by Regulating V-ATPase Activity and Autophagy in UB Cells

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Background: Targeted ablation of the *PRR* in the UB lineage in *Hoxb7*^{Cre}/*PRR*$^{flox/flox}$ (PRRUB-/-) mice causes severe defects in UB branching, leading to decreased nephron endowment and renal hypodysplasia. Since PRR is an accessory subunit of the vacuolar proton pump V-ATPase, we investigated the role of V-ATPase and autophagy in PRR-induced UB branching in mice.

Methods: *UB cells were FACS-isolated from Hoxb7*$^{Cre+/GFP+}$/*PRR*$^{flox/flox}$ (*PRR*$^{UB-/-}$) and control (*PRR*$^{UB+/+}$) littermates at birth (P0). V-ATPase subunit expression in isolated cells was determined by microarray and validated by real-time RT-PCR. PRR knockdown in immortalized UB cells (iUBc) was achieved with adenovirus-driven short hairpin RNA (shPRR). Effect of PRR knockdown on cell pH and V-ATPase activity was determined by staining with Lysotracker (a lysosomal pH marker) and from measurements of Na-independent cell pH recovery rates after intracellular acidification with a NH_4Cl prepulse.

Results: Expression of V-ATPase subunits Atp6ap2 (PRR), V0a4, V0b, V1b1 and V1g1 was reduced in *PRR*$^{UB-/-}$ compared to *PRR*$^{UB+/+}$ UB cells. shPRR decreased mRNA levels of PRR by 80-90% and of kidney-specific α4 V-ATPase subunit by 50% compared to control scrambled control PRR (scPRR) virus in iUBc. shPRR decreased Lysotracker fluorescence in iUBc compared to scPRR ($p<0.001$). Intracellular pH (pHi) measurements (by BCECF fluorescence) indicated slower recovery from acid loads in shPRR-treated cells due to reduced V-ATPase activity. Immunofluorescence of key autophagy protein LAMP2 was increased in the UB of *PRR*$^{UB-/-}$ compared to *PRR*$^{UB+/+}$ kidneys on E14.5, consistent with autophagic defects in UB cells in *PRR*$^{UB-/-}$ kidneys.

Conclusions: PRR knockdown decreases expression of α4 subunit of V-ATPase and suppresses V-ATPase activity in iUB cells in vitro, resulting in deacidification of intracellular vesicles. We propose that endogenous UB PRR regulates normal UB branching morphogenesis through stimulation of V-ATPase activity, control of lysosomal pH and appropriate autophagic flux in UB cells.

SA-PO447

Embryonic Stage Adam10/Notch Pathway Excessive Activation Promotes Ectopic Proximal Tubules Formation and Kidney Fibrosis

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Background: Chronic kidney disease (CKD) is an outstanding public health problem. It is important to elucidate the pathogenesis of CKD and researches on kidney development become a breakthrough. Studies have verified that Notch pathway plays a significant role in kidney development, it is widely believed that Notch promote the formation of proximal tubules. In addition to its role in kidney development, Notch was also found to be involved in kidney fibrosis. Here using prenatal chlorpyrifos (CPF) exposure mouse model we make a further study on the role of Notch in kidney development and fibrosis.

Methods: CPF 5mg/kg/d was administrated by subcutaneous injection in CPF-treated pregnant mice from gestation day 7.5-11.5 while the controls were injected with DMSO. RNA-seq was performed of E12.5, E14.5, E16.5 and E18.5 kidneys, RT-qPCR and WB were performed to verify gene expression. IF and IHC were performed to studied the protein levels and kidney structure changes of offspring mice (4 weeks, 8 weeks and 6 months). Masson staining and fibrosis factor detection were used to evaluate fibrosis. Kidney size and weight, Scr and Bun levels were measured to evaluate renal function.

Results: RNA-seq analysis revealed that Adam10/Notch and Aqp1 were increased in CPF group and nephron progenitor cell (NPC) marker Six2 was decreased. mRNA and protein levels were verified by RT-qPCR, WB, IF and IHC. IF and IHC showed the increasement of proximal tubules. Experiments of offspring mice kidneys showed abnormal embryonic kidney phenotypes persisted in adult kidneys. High activation of Notch also led to impaired kidney function and more severe renal fibrosis.

Conclusions: Excessive activation of Adam10/Notch pathway caused the depletion of $SIX2^+$ NPCs and ectopic proximal tubules formation and aggravate kidney fibrosis.

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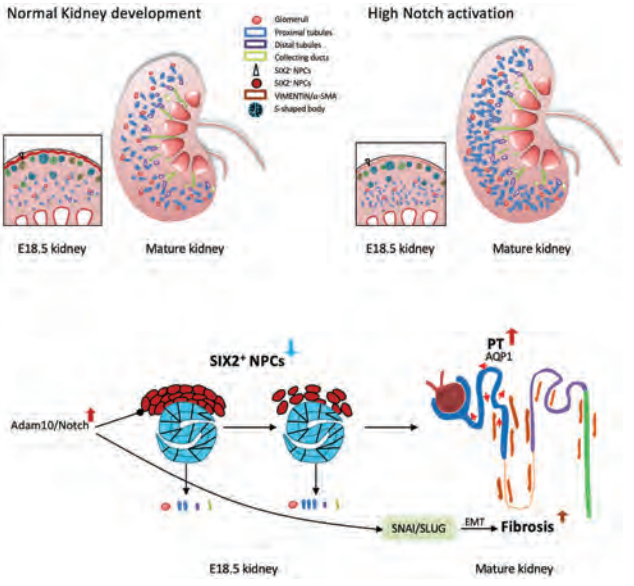

SA-PO448

Toxicodendron vernicifluum Extract Ameliorates Renal Injury in Unilateral Ureteral Obstruction Mice

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Background: Toxicodendron†vernicifluumis used as a traditional herbal medicine in Asia. The physiological properties and antioxidative effects of Toxicodendron vernicifluum extract (TV) have been demonstrated in several experimental studies. The physiological properties and antioxidative effects of Toxicodendron vernicifluum extract (TV) have been demonstrated in several experimental studies. This study evaluated the possible renoprotective effects of TV on UUO induced tubular damage, as well as the mechanism through which it exerts antioxidative and antiapoptotic effects against UUO induced cell death.

Methods: Male Sprague–Dawley rats weighing 180–200 g each were assigned to one of two groups. The first group (UUO+TV) of rats drank TV for 2 weeks before surgery. The second group (UUO) of rats drank water for 2 weeks. Three days later, a morphologic evaluation of renal injury was conducted using hematoxylin and eosin and TUNEL staining. The renal protein expression of PCNA, caspase3, Nrf2, catalase, and phosphorylated p38 as markers of autophagy was determined by immunoblotting.

Results: Obstruction injury caused marked apoptosis and oxidative stress in the UUO group. It also increased the level of phosphorylated p38 and decreased the level of PCNA, suggesting delayed recovery from damage. The number of TUNEL positive cells, which were detected based on DNA fragmentation, was increased in the UUO group. Notably, there was a significant relationship with increased expression of cleaved caspase3, which was counteracted by TV treatment. Moreover, a comparison with the UUO group revealed that TV significantly enhanced the regulation of autophagy and autophagic flux.

Conclusions: Taken together, our findings suggest that the induction of autophagy protects against UUO induced apoptotic damage via ROS and a p38 regulated pathway in this in vivo model.

Funding: Clinical Revenue Support

SA-PO449

A Bottom-Up Approach to Reduce Animal Numbers in Compound Screening Targeting Renal Regeneration After AKI

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Background: Developing new therapeutic approaches to improve kidney regeneration after injury remains a hurdle in translational nephrology, since 96% of in vivo identified drugs drop out due to lack of efficacy or safety concerns in humans. We developed a highly efficient, cost- and animal-saving bottom-up approach to screen compound libraries for their pro-regenerative capacity in tubular cells.

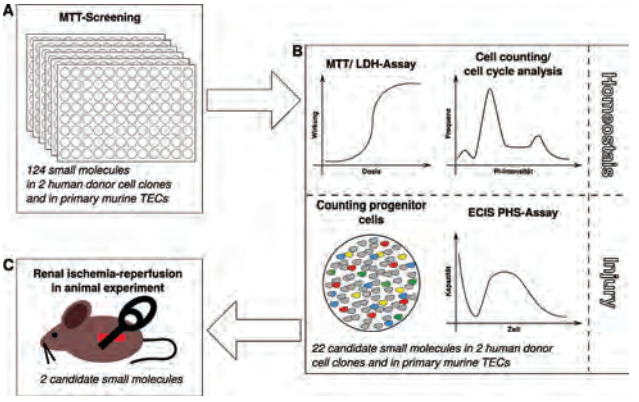
Methods: Using primary human renal progenitor cells (HPCs) and primary murine tubular epithelial cells (TECs) we tested 124 small molecules for their potential to induce

hypertrophy and hyperplasia during homeostasis. We then exposed the cells to PBS and histones (mimicking ischemia/ injury) followed by a return to normal culture conditions (mimicking reperfusion), to test for the compounds pro-regenerative effects. Electric cell impedance sensing and selective progenitor cell expansion were used to monitor effects on wound healing and target cell response, respectively. Only those compounds that proved pro-regenerative in human and murine cells alike were tested in a mouse model of unilateral IRI.

Results: We identified RKI-1447 and SB-525334 in vitro/ ex vivo, and tested both substances in male C57BL/6J, 8-10 weeks of age, at 10 mg/kg every 2nd day for a duration of 3 weeks starting from day 3 after IRI. Both molecules reduced intrarenal mRNA markers of injury, inflammation, and fibrosis. A corresponding trend towards less parenchymal loss and fibrosis was observed in histology.

Conclusions: We were able to show, that an appropriate setup of in vitro and ex vivo experiments using meaningful biological material is suitable for (a) efficiently screening of compound libraries, (b) significantly reducing animal numbers used and (c) predicting outcome in vivo.

Funding: Government Support - Non-U.S.



Bottom-up approach to identify pro-regenerative compounds, that have the capacity to enhance tubular cell healing after injury in human and murine tissue in vitro, ex vivo and in vivo.

SA-PO450

Rapid and Efficient Method to Generate Donor Vectors for Homology-Directed Repair Mediated Genome Editing

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Background: Stem cell-derived kidney organoids are a powerful, tractable tool with numerous potential applications, including the investigation of complex processes underlying human kidney development. To further develop organoids as an embryologic model, it will be essential to generate genetic tools such as fluorescent reporters and lineage tracing systems, which have proven instrumental in rodent studies. With the emergence of CRISPR/Cas9 gene editing via homology directed repair (HDR) is becoming more common in pluripotent stem cells. However, construction of donor vectors that contain gene-specific homology regions remains a time-consuming and often costly endeavor. Thus, we simplified this process through the creation of a modular system to allow rapid and efficient cloning of homology arms into HDR donor vectors.

Methods: We designed and synthesized a plasmid with numerous features and cassettes that are easily interchangeable. These include fluorescent reporters, antibiotic resistance genes and an HSV-TK for use in negative selection. The genes for selection were contained in a floxed cassette to allow easy cre-mediated removal following successful integration. Gene-specific homology arms were created using high fidelity PCR, and final donor vectors were assembled using HiFi Cloning.

Results: To facilitate simultaneous dual and triple knock-in alleles, we used restriction cloning to generate a repertoire of vectors that pair different combinations of reporter and antibiotic resistance genes. The PCR primers designed to amplify the homology arms from genomic DNA of the cell lines of interest also contained sequences of overlap with the sites of insertion on the vector. Thus, in one step using HiFi cloning, we were able to assemble both homology arms into the double-digested vector. This process, including PCR of homology arms, cloning, and sequence validation, can be completed within one week at minimal cost.

Conclusions: Through creation of this vector collection and application of HiFi cloning, we have successfully devised an efficient, streamlined process for cloning donor vectors for use in HDR-mediated gene editing. Given the modular design, these plasmids can also be adapted to permit knock-in of any cDNA of interest. This approach is now broadly applicable for editing of any cell line, including human pluripotent stem cells and hPSC-derived kidney organoids.

Funding: NIDDK Support, Other NIH Support - NCATS

SA-PO451

Defects in the Exocyst-Cilia Machinery Results in Disease Development in the Kidney and Heart

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Background: Patients with polycystic kidney disease such as ADPKD and Joubert syndrome have elevated risk for bicuspid aortic valve disease (BAV). Non-syndromic BAV affects 1% of the population and often leads to aortic stenosis and the need for surgery. We have previously shown a link between these disorders and defects of organelles called primary cilia. Primary cilia are immotile projections of microtubules that act as signaling hubs for numerous pathways. We previously demonstrated in the kidneys that primary cilia are built by a highly-conserved octameric protein-trafficking complex, known as the exocyst. These studies leveraged the expression of the central exocyst protein, EXOC5. Knockdown of EXOC5 in MDCK cells inhibited ciliogenesis and, conversely, EXOC5 overexpression resulted in longer cilia.

Methods: We performed two human GWAS studies, generated two *exoc5*$^{-/-}$ zebrafish knockout lines and two conditional *Exoc5* mouse knockout lines. Phenotypes were characterized through immunohistochemistry, 3D reconstructions, confocal microscopy, and echocardiography.

Results: GWAS identified the exocyst as being near SNPs most associated with BAV. Next we noted that at three days post fertilization, *exoc5*$^{-/-}$ zebrafish embryos had cardiac edema and outflow tract stenosis. This phenotype was rescued in a dose dependent manner by injection of human *EXOC5* mRNA at the one cell stage; however, the rescue was significantly reduced with the introduction of a targeted mutation in the highly-conserved *EXOC5* VxPx ciliary targeting sequence. These findings prompted us to examine the cardiac phenotype following *Exoc5* deletion in mice. We previously reported altered ciliogenesis and nephrogenesis in *Exoc5*$^{f/f}$ mice when bred with a kidney-specific Cre. To examine the heart, we bred these mice with endocardial-specific *NfatC1-Cre*, and later endothelial-specific *Tie2-Cre*, lines This resulted in mice with highly-penetrant BAV and aortic valve calcification. Echocardiography also revealed aortic valve stenosis and increased aortic root diameter similar to what is seen in BAV patients. There was also evidence of significant cilia disruption, and conditional homozygous mutants were embryonic lethal by E15.5, likely due to cardiac defects.

Conclusions: These data for the first time link cilia, BAV, and the exocyst, and explain the clinical association of cardiac valve abnormalities with PKD.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute, Veterans Affairs Support, Private Foundation Support

SA-PO452

Metabolic Syndrome (MetS) Upregulates the Tumour Necrosis Factor Alpha(TNF-α) Transcriptome and Proteome in Swine Adipose Tissue-Derived Mesenchymal Stem Cells (MSC)

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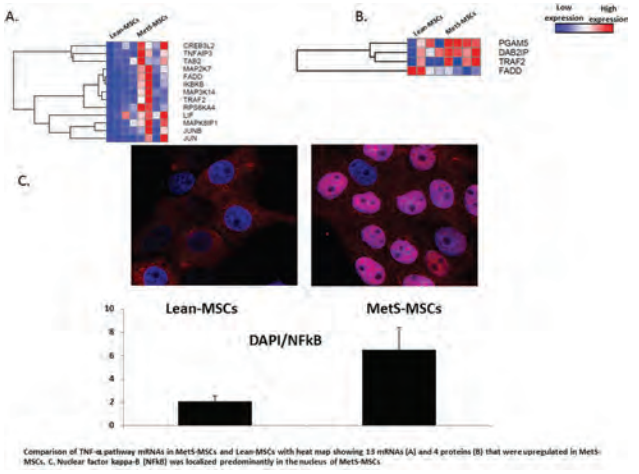
Background: MSC have intrinsic reparative properties, & may serve as an exogenous therapeutic intervention in patients with chronic kidney disease (CKD). This microenvironment of MetS induces fat tissue inflammation, with upregulation of TNFα. MetS may also alter the transcriptome and proteome of adipose tissue-derived MSC, which might affect their reparative potency. We hypothesized that MetS upregulates MSC mRNA and proteins of the TNFα pathway.

Methods: Domestic pigs were fed a 16-week Lean or MetS diet (n=4 each), and MSC were then harvested from abdominal subcutaneous fat. Expression profiles of co-existing mRNAs and proteins in MSC were obtained by high-throughput sequencing and proteomics. DAVID 6.7 was used for functional annotation analysis to rank primary gene ontology categories for the mRNAs and proteins. Cellular location of the pro-inflammatory transcription factor nuclear factor (NF)-kB was evaluated by immunofluorescent staining.

Results: Differential expression after filtering for TNFα pathway genes revealed 13 mRNAs & 4 proteins upregulated in MetS compared to lean MSCs (fold change>1.4, $p<0.05$) (Fig. 1, A & B). Upregulated mRNAs were mostly involved in TNFα-1 receptor pathway. A similar pattern was observed in upregulated proteins, except for Traf2 involved in TNFα-2 receptor pathway. MetS induced changes in MSC TNFα signaling were associated with nuclear translocation of NF-kB(Fig 1, C).

Conclusions: MetS upregulates the TNFα transcriptome & proteome in swine adipose tissue-derived MSCs, leading to activation of NF-kB and inflammatory signaling. Hence, the MetS milieu may affect reparative function of endogenous MSC & limit their use as an exogenous regenerative therapy. Targeting the TNFα pathway might be a novel strategy to restore MSC expression patterns, & in turn function, and permit their use in subjects with MetS & CKD.



Comparison of TNF-α pathway mRNAs in MetS-MSCs and Lean-MSCs with heat map showing 13 mRNAs (A) and 4 proteins (B) that were upregulated in MetS-MSCs. C, Nuclear factor kappa-B (NFkB) was localized predominantly in the nucleus of MetS-MSCs.

SA-PO453

Isolation of Primary Cell Types from the Human Kidney Cortex

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Background: In vitro studies can help elucidate kidney pathophysiology and nephrotoxicity. Cell lines and primary animal cells can be poor representatives of human cell biology. Primary human renal cells are essential tools for studying such mechanisms. Herein we describe isolation of primary cell types from the cortex of whole human kidneys.

Methods: Podocytes, Proximal Tubule Cells (PT), Mesangial, and Glomerular Endothelial Cells were isolated from non-transplantable human kidneys donated for research. The kidney cortex is surgically separated from the medulla, the tissue is minced, glomeruli are separated, and further digested using a collagenase based enzymatic blend to obtain a heterogenous single cell suspension. Cells are cultured and expanded in specialized media to enrich for the target cell populations. Homogenous cell isolates for a. proximal tubules (CD10/CD13) b. mesangial cells (PDGFRB) c. glomerular endothelial cells (CD31) d. podocytes (nephrin) are isolated by immunomagnetic sorting. Proximal tubular cells, mesangial cells and glomerular endothelial cells further expanded in specific media before undergoing a second round of selection to ensure purity. Podocytes are not expanded to avoid de-differentiation. Characterization of the isolated populations is performed by immunofluorescence and flow cytometry for cell-specific proteins.

Results: We successfully obtained pure human proximal tubular cells, podocytes, mesangial cells and glomerular endothelial cells using the outlined methodology. Each population was assessed for viability, attachment, proliferative ability. Purity and cell-specific marker expression were assessed by confocal fluorescent microscopy and flow cytometry; PT: AQ1, cytokeratin, Na/K-ATPase, and ENT1; Mesangial: PDGFRb, CD206, and Vimentin, GEC: EDH3, Ve Cadherin, and CD31; Podocytes: WT1, Synaptopodin, and Podocin. Proximal Tubular cells retained activity demonstrated by enzymatic GGT assay.

Conclusions: We have developed and optimized a streamlined method for isolating target populations from the human kidney. Our process yields highly pure homogenous cell populations that can proliferate in vitro and express population specific surface markers. Furthermore, isolated proximal tubule cells retained functionality and can be used in transporter assays.

Funding: Commercial Support - Parent company, Promethera Biosciences, partially funding the Novabiosis division. Additional funding comes from revenue generation of life science products.

SA-PO454

Renovascular Disease Induces Mitochondrial Damage and Impairs the Reparative Capacity of Swine Scattered Tubular-Like Cells

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Background: Scattered tubular-like cells (STC) contribute to repair neighboring injured renal tubular cells. Mitochondria mediate STC biology and function, but might be injured by the ambient milieu. We hypothesized that the microenviroment induced by the ischemic and metabolic components of renovascular disease (RVD) impairs STC mitochondrial structure and function in swine, which can be attenuated with mitoprotection.

Methods: CD24+/CD133+ STCs were quantified in pig kidneys after 16 weeks of metabolic syndrome (MetS) or Lean diet with or without renal artery stenosis (RAS) (n=6 each). Pig STC were isolated and characterized, and mitochondrial structure and membrane potential were assessed in cells untreated or incubated with the mitoprotective drug elamipretide (ELAM, 1nM for 6hrs). STC protective effects were assessed in-vitro by their capacity to improve viability of injured pig tubular epithelial (PK1) cells.

Results: The percentage of STC was higher in MetS, Lean+RAS, and MetS+RAS kidneys compared to Lean (Fig. A). STC isolated from Lean+RAS and MetS+RAS pigs showed decreased mitochondrial matrix density and membrane potential, which were both restored by mitoprotection (Fig. B). Furthermore, mitoprotection improved the capacity of MetS+RAS-STC to repair injured tubular cells in-vitro (Fig. C).

Conclusions: RVD in swine is associated with a higher percentage of STC, which was predominantly affected by MetS. Ischemia induces structural and functional alterations in STC mitochondria, which can be attenuated by mitoprotection. These observations suggest a key role for mitochondria in the renal reparative capacity of STC.

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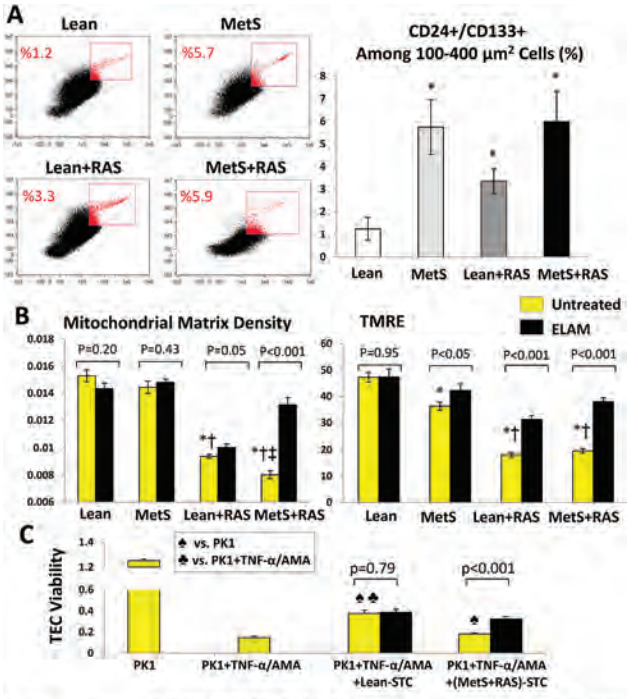

A. The percentage of CD24+/CD133+ STC in the pig kidney was higher in MetS, RAS, and MetS+RAS groups versus Lean. **B.** Mitochondrial matrix density and membrane potential (TMRE) improved after co-incubation with ELAM. **C.** ELAM also improved the capacity of MetS+RAS-STC to increase the viability of PK1 cells that were previously injured with 10ng/mL of tumor necrosis factor (TNF)-α and 10µM of antimycin-A (AMA). **p<0.05 vs. Lean; †p<0.05 vs MetS; ‡p<0.05 vs. Lean+RAS.*

SA-PO455

Mild AKI in a Murine Polymicrobial Sepsis Model and Its Value for Preclinical Testing of Human Cell Therapies

Barbara Fazekas,[1,2] Senthilkumar Alagesan,[2] Luke Watson,[2] Olivia Ng,[2,1] Callum M. Conroy,[2,1] Yolanda Garcia,[1] Stephen J. Elliman,[2] Matthew D. Griffin.[1] [1]*National University of Ireland Galway, Galway, Ireland;* [2]*Orbsen Therapeutics Ltd, Galway, Ireland, Galway, Ireland.*

Background: Even mild AKI greatly worsens the prognosis of sepsis. Allogeneic mesenchymal stem cells (allo-MSC) have potential therapeutic value in sepsis-associated (SA)-AKI but their optimal administration is undetermined. Improved analysis of human MSC effects in pre-clinical models of SA-AKI could improve future clinical trial design. We aimed to develop a model of mild SA-AKI in which to test a human allo-MSC cell product.

Methods: Caecal ligation and puncture (CLP) or Sham surgery with frequent post-procedural monitoring were performed in male C57BL/6 mice. Blood was sampled at 24, 48 and 72 hrs and kidney tissue collected at 72 hrs. Antibody-selected human umbilical cord (UC)-MSC were injected IV at 10^6 cells/animal 4 hours post-CLP. Plasma and renal tubular neutrophil gelatinase-associated lipocalin (NGAL) were quantified by ELISA and IHC. Renal lymphoid and myeloid cells were quantified by multi-color flow cytometry of collagenase/DNAase-digested kidney.

Results: CLP was associated with 10-15% body weight loss and low (10%) mortality by 72 hrs. Plasma liver enzymes were mildly increased in CLP vs Sham but BUN and creatinine were not raised. Plasma (p)NGAL was markedly increased in CLP versus SHAM animals (p<0.001), peaking at 24 hrs and remaing elevated at 48 & 72 hrs. NGAL staining intensity in renal tubular epithelial cells strongly discriminated between CLP and SHAM at 72 hrs (Mean score 2.6±1.2 vs. 0.0±0.0, p=0.0003) and correlated with pNGAL. Intra-renal immune cell profiling indicated that SA-AKI was associated with proportionatley reduced T-cells, increased neutrophils and a complex modulation of MHC II^+ mononuclear phagocytes (MP). A single administration of UC-MSC (compared to saline) resulted in less body weight loss (6.8±3.7% vs. 10.0±5.2%, p<0.05), trends toward lower pNGAL and renal NGAL staining intensity and reversal of SA-AKI-associated alterations to intra-renal T-cells, neutrophls and MP.

Conclusions: Mouse CLP with frequent post-procedural monitoring resulted in mild SA-AKI best detected by pNGAL, renal tubular NGAL staining intensity and altered

intra-renal immune cell repertoire. The model allowed for quantification of the kidney-specific effects of an investigational human allo-MSC product in the setting of subclinical SA-AKI.

Funding: Commercial Support - Orbsen Therapeutics Ltd., Government Support - Non-U.S.

SA-PO456

Intrarenal Hh Signalling Mediates Fibrosis in Aged and Injured Kidneys

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Background: Kidney fibrosis is seen with physiological aging in man and is a feature common to all chronic kidney diseases (CKD), affecting 850 million people worldwide. Both aging and CKD are risk factors for renal injury, and there is an urgent unmet need for novel therapies to prevent subsequent progressive renal fibrosis and renal functional decline. We studied models of renal injury in singleton mice and parabiotic pairings between old and young mice to characterise factors associated with renal fibrosis.

Methods: Young and old C57BL/6J mice were obtained from the NIA. Kidney fibrosis, function and transcriptomes were assessed in baseline singleton and parabiotically paired mice - comparing YY, OY and OO pairings. Serum proteomics were quantified using SOMAscan aptamer panels. Fibrosis was assessed at both a transcriptome and protein level by RNAseq, qPCR and immunohistochemistry, after unilateral ureteric obstruction and ischemia reperfusion injury. Hh signalling was inhibited by the Smo antagonist Cyclopamine, and the Gli antagonist GANT61.

Results: Despite apparently normal function, kidneys from old mice have significantly altered transcriptomes (by RNA sequencing), basal fibrosis levels (by immunohistochemistry) and worsened fibrotic outcomes post injury (using the unilateral ureteric obstruction and ischaemia/reperfusion injury models). Old mice parabiotically paired to young animals demonstrate partial transcriptional normalisation to a young phenotype, revert five serum factors to 'young' levels, and show reduced fibrotic responses to injury. Hh ligands are the most significantly age-associated serum factor, and bulk and single cell transcriptomic assessments demonstrate upregulated renal hedgehog ligand production in the aftermath of injury. In vitro assays demonstrate that Hh induces canonical signalling via the Gli transcription factors leading to renal myofibroblast activation. Pharmacological Hh signalling blockade reduces fibrosis in both the ischaemia reperfusion injury and unilateral ureteric obstruction models of progressive renal fibrosis.

Conclusions: Renal Hh ligand production mediates fibrosis in aging and injury induced kidney disease, via induction of Gli signalling in renal myofibroblasts. The Hh pathway therefore represents a viable therapeutic target in kidney disease, with inhibitors already licenced for clinical use in cancer.

Funding: Private Foundation Support

SA-PO457

Urinary CRK1 Positive Vesicles Yield Novel Insight into Signaling Through Extracellular Vesicles in the Kidney

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Background: While specific functions of extracellular vesicles (EVs) have been discovered in many fields of biology and medicine, very little is known about their role in kidney health and disease. Recently, a new subgroup of EVs was identified in human and murine cell culture as well as a model of glomerulonephritis. These vesicles are shed upon apoptosis and trigger proliferation in neighboring cells, hence named apoptotic compensatory proliferative signaling vesicles (ACPSVs). As these vesicles could be separated from kidney tissue, we aimed to determine whether a fraction is shed into the urine and further analyze their biological properties.

Methods: We established a protocol of differential centrifugation and filtration to separate ACPSVs from urine samples of healthy control subjects. Multiplex immunofluorescence microscopy, Western Blot and FACS were used to validate the presence of CRKI+ EVs, determine their cellular origin and assess the baseline characteristics of these urinary vesicles.

Results: The employed protocol lead to a robust isolation of spherical vesicles ranging between 800nm and 1,8µm in diameter with a subfraction containing the ACPSV marker protein CRKI. Further protein analysis revealed the presence of marker proteins for all segments of the nephron colocalizing with both CRKI positive and negative EVs. FACS analysis and multiplex immunofluorescence enabled us to determine and quantify the specific vesicle fractions originating from i.e podocytes, PECs and collecting duct cells.

Conclusions: Our study represents the first analysis of urinary CRKI containing vesicles of the ACPSV size range. Taken into account the presence of podocyte marker proteins in the separated vesicle fraction, we hypothesize, that these are not only shed upon apoptosis, hence would not call them urinary ACPSVs. Ongoing investigations aim to validate the potential to initiate proliferation on different renal cell types and to determine differences in their function and content in the state of renal diseases. As these vesicles can be easily isolated in a high purity, they also represent a valuable source for biomarker research in various nephropathies.

SA-PO458

Interferon Regulatory Factor 5 Expressed in Kidney Resident Macrophages Promotes Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by genetic mutations in *Pkd1* or *Pkd2*. Previous data indicate that pro-inflammatory cytokines including TNFα, IL-6, and MCP1, as well as their downstream signaling components, are associated with macrophages and accelerated cystogenesis. Recent data indicate that the *Irf5* transcription factor promotes a pro-inflammatory macrophage phenotype.

Methods: In these studies, we assess the importance of macrophage-derived *Irf5* during accelerated cystogenesis induced by unilateral nephrectomy (1K) in conditional *Pkd1* mice.

Results: Analyses of RNA sequencing, qRT-PCR, and flow cytometry data from whole kidney tissue collected three weeks post nephrectomy, a time point prior to the onset of severe cystogenesis, indicate an enriched inflammatory macrophage signature, including increased *Irf5* expression, in 1K *Pkd1* mice compared to controls. To determine the importance of *Irf5* in cyst progression, we injected scrambled or IRF5 antisense oligonucleotide (ASO) in 1K *Pkd1* mice and analyzed the effect on cytokine production and renal cystogenesis 6 weeks post nephrectomy. Our data indicate that IRF5 ASO treatment significantly reduced macrophage numbers, *Irf5* expression in resident, but not infiltrating, macrophages, and reduced the severity of cystic disease. In addition, IRF5 ASO treatment reduced the expression of the pro-inflammatory cytokine *Il6* in resident macrophages, which correlated with reduced STAT3 phosphorylation and downstream p-STAT3 target gene expression in 1K *Pkd1* mice.

Conclusions: These data indicate that *Irf5* expressed in resident macrophages promotes accelerated cystogenesis.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO459

Genetic Strain Influences Infiltrating Macrophage Subtype, Accumulation, and Gene Expression in the Liver of a Mouse Model of Hepatorenal Fibrocystic Disease

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Background: Hepatorenal fibrocystic disease (HRFCD) is a genetically inherited disorder in which patients display significant heterogeneity in disease severity and progression with varying levels of fibrosis, cyst development, and inflammation. Recent data indicate that macrophage subtypes promote renal cystic disease suggesting that the subtype of macrophage present controls phenotypic outcome.

Methods: Herein, we utilize a mouse model of HRFCD ($Ift88^{Orpk}$ mice) on the C57BL/6 and BALB/C inbred backgrounds to study the influence of genetic strain on macrophage accumulation and disease progression in the liver.

Results: Phenotypic analysis of liver tissue shows that C57BL/6 $Ift88^{Orpk}$ livers have increased cystic severity but reduced levels of fibrosis compared to BALB/c $Ift88^{Orpk}$ livers. Further, our data show that genetic strain influences the subtype of infiltrating macrophage present during normal postnatal liver development and in $Ift88^{Orpk}$ mice ($Ly6c^{lo}$ in C57BL/6 vs $Ly6c^{hi}$ in BALB/c). RNA sequencing data indicate that macrophages and cholangiocytes express unique ligand receptor pairs, dependent on genetic strain, that may facilitate epithelial cyst expansion or fibrosis. To test the importance of $Ly6c^{hi}$ infiltrating macrophages in promoting the fibrosis observed in BALB/c $Ift88^{Orpk}$ mice, we crossed these mice onto a CCR2-/- background. Our data indicate that CCR2 deficiency reduces $Ly6c^{hi}$ macrophage accumulation and prevents the increase in *Col1a1* and *Col3a1* gene expression in $Ift88^{Orpk}$ mice.

Conclusions: Collectively, our data suggest that the heterogeneity in the hepatic phenotype associated with ciliopathies is influenced by the subtype of infiltrating macrophage that is present.

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SA-PO460

CD206+ Resident Macrophages Are Associated with Cyst Progression in Juvenile-Induced Cilia Mutant Mouse Models

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Background: Abnormalities in the function (*Pkd1* or *Pkd2* mutation) or structure (*Ift88* mutation) of primary cilia result in renal cysts in animal models and human patients. Recent studies show that removing cilia in mouse models of *Pkd1*or *Pkd2* inactivation suppresses cyst growth suggesting a primary cilia-dependent suppressor function in cystogenesis. It has been reported that renal resident macrophages are associated with cyst formation; however, the importance of resident macrophage subsets in promoting renal

cyst formation and their relationship with cystic disease caused by mutations in proteins required for cilia formation (*Ift88*) or function (*Pkd2*) is unknown.

Methods: To test the association of resident macrophage subtypes with the type of cilia mutation, we performed flow cytometry analysis of kidneys harvested from juvenile induced conditional *Ift88, Pkd2*,or *Ifi88:Pkd2* mutant mice. We also used pharmacological (CSF1R kinase inhibitor) and genetic (CX3CR1$^{gfp/gfp}$) approaches to test the functional importance of resident macrophages in juvenile-induced cyst formation.

Results: Our data indicate that induction of cilia dysfunction (*Pkd2* mutation) in juvenile mice results in more severe cysts 21 days post induction compared to mice lacking primary cilia alone (*Ift88* mutation) or mice lacking both *Pkd*2 and *Ift88*. Analysis of flow cytometry data indicate that the number of CD206+ resident macrophages is directly correlated with the severity of cystic disease with juvenile-induced *Pkd2* deficient mice having the greatest number of CD206+ resident macrophages. Further, we show that *Ifi88:Pkd2* double mutant mice have an intermediate cystic severity and number of CD206+ resident macrophages compared to single *Ift88* and*Pkd2* mutant mice. Finally, our preliminary data indicate that inhibition of CD206+ resident macrophage accumulation using a CSF1R kinase inhibitor or genetic reduction of CD206+ resident macrophages using a CX3CR1$^{gfp/gfp}$ mouse reduced the severity of cystic disease in juvenile-induced *Ift88* mutant mice.

Conclusions: These data suggest that the type of primary cilia mutation controls the abundance of CD206+ resident macrophages and these resident macrophages are important in promoting cyst progression.

SA-PO461

Targeting Immunosuppressive Pathways Reduces ADPKD Progression in a Relevant Murine Model

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) shares many parallels with cancer, where tumor microenvironmental immune cells considerably impact disease progression. Similarly, both macrophages and T cells within the cystic microenvironment (CME) regulate cystogenesis in ADPKD murine models. But, how the interplay among these cells impacts cyst progression remains elusive. The goal of this study was to understand this dynamic interplay better.

Methods: We utilized flow cytometry to quantify renal immune cells in the murine ADPKD C57Bl/6 *Pkd1* p.R3277C (RC) model, strain matched wildtypes (WT), and *Pkd1* RC mice treated with either an inhibitor to the CSF1 receptor (CSF1R) or IDO1 (treatment regimen: 30 days starting at 1-month of age). CSF1 binding to CSF1R regulates macrophage proliferation and IDO1 regulates T cell function.

Results: IDO1 levels were increased in our *Pkd1*$^{RC/RC}$ mice, a *Pkd1*$^{-/-}$ cell line, and in ADPKD patient cyst cells vs. controls. Further, resident macrophage numbers were significantly increased in *Pkd1*$^{RC/RC}$ vs. WT mice. These findings led us to investigate if CSF1R or IDO1 inhibition slows ADPKD and how targeting different immune cell populations modulates the CME. Intriguingly, blocking of either protein reduced PKD severity (%kidney weight [W]/body W) in our mild, slowly progressive model and altered the CME significantly. Both treatments significantly reduced renal resident but not infiltrating macrophage as well as T cell numbers; renal neutrophil or dendritic cell numbers were not impacted. Most interestingly, while overall significantly reduced, the CD4 T cell population shifted, with regulatory T cells (T_{Regs}; known to be immunosuppressive) being significantly reduced two-fold by both treatments. This is of notable importance as we found T_{Regs} to be significantly enriched four-fold in the CD4 population in early disease when comparing *Pkd1*$^{RC/RC}$ vs. WT mice.

Conclusions: Using a relevant disease model, we show that targeting resident macrophages or modulators of T cell function can reduce PKD progression. Inhibition of both pathways resulted in reduced numbers of renal T_{Regs}, suggesting that they may be a unifying key effector of cystogenesis and a viable target for ADPKD immune therapy.

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SA-PO462

Knockout of Caspase-1 Gene Restrains Polycystic Kidney Disease in Pkd1$^{RC/RC}$ Mice

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Background: Two stimuli shown to accelerate disease in PKD model mice are acute kidney injury and exposure to commensal microbes. A commonality of these two stimuli is that they both promote activation of the inflammasome, a multi-protein scaffold that assembles in a range of cell types as an innate immune response to either microbe-associated or cell damage-associated molecular motifs. Inflammasome assembly results in activation of the protease Caspase 1. Activated Caspase 1 promotes the cleavage and secretion of multiple protein substrates to create an inflammatory environment that can be pathological. We hypothesized that inflammasome activation promotes disease progression during the natural course of PKD.

Methods: To identify whether inflammasomes were activated during PKD progression, the expression of known inflammasome sensors/markers was assessed by qRT-PCR and western blotting of samples from the kidneys of human ADPKD patients, cystic *jck* and *Pkd1*$^{RC/RC}$ mice, and from non-cystic human and mouse kidneys. The *jck* mice were treated during an early stage of disease with adenine (2.5% in the chow), an agent known to activate inflammasomes, and the effects on PKD progression were examined at PN43. Caspase-1 (*Casp1*) was knocked out in the *Pkd1*$^{RC/RC}$ mice (*Pkd1*$^{RC/RC}$:Casp1$^{\Delta/\Delta}$). The effects on cystic kidney disease in Pkd1$^{RC/RC}$ and Pkd1$^{RC/RC}$:Casp1$^{\Delta/\Delta}$ mice were assessed at 6 months of age.

Results: Elevated expression of inflammasome components was found in the *jck* and *Pkd1*$^{RC/RC}$ mice and human ADPKD kidneys (*Nlrp3, Nlrp10, Mefv, Casp1, Il1b,* NLRP3, CASP1 in *jck; Nlrp1, Nlrp3, Aim2, Mefv, Casp1, Il1b* in *Pkd1*$^{RC/RC}$; *NLRP1, NLRP3, NLP10, AIM2, CASP1, IL1B,* NLRP3, IL1β in ADPKD). Adenine consumption promoted elevated 2K/TBW and cystic index in *jck* mice. *Casp1* knockout lowered 2K/TBW (*Pkd1*$^{RC/RC}$ =2.2 ± 0.4, *Pkd1*$^{RC/RC}$*:Casp1*$^{\Delta/\Delta}$=1.8 ± 0.15, p=0.01; compared with WT=1.2 ± 0.13) and cystic index in *Pkd1*$^{RC/RC}$ mice.

Conclusions: These preclinical studies identify Caspase1 as a promoter of PKD progression and a potential therapeutic target for cystic kidney disease.

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SA-PO463

Autosomal Dominant Polycystic Kidney Disease Shows a Tumor-Like Microenvironment

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Background: Polycystic kidney disease (PKD) is an inherited genetic disorder characterized by progressive growth of cysts in the kidneys. Despite not being a cancer, PKD shares many features with tumors. For instance, recent studies suggest a role of immune cells in PKD progression. Tumor modifies infiltrating cells functions to create the microenvironment favorable to tumor progression. Principal components of the Tumor Microenvironment (TME) are immune-inflammatory cells, Cancer-Associated Fibroblasts (CAFs), blood vessels and ECM. We investigated whether a similar environment might be present in PKD murine models.

Methods: We have characterized the renal tissue microenvironment of a *Pkd1*$^{flox/-}$*:TmCre* inducible and the *Pkd1*$^{flox/-}$*:KspCre* ADPKD mouse models. We have analyzed the presence of infiltrating immune cells and CAFs, and the state of the ECM through histological analysis and quantitative Real Time-PCR. In addition fluorometric analysis following dissociation of cells from total kidneys was used to analyze interstitial inflammation. For the *pan* macrophages quantification, we have performed an *in situ* quantification employing an F4/80 detection algorithm.

Results: We have detected a statistically significant increased level of CD45^{+} leukocytes in the ADPKD kidneys compared to the controls. In contrast, B and T lymphocytes could not be detected in late PKD models. Macrophages, activated myofibroblasts (potentially corresponding to CAFs), and extensive fibrosis in the kidneys of the ADPKD affected mice could be detected. In particular, while M1-macrophages (expressing *Nos2*) did not significantly change between the PKD kidneys and the controls, M2-macrophages (expressing *Arg1*) were found significantly increased in the kidneys of PKD mice compared to controls.

Conclusions: Our analysis on the kidneys of the ADPKD mouse models reveals the presence of a tumor-like microenvironment (T-LME), which could promote disease progression. The analysis of the crosstalk among the different components of the microenvironment might provide important insights into disease progression in PKD.

SA-PO464

Peptides Derived from the Stalk Region of Polycystin 1 Function as Ligands to Activate Signaling by the C-Terminal Fragment and to Ameliorate Cystogenesis

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Background: Polycystin-1 (PC1) modulates G protein signaling by as yet unknown regulatory mechanisms. Like the Adhesion class of GPCRs, PC1 undergoes auto-catalyzed cleavage at a GPS motif, which generates a large extracellular, N-terminal fragment and a membrane-embedded, C-terminal fragment (CTF) composed of 11 transmembrane domains preceded by an N-terminal extracellular stalk of 25 residues. We previously reported that PC1 CTF-mediated signaling to an NFAT reporter is dependent on the presence of the stalk, and is reduced by specific amino acid substitutions within its sequence. To determine if this stalk-dependent mechanism contributes to the inhibition of cyst formation, the ability of stalk-derived peptides to rescue signaling by a 'stalk-less' CTF expression construct (ΔCTF) and to ameliorate cAMP-driven cystogenesis was determined.

Methods: HEK293T cells transiently transfected with the ΔCTF construct lacking the first 21 residues of the stalk region were treated with soluble peptides (P) ranging from 7 to 21 residues in length whose sequences were derived from the stalk region. Activation of a co-transfected NFAT promoter-luciferase reporter was compared between ΔCTF- and empty expression vector control-transfected cells. Metanephric organ cultures derived from E15.5 Pkd1$^{RC/RC}$ fetal mice were stimulated with 8-Br-cAMP, and were treated with stalk peptides for up to 4 days in culture. The cystic area was compared between non-treated and peptide-treated kidneys.

Results: All of the stalk peptides (P7-P21) enhanced signaling from ΔCTF to the NFAT reporter, albeit to varying degrees, possibly due to differences in peptide structure. Peptides P7, P9, P13, P15 and P17 significantly reduced the cystic index of treated embryonic kidneys to different extents (e.g., ~25% for P7 to ~90% for P17), while P11 had no ameliorating effect. Treatment with P19 or P21 prevented kidney growth and decreased kidney survival. A mutant peptide containing a human ADPKD-associated missense mutation was also detrimental in organ culture unlike its wild type parental peptide.

Conclusions: These results support an Adhesion GPCR-like, stalk-dependent mechanism for regulation of signaling by PC1, implicate a physiological and disease-relevant role for this mechanism in renal tubulogenesis, and suggest a novel therapeutic avenue for ADPKD.

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SA-PO465

RNA Helicase p68 Inhibits Pkd1 Transcription and Promotes Cyst Growth in ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations of PKD1 and PKD2, resulting in progressive deterioration of kidney function due to the formation of thousands of cysts. Expression of PKD1 is high in the fetal kidney, which is essential for kidney development, and then is reduced after nephron formation has completed. However, the transcriptional regulation of PKD1 remains elusive. In this study, we investigate the roles and underlying mechanisms of p68, a DEAD box RNA helicase, in regulating Pkd1 gene expression.

Methods: To understand the role of p68 in ADPKD, we examined the expression of p68 and its regulation in Pkd1 mutant renal epithelial cells and ADPKD patient kidneys by qRT-PCR, Western blot and immunostaining/immunohistochemistry, and investigated how p68 regulates cystic cell proliferation, oxidative stress and renal fibrosis. To investigate if and how p68 regulates the transcriptional and post-transcriptional processing of the Pkd1 gene, we performed co-IP and ChIP assays in renal epithelial cells with and without knockdown of p68.

Results: We found that p68 was upregulated in Pkd1 mutant renal epithelial cells compared to that in Pkd1 wild type control cells as examined by Western blot and qRT-PCR analysis. The level of p68 was also increased in cyst lining epithelial cells in kidneys from Pkd1 mutant mice and ADPKD patients. Knockdown of p68 increased Pkd1 gene transcription, whereas upregulation of p68 decreased Pkd1 transcription, which involved 1) interaction of p68 with p53 and Drosha to form a ternary complex on the promoter of the Pkd1 gene, and 2) increased p68 mediated microRNA 182 (miR182). Inhibition of miR182 increased Pkd1 mRNA and protein levels. In addition, we found that oxidative stress decreased Pkd1 expression in a p68-dependent manner. We further found that p68 regulated cystic epithelial cell proliferation via the activation of ERK, mTOR and Rb signaling, and regulated renal fibrosis via TGFβ1 signaling.

Conclusions: This is the first study to show that one of the RNA helicases, p68, inhibits the transcription of the Pkd1 gene and promotes cystic renal cell proliferation and the expression of fibrotic markers in these cells. Oxidative stress promotes renal cyst progression via p68 mediated Pkd1 downregulation. Targeting p68 with its inhibitor may be a potent therapeutic strategy for ADPKD treatment.

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SA-PO466

The Consequences of Decreased Cap-Dependent Translation in Polycystic Kidney Disease

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Background: Autosomal Dominant Polycystic kidney disease (ADPKD) is the most common life-threatening hereditary disease, characterized by cyst formation and growth. Unchecked proliferation of cystic epithelial cells is a major contributor to cyst growth. At the nexus of regulating proliferation is the 4E-BP1 pathway, a crucial checkpoint in cap-dependent protein translation and proliferation. We demonstrate on immunohistochemistry staining that ADPKD mice and rat models, ADPKD patient renal biopsies, and PKD1$^{-/-}$ cells exhibit hyperphosphorylated 4E-BP1, a biomarker of increased translation and proliferation. We hypothesized that expression of constitutively active 4E-BP1 constructs (4E-BP1^{F113A} and 4E-BP1R13A^{F113A}) would repress translation, decrease proliferation, and reduce cyst expansion.

Methods: In the orthologous ADPKD model, the C57BL/6 Pkd1$^{RC/RC}$ mouse, we determined the effect of 4E-BP1^{F113A} on cystic disease (on MRI scan).

Results: Unexpectedly, relative to controls, 4E-BP1^{F113A} resulted in increased cyst burden (%) (48±5 vs. 72±6*), decreased functional parenchyma (%) (46±7 vs 22±5*, suppressed TUNEL staining (% positive cyst epithelium, 24±9 vs. 36±14*), and increased Bcl-2 expression (relative densitometry units, 12±2 vs. 8±2*). Values are means of control treated, and 4E-BP1^{F113A} treated Pkd1$^{RC/RC}$ ± SEM, *p<0.05.

Conclusions: To determine the mechanism of 4E-BP1^{F113A} enhanced PKD, we performed *in vitro* studies in ADPKD patient cells. *In vitro*, 4E-BP1^{F113A} and 4E-BP1^{R13AF113A} significantly repressed cap-dependent translation as anticipated (57% mean reduction across 3 cyst cell lines). However, 4E-BP1 transduction increased mTOR signaling, enhanced proliferation, decreased apoptosis, impaired NADPH oxidoreductase activity and increased superoxide production. Reduced 4E-BP1 expression reversed the *in vitro* phenotype. These results demonstrate the importance of cap-dependent translation in PKD cyst lining epithelial cells

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SA-PO467

Elevated Calcium/Calmodulin-Dependent Protein Kinase IV (CaMK4) Promotes mTOR-Dependent Cell Proliferation in ADPKD

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Background: Mammalian target of rapamycin (mTOR), a central integration site for pathways involved in cell growth and proliferation, is abnormally activated in cyst-lining cells in ADPKD. mTOR inhibition reduces cell proliferation and PKD progression in rodents; however, the therapeutic value of targeting mTOR with rapalogues in ADPKD patients remains unclear due to dose-limiting side effects. The development of new therapies requires a better understanding of pathways responsible for aberrant mTOR activation in cystic epithelial cells. Calcium/calmodulin-dependent kinase type IV (CaM4) stimulates mTOR signaling in various cell types including hepatic cancer cells and immune cells; however, the role of CaMK4 on mTOR signaling and cyst growth in PKD has not been examined.

Methods: CaMK4 levels were measured in primary ADPKD and normal human kidney (NHK) cells, and in *Pkd1*$^{RC/RC}$ (slow onset), *Pkd1*$^{RC/RC}$*; Pkd2*$^{+/-}$ (rapid onset) and normal mouse kidneys by Western blot analysis. The effect of KN-93, a CaMK4 inhibitor, on mTOR signaling was evaluated in ADPKD cells. To determine if CaMK4 regulation of mTOR was dependent on the LKB1/AMPK pathway, we tested KN-93 on renal cells with an inducible knockout of *Lkb1*. *pcy/pcy* mice, a well-characterized PKD model, received 10 mg/kg KN-93 every day for one week to determine the effect of CaMK4 inhibition on renal mTOR signaling.

Results: CaMK4 levels were 2.5-fold higher in human ADPKD cells compared to NHK cells. Renal CaMK4 levels were also elevated in *Pkd1*$^{RC/RC}$ and *Pkd1*$^{RC/RC}$*; Pkd2*$^{+/-}$ mouse kidneys compared to age-matched normal littermates. Incubation with KN-93 decreased P-mTOR, P-S6K and P-S6, downstream targets of mTOR, and proliferation of ADPKD cells. mTOR inhibition by KN-93 was not affected by LKB1 knockout in renal epithelial cells, consistent with a direct effect of CaMK4 on the mTOR complex. CaMK4 inhibition with KN-93 decreased renal levels of P-S6 in *pcy/pcy* mice.

Conclusions: Elevated CaMK4 promotes mTOR signaling in PKD kidneys and may be a potential target to reduce mTOR-dependent cell proliferation and cyst growth.

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SA-PO468

Polycystin 1 Regulates Cilia Length and Cyst Formation by Controlling Centrosomal ARHGAP35-Dependent RhoA Activation

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Background: Mutations in *PKD1* (encoding for PC1) account for most patients with ADPKD but it is still unclear how these result in the highly complex cellular phenotype of ADPKD. It had been reported that primary cilia length is normal in ADPKD cells implying an abnormality in function (flow-dependent signalling); however this hypothesis has been recently challenged. Unexpectedly, we observed consistently shorter cilia in patient-derived *PKD1* cystic cells compared to normal tubular cells and its correction by cytochalasin-D, an inhibitor of actin polymerisation.

Methods: RhoA activity (GST pulldown) and its localisation (RhoA biosensor) were determined in ciliated cells; siRNA knockdown of reported centrosomal ARHGAPs identified from ciliome and centrosome databases and their effect on cilia length; *PKD1* null human tubular cells were generated by CrispR/Cas9 mutagenesis; BioID proximity assay using a centrosome targeting sequence (PACT) to confirm centrosomal localisation of ARHGAPs; effect of a selective ROCK inhibitor (hydroxyfasudil) in a *Pkd1* mouse model.

Results: We confirmed that primary cilia are shorter *in vivo* (human ADPKD and mouse *Pkd1* kidneys) and in *PKD1* null CrispR cells. In ciliated cells, increased RhoA (but not Cdc42 or Rac1) activation was observed in *PKD1* cystic cells with a localised increase at the cilia base. Cilia length could be normalised by Rho kinase (ROCK) inhibitors or expression of dominant negative RhoA (but not Cdc42 or Rac1). Knockdown of several centrosomal ARHGAPs (5, 29, 35) resulted in shorter cilia but only ARHGAP35 centrosomal localisation was reduced in the absence of *PKD1*. Specific binding of ARHGAP35 to the PC1 C-terminal domain was shown by co-IP. Finally, we demonstrate that selective ROCK inhibition reduced cyst growth *in vitro* (*PKD1* human cystic cells) and *in vivo* (*Pkd1* mouse).

Conclusions: PC1 appears to regulate centrosomal RhoA activity through the recruitment or stabilisation of ARHGAP35. Mutations in *PKD1* lead to shorter cilia due to increased RhoA and ROCK activity. Interestingly a recently reported ARHGAP35 hypomorphic mouse develops shorter cilia and glomerular cysts. Inhibition of ROCK normalised cilia length and reduced cyst expansion suggesting that the RhoA/ROCK pathway is a potential new axis to develop therapies to inhibit cyst initiation in ADPKD.

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SA-PO469

Genetic Reduction of Cilium Length by Targeting Ift88 Impedes Kidney and Liver Cyst Formation in Autosomal Polycystic Kidney Disease Mouse Models

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Background: Mutations in polycystin-1 (PC1) and -2 (PC2), products of the PKD1 and PKD2 genes, cause autosomal dominant polycystic kidney disease (ADPKD). They localize to the primary cilia; however, their ciliary function is in dispute. The loss of either the cilia or PC1 or PC2 causes cyst in orthologous mouse models. Cystogenesis is inhibited in the absence of both cilia and PC1 or PC2. How the cilia and PC1 or PC2 interact to regulate cystogenesis is still unknown. The role of intraflagellar transport proteins in Pkd1-deficient mice is also unknown.

Methods: In this study we used human and mouse kidney tissues to study the correlation between cilia length and cyst formation. We developed Pkd1 and Pkd2 single and double knockouts with Ift88 to thoroughly investigate the correlation between cilia length and cystogenesis in mice and to identify downstream signaling targets.

Results: 1) We report, for the first-time that cilium length is elongated in human ADPKD kidneys. 2) We found similar elongation in Pkd1 and Pkd2 knockout mice following polycystin inactivation. 3) We show that inactivating the intraflagellar transport protein Ift88 in Pkd1-deficient mice and Pkd2-deficient mice shortens the elongated cilia, impedes kidney and liver cystogenesis and reduces cell proliferation. 4) Multi-stage in vivo analysis of signaling pathways revealed a novel early, and sustained activator in disease onset and progression in Pkd2 single knockout (SKO) which is rescued in Pkd2 and Ift88 double knockout (DKO) mouse kidneys. 5) On the other hand, ERK pathway was activated in the SKO but no rescue was observed in the DKO mouse kidneys.

Conclusions: Our findings advocate an essential role of polycystins in the structure and function of the primary cilia and implicate a novel target as a key inducer of cystogenesis downstream of the primary cilia. These data suggest that modulating cilium length and/or its associated signaling events may offer novel therapeutic approaches for ADPKD.

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SA-PO470

SMYD3: A Novel Regulator of Cystogenesis and Ciliogenesis in ADPKD

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Background: Deregulation of lysine methylation signaling has emerged as a common aetiological factor in disease pathogenesis, such as cancers. We found that the lysine methyltransferase, SMYD3, is upregulated in ADPKD, a genetic and "ciliopathy" disease characterized by renal cyst formation and ciliogenesis defects. However, if and how SMYD3 regulates cyst formation and its relationship to ciliogenesis remains elusive.

Methods: We investigate the role of Smyd3 on renal cystogenesis by knockout of Smyd3 in *Pkd1* conditional knockout mouse kidneys, and investigate if Smyd3 regulates ciliogenesis in mIMCD3 and RCTE cells with and without knockdown of Smyd3 and in primary renal cells isolated from *Smyd3 fl/fl:Ksp-Cre* mouse kidneys. We determine the effect of Smyd3 on the localization of proteins on the basal body and ciliary axoneme by immunofluorescence.

Results: We found that knockout of Smyd3 delayed cyst growth as seen by decreased cystic index, kidney weight (KW)/body weight (BW) ratios, blood urea nitrogen (BUN) levels, and cyst lining epithelial cell proliferation in Pkd1 mutant mice (all $p < 0.05$). We further found that knockout of Smyd3 decreased the activity of STAT3 and β-Catenin. In addition, we found that Smyd3 interacted with CDK2, a direct regulator of the cell cycle, and knockout of Smyd3 decreased the phosphorylation of CDK2 in *Pkd1* mutant mouse kidneys. We further found that Smyd3 is localized on the centrosome and basal body and silencing or knockout of Smyd3 inhibits primary cilia assembly in renal cells. Smyd3 is co-localized with centriolar distal appendage proteins, Cep164, C2CD3 and Ofd1, and interacts with Ofd1, Ift88 and TTBK2 proteins, known to play an essential role in ciliogenesis. Depletion of Smyd3 increased the recruitment of Ift140, but decreased the recruitment of Rab8a and Cep164 to the ciliary axoneme. Last, knockdown of Smyd3 regulated the expression of key distal appendage and trafficking related proteins at the transcript and protein levels.

Conclusions: Smyd3 regulates cystic renal epithelial cell proliferation via STAT3, β-catenin and Cdk2 signaling to promote cystogenesis, and regulates ciliogenesis by acting as a gate protein, controlling the trafficking of proteins in and out of the cilia. The interactions between Smyd3 and its novel binding partners provide novel mechanisms of Smyd3 in regulating cystogenesis and ciliogenesis in ADPKD.

Funding: NIDDK Support

SA-PO471

Protein Phosphatase 1 Alpha Interacts with Polycystin-1 and Regulates Polycystin-1 Targeting to Primary Cilium

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease, which is mostly caused by mutations in *PKD1* or *PKD2* genes. However, how mutations in these two genes lead to ADPKD remains partially understood. Recent studies have indicated that defective ciliary trafficking of polycystin-1/2 (PC1/2, encoded by *PKD1* and *PKD2*, respectively) underlies the pathogenesis of a subgroup of ADPKD cases. We have recently identified a novel ciliary targeting sequence (CTS) in the C-terminus of PC1. We found that this CTS interacts with protein phosphatase 1-a (PP1a), a ubiquitously expressed phosphatase in the PPP family. Short hairpin RNA mediated knockdown of PP1a in IMCD3 cells results in reduced PC1 ciliary localization and elongated cilia without affecting GPS cleavage or protein maturation of PC1. Nevertheless, the precise mechanism under which PP1a regulates ciliary targeting of PC1 is still obscure.

Methods: Four PC1 constructs with phosphomimic or phosphodeficient mutantions were transfected into IMCD3 cells and co-stained with cilia marker. HA-tagged PC1 and flag-tagged PP1a were co-transfected into IMCD3 cells and then stained to detect the subcellular localization of PP1a/PC1 complex. PC1 and 2 were co-transfected into PP1a knockdown cells and then the ciliary targeting efficiency of PC1 was analyzed.

Results: Ciliary localization of all the four PC1 mutations was not affected compared with wild type control. PP1a and PC1 do not co-localize on the primary cilium but in the cytosol. Overexpression of PC2 is able to rescue the ciliary targeting defect of PC1 in PP1a knockdown cells.

Conclusions: Preliminary results suggest PP1a bind with PC1 in the cytosol and regulates PC1 trafficking. This regulation is probably not caused by PP1a mediated PC1 dephosphorylation. PP1a might function in this process via modifying PC2, a prerequisite for PC1 targeting to cilia. Further investigation is required to delineate the exact role of PP1a in PC1 trafficking.

SA-PO472

Pannexin-1 Mediates Fluid Shear Stress-Sensitive Purinergic Signaling and Cyst Growth in Polycystic Kidney Disease

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Background: Tubular ATP release is regulated by mechanosensation of fluid shear stress (FSS), but the molecular mechanism mediating this process is poorly understood. Extracellular ATP is implicated in polycystic kidney disease (PKD), where polycystin-1/polycystin-2 (PC1/PC2) is dysfunctional. In health, PC1/PC2 functions as a mechanosensory complex in the kidney. This study aims to provide new insights into renal ATP signaling under physiological conditions and PKD.

Methods: Microfluidic setups, pharmacologic inhibition of mTORC1 and pannexin-1 by rapamycin and brilliant blue FCF, respectively, and CRISPR/Cas9 loss-of-function approaches were combined to assess the ATP release by renal cells. Acute water loading by healthy human subjects was used to evaluate the ATP release under variable urinary flow. PKD models, using inducible kidney-specific *Pkd1* knockout mice (iKsp-*Pkd1*$^{lox/lox}$) and zebrafish with translation blocking morpholino targeting the ortholog of human *PKD2* (*pkd2*), were employed to study *in vivo* the relevance of the mechanisms disclosed *in vitro*.

Results: Immortalized renal mouse distal convoluted tubule 15 (mDCT15) cells subjected to FSS displayed an increased ATP release. Furthermore, inhibition of mTORC1 amplified this FSS-modulated ATP release. Inhibition of pannexin-1 decreased the FSS-modulated ATP release by these renal cells. To translate this *in vitro* phenomenon to the *in vivo* situation, healthy human subjects were exposed to acute water loading resulting in an increased urine production and ATP excretion. In precystic iKsp-*Pkd1*$^{-/-}$ mice, increased renal pannexin-1 mRNA expression and urinary ATP were observed. Similarly, in renal *Pkd1*$^{-/-}$ mDCT15 cells, elevated ATP release was observed upon FSS mechanosensation. In these cells, inhibition of mTORC1 failed to enhance ATP extrusion, but an increase in pannexin-1 mRNA expression was observed compared to renal *Pkd1*$^{+/+}$ mDCT15 cells. Importantly, inhibition of pannexin-1 in a zebrafish PKD model decreased renal cyst growth.

Conclusions: Our results suggest that renal pannexin-1 channels mediate ATP release from epithelial cells towards the tubular lumen. The redundancy of this mechanism in PKD, where urinary ATP levels are elevated, presents pannexin-1 as a new therapeutic target to prevent cyst growth in PKD.

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SA-PO473

Trans-Epithelial Fluid Pumping Performance of Renal Epithelial Cells and the Mechanistic Basis of Polycystic Kidney Disease

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Background: The epithelial cells lining nephrons in kidneys are highly efficient fluid reabsorption and secretion units. Imbalance in the trans-epithelial fluid flow leads to various renal diseases including polycystic kidney disease (PKD), which is characterized by development of numerous fluid-filled cysts in the renal tubules. Surprisingly, no work has been done so far to quantify the fluid pumping performance of renal epithelial cells in a physiologically relevant setup. To make progress, we developed a *micro-fluidic kidney pump* (MFKP) device, to measure the trans-epithelial fluid flow as a function of the hydrostatic pressure gradient generated by cells.

Methods: MFKP mimics a tubular segment of the nephron as it has two microfluidic channels separated by a porous membrane. A microcapillary connected to the basal side acts a sensor to measure both the trans-epithelial fluid flow (J) with a resolution of 0.31 μL and corresponding hydrostatic pressure gradient (ΔP) with a resolution of 10 Pa. This

setup was placed inside the incubator and fluid flow in the microcapillary was recorded using videography. J_0 is the fluid flow at $\Delta P = 0$ and ΔP^* is the stall pressure when $J = 0$.

Results: Here we report that normal human cells pump fluid from apical to basal side with J_0 in the range of 10 μL/min/cm^2 and ΔP^* of 250 Pa. Interestingly the PKD cystic cells pump fluid in the reverse direction (basal to apical) with J_0 of 5 μL/min/cm^2 and ΔP^* of -300 Pa. However, basolateral treatment with 1 nM Tolvaptan caused a decrease in both in J_0 and ΔP^*. The developed pressure gradient translates to a force of 50-100 nanoNewtons per cell, which can potentially expand the cyst lumen. In both normal and PKD cells, the trans-epithelial fluid flux (J) and the PPCs are modulated by mechanical (fluid shear stress), chemical (arginine vasopressin) and apical hypo-osmotic perturbations.

Conclusions: Our combined results offer insights into kidney fluidic pumping action and ADPKD cyst formation. To our knowledge this is the first demonstration of a decrease in secretory fluid flow and hydrostatic pressure gradient by PKD cells in response to a Tolvaptan. Our results demonstrate that secretory and absorptive functions of epithelia can generate significant mechanical forces, and maybe a general phenomenon in tubular morphogenesis in other contexts.

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Defective Glomerulotubular Balance (GTB) in PKD2 Mutant and Conditional PKD2 Knockout Mice Before Renal Cyst Formation

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Background: PC2 (*Pkd2*) is a nonselective calcium permeable cation channel belonging to the TRP channel family, at the cilia and ER, and functions as a Ca^{2+} channel in the ER. Previous studies showed *Pkd2* mutation or knockout resulted in an absence of IP3 receptor mediated calcium release from the ER. We have reported that blocking IP3 receptor abolished the flow-modulation of Na^+ and HCO_3^- transport in mouse proximal tubules. We investigated whether *Pkd2* has a physiological function in response to flow-mediated PT transport.

Methods: The flow-mediated Na^+ and HCO_3^- transport were studied by microperfusion of proximal tubules in vitro in WT, *Pkd2*$^{+/-}$ and *Pkd2* conditional KO (*Pkd2*$^{fx/fl}$*;Pax8-rtTA;Tet-O-Cre*) mice. The KO mice were induced with doxycycline from 4-6 and used 3-4 weeks after the end of induction (9-10 week old mice), before renal cysts have formed. Proximal tubules were perfused *in vitro*at low (5 nl/min) and high (20 nl/min) perfusion rates, and the fluid (J_v) and HCO_3^- (J_{HCO3}) absorption were measured by the changes of ^{3} H-Inulin and total CO_2 in the original and collected fluid. J_{Na} was estimated from the change of J_v and the assumption of isotonic transport.

Results: When perfusion was increased from 5 to 20 nl/min, J_v and J_{Na} increased 48% and J_{HCO3} doubled in WT. In contrast, the flow-stimulated component of J_v and J_{Na} could not be detected, and that of J_{HCO3} was significantly reduced in both *Pkd2*$^{+/-}$ and the *Pkd2*$^{-/-}$ mice, similar to the effect of the IP3 receptor antagonist (2-APB).

Conclusions: These results indicate that *Pkd2* is necessary for normal flow-mediated PT transport, and support the hypothesis that impaired GTB may contribute to renal cyst formation.

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Effect of Axial Flow on Sodium and Bicarbonate Absorption in PTs of WT and *Pkd2* Mutant Mice

	n	J_v (nl/min/mm)	J_{Na} (pmole/min/mm)	J_{HCO3} (pmole/min/mm)
Flow rates		5nl/min │ 20nl/min	5nl/min │ 20nl/min	5nl/min │ 20nl/min
WT	13	0.95±0.1 │ 1.44±0.1*	134.2±5 │ 197.8±6*	70.8±4 │ 138.7±5*
Pkd2 $^{+/-}$	11	0.74±0.1† │ 0.67±0.1†	108.9±11 │ 98.8±7†	68.6±6 │ 87.9±4†
Pkd2 $^{-/-}$	7	0.64±0.1† │ 0.89±0.2†	94.5±12 │130.2±23†	60.8±7 │ 76.9±5†

* P< 0.05 compared from low flow rate; †P<0.05 compared with WT control at the same flow rate.

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ATP Release into Renal Cysts Via Pannexin-1/P2X7 Channels Decreases ENaC Activity

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Background: Genetic predisposition is necessary for polycystic kidney disease (PKD) initiation, although there are other, incompletely identified downstream processes that are required for cyst growth. Their characterization may provide a unique opportunity for clinical interventions. One of the poorly studied phenomena in PKD is high ATP content in cysts. Unfortunately, neither origins of uncontrolled ATP release, nor consequences of abnormal purinergic signaling in relation to epithelial transport are well explored in the polycystic kidney.

Methods: We tested the distribution of pannexin-1 (Panx1) and P2X7, two proteins potentially involved in ATP release, in the kidneys of the *Pkd1*$^{RC/RC}$ mice, a model of autosomal dominant PKD (ADPKD). To establish if pannexin-1 contributes to ATP release in the collecting ducts (CD), we measured luminal accumulation of ATP in M1 cell renal CD monolayers. Also, single channel patch clamp analysis of polarized M1 cells was employed to study how P2X stimulation affects ENaC activity.

Results: Abundance of both Panx1 and P2X7 proteins were abnormally increased in the cyst lining cells compared to non-dilated collecting ducts. Mechanical stimulation increases ATP release by polirized M1 cells to the luminal side and this effect was significantly blunted by treatment with probenecid, a pannexin-1 blocker. Patch-clamp studies reveal that apical stimulation of P2X receptors with αβ-MeATP acutely reduces ENaC activity.

Conclusions: We conclude that in ADPKD progression, an abnormal hyperexpression of both PANX1 and P2RX7 occurs in the cyst lining epithelial cells. High abundance of both proteins is not typical for non-dilated CDs but, when happens in cysts, pannexin1/P2X7 cooperation elevates ATP release into the luminal space. High ATP level is a pathogenic factor facilitating cystogenesis by reducing ENaC-mediated reabsorption from the lumen.

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SA-PO476

Novel PC2 Regulation of Ezrin in Renal Epithelia Reveals Insight into ADPKD Cystogenesis

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Background: Ezrin plays the role of master scaffold of the apical compartment in epithelial cells and is critical in regulation of polarity, cytoskeleton organization, and protein trafficking. Ezrin regulation and the downstream consequences of its disruption have not been elucidated. Investigation into the initiating events of cystogenesis in autosomal dominant polycystic kidney disease (ADPKD) revealed a dramatic change in ezrin, following loss of polycystin-2 (PC2). ADPKD is caused by loss of function mutations in *PKD1* and *PKD2*, which encode for transmembrane proteins PC1 and PC2, respectively.

Methods: Using an inducible *Cre* system (*Pkd2fl/fl Pax8rtTA TeTOCre*), PC2 loss in a three dimensional renal epithelial model resulted in decreased ezrin abundance. Furthermore, an *in vivo* mouse ADPKD model (*Pkd2fl/fl Pax8rtTA TetOCre*) of rapid cystogenesis exhibits significant changes in ezrin at the apical membrane of renal tubules after a short induction period of five days, and before the manifestation of cysts. Human ADPKD tissue also confirms changes in the structure of the apical compartment in emergent cystic cells, which correlated with significant alterations in the localization and abundance of ezrin in comparison to controls. A potential regulatory relationship between PC2 and ezrin is supported by experiments that demonstrated PC2 and ezrin interact in an overexpression system and share a similar phosphoinositide binding profile in a lipid overlay assay. Based on this novel regulatory relationship between PC2 and ezrin, as well as the antecedent loss of ezrin to cyst formation, human ezrin was overexpressed in the *pkd2* morpholino pronephric cyst model of zebrafish. Increased expression of ezrin abolished the formation of pronephric cysts.

Results: The interaction profile of PC2 and ezrin, disruption of ezrin in *Pkd2* inducible *in vitro* and *in vivo* model systems, changes in ADPKD patient tissue, and rescue of pronephric cysts in the *pkd2* MO suggest there is a significant role of ezrin in renal cystogenesis.

Conclusions: Understanding the relationship of a master scaffold, ezrin, with PC2 in renal epithelial cells will help elucidate the mechanism of ADPKD cystogenesis and define important downstream pathways necessary for epithelial functions.

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SA-PO477

Myosin Activation as a Novel Therapeutic Strategy to Treat PKD in Human Kidney Organoids and Mice

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Background: Polycystic kidney disease (PKD) is an autosomal dominant disorder that manifests from loss of function mutations in *PKD1* or *PKD2*, encoding the proteins polycystin-1 (PC1) and polycystin-2 (PC2) respectively. The function of these proteins remain poorly understood and no curative therapeutics have been developed. Blebbistatin, a myosin inhibitor, was found to rapidly increase cyst proliferation in stem cell derived kidney organoids lacking PC1 or PC2. We hypothesize that non-muscle myosin II (NMII) activation will increase tubule epithelial cell contracility to reduce and prevent cystogenesis in PKD organoids and mice.

Methods: Stem cell derived kidney organoids genetically lacking PC1 or PC2 were differentiated over 18 days, picked, placed in suspension, and treated with blebbistatin or EMD, a small molecule myosin activator, every two days for two weeks. Organoids were measured for area, cystic index, stained for NMII, and toxicologically assessed. *Pkd1*$^{RC/RC}$ mice at 20 weeks were intra-peritoneally injected with EMD every two days for four weeks, with blood urea nitrogen (BUN) levels measured. Post-sacrifice, mice kidneys were dissected, imaged, measured for weight and cyst number and histologically analyzed.

Results: In pre-cystic PC2 null organoids, EMD was able to reduce the total number of cysts in the organoids, as well as inhibiting the growth of cysts treated with blebbistatin in tandem. Cystic PC1 null organoids were treated with EMD resulting in the halt of cyst progression and gradual cyst reduction. NMII was enriched at the apical surface of tubules and showed dramatic stretching upon cyst initiation. No added toxicity was observed from EMD treatment. In *Pkd1*$^{RC/RC}$ mice treated with EMD, EMD reduced the total burden of cysts, and reduced total kidney weight and BUN levels relative to their vehicle treated counterparts.

Conclusions: We have discovered a myosin activator that can prevent cysts from progressing in pre-cystic organoids, reduce cysts in post-cystic organoids, and shows efficacy in the *Pkd1*$^{RC/RC}$ mouse model. Collectively, this supports our hypothesis that NMII contractility counteracts PKD cyst formation by stabilizing tubules. Myosin activation has significant potential to spur therapeutic progress for PKD in humans, and elucidate new mechanisms linking myosin to PKD pathogenesis.

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ADAM10-MMP14 Complex Regulates Adherens Junction Integrity at Renal Cystogenesis in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common life-threatening genetic kidney disease and currently do not have relevant therapeutic methods, which eventually results in end-stage renal disease. We previous reported ADPKD is associated with mutations in polycystins, alterations in cell-cell junctions, and disruption of cell polarity in renal epithelial cells. Moreover, our data indicated that Gα12 increase the shedding of E-cadherin, and the inhibition of ADAM10 can block the cystogenesis in renal cells through the preservation of E-Cadherin. In addition, studies also indicate that Matrix metalloproteinase-14 (MMP14) promotes cystogenesis, which was blocked by its inhibitors. However, mechanisms of ADAM10 and MMP14 regulated cystogenesis in ADPKD are not fully understood. In this study, we investigate these two major sheddases association and their roles in renal cystogenesis

Methods: Immunoprecipitation, immunostaining and 3-dimensional (3D) cell culture technologies are used to analyze the interaction between metalloproteinase ADAM10 and MMP14 in Madin-Darby Canine Kidney (MDCK) cells.

Results: Our data shows that ADAM10 and MMP14 associated at hemopexin domain of MMP14 to form a complex, and activation of MMP14 is required for ADAM10 in shedding of E-Cadherin. The enzyme-inactive mutant MMP14^{E240A} (Glu240 to Ala) or the deletion of the catalytic domain of MMP14 (MMP14CAT) significantly decreases the sheddase activity of ADAM10. In addition, ectopic expression of MMP14 increases the proliferation of MDCK cells, alters the cell-cell adhesion and promotes the cystogenesis of renal epithelial cells in our 3D cell model, *in vitro*. Our data also shows that knockdown of MMP14 decreases the cleavage of E-Cadherin by ADAM10, and knockdown of ADAM10 enhances the activation of proMMP2 by MMP14. Furthermore, ectopic expression of the MMP14E^{240A} mutant promotes inhibition of cystogenesis in our 3D epithelial cell models.

Conclusions: Our study shows for the first time that ADAM10 form a unique, stable complex at hemopexin domain of MMP14, and the ADAM10-MMP14 complex play a pivotal role in regulation of their sheddase activity on various cell-cell junctional proteins and cystogenesis in renal epithelial cells. Our data provide a potential therapeutic target in ADPKD through the modulation of ADAM10-MMP14 complex.

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SA-PO479

Persistent Upregulation of Homologous Recombination Repair Signalling in Cystic Epithelial Cells in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: In ADPKD, homologous recombination repair (HRR) of the *PKD* allele in response to DNA damage might explain the postnatal reduction in gene dose and triggering of focal kidney cyst formation. In this study, the hypothesis that HRR signaling is increased in ADPKD and correlates with kidney cyst formation, was investigated.

Methods: Markers of HRR [H2AX, γH2AX, phosphorylated Ataxia Telangiectasia and Rad3-related; pATR and AT Mutated; pATM] were assessed in immortalised ADPKD (WT9-7 and WT9-12) and normal (HK-2) kidney cells; *Pkd1$^{RC/RC}$* mice (1, 3, 6, 9 and 12 months), and end-stage human ADPKD. In addition, the expression of genes encoding proteins upstream (n=88) and downstream of HRR (n=355) was determined from normal and ADPKD kidney tissue [the latter divided into minimal cystic tissue, (MCT), small cysts (SC), medium cysts (MC) and large cysts (LC)] using public transcriptomic datasets (GSE7869; GSE9493).

Results: *In vitro*, pATR increased 1.7- and 2.2-fold in unstimulated WT9-7 and WT9-12 cells respectively compared to HK-2 cells (P<0.05). Similarly, pATM increased 9.6-(WT9-7) and 6.8-fold (WT9-12) compared to HK-2 cells (P<0.05). In *Pkd1$^{RC/RC}$* mice, cyst-lining epithelial cells (CECs) were positive for pATR and γH2AX at all timepoints, with higher frequency at 1 month of age. In end-stage human ADPKD tissue, CECs of kidney cysts were positive diffusely for pATR and pATM. Further analysis showed that dysregulation of HRR-related genes (>1.5-fold, q<0.05) varied by cyst size. The percentage of dysregulated genes encoding upstream HRR mediators (including *MRN*, *TOPBP1* and *RPA1*) increased 22% (in MCT), 47% (in SC) and 52% (in LC), compared to control kidneys. Similarly, genes encoding downstream HRR factors were also dysregulated according to kidney cyst size [MCT (12%), SC (36%), MC (37%) and LC (45%)]. *ATR* was highest in MCT (1.6-fold; q=0.01), and *H2AX* increased 1.4-fold (q=0.07) in MCT and 3.0-fold in LC (q=0.0001).

Conclusions: Kidney cystic epithelial cells exhibit DNA damage and the persistent upregulation of HRR signalling which correlates with cyst size. These data suggest that low-dose inhibition of HRR pathways using sub-lethal dose of ATR or ATM inhibitors could be used to selectively target kidney cyst growth.

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Loss of Mitochondrial Transcription TFAM in Renal Tubular Epithelial Cells Is Associated with Cyst Development

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Background: Mitochondrial dysfunction plays an important role in the pathogenesis of kidney disease. In fact, certain kidney diseases are associated with genetic mitochondrial disorders, indicating that mitochondrial dysfunction can initiate and promote kidney disease.

Methods: In the kidney, mitochondria (mt) are highly abundant in renal tubular epithelial cells due to their high energy demands. In order to gain insights into mt function during renal pathogenesis, we inactivated the gene encoding mt transcription factor A (*TFAM*) in *Six2*-expressing progenitor cells, resulting in TFAM function loss in all nephron segments except collecting ducts; mutant mice are from hereon refered to as *Six2-Tfam$^{-/-}$* mutants. TFAM is required for mt DNA replication and gene transcription and is thus essential for the maintenance of mt mass and function.

Results: We found that *Six2-Tfam$^{-/-}$* mice developed severe renal cystic disease and died by postnatal day (P) 30 from renal failure (76.0 ± 3.46 mg/dL for mutants vs. 22.0 ± 2.0 mg/dL BUN for control; n=4 and n=3, respectively; p<0.0001). Although nephrogenesis was not affected (normal morphology at P0), the expression of proximal and distal renal differentiation markers was severely reduced by P7. Furthermore, *Six2-Tfam$^{-/-}$* mice were characterized by significant changes in mt morphology {EM and structured illumination microscopy (SIM)}, as well as alterations in cellular energy metabolism; increase in glycolysis and decrease in oxygen consumption in isolated proximal tubule epithelial cells using Seahorse XF-24 instrument. To investigate TFAM in autosomal dominant polycystic kidney disease (ADPKD), we examined two mouse models of ADPKD, ROSA26-Cre^{ERT}*Pkd1$^{-/-}$* and *Cys$^{cpk/cpk}$* mice as well as human nephrectomy tissues by immunohistochemistry and RNA in situ hybridization. We observed that TFAM as well as TFAM-regulated mt genes were signifcantly downregulated in cyst-lining epithelial cells in both mouse and human PKD tissues. Consistent with reduced TFAM expression was a decrease in mt volume in cyst-lining epithelial cells compared to non-cystic tubular epithelium using SIM.

Conclusions: Taken together, our data establish that loss of TFAM is associated with the development of polycystic renal disease providing strong rational for developing strategies that target mt function for ADPKD therapy.

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SA-PO481

Investigating the Centrality of the Asparagine Synthetase Enzyme in the Metabolic Reprogramming and Glutamine Usage in ADPKD

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Background: We showed that metabolic alterations in the TCA cycle and increased glutaminolysis interlinked with asparagine metabolism are important features of ADPKD (Podrini et al. Commun Biol, 2018). Tracing studies with labelled [$^{13}C_5$,$^{15}N_2$] glutamine showed that *Pkd1$^{-/-}$* cells increased glutamine uptake and ^{15}N-labelled asparagine, indicating a central role for asparagine synthase (ASNS). Indeed, *siAsns in vitro* abrogated glutamine contribution to the TCA cycle. Here, we explore ASNS as an ER-bound protein activator of the integrated stress response (ISR) sitting at the intercross of metabolic and ER stress response. Further, we propose ASNS as a novel therapeutic target for ADPKD.

Methods: Protein expression for ISR targets, metabolomics, tracing with *siAsns* in *Pkd1*-mutant cells. Given the absence of inhibitors for ASNS we developed a strategy using Antisense LNA GapmeRs to achieve stable downregulation *in vitro* and *in vivo.*

Results: Central to the ISR is the eIF2α/ATF4 axis which drive ASNS transcription. Elevated expression of ASNS was associated with increased ATF4 protein expression in cystic kidneys (*KspCre;Pkd1*) compared to controls. p-eIF2α, which promotes ATF4 synthesis, was increased in *Pkd1*-mutant cells. However, when *Pkd1*-mutant cells were deprived from glucose, p-eIF2α was decreased, suggesting the induction of a pathway involved in ROS production. This was supported by increased GSH (reduced glutathione) in metabolomics studies in cystic kidneys *(KspCre;Pkd1*) and *Pkd1*-mutant cells compared to respective controls. Further, amino acids availability for ROS production was significantly decreased, suggesting that eIF2α/ATF4 axis might be responsive to amino acids depletion. Importantly, downregulation of *Asns* in *Pkd1*-mutant cells causes cell death and rescues the accumulation of metabolites of the TCA cycle, suggesting a potential dual role for ASNS in glutaminolysis and cross-talk with ROS production. To validate ASNS as a therapeutic target, we have designed specifically the silencing of ASNS by LNA GapmeR. Initial testing *in vitro* was done in *Pkd1*-mutant cells on five different GapmeRs. The most effective is currently being tested *in vivo* in an inducible *Pkd1* KO mouse model.

Conclusions: Our data raises the possibility that asparagine metabolism interlinked with the ISR might offer a novel therapeutic intervention in PKD.

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SA-PO482

Investigating the Role of Peroxisomal Metabolism in Polycystic Kidney Disease

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Background: Our group recently reported impaired fatty acid oxidation and abnormal mitochondria in *Pkd1* mutants. However, how these phenomena contribute to cystogenesis in ADPKD is unclear. Peroxisomes interact with mitochondria physically and functionally, and congenital peroxisome biogenesis disorders cause developmental/metabolic phenotypes including renal cysts and aberrant mitochondria. Given the features observed in both PKD and the peroxisome diseases, we hypothesized *PKD1* might affect peroxisomal activity thus may alter mitochondrial behavior.

Methods: Peroxisome biogenesis in control and *Pkd1-/-* kidney epithelial cells was studied by evaluating the abundance of peroxisomes using staining of PMP70 and the peroxisome matrix import was assayed using GFP-SKL. We also investigated whether a tagged PC1 C-terminus (CTT) that localizes to mitochondria also co-localizes with peroxisome markers using live cell imaging. In addition, peroxisome-specific β-oxidation in control and *Pkd1-/-* cells was studied by mass spectrometry (MS) using deuterium-labeled behenic acid. Lastly, comprehensive analyzes of long-chain/very long-chain fatty acids were performed by MS of cystic kidneys of *Pkd1$^{fl/fl}$; Ksp-Cre* mice.

Results: There was no significant difference in peroxisomal abundance in control and *Pkd1 -/-* cells [peroxisome number per cell: 96784LTL WT 49.0±13.2 vs MUT 43.0±18.1 (p=0.4), 121112LTL WT 30.4±9.0 vs MUT 25.9±3.8 (p=0.2)]. GFP-SKL was equally well-recruited into peroxisomes in WT and MUT cells, suggesting peroxisome biogenesis is not defective. Exogenously expressed PC1 CTT exclusively localized to mitochondria. In the labeled behenic study, peroxisome β-oxidation was not significantlly different in *Pkd1-/-* cells (n=3 each cell line pair (each with 3–5 replicates), 89.6±6.7 vs 84.2±7.6%, p=0.3). In the kidney tissues, total levels of fatty acids (C10–C24) were lower in *Pkd1* mutant mice (control n=23, MUT n=12, 104.6±7.7 vs 83.9±7.1 μg/mg, p<6.3e^{-9}), while the ratio of C24:0/C22:0, used as a readout of peroxisome disorder was not changed in the mutant mice (0.56±0.11 vs 0.58±0.11, p=0.5).

Conclusions: These data suggest that peroxisome dysfunction is not responsible for the fatty acid oxidation defect previously described in *Pkd1* mutant cells. On the other hand, further study will be required to figure out the role of the observed reduction of fatty acids levels *in vivo*.

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Evidence for Genetic Compensation for Cilia Membrane Delivery Defects in cep290/NPHP6 Mutants

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Background: Apical cilia move fluid and participate in sensing the extracellular environment. Cilia dysfunction or "ciliopathy" results from disruptions in cilia structure or failed localization of ciliary proteins. Mutations in the *centrosomal protein of 290* kDa (*CEP290/NPHP6*) gene are linked to ciliopathy syndromes including Juvenile nephronophthisis. CEP290 has been proposed to form a "ciliary gate" at the transition zone in *Chlamydomonas reinhardtii* however its roles in cilia appear to be more complex.

Methods: We generated antibodies to the cep290 N terminus and C terminus to assay localization in different cell types. cep290 was acutely disrupted using antisense morpholino oligos and phenotypes were compared with Enu or Crispr/Cas9-generated genetic *cep290* mutants. RNA Seq was performed to test for upregulation of compensatory gene expression in mutants.

Results: Cep290 was localized in different cell types to the transition zone or pericentriolar satellites. Pericentriolar satellite Cep290 correlated with axoneme length defects in photoreceptors and KV cilia of morphants and mutants. In cep290 mutants, photoreceptors showed an abnormal accumulation of cytoplasmic vesicles. Cilia length defects in the KV could be rescued by over-expression of exogenous cilia membrane protein mRNAs (pkd2 or sstr3). cep290 mutants, which show a mild phenotype compared to morphants, exhibited upregulation of multiple mRNAs encoding proteins essential for cilia membrane transport (Arl3, unc119b, Arl13b). Overexpression of upregulated mRNAs partially rescued cep290 deficiency phenotypes in cep290 morphants.

Conclusions: Cep290 plays a key role in facilitating cilia membrane transport, particularly in cells where it localizes to pericentriolar satellites. Long term vs. acute loss of cep290 induces upregulation of genes encoding proteins involved in cilia membrane transport, suggesting genetic compensation in cep290 mutants. Overexpression of cilia GTPases (Arl3, unc119b, Arl13b) in cep290 human patients may provide a new route to ciliopathy gene therapy.

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SA-PO484

Fibrocystin Is Central to Cellular Control of Adhesion Forces and Epithelial Polarity

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Background: Mutations of the *Pkhd1* gene cause autosomal recessive polycystic kidney disease (ARPKD). *Pkhd1* encodes fibrocystin/polyductin (FPC), a ciliary type I membrane protein of largely uncharacterized function, suggested to affect adhesion signaling of cells. Contributions of altered epithelial cell adhesion and contractility to the disease process of ARPKD are elusive. Here, we study how loss of FPC (function) modifies epithelial cell response to adhesion stimuli and contractile force distribution leading to defective control of epithelial polarity.

Methods: To address FPC function in cells with renal collecting duct characteristics, we study *Pkhd1*-silenced Madin-Darby canine kidney cells (MDCKII) and human urine-derived renal epithelial cells (UREC) with normal and defective FPC. Consequences of FPC-deficiency are addressed by proteomics analysis and in cells studied in 2D/3D cell culture conditions, which includes micro-pattered chips and allows analysis of polarity, lumen formation and ciliogenesis in epithelial spheroids. Adhesion forces are studied via RhoA activation and myosin IIa phosphorylation and linked to adhesion signaling.

Results: FPC-mediated changes in epithelial cell characteristics, as revealed in proteomics-based pathway analysis, are linked to altered adhesion behavior and cellular capacity to form polarized epithelia. Their impact can be confirmed using selective inhibitors of cell contractility and FAK/Src signaling. FPC-deficient cells are characterized by defects in the formation of correctly polarized epithelial spheroids, which is restored upon transient reduction of cell contractility and adhesion forces during the initial phase of epithelial morphogenesis.

Conclusions: In FPC-deficient epithelial cells, altered control of pathway activity leads to enhanced integrin adhesion signals, impaired epithelial morphogenesis and by implication homeostasis, which are presumably related to progressive epithelial defects in ARPKD. Epithelial cell-based models with selective genetic alterations allow a better molecular understanding and furthermore may provide means to test pharmacological correction of epithelial defects in PKD.

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SA-PO485

Human and Mouse FPC-CTD Activate the MYC/Myc P1 Promoter: Implications for Renal Cystogenesis in ARPKD

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Background: Human ARPKD (MIM 263200) results from mutations in *PKHD1*, but mouse *Pkhd1* models express limited or no renal cystic disease. The protein product, FPC, undergoes Notch-like processing with regulated membrane-release and nuclear translocation of the intracellular C-terminal domain (FPC-CTD) (Kaimori, 2007). We have previously shown that c-Myc is overexpressed in human ARPKD and mouse *Cys1^{cpk}* cystic kidneys, but not in *Pkhd1^{cyli}*, *Pkhd1^{del67}*, or *Pkhd1$^{del3-67}$* kidneys (ASN 2018). Trudel (2019) has demonstrated that c-Myc plays a dual role in *Pkd1*-induced pathogenesis, through *Myc*-mediated mechanisms and a feed-forward regulatory *Pkd1–Myc* loop. The current *in vitro* study was designed to compare *MYC*/*Myc* regulation by human and mouse FPC-CTD in collecting duct cell lines.

Methods: We generated immortalized normal human (hTERT) and mouse (mTERT) kidney collecting duct cell lines; V5-tagged hFPC-CTD and V5-tagged mFPC-CTD constructs; and luciferase constructs of the P1 promoter for human *MYC* and mouse *Myc*. Luciferase reporter assays were performed as previously described (Wu, 2013).

Results: Sequence analysis revealed 74% identity between the human *MYC* and mouse *Myc* P1 promoters and 55% identity between hFPC-CTD and mFPC-CTD. Combinatorial luciferase assays demonstrated that the hFPC-CTD and mFPC-CTD constructs enhanced *MYC* and *Myc* P1 promoter activity in both human and mouse collecting duct cell lines.

Conclusions: These *in vitro* data demonstrate that FPC-CTD activates *MYC/Myc* expression in both human and mouse collecting duct cells. Paradoxically, we have previously shown that loss of FPC-CTD leads to cystogenesis and c-Myc overexpression in human ARPKD kidneys, but not in mouse *Pkhd1* models. We speculate that in renal collecting duct cells, FPC-CTD regulation of *MYC/Myc* transcription is differentially modulated by species-specific mechanisms. In the mouse, we propose that in normal collecting duct cells, FPC-CTD function at the P1 promoter is constrained by mouse-specific co-factors and overexpression of mFPC-CTD would stimulate *Myc*-induced cystogenesis. Current efforts are focused on *ex vivo* studies in mouse metanephroi to test this model.

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SA-PO486

Intrahepatic Bile Duct Morphogenesis in Pkhd1 Mutant Mice

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Background: ARPKD is a complex disease caused by mutations in the PKHD1 gene (encoding the Fibrocystin/Polyductin protein, or FPC). The predominant clinical manifestations are enlarged echogenic kidneys with distal tubule dilatation and cysts in the biliary tract with congenital hepatic fibrosis. The pathognomonic liver defect in ARPKD is the ductal plate malformation (DPM), which is characterized by the presence of increased numbers of tortuous, irregular bile ducts within the portal tract and fibrosis. In mice, as in humans, the biliary tract development is initiated by the induction of bi-potential hepatoblasts adjacent to the portal vein mesenchyme expressing Sox9 that eventually will form the primitive ductal structures (PDS) by recruiting Sox9– HNF4α+ cells from the surrounding parenchyma that will mature into symmetric structures with all the cells Sox9+ HNF4α–. From around E17 onwards, in a process termed ductal plate remodeling, these dilatations become surrounded by portal mesenchyme to eventually give rise to mature IHBD (intrahepatic biliary ducts). To date, few studies have characterized the DPM

associated with ARPKD in either humans or mouse models and the precise cellular defect remains undefined.

Methods: To gain insights into the mechanism altered during the development of the DPM we harvested livers from homozygous *Pkhd1*$^{\Delta 3\text{-}4}$ and control littermates at E18.5, P0, P7, and P15 and performed H&E staining.

Results: We observed dilated biliary ducts in homozygous mutants starting at P7. Immunofluorescence staining using Sox9 and Ki67 revealed an increased number of Sox9+ cells surrounding the portal vein in mutant homozygous mice although the number of proliferative cells Sox9+ was the same. In order to gain further insights into the role of FPC regulating the biliary tract development we isolated biliary duct cells using anti-EpCAM+ (cholangiocytes specific marker) coated magnetic beads from homozygous mutants and control littermates at P5 (N=16) and performed RNA sequencing (RNA-seq). We identified more than 50 genes that were differentially expressed (Log2 (FC)≤ ± 0.25 and a corrected p-value of <0.05).

Conclusions: Our study revealed that mutant mice develop a biliary expansion independent of the biliary precursors' proliferation. We also detected transcriptional changes in *Pkhd1* mutant cholangiocytes supporting the importance of FPC signaling in the biliary tract development.

SA-PO487

The Impact of Uraemia on Oxidative Stress Signalling Pathways in the Presence of NPHP Mutations

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Background: Mutations in the *Nek8* gene, encoding a member of the serine/threonine protein kinase family related to NIMA (never in mitosis, gene A), are associated with nephronophthisis (NPHP9); a juvenile form of autosomal recessive cystic kidney disease. With the onset of cystic disease due to the genetic mutation, deteriorating renal health leads to accumulation and circulation of several toxins acting as a double-edged sword. This study investigates any synergistic effect between mutation in the *Nek8* gene and the uraemic toxin, indoxyl sulphate (IS) in driving an unfolded protein response (UPR) as an indicator of cellular stress.

Methods: Hek293 cells transiently expressing wild-type (WT) or H425Y mutant *Nek8* found in human NPHP patients were used. UPR was investigated by monitoring expression of BiP and XBP1s using protein and RNA, respectively, from cells expressing WT and H425Y Nek8 alone, and in the presence of 5mM IS for 8hr (n = 3). Tunicamycin treated Hek293 cells were used as positive control (2.5μg/ml, 4hr). Data was analyzed using 2-way ANOVA.

Results: Overexpression of H425Y *Nek8* did not result in elevating UPR markers (BiP and XBP1s) in comparison to WT. However, presence of IS, resulted in upregulation of BiP in WT by 1.45-fold and H425Y by 1.54-fold (calculated as mean ± SEM, $p < 0.05$, n=3) in comparison to untreated WT. XBP1s was upregulated by 2-fold in treated WT and 3.1-fold in treated H425Y cells (calculated as mean ± SEM, $p < 0.05$, n=3), in comparison to WT untreated cells, such that this increased expression was significantly greater in H425Y *Nek8* mutant cells.

Conclusions: Results from this study indicate that overexpression of the human variant of the *Nek8* mutation, as a standalone, is unable to trigger the UPR pathway. However, in presence of uraemic toxin IS, expressions of both BiP and XBP1s in WT and H425Y cells are elevated. The greater elevation of XBP1s expression in treated H425Y compared to treated WT cells is consistent with the hypothesis that UPR responses triggered by uraemic toxins are potentiated in presence of the *Nek8* mutation. Further studies examining additional markers of UPR and measures of cellular stress will further elucidate the impact of uraemic toxins and their interaction with PKD mutations and their potential impact on kidney function.

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SA-PO488

Proximal Tubular Intracellular Pathways Leading to Cystogenesis and Tubular Damage in Tuberous Sclerosis

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Background: Tuberous sclerosis (TS) is a genetic disorder caused by inactivating mutations in either the *Tsc1* or *Tsc2* genes. These mutations induce mTOR activation resulting in cell growth and tumorigenesis. The renal presentation of TS includes angiomyolipoma and cystic disease and is associated with high morbidity and mortality. The exact molecular mechanisms leading to the tubular cell damage and cyst formation remain poorly understood.

Methods: *Tsc1* was deleted in nephron progenitor cells (NPCs) by mating Six2 *Cre*$^{tg/+}$ /*Tsc*$^{-/+}$ males with *Tsc1*$^{f/f}$ females. Tubular damage and cyst formation were examined by H&E staining of kidney sections and IHC for the proximal tubule marker LTL and the proliferation marker KI-67. c-Myc expression was examined by IHC and western blots. c-Myc - hamartin protein interaction was demonstrated by Co-Immunoprecipitation. Rapamycin (IP, 1 mg/kg every other day) was injected to pregnant females between gestation days E12.5-E16.5. For isolation of proximal tubule cells, kidneys from embryos at gestation date E18.5, were digested using Collagenase/Dispase and cells stained for Prominin1 (a marker for proximal tubule cells) and sorted by flow cytometry.

Results: *Tsc1* knockout in NPCs led to a lethal phenotype of severe renal cystic disease. The tubular damage was demonstrated already at E15.5 with a modified ciliary structure in the cyst lying epithelial cells. The tubular damage and cyst formation were associated with an increased proliferation as measured by Ki-67 staining, as well as c-Myc overexpression. Moreover, c-Myc interacted with hamartin which directly affects *c-Myc* expression. Rapamycin injection throughout pregnancy prevented tubular damage and cyst formation and prolonged offspring life span from P2 to P14 days. Rapamycin also prevented the increase in Ki67 and c-Myc overexpression. To uncover the molecular pathways involved in this process, we isolated embryonic proximal tubular cells from control and *Tsc1* KO mice without or with mTOR inhibition by rapamycin Expression profiling confirmed the increase in *c-Myc* expression, as above. In addition, it identified specific target genes that can contribute to the tubular cell damage and cytogenesis.

Conclusions: Tubular damage and cyst formation in TS correlate with increased cell proliferation and *c-Myc* expression, as well as modifications of specific molecular and biochemical pathways.

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SA-PO489

Pattern of Urinary Inflammatory Markers in Longstanding Type 1 Diabetes with and Without Diabetic Kidney Disease: Results from the Canadian Study of Longevity in Type 1 Diabetes

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Background: Diabetic kidney disease (DKD) contributes to significant mortality and morbidity in type 1 diabetes (T1D). Inflammation is a contributing factor to the pathogenesis of DKD, even during its early stages. Urinary inflammatory markers have been used to determine distinct urinary secretion phenotypes in different stages of DKD in T1D. The nature of urinary inflammatory markers in longstanding T1D is, however, unknown. Our objective was to study changes in urine inflammatory markers within the normal range of albuminuria in longstanding T1D, and to quantify the differential urinary excretion of inflammatory markers in participants with DKD versus those without DKD (resistors).

Methods: A 42-plex human urinary inflammatory markers was analyzed from participants of Canadian study of longevity in T1D of more than 50 years duration (n=74) and compared to age and sex matched comparators (n=73). Normoalbuminuric T1D participants (n=44) were categorized into tertiles of albumin:creatinine ratio (<0.8, 0.8-1.2, 1.2-2 mg/mmol). T1D subjects were grouped as those with and without DKD (n=25 vs. n=49).

Results: A stepwise increase was observed in 27 of 42 urine inflammatory markers across tertiles of normoalbuminuria. Urinary inflammatory marker excretion was *lower* in both DKD and DKD-resistors vs. controls. When comparing participants with DKD vs. DKD-resistors, IL-6, a potent inflammatory cytokine, was significantly different, with higher urinary excretion in DKD versus resistors (0.24±0.25 vs 0.13±0.16, P=0.03).

Conclusions: Urinary excretion of inflammatory markers increases with the degree of albuminuria within the normal range in participants with longstanding T1D. This is consistent with our previous observation in an adolescent T1D cohort with shorter disease duration. Lower urine inflammatory marker excretion in longstanding T1D versus comparators may represent as yet unidentified protective factors in these long-term survivors, irrespective of DKD status, and needs further exploration. DKD participants had higher urinary excretion of IL-6 compared to resistors, highlighting a possible role of inflammation in DKD risk.

SA-PO490

Tim-3 Aggravates Podocyte Injury in Diabetic Nephropathy by Promoting Macrophage Activation via the NF-κB/TNF-α Pathway

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Background: Macrophage-mediated inflammation plays a significant role in the development and progression of diabetic nephropathy (DN). However, the underlying mechanisms remain unclear. Studies suggest that T cell immunoglobulin domain and mucin domain-3 (Tim-3) has complicated roles in regulating macrophage activation, but its roles in the progression of DN are still completely unknown.

Methods: We downregulated Tim-3 expression in kidney (intrarenal injection of Tim-3 shRNA expressing lentivirus or global Tim-3 knockout mice) and induced DN by streptozotocin (STZ). We analyzed the degree of renal injury, especially the podocyte injury induced by activated macrophages in vitro and in vivo. Then, we transferred different bone marrow derived macrophages (BMs) into STZ-induced Tim-3 knockdown mice to examine the effects of Tim-3 on macrophages in DN.

Results: First, we found that Tim-3 expression on renal macrophages was increased in patients with DN and in two diabetic mouse models, i.e. STZ-induced diabetic mice and db/db mice, and positively correlated with renal dysfunction of DN patients. Tim-3 deficiency ameliorated renal damage in STZ-induced diabetes with concurrent increase in protein levels of Nephrin and WT-1. Similar effects were observed in mice with Tim-3 knockdown diabetic mice. Second, adoptive transfer of Tim-3-expressing macrophages,

but not Tim-3 knockout macrophages, accelerated diabetic renal injury in DN mice, suggesting a key role for Tim-3 on macrophages in the development of DN. Furthermore, we found NF-κB activation and TNF-α excretion were upregulated by Tim-3 in diabetic kidneys, and podocyte injury was associated with the Tim-3-mediated activation of the NF-κB/TNF-α signaling pathway in DN macrophages both in vivo and in vitro.

Conclusions: These results suggest that Tim-3 functions as a key regulator in renal inflammatory processes and serves as a potential therapeutic target for renal injury in DN.

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SA-PO491

Prolyl Hydroxylase Domain Inhibitor Protects Against Metabolic Disorder-Related Kidney Disease by Suppressing Monocyte Chemoattractant Protein 1 Expression in Mesangial Cells

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Background: We previously showed that administration of a prolyl hydroxylase domain (PHD) inhibitor, enarodustat, improved glucose/lipid metabolism and restored adiponectin levels in BTBR *ob/ob* mice. It also reduced albuminuria and ameliorated glomerular epithelial and endothelial damage (TH-PO450, ASN Kidney Week 2016). To elucidate the mechanism of renoprotection, we performed transcriptome analysis of isolated glomeruli and *in vitro* experiments using murine mesangial cells.

Methods: Four-week-old male BTBR *ob/ob* mice were divided into vehicle and enarodustat groups. Enarodustat (0.005%; in feed) was administered from 4 weeks of age until euthanasia at 22 weeks. cDNA samples from isolated glomeruli were hybridized using Agilent SurePrint G3 Mouse GE Microarray 8x60K ver. 2.0. SV40 MES 13 cells were stimulated by palmitate with either enarodustat or AdipoRon (adiponectin receptor agonist).

Results: Enarodustat-treated mice tended to exhibit lower blood glucose (HbA1c: 8.9±0.3 vs 8.2±0.2%, p = 0.060) and significantly lower total cholesterol levels (260±26 vs 164±19 mg/dl, p = 0.019) with comparable intake. Plasma adiponectin was increased in enarodustat-treated mice (6.7±0.6 vs 9.8±0.8 ng/ml, p = 0.014). Enarodustat significantly decreased albuminuria (5.9±1.3 vs 2.3±0.5 mg/mgCr, p = 0.017) without affecting GFR. Electron microscopic examination revealed amelioration of glomerular epithelial and endothelial damage in enarodustat-treated mice. Transcriptome analysis of isolated glomeruli revealed reduced expression of monocyte chemoattractant protein-1 (MCP-1) in enarodustat-treated mice. Urinary MCP-1 was decreased in enarodustat-treated mice (317±62 vs 173±25 pg/mgCr, p = 0.064), accompanied by reduced glomerular macrophage infiltration (2.7±0.5 vs 1.1±0.2/glomerulus, p = 0.006). *In vitro* experiments demonstrated that both enarodustat and AdipoRon suppressed palmitate-induced MCP-1 production in mesangial cells. Enarodustat's suppressive effect was abolished when HIF-1α was knocked down by siRNA.

Conclusions: Enarodustat conferred renoprotection through both indirect and direct pathways: improvement in glucose/lipid metabolism and suppression of MCP-1 production in mesangial cells via HIF-1 activation.

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SA-PO492

Effects of Triptolide on Macrophage Function and Phenotype by Modulating Autophagy

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Background: Macrophage infiltration process including capacity of adhesion migration and phenotype transformation are key points in diabetic nephropathy (DN). Triptolide (TP), a classic Chinese immunosuppressor, can alleviate macrophage infiltration effectively in renal inflammatory diseases. However, the relationships between autophagy and Triptolide are unknown. This study aims to investigate whether Triptolide affects macrophage function and phenotype through modulating autophagy.

Methods: RAW264.7 cells were divided into normal (NC) and high glucose treatment groups (HG). Triptolide (10.0ng/mL) was added to respective groups after 24 hours of cell incubated. Western blot and immunofluorescence staining were used to detect the expression of M1 macrophage marker (iNOS, TNF-α), M2 macrophage markers (MR, Arg-1) and autophagy markers (LC3, Beclin-1 and p62). The capacity of macrophage adhesion and migration with and without Triptolide treatment were assessed.

Results: Our study showed that macrophage autophagy was inhibited by HG, which results revealed a decrease expression of LC3 and Beclin-1, but increase expression of P62. Subsequently, the numbers of macrophage adhesion and migration were increased ($P<0.05$). HG induces M1 activation (with increase expression of iNOS and TNF-α) and inhibits M2 transformation (with increase expression of MR and Arg-1)($P<0.05$). However, TP recovers macrophage autophagy level that inhibited by HG (with increase expression of LC3 and Beclin-1, whereas a reduction expression of P62), which lead to inhibition of macrophage adhesion and migration under HG ($P<0.05$). In addition, TP inhibits M1 macrophage transformation (with decrease expression of iNOS and TNF-α) while induces M2 macrophage activation (with increase expression of MR and Arg-1) ($P<0.05$).

Conclusions: HG induces classical activation of M1 macrophages and promotes macrophage adhesion and migration, which is associated with decreased autophagy level. TP promotes M2 macrophage transformation under HG through reducing expression of inflammatory factors may affect macrophage adhesion and migration, which is related to the recovery of autophagy.

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SA-PO493

Decay Accelerating Factor (DAF), a Local Complement Inhibitor, Protects from Streptozotocin (STZ)-Induced Diabetic Nephropathy (DN)

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Background: Glomerular deposition of complement components has been described in individuals with DN. Whether altered expression of DAF on podocytes mediates complement deposition in DN and affects disease severity is unknown.

Methods: We injected STZ (50 mg/kg, i.p.) into male WT and germline $DAF^{-/-}$ BALB/c mice and in B6 $DAF^{fl/fl}$ crossed to podocin Cre-transgenics (the B6 strain is resistant to STZ nephropathy). We serially measured urine albumin/creatinine ratio (ACR) and at 20 weeks we quantified histological injury and stained sections for C3b.

Results: STZ-induced nephropathy was associated with C3b deposition (**Fig. 1A**). In BALB/c mice, STZ caused more severe proteinuria in $DAF^{-/-}$ than in WT animals (**Fig. 1B**), a finding associated with more severe histological changes (**Fig. 1C**). Newly developed $DAF^{fl/fl}$-podocin-Cre^{POS} animals lacking DAF conditionally in podocytes showed albuminuria and histological changes of DN, while $DAF^{fl/fl}$-podocin-Cre^{NEG} did not develop the disease (**Fig. 1D-E**). DAF-deficiency-induced proteinuria correlated with glomerular staining for C3b (**Fig. 1E**), mechanistically implicating DAF-dependent restraint on complement activation in the disease process.

Conclusions: Podocyte-expressed DAF mediates resistance to STZ-induced glomerular injury in B6 mice. In the absence of DAF, STZ-induced kidney injury is propagated by local deposition of complement. These data provide the rationale for further studies addressing a role for DAF/complement in human diabetic nephropathy.

Funding: NIDDK Support

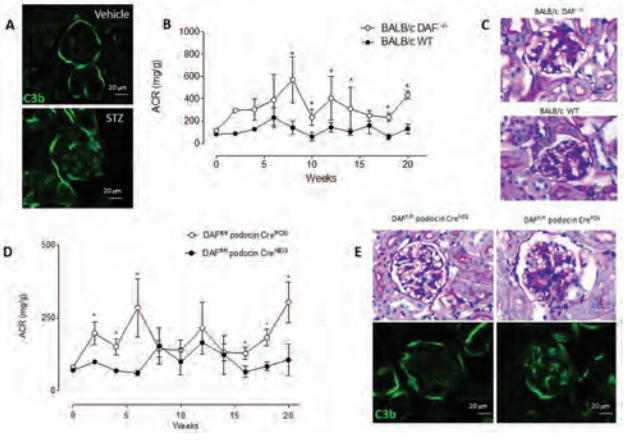

Figure 1. A) C3b deposition in the glomeruli of BALB/c mice at 20 weeks after vehicle or STZ injection. **B)** Serial ACR in WT and $DAF^{-/-}$ BALB/c mice injected with STZ. **C)** H&E staining of kidney tissue of the same mice at 20 wks after STZ injection. **D)** Serial ACR in $DAF^{fl/fl}$ podocin-Cre^{NEG} and Cre^{POS} WT B6 mice injected with STZ. **E)** Renal histology of the same mice at 20 wks after STZ injection. H&E (top) or C3b (bottom) staining. *$P<0.05$ vs. controls at the same time-point.

SA-PO494

The Contact Pathway of Coagulation and Complement Activation Participates in the Progression of CKD in Obese Diabetic Rats

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Background: Diabetic nephropathy is the leading cause of end stage renal disease. Obese diabetic ZS rats become nephrotic at age 12 weeks and develop advanced chronic renal failure (CKD), the hallmark of human diabetic nephropathy, by 24 weeks. We have proposed that episodes of ischemic acute kidney injury (AKI) are key in the progression of CKD. We have also found that, in AKI, disordered clotting and inflammation prevent reflow and promote ongoing ischemia, leading to loss of functional tissue and fibrosis. We hypothesize that activation of the contact pathway of intrinsic coagulation with complement activation is involved in the development of CKD.

Methods: Male lean (L) and obese, diabetic ZS rats were subjected to sham surgery (DS) or bilateral renal ischemia (DI) at 10 weeks of age (total n=24). The rats

were terminated at 28 weeks of age. Renal function and structure were assessed and comprehensive genomic sequencing was performed.

Results: The nephropathy in the diabetic rats postischemia was characterized by renal failure, the sin que non of human disease. The relevant renal transcripts (table) included activation of the contact pathway with increases in F9, 10, 12 and 13 as well as fibrinogen chains A, B, G, platelet MRNA pg1B, F2R, PF4 and C3.

Conclusions: This rat renal transcript profile strongly points to a persistent disorder of renal coagulation and immunity consistent with activation of renal contact pathway. This pathway is a critical juncture of coagulation and inflammation and has multiple therapeutic target opportunities for diabetic nephropathy.

Funding: Veterans Affairs Support, Private Foundation Support

Coagulation Contact Pathway

transcript	Fold change (DI v L)	P value
F12	2.2	≤0.04
F10	2.2	≤0.02
F9	7.7	0.15
F2	--	NS
F7	--	NS
fibrinogen (F) A	1.2	≤0.04
FB	1.5	≤0.04
FC	3.5	≤0.04
F13	1.2	0.005
gp1B	1.8	0.007
F2R	1.2	0.002
PF4	1.3	≤0.007
C3	1.6	0.002
kininogen	1.7	0.003

SA-PO495

Transcriptional Inhibitory Peptides of NFκB and JAK/STAT Pathways Improve Renal Damage in BTBR ob/ob Model

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Background: Diabetic nephropathy (DN) is the leading cause of chronic kidney disease and despite improvements in glycemic and blood pressure control by RAAS inhibitors, end-stage renal disease still remains a growing issue. Chronic inflammation plays a key role in the DN progression, but the underlying mechanisms are largely unknown. Therapeutic modulation of inflammation can be assessed by targeting soluble cytokines, their receptors or the involved cell signaling. In the BTBR ob/ob mice, a model of progressive DN that recapitulates the lesions seen in human DN, we have examined and compared the modulation of NFκB and JAK/STAT, two major inflammatory signaling pathways involved in the pathogenesis of DN. To do that we have employed inhibitory peptides targeting key domains of regulatory proteins such as Nemo-Binding Domain of IKK complex (NBD peptide) and the kinase-inhibitory region of SOCS1 (MiS1 peptidomimetic), which respectively prevent the nuclear translocation of p65 and STAT1/3 transcription factors.

Methods: Six-weeks old BTBR ob/ob mice were given intraperitoneal injections of active peptides (NBD, 6 and 10μg; MiS1, 2 and 4μg), inactive mutant peptides (10μg and 4μg, respectively) and vehicle for 7 weeks (n=6-8/group). At the end of the study, animals were sacrificed to obtain blood, urine and kidney tissue samples for further analysis.

Results: *In vivo* and *ex vivo* imaging revealed efficient peptide delivery and rapid systemic biodistribution, with selective renal metabolization in BTBR ob/ob mice. Although both active peptides significantly reduced albuminuria (ACR) in diabetic mice, a greater effect was observed with MiS1 (decrease 57% with 2μg and 66% with 4μg vs vehicle). Both NBD and MiS1 treatment improved glomerular and tubulointerstitial damage (49% with NBD and 48% with MiS1 vs vehicle) and increased the number of podocytes (46% with NBD and 55% with MiS1 vs vehicle), without changes in metabolic parameters (glycemia and lipid profile) and body weight. Additionally, high dose of MiS1 significantly reduced renal weight in compared to controls.

Conclusions: Transcriptional inhibitory peptides NBD and MiS1 significantly improve albuminuria and alleviate DN in BTBR ob/ob mice, being the inhibition of JAK/STAT pathway more effective in achieving these objectives.

Funding: Government Support - Non-U.S.

SA-PO496

TNF-α Inhibition Protects Against Renal Tubulointerstitial Injury Associated with Suppressing NLRP3 Inflammasome in Diabetic Rats

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Background: Tubular injury exerts a pivotal role in the development of diabetic nephropathy (DN), but current therapies used to treat DN do not combat tubular injury. This study was conducted to investigate whether TNF-α inhibition protected against tubular injury in diabetic rats and examine the associated mechanisms.

Methods: Kidney biopsy tissues, taken from twelve patients with DN and five control subjects, were analyzed. STZ-induced diabetic rats were treated with a TNF-α inhibitor (Humira) for twelve weeks. Renal function, albuminuria, histological injury, renal TNF-α mRNA, and NLRP3 inflammasome was assessed.

Results: Diabetic patients with tubulointerstitial injury presented with higher renal tubular expression of TNF-α mRNA and NLRP3 inflammasome. TNF-α inhibition reduced albuminuria, glomerular injury, and tubular injury in STZ-induced diabetic rats. Importantly, TNF-α inhibition significantly reduced NLRP3 inflammasome in tubules. Moreover, TNF-α inhibition decreased expression of tubular IL-6 and IL-17A, which could activate NLRP3 inflammasome.

Conclusions: TNF-α inhibitor can protect against tubulointerstitial injury associated with suppressing NLRP3 inflammasome in diabetic rats.

SA-PO497

Comparison of Nrf2-Inducing Compounds on Renal Tubule Cell Responses Associated with Diabetes

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Background: The transcription factor Nrf2 regulates cell stress responses. Though many reports suggest the therapeutic potential of Nrf2 inducing compounds in models of kidney disease, use of these agents in clinical settings is limited. Our lab found disparate effects of two Nrf2 inducing compounds, Dimethyl fumarate (DMF) and Protandim (a dietary supplement with no previously reported findings in renal cells), on renal tubule cell morphology and actin cytoskeleton. Due to varying interactions of inducers with the Nrf2 inhibitor, Keap1, and ultimately Nrf2 target gene induction, this study tested the hypothesis that DMF and Protandim differentially regulate renal tubule cell responses associated with disease.

Methods: Human renal proximal tubule cells were treated with 5μg/ml Protandim or 10μM DMF, before or after culture in high glucose (HG; 25mM) concentrations to mimic diabetes. Cell viability was examined via MTT Assay (reduction of (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide [MTT] in viable cells), matrix protein secretion tested via fibronectin immunoblot of cell culture medium, and cell structural proteins (E-Cadherin and α/β tubulin) analyzed via Immunofluorescent staining. Results analyzed by two-way ANOVA with post hoc.

Results: Culture in HG for 24h increased MTT reduction. When cells were treated with inducers for an additional 24h after culture in HG, DMF reversed the effects of HG on MTT reduction. When cells were instead pre-treated with inducers for 24h prior to culture in HG for an additional 24h, DMF again tended to reverse the effects of HG on MTT reduction. Pre-treatment with DMF and Protandim prior to culture in HG showed a trend (P=0.07) of lowering HG-induced fibronectin production. Alternatively, treatment with inducers after HG conditions exhibited the same trend with Protandim but an opposing trend with DMF. Expression of E-cadherin decreased with DMF and protein distribution was more punctate, while α/β tubulin expression and/or polymerization increased with Protandim.

Conclusions: Protandim and DMF differentially regulate renal tubule cell matrix protein secretion and cell structural protein expression and distribution, responses known to be altered with diabetes. The differential effects of Nrf2 inducers on renal cells may lead to different outcomes if/when used for treatment of kidney diseases.

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SA-PO498

Serpinc1/Antithrombin III Protects Against Diabetic Nephropathy

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Background: Antithrombin III (ATIII), encoded by the gene *Serpinc1*, is a serine protease inhibitor in the coagulation cascade and exhibits significant anti-inflammatory properties. Inflammation contributes to the development of diabetic nephropathy. The aim of this study was to investigate the effect of *Serpinc1*/ATIII on diabetic nephropathy.

Methods: ATIII activity was analyzed in patients with diabetic nephropathy. Kidney injury and inflammation were evaluated in streptozotocin (STZ)-treated *Serpinc1* heterozygous knockout (*Serpinc1*$^{+/-}$) rats and in db/db mice treated with adeno-associated virus (AAV, serotype 8) carrying *Serpinc1* gene. The effects of ATIII on macrophages and podocytes treated with high glucose were also examined in vitro.

Results: Diabetic patients with lower ATIII activities had a significantly higher incidence of macroalbuminuria and microalbuminuria (n=328, P<0.05). Albuminuria was exacerbated in STZ-treated *Serpinc1*$^{+/-}$ rats compared with STZ-treated wild-type littermates 8 weeks after diabetes induction (albuminuria 76.1±7.1mg/24hr in *Serpinc1*$^{+/-}$ rats vs 26.6±4.7mg/24hr in wild-type controls, n=6, P<0.05). *Serpinc1* heterozygous knockout significantly exacerbated renal infiltration of macrophages and increased renal NF-κB activity and IL-6 and MCP-1 mRNA abundance in rats with STZ-induced diabetes. *Serpinc1* overexpression in db/db mice reduced albuminuria (273.4±21.7μg/24hr in db/db mice treated with AAV-*Serpinc1* vs 430.9±26.8μg/24hr db/db mice treated with AAV-control, n=6, P<0.05) and attenuated renal infiltration of macrophages and decreased renal NF-κB activity and IL-6 and MCP-1 abundance. Treatment with high glucose (25mM) significantly increased NF-κB activation and IL-6 abundance in macrophages and podocytes in vitro. Treatment with ATIII protein attenuated these effects of high glucose.

Conclusions: In conclusion, *Serpinc1*/ATIII reduces inflammation and attenuates diabetic nephropathy.

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SA-PO499

Immunosenescence in Type 2 Diabetic Patients with Chronic Renal Disease

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Background: Immunosenescence is an important challenge for an aging population. It is known that patients with end-stage renal disease suffer from immunosenescence and premature T cell aging but whether such changes occur in diabetic patients with less severe chronic renal disease is unclear.

Methods: 832 patients with type 2 diabetes with different levels of renal function were recruited in this study. Immunosenescence was analyzed by staining peripheral blood with two immunophenotyping panels and analyzed by multicolor flow cytometry.

Results: Out of all the 832 participants, there were 171 patients with stage 3 CKD and 46 patients with 4/5 CKD. Compared to patients with eGFR>60 ml/min, patients with more severe CKD showed progressive decreased total CD3+ T cell and CD4+ and CD8+ T cell, but not monocyte numbers. In addition, immunosenescence, as defined by various phenotypic markers, showed significant upregulation in both stage 3 and stage 4/5 patients. However, immunosenescence was not associated with proteinuria level nor worse glucose control. In age and sex adjusted regression models, stage 3 CKD patients already exhibited significant elevated percentages of CD28-, CD127- and CD57+ cells among CD8+ T cells when compared to patients with eGFR>60 ml/min. In addition, stage 3 CKD patients exhibited depressed HLA-DR and CX3CR1 expression in specific monocyte subpopulations.

Conclusions: Level of immunosenescence is not significantly associated with proteinuria nor glucose control in type 2 diabetes patients. Both T cell and monocyte compartment exhibit characteristics of immunosenescence during renal function decline, starting from stage 3 CKD.

SA-PO500

Targeted Transgenic Expression of Catalase to Mitochondria Reduces Reactive Oxygen Species and Ameliorates Diabetic Nephropathy in BTBR ob/ob Mice

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Background: Diabetes induced mitochondrial dysfunction from increased generation of reactive oxygen species (ROS) is pathogenic for diabetic complications including diabetic nephropathy (DN). Catalase is a major scavenger of ROS and prevents tissue damage from oxidative stress. To explore pathogenic mechanisms and to test a targeted ROS reduction strategy for treating DN, we created diabetic BTBR *ob/ob* mice with inducible transgenic human catalase expressed only in mitochondria (mCAT) to determine the efficacy of reducing mitochondrial ROS in a murine model of DN.

Methods: Transgenic Rosa 26 mice containing loxP-stop-loxP-mCAT and tamoxifen-inducible Cre mice (B6.129-Gt(ROSA)26Sor$^{tm1(cre/ERT2)Tyj}$/J) were backcrossed into the BTBR mouse strain. The heterozygous *ob*/+ mice of each strain were crossed to obtain *ob/ob* double transgenic mice. At 16 weeks of age, the mCAT gene expression was induced by oral administration of tamoxifen and the induced mice were referred as mCAT *ob/ob*. The double transgenic mice without tamoxifen treatment were used as control group (Rosa *ob/ob*). Fasting glucose levels were monitored and timed (6 hour) urine samples were collected at weeks of 18 and 24. At the end of the study (24wks), mice were sacrificed and blood and organs harvested.

Results: Both mCAT *ob/ob* and Rosa *ob/ob* were hyperglycemic (499.2 vs 566.7mg/dl) and obese. mCAT *ob/ob* mice exhibited a significant decrease in albumin-creatinine ratio (ACR) compared with control mice (196.1 vs 305.9 ug/mg, $p < 0.05$). Morphometry revealed a marked reduction of mesangial matrix accumulation assessed by collagen IV staining (15.4 vs 22.3% glomerular tuft area, $p < 0.01$). mCAT expression also reduced the extent of mesangiolysis vs. control mice (20.5 vs 29.4% of glomeruli, $p < 0.05$). The levels of urinary 8OHdG (a DNA/RNA marker of oxidative stress) were also reduced in mCAT *ob/ob* mice vs. Rosa *ob/ob* (72.9 vs 129.2 ng/mg creatinine, $p < 0.05$). Measures of podocyte density are pending.

Conclusions: Reduction of ROS specifically in mitochondria by targeted expression of catalase in BTBR *ob/ob* mice ameliorates albuminuria and dramatically improves mesangial expansion and mesangiolysis, thereby offering a new approach for DN therapeutics.

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SA-PO501

Lysyl Oxidase-Like 4 Acts as a Deacetylase to Regulate Mitochondrial Respiration in Diabetic Kidney Tubule

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Background: Dysfunctions in mitochondrial respiration and energy production are quite evident in the pathogenesis of diabetic kidney disease; however, the underlying mechanism remains unclear. Acetylation negatively regulates the activity of enzymes involved in the process of mitochondrial respiration. With the N-terminal scavenger receptor cysteine-rich (SRCR) repeats, lysyl oxidase-like 4 (LOXL4) may act as a deacetylase. In the present study, we aimed to investigate whether the LOXL4 regulates enzyme acetylation and mitochondrial respiration of renal tubular cells in diabetes.

Methods: Kidney biopsy samples were obtained from patients without or with diabetes. Protein acetylation was determined by mass spectrometry of isolated kidney tubule from control and STZ-induce diabetic mice. Mitochondrial respiration was measured by oxygen consumption rate (OCR) and extracellular acidification rate (ECAR). Protein expression and localization of LOXL4 were examined by western blot and immunofluorescence staining. Expression of LOXL4 was modulated by plasmid or siRNA in primary cultured tubular epithelial cells to determine the effect of LOXL4 on acetylation.

Results: In kidney tubule of diabetic mice, the acetylation was upregulated and downregulated in 588 and 105 proteins, respectively. Besides cyroplasm, abundant of these acetylated/deacetylated proteins locate in mitochondria. Bioinformatics analysis suggested that these proteins are evolved in mitochondrial respiration and probably regulate metabolic process and energy production. Consistently, mitochondrial respiration capacity was impaired in tubular cells treated with high glucose. The expression of LOXL4 was markedly increased in kidney tubule of both diabetic patients and mouse model. Moreover, immune staining showed the colocalization of LOXL4 and mitochondria. Modulation of the expression of LOXL4 regulated the acetylation of mitochondrial proteins and affected mitochondrial respiration and energy production.

Conclusions: Collectively, lysyl oxidase-like 4 may regulate the acetylation/deacetylation of mitochondrial proteins and protects mitochondrial respiration and function in diabetic kidney tubule.

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SA-PO502

CD248 Modulates Unfolded Protein Response in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is a major cause of end-stage renal disease and a growing public health burden. Recently DN has been linked with maladaptive unfolded protein response (UPR) and sterile inflammation, but the underlying mechanism triggering the glucose induced maladaptive UPR and sterile inflammation remain poorly defined. We focused on CD248, a type I transmembrane glycoprotein expressed by pericytes, such as glomerular mesangial cells and tubulointerstitial fibroblasts whose expression correlates with renal fibrosis in chronic kidney disease. Hence, the aim of our study is to investigate the role of CD248 in regulating UPR and sterile inflammation in DN.

Methods: C57Bl/6 (WT) mice and CD248$^{-/-}$ mice were used for the study. Diabetes was induced using streptozotocin (STZ) and samples were obtained after 26 weeks. Albuminuria (UACR), PAS staining and WT-1 immunostaining of kidney sections were done to study development of renal disease. To evaluate mechanistic insights, genetic knockdown or overexpression of CD248 was done followed by immunoblotting and co-immunoprecipitation approaches.

Results: We detected a marked increase of renal CD248 expression after 26 weeks in diabetic mice versus nondiabetic controls. CD248 knockout protected mice from diabetes induced albuminuria, podocyte loss and mesangial expansion. In vitro, shRNA mediated CD248 knockdown in renal pericytes prevented high glucose induced maladaptive UPR signaling (lower levels of CHOP, ATF4, cATF6α), inflammasome activation (lower levels of NLRP3, cleaved IL-1β), SMAD2/3 phosphorylation and mTORC1 activation (lower levels of p-Raptor and p-p70S6Kinase). Vice versa, overexpression of CD248 amplifies these glucose induced cellular responses. Mechanistically, the chaperone HSP90 interacts with the transmembrane receptor CD248 and may thus transduce extracellular glucose-dependent stress signals to the ER via IRE-1α.

Conclusions: CD248 modulates hyperglycemia induced UPR, inflammasome activation and renal fibrosis. HSP90 appears to serve as the cytosolic mediator linking the receptor CD248 with ER membrane proteins such as IRE1α. Our findings identify pericyte-specific CD248 as a potential target for therapeutic interventions of DN.

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SA-PO503

Spexin: Is It Another Bystander or a New Biomarker in Diabetic Kidney Disease?

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Background: Spexin is a highly conserved active neuropeptide that has been recently identified in the involvement of controlling appetite and energy balance. Although few is known regarding to the role of spexin, spexin level was noted to be significantly lower in obese and diabetic patients. Recent study has shown that spexin mRNA was significantly detected in human kidney tissue. Therefore, we investigated the expression of spexin in diabetic kidney disease in clinical and experimental model.

Methods: Serum samples from patients who were diagnosed as type 2 diabetes were examined for circulating spexin level using commercially available ELISA kit (Spexin/neuropeptide Q(NQP)). Serum and renal expression of spexin was examined in experimental mice models; ü1) normal control, 2) db/db mice, 3) fat chow diet induced obesity mice and 4) non-diabetic UUO-induced mice.

Results: Total 89 diabetic patients participated in the study. The circulating spexin level was significantly increased in patients on dialysis (both peritoneal and hemodialysis) compared to patients with estimated GFR ≥60 ml/min/1.73m^2. In diabetic patients with chronic kidney disease stage 1 to 3, spexin level was significantly increased in patients with overt proteinuria (urine protein to creatinine ratio). There was significant correlation between serum spexin and proteinuria, however no correlations were observed in age, gender, BMI, blood glucose, lipid profiles and HOMA-IR or estimated GFR with serum spexin level. Spexin was detectable in serum and kidney tissue of murine models. In experimental mice of obese type 2 diabetes (db/db), serum spexin level was significantly increased, whereas its renal expression was not significantly different compared to normal and obstructed kidney control.

Conclusions: The spexin expression in the kidney from experimental mice and circulating spexin level in diabetic patients may indicate that spexin may be a biomarker of diabetic kidney disease. However, further study is needed to elucidate the specific role and mechanism of spexin in metabolic kidney disease.

SA-PO504

Hyperinsulinemia Contributes to High Fat-Induced Kidney Injury in Mice

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Background: The mechanism of obesity-induced kidney injury is not well understood. We hypothesized that hyperinsulinemia activates kidney proximal tubular epithelial insulin receptor (IR) and contributes to obesity-induced kidney injury in high fat diet fed mice.

Methods: We generated kidney proximal tubule IR knock out (KPTIRKO) mice by crossing IR lox mice with Sglt2-Cre mice. We administered normal fat diet (NFD) or high fat diet (HFD) to 5-8 month old male Control and KPTIRKO mice for 4 months (n=9-10/group, 2 batches) and evaluated changes in albuminuria, blood pressure (BP), renal matrix proteins, signaling pathways and intraperitoneal GTT.

Results: KPTIRKO mice grew normally. In KPTIRKO mice renal cortical IR expression was decreased by more than 60% although it was unchanged in other tissues. Serum insulin, creatinine, urinary albumin to creatinine ratio (ACR) and renal cortical IGF-1 receptor expression in KPTIRKO mice were similar to Controls. On HFD, food consumption, increase in body weight and serum cholesterol were similar in Control and KPTIRKO mice. HFD increased the following in Control mice: renal cortical content of tyrosine phosphorylated IR indicating IR activation, matrix proteins laminin, fibronectin and collagen I, urinary and renal cortical KIM-1 content, urinary ACR, systolic BP; these changes were significantly ameliorated in HFD-fed KPTIRKO mice ($p<0.05$-0.001). HFD activated renal cortical IR-Akt axis in Control but not KPTIRKO mice. HFD increased serum insulin and C-peptide levels in Control but not in KPTIRKO mice. To explore if improved glucose tolerance was the reason for lack of hyperinsulinemia in KPTIRKO mice on HFD, GTT was done. KPTIRKO mice on NFD had lower fasting glucose and improved glucose tolerance; however, glucose intolerance was similar in Controls and KPTIRKO mice on HFD.

Conclusions: HFD-induced hyperinsulinemia activates renal cortical IR and contributes to kidney injury manifesting as albuminuria, elevated BP, and matrix protein accumulation in male mice. These results provide a mechanistic explanation for obesity-induced kidney injury. The reason for lack of hyperinsulinemia in HFD fed KTPTIRKO mice needs further investigation.

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SA-PO505

Deletion of Peroxisome-Proliferator-Activated Receptor δ in Mice Promotes High-Fat-Diet-Induced Renal Injury

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Background: Peroxisome proliferator-activated receptor δ (PPARδ), the least studied member of the PPAR group in the nuclear receptor superfamily, plays a crucial role in cellular metabolic functions and other physiological processes. Recent evidence highlights the therapeutic potential of PPARδ agonists in obesity, dyslipidaemia, insulin resistance/type 2 diabetes. However, little is known the role of PPARδ in the pathogenesis of obesity related renal injury. It is reported that *PPAR*δ gene is a primary target of 1a,25-dihydroxyvitamin D3 (calcitriol), the aim of this study is to investigate the effects of calcitriol on the role of PPARδ in HFD-induced renal injury.

Methods: Diet-induced obese (DIO) micewere generated on *PPAR*δ KO, age-matched *PPAR*δ wildtype (WT) littermates at the 6 weeks of age and were fed with high-fat-diet (HFD) for 12 weeks. In addition, 12 weeks after HFD feeding, mice were treated with 1a, 25-dihydroxyvitamin D3 (calcitriol) or vehicle by intraperitoneal injection at the dosage of 100 ng/kg three times a week for 4 weeks. The effects of calcitriol on the role of PPARδ in HFD-induced renal injury were evaluated by real-time quantitative polymerase-chain-reaction (qRT-PCR), western blot analysis, as well as a histological examination.

Results: Compared with control mice on a normal diet, DIO *PPAR*δ WT mice exhibited significant renal injury, which were further exacerbated in DIO *PPAR*δ KO mice: including 1) obviously increased expression of kidney injury molecule-1 (KIM-1), as well as histological injury revealed by Masson's Trichrome &PAS Staining; 2) marked up-regulation of pro-inflammatory cytokines TNF-a; 3) exacerbated renal fibrosis as demonstrated by significantly up-regulation of fibrotic matrix proteins deposition, such as a-smooth muscle actin (a-SMA), collagen 1 and fibronectin. However, all these changes were dramatically attenuated after administration of calcitriol.

Conclusions: In conclusion, deletion of PPARδ promotes HFD-induced renal fibrosis and inflammation, and these changes could be partially attenuated by calcitriol treatment. Targeting *PPAR*δ gene may offer a new treatment approach for obesity-related renal injury.

SA-PO506

Increased Expression of NMN Transporter in the Kidneys in Diabetic Nephropathy

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Background: In diabetic nephropathy (**DN**) and aging kidney, renal tissue concentration of nicotinamide adenine dinucleotide (**NAD$^+$**) decreased, which is associated with renal dysfunction and albuminuria. The regulatory systems of NAD$^+$ and its precursor, nicotinamide mononucleotide (**NMN**) are considered to play a crucial role in the maintenance of tissue NAD$^+$ levels and the pathogenesis of DN. Recent study identified novel **NMN transporter,** Solute Carrier Family 12 Member 8 (**Slc12a8**). However, the role and location of NMN transporter in the kidneys as well as diabetic kidney remain unclear.

Methods: Type 2 diabetic db/db and **control db/m** mice were given regular chow diet ad libitum and euthanized at 24 weeks of age. We performed immunohistochemistry (IHC) of renal Slc12a8. Further, we measured serum and urinary NAD$^+$ metabolites at 24 weeks of age. We evaluated renal NAD$^+$ loss by calculating urine NAD$^+$ to creatinine ratio (**NAD$^+$/Cr**). NMN resorption was evaluated by the calculation of the fractional excretion of NMN (**FeNMN**).

Results: Tissue concentration of NAD$^+$ decreased in db/db mice as compared to that in db/m mice at the age of 8 weeks, although that of NMN was not different. Urine NAD$^+$/Cr ratios were higher in db/db mice than in db/m mice, suggesting an increased renal loss of NAD$^+$ in db/db mice. IHC revealed weak staining of Slc12a8 in the glomerulus and proximal tubules, while strong staining in the distal tubules. Slc12a8 expression was higher in db/db mice than in db/m mice. While the expression of Slc12a8 was detected mostly on the **basolateral** side in db/m mice, it was expressed on both **apical** and basolateral side in db/db mice. These findings suggested the increased translocation of Slc12a8 towards apical side of distal tubular cells in DN. Consistently, FeNMN was lower in db/db mice than that in db/m mice, indicating increased resorption NMN at the tubules in db/db mice.

Conclusions: Novel NMN transporter, Slc12a8 was dominantly expressed in the distal tubules. In DN, Slc12a8 translocation to apical side was enhanced, which can be the compensatory mechanism for NAD$^+$ loss in diabetic mice.

SA-PO507

Molecular Mechanism of Regulatory Effect of Vitamin D Receptor on Mitophagy of Proximal Tubular Epithelial Cells in Diabetic Nephropathy

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Background: Vitamin D receptor (VDR) is a kind of nuclear transcription factor, which is widely expressed in proximal tubular epithelial cells (PTECs). Our previous study found that VDR has anti-inflammatory and anti-fibrotic effects. Given the previous evidence that the expression of VDR decreased in PTECs of DN patients and VDR can regulate the mitophagy, how VDR contribute to the development of renal tubulointerstitial mitophagy in diabetic nephropathy is not entirely clear. In this study, we tend to investigate the effect of VDR on mitophagy dysfunction in diabetic nephropathy and its molecular mechanism.

Methods: VDR-knockout mice in C57BL/6 background were generated and streptozotocin (STZ)-induced diabetic mice were used in these experiments. Mitophagy in the PTECs was observed by electron microscope, and the pathological changes of the kidneys were delineated by periodic acid–Schiff (PAS) staining. Immunohistochemistry and Western blotting were performed to identify the expression of VDR, Collagen 1, Fibrinogen, α-SMA,TGF-β, Drp1, mitofusin 2, Pink1 and Bnip3.

Results: 1. The blood glucose of the mice was significantly increased in the first week after the injection of STZ. 16 weeks after STZ injection, PAS staining revealed the glomerulomegaly and renal tubular injury of diabetic mice, suggesting that STZ-induced diabetic mice were generated successfully. 2. The accumulation of collagen in glomeruli and tubulointerstitium revealed the occurrence of renal fibrosis in the STZ-induced mice. The expression of Collagen 1, Fibrinogen and α-SMA in wild-type diabetic mice was lower than that in VDR-KO diabetic mice, thus confirming the anti-fibrotic effect of VDR in the pathogenesis of DN. In the diabetic model induced by STZ, there is severer mitophagy dysfunction in VDR-KO mouse than that in the wide type diabetic mouse, which indicates that VDR may regulate the mitophagy in diabetic nephropathy.

Conclusions: VDR can control the renal fibrosis and the progression of diabetics by regulating the mitophagy. VDR overexpression may act as a new target for the prevention and treatment of DN.

Funding: Government Support - Non-U.S.

SA-PO508

Activation of Vitamin D Receptor Attenuates High Glucose-Induced Cellular Injury Partially Dependent on CYP2J5 in Murine Renal Tubule Epithelial Cell

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Background: Vitamin D receptor (VDR), have renoprotection effect against diabetic nephropathy (DN). Paricalcitol is a VDR activator. Epoxyeicosatrienoic acids (EETs) are cytochrome P450 (CYP) protecting against diabetes and DN. Our objective is to investigate whether activation of vitamin D receptor protect nephropathy partially dependent on CYP2J5 in murine renal tubule epithelial cell.

Methods: Adult male wile type (WT) and *Vdr*$^{-/-}$ mice were used,. STZ-induced diabetic nephropathy model was established and paricalcitol was injected. 12 weeks after the STZ injection, mice were sacrificed. Kidneys were collected for histology and immunohistochemistry staining. Murine kidney proximal tubule epithelial cell line (BU. MPT) was used in this study, incubated with high glucose and paricalcitol. supernatent, mRNA and protein were collected. Real-time PCR and Western blot were used to detect the RNA and protein levels.

Results: 1. STZ, VDR-/-,VDR-/-+STZ mice tubulointerstitial injury were more severe than WT, the expression of CYP2J5 and VDR decreased. But STZ mice treated with paricalcitol had attenuated tubulointerstitial injury and increased CYP2J5 and VDR than STZ 2. Activation of VDR attenuated high glucose-induced cellular injury in renal tubular epithelial cells partially though up-regulating CYP2J5 expression. High glucose treatment strongly reduced the CYP2J5 expression and the synthesis of 14,15-EET in murine renal tubular epithelial cells. Supplement of 14,15-EET significantly reduced the lactate dehydrogenase (LDH) release induced by high glucose in renal tubular epithelial cells. Treatment with an activator of VDR, paricalcitol, restored the expression of CYP2J5 reduced by high glucose treatment in renal tubular epithelial cells. And we found that paricalcitol attenuated cellular injury induced by high glucose partially dependent on the up-regulation of CYP2J5 in renal tubular epithelial cells 3. WT and a mutant-Cyp2j5 luciferase reporter plasmid were constructed. We found that paricalcitol treatment (0.1 mM) significantly increased relative luciferase activity in the WT plasmid, compared with the pGL3 basic plasmid

Conclusions: Activation of VDR attenuates high glucose-induced cellular injury partially dependent on CYP2J5 in murine renal tubule epithelial cells and paricalcitol may represent a potential therapy for DN.

SA-PO509

The Potential Therapeutic Effect of Active Vitamin D Supplementation in Preventing Initiation and Progression of Diabetic Nephropathy in a Diabetic Mice Model

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Background: Diabetiv Nephropathy (DN) is characterized by morphological changes in podocytes and proximal tubule cells (PCT), and are characterized by hyperfiltration, albuminuria, glomerular sclerosis to ESRD. DN mice suffer from an active vitamin D deficiency, which results in podocytopathy and PCT injury. We hypothesize that supplementation of **active vitamin D paricalcitol(P**) to DN mice may slow the development & progression of DN.

Methods: Renal injury in diabetic mice with and without **P** treatment (TX), and control mice, were evaluated for albuminuria, blood Creatinine and BUN levels. The kidney biopsies were subjected to PAS & IHD staining: of **vitamin D receptor (VDR) expression,** villin, nephrin, podocin and fibronectin proteins. We used 4 groups of mice:**(1)** CON-wild type **(2) DM group** after DM induction with STZ were treated with vehicle for 12 weeks.**(3) DM+P after STZ group** - diabetic mice treated with P **before** the onset of DN, and one week after DM induction, i.p. 3 times a W for 12 wkss, **(4) DM+P group** - 3 weeks **after** diabetes induction, the mice were treated with P i.p. 3 times a W for 12 wks.

Results: 1. VDR expression increased in DM+P after STZ (1.08±0.13) compared with DM+P group (0.59±0.13), **2**, **Renal villin expression of DM mice** was significantly decreased (0.53±0.09) compared with control mice (1.14±0.05, p<0.001), but **P** TX before and after the onset of DN (DM+P and DM+P after STZ groups) restored villin expression, **3. P** TX (DM+P and DM+P after STZ) **decreased fibronectin expression. 4. Nephrin expression levels were decreased in DM group** (0.5±0.11) compared with control group (1.03±0.09). **P treatment** (DM+P, DM+P after STZ) restore nephrin levels to normal (1.26±0.22) VS (0.99±0.04) respectively. 5. Renal expression of podocin was decreased in DM mice compared with control mice. **P** TX restore podocin expression in DM+P after STZ TX.

Conclusions: 1. Significant protective effect of Paricalcitol treatment in preventing the initiation and progression of DN in STZ-induced diabetic mice mode. 2. Increasing the expression of VDR and restoration of nephrin-podocine proteins with decreasing fibronectin, prevent the progression of DN **3**. Our findings can be proposed as a new approach to deal with DM complications by selective Vitamin D supplementation in early stages of DN.

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SA-PO510

Downregulation of EHHADH and Tubular Dysfunction in Diabetic Nephropathy

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Background: The pathophysiology of diabetic nephropathy (DN) is not well understood. In a previous study, we analyzed renal cortical tissue from the db/db/eNOS$^{-/-}$ murine DN model by RNA-seq, identified altered novel genes with human orthologs, and assessed mRNA expression of these genes in human DN versus control. Ehhadh was downregulated in human DN. Ehhadh encodes for a peroxisomal protein that catalyzes the second and third committed steps in the peroxisomal beta-oxidation pathway (PBO), which is responsible for oxidizing long-chain and complex fatty acids. We investigated the potential role of Ehhadh in DN.

Methods: Biopsies with mild (n=20), moderate (n=19), or severe (n=20) DN were compared to normal controls (n=20). Ehhadh protein expression and localization were scored and compared to morphologic lesions, clinical data, and follow-up. Multiplex analyses examined the relationship of Ehhadh and KIM1 expression. Subcellular localization of Ehhadh and peroxisomal membrane protein ABCD3 was analyzed via super-resolution microscopy (SIM). Ehhadh mRNA expression in a high-glucose assay of cultured human proximal tubular cells (PTC) was assessed by qPCR.

Results: In normal controls, Ehhadh protein was strongly expressed in tubular epithelium and was significantly reduced in moderate and severe DN groups versus control. Downregulation of tubular Ehhadh significantly correlated with increased interstitial fibrosis (r^2=0.587, p<0.0001), increased serum creatinine (r^2=0.488, p<0.0001), and increased UPCR (r^2=0.327, p<0.005). Ehhadh expression correlated positively with renal survival (p=0.054). Ehhadh exhibited complementary expression with KIM1 with no co-localization in tubules. SIM analyses of Ehhadh and ABCD3 indicated that tubular downregulation of Ehhadh in DN precedes loss of peroxisomal membranes. Ehhadh transcription was significantly downregulated in PTC under high-glucose conditions.

Conclusions: Ehhadh downregulation is associated with tubular injury and worse renal survival in human diabetic nephropathy. We postulate that the dysmetabolism caused by downregulation of Ehhadh and PBO promotes increased levels of complex lipid products in PTC, possibly contributing to progression and tubulointerstitial fibrosis.

Funding: Other NIH Support - R24 Grant

SA-PO511

Cell Proliferation of Proximal Tubular Epithelia Leads to Renal Hypertrophy in Early Diabetic Nephropathy

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Background: The initial phenotypes of diabetic nephropathy are renal hypertrophy accompanying an increase in GFR, resulting in an increase in glucose reabsorption at proximal tubules. However, the detailed morphological changes and underlying mechanisms are not fully understood.

Methods: To investigate the proximal tubule-specific phenotypes in type 2 diabetic mice, we generated transgenic db/db mice carrying tamoxifen-inducible proximal tubule-specific tdTomato reporter genes (SLC34a1CreER/R26tdTomato). We isolated tubular epithelial cells by FACS from mice in which the proximal tubular epithelium was exclusively labeled by tdTomato, and evaluated the tubule-specific molecular mechanisms of the development of diabetic nephropathy. To assess the proliferation of tubular epithelial cells, we also performed lineage tracing analysis of single-labeled proximal tubular epithelial cells in db/db mice by low-dose tamoxifen injection.

Results: Histological analysis of 18-week-old diabetic mouse kidneys revealed expansion of the renal cortex and enlargement of the cross-sectional area in each tubule. The protein/DNA ratio, a marker of cellular hypertrophy, was not increased in FACS-isolated tubular epithelial cells from the diabetic mouse kidney. qPCR analysis revealed that SGLT2 and GLUT2 expression in isolated tubular epithelial cells was not increased in diabetic mice. Lastly, lineage tracing analysis of single-labeled proximal tubular epithelia cells revealed significant clonal expansion of the labeled epithelium in db/db mice, suggesting increased cell proliferation during the observational period.

Conclusions: Our study using a proximal tubule-specific reporter demonstrated that cell proliferation, rather than cellular hypertrophy, plays a role in the enlargement of the tubular lumen and subsequent kidney hypertrophy in early diabetic nephropathy. This suggests that the increase in glucose reabsorption under diabetic conditions is due to the proliferation of proximal tubular epithelial cells, which predominantly express SGLT2, and not to the overexpression of SGLT2 in individual cells.

SA-PO512

VEGFR2 Blockade Improves Renal Damage in the Experimental Model of Diabetic Nephropathy

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Background: Chronic inflammation is the main feature of progressive kidney disease, including Diabetic Nephropathy (DN). Among the potential therapeutic targets of renal damage induced by diabetes, a pathogenic role for Gremlin has been described. Recent

studies in our group have described that Gremlin activates the vascular endothelial growth factor-2 receptor (VEGFR2) associated with renal inflammation. The animal model BTBR ob/ob has been widely used for the study of DN, since it develops histological characteristics that resemble the human DN. In these mice, Gremlin expression increases at week 8 and remains elevated until week 20 of life. This model offers an opportunity to study the mechanisms that could lead to more specific therapies that lead to the regression of the DN. Our aim was to evaluate the role of VEGFR2 blockade in the progression of the DN in the BTBR ob/ob model.

Methods: In this animal model, VEGFR2 was blocked with the pharmacological inhibitor SU5416. The inhibitor was administered to mice of 15 weeks of life, 3 times a week for 5 weeks and then sacrificed (0.1 mg per mouse, i.p). The parameters of weight and glycemia, the ratio of Albumin/Creatinine (ACR) in urine, glomerular and tubulointerstitial damage at the microscopic and ultrastructural level, as well as inflammatory and podocyte damage markers by real-time PCR and IHC were evaluated in non-diabetic, diabetic and diabetic SU5416-treated groups. (n:6-8 animals per group).

Results: VEGFR2 blockade improved the ACR during all period of study compared to diabetic group. At glomerular level, SU5416-treated mice showed lower cellularity and lower mesangial matrix expansion and decreased thickening of the glomerular basement membrane. Also, in the tubulointerstitial compartment, the inflammatory infiltrate decreased and some foci of tubular atrophy were observed. In response to VEGFR2 blockade, there was a downregulation in the kidney damage markers (KIM1 and Ngal), in podocyte markers WT-1, Nphs-1 and Nphs2 and in the pro-inflammatory factors MCP-1, Rantes, IL-17A and IL-6. However, Gremlin levels were not affected. Decreased inflammatory infiltrating cells in SU5416-treated mice was histologically observed.

Conclusions: These data show that the Gremlin/VEGFR2 axis would be involved in kidney damage mediated by diabetes and could be a new therapeutic target for ND.

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SA-PO513

Soluble Klotho Anchors TRPV5 on Membrane Independent of FGFR1 by Binding TRPV5 and Galectin 1 Simultaneously

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Background: Hypercalciuria is one of the early disturbances of diabetic nephropathy (DN). This is partially due to decrease of renal transient receptor potential vanilloid type 5 (TRPV5) expression, which is responsible for renal calcium reabsorption. Soluble klotho was previously known to increase TRPV5 by cleaving sialic acid, causing TRPV5 to bind to a membrane protein galectin 1. However, recent study showed that soluble klotho binds to a2-3-sialyllactose - where sialic acid is located - on TRPV5, rather than cleave it.

Methods: We injected recombinant soluble klotho protein(rKL) into db/db and db/m mice for 8 weeks, and collected urine and the kidney. We treated rKL, AZD4547 (FGFR1 inhibitor), and OTX008 (Galectin 1 inhibitor) to mouse distal tubular cells, with or without 30mM high glucose (HG) exposed.

Results: db/db mice showed increased renal calcium excretion, and decreased renal TRPV5 expression. rKL treatment reversed this change. In vitro, TRPV5 expression in distal tubular cells decreased in HG situation, and rKL successfully upregulated TRPV5 with or without AZD4547. Also, immunofluorescence for klotho, TRPV5 and glaectin 1 are the same location in distal tubule cells, suggesting that klotho binds to both TRPV5 and galectin 1. However, when AZD4547 and OTX008 are both treated, rKL failed to increase TRPV5 in HG condition.

Conclusions: rKL binds to both TRPV5 and galectin1, thereby tethers TRPV5 on apical membrane. This soluble klotho-mediated holding TRPV5 on apical membrane is FGFR1 independent, but galectin 1 dependent.

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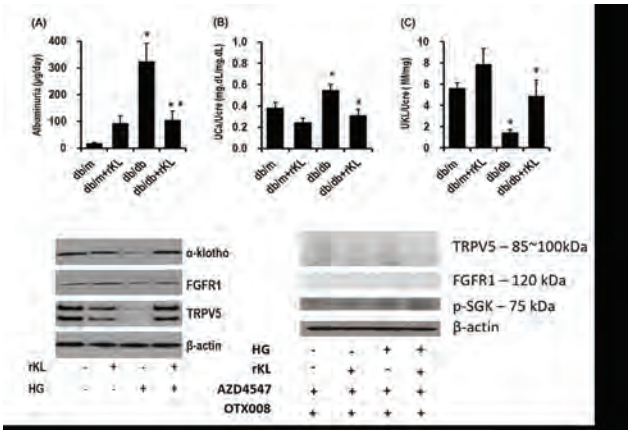

in db/db mice, rKL increased renal TRPV5 and decreased urinary calcium excretion. In vitro, rKL failed to increase TRPV5 when both FGFR1 and galectin 1 are inhibited.

SA-PO514

Function of Protein X as a Novel Regulator of NADPH Oxidase 4 in Diabetic Nephropathy

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Background: Several lines of evidence indicate that NADPH oxidase (Nox)-derived excessive reactive oxygen species (ROS) play important role in diabetes complication such as diabetic nephropathy. It has been reprted that Nox4 isozyme is major source of ROS in pathological stage of kidney. Nox4, the isozyme highly expressed in kidney, is known to be constitutively active, but its activity is associated with diabetic nephropathy. We recently identified a novel regulator of Nox4, PX which interacts and activates Nox4. Here, we show that association of Nox4 with PX is involved in chronic kidney disease.

Methods: Eight week-old male wild type (WT), PX KO, Nox4 KO mice were subjected into the development of type I diabetes by injection of streptozotocin (STZ). Kidney tissues of the mice were analyzed with histological analyses, PAS-staining and collagen with immunohistochemistry (IHC) staining. Oxidative stress was assessed with urinary 8-isoprstane. Furthermore, renal functions were investigated by measurement of urinary albumin excretion and creatinine clearance rate (CCR).

Results: Mesangial expansion as a marker of glomerulosclerosis was reduced in PX KO and Nox4 KO mice. Albumin to creatinine ratio (ACR), urinary albumin excretion, and blood urea nitrogen (BUN) of protein X KO and Nox4 KO mice markedly decreased, compared to diabetic WT. Extracellular matrix (ECM) including collagen type I, type IV, TGF-β and α-SMA were significantly reduced in PX KO and Nox4 KO mice. Levels of H_2O_2 and urinary 8-isoprostane were suppressed in PX KO and Nox4 KO mice, compared to diabetic WT. To investigate clinical significance of PX-induced H_2O_2 generation, we evaluated the level of PX expression in type II diabetic patients. Interestingly, significantly elevated levels of PX were seen in type II diabetic patients. It strongly suggests that PX is involved in renal damage in type II diabetic patients.

Conclusions: In conclusion, PX as a Nox4 regulator plays important role in progression of diabetic nephropathy.

SA-PO515

Thioredoxin-Interacting Protein (TXNIP) Promotes GAPDH Nuclear Translocation by High Glucose

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Background: Thioredoxin-interacting protein (TXNIP) is a multifunctional protein that regulates glucose metabolism and the cellular redox state, the latter by binding and inhibiting the endogenous antioxidant thioredoxin. TXNIP is markedly upregulated by high glucose and we previously showed that STZ-induced diabetic TXNIP-/- mice are protected from developing features of Diabetic Nephropathy (DN). The pathogenesis of diabetes complications involves the oxidative inhibition of the glycolytic enzyme GAPDH, resulting in aberrant glucose metabolism. However, nitrosylation and oxidation (N/O) of GAPDH was found in neuronal cells to cause its nuclear translocation by binding the E3 ligase Siah1, followed by activation of proapoptotic gene expression. We postulated that TXNIP would promote GAPDH N/O and nuclear translocation in HG by inhibiting redox balance.

Methods: To study TXNIP signalling in vitro, primary mesangial cells (MCs) from TXNIP+/+ (WT) and TXNIP-/- (KO) mice were cultured in normal (5mM) and high glucose (25mM; HG). GAPDH activity, GAPDH/Siah1 nuclear translocation, caspase-3 cleavage, and Bax/Bcl-2 expression were examined via immunoblotting. To test our hypothesis in vivo, STZ-induced diabetic DBA/2J mice were orally treated with deprenyl, a drug used in Parkinson's disease and shown to inhibit GAPDH-Siah1 binding, or the vehicle as a control. Structural outcomes including glomerular mesangial expansion and fibrosis, basement membrane thickening, podocyte foot process effacement, and NOX4 expression were assessed by histology. Functional outcomes such as albuminuria were assessed by ELISA.

Results: In vitro, exposure of primary cultured WT MCs to HG significantly decreased GAPDH activity, caused nuclear localization of both GAPDH and Siah1 at 24h and 48h, and increased caspase-3 cleavage and the Bax/Bcl-2 ratio at 12h and 24h, while TXNIP-/- MC showed no HG-mediated effect. In vivo, deprenyl treatment significantly reduced diabetes-induced albuminuria, glomerular mesangial expansion and fibrosis, basement membrane thickening, podocyte foot process effacement, and NOX4 expression.

Conclusions: These data suggest that GAPDH has a direct pathogenic role in DN via the GAPDH-Siah1 signalling pathway and that TXNIP is a critical modulator of this pathway that promotes DN.

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SA-PO516

L-Homoarginine Supplementation Prevents Diabetic Kidney Damage

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Background: Diabetes is the major cause of end stage renal disease, with heavy burden for the health care system. L-homoarginine (**HA**) is an endogenous, non-proteinogenic amino acid that is associated with renal and cardiovascular disease. Specifically, low HA levels are associated with cardiovascular diseases, stroke and reduced kidney function. However, the role of HA in diabetic nephropathy is unknown.

Methods: Six-week-old diabetic DBA *Ins2*^{Akita} and their controls were treated with or without HA supplementation via drinking water or mini osmotic pump for twelve weeks.

Results: Plasma and kidney HA levels were significantly reduced by 25% (p<0.05) and 65% (p<0.05) in *Ins2*^{Akita}; respectively compared to control mice. Vehicle-treated *Ins2*^{Akita} mice showed significant increases in urine albumin excretion (UAER) (p<0.01), renal histological changes (score: 1.5 vs. 0.25), glomerular macrophage recruitment (p<0.01), inflammatory KC-GRO/CXCL1 (p<0.0005), and urinary TBARS (p<0.0001); a marker of oxidative stress, along with reduction in kidney nitrate and nitrite levels (p<0.01) compared to non-diabetic controls. HA supplementation by either drinking water or osmotic pumps for 12 weeks in *Ins2*^{Akita} mice significantly reduced UAER (p<0.05), renal histological changes (score: 0.625 and 0.375), glomerular macrophage recruitment (p<0.05), KC-GRO/CXCL1 (p<0.005), and urinary TBARS (p<0.05), along with significant increase in kidney nitrate and nitrite levels (p<0.05) compared to vehicle-treated *Ins2*^{Akita} mice.

Conclusions: These data demonstrate that L-homoarginine supplementation attenuates specific features of diabetic nephropathy in mice and could be a potential new therapeutic tool for treating diabetic patients.

Funding: NIDDK Support

SA-PO517

Parkin Accelerates Tubular Cell Senescence Through GATA4/GAS1 in Diabetic Nephropathy

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Background: Accelerated senescence of renal tubular epithelial cell (RTEC) plays a fundamental role in the pathogenesis of diabetic nephropathy (DN). Gene mutation of Parkin, an E3 ubiquitin ligase, can accelerate neuron degeneration in familial aging-related diseases. We investigated the role of Parkin in accelerating senescence of RTEC and its mechanism.

Methods: 149 cases of patients with DN diagnosed by renal biopsy were recruited in our study. 32 normal kidney samples were obtained from renal carcinoma as control. Renal Parkin expression was detected by immunohistochemistry. In vivo, we used C57BL/6 Parkin$^{-/-}$ knockout mice, Parkin overexpression mice and wild-type controls with or without streptozotocin-induced diabetes over 5 months of follow-up. In vitro, mouse primary RTEC were exposed to high glucose (HG) for 48h. Moreover, co-immunoprecipitation and ubiquitination experiments were applied to evaluate the relationship of GATA4 with Parkin.

Results: Expression of Parkin was gradually decreased with development of tubulointerstitial injury and positively correlated with eGFR. Parkin KO+STZ mice showed significantly higher plasma BUN, SCr and urinary NAG than those in wild-type STZ mice. The degree of renal interstitial fibrosis in the STZ+Parkin overexpression group was significantly lower than that in STZ mice. The proportion of P16-positive renal tubular cells and renal P21 expression in Parkin overexpression + STZ group were significantly lower than those in STZ group. In vitro, overexpression of Parkin attenuates high glucose-induced tubular senescence and GATA4 accumulation. Parkin co-immunoprecipitated with GATA4 in renal biopsy samples of DN patients and mouse tubular cells. Furthermore, Parkin ubiquitinated GATA4 in vivo and in vitro. Parkin KO diabetic nephropathy mice have significantly higher GAS1 mRNA and protein levels in kidneys than WT mice. Overexpression of GATA4 enhanced GAS1 mRNA and protein levels in renal tubular cells. Overexpression of GAS1 can directly inhibit the expression of a key negative regulator of cell senescence, cyclin dependent kinase 2 (CDK2) and inhibit the anti-senescence effect of Parkin in mouse primary RTCs stimulated by high glucose.

Conclusions: Parkin inhibits RTEC senescence in diabetic nephropathy by inhibiting GATA4/GAS1 pathway. Parkin is a potential anti-senescence factor in the development of diabetic nephropathy.

Funding: Government Support - Non-U.S.

SA-PO518

Tubular Secretory Clearance Is Associated with Whole-Body Insulin Clearance

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Background: The kidneys eliminate insulin via glomerular filtration plus tubular reabsorption and by extraction from the basolateral surface of proximal tubule cells. The relative contributions of each mechanism are incompletely understood. We tested associations of proximal tubular secretory clearances and estimated glomerular filtration rate (eGFR) with whole-body insulin clearance.

Methods: The Study of Glucose and Insulin in Renal Disease performed the hyperinsulinemic-euglycemic clamp in 57 non-diabetic persons with CKD (eGFR <60 mL/min/1.73m^2) and 38 persons without kidney disease or diabetes (eGFR ≧60 mL/min/1.73m^2). We defined insulin clearance as the intravenous insulin infusion rate divided by the steady-state plasma insulin concentration. We measured plasma and 24-hour urine concentrations of 7 tubular secretory solutes using targeted liquid chromatography-tandem mass spectrometry. We estimated GFR using the CKD Epidemiology Collaboration equation.

Results: Mean age was 63 ± 13 years and mean insulin clearance was 924 ± 228 mL/min. After adjustment for demographics and body composition, lower eGFR and lower kidney clearances of 3 solutes were associated with lower insulin clearance accounting for multiple comparisons (Table). Lower kidney clearances of isovalerylglycine and xanthosine remained associated with lower insulin clearance after further adjustment for eGFR.

Conclusions: Lower kidney clearances of tubular secretory solutes are associated with lower insulin clearance, suggesting an important role of tubular secretory pathways in renal insulin metabolism.

Funding: NIDDK Support

Associations of kidney functions with insulin clearance

	Insulin Clearance (mL/min)			
	Model 1		Model 2	
	Difference (95% CI)*	p-value	Difference (95% CI)*	p-value
eGFR	-28 (-50, -6)	0.01**	--	--
Cinnamoylglycine	-6 (-15, 4)	0.27	1 (-10, 12)	0.87
Indoxyl sulfate	-17 (-32, -2)	0.02	-12 (-27, 3)	0.10
Isovalerylglycine	-17 (-28, -6)	0.002**	-14 (-27, -1)	0.04
Kynurenic acid	-14 (-30, 2)	0.09	1 (-22, 23)	0.94
Pyridoxic acid	-13 (-26, 0)	0.05	-6 (-22, 9)	0.43
Tiglylglycine	-19 (-30, -7)	0.001**	-15 (-30, 1)	0.06
Xanthosine	-24 (-34, -13)	< 0.0001**	-21 (-32, -9)	0.0004**

Model 1: Adjusted for age, sex, Black race, fat mass, fat free mass, and log (albumin excretion rate).

Model 2: Model 1 + log(eGFR).

*Difference in insulin clearance (mL/min) per 20% lower kidney function.

**Statistical significance after accounting for multiple comparisons (Bonferroni adjustment).

SA-PO519

Effects of RAAS Activation on Intrarenal Inflammation and Intrarenal Hemodynamics: Results from the Canadian Study of Longevity in Type I Diabetes

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Background: Inflammation and pro-fibrotic pathways are implicated in the pathogenesis of diabetic kidney disease (DKD) and are activated by chronic hyperglycemia and renin angiotensin aldosterone system (RAAS) stimulation. Quantification of urinary inflammatory markers has been used in type I diabetes (T1D) to determine renal tissue inflammation. The relationship between RAAS activation, intrarenal inflammation and hemodynamics is unknown. To study this, we measured the excretion of urine inflammatory markers and GFR in participants with longstanding T1D compared to adult comparators without diabetes following exogenous RAAS activation.

Methods: A urinary cytokine 42-plex panel adjusted for urine creatinine was analyzed from participants of the Canadian Study of Longevity in T1D of more than 50 years duration (n=74) and compared to age and sex matched adult comparators without diabetes (n=73). Renal hemodynamic function was measured using inulin and *p*-aminohippurate (PAH). Changes in urinary inflammatory marker excretion post angiotensin II (AngII) infusion were compared between comparators, and T1D participants with and without DKD (resistors). Renal hemodynamic function was correlated with urinary inflammatory markers independent of A1c, T1D duration, and systolic blood pressure.

Results: The renal hemodynamic response to AngII in this cohort has been previously published, with an attenuated response in DKD vs. DKD resistors and controls, likely signifying high baseline RAAS activation. Conversely, in this analysis, RAAS activation stimulated a significant increase in the urinary excretion of 31 inflammatory markers in both DKD and DKD resistors, compared to adults without diabetes (p<0.05). There were no differences in inflammatory marker excretion between participants with DKD and resistors. $Inulin_{GFR}$ inversely correlated with urinary excretion of proinflammatory markers (IL-18, IP-10, & RANTES), growth factor receptors (PDGF-AA & VEGFAA), and chemokines (Eotaxin & MCP-1).

Conclusions: RAAS activation was associated with increased markers of intrarenal inflammation in T1D participants with and without DKD, suggesting a consistent role for RAAS activation at the renal tissue level leading to inflammation even after longstanding T1D.

SA-PO520

ManNAc Improves Nephropathy but Worsens Hyperglycemia in Diabetic Rats by Inducing O-GlcNAcylation

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Background: The sialylation inducing compound N-acetyl Mannosamine (ManNAc) improved renal function in Nephrotic syndrome rats model (Clement LC et al Nature Medicine Jan 2011). We compared the overall efficacy and side effect profile of ManNAc with another sialylation inducing compound GDT01 in diabetic rats.

Methods: MManNAc study: 5 month old ZDF male rats (n = 5 rats / group) were treated for 5 months with tap water or ManNAc in drinking water. Changes in proteinuria, BUN, creatinine, hyperglycemia and histology were assessed. GDT01 study: 5 month old male ZSF1 rats (n = 6 rats / group) were treated with plain tap water or GDT-01 over a period of 7 months. Same parameters as above were assessed. Muscle protein content of the diabetogenic sugar O-GlcNAc was assessed using 1D and 2D gel Western blots for both studies. O-GlcNAcylation occurs at the same amino acid residues as O- glycosylation and phosphorylation.

Results: ManNAc reduces proteinuria in ZDF rats significantly ($P<0.05$, $P<0.01$) when compared to water control group. The blood glucose level in ManNAc treated animals was also significantly ($P<0.05$) increased. GDT01 treated rats showed a significant reduction in proteinuria ($P<0.05$ to $P<0.01$) without any increase in blood glucose levels. Analysis of BUN and creatinine levels showed no significant changes in the ManNAc study, but improved in the treated group in the GDT01 study ($P<0.05$, $P<0.01$). In addition, renal histology was remarkably better in GDT01 treated rats. Assessment of O-GlcNAc showed increased levels in skeletal muscle in ManNAc treated rats, but no change in GDT01 treatment. This suggests that shuttling of ManNAc into O-GlcNAc induces diabetogenic changes, that negate otherwise potentially beneficial effects in treating diabetic nephropathy. It is likely that this phenomenon is noted also in non-diabetic rats, suggesting "diabetes like" side effect profile in the absence of diabetes.

Conclusions: The sialic acid precursor ManNAc is diabetogenic and should be avoided as a sialylation inducing agent. GDT01 improves diabetic CKD without being diabetogenic, and remains the preferred sialylation inducing agent

Funding: NIDDK Support

SA-PO521

Urinary L Type Fatty Acid Binding Protein Reflects the Degree of Renal Hypoxia in Spontaneously Diabetic Torii Fatty Rats

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Background: Tubulointerstitial damage is known to be strongly associated with renal prognosis in diabetic kidney disease (DKD). Because renal hypoxia is an aggravated factor for the tubulointerstitial damage, urinary marker which is capable of detecting the renal hypoxia, is useful for monitoring the DKD. The aim of this study is to reveal the correlation between urinary liver-type fatty acid binding protein (L-FABP) and renal hypoxia using novel model of type 2 diabetes with obesity.

Methods: Male spontaneously diabetic torii (SDT) fatty rats (n =6) were used as an animal model of type 2 diabetes with obesity. Age- and sex-matched Sprague–Dawley rats (SD) (n = 8) were used as controls. Body weight, systolic blood pressure and blood glucose levels were measured at 8, 12, 16 and 24 weeks of age. Urine samples, serum and kidney tissues were obtained at 24 weeks of age. Microvascular blood flow index (BFI) in renal cortex was measured using diffuse correlation spectroscopy (DCS) before removing the kidney at 24weeks of age.

Results: Obesity, hyperglycemia and hypertension were observed in the SDT fatty rats. Mild glomerular hypertrophy and sclerosis, moderate interstitial inflammation and fibrosis, and accumulation of renal oxidative protein were significantly observed in the SDT fatty rats compared to the SD rats. While frequency of peritubular endothelial cells and phospho- endothelial nitric oxide synthase levels were similar between the SDT fatty rats and the SD rats, the degrees of renal hypoxia-inducible factor-1a expression significantly increased and renal vascular endothelial growth factor expression levels did not increase in the SDT fatty rats compared to the SD rats. Urinary L-FABP levels in the SDT fatty rats were significantly higher and renal microvascular BFIs in the SDT fatty rats were significantly lower compared to the SD rats. The levels of urinary L-FABP were significantly positively correlated with renal HIF-1a expression levels and were negatively correlated with renal microvascular BFIs.

Conclusions: Urinary L-FABP levels reflected the degree of renal hypoxia in DKD of type 2 diabetic animal model. In clinical practice, urinary L-FABP may be useful for monitoring DKD in type 2 diabetic patients as a renal hypoxic marker.

SA-PO522

A Protective Role of Renalase in Nephropathy

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Background: Renalase, a recently discovered secreted flavoprotein, exerts anti-apoptotic and anti-inflammatory effects against renal injury in acute and chronic animal models. However, whether Renalase elicits similar effects in the development of diabetic nephropathy (DN) remains unclear. The studies presented here tested the hypothesis that Renalase may play a key role in the development of DN and have therapeutic potential for DN.

Methods: Renalase expression was determined in human kidney biopsies with diabetic nephropathy. The role of Renalase in the development of diabetic nephropathy were examined using Renalase heterozygous knockout mice with db/db background and db/db mice with Renalase overexpression. In addition, the effects of Renalase on high glucose induced podocytes were investigated.

Results: Renalase was downregulated in human diabetic kidneys compared with healthy controls. Our data demonstrated that Renalase heterozygous knockout resulted in elevated albuminuria and increased renal mesangial expansion in db/db mice. However, overexpression of Renalase significantly ameliorated renal injury in db/db mice. Renalase could inhibit high glucose-induced podocyte injury in vitro.

Conclusions: This study suggested that Renalase protected against the progression of DN and Renalase may represent as a novel therapeutic target for the treatment of DN.

SA-PO523

The Role of ABCA1 on the Glomerular Lipid Accumulation and Renal Injury in Diabetic Kidney Disease

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Background: Glomerular lipid accumulation is one of the pathologic characteristics of diabetic kidney disease (DKD). Recent evidences suggested that ATP-binding cassette transporters A1 (ABCA1) has a particular effect on the cellular lipid homeostasis. We aimed to evaluate the role of ABCA1 on the lipid accumulation in glomeruli and podocyte under the diabetic conditions.

Methods: *In vitro,* mouse podocytes were stimulated with high glucose (HG) and palmitic acid (PA), and treated an GW683965, agonist of ABCA1. In vivo, C57BL/6 and ABCA1 knockout (KO) mice were maintained with high fat diet for 12 weeks with low dose streptozocin intraperitoneal injection. GW683965 was administered via osmotic pump in *db/m* or *db/db* mice. Urinary albumin-to-creatinine ratio (ACR), total cholesterol and triglyceride in kidney tissues were measured. RhoA activity and BODIPY 493/503 staining were performed in the kidney. Foot process effacement in glomeruli was evaluated by transmission electron microscopy. Apoptosis, mitochondrial morphology and energy metabolic key enzymes were evaluated both *in vitro* and *vivo*.

Results: Blood glucose, ACR, serum cholesterol and triglyceride were significantly increased and foot process effacement was prominent in diabetic mice. These changes were exaggerated in the ABCA1 KO mouse with diabetes, whereas abrogated by GW683965 treatment. Renal cholesterol and triglyceride contents were higher in ABCA1 KO mice with diabetes or lower in GW683965 treated mice than those in control and diabetic mice. Mitochondrial morphology and the expression of energy metabolic enzymes were changed in the kidneys of diabetic ABCA1 KO mice or GW683965 treated mice. In vitro, the intracellular lipid contents were increased and apoptosis combined with mitochondrial swelling and crista disruption were also increased in podocytes with HG and PA stimuli. All of these changes were ameliorated through GW683965 treatment.

Conclusions: These findings suggest that ABCA1 plays an important role in the glomerular lipid accumulation and renal injury under diabetic conditions and that ABCA1 can be a promising therapeutic target in patients with DKD.

SA-PO524

Intrarenal Enhancement of Leucine-Rich α-2-Glycoprotein-1 in the Early Stage of Diabetic Nephropathy

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Background: Abnormal angiogenesis plays a major role in the development of early stage diabetic nephropathy. Vascular endothelial growth factor (VEGF) is a classical proangiogenic factor that regulates abnormal glomerular angiogenesis linked to glomerular hypertrophy in the early stage of diabetic nephropathy. Very recently, Leucine-rich α-2-glycoprotein-1 (LRG1), a novel proangiogenic factor expressed in endothelial cells, has been reported to be involved in the development of diabetic nephropathy. The aim of this study was to compare glomerular expression of the classical proangiogenic factor VEGF and novel proangiogenic factor LRG1 in the early stage of diabetic nephropathy.

Methods: We investigated intrarenal expression of VEGF and LRG1 in a mouse model of diabetes (*db/db* mouse) by immunohistochemistry and a laser capture microdissection method, and compared the changes in expression at 16 and 24 weeks of age to evaluate their association with diabetic nephropathy development.

Results: At 16 weeks, diabetic *db/db* mice exhibited glomerular hypertrophy with abnormal angiogenesis characterized by endothelial cell proliferation, which was concomitant with an increase in LRG1 expression of glomerular endothelial cells. However, glomerular VEGF expression was not increased at this early stage. At 24 weeks, the features of early diabetic nephropathy in *db/db* mice had developed further, along with further enhanced glomerular LRG1 expression. At this late stage, glomerular VEGF and fibrosis related-gene expression was also significantly increased compared with nondiabetic *db/m* mice.

Conclusions: These results suggest that LRG1 plays a pivotal role in the initial development of diabetic nephropathy by promoting abnormal angiogenesis, thereby suggesting that LRG1 is a potential preemptive therapeutic target of diabetic nephropathy.

SA-PO525

Deletion of Endothelial Nitric Oxide Synthase in BTBR ob/ob Mice Enhances Mesangiolysis and Worsens Diabetic Nephropathy

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Background: Leptin receptor deficient *db/db* mice with endothelial nitric oxide synthase (eNOS) deficiency and leptin deficient BTBR *ob/ob* mice have been useful models of moderately advanced diabetic nephropathy (DN). eNOS is essential for maintaining integrity and health of endothelial cells and podocytes. We postulated eNOS deficiency in BTBR *ob/ob* mice would exacerbate the severity of DN, allow testing of whether intact eNOS is essential or not to enable regression of DN with leptin replacement.

Methods: CRISPR/Cas9 was used to delete eNOS in BTBR *ob* +/- heterozygous mice. The resultant BTBR *ob* +/- /eNOS-/-mice were crossed to obtain BTBR *ob/ob*/ eNOS-/- homozygous mice (eNOS *ob/ob*), and control BTBR wt eNOS-/- mice (eNOS BTBR). At 18 weeks, fasting glucose levels and timed (6 hour) urine samples were collected. The mice were then euthanized, and blood, urine and tissue samples collected.

Results: eNOS *ob/ob* mice exhibited robust hyperglycemia (517.5 mg/dl) and a marked increase in urine albumin-creatinine ratio (ACR) (791.9 vs 172.3 ug/mg in eNOS BTBR, $p < 0.01$). Compared to control mice, eNOS *ob/ob* mice had significantly higher mesangial matrix accumulation (29.5% vs 15.9%, $p < 0.01$, assessed as fraction of collagen IV staining of glomerular tuft area). Silver methenamine stain revealed striking mesangiolysis, affecting 31.1% of glomeruli in eNOS *ob/ob* vs. 9.5% in control mice ($p < 0.01$). Podocyte density decreased in eNOS ob/ob compared to control mice (90.5 vs 149.8 podos/x10^6 um^3, $p < 0.01$). In addition, significantly higher amounts of urinary 8OHdG (a DNA/RNA marker of oxidative stress) were detected in eNOS *ob/ob* mice than in control mice (511.2 vs 35.9 ng/mg creatinine, $p < 0.05$).

Conclusions: BTBR *ob/ob* mice with further knockout of eNOS exhibit dramatic albuminuria, reduced podocyte density, mesangial expansion and more extensive mesangiolysis than is featured in other models of murine DN including BTBR *ob/ob* mice of similar age. These characteristics more closely resemble advanced human DN. This mouse model could be useful for the development of drugs targeting mesangiolysis as well as for understanding the pathogenesis of DN.

Funding: NIDDK Support, Other NIH Support - University of Washington

SA-PO526

Low Expression of Autophagy-Related Protein 5 (ATG5) Leads to Suppression of Autophagy in Patients with Diabetic Nephropathy and Retinopathy

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Background: Autophagy is a catabolic mechanism that involves lysosomal-dependent degradation of unnecessary or dysfunctional intracellular components, plays role in diabetic nephropathy (DN) and retinopathy (DR). ATG5 is one of the most important participants in the autophagy mechanism. Our study's aim was to investigate if aberrant expression of ATG5 protein/ *Atg5* gene is associated with DN or DR.

Methods: The study included 120 human participants in 4 groups – Healthy, diabetic (DM), DN and DR; 10 mice in 2 groups – healthy and DN. Western blot analyses of ATG5 and its downstream collaborator LC3-II were performed on human white blood cell lysates and murine renal lysates. Immunohistochemical analysis was performed on mice renal tissues. qRT-PCR analysis of ATG5 was performed on total mRNA isolated from human WBC.

Results: 1. ATG5 protein expression was decreased in DM patients, with and without complications [0.66 ± 0.06 A.U in DM patients (n=30) $p < 0.01$), 0.62 ± **0.06** A.U in DN, (n=30) $p<0.001$), 0.67± 0.05 A.U in DR patients (n=30) $p<0.01$)], compared with the healthy control 0.97 ± 0.04 A.U. **2. A** 2.5-fold decrease in the percentage of ATG5-stained areas in the PCT of DN mice (4.42 ± 1.08%) compared with W.T mice (10.87 ± 1.01%). **3.** The expression of *Atg5* gene between the groups by qRT-PCR analyses: in the DN (0.0069 ± 0.0005) and DR patients (0.0069 ± 0.0004) was down regulated at the mRNA levels, compared with healthy controls (0.0083 ± 0.0008). **4. Decreased** LC3-II levels in DM patients (0.50 ± 0.04 A.U (n=18) $p < 0.001$) DN patients (0.44 ± 0.05 A.U, (n=19) $p < 0.001$) and DR patients (0.43 ± 0.05 A.U (n=18) $p < 0.001$) compared with the healthy control (0.81 ± 0.05 A.U (n=19). 5. The renal LC3-II protein expression was found to be greatly decreased in the tubules of DN mice when compared with W.T mice.

Conclusions: 1. ATG5, as well as its downstream collaborator LC3-II, are down-regulated in DN & DR patients, which contributes to deficiencies in autophagy process. 2. Impairment of this process can lead to accumulation of abnormal proteins and molecules that can lead to the development and progression of DN &DR. 3. Therapeutic potential of ATG5 modulations as a novel treatment strategy for DN/DR patients through the autophagy mechanism may serve as a goal in the development of drugs for diabetic complications.

Funding: Government Support - Non-U.S.

SA-PO527

Semicarbazide-Sensitive Amine Oxidase (SSAO) Inhibition Ameliorates Albuminuria and Glomerulosclerosis but Does Not Significantly Improve Tubulointerstitial Fibrosis in Diabetic Nephropathy

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Background: SSAO is an enzyme known for its dual function in mediating inflammation and reactive oxygen species production. However, the role of SSAO inhibitors in chronic kidney disease is unclear. We aimed to determine the effectiveness of a SSAO inhibitor (PXS4728A) as an antifibrotic agent using a diabetic model of chronic kidney fibrosis.

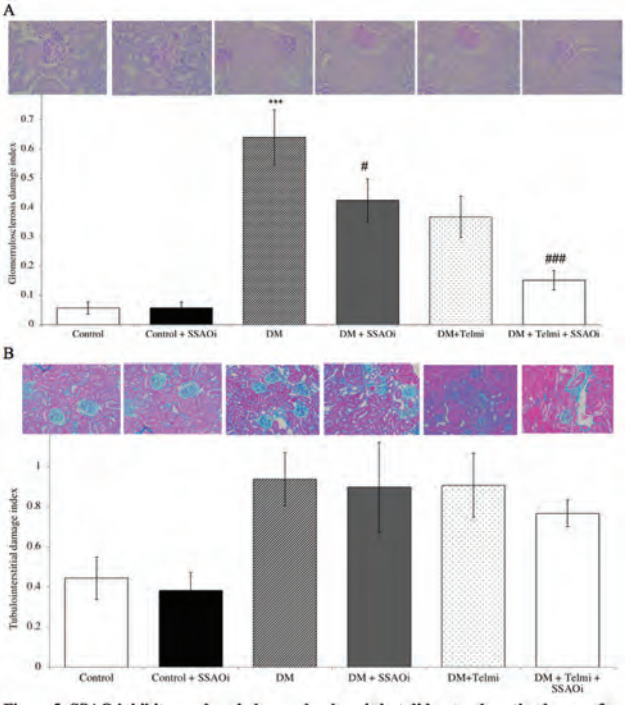
Methods: A streptozotocin-induced diabetic model in male $eNOS^{-/-}$ mice on a C57BL/6 background. Diabetic mice were treated with SSAOi for 24 weeks and outcomes compared with untreated diabetic mice and telmisartan treated animals as a comparator of current standard of care.

Results: Albuminuria, the extracellular matrix marker fibronectin, inflammatory marker expression of CD45 and oxidative stress, assessed by nitrotyrosine staining, were lower in diabetic mice treated with SSAOi compared with untreated diabetic mice. Glomerulosclerosis was reduced to a greater extent by SSAOi compared to telmisartan.

Conclusions: The effect of SSAO inhibition in diabetic mice resulted in a significant reduction in inflammation, oxidative stress, glomerulosclerosis and associated albuminuria compared to untreated diabetic mice. However, the effect of SSAOi was less obvious in the tubulointerstitial compartment than in the glomeruli. Therefore, SSAOi may be a potential target for diabetic glomerulosclerosis.

Parameters of studied animals

n=6-8	Control	Control + SSAOi	DM	DM+ SSAOi	DM + Telmi	DM+ Telmi+ SSAOi
Fasting Blood glucose level (mmol/L)	9.5±0.44	10.2±0.41	20.0±0.60*	20.7±0.77*	24.2±1.06*	20.2±1.0*
HbA1c (%)	4.3±0.05		7.0±0.26*	7.1±0.49*	7.7±0.40*	7.9±0.44*
Weekly Insulin requirement (IU)			0.1±0.05	0.04±0.02	0.3±0.09	0.1±0.04
Urinary Albumin: Creatinine (ug/mg)	113±17	104±13	597±163*	401±123#	187±42#	345±74



SSAO inhibiton reduced glomerulosclerosis but not degree of tubulointerstitial fibrosis

SA-PO528

Chloride Channel Accessory 1 (CLCA1)-TMEM16A-Chloride Current Axis: A Novel Kidney Injury Pathway in Aging and Diabetes

Hak Joo Lee,[1] Yuyang Sun,[1] Andrew Donati,[1] Christopher G. Kevil,[2] Adam Salmon,[1] Muniswamy Madesh,[1] Goutam Ghosh-Choudhury,[1] Brij Singh,[1] Kumar Sharma,[1] Balakuntalam S. Kasinath.[1] *[1]University of Texas Health San Antonio, San Antonio, TX; [2]LSU Health Shreveport, Shreveport, LA.*

Background: CLCA1 activates TMEM16A, a Ca^{++}-dependent chloride channel. RNA Seq showed increased expression of CLCA1 in renal cortex of old vs. young mice. We have reported that renal changes in aging and diabetes are associated with deficient generation of hydrogen sulfide (H_2S) (Lee, 2012, Lee, 2018). We studied role of CLCA1 in kidney injury in aging and diabetes.

Methods: We employed young and aging mice (n=10 per group). We also studied aging mice treated with (n=20) or without sodium hydrosulfide (NaHS) (n=14), a source of H_2S. Diabetic db/db mice with littermate controls (n=3 per group) were studied after being treated with or without NaHS. We overexpressed human CLCA1 (hCLCA1) in proximal tubular epithelial MCT cells.

Results: In aging mice renal CLCA1 expression was increased but not TMEM16A in association with mTORC1 activation, senescence associated secretory phenotype (SASP, consisting of increase in p53, p21, p16, IL-1and IL-6), albuminuria and fibrosis; all these were ameliorated by NaHS administration. Overexpression of hCLCA1 in MCT cells resulted in increase in chloride current by patch clamp, mTORC1 activation, induction of SASP and increase in matrix protein fibronectin. TMEM16A inhibitor and NaHS individually abolished these changes. In diabetic mice renal cortical expression of CLCA1 and TMEM16A was increased in association with mTORC1 activation, SASP, albuminuria, and matrix increase; these changes were ameliorated by NaHS. In MCT cells, high glucose augmented renal cortical expression of CLCA1 and TMEM16A. siRNA against CLCA1 and TMEM16A individually abolished high glucose-induced fibronectin and collagen 1 protein increase. Patch clamp showed high glucose increased chloride current that was abolished by NaHS and TMEM16A inhibitor.

Conclusions: Renal cortical H_2S deficiency in aging and diabetes is associated with increased CLCA1 expression; it is ameliorated by H_2S administration. Overexpression of hCLCA1 activates chloride current, mTORC1, induces SASP and matrix protein increase in renal cells. High glucose induced mTORC1 and matrix increase requires activation of CLCA1-TMEM16A-chloride current. These data suggest that CLCA1-TMEM16A-chloride current pathway is a novel contributor to kidney injury in aging and diabetes.

Funding: Veterans Affairs Support

SA-PO529

Redosing of Dysglycemic, Diabetic Mice with Neo-Islets, Aggregates of Adipose Stem Cells and Pancreatic Islet Cells, Achieves Euglycemia: Relevance to the Therapy of Diabetic Dogs

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Background: We demonstrated that allogeneic, ip administered "Neo-Islets" (NIs), aggregates of cultured islet cells and immune- and cyto-protective Adipose Derived Stem Cells, reestablished durable normoglycemia through omental engraftment and splenic and omental upregulation of Tregs, in autoimmune T1DM NOD mice without immunosuppressive agents (*SCTM* 2017;6:1631). Similarly, our FDA pilot study in insulin dependent pet dogs (INAD 012-0776) demonstrates that allogeneic NI therapy (i) is effective in significantly improving both glycemic control and the need for insulin (> 1 year); and (ii) does so without eliciting an allo-immune response (see abstract this session). Because the need for insulin is not eliminated in dogs, the current study was conducted to test whether redosing, independent of modulating an allo-immune response, is effective in further reducing the need for insulin. Redosing was therefore tested using Streptozoticin-diabetic (STZ) NOD/SCID mice.

Methods: Blood glucose levels were initially controlled with insulin pellets (Linbits) in 12 STZ-diabetic mice prior to i.p. NI or vehicle treatment (2x10e5 NIs/kg bw) (n=6 per group). Mice were followed (blood glucose; weight, ip Glucose Tolerance Test [GTT]) for ~8 weeks.

Results: No mice in the treated group died vs. 4 controls. NI therapy significantly improved glycemic control without achieving euglycemia vs controls x50 days. Therefore, on day 60, mice were redosed and followed as detailed above. This second dose of normalized both blood glucose levels and GTTs.

Conclusions: We conclude that these data support the planned redosing of dogs whose need for insulin has been reduced but not eliminated through allogeneic NI treatment, as initial allogeneic treatment of these dogs failed to elicit an immune response. We expect that doing so may lead to insulin independence, i.e., in analogy to islet transplant recipients who require several doses of islets but who are, however, treated with anti-rejection drugs.

Funding: Commercial Support - SymbioCellTech, LLC

SA-PO530

Allogeneic "Neo-Islets" Composed of Adipose-Derived Stem and Islet Cells Durably Reduce Diabetic Pet Dogs' Insulin Needs Without Requiring Immunosuppression (INAD 012-776)

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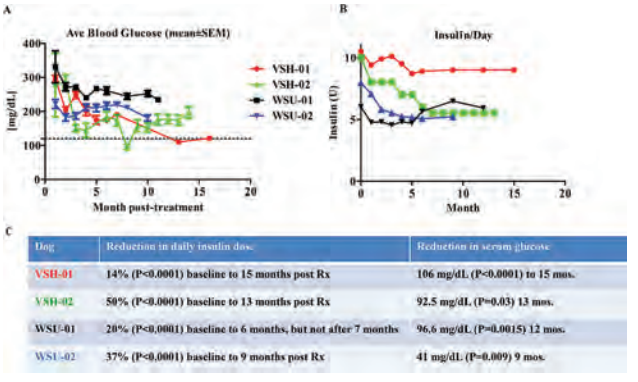
Background: We demonstrated that allogeneic, ip administered "Neo-Islets" (NIs), aggregates of cultured islet cells (ICs) and immune- and cyto-protective Adipose Derived Stem Cells (ASCs), reestablished durable normoglycemia through omental engraftment and splenic and omental upregulation of Tregs, in autoimmune T1DM NOD mice without immunosuppressive agents (*SCTM* 2017;6:1631). Comparable euglycemia was achieved with dog- or human-derived NIs in STZ-diabetic NOD/SCID mice. Here we update our report on an FDA supervised study using NI therapy in diabetic pet dogs.

Methods: Insulin dependent, diabetic pet dogs were included; 8 enrolled; 6 treated; and 4 followed for ≥ 6 mos. Pre-treatment serum samples were tested for islet autoantibodies. Comorbidities and blood glucose levels were treated. Allogeneic NIs were given once ip (2.5x10e5/kg bw). No encapsulation or antirejection agents were used. Blood glucose levels, insulin need and antibody responses were monitored.

Results: Prior to treatment 3 dogs had islet autoantibodies indicating autoimmunity. NIs appear to engraft, redifferentiate and physiologically produce insulin, and are neither rejected by auto- or allo-immune attacks, as evidenced by (i) an absent IgG response to the administered NIs, and (ii) progressively, durably (≥ 12 mos) and improved glycemic control, achieved with an up to 50% reduction in daily insulin need paralleled by a fall in serum glucose (See Figure). No adverse events attributable to therapy have been observed to date. While no dog has achieved insulin independence, preclinical results using human NIs indicate that redosing could accomplish this.

Conclusions: Allogeneic NI therapy is feasible, safe, and durably effective. We conclude that this therapy has significant translational relevance for dog and human T1DM.

Funding: Commercial Support - SymbioCellTech, LLC



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Dog	Reduction in daily insulin dose	Reduction in serum glucose
VSH-01	14% (P<0.0001) baseline to 15 months post Rx	106 mg/dL (P<0.0001) to 15 mos.
VSH-02	50% (P<0.0001) baseline to 13 months post Rx	92.5 mg/dL (P=0.03) 13 mos.
WSU-01	20% (P<0.0001) baseline to 6 months, but not after 7 months	96.6 mg/dL (P=0.0015) 12 mos.
WSU-02	37% (P<0.0001) baseline to 9 months post Rx	41 mg/dL (P=0.009) 9 mos.

(A) Serum glucose levels and (B) insulin need over time. (C) Percent reduction and statistical significance in reductions for each dog.

SA-PO531

Hyperglycemia Reduced DUSP4 Expression Leads to JNK MAPK Activation, Increased NOX4 Expression, and Insulin Resistance in Podocytes and Diabetic Nephropathy

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Background: Podocyte dysfunction is an early event in the development of diabetic nephropathy (DN) with multiple causes including insulin resistance and increased oxidative stress (ROS via NOX4) which lead to the activation of p38 and JNK MAPK pathways. A previous study has shown that JNK activation leads to serine 307 (ser307) phosphorylation of IRS1 (inhibitory phosphorylation) in insulin-resistant ob/ob mice. Our laboratory recently reported a decrease in the expression of DUSP4, a dual specificity phosphatase known to inhibit the MAPKs, which was associated with elevated JNK activation and NOX4 expression in podocytes exposed to high glucose. Thus, we hypothesized that hyperglycemia-induced DUSP4 expression reduction leads to insulin resistance in podocytes and DN via JNK activation and NOX4 expression.

Methods: Cultured podocytes were exposed to normal (5.6 mM) or high (HG; 25 mM) levels of glucose for 72h with either an overexpression of DUSP4 (adenovirus) or an inhibition of JNK (JNK inhibitor SP600125). *In vivo*, insulin injection was performed 15min prior to euthanasia where renal cortex was extracted from nondiabetic and diabetic ($Ins2^{+/C96Y}$) mice, with or without a deletion of DUSP4 ($Dusp4^{-/-}$).

Results: Podocytes exposed to HG showed reduced DUSP4 expression, increased JNK activation and increased ser307 phosphorylation of IRS1, which contributed to a decrease in the phosphorylation of Akt after insulin stimulation. Both DUSP4 overexpression and JNK inhibition blocked ser307 phosphorylation of IRS1 induced by HG and reestablished downstream insulin signaling cascade (tyrosine 612 phosphorylation of IRS1 and Akt phosphorylation). HG reduced DUSP4 expression was prevented using antioxidant N-acetyl cysteine and HG increased NOX4 expression was diminished with DUSP4 overexpression

and JNK inhibition in podocytes. *In vivo*, DUSP4 reduction in renal cortex of *Ins2*$^{+/C96Y}$ mice correlated with JNK activation, increased ser307 phosphorylation of IRS1 and reduced Akt phosphorylation, reduction exacerbated in *Ins2*$^{+/C96Y}$ mice deficient for DUSP4.

Conclusions: HG induced JNK activation by reduced DUSP4 expression mediates an increase in the production of ROS via NOX4 as well as insulin resistance in DN.

Funding: Government Support - Non-U.S.

SA-PO532

Transgenic LPA Expression Does Not Exacerbate Albuminuria in Diabetic Mice

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Background: Lipoprotein(a) [Lp(a)] is a unique primate-specific and liver-specific lipoprotein consisting of a low-density lipoprotein molecule covalently bonded to an apo(a) protein. Genetically elevated circulating Lp(a) has been identified as an independent causal risk factor for developing coronary heart disease and stroke. We previously showed in a cross-sectional study of patients with type 2 diabetes mellitus that elevated baseline Lp(a) associates with steeper eGFR decline, although no causal link has been firmly established. Here we describe kidney phenotypes resulting from transient adenovirus-induced expression of two different Lp(a) isoforms in diabetic mice.

Methods: In 26-week old DBA/2J mice fed a high-fat diet for 14 weeks, we induced transient liver-specific expression of Lp(a) (truncated or full-length isoform) by adenovirus delivery under a TBG promoter. These sizes were tested due to the proposed role of isoform size in altering Lp(a) plasma concentrations. Plasma and urine samples were serially collected and assayed for metabolic analytes.

Results: Within seven days of adenovirus injection, mice receiving plasmid encoding the truncated LPA isoform or the full-length isoform had robust induction of circulating Lp(a) compared to mice receiving the null plasmid control (1693 +/- 714.3 mg/dL and 207.8 +/- 132.4 mg/dL, respectively, vs. < 6 mg/dL). Baseline mean fasting glucose, blood urea nitrogen, and urinary albumin to creatinine ratios (ACR) were 206.4 mg/dL, 20.3 mg/dL, and 202.9 ug/mg, respectively. Although all mice had increased urinary ACR 4 days post-adenoviral injection, no significant increases in urinary ACR for LPA-expressing mice were seen on days 2, 4, 6, and 7. Consistent with this result, we also did not observe changes in BUN between the LPA-expressing mice and control. No structural differences were observed on histology of kidneys collected 7 days after injection.

Conclusions: Taken together, our results suggest that transient overexpression of Lp(a), does not induce significant worsening of renal function in the short-term. Further studies are needed establish whether a more significant causal effect would be observed with chronic overexpression.

Funding: Other NIH Support - K08 HL135348

SA-PO533

Clinicopathological Features of a Rapid Decliner in Diabetic Nephropathy

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Background: Declining speed of kidney function in diabetic nephropathy is different in each case. It is well known that there are characteristic groups; “rapid decliner” and “no or slow decliner”. Although, many studies of kidney prognosis and cardiovascular events in cases of diabetic nephropathy have been reported, clinical and pathological features of these groups are unclear so far.

Methods: Biopsy proven 600 diabetic nephropathy cases were enrolled in this study. Among them, 385 cases were able to calculate the eGTR decline speed 3 years after kidney biopsy. The cases were classified into 4 groups in accordance with the eGFR declining speed. The first quartile, that is the fastest declining speed group, contains 97 cases, and the fourth quartile, that is the slowest declining speed group, contains 96 cases. Clinical data and kidney biopsy data of these two groups were evaluated. The pathological findings (Nine glomerular lesions, two interstitial lesions, and two vascular lesions) were followed by the previous paper (Nephrol Dial Transplant. 2018;33:138-148).

Results: Declining speed op the first quartile group (rapid declining) was 13.9 mL / min / 1.73 m 2 / year or more (median 21.3), and that of the fourth quartile (slow declining) group was 1.9 mL / min / 1.73 m 2 / year or less (median -1.96). The incidence of renal composite events and renal deaths, 40.0 and 4.6 (100 persons / year) in the first quartile, and 3.12 and 0.5 in the fourth quartile, respectively. In background analysis at biopsy, ten pathological factors and three clinical factors were statistically difference between two groups. Using multivariate logistic analysis showed that three pathological factors (nodular lesion, mesangiolysis, and polar vasculosis) and one clinical factor (urinary albumin) were statistically significant, and odds ratio of these factors were 4.4, 3.0, 6.9 and 4.0, respectively. We evaluate the cohort with tertile, in the same way of the quartile as the tertile. The result of tertile analysis an almost similar to the results of quartile.

Conclusions: Through this analysis, large amounts of urinary albuminuria, and three pathological findings (nodular lesion, mesangiolysis, and polar vasculosis) were characteristic features of patients with rapid kidney function declining.

Funding: Government Support - Non-U.S.

SA-PO534

Diversity of Biopsy-Proven Kidney Diseases in Japanese Patients with Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD), including diabetic nephropathy (DN), is the leading cause of chronic kidney disease worldwide including Japan. However, there is also increasing recognized diagnosis of non-diabetic renal diseases (NDRD) in diabetic patients, which may influence in the different treatments and outcomes. This study reported the spectrum and clinical characteristics of NDRD and NDRD superimposed DN in Japanese diabetic population.

Methods: Clinical data of the diabetic patients with aged > 18 years undergone kidney biopsy in Kochi Medical School hospital during 2001-2017 were collected. These data including the and laboratory data together with renal biopsy pathological findings.

Results: The 165 from 872 patients were recruited in this study; 108 cases were male (65.4%). The mean age was 61.1±1.1 years, and the median serum creatinine was 1.86 mg/dL (0.96-2.76). The 48 cases (29.0%) were diagnosed NDRD, while 50 cases (30.3%) were diagnosed NDRD superimposed DN. The rest of the patients were diagnosed isolated diabetic nephropathy; DN (40.6%). IgA nephropathy was either the most prevalent glomerular disease in NDRD (39.5%) and NDRD superimposed DN (34.0%). The second and third kidney biopsy findings in NDRD were lupus nephritis (18.7%), membranous nephropathy (12.5%), respectively. In NDRD superimposed DN, membranous nephropathy (18.0%), and ANCA associated vasculitis (14.0%) were the second and third pathological findings. The serum creatinine levels were higher in DN than in NDRD and NDRD superimposed DN (2.47 mg/dL, 1.25 mg/dL, and 1.63 mg/dL, respectively). Nephrotic syndrome was more common in NDRD superimposed DN, following DN and NDRD (38.0%, 37.3%, and 31.2%, respectively, $p<0.05$). Moreover, the quantity of proteinuria was found to be higher in DN and NDRD superimposed DN than in NDRD (4.0, 3.2, and 2.8 g/gCr, respectively, $p<0.05$).

Conclusions: This study disclosed the diversity and prevalence of NDRD that was diagnosed in almost 60% of DKD in Japanese diabetic patients. Presence of nephrotic syndrome was the more suggestive diagnosis of DN or NDRD superimposed DN. Kidney biopsy is the important means for the definite diagnosis and the proper treatment of glomerular disease in diabetic patients.

SA-PO535

Synergistic Effects of Glomerular Lesion and Interstitial Lesion on Increased Proteinuria But Not on Renal Prognosis

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Background: Diabetic kidney disease (DKD), a recently proposed concept, is associated with various proteinuria level and heterogeneous renal prognosis; however, these patients are rarely examined by renal biopsy. We have biopsy-proven diabetic nephropathy (DN) cohort including many patients with relatively mild proteinuria. That encouraged us to examine the association between histological findings and variation in proteinuria level and renal prognosis in DKD.

Methods: This is a longitudinal study of 396 adults with biopsy-proven DN from 1981 to 2014. Predictors were renal pathological findings. DN was evaluated by two renal pathologists according to 13 histological findings (9 glomerular lesions, 2 tubulointerstitial lesions and 2 vascular lesions). Cross-sectional association with proteinuria level was examined with multivariable general linear model and two-way analyses of covariate and variance, and longitudinal association with renal prognosis was examined with Cox regression model.

Results: Median proteinuria level was 0.5 g/day (25th and 75th percentile: 0.2 and 2.6 g/day) at the time of renal biopsy. During mean follow-up of 9.7 years, 99 patients reached end-stage kidney disease (ESKD). Among thirteen histological findings, nodular lesion (NL) and interstitial fibrosis and tubular atrophy (IFTA) were significant predictors for proteinuria levels after adjustment for clinical risk factors. Among patients with NL or >25% IFTA, 31% of patients had only IFTA and 20% had only NL. NL and IFTA had a synergetic effect on increased proteinuria after adjustment with clinical parameters (p for interaction=0.07). Cox regression analysis showed NL and IFTA were significantly associated with a development of ESKD but there was not a synergetic effect on renal prognosis between these two factors (p for interaction=0.94).

Conclusions: These data suggest the fluctuation in the balance between glomerular and interstitial damages could interpret various degrees of proteinuria and heterogeneous renal prognosis in DKD.

SA-PO536

Implications of Solidified Glomerulosclerosis and Extracapillary Hypercellularity in Chinese Patients with Type 2 Diabetes and Diabetic Nephropathy

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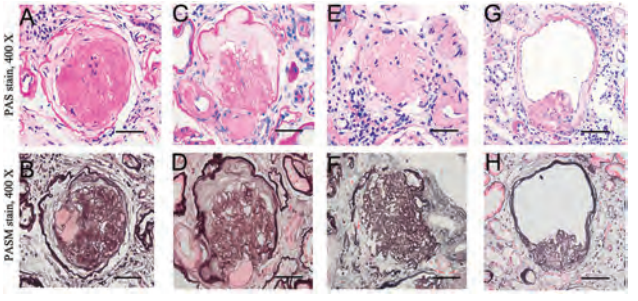
Background: This study was aimed to determine nephropathologic markers for time to end-stage renal disease (ESRD) in Chinese patients with type 2 diabetes and diabetic nephropathy (DN).

Methods: This retrospective cohort study recruited 322 Chinese type 2 diabetic patients from 2003 to 2017 with biopsy-proven diabetic nephropathy who received follow-up over 12months. All kidney biopsy specimens were fully assessed under a uniform scale. Competing risk models with death as the competing risk was used to estimate the sub-distribution hazard ratios (SHRs) for ESRD.

Results: During a median follow up of 26.0 months, 144 (44.7%) patients progressed to ESRD and 17 (5.3%) patients died before entering ESRD. Global glomerulosclerosis was further separated into three categories: solidified glomerulosclerosis (Figure 1 A-B), ischemic obsolescent glomerulosclerosis (Figure 1 C-D) and not otherwise specified glomerulosclerosis (Figure 1 E-H). Pathological parameters in Renal Pathology Society system were associated with ESRD in univariate analysis but failed to predict ESRD in multivariable models. After adjusting for parameters of demographics, baseline kidney functions, nutritional status, and medications in the multivariable model, solidified glomerulosclerosis and extracapillary hypercellularity (SHR, 1.77; 95% CI, 1.11-2.80; and SHR, 2.48; 95% CI, 1.58-3.90, respectively) were identified as risk factors for ESRD. Moreover, patients in RPS class III with a higher proportion of solidified glomerulosclerosis had a lower 5-year renal survival rate than class IV.

Conclusions: In Chinese type 2 diabetic patients with DN, solidified glomerulosclerosis and EXHC were prognostic indicators for ESRD. Solidified glomerulosclerosis contributed partly to the worse renal outcome of patients in class III.

Funding: Government Support - Non-U.S.



A-B, Solidified glomerulosclerosis. **C-D,** Ischemia obsolescent glomerulosclerosis. **E-F,** One type of not otherwise specified glomerulosclerosis. **G-H,** Another type of not otherwise specified glomerulosclerosis. Bar= 50 μm.

SA-PO537

Association Between Renal Fibrosis and Early Renal Decline in Type 2 Diabetes

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Background: The association between fibrosis and early progressive renal decline in diabetes is unclear. Recently, MMP-7 (Matrilysin) and WFDC2 (WAP four-disulfide core domain protein 2) were postulated to be markers of renal fibrosis. We hypothesized that renal fibrosis may be involved in early renal decline in type 2 diabetes (T2D).

Methods: Patients for this nested case-controls study were selected from among those participating in the 2nd Joslin Kidney Study with T2D, CKD stage 1 and 2, and normo-/microalbuminuria at enrollment. Patients were followed for 6-12 years. The primary outcome was eGFR decline defined as eGFR slope ≤-5 mL/min/1.73m^2/year. We developed the fibrosis index by integrating serum and urinary MMP-7 and plasma WFDC2 into a predictive probability model of renal decline using logistic regression, after verifying that these markers were not highly correlated between each other. To estimate the effect of fibrosis index on eGFR decline, multivariable logistic regression was applied adjusting for eGFR, ACR, plasma TNF-R1, plasma KIM-1, and urinary EGF/MCP-1 ratio at baseline. The markers included in our model were based on our previous prediction model (Nowak et al. Kidney Int 2018).

Results: One hundred sixty patients were enrolled. Median age was 57.5, 43.1% were women, 75.6% were Caucasian, median HbA_{1c} was 7.7%, and median duration of diabetes was 10.0 years. eGFR and ACR at baseline were 97.0 mL/min/1.73m^2 and 24.1 mg/g, respectively. One hundred patients experienced eGFR decline, and 60 were non-decliners. In comparison with non-decliners the group of eGFR decline at baseline had elevated plasma TNF-R1, KIM-1, WFDC2, serum and urinary MMP-7, whereas urinary EGF/MCP-1 ratio was decreased. Quartile change of the fibrosis index was significantly associated with eGFR decline [odds ratio (OR) 2.04; 95% confidence interval (CI) 1.38-3.03] and was consistent in patients with normoalbuminuria (OR 5.18; 95% CI 2.00-13.41) and microalbuminuria (OR 2.33; 95% CI 1.38-3.96). The effects of the fibrosis index on eGFR decline were robust across sex, HbA_{1c}, duration of diabetes, and use of renin-angiotensin system inhibitors in subgroup analyses.

Conclusions: Renal fibrosis is associated with early progressive renal decline in type 2 diabetes, even in patients without albuminuria.

Funding: NIDDK Support, Private Foundation Support

SA-PO538

Effects of Tubulointerstitial Plasmocyte Infiltration on Hard Clinical Renal Outcomes in Subjects with Diabetic Kidney Disease

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Background: Identification of the tubulointerstitial inflammatory features has the potential to the prediction of renal prognosis of diabetic kidney disease (DKD); however, the influence of plasmocyte infiltration on the DKD is unclear. This study was conducted to determine the association between the tubulointerstitial plasmocyte infiltration and DKD in a cohort of Chinese patients with type 2 diabetes mellitus (T2DM).

Methods: We enrolled 226 adult patients with biopsy-proven DKD for a follow-up time more than 12 months. Tubulointerstitial plasma cells in kidney biopsy tissues were detected by immunohistochemistry and immunofluorescence. The patients then were divided into two groups based on tubulointerstitial plasmocyte infiltration: plasmocyte group (n=117) and non-plasmocyte group (n=109). Hard renal outcome was defined as end stage renal disease (ESRD). A comparison of the baseline features and renal prognosis between the two groups was performed.

Results: The accumulation of tubulointerstitial plasma cells was found to be related with more serious anemia, heavy proteinuria, renal function decline, and more serious glomerular, interstitial and arterial lesions. During the follow up (12-85 months), 42.5% (96) of patients developed ESRD. Patients in plasmocyte group exhibited a high percentage of incident ESRD (53%) than those (31.2%) in non-plasmocyte group ($p<0.05$). A Cox regression showed that the plasmocyte infiltration had a significant effect on the renal endpoint (HR, 1.969; 95%CI, 1.292-3.000), though it was not an independent risk factor.

Conclusions: As one of contributors to the renal inflammatory response, the tubulointerstitial infiltration of plasmocyte was associated with severity of glomerular, interstitial, and arterial lesions as well as DKD hard clinical renal outcome.

Funding: Government Support - Non-U.S.

SA-PO539

Impact on Kidney Function with Focal and Segmental Glomerulosclerosis (Tip) in Patients with Diabetic Nephropathy

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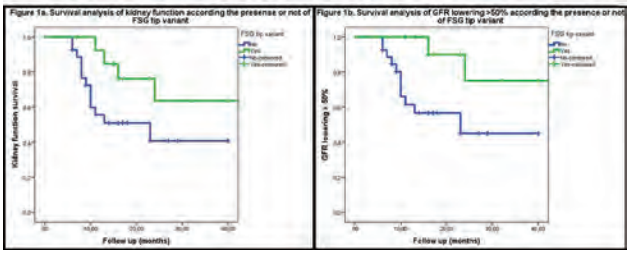
Background: Type 2 Diabetes Mellitus is the first cause of end stage kidney disease (ESKD). Focal and Segmental Glomeruloesclerosis (FSG) is the most common glomerulopathy in western world. Tip variant is the most common glomerulopathy associated with Diabetic Nephropathy (DN). By now, only mathematic and experimental models tried to explain the association between DN and FSG (tip) without including the clinical impact and the prognosis of these patients. This study is the first in Mexico which evaluates this combination and the clinical impact.

Methods: Retrospective cohort with patients over 18 years with renal biopsy who at that moment, didn't had ESKD. We did descriptive and analytic statistics and a survival analysis with Kaplan Meier. We considered as primary outcome, the need of dialysis, lowering glomerular filtration rate (GFR) >50% of basal value and/or doubling the basal serum creatinine.

Results: 41 patients included, 64% (26) male, 73% (30) had hypertension at the moment of the biopsy, 83% (34) had nephrotic syndrome, the chronic changes score (CCS) were moderate or severe in >90% of patients. The age was 51±13, follow up of 18±12 months, the initial proteinuria was 8.8±4.3 gr/24h in the group without FSG and 8.3±5.7 gr/24h in the other group. The proteinuria at 6 months after the biopsy was different between groups (p= 0.03). The group without FSG had worse GFR, but with no difference in the analysis of the primary outcome, (Figure 1)

Conclusions: There was no difference between groups in the primary outcome, but we observe some clinical differences. The CCS did evaluate better the outcomes than the histologic changes in both groups. Maybe further studies with more patients, could find a difference in the impact of FSG on kidney function proposed in our study.

Figure 1. Survival analysis according the presence or not of FSG tip variant, complex outcome and GFR lowering >50%



SA-PO540

Interstitial Eosinophilic Infiltration in Diabetic Nephropathy Is Indicative of Poor Prognosis with No Therapy Benefit from Steroid

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Background: Recent data suggested that eosinophils in diabetes might be associated with severity of diabetic nephropathy (DN). In a retrospective study of 102 Chinese patients with biopsy proven DN, we aimed to evaluate relationships of both blood and renal eosinophils(Eos) to the severity of DN, and check whether it can be served as an independent indicator of prognosis as well as therapeutic effect of steroids in these patients.

Methods: A total of 102 patients with a single diagnosis of glomerulopathy with DN were enrolled. Demographical and clinical data as well as histopathological scores were associated. Interstitial eosinophilic aggregates (IEA) were defined as the presence of ≥10 Eos in at least one high-power field (×400). End stage renal disease was defined as the end point. Urinary eosinophil cationic protein (ECP) levels were also analyzed to evaluate its biomarker role in DN

Results: We observed that $\log_2$(blood eosinophil counts) correlated with neutrophil counts, proteinuria and interstitial inflammation. IEA was observed in 33.3% of the DN patients and was associated with higher serum creatinine (2.3 vs. 1.5mg/dL, p=0.021), lower estimated glomerular filtration rate (39.8 ± 27.3 vs. 51.9 ± 30.3ml/min/1.73 m^2, p=0.053), higher proteinuria (7.5 ± 4.8 vs. 4.9 ± 3.6g/d, p=0.004), more prevalence of hematuria (82.4% vs. 43.9%, p<0.001), higher HbA1c (7.5 ± 1.9% vs. 6.7 ± 1.4%, p=0.026), higher blood eosinophil counts (0.22×10^9 vs. 0.16×10^9/L, p=0.001), severer tubulointerstitial injury including tubular injury (p=0.004), interstitial inflammation(p=0.004), tubular atrophy (p= 0.007) and interstitial fibrosis (p=0.020). IEA was associated with worse renal prognosis (HR 2.424, p=0.008). Consistently, urine ECP (ng/mgCr) was associated with renal injury and poor renal prognosis (HR 1.160, p=0.024). Patients with IEA were more likely to be treated with steroid (IEA vs. non-IEA, 47.1% vs. 14.7%, p=0.001) but did not show renal benefit.

Conclusions: It suggested that both blood and renal infiltrated eosinophils were prevalent in DN and associated with severity of DN. But IEA in renal pathology showed better fit in correlation with renal prognosis. Treatment with steroid/immunosuppressant showed no significant improvement regarding renal prognosis.

Funding: Government Support - Non-U.S.

SA-PO541

The Feasibility and Safety of Obtaining Research Kidney Biopsy Cores in Patients with Diabetes: An Interim Analysis of the TRIDENT Study

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Background: Obtaining additional kidney tissue for research is essential for advancing the understanding and treatment of kidney disease. The Transforming Research in Diabetic Nephropathy (TRIDENT) Study is a multi-center, longitudinal, observational cohort study for adults with diabetes who are undergoing a clinically indicated kidney biopsy, and requires an additional research biopsy core. We present an interim analysis of the feasibility and safety of obtaining research kidney biopsy cores in the TRIDENT study.

Methods: The TRIDENT database was analyzed for data acquired as of May 1, 2019. Data on adverse events (AEs) were obtained for cases where a research core was successfully obtained and a central pathologist confirmed the histologic diagnosis (N=134). Clinical and demographic data was obtained at the enrollment visit, which occurred within 45 days of biopsy. We defined AEs as hematoma >5cm, gross hematuria and prolonged hospital stay. Serious AEs included unplanned blood transfusion, transfer to an intensive care unit (ICU), respiratory distress requiring intubation or vascular radiology intervention to halt bleeding.

Results: As of May 1, 2019, 160 patients were consented and underwent kidney biopsy at 15 centers, with a research biopsy core successfully obtained in 143 cases (89%). Diabetic glomerulopathy was found in 110 (82%) of cases. Patients had a mean age of 54.7 (SD 12.6) years, with 45% female, 32% African American race and 34% Hispanic ethnicity. The mean serum creatinine was 2.9 (SD 1.9) mg/dL. A 16 gauge needle was used in 72 (54%) of biopsies and the mean number of biopsy passes was 3.6 (SD 1.0). Serious AEs occurred in 4 patients (3%): blood transfusion in 2 (1.5%), post-biopsy aspiration leading to respiratory failure and prolonged hospitalization in 1 (0.7%)) and ICU observation in 1 (0.7%). Post-biopsy hematoma >5 cm was noted in 7 (5.2%), 2 developed transient gross hematuria (1.5%) and 5 (3.7%) patients required a prolonged hospital stay.

Conclusions: This interim analysis of the TRIDENT study suggests that obtaining tissue for research purposes in adults with diabetes undergoing clinical kidney biopsies is feasible and is associated with an acceptable complication rate.

Funding: Commercial Support - Boeringer Ingelheim, Gilead, GSK, Regeneron Pharmaceuticals

SA-PO542

Incidence in Kidney Failure from Diabetes Among Native Americans, 2000-2016

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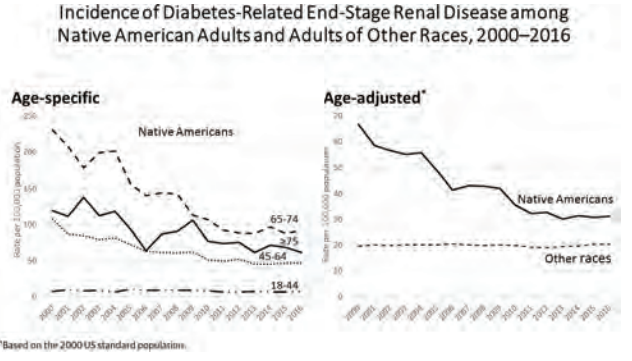
Background: Diabetes-related end-stage renal disease (ESRD-D) among Native Americans (NAs) declined from 1996 to 2013. We assessed recent data to determine if the rates have continued to decline.

Methods: From the US Renal Data System, we obtained the number of NA adults and adults of other races (whites, blacks, Asians, Native Hawaiians/Pacific Islanders, and others) aged ≥18 years with newly treated ESRD-D (with diabetes listed as primary cause of ESRD) between 2000 and 2016. ESRD-D rates by age and sex were calculated using general population estimates from the US Census and age-adjusted based on the 2000 US standard population. Joinpoint regression was used to assess trends and estimate the annual percentage change (APC).

Results: From 2000 to 2016, the number of US adults starting ESRD-D therapy decreased from 878 to 825 for NAs and increased from 40,632 to 56,170 for other races. For NAs, the age-adjusted ESRD-D rate decreased from 66.7 per 100,000 population in 2000 to 30.3 in 2013 (APC= -5.6%, p<0.001) and then leveled off (Figure). Trends for NA men and women were similar to the overall trend. For other races, the age-adjusted rate increased slightly from 2000 to 2006 (from 19.7 to 20.7, APC=0.6%, p=0.04), decreased from 2006 to 2012 (20.7 to 19.1, APC= -1.1%, p=0.007), and again increased from 2012 to 2016 (19.1 to 20.3, APC=1.5%, p=0.009). By age group, ESRD-D rates showed no change for NAs aged 18-44 (from 7.7 in 2000 to 7.6 in 2016), declined for NAs aged 45-64 (from 108.3 in 2000 to 45.2 in 2013, APC= -5.8%, p<0.001) and 65-74 (from 231.2 in 2000 to 88.6 in 2012, APC= -7.6%, p<0.001) and then leveled off, and declined throughout the period for NAs aged ≥75 (119.3 to 61.9, APC= -4.2%, p<0.001).

Conclusions: From 2000 to 2016, ESRD-D continued to decline in NAs aged ≥75 years but, after an initial decline, has leveled off in more recent years in NAs aged 45-74 years. During the period, the disparity gap between NAs and other races was reduced more than 2-fold. Continued efforts might be considered to sustain and improve ESRD-D trends in NAs.

Funding: Government Support - Non-U.S.



SA-PO543

Genetic Determinants of CKD Progression Among Individuals with Diabetes: The Million Veteran Program

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Background: The rate of CKD progression among individuals with diabetes varies widely and is incompletely explained by known risk factors. While the genetic determinants of cross-sectional eGFR have been identified, only one small analysis of longitudinal change in eGFR among individuals with CKD has been conducted.

Methods: We performed a genome-wide association study of the relative rate of decline in estimated glomerular filtration rate (eGFR, % decline/year) among individuals with CKD and diabetes participating in the Million Veteran Program. Our study included participants

with genetic data available from the MVP second data release, with 351,510 participants from whom 91,523 individuals had type 2 diabetes. Analyses were stratified by race.

Results: There were 28,368 individuals with CKD and diabetes. 21% (n=5904) were of non-hispanic black race /ethnicity. Mean (SD) eGFR at baseline was 51.1 (±8.1) ml/min/1.73m^2 and median relative kidney function decline was -0.5%/year. Trans-ethnic meta-analysis uncovered 6 SNPs from only one region significantly associated with decline in kidney function. The SNP with the strongest association, rs6047460, lies 45kb upstream of *UGT2A1*; every additional minor allele was associated with a 1%/year faster decline in eGFR ($p=1.1 \times 10^{-7}$). Among blacks, we were able to replicate one of four previously identified SNP, rs116356141, which lies between *SH2D4B* and *NRG3* (p=0.03). Among whites, we were able to replicate 2 of 11 SNPs previously associated with incident CKD, rs12917707 (near *UMOD*, $p=6x10^{-4}$) and rs7805747 (intronic for *PRKAG2*, $p=9x10^{-3}$).

Conclusions: Our data suggest that while there is genetic basis for diabetic kidney disease progression, the discovery of the genetic variants involved has been difficult. The etiological heterogeneity of the phenotype could preclude true associations from being detected.

Funding: Veterans Affairs Support

SA-PO544

Poor Renal and Cardiovascular Outcomes in Patients with Biopsy-Proven Diabetic Nephropathy

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Background: Despite high level of mortality related to cardiovascular disease (CVD) in diabetic patients with renal injury, few studies have compared cardiovascular characteristics and outcomes between patients with diabetic nephropathy (DN) and non-diabetic renal disease(NDRD).

Methods: A total of 370 T2DM patients with renal biopsy were assigned to one of three groups (DN, NDRD, and NDRD with underlying DN). Echocardiography and Doppler ultrasound were performed to evaluate left ventricle hypertrophy(LVH) and peripheral atherosclerosis disease(PAD). Renal and cardiovascular survival rates were compared between the DN and NDRD groups by Kaplan-Meier analysis (medium follow-up, 29 months). Risk factors for renal and cardiovascular events were identified by Cox proportional hazards model.

Results: DN patients were more vulnerable to developing LVH than NDRD patients (37.3% vs 6.8%, $P < 0.001$). PAD was more severe in DN group, with thicker intima-medium and more atherosclerotic plaques ($P < 0.001$). Poorer renal (log Rank $X^2 = 22.089$, $P < 0.001$) and cardiovascular (log Rank $X^2 = 9.346$, $P = 0.002$) prognosis were seen in DN group. Low estimated glomerular filtration rate at baseline was associated with renal events (HR = 0.962 [0.942–0.983], P = 0.001), while elevated levels of glycosylated hemoglobin A1c (HR = 1.599 [1.256–2.635], P = 0.041) and postprandial blood glucose (HR = 1.321 [1.072–1.626], P = 0.009) were identified as risk factors for cardiovascular events.

Conclusions: Patients with DN had more severe CVD along with poorer renal and cardiovascular prognosis than those with NDRD.

Funding: Government Support - Non-U.S.

SA-PO545

Association of Urinary Acidification Function with the Progression of Diabetic Kidney Disease in Patients with Type 2 Diabetes

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Background: Although diabetic kidney disease (DKD) has been considered as a glomerulocentric disease in the past few decades, growing evidence demonstrated that tubular damage is indispensable in its pathogenesis and progression. This study was designed to investigate the association of urinary acidification dysfunction with the progression of DKD in type 2 diabetic patients.

Methods: Here we measured the urinary acidification function from 80 participants with renal biopsy-proven DKD. The different kinds of renal tubular transportation dysfunction were analyzed by urinary acidification function, including the dysfunction of bicarbonate reabsorption, titratable acid secretion, and ammonium secretion. In addition, patients were followed up for 17 (interquartile range, 11-32) months to evaluate the effect of urinary acidification dysfunction in the progression of DKD.

Results: The dysfunction of ammonium secretion was the most common, accounting for 53.75%. The more proteinuria excretion and the lower glomerular filtration rate (GFR) were observed in the urinary titratable acid secretion disorder group than the normal group, and the same results were obtained for ammonium secretion disorder. Urine titratable acid was positively correlated with eGFR whereas it was inversely correlated with proteinuria, serum creatinine, and BUN. Moreover, 24h urine protein, serum creatinine, BUN and cystatin C increased from DKD stage II to stage IV, whereas the eGFR and urine titratable acid decreased in the same way. Furthermore, Kaplan-Meier analysis and Cox regression showed that the dysfunction of titratable acid secretion was an independent risk factor of DKD progression.

Conclusions: The dysfunction of titratable acid secretion is a potential biomarker for the severity of proteinuria, eGFR and glomerular lesions in patients with DKD. Moreover, the titratable acid secretion disorder is an independent risk factor of the DKD progression.

SA-PO546

Influence of Metabolic Phenotype and Non-Alcoholic Fatty Liver Disease in the Evolution of Renal Function in Diabetic Patients

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Background: It has been described the albuminuric and normoalbuminuric phenotypes in diabetic nephropathy (DN). However, there is little information on the influence of non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome (MSd) on renal function in patients with type 2 diabetes mellitus (DM). The aim of this study was to compare the effect on renal function and proteinuria in patients with type 2 DM according to the presence of MSd.

Methods: Retrospective and observational study, including patients with type 2 DM, < 70 years of age and estimated glomerular filtration rate (eGFR) > 30 ml/min/1,73 m^2. MSd was defined as: obesity (body mass index > 30 kg/m^2), hypertension and dyslipidaemia. Patients were classified according to the presence or absence of MSd. We analysed different clinical and analytical variables along the follow up.

Results: A total of 90 patients were included (61% males) with mean age of 57.9 7.6 years. The median evolution of type 2 DM was 64.8 months (38.7 – 117.8 months). When comparing patients with (group 1, n=39) and without (group 2, n=51) MSd at the beginning of this study, we found no significant difference in eGFR (80.5 39.7 ml/min vs 71.3 29.4 ml/min), proteinuria (1.4 1.1 g/24h vs 2.2 3.1 g/24h) and glycated haemoglobin (7.4 1.7% vs 6.8 1.2%). After a mean follow-up time of 74 months, we found significant differences in the loss of eFGR (group 1 4.9 ml/min/year vs group 2 2.6 ml/min/year; .013) and in increase of proteinuria (2.7 3.5 g/24h vs 1.0 1.3 g/24h; .02). We found an increase in incidence of chronic kidney disease in group 1 (26%) vs group 2 (16%). There were no differences in the need to initiate renal replacement therapy or all-cause mortality. On a post hoc analysis, we evaluated the influence on renal function and proteinuria of NAFLD. Twenty eight out of 59 patients had NAFLD, observing a significant difference in loss of eFGR between those with and without NAFLD (32.7 ± 4.9 vs 29.7 ± 5.3; .03). There was also an increase in incidence of chronic kidney disease (32% vs 10%).

Conclusions: Metabolic phenotype and NAFLD in type 2 DM caused a mayor decline in renal function and increase in 24-hour proteinuria. Therefore, we should stratify patients with DKD to optimise treatment of associated risk factors.

SA-PO547

Prognostic Importance of Serum Alkaline Phosphatase in Type 2 Diabetic Patients with Diabetic Nephropathy

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Background: This study was aimed to investigate the impact of circulating alkaline phosphatase (ALP) on renal outcomes in type 2 diabetic patients with diabetic nephropathy (DN).

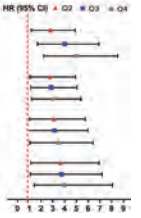
Methods: This longitudinal observational study enrolled 299 type 2 diabetic patients with biopsy-proven diabetic nephropathy. Patients were divided into two groups: nephrotic-range proteinuria group (NPU, 24h proteinuria≥3.5 g/d, n=179), and non nephrotic-range proteinuria group (non-NPU: 24h proteinuria<3.5 g/d, n=121). Multivariable adjusted Cox models were used to estimate the association of serum ALP with end-stage renal disease (ESRD).

Results: During a median follow up of 26.0 months, 133 (44.5%) patients progressed to ESRD. The median ALP was much higher in NPU group than non-NPU group (87 IU/L vs. 76 IU/L, P=0.009). In NPU group, higher ALP levels were incrementally associated with higher risks of ESRD after adjusted for demographics, kidney functions, nutritional status and medications. The highest quartile of ALP was associated with a hazard ratio for ESRD of 3.37 [95% confidence interval (CI), 1.41-8.07] (Figure 1). Moreover, ALP level was positively correlated with proteinuria (r=0.21) and interstitial fibrosis and tubular atrophy (r=0.37). In non-NPU group, only the highest ALP quartile was associated with a hazard ratio for ESRD of 2.94 (95% CI, 1.08-9.36).

Conclusions: Elevated serum ALP was an independent predictor for time to renal events in type 2 diabetic patients with nephrotic-range proteinuria. Our findings suggested ALP might play a role in kidney fibrosis and interstitial injury. Further studies are warranted to clarify the potential mechanisms.

Funding: Government Support - Non-U.S.

	Per 1SD ln ALP	Hazard ratio (95% Confidence Interval) & P-value Serum ALP (U/L) Q1 (n = 43) ≤67 IU/L	Q2 (n = 46) 68-87 IU/L	Q3 (n = 44) 88-102 IU/L	Q4 (n = 45) ≥103 IU/L
Unadjusted model	1.67 (1.36-2.05)	1 (reference)	2.59 (1.16-4.91)	3.43 (1.7-6.92)	4.35 (2.22-8.52)
	< 0.001		0.018	0.001	< 0.001
Model 1 *	1.30 (1.01-1.67)	1 (reference)	2.28 (1.05-4.94)	2.38 (1.12-5.05)	2.53 (1.19-5.39)
	0.039		0.036	0.024	0.016
Model 2 #	1.27 (0.96-1.67)	1 (reference)	2.41 (1.01-5.76)	2.57 (0.86-5.97)	2.98 (1.05-8.42)
	0.094		0.049	0.104	0.039
Model 3 †	1.57 (1.12-2.21)	1 (reference)	2.79 (1.12-6.94)	2.92 (1.08-7.18)	3.37 (1.41-8.07)
	0.010		0.028	0.034	0.006



Model 1 *, adjusted for baseline age, gender, ethnicity, smoking, CVD morbidity, diabetic retinopathy, SBP, DM duration, hemoglobin, albumin, cholesterol, eGFR and proteinuria, Renin-angiotensin-aldosterone system inhibitor use.Model 2 #, adjusted for covariates in model 1 plus renal pathological findings according to Renal Pathology Society system.

Model 3 †, adjusted for covariates in model 2 plus Calcium, Phosphorus, ALT, AST, γ-glutamyltransferase.

SA-PO548

Diabetic Retinopathy and Progression of Diabetic Kidney Disease in Asians

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Background: Diabetic kidney disease (DKD) and diabetic retinopathy (DR) share similar risk factors and pathogenic mechanisms. We examined the prospective relationship between DR and incidence and progression of DKD in a multi-ethnic Asian population in Singapore.

Methods: We analysed data from 2981 Chinese, Malay and Indian adults with diabetes aged 17-90 years who attended annual screening visits (3-6 visits) at primary care clinics from 2010-2015 as part of the Singapore Integrated DR Screening Program (SiDRP). DR (n=297) was assessed from retinal photographs graded using a standard protocol and defined as presence of mild/moderate/severe DR. Incident DKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2+ 25% decrease in eGFR at follow-up in those with eGFR≥60 at baseline and DKD progression as decline in eGFR by ≥30% from baseline to follow-up. We examined the association between DR and incidence/progression of DKD using logistic regression models adjusted for age, sex, ethnicity, systolic blood pressure (SBP), baseline eGFR, HbA1c, and duration of diabetes. We assessed if addition of DR improved prediction of DKD incidence or progression to traditional risk factor model by comparing the area under the receiver operating characteristic curve (AUC-ROC).

Results: The 3-5 year cumulative incidence and progression of DKD were 6.4% and 2.1%. Progression was significantly higher in Malays compared to Chinese and Indians (4.4%, 1.9%, 1.9%, p=0.04), incidence was not significantly different (7.1%, 6.8%, 3.8%, p=0.09). In multivariable models, DR was significantly associated with both incident and progressive DKD, (odds ratio [95% confidence interval] = 2.29 [1.50-3.48]) and 2.20 [1.18-4.09]) compared to no DR. Addition of DR, did not significantly improve prediction of incidence (AUC= 0.824 vs. 0.818, p=0.1) or progression (0.737 vs. 0.726, p=0.4) compared to traditional model, probably due to the small number of events. Other than DR, SBP and baseline eGFR were significant predictors for incidence and progression and Malay ethnicity for progression (all p<0.05).

Conclusions: We found that presence of DR was independently associated with increased risk of onset and progression of DKD. Our findings emphasize the importance of assessing DR status in DKD management and control of blood pressure in DR patients.

Funding: Government Support - Non-U.S.

SA-PO549

Relationship Between Waist Circumference and Renal Function Decline Rate

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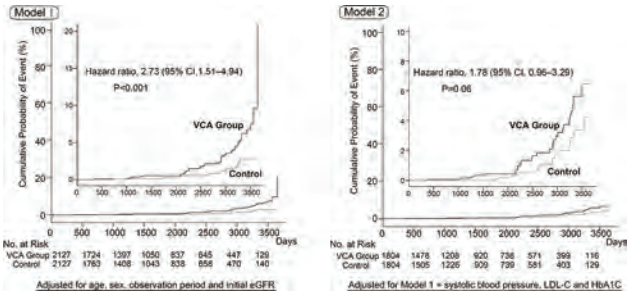
Background: As hyperinsulinemia correction is one of the renal protective effects of SGLT2 inhibitors, we hypothesized that hyperinsulinemia-insulin resistance deteriorates renal function. Therefore, we investigated the relationship between waist circumference, a marker of visceral fat and an indicator of insulin resistance, and renal function decline rate.

Methods: In this single-institutional observational study in Japan, subjects were selected from those who underwent creatinine and waist circumference measurements at annual health examinations from 2008 to 2018. Subjects had undergone examinations for ≥2 years; their estimated glomerular filtration rate (eGFR) in the first year was > 60 ml/min/1.73 m^2. The subjects were divided into two groups: visceral adiposity group (VCA group) and control group, by the initial abdominal circumference based on diagnostic criteria for metabolic syndrome in Japan. We adjusted for the following baseline variables: model 1: age, sex, observation period, and initial eGFR; model 2: model 1 + systolic blood pressure, low-density lipoprotein cholesterol, and hemoglobin A1C during the observation period. We evaluated both groups by time-to-event analysis for 30% eGFR decline.

Results: Totally, 8390 subjects (56.4% men, mean age: 47.7 years, mean observation period: 1751.1 days) met the criteria. The mean waist circumference was 77.0 cm in the control group and 92.3 cm in the VCA group. When adjusted using propensity score, 2127 (model 1) and 1804 (model 2) subjects in each group were extracted. In the time-to-event analysis for 30% eGFR decline, there was a significantly difference in model 1 (hazard ratio, 2.73 [95% CI, 1.51-4.94]; P<0.001), but not model 2 (hazard ratio, 1.78 [95% CI, 0.96-3.29]; P=0.06).

Conclusions: Excess visceral fat is associated with decreased renal function. However, after adjustment for hypertension, lipids, and glucose intolerance, this study failed to establish a relationship between hyperinsulinemia-insulin resistance and decreased renal function.



SA-PO550

Development of an Exhaustive-Risk-Prediction System Using Deep Learning and Different Patterns of Diabetic Kidney Disease Progression Based on Patient Characteristics

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Background: Diabetic kidney disease (DKD) is a risk factor for end-stage kidney disease (ESKD) and death. An accurate prediction of these risks at an individual level is required to improve DKD patients' prognosis. In this study, we developed a new system for the prediction of chronic kidney disease (CKD) progression using deep learning (DL) and the CKD big database in Japan, and investigated DKD progression patterns based on their characteristics.

Methods: The associations among patients' characteristics, laboratory data and an outcome (ESKD or death) in five years were evaluated by DL. The kidney disease progression risk for a virtual patient was simulated using the trained DL model.

Results: Among the patients (n=3877, 83701 measured data), 53.0% were male; average age, 59.8±17.9 years; estimated glomerular filtration rate (eGFR), 51.1±29.0 ml/min/1.73 m^2; and diabetes mellitus, 18.8%. In the test dataset, the accuracy of DL was 0.95, which was higher than those of multivariate logistic regression models (0.84) and support vector machine models (0.84). Then, various patterns of characteristics of a 60-year-male patient were evaluated. The predicted risk of the outcome is shown in heat maps (Figure 1), and various patterns are observed. A basic pattern (e.g., CKD severity category) shows high risks in categories of low eGFR and high urinary protein level. And, the nephrosclerosis-like pattern shows higher risks at low urinary protein levels than at high urinary protein levels. Moreover, DKD shows a mix pattern, which suggests that DKD patients are a heterogenous population.

Conclusions: We developed a new exhaustive risk-prediction system using DL and found different patterns of kidney disease progression based on patient characteristics. This system may be useful for identifying patients at an increased risk of DKD progression for early treatment.

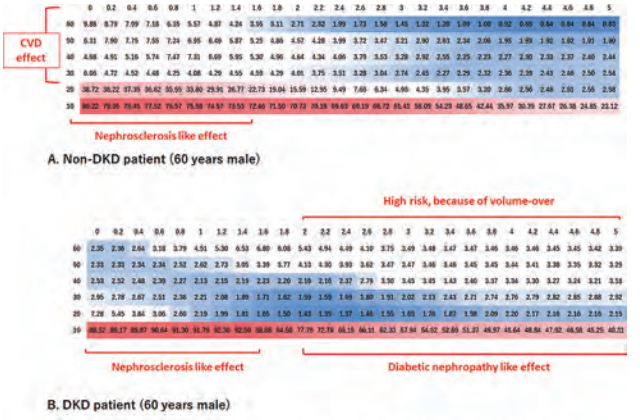

Figure 1 Risks of CKD progression predicted on the basis of patients' characteristics

SA-PO551

Trimethylamine-N-Oxide and Renal Complications, Cardiovascular Disease, and Mortality in Individuals with Type 2 Diabetes and Microalbuminuria

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Background: Trimethylamine-N-Oxide (TMAO) is suggested as an independent gut microbiota derived risk marker for several diseases. We investigated associations between plasma TMAO concentrations and all-cause mortality, cardiovascular disease (CVD) and deterioration in renal function in individuals with type 2 diabetes and microalbuminuria.

Methods: Plasma TMAO was measured at baseline in 311 individuals with type 2 diabetes and microalbuminuria. All-cause mortality and CVD (fatal and non-fatal) were tracked from national registries. Yearly p-creatinine was measured after baseline in 166 of the participants, the renal endpoint was defined as eGFR-decline of >30%. Associations between TMAO and events were analyzed using Cox regression models. Adjusted models included age, sex, HbA1c, systolic blood pressure, total cholesterol, urine albumin excretion rate and eGFR.

Results: Baseline mean (SD) age was 57.2 (8.2) years, 75% were male and median [IQR] of TMAO was 5.87 [3.79-9.04] μM. TMAO was negatively associated with eGFR at baseline (R^2=0.108, p<0.0001). Follow-up was up to 21.8 years for all-cause mortality and CVD events (median 6.8 and 6.5 years) and for renal events up to 5.8 years (median 4.6 years). We recorded 106 cases of mortality, 116 CVD events and 41 renal events. Higher plasma TMAO concentrations were associated with renal events in unadjusted analyses (p=0.03), but not after adjustment p=0.17. TMAO was not associated with mortality (unadjusted p=0.53; adjusted p=0.87) or CVD events (unadjusted p=0.14; adjusted p=0.24).

Conclusions: In individuals with type 2 diabetes and microalbuminuria, plasma TMAO was negatively correlated with eGFR at baseline. Moreover, higher plasma TMAO was in unadjusted analysis associated with renal events, but not after adjustment. Plasma TMAO was not associated with mortality and CVD events.

Funding: Private Foundation Support

SA-PO552

Visit-to-Visit Variability of Albuminuria and eGFR as Risk Markers for Renal Complications, Cardiovascular Events, and Mortality in Type 1 Diabetes

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Background: Clinicians strive towards determining stable and reliable measures for monitoring risk of diabetic complications. The impact of visit-to-visit variability (VVV) of albuminuria (ALB) and eGFR needs further clarification. We investigated VVV in ALB and eGFR as risk markers of renal complications, cardiovascular events (CVE), and mortality in subjects with type 1 diabetes (T1D).

Methods: 1077 individuals with T1D a range of albuminuria were included. VVV was defined as the standard deviation (SD) of the residuals in individual linear regression models, calculated using all measures of ALB or eGFR from 1998-2016. Data on end-stage renal disease (ESRD), CVE and mortality were gathered through national registers. eGFR and ALB was traced through laboratory records from ambulatory care. Endpoints were ESRD (CKD stage 5, dialysis or transplantation), eGFR-decline ≥30%, CVE (cardiac death, myocardial infarction, stroke and arterial interventions) and mortality. Hazard ratios (HR) were calculated using Cox models and are presented per doubling of VVV. Adjustment included sex, age, total cholesterol, HbA_{1c}, systolic blood pressure, body mass index, smoking, 24h ALB, eGFR, and the intercept and slope of the respective linear models.

Results: Median follow-up ranged from 6.1-13.4 years for ALB and 6.8-16.2 years for eGFR, depending on endpoint. Subjects had a mean (SD) age and diabetes duration of 47 (13) and 27 (13) years, respectively, at baseline. Depending on availability of data, between 848-1077 subjects were included in the respective models. Adjusted HR (95% CI, p) for ALB VVV were 1.68 (1.38-2.05, p<0.001), 1.34 (1.25-1.44, p<0.001), 1.12 (1.04-1.20, p=0.002) and 1.10 (1.01-1.19, p=0.029) for development of ESRD, eGFR decline ≥30%, CVE and mortality, respectively. Adjusted HR (95% CI, p) for eGFR VVV were 1.78 (1.29-2.45, p<0.001), 2.02 (1.68-2.43, p<0.001), 0.96 (0.85-1.08, p=0.091) and 0.93 (0.79-1.11, p=0.424) respectively.

Conclusions: We demonstrate an independent association between long term VVV in ALB and development of renal complications, CVE and mortality in T1D, and in eGFR VVV for development of renal complications. Studies addressing stabilization of VVV and reduction of endpoints, are warranted.

SA-PO553

Poor Glycemic Control Increases Mortality in Elderly Dialysis Patients with Diabetes: A Nationwide Prospective Cohort in Korea

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Background: Glycemic control, defined as glycated hemoglobin (HbA1c), was known to be an important factor for mortality in diabetic end-stage renal disease (ESRD) patients. However, the clinical impacts of glycemic control had not been fully elucidated in the elderly diabetic ESRD patients. We investigated whether glycemic control had clinical impact on all-cause mortality of elderly dialysis patients with diabetes.

Methods: A total of 755 elderly diabetic patients (≥ 65 years) who had a value of HbA1c at the time of cohort enrollment were extracted from a nationwide prospective ESRD cohort in Korea between August 2008 and February 2015. The patients were divided into three groups according to the degree of glycemic control (< 6.5%, 6.5-7.9%, and ≥ 8.0%).

Results: The patients in the highest group of HbA1c (≥ 8.0%) were 132 (17.5%), which were younger, had higher vintages of dialysis, and higher percentage of peritoneal dialysis than the other two groups. Mortality rate was 57.2% during the median follow-up of 56.3 months. Patients with poor glycemic control (≥ 8.0%) had a higher risk of mortality compared with those in the HbA1c < 6.5% (hazard ratio [HR] 1.37; 95% confidence interval [CI] 1.06-1.77; P = 0.016). In subgroup analysis by dialysis modality, HbA1c ≥ 8.0% was a risk factor for mortality in the patients on peritoneal dialysis (HR 1.66; 95% CI 1.02-2.70; P = 0.041). Multivariate analysis adjusting for age, sex, comorbidity, dialysis vintage, and dialysis modality verified a significant association between poor glycemic control (≥ 8.0%) and mortality rate in the elderly diabetic ESRD patients (HR 1.53; 95% CI 1.17-2.00; P = 0.002).

Conclusions: Poor glycemic control was significantly associated with mortality in the elderly dialysis patients, which suggests that lowering HbA1c to at least less than 8.0% might decrease mortality rate.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO554

Hypoglycemia and Mortality Risk in Incident Hemodialysis Patients

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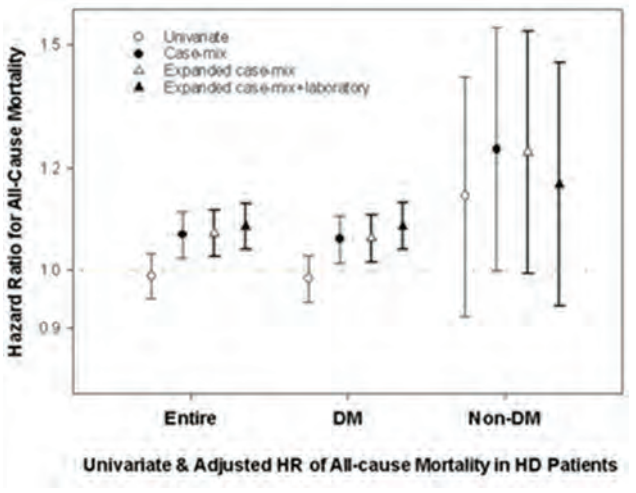
Background: Hypoglycemia is a frequent occurrence in chronic kidney disease (CKD) patients due to alterations in glucose and insulin metabolism. Yet there are sparse data examining the predictors and clinical implications of hypoglycemia, including mortality risk, among incident hemodialysis patients.

Methods: Among 58,304 incident hemodialysis patients receiving care from a large national dialysis organization over the period 2007-2011, we first examined clinical characteristics associated with risk of hypoglycemia, defined as a blood glucose concentration of <70 mg/dL, in the first year of dialysis using expanded case-mix and laboratory-adjusted logistic regression models. We then examined the association between hypoglycemia during the first year of dialysis with all-cause mortality risk using expanded case-mix and laboratory adjusted Cox models.

Results: In the first year of dialysis, hypoglycemia was observed among 16.8% of diabetic and 6.9% of non-diabetic incident hemodialysis patients. In adjusted logistic regression models, clinical characteristics associated with higher risk of hypoglycemia included younger age, female sex, African-American race, presence of a central venous catheter, lower residual renal function, and longer dialysis session length. In the overall cohort, patients who experienced hypoglycemia had a higher risk of all-cause mortality (reference: absence of hypoglycemia): adjusted HR (95% CI) 1.08 (1.04, 1.13). In stratified analyses, hypoglycemia was also associated with higher mortality risk in the diabetic and non-diabetic subgroups: adjusted HRs (95% CIs) 1.08 (1.04-1.13) and 1.17 (0.94-1.45), respectively.

Conclusions: Hypoglycemia was a frequent occurrence among both diabetic and non-diabetic hemodialysis patients, and was associated with higher mortality risk. Further studies are needed to identify approaches that ameliorate risk of hypoglycemia in hemodialysis patients.

Funding: NIDDK Support



SA-PO555

Diabetic Retinopathy and the Risk of Renal, Cardiovascular, and Death Events: Results from a Longitudinal Japanese Cohort of 232 Patients with Type 2 Diabetes and Biopsy-Proven Diabetic Kidney Disease

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Background: The predictive value of diabetic retinopathy on end-stage kidney disease (ESKD), cardiovascular disease (CVD), and death has not been fully addressed in patients with type 2 diabetes and diabetic kidney disease.

Methods: We studied 232 patients with type 2 diabetes and biopsy-proven diabetic kidney disease, stratified into five groups according to the International Clinical Disease Severity Scale for Diabetic Retinopathy. The association between retinal grading and kidney lesions was examined. The risks of ESKD, CVD, and all-cause death, were explored using Cox regression analyses adjusted for known risk demographic and clinical variables. The incremental prognostic value of ESKD was assessed by adding diabetic retinopathy to the clinical variables.

Results: The severity scale of diabetic retinopathy positively correlated with all scores of renal lesions, especially with the glomerular-based classification (r =0.41), and scores of interstitial fibrosis (r =0.41) and diffuse lesion (r =0.47). During median follow-up of 5.7 years, 114 patients developed ESKD, 45 patients developed CVD, and 42 patients died, respectively. Compared to patients with no apparent retinopathy, the adjusted hazard ratio (HR) for ESKD were 1.96 (95% confidence interval (CI), 0.62-6.17) for patients with mild non-proliferative diabetic retinopathy (NPDR), 3.10 (95% CI, 1.45-6.65) for patients with moderate NPDR, 3.03 (95% CI, 1.44-6.37) for patients with severe NPDR, and 3.43 (95% CI, 1.68-7.03) for patients with proliferative diabetic retinopathy, respectively. The risks of CVD and all-cause mortality were not shown to be significant. The global chi-square statistic increased from 155.21 to 164.48 (p <0.001) with the addition of diabetic retinopathy severity scale to the clinical model alone.

Conclusions: Diabetic retinopathy appeared to be associated with developing ESKD but not with developing CVD or all-cause mortality. Since diabetic retinopathy and diabetic kidney disease share the same magnitude of microvascular changes, diabetic retinopathy may predict renal prognosis in patients with diabetic kidney disease.

SA-PO556

Prevalence and Risk Factor Analysis of Microalbuminuria in Type 2 Diabetic Patients: Data from Nationwide Registry of Primary Care Cohort of Thailand

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Background: Microalbuminuria (MAU), an indicator of glomerular injury, is associated with an increased risk of progressive renal deterioration, cardiovascular disease, and mortality. However, the prevalence of MAU in Asian populations is unclear, especially during various stages of chronic kidney disease (CKD). Thus, we examined the prevalence of microalbuminuria and its associated risk factors in Asian patients with type 2 diabetes mellitus (T2DM).

Methods: This study evaluated patients between 18 and 85 years old from the most extensive National Health Security System (NHS) of Thailand from 2011 to 2014. Multivariate regression analyses, including linear and logistic regression, were performed to assess the association between MAU and risk factors.

Results: A total of 7,587 T2DM patients were included. Sixty-four percent were female. The mean age was 63 ±11 years old. The prevalence of MAU was presented by percentage and 95% confidence interval (CI): CKD stage G1 32% (30–34); stage G2 34% (32–35); stage G3a 41% (39–44); stage G3b 47% (43–50); stage G4 70% (63–77); and stage G5 73% (60–82) **(Figure1)**. The multivariate analysis identified the odds ratio (OR) of time-average systolic blood pressure (adjusted OR; 95% CI; P-value) as an independent risk factor for MAU presence. After adjusting for age, gender, body mass index, occupation, provinces, religions, categories of cholesterol, and % glycosylated hemoglobin, the resulting levels were 1.12; 0.94–1.32; 0.20 (<120 mm Hg group), reference group (120–140 mm Hg group), 1.21;1.07–1.36; 0.003 (140–160 mm Hg group), and 1.45; 1.21–1.75; <0.0001 (>160 mm Hg group).

Conclusions: Several factors demonstrated independent correlations with MAU in Asian populations. Higher time-average systolic blood pressure was associated with MAU, which may lead to further target organ damage in T2DM. MAU has also been observed to be much more prevalent in later CKD stages.

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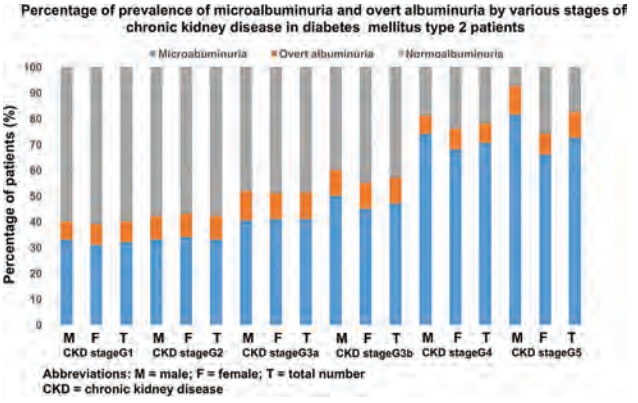

Figure1

SA-PO557

The Association Between Vitamin D Level and Microvascular Complications in Persons with Type 2 Diabetes

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Background: The objective of this study is to examine the association between vitamin D level and presence of microvascular complications in persons with type 2 diabetes.

Methods: Cross-sectional study including 789 persons with type 2 diabetes followed at Steno Diabetes Center Copenhagen with information on plasma concentration of vitamin D and relevant clinical data. Peripheral neuropathy was defined as bilaterally decreased sensibility of vibration and minimum one symptom.

Results: The cohort included 378 persons with normoalbuminuria (NA) (mean (SD) age 63.7 (11.5) years), 260 with moderately increased albuminuria (MA) (mean age 68.3 (10.9) years) and 148 with severely increased albuminuria (SA) (mean age 67.2 (11.0) years). The overall prevalence of vitamin D deficiency (25-49 nmol/L) and severe deficiency (<25 nmol/L) was 19.3% and 6.6%, respectively. In persons with NA, MA and SA, the mean (SD) of vitamin D level was 78.1 (35.7), 75.7 (33.6) and 65.2 (35.0) nmol/L, respectively. There was no difference between the NA and MA group (p=0.41), but the difference between the NA and SA group was significant both unadjusted (p=0.0002) and after adjustment for age, sex, seasonal variation, HbA_{1c}, smoking, BMI, systolic BP and eGFR (p=0.005). In linear regression analysis, vitamin D level was negatively associated with albuminuria unadjusted and after adjustment (both p<0.0001). When stratified into CKD stage 1 to 5; including 254, 309, 195, 20 and 11 persons, respectively, the mean (SD) vitamin D level was 70.3 (34.5), 78.6 (33.9), 74.2 (36.7), 81.5 (43.7) and 67.4 (25.9) nmol/L in stage 1 to 5. There was no difference between groups (p=0.25). The mean (SD) vitamin D level was 81.4 (41.2) nmol/L in persons with proliferative retinopathy (n=48) and 75.3 (35.0) nmol/L in persons without (n=621) (p=0.25). In persons with peripheral neuropathy (n=153), the mean (SD) vitamin D level was 74.3 (34.4) nmol/L, and 74.7 (35.4) nmol/L in persons without (n=470) (p=0.91).

Conclusions: Among persons with type 2 diabetes, persons with severely increased albuminuria had a lower vitamin D level; moreover, an inverse relationship between vitamin D level and albuminuria was demonstrated. Interestingly, no association between vitamin D level and CKD stage, proliferative retinopathy or peripheral neuropathy was observed.

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The Target Glycated Albumin Level May Differ According to Dialysis Patients' Nutritional Status and Use of Hypoglycemic Agents: A 3-Year Nationwide Cohort Study

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Background: We previously reported a J-shaped association between glycated albumin (GA) and mortality in diabetic patients on dialysis. However, it remains unclear what GA level is associated with the cause-specific mortality among patients taking or not taking hypoglycemic agents and among those with or without malnutrition.

Methods: We examined 40,417 diabetic patients on maintenance hemodialysis in a cohort studied by the Japanese Society for Dialysis Therapy (female, 30.8%; mean age, 67.3±11.2 years; mean dialysis duration, 5.4±4.6 years) and followed up for 3 years from 2013-2016. GLIM criteria were used to assess malnutrition. Patients on PD, who had history of kidney transplantation, or who did not have data of baseline GA or hypoglycemic agent use were excluded. We used Cox regression to calculate adjusted hazard ratios (HRs) and 95% confidence limits (95% CL) for 3-year mortality after adjusting for 18 potential confounders. Subdistribution hazard ratios (SHRs) were used to explore cause-specific mortality.

Results: Using GA levels of 15.9–17.2% as the reference, patients not taking hypoglycemic agents in the lowest GA deciles (≤15.8%) had slightly worse mortality (HR 1.10 [0.94–1.30]), mainly due to increased deaths from cancer (SHR 1.64 [0.99–2.68]), which was not observed in those patients taking hypoglycemic agents. Malnourished patients taking hypoglycemic agents in the lowest GA deciles had slightly worse mortality (HR 1.05 [0.75–1.46]), mainly due to increased deaths due to infections (SHR 1.31 [0.70–2.44]). In addition, their lowest mortality was observed at a GA level of around 21.5%, which was higher than that seen in other patients.

Conclusions: These data suggests that GA levels may differ according to patients' hypoglycemic agent use, nutritional status, and cancer status. Target GA levels in malnourished patients may be higher than in other diabetic patients, and a very low GA level in dialysis patients not taking hypoglycemic agents may be associated with an increased risk of cancer.

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SA-PO559

Predictors of CKD Progression, Mortality, and Cardiovascular Outcomes in Patients with and Without Diabetes

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Background: Diabetes and CKD are a growing burden for health systems, both in the US and internationally. Diabetes is thought to be responsible for approximately half of all end-stage renal disease (ESRD) cases. Also, the number of people with diabetes and CKD has increased dramatically along with the increase in diabetes itself. The role of albuminuria in CKD progression and cardiovascular (CV) outcomes is still underappreciated. This study examines CKD progression and CV outcomes in a contemporary real-world setting.

Methods: This retrospective cohort study used administrative data in Henry Ford Health System. eGFR lab results were used to identify patients with stage 2-4 CKD (index date) from 2006-2016 and followed through 2018. A second eGFR >90 days from index date excluded acute kidney injury. Patients with a history of renal transplant, death within 30 days of index date, or progression to ESRD within 6 months of index date were excluded. Logistic regression models were used to identify factors associated with ESRD and occurrence of a composite of myocardial infarction (MI), stroke, and all-cause mortality at 5 yrs of follow-up.

Results: The final cohort consisted of 29,303 patients. The population was 45% male, 38% African American (AA), 48% white, and had a mean age of 61 yrs. At baseline, 72% of patients had stage 2 CKD and 64% had type 2 diabetes (T2D). At 5 yrs of follow-up, ESRD occurred in 3.8%, heart failure (HF) in 17.6%, and the composite outcome in 17.5% (MI 5.8%, stroke 5.0%, all-cause mortality 9.4%). In the ESRD regression model, male gender, AA race, baseline eGFR, and diabetes were associated with high risk, and older age with lower risk. For the composite outcome, male gender, AA race, older age, T2D, and baseline eGFR were all associated with greater risk. In additional models examining the subset of patients with UACR (48% of patients), elevated UACR became the strongest predictor, with a 4-fold increased risk for both ESRD and the composite outcome.

Conclusions: There was a moderate risk of progression to ESRD, but a significant risk of the CV composite and HF outcomes over a 5-yr period. Traditional factors (eg, male gender, increasing age) were observed, but albuminuria was further identified as a strong independent risk factor.

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SA-PO560

Modifiable Factors Associated with Health-Related Quality of Life in Patients with Diabetic Kidney Disease

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Background: Poor health-related quality of life (HRQOL) is associated with increased cardiovascular risk and mortality in patients with kidney disease. Therefore, it is critical to identify potentially modifiable clinical factors contributing to poor HRQOL. This study examined clinical factors associated with poor HRQOL in patients with diabetic kidney disease (DKD) focusing on depression, anxiety, sleep quality, and physical activity.

Methods: Between April 2017 and March 2018, 141 adults (aged ≥18 years) with DKD were recruited in single tertiary hospital. HRQOL was assessed at baseline with the Short Form 36 (SF – 36) Health Survey Questionnaire. Poor HRQOL was defined as baseline scores blow the median value. Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS). Sleep quality and physical activity were measured using Korean version of the Pittsburgh Sleep Quality Index (PSQI-K) and Short form of Global Physical Activity Questionnaire (GPAQ) respectively.

Results: The age was 65 [57-72] years old, and 73% (n=103) of participants were men. Prevalence of anxiety and depression were 17% (n=24) and 7% (n=10) respectively. Forty-eight (34%) subjects corresponded to poor sleepers and 40 (28%) subjects showed low physical activity. SF-36 scores were decreased with advanced CKD stages (stage 3, 79 [71-82]; stage 4, 71 [56-82]; stage 5, 70 [57-82]; $p = 0.029$ for trend). Anxiety, depression, and poor sleep quality were negatively correlated with SF-36 scores ($p < 0.05$). eGFR and physical activity were positively correlated with HRQOL scores ($p < 0.05$). In multivariable logistic analysis, depression scores were associated with poor HRQOL independently of age, sex, comorbidity, eGFR, anemia, sleep quality, anxiety and physical activity (odds ratio per 1-score increment, 1.51; 95% CI, 1.27-1.80, $p < 0.001$).

Conclusions: In patients with DKD, depression was a major determinant of poor HRQOL among the modifiable clinical factors such as anxiety, sleep and physical activity. Active surveillance of depression and psychosocial intervention should be considered to improve the well-being of these patients.

SA-PO561

Characterization of Extracellular Vesicles Derived from Human Amniotic Fluid Stem Cells (hAFSC-EVs) and Their Therapeutic Effect in Alport Syndrome

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Background: Alport Syndrome (AS) is an inherited disease characterized by a loss of glomeruli cells and kidney function. Based on our previous results that EVs from AFSC modulated glomerular crosstalk, we proposed that AFSC-EVs might represent a new therapeutic approach to treat AS. In light of clinical translation, we characterized AFSC-EVs of human origin and evaluated whether they would present a therapeutic effect in an AS mouse model.

Methods: Human clonal AFSC were derived from amniotic fluid collected after volunteer donors provided consent. EVs were obtained from AFSC and characterized by RNA-seq and proteomics. hAFSC-EVs were injected into Alport mice and their therapeutic effect was studied by evaluation of renal function and life-span. RNA-seq was performed on glomeruli obtained from injected and non-injected mice.

Results: Proteomic profiling identified 675 intact proteins and RNA-seq data identified 2,535 miRs in hAFSC-EVs. hAFSC-EV "fingerprint" was assessed by performing GO analysis on the 100 most highly expressed proteins and miRs. The results identified pathways involved in tissue homeostasis, the mTOR pathway, and TGFβ and VEGF pathways. When injected in vivo into AS mice, biodistribution studies showed hAFSC-EVs localized in the kidney, corrected proteinuria and prolonged the life-span of treated mice. No side effects (including teratoma) were noted in the treated mice. RNA-seq of glomeruli obtained from treated AS mice showed similar gene expression patterns to WT, by cluster analysis. Our data indicated that hEVs highly modulated pathways involved in collagen deposition remodeling, in addition to downstream targets of VEGF, FGF, TNF, angiotensin and preserved glomerular cells structure and function.

Conclusions: Our protocol for hEVs derivation is reproducible and allows derivation of EV lots with the same identity (specific cargo of proteins and miRs), purity (absence of contaminants) and potency (present therapeutic effect in AS). hAFSC-EVs modulated signaling pathways that are central to maintaining glomerular homeostasis and preserved glomeruli structure with improved kidney function. This suggests the possibility of using hAFSC-EVs as a new therapeutic option for treating AS in humans.

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SA-PO562

Macula Densa mTOR Signaling Regulates Renin Cell and Glomerular Endothelial Remodeling

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Background: Macula densa (MD) cells are critical regulators of glomerular filtration rate, renal blood flow and renin release via paracrine signaling that involves MD MAP kinases ERK1/2 and p38, and the MD-specific enzymes COX2 and nNOS. The mTOR complex is known to act as a central mediator, integrating the downstream effects of several cell signaling pathways to promote cell growth and protein synthesis. The present study aimed to examine the role of mTOR signaling in regulating MD cell function and its effect on glomerular tissue remodeling.

Methods: An MD-specific genetic mouse model for upregulated mTOR signaling was developed by crossing nNOS Cre mice and mice with a truncated form of TSC2 that upon tamoxifen induction results in mTOR gain-of-function in MD cells (MD-mTOR^{gof}). Changes in expression of MD molecular players controlling renin release (ERK1/2, COX2, mPGES1, etc.) was quantified in renal cortical tissue homogenates. To test the effect of MD-mTOR signaling on renal tissue remodeling, kidney slices were stained for endothelial cell (Meis2 and CD34) and podocyte markers (WT1) using 3D tissue clearing and histological analysis.

Results: Compared to control WT mice, a significant increase in glomerular diameter, robust expansion of the glomerular mesangium, and hypercellularity at the glomerular vascular pole were observed in MD-mTOR^{gof}mice. MD-mTOR^{gof}mice had increased expression of ERK1/2, phospho ERK1/2, COX2 and mPGES1, as well as increased renin expression quantified with immunofluorescence labeling for renin granules and on immunoblots. MD-mTOR^{gof}mice featured significantly increased number of Meis2^{+} glomerular endothelial cells as well as CD34^{+} endothelial precursor cells with the highest density close to the MD.

Conclusions: In summary, upregulation of MD-mTOR signaling has robust effects on both the traditional MD cell functions (renin control), and their newly emerging role in long-term glomerular tissue remodeling. Since MD-mTOR signaling significantly affects the glomerular architecture, it may be targeted to develop future therapeutic strategies for endogenous tissue remodeling and repair in glomerular diseases.

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SA-PO563

Extent of Glomerular Filtrate Determines the Pattern of Podocyte Detachment

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Background: Podocyte detachment is a hallmark of segmental glomerulosclerosis. In ASN Kidney Week 2018, we presented that the cell detachment occurred locally and dominantly at the side of urinary pole even in diffuse cell injury in NEP25 mouse. In addition, by adding unilateral ureter obstruction (UUO) in the mouse model, we showed that glomerular filtrate was essential for detachment. In the present study, we focused on the effects of hyperfiltration to the changes of detachment pattern in diffuse podocyte injury model.

Methods: We used NEP25 mouse, a model of podocyte-specific injury by immunotoxin (LMB2) injection. We performed UUO at 5 days or uninephrectomy (UNx) at 1 day after LMB2 injection. Whole glomerular profiles were photographed by TEM from LMB2+UUO contralateral kidney (61 glomeruli, n=3) and LMB2+UNx model (65 glomeruli, n=3) and compared with the data from LMB2 model (47 glomeruli, n=4). Entire GBM in all glomeruli were classified into normal, foot process effacement or detachment and each length per glomerulus was measured. This method enabled us to identify the localization, continuity and relationship of each change. The relationships between the depth of the glomerulus and the severity of detachment were also analyzed in all models.

Results: The average lengths of detachment were significantly longer in both LMB2+UUO contralateral kidney (12.27%) and LMB2+UNx model (14.21%) than in LMB2 model (5.20%). The tendency of detachment to occur near the urinary pole was enhanced in LMB2+UUO contralateral kidney. By contrast, detachment occurred globally without the tendency in LMB2+UNx model. Detachment was most severe not at the deepest area (750-1000 um) but at 500-750 um from the surface in all models. In comparison with LMB2 model, detachment was severer at all range of the depth of the glomeruli in LMB2+UUO contralateral kidney and LMB2+UNx model.

Conclusions: Extent of glomerular filtrate may regulate the length and the localization of detachment of injured podocyte. Up to some threshold, increase in glomerular filtrate may enhance the tendency of the lesion as a local event. Excessive glomerular filtrate beyond the autoregulation by glomerulus, as presumed in LMB2+UNx model in the study, may change the pattern of podocyte detachment that accelerates FSGS.

SA-PO564

Dynamic regulation of macrophage subpopulations in mouse models of kidney injury

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Background: Macrophages are key drivers of kidney fibrosis and therapeutic efforts have been made to manipulate immuno-regulatory macrophage functions *in vivo*. However, the moderate success of these approaches might be explained by a poor understanding of macrophage kinetics, functional relevance of distinct macrophage subpopulations, and model specific differences.

Methods: We analyzed kidney macrophages in healthy mice and two models of kidney damage, unilateral ureteral obstruction (UUO) and ischemia reperfusion injury (IRI) by a flow cytometry strategy. We identified five kidney macrophage subpopulations with distinct expression of myeloid markers CD11b and CD11c, based on a strategy by Kawakami et al. (2013; J Immunol.).

Results: All macrophage populations, particularly CD11b^{high} CD11c^{high} macrophages, were increased in diseased mice compared to healthy mice. Model specific differences revealed 8-fold more blood-derived monocytes (CD11b^{high} CD11c^{low}) after eight days of UUO than after six days of IRI (840 vs 110 cells/mg kidney). Surface markers MHCII and CD206 allowed further distinction between more pro-inflammatory "M1"- and immuno-regulatory "M2"-like macrophages, illustrating dynamic contribution of each of the five macrophage populations. Treatment with the VEGF receptor tyrosine kinase inhibitor tivozanib effectively reduced total numbers of MHCII-positive and CD11b^{high} CD11c^{high} macrophages after eight days of UUO.

Conclusions: In conclusion, we were able to reveal kinetic and model specific changes in kidney macrophage subpopulations occurring under damage. Being able to monitor and understand the dynamics of different macrophage subsets within diseased organs could help in finding new therapeutic angles.

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SA-PO565

Anti-KITLG Therapy in Renal Injury

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Background: Activation of TGFB signaling promotes organ fibrosis. KIT/KITLG signaling regulates inflammation and fibrosis in humans and animal models and cross-talks with TGFB signaling, but its role in mediating kidney fibrosis remains unclear. Isoform-specific anti-KITLG-antibody therapy is in preclinical development. Therefore, we examined the effect of KITLG inhibition on glomerulosclerosis and interstitial fibrosis in ALB-TGFB1 transgenic mice (TGFB1-TG).

Methods: Ten-day old TGFB1-TG mice were treated biweekly with a monoclonal antibody against KITLG (aKITLG) (n=17) or control-IgG (IgG) (n=15) and euthanized after two weeks. Six wild-type mice were used as non-diseased controls. Pathologic phenotype was assessed blindly by an experienced nephropathologist using trichrome stained sections. RNA-sequencing was performed on HiSeq4000 and analyzed using dseq2 and limma-voom, and further assessed using Ingenuity pathway analysis (IPA). IgG and aKITLG-treated mice were separated into mild (n=6) and severe (n=9-10) groups using previously published parameters (PMID 19465643) and principal component analysis of gene expression profiles. Podocyte density, mesangial index and glomerulosclerosis were quantitated morphometrically and plasma KITLG (pKITLG) levels measured by ELISA.

Results: Severe IgG mice had significantly higher pKITLG and mesangial index and lower podocyte density compared to mild IgG mice ($p<0.01$). pKITLG levels significantly correlated to podocyte density (inversely) and mesangial index (positively) ($p<0.05$). aKITLG mice had no change in body weight and trended towards improved survival. aKITLG mice demonstrated significantly reduced fibrosis and mesangial index ($p<0.05$) and a trend towards improved podocyte density compared with IgG mice. Expression of extracellular matrix genes *Col1a1*, *Col3a1* and *Col6a3* was significantly reduced in kidney cortex of aKITLG vs IgG mice ($p<0.05$). IPA identified several candidate signaling pathways altered by aKITLG.

Conclusions: Our findings that pKITLG increased with severity and aKITLG antibody ameliorated kidney damage in TGFB1-TG mice support aKITLG therapy as a candidate intervention for fibrotic kidney disease. Studies examining human biofluids and aKITLG therapy in other mouse models of kidney injury are ongoing.

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SA-PO566

Inhibition of Human Antigen R Reduces Glomerular Injury in Experimental Glomerulonephritis

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Background: Recent identification of a mRNA-binding protein (human antigen R (HuR)) that regulates mRNA turnover and translation of numerous genes involved in immune response, inflammation, fibrosis and oncogenic signaling and is abnormally elevated in varied kidney diseases offers a novel target for the treatment of renal fibrosis. Thus, we hypothesized that therapy with a selective inhibition of HuR function with a small molecule, KH3, would reduce inflammation and profibrotic factors thereby improving glomerulosclerosis in experimental glomerulonephritis.

Methods: Three experimental groups included normal, untreated disease control, and KH3-treated nephritic rats. Disease was induced in rats with monoclonal anti-thy 1.1 antibody. KH3 was given via daily intraperitoneal injection from day 1 after disease induction at the dose of 50mg/kg BW/day.

Results: At day 6, animals treated with KH3 showed significant reductions in proteinuria, podocyte injury determined by ameliorated podocyte loss and glomerular podocin expression, glomerular staining for periodic acid-Schiff positive material (41%), fibronectin (52%) and collagen IV (48%) and in collagen and fibronectin mRNA levels and protein production. Treatment with KH3 also reduced disease-induced increases in

renal TGF-ß1 and PAI-1 mRNA levels and protein levels. Additionally, a marked increase in renal production of NF-kb-p65 and Nox4 and glomerular macrophage cell infiltration observed in disease control group was largely reversed by treatment with KH3.

Conclusions: These observations strongly support our hypothesis that inhibition of HuR with KH3 has therapeutic potential for reversing glomerulosclerosis by inhibiting inflammatory cell infiltration, decreasing local NAPDH oxidase-mediated oxidative stress, and TGFß and PAI-1's expression and action.

SA-PO567

D-Site Binding Protein Regulates Cell Proliferation Through Mediating Cell Cycle Progression in Rat Mesangial Cells

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Background: Over proliferation of glomerular mesangial cells (MCs) disturbs mesangial homeostasis and leads to renal damage in mesangioproliferative glomerulonephritis. It is documented that transcriptional factors may be involved in the proliferation of MCs. This study aims to identify the key transcriptional factor that prevents the MCs from over proliferation and to clarify its regulatory mechanism.

Methods: Glomeruli were isolated from rats subjected to anti-Thy1 antibody or phosphate-buffered saline. Total RNA was extracted and subjected to microarray analysis. Lentiviral transfection and siRNA transfection were used to obtain D-site binding protein (DBP)-over expressed and DBP-knockdown rat primary MCs, respectively. The cell proliferative capacity was measured by 5-Ethynyl-2′-deoxyuridine (EdU) assay. Flow cytometry was conducted for cell cycle analysis. Histology, immunohistochemistry, and western blot analysis were performed to detect the expression of selected gene and cell cycle regulators.

Results: The cell cycle pathway was the most enriched pathway in the anti-Thy1N model, and the DBP ranked first in the cluster of transcription factors, which was markedly decreased accompanied by an over proliferation of MCs in anti-Thy1N model rats. The knockdown of DBP significantly promoted the proliferation of primary rat MCs, whereas the DBP over expression inhibited the MCs' proliferative capacity in vitro, compared to that of the control cells. DBP arrested G1/S-phase transition by inhibiting the expression of p21, p27 and inducing the Cyclin D1 expression in MCs.

Conclusions: DBP effectively inhibits the proliferation of MCs through G0/G1 phase arrest, and the decrease of DBP may induce mesangial over proliferation in the anti-Thy1N model.

SA-PO568

Integrin β6 Knockout Ameliorates Glomerular Sensitization to Podocyte-Specific Injury

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Background: We previously showed that even mild tubulointerstitial injury sensitized glomeruli to subsequent podocyte-specific injury. We also showed that tubulointerstitial fibrosis was decreased in integrin $\beta6^{-/-}$ mice. Integrin avβ6 is expressed on some tubular epithelial cells, including macula densa, but not on glomerular tufts, and activates latent TGFβ. We aimed to investigate whether $\beta6^{-/-}$ mice had ameliorated sensitization to glomerular injury induced by initial tubular injury, and possible mechanisms of β6 in tubuloglomerular crosstalk.

Methods: Wild type (WT) or $\beta6^{-/-}$ mice were mated with NEP25 mice which express human CD25 on podocytes that can be injured with specific toxin (LMB2) injection. A sequential tubular-glomerular injury model was performed by inducing acute tubular injury by aristolochic acid injection at wk 0, followed by podocyte injury by LMB2 injection at wk 8, when tubular injury had functionally recovered. Uninephrectomy was performed at wk 9 and mice sacrificed at wk 12. Effects of β6 on tubuloglomerular feedback were assessed by adding high salt from wk 6 in subgroups.

Results: KIM-1 expression in tubules was decreased in $\beta6^{-/-}$ at wk 8 after tubular injury but with only numerically reduced interstitial fibrosis (Sirius red morphometry). However, even this minor tubulointerstitial protection by β6 deficiency resulted in a marked effect on glomerular sensitization to podocyte injury. $\beta6^{-/-}$ mice had less albuminuria and glomerulosclerosis with more preserved GFR and $WT1^{+}$ cells vs WT, with less TGFβ activation. Further, WT subgroups treated with high salt had greater increase in urinary sodium excretion, compared to normal salt, vs $\beta6^{-/-}$. High salt increased calculated single-nephron GFR (SNGFR) in $\beta6^{-/-}$ but not in WT, with less decrease in renin RNA and protein in $\beta6^{-/-}$. NKCC2 activity (measured by OXSR1 and VAMP2 expression), adenosine formation enzyme (ecto-5–nucleotidase) and A1 adenosine receptor were lower in high salt exposed $\beta6^{-/-}$ vs WT.

Conclusions: We conclude that integrin $\beta6^{-/-}$ show very mild amelioration of acute tubular injury and interstitial fibrosis vs WT, but still show markedly less glomerular sensitization to subsequent podocyte-specific injury, which is contributed to by blunted tubuloglomerular feedback. We postulate that β6 may, in addition to effects on tubulointerstitial injury, also modulate macula densa function.

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SA-PO569

PBI-4050 Reduces Renal Injury in a Mouse Model of Aristolochic Acid-Induced Nephropathy

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Background: PBI-4050 is a novel therapeutic compound with excellent safety and efficacy profiles in both experimental and clinical settings. Treatment with PBI-4050, a dual GPR40 agonist and GPR84 antagonist, is beneficial in diseases where sustained inflammation and fibrosis are involved, including chronic kidney disease (CKD). Here we used the aristolochic acid (AA) model of CKD and tested whether treatment with PBI-4050 could mitigate renal injury progression.

Methods: Eight-week old male C57BL/6 mice were challenged with AA (4 days, 3.5 mg/kg/day, i.p.) and were treated with PBI-4050 (200 mg/kg/day, p.o.) or vehicle (H_2O) seven days later for four weeks. Plasma creatinine was measured weekly by HPLC. Twenty-four hour urine collection was performed at endpoint. Tubulointerstitial injury was assessed using Sirius-red and PAS-stained kidney sections. Lipid accumulation was observed using Oil Red-O stained frozen kidney sections.

Results: At endpoint, renal function was significantly improved in PBI-4050 treated AA-mice, as plasma creatinine and urea were reduced compared to vehicle treated mice. This was accompanied by significant improvements in polyuria and tubular function as fractional excretion of Na^{+}, K^{+}, Ca^{2+} was maintained by PBI-4050. Moreover, AA-induced reduction in hematocrit was significantly improved as early as one week-post treatment with PBI-4050 and maintained until endpoint. Consistent with improved renal function, tubulointerstitial fibrosis (% collagen area) was apparent in AA-mice and was significantly reduced in PBI-4050-treated mice. Interestingly, AA-challenged mice had significant lipid deposition in kidney tissue along with reduced PGC1α mRNA expression, and this effect was also improved by PBI-4050. Finally, inflammatory cell infiltration and F4/80 mRNA levels were decreased in PBI-4050 treated AA-mice.

Conclusions: Overall, treatment with PBI-4050 improved several key renal functional and structural abnormalities in AA-induced CKD including anemia, fibrosis, renal lipid handling and functional decline. Results from the above and previous studies suggest treatment with PBI-4050 has the potential to slow the progression of CKD due to various diseases with different etiologies.

Funding: Commercial Support - Prometic Life Sciences Inc.

SA-PO570

Persistent Mechano-Growth Factor (MGF) Upregulation in Glomeruli of Diabetic or MGF-Transgenic Mice Induces Mesangial Cell (MC) Glucose Transport, PKC Activation, and Extracellular Matrix Production

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Background: Mechano-Growth Factor (MGF) is expressed at baseline in normal mouse glomeruli, and is increased in type 2 and type 1 diabetic mice. Here we investigated glomerular MGF expression at both 18 and 26 weeks of Type 2 diabetes mellitus in db/db mice vs db/+ controls and the role of MC glucose uptake and PKC in this process. Mice overexpressing MGF in the glomerular MC were produced to determine its role in glomerulosclerosis (GS).

Methods: IHC for glomerular proteins using specific antibodies, with 0-4+ scoring. P<.05 for changes. 3H2-Deoxyglucose glucose uptake rates in cultured MC. PAS stain for GS. Western analyses for MC proteins.

Results: Db/db Type 2 diabetic mice had developed GS at 18 and 26 weeks of age (increased 45%). They also had 1.9-fold increased glomerular GLUT1 and 1.7-fold increased active PKCß1, resulting in 2.4-fold excess Fibronectin (FN) and 1.7-fold excess Collagen Type IV (Col-IV). Glomerular MGF increased > 3-fold in the diabetic mice at 18 and 26 weeks. MGF-overexpression in cultured MC (i.e. MGF-S) increased GLUT1 2.6-fold, with a 67% increased glucose uptake rate and increased fibronectin (FN) 95%. 0.1mM Phloretin inhibited the excess glucose uptake in MGF-S by 57%, and suppressed the excess FN by 43%. This implicated MGF-induced glucose uptake in the excess FN production of MGF-S. 1μM Staurosporine (PKC inhibitor) suppressed the excess GLUT1 in MGF-S by 77%, and suppressed the excess glucose uptake rate by 64%. This implicated PKC activation in MGF-induced GLUT1 expression and glucose uptake. Transgenic overexpression of MGF in mouse glomerular MC's in vivo by 2.7-fold vs controls, led to 2.3-fold increased glomerular GLUT1 and 2.4-fold increased fibronectin (FN) accumulation. MGF-transgenic adult mice exhibit 2-fold increased GS on PAS staining.

Conclusions: 1. Glomerular MGF is induced in Type 2 diabetic mice at age 18 weeks and persists at 26 weeks, with increased PKCB1, GLUT1, FN and Col-IV. 2. Enhanced glucose uptake and PKC activation are involved in MGF-induced GLUT1 and FN expression in MC; 3. Transgenic mice overexpressing MGF in glomerular MC exhibited increased glomerular GLUT1 and GS with excess FN, similar to diabetic GS where glomerular MGF is also elevated.

Funding: Commercial Support - Dialysis Clinics Inc., Private Foundation Support

SA-PO571

Lipopolysaccharide from Gut Microbiota Contributes to Pathogenesis of Murine Lupus Nephritis

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Background: Bacterial products from the gut may enter the circulation and induce inflammatory responses at distant sites, and gut microbiota has been implicated in the pathogenesis of autoimmune diseases. Lipopolysaccharide (LPS) is a component of the outer wall of Gram-negative bacteria. We previously showed that lupus nephritis patients had higher circulating LPS levels compared with healthy subjects. We investigated the role of LPS in the pathogenesis of murine lupus nephritis

Methods: NZB/W F1 mice at 16-wk were randomized to receive saline or LPS (0.5 mg/kg body weight) once daily for 4 weeks, and their renal and colonic histopathology was examined. Intestinal mucosal permeability was investigated with LPS-FITC. Expression of LPS-binding protein (LBP), CD14 and TLR-4 was investigated with cytochemistry.

Results: Serum LPS level was significantly higher in NZB/W F1 mice with active nephritis compared with age-matched BALB/c mice ($P<0.05$). Histopathologic features of active nephritis in NZB/W F1 mice were accompanied by increased LBP, CD14 and TLR-4 expression in proximal renal tubular epithelial cells. Mice with active nephritis also showed increased gut permeability, with orally fed LPS-FITC detected in renal proximal tubules. NZB/W F1 mice that received LPS showed increased proteinuria, and increased IgG and collagen deposition in glomeruli, compared with controls that received saline. Mice given LPS also showed decreased neutral mucin expression in goblet cells, and reduced ZO-1 and LBP expression, in the colonic epithelium, and also increased α-smooth muscle actin expression in the lamina propria.

Conclusions: The data demonstrate that active murine lupus nephritis is associated with increased circulating LPS likely of gut origin, which may contribute to the pathogenesis of renal histopathologic features.

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SA-PO572

Kidney Biopsy in Initial Presentation of Markedly Reduced Kidney Function: Is It Safe? Will It Make a Difference?

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Background: One of the dilemmas faced by nephrologist is a patient presenting for the first time with elevated creatinine and unknown baseline renal function. It is usually unclear whether this represents an acute or chronic kidney disease, especially when the size of kidneys is normal and immunologic workup is negative. The aim of this study is to retrospectively determine the risks and benefits of obtaining a kidney biopsy in patients presenting with elevated creatinine and negative immunologic workup.

Methods: We included patients who presented with serum creatinine higher than 4.5 mg/dL and underwent kidney biopsy between April 1st, 2017 and April 1st, 2019. Patients who had known baseline creatinine or positive serologic studies were excluded from the study.

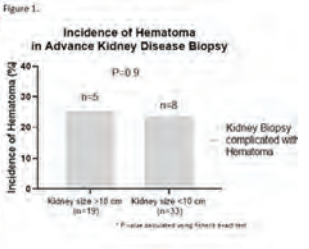
Results: 52 patients were included in the study and their baseline characteristics are summarized in Figure 1. 54% of patients were initiated on chronic hemodialysis during hospitalization. All kidney biopsies were ultrasound-guided and were done with blood pressure <140/80. 29% of kidney biopsies were considered suboptimal or inadequate to make a diagnosis. Only two biopsies (4%) showed treatable acute pathology (1 multiple myeloma and 1 proliferative GN). All the remaining biopsies had at least moderate IFTA and 86% had diffuse global glomerulosclerosis. IgA nephropathy was the most common etiology (n=11; 21%) followed by hypertension (n=5) and diabetic nephropathy (n=4). 13 patients (25%) developed hematoma post procedure: 6 patients (46%) required no intervention, 6 patients (46%) required blood transfusion, and 1 patient (8%) required embolization to control bleeding. Figure 1 compares kidney size and incidence of hematoma.

Conclusions: Initial presentation of markedly reduced renal function with insignificant history and negative work up are at high risk for native kidney biopsy complications and have low yield to diagnose a reversable disease even if kidney size is normal. Benefits and risks of kidney biopsy should be carefully discussed with patients.

Table 1.

Baseline characteristics	N = 52
Age at presentation, years, median (IQR)	32.5 (29-40)
Male gender, n (%)	39 (75)
Asian ethnicity, n (%)	43 (83)
Diabetes, n (%)	8 (15)
SBP on presentation, mm Hg, median (IQR)	174 (160-190)
DBP on presentation, mm Hg, median (IQR)	105 (97-114)
Serum creatinine at presentation, mg/dL, median (IQR)	8.8 (5.8-13.2)
Hemoglobin, g/dL, median (IQR)	8.95 (7.4-10.9)
Serum Calcium, mg/dL, median (IQR)	8.52 (8-9.6)
Serum Phosphorus, mg/dL, median (IQR)	5.9 (4.9-7.5)
PTH, pg/mL, median (IQR)	371 (250-649)
Urine protein: creatinine ratio, mg/mmol, median (IQR)	572 (361-705)
Serum C3, mg/dL, median (IQR)	99 (84-114)
Serum C4, mg/dL, median (IQR)	32 (27-40)
Hematuria, n (%)	36 (69)
Right kidney size, cm, Median (IQR)	9.7 (9.3-10.1)
Left kidney size, cm, Median (IQR)	9.7 (9.2-10.1)
Dialysis during hospitalization, n (%)	28 (54%)

Figure 1.



SA-PO573

MiRNA-424 in Exosomes from Podocytes Promote Apoptosis of Renal Tubular Epithelial Cells Through p38 Activation

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Background: Tubular injury and fibrosis is associated with progressive kidney function decline in advanced glomerular disease. Glomerulo-tubular crosstalk is believed to contribute to tubular injury. Exosomal micro RNAs (miRNAs) are capable of modulation of distant cells. We hypothesized the exosomal miRNAs derived from injured podocyte lead to tubular epithelial cell damage.

Methods: As proof of concept, tubular epithelial cells (HK2 cell) were cultured with exosomes from puromycin-treated human podocytes or healthy podocytes. Damage to the HK2 cells was assessed. Through sequencing we identified the miRNA repertoire from podocyte exosomes. To validate the effect of the miRNAs, HK2 cells were treated with miRNA mimics.

Results: Exosomes from injured podocytes induced apoptosis and p38 phosphorylation of HK2 cells. RNAseq identified up-regulated 63 miRNAs in the exosomes from puromycin treated podocytes. Among them, 5 miRNAs (miR-149, 424, 542, 582 and 874) were selected as candidate miRNAs for tubular apoptosis according to a literature-based search. miRNA-424 mimics led to apoptosis of HK2 cells.

Conclusions: Exosomes from injured podocytes lead to damage in tubular epithelial cells. This may contribute to the development of tubular injury in glomerular disease.

SA-PO574

Cell Fraction Changes Show Strong Correlation with Kidney Disease Severity in Mice and in Patients

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Background: A revolution in cellular measurement technology is under way. While prior studies have only been able to analyze averaged outputs from whole kidneys, now we can accurately monitor genome-wide gene expression, regulation, function, cellular history and cellular interactions in thousands of individual cells in a single experiment. We used single cell RNA analysis to unravel the kidney and immune cell diversity and cell plasticity in healthy and diseased kidneys.

Methods: Five to 8-week-old male FvB wild-type mice underwent ligation of the left ureter and were sacrificed on day 7. Single cell RNA sequencing was performed using the 10X Genomics Chromium System. Data was aligned using Cell Ranger Software and processed using the Seurat package.

Results: We analyzed the transcriptome of 59,609 individual cells from 6 control and 2 UUO kidneys. We identified 30 different major cell populations and multiple subpopulations. Specifically, we found that immune cell diversity was much greater in disease tissue compared to control animals and we identified 16 different immune cell types, including neutrophils, basophils, macrophages, B-cells, plasma cells, CD4 T cells, Th17 cells, T regulatory cells, NK cells, CD8 cells, CD8 effector cells, dendritic cells and plasmacytoid dendritic cells. We found that the fraction of immune cells were also significantly increased in UUO kidneys by single cell analysis. In silico cell deconvolution analysis of bulk RNA sequencing further confirmed loss of epithelial cells and increased in immune cell numbers in UUO mice. Cell-cell interaction analysis indicated that cytokines secreted by injured epithelial cells play key role in immune cell recruitment into disease samples, for example the expression of CD34 responsible for myeloid cell recruitment, Cxc10 and Cxc16 for lymphocyte recruitment. In silico cell deconvolution analysis of 91 human kidney biopsy samples indicated significant cell proportion changes in patient samples. We found that cell proportion changes correlated with the degree of kidney disease such as GFR or fibrosis.

Conclusions: Comparing to health kidneys, UUO kidneys are characterized by increase cell diversity and cell type specific changes. Cell fraction changes show strong correlation with the degree of fibrosis in mice and in patients.

Funding: NIDDK Support

SA-PO575

Kidney Expression of Quantitative Trait Analysis Identified Tubule Caspase9 as a Kidney Disease Gene

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Background: Genome-wide association studies (GWAS) have identified sequence variations associated with kidney disease. However, finding causal genes, cell types and biological mechanisms underlying these associations remains a challenge. We generated expression of quantitative trait (eQTL) information for human kidney compartments to identify likely causal genes. Computational integration of the GWAS and eQTL datasets

identified caspase 9 as a kidney disease risk gene. Caspase 9 is an initiator caspase in the apoptosis pathway found in many cells. Here we analyzed the role of caspase9 in kidney disease development.

Methods: We used a Bayesian colocalization method to integrate kidney eQTL data from 151 healthy individuals of European descent with CKD GWAS. We complemented our compartment-based eQTL studies with kidney-specific epigenome maps and single-cell specific RNA-sequencing results. We generated mice with heterozygous loss of caspase 9 (Casp9+/-). We characterized wild type and Casp9+/- mice at baseline and following folic acid induced kidney injury. Transcript levels for Caspase9 and fibrosis markers were determined by qPCR. Histological changes were characterized by Sirius Red and PAS staining.

Results: We found that the CKD risk variant of rs12124078 was associated with higher expression of caspase9 in microdissected human kidney glomerular and tubule samples. Similarly, in the folic acid kidney fibrosis model and in the APOL1 transgenic mouse model but not in the UUO induced kidney fibrosis model, the expression of cleaved Caspase9 was increased. Caspase 9 heterozygous mice appeared healthy without renal abnormalities. In the folic acid induce kidney injury model, not only the expression of cleaved Caspase9, but other effector caspases such as caspase3, caspase7, and expression of profibrotic genes were lower in Caspase 9 heterozygous mice.

Conclusions: GWAS and eQTL integration identified caspase 9 as CKD risk gene. Heterozygous loss of Caspase9 decreases apoptosis and fibrosis in models of kidney injury, indicating that Caspase9 is a kidney disease risk gene.

Funding: NIDDK Support, Private Foundation Support

SA-PO576

The Dual AT_1R/ET_AR Blocker Sparsentan Slows Renal Disease, Improves Lifespan, and Prevents Hearing Loss in Alport Mice

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Background: In Alport syndrome (AS), ET_AR activation in mesangial cells results in subendothelial invasion of glomerular capillaries by mesangial filopodia and induction of inflammatory cytokines culminating in glomerulosclerosis (GS) and tubulointerstitial fibrosis (TIF). Hearing loss in AS is also a consequence of ET_AR-mediated changes in the inner ear. We compared the effect of sparsentan (SP) with AT_1R blocker losartan (LS) on the development of nephropathy and explored the effect of SP on hearing loss-associated inner ear pathology in Alport (AP) mice.

Methods: Wild type (WT) and AP mice were treated daily with vehicle (V), 120 mg/kg SP, or 10 mg/kg LS in 3 studies; early intervention (EI) from 3-7 weeks of age (W) (n=7-8), late intervention (LI) from 5-7W (n=8), or for lifespan (n=10). Proteinuria (UP/C) was assessed weekly, and immunostaining for fibronectin and collagen 1 was used to assess GS and TIF. Glomerular basement membrane dysmorphology was examined by electron microscopy (EM). For hearing, WT and AP mice were treated with V or SP in EI (n=5). Strial capillary basement membrane (SCBM) width was analyzed by EM. Hearing was assessed at 7W (n=5) by auditory brainstem response pre- and 5 days post-exposure to noise.

Results: SP or LS treatment in AP mice in EI ($p<0.05$ vs APV) attenuated increases in UP/C observed in APV at 7W and showed little to no TIF or GS. In LI, SP but not LS prevented a significant increase in GS compared to 5W untreated AP mice and significantly attenuated ($p<0.05$ vs APV 7W) UP/C and TIF compared to APV. Lifespan was significantly longer ($p<0.05$) for both SP- and LS-treated AP mice compared to APV. SP prevented both SCBM thickening and post-noise hearing loss at 16 kHz in AP mice (mean SCBM width±SD nm: 57.8±2.1 WTV, 67.6±5.5 APV, 54.7±2.4 APSP [$p<0.05$ APSP vs APV]; hearing loss: $p<0.05$ APSP vs APV).

Conclusions: In the LI studies, SP provided significant nephroprotection in AP mice, and to a greater extent than in the LS group. SP also significantly attenuated inner ear pathologies. Results from this study, if translated to the clinic, may present a therapeutic approach to reduction in both hearing and renal injury for AS patients.

Funding: Commercial Support - Retrophin, Inc., San Diego, CA

SA-PO577

Acetate from Microbiota Contributes to the Pathogenesis of Murine Lupus Nephritis

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Background: Pathogenesis of lupus nephritis is complex, and involves both genetic and environmental factors. Emerging evidence suggests that translocation of microbial products from the gastrointestinal (GI) tract into the circulation may have impact on distant organs. Acetate is a short chain fatty acid (SCFA) generated by gut microbiota. We previously showed that lupus nephritis patients had higher serum acetate levels compared to healthy subjects, and serum acetate level correlated with lupus disease activity. We investigated the role of acetate in the pathogenesis of murine lupus nephritis.

Methods: Eight week old NZB/W F1 mice were randomized to receive (a) drinking water, (b) sodium acetate, or (c) ampicillin and neomycin for 20 weeks. Intestinal mucosal permeability was investigated with dextran-FITC administration, and ZO-1 and claudin-1 expression. Expression of SCFA receptors GPR-41 and GPR-43 was investigated with cytochemical staining. The effect of acetate on mediators of inflammation was investigated in HK-2 cells.

Results: Serum acetate level was significantly higher in NZB/W F1 mice with active disease compared with age-matched BALB/c mice ($P<0.05$). Renal histology in untreated NZB/W F1 mice showed mesangial expansion, immune cell infiltration, progressive glomerulosclerosis, tubular atrophy and interstitial fibrosis; and increased GPR-41 and GPR-43 expression in proximal renal tubular epithelial cells. Also, active lupus nephritis was accompanied by increased gut permeability and decreased ZO-1, claudin-1, GPR-41 and GPR-43 expression in colonic epithelium. 16S rRNA analysis showed a progressive decrease in Gram-positive bacteria phyla *Actinobacteria* and *Firmicutes* and an increase in Gram-negative bacteria phyla *Bacteroides* and *Proteobacteria* as lupus nephritis progressed. Mice fed acetate showed higher level of proteinuria and reduced survival. In contrast, antibiotic treatment attenuated abnormalities observed in the colon and kidney, and significantly decreased serum acetate level and proteinuria ($P<0.05$, for both). HK-2 cells exposed to acetate for 24h showed induction of IL-6, IL-8, TNF-α, TGF-β1 and SNAIL mRNA.

Conclusions: The data demonstrate that murine lupus nephritis is associated with a change in gut microbiota and increased circulating microbial acetate, which may contribute to renal tubulo-interstitial inflammation and fibrosis.

Funding: Government Support - Non-U.S.

SA-PO578

Irradiation-Induced Glomerular Endothelial Cellular Senescence May Contribute to the Senescence-Associated Secretory Phenotype by Activating the NF-kB Signaling Pathway

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Background: Cellular senescence is one of the major risk factors for chronic kidney disease. We recently reported that ionizing radiation (IR) can cause cellular senescence in the kidney and lead to kidney dysfunction. In this report, we investigated the precise characteristics of radiation-induced cellular senescence in glomerular endothelial cells.

Methods: Male 7-8-week-old rats received unilateral IR of 18 Gy on the kidney (irradiated kidney) or sham IR (normal kidney). We analyzed the presence of cellular senescence and pathological changes until 9 months post IR. In an in vitro experiment, rat glomerular endothelial cells received a single dose of 20 Gy (irradiated cells). Cellular senescence was defined by the combination of senescence-associated β-galactosidase (SA-β-gal), p21, p53, p16 and the senescence-associated secretory phenotype (SASP). The DNA damage response (γH2AX, a marker of DNA double strand breaks) and nuclear factor-kappa B (NF-κB) signaling pathway were also evaluated.

Results: As previously reported, irradiation-induced cellular senescence was demonstrated in the irradiated kidneys. Notably, glomerular endothelial cells in irradiated kidneys displayed more cells that were positively stained for p21 at an earlier time (from 3 months) compared to podocytes. In vitro, irradiation-induced cellular senescence in glomerular endothelial cells was also confirmed. Recent studies reported that the DNA damage response could trigger the NF-kB signaling pathway, resulting in a cascade of inflammation. In our study, irradiated cells showed DNA damage response, and a gradual increase in the expression level of NF-kB mRNA. Irradiated cells also showed nuclear localization of NF-κB and positive staining for phosphorylated IκBα. Once IκBα is phosphorylated, IκB proteins are released from NF-κB. Subsequently, NF-κB translocates to the nucleus and transactivates the expression of target genes. Following the activation of the NF-κB pathway, the various SASP was upregulated at days 20.

Conclusions: Taken together, these data suggest that IR could cause cellular senescence in the kidney. In particular, glomerular endothelial cells may play an important role in production of SASP that might be triggered by the activated NF-kB signaling pathway.

SA-PO579

DCR2, a Cellular Senescent Molecule, Is a Novel Marker for Assessing Tubulointerstitial Fibrosis in Patients with Immunoglobulin A Nephropathy

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Background: DcR2 is a senescent marker expressed exclusively in senescent tubular epithelia. We calculated the ratio of urinary levels of Dcr2 to creatinine (uDcr2/Cr) and renal tissue DcR2 levels, in order to analyze the relationship between DcR2 levels and the severity of tubulointerstitial fibrosis (TIF) in patients with immunoglobulin A nephropathy (IgAN).

Methods: This study included 210 IgAN patients and 80 healthy volunteers, with uDcR2 levels measured using enzyme-linked immunosorbent assay. Renal DcR2 expression was quantified by immunohistochemistry. Co-expression of DcR2 with senescent (interleukin-6 [IL-6], tissue inhibitors of metalloproteinase [TIMP]-2) and fibrotic markers (α-smooth muscle actin [α-SMA], collagen III) were analyzed by confocal microscopy. We examined the relationship among uDcR2/Cr levels, renal function, and pathological findings, using the area under the curve (AUC) approach to predict tubulointerstitial fibrosis.

Results: Levels of uDcR2/Cr were significantly higher in IgAN patients and in those with more severe TIF, compared with healthy controls. Serum DcR2 levels were similar across groups. The proportion of IgAN patients with stage 1-2 chronic kidney disease (CKD) and T0 was highest among those with uDcR2/Cr < 130 ng/g. In contrast, the majority of those with uDcR2/Cr > 201 ng/g had stage 4-5 CKD and T2. Levels of uDcR2

were positively associated with urinary albumin/creatinine ratio (ACR), N-acetyl-β-D-glucosaminidase (uNAG)/Cr, and TIF scores. Levels of uDcR2 were negatively associated with estimated glomerular filtration rate (eGFR). uDcR2/Cr, uNAG, ACR and eGFR were independent predictors for TIF, with AUC of 0.907 for uDcR2/Cr. This AUC value was higher than that observed for eGFR, uNAG/Cr, or ACR. The sensitivity and specificity of uDcR2/Cr in predicting TIF were 87.0% and 80.5%, respectively. Renal DcR2 co-expressed with IL-6 and TIMP-2 in tubules and co-localized with α-SMA and collagen III in the kidneys of IgAN patients.

Conclusions: Levels of uDcR2/Cr were closely associated with the severity of TIF and renal function parameters. uDcR2/Cr represents a potential biomarker for predicting chronic TIF in IgAN patients.

Funding: Government Support - Non-U.S.

SA-PO580

Epigenetic Factors Regulate APOL1-miR193a Axis in Parietal Epithelial Cells

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Background: Bifunctional APOL1-mIR193 axis plays a vital role in the podocyte renewal during normal physiology and pathological states. Parietal epithelial cells (PECs) serve as progenitor cells for podocytes in juvenile. We have recently demonstrated the role of APOL1 wild-type (G0) in the transition of PECs. Since PECs have a higher expression of miR193a, they do not express APOL1. However, downregulation of miR193a induces APOL1 expression in PECs. We hypothesize that epigenetic factors regulate APOL1-miR193 axis through modulation of miR193a expression in PECs.

Methods: Immortalized human PECs underwent several experimental designs: PECs were transduced with either vector (V) or HIV (NL4 (n=4); PECs were incubated in media containing variable concentration of IFN-γ (0, 5, 10, and 20 nM) for 48 hours (n=4); PECs were treated with either empty vector (EV) of a specific miR193 inhibitor (20 nM) for 48 hours (n=4); PECs were treated with either buffer, azacytidine (5 μM, a demethylating agent), or SAHA (10μM, an histone deacetylation inhibitor) for 48 Hours (n=4). Protein blots were probed for APOL1, DNMT 1-3, HDAC 1-4, H3K27me3, H3K4me3, H3K8/9ac, and reprobed for actin. cDNAs were amplified for DNMT1-4, HDAC1-4, and APOL1. RNAs were assayed for miR193a. ChiP assay was carried out to evaluate histone acetylation at miR193a promoter. The RIP-ChIP assay was performed to examine the binding of miR193a at APOL1 gene promoter. In PECVs and PECHIVs, methylation of CpG islands at miR193a gene was detected by Bisulphite sequencing.

Results: HIV, as well as IFN-γ, induced APOL1 expression in PECs. PECHIV and IFN-γ-treated PECs showed 2.0-2.5-fold decrease in miR193a expressions, respectively; inhibition of miR193a in PECs by a specific miR193a inhibitor also resulted in the induction of APOL1 expression. The treatment of PECs with either azacytidine or SAHA induced the expression of APOL1 as well as decreased (three-fold) miR193a levels. HIV and IFN-γ enhanced the expression of DNMT3b, HDAC4, HK4me3, and H3K27me3 but down-regulated the expression of H3K8/9ac. ChIP assay revealed histone methylation at 27 lysine residues. RIP-ChIP assay confirmed the binding of miR193a on APOL1 gene promoter. Bisulfite sequencing displayed enhanced methylation of CpG islands at miR193a gene in PECHIV.

Conclusions: Epigenetic factors regulate APOL1-miR193a axis in PECs.

Funding: NIDDK Support

SA-PO581

Efficacy of Low-Intensity Pulsed Ultrasound on Renal Fibrosis and Progression of CKD in a Mouse Model

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Background: The prevalence of chronic kidney disease (CKD) has been increasing in recent years. Proliferation of fibroblasts and excessive deposition of extracellular matrix including collagen in renal tissues after ischemia/reperfusion injury (IRI) contribute to renal fibrosis and progression of CKD. Low intensity pulsed ultrasound (LIPUS) has been recognized to elevate bone fracture repair process and help in some soft tissues healing such as cartilage and cardiac tissues. Here, we tested the prevention of renal fibrosis and progression of CKD by LIPUS in a mouse model of unilateral IRI with contralateral nephrectomy.

Methods: Animals were randomized into the sham, IRI, and IRI+LIPUS groups. In the IRI group, the left renal artery was isolated and clamped fir 30 mins. They were sacrificed 14 days after IRI as an AKI to CKD transition model in the presence or absence of LIPUS treatment (3 MHz, intensity 0.1 W/cm^2, 20 min, 50% duty factor) 5 days before and 14 days after IRI. Serum biochemical measurement, including BUN, Cr and Cystatin C, Histological analysis, Immunoblotting, including GRP78, Chop, Bax, cleaved caspase-3, p21, Sirtuin-1, E-cadherin, vimentin, catalase, superoxide dismutase 1 (SOD1), Klotho, etc., and Malondialdehyde (MDA) were examined

Results: LIPUS treatment significantly alleviated the increases in the serum levels of BUN, creatinine, and fibroblast growth factor (FGF)-23, and renal pathological changes and fibrosis (n=8, p<0.05). The development of epithelial-mesenchymal transition was alleviated by LIPUS treatment (n=8, p<0.05). LIPUS treatment could also inhibit the induction of renal senescence-related molecular signals such as p53, p21, and p16 (n=8, p<0.05). Interestingly, LIPUS significantly reversed the decreased α-Klotho protein expression in the kidneys (n=8, p<0.05). LIPUS treatment significantly reversed the decrease in renal endogenous antioxidant enzymes (n=8, p<0.05). Taken together, LIPUS treatment showed the benefits for renal protection in IRI mice.

Conclusions: These findings suggest that LIPUS therapy may be used to serve as an auxiliary tool for the management of renal fibrosis and progression of CKD.

Funding: Government Support - Non-U.S.

SA-PO582

Remodeling of the Glomerular Tuft in Proteinuric Kidney Disease

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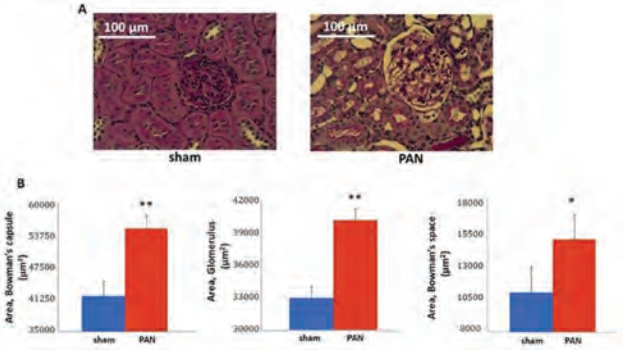
Background: Glomerular hypertrophy is associated with proteinuric kidney disease and progression to renal failure. The present study sought to quantify the association between remodeling of the glomerular tuft and proteinuria.

Methods: Adult male Wistar rats (sensitive strain, ~75 g) were administered puromycin aminonucleoside (PAN, 167 mg/kg, n=8) or water (n=3, sham cohort). On Day 14 after PAN administration, 24-hour urine was collected for determination of proteinuria. Left kidneys were removed, sectioned and stained with hematoxylin-eosin and glomeruli (14 per kidney) photographed at 40X. Areas of the Bowman's capsule and glomeruli were measured using ImageJ by an observer blinded to the experiment groups and the area of the Bowman's space calculated.

Results: Compared to the sham cohort, PAN-administered animals exhibited a 3-fold increase in proteinuria (p<0.01) and changes in glomerular tuft morphology (A). Significant increases (B) were observed in the areas of the Bowman's capsule (**, p<0.01), the glomerulus (**, p<0.01), and the Bowman's space (*, p<0.05) with PAN administration.

Conclusions: Remodeling of the glomerular tuft, including hypertrophy of the Bowman's capsule and glomerulus, and an increase in Bowman's space, accompanies proteinuric kidney disease. These findings might be an important consideration in the development of therapies for the treatment of kidney disease.

Funding: Private Foundation Support



The PAN model of proteinuric kidney disease is associated with an increase in the area of the Bowman's capsule, hypertrophy of the glomerulus, and an increase in the Bowman's space.

SA-PO583

Molecular Mechanisms of Renal Fibrosis in Alport Syndrome

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Background: Alport Syndrome is a rare hereditary disease caused by mutations in glomerular basement membrane (GBM) type IV collagen and characterized by progressive renal fibrosis and early onset ESRD. Collagen IV dysregulation and loss of GBM integrity allows passage of albumin to the tubular lumen causing injury and ultimately tubulointerstitial fibrosis in advanced Alport Syndrome. To date, the signaling pathways and molecular targets in albuminuria-induced fibrosis in Alport Syndrome have not been elucidated.

Methods: We evaluated the kinetics and potential mechanisms of renal fibrosis in Col4a3 knock out (Col4a3KO) mice, a model of autosomal recessive Alport Syndrome compared to age-matched Wild Type (WT) controls. Approximately equal numbers of male and female Mice were studied from 5–10 wks age to evaluate the renal fibrotic response to progressive albuminuria. At 6, 8 and 10 wks, representative cohorts of mice were euthanized and kidneys were harvested for biochemical and histological analyses. mRNA expression was analyzed using a Quantigene pro-inflammatory and fibrotic gene multiplex (MCP-1, CTGF, TGF-β1, α-SMA, FN1 and Collagens 1a1 and 3a1). Renal cortical hydroxyproline (OH-P) content and Collagen Volume Fraction (CVF) via Picrosirius Red (PSR) histology were also evaluated. Renal cortical lysates were evaluated for TGF-β1 content and phospho- p38, JNK and Erk to elucidate potential pathways in albuminuria-induced fibrosis.

Results: Col4a3KO had age-dependent polyuria and fulminant albuminuria (5 wks: 360-fold; 10 wks: ~2,500-fold) compared to WT. Renal cortical OH-P content was not increased by 6 wks but increased thereafter. Associated with progressive albuminuria, CVF was age-dependently increased in Col4a3KO (8 wks: 10-fold; 10 wks: 25-fold). Although pro-inflammatory and fibrotic mRNA species were increased by 6 wks in Col4a3KO, peak expression occurred at 8 wks, in advance of peak fibrosis. Renal cortical TGF-β1 content was age-dependently increased while pJNK and pERK peaked at 8–10 wks.

Conclusions: This study demonstrates albuminuria precedes renal fibrosis in the Col4a3KO model of Alport Syndrome and identifies potential mechanisms related to disease progression. These results enable future investigations of inflammatory and stress-signaling pathways in Alport Syndrome, and evaluation of novel therapies to attenuate albuminuria-induced renal fibrosis.

Funding: Commercial Support - Plato BioPharma, Inc.

SA-PO584

Established Human Mesenchymal Stem Cell Lines Stably Secreting Matrix Metallopeptidase 7 to Treat Glomerulosclerosis in Light Chain Deposition Disease

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Background: Light chain deposition disease (LCDD) is a rare systemic disorder, caused by the overproduction and extracellular deposition of monoclonal immunoglobin light chain. The clinical manifestation is dominated by renal disease. The affected glomeruli are enlarged. The deposition of PAS-positive material produces capillary wall thickening and nodular expansion of the mesangium. The extent of glomerular involvement can vary from minimal mesangial expansion to a fully developed nodular glomerulosclerosis. Although the pathogenesis of the glomerulosclerosis in LCDD is not entirely clear, experimental studies have shown that mesangial cells incubated with monoclonal light chains obtained from patients with LCDD produce transforming growth factor β, which triggers the production of extracellular matrix proteins. Tenascin is the most common protein in expanded mesangium in LCDD and is degraded mostly by Matrix Metallopeptidase 7 (MMP7). This finding suggests that inducing MMP7 secretion by stem cells might be a possible therapeutic intervention to reverse nodular glomerulosclerosis in LCDD. In this study, we aimed to establish stable stem cell lines to facilitate degradation of tenascin.

Methods: 1) pcDNA3-GFP-MMP-7 plasmid was purified using ***QIAprep Spin Miniprep Kit.*** The products are confirmed by gel electrophoresis. 2) HMSC was cultured in 6-well plate with 5% FBS specific medium. When 80% confluences was reached, the HMSCs were transfected by purified GFP-MMP7 plasmid using ***lipofectinamine 2000***. Immunofluorescence microscopy was used to test the transfection efficiency. 3) 48 hours after transfection, the HMSCs were transferred into 10cm dishes. 72 hours later, G418 600ug/ml was added in to medium. Cell clones formed in 3-4 weeks and then were picked up to amplify. Confocal microscopy and western blot analysis were used to identify MMP-7 expression and secretion.

Results: 1) GFP-MMP-7 plasmid was successfully amplified and purified. 2) HMSC were successfully transfected by GFP-MMP7 plasmid using *lipofectinamine 2000*. The transfection efficiency was about 30%, including 10% highly expressed cells.

Conclusions: We successfully established HMSC cell lines which highly express and secret MMP7. In our future study, the cell line will be used to treat kidney diseases caused by LCDD in animal model.

SA-PO585

IL-17 Signaling in CD4$^+$ T Cells Controls TH17 Immune Response

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Background: The IL-17/IL-17 receptor system plays a crucial role in autoimmune and chronic inflammatory diseases. The biological effects on residential cells are mediated through a heterodimeric receptor complex consisting of IL-17RA and a ligand specific IL-17 receptor subunit (IL-17RB - IL-17RE). However, the expression and function of IL-17 receptors on hematopoietic cells as CD4$^+$ T cells have not been elucidated.

Methods: Crescentic GN (NTN), Psoriasis and C. rodentium colitis were induced in IL-17RA$^{-/-}$, IL-17RC$^{-/-}$ and in IL-17A, IFNγ and Foxp3 triple-reporter mice for *in vivo* cell sorting of CD4$^+$ T cell subsets. Single cell RNAseq of CD4$^+$ T cells from the nephritic kidney was performed using the 10X single cell system. pLIVE-plasmid was used to induce IL-17A overexpression *in vivo*. Moreover, we generated T_H17 cell specific IL-17RA gene-deficient mice to study the role of IL-17 signaling in T_H17 cells in the NTN model.

Results: Induction of inflammation in the kidney, skin and intestine in IL-17RA$^{-/-}$ mice resulted in an aggravated T_H17 cell immune response. Transfer of IL-17RA$^{-/-}$ bone marrow cells in irradiated WT mice indicated IL-17 signaling on hematopoietic cells. CD4$^+$ IL-17 producing WT cells from the inflamed kidney, analyzed with single cell RNAseq, demonstrated a highly activated IL-17 signaling score. mRNA expression analysis of FACS-sorted T cells revealed predominant expression of IL-17RC and IL-17RE by IL-17A$^+$ T_H17 cells, whereas IL-17RA is ubiquitously expressed by all CD4$^+$ T cell subsets, demonstrating a T cell specific expression pattern of IL-17 receptors. Systemic overexpression of IL-17A showed a reduction of CD4$^+$ IL-17A$^+$ cells in the kidneys of nephritic mice. Moreover, competitive adoptive transfer experiments of wildtype and IL-17RA$^{-/-}$ or IL-17RC$^{-/-}$ CD4$^+$ T cells into nephritic Rag1$^{-/-}$ mice showed that IL-17 signaling on CD4$^+$ T cells is critically for the control of the pathogenic T_H17 response. Mice specifically lacking the IL-17RA receptor in IL-17A$^+$ cells also present an enhanced T_H17 cell immune response.

Conclusions: Our findings indicate intrinsic IL-17RA/RC signaling on CD4$^+$ T cells, which regulates the T_H17 cell immune response. This novel mechanism might lead to more efficient therapeutic options in targeting IL-17 signaling pathways.

SA-PO586

Establishment of a Preparative Method and Gating Strategy for Renal Mononuclear Phagocytes (rMophs) and Analysis of rMophs in CD11c-Specifc Shp-1 Knockout Mice

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Background: Recent studies demonstrated the existence of renal mononuclear phagocytes (rMophs), which express both macrophage markers, CD11b and F4/80, and dendritic cell marker, CD11c. However, standardized procedures to isolate and characterize rMophs have not been adopted; therefore, the function of rMophs is not fully understood. In this study, we aimed to provide a preparative method of rMophs and optimize gating strategy for flow cytometry (FCM). We further examined the contribution of rMophs in renal injury by inducing nephritis in CD11c-specific Shp-1 knockout mice (Shp-1 CKO), in which certain population of rMophs lack Shp-1, a negative regulator of hematopoietic cell signaling.

Methods: C57BL/6J mice were used to establish the preparative method of rMophs. To induce nephritis, Shp-1 CKO and control littermates mice (Ctrl) at the age of 8-10 weeks were immunized by subcutaneous injection with bovine serum albumin (BSA) at 2-week intervals.

Results: We first determined the efficacy of renal cell collections from the mouse kidney. Higher yield of CD45.2$^+$ cells and F4/80^{high} cells was achieved by collagenase digestion compared to simple mechanical dissociation. We then characterized the isolated cells by FCM. A significant number of neutrophils, which expressed Ly6G, mixed up into F4/80^{low} cells. Therefore, isolated renal cells expressing CD45.2 and CD11b, but not Ly6G, could be referred as rMophs. These CD45.2$^+$ CD11b$^+$ Ly6G$^-$ rMophs were, then, divided into 3 subpopulations: F4/80^{high} CD11c^{int} rMophs, F4/80^{low} CD11c^{high} rMophs and F4/80^{low} CD11c^{low} rMophs. In animal experiments, Shp1-CKO developed proteinuria at 6-8 weeks after the first BSA injection, when Ctrl did not develop proteinuria yet. Proliferative glomerulonephritis was also developed at this early time point in Shp-1 CKO. Finally using the isolation and gating methods, the FCM analysis revealed that proportion as well as absolute number of F4/80^{high} rMophs increased in Shp-1 CKO treated with BSA.

Conclusions: We found that the use of collagenase digestion is necessary to collect rMophs and the gating strategy of eliminating neutrophils is important for the analysis of rMophs. We also showed that Shp-1 may regulate rMophs and protect against renal injury.

SA-PO587

Neutrophil Elastase-Deficient Mice Are Protected from Experimental Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody Vasculitis

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Background: Neutrophil extracellular trap (NETs) are implicated in the pathogenesis of myeloperoxidase anti neutrophil cytoplasmic antibody vasculitis (MPO-AAV). Neutrophil elastase (NE) is implicated in initiating NET formation through proteolytic degradation of the nuclear envelope, histone degradation and chromatin decondensation in concert with other neutrophil enzymes to facilitate DNA release. NETs are decorated with multiple proinflammatory enzymes including MPO (the autoantigen in this disease) and NE. NE released through degranulation is degraded by endogenous NE inhibitors, however NE bound to NET derived DNA is protected providing a reservoir of proteolytic NE enabling tissue destruction, microvascular injury and further recruitment of neutrophils. This study investigates the pathogenic contribution of NE release through NET formation in experimental MPO-AAV using animals deficient in neutrophil elastase.

Methods: A 20 day experimental model of anti-MPO GN was induced in B6.129X1-Elane^{tm1Sds}/J mice (neutrophil elastase knock out mice) and wild-type (WT) litter mate controls by myeloperoxidase (MPO) immunisation and GN triggered using a sub-nephritogenic dose of anti-glomerular basement membrane globulin (anti GBM Ig), [*n*=10 (WT) and *n*=10 (*Elane*-/-)].

Results: *Elane*-/- animals were protected from excessive NET production and glomerular injury with significantly reduced numbers of glomerular neutrophils, extracellular MPO deposition, CD4 T cells and macrophages influx (all, P <0.05 compared to WT). Histological assessment of kidneys demonstrated a reduction in segmental necrosis in the *Elane*-/- group compared to the WT group (P<0.05). Functional injury measured by creatinine/albuminuria ratio was significantly reduced in the *Elane* -/- group compared to the WT group (P=0.04). Systemic autoimmunity to MPO was significantly reduced in *Elane*-/- mice with reduced frequency of MPO specific CD4 effector T cells from the draining lymph nodes and a significant reduction in dermal DTH, measured by a 24 hour footpad challenge with MPO (P<0.05, compared with WT).

Conclusions: Reduced NET formation in *Elane -/-* mice attenuated glomerular injury through the reduction in NET associated MPO and NE. This data provides proof of concept evidence that targeting NE therapeutically may be of potential benefit in MPO-AAV.

SA-PO588

Urinary Treg and Th17 Cells Identify Active Renal Disease in Patients with ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitides (AAV) cause necrotizing crescentic glomerulonephritis which is a major contributor to morbidity and mortality in AAV. As therapy relies on immunosuppressive agents with potential adverse effects, a reliable non-invasive biomarker of disease activity is needed to determine the right balance between over- and undertreatment. Since the pathogenic role of Tcells in AAV is emerging, we hypothesized that these subsets are increased in urine in active renal AAV and represent a reliable biomarker of disease activity.

Methods: Levels of Tcells and their subsets were measured in peripheral blood and urine samples from patients with active renal AAV (n=39), active non-renal AAV (n=9), AAV in remission (n=22), and healthy controls (n=9) using flow-cytometry. Urinary metabolites and cytokines (MCP-1, sCD163, sCD25, and C5a) were quantified by multiplex-analysis.

Results: Patients with active renal vasculitis show significantly higher urinary T cell counts than active non-renal, inactive, and healthy controls. In particular CD4+ T cells, T regulatory cells, and Th17 cells are significantly elevated compared to all controls. No significant difference could be shown for CD8+ T cells between active renal and remission. The only significant difference for Th1 cells was was found between active renal vasculitis and healthy controls. sCD163, MCP-1, and C5a all show a significantly elevated concentration compared to patients in remission only sCD163 reaches significance for active renal vs. active non-renal. Analysis of receiver operator characteristics (ROC) reveals that urinary T cells identify active renal vasculitis with at least comparable diagnostic accuracy, CD3+, CD4+, CD8+ and Treg outperform soluble markers based on area under the curve (Treg AUC 0.93, sensitivity 79%, specificity 95%; CD3 Tcells AUC 0.95; sensitivity 92%, specificity 95%; MCP-1 AUC 0.9; sensitivity 60% specificity 100%, sCD163 AUC 0.92, sensitivity 96%, specificity 85%).

Conclusions: Urinary Tcells are significantly elevated in active renal AAV and reliably determine renal disease activity. Biomarker performance for Tregs is comparable to published results of urinary MCP-1 and sCD163 and exceeds sCD25 and C5a while Th17 outperforms only sCD25 and C5a. Hence, urinary Tregs and Th17 are new potential biomarkers in AAV.

SA-PO589

Fostamatinib Treatment of a New Model of Myeloperoxidase-ANCA Vasculitis

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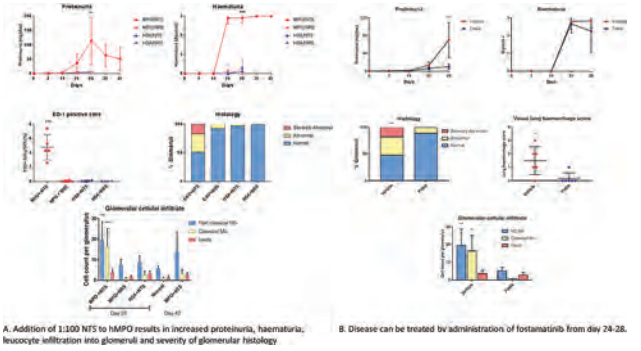
Background: EAV is a model of MPO-AAV induced by immunising rats with human myeloperoxidase (hMPO). Animals develop lung haemorrhage and proliferative GN, but disease is milder than human AAV. To augment disease severity, we immunised animals with an additional subnephritogenic dose of rabbit nephrotoxic serum (NTS). Fostamatinib, a small molecule Syk inhibitor, was used to evaluate therapeutic manipulation in this new model.

Methods: WKY rats were immunised IV with diluted NTS to establish a subnephritogenic dose. For EAV+NTS experiments, animals were immunised IM with hMPO (or human serum albumin (HSA)) on day 0 and 1:100 NTS IV (or normal rabbit serum (NRS)) at day 14. When fostamatinib was used, this (or vehicle) was administered by oral gavage from day 24-27, and animals culled on day 28. Infiltrating glomerular leucocytes were isolated and analysed by flow cytometry.

Results: A sub-nephritogenic dose of NTS was identified as a 1:100 dilution. Animals immunised with hMPO and 1:100 NTS had significantly more proteinuria and glomerular abnormalities at day 28 than the hMPO+NRS group or HSA controls (Fig1A). There was no detectable immune deposits by immunofluorescence or electron microscopy in any of the groups. In animals immunised with hMPO and 1:100 NTS, there were significantly more infiltrating glomerular leukocytes with greater increase in classical compared to non-classical monocytes (Fig1A). Fostamatinib treatment significantly reduced lung haemorrhage, glomerular, urinary abnormalities and infiltrating gloemrular leucocytes (Fig1B).

Conclusions: A subnephritogenic dose of NTS 14 days after hMPO significantly augments disease severity without evidence of deposited antibody or immune complexes. Characterisation of glomerular infiltrating cells shows significant infiltration of classical monocytes and we suggest it may be these cells which are stimulating crescent formation. Administration of fostamatinib for 4 days was sufficient to significantly decrease disease severity.



A. Addition of 1:100 NTS to hMPO results in increased proteinuria, haematuria, leucocyte infiltration into glomeruli and severity of glomerular histology

B. Disease can be treated by administration of fostamatinib from day 24-28.

SA-PO590

In ANCA Vasculitis, Low-Density Neutrophils Express High Levels of Autoantigen Genes, but Expression in Normal-Density Neutrophils Correlates with Activation by ANCA

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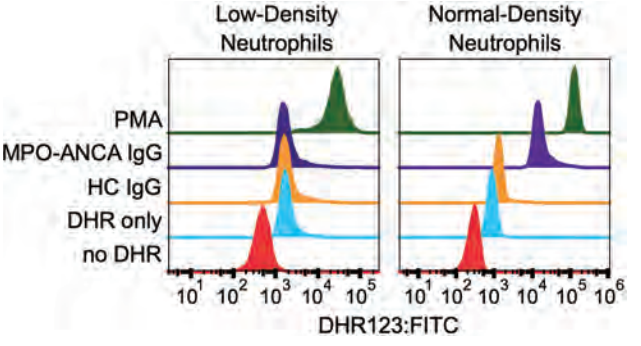
Background: Neutrophils are a heterogenous cell population, a primary source of expression of autoantigen genes in ANCA vasculitis, and central to the pathology of ANCA vasculitis; however, it is unclear the impact neutrophil heterogeneity and expression has on disease pathology.

Methods: Low-density neutrophils (LDNs) and normal-density neutrophils (NDNs) were isolated from peripheral blood of 137 ANCA vasculitis patients and 54 healthy controls (HC). Expression of *MPO* and *PRTN3* was measured by quantitative RT-PCR. LDNs were immunophenotyped by flowcytometry. Oxidative burst in response to MPO-ANCA was measured with dihydrorhodamine assay in LDNs and NDNs without *in vitro* priming.

Results: Increased *MPO* and *PRTN3* expression was detected in LDNs and NDNs from patients during active disease compared to HC, with the largest difference in LDNs. Surface markers CD10 and CD15 revealed LDNs contained mature and immature neutrophils; both contributed to autoantigen expression. The frequency of LDN subtypes was similar between HC and patients regardless of disease activity. The frequency of immature LDNs did not correlate with *MPO* or *PRTN3* expression in LDNs. LDNs were refractory to MPO-ANCA induced oxidative burst, while MPO-ANCA induced robust activation of NDNs, that correlated with *MPO*expression.

Conclusions: LDNs may be a bystander of chronic inflammation or contribute to alternative mechanisms of disease pathology. In NDNs the association between *MPO* gene expression and MPO-ANCA induced NDN activation argues autoantigen gene expression influences disease pathogenesis and a therapeutic strategy could be suppressing expression.

Funding: NIDDK Support



Oxidative burst in LDNs (left) and NDNs (right) from ANCA vasculitis patients. Histograms show DHR fluorescence following activation with HC IgG (organge), MPO-ANCA IgG (purple), or PMA (green).

SA-PO591

Platelet Activation Is Induced via Myeloperoxidase Production and Anti-Myeloperoxidase Antibodies Primed by Thrombin

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Background: In addition to their central role in hemostasis and thrombosis, platelets involve in inflammatory responses. Anti-neutrophil cytoplasmic autoantibodies (ANCAs) directed to myeloperoxidase (MPO-ANCAs) are the main serological markers of ANCA-associated vasculitis.

Methods: Platelets were stimulated by purified total IgG and MPO-ANCA from patients with or without low doses of thrombin. The fragments from MPO-ANCAs, $F(ab')_2$ and Fc, were digested and isolated, then incubated with thrombin-primed platelets. The $F(ab')_2$ pull-downed proteins were analyzed using mass spectrometry. The concentration of MPO was detected in active platelets and AAV patients.

Results: The current study demonstrated that MPO-ANCAs caused normal human platelets to activate, primed by low doses of thrombin. Purified immunoglobulin G, MPO-ANCAs and their $F(ab')_2$ fragments evidently increased the CD62P expression of platelets compared with controls. The existence of MPO in platelets was confirmed with mass spectrometry technology, after analyzing the $F(ab')_2$ fragment pull-downed proteins. After thrombin priming, platelets not only expressed MPO on the surface with an activation-dependent manner, but also released the enzyme to extracellular space. These effects markedly enhanced the activation of platelets. Additionally, there was no apparently increased CD62P-expression on platelets in MPO-ANCAs group compared with controls when adding MPO inhibitor, proving that primed platelets have ANCA antigen at their surfaces interacting with the autoantibodies.

Conclusions: These findings suggest a previously unappreciated character for platelets as immune cells and the autoantibodies-induced activation in an acute inflammatory disease.

SA-PO592

SUMO1 Promote Mesangial Cell Proliferation Through Inhibiting Autophagy in a Cell Model of IgA Nephropathy

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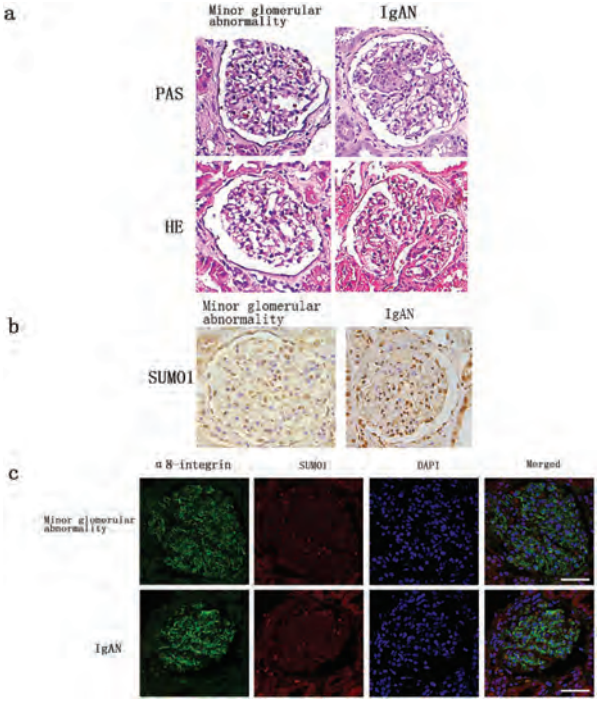
Background: IgA nephropathy(IgAN) is a common form of primary glomerulonephritis and its main pathological changes are mesangial cell proliferation and matrix expansion. Autophagy inhibition may result in its mesangial cell proliferation and renal lesions. SUMOylation is a eukaryotic-reversible post-translational modification where SUMO are covalently attached to target proteins to regulate their properties. It is largely unclear if SUMOylation contributes to the pathogenesis of IgAN.

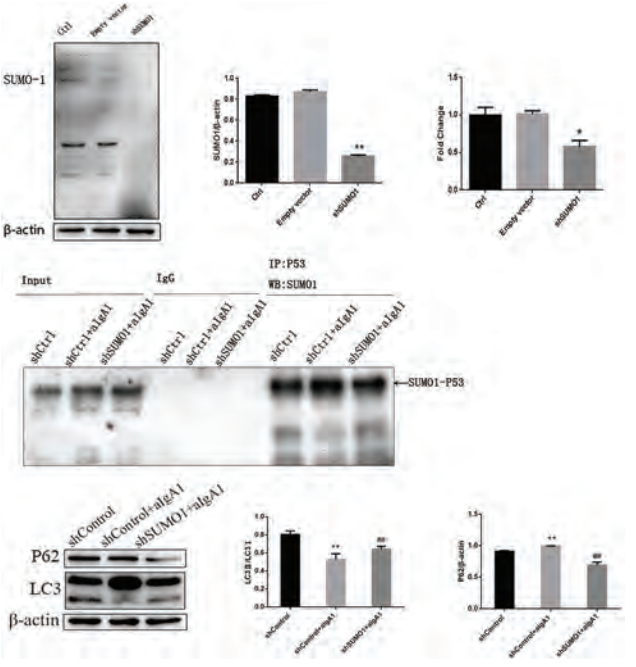
Methods: This study was designed to investigate the change of protein SUMO1 in mesangial cells of IgAN and its association with autophagy.

Results: We found the expression of SUMO1 was up-regulated in IgAN and aIgA1 stimulated mesangial cells. In aIgA1 stimulated mesangial cell model, we tested LC3 and p62, the autophagy-related proteins suggested the inhibition of autophagy. Silencing SUMO1 could down-regulate SUMO1 and SUMO1-p53, promote autophagy and lessen cell proliferation.

Conclusions: In the mesangial cells stimulated with aIgA1, SUMO1 may contribute to its cell proliferation through inhibited autophagy and SUMO1-p53 may play a role in this process.



The expression of SUMO1 in IgAN patients.



The expression of autophagy related proteins in mesangial cells stimulated with aIgA1.

SA-PO593

IgA1 from Sera of Patients with IgA Nephropathy, but Not Purified Monomeric or Polymeric IgA1, Associates with Cultured Primary Human Mesangial Cells and Induces Cellular Signaling

Zhi qiang Huang, Stacy D. Hall, Bruce A. Julian, Jan Novak. *University of Alabama at Birmingham, Birmingham, AL.*

Background: Circulating immune complexes (CIC) containing galactose-deficient IgA1 (Gd-IgA1) bound by Gd-IgA1-specific autoantibodies play a key role in the pathogenesis of IgA nephropathy (IgAN). Using a model of cultured primary human mesangial cells (hMC), we have previously shown that Gd-IgA1-containing CIC are biologically active, as they activate multiple protein-tyrosine kinases, lead to ERK1/2 phosphorylation, and stimulate cellular proliferation. In this study, we assessed how purified IgA1 of different molecular forms and serum IgA1 associate with and activate hMC.

Methods: Monomeric and polymeric forms of Gd-IgA1 were isolated from plasma of a patient with multiple myeloma by size-exclusion chromatography. IgA concentrations in serum samples from IgAN patients were measured by ELISA. Primary hMCs were incubated for 15 min at 37°C with 5% sera from IgAN patients or with the corresponding amount of monomeric or polymeric IgA1; hMC without any IgA1 served as a negative control. Cell lysates obtained after the incubation were used for pull-down using antibody specific for integrin β1 followed by protein G agarose. Cell lysates and pull-down samples were subjected to SDS-PAGE/Western blotting to detect IgA and phospho-ERK1/2.

Results: Purified monomeric as well as polymeric Gd-IgA1 exhibited minimal interactions with hMC, as only small amounts of IgA1 appeared in the hMC lysates and no induction of ERK1/2 phosphorylation was observed. In contrast, when sera from IgAN patients were used, we observed more IgA1 in hMC lysates (4 times more compared to monomeric Gd-IgA1, 8 times more compared to polymeric Gd-IgA1) as well as robust ERK1/2 phosphorylation. Preliminary pull-down experiments indicated that a fraction of IgA1 was associated with integrin β1, a previously described hMC receptor for IgA1. Moreover, we found that hMC formed α1β1 and α5β1 integrin complexes.

Conclusions: IgA1 from sera of IgAN patients, but not free monomeric or polymeric Gd-IgA1, associates with hMC and activates hMC. Integrin β1 may be involved in this process and may provide clues for development of future targeted therapy of IgAN.

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SA-PO594

C-Reactive Protein Is Renoprotective in Experimental IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common glomerulonephritis in the world. Although the pathogenesis of the renal disorder remains largely unknown, NLRP3 inflammasome-mediated IL-1b production and subsequent activation of adaptive immunity is implicated in the development of IgAN. C-reactive protein (CRP) is a serum biomarker for various inflammatory conditions and has been shown to inhibit the activation of the NLRP3 inflammasome.

Methods: In the present study, we examined the role that CRP could play in the evolution of IgAN using an experimental model of IgAN in CRP knockout (KO) mice, and dissected the mechanisms involved.

Results: The results show that the experimental IgAN in CRP KO mice revealed significantly increased magnitudes in **(1)** renal pathology, including marked mesangial cell proliferation and mononuclear leukocyte infiltration in the glomeruli and peri-glomerular interstitial tissue, **(2)** glomerular deposition of IgA and C3, **(3)** NLRP3 inflamamsome activation in the kidney, and **(4)** renal function impairment and proteinuria compared to their wild type (WT) counterparts equally induced of IgAN. Moreover, IL-10 levels in both sera and renal tissues were significantly elevated in IgAN in CRP KO mice, compared with WT counterparts.

Conclusions: In conclusion, CRP may serve as a protective role in the development of IgAN by inhibiting NLRP3 inflammasome and enhancing the production of IL-10. The results suggest that CRP may be a potential therapeutic agent for IgAN.

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SA-PO595

Tris DBA Ameliorates IgA Nephropathy by Blunting the Activating Signal of NLRP3 Inflammasome Through SIRT1- and SIRT3-Mediated Autophagy Induction

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Background: Tris (Dibenzylideneacetone) dipalladium (Tris DBA), a small molecule palladium complex, can inhibit cell growth and proliferation in pancreatic cancer, lymphocytic leukemia and multiple myeloma. Given that this compound is particularly active against B cell malignancies (Chronic lymphocytic leukemia and multiple myeloma), we hypothesized that it can alleviate immune complex-mediated conditions, including IgA nephropathy (IgAN)

Methods: C57BL/6 mice were induced IgAN by consecutive 28 daily injections of purified IgA anti-phosphorylcholine antibodies and pneumococcal C-polysaccharide antigen (PnC), followed by clinical, pathological, and molecular mechanism analyses. On day 7 after disease induction, the mice were divided into 2 groups and administered daily either Tris DBA (30 mg/kg body weight) or vehicle (KATIMIN) via an intraperitoneal route throughout the study. The animals were killed at days 14 and 28, respectively. Cultured of macrophages were analysis for activating signal of NLRP3 inflammasome and SIRT1- and SIRT3-mediated autophagy induction.

Results: In the present study, we examined the therapeutic effects of Tris DBA on glomerular cell proliferation and renal inflammation in a mouse model of IgAN. The results show that treatment of IgAN mice with Tris DBA resulted in markedly improved renal function, albuminuria and renal pathology, including glomerular cell proliferation, neutrophil infiltration, sclerosis and peri-glomerular inflammation in the renal interstitium, together with [1] reduced mitochondrial ROS generation; [2] differentially regulated autophagy and NLRP3 inflammasome, [3] inhibited phosphorylation of JNK, ERK, and p38 MAPK signaling pathways, and priming signal of the NLRP3 inflammasome, and [4] blunted NLRP3 inflammasome activation through SIRT1- and SIRT3-mediated autophagy induction, in renal tissues or macrophages.

Conclusions: Tris DBA was able to effectively ameliorate the mouse IgAN model; this beneficial effect involves blunting of mitochondrial ROS production, a MAPK (ERK, JNK)-mediated priming signal of the NLRP3 inflammasome, and differentially regulating the autophagy/NLRP3 inflammasome axis through SIRT1 and SIRT3. Thus, Tris DBA can be considered a therapeutic candidate for IgAN.

SA-PO596

Quantitative Assessment of Sites with Galactose-Deficient O-Glycans in the Hinge Region of IgA1

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Background: Serum level of IgA1 with galactose (Gal)-deficient hinge-region (HR) *O*-glycans (Gd-IgA1) is elevated in patient with IgA nephropathy (IgAN) and the glomerular immunodeposits of IgAN patients are enriched for Gd-IgA1. Lectins and a monoclonal antibody (mAb) specific for Gd-IgA1 have been used in ELISA to measure Gd-IgA1 serum levels. mAb specific for Gd-IgA1 stained glomerular immunodeposits in IgAN, further supporting the role of Gd-IgA1 in pathogenesis of IgAN. As mAb for Gd-IgA1 recognizes Gal-deficient *O*-glycans at a specific site(s), quantitative assessment of Gal-deficient sites is needed to identify disease-specific IgA1 HR *O*-glycoforms. Here, we describe a new method for quantitative assessment of sites with Gal- deficient *O*-glycans in IgA1 HR.

Methods: IgA1 from sera of 5 healthy controls was purified by affinity chromatography. After neuraminidase treatment and trypsin digestion, IgA1 HR glycosylation heterogeneity was analyzed by liquid chromatography-high-resolution mass spectrometry (LC-MS). Area under the peaks of extracted ion chromatogram (XIC) of identified IgA1 HR *O*-glycopeptides was calculated and expressed as relative abundance (RA) for each glycopeptide. The sites with Gal-deficient *O*-glycans were identified after selective quantitative removal of galactosylated *O*-glycans with *O*-glycanase by electron-transfer dissociation (ETD) tandem MS.

Results: Approximately 60% of IgA1 HR *O*-glycoforms contained one to three Gal-deficient *O*-glycans. ETD tandem MS unambiguously identify sites with Gal-deficient *O*-glycans and XIC based on isomeric glycoforms enabled quantitative assessment of Gal-deficient sites. The most common Gal-deficient sites included T^{236} followed by S^{230}, S^{232}/T^{233} and T^{228}. HR *O*-glycoforms with 2 or 3 Gal-deficient *O*-glycans predominantly included combinations of Gal-deficient sites at S^{230}, T^{233}, and/or T^{236}.

Conclusions: The quantitative assessment of sites with Gal-deficient *O*-glycans in IgA1 HR of healthy controls will enable future differentiation of IgAN *vs.* controls and identification of disease-specific IgA1 HR *O*-glycoforms associated with IgA1 glomerular deposition.

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SA-PO597

Characteristics of B Cells in IgA Nephropathy Model Mice

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Background: The pathogenesis of IgA nephropathy (IgAN) is associated with dysregulation of immune system, however the characteristics of B cells that are responsible for production of nephritogenic IgA have been elusive. Recently, we have reported the abnormal B cells expressing APRIL are present in tonsils of human IgAN (JASN 28; 1227, 2017). Since abnormal antibody production seems to be the key feature in the pathogenesis of IgAN, we investigated characteristics of B cells in IgAN model mice, gddY mice, which we have established. Furthermore, we recently developed a novel culture system mimicking germinal center in mucosa, by which nearly 50 % of B cells undergo class switch (CS) to IgA. Therefore, the present study aimed to evaluate characteristics of B cells in gddY mice by using this novel culture system. First, we analyzed the proliferation of splenic B cells upon stimulation in vitro. Next, we examined their CS to IgA.

Methods: The proliferation of splenic B cells upon stimulation with membrane-bound IgM and CD40 were evaluated by Thymidine-uptake analysis. Naïve B cells from wild type mice and gddY mice were cultured for seven days by using newly developed culture system and the IgA CS was evaluated by flow cytometry.

Results: We found that B cells of gddY mice exhibited elevated proliferation rate than those of wild type mice in response to stimuli through CD40 and membrane-bound IgM. There was no significant difference in the frequency of CS to IgA between splenic B cells from gddY mice and those from wild mice.

Conclusions: These data indicate B cells in gddY mice may be hyper-sensitive to stimuli by antigen and T-cell help without increasing the frequency of IgA CS and suggest such a B-cell intrinsic factor may be involved in the pathology of IgAN.

SA-PO598

A New Insight into the Pathogenesis of IgAN: Dissecting the Disease in Single Cells

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Molecular mechanisms driving glomerular damage in the disease are poorly understood. In this study, we analysed individual glomerular cell from ddY mice, a well-established genetic model of IgAN, by using scRNA-seq.

Methods: 5 control (non-proteinuric) and 5 IgAN (proteinuric) ddY mice were included in the study. Animals were sacrificed at 4 weeks of age and glomeruli isolated using the perfusion of magnetic beads. The glomeruli were treated mechanically and enzymatically to obtain single cells. Viable single cells of enriched glomeruli were unbiasedly sorted to 384-well plates and scRNA-seq performed using the Smart-seq2 protocol.

Results: A total of 3096 cells passed Quality Control. Unsupervised cell clustering demonstrated the inclusion of 11 cell types in both control and IgAN (glomerular endothelial (GEC), mesangial, parietal epithelial, podocyte, juxtaglomerular, macrophage, NK, T and B cells, as well as small contamination with tubular cells). The results showed a significant loss of podocytes in IgAN animals and revealed a number of new IgAN-associated genes/pathways in individual cell types. In podocytes, the Gene Ontology analysis revealed the emission of chemoattractant and pro-inflammatory cytokines, a role classically attributed to mesangial cells in this disease. In GECs, several cell subpopulations were detected and they showed a proinflammatory phenotype in IgAN, including for instance the up-regulation of selectin and MHC class 2 molecules. Mesangial cells seemed to be get activated and gain a migratory phenotype, which included, for instance, the up-regulation of ACTA2 expression. Moreover, several novel ligand-receptor pairs were identified in glomerular cells that are likely to play a role in the disease progression.

Conclusions: The preliminary analysis of our data suggests a crucial role of podocytes and GECs in the initiation of glomerular injury in ddY IgAN mice. Further analyses are ongoing to understand the crosstalk between the different glomerular cell types in both disease and healthy state.

SA-PO599

Intravenous Infection with Cnm-Positive Streptococcus mutans, a Dental Pathogen, Induces IgA Nephropathy-Like Lesions in Rats

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Background: IgA nephropathy (IgAN) is one of most common types of primary glomerulonephritis worldwide, but its precise pathogenesis remains unclear. Previously, we reported that *Streptococcus mutans*, a major pathogen of dental caries was frequently isolated from the oral cavity of IgAN patients; these isolates showed surface expression of collagen-binding protein (Cnm). However, there is no direct evidence that Cnm-positive *S. mutans* induces IgAN. In the present study, we evaluated renal lesions in rats that were intravenously infected with Cnm-positive *S. mutans* isolated from an IgAN patient.

Methods: Cnm-positive *S. mutans* strain SN74, isolated from the saliva of an IgAN patient, was intravenously administered to 4-week-old male specific pathogen-free Sprague-Dawley rats. At 15, 30, 45, and 60 days post-infection, kidney specimens were evaluated. Periodic acid-Schiff staining and fluorescent immunostaining with IgA, C3, and CD68 antibodies was performed; electron microscopy analysis was also performed.

Results: Proteinuria in the *S. mutans* group was significantly elevated, compared with that in the control group at 30 days post-infection ($p < 0.05$). Histopathological examinations revealed increased presence of mesangial cells and matrix at 30 days post-infection in the *S. mutans* group. Immunochemical examinations demonstrated that combined IgA/C3 deposition in mesangial cells was significantly greater in the *S. mutans* group than in the control group at 45 days post-infection ($p < 0.05$). Electron microscopy analysis showed electron-dense deposits in the mesangial area and hump in subepithelial areas in the *S. mutans* group at 45 days post-infection. Furthermore, the numbers of CD68-positive cells (i.e., macrophages) in the glomeruli of the *S. mutans* group were significantly higher than those in the control group at 30, 45, and 60 days post-infection ($p < 0.01$).

Conclusions: Intravenous infection with Cnm-positive *S. mutans* isolated from an IgAN patient could induce IgAN or infection-related glomerulonephritis in rats.

SA-PO600

Upregulation of miR-98-5p Enhance the Level of Galactose-Deficient IgA1 Through Chemokines in IgA Nephropathy

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Background: The increase of galactose-deficient IgA1 (Gd-IgA1) plays a crucial role in the pathogenesis of IgA nephropathy (IgAN). The aim of this study was to find the miRNA which could affect the pathogenesis of IgAN and reveal its regulation mechanism of Gd-IgA1 expression in peripheral blood.

Methods: The differentially expressed miRNAs in peripheral blood mononuclear cell (PBMC) between IgAN patients and healthy controls were screened by high-throughput sequencing. Confirm the results of the sequencing in a larger sample size. And explore the mechanism of the regulation of Gd-IgA1 caused by miRNA through transfecting miRNA mimic and related plasmid.

Results: High-throughput sequencing results showed that miR-98-5p is highly expressed in PBMC of IgA nephropathy patients compared with healthy controls, and the luciferase reporter gene system confirmed that miR-98-5p may target CCL3. miR-98-5p was increased and CCL3 was decreased in PBMC of IgAN patients were confirmed in a larger sample size, which was consistent with the sequencing results. It was confirmed by transfecting si-CCL3 that the decrease of CCL3 can affect the expression of interleukin-6 (IL-6) and C1GALT1. The overexpression of miR-98-5p in PBMC through transfecting the miR-98-5p mimic led to a reduction in CCL3 and C1GALT1 levels and an increase in IL-6 and Gd-IgA1 levels. But when co-transfected with the CCL3 plasmid, these changes in PBMC could be attenuated.

Conclusions: Hsa-miR-98-5p may be involved in the development of IgA nephropathy and is expected to become a biomarker and a new therapeutic target.

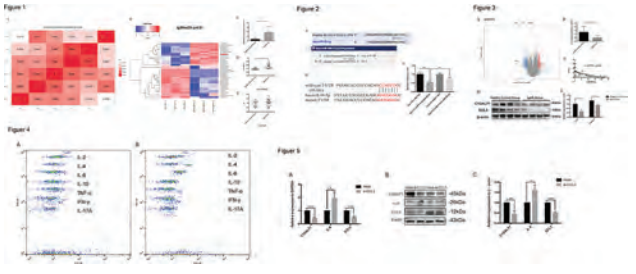

Figure 1. The changes in miR-98-5p expression of PBMCs in IgAN patients. Figure 2. miR-98-5p targets CCL3. Figure 3. CCL3 was down-regulated in IgAN patients. Figure 4. Th1/Th2/Th17 cytokines expression. Figure 5 CCL3 affects the expression of IL-6 and C1GALT1

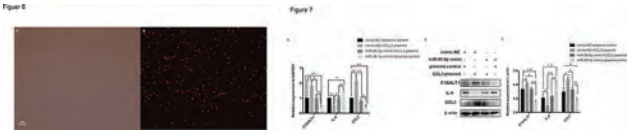

Figure 6 PBMCs transfected with mimic-Cy3Figure 7 miR-98-5p affects the expression of IL-6 and C1GALT1 and the level of Gd-IgA1 through CCL3

SA-PO601

Macrophage Interactions with Collecting Ducts May Contribute to the Interstitial Fibrosis Observed in IgA Nephropathy Progression

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Background: Tubulo-interstitial fibrosis is a powerful predictor of future progression in IgA nephropathy (IgAN). Proximal tubules, in concert with infiltrating macrophages, are regarded as the *agents provocateurs* for driving this process. However, evidence is now emerging for a contributory role of the distal nephron. The aim of this study was to examine the potential influence of macrophages on renal collecting ducts (CDEC) in the progression of IgAN.

Methods: Macrophage-conditioned media (MCM) were generated from U937 and THP-1 cells, cultured in the presence or absence of 100μg/ml IgA1. Collecting duct epithelial cells (CDEC) exposed to the MCMs were analysed for evidence of inflammation and fibrosis.

Results: Staining of IgAN biopsies for the macrophage marker CD68 demonstrated that macrophages were principally observed in and around proximal tubules. However, CD68+ macrophages were also observed in areas of medullary collecting ducts and within their lumens. CDEC exposure to THP-1-IgA-MCM exhibited markedly increased expression of the tubular injury marker neutrophil-associated gelatinase (NGAL) and raised levels of IL1β, TNFα, IL6 and IL8; effects that were replicated by 5ng/ml IL1ß alone. U937-IgA-MCM, on the other hand, significantly increased MCP-1 and fibronectin levels and reduced E-cadherin mRNA expression. Exosomes extracted from THP-1-IgA-MCMs stimulated similar increases in NGAL and cytokine expression to the source MCM, while in cross over experiments exosomes extracted from CDECs induced IL1β and IL6 mRNA expression in macrophages. MiRnome analysis using nanostring technology revealed that miR-146a was expressed more than 2 fold in CDECs treated with THP-1-IgA-MCM compared to THP-1-MCM. Enforced miR-146a suppression with a specific inhibitor further enhanced NGAL expression in CDECs in the presence of MCM while ectopic miR-146a over expression down-regulated it. Both NGAL mRNA and miR-146a were found, by RT-PCR, to be upregulated in the biopsies of progressive forms of IgAN compared to CKD controls.

Conclusions: Taken together these data suggest that macrophages and collecting ducts could interact to contribute to the tubulo-interstitial fibrosis and inflammation found in progressive forms of IgAN.

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SA-PO602

CARD9 Risk Allele and IgA Nephropathy

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Background: IgA nephropathy (IgAN) is a common cause of primary glomerulonephritis and is most prevalent in East Asian populations. The pathogenesis of IgAN is not well understood. IgAN GWAS studies have revealed an association with rs4077515, a SNP within the coding sequence of CARD9, an essential mediator of the innate immune system. However the place of CARD9 in the pathogenesis of IgAN has yet to be defined. The aim of this study was to investigate the expression of CARD9 in the kidney and determine whether it has an intrarenal role in IgAN.

Methods: Screening kidney cell lines for synthesis of CARD9 by western blotting revealed greatest CARD9 synthesis in human mesangial cells (hMC). To test the significance of the risk allele we incubated hMC that were heterozygous or homozygous negative or positive for the risk allele rs4077515-T with IgA1 isolated from 5 individuals (3 IgAN, 2 healthy subjects) and measured IL-6 synthesis using ELIZA.

Results: We observed increased expression of CARD9 mRNA in whole kidney biopsies in IgAN compared to kidney disease controls ($p<0.005$). Immunohistochemistry demonstrated CARD9 protein in both the glomerular and tubulointerstitial compartments in IgAN. The presence of rs4077515-T resulted in significantly increased production of the pro-inflammatory cytokine IL-6 following exposure to IgA1 ($p<0.0001$: TT:CC and $p<0.001$: CT:CC). In parallel, similar increases were seen in mRNA coding for IL-6 IgA1 ($p<0.001$: TT:CC and $p=0.0109$: CT:CC), the signal transducer, IL-6ST ($p<0.0001$: TT:CC and $p<0.0023$: CT:CC) and monocyte chemoattractant protein 1 ($p<0.0001$: TT:CC and

p=0.0004: CT:CC). This *in vitro* data suggests that the presence of rs4077515-T could result in a greater inflammatory response to mesangial IgA deposition in IgAN and therefore rs4077515-T may play a role in determining the rate of renal function decline in IgAN. To test this hypothesis we analysed the association of rs4077515-T with renal function outcome in 1,279 Chinese IgAN patients. There was a significant association between rs4077515-T and the likelihood of renal function decline in this population (HR values of 1.85 (95% CI 1.17-2.93) TT:CC and 1.33 (95% CI 0.98-1.82) CT:CC).

Conclusions: This data suggests intrarenal CARD9 may play a significant role in determining mesangial response to IgA deposition in IgAN and ultimately influence the likelihood of renal function decline.

SA-PO603

The Role of Angiogenin/miR-141 Axis in Glomerular Injury of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common primary chronic glomerular disease worldwide. Gal-deficient IgA1 (Gd-IgA1) containing immune complex is the important factor involved in the pathogenesis of IgAN, which mechanism has not yet been clarified. Angiogenin is a secreted ribonuclease, and it plays biological functions through selectively cutting RNA substrates, including miRNAs.

Methods: The concentration of Angiogenin in plasma and cell medium was examined by Elisa. Overexpression of Angiogenin was conducted by infection of lentivirus with Angiogenin overexpression plasmid. Knockdown of Angiogenin was conducted by infection of lentivirus with shRNA. Cell proliferation activity was carried out by CCK-8. Cell apoptosis was carried out by Flow cytometry. The protein were measured by western blotting, mRNA and miRNA were measured by RT-qPCR. The cleavage of miR-141 by Angiogenin was carried out by a cell-free cleavage assay.

Results: The level of Angiogenin in plasma was elevated in IgAN patients than healthy controls. When the glomerular mesangial cell was stimulated by Gd-IgA1 immune complex, the secretion of Angiogenin and some inflammatory cytokines were upregulated. When the expression of Angiogenin in mesangial cell was knock-down by shRNA, the proliferative activity of mesangial cells was inhibited. The expression level of miR-141 was affected by Angiogenin expression in mesangial cells, high expression of Angiogenin downregulated miR-141 and knockdown of Angiogenin upregulated the level of miR-141. In addition, Angiogenin digest miR-141 as an endoribonuclease *in vitro*.

Conclusions: Angiogenin was upregulated in IgAN. Gd-IgA1 complex stimulation increased the secretion of Angiogenin and inflammatory cytokines of mesangial cell. Down-regulation of Angiogenin inhibits the proliferative activity of mesangial cells. Angiogenin regulates the level of miR-141 in mesangial cell and digests miR-141 as an endoribonuclease *in vitro*. Thus, Angiognein/miR-141 axis may regulate IgAN through affecting mesangial cell proliferation and inflammatory cytokines secretion.

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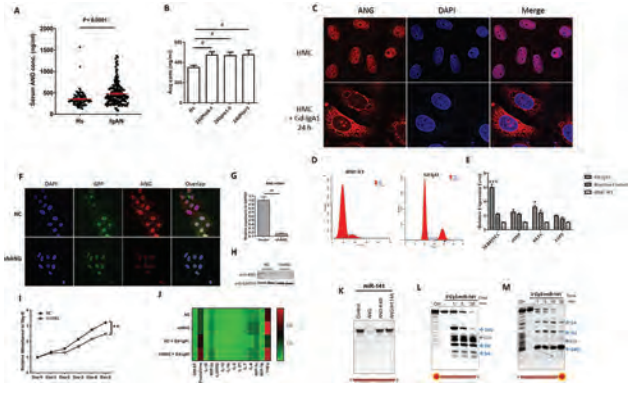

SA-PO604

TLR3 Activation Contributes to Pathogenesis of Mesangial Proliferative Glomerulonephritis

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Background: It is assumed that Toll-like receptor (TLR) is activated by ligands released from damaged tissue, and the TLR-mediated signaling is involved in the development of mesangial proliferative glomerulonephritis (MGN). However, how TLR detects signals from the damaged tissue and the pathogenic mechanism initiated by the TLR activation in MGN are poorly understood. Thy1.1. GN, a widely used rat experimental model for MGN, is caused by the injection of the antibody against Thy1.1 expressed on mesangial cell surface. Thy1.1. GN is characterized by diffuse mesangiolysis at 24h and consequent accumulation of inflammatory cells and mesangial cell proliferation.

Methods: The kinetics of the expression of TLR2, TLR3, TLR4 in Thy1.1. GN were analyzed by RT-PCR and immune-histochemical analyses. The cells expressing TLRs were analyzed.

Results: The increase in mRNA expression of TLR3 was already detected at 1 h (3.4 times to control) and the increase is promoted on day 7 (11.4 times to control). However, such a clear increase is not detected in TLR2 or TLR4. Immunostaining of TLR3 was not detected in normal glomeruli, and the clear positive staining of TLR3 was detected at mesangial area at 1h, and at 24h and day 7 the positive staining was detected at the expanded mesangial area and in capillary lumen. In Thy1.1. GN at the early recovery phase after mesangiolysis Thy1.1. negative cells were mainly accumulated in mesangial area and the population of Thy1.1 positive cells gradually increased with time. ED1+ macrophage (4.3±0.45/glom.), ED3+ activated macrophages (4.5±0.90/glom) and NKRP1+ NK cells (1.6±0.45/glom) were accumulated in glomeruli on day 7 of Thy1.1. GN. Dual labeling immune-histochemical analysis showed that TLR3 was detected on Thy1.1. negative cells localized at mesangial area but not detected on Thy1.1. positive cell, and some portions of ED3+ cells express TLR3 but no NKRP1+ cells express TLR3. mRNA expression IFN-β, which is mainly activated by TRL3-mediated signaling, was increased (2.8 times to control) in this GN model.

Conclusions: Not TLR2 or TLR4 but TLR3 was dominantly activated in Thy1.1. GN. It is conceivable that TLR3 responds to molecules released by damaged mesangial cell, and TLR3-mediated signaling participates in the pathogenesis of mesangial proliferative nephritis.

Funding: Government Support - Non-U.S.

SA-PO605

THSD7A Knockout Mice as a Valuable Tool for the Generation of Domain-Specific Monoclonal Antibodies

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Background: Autoantibodies against multiple domains in THSD7A cause membranous nephropathy (MN). However, the function of THSD7A in podocytes, the precise mechanisms of antibody-induced glomerular injury and the role of the targeted epitopes are largely unknown.

Methods: Embryonic stem cells for generation of THSD7A-ko first mice were purchased from UCDavis KOMP. Since ko first mice were found to contain residual expression of THSD7A in podocytes, mice were further bred to obtain a true constitutive THSD7A ko status (THSD7A$^{-/-}$). For the generation of poly- and monoclonal antibodies (MABs), 12w-old THSD7A$^{-/-}$ mice were immunized using the purified murine antigen fragments d1_d2 and d15_d16, corresponding to the domains most frequently recognized by patient autoantibodies. Spleen and lymph nodes were collected 7w after immunization and fused with SP2/0 myeloma cells. Cell clones expressing anti-THSD7A antibodies were selected using an immunofluorescence test on THSD7A-transfected CHO cells. Positive clones were cultured and IgG was purified from cell culture supernatant.

Results: THSD7A$^{-/-}$ mice showed no glomerular expression of THSD7A in immunofluorescence and Western blot. Glomeruli appeared normal in PAS staining and no ultrastructural changes were observed by EM. Mice had no proteinuria by the age of 1y. Immunization of THSD7A$^{-/-}$ mice induced high levels of domain-specific anti-THSD7A antibodies. Fusion of splenic cells with myeloma cells resulted in 3 clones producing antibodies against THSD7A. One MAB recognized d1_d2 (IgG1) and two MABs recognized d15_d16 (IgG1 and IgG2b). These MABs were suitable for the detection of THSD7A in immunofluorescence, Western and dot blot. Transfer of individual MABs to WT BALB/c mice resulted in glomerular binding of mouse IgG, but no complement deposition and no proteinuria.

Conclusions: In preliminary investigations, THSD7A$^{-/-}$ mice do not show significant glomerular alterations, suggesting that THSD7A expression is not integral for basal glomerular function or that other unidentified molecules can compensate for the lack of THSD7A. THSD7A$^{-/-}$ mice are a powerful tool for the generation of poly- and monoclonal antibodies and these antibodies can potentially be used to dissect the mode of antibody-induced glomerular damage and the role of targeted epitopes in MN.

SA-PO606

IL233 Regulates Mitochondrial Function and WNT Signaling for Lupus Glomerulonephritis Remission

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Background: We showed that the hybrid cytokine IL233 induced persistent remission in ongoing lupus glomerulonephritis (GN) in NZM2328 mice. The progression of GN in NZM2328 animals involves stages of acute (aGN), transitional (tGN) and chronic GN (cGN). As a means to further understand the mechanisms involved in IL233-rendered protection, we investigated modulation of mitochondrial function and canonical Wnt signaling that is understudied in the setting of aGN to cGN progression, utilizing both *in vitro* and *in vivo* approaches.

Methods: Mouse glomerular endothelial cells (mGECs) and proximal tubular TKPTS cells were treated with varying concentrations of IL233 and investigated for mitochondrial membrane potential and for genes and proteins associated with mitochondrial function. *In vivo*, kidney lysates from treated NZM2328 animals were screened for transcripts of mitochondrial genes by real time PCR. Canonical Wnt signaling proteins were studied by Western blotting. Seahorse XF Cell Mito Stress assay was performed with isolated regulatory T cells (Tregs) from treated animals.

Results: IL233 treatment induced a marked elevation of genes related to mitochondrial function and biogenesis (*Pgc1α*, *Mfn1*, *Nrf1*, *Nrf2*, *Tfam* and *Drp1*) in mGECs and TKPTS cells indicating a direct regulation of mitochondrial function. These cells also displayed higher mitochondrial membrane potential by flow cytometry. IL233-treated mice with established GN had higher expression of genes related to mitochondrial function and biogenesis, thus, complementing *in vitro* observations. Levels of canonical Wnt activators (*LRP6* and *Dvl3*) and □□-catenin were significantly reduced in IL233 treated kidneys. Tregs isolated from saline, IL-2, IL-33, IL2+IL-33 and IL233 treated animals were investigated for oxidative respiration with Seahorse. Although there was a trend of a higher rate of oxidative respiration in mice treated with IL-2 or IL-33 only or the combination of IL-2 and IL-33, the Tregs isolated from IL233 treated mice had a significantly higher basal and burst respiration rate.

Conclusions: We present evidence for the use of IL233 for therapy of lupus GN in a murine model. *In vitro* and *in vivo* data reveals enhancement of mitochondrial function and modulation of canonical Wnt signaling as possible mechanisms of IL233-mediated remission from lupus GN.

Funding: NIDDK Support

SA-PO607

Epidermal Growth Factor Receptor-Dependent TLR7 Signaling in Macrophages Promotes Kidney Injury in Crescentic Glomerulonephritis

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Background: Epidermal growth factor receptor (EGFR) has been shown to promote glomerular injury in crescentic glomerulonephritis (CRGN) and we showed that EGFR plays pivotal roles in the signaling of endosomal Toll-like receptors (TLRs): TLR3 (*Sci Signal. 2012*), TLR4 (*EMBO Rep. 2015*), and TLR9 (*J Immunol. 2018*). Polymorphisms in TLR7, a sensor for endogenous danger signal, are linked with the development of SLE, and TLR7 activation is implicated in lupus nephritis. Here, we show that EGFR has a critical role in macrophages (MΦs) for TLR7-dependent CRGN.

Methods: To induce nephrotoxic serum nephritis (NTN), a model of CRGN, C57Bl/6 (WT) mice or TLR7-/- mice were immunized with normal rabbit IgG and IFA, and injected with nephrotoxic serum (NTS). These mice were also treated with or without treatment of Gefitinib, an EGFR inhibitor. Seven days after NTS injection, kidney injury was analyzed by proteinuria and histology. In cell culture system, TLR7-mediated gene induction, cytokine production, and cell migration were assessed using bone marrow-derived MΦs and RAW 264.7 cells. The physical interaction between EGFR and TLR7, and tyrosine phosphorylation of TLR7 were analyzed by immunoprecipitation assay.

Results: TLR7-/- mice were resistant to NTN compared to WT mice: TLR7-/- mice showed less severe proteinuria, GBM rupture, crescent formation, and less number of Mac-2 positive MΦs infiltration into glomeruli. None of the glomerular resident cells expressed TLR7 confirmed by protein expression and functional assays *in vitro* and *ex vivo*. Only inflammatory MΦs expressed significant amount of functional TLR7. Mechanistically, upon a TLR7 ligand stimulation, TLR7 physically interacted with EGFR in MΦs by co-immunoprecipitation, and tyrosine residue(s) of TLR7 is phosphorylated. However, such a TLR7 phosphorylation is completely blocked by Gefitinib, an EGFR kinase inhibitor. In addition, Gefitinib blocked subsequent cellular function (e.g. cell migration) and cytokine production (e.g. IL-6 production). Finally, Gefitinib treatment on TLR7-/- mice did not show significant additional protective effects on NTN at an early time point (Day 7), compared to TLR7-/- mice without Gefitinib.

Conclusions: These results indicate that regulation of TLR7 signaling in MΦs by EGFR has a critical role in the early pathogenesis of CRGN.

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SA-PO608

Glomerular Endothelial Cell Heterogeneity and Contribution to Kidney Disease

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Background: Glomerular endothelial dysfunction plays a key role in the development of chronic kidney disease (CKD), but its impact on Alport syndrome (AS, characterized by mutations in collagen IVα3α4α5) is unknown. In AS, we reported structural changed and upregulation of VEGF pathway in the glomerular endothelial cells (GEC) in the early stage of the disease and we hypothesized that GEC dysfunction is important in AS pathogenesis.

Methods: To test our hypothesis, we generated GEC specific (Tek-Cre driven) *td*Tomato reporter AS mice and isolated GEC by FACS. We studied GEC by flow cytometry, WB, and by multiphoton and confocal microscopy, and by RNA-seq analysis. Data were analyzed and AS-GEC compared to WT-GEC in terms of their morphology and gene expression.

Results: *td*Tomato signal identified two distinct GEC subsets (*bright* and *dim*) in both wild type and AS mice, which presented with transcriptional heterogeneity in ECM and glycocalyx-associated proteins, immune cell activation and cellular metabolism. In AS-GEC vs WT-GEC, genes with a well-established functional role in mitochondrial dysfunction, glucose and lipid metabolism, and inflammation were most significantly enriched. In particular, the *bright* cells were enriched in (upregulated) genes controlling cytoskeleton organization and inflammatory cell-cell adhesion (such as Icam1, Vcam1, Ccl2, Spon2, Sele, etc). In contrast, the *dim* cells were highly enriched in (upregulated) genes related to chemokine signaling but downregulated for genes and pathways associated with mitochondrial function. Both *bright* and *dim* cells were enriched in downregulated genes linked to glucose and lipid metabolism. In terms of cell-ECM interactions, Itgβ9 was highly reduced in both subsets in AS. Among other differentially expressed genes related to ECM composition, Svep1 expression was highly increased in the *bright* cells and Col17α1 in the *dim* cells exclusively.

Conclusions: In conclusion, we identified two GEC subpopulations and showed glomerular endothelial dysfunction in the early stages of AS. Importantly, GEC subsets contributed to endothelial dysfunction differently. A better understanding of the functional role of the glomerular endothelium could lead to the development of targeted new therapies for the treatment of CKD.

Funding: Private Foundation Support

SA-PO609

APL-2 Prevents Both C3 and C5 Convertase Formation and Activity: A Potential Therapeutic for Renal Diseases

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Background: C3 glomerulopathy (C3G) is a group of renal diseases characterized by isolated glomerular deposits of C3 fragments as a result of an uncontrolled activation of the complement alternative pathways (AP). The excessive activation of C3 and C5 convertases leading to C3b production and formation of the membrane attack complex is associated with renal function impairment. About 50% of the patients progress to end stage renal disease within 10 years of the diagnosis. The disease is caused either by genetic abnormalities in complement regulatory proteins or by the presence of autoantibodies, C3 or C5 nephritic factors (NeFs), that bind and stabilize the convertases. APL-2 is a small, synthetic, cyclic peptide that binds and inhibits C3 and C3b. The objective of this study was to better understand the impact of APL-2 on the formation of the AP C3 and the C5 convertases and on the activity of pre-formed convertases. We also evaluated the ability of APL-2 toinhibit NeFs-mediated overactivation of both convertases.

Methods: This study was performed in *in vitro*model of hemolysis using C3b-recovered sheep erythrocytes and purified complement proteins. IgG positive for C3NeF (n=14) and C3/C5NeF (n=9) were isolated from patients with C3G and added with or without APL-2 (25 μg/ml).

Results: APL-2 prevents the formation of AP C3 and C5 convertases and inhibits the activity of both pre-formed convertases. APL-2 also decreased the prolonged convertase activity mediated by C3NeF and C5NeF. In 6/14 C3NeF and 7/9 C5NeF the stabilizing effect of the autoantibodies became undetectable demonstrating that APL-2 is still effective to inhibit the convertase hyperactivity in the presence of NeFs.

Conclusions: APL-2 is a C3 inhibitor that also interrupts the formation and inhibits the activity of pre-formed AP C3 and C5 convertases, therefore blocking the activation of both C3 and C5. The effect of APL-2 on the convertases occurs also in the presence of NeFs. This data supports potential therapeutic effects of APL-2 in patients with C3G as well as for other renal diseases associated with overactivation of complement.

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SA-PO610

Micromanaging Autoimmune Nephritis: miR-17-92 Modulates T_{FH} Development and Regulatory T Cell Activity

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Background: T follicular helper (T_{FH}) cell provide crucial growth signals to germinal center (GC) B cells supporting antibody production. Tight control of T_{FH} numbers maintains self-tolerance. Regulatory T (Treg) cells play a critical role in maintaining self-tolerance and controlling the magnitude of physiologic immune response. The Treg transcription factor forkhead box P3 (Foxp3) works in concert with other co-regulator molecules to determine suppressive phenotype of Treg. Compiling evidence show that aberrant T_{FH}, GC responses and deficiencies of Treg are associated with systemic lupus erythematousand autoantibody production.

Methods: We generated T cell specific miR-17-92 knockout (miR-17-92-/-) mice, followed by induction of pristane nephropathy in miR-17-92 -/- and wild type littermates. By bioinformatics study, possible targets of mir-17-92, related to Treg function was evaluated. Luciferase reporter assay was utilized for verification. Forced expression and knockdown of miRNA in Treg and TFH was performed by lentivirus.

Results: We induce pristane nephropathy on T cell specific miR-17-92 knockout (miR-17-92$^{-/-}$) mice. Mir17-92 CD4 T cell specific deficiencymitigates pristane induced-lupus nephropathy in mice. The mice showed less T_{FH} cells, less GC B cells and lower autoantibody formation. Consistent with the reduction in autoantibody production, histological analysis revealed a lower mean renal histopathology score and less IgG deposition. We further demonstrate that the miR-17 regulates T_{FH} development by targeting Akt pathway. Moreover, miR17-92 mitigate the suppression function of Tregs

by targeting Foxp3 co-regulators. Ectopic expression of miR-17 downmodulates the suppression functions of Tregs in the colitis model. In addition, Tregs from patient with lupus nephritis and lupus mice both showed increased miR-17 expression.

Conclusions: Our studies suggest that miR-17-92 modulates aberrant immune response through critical regulation in T cells subsets, unveiling the future therapeutic potential of microRNA manipulation in lupus nephritis.

Funding: Private Foundation Support

SA-PO611

Evaluation of the Renoprotective Role of Endogenous Galectin-3 and Mechanism in Lupus Nephritis

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Background: Lupus nephritis (LN) is a major complication of systemic lupus erythematosus. Current therapeutic regimens to control the acute onset of LN progression include high doses of corticosteroids, cytotoxic agents and disease-modifying antirheumatic drugs. However, there is still a major concern about the potential, systemic adverse events of these drugs. Thus, the development of pathogenic pathway-based new therapies with much fewer and more tolerable side effects is clinically warranted. Galectin-3 (Gal-3) is a β-galactoside-binding protein and implicated in diverse biological processes in macrophages, dendritic cells (DCs), activated lymphocytes, and epithelial cells. However, the role of Gal-3 and exact mechanisms involved in the development and progression/deterioration of LN has yet to be determined, although renal expression of the protein is observed in LN patients.

Methods: Gal-3 KO-Y chromosome-linked autoimmune acceleration (Yaa) mutation was introduced in KO1 strain (KO1.Yaa) mice, a spontaneous mouse model of LN, which is deficient of Gal-3 were generated to investigate the renoprotective effects of Gal-3 in two complementary LN mouse models. Moreover, lupus-like nephritis in Gal-3 KO mice induced by LPS injections. Renal function, pathology and pathogenesis-based experiments galactoside-binding.

Results: In the present study, the results show that [1] the distribution and expression levels of Gal-3 were increased in renal biopsy specimens from LN patients, compared to normal control subjects; [2] deficiency of endogenous Gal-3 resulted in markedly increased severity in clinical and pathological alterations in both the LPS-induced LN in Gal-3 KO mice and spontaneous LN in Gal-3 KO-KO1. Yaa mice, compared to their respective wild type counterparts that equally induced of or developed galactoside-binding; and [3] greatly enhanced activation of T cells and B cells as well increased monocytosis in peripheral blood mononuclear cells were observed in the spontaneous LN in Gal-3 KO-KO1. Yaa mice, compared to KO1.Yaa mice.

Conclusions: Gal-3 played a protective role in the development of LN, and justify the protein as a potential drug candidate for LN.

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SA-PO612

Urinary Levels of CD11b and CD163 Determine Rapid Responders to Remission Induction Therapy in Proliferative Lupus Nephritis

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Background: Drastic elevations of urinary CD11b (U-CD11b), α_m subunit of integrin Mac-1, and CD163 (U-CD163), a scavenger receptor for hemoglobin-haptoglobin complex, have been demonstrated in proliferative lupus nephritis (LN). The current study aims the further verifications of U-CD11b and U-CD163 as the potential LN biomarkers to predict longitudinal response of proliferative LN patients to the remission induction therapy.

Methods: We examined CD11b and CD163 by enzyme-linked immunosorbent assay in urine samples collected from proliferative LN class III or IV patients confirmed by renal biopsy in Nagoya Kidney Disease Registry (N-KDR) cohort between 2004 and 2014, and retrospectively analyzed those associations with longitudinal achievement of complete remission (CR) following the remission induction therapy. Based on the cut-off values of U-CD11b and U-CD163 respectively determined by receiver operation curves to predict CR, univariate analysis by log-rank test and multivariate analysis by cox proportional hazards regression model were performed to evaluate patient susceptibility to the remission induction therapy.

Results: Among 63 patients with proliferative LN for 52 months observation period on average, U-CD11b and U-CD163 levels were significantly higher in patients who achieved CR within 3 months ($p<0.001$ in U-CD11b, $p=0.003$ in U-CD163) and 12 months ($p=0.02$ in U-CD11b, $p=0.03$ in U-CD163) compared with those who did not. In univariate analysis, the cumulative CR rates within 3 months in patients presenting low levels of U-CD11b and U-CD163 were significantly higher than their respective high levels. Multivariate analysis revealed low level of U-CD11b (hazard ratio [HR], 5.68; 95% confidence interval [95% CI], 1.65 to 19.4) and eGFR per 10ml/min/1.73m^2 (HR, 1.30; 95% CI, 1.11 to 1.52) as independent predictors for the achievement of CR within 3 months. Moreover, low level of U-CD11b (HR, 4.69; 95% CI, 1.35 to 16.2) still demonstrated the significance even in the subpopulation with preserved renal function.

Conclusions: U-CD11b, rather than U-CD163, serve the clinical values for the prediction of early response to the remission induction therapy in LN patients.

SA-PO613

The Role of Plasmacytoid Dendritic Cells in Pathogenesis of Systemic Lupus Erythematosus

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Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease accompanied by production and deposition of immune complexes (IC) in multiple organs. Especially in the kidney, lupus nephritis (LN) due to deposition of IC occurs in about 40-70% of SLE patients, and about 10-30% of these patients progress to end stage renal disease. Plasmacytoid dendritic cells (pDCs) which recognize viral nucleic acids by endosomal toll-like receptor (TLR) 7/9 and secrete large amounts of IFN- I are considered as important mediators of antiviral responses, while inappropriate recognition of self nucleic acids with IFN- I responses is linked to autoimmunity. Therefore, this subset of DCs are attracting an attention for novel therapeutic target. But so far, little is known about the mechanisms how pDCs contribute pathogenesis of SLE and LN. TLR7 agonist, imiquimod (IMQ) induced mice SLE model is deeply involved with IFN- I secretion, and present LN which is similar to those of human. With this model, we investigated pathogenesis of SLE focusing on pDCs.

Methods: We isolated pDCs from spleen of 4weeks IMQ model, and performed miRNA array. We extracted miRNA which was up or down-regulated, and searched mRNAs target of these miRNAs on database. Then predicted mRNA targets were confirmed by qPCR. Using human pDCs cell line, CAL-1, we performed TLR7, 9 and IC stimulation experiment.

Results: As a target of miRNAs that shows down-regulation, we found zinc finger transcription factor: Kruppel-Like Factor 4 (KLF4). By qPCR, we confirmed that KLF4 was up-regulated in mice pDCs. Similar results were observed in the pristine-induced mice SLE model. We found that the protein levels of KLF4 was also up-regulated in TLR7 stimulation group compare with control group.

Conclusions: The production of autoantibody in SLE requires sustained production of IFN- I, but the pathogenesis of sustained IFN- I production in pDCs is not fully understood. From our study, it was suggested that the up-regulation of KLF4 in pDCs plays some roles in the pathogenesis of SLE. Further studies are needed to elucidate the precise roll of KLF4 in pDCs.

SA-PO614

Circulating MiRNAs as Potential Biomarkers of Kidney Damage in Patients with Systemic Lupus Erythematosus

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Background: Renal involvement is one of the most severe manifestations of systemic lupus erythematosus (SLE). Renal biopsy is the gold standard when it comes to knowing whether a patient has lupus nephritis and the degree of renal disease present. However, the biopsy has various complications, bleeding being the most common. Therefore, the development of alternative, non-invasive diagnostic tests for kidney disease in patients with SLE is a priority. Micro RNAs (miRNAs) are differentially expressed in various tissues, and changes in their expression have been associated with several pathological processes. The aim of this study was to identify changes in the abundance of miRNAs in plasma samples from patients with lupus nephritis that could potentially allow the diagnosis of renal damage in SLE patients.

Methods: This is an observational case-control cross-sectional study, in which we characterized the differential abundance profiles of miRNAs among patients with different degrees of lupus compared with SLE patients without renal involvement and healthy control individuals.

Results: We found 89 miRNAs with changes in their abundance between lupus nephritis patients and healthy controls, and 17 miRNAs that showed significant variations between SLE patients with or without renal involvement. Validation for qPCR of a group of miRNAs on additional samples from lupus patients with or without nephritis, and from healthy individuals, showed that five miRNAs presented an average detection sensitivity of 97%, a specificity of 70.3%, a positive predictive value of 82.5%, a negative predictive value of 96% and a diagnosis efficiency of 87.9%.

Conclusions: These results strongly suggest that miR-221-5p, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p are potential diagnostic biomarkers of lupus nephritis in patients with SLE. The observed differential pattern of miRNA abundance may have functional implications in the pathophysiology of SLE renal damage.

SA-PO615

Pneumococcal Polysaccharide Vaccine Regulates Murine Lupus

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Background: Current guidelines suggest the use of anti-pneumococcal vaccine Prevnar13 in patients with lupus, but the effects of such vaccination on disease severity are unknown.

Methods: We injected Prevnar13 (0.5 ml) or vehicle control into 8wk-old female MRL-*lpr* that spontaneously develop lupus. After 3mo, we measured circulating anti-PS IgG. In another set of animals, we quantified disease severity at 3 mo after Prevnar13 injection, including albuminuria, renal histology, and skin lesions. We also measured phenotype and function of splenocytes from treated and untreated mice, as well as renal STAT1 and STAT3 protein levels (WB).

Results: Prevnar13 induced the formation of anti-pneumococcal IgG (**Fig. 1A**). Prevnar13 treated animals showed less albuminuria, renal histological lesions, and milder dermatitis compared to controls (**Fig. 1B-D**). Improved disease severity in Prevnar13-treated animals was associated with reduced T follicular helper cells (T_{FH}) and more T follicular regulatory cells (Tfr) and regulatory T cells (Treg) (**Fig. 1E**). After aCD3/aCD28 stimulation, T lymphocytes from vaccinated mice showed less IL-17 and IL-4 production than non-vaccinated controls, while IL-10 production was significantly increased. Vaccinated mice had significantly decreased expression of STAT1 compared to controls, whereas STAT3 levels did not differ.

Conclusions: Anti-pneumococcal vaccination elicits anti-pneumococcal antibody response and ameliorates disease severity in MRL-*lpr* mice, which associates with increased fewer T_{FH} and increased Tregs. These data strongly support the use of Prevnar vaccination in individuals with lupus.

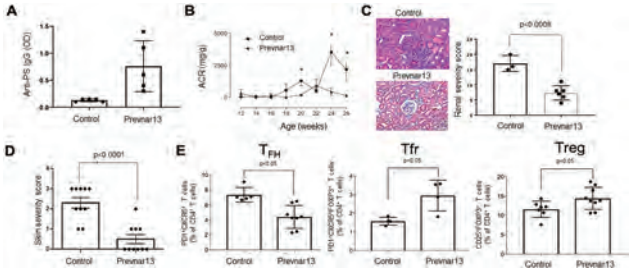

Fig. 1. Anti-PS IgG in MRL-*lpr* mice at 3 months after Prevnar13 injection (**A**). Urinary albumin/creatinine ratio (ACR) at serial time points after vehicle control or Prevnar13 injection in MRL-*lpr* mice (**B**). Representative H&E staining and kidney (**C**) and skin (**D**) severity score at 3 months after injection. T_{FH}, Tfr, and Treg in the spleens of the same mice (**E**). *P < 0.05 vs. control at the same time-point.

SA-PO616

Patients with Membranous Nephropathy Show Increased Circulating T Follicular Helper (T_{FH}), T_H17, and Exhausted T Cells (T_{EXH}): Results from a Cross-Sectional Study Including Healthy and CKD Controls

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Background: Primary membranous nephropathy (MN) is characterized by the presence of antibodies to the podocyte, but studies characterizing abnormalities in circulating T and B cell populations are limited and generally include only healthy controls.

Methods: We performed a comprehensive flow-cytometric analyses of 38 T and B lymphocyte subpopulations, including intracellular staining for IFN-g, IL-4, and IL-17 production in 27 patients with MN (before initiating immunosuppressive therapy) and compared them with 12 healthy individuals and 22 patients with non-immune mediated chronic kidney disease (CKD) including diabetic nephropathy, hypertension, and APKD. We also measured 19 serum cytokines in MN patients and healthy controls.

Results: 9 T and B cell subsets varied between MN and healthy subjects, but the only ones that differed between MN and both healthy and CKD controls included: $CD4^+$ $CXCR5^+$ $PD1^+$ T follicular helper (T_{FH}), $CD4^+$ $PD1^+$ $CD57^-$ T exhausted (T_{EXH}), and $CD4^+$ $IL17^+$ T cells (T_H17) that were significantly higher in MN patients (**Fig. 1A-D**). TNF-a and IL-7 were also significantly higher in MN patients than in healthy controls (**Fig. 1E-F**).

Conclusions: Patients with MN display a unique immune phenotype characterized by increased T_{FH}, T_{EXH}, and T_H17 cells. Despite the associative nature of the study, inclusion of both healthy and CKD controls, strongly supports a pathogenic role for these cells.

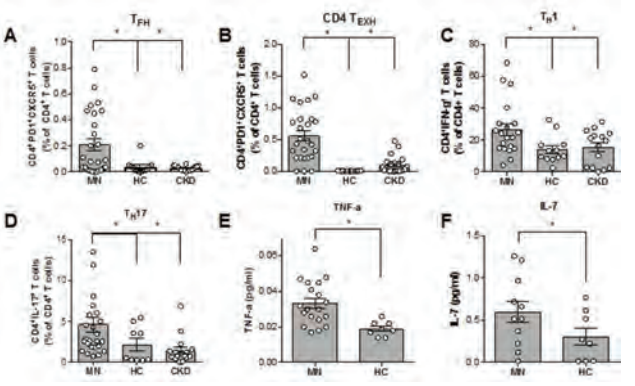

Fig. 1. Percentages of T_{FH} (**A**), $CD4^+$ T_{EXH} (**B**), T_H1 (**C**), T_H17 (**D**) cells in patients with membranous nephropathy (MN), in healthy controls (HC), and in patients with non-immune mediated chronic kidney disease (CKD). Serum TNF-a (**E**) and IL-7 (**F**) levels in MN patients and in HC.

SA-PO617

Ablation of MRP8 in Myeloid Cells Ameliorates Glomerulonephritis by Affecting Macrophage Characterization

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Background: We previously reported that toll-like receptor 4 (TLR4) and its endogenous ligand, myeloid-related protein 8 (MRP8, S100A8), play important roles in the progression of diabetic nephropathy in mice. During these experiments, we unexpectedly observed that glomerular-infiltrated macrophages (MΦ) expressed MRP8 much more robustly than tubulointerstitial MΦ. However, the mechanisms and roles remain elusive.

Methods: We generated myeloid-lineage cell-specific MRP8 knockout mice (MyM8KO), and induced experimental nephrotoxic glomerulonephritis (NTN). Co-culture of MΦ with mesangial cells (Mes) or proximal tubular cells (PT) was performed to investigate the potential cellular crosstalk within glomeruli. Phalloidin staining was performed to evaluate the effects of MRP8 on bone marrow-derived MΦ (BMDM) generated from MyM8KO. BMDM was characterized as the M1/M2 ratio (M1/M2) determined by real-time PCR. Cell surface markers of peripheral leukocytes and glomerular-infiltrated MΦ were analyzed by flow cytometry (FCM). For effective sorting of MRP8-targeted cells, MyM8KO were crossed with floxed-STOP ZsGreen transgenic mice (MyM8KO-ZsG).

Results: In the NTN mice, ablation of MRP8 in myeloid-lineage cells significantly ameliorated glomerulonephritis as indicated by the reduction in proteinuria, glomerular exudative lesions, pro-inflammatory gene expressions and M1 dominancy in isolated glomeruli. In vitro, MRP8 expression was markedly induced in BMDM by co-culture with Mes but not with PT. This finding was recapitulated by stimulation with Mes-cultured supernatant (Mes-sup). Moreover, Mes-sup stimulation increased M1/M2 in wild-type BMDM, but such effect was blunted in BMDM obtained from MyM8KO. In BMDM stimulated with Mes-sup, deletion of MRP8 resulted in less stress fiber formation. FCM revealed that MyM8KO-ZsG NTN mice exhibited less ICAM-1 expression in both peripheral blood monocytes and glomerular-infiltrated MΦ.

Conclusions: These results indicate that myeloid-lineage cell-derived MRP8 could potentially contribute to glomerular injury upon NTN through intraglomerular cell-cell crosstalk, affecting MΦ characterization.

SA-PO618

A Modified Peptide Derived from Goodpasture Autoantigen Arrested and Attenuated Kidney Injuries in Experimental Anti-GBM Glomerulonephritis

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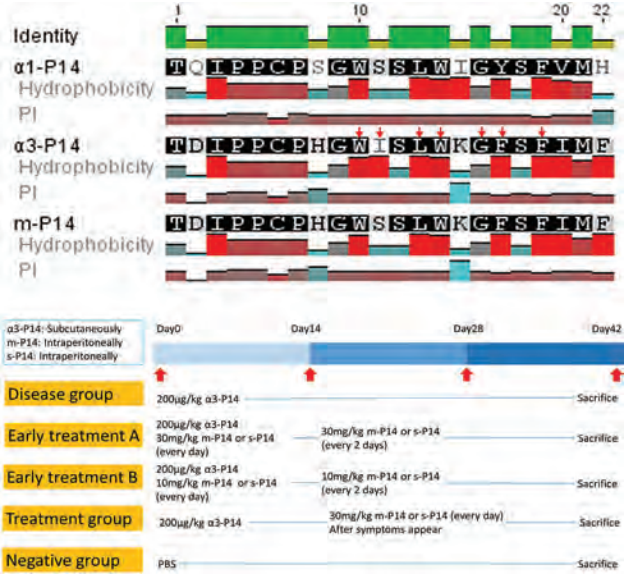
Background: P14 ($\alpha3_{127\text{-}148}$) was a nephritogenic epitope on human α3(IV)NC1, inducing EAG with its core motif $W_{136}I_{137}L_{139}W_{140}G_{142}F_{143}F_{145}$. Based on the sequences of α1-P14 and α3-P14, a modified peptide (m-P14) was designed by the substitution of $\alpha3\text{-}I_{137}$ to $\alpha1\text{-}S_{137}$.

Methods: m-P14 was injected into P14-immunized WKY rats either on immunization or upon disease onset. PAS staining, ELISA, Flow cytometry, ELISpot were also applied in this study.

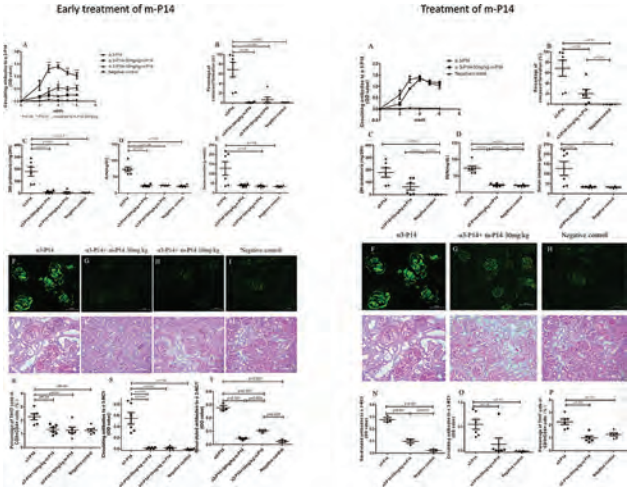
Results: m-P14 intervention attenuated the α3-P14 induced anti-GBM disease in early-treatment groups and treatment group with decreased crescent formation(30mg/kg m-P14: 0.5±0.4 *vs.* 68.8±15.4 %; *P*=0.002; 10mg/kg m-P14: 6.3±5.6 *vs.* 68.8±15.4%, *P*=0.009; treatment: 20.1±8.4 *vs.* 68.8±15.4%, *P*=0.026). m-P14 could inhibited the binding of α3-P14 to MHC molecules and abated the forming of splenic Th17 in

intervention groups. m-P14 also inhibited the binding between α3-P14 to antibodies and impeded intra-molecular epitope spreading.

Conclusions: m-P14 could arrest and attenuate the kidney injuries of anti-GBM disease in rat model through cellular and humoral immunity regulation. This approach confirmed the feasibility of modulating T cell activation for the treatments of Goodpasture's disease.

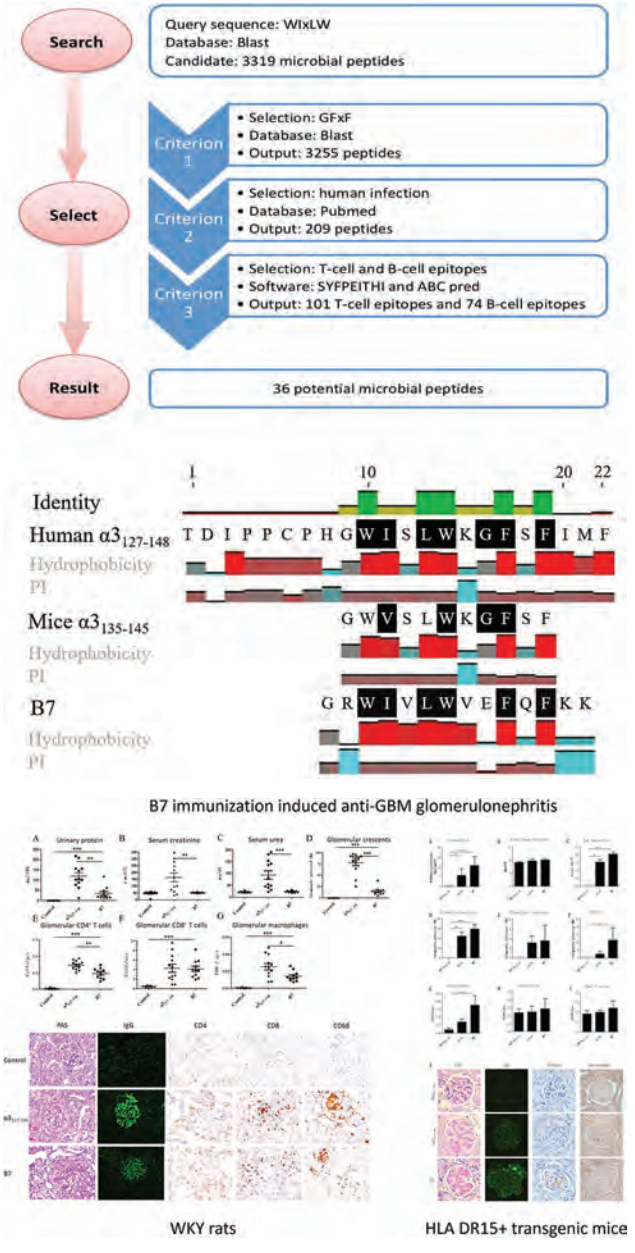


The design of m-P14 and the flowcharts of m-P14 intervention in experimental anti-GBM disease.



Early-treatment and treatment of m-P14 in experimental anti-GBM glomerulonephritis.

HLA-DR15 transgenic mice. These results indicate that infections may initiate anti-GBM disease through molecular mimicry.



SA-PO619

Experimental Anti-Glomerular Basement Membrane Glomerulonephritis Induced by a Peptide from Actinomyces

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Background: P14 ($\alpha3_{127}$-$_{148}$) was a nephritogenic epitope for anti-GBM disease, with its core motif $W_{136}I_{137}L_{139}W_{140}G_{142}F_{143}F_{145}$. Infections has been suspected as the "second hit" for the onset of anti-GBM disease. We aimed to search for mimicking microbial peptides that may participate in anti-GBM disease.

Methods: Blast, SYFPEITHI, ABCpred were used for searching P14-mimic microbial peptides. WKY rats and HLA-DR15$^+$ transgenic mice were immunized with peptide B7. IHC staining, ELISA and ELISpot were applied.

Results: Peptide B7 derived from actinomyces was screened from 3319 microbial peptide under the criteria of containing the critical motif of P14, related with human infection, included both T cell and B cell epitope and high recognition for sera of anti-GBM patients. All B7-immunized rats exhibited linear deposits of IgG on the GBM. The percentage of crescent formation in glomeruli was 14.6±2.7%. For HLA-DR15$^+$ transgenic mice, all mice immunized with B7 exhibited linear IgG deposits along the GBM and focal glomerular necrosis, two of them (28.6%) developed glomerular crescent formation. B7 also had cross-reaction with $\alpha3_{135-145}$ immunized rat splenocytes on T cell level for WKY rats model.

Conclusions: We found one microbial peptide derived from actinomyces could induce crescentic anti-GBM glomerulonephritis in both WKY rats and humanized

SA-PO620

Human Hypoxic Proximal Tubule Epithelial Cells (PTECs) Trigger NLRP3 Inflammasome Activation in CD1c$^+$ Dendritic Cells (DC)

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Background: Chronic kidney disease (CKD) is characterised by inflammation and tubulointerstitial fibrosis. Hypoxia is a key driver of this pathology. Kidney proximal tubule epithelial cells (PTEC) are particularly susceptible to oxygen imbalances due to their high rates of aerobic respiration. We have reported activated CD1c$^+$ dendritic cells (DC) adjacent to PTEC in fibrotic kidney tissue, where they are well positioned to sense PTEC-derived danger signals via the NLRP3 inflammasome. In this study, we examined the hypoxic response in human PTEC and their functional role in CD1c$^+$ DC activation.

Methods: Primary human PTEC were cultured under normoxia (21% O_2) or hypoxia (1% O_2) and assessed for mitochondrial function, proliferation and viability. PTEC-CD1c$^+$ DC interactions were examined by *in vitro* co-culture in the absence or presence of NLRP3 inflammasome inhibitor MCC950. DC activation was assessed by mRNA profiling and cytokine secretion. *In vivo* cellular interactions in fibrotic kidney tissue were examined by immunofluorescence microscopy.

Results: Hypoxic PTEC displayed significant mitochondrial dysfunction, significantly reduced proliferation and significantly increased cell death compared to normoxic PTEC. $CD1c^+$ DC matured in the presence of hypoxic PTEC showed increased NLRP3 mRNA expression and secreted significantly elevated levels of inflammasome-related cytokines (IL-1β, IL-18). Notably, this pro-inflammatory response was significantly reduced in the presence of the NLRP3 inflammasome inhibitor, MCC950. Immunofluorescence staining of fibrotic kidney tissue identified PTEC co-localized with $CD1c^+$ DC expressing downstream signalling markers of NLRP3 inflammasome activation (active Caspase-1).

Conclusions: Our data demonstrate that hypoxic PTEC trigger and activate $CD1c^+$ DC via the NLRP3 inflammasome, resulting in the secretion of pro-inflammatory cytokines. Future studies will examine the putative role of mitochondrial danger signals generated by hypoxic PTEC for therapeutic targeting in human CKD.

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SA-PO621

HIV-Induced Podocyte Pyroptosis Contributes to Proliferation of Parietal Epithelial Cells

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Background: The lack of or abundance of proliferating parietal epithelial cells (PECs) in Bowman's space determines the glomerular phenotype in focal segmental glomerulosclerosis. Proliferating PECs in Bowman's space characterize the HIV-associated nephropathy. The involved mechanism of PECs proliferation in HIV milieu is not understood. Interleukin (IL)-1 β has been reported to stimulate PECs proliferation. We have recently demonstrated that HIV infection stimulates the generation of IL-1β by podocytes. We hypothesize that massive injury of HIV-infected podocytes would stimulate PECs proliferation.

Methods: Immortalized human podocytes were differentiated and transduced with either vector (V-PDs) or HIV (NL4-3, HIV-PDs) and evaluated for pyroptosis (morphologic assay). V-PDs and HIV-PDs were incubated in serum-free media for 24 hours. Incubation (conditioned, C) media was collected and stored at -80°C. PECs were incubated in serum-free media containing 10% of control (V-PDs), and experimental (HIV-PDs) conditioned media for 48 hours. In another set of experiments, PECs were incubated in serum-free media containing 10% control and experimental media with or without IL-1β (neutralizing) antibodies for 48 hours. Cells were evaluated for proliferation by MTT cell viability assay. To establish an interaction, PECs were grown in outer wells, and V-PDs/HIV-PDs were seeded into inner wells (Trans-well plates). After 48 hours,-PDs were assayed for IL-1β by ELISA. Additionally, PECs grown on coverslips were treated with 10% control and experimental media for 48 hours, followed by immunolabeling for either PCNA or Ki67.

Results: HIV-PDs showed a higher percentage of pyroptosed cells ($P<0.01$ vs. V-PDs). Cellular lysates and incubation media of HIV-PDs showed increased ($P<0.05$ vs.V-PDs) generation of IL-1β. Conditioned media of HIV-PDs stimulated PECs proliferation; however, anti-IL-1β antibody partially inhibited HIV-PDs conditioned media-mediated proliferation. PECs growing in outer wells of trans-well plates containing HIV-PDs showed increased proliferation. PECs treated with HIV-PDs conditioned media showed a higher percentage ($P<0.01$ vs. V-PDs) of PCNA/Ki67 +ve cells.

Conclusions: HIV-induced podocyte pyroptosis contributes to PECs proliferation.

Funding: NIDDK Support

SA-PO622

Glomerular Gene Coexpression Networks Suggest Pathogenic Mechanisms in a Mouse Model of HIV-Associated Nephropathy

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Background: HIV-associated nephropathy (HIVAN) is an important cause of renal failure in African-Americans. The Tg26-transgenic mouse replicates key features of HIVAN including podocyte dedifferentiation. We hypothesize that glomerular gene coexpression networks from Tg26 mice will provide insights into HIVAN pathogenesis.

Methods: Glomerular-transcriptomes were obtained from 6-week old wild-type and Tg26-HIVAN4 mice of both sexes. Preliminary analysis demonstrated a strong sex effect on gene expression. In order to control the covariate sex, two networks were generated using weighted gene-correlation network analysis (WGCNA): 1) all mice sex-adjusted, 2) Consensus network between unadjusted gene expression form female and male mice. Coexpression modules significantly correlated with HIV-transgenes in both analysis were compared, identifying overlapping gene lists. These lists were evaluated for canonical pathway enrichment with IPA.

Results: 1113 overlapping genes were found between 2 consensus and 5 sex-adjusted modules significantly correlated with HIV transgenes. Intersecting genes were pooled into 4 functional groups based on pathways enrichment. The first group represented the initial response to HIV transgenes with pathways leading to the activation of macrophages and secretion of chemoattractant molecules. The second group represented the migration of immune cells to the "infection" site and the activation of the inflammasome. The third group was enriched with integrin signaling pathways. As integrin interactions are widely used by migrating immune cells, this group likely supports the immune response on groups 1 and 2. Finally, the fourth functional group was largely enriched with cell cycle pathways, reflecting that in collapsing forms of focal segmental glomerulosclerosis such as HIVAN, differentiated glomerular cells are recruited back into the cell cycle.

Conclusions: Gene-coexpression network analysis detected modules matching the chain of events in the progression of HIVAN in the Tg26-HIVAN4 mice. We also identified sex as a strong driver of gene expression. However, this sex effect did not impact disease pathways in Tg26-HIVAN4 mice, but could be relevant in understanding sexual dimorphism in other kidney diseases.

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SA-PO623

APOL1 and JAK1/2 Are Required for Interferon Gamma-Stimulated Inflammatory Responses in Human Kidney Cells

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Background: Chronic inflammation contributes to progression of glomerular diseases including diabetic kidney disease (DKD). Recent data suggest that APOL1 and JAK1/2 signaling contribute to the pro-inflammatory milieu in FSGS and DKD, respectively. Based on systems genetic and transcriptomic analyses of humans and of murine models of glomerular diseases, the expression of CXCL9, a T-cell chemoattractant belonging to the CXC chemokine family, is increased by APOL1 high risk genotype expression in FSGS and by JAK2 overexpression in diabetic podocytes. We therefore determined whether and how APOL1 and JAK signaling interact to stimulate CXCL9 in a human kidney cell.

Methods: Human kidney 2 (HK-2) cell monolayers were grown to confluence and treated with interferon gamma (IFNg) (30ng/ml), interleukin-6 (10ng/ml), or tumor necrosis factor-alpha (10ng/ml) from 30 min to 48 hr. Levels of JAK2, APOL1 and CXCL9 mRNAs were determined in response to agonists. Inhibition of JAK1 and JAK2, with baricitinib (500nM) or siRNA knockdown of APOL1 expression was performed in some experiments befpre IFNg exposure. Effects of APOL1 knockdown on IFNg-stimulated gene expression were examined. These genes were identified by transcriptomic analysis of IFNg-treated podocytes.

Results: HK-2 cells express APOL1, JAK2 and CXCL9. Stimulation of HK-2 cell monolayers with IFNg, but not IL-6 or TNF, resulted in a rapid and sustained 4-50-fold increase in mRNA expression of JAK2, APOL1 and CXCL9. These increases were largely abrogated by pretreatment with the JAK1/2 inhibitor as were IFNg-induced increases in STAT3 phosphorylation and APOL1 protein levels. APOL1 knockdown resulted in an 80% reduction in CXCL9 expression and a 40-50% reduction in interferon-induced guanylate-binding protein 2, HLA class II histocompatibility antigen, DR alpha chain and ubiquitin D. Expression of other IFNg-stimulated genes was not consistently affected by APOL1 knockdown.

Conclusions: In cultured human kidney cells, IFNg triggered responses in kidney cells resulting in increased expression of pro-inflammatory mediators and APOL1. This cascade was largely abrogated by specific inhibition of JAK1/2 signaling and selectively inhibited by knockdown of APOL1. These findings suggest that APOL1 plays an important role in the IFNg-mediated inflammatory response in kidney cells.

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SA-PO624

Lipoxins Promote Tissue Repair And Regeneration

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Background: Inflammation and its timely resolution is essential in maintaining tissue homeostasis during injury and infection. Chronic low-grade inflammation contributes to the pathogenesis of CKD and failure to resolve this leads to impaired tissue repair. Conventional therapeutics such as steroids and non–steroidal anti-inflammatory drugs target the key drivers of the inflammation to dampen the inflammatory response but fail promote inflammation resolution or tissue repair. The resolution phase of inflammation is dynamically regulated by endogenously generated mediators including bioactive lipids such as lipoxins and deficits in these mediator networks may underlie chronic inflammation. We have previously demonstrated reno-protection by lipoxins in experimental models of acute and chronic renal injury (Brennan et al, JASN 2018). Now we wish to explore the therapeutic potential of lipoxins to promote tissue repair and regeneration.

Methods: To investigate the potential of lipoxins to promote tissue repair and regeneration the median tail fin of wild-type 3dpf zebrafish larvae was transected. 4 hours post-injury larvae were treated with LXA4 or vehicle and tissue regeneration tracked by time lapse imaging over 48 hours. The effect of lipoxins on the activation and recruitment of PMNs during tail fin injury was monitored using fluorescent imaging in the transgenic zebrafish lines Tg(mpx:EGFP) and Tg(MPEG1:mCherry). The effect of lipoxins on macrophage subsets was further investigated in human THP-1 derived macrophages treated with TNFα.

Results: Treatment with LXA4 significantly enhanced tail fin regeneration and promoted the resolution of inflammation in the zebrafish model. Furthermore, in THP-1 derived macrophages LXA4 treatment significantly reduced TNF induced inflammation, reprogramming macrophages towards a pro-resolution phenotype as evidenced by up-regulation of IL-4 and MRC1.

Conclusions: These findings suggest that lipoxins promote tissue repair and regeneration by reprogramming macrophages towards a pro-resolution phenotype and may have therapeutic potential for the treatment of chronic inflammation associated with diseases such as CKD.

SA-PO625

Mitochondrial Damage in Tubule Cells Activates the cGAS-STING Innate Immune Pathway and Leads to Fibrosis

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Background: Mitochondrial damage, defective bioenergetics, and immune system activation play key role in chronic kidney disease (CKD) and fibrosis. As the mitochondria retained ancient circular bacterial DNA, we hypothesized that the mitochondrial defects observed in kidney fibrosis lead to cytoplasmic leakage of the mitochondrial DNA and then recognized by the intracellular bacterial DNA recognition pathway; cGAS-STING signaling cascade resulting in activation of inflammatory pathways and CKD.

Methods: Here, we analyzed gene expression data by RNA sequencing of 433 microdissected human kidney tissue samples with varying degree of kidney fibrosis and kidney function. To model mitochondrial damage, we generated mice with tubule-specific mitochondrial transcription factor (*Tfam)* deletion (Ksp-Cre/Tfam$^{f/f}$). To explore the role of STING we crossed these mice with STING knock-out mice and treated with STING inhibitor. To understand the therapeutic potential of STING inhibition in CKD, we examined the renal phenotype of the STING knock-out mice following folic acid (FA) induced kidney injury and treated mice with a STING inhibitor.

Results: We found that expression of mitochondrial genes and its transcriptional regulator TFAM was significantly decreased in patients and mouse models with kidney disease. *Ksp-Cre/Tfam $^{f/f}$* developed severe mitochondrial loss and decline of ATP content by 6 weeks of age. Progressive azotemia, kidney fibrosis and death of the animals was only observed after 12 weeks of age. Mechanistic studies demonstrated that aberrant mtDNA packaging upon TFAM deficiency in tubule cells resulted in escape of mtDNA into the cytosol, activation of the cytosolic DNA sensing pathway, STING, resulting in cytokine expression and immune cell recruitment. Genetic deletion or pharmacological inhibition of STING ameliorated TFAM-loss induced kidney fibrosis. Genetic deletion of STING and to lesser degree the STING inhibitor ameliorated kidney fibrosis in the FA induced model of kidney disease.

Conclusions: We concluded that in addition to its essential role in metabolism, TFAM sequesters mtDNA to prevent the activation of innate immune pathways and fibrosis. Cytosolic aberrant DNA in CKD activates the cGAS-STING pathway. Limiting STING activity can ameliorates kidney disease development.

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SA-PO626

Decreased Monocyte Costimulatory Molecule CD86 Expression in Focal Segmental Glomerulosclerosis Predicts Early Relapse Following Rituximab Therapy

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Background: We recently reported a subgroup of focal segmental glomerulosclerosis (FSGS) patients bearing an immunological signature of T-cell hyporesponsiveness who responded to rituximab treatment. This study aimed to characterize the immunological subsets in FSGS patients who responded to treatment in order to predict early relapse within the first year following rituximab therapy.

Methods: A total of 29 FSGS patients (median age 14.7 years, range 6.1-25.0 years) receiving rituximab were recruited in this study. Rituximab was administered to patients at a dose of 375 mg/m^2 fortnightly to a maximum of 4 doses, and followed up longitudinally. Immunological subsets were monitored at baseline, and 6 months post-rituximab. Statistical analyses was done using Mann-Whitney U test and Wilcoxon signed rank test for paired analysis prior and 6-months post-rituximab. Receiver-operating characteristic (ROC) curve analysis was used to determine predictive utility of the subset for early relapse.

Results: 51.7% (15/29) responded to rituximab therapy with characteristic significant downregulation of IFNγ (P<0.01) following PMA/ionomycin stimulation. Of the 15 FSGS patients who responded to treatment, 60% (9/15) had no relapses within the first year post-rituximab (Group I), while 40% (6/15) relapsed (Group II) with comparable median B-cell recovery of 6.0 months and 5.0 months respectively (P=0.41). Patients in Group II had significant lower percent CD86 (75.5±7.0%) on monocytes compared with Group I (91.8±2.5%) (P=0.03). ROC analysis showed that monocyte expression of CD86 (AUC 0.88, 95% CI 0.67-1.00) fared well as a good predictor for relapse (sensitivity 80.0%, specificity 87.5%, PPV 80.0%, NPV 87.5%, with discriminatory threshold <90.2%). CD86 expression in Group II was significantly upregulated 6-months post-rituximab treatment (91.6±2.1%), (P=0.04).

Conclusions: We identified a distinct immunological subset of FSGS patients with decreased monocyte CD86 (B7-2) expression at baseline, who are likely to relapse within a year post-rituximab therapy and hence could benefit from early re-treatment with rituximab. CD86 is a receptor which provides costimulatory signal to T-cell activation, deciding between T-cell fate of immunity or anergy. The role of monocytes in FSGS however remains to be elucidated.

Funding: Government Support - Non-U.S.

SA-PO627

Differential Roles of RAGE Species for Renal Tubular Damages

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Background: Receptor for advanced glycation end-products (receptor for AGEs, RAGE) is a transmembrane and multiligand pattern recognition receptor, which binds AGEs, S100 proteins, and high mobility group box 1 protein (HMGB1), eliciting inflammatory signal transductions. Soluble and decoy forms of RAGE (sRAGE) are, otherwise, generated by a cleavage of RAGE or by an alternative splicing, which forms an endogenous secretary RAGE (esRAGE). However, roles of sRAGE in the pathogenesis of kidney diseases remains unclear. We here examined whether RAGE and sRAGE could be implicated in renal tubular damages using a mouse kidney ischemia/reperfusion (I/R) model.

Methods: Unilateral renal I/R was introduced in RAGE knockout (*Ager$^{-/-}$*) mice with or without administration of sRAGE. Tubular damages, interstitial cell accumulation and fibrosis were assessed at day 2 or 7. We also assessed tubular damages using anti-glomerular basement membrane nephritis models with or without sRAGE treatment at day 7. We checked the expression of genes coding RAGE, esRAGE and proinflammatory mediators after hypoxia using murine renal proximal tubular epithelial (mProx24) cells. Cellular damages and proliferation were also assessed in hypoxia-induced mProx24 cells with or without an sRAGE addition.

Results: We found that tubular damages were severer in *Ager$^{-/-}$* mice than in *Ager$^{+/+}$* mice at day 2 and 7 after I/R. Kidney fibrosis and macrophage infiltration were also exaggerated in *Ager$^{-/-}$* mice at day7. In vitro, hypoxia-exposure decreased the expression of genes coding RAGE and esRAGE in mProx24 cells, while *Hmgb1* and *Tnfa* mRNAs were paradoxically upregulated. However, an sRAGE addition significantly decreased *Hmgb1* and *Tnfa* mRNA expressions and induced the proliferation in hypoxia-induced mProx24 cells. Moreover, an sRAGE administration protected from tubular damages of I/R-performed mice and of the anti-GBM glomerulonephritis models.

Conclusions: We demonstrated that the hypoxic condition could induce the downregulation of genes coding RAGE and esRAGE in renal tubular cells. Administration of sRAGE could protect the kidney from I/R injury.

SA-PO628

Detection and Characterization of Prolonged Classical Pathway Convertase Activity: C4 Nephritic Factor and a Non-Autoantibody Serum Factor

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Background: C3 glomerulopathy (C3G) is a renal disease caused by overactivity of the complement system, particularly of the alternative pathway (AP). Autoantibodies such as C3 nephritic factors (C3NeFs) or mutations in complement genes are commonly found as pathogenic causes. Recent findings also reveal the presence of C4 nephritic factors (C4NeFs) in some C3G cases. By stabilizing the convertases of the classical pathway (CP), these autoantibodies contribute to the complement dysregulation in C3G. In this study, we investigated C4NeF activity in a cohort of patients with complement-mediated renal diseases.

Methods: We used a recently described hemolytic method to measure convertase activity directly in serum, using a C5-blocker to separate the CP into 2 steps: a time-variable first step for convertase formation out of test serum and a standardized second step for hemolysis readout.

Results: Serum samples of 17 healthy controls and 47 patients with (suspected) C3G and closely related complement-mediated disorders were analyzed. Convertase activity levels in controls consistently returned to background levels after 10 min. In contrast, convertase activity was significantly prolonged until 20 min in 2/47 (4%) patients (P1 and P2), indicating the presence of CP convertase-stabilizing factors. Addition of purified Igs from P1 to control serum supported prolonged convertase activity, confirming the autoantibody nature of the stabilizing factor. Previously, the Igs of this patient were also shown to have AP convertase-stabilizing activity, i.e. C3NeF activity. Further investigation showed that both the C3NeF and C4NeF activity resided in the Ig fractions of the kappa light chain type. In addition, both the AP and CP convertase-stabilizing activities remained present over the disease course of the patient. In contrast to P1, the Igs of P2 did not support convertase stabilization when added to control serum, indicating a non-autoantibody factor caused the increased convertase half-life. The nature of this factor, possibly genetic, is currently under investigation.

Conclusions: This study offers new opportunities for the detection and characterization of (previously unrecognized) CP convertase-dysregulating factors in patients with complement-mediated renal diseases.

SA-PO629

Trending Complement C3 in C3 Glomerulopathy Patients Before and After Renal Transplant

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Background: C3 Glomerulopathy (C3G) is characterized by dysregulation of the alternative pathway of complement. Most patients will approach ESRD within 10 years of diagnosis. Recurrence in renal transplants is as high as 84%. Little is known about the natural history of transplant recurrence or predictors of poor renal outcome. The degree of C3 consumption (represented by a low C3) has been postulated as a predictor of disease activity in the setting of native kidney disease. Whether C3 abnormality plays a similar role in the transplant setting is unknown. Similarly, the predictive value of other complement biomarkers is unknown.

Methods: We studied a sub-cohort of the University of Iowa's C3G Natural History Study. All patients met biopsy criteria for C3G. Reviewed patients had at least 3 pre-transplant and 3 post-transplant C3 values. Using our standard assays, we tested all patients in the cohort for complement gene abnormalities and for longitudinal nephritic factor trend. Phenotypic results were correlated with recurrence of C3G in a renal allograft.

Results: Average age at diagnosis was 24 years. Average time to ESRD was 2 years. Drivers of disease included nephritic factors (NF, n=5), gene mutations (n=2), and a monoclonal protein (n=1). Median follow-up time post-transplant was 5 years. At transplantation, 6 patients had a low C3 level. In the five patients with a NF at the time of transplant, the NF remained positive at follow-up. Disease recurrence was noted in 2 patients (both within the first year of transplant). One was positive for a nephritic factor, one has a C3 mutation. One patient had histologic recurrence. This patient was both nephritic factor negative and with normal genetics. All patients with recurrence had a low C3 at the time of recurrence. All nonrecurring patients have a normal C3.

Conclusions: Considering this preliminary data, having a low C3 appears to predict risk for C3G recurrence. It remains unclear what role a persistent nephritic factor titer may have. Our data suggest the impact of this titer may change over time. We have extended the collection of the clinical parameters and the complement biomarker evaluation for each subject in this cohort - with the express goal of creating a predictive model for C3G recurrence.

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SA-PO630

Risk Factors for Biopsy Complications in Initial vs. Subsequent Biopsies in Native and Transplant Kidneys

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Background: There are few studies about risk factors for complications in initial (ib) versus subsequent (sb) biopsies. Biopsy complications are divided in major (require an intervention) and minor (resolve without intervention). The aim of the study was to explore the risk factors for complications in ib versus sb in native (nkb) and transplant kidney biopsies (tkb) which may serve as predictors for biopsy complications.

Methods: In a multi-center study, 2830 nkb (4.3% sb) were analyzed for major and 667 tkb (29% sb) for major and minor complications. No death or nephrectomy was described. Fisher's exact, t-test (mean values) and $\chi 2$ test were used. A two sided p-value <0.05 was considered significant.

Results: In nkb, the frequency for major biopsy complications was 5.6% in ib and 4.9% in sb. In tkb, the biopsy complication frequency was 4% major and 2.3% minor in ib; in sb 3.5% major and 3.5% minor. In initial nkb, the frequency of major complications were higher in women compared to men (7.1% vs 4.6%;Odds Ratio 1.6, Confidence Interval 1.1-2.2), in younger patients (50 vs 54years, p=0.007) and in patients with lower weight (78 vs 82kg, p=0.005). In subsequent nkb, patients with major complications had a higher systolic blood pressure (145 vs 132mmHg, p=0.03). In initial tkb, biopsies with major complications had less glomeruli in the biopsy (17 vs 24, p=0.046) and biopsies with minor complications were from younger patients (42.5 vs 52years, p=0.027) and patients with lower BMI (22 vs 26, p=0.049). Risk factors for overall complications in initial txb were younger age (46 vs 52years, p=0.028) and less glomeruli in the biopsies (18 vs 24, p=0.04). In subsequent tkb, patients with major complications had a higher systolic (151 vs 136mmHg, p=0.03) and diastolic blood pressure (93 vs 79mmHg, p=0.003). For minor and overall complications in subsequent nkb, no risk factors were found. In nkb, in sb there was a higher number of SLE-nephritis (12% vs 4.6%, p=0.001), a lower number of nephrosclerosis (4.3% vs 10.3%, p=0.02) and diabetic nephropathy (3.4% vs 9.3%, p=0.02) compared to ib; in tkb no differences were found.

Conclusions: The different types of risk factors for biopsy complications in initial versus subsequent biopsies in native and transplant kidneys could be important for the clinicians to improve patients' safety.

SA-PO631

Infection-Related Glomerulonephritis and Analysis of Clinical Outcomes: Experience in South India

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Background: There has been a major shift in the causative agents, clinical presentation, epidemiology and the treatment outcomes of IRGN in the developing nations.

Methods: A retrospective analysis of 100 IRGN consecutive cases were studied from our hospital records. percutaneous renal biopsy was done in all the patients and the tissue has been processed for LM IF and EM after appropriate staining for clinical and pathological characteristics

Results: A retrospective analysis of 100 IRGN consecutive cases were studied from our hospital records. percutaneous renal biopsy was done in all the patients and the tissue has been processed for light microscopy, immunofluorescence and electron microscopy after appropriate staining for clinical and pathological characteristics Results: A total of 73 patients were analyzed after exclusion. The mean age of the presentation was 41.89±14.58 years. 51% were males. Common infection sources were UTI (33%) and foot ulcer (33%). Most common clinical presentations were shortness of breath (45%), Anasarca (38%) and fever (36%). All the patients had micro hematuria (100%). The mean creatinine at presentation was 3.37± 2.47 mg/dl with an average proteinuria of 2.43 ± 1.28 g/24hr. 94% had low C3, 8% had low C4,8 % had low C3+C4.55% c4d negative out of c4d negative, 38% are c3 codominant and 63% are c3 dominant. Mean serum creatinine at presentation 4.1±2.6 and 3.3±2.5 (p value:0.8). Proteinuria between two groups was statistically significant. On light microscopy, the most common histological pattern of injury is endocapillary proliferation with neutrophil in mesangial tufts. Immunofluoresence pattern revealed immunoglobulin and C3 dominant staining commonly. Mean GBM thickness was seen in 358.95±99.2. Diffuse effacement was seen in 13 patients, focal effacement was seen in 27 patients. 23% patients needed hemodialysis and 8% needed plasmapheresis at presentation. 20% patients needed immunosuppression. At the end of 12months, 35% patients had persistent hypertension and 30% patients had persistent renal dysfunction. Persistent proteinuria was noted in 17 % of patients and persistent hematuria was seen in 30 % of patients at 1 year follow up. Spot PCR and creatinine between C4d negative C3 dominant and codominant groups was not significant at 1 year.

Conclusions: Male sex, age>40 years, creatinine>5 mg/dl, dialysis requirement at presentation were independently associated with poor renal outcomes.

SA-PO632

Success and Safety of Native Kidney Biopsies Guided and Performed by Nephrologists

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Background: Percutaneous kidney biopsy is a key procedure in nephrology and a requirement for training, but is often not performed by nephrologists, even in training programs. The reasons are manifold but include concerns about competence and safety, particularly the perceived need for real-time ultrasound guidance. To address this, we examined the outcomes of ultrasound-guided biopsies performed in their entirety by nephrologists at this institution.

Methods: All native kidney biopsies performed by the Renal Division at Emory University Hospital for clinical indications from 1/1/2008 to 9/30/2018 were identified from a database of ultrasound studies performed by the Division. Medical records were reviewed to determine clinical characteristics and outcomes. Large hematomas, gross hematuria, hypotension, transfusion, or endovascular intervention were considered clinically important complications.

Results: We identified 422 biopsies that were performed by 70 trainees (1-12 procedures each; median: 5) with the supervision or assistance of 22 faculty (1-105 procedures each; median: 5). Forty three were performed by faculty alone. Patient age was 45.6 + 0.8 (13-84) and body mass index (BMI) 27.2 + 0.3 kg/m^2 (16.2-52.3). All biopsies were performed with a Monopty 18g device with a 1.7 cm sampling length (Bard Peripheral Vascular, Tempe, AZ). In 93%, the kidney was located by ultrasound prior to but not during the biopsy, with an 18.8 cm, 20g needle used to confirm the location and provide deep anesthesia. In 7%, ultrasound was used during the procedure (real-time guidance). Other characteristics of the biopsies were: left kidney 91%; prone position 99%; end-inspiration 51%; end-expiration 44%; depth 5.4 + 0.08 cm (2-11). Tissue was obtained in 98.6% (adequate for diagnosis in 96.9%) with 3.56 +0.07 (1-10) passes and 2.54 + 0.04 (1-5) tissue cores. The BMI was 40 kg/m^2 or greater in 2 of the 6 unsuccessful procedures. Clinically significant complications occurred in 7 patients (1.7%), requiring transfusions in 3 and intervention in 2. These patients did not differ in characteristics or biopsy parameters from those with no complications.

Conclusions: Percutaneous renal biopsies can be performed in their entirety by nephrologists with excellent success and complication rates. Real-time ultrasound guidance is not essential and should not deter nephrologists from performing this important procedure.

Funding: Clinical Revenue Support

SA-PO633

The Effect of Intravenous Tranexamic Acid in Percutaneous Renal Biopsy: A Randomized Controlled Trial

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Background: Tranexamic acid is an anti-fibrinolytic agent, and the evidence of its benefit for major surgery and trauma has accumulated. We aimed to assess whether intravenous tranexamic acid reduces hematoma sizes after percutaneous renal biopsy.

Methods: We conducted a randomized, triple-blind, placebo-controlled trial at a teaching hospital in Japan between January 2016 and July 2018. We included adult patients who had a clinical indication of percutaneous renal biopsy. High-dose tranexamic acid (500 mg), low-dose tranexamic acid (250 mg) or counterpart saline (placebo) was intravenously injected twice, with bolus just before the biopsy and continuous infusion initiated just after the biopsy. On the morning of the biopsy day, patients were randomly assigned to either of the three groups. The primary outcome was the post-biopsy perirenal hematoma size measured by ultrasound on the next morning of the biopsy. According to the predefined protocol, a closed testing procedure with Wilcoxon rank sum test was used to adjust the multiple comparisons of the tranexamic acid groups (high-dose and low-dose) with the placebo control group. Thus, if the high-dose group was statistically significant against the control group, the low dose group was compared with the placebo group. All analyses were done on an intention-to-treat basis. The trial was registered with UMIN-CTR, number UMIN000019830.

Results: We randomly allocated 56 patients into the three groups: 20 in the high dose group, 19 in the low dose group, and 17 in the placebo group. The median post-biopsy hematoma sizes were 200 mm^2 (IQR 21–650) in the high dose group, 52 mm^2 (0–139) in the low dose group, and 0 mm^2 (0–339) in the placebo group. The results of Wilcoxon rank sum test for the comparison of the high dose group with the placebo group was p=0.047 and that of the low dose group with the placebo group was p=0.80.

Conclusions: High dose tranexamic acid compared to placebo increased perirenal hematoma size after percutaneous renal biopsy. Since the mechanism of increased bleeding in this drug is unknown, we need to confirm the findings in further large randomized controlled trials.

SA-PO634

Biofluid MicroRNA Expression Patterns in Three Types of Naturally Occurring Canine Models for Glomerular Disease

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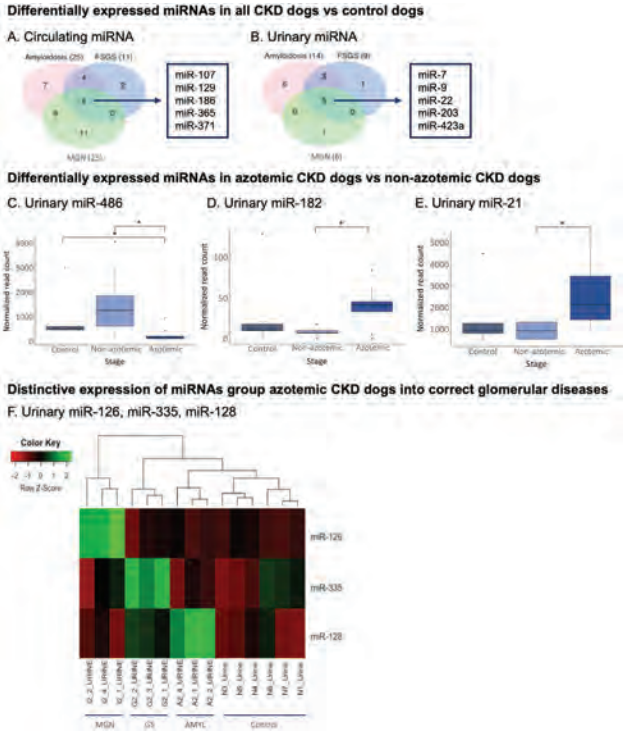
Background: The majority of proteinuric dogs with naturally-occurring chronic kidney disease (CKD) have one of three categories of glomerular diseases: immune complex-mediated (often membranous glomerulopathy [MGN]), glomerulosclerosis (GS), or amyloidosis (AMYL). As in humans, proper treatment of glomerular disease relies on an accurate diagnosis largely based on a renal biopsy and comprehensive pathologic examination. We hypothesized that the expression pattern of biofluid microRNA (miRNAs) would correlate with disease progression and categorization.

Methods: Archived serum and urine samples from 24 dogs, 6 proteinuric dogs from each glomerular disease category (MGN, GS, and AMYL) and 6 clinically healthy dogs were selected. Within each glomerular disease category, equal numbers of non-azotemic and azotemic dogs were included. Circulating and urinary miRNAs were isolated and profiled using small RNA sequencing.

Results: Overall, 38 circulating miRNAs and 16 urinary miRNAs were differentially expressed (DE) in CKD dogs versus controls. When all CKD dogs were combined regardless of glomerular disease category, no circulating DE miRs were identified between azotemic and non-azotemic CKD dogs. However, DE urinary miR-182, miR-21, and miR-486 were identified comparing azotemic dogs versus non-azotemic CKD dogs. Notably, the distinctive expression of urinary miR-126, miR-335, and miR-128 could correctly group azotemic, proteinuric dogs into MGN, GS, or AMYL.

Conclusions: This unique finding supports that urinary miRNAs might help establish a diagnosis in azotemic dogs with suspected glomerular disease. These highly conserved miRNAs are potential non-invasive biomarkers for human patients.

Funding: Private Foundation Support



Differentially expressed miRNAs in proteinuric dogs with three types of glomerular disease

SA-PO635

Percutaneous Native Kidney Biopsy in Obese Patients: Feasibility and Histological Findings

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Background: Body Mass Index (BMI) > 30 kg/m^2 is an independent risk factor for proteinuria and Chronic Kidney Disease. There are few studies on kidney biopsy of obese patients (OP). This study assessed the results of renal biopsies and their complications in this group as compared to nonobese patients (NOP).

Methods: This is a retrospective cohort study of native kidney biopsies performed between January/2009 and December/2018 at a tertiary university center. Clinical and laboratory data were collected at the time of the procedure. Biopsy indication, sample quality, procedural complications and histological diagnoses were analyzed, comparing OP and NOP.

Results: A total of 171 biopsies were performed in OP (mean BMI 33.1±2.8 kg/m^2) and 780 in NOP (mean BMI 23.8±3 kg/m^2). When compared to NOP, we found a higher proportion of women (68% x 60%, p=0.04) and higher age (45±14 x 39±16, p<0.001) in OP. The indications for biopsy did not differ significantly between groups. Although a higher number of OP required more than 3 needle shots (23% x 12%, p=0.0002), the representativeness of samples did not differ between groups: an average of 17±9 glomeruli for light microscopy and 11±8 for immunofluorescence was obtained in OP, compared to 18±9 and 11±8 in NOP (p>0.05). The incidence of complications such as hematuria (6% x 7%), need for arteriography (1% x 2%) and blood transfusion (2% x 3%) was also similar in OP and NOP (p>0.05). The most common histological diagnoses in OP were Lupus Nephritis (LN, n=42, 25%); Focal Segmental Glomerulosclerosis (FSGS, n=33, 19%); Membranous Glomerulopathy (MG, n=20, 12%); Diabetic Nephropathy (n=13, 8%) and IgA Nephropathy (IgAN, n=13, 8%), whereas in NOP LN (n=128, 16%); FSGS (n=79, 10%); MG (n=45, 6%) and IgAN (n=34, 4%) were the main diagnoses.

Conclusions: Kidney biopsy of obese patients is safe, feasible and effective. In our cohort, despite the need for more needle shots, the representativeness of samples and the rate of complications were similar between OP and NOP. Of note, FSGS was not the most frequent histologic finding. A broad spectrum of patterns was observed, implying equally variable therapeutic schemes and reinforcing the appropriateness of performing renal biopsies in this particular group of patients.

SA-PO636

The Impact of Desmopressin on Native Kidney Biopsy Complications

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Background: As bleeding is a feared complication of native kidney biopsy (NKB), nephrologists often prescribe desmopressin in an attempt to lower its occurrence, especially for patients with reduced estimated glomerular filtration rate (eGFR) at risk of uremia-related platelet dysfunction. However, only one randomized study has analyzed its effect before NKB on patients with eGFR >60 mL/min/m^2 whereas retrospective studies on patients with eGFR <60 mL/min/m^2 are contradictory.

Methods: This study aims to evaluate the impact of desmopressin on complications after NKB. We reviewed medical records of every adult patient who had a NKB at our tertiary teaching hospital from April 2013 to April 2018. We collected data concerning the medical history of each patient and their clinical parameters before and after each NKB. We used multivariate logistic regressions to evaluate the effect of desmopressin on the occurrence of hemoglobin fall, transfusions, hypotension, acute kidney injury (AKI), hematomas and additional radiologic examinations.

Results: Among the 413 NKB analyzed, 79.4% were done after a dose of desmopressin. Patients who received desmopressin had more severe chronic kidney disease at baseline (eGFR 39 vs 54 mL/min/m^2; p=0.0003) and were more often hospitalized before the biopsy (48% vs 32%; p=0.009). There was a tendency for a reduction in symptomatic hematomas (OR=0.34; 95%CI: 0.11-1.19; p=0.08) and a significant reduction of post-biopsy additional radiologic examinations (OR=0.22; 95%CI: 0.07-0.73; p=0.01) in the desmopressin group. Desmopressin had a neutral effect on other complications (see table) and on hyponatremia.

Conclusions: Our results were affected by an indication bias, because sicker patients were more likely to receive desmopressin and IV fluids causing hemodilution. However, after adjustment for potential cofounders, desmopressin seems to reduce post-biopsy symptomatic hematomas and additional radiologic examinations, implying important clinical and financial benefits.

	OR	CI 95%	p
Hemoglobin fall > 15	1.54	[0.78;3.23]	0.23
Hemoglobin fall > 20	1.29	[0.58;4.36]	0.43
Transfusion	1.63	[0.19;8.59]	0.46
Radiologic hematomas	0.86	[0.39;2.01]	0.70
Hypotension	1.08	[0.41;3.11]	0.88
AKI	2.04	[0.35;38.72]	0.51

SA-PO637

Proximity of Residence to Silica Mines as a Risk Factor for Anti-Neutrophil Cytoplasmic Antibody-Associated (ANCA) Vasculitis

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Background: Anti-neutrophil cytoplasmic antibody-associated (ANCA) vasculitis is a rare necrotizing vasculitis affecting small to medium-sized vessels, with renal involvement usually presenting with a rapidly progressive glomerulonephritis. There is evidence to suggest that silica exposure is associated with the development of ANCA vasculitis. The incidence of ANCA vasculitis in Queensland, Australia was 0.47 per 100,000 people/year from 2002 to 2011; and there is a high density of silica mines, with approximately 2 per 1,000,000 population in 2011. The aim of the study was to examine whether residing close to silica mines is associated with development of ANCA vasculitis.

Methods: This retrospective cohort study compared patients with a biopsy-proven diagnosis of ANCA vasculitis and a control cohort of IgA nephropathy (IgAN) from 2009 to 2011. IgAN was selected as there is no known association between silica exposure and its development. A pathology database of renal biopsies was used to identify cases of ANCA vasculitis and IgAN. Age, gender, postcode and suburb of the patient at the time of biopsy were obtained. The distance between the suburb and closest silica mine in Queensland was calculated using Quantum GIS 3.4 software. Distance to silica mines was categorised into ≤50km, 51-99km and ≥ 100km. SPSS was used, with a X^2 test for independence to determine association between distance to silica mines and ANCA vasculitis.

Results: 135 patients were identified, with a mean age of 48 years and 60% were male. There were 44 cases of ANCA vasculitis and 91 cases of IgAN. Patients diagnosed with ANCA vasculitis were significantly older (63.5 years v 40.9 years, p<0.05). 50% of ANCA vasculitis patients resided within 50km of a silica mine, compared to 44% of patients with IgAN. 20.5% and 29.5% of ANCA vasculitis patients resided 51-99km and ≥ 100km respectively; compared to 22% and 34.1% of patients with IgAN respectively. There was no evidence of association between distance from suburb to silica mine and ANCA vasculitis ($X^2_{(2,135)}=0.45$, p=0.8).

Conclusions: There was no evidence that proximity of residence to silica mines was associated with ANCA vasculitis compared to IgAN in this cohort of patients. Limitations include small sample size and inability to account for patient relocation prior to biopsy.

SA-PO638

Urine Aquaporin-2 Messenger RNA Predicts Global Glomerulosclerosis and Renal Outcome in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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Background: Despite substantial progress in the treatment for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), the prognosis of patients with AAV has not sufficiently improved. The poor prognosis is not only caused by the activity of AAV but also caused by adverse events due to the therapeutic agents. Avoiding excessive immunosuppression can lead to an improvement in the prognosis. Useful and noninvasive predictor for renal outcome is needed. We recently announced that urine aquaporin 2 (U-AQP2), which is a water channel localized in the renal collecting ducts, mRNA predicts the renal outcome in AAV at the 56th ERA-EDTA Congress in Budapest, 2019. Here, we examined the association between U-AQP2 mRNA and renal biopsy tissue.

Methods: We enrolled 33 patients with AAV diagnosed at Miyazaki University Hospital from January 2009 to March 2016. Their U-AQP2 mRNA levels at the onset of AAV were evaluated by real-time polymerase chain reaction, and normalized by urine creatinine concentration. We divided them into two groups (High U-AQP-2 group (n=7) and Low U-AQP-2 group (n=26)) based on mean value of U-AQP2 mRNA and performed Kaplan-Meier analysis to assess renal survival in two groups. We also examined the renal biopsy tissues of each group.

Results: High U-AQP2 group showed poorer renal prognosis than Low U-AQP2 group (p<0.001). In analysis of renal biopsy tissue, the percentage of global glomerulosclerosis in High U-AQP2 group was significantly higher than in Low U-AQP2 group (32.9 % vs. 16.8 %, p=0.02). The percentage of crescentic lesions in High AQP2 group was not significantly different from Low AQP2 group (39.8 % vs. 33.3 %, p=0.44). The degree of tubulointerstitial lesion in High AQP2 group was also not significantly different from Low AQP2 group. Urinary NAG concentration, which is an indicator of tubular injury, did not change between the two groups.

Conclusions: This result could suggest severe glomerular damage caused by AAV affects distal nephron. U-AQP2 mRNA may be able to detect deep lesions that are difficult to diagnose in kidney biopsy tissue. U-AQP2 could predict irreversible damage by AAV.

SA-PO639

Improved Survival due to Better Renal Outcomes in Danish Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis (AAV) During the Years 2000-2015: A Nationwide Study

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Background: AAV (Granulomatosis with polyangiitis and microscopic polyangiitis) carries significant risk of morbidity and mortality, notwithstanding adequate treatment. Contemporary large-scale descriptive studies have been challenged by the rare occurrence of these diseases. Accordingly, by use of Danish nationwide healthcare registries, we examined the temporal progression of incidence and prognosis of AAV during 2000-2015.

Methods: All patients with incident AAV, regardless of primary organ manifestation were included by use of ICD10 diagnostic codes (positive predictive value of > 90%) and grouped in five-year intervals (P1: 2000-2004, P2: 2005-2009, P3: 2010-1015). Absolute risk ratios (ARR) adjusted for age, sex and advanced disease severity (>10 days of initial hospital stay), as well as cumulative incidences were computed in R version 3.5.0.

Results: We identified 1634 patients (52% male), corresponding to an overall incidence of 18.2 persons/million/year (P1: 12.1; P2: 16.3; P3: 21.0), and 425 (26% [P1: 34.6%; P2: 28.5%; P3: 19.4%]) met the criteria of advanced disease severity. Mean age was 60.3 (IQR 21.0) years and mean follow-up was 5.9 (IQR 4.0) years. 571 (34.9%) patients died (uncensored 5-year mortality of 20.3%) resulting in an ARR for P2 and P3 as compared to P1 of 0.80 (CI 0.65-0.97, P=0.028), and 0.40 (CI 0.30-0.51, P<0.001). 274 patients developed end-stage renal disease (16.8 % [P1: 23.3%; P2: 17.6%; P3: 12.5%]), similarly with ARR decreasing over time: P2 0.62 (CI 0.43-0.89, P=0.009) and P3 0.54 (CI 0.37-0.78, P=0.001) relative to P1. The overall risk of death associated with need of dialysis or chronic kidney involvement within 30 days of discharge as compared to no renal involvement was 1.81 (CI 1.41-2.33, P<0.001) and 1.39 (CI 1.11-1.76, P=0.005). During follow-up 526 (32.2% [P1: 39.6%; P2: 30.4%; P3: 29.3%]) patients developed chronic kidney disease.

Conclusions: AAV remain a group of diseases associated with high morbidity and mortality; however, although incidence of AAV is increasing, the absolute risk of death appears to be declining, putatively in part due to earlier detection of incident episodes and better renal outcomes.

SA-PO640

Predictors of Renal Involvement in ANCA-Associated Vasculitis

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Background: Renal involvement in the context of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is associated with significant morbidity and higher mortality rates. This study examined predictive factors associated of renal involvement in AAV within a large, international cross-sectional cohort.

Methods: Univariate and multivariate analyses were performed to identify risk factors associated with renal disease, which was defined as i) an increase of serum-creatinine > 30%; ii) a fall in creatinine-clearance < 25%; or iii) haematuria attributable to active vasculitis.

Results: Of the 1230 patients eligible, 723 patients (58.8%) presented with renal involvement. The majority of patients with microscopic polyangiitis (82.2%) and granulomatosis with polyangiitis (58.6%) had renal involvement, while 26.4% with eosinophilic granulomatosis with polyangiitis presented with renalvasculitis. The following clinical factors were more common among patients with renal disease that among patients without renal disease. Older age (p=0.001), fever (p<0.001), fatigue (p=0.005), weight loss (p=0.001), polyarthritis (p=0.036), petechiae/purpura (p=0.022), pulmonary haemorrhage (p=0.014), gastrointestinal symptoms (p=0.002), serum albumin below 30 g/L (p<0.001), higher CRP (p=0.038), low C3 at baseline (p=0.015), ANCA positivity (p<0.001), myeloperoxidase-ANCA (p<0.001) and proteinase 3-ANCA (p=0.020). Patients with proptosis/exophthalmos (p=0.001), saddle nose deformity (p=0.015), nasal polyps and nasal septal defect/perforation (p<0.001 each), respiratory distress/pulmonary fibrosis/asthma (p<0.001) or wheeze/obstructive airway disease (p<0.001) had a lower likelihood of developing renal involvement.

Conclusions: In this large international study, we identified clinical factors associated with renal involvement in AAV, including concomitant pulmonary alveolar haemorrhage, low C3, and elevated C-reactive protein. Further large studies arenecessary to confirm our findings.

SA-PO641

Chorioretinal Thickness Reflects Disease Activity in ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) is characterised by autoimmune-mediated injury of small blood vessels and often requires renal biopsy for diagnosis. A non-invasive means of detecting this microvascular injury would be of major clinical value. The eye acts as a window to the systemic microvasculature. Retinal optical coherence tomography (OCT) provides cross-sectional imaging of the retina and highly vascularized choroid with near-histological resolution. We have shown that systemic and renal inflammation associates with choroidal thinning. We hypothesized that OCT metrics would reflect disease activity in AAV and be modified with treatment.

Methods: We prospectively recruited 50 patients with active AAV and 50 age-and sex-matched healthy controls, excluding those with diabetes and previous eye disease. AAV patients were studied prior to receiving immunosuppression and once in disease remission, defined by a Birmingham Vasculitis Activity Score (BVAS) of 0 for a least 2 months on low dose steroid. All subjects were imaged with the Heidelberg SPECTRALIS® OCT device. Choroidal thickness was measured blinded at three locations: 2mm nasal to fovea (location I), subfoveal (location II) and 2mm temporal to the fovea (location III), Figure 1.

Results: AAV patients had a mean (±SD) age of 60±14 years, 20 (50%) were male and 24 (60%) were PR3+. Median (range) BVAS at entry was 13 (3-21). 30 (75%) patients were new presentations and 26 (65%) had renal involvement. Mean (±SD) choroidal thickness was thinner in active AAV patients compared to health: location I 202±84 *vs.* 248±76mm; location II 279±90 *vs.* 331±69mm; location III 276±90 *vs.* 309±65mm; all p<0.05. Choroidal thickness correlated negatively with baseline BVAS, *r*=0.57, p<0.05. Following disease remission, choroidal thickness increased by ~10% compared to active disease, p<0.01 at all locations, Figure 1.

Conclusions: Active AAV is associated with choroidal thinning compared to health. This improves with successful treatment. OCT-derived metrics may be a novel means of assessing disease activity and treatment response in AAV. Larger studies will explore these findings further.

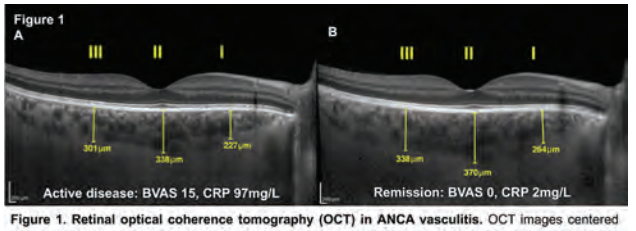

Figure 1. Retinal optical coherence tomography (OCT) in ANCA vasculitis. OCT images centered over the macula of the right eye from the same patient with ANCA vasculitis during active disease (**A**) and following successful treatment and disease remission (**B**). OCT images taken at the level of the macula. Yellow callipers indicate choroidal thickness measured at locations I, II and III.

SA-PO642

Venous Thromboembolisms in ANCA-Associated Vasculitis: Incidence and Risk Factors

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Background: The incidence of venous thromboembolism (VTE) is increased in ANCA associated vasculitis (AAV). We aimed to assess the frequency of VTEs observed in our center and identify risk factors.

Methods: VTEs in 155 AAV patients with diagnosed Granulomatosis with Polyangiitis and Microscopic Polyangiitis were analyzed. Baseline demographics, clinical and serologic data were extracted. Univariate and multivariate analyses were performed to identify factors associated with VTE in AAV.

Results: Of the 155 AAV patients, the mean age was 55.1 ± 17.5 years, 61% females, 55% PR3-ANCA positive, 45% MPO-ANCA, with a total mean BMI of 28.9 ± 6.3 kg/m^2. The mean Birmingham Vasculitis Activity Score (BVAS) was 14.3 ± 6.0. VTEs occurred in 21 (14%) patients and the mean time to VTE was 1.8 months. Univariate analyses identified PR3-ANCA as significantly associated with the onset of VTE (17/85, p=0.02). In multivariate models, each adjusted for age, sex, hyperlipidemia/hypertension medications, smoking status, diagnosis (GPA/MPA), **the associations of PR3-ANCA (p=0.018), BMI (p=0.0015), and RPGN (p=0.015) with VTE incidence remained significant, while there was no statistically significant correlation of alveolar hemorrhage or BVAS severity with VTE.**

Conclusions: The incidence of VTE in AAV was 21/155 (14%). PR3-ANCA, RPGN, and increased BMI are risk factors for developing VTEs. BVAS severity or alveolar hemorrhage does not increase risk of venous thromboembolic events. Further studies are needed to confirm these findings.

Logistic Regression				
Coefficients:	**Estimate**	**Standard Error**	**z-value**	**Pr(>|z|)**
BMI (kg/m^2)	0.14869	0.04680	3.177	0.0015 **
ANCA Serology (PR3/MPO)	-1.64706	0.69727	-2.362	0.018 *
RPGN	1.59363	0.65311	2.440	0.015 *
Alveolar Hemorrhage	0.81914	0.75023	1.092	0.27
Age of diagnosis	0.02996	0.01863	1.608	0.11
BVAS < 10	0.85613	1.84096	0.465	0.64
10 < BVAS < 20	0.82044	1.76084	0.466	0.64
20 < BVAS < 30	1.82693	1.90066	0.961	0.34

BMI (kg/m^2), ANCA serology (PR3 vs MPO), RPGN are significantly correlated with incidence of venous thromboembolisms. BVAS severity and presence of alveolar hemorrhage do not appear to contribute to VTE risk.

SA-PO643

Outcomes by Etiology in Pediatric Glomerulonephritis with Crescents

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Background: Etiologies of Glomerulonephritis (GN) with crescents in Pediatrics differ from those in adults. Many of the typical etiologies can be categorized into diseases with or without involvement of immune complex (IC) deposition leading to damage and inflammation of glomeruli. Our previous work had identified a composite risk index, involving 4 disease markers: % crescents, presence of fibrous crescents, HTN, and eGFR at biopsy. However, it is unknown whether these 4 markers predict 1 year outcomes in specific classes of glomerulonephritis.

Methods: We reviewed the Pediatric GN with crescents registry which is a multicenter, retrospective (2004-2016) review of subjects < 21 y, with GN with crescents, followed for at least 12 mo. across the US as part of the Midwest Pediatric Nephrology Consortium. Crescentic GN was defined as > 1 crescent per core biopsy according to local pathologist read. Primary outcome of interest was end stage kidney disease (ESKD) at 1 year.

Results: We reviewed records on 305 patients, mean age 11 y, 58% female. There were 53 with pauci immune GN (17%) and 252 with IC GN (82%). 21% of patients in the pauci-immune group reached ESKD at 1 year, as compared to 9.5% in the immune complex group (p-value 0.031). On bivariate analysis in the pauci immune group, variables at time of biopsy associated with ESKD at 1 y. were estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m2 (58 vs. 10% p= 0.001), hypertension (44 vs. 8.6%, p= 0.006), and > 43% crescents (39 vs. 6.7%, p=0.006). Percentage drop in eGFR at 1 year was also higher in the pauci-immune group (20 vs. 10.7%), as compared to the immune complex group, but these results were not statistically significant. In the immune complex group, variables at time of biopsy associated with ESKD at 1 y. were estimated glomerular filtration rate (eGFR) below 15 ml/min/1.73m2 (59 vs. 5.1% p< 0.001), presence of fibrous crescents (16 vs. 6.9% p = 0.034), hypertension (17 vs 3.1% p < 0.001), > 43% crescents (33 vs. 3.9%, p<0.001), and presence of generalized edema (17 vs 5.7% p=0.007

Conclusions: Pauci-immune GN, which constituted only 17% of our cohort, was associated with a significant risk of ESKD at 1 year. Different risk factors at time of biopsy are associated with ESKD at 1 year in pauci immune GN compared to IC GN.

SA-PO644

Benefit or Burden: A Systematic Review and Meta-Analysis of Treatment Outcomes of ANCA-Associated Vasculitis in Patients Older Than 75 Years

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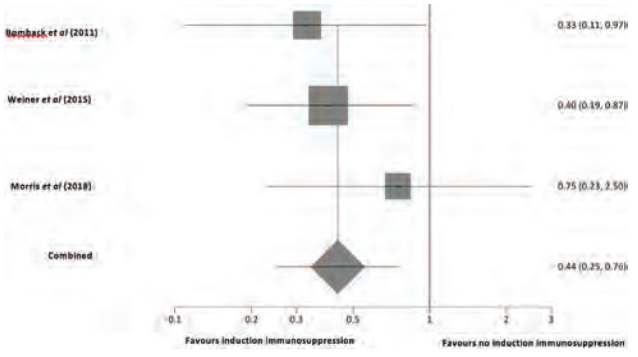
Background: Despite a peak incidence of 64-75 years, the benefit of treating ANCA-associated vasculitis (AAV) in older patients remains unclear with most published studies defining elderly as ≥65 years. This study aims to determine outcomes of induction immunosuppression in patients aged ≥75 years.

Methods: A cohort aged ≥75 years with biopsy proven AAV was constructed from a single centre between 2006–2016. Follow up was to two years or death. Analysis included multivariate Cox regression to compare mortality and ESRD based on induction immunosuppression therapy. A systematic review of outcome studies was subsequently undertaken amongst this patient group through Pubmed, Cochrane and Embase databases from inception until 13/09/18.

Results: From 145 patients, 59 were ≥75 years, of which 51 had completed data. Mean age was 78.9±2.7, 54.9% were male and mean modified Charlson comorbidity index was 1±1.3. 76% (n=39) received induction therapy. The systematic review identified 1943 citations. Four studies were eligible for inclusion, yielding a combined total of 274 patients inclusive of our cohort. The aggregated one year mortality irrespective of treatment was 36% (CI 27–47%). Within our cohort, induction immunosuppression therapy was associated with a lower two-year mortality risk, although not statistically significant [HR 0.75 (95% CI 0.23–2.49)]. However, the pooled HR by meta-analysis revealed a significant risk reduction for death [HR 0.44 (95% CI 0.25–0.76), I^2=0%]. Treated patients had a lower pooled rate of ESRD, but was not statistically significant [HR 0.76 (95% CI 0.37–1.59)].

Conclusions: This meta-analysis suggests that patients ≥75 years with AAV do benefit from induction immunosuppression with a significant survival benefit. Age should not be a limiting factor when considering treatment. Further trials are required to better evaluate renal outcomes amongst this age group.



Forest plot of mortality risk in patients with AAV ≥75 years based on the use of induction immunosuppression

SA-PO645

ANCA-Associated Vasculitis with AKI: KDIGO AKI Stage, Short-Term Recovery, and Long-Term Outcome

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Background: To study KDIGO AKI stages and its association with short-term and long-term outcome in patients with ANCA associated vasculitis.

Methods: We retrieved data of 154 patients who combined with AKI (including AKI on chronic kidney disease) and not requiring maintaining renal replacement therapy 3 months after admission. In these 154 patients, 14 were lost to follow up. The remaining 140 patients were staged from 1 to 3 according to AKI criteria based on KDIGO guideline. Short-term recovery was assessed according to the serum creatinine level change, and patients were divided in to 2 groups: ≥30% decline(G1), and <30% decline or rise (G1) at 3 month comparing to pre-episode baseline. Long term renal endpoint was defined as: reaching an eGFR level of <15ml/min/1.72m2 or requiring maintaining renal replacement therapy for more than 3 months. Univariate analysis and multivariate analysis were used to compare the outcome.

Results: At admission, 49(35%) were in AKI stage 1, 53(37.0%) in stage 2 and 38(27.1%) were in stage 3. Three months after admission, there were 75 patients in G1, and 65 patients in G2(including 24 patients with rising serum creatine level). No significant differences in age and gender(p>0.05) were found. AKI stage(p<0.001), 24h urine protein(p=0.012) and urine red blood cell per μl(p=0.015) were found associated with short-term recovery. Twenty-three patients reached the renal endpoint during the median follow-up duration of 54(32,79) months. The renal survival rates of AKI stage 1 patients were 91.90%, 79.07 % in stage 2 and 71.80% in stage 3, Kaplan-Meier analysis suggested significant difference (p=0.034). Additionally, renal survival rates were 90.7% in G1 and 75.4% in G2, and Kaplan-Meier analysis showed significant difference between the two groups (p=0.013). The COX model suggested that high AKI stage (OR=5.765, 95%CI 1.886-17.619; p=0.002), high baseline serum creatine (OR=1.008,95%CI 1.001-1.016, P=0.027), and G1(OR=0.084, 95%CI 0.019-0.37) were independent risk factors of renal outcome in patients with ANCA associated vasculitis.

Conclusions: In patients with ANCA associated vasculitis, AKI stage, 24h urine protein and hematuria were associated with short-term outcome; AKI stage, baseline scr, and serum creatinine recovery level at 3 months were independent risk factors of long-term renal outcome.

SA-PO646

Analysis of Clinical Features in ANCA-Associated Vasculitis with Rapidly Progressive Glomerulonephritis: Thirty-Five Years of a Single-Center Experience

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Background: The clinical features of AAV, with respect to renal involvement, may have been changing recently in Japan, where MPO-ANCA-associated vasculitis (MPO-AAV) are dominant in contrast to the Western countries. Thus, we retrospectively analyzed the clinical database of the141 AAV-patients with RPGN who were admitted to our hospital for the last 35 years.

Methods: At the onset, all patients fulfilled the Chapel Hill Consensus Conference (CHCC) classification criteria for MPA, GPA and EGPA. 141 patients (56 male, 85 female: MPA 118, MPO-GPA 12, PR3-GPA 7, EGPA 4) who underwent initial treatment diagnosed with AAV and presented rapidly progressive glomerulonephritis (RPGN) at our hospital from 1983 to 2018. We divided the AAV patients into the 3 groups(Group1 (1983-2000: 31 cases), Group2 (2001-2010: 56 cases), 3 (2011-2018: 54 cases)), and compared the clinical features and renal prognosis.

Results: The frequencies of RPGN in AAV were 76% (31/41) in group1, 50% (56/111) in group2 and 47% (54/115) in group 3, respectively. The average ages at the first onset were 67.2 ± 10.9, 69.1 ± 12, 75.4 ± 9.1 years (mean±SD). The BVAS were 24.8 ± 3.9, 22.8 ± 8.1, and 17.8 ± 4.7. Serum creatinine levels (mg/dl) were 6.5 ± 4.2, 4.6 ± 3.5, 3.2 ± 2.1, and the frequencies of renal death were 71% (22/31), 46% (26/56), 22% (12/54). The dialysis withdrawal rates were 0% (0/22), 7% (2/28), 20% (3/15). The immunosuppressants were used in the 19% (6/31), 25% (14/56), 44% (24/54) of the patients in initial treatment. Cyclophosphamide (CY) was used for 16% (5/31), 23% (13/56), 33% (18/54) of the patients. RTX was used only in group III for 9% of the patients (5/54). PE were used 3% (1/31), 2% (1/56), 6% (3/54). One-year survival rates were 52% (16/31), 85% (47/55), 88% (36/41), with the survival observation period for 40.0 ± 56.2 months, 47.3 ± 42.7 months, 29.6 ± 29.5 months, respectively. Death due to vasculitis was seen in 30% (8/27), 17% (4/24), 11% (1/9), and death due to infection in 30% (8/27), 21% (5/24), 56% (5/9). Relapse rates were 32% (10/31), 21% (12/56), 11% (6/54).

Conclusions: These results clearly show the changing features of ANCA-associated renal vasculitis, with an earlier detection and the improvement of renal and patient survival during the last decades in Japan.

SA-PO647

ANCA-Associated Glomerulonephritis Without Crescent Formation Has Atypical Clinicopathological Features: A Multicenter Retrospective Study

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Background: The most typical histopathological feature of ANCA-associated glomerulonephritis (ANCA-GN) is crescentic GN. However, ANCA-GN sometimes includes tubulointerstitial or vascular-dominant inflammation without crescent (C) formation. Few reports have focused on ANCA-GN without C in a large multicenter study. We aimed to identify the clinicopathological features of ANCA-GN without C.

Methods: We enrolled 147 Japanese ANCA-GN patients who were subjected to renal biopsy in 17 hospitals from 2001 to 2018. We measured various clinical parameters at the time of renal biopsy, and determined the presence of comorbidities. We also measured serum Cr and eGFR at the last patient visit, and recorded medications prescribed for ANCA-GN. We retrospectively compared these clinical and histological findings between those with C (C+ group) and without C (C- group). The endpoint was the cumulative percentage of patients who died from any cause.

Results: Of 147 patients (76 females; mean age 69.2 years; observational period 39.5 months), 25 (17.1%) were in C- group. Although C- group had less proteinuria (0.7±0.8 vs 1.7±1.6 g/gCr, p<0.01) and hematuria (75.0% vs 99.1%, p<0.01) with better renal function (eGFR; 53.9±28.7 vs 32.2±24.6 ml/min/1.73m^2, p<0.01), they had higher CRP levels (10.9±7.9 vs 6.6±6.1 mg/dl, p<0.01) than C+ group. There were no significant differences in any other clinical findings including ANCA serology. In histological findings, C- group had a higher frequency of arteritis (41.7% vs 17.5%, p=0.01), while other histological findings such as arteriolitis and tubulointerstitial lesions did not differ. Corticosteroid was less often prescribed in C- group (84.0% vs 100%, p<0.01). There was no significant difference in observational period, and C- group had better latest renal function (eGFR;

53.9±32.1 vs 40.6±29.4 ml/min/1.73m^2, p=0.05) than C+ group. However, overall survival rate did not differ (76.0% vs 79.6%, p=0.78).

Conclusions: ANCA-GN without C had specific clinicopathological features including higher systemic inflammation and frequency of renal arteritis than ANCA-GN with C. Though renal function throughout the clinical course was better in ANCA-GN without C, overall survival rate was similar with ANCA-GN with C.

SA-PO648

The Clinical and Pathological Features of Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitides Concomitant with IgG4-Related Disease

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Background: Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) and IgG4-related disease (IgG4-RD) have similarities in clinical features. The characteristics and the pathogenesis of the concomitant AAV and IgG4-RD disease have not been elucidated.

Methods: We included 92 AAV patients with renal biopsy results. Among them, 10 patients met both AAV and IgG4-RD criteria (concomitant group). The IgG subclasses of myeloperoxidase (MPO)-ANCA in both serum and renal tissue were measured and complement activation components were detected in serum.

Results: Patients in concomitant group had both elevated serum IgG4 level and positive MPO-ANCA. They had higher levels of eosinophil counts, serum globulin, IgG, IgE and CRP than patients in AAV alone group. All 10 patients had glomerulonephritis with crescents and 7 patients also had segmental necrosis of glomerular capillary wall. Most of them also presented storiform fibrosis and lymphoplasmocytic infiltration in renal interstitium with IgG4 positive plasma cells more than 10/HPF. The percentages of glomerular global sclerosis and crescent were 36.6%±25.7% and 23.2%±15.4% respectively. Eight patients received combined therapy of glucocorticoids and cyclophosphamide, one patient received glucocorticoids only and another patient received glucocorticoids and rituximab. Eight patients achieved remission with improved renal function, the other two patients were on maintaining dialysis. The IgG4 subclass of MPO-ANCA was higher in concomitant group than that in AAV alone group. A merge of IgG4 and MPO immunofluorescence was observed in parts of glomerular mesangium of concomitant AAV and IgG4-RD patients. For complement components, Bb and mannose-binding lectin (MBL) were elevated in serum of concomitant AAV and IgG4-RD patients.

Conclusions: We showed a new overlap syndrome of AAV and IgG4-RD, in which the IgG4 subclass of ANCA may be a pathogenic factor, and alternative complement pathway and MBL pathway may be involved.

SA-PO649

Histopathological Findings and Clinical Outcomes of ANCA-Negative vs. ANCA-Positive Pauci-Immune Glomerulonephritis

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Background: It has been suggested that pauci-immune small vessel vasculitis exhibits a different spectrum of disease in the absence of detectable ANCA. We investigated differences in clinical phenotypes, renal histology and clinical outcomes amongst patients with or without ANCA positive disease.

Methods: A cohort with biopsy proven pauci-immune glomerulonephritis was constructed from a single centre between 2006-2016 and followed until December 2018. Patients were stratified by ANCA status at the time of diagnosis with comparative analysis of demographics, clinical characteristics and histopathological variants. Multivariate survival and logistic models compared remission rates, ESRD and mortality risk.

Results: From 143 patients, 20% (n=29) had ANCA negative disease with a male predominance of 66% (n=19) and a younger mean age at diagnosis compared to those with positive ANCA serology; 53±19 years vs. 66±12 years respectively (p=<0.001). The presence of extra-renal disease with ENT and constitutional symptoms occurred more frequently in ANCA positive patients; 25% (n=27) vs. 0% (p=0.0012) and 27% (n= 30) vs. 3% (n=1) (p=0.0049) respectively. Conversely, ANCA negative serology was associated with renal limited disease (p=0.039). There was no association between histological features on biopsy and ANCA serology (Table 1). ANCA positive disease was associated with a significantly higher remission rate [OR 3.9 (95% CI 1.12-13.5)]. However, this did not confer any renal or overall survival benefit; [HR 0.45 (95% CI 0.15 – 1.33)] for ESRD and [HR 0.68 (95% CI 0.25 – 1.81)] for death.

Conclusions: Our single centre experience suggests that ANCA negative disease tends to occur in younger patients, with a higher rate of renal limited disease and no significant differences in histopathologial variants. Seronegative disease is less likely to remit, but is associated with similar survival risks in compassion to ANCA positive disease.

Table 1: Histopahtological Variants by ANCA status

Histological feature	ANCA negative	ANCA positive	p-value
< 10% Normal Glomeruli	10 (34.48%)	22 (19.30%)	0.22
Berden Classification:	.	.	.
Crescentic class	3 (10.34%)	21 (18.42%)	0.73
Sclerosed class	2 (6.90%)	5 (4.39%)	0.73
Focal class	13 (44.83%)	47 (41.23%)	0.73
Mixed class	11 (37.93%)	41 (35.96%)	0.73
Extra-glomeruli arteritis	4 (13.79%)	16 (14.04%)	1
Vessel wall necrosis	4 (13.79%)	11 (9.65%)	0.51
>50% IFTA	0	3 (2.63%)	0.53

SA-PO650

Absence of Fibrinoid Necrosis in ANCA-Glomerulonephritis Is Associated with Increased Risk of Vasculitis Relapses

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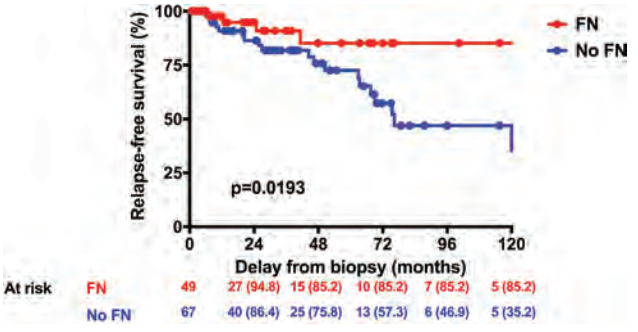
Background: Fibrinoid necrosis (FN) is a cornerstone lesion of ANCA-associated glomerulonephritis (ANCA-GN). However, its significance in kidney biopsy of ANCA-GN patients has not yet been fully established. The objective of the present study was to analyze its association with baseline characteristics and outcomes of ANCA-GN patients.

Methods: All consecutive AAV patients diagnosed between 2000 and 2018 from the Maine-Anjou ANCA-associated vasculitis (AAV) registry with a contributive kidney biopsy showing pauci-immune glomerulonephritis at onset or relapse of AAV were included in the present study. Among the 146 patients on the registry, 116 patients fulfilled the inclusion criteria and were analyzed.

Results: Patients were predominatly males with a mean age of 63.7 years-old and a mena eGFR at diagnosis of 33.1mL/min/1.73m^2. FN was detected at kidney biopsy in 42.2% of patients. Patients with FN had lower eGFR (p=0.008), needed more frequently renal replacement therapy at kidney biopsy (p=0.018) and had a lower rate of AAV relapse (p=0.005) as compared to patients without FN. Attack and maintenance regimen, and extra-renal involvment was not significantly different between groups. FN was not significantly associated with other glomerular lesions. Relapse-free survival was significantly higher in patients with FN at biopsy, as was the survival-free of major and renal relapses. Univariate analysis showed granulomatosis with polyangiitis (GPA; HR 2.32, p=0.045), ear-nose-throat involvement (HR 2.47, p=0.032) and absence of FN (HR 3.35, p=0.027) to be significant risk factors of relapse. In multivariate Cox analysis, absence of FN at kidney biopsy conferred a 3-fold increased risk of developing relapse, after adjustment for other risk factors.

Conclusions: FN could be a reliable marker to assess the risk of AAV relapse and we propose that it should be evaluated as a tool to manage immunosuppressive regimen, especially in the long term.



Relapse-free survival according to FN status

SA-PO651

C3 Dominant Deposition in ANCA-Associated Glomerulonephritis

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Background: It has been reported that Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (ANCA-GN) is characterized by necrotizing crescentic glomerulonephritis with few immune and complement deposits. Several recent studies have implied that complement activation plays an important role in the pathogenesis of ANCA-GN. However, the clinical and pathological significance of C3 deposits in patients with ANCA-GN has not been fully elucidated. This current study investigated the characteristics of C3 dominant deposition in ANCA-GN.

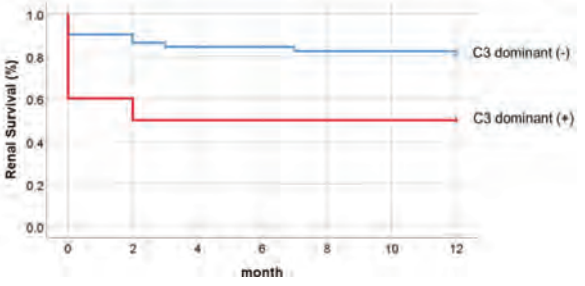
Methods: Kidneys specimens from 61 subjects with ANCA-GN were retrospectively evaluated at Jikei University School of Medicine Hospital, Atsugi City Hospital and Japanese Red Cross Ashikaga Hospital, Japan, during biopsy performed between 2004 and 2019. Clinical and histopathological data at kidney biopsy were compared between the patients with and without C3 deposits. The dominant deposition was defined as the presence of C3 for at least 1+ in a 0–3+ scale without other immune and complement deposits.

Results: **Figure** provides clinical and histopathological data for the ANCA-GN patients with and without C3 dominant deposits. Demographic data, estimated glomerular filtration rate (eGFR), and urine protein were similar between the two groups, indicating that renal function at biopsy was unlikely to associate with C3 deposition. Compared with patients without C3 dominant deposition, patients with C3 dominant deposition had a higher level of C3 (P=0.003) and a poorer renal outcome at one year after biopsy (P=0.025). Although there was no difference in the rate of glomerular cellular crescent

formation or global sclerosis, the patients with C3 dominant deposition had a higher percentage of fibrocellular or fibrous crescent.

Conclusions: These results suggest that C3 deposition and complement activation would be associated with chronic histological changes and poor renal outcome in ANCA-GN.

Figure : Kaplan-Meier plot of the renal survival curve comparing C3 dominant and negative



SA-PO652

Prognostic Impact of Interstitial Fibrosis for Progression to ESRD in ANCA-GN

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Background: Interstitial fibrosis (IF) is a well-known risk factor for progression to ESRD in patients with glomerulonephritis (GN). However, few studies have reported its role as an independent risk factor as determined by multivariate analysis on patients with ANCA-GN.

Methods: Patients with ANCA-GN and IF graded as none-mild focal (<25%)/severe focal (25-50%)/diffuse (>50%) and other base-line risk factors, were obtained from the Norwegian Kidney Biopsy Registry. The observation period was from the date of biopsy to date of ESRD/death/end of 2013. ESRD and deaths during follow-up were identified by record linkage with The Norwegian Renal Registry. The primary end-point of the study was progression to ESRD within 3-years after diagnosis of ANCA-GN. Cox-regression statistics with and without adjustment for eGFR, glomerular classification (focal/crescentic/mixed/sclerotic), age, gender, ANCA sero-type was used to calculate HR's of ESRD between the different grades of IF.

Results: Two-hundred-fifty patients were identified of whom 43 progressed to ESRD within 3-years after diagnosis of ANCA-GN. Severe focal versus mild focal IF: Unadjusted HR 3.1 (1.6-6.1) p<0.001 and adjusted HR 2.1 (1.0-4.2) p=0.04. Diffuse versus mild focal IF: Unadjusted HR 5.7 (2.6-12.6) p<0.001 and adjusted HR 2.3 (0.9-5.6) p=0.07. Diffuse or severe focal versus mild focal IF: Unadjusted HR 3.8 (2.1-7.0) p<0.001 and adjusted HR 2.0 (1.1-3.9) p=0.03. Diffuse versus severe focal: Unadjusted HR 1.9 (0.9-4.4) p=0.11 and adjusted HR 0.8 (0.3-2.0) p=0.63.

Conclusions: Unadjusted, increasing degrees of IF is a strong risk factor for progression to ESRD in ANCA-GN. Adjusted for other known risk factors IF < versus ≥25% is a moderate independent predictor of progression to ESRD in ANCA-GN. Our finding suggests that IF should be included in multi-factor models aiming at predicting risk of progression to ESRD in ANCA-GN.

SA-PO653

Histopathologic Predictors for Renal Outcome in Crescentic Glomerulonephritis

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Background: Crescentic glomerulonephritis (CGN) results in serious decline of renal function, but the prognostic factors are not known in detail. We evaluated the long-term renal outcome and prognostic predictors of CGN according to histopathologic information obtained by renal biopsy.

Methods: Among 133 patients diagnosed as CGN between 2010 and 2018 from two university-based hospitals, we retrospectively analyzed 117 patients whose biopsy specimen contained more than 10 glomeruli. Specimens were categorized into four classes according to anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis classification. The severity of arterial fibrointimal thickening was assessed by semi-quantitative method between grade 0 and 3. Cox proportional analysis was used to calculate hazard ratio (HR) for renal survival and linear regression analysis was performed for one-year estimated glomerular filtration rate (eGFR).

Results: The mean age was 60.9 ± 15.5 years and male was 49.6%. The mean eGFR was 19.5 ± 16.5 mL/min/1.73m^2 and hemodialysis was required in 38 patients (32.5%) initially. Ninety-one patients (77.8%) showed positive for ANCA and 11 patients (9.4%) showed positive for anti-glomerular basement membrane antibody. Fifty-nine patients (50.4%) had advanced to end-stage renal disease (ESRD) during the mean follow-up of 34.1 month. Patients with sclerotic type had worse renal survival than focal type (HR, 3.30 [95% CI, 1.18–9.17], *P*=0.022), and moderate to severe arterial fibrointimal thickening was also associated with poor renal survival (grade 2: HR, 2.51 [95% CI, 1.18–5.37], *P*=0.017; grade 3: HR, 2.82 [95% CI, 1.21–6.57], *P*=0.016). Tubulointerstitial rounded dense lymphocyte aggregation was observed in 42 patients (35.9%) and was also a prognostic factor for ESRD (HR, 1.76 [95% CI, 1.03–2.99], *P*=0.039). In the multivariate linear regression analysis, sclerotic type, severe tubular atrophy, age, and baseline eGFR were independent predictors of eGFR at one year after biopsy (all, *P*<0.05).

Conclusions: Specific histopathologic findings, such as higher proportion of sclerotic glomeruli, moderate to severe arterial fibrointimal thickening, and presence of tubulointerstitial lymphocyte aggregation, provide helpful information for predicting the renal outcome in patients with CGN.

SA-PO654

Validation of a New Renal Risk Score for Patients with ANCA-GN

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Background: A new predicting model, renal risk score in ANCA associated GN, was published by Brix et al. in Kidney International Dec. 2018. It is a general principle that prognostic models need external validation for determination of generalizability.

Methods: Patients with ANCA-GN and risk factors included in the prognostic model; GFR > (G0) vs ≤15 ml/min/1,73m^2(G1), IF ≤ (T0) vs >25%(T1), and percentage of normal glomeruli (N0 >25%/N1 10-25%/N2 <10%), were identified in the Norwegian Kidney Biopsy Registry. According to the model, risk score points were assigned: G1=3, N1=4, N2=6, T1=2. Further, risk stratification was performed according to the model as follows: Low risk = 0-point, intermediate risk = 2-7 point, high-risk 8-11. Observation period was from the date of biopsy to date of ESRD/death/3 years post biopsy. ESRD during follow-up were identified by record linkage with The Norwegian Renal Registry. Kaplan-Meier and the ROC statistics were used to evaluate the prognostic performance of the model.

Results: We identified 250 patients with ANCA-GN of whom 43 progressed to ESRD during follow up. At 3-years of follow up cumulative risk of ESRD was 3.3% in low-, 22.4% in intermediate- and 44.0% in the high-risk group, p<0.001. In the ROC analysis AUC was 0.77 when assessed as 3 risk groups and 0.78 when assessed according to number of risk points.

Conclusions: We demonstrate that the prognostic value of this new prediction model for patients with ANCA-GN is good with an AUC of nearly 0.8 in the ROC analysis. However, the use of percentage normal glomeruli instead of glomerular classification (focal/crescentic/mixed/sclerotic) needs confirmation in larger cohorts. Further, the choice of grading initial eGFR in only 2 groups > versus ≤15 ml/min/1.73 m2 can also be questioned. It is also slightly surprising that demographic risk factors like age and gender are not included.

SA-PO655

Pauci-Immune Glomerulonephritis (PIGN) with Low Clearance at Clinical Presentation: Predictors of Treatment Response and Long-Term Outcomes

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Background: Pauci-immune vasculitis often presents with severe kidney involvement requiring hemodialysis. Considering the poor prognosis in this setting, we aimed to explore the factors which are associated with response to therapy.

Methods: Patients were included if they had biopsy proven PIGN with estimated GFR<20 ml/min/1.73 m^2 or required dialysis at presentation, received standard immunosuppression and had a follow up > 6 months. We recorded clinical, laboratory and histopathological parameters at diagnosis, at 3 months, at 1 year and at the end of follow up. Outcomes of interest included response to treatment, ESKD, and death. Treatment response was defined by the ability to come off dialysis with an eGFR>20 ml/min/1.73 m^2 with no signs of vasculitis. Histopathological evaluation included arteriosclerosis, % of normal glomeruli, activity index, chronicity index.

Results: A total of 77 patients, with a mean age of 60.6(16.05) years were included. There were, 42 males (54.5%). After 3 months, 55 patients (74.6%) had responded to immunosuppressive therapy, 15 (20%) were dialysis depended, 5(6.7%) died and 2 were lost in follow up. By the end of the 1st year, 54 patients (71.4%) achieved remission, 15(20%) ended up in ESKD and 6(8%) died. Factors which were associated with treatment response included MPO-ANCA positivity [odds ratio OR:3.9, 95%CI(1.13-13.37) p=0.03], eGFR>10ml/min/1.73m^2 at presentation [OR:2.5, 95% CI(0.86-7.30), p=0.009], normal glomeruli >10% [OR:3.8, 95%CI(1.24-12.1), p=0.02], and chronicity index more than 6 [OR:6.2, 95% CI(1.77-22.4), p=0.004]. Risk factors associated with ESKD included non-response to immunosuppressive therapy [Relative Risk RR:0.05, 95%CI(0.01-0.2) p<0.0001)], normal glomeruli<10% in the diagnostic biopsy [RR: 2.9, 95% CI(1.38-6.32), p=0.005] and age>75 years [RR:3.2, 95% CI(0.9-10.6) p=0.055]. Two of the 6 deaths were disease related.

Conclusions: A significant proportion of patients with PIGN who presented with severe renal dysfunction, responded to immunosuppresive therapy and recovered renal function approximately 3 months after initiation of therapy. Risk factors for ESKD were age>75 years, <10% normal glomeruli in the diagnostic biopsy and non-response to immunosuppressive therapy.

SA-PO656

Long-Term Outcomes of Patients with ANCA-Associated Vasculitis (AAV) Presenting with Severe Renal Dysfunction

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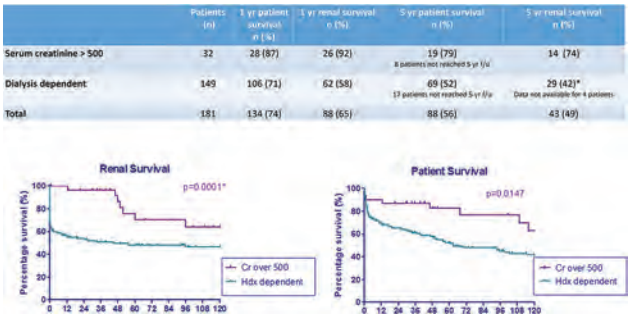
Background: Rapidly progressive glomerulonephritis (RPGN) is an important cause of morbidity and mortality in AAV. Few studies have specifically addressed the outcome of patients presenting with severe RPGN, traditionally defined as dialysis-dependence or a serum creatinine (SCr) of over 500µmol/l, and in particular the benefit of plasma exchange (PEX). Recent research has challenged the role of PEX in this patient set. Here we describe the long-term patient and renal outcomes in a large cohort of patients with severe RPGN treated with PEX at our centre.

Methods: This is a retrospective analysis of patients treated from 1977-2017 with newly presenting AAV and severe RPGN. Patients were classified as being dialysis-independent with a sCr>500µmol/l or as dialysis-dependent (defined as the need for dialysis within 72 hours of admission). Patients were treated consistently with steroids, cyclophosphamide and plasma exchange (with Rituximab post 2011) and with azathioprine as first line maintenance.

Results: Data were obtained for 181 patients, 149 of whom presented with dialysis-dependence. There were no demographic or treatment differences between the two groups. Patients who were not dialysed at presentation had significantly improved renal and patient survival at 1 and 5 years when compared to patients who presented dialysis dependent (Figure 1).

Conclusions: Renal and patient outcomes were favourable compared to other studies of this patient group. There was a striking difference in outcomes for dialysis-dependent patients when compared to those who had a sCr of >500µmol/l with independent renal function; it may be relevant to analyse patients with severe renal dysfunction according to these criteria in future therapeutic trials.

	Patients (n)	1 yr patient survival n (%)	1 yr renal survival n (%)	5 yr patient survival n (%)	5 yr renal survival n (%)
Serum creatinine > 500	32	28 (87)	26 (92)	19 (79) 8 patients not reached 5 yr f/u	14 (74)
Dialysis dependent	149	106 (71)	62 (58)	69 (52) 13 patients not reached 5 yr f/u	29 (42)* Data not available for 4 patients
Total	181	134 (74)	88 (65)	88 (56)	43 (49)



SA-PO657

A Dutch Consensus Statement on the Diagnosis and Treatment of ANCA-Associated Vasculitis

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Background: Several guidelines have been published on the diagnosis and treatment of anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV). These guidelines provide an evidence-based approach to support clinical-decision making and adequate implementation is needed to improve care. As part of an implementation strategy, national consensus meetings in the Netherlands were initiated in order to establish consensus on broad aspects of the diagnosis and treatment of AAV based upon the recently published guidelines, relevant to daily clinical practice.

Methods: A national, multidisciplinary working group of physicians (nephrologists, rheumatologists, immunologists, pulmonologist, pathologist) with expertise on AAV addressed the broad spectrum of diagnosing, treating and organisation of care for AAV patients. Consensus was established using a Delphi-based method in a national conference in conjunction with a nationally distributed online consensus survey. This survey was distilled from the current published international guidelines. Cut-off for consensus was 70% (dis-)agreement.

Results: Ninety-eight professionals were involved in the Delphi procedure to assess consensus on 52 statements regarding diagnosis, treatment and organisation of care for AAV patients. From 52 statements, consensus was achieved for 39 statements (75%). Consensus was achieved on aspects of AAV disease definition, nomenclature, distinct disease states through follow-up, treatment algorithm and organisation of care for AAV. No consensus was achieved on the necessity of histopathological evidence, regular blood testing for ANCAs and standard BVAS, VDI and PROMs assessment.

Conclusions: This study describes the results of a national consensus statement on diagnosing and treatment of AAV patients as part of an implementation strategy in the Netherlands of (inter-)national guideline-derived recommendations. Future studies should evaluate whether the consensus statement has facilitated local implementation, reduced clinical practice variation and, ultimately, improved care for AAV patients in the Netherlands.

SA-PO658

A Proposal of a Stepwise Algorithm for Therapeutic Intervention Using a Modified EUVAS Classification

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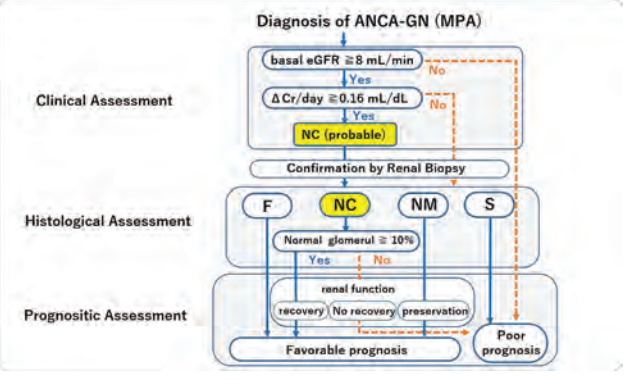
Background: Prediction of treatment's response is useful for minimizing the side effects of immunosuppression therapy for elderly patients. We proposed the Modified EUVAS histological classification of ANCA-associated glomerulonephritis (AAGN), in which New Crescent class (NC) was categorized by active crescents with more than 50% after eliminating a number of global sclerosis and the rest was categorized as New Mixed class (NM) (ASN2018). The purpose was to produce a stepwise algorithm consisting of clinical, histological, and prognostic assessments using the modified EUVAS classification.

Methods: The 51 patients with MPO-AAGN (male 45%, 68 +-9.1years old), who were followed more than 2 years were the cohort in the present retrospective study. All patients were treated according to the Japanese guideline (JSN 2011). In the clinical assessment, cut off values of basal eGFR and increases in sCr per day (ΔCr/day) predicting NC were decided using ROC analysis. In the second step, prognosis as well as treatment's response of each subclass of modified EUVAS classification was analyzed.

Results: F:NC:NM:S was 18:11:11:11, respectively. In clinical assessment, 8 mL/min of $eGFR_0$ and 0.16 mg/dL/day of ΔCr were cut off values for renal prognosis and estimation of NC, respectively. In subtype NC, the proportion of normal glomeruli more than 10% was valuable indicator for prediction of treatment response ($\Delta eGFR_{0\text{-}2}$). The renal function of NM was preserved without correlation with the proportion of normal glomeruli.

Conclusions: Patient with F or S will be treated conventionally. However, histological quantative assessment of NC and NM provides an idea of concrete immunosuppressant's therapy. Stepwise algorism consisting of clinical, histological and prognostic assessment as shown in Figure, is useful for minimizing the side effects of immunosuppression therapy for elderly patients.



Stepwise Algorithm using the modified EUVAS classification.

SA-PO659

Glucocorticoids for Remission Induction in Incident ANCA-Associated Vasculitis (AAV) Patients in Real-World Practice: High Exposure and Temporal Relationship to Adverse Events

Peter A. Rutherford, Dieter K. Goette. *Vifor Pharma, Glattbrugg, Switzerland.*

Background: Rapid induction of remission in AAV is desirable and typically includes high dose glucocorticoids (GC). While achieving remission is critical, patients are also at risk from GC-related adverse events (AEs) leading to long term organ damage as well as acute morbidity and mortality. This study examined GC prescribing, AAV response and AEs in incident AAV patients managed in routine clinical practice

Methods: 929 incident AAV patients from 4 European countries (399 physicians) were diagnosed between 2014-17 and data collected at baseline, 1, 3, 6 and 12 months following induction therapy start were reviewed

Results: 54% of patients had granulomatosis with polyangiitis, and 46% had microscopic polyangiitis; mean age was 56.82 years (SD 14.2) with 53.7% male. Physicians reported 12% patients as mild/localized, 54% as moderate systemic and 34%

as severe life threatening vasculitis. 83% of patients received GCs – 49% IV followed by oral, 17% oral only and 17% IV only. 43% used cyclophosphamide and GC, 13% rituximab and GC, 10% only GC with remainder using other regimes. As BVAS was not used, full clinical response was assessed as no vasculitis activity and GC taper on track. Most patients remained on GCs over 12 months, AAV response was incomplete and AEs were common especially in first 3 months when GC dose highest. Dose change practice varied and more UK patients had GC reductions at 3 (55%) and 6 months (46%) compared to other countries. At 12 months, of the 61% patients still receiving GCs, 34% were taking < 5mg, 56% 5-10mg, 9% 10-20mg and 2% > 20mg. 67% had no AAV activity, 17% local disease only, 11% mild/moderate systemic disease and 6% moderate/severe systemic disease

Conclusions: Most incident AAV patients receive high dose GCs, commonly IV, and most remain on GCs over 12 months. AEs and infections are common especially in the first months when GC dose is high. Remission is variable and only a minority of patients at 12 months have full control of AAV without steroids. New treatments are needed to address this unmet medical need

Funding: Commercial Support - Vifor Pharma

	1 month	3 months	6 months	12 months
Full response %	22	43	61	68
Still receiving GC %	82	79	67	61
Decrease/stop GC at visit %	38/1	45/4	38/5	26/8
At least one AE/infection %	64/46	42/28	35/23	30/20

SA-PO660

Maintenance Treatment in ANCA-Associated Vasculitis (AAV): Definition, Clinical Outcomes, and Significant Burden of Disease in Real-World Clinical Practice

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Background: After remission induction AAV is a relapsing remitting long term condition and patients are at risk of organ damage from both active AAV and therapy in particular glucocorticoids (GC). This maintenance phase of AAV is critical for good long term outcomes. This retrospective study examined the definition of maintenance, therapies and clinical outcomes in AAV patients in routine clinical practice.

Methods: AAV patients from 4 European countries (310 physicians) who completed induction therapy for organ/life threatening AAV and initiated maintenance therapy between 2014-16 were studied. Data were collected from when maintenance was determined to begin by the physician and at 6, 12, 18 and 36 months.

Results: 929 patients were studied - 51% had granulomatosis with polyangiitis, mean age 54 years with 54% male. 49% were incident AAV patients and 51% relapsing. Physicians defined maintenance beginning at mean of 5.6 months from induction start on basis of fixed time point 38%, starting of new drug for maintenance 27%, reaching full remission 26% and no specific criteria 9%. At this time 45% were in full remission vs 49% in partial and 6% refractory. Over 36 months after maintenance was defined, 84% were still in remission but 10% had major relapse requiring re-induction and left follow up, 6% died (2/3 at time of relapse). There is variation in maintenance drug regimes, initially in 929 patients GC 62%, Azathioprine 37%, Rituximab 19% and MMF 18%. At 36 months, 9% of AAV patients were receiving renal replacement therapy and CKD was reported as a comorbidity in 17% vs 7% at start of remission induction therapy.

Conclusions: Maintenance therapy in AAV is variably defined but typically 6 months after start of remission induction. Relapse severity varies and is still a problem and many patients require ongoing GC therapy to maintain remission. Infections and renal complications are an unmet need in AAV maintenance. There is a need for new targeted therapies in AAV to improve clinical outcomes in the maintenance phase.

Funding: Commercial Support - Vifor Pharma

	6 months	12 months	18 months	36 months
Remission n	817	789	777	742
Total relapse %/ major %	12/46	10/53	6/51	7/66
GC/Azathioprine/Rituximab/ MMF %	59/36/20/19	49/31/17/18	40/28/15/16	33/23/13/12
GC dose > 7.5mg %	59	41	30	29
At least 1 infection %	43	34	28	26

SA-PO661

ANCA Response on Rituximab or Cyclophosphamide in ANCA-Associated Vasculitis Patients

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Background: Recent studies have demonstrated that in patients with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) with successful remission-induction (RI) after cyclophosphamide (CYC), maintenance treatment with ANCA-guided rituximab (RTX), improved relapse free survival (RFS). However, current recommended RI therapy is RTX, CYC or the combination. As yet it is unclear how these different RI therapies affect ANCA levels. Therefore, this study aimed to investigate the potential of RTX, CYC, or RTX+CYC to achieve an ANCA-negative status and its effect on RFS to further improve the insight on ANCA-guided treatment in AAV patients.

Methods: This retrospective cohort study involved 129 ANCA-positive AAV patients treated with 200 remission-induction regimens, including RTX (n=109), CYC (n=66), or RTX+CYC (n=25) between 1990 – 2018 with a mean follow-up of 328 weeks. ANCA serum levels and major RFS were assessed.

Results: Within 6 months, 23% of RTX-treated, 50% of CYC-treated and 40% of RTX+CYC-treated AAV patients achieved an ANCA-negative status (p=0.0001). Time to ANCA negativity was significantly shorter after CYC+/- RTX (mean±SD: 11±6 weeks) as compared to RTX (16±6 weeks; p=0.02). ANCA reappearance within 1 year after achieving ANCA negativity, occurred in 9 out of 31 (29%) RTX-treated, 17 out of 43 (39%) CYC-treated and 2 out of 12 (17%) RTX+CYC-treated patients (p=0.2), which happened significantly faster in CYC-treated patients at an average of 18 weeks as compared to RTX+/- CYC at an average of 30 weeks (p=0.003). Both 1yr and 2yr major RFS was significantly less for RTX-treated (86% and 68%) as compared to CYC-treated (97% and 91%) and RTX+CYC-treated patients (100%, 91%) (p=0.02, p=0.005). Overall, patients that reached an ANCA-negative status had a better 2yr-RFS. ANCA reappearance associated with major relapses in RTX-treated group (67% vs 0%; p=0.001) but not in CYC-treated group (12% vs 4%; p=0.38).

Conclusions: This study demonstrates that an ANCA-negative status was achieved more frequently and quicker with CYC +/- RTX as compared to RTX and associated with a better 2yr-RFS. ANCA reappearance was associated with relapses in RTX-treated patients but not in CYC-treated patients. Thus, monitoring ANCAs to guide tailored maintenance treatment is most relevant in RTX-treated AAV patients.

SA-PO662

Harmful Effects of Cyclophosphamide on Japanese Patients with Renal Vasculitis Associated with Myeloperoxidase-Antineutrophil Cytoplasmic Antibody-Positive Microscopic Polyangiitis

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Background: In Europe, combination of glucocorticoid (GC) and cyclophosphamide (CY) or rituximab is recommended as an induction therapy in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. However, many Japanese patients with myeloperoxidase (MPO)-ANCA-positive microscopic polyangiitis (MPA) are treated with only GC.

Methods: We retrospectively reviewed patients with newly diagnosed MPO-ANCA-positive MPA in two Japanese institutes between April 2000 and March 2017. Patients with serum creatinine levels > 5.0 mg/dL or those <20 years of age were excluded. Patients were divided into two groups based on whether they received combination therapy of GC plus CY (CY group), therapy with only GC, or GC plus other therapies excepting CY for remission induction (non-CY group). Primary endpoint was a combination of death and end-stage renal disease (ESRD). Pairwise 1:2 propensity-score matching was used to assemble a cohort of patients with similar baseline characteristics.

Results: Among 121 eligible patients, 27 [17 men (63.0%), average age 66.9 ± 10.2 (mean ± SD) years] were assigned to the CY group, whereas 54 [32 men (59.3%), average age 67.0 ± 14.7 years] were assigned to the non-CY group. Both groups had similar propensity scores. In the CY group, 22 patients were treated with oral CY and five with intravenous CY. In the non-CY group, 42 patients were treated with GC alone and 12 with a combination of GC and other therapeutics, including intravenous immunoglobulin, mizoribine, and lymphocyte apheresis. No patient was treated with rituximab. Fifteen primary endpoints (8 deaths and 7 ESRDs) occurred in the CY group, whereas 14 (10 deaths and 4 ESRDs) occurred in the non-CY group. The 1- and 5-year survival rates were 0.89 and 0.60 in the CY group and 0.93 and 0.79 in the non-CY group (p = 0.039), respectively. Hazard ratio in the CY group was 2.14 (95% confidential interval, 1.02–4.52) as compared with the non-CY group.

Conclusions: Induction therapy with CY increased the risk of death and ESRD by 114% as compared with therapy without CY in Japanese patients with renal vasculitis associated with MPO-ANCA-positive MPA. Therefore, CY should not be used for induction therapy in these patients.

SA-PO663

The Use of Rituximab in ANCA-Negative Pauci-Immune Small Vessel Vasculitis: A Comparative Analysis

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Background: Rituximab has been established as an effective treatment strategy for induction-remission of ANCA associated vasculitis, although little is known about its use in the absence of detectable circulating ANCA with respect to its accepted mechanism of action. Due the rare nature of the disease and even smaller subcategory of patients with ANCA negative disease, trials in this area are likely to be challenging. This study aims to determine the treatment outcomes of rituximab as induction therapy in ANCA negative disease.

Methods: A cohort of patients treated with rituximab for induction-remission of pauci-immune small vessel vasculitis was constructed from a single centre between 2006-2018 and followed up until May 2019. Multivariate Cox regression was used to compare treatment outcomes of rituximab between patients with or without detectable circulating ANCA. Primary study outcomes were patient survival, renal survival and disease remission.

Results: 58 patients with active disease who required treatment with rituximab were identified. Mean age was 59±14 with a male predominance of 53%. 29% (n=17) had ANCA negative disease at the time of treatment. The overall remission rate irrespective

of ANCA serology was 91% (n=53), with a relapse rate of 23% (n=12). On comparative multivariate analysis, ANCA negative disease was not associated with a lower likelihood of remission [HR 0.6 (95% CI 0.19 - 1.85)]. There was no significant difference in subsequent relapse rates between ANCA positive and ANCA negative patients; 21% vs. 27%, respectively (p=0.67). Moreover, the risk of death [HR 2.65 (95% CI 0.32 – 21.76)] and ESRD [HR 0.25 (95% CI 0.03 – 2.04)] were similar between the two groups. Adverse events did not differ between the two groups (p=0.96).

Conclusions: Our centre experience suggests that the use of rituximab is an effective treatment for induction-remission of ANCA negative pauci-immune small vessel vasculitis. To our knowledge, this is the largest cohort analysis of rituximab therapy in seronegative disease reported to date.

SA-PO664

Rituximab-Associated Hypogammaglobulinemia in ANCA Vasculitis: Incidence and Time Course

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Background: Rituximab (RTX) is approved for remission induction (I) and maintenance (M) in ANCA vasculitis (AAV). RTX depletes B cells that express CD20 but does not affect B cell precursors or antibody producing plasma cells. Persistent production of protective antibodies and replenishment of peripheral B cells by B cell precursors renders RTX a relatively safe and effective treatment option. However, several observational studies have demonstrated a decline in serum immunoglobulin (IgG) in AAV patients treated with RTX. We evaluated the risk of hypogammaglobulinemia (Hypo-IgG) among RTX-treated AAV patients.

Methods: AAV patients treated with RTX were included in this single-center observational study. Demographics, clinical and post RTX IgG levels were extracted and analyzed. Severity of Hypo-IgG was defined as mild (501-700mg/dL), moderate (301-500mg/dL), and severe (≤300mg/dL). Descriptive data are presented as mean with SD and median with IQR.

Results: Between 2013 to 2018, we investigated 105 RTX treated AAV patients, with mean (SD) age 56 (16) years, 84% Caucasians, 57% females and 64% diagnosed with Granulomatosis with Polyangiitis. Post RTX IgG were measured in 74 patients of which 50 had repeat IgG. 27 patients received RTX for remission I, 8 for remission M and the remainder received RTX for remission I and M. Hypo-IgG occurred in 43 (58%) patients and 19 (44%) had moderate to severe hypo-IgG. Overall, IgG remained stable over time (Figure). Of the 50 patients with repeat IgG, 11 (36%) had moderate to severe hypo-IgG. Infections requiring hospitalization occurred in 10 patients with hypo-IgG.

Conclusions: Hypo-IgG is common in RTX treated AAV patients. Although limited by sample size, IgG trend suggests that nadir IgG levels occur during I dosing and the IgG levels remain stable or increase over time in those receiving M.

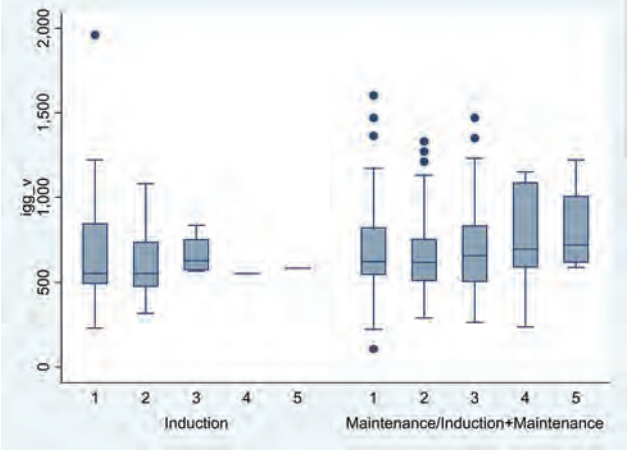

Figure: IgG levels over time in patients receiving induction and continous Rituximab

SA-PO665

The Factors for Maintenance of B Cell Depletion After Use of Rituximab in Renal Disorders

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Background: The duration of B-cell depletion(BCD) after rituximab administration may be related to the disease recurrence. We aimed to explore the factors which may influence the duration of BCD(CD19 positive B cell count<5/μL) after the use of rituximab in patients with kidney diseases.

Methods: Patients received rituximab for renal causes and were regularly monitored every 2-3 months on B cell counts were enrolled. Prognostic factors for maintenance of BCD were identified through Cox proportional hazards model where the optimal cutoff values were determined using an online statistical tool Cutoff Finder.

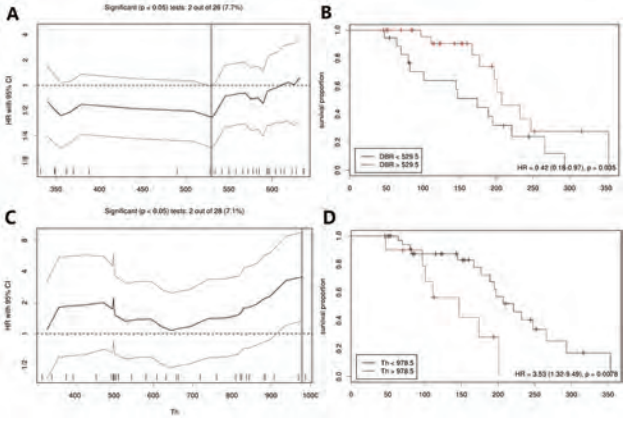
Results: There were 47 patients who received a median of 900mg (range,300-1500mg) of rituximab with 100% achieving BCD and 49% experiencing B cell reconstitution during follow-up. The optimal cutoff value of dose to body-surface-area ratio (DBR) was 529.5mg/m^2 in total and that of circulating T helper (Th) cell count was 978.5/μL. In multivariate analyses, high DBR(>529.5mg/m^2) was identified as an independent protective factor (HR0.42,p=0.024) and high circulating Th cell count (>978.5/μL) was identified as an independent risk factor (HR2.98,p=0.037) for maintenance of BCD. High Th cell count (>978.5/μL) was also associated with manifestation of nephrotic syndrome, increased CD19 positive B cell counts and T killer cell counts.

Conclusions: DBR and Th cell counts were of predictive values for maintenance of BCD after use of rituximab in patients with renal disorders.

Funding: Government Support - Non-U.S.

	Cutoff point	Univariate analysis			Multivariate analysis		
		HR	95%CI	P	HR	95%CI	P
Age,years	44.5	0.66	0.26-1.68	0.38			
Sex	1=male,0=female	0.82	0.36-1.90	0.65			
Nephrotic syndrome	1=yes,0=no	2.13	0.92-4.92	0.08			
Immunosuppressant	1=yes,0=no	0.45	0.19-1.07	0.07			
DBR,mg/m^2	529.5	0.42	0.18-0.97	0.035	0.37	0.16-0.88	0.024
SCr,μmol/L	142	0.42	0.16-1.11	0.072			
Albumin,g/L	18.15	0.48	0.2-1.2	0.11			
Globulin,g/L	23.75	0.45	0.13-1.54	0.19			
Urine protein,g/24h	4.875	0.52	0.22-1.26	0.14			
White cell,10^9/L	7.4	0.52	0.21-1.29	0.15			
Lymphocyte,10^9/L	2.315	2.53	1.04-6.13	0.034			
T helper cell,/μL	978.5	3.53	1.32-9.49	0.008	2.98	1.07-8.31	0.037
T Killer cell,/μL	765	2.14	0.91-5.08	0.076			
CD4/CD8 T cell	1.675	1.7	0.6-4.82	0.31			
NK cell,/μL	94	4.15	1.18-14.61	0.018	3.51	0.98-12.51	0.053
CD19+ B cell,/μL	328	0.62	0.26-1.49	0.28			
IgG,mg/dl	921.5	2.91	1.04-8.17	0.034			
IgM,mg/dl	45.5	2.47	0.73-8.34	0.13			
IgA,mg/dl	161.5	1.96	0.8-4.81	0.14			

Prognostic parameters for maintenance of B cell depletion (BCD) via Cox proportional hazards model



SA-PO666

The Short-Time Efficacy and Safety of Immunoadsorption onto Protein A, Compared with Plasma Exchange, in the Treatment of Severe Immunological Nephropathy

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Background: The efficacy and safety of immunoadsorption onto protein A (IA), compared to plasma exchange (PE), in the treatment of severe anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) and lupus nephritis (LN), are few reported.

Methods: The clinical data of 42 patients with severe immunological nephropathy, including 21 treated with IA from Nov 1, 2016 to Nov 31, 2018 and 21 treated with plasma exchange (PE) from Nov 1, 2014 to Nov 31, 2018 in our hospital were retrospectively analyzed. IA or PE was combined glucocorticoid, with or without immunosuppressant regimen as induction immunosuppression. IA was performed 10 cycles every time and was done 3-7 times. PE was performed 3-6 times with plasma and albumin. All the patients were followed up prospectively for 3 months.

Results: In AAV patients, Hb, PLT, Glb, SCr, IgA, IgG, IgM, C3, C4, Fg and BVAS were significantly decreased after IA treatment, $P<0.05$. The decline of ANCA and IgG were 46.11% and 53.76% after the first time IA treatment. After the 3-7 times IA treatment, ANCA and IgG decreased by 82.48%, 77.81%, respectively. In LN patients, Glb, SCr, IgA, IgG, IgM, Fg and SLEDAI-2k were significantly lower after IA treatment, $P<0.05$, while eGFR was increased, $P<0.05$. After IA treatment, the reduction rates of anti-dsDNA Ab and IgG were 72.14%, 44.31%, respectively. There was no significant change in PT and INR in IA group, but in PE group PT and INR were longer than that before treatment, $P<0.05$. The Fg decline in IA and PE group were 46.74±25.32%, 66.01±13.98%, respectively, $P<0.05$. There were 4 patients in the PE group who were transfused with cryoprecipitate due to

poor coagulation function but no one in IA group, *P*<0.05. The main adverse event of IA treatment is hypotension during processes, but for PE treatment is allergies, manifested as rashes. There was no difference in the incidence of adverse events, *P*>0.05. After 3 month follow-up, albumin in IA group was higher than that in PE group, *P*<0.05.

Conclusions: IA combined with glucocorticoid, with or without immunosuppressant, resulted in similar rapid removement of pathogenic autoantibodies and similar rapid improvement of renal function as PE did in the short term, but IA treatment induced less coagulation disorders, which potentially decreased the risk for bleeding, compared to PE treatment.

Funding: Government Support - Non-U.S.

SA-PO667

Rescue Therapy with Extracorporeal Membrane Oxygenation (ECMO) for Diffuse Alveolar Haemorrhage in Patients with Systemic Vasculitis

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Background: Diffuse alveolar haemorrhage (DAH) is a life threatening condition and common causes include autoimmune diseases, infections and medications among others. DAH is a severe manifestation of systemic vasculitis, particularly in patients with ANCA and anti-GBM antibodies. This is mediated through inflammation, occupation and destruction of the alveoli. In extreme cases, even mechanical ventilation is ineffective and ECMO is required to oxygenate the blood whilst the immunosuppressive treatment takes effect.

Methods: We performed a retrospective review of the patients with confirmed DAH which required ECMO at our centre between 01/2016 and 04/2019. Each case was reviewed and we assessed baseline characteristics, cause of vasculitis, duration of ECMO, immunosuppressive therapies used, renal outcome and mortality.

Results: 8 patients met the inclusion criteria making this the largest single centre case series to date of patients with DAH requiring ECMO. 6 patients were female and 2 male with a median age of 42.5 years. 6 patients had ANCA associated vasculitis (5 PR3, 1 MPO), 1 had systemic lupus erythematosus (SLE) and 1 was ANCA and anti-GBM negative. After commencing ECMO, 7 patients survived; of those 4 received IV cyclophosphamide, and 5 received rituximab; all had IV methylprednisolone and plasmapheresis (PLEX). 6 of the 8 patients presented AKI and 5 required continuous renal replacement therapy (CRRT); at discharge 5 patients had renal recovery with a GFR back to baseline.

Conclusions: The majority of cases with catastrophic DAH are related to AAV and in those failing invasive mechanical ventilation, ECMO would appear to be a valid rescue therapy with good overall outcomes. Immunosuppression with IV CYC and/or IV RTX appears to be safe and effective in this setting. Despite a high incidence of AKI requiring RRT, the majority of patients achieved renal recovery.

Gender	Age	Aetiology	Days ECMO	CRRT	Immunosuppression	PLEX sessions	ICU length of stay	Renal recovery	Survival
M	47	AAV	7	Yes	MPDN + CYC	7	21	Yes	Yes
M	48	AAV	7	Yes	MPDN + RTX	7	14	No	Yes
F	24	SLE	4	No	MPDN	3	5	No	No
F	36	MAHA	6	Yes	MPDN + RTX	7	13	Yes	Yes
F	38	AAV	5	No	MPDN + CYC	7	13	Yes	Yes
F	34	AAV	4	No	MPDN + RTX	7	10	Yes	Yes
F	63	AAV	10	Yes	MPDN + CYC + RTX	7	23	No	Yes
F	50	AAV	5	Yes	MPDN + CYC + RTX	7	11	Yes	Yes

SA-PO668

Clinical Features and Outcomes in Anti-Glomerular Basement Membrane Glomerulonephritis Patients with Onset of Noninfectious Fever

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Background: To summarize the clinical features and outcomes of anti-glomerular basement membrane (anti-GBM) glomerulonephritis (GN) with onset of non-infectious fever.

Methods: We retrospectively reviewed the clinical records and follow-up data of 58 patients with anti-GBM GN in our hospital from May 2010 to May 2019.

Results: Among the 58 anti-GBM GN patients, 39 patients (67.2%) presented with fever initially. After careful screening of serological and urinary tests, pathogenic cultures, and CT scans, 28 (48.3%) patients had no evidence of infections. These non-infectious febrile patients had a female/male ratio of 1.3:1, and the average age was 46±18 years old. Six (21.4%) patients were complicated with pulmonary hemorrhage. Compared to the non-febrile anti-GBM GN patients (n=19), they showed higher CRP levels (65.4 vs. 24.5 mg/L, *P*=0.045) and higher anti-GBM antibody titers (175±41 vs. 132±62 EU/ml, *P*=0.012). In kidney, they presented milder proteinuria (2.51±2.51 vs. 4.69±2.41 g/d, *P*=0.016), despite similar serum creatinine (906±414 vs. 995±604 μmol/L) and eGFR (4.66 vs. 4.40 mL/min/1.73m^2) levels (*P*>0.05). Crescentic GN was diagnosed in 11 (84.6%) of 13 patients who had renal biopsy. At onset, 82.1% patients were treated by antibiotics which didn't work. All patients received immunosuppressive treatment later, and 26 of them had combined plasma exchange therapy. They received more plasma exchanges (7.2±3.9 vs. 4.0±3.5, *P*=0.006) and had a longer hospital stay (42±21 vs. 29±15 days, *P*=0.020) compared to the non-febrile group. During follow-up, the renal survival rate at 1, 3 and 5 year was 20.8%, 13.6% and 10.0%, which were similar with the non-febrile group (18.8%, 7.1%, 0%) (*P*>0.05). Among all the 58 anti-GBM GN patients, Kaplan-Meier survival analysis showed that oliguria, pulmonary hemorrhage, initial eGFR, and anti-GBM antibody titers were prognostic factors for renal outcome (*P*<0.05), but fever was not a predictor of it. Multivariate Cox regression analysis showed higher initial eGFR was an independent risk factor for ESRD (RR=0.80, 95%CI (0.69, 0.93), *P*=0.004).

Conclusions: Fever in anti-GBM GN may be part of systemic inflammations instead of infections. Anti-GBM GN patients with onset of non-infectious fever presented more severe systemic inflammations and needed more intensive treatment.

SA-PO669

Anti-Glomerular Basement Membrane Disease: A Real-World Experience

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Background: Anti-glomerular basement membrane (Anti-GBM) disease is associated with deleterious renal outcomes, with the majority of patients remaining dialysis dependent. There is a paucity of evidence regarding optimal treatment and factors predicting outcomes in this cohort. We aim to describe our real-world experience and evaluate factors associated with end-stage renal disease (ESRD).

Methods: A multi-centre, retrospective cohort study was performed using existing databases from 3 centers in Ireland, Czech Republic and North America (N= 52). All patients, recruited between 1998-2018, had biopsy proven Anti-GBM disease. We describe the clinical characteristics and evaluate factors associated with ESRD using chi-square and independent sample t-tests.

Results: 48 (92%) were Caucasian and 33 (64%) female, with a mean (SD) age of 58 (16) years. Table 1 depicts baseline characteristics for the total cohort stratified for presence of ESRD. 43 (83%) required renal replacement therapy (RRT) at presentation and 22 (42%) displayed ANCA positivity. Patients reaching ESRD had higher need for RRT at entry, were more often ANCA negative and had a lower percentage of normal glomeruli compared to those who did not. Overall, renal recovery occurred in 14 (33%), over a median follow-up of 39 months (IQR 79.5).

Conclusions: The need for RRT at diagnosis, ANCA negativity and a lower percentage of normal glomeruli are associated with an increased trend towards ESRD. Renal recovery occurred in 1/3 of patients, suggesting a possible beneficial role in modulating acute renal inflammation, even with apparent poor prognostic features. Individualization of treatment, stratified by prognostic factors is paramount and requires larger scale collaborative studies to explore this further.

Variable	ESRD Yes (n = 31)	ESRD No (n = 21)	p value
Female (%)	51	48	0.12
RRT requirement at diagnosis (%)	72	28	0.0001
Alveolar haemorrhage (%)	47	53	0.23
eGFR (MDRD) at diagnosis, ml/min/1.73m2 (SD)	7 (6)	14 (15)	0.06
ANCA negative (%)	70	30	0.08
Percentage normal glomeruli (SD)	5 (8)	15 (22)	0.05
Crescentic Berden class (%)	67	33	0.07
Immunosuppression use (%)	58	42	0.24
Plasmapheresis use (%)	60	40	0.89

SA-PO670

Intravenous Cyclophosphamide for Treatment of Anti-GBM Disease

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Background: Anti-GBM disease is a condition caused by antibodies to type IV collagen. We report a single centre experience of the use of pulsed intravenous cyclophosphamide (IV Cyc), steroids and plasma exchange (PEX) for induction treatment. There is a paucity of data on the use of IV Cyc for induction. Standard therapy involves daily oral cyclophosphamide.

Methods: Retrospective review of patient records from Jan 2006 to Dec 2018. Primary aim was to compare the outcomes of our treatment regimen on mortality and preservation of renal function with published outcomes.

Results: 33 patients were identified. Complete data was not available in 4. Of the remaining 29, 24 had renal disease, 2 had pulmonary disease and 3 had both renal and pulmonary involvement. Iv Cyclophosphamide was dosed adjusted for age and renal function. Maintenance was predominantly with steroids and Azathioprine. The median age was 67 years (range 17-86), 41% were female. Plasma exchange was done in 25 patients who received between 4 and 25 sessions. 14 patients were dialysis dependent at presentation. Renal survival was 10% in dialysis dependent patients and in those who did not require dialysis, it was 75%. Patient survival was 90% at 1-year for treated patients. 8 out of 29 patients were deemed too frail to receive induction therapy. 14 of 27 (52%) with renal involvement required dialysis at the time of discharge after their first presentation. 3 of the 13 dialysis independent patients later went on to require dialysis.

Conclusions: Published data suggests 1 year patient survival of 87 to 100% and 1 year renal survival of 94% in those with creatinine < 500 umol/[1-3]. Our cohort had higher proportion of patients who were dialysis dependent at presentation. Our data suggest that pulsed intravenous cyclophosphamide is as effective a therapy as oral cyclophosphamide with comparable outcomes at 1 year. This may make it a suitable option when consideration to cumulative dose exposure is made. As it is a rare disease further collaborative prospective study with other centres will likely be needed. 1. Huart A et al. *J Autoimmun* 2016;73:24-29 2. Alchi B et al *Nephrol Dial Transplant*. 2015;30(5):814-821. 3. Levy JB et al *Ann Intern Med*. 2001;134(11):1033

SA-PO671

Therapy and Outcome of Anti-Glomerular Basement Membrane Disease: A Single-Center Experience

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Background: Patients with anti-glomerular basement membrane (GBM) disease are at high risk of morbidity and mortality from renal failure or severe complications. Reviews revealed one-third patients have circulating anti-neutrophil cytoplasmic antibodies (ANCA). Phospholipase A_2 receptor (PLA_2R) antibody can also be positive. The aim of this study was to analyze the therapy differences of patient and renal outcomes in anti-GBM disease with or without ANCA or PLA_2R antibody.

Methods: We screened the patients from December 2014 to April 2019 in the First Affiliated Hospital of Xi'an Jiaotong University. The patients with anti-GBM disease were reviewed. Renal biopsies were scored for the presence of active and chronic lesions. The correlation between survival with clinical characteristics and regimens were analyzed.

Results: A total of 40 patients (18 M/ 22 F) were identified with anti-GBM glomerulonephritis. The average age was 57.4±16.8 years old. The duration of symptoms before diagnosing was 1.3±1.5 months. 35 patients (87.5%) presented with rapidly progressive glomerulonephritis. The SCr level was 10.0±5.2 mg/dL. Serological screening showed anti-GBM antibody titer 180.2±87.4 RU/mL, 11 cases with ANCA positivity (27.5%, 10 cases of pANCA-MPO, 1 case of cANCA-PR3), 5 cases with PLA_2R antibody positivity (12.5%). 23 patients accepted renal biopsy. 82.6% were compatible with crescentic glomerulonephritis. 30 patients (75%) received Plasmapheresis (PE). The patients were followed up for 9.98±10.5 months (range 0.5-28.5 months). Except 3 cases lost data and 14 death, 14 patients underwent maintenance hemodialysis, 2 patients underwent peritoneal dialysis, 3 cases had kidney transplantation, renal function recovered in 4 cases and 4 cases to chronic kidney disease. Multivariate Cox regression revealed female (hazard ratio [HR], 3.21; 95% confidence interval [95% CI], 1.41 to 7.30; *P*=0.005) and regimen with PE (HR, 2.89; 95% CI, 1.32 to6.35; *P*=0.008) were independent predictors of survival. SCr >6mg/dL was a risk factor for the ESRD and all-cause mortality.

Conclusions: Unlike previous data, our study shows that 55% of the patients with anti-GBM disease were female (considered a district bias). Multivariate analysis reveals female and PE therapy are predictors of renal and patient survival while high SCr (>6mg/dL) is associated with poor renal outcome and high risk of all-cause mortality.

Funding: Government Support - Non-U.S.

SA-PO672

Predictors of Kidney Function Recovery in Glomerular Disease After Dialysis Initiation

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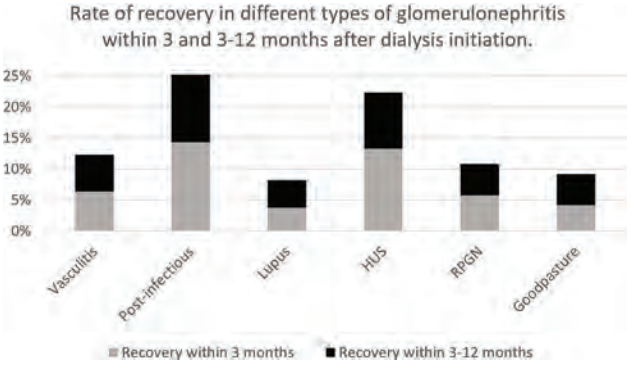
Background: Many patients with glomerulonephritis (GN) may require dialysis acutely, but the proportion of patients who recover kidney function has not been well-described. We examined characteristics of patients with GN who initiated outpatient dialysis and recovered sufficient function to become dialysis independent as well as trends in rates of recovery by GN type over time.

Methods: We performed a retrospective cohort study of adults ≥18 years who initiated outpatient dialysis between 1995-2015 and had a GN as cause of ESKD according to the USRDS. We defined recovery as a 60-day dialysis-free period and alive for at least 90 days after stopping dialysis within one year of dialysis initiation. We used adjusted Cox models to examine predictors of recovery.

Results: Of 173,348 patients, 4.6% recovered renal function and 13.3% died within one year after dialysis initiation. Recovery within the first 90 days of dialysis initiation was most likely among those with post-infectious GN or hemolytic uremic syndrome (HUS) [Figure]. Younger age, female gender, non-Hispanic white race, and having post-infectious, lupus and vasculitis as the cause of ESKD were associated with higher odds of recovery [Table].

Conclusions: Nearly one in four patients who initiated outpatient dialysis due to post-infectious and HUS diagnoses recovered kidney function within one year. Close follow-up after dialysis initiation is warranted.



Odds of kidney function recovery in adjusted model.

	OR (95% CI)
Age	
18-<30	Reference
30-<65	0.98 (0.91-1.05)
≥65	0.77 (0.71-0.84)
Women (vs. men)	1.08 (1.03-1.14)
Race/ethnicity	
Non-Hispanic White	Reference
Black	0.63 (0.59-0.68)
Hispanic	0.70 (0.64-0.75)
Asian	0.62 (0.54-0.70)
Native American	0.68 (0.54-0.86)
Calendar period	
1995-2000	Reference
2000-2005	1.25 (1.17-1.34)
2005-2010	1.63 (1.52-1.74)
2010-2015	1.55 (1.45-1.66)
GN type (gross categories)	
Post-infectious	Reference
GN (not biopsied or unspecified)	0.11 (0.10-0.13)
FSGS	0.07 (0.06-0.07)
Membranous	0.12 (0.10-0.14)
Dense deposit	0.17 (0.14-0.21)
IgA	0.07 (0.06-0.09)
IgM	0.14 (0.10-0.18)
RPGN	0.45 (0.39-0.53)
Goodpasture	0.26 (0.23 -0.31)
Lupus	0.45 (0.39-0.53)
HSP	0.26 (0.23-0.31)
HUS	0.29 (0.25-0.32)
Vasculitis	0.42 (0.37-0.48)

SA-PO673

Predictors of Treatment Resistance and Relapse in Childhood-Onset ANCA-Associated Vasculitis: A Nationwide Japanese Survey

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Background: Treatment resistance and relapse in childhood-onset antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) are major challenges for pediatricians. The aim of this study was to assess the predictive factors for treatment resistance and relapse in a nationwide cohort of Japanese patients with childhood-onset AAV.

Methods: Forty-five consecutive patients with childhood-onset AAV were recruited for inclusion in this study. The value of various demographic and clinical parameters for the prediction of treatment resistance and relapse were analyzed.

Results: The cohort consisted of 45 children; 34 (76%) were female, 36 (80%) had MPA, 9 (20%) had GPA, 78% were MPO-ANCA-positive, 20% were PR3-ANCA-positive. After the induction phase treatment, treatment resistance occurred in 20 (44%). Multivariable logistic regression models revealed that decreased estimated glomerular filtration rate (eGFR) at presentation predicted treatment resistance (odds ratio [OR] 30.71, 95% confidence interval [95% CI] 2.30-410.43, P = 0.010). Relapse occurred in 14 (31%) of 45 patients in whom remission was achieved and was independently associated with PR3-ANCA (OR 6.95, 95% CI 1.05-46.04, P = 0.044). Although not significant, male tended to be associated with relapse (p = 0.05).

Conclusions: Our findings highlight the important effect of severity of renal disease at presentation as predictors of treatment resistance. Increased risk for relapse appears to be related to the presence of anti-PR3 antibody seropositivity.

SA-PO674

The Role of TNFα/TNF Receptor 2 Pathway Activation in the Modulation of Childhood Nephrotic Syndrome

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Background: Primary Nephrotic Syndrome (NS) is considered T cell pathology; however, the pathogenesis still remains poorly defined. There is increasing evidence pointing to the important role of tumor necrosis factor-alpha (TNFα), a key inflammatory mediator, in pediatric nephrotic syndrome. We recently showed that elevated serum TNFα levels were associated with worse prognosis and lack of response to corticosteroids in children with NS. TNFα exerts its biological effect via interaction with two main cell surface receptors: tumor necrosis factor receptor 1 (TNFR1), and tumor necrosis factor receptor 2 (TNFR2), that contribute differently to glomerular inflammation. The aim of the present study was to investigate the expression and the role of different TNFα receptors and TNFα signaling pathways in kidney biopsies of children with steroid responsive and steroid resistant nephrotic syndrome.

Methods: TNFα and TNFα receptors expression were studied by immunofluorescence staining and RNA isolation from formalin-fixed, paraffin-embedded (FFPE) renal biopsies of children with nephrotic syndrome who were treated in our department (n=40) versus normal kidneys (n=12).

Results: TNFα and TNFR2 expression was significantly elevated in both children with steroid sensitive and resistant nephrotic syndrome, versus control group. Furthermore, TNF protein and mRNA abundancey were increased in steroid resistant nephrotic syndrome kidneys compared with steroid sensitive nephrotic syndrome kidneys. TNFα and TNFR2 but not TNFR1 expression positively correlated with steroid resistance and disease progression. In addition, TNFα signaling proteins (TRAF1, TRAF2, CCL2, CCL4, CCL10, CCL11, MMP2, MMP9, TIMP1, ADAM17, IL1b, IL6 and others) were also increased in children with NS and predicted prognosis and steroid responsivness.

Conclusions: As yet there is little information regarding the pathogenesis and optimal treatment of pediatric nephrotic syndrome, our results may indicate that TNFα pathway has a role in the pathogenesis of steroid resistant nephrotic syndrome, and may serve as a target for future therapy.

SA-PO675

Efficacy of a Gluten-Free Diet (GFD) in Children with Difficult-to-Manage Nephrotic Syndrome (NS)

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Background: Zonulin (ZON) increases gut permeability after exposure to gliadin in children with celiac disease. Plasma zonulin levels are increased in children with NS. Protease activated receptor-2, which mediates ZON effect in enterocytes, is present on podocytes. Thus, gluten-induced elevations in ZON may affect glomerular permeability and mediate proteinuria in children with NS. We conducted this study to assess the efficacy of a GFD in controlling disease in children with difficult-to-manage NS.

Methods: This multicenter, open-label trial tested the efficacy of a GFD in children with steroid-responsive, difficult-to-manage NS. The Treatment Period was 6 months. A positive response was defined as ≥50% reduction in relapse rate versus the prior 6 months or discontinuation of ≥1 immunosuppressive medication. The following data were tabulated: age, gender, race/ethnicity, serum creatinine, proteinuria, histopathology if available, and treatment. Serum was collected prior to and at completion of the Treatment Period to assess the effect on the glomerular cytoskeleton in vitro. Data are provided as mean±SD.

Results: 14 children (8F:6M) were enrolled, age 7.8±4.6 yr, baseline serum creatinine 0.46±0.12 mg/dl, and Up/c 0.45±0.49 (mg:mg). There were 11 Whites, 1 Black and 3 other racial groups and 2 children were Hispanic/Latino. The underlying disease was MCD in 10 and FSGS in 4 cases. At the end of the Treatment Period, 4 participants had a positive response (2 reduced relapse rate and 2 reduced medication burden), 5 had no benefit (2 withdrew before 6 months), 3 patients are in the 6-month Treatment Period, and 1 child was lost to follow-up. One adolescent had no change in relapse rate but responded to corticosteroids more rapidly on the GFD. Baseline plasma zonulin concentration was 19.4±1.7 vs 13.4±0.9 pg/mL in non-responders (n=4) vs GFD responders (n=2), respectively, P=0.01.

Conclusions: Up to a third of patients with difficult-to-manage NS have a favorable response to implementation of a GFD. An elevated plasma zonulin level may predict a poor response to the maneuver. A trial of this dietary intervention may be warranted in children with frequently relapsing or steroid dependent NS to minimize the need for immunosuppressive agents.

Funding: NIDDK Support

SA-PO676

Unbiased Transcriptional Analysis of the Nail-Patella-Like Renal Disease Inducing LMX1B R246Q Variant Reveals Dysregulation of Several Genes Critical to Homeostasis of Podocytes and the Glomerular Basement Membrane

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Background: While most genetic variants in LIM Homeobox Transcription Factor 1 Beta (*LMX1B)* are associated with the development of Nail Patella Syndrome, select variants such as *R246Q* produce renal limited phenotypes known as Nail Patella Like Renal Disease (NPLRD). Using a targeted analysis of key podocyte genes, we have previously identified several candidates that are downregulated by *R246Q* in cultured human podocytes. However, a more comprehensive transcriptional analysis is needed to understand the pathological mechanisms driving kidney specific disease development in NPLRD patients and to identify possible theraputic targets.

Methods: Differentiated conditionally immortalized human podocytes cell lines stably overexpressing equivalent levels of wild type *LMX1B* or the *R246Q* variant were analyzed using Illumina RNAseq technology.

Results: The analysis of *LMX1B R246Q* revealed significant reductions in genes that have been previously implicated in renal disease, including *SULF1* and *CLIC5*, (fold changes of -7.6, and -7.1 respectively). These genes as well as *FIBIN* (-24.1), *COL3A1* (-4.6), *ODAM* (-5.3), *TNIP3* (-5.2), *PRKG2* (-5.0), *RGS5* (-3.3), *ADRA1D* (-3.1), and *CDH11* (-2.8) were the most highly downregulated targets by the *R246Q* variant in a kidney focused analysis of the data. The most highly upregulated genes include *ANKHD1* (2.9), *CCL2* (2.1), *C8ORF4* (2.1), *ST14* (2.0), *MMP9* (1.7), *MMP2* (1.7), *MMP7* (1.7), and *CSF2* (1.7). A kidney focused pathway analysis of the transcriptional data in this study revealed that Matrix Metalloproteinase (MMP) inhibition was the top candidate pathway affected.

Conclusions: While downregulation of key podocyte genes was observed in the transcriptional analysis of *LMX1B R246Q*, the milieu of affected genes suggest additional pathogenic mechanisms may exist. The upregulation of *MMP* genes as well as a downregulation of critical basement membrane genes including *SULF1* and *COL3A1* suggests that glomerular basement membrane (GBM) modification is a key component of *R246Q* mediated renal disease.

Funding: NIDDK Support

SA-PO677

CD44 Isoform Status Predicts Response to Treatment in Childhood Nephrotic Syndrome

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Background: Standard CD44 (sCD44) and variant (vCD44) isoforms are hyaluronic receptors, known as stem cell markers that play a role in stem cell activation, migration, and shaping of extracellular matrix and fibrosis. De-novo expression of CD44 is a marker of activated glomerular parietal cells (PECs), which predicts the development of focal segmental glomerulosclerosis (FSGS). Upregulation of CD44 in nephrotic syndrome (NS) has been linked to poor prognosis in minimal-change disease (MCD) and has been shown to be an early marker of glomerular sclerosis prior to the development of visible lesions by light microscopy. Multiple CD44 isoforms are known to produce by alternative RNA splicing with different functions related to cell-cell, cell-matrix interaction and also to renal fibrosis, however, there are no reports on which isoforms are expressed on activated PECs in NS and whether changing profile of CD44 isoforms expression is associated with renal disease progression. This study was addressed to investigate the role of different CD44 splicing variant isoforms expression in pediatric kidney biopsies of steroid responsive vs steroid resistant NS.

Methods: Here we investigate the expression patterns of CD44S (which does not contain any alternative exon) and CD44 splice variants using rtPCR in RNA isolated from formalin-fixed, paraffin-embedded (FFPE) of renal biopsies from children with nephrotic syndrome (n=40) versus normal kidneys (n=12), all were treated in our department.

Results: The expression of CD44S and CD44 splice variants CD44v2, CD44v6, and CD44v9/10, were significantly higher in NS kidneys compeerd with normal kidneys and were negatively correlated with disease progression and overall immunosuppressive response. In contrast, there was no significant difference in the expression of CD44v3, CD44v4/5, and CD44v7.

Conclusions: These data indicate that certain standart CD44 and CD44 splice variants may contribute to NS pathology and to disease progression and glomerulosclerosis.

SA-PO678

Response to Glucocorticoids Remains a Valid Approach to Initial Evaluation of Children with Idiopathic Nephrotic Syndrome

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Background: The therapeutic approach to childhood Idiopathic Nephrotic Syndrome (INS) is based on the ISKDC and APN studiesfrom the 1960's and 1970's. Because most patients had minimal change disease (MCD) sensitive to glucocorticoids, the therapeutic response to the medication was recommended for initial evaluation and therapy. Since the 1990's, several single-center studies have reported greater frequency of resistance to glucocorticoids among MCD patients and of Focal Segmental Glomerulosclerosis (FSGS). The trend is concerning, causes are unknown, and data are limited. Although initially considered a resistant lesion, more aggressive therapy can induce a response in more than 50% of FSGS patients. However, unnecessary exposure to long-term glucocorticoid therapy in resistant patients may cause side effects without a benefit. Our objective was to determine whether response to glucocorticoids remains a valid approach to initial evaluation of INS children.

Methods: A retrospective review identified 110 patients with INS treated at our center. Glucocorticoid doses and definitions of steroid sensitive (SS) and steroid resistance (SR) INS were according to ISKDC. Statistical analysis was performed by fisher exact test.

Results: The mean age was 5.9 years with equal number of males and females. Caucasians (80%) and African Americans (15%) were the predominant ethnicities. The proportion of SRINS in our study was higher, compared to ISKDC (33% vs. 20%). However, it has not been increasing with time (35% during 2003-2007 compared to 30% during 2008-2012). MCD was almost 3 times as common among the SRINS patients in our study, compared to ISKDC (52% vs. 18%). FSGS was similar among SRINS patients, compared to ISKDC (39% vs. 36%). Among patients with kidney biopsy, SSINS characterized 77% of MCD and 42% of FSGS, compared to 93-98% and 17-30% in the ISKDC studies.

Conclusions: In summary, despite the changing characteristics and different study populations, the therapeutic response to glucocorticoids is a valid approach for the initial evaluation and therapy for INS children at our center. An international study would help to monitor the changing characteristics and elucidate the role of patient demographics, ethnicity, and environmental factors that cannot be assessed by smaller studies.

Funding: Clinical Revenue Support

SA-PO679

Pioglitazone (Pio) in Pediatric Nephrotic Syndrome (NS)

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Introduction: Thiazolidinediones (TZD) may exert direct protective effects on injured podocytes. PPARγ agonists have been shown to reduce proteinuria in adults with non-diabetic kidney disease. We report our experience with off label, adjuvant use of Pio in pediatric patients with NS.

Case Description: Case 1 A 4 yr old boy was diagnosed with steroid resistant NS (biopsy minimal change). Despite ongoing treatment with prednisone (Pred), lisinopril, tacrolimus, mycophenolate (MMF), losartan, rituximab (Ritux), and Acthar he required twice weekly admissions for diuresis. Pio 15 mg/day was added and increased after 4 wks to 30 mg/day. U P/C decreased from 6 - 8 to 0.2 - 1 mg/mg over the next 7 months and cumulative immunosuppression was decreased considerably. Case 2 A 13 yo female with obesity was found to have NS (Ur P/C 11 mg/mg, S_{Alb} 1.7 g/dL, S_{creat} 0.56 mg/dL), normal C3, and negative ANA. Biopsy showed collapsing FSGS. Glomerular size was normal. She was treated with Pred 40 mg, valsartan 80 mg, simvastatin 20 mg, and Pio 15 mg daily. After 7 wks, U P/C was 3.8 mg/mg and edema had resolved. Pred was decreased to 20 mg and Pio increased to 30 mg daily. After 6 months of treatment, U P/C was 0.5 mg/mg. Case 3 A 6½ yo boy was diagnosed with NS and renal dysfunction after 3 months of intermittent edema (4+ proteinuria, S_{Alb} 1.2 g/dL, S_{creat} 0.93 mg/dL [eGFR 51 ml/min/1.73 m^2]). He was born at 29 weeks gestation with a single right kidney. After 1 1/2 weeks of Pred 2 mg/kg/day, he was readmitted with anasarca and worse renal dysfunction (S_{creat} 2.02 mg/dL [eGFR 24 ml/min/1.73 m^2]. Biopsy showed collapsing FSGS. HIV and parvovirus evaluations were negative. Pred was continued and daily Pio 7.5 mg and pravastatin 20 mg were added. He received 2 doses of Ritux. Renal dysfunction progressed and he required dialysis 3 wks later, 6 ½ wks after presentation. During Pio, blood glucose ranged 93 – 159 mg/dL. Case 4 A 5 yo boy was diagnosed with steroid sensitive but dependent NS. Addition of MMF did not allow Pred taper which was kept at 30 mg/d. Pio 15 mg daily was added for 16 weeks. During this time, Pred was successfully tapered to 5 mg qod while maintaining remission.

Discussion: In pediatric NS, the addition of Pioglitazone may improve proteinuria and allow reduction in corticosteroid and other immunosuppressant medications. In this case series, no hypoglycemia or other adverse events occurred.

SA-PO680

Initial Steroid Resistance Is Not Predictor of a Worst Prognosis in Children with Nephrotic Syndrome Sensitive to Calcineurin Inhibitors

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Background: Children with steroid resistant nephrotic syndrome (SRNS) have a high risk of progressing to end-stage renal disease (ESRD). While Calcineurin inhibitors (CNIs) effectively induce remission in >30% patients, long-term management of SRNS presents a significant clinical challenge. Very little is known about the evolution of SRNS in children, prognosis and the potential role of cortisteroid for relapse(s).

Methods: We performed a retrospective observational study of all paediatric patients treated with CNI for SRNS at our institution between 2008 and 2018. The data was collected about remissions achieved with CNIs, subsequent relapses, their treatment and remission, and long-term renal function.

Results: 54 patients were included (41% males), with a median age of 12.5 years. After a median follow-up of 49 months, 38/54 patients (70.37%) achieved remission with CNIs, while the remaining 16 patients (29.63%) were unresponsive.18/38 patients (47.4%) had one or more relapse(s), (range:1-7). The total number of relapses was 48, out of which, 46 (95.8%) achieved remission. Of these, 38/46 (82.60%) were treated with corticosteroids only, 2/46 were treated with an increased dose of CNI only (>50% of initial dose), 5/46 (10.87%) were treated with both increased CNI dose and corticosteroids, and 1 patient achieved remission with mesenchymal stromal cell infusion. In total, 43 relapses were treated with steroids and 41 of these achieved a new remission. 2/48 relapses did not achieve remission despite different lines of treatment, but none had an impairment of renal function.

Conclusions: SRNS patients responsive to CNIs appear to have a good long-term prognosis, with no patient developing chronic kidey disease after a median follow-up of 49 months. 41/43 (95.3%) relapses were sensitive to corticosteroid therapy, despite the patient being SRNS at the onset of the disease. Therefore, corticosteroids can be considered an option for relapses of SRNS patients sensitive to CNIs. Steroid-sensitive and steroid-resistant NS responsive to CNIs are essentially a part of the spectrum of the same disease.

SA-PO681

Oval Fat Bodies in Urinary Sediment Microscopy Can Be a Convenient Prognostic Marker for Idiopathic Nephrotic Syndrome in Children

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Background: Recently, genetic testing for steroid-resistant nephrotic syndrome has been applied to diagnosis and treatment, but it is not a simple test because of the time and cost. Meanwhile, urine microscopy is the oldest and one of the most commonly used tests for diagnosis of kidney disease. It is generally considered that oval fat bodies and fatty casts in urine sediments are seen in nephrotic syndrome, but in fact oval fat bodies and fatty casts are rarely detected in pediatric idiopathic nephrotic syndrome, and sometimes they are detected in steroid-resistant nephrotic syndrome. However, the significance of oval fat bodies and fatty casts in pediatric idiopathic nephrotic syndrome has rarely been investigated. In this study, we investigated whether oval fat bodies and fatty casts could be a prognostic predictor of steroid-resistant nephrotic syndrome in children with idiopathic nephrotic syndrome.

Methods: We retrospectively reviewed medical records of pediatric patients with idiopathic nephrotic syndrome who were being treated at our department. The study items were steroid sensitivity in the nephrotic syndrome, the grade of CKD, and the presence of oval fat bodies and fatty casts in the urine sediments at the onset and recurrence.

Results: Of the 45 patients, 11 had oval fatty bodies and/or fatty casts. These sediments were present in 8/13 (62%) of patients with steroid-resistant nephrotic syndrome versus only 3/32 (13%) of patients with steroid-sensitive nephrotic syndrome. In patients with CKD, they were observed continuously in all patients, while in those with steroid-sensitive nephrotic syndrome, they were observed only once or twice.

Conclusions: In children with idiopathic nephrotic syndrome, those who continue to have oval fat bodies or fatty casts are more likely to be steroid-resistant and have a poor kidney prognosis. In the present study, oval fat bodies and fatty casts in the urine sediment were found to be poor prognostic markers in children with idiopathic nephrotic syndrome.

SA-PO682

A Pilot Study of Urinary Podocyte-Derived Microparticles (MP) as a Marker for Podocyte Injury in Youth with Type 1 Diabetes

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Background: Podocyte injury plays a crucial role in the development of diabetic nephropathy. Recent animal and clinical studies have shown that podocytes release microparticles under conditions of stress, and may be an early marker of podocyte injury.

Our objectives were to assess MP in youth with Type 1 (T1DM) and healthy controls (HC), and investigate associations with clinical characteristics, including glycemia and renal function. We included youth with T1DM (n= 53), mean age of 14.7 ±1.6 years and age matched (12.9±1.9years) healthy control (HC) subjects, (n=52).

Methods: MP were extracted from first am urine, processed immediately and frozen. MP were identified as of podocyte origin by co-labelling with Annexin V and Podoplanin. ACR was measured on two sets of first morning samples, albuminuria defined as >3.5mg/mmol in males and >4mg/mmol females. eGFR was calculated using the Larsson Equation, previously validated in the Type 1 population. MP numbers were normalised to urinary creatinine (MP/umol Cr). Data distribution was skewed, so groups were compared using non parametric analyses, and expressed as median (IQR).

Results: There was no difference observed in MP number between T1DM with no albuminuria, T1DM with albuminuria and HC 8.28 (8.87), 6.39 (8.90), & 10.39 (8.93); p=0.1530. Unexpectedly, there was only a modest positive correlation between MP number and blood glucose levels (r=0.21, p=0.04) in the T1DM subjects, and trends for MP number and eGFR (r=0.25, p=0.07). A modest positive correlation was also seen for HDL level (r=0.30, p=0.03). There was a more robust negative correlation with serum uric acid (r= -0.46, p=0.0007). Finally, MP number correlated with the urinary albumin excretion rate (r = 0.48, p=0.0029) in T1DM, but only in subjects with normal albumin excretion rates.

Conclusions: Podocyte-derived MP numbers are similar in youth with early T1DM and age-matched healthy subjects, although within the T1DM cohort, MP numbers associate with both glycemia and ACR. These findings suggest that podocyte injury cannot be detected by MP enumeration in the urine at this early stage of diabetes. Future will be necessary to define changes in podocyte MPs over time and their relationship to long term kidney outcomes.

SA-PO683

Urine Exosome Protein Signatures Differentiate Disease Type and Activity in Children with Steroid-Resistant Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) is an etiologically and prognostically heterogeneous condition. In 40-50% of children with SRNS remission is achieved by intensified immunosuppressive (IIS) therapy, 20-25% suffer from hereditary podocytopathies, and 30-40% turn out multidrug resistant (MDR) without an identifiable genetic cause. Long-term renal outcomes are excellent for IIS, poor for genetic, and intermediate for MDR-SRNS. No biomarkers differentiating these entities early in the disease course are available to date. Urinary exosome analysis is a promising non-invasive methodology to obtain information about pathobiological processes in the cells lining the nephron.

Methods: Urine samples were obtained from patients with IIS-SRNS (n=4) and MDR-SRNS with or without an identified genetic cause (n=4 each). IIS patients were studied both during relapse and in remission. Exosomes were isolated by ultracentrifugation followed by size exclusion HPLC. Protein isolates were digested with trypsin and LysC, labeled with isobaric tags (TMT 10-plex) and subjected to two-dimensional LC-MS analysis. Ingenuity software was used to identify enriched pathways and functions.

Results: We identified 2,713 proteins with high confidence in urinary exosomes. Comparison of samples from patients with active disease (IIS-relapse/MDR/genetic) vs remission yielded 739 differentially abundant proteins, respectively, with glomerular and tubular cell damage as the most prominent disease functions. Exosomal fractions from active IIS and MDR/genetic patients differed in 124 proteins (most prominently of complement and coagulation pathways and proteins indicating glomerular and proximal tubule damage), whereas only 16 proteins were differentially abundant in MDR with and without an identified genetic cause. Biomarker filter analysis for individual proteins discriminating between disease states yielded highly significant candidates.

Conclusions: Urinary exosome analysis is technically feasible and provides a reflection of disease-related tissue alterations on the proteome level. The deregulated molecular pathways identified in this study might allow to differentiate etiologically and prognostically distinct entities in SRNS.

SA-PO684

Obinutuzumab in Pediatric Idiopathic Nephrotic Syndrome Resistant to Rituximab

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Background: B-cell depletion with rituximab (RTX) induces sustained remission in children with Steroid Dependant or Frequent Relapsing Nephrotic Syndrome (SD/FRNS). However, most patients relapse after B-cell recovery and some patients do not achieve B-cell depletion. Obinutuzumab (OBZ) is a 2nd generation glycoengineered anti CD20 monoclonal antibody, with higher in vitro B-cell cytotoxicity, that might be more effective in patients with autoimmune diseases. We report the results of a pilot study of OBZ in pediatric patients with FR/SDNS aiming at assessing both the safety and efficacy of OBZ in patients with prior resistance, intolerance or failure to rituximab.

Methods: Patients received an infusion of 300mg/1,73m^2 of obinutuzumab, after premedication. All other immunosuppressive therapies were discontinued within two months, and biological monitoring performed monthly until B-cell recovery.

Results: 12 patients with SD/FRNS were included and followed for a median duration of 8.0 months [IQ 5.9-12.1]. Median ages at INS onset, first RTX and first OBZ injection were of 3.8, 8.8 and 9.3 years old, respectively. Indication for OBZ were intolerance to RTX (n=1), no B-cell depletion (n=4) or short depletion <3 months (n=4) or early relapse after prolonged B-cell depletion (n=3). B-cell depletion was achieved in all patients. At last follow up, B-cell recovery had occurred in 7 patients after a median depletion of 6 months [IQ 5.2-7.9]. B-cell depletion after OBZ was longer in all patients compared to prior RTX (p = 0,0013). 6/7 patients remained relapse-free with median follow up of 3.6 months after B-cell recovery. Mild infusion reactions were reported in 3/12 patients. Neutropenia within 500-1000/mm^3 occurred in 3/12 patients. 2 patients received IV immunoglobulins because of hypo-IgG and 5 patients had hypo-IgM. One patient was hospitalised for pneumonia, with negative bacterial and viral testing and improved with antibiotics.

Conclusions: Obinutuzumab induced peripheral B-cell depletion in SD/FRNS patients resistant to rituximab. A single low dose injection resulted in longer B-cell depletion compared to rituximab. However, short term and long term immunological and infectious side effects have to be closely monitored.

SA-PO685

Bloody Diarrhea and Shiga Toxin-Producing Escherichia coli Infection in Children: Data from the ItalKid-HUS Network

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Background: Shiga toxin-producing Escherichia coli (STEC) are responsible for STEC-HUS. The few days before the development of the renal complication, when bloody diahrrea (BD) is the only symptom, represent a window of therapeutic opportunities for preventing or mitigating HUS.

Methods: In order to identify patients at risk for HUS early in the course of the disease, a network connecting >60 pediatric hospitals in Northern Italy (12 millions gp; 2.3 million children) has been developed since May 2010, aimed at identifying patients with STEC infections with the aim of an early management of the severe renal complication. Children (<18 yrs old) with BD were centrally screened for the presence of Stx genes in stools using a Reverse Dot blot assays (Genotype EHEC-Arnika) until 2018 and Real-Time PCR (RIDA Gene-Relab) thereafter.

Results: Out of 4239 analyzed samples, 216 (5.1%) were positive for Stx (1: 63 (29.2%), 2: 92 (42.6%) and 1&2: 61 (28.2%)). Forty patients (0.9% of BD) developed HUS (Stx1 alone was found in 1 eHUS only). The most frequent serogroup identified was the O26 (29%), followed by the O157 (19%) and the other top5 (18%), while a significant proportion were "non top5" (19.7%). In late Summer, the probability that BD is associated with Stx, increases from the year average of 5.1% to around 15%. BD was more common in younger children (85% of cases < 10 yo) but the likelihood that BD was caused by STEC infection was not different in different age groups. Finally, the probability of developing HUS in case of STEC infection decreases with age.

Conclusions: The present analysis provides important information about the epidemiology of BD and gives the evidence that STEC is everything but a rare cause of BD that should therefore always be screened for Stx given the severity of its complication.

Funding: Private Foundation Support

SA-PO686

Disease Risk Among Family Members of Patients with aHUS Carrying Complement Regulatory Gene Abnormality

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Background: Atypical hemolytic uremic syndrome (aHUS) is a severe thrombotic microangiopathy mainly due to mutations in complement regulatory genes (MCRG) with a dominant pattern (heterozygous can exhibit the disease) but incomplete penetrance thus a number of healthy carriers (HC) can be identified in any family of aHUS patients but it is not clear which, when or why HC will eventually turn into patient. Patients with aHUS referred to our Center are screened for all of the known MCRG and once a genetic

abnormality is identified, the search is extended to all the at-risk family members interested in being tested.

Methods: Among all the patients with primary aHUS diagnosed at or referred to our centre, only those with a documented MCRG and their relatives were included: 276 subjects (141 females) with 104 aHUS patients and 172 HC, from 75 families.

Results: Fourteen families(18.7%) experienced multiple cases, 9 subjects had multiple mutations. The mean age at presentation (for patients) or at the time of analysis was 35.2+24.1 years. Over a cumulative observation period of 6408 patient-year, only 29 family members carrying gene mutations experienced aHUS (overall penetrance of 14.4%) leading to a disease rate of 4.5 events for 1000 patient-year. The disease rate was 13.4 among siblings, 10.7 among offsprings and only 3.5 among parents.

Conclusions: In conclusion, the overall penetrance of aHUS seems a lot lower than previously reported, the risk of developing the disease in any given relative carrying MCRG is low but it is not equally distributed among generations: siblings and the offspring of patients have a much greater disease risk compared to parents. This piece of information is very important for genetic counseling and clearly supports the concept of a second hit as a cofactor of aHUS which, most likely, should be searched for in the parent who does not carry the MCRG.

Funding: Private Foundation Support

SA-PO687

Biomarkers of Disease Activity in Childhood-Onset Lupus Nephritis

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Background: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects children and adults, but is more severe and more often involves the kidneys in children. The traditional clinical signs of renal injury do not adequately reflect kidney histology in lupus nephritis (LN), but repeating biopsies frequently is not practical. In adults with LN urine levels of CD163 and epidermal growth factor (EGF) correlate with histologic activity and chronic damage, respectively. These putative biomarkers were examined in a cohort of SLE patients from the Midwest Pediatric Nephrology Consortium.

Methods: Urine was collected prospectively from 37 pediatric patients with active LN, 27 with active extra-renal lupus, and 34 with inactive SLE. Urine CD163 (uCD163) and urine EGF (uEGF) were measured by ELISA and analyzed using JMP14 Pro.

Results: uCD163 was higher in children with active LN compared to those with active non-renal lupus and inactive disease (p=0.0011, p=0.0004, respectively). uCD163 fell significantly in patients who had a complete renal response or in whom renal inflammation resolved on repeat biopsy after 6 months of treatment (328±350 ng/mg urine creatinine vs 15±31 ng/mg, P<0.03). uCD163 correlated with the biopsy NIH activity index (r^2=0.452, p=0.002), and specifically capillary hypercellularity, WBC infiltration, hyaline deposits, karyorrhexis, and interstitial inflammation. uCD163 did not correlate with chronic damage. uEGF was significantly lower in children with active LN compared to those with active non-renal lupus and inactive disease (p=0.0008, p=0.0004, respectively). In patients with eGFR <60 ml/min/m^2 uEGF was 24±8 ng/mg compared to 129±44 ng/mg in those with eGFR >60 (p<0.0001). In the patients with eGFR <60, the biopsy chronicity index (CI) was 0 (n=2), 2 (n=1), 3 (n=1). uEGF did not correlate with CI, interstitial fibrosis, or tubular atrophy. uEGF tended to increase in treated patients as eGFR improved (p=0.06).

Conclusions: uCD163 reflects histologic activity in pediatric patients with LN. In children uEGF does not reflect histologic chronicity, but appears to be a marker of acute kidney injury.

SA-PO688

Silent Lupus Nephritis vs. Overt Lupus Nephritis in a Pediatric Lupus Cohort

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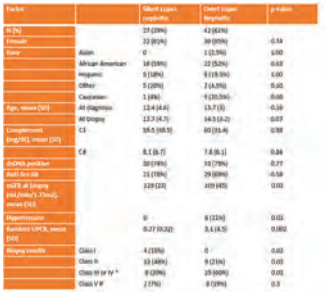
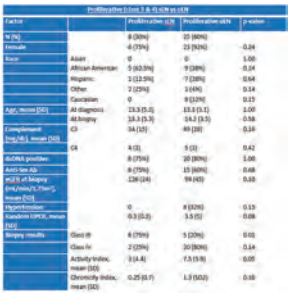
Background: Lupus nephritis (LN) is seen in 20–75% of childhood onset Systemic Lupus Erythematosus (cSLE) and is a predictor of poor prognosis. LN may present with active urinary sediment and/or renal impairment (overt LN- oLN) or be apparent only upon renal biopsy (silent LN-sLN). There is limited data regarding sLN in pediatric lupus. We describe and compare features of sLN and oLN.

Methods: Our retrospective review included patients followed at the University of Florida, Gainesville, diagnosed with cSLE < 18 years of age (≥ 4/11 ACR and/or ≥ 4/11 SLICC classification criteria) who underwent renal biopsy between January 2011 and October 2018. Continuous variables were compared using Student's t test and categorical variables were compared using Fisher's test.

Results: Out of 69 patients, 39% (n=27) were found to have sLN and 61% (n=42) had oLN. The most common histopathology [ISN/RPS] was Class II LN in sLN group (48%, n=13) and proliferative Class III/IV LN in oLN group (60%, n=25). However, 30% (n=8) of sLN had proliferative LN [Class III/IV]. The two groups had similar demographic features. Most of the patients were African American in both groups. There was no significant differences in C3, C4 levels and anti ds-DNA titers. Patients with oLN had more hypertension (p=0.01), deceased eGFR (p=0.03) and higher UPCR (p=0.002) when compared to sLN group. (refer to tables).

Conclusions: In our pediatric cohort, 39% were found to have sLN and 30% of them had proliferative LN, which was more prevalent in African American females with low C3. Renal biopsy should be considered in patients with very low C3 and before development of renal manifestations like hypertension, and decreased eGFR. However, more studies are needed to see if early diagnosis and treatment would modify the long-term renal outcomes.





SA-PO689

Clinical Characteristics and Risk Factors for Thrombotic Microangiopathy in Children with Lupus Nephritis

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Background: Thrombotic microangiopathy (TMA) presents with the most severe clinical manifestations and high mortality. The aim of this study is to find the risk factors for TMA in children with lupus nephritis (LN) after analyzing their clinical characteristics.

Methods: We retrospectively reviewed the clinical data of 12 LN patients complicated with TMA hospitalized from January 2006 to December 2018.

Results: TMA occurred in 8.28% (12/145) of the hospitalized patients with LN. Four patients were boys and 8 patients were girls. One boy was 6-year-old and the other 11 patients were from 11 to 18-year-old. Their SLEDAI scores ranged from 14 to 31, 92% of them were in severe activity. Renal biopsy was performed in 11 patients, and the results of renal pathology showed all of them had type IV or type IV plus type V LN (type IV, n=8; type IV+V, n=3). All the patients were diagnosed with TMA within 1 week to 2 months after admission. At the beginning of the hospitalization, seven of them (58%) had both anemia and thrombocytopenia, while 5 patients (42%) only had moderate anemia. All of them had obvious hypocomplementemia. Especially in all of the 8 patients with first onset of SLE, there serum levels of C3 were lower than 0.18g/L and C4 were lower than 0.07g/L. Moreover, GFR of them were much lower than normal range. Most of the patients had heavy proteinuria (11/12) and positive anti-ds-DNA antibody (10/12). All of the patients accepted the treatment of methylprednisolone pulse therapy, ten of the them were treated with cyclophosphamide, five patients were treated with plasmapheresis (PE). After 6 months of treatment, five patients obtained complete response, five patients obtained partial response. One patient relieved after 3 times of PE but died during the fourth PE may because of intracranial hemorrhage. The other patient was unwilling to accept renal biopsy and the diagnosis of TMA was not confirmed until 2 months after onset. Although she was treated with PE for 10 times and two doses of Rituximab, she deteriorated continuously.

Conclusions: Children with LN complicated with TMA are mostly in severe disease activity, and the main pathological change of them is type IV LN. Anemia and extremely low level of serum complement occur simultaneously maybe the risk factors for TMA in children with LN whether they have thrombocytopenia or not.

SA-PO690

Recapitulating Shiga Toxin-Mediated Renal Injury in Engineered Microvessels

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Background: Hemolytic-Uremic Syndrome (HUS) presents as a severe form of thrombotic microangiopathy (TMA), and the endothelial injuries that precipitate HUS/TMA are caused by a wide range of insults, including metabolic, immunologic, pharmacologic, and infection-associated etiologies. Shigatoxin-producing E. Coli HUS (STEC-HUS) is an infectious TMA that results in renal injury, leading to AKI, permanent renal damage and death, and is the leading cause of dialysis initiation in otherwise healthy children. Despite severe long-term consequences with STEC-HUS, no targeted therapies to-date have demonstrated any clinical benefit. Use of perfusable vascular models previously developed in our lab provide physiologically relevant platforms to evaluate specific cellular injury mechanisms responsible for the endothelial injury in STEC-HUS. These models also provide a well-controlled and efficient platform for evaluating novel therapeutic interventions.

Methods: Human primary renal endothelial cells were treated with Stx1 and Stx2, the principal toxins responsible for STEC-HUS, and evaluated for cell death, cell injury, and morphology. Studies were performed in both 2D tissue culture and 3D microvessel platforms.

Results: Treatment of isolated human primary renal endothelial cells with either Stx1 or Stx2 demonstrated effective binding, toxin internalization and death. Significant increases in both apoptosis and necrosis were appreciated in a dose-dependent manner in these microvascular cells, with non-renal endothelial cell lines demonstrating insensitivity to Stx1 or Stx2 treatment at equivalent or higher doses. Engineered microvessels using primary renal endothelial cells were generated and maintained under flow for several days. In these models, treatment with Stx1 and Stx2 demonstrated effective binding to luminal endothelia, with evidence of a greater degree of endothelial injury and endothelial denudation observed with Stx2 than Stx1.

Conclusions: Human primary renal endothelial cells exhibit dose-specific responses to Shigatoxin consistent with clinical presentation of STEC-HUS. Notably, engineered renal microvessels also exhibited endothelial injury consistent with Shigatoxin toxicity. Ongoing phenotypic and transcriptional studies will use these models to delineate the specific injury pathways responsible for endothelial injury that result in vascular damage and progression to TMA.

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SA-PO691

Immunostaining for Galactose-Deficient IgA1 in Routine Kidney Biopsies

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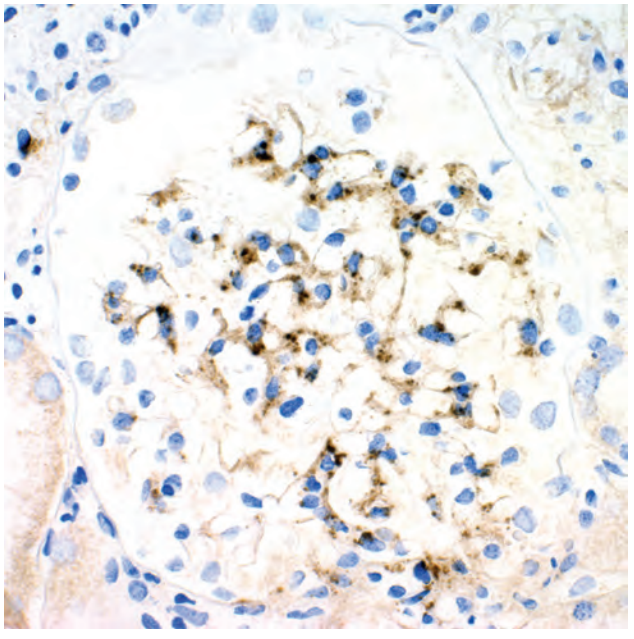
Background: Recently, an antibody against galactose-deficient IgA1 (gdIgA1) became commercially available. Very little is known about the specific staining patterns of this KM55 antibody in routine diagnostics. Here we report the staining pattern in routine native and transplant biopsies with various forms of IgA-codominant glomerulonephritis and controls.

Methods: We established a protocol for formalin-fixated paraffin embedded (FFPE) tissue with protease antigen retrieval (Fast Enzyme, Zytomed Systems, Germany). Primary antibody KM55 was incubated overnight at 1:5 dilution and visualized with a standard peroxidase system and reported as 0, 1+, 2+, 3+ on 58 consecutive renal biopsies with IgA-codominant glomerular staining (50 native, 8 transplant) and controls (7 IgM glomerulopathy, 3 infectious associated glomerulonephritis) together with immunostaining for IgA1 and IgA2.

Results: 26/43 (60%) primary IgA-GN (pIgA-GN), 7/9 (78%) Henoch-Schönlein Purpura (HSP) and 2/4 (50%) cirrhotic IgA-GN (cirrhIgA-GN), 0/1 (0%) staphylococcus-associated GN (staphGN), 0/1 (0%) monoclonal IgA-GN were positive for gdIgA1. IgA1 was dominant over IgA2 in 40/43 pIgA-GN, 7/9 (78%) HSP, 4/4 (100%) cirrhIgA-GN, 1/1 (100%) staphGN; IgA2 over IgA1 in 1/43 (2%) pIgA-GN, 0/9 (0%) HSP and 0/4 (0%) cirrhIgA-GN. gdIgA1 was negative in all controls. Repeat biopsies in transplants showed consistent staining.

Conclusions: We report an immunohistochemical staining method for gdIgA on FFPE kidney biopsies. Together with serum tests for gdIgA1 and anti-gdIgA1 autoantibodies, this ancillary staining method could be useful for a pathogenesis-driven classification of glomerular diseases with IgA-codominant deposits.



3+ mesangial staining (brown) for gdIgA1 in a FFPE biopsy which was classified as primary IgA-GN. Immunoperoxidase, original magnification x400.

SA-PO692

Circulating Endothelial Microparticles and Correlation with MEST-C Scores in IgA Nephropathy

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Background: Renal endothelial injury or activation can lead to a cascade of pathways that contribute to loss of renal function and fibrosis. Recent reports suggest that endothelial injury may play a role in the pathophysiology of IgAN. Microparticles (MPs) are 0.1 to 1.0 μm membrane vesicles shed from the damaged or activated cell surface following injury. Microparticles derived from endothelial cells are called endothelial microparticles (EMPs) and play an important role in promoting endothelial dysfunction. They can act as biomarkers of disease state and progression. The aim of this study was to study the presence and quantify the levels of circulating MPs of endothelial origin in plasma from patients with IgAN and healthy controls.

Methods: 25 biopsy-proven IgA nephropathy (Mean age=32.8±8.2 years) and 25 healthy controls (Mean age=30±7.6 years) were recruited in this study. Platelet-poor-plasma from citrated blood was isolated and centrifuged at 20,000g (90 min) at 4 degree C. EMPs were analyzed by Flow cytometry using EMP specific antibodies for antiCD31-FITC and antiCD146-PE. All quantification related to size and number was done by using cell count beads of known concentration. The levels of circulating endothelial MPs were correlated with renal biopsy features of the Oxford classification (MEST-C scores). The study was reviewed and approved by the Institutional Ethics Committee.

Results: There are significantly higher levels of total circulating MPs and EMPs in IgAN compared to healthy controls ($p<0.05$). EMPs levels were increased in patients with hypertension and correlated with presence of mesangial and endocapillary hypercellularity ($p<0.05$) on renal biopsy (Table 1).

Conclusions: IgAN shows evidence of significant endothelial injury/dysfunction. A non-invasive method of detection of levels of circulating EMPs can predict the severity of glomerular injury and may be a simple method useful for monitoring endothelial injury in IgAN.

Funding: Government Support - Non-U.S.

Table 1. Correlation of Circulating Endothelial Microparticle (EMP) counts with MEST-C scores in IgAN

MEST-C score on Renal Biopsy	MPs/μl plasma	Circulating EMPs/μl plasma (CD31+/CD146+)	P value
Mesangial Proliferation M0 M1	105±12 187±107	21±2.8 44±27	0.04
Endocapillary Proliferation E0 E1	141±49 242±141	31±14 60±33	0.001
Segmental sclerosis S0 S1	168±93.3 188±116	40±26 43±26	0.614
Tubular Atrophy Absent Present	126±34 156±89	37±13 44±29	0.433
Crescent Absent Present	164±82 200±140	39±26 45±27	0.512

SA-PO693

Histological Classifications in IgA Nephropathy Should be Considered for Predicting Not Only Renal Functional Decline but Also Treatment Response

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Background: In IgA nephropathy, Oxford classification (Oxford) (MESTC) and Japanese Histological Grade Classification (JHGC) (Gr1-Gr4, A: active crescent, C: global or segmental sclerosis) are evidence-based classification, which have been produced for predicting renal functional decline (RFD). However, clinical parameters are also selected as independent parameters besides histological parameters for RFD. The purpose was to detect the histological parameters, which show a significant correlation with these clinical parameters, because the detected histological parameters can be main indicators for the choice of therapy.

Methods: The 906 Japanese patients with IgA nephropathy (male : 49%, median age: 38 yrs) were prospectively followed for a median of 62 months. First, histological and clinical parameters were evaluated by multivariate Cox regression analysis for 1.5 time's increase of serum creatinine to find clinical independent parameters. Thereafter, structural equation modeling (SEM) (STATA, Light Stone, USA) was used to find histological parameters which correlate with the independent clinical parameters for RFD.

Results: Besides M, T1, T2 in Oxford and Gr1-Gr4 in JHGC as the independent histological parameters, amount of proteinuria at renal biopsy (PU0) and steroid therapy (ST) were selected as the independent clinical parameters in both classifications. In SEM, histological parameters which correlated with ST were S(coefficient 0.10), C1(0.20), C2(0.30), and E(0.11)in Oxford and AorA/C(0.27)in JHGC for renal functional

improvement (RFI: 0.75 in Oxford and 0.81 in JHGC). The histological parameters which correlated with PU0 were C1 (0.39), M(1.08) and eGFR0 (-0.01) in Oxford and Gr3(1.03), Gr4(1.61), eGFR0 (-0.01), AorA/C(0.27)in JHGC for RFD (-0.06 in Oxford and -0.06 in JHGC).

Conclusions: Since S, C1, C2, and E in Oxford and AorA/C in JHGC were treatment's targets for ST resulting in RFI, these histological parameters in each classification are reasonable indicators for a choice of ST. The histological parameters, which correlated with PU0, consisted of ST-related parameters and non-ST related parameters. Therefore, both histological classifications can be more practical considering aforementioned histology-based choice of therapy.

SA-PO694

Validation of the Renal Risk Score for ANCA-Associated Glomerulonephritis

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Background: Recently, Brix *et al*. proposed a clinicopathologic score to predict renal outcome in ANCA-associated glomerulonephritis (AAGN). This score was based on data from 205 German patients. We here show results of a validation study of this risk score in an international cohort of patients.

Methods: This study included 143 adult patients with AAGN from centers in the U.S., Europe and Asia. Percentage of normal glomeruli (>25%, 10-25% or <10%), percentage tubular atrophy and interstitial fibrosis (≤25% or >25%) and estimated glomerular filtration rate at the time of diagnosis (>15 or ≤15) were determined for each patient. Following the risk score, each parameter was assigned points, resulting in a low, intermediate or high risk to develop end-stage renal disease.

Results: At 36 months follow-up, renal survival in our cohort was substantially higher compared to the Brix *et al*. cohort (table 1). Although renal survival differed significantly between the three risk groups (P<0.001), the clinical relevance between low and medium risk is doubtful, being 100% and 96% respectively. In the high risk group, there was a substantial difference in the renal survival of our cohort (77%) in comparison to the reported renal survival from the Brix study (32%). Only one patient from five with the maximum risk score of 11 developed ESRD in our cohort versus all patients with a maximum score in the German cohort.

Conclusions: In this international cohort, we validated the renal risk score proposed by Brix *et al*. and demonstrated significantly different renal survival between the three risk groups. The renal survival in our cohort was much higher than in the cohort from Brix. Their relatively poor renal survival might result from the German practice of early dialysis initiation which questions the applicability of the renal risk score to other populations.

Table 1. Renal survival at 36 months in our cohort and the cohort of Brix et al.

	The present cohort		The training cohort by Brix et al.	
Risk group	N of patients	Renal survival 36 months	N of patiens	Renal survival 36 months
Low (0 points)	6	100%	30	100%
Medium (2-7 points)	90	96%	64	84%
High (8-11 points)	47	77%	21	32%

SA-PO695

The Clinicopathologic Characteristics and Complement Activation of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitides with Glomerular IgA Deposition

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Background: The renal injury caused by anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are characterized by few or no immune deposits in glomerulus. A growing number of AAV patients with glomerular IgA deposits have been reported.

Methods: We retrospectively investigated all AAV patients with glomerular IgA deposits diagnosed in our center. Serum Galactose-deficient IgA1 (Gd-IgA1) level and glomerular Gd-IgA1 and IgA staining were measured. Moreover, we detected complement pathway components in their sera.

Results: A total of 168 AAV patients were enrolled, including 26 patients with glomerular IgA deposition and 142 patients with pauci-immune complex deposition. The AAV patients with IgA deposition had a tendency of lower systemic disease activity, presenting with lower ESR, lower MPO-ANCA, tendency of lower CRP and BVAS. For renal injury, there were no significant differences in clinical data, renal pathological parameters or renal outcome between groups. The serum level of Gd-IgA1 and intensity of glomerular Gd-IgA1 staining in IgA deposition AAV patients were similar with IgA nephropathy patients. All patients in IgA nephropathy group, AAV groups with or without IgA deposition had the activation of alternative complement pathway, while AAV patients with IgA deposition also had the activation of classical complement pathway. Correlation analysis showed serum C1q level correlated directly with serum globulin and IgA levels.

Conclusions: AAV patients with IgA deposition had the basis of IgA nephropathy, and may present lower systemic disease activity. But it differs from pauci-immune AAV or IgA nephropathy by the possible activation of classical complement pathway.

SA-PO696

The Modern Spectrum of Kidney Biopsy Findings in HIV-Infected Patients

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Background: The epidemiology of HIV-associated kidney disease is evolving rapidly. However, few North American studies address modern trends and none has applied the pathologic classification proposed by the 2018 Kidney Disease Improving Global Outcomes (KDIGO) consensus.

Methods: To characterize the modern spectrum, we performed a retrospective analysis of all HIV-positive patients (pts) with kidney biopsy interpreted at Columbia University from 2010-2018 using KDIGO guidelines.

Results: The biopsy cohort of 437 HIV pts had median age 53 years, including 66% male, 78% on anti-retroviral therapy (ART), 27% with hepatitis C (HCV), 6% with hepatitis B coinfection, 57% with hypertension, and 31% with diabetes. Race, known in 308 pts, included 179 African American (AA), 77 White, 51 Hispanic and 1 Asian. The frequency of diabetic nephropathy and immune complex (IC)GN each outnumbered classic HIVAN, followed by tenofovir nephrotoxicity (Table 1). However, classic HIVAN was the most common disease in ART-naïve or noncompliant pts (43%) and associated with AA race (95%). The association of FSGS (NOS) with AA race (62%) and ART (79%) suggests that some FSGS (NOS) may represent an attenuated form of HIVAN. The most common ICGNs were IgA nephropathy and membranous GN, both associating with ART (>90% pts). Of the 26 cases of unclassified ICGN, 54% were not on ART and 54% lacked an identifiable etiology, a subset of which may represent true HIVICK. IgM-dominant ICGN was most common in hypocomplementemic and HCV-infected pts. The presence of dual diagnoses in 88 (20%) pts underscores lesion complexity.

Conclusions: ART is changing the landscape of HIV-associated kidney diseases in the U.S. towards diabetic nephropathy, diverse ICGN and tenofovir nephrotoxicity, but has not eradicated classic HIVAN.

Table 1. Kidney Biopsy Findings in HIV-infected Patients (N=437).

Diagnosis		N (%)
Glomerular-dominant		**190 (43%)**
Podocytopathy		**116 (28%)**
	Classic HIVAN	64 (15%)
	FSGS NOS in the setting of HIV	49 (11%)
	Minimal change disease in the setting of HIV	3 (1%)
Immune complex-mediated glomerular disease		**74 (17%)**
	IgA nephropathy in the setting of HIV	21 (5%)
	Membranous nephropathy in the setting of HIV	14 (3%)
	ICGN NOS	26 (6%)
	Lupus-like nephritis in the setting of HIV	5
	IgG-dominant ICGN	9
	IgM-dominant ICGN	8
	IgG and IgM-codominant ICGN	3
	Other ICGN NOS	1
	Lupus nephritis in the setting of HIV	4 (1%)
	Infection-related glomerulonephritis	4 (1%)
	Fibrillary glomerulonephritis in the setting of HIV	1 (<1%)
	Other IC disease in the setting of HIV (2 cryoglobulinemic GN, 1 C1q nephropathy, 1 PGNMID)	4 (1%)
Tubulointerstitial-dominant		**99 (23%)**
	Tubulopathy associated with tenofovir	54 (12%)
	ATI due to other causes	33 (8%)
	Tubulointerstitial nephritis	12 (3%)
Vascular-dominant		**5 (1%)**
	Thrombotic microangiopathy in the setting of HIV	5 (1%)
Others, in the setting of HIV infection		**143 (33%)**
	Diabetic nephropathy	69 (16%)
	Global glomerulosclerosis NOS	41 (9%)
	Diverse other diseases	33 (8%)

SA-PO697

Clinicopathologic Features and Outcomes of Endocarditis-Associated Glomerulonephritis (ECGN)

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Background: ECGN is a well-documented entity but may be under recognized due to its overlapping features with other glomerulonephridities. The aim of this study was to analyze clinical and pathologic characteristics of patients with ECGN.

Methods: Clinical and renal histopathologic data of 12 patients from a single center with biopsy-proven ECGN from 2009 to 2019 were retrospectively analyzed.

Results: Among the 12 patients with ECGN, all presented with acute kidney injury, the male-to-female ratio was 5:1 and mean age was 60 years. Mean serum creatinine at the time of presentation was 4.8 mg/dL. On urine dipstick, 92% of the patients presented with at least 2+ hematuria and 84% had 1+ proteinuria. There were no known cardiac abnormalities in 7 of 12 patients. The most common comorbidities were cardiac valve disease (42%), intravenous drug abuse (17%), and hepatitis C (8%). Infective bacteria were *Bartonella* (5/12), *Staphylococcus* (4/12), *Enterococcus* (2/12) and *Streptococcus* (1/12). All cases associated with hypocomplementemia (5/10) and/or ANCA antibody (5/10) in the patients tested were found in association with the following bacteria: *Bartonella*, *Enterococcus* or *Streptococcus viridans*. Cryoglobulins were positive in 9 of 11 patients tested. Light microscopy showed either focal or diffuse endocapillary proliferative features in 92% of the cases and 83% of cases showed at least focal necrotizing crescent formation. An active tubulointerstitial infiltrate was seen in 67% of the cases. No cases showed arteritis. Immunofluorescence revealed either dominant or co-dominant C3 staining (10/12 cases) and IgM was the most commonly deposited immunoglobulin with polyclonal 2-3+ staining seen in 58% of the cases. Strong IgM staining was associated with all tested cases of *Bartonella* (5), *Enterococcus* (1) and *Streptococcus* (1). Treatment included long term antibiotics (12/12), heart valve replacement (6/12), immunosuppression (4/12) and dialysis (4/12).

Conclusions: ECGN most commonly presents with AKI. Particularly in subacute endocarditis, positive ANCA serologies and biopsy findings of crescentic GN can lead to missed diagnosis. Strong staining for IgM as well as C3 was seen commonly in cases of ECGN associated with *Bartonella* and other subacute organisms. A high index of suspicion on renal biopsy was important to timely diagnosis as *Bartonella* is not detectable on routine blood culture.

SA-PO698

Gender, Ethnicity, and Outcome in Thrombotic Microangiopathy (TMA) on Renal Biopsy: A Retrospective Study Evaluating the Demographic and Etiologic Spectrum

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Background: TMA is a systemic disease with diverse etiologies, characterized histologically by endothelial injury. Studies have reported an increased incidence and mortality rate in African American (AA) females with TMA. Our study seeks to determine if this finding is reproducible in a population of patients with evidence of TMA on renal biopsy.

Methods: A retrospective search of our pathology data system was conducted to identify all renal biopsies with a diagnosis of TMA from January of 2015 to May of 2018. Groups were analyzed in terms of gender, ethnicity, native versus allograft, presence of associated rejection and cause of ESRD in the allograft population. The presence of ESRD or a doubling of the serum creatinine from the time of the biopsy until the latest follow up date was defined as an unfavorable outcome.

Results: Sixty-six cases were reviewed with the demographic data. Number of total and (allograft) biopsies is shown in the table. There was no statistically significant difference between the groups in terms of gender, ethnicity, unfavorable or favorable outcome, numbers of native versus allograft biopsies or the presence or absence of cell or antibody mediated rejection in biopsies showing histopathologic findings of TMA. However, in allograft biopies, 9/14 males and 2/12 females had ESRD due to HTN and/or DM (p=0.014). Other cases of ESRD in women included scleroderma, SLE, complications of pregnancy, drug toxicity, multiple myeloma and polycystic kidney disease.

Conclusions: In summary, we found that kidney biopsies showing histologic findings of TMA are indeed, more common in AA females, but this was not associated with a significantly worse outcome as the data suggests. We also note that in the transplant population of biopsies with TMA, hypertension and/or diabetes was a more common cause of ESRD in males of either ethnicity, rather than mirroring the general population with a higher preponderance in AA overall. This finding suggests that in women, allograft associated TMA could be related to predisposing factors. Further investigation with a larger cohort is required to support these findings.

Results

	Males (# allograft)	Females (# allograft)
AA	13 (8)	28 (10)
C	14 (6)	11 (2)

SA-PO699

Lithium Nephrotoxicity Is Associated with Dysmorphic Proximal Tubule Cell Lysosomes

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Background: Long term lithium (L) use is associated with tubulointerstitial fibrosis, renal dysfunction and ESRD in select patients. The mechanisms resulting in parenchymal fibrosis are not well understood. We have described proximal tubular cell (PTC) dysmorphic lysosomes (DLs) in calcineurin inhibitor (CNI) toxicity and chronic interstitial nephritis in agricultural communities (CINAC), suggesting this is a marker of tubulotoxic exposure. Similar lysosomes were identified in cases of chronic interstitial nephritis due to lithium toxicity (LT) used as controls for our CINAC studies, prompting further assessment of this finding.

Methods: 9 kidney biopsies from patients with clinical LT were reviewed, Ki67 staining was performed and clinical data were obtained from the medical records.

Results: Patient data are in the Table. 7 patients discontinued L for 0.15 to 31 years prior to biopsy. All biopsies showed tubulointerstitial fibrosis and tubular microcysts diagnostic of LT. 7 biopsies had PTCs with cytoplasmic large DLs containing electron dense aggregates, identical to patients with CINAC and CNI toxicity. Ki67 staining showed no to few positive proximal and distal tubular cells in 8 biopsies, demonstrating reduction in tubular cell proliferation and repair. The 1 patient with moderate numbers of Ki67 positive tubular cells had scattered PTC DLs and had discontinued L 14 years before biopsy, possibly indicating evolving tubular cell repair. The patient off L for 31 years had no DLs or Ki67, suggesting completed recovery from LT.

Conclusions: PTC DLs are a marker of tubulotoxic exposure to L and are associated with a reduction in PTC regenerative capacity. In the setting of LT, PTCs are senescent and the DLs may persist for up to 14 years after drug discontinuation. As tubular cell mitotic arrest has been associated with tubulointerstitial fibrosis, further evaluation of the relationships between DL development, DL cargo, and loss of PTC proliferative capacity may help elucidate mechanisms of L-induced tubulointerstitial fibrosis, which currently are poorly understood.

Clinical and Biopsy Data

PT dysmorphic lysosomes	Age	Gender	Time on L	L stopped before biopsy	Cr (mg/dL)	Tubulointerstitial fibrosis
Yes (n=7)	46+/-18	2M:5F	7->25 yrs	0-14 yrs	1.8+/-0.1	35+/-15%
No (n=2)	67+/-25	2M	15->25 yrs	0-31 yrs	2.8+/-0.8	27.5+/-10.5%

SA-PO700

Renal Oxalosis in Adult Patients: A Relatively Common Entity of Often Unclear Etiology

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Background: The prevalence, manifestation and outcome of secondary oxalate nephropathy have not been extensively studied.

Methods: Retrospectively reviewed kidney biopsy cases with oxalate deposition (7/1/2017-12/31/2018).

Results: The prevalence of oxalate deposition on a kidney biopsy was 4.07%(25/615). Prior to biopsy, oxalate was anticipated in only 1 case. The etiology of oxalosis was clarified retrospectively in 14 cases, most commonly due to GI surgery (n=10) and increased oxalate intake (n=4). In 11 cases, etiology remained unknown, although at least 3 cases were exposed to antibiotics associated with secondary oxalosis. There was no significant clinical/pathological or survival difference between known vs. unknown cause groups. Multivariate COX regression showed that Cr at the time of biopsy (HR1.79,95%CI 0.71-4.51), background histological chronicity change(HR1.82, 95%CI 0.70-4.72) and oxalate density (HR2.27,95%CI 0.49-10.55) are associated with ESRD and patient death(-2LogLikelihood: 20.15 to 16.99, forward selection).

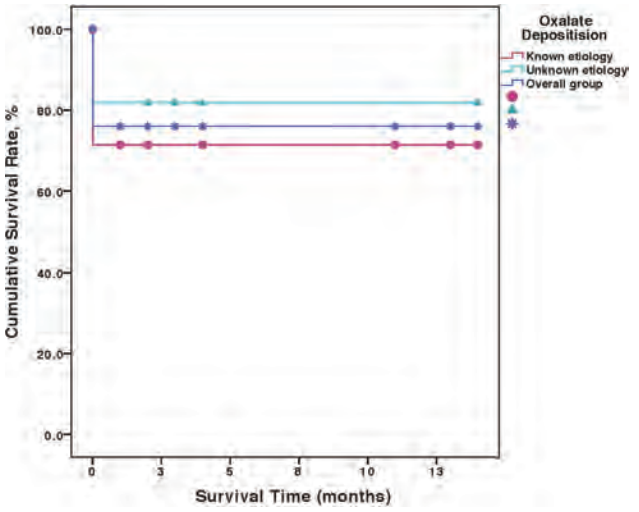
Conclusions: Oxalate deposition is common but rarely anticipated biopsy finding. Nephrologists need to consider surgical history and other secondary causes of oxalosis as causes of AKI and CKD.

Table 1: Clinical and histological characteristics of patients with renal oxalosis

	Overall	Oxalosis with known etiology	Oxalosis with unknown etiology	p
N of patients	25	14	11	
N of renal biopsy	27	14	13	
Age (y)	63.6 ± 9.1	64.6±9.7	62.4±8.5	0.54
Male sex	13 (52%)	6 (42.9%)	7 (63.6%)	0.32
BMI (kg/m^2)	30.6±8.6	29.9±9.3	31.8±8.4	0.64
Diabetic	16 (64%)	10 (71.4%)	6 (54.5%)	0.38
Hypertension	19 (76%)	10 (71.4%)	9 (81.8%)	0.55
Cr at renal biopsy (mg/dL)	6.31±3.23	5.92±3.43	6.86±3.04	0.50
Cr at last follow-up (mg/dL) *	2.86±1.53	2.71±1.59	3.09±1.57	0.66
Follow-up time (months)**	3.1±4.7	3.7±5.1	2.4±4.2	0.48
ESRD or Death	6 (24%)	4 (26.8%)	2 (18.2%)	N.A.
Histological Parameters				
Presence of diabetic nephropathy	8 (29.6%)	6 (42.9%)	2 (15.3%)	0.12
Presence of acute tubular injury	17 (63.0%)	7 (50%)	10 (76.9%)	0.15
Presence of acute interstitial inflammation	9 (33.3%)	3 (21.4%)	6 (46.2%)	0.09
Presence of interstitial fibrosis	3 (11.1%)	2 (14.3%)	1 (7.7%)	0.59
Global sclerosis (%)	26.27±20.60	29.92±20.53	21.90±20.89	0.38
Tubular atrophy (%)	37.27±20.80	47.50±19.25	25.00±15.81	0.01
Mild artery and arteriolar sclerosis	2 (7.4%)	2 (14.3%)	0	0.38
Moderate artery and arteriolar sclerosis	9 (33.3%)	3 (21.4%)	6 (46.2%)	
Severe artery and arteriolar sclerosis	11 (40.7%)	7 (50%)	4 (30.8%)	
Oxalate density (per cm)	15.49±18.68	19.20±23.65	11.45±10.86	0.33

*only patients not progressed into ESRD are included in this calculation.

**time from renal biopsy to the last follow-up or ESRD/death.



SA-PO701

Clinicopathologic Spectrum of Renal Lesions Following Anti-TNF Alpha Inhibitor Therapy: A Single-Center Experience

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Background: Anti-tumor necrosis factor (TNF)-alpha inhibitors, as biological agents, are used in a number of chronic immune mediated inflammatory states such as rheumatoid arthritis (RA), psoriatic arthritis (PA), and Crohns disease. This therapy can induce several autoimmune serologic markers and disorders including systemic vasculitis and lupus-like diseases, which may affect the kidney.

Methods: We studied the clinicopathologic features of kidney disease from our renal biopsy files from 2000-2018 and categorized them into pathogenic groups.

Results: 45 patients using anti-TNF alpha inhibitors had renal biopsies, RA in 30, PA in 6, Crohns disease 7, RA and PA 1, RA and Crohns 1. Among these, 21 received etanercept, 16 adalimumab, 8 infliximab and 4 had 2 kinds of anti-TNF alpha inhibitors. The patients presented mostly with nephritic syndrome or CKD plus 1 case of AKI and 6 nephrotic syndrome. The main renal lesions on biopsy were classified into 3 groups: autoimmune and anti-TNF alpha induced lesions in 15, autoimmune disease-only 8, a variety of renal lesions unrelated to autoimmune or anti-TNF alpha therapy in 22 (diabetic nephropathy, interstitial nephritis, acute tubular injury, infection-related GN). Crescentic glomerulonephritis was seen in 6, 5 being pauci-immune type with 4 ANCA positive serology. Lupus or lupus-like nephritis was diagnosed in 6: ISN/RPS 2018 class II-2, class V-2, class III+V-1, class IV+V-1. Concurrent fibrillary GN, scleroderma renal crisis and renal amyloidosis were noted in 3 cases. In addition, active or chronic thrombotic microangiopathy was noted in 5, possibly associated to scleroderma or antiphospholipid antibodies, and nephrotic syndrome secondary podocytopathy in 2 cases.

Conclusions: The renal lesions during anti-TNF alpha therapy may have an autoimmune basis such as lupus, lupus-like or ANCA mediated disease, as well as secondary to endothelial or podocyte injury or related to the primary underlying systemic disease.

SA-PO702

Pathological Value of Lysozyme Staining for Diagnosing Renal Sarcoidosis

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Background: Sarcoidosis is a systemic inflammatory disease of unknown etiology. Pathological findings of the kidney show interstitial fibrosis with or without granulomatous formation, whereas low detection rates of granulomas make it difficult to diagnose renal sarcoidosis. We have found positive lysozyme staining of kidney tubular cells in sarcoidosis and assessed the diagnostic value of lysozyme staining for sarcoidosis.

Methods: Kidney biopsy specimens of 41 cases of pathological diagnosed tubulointerstitial nephritis (TIN) obtained in Japan Health Care Organization Sendai Hospital between 2013 to 2019 were analyzed retrospectively by immunohistochemistry. Diagnosis of sarcoidosis was made by clinical, radiational, and histopathological examinations. Samples of representative skin sarcoidosis were also stained by lysozyme. Three specimens from sarcoidosis, chronic myelomonocytic leukemia (CMML) and IgG4-related nephritis were analyzed by electron microscopy.

Results: All six cases of sarcoidosis showed positive staining of lysozyme in proximal tubular cells (100%), however, 25 TIN specimens, including drug-induced, IgG4-related, aristolochic acid toxicity, ischemia and Sjogren syndrome showed blunted stains (0%). The specimen of CMML-related TIN, representative of lysozyme-induced nephropathy, showed strikingly positive lysozyme staining in the proximal tubules. Among nine idiopathic TIN, two cases revealed lysozyme positive. These cases did not meet the diagnostic criteria of sarcoidosis clinically, but the possibility of sarcoidosis cannot be denied. In electron microscopy, an increased number of lysosomes in proximal tubules was observed in CMML and sarcoidosis, however, no lysosome was found in IgG4-related nephritis. In skin sarcoidosis, positive lysozyme staining was shown in basal layer of epidermis and dermis while no stain was found in skin samples from different subjects.

Conclusions: Lysozyme staining can aid in the diagnosis of renal sarcoidosis by distinguishing from sarcoidosis to other TIN diseases. Lysozyme induced tubular injury could be an underlying mechanism of TIN in sarcoidosis. In addition, this method could be a useful tool to detect clinically underdiagnosed sarcoidosis including skin and kidney lesions.

SA-PO703

Endothelial Cell Injury Can Be Significant in Cases of Membranoproliferative Glomerulonephritis with Monoclonal IgG Deposition

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Background: Pathological and clinical features of proliferative glomerulonephritis with monoclonal IgG deposition (PGNMID) are not fully revealed. This study focused on glomerular endothelial alterations characterized by plasmalemmal vesicle associated protein-1 (PV-1) and Weibel–Palade body. PV-1 is a component of caveolae and considered an indicator of endothelial injury and Weibel–Palade body.

Methods: A total of 23 cases of PGNMID were compared with cases of lupus nephritis (n = 52), primary membranoproliferative glomerulonephritis (MPGN) (n = 7), and IgA nephropathy (n = 25). Informed consent from the patients and ethical approval from Tokyo Women's Medical University was obtained. PV-1 expression in the glomerular endothelium was evaluated using PAL-e antibody to verify endothelial changes in both PGNMID and control groups. Further, we compared monoclonal IgG patterns and complement deposition. We also examined histological types of MPGN and endothelial alterations as Weibel–Palade body using electron microscopy.

Results: Histological analysis in PGNMID group revealed MPGN type I (n = 10), MPGN type III (n = 8), membranous nephropathy (n = 3), endocapillary proliferative glomerulonephritis, and minor glomerular abnormality (n = 1). Deposit patterns were identified as IgG1 (IgG1κ, n = 6), IgG2 (IgG2λ, n = 1), and IgG3 (IgG3κ, n = 13; IgG3λ, n = 3). Further, 16 cases showed C1q deposition, and 21 cases showed C3 deposition. Electron dense deposits were located in subepithelial (n = 11), intramembranous (n = 16), subendothelial (n = 21), and mesangial (n = 19) sites. The percentage of PAL-e antibody-positive patients was significantly higher in PGNMID group (69.6%, n = 23) than in control groups (19.0%, n = 84). Weibel–Palade body density and caveolae were considerably elevated in PGNMID groups.

Conclusions: These results suggest that PGNMID-related damage is characterized by glomerular endothelium alterations; further studies are required to investigate whether such endothelial alterations are associated with clinical prognosis.

SA-PO704

Monoclonal IgG Deposit on Tubular Basement Membrane in Original Kidney

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Background: Tubular basement membrane immune deposit (TBMID) are often observed during renal biopsies. We recently reported that monoclonal IgG TBMID is associated with the progression of interstitial fibrosis and tubular atrophy (IFTA) in renal allografts; however, its significance in original kidneys remains unclear.

Methods: This retrospective study includes 3,126 patients who underwent native renal biopsy and 1,724 patients who underwent 0-hour biopsy between 2008 and 2018 at Tokyo Women's Medical University. We performed light microscopic, electron microscopic, and immunofluorescence studies.

Results: IgG TBMID was identified in 164 (5.2%) patients who had undergone native renal biopsy and in six (0.4%) patients who underwent 0-hour biopsy. The IgG subclass was identified in 94 patients. Monoclonal IgG TBMID was found in seven patients, including three patients who underwent 0-hour biopsy. Pathological diagnosis was that of IgA nephropathy (n = 3, including one patient who underwent of 0-hour biopsy), minor glomerular abnormalities (n = 2), antineutrophil cytoplasmic antibody-related vasculitis (n = 1), and light and heavy chain deposition disease (LHCDD) (n = 1). Upon IF, glomerular IgG deposition was negative for all patients. The combinations of IgG subclass and light chain were IgG1κ (n = 2), IgG1λ (n = 3), and IgG2κ (n = 2). Complement C3, C4, and C1q staining in the tubular basement membrane (TBM) was negative for all patients. Upon electron microscopy (EM), all patients showed a powdery electron-dense deposition (EDD). Median IFTA was 5% (range: 0–30%). Based on bone marrow examination, the diagnosis of monoclonal gammopathy of undetermined significance was

made in one patient, which was different from the patient with LHCDD. Median follow-up period from biopsy was 3.5 (range: 0.5–6) years. Although one patient with LHCDD developed renal graft failure, all other patients had stable renal function.

Conclusions: Unlike cases of renal allograft, IgG TBMID in the original kidneys does not appear to be associated with renal prognosis. However, it is necessary to investigate for hematological disorders and evaluate the type of deposit in the TBM by EM.

SA-PO705

Adenovirus Immunohistochemistry in Renal Transplantation

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Background: Human adenovirus, a linear double-stranded DNA virus, is a common cause of mild respiratory and gastrointestinal disease in otherwise healthy people. In immunocompromised patients, such as renal transplant patients, it may cause severe infections including hemorrhagic cystitis, hepatitis and interstitial nephritis. Adenovirus immunohistochemistry is a technique frequently used in the clinic to aid the diagnosis of adenovirus infections, next to PCR. Based on clinical experience, we recently questioned the specificity of immunohistochemical adenovirus detection in renal tissue as currently used in laboratories worldwide.

Methods: Adenovirus immunohistochemistry was performed on 25 pre-transplantation biopsies of donor kidneys, eight autopsy controls and one renal allograft which was removed as a result of renal failure caused by infection. Adenovirus PCR targeting Adenovirus species A, B, C, E and F was performed in quadruple on those biopsies staining positive for adenovirus. In addition, electron microscopy was performed on the renal allograft.

Results: The renal allograft and 4 out of 25 pre-transplantation kidney biopsies were positive for adenovirus on immunohistochemistry, showing typical nuclear and perinuclear staining in tubular epithelium as previously reported in the literature. However, adenovirus PCR remained negative in all cases. Electron microscopy of the renal allograft showed particles with a width ranging from 75 to 95 nm, which could be compatible with adenovirus virions.

Conclusions: In cases in which adenovirus infection is clinically suspected and a positive immunohistochemical staining for adenovirus supports this notion, an additional workup (PCR and/or EM) is usually not performed. It appears that by immunohistochemistry, positivity for adenovirus is present in normal donor kidney samples without clinical suspicion for adenovirus infection. Because of lack of confirmation by PCR, we question whether immunohistochemistry for adenovirus is specific and clinically relevant. Alternatively, adenovirus could be present (latently?) in the otherwise healthy population – but little is known about its prevalence.

SA-PO706

Kidney Function and Histopathology in Patients Undergoing Nephrectomy

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Background: Existing data on kidney histopathologic findings and estimated glomerular filtration rate (eGFR) are derived largely from studies from kidney donor nephrectomy specimens. Our objective was to use non-neoplastic tissue from nephrectomy specimens to examine the association between eGFR and the degree of glomerulosclerosis (GS), interstitial fibrosis/tubular atrophy (IF/TA), and arteriosclerosis (AS).

Methods: We reviewed non-neoplastic kidney pathology reports from patients who underwent nephrectomy between 1999 and 2018 (n=1,195). We used linear regression models to determine the association between the degree of GS, IFTA, and AS, with eGFR at the time of nephrectomy. We also assessed the relation between age and eGFR, stratifying by the degree of GS, IFTA, and AS.

Results: Greater %GS, IFTA, and AS were associated with lower eGFR (Figure 1). After MV-adjustment, eGFR was most strongly associated with greater degrees of IFTA [-29.0 ml/min/1.73m^2 (95% CI -34.2, -24.0), p <0.001 among those with >50% vs <10% IFTA]. The slope of decline in eGFR within each category of GS, IFTA, AS, and chronicity score did not differ based on age (Figure 2) (interaction term p >0.05).

Conclusions: Independent of age, lower eGFR was associated with a greater severity of histopathologic changes.

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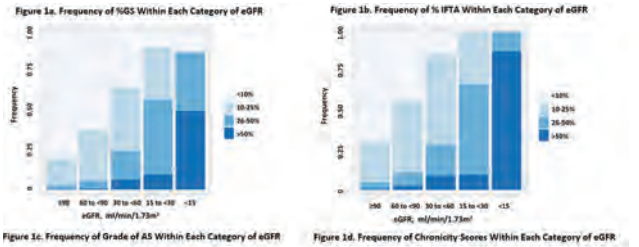
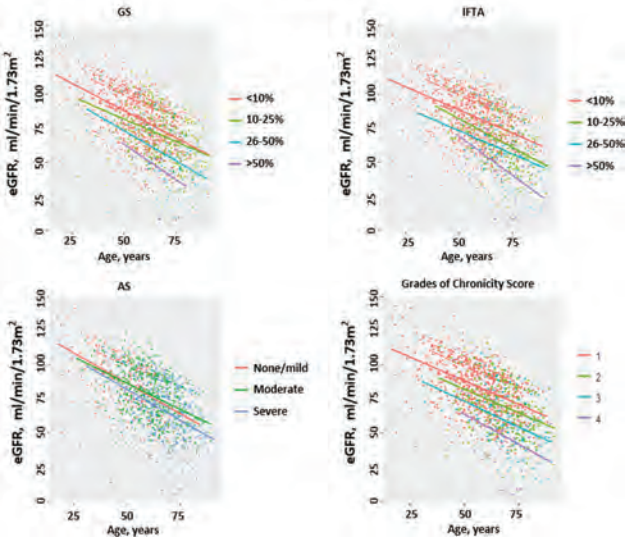


Figure 2a-2d



SA-PO707

Percutaneous Renal Biopsy Using an 18-Gauge Automated Needle Is Not Optimal

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Background: As percutaneous renal biopsies (PRB) are increasingly performed by interventional radiologists, an increase in the use of the smaller 18-gauge (G) automated biopsy needle has been observed. The use of smaller needles stands to compromise biopsy adequacy, ideally >20 glomeuli per biopsy. We compare the adequacy and safety of PRB with a 14, 16 and 18G automated needles.

Methods: PRB of native (N) kidneys (N-557) and transplant (T) kidneys (N-991) was performed by a Nephrologist or supervised Fellow at Rush University Medical Center from 1/2002 to 12/2018 using automated biopsy needles and with real-time ultrasound guidance. Baseline clinical and laboratory data, biopsy data (number of cores, glomeruli on light (LM) and immunofluorescence (IM) microscopy, total glomeruli (LM+IM) and total glomeruli per core (LM+IM)/cores)) and outcome data (hematoma on renal US 1-hr post-PRB, complications and procedures post-PRB) was collected prospectively. PRB with N14G (n=337) vs N16G (n=220) vs T16G (n=892) vs T18G (n=99) needles were compared. A P value of <0.05 was significant.

Results: PRBs with an 18G needle were less likely to be performed by fellows (N14 vs N16 vs T16 vs T18G: 94% vs 85% vs 62% vs 22%, <0.0001). Despite this, PRB with an 18G needle was associated with the lowest number of glomeruli on LM (23±11 vs 20±10 vs 26±14 vs 16±10, <0.0001), IM (9±5 vs 9±5 vs 8±5 vs 6±, <0.0001) and LM+IM (32±13 vs 29±12 vs 34±6 vs 22±12, <0.0001). PRBs with an 18G needle were less likely to have >10 (99% vs 98% vs 98% vs 89%, <0.0001) and >20 (81% vs 79% vs 83% vs 48%, <0.0001) total glomeruli (LM+IM) per biopsy. The total glomeruli per core ((LM+IM)/cores) was also significantly less with an 18G needle (15±8 vs 14±6 vs 13±6 vs 10±5, <0.0001). A hematoma by renal US 1-hr post-PRB was similar for native biopsies (14G-35% vs 16G-29%, P=0.16), and transplant biopsy (16G-10% vs 18G-10%, P=0.71) irrespective of needle size. The complication rate for native biopsies (14G-8.9% vs 16G-7.2%, P=0.53), and transplant biopsies (16G-4.6% vs 18G-2.0%, P=0.30) and the transfusion rate for native biopsies (14G-7.7% vs 16G-5.9%, P=0.49), and transplant

biopsies (16G-3.8% vs 18G-1.0%, P=0.25) were not significantly different irrespective of needle size.

Conclusions: The use of 18G biopsy needles significantly compromise the adequacy and thus, quality of the PRB while not significantly enhancing safety.

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SA-PO708

Necessity Drives Innovation: Using Transjugular Liver Biopsy Sets for Renal Biopsies

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Background: Renal biopsies are a cornerstone of nephrology, providing valuable diagnosis and treatment information. In some cases, traditional percutaneous biopsies are limited by factors such as obesity, coagulopathy and critical illness. Previously, an intravascular transjugular approach using a renal biopsy set from Cook Medical (Bloomington, IN) was used. However, the Cook set was discontinued in 2016, leaving few options for such patients in the United States. As a solution to this problem, our institution has employed a liver biopsy set manufactured by Argon Medical Devices (Frisco, TX). Our case series describes the novel and successful use of a transjugular liver biopsy set for renal biopsies in complex patients.

Methods: We reviewed patients undergoing transjugular renal biopsy using the Argon liver biopsy set at our center from 2017-2018. Indications, demographics, and outcomes were noted. Briefly, the procedure involves catheterization of the right internal jugular vein and subsequent right renal vein catheterization with renal cortex identification by venography. Biopsy specimens are then obtained using the Argon core biopsy needle set.

Results: Eighteen patients underwent a transjugular renal biopsy with the liver set. Biopsy adequacy was 95% as judged by interpreting pathologists. Complications were rare, with only one patient experiencing bleeding which was self-limited. Results are summarized in Table 1.

Conclusions: Our novel case series demonstrates that a transjugular liver biopsy set is safe and effective for renal biopsies in patients unsuitable for percutaneous biopsy. These findings are significant as there are limited options for transjugular renal biopsies in the United States. Hopefully this will lead to wider use of such techniques.

Age	Sex	Transjugular Indication	Adequacy	Complication	Pre BP	Post BP	Pre Hgb	Post Hgb	Admission
57	M	Availability	yes/cortex and medulla	none	144/27	137/72	7.2	7.4	inpatient
58	M	Obesity, solitary kidney	yes/cortex and medulla	none	173/83	163/103	9.4	9.6	inpatient
65	M	Coagulopathy, cirrhosis	yes/cortex and medulla	none	164/95	155/107	8.1	8	inpatient
23	F	Obesity	yes/cortex and medulla	none	150/114	128/69	8.2	9.1	inpatient
47	F	Liver biopsy, RHC	yes/cortex and medulla	none	107/77	113/74	14.1	13.6	inpatient
36	F	Obesity	yes/mainly cortex	none	129/84	134/89	–	–	observation
55	F	Anticoagulation, RHC	yes/cortex and medulla	none	125/85	115/84	10.7	10.4	observation
59	M	Availability	yes/cortex and medulla	None	157/84	155/93	12.1	12	inpatient
34	M	Obesity, Anticoag (LVAD)	borderline/mainly cortex	none	78/55	68/46	8.9	9	inpatient
55	M	Anticoagulation, HD access	no/cortex and medulla	bleeding	160/93	161/80	9	7.9	inpatient
54	M	Coagulopathy, thrombocytopenia	yes/mainly cortex	none	170/92	163/83	8.5	7.9	observation
74	F	Anticoagulation, HD access	yes/mainly medula	none	162/69	160/61	7.2	7.9	inpatient
56	M	Availability	yes/cortex and medulla	none	110/90	104/69	12	12.4	observation
69	M	Anticoagulation	yes/cortex and medulla	none	150/107	142/84	7.5	7.3	inpatient
35	F	Anticoagulation	yes/cortex	none	94/64	99/77	9.8	9.4	inpatient
43	F	Thrombocytpenia, critical illness	yes/cortex and medulla	none	161/100	139/93	9	9	inpatient
30	F	Obesity	yes/cortex and medulla	none	136/77	144/82	10.1	10.1	observation
Average Age: 49.9yrs	Male: 9 Female: 9		Adequacy Rate: 17/18 (94%)	Complication Rate: 1/18 (5%)			Mean: 9.4	Mean: 9.4	Inpatient: 13/18 Observation: 5/18

Table 1

SA-PO709

The Accuracy of Equations That Estimate Glomerular Filtration Rate Compared with Measured Creatinine Clearance in Critically Ill Patients

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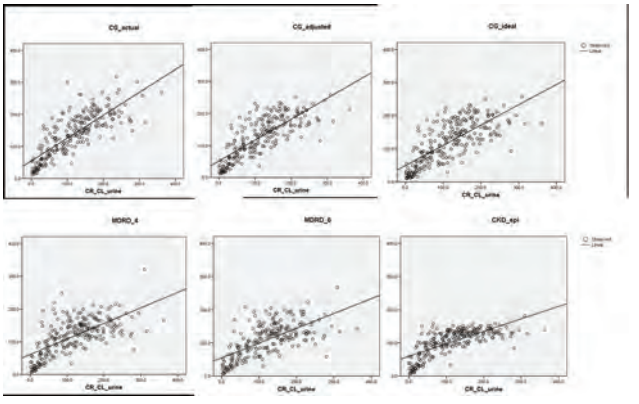
Background: The accuracy of glomerular filtration rate estimates has been questioned. This study compared estimates of GFR by commonly used equations with creatinine clearance measured by 24-hour urine collection in critically ill patients.

Methods: This sub-study of the PermiT trial included the patients enrolled at KAMC-Riyadh who had 24-hr urine collection. We estimated GFR using the Cockroft–Gault (CG), Modification of Diet in Renal Disease(MDRD4-MDRD6) and Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI) equations. For the CG equation, we entered actual weight in one calculation(CG actual-wt), and for BMI ≥30 kg/m2, the ideal body weight and the adjusted body weight in two calculations.

Results: The cohort consisted of 238 patients (age 45.2±20.2 years, DM 31.9%, CKD 2.9%, APACHE II 20.3±8.1, mechanical ventilation 98.7% and serum Cr 214±128 micromol/L). The measured CrCl24h-urine was 117.0±75.0 ml/min. The correlations between the different formulae were all significant (p<0.0001).

Conclusions: There was a modest correlation between the formulae estimating GFR with CrCl24hr-urine. CGactual-wt had the best correlation. Strength of correlation changed within the different ranges of CrCl24h-urine.

	Estimated GFR(ml/min)	Correlation(r) with CrCl(24h-urine)
CG (Actual-wt)	138.3 67.2	0.80
CG(Ideal-wt)	121.0 62.4	0.74
CG(Adjusted-wt)	127.9 62.4	0.78
MDRD-4	116.8 54.1	0.66
MDRD-6	109.2 51.0	0.65
CKD-EPI	103.5 39.5	0.71



CrCl24h-urine (ml/min)	Correlation (r) based on the equation
20-60 (ml/min)	CKD-EPI (r=0.42) MDRD-4 (r=0.37)
60-130 (ml/min)	$CG_{ideal-wt}$ (r=0.29) $CG_{adjusted-wt}$ (r=0.29)
> 130 (ml/min)	$CG_{actual-wt}$ (r=0.41) $CG_{adjusted-wt}$ (r=0.35)

SA-PO710

Performance of StatSensor Point-of-Care Device for Measuring Creatinine in Patients with CKD or Post-Kidney Transplantation

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Background: The StatSensor measures creatinine in "fingerstick" capillary blood samples. Previous studies reported a negative bias at higher creatinine concentrations. The current accuracy-based study evaluates the use of this device in kidney transplanted patients and those with CKD.

Methods: Duplicate StatSensor creatinine measurements were performed on direct fingerstick samples from 60 participants (mean age 61.9 years, 55% male, 33% transplant, mean plasma creatinine 137 μmol/L) and compared to plasma creatinine values obtained from simultaneous venous blood sampling using a Roche Integra 400 mainframe analyser.

Results: Bland-Altman analysis indicated a positive mean difference (bias) of 25.4 μmol/L between StatSensor fingerstick creatinine measurement and plasma creatinine. Comparison of eGFR (CKD-EPI) calculated from the StatSensor fingerstick creatinine versus plasma creatinine revealed misclassification across all KDIGO CKD stages (Figure 1). Post-analytical correction of the bias did not improve misclassification. Use of mean of duplicate StatSensor creatinine results did not improve performance compared to use of singlet results.

Conclusions: Our results suggest that the limiting characteristics of the StatSensor are not only bias, but also imprecision. The level of imprecision observed would likely

influence clinical decision making and limits the StatSensor's usefulness as a CKD screening tool. If choosing to utilise it for either screening for or monitoring CKD, it is essential that clinicians understand the limitations of point-of-care devices and apply this knowledge to test interpretation.

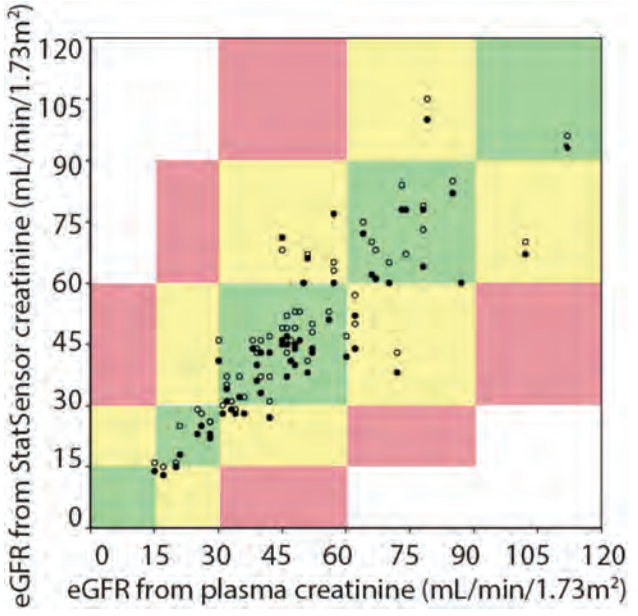

Figure 1. eGFR with StatSensor creatinine vs plasma (● Uncorrected creatinine; ○ Bias corrected creatinine)

SA-PO711

B and T Cell Subsets in Patients with Membranous Nephropathy: Comparison of Frozen Stored vs. Freshly Collected Blood Samples

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Background: It is suggested that characterisation of B and T cell subsets may provide relevant information in auto-immune diseases. Rosenzwajg et al (Kidney Int 2017; 92,277-237) studied B and T cell subsets in Rituximab treated patients with primary membranous nephropathy (pMN). They observed a decrease of regulatory T cells as well as NK cells in active disease, whereas numbers of naive B cells were increased. The increase in Treg after Rituximab predicted treatment response. In the literature B and T cell subsets are evaluated using frozen peripheral blood mononuclear cells (PBMCs) or freshly isolated blood samples. We compared these conditions, a comparison which is lacking in the literature.

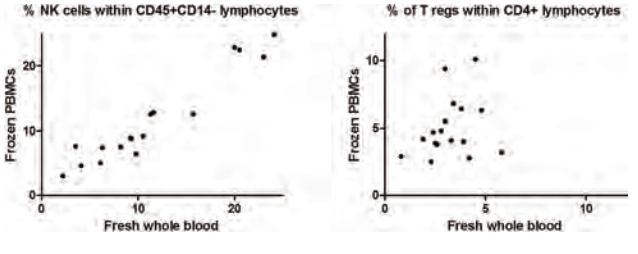
Methods: In 18 patients with pMN, we collected 20 mL of EDTA plasma. 10mL was used for fresh whole blood analysis and 10mL was used for isolation of PBMCs, and samples were stored in liquid nitrogen for 6 – 12 months. We characterised immune cell subsets with flowcytometry with fluorescently labelled cell surface markers: CD3, CD4, CD5, CD8, CD14, CD16, CD19, CD20, CD24, CD25, CD27, CD38, CD45, CD45 RA, CD45RO, CD56, CD127, HLA-DR, IgD, IgM.

Results: The distribution of the various B and T cell subsets when comparing both conditions showed a good correlation(table). The figure shows the correlation for NK cells and Tregs respectively. Our data show a weak correlation specifically within the Treg subset.

Conclusions: Our study suggests that frozen PBMC samples can be used for the characterisation of T and B lymphocytes and NK-cells, except for the Treg population. This may be improved by intracellular staining techniques. Further validation is needed.

Comparison of fresh and frozen immune cell subsets

Cell type	Fresh whole blood	Frozen PBMCs	Spearman correlation coefficient (P value)
Monocytes	20.3%	31%	0.631 (0.005)
Lymphocytes	79.7%	69%	0.631 (0.005)
total T-cells (within lymphocytes)	73.4%	67.9%	0.811 (0.000)
CD4 (within T-cells)	69.2%	68.1%	0.934 (0.000)
Treg (within T-cells)	3.1%	4.4%	0.421 (0.082)
CD8 (within T-cells)	26.6%	27.6%	0.935 (0.000)
total B-cells (within lymphocytes)	3.8%	6.5%	0.824 (0.000)
NK-cells (within lymphocytes)	10.9%	9.0%	0.939 (0.000)



SA-PO712

Vasculopathy Plays an Essential Role During the Development and Relapse of Encapsulating Peritoneal Sclerosis in Conventional PD Solutions

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Background: Encapsulating peritoneal sclerosis (EPS) is a rare, but life-threatening complication of peritoneal dialysis (PD) therapy. The precise pathogenesis remains unknown, making it difficult to prevent the development of EPS. The aim of this study is to examine the peritoneal samples of EPS patients and identify the association of the peritoneal pathology with different clinical factors.

Methods: Peritoneal samples were obtained at the time of surgical enterolysis in Tsuchiya General Hospital from 1993 to 2016. Total 283 peritoneal samples were screened. This study used pathological and immunopathological techniques to assess EPS peritoneum samples.

Results: 214 in 283 samples were evaluable. In conventional PD solution group, the ratio of lumen diameter to vessel diameter (L/V ratio) was significantly smaller (P<0.01) and less angiogenesis (P=0.014). Lower L/V ratio was also found to be related to the relapse of EPS (P=0.014). Univariate analysis demonstrated that L/V ratio was significantly associated with EPS relapse (P=0.024). Multivariate logistic regression analysis suggested that more sever vasculopathy with low L/V ratio was identified as a risk factor of EPS relapse (per 0.1 increase, HR 0.87, P= 0.025)

Conclusions: Pathophysiology of the development of EPS was different between conventional solution and pH-neutral solution. Vasculopathy was related to the development and relapse of EPS in conventional solutions.

SA-PO713

Assessing Bleeding Risk in CKD Using Global Coagulation Assays

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Background: Later stage CKD patients are often clinically hypocoaguable. Current coagulation studies do not sufficiently assess this risk. Global coagulation studies (GCA) are functional studies that can better describe bleeding and thrombosis risk. GCA includes whole blood thromboelastography (TEG), platelet-poor calibrated automated thrombogram (CAT), overall haemostatic potential (OHP). TEG is well established in the management of major haemorrhage and massive transfusion. We aim to evaluate using GCA in CKD patients to help define bleeding or thrombosis risks.

Methods: We prospectively recruited 2 groups of stable CKD patients. Pre-dialysis with eGFR<30 ml/min/1.73m² (n=24) and dialysis patients (n=46 haemodialysis, n=10 peritoneal dialysis) were compared to healthy controls (n=138). Baseline renal, hematological investigations and GCA were compared using t-test and chi-square statistics.

Results: Compared to controls (67% female, mean age 42, creatinine 70umol/L) predialysis CKD (46% female, mean age 70, creatinine 237umol/L, urea 18.6mmol/L, eGFR 22 ml/min/1.7m2) had increased von Willebrand factor (VWF) antigen (223 vs 102%, p<0.001), factor VIII (208 vs 108%, p<0.001) and D-dimer (1188 vs 430, p<0.001). Pre-dialysis CKD were prothrombotic with increased maximum amplitude (MA, a measure of clot strength) of 68 vs 60mm (p<0.01) compared to controls. In predialysis CKD, there was no association between urea or eGFR and MA. Thrombin generation (peak thrombin 269 vs 219nM, p<0.01) and fibrin generation (OHP 41 vs 29, p<0.01) were increased with impaired fibrinolysis (OFP 42 vs 50%, p<0.01) compared with controls. Dialysis patients (38% female, mean age 66) also had increased clot strength (MA 70mm, p<0.01) and reduced fibrinolysis (OHP 41 U, OFP 40%, p<0.01) compared to controls. Measures of clot strength and overall fibrinolysis were not significantly different between pre-dialysis and dialysis patients.

Conclusions: Contrary to expectation, pre-dialysis CKD and dialysis patients were not found to be hypocoaguable using functional coagulation tests. Both groups were found to have markers conferring increased prothrombotic risk: elevated vWF, increased TEG measures and impaired fibrinolysis. The clinical significance of these results and the use of GCA to stratify both thrombotic and bleeding risk warrants further investigation.

SA-PO714

Usefulness of Urinary-Soluble CD163 as a Biomarker of Disease Activity in Patients with Glomerulonephritis

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Background: Although histopathological examination of kidney tissues can be useful for understanding of disease activity of glomerulonephritis, there are undiagnosed cases because of the difficulties in performing invasive biopsies. Therefore, noninvasive

biomarkers are needed to reflect disease activity and monitor response to therapy in patients with glomerulonephritis. Recently, it is suggested that the level of urinary soluble CD163 (sCD163), a marker of M2 macrophage infiltration, associated very tightly with active renal vasculitis, but the usefulness of urinary sCD163 as a surrogate marker of disease activity in glomerulonephritis is unclear. In this study, we investigated whether urinary sCD163 is useful for reflecting disease activity and monitoring response to therapy in patients with glomerulonephritis.

Methods: Subjects were forty-five patients with biopsy-proven glomerulonephritis including IgA nephropathy (n=24), IgA vasculitis (n=7), ANCA-associated glomerulonephritis (n=8), and lupus nephritis (n=6). In all patients, urinary excretion of sCD163 and protein, and quantitative urinary occult blood were measured at two points (baseline and follow-up). The relationships between change in urinary sCD163, reflecting follow-up value minus baseline value, and changes in other measurements were evaluated.

Results: Patients except for 8 cases of IgA nephropathy were treated with steroid therapy. At the point of follow-up, urinary sCD163 significantly decreased compared with baseline (6582±10827 to 1837±4510 pg/mgCr, p <0.01). Change in urinary sCD163 positively correlated with change in urinary protein (r = 0.60, p <0.01), whereas change in urinary sCD163 did not associate with change in urinary occult blood. ROC curve analysis revealed that a reduction of urinary sCD163 by more than 60% predicted remission of proteinuria defined as urinary protein < 0.3 g/gCr (71.4% sensitivity and 87.1% specificity), and a reduction of urinary sCD163 by more than 86% predicted remission of hematuria remission (86.4% sensitivity and 54.5% specificity).

Conclusions: Urinary sCD163 levels reflected disease activity of glomerulonephritis and thus may be useful for monitoring disease activity in patients with glomerulonephritis.

SA-PO715

In Situ Visualization of C3/C5 Convertases: A New Diagnostic Tool to Differentiate Complement Activation in Kidney Biopsies

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Background: Deregulated complement activation contributes to or drives the pathogenesis of various kidney diseases. Currently, the diagnosis of complement activation in kidney diseases is primarily based on detection of complement activation products in glomerular tissue and of consumption of complement components or generation of split products in plasma. Up to now a method to directly identify, localize and differentiate complement convertases in tissue has been lacking.

Methods: We established a new *in situ* method for the detection of the assembled C3/C5-Convertases of the classical/lectin and alternative pathways using the bright field proximity ligation assay. We compared kidney biopsies derived from cases of systemic lupus nephritis (SLE, n=10) with cases of thrombotic microangiopathy (TMA, n=9) due to atypical hemolytic syndrome, using zero hour transplant biopsies as normal controls (n=5).

Results: As expected, SLE cases revealed a higher density of classical pathway C3/C5 convertases, while TMA cases showed less classical pathway enzymes and a higher density of alternative pathway C3/C5 convertase signals.

Conclusions: We introduce the first methodological workflow for the visualization, differentiation and quantification of classical/lectin and alternative C3/C5 convertases directly within the tissue specimen.

SA-PO716

Massive Ex Vivo C5b9 Formation on Endothelium Indicates Complement Defects and a Clinical Response to Complement Inhibition in Patients with Thrombotic Microangiopathy

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Background: The syndromes of thrombotic microangiopathy (TMA) are extraordinarily diverse, some of which have been linked to defects in complement regulation. The correct recognition of such defects in patients with TMA is critical for treatment and prognosis, although challenging in patients with coexisting conditions, i.e., so-called secondary TMAs. We evaluated the clinical value of an *ex vivo* test to detect complement defects in a well-defined cohort of patients with TMA.

Methods: Sixty-three patients with TMA on kidney biopsy and/or peripheral blood smear were analyzed for serum-induced *ex vivo* C5b9 formation on microvascular endothelial cells and compared to pooled normal human serum. Patients with TMA also were screened for rare variants in genes linked to complement regulation. In addition, renal survival at 1 year was assessed.

Results: At diagnosis, massive *ex vivo* C5b9 formation was found in *n*/*N*=40/63 (63%) patients with TMA, including *n*/*N*=15/15 with atypical hemolytic uremic syndrome, *n*/*N*=17/25 with hypertensive emergency, *n*/*N*=6/6 with pregnancy, *n*/*N*=1/1 with invasive Streptococcus pneumonia infection, and *n*/*N*=1/1 after an endovascular aortic repair, but neither in those with coexisting autoimmunity (n=9) nor thrombotic thrombocytopenic purpura (n=6). Patients with massive *ex vivo* C5b9 formation presented with severe acute kidney injury (median serum creatinine of 538 versus 197 μmol/L, *P*<0.01) and a high prevalence of rare variants in complement genes (23 [58%] versus 0, *P*<0.001) as compared to those with normal *ex vivo* C5b9 formation. Seventeen patients with massive *ex vivo* C5b9 formation were treated with eculizumab (median number of treatment was 14); renal survival at 1 year was *n*/*N*=14/17 (82%) and *n*/*N*=9/23 (39%) for treated and untreated patients (*P*<0.01), respectively. Notably, 3 patients with normal *ex vivo* C5b9 formation who had been treated with eculizumab progressed to end-stage renal disease.

Conclusions: Massive *ex vivo* C5b9 formation indicates defects in complement regulation as the dominant cause of TMA, including TMAs that present with coexisting conditions. Patients with TMA and massive *ex vivo* C5b9 formation may benefit from complement inhibition.

SA-PO717

Direct and Indirect Effects of Macrophage Compartmental Localization and Salt Concentration in the Kidney Graft

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Background: Recent data have delineated a role for sodium chloride in immune regulation. The kidney is characterized by a marked cortico-medullary salt gradient. A better understanding of local immunoregulatory mechanisms is especially relevant in the transplanted kidney, where the balance between detrimental inflammation in rejection and beneficial inflammation for host response is frequently lost.

Methods: Primary human macrophage and tubular cell culture single and co-cultures was performed in defined sodium chloride and urea concentrations serving as osmolarity control with an without therapeutic dose calcineurin inhibitors and analyzed by flow cytometry, qPCR and microscopy. In a cohort of 112 adult renal allograft recipients, renal cortical and medullary macrophage polarization markers and MCP-1 chemokine production were analyzed by digitally assisted immunohistology of surveillance biopsies. Incidence of urinary tract infection during five years after transplantation was extracted from the records.

Results: Under defined conditions in vitro, an elevated sodium chloride concentration dose-dependently increased chemotactic cytokine MCP-1 production in human renal tubular epithelial cells and also in monocyte derived macrophages. Patients who received loop diuretic therapy, which depletes the renal cortico-medullary salt gradient, had significantly lower MCP-1 serum levels and no gradient between renal medullary and cortical MCP-1 protein, in contrast to patients without diuretic therapy, where it was significant. The renal medullary M1/M2 macrophage marker ratio decreased with increasing loop diuretic dose. Clinically, diuretic therapy significantly correlated with urinary tract infection rate in uni- and multivariable regression analysis in this cohort of renal allograft recipients.

Conclusions: Renal medullary M1/M2 macrophage marker ratio and MCP-1 gradient significantly associated with loop diuretic therapy as did urinary tract infection rate. Modulation of the renal salt gradient should be considered and further investigated in patients at a high risk of urinary tract infections.

Funding: Government Support - Non-U.S.

SA-PO718

From Baseline Serum Creatinine to Creatinine-Based AKI: Different Definitions for Different Results

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Background: The lack of consensus on the definition of baseline serum creatinine(bsCr) influences the creatinine-based acute kidney injury(AKI) diagnosis, leading to problems relating to both research and clinical purpose. Pre-admission bsCr, measured in a time-period of a maximum of 365 days and minimum of 7 days from hospitalization, is considered the gold standard, but is rarely available in unscheduled patients. Our study aims at evaluating sensitivity and specificity of different bsCr.

Methods: We retrospectively enrolled patients admitted to our intensive care unit(ICU) over 6-month period. Inclusion criteria were:(i)availability of pre-admission bsCr;(ii)length of ICU stay≧72hrs. According to the bsCr definitions derived from literature, we recorded:(i)sCr measured at ICU admission(admission bsCr);(ii)the lowest sCr achieved during the first 3 days of ICU stay(nadir bsCr);(iii)sCr calculated using the MDRD equation(back-estimation formula)(estimated bsCr), thus resulting 4 different bsCr for each patient. The occurrence of AKI was evaluated according to KDIGO criteria considering each of the 4 bsCr.

Results: Of 490 patients, 195 had pre-admission bsCr. 14 patients were excluded because daily sCr was not available. Using pre-admission bsCr, we identified 79 patients who developed AKI(43.6%). Results are summarized in table 1.

Conclusions: Admission bsCr, frequently used in ICU, has the lowest sensitivity for AKI, missing almost entirely the diagnosis of community-acquired AKI. In previous studies, estimated bsCr has been demonstrated to overestimate the incidence of AKI in patients with pre-existent chronic kidney disease. In the absence of pre-admission bsCr,

nadir bsCr seems to be the most accurate bsCr for diagnosis of AKI. Future efforts should focus on identifying a shared definition of bsCr.

	pre-admission bsCr	admission bsCr	nadir bsCr	estimated bsCr
AKI(pts)	79	37	63	69
no AKI(pts)	102	96	86	91
sensitivity(%)		46.8	87.3	79.7
specificity(%)		94.1	84.3	89.2

SA-PO719

New Approach to the Urinary Sediments: Strange Crystals in Urine

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Background: Low vacuum scanning electron microscopy (LVSEM) is a non-perturbing technology that requires minimal sample preparation. Compared with conventional SEM, it is possible to observe wet samples directly without freeze-drying and vacuum evaporated carbon deposition process, thus, there is no loss of small parts of the samples during processing and can obtain more detail structure.

Methods: LVSEM was used to study the 3D structure of the urinary sediment from the patients undergone renal biopsy. Ten mL urine samples from renal biopsy patients were fixed with 1mL of 10% formalin and centrifuged at 500g for 5 minutes. The urinary sediments were stained with 1% Ponseau solution and mounted on the carbon filter membrane and observed with the LVSEM (Hitachi TM4000 Plus, Tokyo, Japan).

Results: Typical bipyramids calcium oxalate crystals and dodecahedrons crystals of various sizes were observed by LVSEM. Interestingly, dodecahedral calcium oxalate crystal shows multilayer configuration resembling a thread winding. Urine samples collected from the bladder catheter's bag showed curious honeycomb and tubular structures with spikes. It revealed that these structures were shed from the luminal walls of bladder catheter. These walls are composed of silicon-elastomer coated rubber to strengthen the tube.

Conclusions: LVSEM is a useful tool to obtain 3D views of the urinary sediment and can provide a new understanding of the urinary sediment, especially of the urinary crystals.

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SA-PO720

Clinical Verification of Urine Protein/Creatinine Ratio Instead of 24-Hour Urinary Protein Evaluated the Different Levels of Proteinuria in Children

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Background: To evaluate the correlation and consistency between urine protein/creatinine ratio (UPCR) and 24 hour urinary protein (24hUP) in children, and to determine cutoff values of UPCR relative to 24hUP at 150mg(>150mg is pathological proteinuria) and 50mg/kg (>50mg/kg is nephrotic-range proteinuria) respectively.

Methods: 370 children were enrolled, including 85 normal children, 109 Henoch-Schönlein purpura nephritis, 167 nephrotic syndrome, 5 IgA nephropathy, and 4 lupus nephritis. These patients were divided into three groups: normal group: 24hUP≤150mg, *n* =85; non-nephrotic range proteinuria group: 150mg<24hUP≤50mg/kg, *n* =120; nephrotic-range proteinuria group: 24hUP>50mg,kg, *n* =165. Clinical symptoms and laboratory examination data were collected. The correlation between UPCR and 24hUP were evaluated by spearman correlation analysis. The consistency between UPCR and 24hUP was analyzed by Bland-Altman technique. The cutoff values of UPCR in predicting non-nephrotic range proteinuria group and nephrotic-range proteinuria were determined using receiver operating characteristics (ROC) curve, respectively.

Results: UPCR was positively correlated with 24hUP (r =0.885, *P*<0.01). Bland-altman diagrams showed that UPCR and 24hUP had good consistency, and >95% spots of UPCR and 24hUP were within the 95% consistency area. Relative to 24hUP (150mg), the cutoff value (0.23g/g Cr) with the highest sensitivity (92.8%) and specificity (92.9%) was close to the UPCR>0.2g/g Cr proposed by American rheumatic society in 2006 as the diagnositic standard of pathological proteinuria. Relative to 24hUP (50mg/kg), the cutoff value (2.09g/g Cr) with the highest sensitivity (94.5%) and specificity (88.6%) was close to the UPCR>2.0g/g Cr proposed in 2012 KDIGO guidelines as the diagnositic standard of nephrotic syndrome and nephrotic-range proteinuria.

Conclusions: There are good correlation and consistency between UPCR and 24hUP. UPCR can be used to evaluate the different levels of proteinuria in children.

SA-PO721

Alteration of Structural and Functional Connectivity in Neurologically Asymptomatic Patients with ESRD

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Background: The aim of this study was to evaluate the alterations of structural and functional connectivity using graph theoretical analysis in the neurologically asymptomatic patients with end-stage renal disease (ESRD). In addition, we investigated the prevalence of cognitive impairment (CI) in the patients with ESRD, and analyzed the association between the network measures of brain connectivity and cognitive function.

Methods: We prospectively enrolled neurologically asymptomatic 40 patients with ESRD and 40 healthy controls, and all of the subjects underwent diffusion tensor imaging (DTI) and resting state functional MRI (rs-fMRI). We calculated the measures of structural and functional connectivity based on DTI and rs-fMRI, respectively, and investigated the differences between the patients with ESRD and healthy controls. We assessed cognitive function in the patients with ESRD with the MMSE, MoCA, and CERAD neuropsychological battery.

Results: The patients with ESRD had decreased global structural and functional brain connectivity, and they had also alterations of network hubs compared to healthy controls. About 70% of patients with ESRD had CI. Even without CI, patients with ESRD had decreased global connectivity and alterations of network hubs. Furthermore, there was significant positive association between measures of brain connectivity and cognitive function.

Conclusions: We found that patients with ESRD had decreased structural and functional brain connectivity, and there was significant association between brain connectivity and cognitive function. These alterations of brain network may contribute to the pathophysiological mechanism of CI in the patients with ESRD.

SA-PO722

Brain Structural and Functional Dissociated Connectivity Patterns Between ESRD Patients with Peritoneal Dialysis and Hemodialysis

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Background: The aim of this study was to investigate and compare the alterations of structural and functional connectivity between peritoneal dialysis(PD) patients and hemodialysis (HD) patietnts.

Methods: We prospectively enrolled neurologically asymptomatic 20 maintenance PD patients, 20 maintenance HD patients and 40 healthy controls, and all of the subjects underwent diffusion tensor imaging (DTI) and resting state functional MRI (rs-fMRI) to investigate the alterations of structural and functional connectivity. We calculated the measures of structural and functional connectivity based on DTI and rs-fMRI, respectively. We assessed cognitive function in the patients with ESRD with the MMSE, MoCA, and CERAD neuropsychological battery.

Results: The main findings of our study were that PD patients had decreased global structural connectivity compared to healthy controls and HD patients had decreased global functional connectivity compared to healthy controls. In addition, we found that there are many regions in the alteration of local structural and functional connectivity between PD patients compared to healthy subjects and HD patients compared to healthy subjects.

Conclusions: We found that patients with ESRD had decreased structural and functional brain connectivity, and there are important differences of the structural and functional connectivity in brain networks according to the dialysis modality

SA-PO723

Prediction of Baseline Renal Function in Lupus Nephritis Using Deep Learning on Histology Images

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Background: Lupus nephritis (LN) is a heterogeneous disease that might be an ideal case to use artificial intelligence such as deep learning (DL) to provide a more precise and objective assessment of biopsy. The aim of the study is to assess DL performance on kidney biopsy whole-slide images in predicting baseline renal function in LN stage II-IV patients.

Methods: Kidney biopsies from 98 LN patients were used to train an agnostic DL algorithm called Chowder using multitask learning. Additionally, a Mask Region-based Convolutional Neural Network instance segmentation model was used to segment renal structures, trained using expert annotations and validated before applying it to patient biopsies. Histomic features from the algorithm predictions were extracted to predict renal function. Cross-validation AUC was calculated.

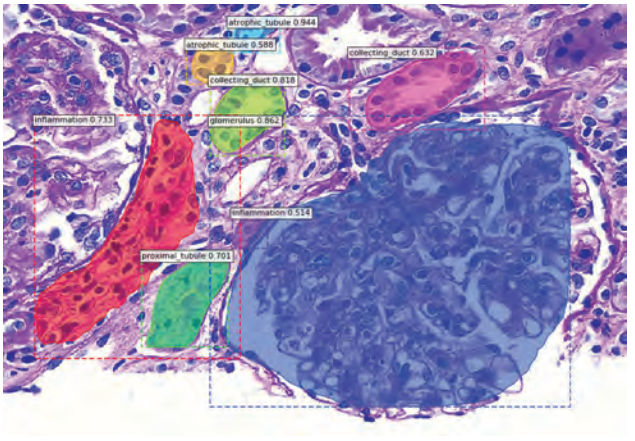
Results: Chowder was able to predict baseline eGFR and creatinine (Table). The structure segmentation model has an average precision of 0.68 and 0.76 for proximal tubules and glomeruli, respectively (Figure). Histomic feature of inflammation area outperforms Chowder in proteinuria and tubulointerstitial fibrosis prediction (Table).

Conclusions: Preliminary results show that DL on renal biopsy can predict baseline renal function. Histomic features from structure segmentation prediction provided additional insights into histological manifestations. This methodology can be extended to disease outcome prediction.

Funding: Commercial Support - Hoffmann-La Roche Ltd

Renal function prediction performances. AUC values shown.

Renal Function	ISN/RPS Grade	Chowder	Histomics (inflammation area)
eGFR (<60 ml/min/1.73m2)	0.70	0.91	0.77
Serum Creatinine (>83 µmol/l)	0.64	0.74	0.74
Proteinuria (>0.35 g/l)	0.82	0.62	0.75
Tubulointerstitial fibrosis (>10%)	0.69	0.55	0.75



An example of structure segmentation prediction on a test image in validation set. Classes and confidence values shown.

SA-PO724

Urine Red Blood Cell-Derived Microparticle by Flow Cytometry as a Novel Biomarker for Diagnosis of Glomerular Hematuria

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Background: Differentiating glomerular hematuria (GH) from non-glomerular hematuria (NGH) is based on the identification of dysmorphic red blood cell (RBC) by bright field microscopy which is operator-dependent and insensitive. Whether the detection of RBC-derived microparticle (RMP) by flow cytometry which indicates specific injury to RBC can differentiate GH from NGH has never been validated.

Methods: Spot urine was collected from patients with GH, NGH, and healthy non-hematuria volunteers. GH patients were patients with biopsy-proven glomerular disease diagnosed within 3 months while NGH were patients with urinary tract cancer, nephrolithiasis, and post-operative bleeding. Urine was submitted for microscopic study to identify percentage of dysmorphic RBC, and flow cytometry to detect urine RMP. RMP was defined by size (<1 μm) and positive labeling for CD235a and annexin V. The RMP number was normalized by total RBC number (RMP/RBC ratio). All analyses were performed by blinded technician within 2 hours after specimen collection. Receiver Operating Characteristics (ROC) curve analysis was used to demonstrate diagnostic performance of RMP/RBC ratio in diagnosing GH.

Results: There were 29, 29, and 19 participants in GH, NGH, and healthy groups. The most common diagnoses in GH group were lupus nephritis (48.3%), ANCA-associated glomerulonephritis (13.8%), and IgA nephropathy (10.3%) while majority of NGH group were post-operative hematuria (55.2%) and urinary tract cancers (17.2%). RMP was not present in urine from healthy volunteers but were detected in both GH and NGH patients. The RMP/RBC ratio was significantly higher in GH compared to NGH patients (1.06±0.19 vs 0.18±0.04; p<0.001). RMP/RBC ratio at a cut point of 0.40 provided a sensitivity and specificity of 82.8% and 82.8% for diagnosis of GH, respectively. Performance of RMP/RBC ratio was better than the conventional use of dysmorphic RBC percentage according to the area of under the curve of ROC curve analysis (0.90 vs 0.87).

Conclusions: Measurement of urine RMP/RBC ratio by flow cytometry is a more accurate biomarker for diagnosing GH. This biomarker is operator-independent and can serve as a useful test for clinical practice.

Funding: Government Support - Non-U.S.

SA-PO725

A Nuclear Magnetic Resonance-Based Biomarker Constellation for GFR Prediction Enables Metabolic Phenotyping

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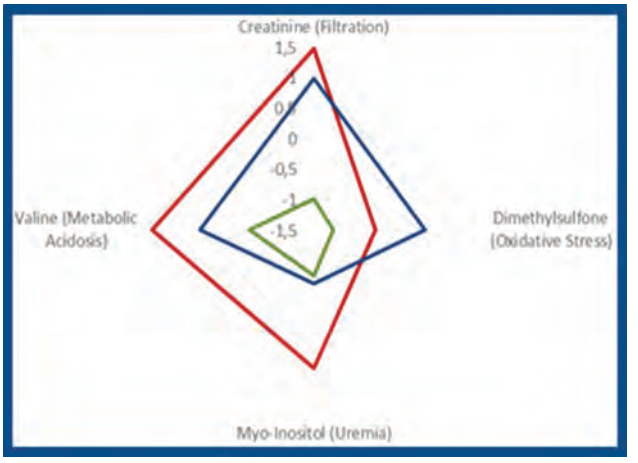
Background: Assessment of kidney function does either entail high burden for patients as part of clearance measurements (mGFR) or estimated GFR by moderately-performing equations (eGFR). Recently, we developed a novel method for accurate prediction of mGFR, based on a serum biomarker constellation of creatinine, myo-inositol, valine and dimethyl sulfone (DMS) analyzed by nuclear magnetic resonance (NMR) spectroscopy. This metabolomic constellation was tested and validated in three separate cohorts in a multi-center study.

Methods: In order to characterize the role of these biomarkers in renal dysfunction and pathogenesis of CKD and to test their value for metabolic phenotyping, biomarker profiling was applied to sets of three age-, sex-, and mGFR-matched male patients with CKD stage II during end-stage liver disease. To compare the obtained profiles, measured biomarker concentrations were transformed into z-scores and plotted into a radar chart with four axes, one each for creatinine (marker for filtration), dimethyl sulfone (marker of oxidative stress), myo-inositol (marker of uremia), and valine (marker of metabolic acidosis).

Results: Within these age-, sex-, and mGFR-matched sets, the metabolic profiles of clinically similar patients differed significantly concerning single markers reflecting filtration, uremic toxins, oxidative stress, and acidosis. An exemplary set of patients with an mGFR of 62 ml/min/1.73m^2 is depicted in the figure where every color indicates the distinct metabolic profile of one matched patient.

Conclusions: These observations suggest that the set of renal biomarkers enables molecular phenotyping of clinically highly selected age-, sex-, and mGFR-matched patients of homogenous clinical etiology providing further insights into their individual renal comorbidities based upon complex design thinking and a single diagnostic method using one serum sample.

Funding: Commercial Support - numares AG



z-score radar chart

SA-PO726

Artificial Intelligence Is Useful for Quantitative Analyses of Human Kidney Biopsy Images

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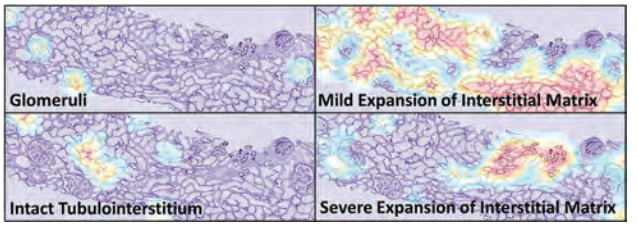
Background: The kidney biopsy is a valuable clinical examination that provides profound insight into the diagnosis, prognosis, and treatment of kidney diseases. However, appropriate quantitative analyses of the kidney biopsy images require trained nephrologists and pathologists. Artificial intelligence, an emerging technology in the field of computer science, may help analyses of pathology images.

Methods: PAS, PAM, or Masson-stained human kidney biopsy samples were obtained from four hospitals in Japan. The kidney biopsy images were digitalized by virtual slide system. Convolutional neural network (CNN), a deep neural network for computer vision, was trained to segment the kidney biopsy images.

Results: The CNN was almost well trained to identify glomerular and global sclerosis regions in various kidney diseases. However, Kimmelstiel-Wilson nodules were tended to be identified as global sclerosis. The CNN could also segment kidney biopsy images into intact tubulointerstitium, mild expansion of interstitial matrix, severe expansion of interstitial matrix, inflammation, arteries, and capsule of the kidney. Because PAS, PAM, and Masson-staining techniques were slightly different among the four hospitals, the training of the CNN required data from all four hospitals to obtain better accuracy of segmentation.

Conclusions: The artificial intelligence could segment human kidney biopsy images. The segmentation by artificial intelligence can provide novel quantitative methods for the analyses of human kidney biopsy images.



Segmentation of kidney biopsy images by artificial intelligence

SA-PO727

Primary and Secondary Podocyte Infolding and Microparticles: An Ultrastructural Diagnosis

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Background: Podocyte Infolding Glomerulopathy (PIG) is a recently described pathologic entity with ultrastructural alterations of glomerular basement membrane (GBM) and podocytes. It is characterized by the presence of podocyte invaginations, podocyte infolding, spherical microparticles and microtubules in the GBM. It was first reported from Japan. Since then there are case reports describing it more commonly among women with membranous nephropathy and autoimmune diseases. This study describes the author's experience of finding PIG-like changes in a spectrum of glomerular diseases.

Methods: The ultrastructural features in renal biopsies received for routine electron microscopy during a 6-month period, in a tertiary care referral center in North India, were evaluated for PIG-like changes. Biopsies showing both podocyte infolding and microtubules and microparticles were included. The changes were evaluated as segmental/global and focal/diffuse.

Results: On ultrastructure, focal and segmental podocyte infolding and microparticles were seen in four biopsies including Membranous Nephropathy with FSGS (n=2), post-transplant IgAN with transplant glomerulopathy (n=1), and unspecified connective tissue disease (n=1). Electron dense deposits were present in all. Mean age was 29 years (range 20-47) with three males. Diffuse PIG was seen in a renal biopsy from a 43-year old woman, diagnosed as FSGS on light microscopy. No electron dense deposits were seen. The microparticles were round or oval and the size varied widely, measuring 40-170 nm. All biopsies showed diffuse foot process effacement and evidence of GBM remodeling with lamellation and splitting of lamina densa. Nephrotic proteinuria was present in all patients.

Conclusions: As is true for other pathological morphological entities in renal glomerular diseases like FSGS, MPGN etc., PIG is also a morphological; pattern which may exist in a primary diffuse form with no electron dense deposits, predominantly in females and a secondary form with focal and segmental changes associated with other glomerular diseases with electron dense deposits without any gender predilection. It is useful to recognize that PIG-like changes can be seen in various glomerular diseases and this may be referred to as focal and segmental-PIG (FSPIG) instead of PIG.

SA-PO728

Podocytic Infolding Glomerulopathy: The Clinical Secrets of Hidden Disease

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Background: Several cases of Podocytic infolding glomerulopathy (PIG) has been reported from Japan as a new disease entity since 2008. It is a rare glomerular abnormality seen predominantly among women in associaciation with membranous nephropathy and autoimmune diseases involving glomerular basement membrane (GBM) bubbling visualised by light microscopy (LM), invagination of the podocyte membrane, and the presence of microspheres viewable by electron microscopy (EM). The clinical features and pathogenesis of this condition are still unclear. We reviewed clinical, biochemical, and pathological features of cases of PIG at our institute.

Methods: We retrospectively analysed cases of PIG as per the diagnostic criteria during preceding two years.

Results: Seven cases of PIG have been reported from our institute. The mean age of the patients was 48, (43-65) years, and all were men. Both hypertension and diabetes were seen in five, one each had hypertension and diabetes. Four patients had nephrotic range proteinuria and two had insignificant proteinuria. All had increased creatinine with a mean of 4.3mg%. Autoimmune workup and viral markers were negative in all. LM showed diabetic nephropathy (DN) in 5 cases and hypertensive changes in 1 case and secondary FSGS in 1 case. Microspheres were present in all but podocyte infolding was present in 1 and cluster formation of microspheres was found in 3 cases

Conclusions: PIG in our case series differs from that of Japan in male preponderance and is associated with diabetic nephropathy. The clinical significance of PIG in south Indian population is yet to be elucidated.

SA-PO729

Single-Cell RNA Sequencing of Myofibroblasts to Identify Therapeutic Targets in CKD

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Background: Renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function, independent of underlying disease. It is characterized by an increase in activated cells, myofibroblasts, which produce and deposit extracellular matrix. This project aim at an in depth analysis of myofibroblasts to further understand the progression of fibrosis and to identify novel targets for development of therapeutics.

Methods: Mice with Pdgfra-GFP and Pdgfrb-GFP reporters were utilized to identify pericytes, fibroblasts and myofibroblasts. Mice were subjected to unilateral ureter obstruction (UUO) and analyzed at different time points after UUO. GFP positive cells from UUO and contralateral (CL) kidneys were enzymatically digested and sorted into 384-well plates by FACS for single cell RNA-seq using SmartSeq2. Cluster analysis was performed with BackSPIN and Pagoda2.

Results: Pdgfra-GFP and Pdgfrb-GFP positive cells were significantly increased after UUO and colocalized with markers of fibrosis (ASMA and vimentin). Analysis of the single cell transcriptomes from Pdgfra-GFP and Pdgfrb-GFP cells clustered CL cells and UUO cells separately. Several genes were exclusively expressed in cells from UUO kidneys, while some genes were seen in CL kidneys but lost in UUO kidneys. Ongoing studies include trajectory analysis from the different time point as well as confirmation of results with immunohistochemistry and RNAScope.

Conclusions: Our study will give insight into the temporal changes of fibroblast and pericytes transcriptomes on the single cell level during fibrosis progression.

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

SA-PO730

Endoglin Promotes Interstitial Fibrosis in CKD

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Background: Tubulointerstitial fibrosis is a common process leading to chronic renal damage. It is characterized by extracellular matrix (ECM) deposition and pathological scar formation driven by transforming growth factor beta (TGF-β). Inhibiting excessive ECM production could be a strategy to reduce the functional decline of the kidney and thereby the progression towards end-stage renal disease. Endoglin, a co-receptor of the TGF-β-receptor, could be an interesting target to inhibit fibrosis formation.

Methods: Biopsies of patients with kidney diseases characterized by interstitial fibrosis, such as focal segmental glomerular sclerosis (FSGS; n=48), diabetic nephropathy (DN; n=11) and chronic allograft dysfunction (CAD; n=43) were selected; healthy kidneys were used as controls (n=8). Sections were stained for endoglin and the positively-stained area was measured. DN and CAD sequential sections were stained for Sirius Red, a marker for interstitial fibrosis. Endoglin mRNA expression in whole kidney tissue of another DN cohort (n=23) was measured with qPCR; healthy kidneys were used as controls (n=12). Lastly, collagen type I production was measured with western blot in TGF-β stimulated lentivirally transduced fibroblasts that were either wild type or knock down for endoglin.

Results: Endoglin was increased in the interstitium of patients with FSGS, DN and chronic allograft dysfunction compared to controls ($p<0.001$). The endoglin-positive area colocalized with the Sirius Red-positive area. qPCR showed upregulation of endoglin mRNA in patients with DN compared to healthy controls ($p<0.05$). The western blot analysis demonstrated that collagen type I production after TGF-β stimulation was less upregulated in the endoglin knockdown fibroblasts compared to wild type fibroblasts.

Conclusions: We show that endoglin is overexpressed in different patient cohorts with interstitial kidney fibrosis and that it colocalizes with Sirius Red-positive areas. We also show that lowering endoglin levels reduces TGF-β-induced collagen type I production. These results suggest that endoglin could be a potential target reduce the development of fibrosis. This offers an interesting opportunity to treat patients with declining renal function.

SA-PO731

Hypothermic Protection Attenuates Renal Fibrosis After Renal Ischemia-Reperfusion

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Background: Hypothermia attenuates acute renal injury including tubular necrosis, detachment, and apoptosis after ischemia-reperfusion. However, it remains unknown whether hypothermia improve renal fibrosis. Although some reports showed cold ischemia activate TGF-bata signals, it is unclear that it induce the renal fibrosis. We evaluated the hypothermia reduced the renal fibrosis after renal ischemia-reperfusion injury.

Methods: C57Bl/6 mice were divided into the following groups: sham-operated (cold, 32C) vs normal temperature (37C); ischemia-reperfusion mice (32C vs 37C). Kidneys were harvested 20 minutes after induction of renal ischemia, 4hr, 24 hours, 72hr, and 168hr after ischemiareperfusion injury. Functional and molecular markers of kidney injury were evaluated. To explore the molecular mechanism involved the expression levels of renal HIF-1 and associated proteins were evaluated.

Results: The blood urea nitrogen and serum creatinine levels and the histologic renal injury scores were significantly lower in 32C ischemia-reperfusion than 37C ischemia-reperfusion kidneys (all P values < .05) at 24hr and 72hr after IR. Microscopic evaluation showed that renal fibrosis were significantly decrased in the kidneys of 32C compared to 37C ischemia-reperfusion mice at 4hr and 24hr after IR. The expression levels of Bax and caspase-3 and the extent of TUNEL and 8-OHdG cell positivity decreased, whereas the renal Bcl-2 level increased, in 32C ischemia-reperfusion compared to 37C ischemia-reperfusion mice. ERK and HIF1 phosphorylation was significantly increased in the kidneys of 32C compared to 37C ischemia-reperfusion mice at 4hr and 24hr after IR. However, TGF beta, SOX9, fibronectin, and collagen IV were significantly decrased in the kidneys of 32C compared to 37C ischemia-reperfusion mice at 4hr and 24hr after IR.

Conclusions: Hypothermic Protection increased the HIF1 and ERK phosphorylation. however it decreased the SOX9 and TGF beta signals. Hypothemia reduced the renal fibrosis after IR renal injury.

Funding: Government Support - Non-U.S.

SA-PO732

Effects of AMPK Deficiency and Sex-Differences in Kidney Parameters Post Uninephrectomy

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Background: Living donor (LD) kidney transplant is the preferred therapy for end-stage kidney disease. LDs have generally excellent outcomes, yet some show that in the first year post-UNX there is an increased risk of hypertension and microalbuminuria. It is unclear whether compensatory kidney changes are beneficial to the LD long term. In some chronic kidney disease (CKD) models activity of the metabolic sensor AMP-activated kinase (AMPK) is lower compared to healthy kidneys. We hypothesized that low AMPK activity pre-UNX could worsen CKD post-UNX when combined with a high-Na^+ diet in both male and female mice. Our work aims to inform mechanisms that could lead to protective interventions for LDs with AMPK activation.

Methods: We used adult male and female mice with double-floxed AMPK alpha subunit (AMPKfl) and ± tamoxifen-driven (tam) expression of Cag-Cre recombinase (Cre+ vs. Cre-AMPKfl). Mice underwent UNX 5 wks post-Tam (vs. Sham surgery) and were all placed on a high-Na^+ (HNa) diet at that time (intervention). We measured GFR, urine albumin and plasma electrolytes at different time points. Kidneys were examined by immunoblot and qPCR.

Results: Cre+AMPKfl males and females kidneys had significant AMPK knockdown (KD) compared to Cre-AMPKfl mice after tam. Females. AMPK-KD (Cre+ mice) females had a significant increase in albuminuria compared to AMPK-sufficient mice, although we did not detect such change in males. AMPK-KD mice had significantly worse anemia compared to AMPK-sufficient mice in both males and females. Although we found that GFR increased after UNX+HNa in AMPK-sufficient females, this compensatory hyperfiltration was not evident in the AMPK-D female mice. In male mice that were AMPK-sufficient we did not observe compensatory hyperfiltration post UNX+HNA (as estimated by blood urea nitrogen (BUN). In contrast, in AMPK-D mice, UNX+HNa had a detrimental effect on BUN.

Conclusions: AMPK KD in both male and female mice worsens kidney injury in a model of kidney donation and HNa diet. These findings implicate AMPK as an important target for potential pharmacological interventions to prevent CKD in men and women LDs.

Funding: Private Foundation Support

SA-PO733

Renal Epithelia Regulate Clearance and Homeostasis of Amyloid-β

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Background: Accumulation of circulating amyloid-β (Aβ) molecules is associated with accelerated Aβ deposition in the brain, thereby accelerating cognitive impairment and dementia. Aβ molecules undergo renal clearance to ensure proper Aβ homeostasis. In chronic kidney disease (CKD), impaired kidney function contributes to accumulation of circulating Aβ and accelerates cognitive impairment. Based on these prerequisites, we here aimed to elucidate molecular mechanisms contributing to impaired renal clearance of Aβ molecules.

Methods: Aβ transporters including P-glycoprotein, LRP1, LRP2 and RAGE were analyzed in multiple mouse models of acute/chronic renal failure, human kidneys and cultures of tubular epithelial cells. Genome-wide array datasets was analyzed using NephroSeq database (GSE69438).

Results: We show that Aβ transporters including P-glycoprotein, LRP1, LRP2 and RAGE are present and polarized in tubular compartments in the kidney. Progressive CKD is associated with loss and/or mislocalization of tubular Aβ transporters, implicating that tubular clearance regulates Aβ homeostasis. Finally, analysis of human kidneys and genome-wide array datasets confirmed that Aβ transporters are equally present in human renal epithelia and lost during progressive CKD.

Conclusions: In summary, we here show that Aβ transporters are present and polarized in tubular compartments in the kidney. Furthermore, we provide evidence that CKD is associated with loss of tubular Aβ transporters and impaired renal Aβ clearance. Because impaired kidney function contributes to accumulation of circulating Aβ and accelerates cognitive impairment, these findings provide insights into molecular mechanisms underlying clearance and homeostasis of Aβ.

SA-PO734

1,25-Dihydroxy-Vitamin D3 Regulates M2 Macrophage Polarization via the VDR-PPARγ Signaling Pathway in Lupus Nephritis Mice

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Background: Lupus nephritis (LN) is one of most serious manifestation of systemic lupus erythematosus (SLE). Recent studies have shown besides autoantibodies and complement activation, macrophage polarization play a major role in the pathogenesis of LN. 1,25-Dihydroxyvitamin D (1,25(OH)2D3) has immunomodulatory activity, and 1,25(OH)2D3 deficiency is correlated with SLE, especially with activity of LN. This study aimed to explore whether 1,25(OH)2D3 modulates macrophage polarization in LN and its underlying mechanism.

Methods: We compared the levels of 1,25(OH)2D3, renal injury (proteinuria, serum urea), and inflammatory cytokines (TNF-α, interleukin (IL)-10) in MRL-*Fas*^{lpr} mice expressing VDR and VDR knockout (KO) MRL-*Fas*^{lpr} mice. Infiltration with M1-like (iNOS+/CD68+), M2-like macrophages (CD163+/CD68+) in renal tissue were detected using immunohistochemical analysis. Peripheral blood monocytes were isolated in MRL-*Fas*^{lpr} mice, and were incubated with or without 1,25(OH)2D3 (10^{-8} mol/L). M1 and M2 macrophages in vitro were induced by treating cells with 100 U/mL IFNγ + 5 ng/mL LPS or 10 ng/mL IL-4, respectively. In order to explore the underlying mechanism, these cells were treated with VDR siRNA and the PPARγ antagonist. mRNAs expression levels of iNOS, MR and Arg-1 were assessed by RT-PCR.

Results: In vivo, compared with VDR KO MRL-*Fas*^{lpr} mice, more positive for CD68 and iNOS cells were infiltrated in renal tissues in expressing VDR mice, a phenotype suggestive of M1 macrophages. 1,25(OH)2D3 and IL-10 levels were also observed higher than VDR KO MRL-*Fas*^{lpr} mice, whereas TNF-α, proteinuria, serum urea levels were lower. In vitro, pretreatment with 1,25(OH)2D3 significantly inhibited M1 activation, enhancing M2 macrophage activation. Moreover, it upregulated the expression of anti-inflammatory cytokine IL-10 and MR, Arg-1 mRNA but downregulated the expression of iNOS mRNAs. However, cells treated with VDR siRNA and PPARγ antagonist were decreased the tendency toward M2 polarization. Moreover, the expression of PPARγ was decreased when cells treated with VDR siRNA.

Conclusions: The above results demonstrate that 1,25(OH)2D3 promoted M1 phenotype switching to M2 via the VDR-PPARγ pathway in LN. 1,25(OH)2D3 treatment ameliorated LN-associated renal inflammatory injury.

Funding: Government Support - Non-U.S.

SA-PO735

IL-6-Mediated Phosphorylation of STAT3 at Tyrosine 705 Leads to Proliferation of Pericytes and Fibroblasts

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Background: Fibrosis is a final common pathway that leads to progressive chronic kidney disease (CKD) and end stage renal disease. Inflammation is one of the many events occurrs during the progression of CKD. IL-6, an inflammatory cytokine, contributes to kidney disease by enhancing the signaling response of tubular epithelial cells to profibrotic cytokines. STAT3 is known to be activated following phosphorylation at tyrosine 705 in response to IL-6, which plays a key role in many cellular processes such as cell proliferation and apoptosis. The role of IL-6/STAT3 pathway in the differentiation of specific cell types and its outcome in kidney fibrosis remains largely unknown.

Methods: We used the mouse pericyte cell line 10T1/2 and human fibroblast cells. We treated these cells with different doses (20 ng/ml to 300 ng/ml) of recombinant IL-6 for different time points. Phosphorylation of STAT3 was evaluated by western blot and immunofluorescence using anti-phospho-STAT3 specific antibody. To assess the cellular proliferation, we used MTS assay. The cellular migration was examined by trans well chamber method. The expression of pro-fibrotic markers was detected by RT-PCR, immunofluorescence and western blot analysis.

Results: IL-6 induced the activation of STAT3 in 10T1/2 and human fibroblast cells, and up-regulated the phosphorylation of STAT3 (Tyr705) in a dose and time dependent manner. The dose of IL-6 for activation of STAT3 was different in these two cell types (10T1/2 and human fibroblasts showed pSTAT3 at 20 and 300 ng/ml respectively). After phosphorylation, STAT3 was translocated to the nucleus, which is crucial for its transcriptional activity. IL-6 mediated phosphorylation of STAT3 caused cellular proliferation of human fibroblasts (at 72 hours by 123.88% and of mouse pericytes 10T1/2 (at 96 hours by 131.71%) as compared to respective control cells. pSTAT3 increased the expression levels of α-SMA, Collagen 1 and fibronectin.

Conclusions: IL-6/STAT3 pathway may participate in cellular proliferation of pericytes and fibroblasts during fibrosis development and its inhibition may reduce the proliferation of these cells leading to reduced fibrosis.

Funding: Private Foundation Support

SA-PO736

IL34-Induced M2-Like Macrophage Polarization Promotes Renal Interstitial Fibrosis via Macrophage-to-Myofibroblast Transition

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Background: M2-like macrophages play important roles during the injury and repair phases in kidney diseases. However, the relationship between M2-like macrophages and fibrosis is still controversial, with some studies showing pro-fibrotic effects while others showing anti-fibrotic effects.

Methods: Here, we used the Cre/LoxP system to generate renal tubular epithelial cells-specific IL34-overexpression mice (Cdh16-Cre; LSL-IL34 mice and Tamoxifen-induced Cdh16-iCreERT2; LSL-IL34 mice).

Results: We found that Cdh16-Cre; LSL-IL34 mice spontaneously experienced weight loss, renal injury, decreased survival rates and declined renal function after birth. Furthermore, they automatically developed into renal fibrosis, which was marked by notable intrarenal infiltration of M2-like macrophages. The similar results were also found in the Tamoxifen-induced Cdh16-iCreERT2; LSL-IL34 kidneys. The proteome and transcriptome analysis of Cdh16-Cre; LSL-IL34 kidneys showed a high degree of relationship between the extracellular matrix deposition and the infiltrated macrophages. Meanwhile, transcriptome sequencing of isolated macrophages from Cdh16-Cre; LSL-IL34 kidneys revealed the infiltrated macrophages in Cdh16-Cre; LSL-IL34 kidneys were predominantly M2-like ($CD204^+$ $CD206^+$ $CD163^+$) and characteristically exhibited

a myofibroblast phenotype (Fibronectin$^+$ Acta2$^+$ Collagens$^+$). The M2-like macrophage polarization and macrophage-to-myofibroblast transition were further supported by flow cytometry, immunofluorescence and confocal fluorescence microscopy. On the contrary, Clodronate Liposomes (CLs)-mediated depletion of renal M2-like macrophages in Cdh16-Cre; LSL-IL34 mice alleviated the renal injury and fibrosis.

Conclusions: Tubular IL34 specifically activates M2-like macrophages, which can directly transdifferentiate into myofibroblasts (MMT) and in turn promote renal interstitial fibrosis.

Funding: Government Support - Non-U.S.

SA-PO737

Development of a New Macrophage-Specific TRAP Mouse (Mac^{TRAP}) and Definition of the Renal Macrophage Translational Signature

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Background: Tissue macrophages play an important role in organ homeostasis and immunity as well as pathogenesis of inflammatory-driven diseases including organ fibrosis, atherosclerosis and autoimmune disorders. One major challenge has been as how to selectively study resident macrophages *in vivo* in highly heterogeneous organs such as kidney.

Methods: To address this problem, we adopted a *translational ribosome affinity purification* (TRAP) - approach and designed a transgene that expresses an enhanced green fluorescent protein (eGFP)-tagged ribosomal protein (L10a) under the control of the macrophage-specific c-fms promoter, a driver of the macrophage colony-stimulating factor 1 receptor (Csf1r), to generate c-fms-eGFP-L10a transgenic mice (Mac^{TRAP}).

Results: Rigorous characterization and validation found no gross anatomical, behavioral or developmental abnormalities in Mac^{TRAP} mice and confirmed transgene expression across various organs. Immunohistological analyses of Mac^{TRAP} kidneys identified eGFP-L10a-expressing cells in the tubulointerstitial compartment that stained positive for macrophage marker F4/80. Following induction of kidney fibrosis we observed a robust upregulation of eGFP-L10a along with classical macrophage and fibrotic markers, validating Mac^{TRAP} responsiveness upon proinflammatory challenge. Using TRAP, we successfully extracted macrophage-specific polysomal RNA from Mac^{TRAP} kidneys and conducted RNA sequencing followed by extensive bioinformatical analyses, hereby establishing a comprehensive *in vivo* gene expression and pathway signature of resident renal macrophages and closely related dendritic cells.

Conclusions: In summary, we have created, validated and applied a novel and responsive macrophage-specific TRAP mouse line, defining the translational profile of renal macrophages and dendritic cells. This new and broadly applicable tool may be of great value for the study of macrophage biology in different organs and various models of injury and disease.

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SA-PO738

Disruption of CD40 Attenuates Renal Injury Induced by Acute High Salt Intake in Experimental Hypertensive Renal Disease

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Background: We have recently shown that circulating levels of the pro-inflammatory receptor CD40 predict progression of renal dysfunction in patients with hypertensive renal disease and the soluble ligand for CD40 (sCD40L) is significantly elevated in this setting. In our CD40 knockout (KO) model developed on a background prone to hypertensive renal disease (Dahl S rat), we demonstrated significantly reduced renal fibrosis and improved renal function following a chronic high salt diet. To test the hypothesis that disruption of CD40 attenuates early indicators of renal injury and reduces inflammation, we performed the following acute high salt study.

Methods: Seven-week old Dahl S wild-type and Dahl S CD40KO male rats (n=8 per group) were given a high salt diet (2% NaCl) for 1 week. Blood pressure, urinary protein excretion (UPE), and plasma creatinine were measured. Kidneys were assessed for evidence of inflammation and injury.

Results: After acute high salt diet, blood pressure and plasma creatinine between wild-type Dahl S rats and Dahl S CD40KO rats were similar. UPE was significantly reduced in the Dahl S CD40KO compared to Dahl S rats (33.7±6.8 mg/24h vs. 106.9±28.6 mg/24h, $p<0.05$). Renal cortex gene expression of kidney injury molecule-one (KIM-1) ($p<0.05$), monocyte chemoattractant protein-1 (MCP-1) ($p<0.001$), and chemokine (C-X-C motif) ligand 2 (CXCL-2) ($p<0.05$) were significantly lower in Dahl S CD40KO rats compared to Dah S rats as assessed by quantitative PCR.

Conclusions: Disruption of CD40 significantly reduced proteinuria, KIM-1, and markers of inflammation following acute high salt induced renal injury. Our results indicated that CD40 may serve as a therapeutic target to inhibit acute renal injury and prevent the progression of hypertensive renal disease.

SA-PO739

Protein-Bound Uremic Toxins Induce NLRP3 Inflammasome Activation in Proximal Tubule Cells

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Background: Protein bound-uremic toxins (PBUTs) are not efficiently removed by hemodialysis in chronic kidney disease (CKD) patients. Their accumulation can lead to cellular dysfunction, inflammation and oxidative stress. Moreover, it has been shown that increased intrarenal expression of the NLRP3 receptor and IL-1β are associated with reduced kidney function, suggesting a critical role for the NLRP3 inflammasome in CKD progression. Here, we evaluated the effect of PBUTs on NLRP3 inflammasome activation in human conditionally immortalized proximal tubule epithelial cells (ciPTECs).

Methods: NLRP3 activation was studied after exposing cells to LPS, ATP, indoxyl sulfate (IS), and a mixture of eight anionic PBUTs (UT-mix). Expression levels of inflammasome components (NLRP3, caspase-1, IL-1β), IL-1β secretion, caspase-1 activity and production of reactive oxygen species (ROS) were evaluated.

Results: Exposure to a combination of LPS (1 µg/ml; 24h) and ATP (5 mM; 30 min) showed 3-fold ($p<0.01$) increase in IL-1β secretion, and 2-fold ($p<0.05$) increase in caspase-1 activity, suggesting that the NLRP3 pathway is functional in ciPTECs. Next, 24h exposure to increasing concentrations of IS increased mRNA expression of NLRP3 (2.3-fold; $p<0.01$), caspase-1 (2.2-fold; $p<0.01$) and IL-1β (24-fold; $p<0.01$). Similar results were observed for UT-mix: NLRP3 (1.7-fold increase; $p<0.05$), caspase-1 (1.8-fold increase; $p<0.05$) and IL-1β (4.5-fold increase; $p<0.001$). In addition, exposure to IS and UT-mix led to 10-fold ($p<0.001$) and 3-fold ($p<0.001$) increases in IL-1β secretion, respectively. Similarly, there was 1.9-fold ($p<0.01$) increase of caspase-1 activity upon treatment with IS and 1.8-fold increase after exposure to UT-mix. Furthermore, IS and UT-mix induced the production of intracellular ROS (2.6-fold increase for IS and 1.9-fold increase for UT-mix; $p<0.05$). Finally, IL-1β secretion was reduced when the N-acetylcysteine (1.8 mM; 24h) was added as a pre-treatment (47% reduction for IS and 35% reduction for UT-mix; $p<0.05$), suggesting that inflammasome activation is ROS-mediated.

Conclusions: PBUTs are able to induce NLRP3 inflammasome activation in proximal tubule cells via oxidative stress, suggesting their involvement in a local inflammatory response in kidney disease.

Funding: Government Support - Non-U.S.

SA-PO740

Mint3 Mitigates Renal Fibrosis After Ischemia-Reperfusion Injury Through Protection of Tubular Epithelial Cells from Apoptosis via Upregulation of NF-κB

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Background: Tubulointerstitial fibrosis is a hallmark of chronic kidney disease (CKD), and initiated by tubular epithelial cell (TEC) injury. Hypoxia promotes tubular cell death, fibrosis, and CKD progression. Munc18-1-interacting protein 3 (Mint3) is a molecule that activates hypoxia-inducible factors (HIFs) by binding and suppressing factor inhibiting HIF-1 (FIH). However, the role of Mint3 in tubulointerstitial fibrosis remains unknown.

Methods: We induced fibrosis of the kidney after unilateral ischemia-reperfusion injury (uIRI) in Mint3-knockout and littermate wild-type mice. The function of Mint3 was further investigated by using mouse cortical tubular (MCT) cells, which were treated with Mint3 and/or FIH siRNA and exposed to hypoxia. Apoptosis was assayed with cleaved caspase-3 and TUNEL staining, and flow cytometry with Annexin-V and 7-AAD.

Results: We found that Mint3 was mainly expressed in TECs with immunostaining of the kidney. Knockout of Mint3 did not affect the acute injury induced by uIRI, but exacerbated the tubulointerstitial fibrosis, accompanied by an increase in TEC apoptosis. Consistently, hypoxia-induced apoptosis of MCT was aggravated by Mint3 knockdown. Unexpectedly, the additional knockdown of FIH did not suppress the increase in apoptosis by Mint3 knockdown, demonstrating the irrelevance of the FIH/HIF pathway. Hence, we focused on NF-κB, a transcription factor which has an anti-apoptotic role, as well as a well-known proinflammatory role. While NF-κB forms a dimer and usually promotes transcription, a homodimer of p50 or p52, which lacks a transactivation domain, can suppress transcription. Indeed, the expression of the inhibitory NF-κB p50 and the protein in nuclei were increased by knockdown of Mint3 in the TECs and by its knockout in the kidney, along with the decreased expressions of the NF-κB-targeted anti-apoptotic genes.

Conclusions: This study demonstrated the importance of TEC injury as a primary event leading to renal fibrosis, as well as unexpected relationship of Mint3 and NF-κB. Mint3 protects the cells from apoptosis by decreasing inhibitory effects of NF-κB, leading to fibrosis suppression. This new pathophysiology of tubulointerstitial fibrosis can be a target of the future therapy for CKD.

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SA-PO741

Nrf2 Deletion Attenuates Kidney Injury Caused by Cullin Ring Ligase Dysfunction

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Background: Nrf2 is postulated to play a protective role in oxidative stress-induced kidney injury; conversely, multiple studies have shown that aberrant Nrf2 activity can be damaging. Nrf2 abundance is determined by cullin-RING ligases (CRLs), which control the regulated degradation of proteins through the ubiquitin proteasome system. CRLs, in turn, are regulated by the COP9 Signalosome (CSN). We previously reported that nephron-specific CSN disruption (KS-*Jab1*$^{-/-}$ mice) causes progressive renal injury, with increased Nrf2. Here, we tested the hypothesis that direct Nrf2 accumulation exacerbates kidney injury in this model, using KS-Jab1 and Nrf2 double knock out mice (DKO).

Methods: The Pax8-rtTA mouse system was used to generate inducible mice with genetic deletion of the catalytically active CSN subunit, *Jab1*, only along the nephron (KS-*Jab1*$^{-/-}$). KS-*Jab1*$^{-/-}$ were bred to mice with global and constitutive deletion of Nrf2 (DKO). Kidney damage was evaluated at 1 week (early) and 8 weeks (late) after *Jab1* deletion.

Results: KS-*Jab1*$^{-/-}$ showed an increase in Nrf2 activity which was attenuated in DKO at both time points. Early KS-*Jab1*$^{-/-}$ demonstrated an increase in blood urea nitrogen (BUN; 34 ± 2 vs. 26 ± 1 mg/dl in controls), and kidney weight (6.8 ± 0.3 vs. 5.3 ± 0.2 mg/g BW in controls). Analysis of the proximal tubule injury marker KIM-1 (kidney injury molecule-1) via Western blot revealed an increase in KS-*Jab1*$^{-/-}$ compared to controls. Furthermore, immunofluorescent staining using antibodies against the proliferation marker Ki-67 demonstrated an increase in the number of proliferating cells located in kidney medulla (208 ± 27 vs. 42 ± 4 cells/field in controls). Nrf2 deletion in early DKO significantly attenuated the rise in BUN (29 ± 2 mg/dl), KIM-1 abundance, and medullary Ki-67 positive cells (96 ± 13 cells/field). Kidney weight trended lower (6.0 ± 0.5 mg/g BW), but was not significantly different. Late DKO showed no significant differences in BUN, kidney weight, or KIM-1 abundance compared to time-matched KS-*Jab1*$^{-/-}$.

Conclusions: Disrupting the CRL pathway in mouse tubules, which leads to kidney damage, also increases Nrf2 activity. Nrf2 deficiency reduces kidney injury after *Jab1* deletion early, but not at later time points. The results suggest that treatment via modulation of Nrf2 activity in progressive kidney disease may have unexpected effects.

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SA-PO742

Unilateral Ureter Obstruction (UUO)-Induced Renal Fibrosis Is Attenuated by Suppression of Indoxyl Sulfate (IS) Accumulation in Sulfotransferase (Sult)1a1-Deficient Mice

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Background: Obstructive nephropathy is the result of functional or anatomic lesions located in the urinary tract, and renal interstitial fibrosis is a common finding associated with long-term nephropathy. Many factors are involved in the pathogenesis of renal fibrosis, such as macrophages, growth factors, oxidative stress and inflammatory cytokines. Indoxyl sulfate (IS), a typical sulfate-conjugated uremic solute, accumulates markedly in serum and kidney of drug or ischemic AKI models, thereby inducing oxidative stress. IS is produced predominantly in the liver by CYP2A6/2E1-mediated oxidative metabolism of gut microflora-derived indole to indoxyl, followed by Sult1a1-mediated sulfate transfer to indoxyl. Thus, we established Sult1a1 gene-deficient (KO) mice to investigate the pathological role of IS in UUO-induced renal interstitial fibrosis.

Methods: The left ureter of C57BL/6J mice (wide type, WT, 8wks-old) and KO (8wks-old) were obstructed last for 2 weeks. IS concentration in serum and renal tissue was determined by LC-MS/MS. BUN was determined as renal damage marker. Changes in interstitial fibrosis formation was histologically examined by Sirius red staining. Renal fibrosis-related factors(Col1a1, α-SMA,TGF-β1)were detected by Western blot analysis or quantitative qRT-PCR.

Results: Elevated BUN in WT-UUO mice was significantly reduced in KO-UUO mice (1.44-fold). By UUO treatment, IS accumulation in serum, kidney and liver were markedly elevated in WT-UUO mice, which were suppressed in KO-UUO mice. IS accumulation in the unobstructed kidney was also decreased in KO-UUO mice. Remarkable interstitial fibrosis was observed in the kidney of WT-UUO, but was partly prevented in the kidney of KO-UUO mice. The medulla portion in the kidney of KO-UUO mice exhibited alleviated atrophy compared with that in WT-UUO mice. The high expression of Col1a1, α-SMA and TGF-β1 in the kidney of WT-UUO was suppressed in KO-UUO mice, 1.40-fold, 2.30-fold and 1.68-fold, respectively.

Conclusions: Sult1a1-deficient mice showed suppressed IS accumulation in the serum and kidney after UUO treatment, suggesting that Sult1a1 is the enzyme responsible for IS production. Renal IS accumulation during progression of UUO nephropathy could enhance interstitial fibrosis.

SA-PO743

Ablation of Polyamine Catabolic Enzymes Protects Against Renal Damage and Fibrosis due to Long-Term Cisplatin Treatment

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Background: Cisplatin is a highly effective anti-neoplastic agent against a variety of solid tumors; however, complications associated with its use such as nephrotoxicity limit its effectiveness. While cisplatin's main anti-tumor activity is via the formation of DNA adducts and disruption of cell cycle progression, its general toxicity is mediated by the induction of oxidative stress. Enhanced polyamine catabolism, mediated via increased expression and activity of spermidine/spermine N1-acetyltransferase (SAT1) and spermine oxidase (SMOX), and generation of toxic products of polyamine degradation (acrolein, H_2O_2 and aldehydes) is important in the mediation of acute kidney injury in mice treated with a single high dose of cisplatin (20mg/kg). We hypothesized that the inhibition of polyamine catabolism will reduce the severity of chronic renal injury caused by long-term cisplatin treatment.

Methods: Using a multiple low dose cisplatin (single weekly cisplatin injection of 7mg/kg for 4 weeks) which more closely simulates the course of cisplatin treatment in cancer patients, we examined the effect of inhibition of polyamine catabolism on the severity of renal injury. The onset and severity of renal damage was determined by assessment of renal function (serum creatinine and blood urea nitrogen levels), damage to the tubular epithelium and renal fibrosis.

Results: Treatment of mice with multiple low doses of cisplatin led to renal tubular damage, interstitial fibrosis and deterioration of renal function. This was associated with increased expression of polyamine catabolizing enzymes *Sat1* and *Smox* transcripts. Comparing the effect of multiple low dose cisplatin treatment in wild type (Wt), *Smox*-KO and *Sat1*-KO mice revealed that *Sat1*-KO and *Smox*-KO mice are significantly protected against renal tubular injury, interstitial fibrosis and loss of renal function.

Conclusions: These studies indicate that: 1) the expression and activity of *Smox* and *Sat1* increase in animals treated with multiple low doses of cisplatin; and 2) the ablation of these genes reduces the severity of renal injury, interstitial fibrosis and loss of renal function. These results suggest that modulating the activity of polyamine catabolic enzymes or neutralizing the toxic products of polyamine catabolism protects against cisplatin-induced chronic renal injury.

Funding: Veterans Affairs Support

SA-PO744

Discovery and Validation of Intestinal Microbiota as Gut Biomarkers for Mirroring Disease Progression and Circulating Nephrotoxin Levels in CKD

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Background: The interplay of the gut microbes with gut-producing nephrotoxins and the renal progression remains unclear in cohorts with different stage of chronic kidney disease (CKD) patients.

Methods: Analysis of intestinal microbiota (16S rRNA gene sequencing) and circulating p-cresyl sulfate/indoxyl sulfate were conducted in 92 (31 mild, 30 moderate and 31 advanced) CKD patients and 30 controls (discovery cohort), and further validated in a cohort comprising 22 controls and 76 peritoneal dialysis patients. Spearman's correlation was used to determine the association of major genera (>0.1% abundance and present in >90% of samples) with serum biomarkers and disease severity. Chao1 index and Bray-Curtis distance were used to assess microbial community diversity. Functional composition of metagenomes was predicted from 16S rRNA data by the phylogenetic reconstruction of unobserved states (PICRUSt).

Results: Significant differences in bacterial composition and diversity were noted among controls and patients at different disease stages. A core CKD-associated microbiota consisted of 7 genera (Escherichia_Shigella, Dialister, Lachnospiraceae_ND3007_group, Pseudobutyrivibrio, Roseburia, Paraprevotella and Ruminiclostridium) and 2 species (Collinsella stercoris and Bacteroides eggerthii) were identified to be highly correlated with the stages of CKD. Paraprevotella, Pseudobutyrivibrio and Collinsella stercoris were superior in discriminating CKD from the controls than the use of urine protein/creatinine ratio, even at very early-stage of disease. The performance was further tested in validation cohort. Bacterial genera highly correlated with indoxyl sulfate and p-cresyl sulfate levels were identified, and predicting the functional capabilities of microbial communities by PICRUSt showed that microbial genes related to the metabolism of aromatic amino acids (phenylalanine, tyrosine, and tryptophan) were differentially enriched among the control and different CKD stages.

Conclusions: Our results provide solid human evidence of the impact of gut-metabolite-kidney axis on the severity of CKD and highlight a usefulness of specific gut microorganisms as possible biomarker or therapeutic target of this global health burden.

Funding: Other NIH Support - Chang Gung Memorial Hospital

SA-PO745

Probiotic Bifidobacterium animalis subsp. lactis Bi-07 Protects Intestinal Barrier by Alleviating Intestinal Oxidative Stress in Uremic Rats

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Background: To investigate whether oral administration of probiotic *Bifidobacterium animalis subsp. lactis Bi-07*(*B. animalis subsp. lactis Bi-07*)could protect intestinal barrier in uremic rats and to explore whether it could alleviate oxidative stress in intestinal tissues.

Methods: Thirty SD rats were randomly divided into 3 groups (n=10). The sham operation group only opened the renal capsules. The uremia group underwent 5/6 nephrectomy. Uremia+probiotics group: *B.animalis subsp. lactis Bi-07* was administered daily to the rats for 5 weeks after 5/6 nephrectomy. Determination of 99mTc-DTPA in blood and urine after intragastric administration of 99mTc-DTPA solution evaluated Intestinal permeability. At the end of the intervention, the intestinal segments were retrieved. The ultrastructure of the intestinal epithelial tight junction (TJ) complex was observed by scanning electron microscopy (SEM) combined with lanthanum nitrate staining. After preparation of intestinal homogenate, malondialdehyde (MDA) content and superoxide dismutase (SOD) activity were detected.

Results: SEM showed that microvilli structure of the intestinal epithelial cells in the uremia group was disordered, sparse and shed. Lanthanum nitrate dye could penetrate into the intestinal epithelial cells gap. Compared with the uremia group, microvilli were neatly arranged and TJ was structurally intact. Little of lanthanum nitrate penetrated cell gap in uremia+ probiotics group. Compared with uremic group, *B. animalis subsp. lactis Bi-07* can significantly reduce intestinal permeability (P<0.05). The content of MDA of the ileal tissue was significantly increased in the uremia group (P<0.05), SOD activity was significantly decreased (P<0.05). Compared with the uremia group, the uremia +probiotic group significantly increased SOD levels, suggesting that *B. animalis subsp. lactis Bi-07* protects the intestinal barrier by alleviating oxidative stress.

Conclusions: The probiotic *B. animalis subsp. lactis Bi-07* can protect the intestinal barrier in uremic rats. The mechanism may be to alleviate intestinal oxidative stress and reduce intestinal barrier damage in uremia.

Funding: Government Support - Non-U.S.

SA-PO746

The Expression of Intestinal Mir-223/NLRP3 Axis in Uremic Rats and the Intervention of Probiotics

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Background: To investigate the role of chronic inflammatory response mediated by NLRP3 inflammasome in uremia intestinal barrier dysfunction by detecting the changes of mir-223 /NLRP3, and to observe the effect of probiotic intervention on it.

Methods: Seventy SD rats were randomly divided into 3 groups and 20 sham group (SH group). 5/6 Nephrectomy was performed on 50 rats in the uremic model group, and the final histopathology confirmed the successful modeling, which were randomly divided into the uremic group (UR group, n=20), probiotics intervention group (UP group, n=20), and intestinal tissue were extraction. The expression of miR-223 mRNA of each group was detected by RT-qPCR. Expression of NLRP3, caspase-1, IL-1β, tight junction protein in intestinal epithelial cells were detected by Western blotting. Bioinformatics software was used to predict the binding site of mir-223-3p and NLRP3 gene. The 3'UTR sequence of NLRP3 gene and its mutants were cloned into the dual luciferase reporter gene vector, and the wild-type and mutant recombinant double luciferase reporter plasmid vector were constructed. PCR and gene sequencing were used to determine whether the vector was successfully constructed, and 293 cells were used for grouping transfection and cell luciferase detection.

Results: Compared with SH group, the expression of miR-223 mRNA in the ileal tissues of the UR group was significantly decreased, while that of UP group was significantly increased (*P*<0.05). Western blotting showed that the expressions of NLRP3, caspase-1 and IL-1β of the UR group were significantly higher than those of the SH group (*P*<0.05), while the expressions of JAM-1, Occludin and claudin-1 proteins were significantly lower (*P*<0.05). However, after probiotics intervention, the expressions of NLRP3, caspase-1 and IL-1b was decreased (*P*<0.05), and the expressions of JAM-1, Occludin and claudin-1was improved. After 293 cells co-transfected with miR-223-3p mimic or inhibitor, NLRP3-3 'UTR wild-type had decreased or increased luciferase activity, with statistically significant differences (P < 0.05).

Conclusions: Probiotics can improve the intestinal barrier function of uremia, which may involve the miR-223 /NLRP3 pathway. The conclusion of this study may provide a new treatment idea for the intestinal barrier dysfunction of uremia and chronic inflammation.

SA-PO747

Omega-3 Polyunsaturated Fatty Acids Reduce Intestinal Inflammation and Enhance Intestinal Motility Associated with Reduced Nitric Oxide Production in CKD

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Background: Previous studies have shown that chronic kidney disease (CKD) could elicit an intestinal inflammation and result in intestinal dysmotility followed by many complications. Increasing evidence suggests that omega-3 polyunsaturated fatty acids can reduce intestinal inflammation and improve intestinal function in many diseases. In this study, we therefore investigated the effect of omega-3 polyunsaturated fatty acids on intestinal inflammation and intestinal motility in CKD and the underlying mechanism.

Methods: CKD was induced by the 5/6 kidney resection, and omega-3 polyunsaturated fatty acids enriched diet or standard diet was administrated for six weeks. Intestinal motility was assessed by charcoal transportassay, and intestinal inflammation was assessed by analyzing myeloperoxidase activity and concentrations and gene expression of TNF-α,IL-1β, and IL-10 in the intestinal tissue. The nitric oxide production was assessed in the intestinal tissue.

Results: The results showed that CKD resulted in a marked delay in intestinal motilityand was associated with a significant increase of intestinal levels of inflammatory parameters (*P*<0.05). However, compared to the standard diet, omega-3 polyunsaturated fatty acids enriched diet administration markedly reduced intestinal inflammatory response, and resulted in a significant improvement in intestinal motility(*P*<0.05). In addition, the intestinal nitric oxide production was inhibited by omega-3 polyunsaturated fatty acids enriched diet treatment (*P*<0.05).

Conclusions: These results suggest that omega-3 polyunsaturated fatty acids could reduce intestinal inflammation and enhance intestinal motility in CKD, and the underlying mechanism may be associated with reduced nitric oxide production.

Funding: Government Support - Non-U.S.

SA-PO748

The Effects of Allopurinol on Xanthine Oxidase Activity and Expression in CKD

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Background: Allopurinol lowers uric acid levels and may improve vascular function in chronic kidney disease (CKD). It is unclear whether the effects of allopurinol are mediated by xanthine oxidase (XO) inhibition, uric acid-lowering, or both. We hypothesized that allopurinol suppresses serum XO activity and reduces endothelial XO protein expression.

Methods: We anlayzed serum and endothelial cells samples from 45 CKD patients who participated in a randomized controlled trial of allopurinol vs placebo. Serum XO activity was determined and the expression of endothelial XO protein was evaluated (immunofluorescence). Serum xanthine levels were measured via mass spectrometry. Change from baseline was compared for both study groups.

Results: Baseline serum uric acid correlated with baseline CKD-EPI estimated GFR (r = 0.57, p value <0.0001) but not with serum XO activity (r =0.10, p value 0.52) or endothelial XO protein expression (r =0.2, p value=0.56). There was no correlation between serum XO activity or endothelial XO protein expression with baseline brachial artery flow-mediated dilation (BA-FMD) or CKD-EPI estimated GFR. As shown in the Table, allopurinol lowered serum uric acid levels and increased serum xanthine levels significantly. However, allopurinol did not decrease serum XO activity or the expression of endothelial XO protein. Change in XO activity and XO protein expression did not correlate with change in BA-FMD.

Conclusions: Our data suggest that allopurinol effectively lowers serum uric acid levels by inhibition of XO activity in the liver. However, contrary to our hypothesis, allopurinol does not significantly affect serum XO activity or XO protein expression in the endothelium. In addition our findings suggest that the main factor for increased serum uric acid in CKD is reduced kidney function.

Funding: NIDDK Support

Changes in serum uric acid, serum XO activity, and endothelial XO expression by study group

	Allopurinol (n=24)	Placebo(n=21)	P value
Serum uric acid (mg/dL)	-3.7(1.0)	0.14(1.46)	<0.0001
Serum xanthine (RSI)	2703(2037)	-4.7(177)	<0.0001
Serum XO activity (mU/mL)	-0.21(0.56)	-0.13(0.34)	0.68
XO endothelial expression*	0.08(0.34)	0.22(0.41)	0.55

RSI: relative signal intensity, *: arbitrary units, normalized to XO expression in human umbilical endothelial cells

SA-PO749

Allopurinol Alters the Metabolome of CKD Patients Beyond Uric Acid-Lowering

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Background: Allopurinol, a xanthine oxidase (XO) inhibitor, is the most commonly prescribed uric acid-lowering agent in patients with chronic kidney disease (CKD). Although experimental evidence suggests allopurinol has broader effects on the metabolome, these potential effects have not been characterized in CKD. Here, we sought to evaluate the effects of allopurinol on the metabolome of CKD patients.

Methods: Gas chromatography mass spectrometry (GC-MS) was performed on the serum of 31 subjects who participated in a 12-week randomized clinical trial of allopurinol vs placebo. Metabolites of central carbon metabolism included the TCA cycle, glycolysis, the pentose phosphate pathway, amino acid metabolism, neurotransmission, reactive oxygen species defense, and energetics. Metabolites were compared at baseline to the end of study for allopurinol and placebo (paired t test). MetaboAnalyst software was utilized to identify metabolic pathways.

Results: Of the 90 metabolites evaluated by GC-MS, 6 were significantly altered after allopurinol treatment but not placebo (Table). MetaboAnalyst indicated the pentose phosphate (PP) pathway and purine and pyrimidine metabolism were the top pathways affected by allopurinol. Allopurinol inhibited purine metabolism, resulting in decreased serum uric acid (-3.7 ± 1.0mg/dL) vs placebo (0.1 ± 1.5 mg/dL) ($p<0.0001$) and increased the precursor xanthine. Allopurinol inhibited PP pathway activity as downstream product ribose-5-phosphate decreased and upstream precursor glucose-6-phosphate increased.

Conclusions: We describe, for the first time, important effects of allopurinol on the metabolome of CKD patients. Specifically, PP pathway inhibition is known to contribute to oxidative stress and pyrimidine pathway inhibition is known to increase ammonia. These findings should be confirmed in larger studies and the clinical implications of these broad effects should be explored.

Funding: NIDDK Support

Changes in metabolites by study group

Metabolite	Pathway	Allopurinol (n=16)		Placebo (n=15)	
		Baseline	End of study		
Dihydroxyphenylalanine	Tyrosine metabolism	1033(267)	787(310)*	1069(256)	1117(312)
Glucose-6-phosphate	PP pathway	1214(896)	1906(1274)#	1328(897)	892(510)
Ribose-5-phosphate	PP pathway, purine metabolism	1132(265)	632(187)*	1147(150)	1200(200)
N-acetyltyrosine	Tyrosine metabolism	1258(312)	497(183)*	1279(355)	1343(400)
Orotate	Pyrimidine metabolism	251(82)	4126(4655)*	258(128)	255(184)
Xanthine	Purine and caffeine metabolism	466(168)	3171(2049)*	511(232)	506(283)
Linoleic acid	Lenoleic acid metabollism	1269(651)	934(355)*	1106(427)	1361(607)

Values are expressed as mean(SD) relative signal intensity

*: P value<0.05, #: P value=0.09

SA-PO750

Hydrogen Sulfide Attenuates CKD Progression by Inducing TET-Dependent DNA Demethylation on Klotho Promoter

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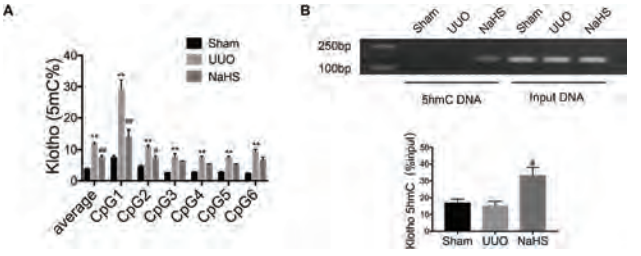
Background: Hydrogen sulfide has been reported to attenuate renal fibrosis. A recent study shows hydrogen sulfide can demethylate its target genes by upregulating TET1 expression in regulatory T cells. Our previous study revealed Klotho hypermethylation in CKD patients, suggesting possible involvement of Klotho promoter hypermethylation in the development of CKD This study aims to investigate whether H_2S can directly change TET hydroxylase expression or activity as well as subsequent DNA demethylation in renal fibrosis.

Methods: C57BL/6 mice underwent unilateral ureter obstruction(UUO) with or without NaHS treatment. Multiple techniques were used to analyze the extent of tubulointerstitial fibrosis and renal hypoxia, the methylation and hydroxymethylation level of renal Klotho promotors, and the expression and activity of TETs. In vitro, HK2 cells received hypoxia treatment. The level of cellular ROS and ferrous ion was examined to further explore the role of hypoxia on TETs enzyme activity and Klotho methylation.

Results: Evidenced by Masson staining and the expression of α-SMA and Fibronectin, NaHS treatment reduced renal fibrosis in UUO mice. Also, it upregulated Klotho expression, decreased Klotho methylation level and increased Klotho hydroxymethylation level, along with increased TETs activity, rather than TETs expression. Moreover, NaHS reduced hypoxic areas of UUO-injured kidney. In vitro, hypoxia increased Klotho methylation level and decreased TET activity. In hypoxic HK2 cells, the level of total ROS and nuclear ROS were raised. Both H_2O_2 and hypoxia reduced the concentration of cellular Fe^{2+}. While ascorbate rescued hypoxia-induced decrease of TETs activity.

Conclusions: Hypoxia causes Klotho hypermethylation by decreasing TETs enzyme activity through ROS-induced Fe^{2+} reduction. And hydrogen sulfide attenuates renal fibrosis by improving hypoxia and enhancing TETs enzyme, which induces Klotho demethylation and restores Klotho.

Funding: Government Support - Non-U.S.



NaHS administration demethylates Klotho in UUO mice.

SA-PO751

The Differential Expression Research of Circular RNAs in Exosomes from Serum and Urine in Patients with Idiopathic Membranous Nephropathy

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Background: To further explore the pathogenesis of IMN, the technique of gene-sequencing was uesd to analyze the differentially expressed circRNAs in exosomes from both the serum and urine of patients with IMN, which may lay the foundation for research of circRNAs as a new class of exosome-base IMN diagnosis biomarkers.

Methods: Ten patients with IMN and ten normal controls were recruited as experimental subjects in our study. The exosomes were extracted from the collected serum and urine. Then, pure circRNAs were extracted from the exosomes with a series of enzymatic reactions. Afterwards, the significantly differentially expressed circRNAs were chosen by the method of gene-sequencing.

Results: Compared with normal controls. the circRNAs were reduced in the exosomes from serum of patients with IMN, which mostly originated from intron gene regions. Meanwhile, a total of 89 circRNAs were significantly differentially expressed, which were also mostly derived from intron gene regions. including 49 up-regulated and 40 down-regulated genes. However, the species were increased in the exosomes from the urine of patients with IMN compared to normal controls, and they mainly originated from exon gene regions. Simultaneously, a total of 60 circRNAs were significantly differentially expressed, which primarily belonged to intron gengeregions, including 54 up-regulated and 6 down-regulated regions.

Conclusions: The significant differential and specific expression of circRNAs in the exosomes from patients with IMN were. For example, MUCA, which originated from chr7:100550808/100551062, could be considered a potential diagnostic biomarker of IMN. Furthermore, these figures may be used as a reference or supplement in the research of the pathogenesis of IMN. Number

SA-PO752

Dietary Phosphate Disturbs of Gut Microbiome In Mice

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Background: Disorder of phosphate metabolism is a common pathological condition in chronic kidney disease (CKD) patients. Excessive intake of dietary phosphate deteliorates CKD and various complications including cardiovascular disease. Recent reports have demonstrated that gut microbiome disturbance is associated with both the etiology and progression of CKD. However, the relationship between dietary phosphate and gut microbiome remains unknown. Here, we examined the effects of excessive intake of phosphate on gut microbiome.

Methods: Five-week-old male C57BL/6J mice were fed either control diet (0.4% phosphate; CP) or high phosphate diet (1.2% phosphate; HP) for eight weeks. Stool samples were collected at eight weeks. After amplifying the V3-V4 region of 16S ribosome RNA by PCR, analysis of the gut microbiota was carried out using MiSeq next generation sequencer (NGS).

Results: Compared with CP diet group, HP diet group significantly decreased in body weight and epididymal fat weight, plasma calcium level, and increased in urinary phosphate excretion. In analysis of gut microbiota, HP diet group increased in *Firmicutes* phylum and decreased in *Bacteroidetes* phylum by PCR and NGS analysis. In particular, significant increase in *Erysipelotrichaceae* genus and decrease in *Clostridia* genus were observed in HP diet group, and NGS analysis showed the decrease in bacterial diversity in HP diet group. In addition, HP diet group decreased colonic tight junction marker mRNA levels.

Conclusions: These results suggest that the excessive intake of dietary phosphate disturbs gut microbiota and decreased in bacterial diversity. Furthermore, it may affect the intestinal barrier function. Such a disturbance may be related to progression of CKD. Adequate management of dietary phosphate would be required to keep healthy environment in gut.

Funding: Government Support - Non-U.S.

SA-PO753

Improvement of the Effect of HIF-1α Stabilizer on the Destruction of Tight Junctions in Intestinal Epithelial Cells Induced by Homocysteine

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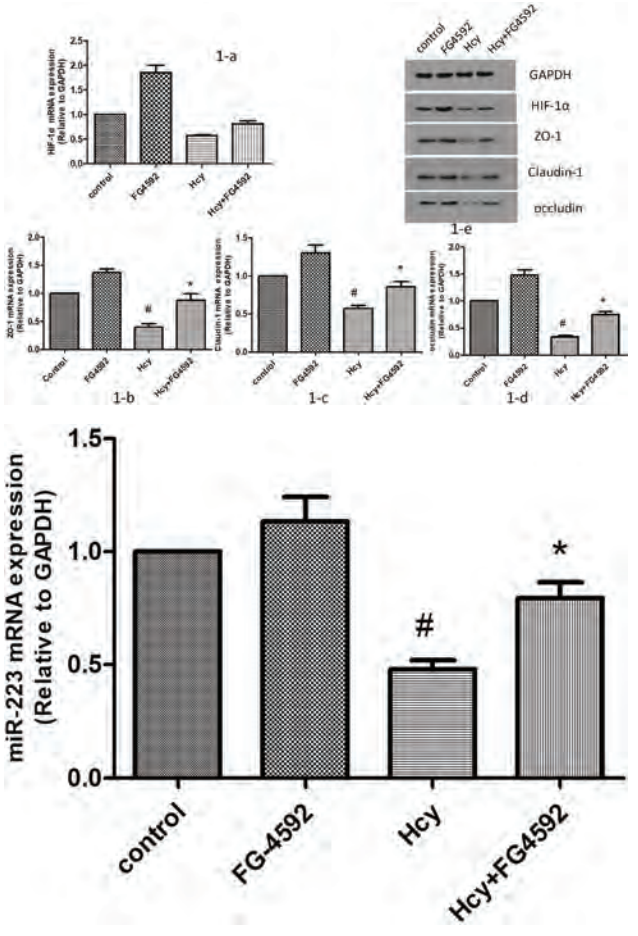
Background: Based on previous findings that homocysteine (Hcy) can increase the permeability of intestinal epithelial Caco2 cell and lead to decreased expression of tight junction molecules, the role of HIF-1α in intestinal barrier dysfunction caused by homocysteine and the mechanism of intervention of HIF-1α stabilizer (FG-4592) on these effects were explored.

Methods: Caco2 cells was cultured and divided into four groups: normal control group, FG4592 group, homocysteine group (Hcy group), Hcy+FG4592 group. mRNA and protein expression levels of HIF-1α, ZO-1, claudin-1, occludin were detected by RT-qPCR and Western blotting. The expression level of miR-223 was detected by RT-qPCR.

Results: Hcy (0.5 mM) can reduce the expression of HIF-1α, claudin-1, occludin and ZO-1mRNA and protein in Caco2 cells, and FG-4592 can improve the expression of these induced by Hcy (P<0.05) through the RT-qPCR or Western bloting method (Fig.1). Hcy can reduce the expression of miR-223 mRNA (P<0.05), while the FG-4592 can increase the expression of miR-223 mRNA (P<0.05) (Fig.2).

Conclusions: miR-223 may be involved in the maintenance of intestinal epithelial barrier function in the experiment of using uremic serum to stimulate Caco2 cells. HIF-1α stabilizer can improve the Hcy-induced reduction expression of HIF-1α, ZO-1, claudin-1, Occludin, up-regulate the expression of miR-223 and down-regulate the expression of NLRP3, the mechanism may involve the mir-223/NLRP3 pathway.



SA-PO754

Effect of Hypoxia-Inducible Factor-1α Stabilizers on the Destruction of Tight Junctions in Uremic Intestinal Epithelial Cells

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Background: Hypoxia-inducible factor-1α (HIF-1α) plays an important role in maintaining the structure and function of the intestinal mucosal barrier and is involved in regulating the expression of intestinal epithelial tight junction proteins. In this study, based on the previous findings, the role of HIF-1α in intestinal barrier dysfunction caused by ureima toxins and the effect of intervention of HIF-1α stabilizer (FG-4592) on the above effects were explored.

Methods: Caco2 cells was cultured and divided into 3 groups, the normal control group, the uremic serum stimulation group, and the uremic serum + HIF-1α stabilizer (FG-4592) intervention group. RT-qPCR and Western blotting method was used to detect the expression of HIF-1α, ZO-1, claudin-1, Occludin, and NLRP3 inflammasome in each group. RT-qPCR was used to detect the effect of miR-223 mimimc and siNLRP3 on NLRP3 expression stimulated by uremia serum. Transfection of miR-223-mimics or miR-223-inhibitor to Caco2 cells followed by downstream gene expression analysis is performed to elucidate the targets and roles of mir-223.

Results: Compared with the control group, the application of uremia serum to Caco2 cells can significantly decrease the expression of HIF-1α, ZO-1, claudin-1, occludin mRNA and protein (P < 0.05), while FG-4592 intervention could reverse the above changes (P < 0.05). On the contrary, stimulation of Caco2 cells by uremia serum can significantly increase the expression of NLRP3, caspase-1 and IL-1β mRNA and protein, while FG-4592 intervention can down-regulate the expression of NLRP3 inflammasome. At the same time, while uremic serum stimulation can increase NLRP3 expression, application of miR-223 mimic or siNLRP3 can reduce NLRP3 expression (P < 0.05). The mRNA and protein expression of NLRP3, caspase-1 and IL-1β of Caco2 cells transfected miR-223-mimic decreased but that increased for tight junction protein, while transfection of miR-223-inhibitor, we got opposite results.

Conclusions: HIF-1α stabilizer (FG-4592) increases the decrease of HIF-1α expression under the stimulation of uremic serum, and its improvement of the expression mechanism of tight junction protein may play a role in the down-regulation of NLRP3 inflammasome caused by the up-regulation of miR-223 expression, thus improving the intestinal barrier function, which needs further experimental verification

SA-PO755

A Guanylate Cyclase C Agonist Linaclotide Reduces Trimethylamine N-Oxide in an Adenine-Induced CKD Model

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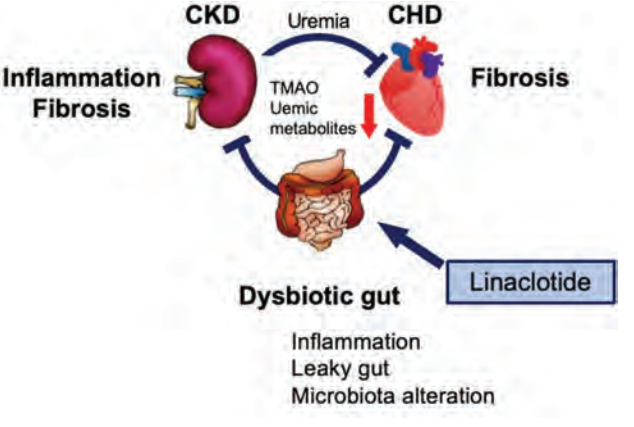
Background: Cardiorenal syndrome is a major cause of mortality in CKD patients. Trimethylamine-*N*-oxide (TMAO), which is a hepatic metabolized product of trimethylamine (TMA) generated from dietary phosphatidylcholine or carnitine derived by gut microbiota, directly linked to the progression of cardiovascular disease and renal dysfunction. Therefore, targeting TMAO may be one of a novel strategy for the prevention of CVD and CKD.

Methods: A guanylate cyclase C agonist linaclotide was administered to adenine-induced renal failure model and the changes of renal function and gut-derived uremic toxins as well as gut microbiota community were analyzed using metabolomic and metagenomic analyses.

Results: Linaclotide decreased the plasma TMAO level at a clinically used dose (10 μg/kg) in an adenine-induced renal failure mouse. In additon, linaclotide (100 μg/kg), significanlty improved renal function and reduced various uremic toxins. Linaclotide reduced renal inflammation and fibrosis, cardiac fibrosis as well as collagen I, TGF-β, galectin-3 and ST2 gene expressions. The plasma galectin-3 and ST2 were also reduced. In the small intestinal crypt, F4/80-positive macrophages were abundant in renal failure and theexpression was decreased by linaclotide. Reduced colonic claudin1 was also restoredby linaclotide, suggesting that linaclotide ameliorated "leaky-gut" in the renal failure. By metagenome analysis, microbial order Clostridiales may have been responsible for the change in TMAO.

Conclusions: Linaclotide reduced TMAO and uremic toxin levelsand be a potent tool for the cardio-renal syndrome by modification of the "gut-cardiorenal axis"

Funding: Government Support - Non-U.S.



gut-cardiorenal axis

SA-PO756

Impaired Secretion of Uremic Solutes in Advanced CKD

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Background: The normal kidney clears many solutes efficiently by proximal tubular secretion. Clearance values are observed to be particularly high relative to the glomerular filtration rate (GFR) when the clearances of protein-bound solutes are calculated in terms of their free, unbound concentrations. This study examined the extent to which high secretory clearances are maintained when kidney function is markedly reduced.

Methods: Simultaneous urine and blood samples were collected from patients with stage V chronic kidney disease not on dialysis (CKD, n=16) and control subjects (control, n=17). The normally secreted and protein-bound solutes indoxyl sulfate (IS) and p-cresol sulfate (PCS) were assayed by LC/MS/MS. Clearances relative to the GFR (fractional clearances) were then estimated by dividing the urine to free plasma concentration ratios for these solutes by the urine to plasma concentration ratio for creatinine.

Results: GFR values estimated by the CKD-EPI equation were 7 ± 2 ml/min/1.73 m^2 in the CKD patients and 86 ± 17 ml/min/1.73 m^2 in the controls. Fractional clearances of IS and PCS were very high in controls in accord with prior results. Fractional clearances for both solutes were greatly reduced in CKD indicating impaired secretion (IS: 5 ± 2 vs. 28 ± 7, p<0.001; PCS: 3 ± 1 vs. 10 ± 3, p<0.001). Impaired kidney secretion was accompanied by prominent plasma accumulation in CKD patients with plasma concentrations of IS and PCS averaging 59 and 27 times greater than those in control subjects as compared to a 9 times greater creatinine concentration.

Conclusions: Secretory clearance of IS and PCS was impaired out of proportion to glomerular filtration in patients with advanced CKD. Prominent accumulation of these and other normally secreted solutes may contribute to uremic illness.

Funding: NIDDK Support, Veterans Affairs Support

	Fractional Clearance			Free Plasma Concentration CKD/Control
	CKD	Control	CKD/Control	
Creatinine				9 *
Indoxyl Sulfate	5 ± 2	28 ± 7	0.2 *	59 *
p-Cresol Sulfate	3 ± 1	10 ± 3	0.3 *	27 *

Values are mean ± sd; * p<0.001 comparing CKD and control

SA-PO757

Association of Tubular Solute Clearances with the Glomerular Filtration Rate and Complications of CKD: The CRIC Study

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Background: The secretion of organic solutes by the proximal tubules is an essential intrinsic kidney function. However, the degree to which secretory solute clearance corresponds with the glomerular filtration rate (GFR) and potential implications of net secretory clearance are largely unknown.

Methods: We evaluated 1240 participants who underwent ^{125} I-iothalamate clearance (iGFR) measurements of GFR in the Chronic Renal Insufficiency Cohort (CRIC) Study. We used targeted mass-spectrometry to quantify 11 secretory solutes in 24-hour urine and plasma samples. We used correlation and linear regression to determine cross-sectional associations of secretory clearances with iGFR and common metabolic complications.

Results: Correlations between iGFR and secretory solute clearances ranged from ρ = 0.21 (p-cresol sulfate) to ρ = 0.55 (kynurenic acid). Lower clearances of most secretory solutes were associated with higher serum concentrations of parathyroid hormone (PTH), triglycerides, and uric acid (Figure). Each 50% lower kynurenic acid clearance was associated with a 16.1 pg/mL higher serum PTH concentration and an 18.2 mg/dL higher serum triglyceride concentration after adjustment for iGFR, albuminuria, and other potential confounders. Secretory solute clearances were not associated with meaningful differences in serum calcium, phosphate, hemoglobin, bicarbonate, or C-reactive protein concentrations.

Conclusions: Patients with CKD differ in their tubular secretory clearance for a given level of GFR. Lower net secretory clearances are associated with higher levels of PTH, triglycerides, and uric acid independent of GFR and albuminuria, suggesting potential clinical and biological relevance of this kidney function.

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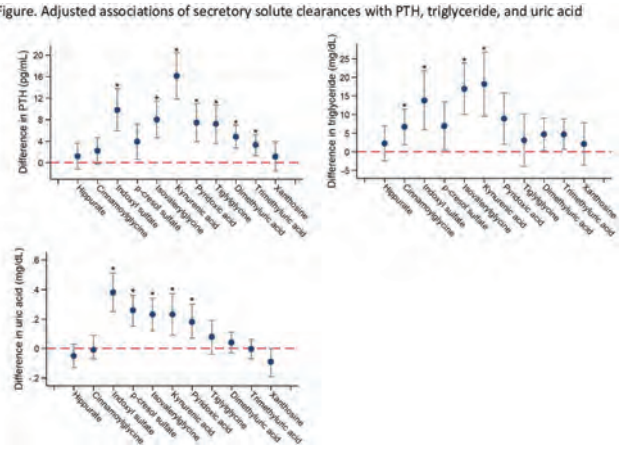
Figure. Adjusted associations of secretory solute clearances with PTH, triglyceride, and uric acid



SA-PO758

Variations in Gut Microbiota May Correlate with Lipid Metabolism in UMOD Knockout Rats

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Background: Tamm-Horsfall protein (THP, uromodulin, UMOD) is an important protective factor during kidney injury. Although it was mainly expressed in the thick ascending limb, uromodulin still can be detected in the serum and in other tissue cells. Study has revealed a crucial role of uromodulin on the M-cell surface for the uptake of SlpA-positive lactic acid bacteria into M cells, possibly leading to subsequent delivery of the bacteria to dendritic cells closely associated with M cells for immunomodulation. In this study we investigated the change of gut microbiome in UMOD ablation rats.

Methods: 10wild type SD male rats and 10 UMOD knockout SD rats (THP-/-) were housed under controlled environment for10 weeks. Same water and diet were provided. All of the rats were anesthetized to collect fecal samples from large intestine directly. The bacterial composition was analyzed based on 16S ribosomal DNA pyrosequencing. Bioinformatics tools, including sequence alignment, abundance, and taxonomic diversity, were used in microbiome data and its products analyses.

Results: There was no difference in mean weight between two groups. The serum triglyceride (TG) decreased significantly in THP-/-rats (0.632&1.473mmol/L, p<0.05). The microbial richness and diversity in composition were different in THP-/- rats compared with WT (PCoA analysis, p=0.036). At the phylum level, there were obvious reductions in Elusimicrobia and Actinobacteria in THP-/- rats (p<0.05). At the genus level, five genera were obviously increased in THP-/- rats(p<0.05), including Helicobacter, Lactobacillus, Roseburia, Clostridium XI and Phascolarctobacterium. While four genera, including Alloprevotella, Elusimicrobium, Intestinimonas and Ruminococcus decreased (p<0.05). Among those changed genera, Ruminococcus and Elusimicrobium presented positive correlation with TG, while Phascolarctobacterium, Lactobacillus and Alloprevotella were negative correlated with TG (P<0.05). Obvious variations were identified in 33 microbial metabolites with the change of microbiota. 22 out of 33 microbial metabolite products were fatty acid.

Conclusions: UMOD ablation led to significant variations in composition of gut microbiota in SD rats. The change of gut microbiota correlated with serum TG, suggested other pathways may be involved the abnormal lipid metabolism in chronic kidney disease

SA-PO759

Carbamylation of Albumin Results in Structural Changes That Minimize Binding to Cubilin and FcRn Resulting in More Rapid Serum Clearance

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Background: Chronic kidney disease results in high serum urea concentrations and leads to increased cardiovascular disease. An increase in urea results in excessive protein carbamylation which has been associated with increased mortality. We hypothesized carbamylation would alter the structure of albumin leading to reduced binding to cubilin and or FcRn resulting in increased serum clearance.

Methods: To test this hypothesis rats were injected at time 0 with RSA or RSA modified with KCN 30min, 2hr or 4hr to induce increasing amounts of carbamylation. Increased serum clearance was observed in a dose dependent fashion. To determine the mechanism we quantified the number of lysine residues modified on RSA using MALDI TOF and showed increasing Lys residues modified with longer KCN incubation times. We then asked whether increased clearance was the result of decreased binding to cubilin, which would result in reduced PTC uptake, and or FcRn which would reduce transcytosis of albumin. Using Microscale Thermophoresis to quantify changes in binding affinity values, Kd, we observed a reduction in both cubilin and FcRn binding with carbamylated RSA, compared to RSA.

Results: Specifically, the Kd of cubilin 7,8 increased from 0.01 mM for unmodified RSA to 1.2 mM for 30min, 1.7 mM for 2hr and 10 mM for 4hr carbamylated RSAs, respectively. For FcRn the Kd for albumin was10 mM for unmodified albumin, while 2hr carbamylated RSA was >100 mM and 4hr had no binding. The decreased binding to both cubilin 7,8 and FcRn can explain the increased serum clearance and is also consistent with our observed increase in carbamylated albumin in the urine. To better understand the changes to albumin mediated by carbamylation we performed a structural characterization analysis of modified albumin using small-angle X-ray scattering (SAXS) to evaluate shape changes with carbamylation. Guinier and P(R) analyses yielded the radius of gyration (R_g) and D_{max} with longer carbamylation time.

Conclusions: These data indicate carbamylation of albumin results in an altered structure that mediates reduced binding to cubilin and FcRn. This results in reduced proximal tubule uptake and transcytosis of albumin resulting in more rapid serum clearance and lysosomal accumulation of carbamylated albumin.

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SA-PO760

The Mechanism of Glutamine Catabolism in the Activation of Renal Fibroblasts

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Background: Glutamine catabolism enhances the activity of tricarboxylic acid cycle and synthesizes key intermediate metabolites required for amino acids. This study will explore the role of glutamine catabolism in the activation of fibroblasts.

Methods: Activation of fibroblasts was induced by TGF-β1, changes of metabolites during fibroblast activation were detected by non-targeted metabolomics. The expression of GLS1, the key enzyme of glutamine catabolism, was detected by western blot. After the inhibition of GLS1 by specific inhibitors or siRNA, the proliferation, activation and migration of fibroblasts were detected. Glutamine was deprived during fibroblast activation, and the effects of glutamine on mitochondrial function were detected by measuring mitochondrial content, morphology, membrane potential, and oxygen consumption rate. The effects of supplementation with α-ketoglutarate after deprivation of glutamine on proliferation, activation, migration and mitochondrial function of fibroblasts were observed. In vivo experiment, intraperitoneal injection of BPTES after the UUO model was constructed, and the effect of BPTES on renal fibrosis was determined by pathological staining and immunohistochemistry.

Results: After TGF-β1 treatment, non-targeted metabolomics suggested that glutamate content increased significantly and pathway analysis highlighted significant enhancement of glutamine metabolism. The expression of GLS1 was significantly increased during fibroblast activation. After inhibition of GLS1, the proliferation, activation and migration of fibroblasts were significantly inhibited. After deprivation of glutamine during fibroblast activation, the mitochondrial content was significantly reduced, mitochondria were fragmented, the mitochondrial membrane potential, mitochondrial oxygen consumption rate, and ATP generation were all significantly reduced. After deprivation of glutamine and supplementation with α-ketoglutarate, the proliferation, activation and migration of fibroblasts were increased, and the mitochondrial content and mitochondrial membrane potential was partially recovered. In UUO model, BPTES could inhibit the activation of renal fibroblasts and alleviate renal fibrosis.

Conclusions: Glutamine catabolism plays an important role during fibroblast activation. Inhibition of glutamine catabolism can inhibit the proliferation and activation of renal fibroblasts and improve renal fibrosis.

SA-PO761

Knockdown of Central (Pro)Renin Receptor Attenuates Renal Injury in a High-Salt-Load CKD Rat Model

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Background: High-salt promotes renal injury in chronic kidney disease (CKD) through activating the RAS axis of the brain and kidney. Simultaneously, (pro)renin receptor (PRR) can exert local physiological effects in brain. However, the mechanism of central PRR in regulating salt-induced renal injury in CKD remains unclear. Therefore, we investigate the role of central PRR on renal injury in salt-loaded CKD rats in this study. Furthermore, we also investigate the potential mechanism of central PRR ameliorating renal injury.

Methods: Protocol A, First, we screened out the sequences that inhibit the central PRR expression in vitro. After the CKD model, which was established by 5/6 nephrectomy, was successfully prepared, intraventricular injection of lentivirus-packaged shRNA was used and a high-salt diet was given for 4 weeks. Finally, renal pathologic change was detected. Protocol B, U0126, Wortmannin and Losartan were used to inhibit MAPK/ERK1/2, PI3K/Akt signaling pathway, and ACE1-Ang II-AT1 axis in CKD model by continuous central administration and a high-salt diet was given for 4 weeks, respectively. Finally, we investigated the central and renal pathological changes.

Results: High-salt diet could aggravate kidney damage and fibrosis, increased RAS activation, oxidative stress, and inflammation. After successful inhibition of central PRR expression, the activity of the sympathetic nervous system (SNA) was decreased, kidney damage, renal fibrosis, RAS activation, oxidative stress, and inflammation were diminished. Furthermore, phosphorylation of ERK1/2 and Akt in central were inhibited. Central administration of U0126, Wortmannin, and Losartan was performed. The results revealed that these interventions ameliorated kidney damage, inflammation, oxidative stress, fibrosis, and SNA. However, decreased phosphorylation of ERK1/2 and Akt signaling in the brain had no significant effect on the expression of PRR, but knocking down PRR can inhibit the phosphorylation of these pathways. It suggested that central PRR may affect renal pathology through these signaling pathways.

Conclusions: Centrally knockdown of PRR expression can ameliorate salt-induced renal damage, as well as reduce RAS activation, inflammation, and oxidative stress, thereby slowing down the progression of CKD. Central PRR may affect renal pathology through the ACE1-Ang II-AT1 axis as well as MAPK/ERK1/2 and PI3K/Akt signaling pathways.

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SA-PO762

A Whole-Genome CRISPR Knockout Positive Screen Reveals Pathways Regulating APOL1-Induced Cytotoxicity

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Background: In humans two genetic variants of Apolipoprotein L1 (APOL1), G1 and G2, are common in African Americans and are strongly associated with chronic kidney disease (CKD). However, little is known about their pathological mechanism(s). APOL1 G1 and G2 are generally more toxic than wild type upon overexpression, with evidence for cellular mechanisms ranging from mitochondrial dysfunction, ER stress, endosome or autophagosome maturation defects, impaired cholesterol efflux, altered suPAR:integrin binding to cation efflux. It is unlikely that all these are primarily responsible for CKD, so an unbiased approach to identifying pathways and/or co-factors that mediate APOL1 variant cell killing should aid our understanding of the actual disease mechanism.

Methods: A pooled genome-wide CRISPR knockout screen, where each cell is deleted of a single gene prior to a phenotype-based selection, is one such powerful unbiased technique, which APOL1-induced *in vitro* cell death renders possible. Here, we show how we performed a genome-scale CRISPR-Cas9 loss-of-function screen in HEK293 cells to discover genes that influence APOL1-induced cell killing. We generated *Tet* inducible APOL1 G0, G1 and G2 HEK-293 cells expressing Cas9-GFP and carefully titrated APOL1 variant dose-dependent cell killing. These cells were infected with a genome-wide lentiviral guide RNA library, followed by APOL1 induction to the pre-determined level.

Results: The cells surviving APOL1 selective pressure were subjected to next-generation sequencing of the integrated sgRNA cassettes. With this approach we identified new and existing pathways affecting APOL1-mediated cell killing.

Conclusions: Here we demonstrated how APOL1 variants over-expression could be used as a selective pressure in a CRISPR KO positive screen to reveal pathways that are directly or indirectly involved in APOL1-induced cell toxicity. The same pathways have the potential to become druggable targets for patients that develop CKD linked to APOL1 variants. Validation and characterization analysis of the discovered factors will be essential to confirm our findings and to demonstrate the feasibility of our screening approach.

Funding: Commercial Support - Genentech

SA-PO763

Putative Endothelial Progenitor Cells Protected Mice from Ischemia-Reperfusion-Induced Renal Fibrosis by Suppressing the Activation of PDGFR-β$^+$ Pericytes via Paracrine Way

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Background: Putative Endothelial progenitor cells (pEPCs) are defined as a group of stem cells which have the potential capacity to differentiate into endothelial cells. When tissues suffer from injury, they secrete factors to recruit pEPCs from bone marrow to injured site, involving in the vascular repair and protecting tissues from damage. However, the mechanism of pEPCs acting on ischemic organs, especially kidneys, is still not clear. Some studies showed that pEPCs participated in angiogenesis by directly intervening in vascular walls and differentiating into endothelial cells. Other studies claimed that pEPCs regulated long-distance targeting recipient cells via paracrine way. This study aimed to investigate the role and mechanism of pEPCs in ischemia reperfusion (IR)-induced renal fibrosis.

Methods: Mice were infused with pEPCs extracted from bone marrow of GFP mice 6 hours after IR surgery and sacrificed at day 5, 10 and 28. GFP+ pEPCs were tracked by immunofluorescence and flowcytometry. The pEPCs-cultured medium (pEPCs-CM) were infused to investigate the paracrine role of pEPCs. Platelet derived growth factor-BB (PDGF-BB), the ligand for platelet derived growth factor receptor-β (PDGFR-β), which is the specific surface receptor on pericytes, was adopted, in a selective pericyte knockout mice (DTR expression in PDGFR-β$^+$ cells), to detect the relationship between pEPCs and pericytes in the progression of IR-induced kidney disease.

Results: The results demonstrated that the adoptive transfer of pEPCs promoted the renal angiogenesis and attenuated renal fibrosis. Cell tracking experiments showed that few pEPCs were detected in IR kidney, suggesting the involvement of paracrine mechanism. We further found the injection of pEPCs-CM had an equal protective effect on kidney as pEPCs did. The transfer of pEPCs or pEPCs-CM inhibited IR-induced PDGFR-β expression, pericyte-endothelial detachment, pericyte proliferation and

pericyte-myofibroblast transition. These protective effect of transferred pEPCs on capillary rarefaction and renal fibrosis was blocked by conditional PDGFR-β^+ cell knockout.

Conclusions: The adoptive transfer of pEPCs ameliorated IR-induced capillary rarefaction and renal fibrosis by suppressing the activation of PDGFR-β^+ pericytes via paracrine way.

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SA-PO764

Basigin/CD147 Facilitates Uptake of Protein into Renal Tubular Epithelium

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Background: CD147/Basigin (Bsg), a glycosylated transmembrane protein, plays a crucial role in processes such as cancer development, inflammation and immune system regulation. We have so far demonstrated that Bsg is involved in the pathogenesis of acute kidney injury and renal fibrosis. In the injured kidneys, this expression is induced strongly in the basolateral sides of TECs, infiltrating inflammatory cells. In a series of prior clinical studies, proteinuric kidney diseases such as minimal change nephrotic syndrome, showed marked increases in urinary Bsg levels, and a close relationship between proteinurea and urinary Bsg levels. Aberrant molecular mechanisms involving Bsg-mediated intracellular metabolism may be a crucial determinant of proteinuric tubular injury. In this study, we investigated whether Bsg deficiency maintains intracellular homeostasis by inhibiting uptake of protein into TECs.

Methods: As a clinical study, diabetic kidney disease (DKD) patients (N=52) registered with UMIN Clinical Trials Registry (8016) were treated with spironolactone 25 mg once daily for 8 weeks. The relationships between urinary Bsg values and clinical indicators were examined. We then induced tubulointerstitial injuries in wild-type ($Bsg^{+/+}$) or Bsg-deficient ($Bsg^{-/-}$) mice using intraperitoneal injections of a large amount of protein for 14 days. Immortalized proximal tubule epithelial cell line from normal adult human kidney (HK2) was exposed to high glucose (40mM) or bovine serum albumin (BSA).

Results: In DKD patients, plasma and urinary CD147 levels showed a correlation with eGFR or proteinuria, but not HbA1c, respectively. In biopsy tissues of patients with DKD, marked CD147 induction was detected in injured lesions representing renal inflammation. In a basic study, $Bsg^{-/-}$ mice induced by protein overload ameliorate the development of tubulointerstitial injuries and kidney dysfunction. In $Bsg^{+/+}$ kidneys with protein overload, several apoptotic factors were enhanced with increased Bsg expression. Bsg silencing in HK2 exposed to BSA suppressed uptake of BSA into the epithelium, and decreased heme oxygenase-1 expression as a marker of oxidative stress. Exposure of high glucose wasn't affected.

Conclusions: Bsg is involved in the pathogenesis of tubulointerstitial injuries by protein overload through promoting uptake of protein into TECs.

SA-PO765

Mechanism of Action of Veverimer, a First-in-Class, Orally Administered, Nonabsorbed, Counterion-Free Hydrochloric Acid Binder for the Treatment of Metabolic Acidosis in CKD

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Background: Current management of metabolic acidosis in patients with CKD relies on dietary protein restriction to reduce metabolic acid production or neutralization of retained acid with orally administered bicarbonate. Veverimer is being developed to provide a novel treatment modality for metabolic acidosis: endogenous acid removal. Veverimer is a free-amine polymer designed to combine high capacity and high selectivity for binding and removing HCl from the GI tract. It does not deliver sodium or other counterions and may therefore be appropriate for all patients with CKD and metabolic acidosis, including those with common sodium-sensitive comorbidities.

Methods: The binding capacity of veverimer and its selectivity for chloride over other anions were assessed in vitro in matrices mimicking the pH and ionic conditions of the human GI tract. Proof-of-concept of the efficacy of veverimer to increase serum bicarbonate was provided using a rat model of adenine-induced nephropathy and chronic metabolic acidosis. The bioavailability of veverimer was assessed in ADME studies in rats and dogs dosed with ^{14}C-labeled veverimer.

Results: In vitro, veverimer had a maximum binding capacity of 10.7 ± 0.4 mmol HCl per gram of polymer with significant binding capacity (> 5 mmol/g) across the entire range of physiologically relevant human GI pH (1.5 to 7). Upon protonation, veverimer bound chloride with high specificity, with little to no binding of phosphate, citrate or taurocholate. Administration of veverimer to rats with adenine-induced nephropathy and chronic metabolic acidosis resulted in a significant increase in fecal chloride excretion and a dose-dependent increase in serum bicarbonate to within the normal range, compared to untreated controls. ADME studies demonstrated that veverimer was not absorbed from the GI tract into the systemic circulation.

Conclusions: Endogenous acid removal through binding to veverimer, an orally-administered, non-absorbed polymer that is then excreted, provides a potential new mechanism for treating metabolic acidosis in patients with CKD.

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SA-PO766

Klotho Protein Supplementation Retards Renal Injury in 5/6-Nephrectomized Rats

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Background: We have previously reported that ronacaleret, a calcilytic agent, retards renal injury by increasing endogenous klotho expression in remnant kidney model (Am J Physiol Renal Physiol. 2015;309:F216-26). Recent studies have demonstrated that FGF23 transduces its signal using klotho as co-receptor to increase renal abundance of Egr-1 and phosphorylated ERK, both of which may control the expression of bone morphogenetic protein (BMP) 7.

Methods: In the present study, the effects of exogenous klotho protein supplementation on renal injury was compared between two groups of rats (n=6 for each group); 5/6-nephrectomized Wister rats (Nx), those treated with klotho (20 μg/kg/day) (Nx+K). Three months later, rats were killed with over-anesthesia, and harvested remnant kidney for analysis.

Results: Albuminuria was lower in Nx+K (42±6 mg/day) than Nx group (132±14 mg/day, $p<0.05$). Glomerular filtration rate and serum calcium were similar between 2 groups. However, fractional phosphate excretion was increased in Nx+K group (13±2 %) than Nx group (7±1 %, $p<0.05$). Serum phosphate (8.1±0.3 mg/dl (Nx+K) vs 9.8±0.3 mg/dl (Nx), $p<0.05$).and FGF23 (361±17 pg/ml (Nx+K) vs 480±31 pg/ml (Nx), $p<0.05$) were reduced in Nx+K group. RT-PCR analysis revealed that compared to Nx ($p<0.05$), renal expressions of klotho (1.8 fold) and BMP7 (1.7 fold) were elevated in Nx+K group. In contrast, renal expression of TGF-β in Nx+K group (2.1±0.2) was lower than Nx group (3.2±0.3, $p<0.05$). Western blot analyses showed that renal abundance of Egr-1 and phosphorylated ERK in Nx+K group was higher than Nx group. Pathological examination revealed that fibrosis index in Nx+K group was smaller than Nx group, and that endogenous klotho and BMP7 were co-localized in both renal tubular and interstitial cells.

Conclusions: The present data indicate that klotho supplementation reduced albuminuria, serum phosphate and FGF23 in 5/6-nephroctomized rats. Our findings demonstrate that exogenous klotho supplementation prevented the declines in endogenous klotho expression to recover normal FGF23-klotho signaling that facilitates phosphate excretion. Finally, the current results provide the evidence that klotho protein, which inhibits renal fibrosis, counteracts against TGF-β in itself as well as induces BMP7 expression by elevating the abundance of Egr-1 and phosphorylated ERK. in remnant kidney.

Funding: Government Support - Non-U.S.

SA-PO767

NAD$^+$ Metabolite, 2-Py Has a Potent Anti-Fibrotic and Anti-Inflammatory Activity in the Mouse Unilaterally Ureter-Obstructed Kidney

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Background: Renal fibrosis is a common pathogenic feature in chronic kidney diseases. Several studies have suggested NAD$^+$ metabolism may be disturbed in the kidney diseases, and we have found that the plasma levels of NAD$^+$ metabolites, N-methyl-2-pyridone-5-carboxamide (2-Py) and 4-Py were markedly increased in the unilateral ureter obstruction (UUO) mice and CKD patients. However, the effect of NAD$^+$ metabolites on renal fibrosis has not been fully elucidated.

Methods: Effects of 2-Py, 4-Py, and NNO (nicotinamide N-oxide) on TGFβ1 (5 ng/mL)-induced fibrosis-related genes (Col1a1, Col3a1, Col4a1, Acta2) and inflammatory gene (IL-6) were evaluated in rat fibroblast cells (NRK49F) and human tubular cells (HK-2). In vivo study was performed by administering 2-Py (300 mg/kg, bid, plus 5 or 10 mg/mL in the drinking water) to the UUO mice. Body weight and food intake were monitored during this study. At day 7, plasma parameters, gene expression, hydroxyproline content in the kidney were analyzed. Fibrotic area was evaluated using Masson's trichrome stained sections.

Results: In NRK49F, 2-Py strongly attenuated TGFβ1-induced Col3a1 expression (IC_{50} 750 μM), and 4-Py showed weak but significant reduction. NNO had no effect. In HK-2, 2-Py prevented TGFβ1-induced Col1a1 expression. 2-Py inhibited TGFβ1-mediated IL-6 gene induction in NRK49F and HK-2. In the UUO mice study, food intake and body weight were not affected by 2-Py treatment, and abnormal behaviors were not observed. At day 7 after UUO treatment, gene expressions of Col1a1, Col3a1, Acta2, IL-6 and TNFα in the kidney were significantly attenuated, and hydroxyproline content and histological fibrotic in the kidney area were significantly lower in the 2-Py-treated group as compared to those in UUO mice with vehicle treatment.

Conclusions: We provide a novel evidence that NAD$^+$ metabolite, 2-Py ameliorates renal fibrosis and inflammatory response in renal tubular and fibroblast cells as well as in UUO mice.

Funding: Commercial Support - Shionogi & Co., Ltd.

SA-PO768

The Bidirectional Relationship Between CKD and Sleep Disordered Breathing

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Background: The prevalence of Sleep Disordered Breathing (SDB) is higher in Chronic kidney disease (CKD) patients compared to the general population. The relationship between these two diseases is complex and bidirectional. SDB is linked to increased risk of hypertension, atherosclerosis and systemic inflammation which can accelerate the deterioration of renal function. On the other hand, CKD is associated with volume overload, metabolic abnormalities and hypertension contributing to the pathogenesis of SDB. Recognizing the association between them can lead to early treatment, better clinical outcomes and higher quality of life.

Methods: A retrospective study included 385 Beaumont Health System patients from 01/01/2012 to 12/31/2017 with diagnosis of both CKD and SDB. The objective was to observe the association of SDB across the CKD stages and proteinuria and to assess the relationship with sleep parameters identifying common predictors associated with these two conditions. SDB was confirmed by polysomnography. CKD diagnosis was based on Glomerular Filtration Rate (GFR) and urine albumin creatinine ratio (UACR).

Results: In patients with both SDB and CKD, there was an association between Apnea Hypopnea Index (AHI) and GFR (p=0.08) but not with UACR (p=0.59). 70 % of the patients with stage G2 & G3 CKD had moderate to severe AHI. The median decline in GFR was 5.5 ml/min/1.73 m2 per year and 12% had accelerated decline in GFR. There was a strong association between Nocturnal Hypoxia (NH) and AHI (p<0.0001) in CKD patients but none with GFR (p=0.60) or UACR (p=0.52). Patients on Renin Angiotensin System (RAAS) inhibitors and on Non-Steroidal Anti-inflammatory (NSAIDs) showed trend towards less severe AHI (p=0.03) and (p=0.06) respectively; those with systolic heart failure (HF) trended towards worse UACR values (p=0.02). There was no evidence that body mass index, gender, antidepressant or narcotic use is related to AHI severity or NH in CKD patients.

Conclusions: Overall, the severity of SDB tended to get worse with advanced CKD and vice versa: patients on RAAS inhibitors and NSAIDs showed less severe AHI, supporting the role of systemic inflammation and hypertension in the pathogenesis of SDB. It was also noted that patients with nocturnal hypoxia tended to have worse AHI and those with systolic HF had higher levels of proteinuria.

SA-PO769

Phenotype or Environment: Mechanisms of CKD Skeletal Muscle Wasting

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Background: Despite its prevalence and impact, mechanisms of skeletal muscle wasting in non-dialysis dependent chronic kidney disease (NDD-CKD) are unclear. The current investigation used human primary skeletal muscle cells (HDMCs) to investigate the effect of CKD derived serum on HDMC proliferation and differentiation *in-vitro*.

Methods: Biopsies were taken from the vastus lateralis of NDD-CKD (n=3, 45.3yrs, eGFR 16ml.min.1.73m^2) and healthy controls (HC, n=3, 48.3yrs, eGFR>90 ml.min.1.73m^2). Isolated HDMCs were cultured for 4 days in medium supplemented with foetal bovine serum (FBS, 20%), HC (sHC) or CKD (sCKD) derived serum (10%). Proliferation was assessed using AlamarBlue™ assay. To assess differentiation, cells were grown to confluence in FBS, followed by 7 days in either 2% horse serum (HS), sHC or sCKD and myotube morphology was analysed.

Results: Proliferation increased significantly from baseline in all conditions in HC and CKD. There was a significant effect of sera in HC, with greater proliferation in sCKD from D2 compared to FBS and D3 compared to sHC (Fig.1a). There was no effect of sera on CKD proliferation (Fig.1b). Fusion index (Fig.1c) and myotube diameter (Fig.1e) was generally higher in CKD, but only significantly in sHC and HS, respectively. There was no significant effect of sera on either outcome. There was no effect of donor or sera on desmin index (Fig.1d).

Conclusions: Preliminary findings indicate similar rates of proliferation between HC and CKD. sCKD increased proliferation compared to FBS and sHC in HC but not CKD. There was no effect of sera on measures of differentiation/maturation. Future work will seek to determine what factors increase HDMC proliferation which may inform targets for therapeutic intervention.

Funding: Government Support - Non-U.S.

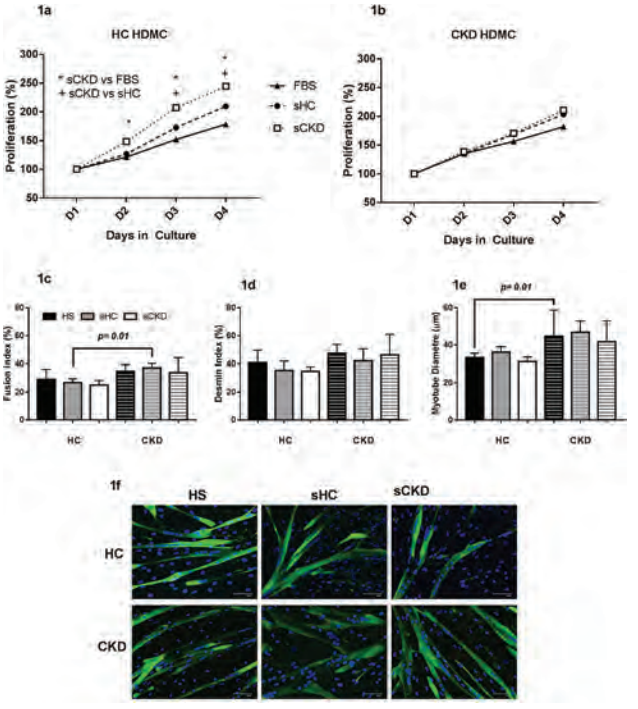

Figure 1. The effect of sCKD on proliferation in HC (a) and CKD (b) and differentiation (c-e).

SA-PO770

Discovery and Validation of Skeletal Muscle MicroRNA Expression in Non-Dialysis CKD

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Background: Skeletal muscle (SM) wasting is a common complication of chronic kidney disease (CKD), and is significantly associated with an increased risk of morbidity and mortality. The precise mechanisms of SM wasting are not fully defined, but multiple studies have identified a major contribution of aberrant microRNA (miR) expression and regulation. The involvement of miRs has been described in animal models of CKD SM wasting, however there is no evidence for their involvement in human CKD SM wasting. Therefore, we investigated SM miR expression in non-dialysis CKD patients compared to matched healthy controls (HCs).

Methods: Next Generation Sequencing (NGS) was performed on lower limb (LL) SM biopsies collected from 5 CKD patients stage 3b-5 (mean eGFR 22.0 ± 8.1 ml/min/1.73m^2; mean age 59.2 ± 9.4 years) and 5 HCs (mean age 54.7 ± 7.9 years). MiR expression was then validated in LL SM biopsies collected from a further 10 CKD patients stage 3a-5 (mean eGFR 30.8 ± 13.6 ml/min/1.73m^2; mean age 61.6 ± 11.8 years) and 10 HCs (mean eGFR 83.2 ± 4.4 ml/min/1.73m^2; mean age 61.5 ± 13.4 years) by qPCR with let-7f as an internal control. Relative expression was calculated by 2^{-DCT}).

Results: NGS identified differential expression of 15 miRs in SM of CKD patients compared to HCs (fold-change ≥1.5; increased: miR-128, 148a, 182, 21, 22, 29c, 92a; decreased: let-7a, 7e, miR-100, 191, 206, 486, 99a, 99b). Upon validation in a larger sample, miR-148a expression was significantly decreased in CKD patients compared to HCs (p=0.03), and there was a non-significant trend towards decreased miR-191 expression in CKD patients (p=0.061). No further differences were maintained upon validation of the other miRs.

Conclusions: Patients with non-dialysis CKD exhibit altered SM miR expression compared to HCs. However, the miR signature reported here does not reflect those previously reported in animal models of CKD SM wasting. For the first time, we report that miR-148a expression is significantly decreased in SM in CKD. Future work will explore the role of dysregulated miR-148a in CKD SM wasting, thus providing a rational for use as a potential therapeutic target in this population.

SA-PO771

Heparin Infusions Contribute to Cardiovascular Damage in CKD by Promoting Pathologic Effects of FGF-23

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Background: Fibroblast growth factor (FGF) 23 is a bone-derived hormone that increases phosphate excretion by targeting the kidney via klotho and FGF receptor (FGFR) 1. Most FGF family members interact with heparin as a co-factor for efficient FGFR activation. Endocrine FGFs, such as FGF23, have reduced heparin binding affinity

and instead require the transmembrane protein klotho as FGFR co-receptor. Patients on hemodialysis (HD) have extremely high serum FGF23 levels and receive high amounts of heparin to prevent blood clotting. We have shown that FGF23 causes cardiac hypertrophy by directly targeting cardiac myocytes via FGFR4 in the absence of klotho, and here we test whether heparin affects this pathologic process.

Methods: We have developed a multi-well assay to measure FGFR binding affinities of FGF23 and test effects of heparin co-incubations. We co-treat cultured cardiac myocytes with FGF23 and heparin and analyze changes in signaling events and in cell area as a readout for hypertrophy. Finally, mimicking a HD-like administration pattern, we inject heparin via the tail vein into two mouse models of FGF23 elevation, i.e. adenine diet-induced kidney failure and repetitive injections of recombinant FGF23.

Results: While purified FGF23 and FGFR4 proteins show only a weak interaction, co-incubation with patient grade heparin increases their binding affinity 10-fold. Heparin increases FGF23-induced signaling and hypertrophic growth of cardiac myocytes. Both mouse models with elevated serum FGF23 levels show increased cardiac hypertrophy when heparin is administered.

Conclusions: We show that heparin can increase the FGFR binding affinity and cellular effects of FGF23. Specifically, heparin aggravates the klotho-independent FGFR4-mediated actions of FGF23 on cardiac myocytes and thereby cardiac injury in mice with systemic FGF23 elevations. Our experiments suggest that in HD patients, administered heparin acts as a biologically active, circulating co-receptor for FGF23 that increases FGF23 affinity for FGFR4 thereby aggravating the pathologic actions of FGF23 on the heart and contributing to the increased cardiovascular mortality.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO772

Novel Truncated ACE2 Fusion Protein with Extended Half-Life Is Delivered to the Kidney and Ameliorates Angiotensin II-Induced Hypertension

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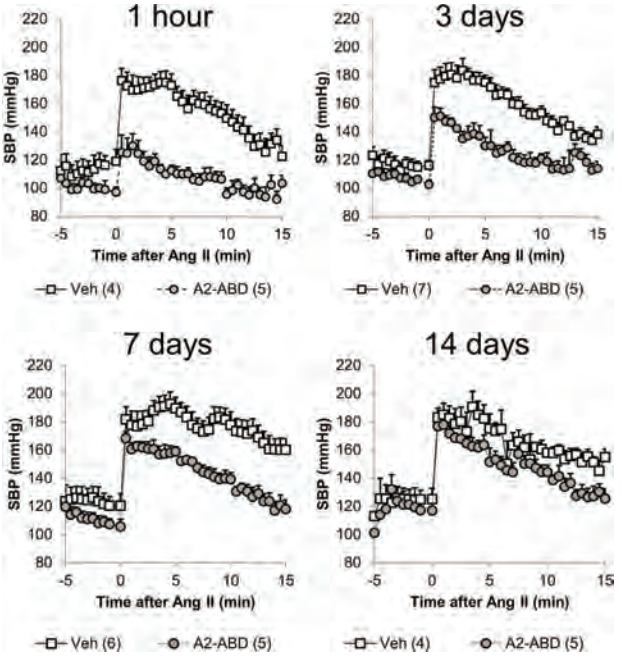
Background: ACE2 converts angiotensin (Ang)II to the renoprotective peptide, Ang (1-7), thereby providing a mechanism to downregulate the renin-angiotensin system (RAS). Targeting kidney RAS using native ACE2 might not be effective due the large size (~110 kDa) that prevents its glomerular filtration and subsequent tubular uptake.

Methods: To circumvent this limitation, ACE2 truncate (ACE2 1-619) was generated through C-terminal truncation of the native ACE2 and subsequently fused with albumin binding domain (ABD). Enzyme activity of the chimeric protein was confirmed using ACE2-specific substrate Mca-APK-Dnp and its inhibition by MLN-4760 (ACE2-specific inhibitor).

Results: In Western blot the fusion protein appeared as a single band at the apparent molecular weight of ~75 kDa, as expected from its amino acid sequence. In keeping with the goal of our original design, ACE2 1-619ABD exhibited a markedly extended circulatory residence longevity than naked ACE2 1-619 or native ACE2 1-740. The extended in vivo half-life was confirmed in a model of angiotensin II-induced hypertension whereby an increase in SBP was mitigated by the ACE2 1-619ABD for up to 7 days after a single i.p. bolus injection (1 ug/g BW) (Figure). In SPECT/CT imaging, after i.v. injection of ^{Tc99m}-labeled ACE2 1-619ABD, there was a significant retention in kidney cortex (6.3 ±0.5% of whole body (WB) radioactivity) as compared to trace retention generated by the native ^{Tc99m}-ACE2 1-740 (1.2±0.2% WB).

Conclusions: The novel ACE2 truncate fused with ABD is enzymatically active, exhibit an extended in vivo half-life, and is taken up by kidney cortex. These features might be potentially favorable for developing a new approach to target kidney disease with intrarenal RAS overactivity.

Funding: NIDDK Support



SA-PO773

Cardio-Renal Protective Effect of the Xanthine Oxidase Inhibitor Febuxostat in the 5/6 Nephrectomy Model with Hyperuricemia

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Background: Previous studies have shown that hyperuricemia can cause cardiovascular dysfunction and chronic kidney disease progression; however, the mechanisms remain unclear. In this study, we addressed the cardio-renal protective effects of xanthine oxidase (XO) inhibition in the rat remnant kidney model with hyperuricemia (RK+HUA).

Methods: Male Sprague-Dawley rats received 5/6 nephrectomy and were fed oxonic acid, the uricase inhibitor, according to the previously described methods (Kang et al., J Am Soc Nephrol 2002; Asakawa et al. Oxid Med Cell Longev 2017). XO inhibitor febuxostat was administered orally via drinking water (30 mg/l). Blood pressure and urinary albumin excretion were monitored during the course of the experiment. At 8 weeks, heart and kidney were removed for the histological evaluation.

Results: Compared with control group, RK+HUA showed significant increase in urinary albumin excretion. However, febuxostat significantly reduced albuminuria in this model, along with the reduction in serum uric acid levels. PAS-stained kidney section revealed that febuxostat attenuated glomerular and tubulointerstitial injury, confirming the renoprotective effects of XO inhibition. There was no significant difference in blood pressure levels between RK+HUA rats and RK+HUA rats that received febuxostat. However, histopathological analysis using HE-stained cardiac sections indicated that left ventricular wall thickness was reduced by febuxostat. Furthermore, quantitative evaluation of myofiber cross-sectional areas in wheat germ agglutinin (WGA)-stained sections revealed that individual myofiber hypertrophy was significantly alleviated. In addition, cardiac fibrosis was also reduced in RK+HUA with febuxostat compared with RK+HUA rats.

Conclusions: XO is involved in the cardiac and renal injury observed in the remnant kidney model with hyperuricemia. These effects can at least in part be mediated through non-hemodynamic mechanisms.

SA-PO774

Elevated Left Ventricular Cardiac LIM Protein (CSRP3) in ESRD

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Background: Emerging evidence suggest that cardiac cytoskeletal components are involved in the pathogenesis of cardiorenal syndromes. We recently identified the cardiomyocyte transcription factor CSRP3 as an endocrine cardiorenal connector in mice. CSRP3 is a critical component of the cytoskeleton and contractile apparatus in the heart. Mutations of CSRP3 have been detected in patients with cardiomyopathy, however the role of CSRP3 in human cardiorenal disease is unknown.

Methods: We analyzed human Left Ventricular (LV) tissues from donors with end-stage renal disease (ESRD, n=15) compared to hypertensive (HTN, n=11) and healthy controls (n=18) in a 3-arm cross-sectional controlled study using The CAIN (Cardiac Aging in CKD) Cohort. All tissues underwent gross pathologic examination. LV free wall thickness (LVWT) was assessed as an index for left ventricular hypertrophy (LVH). RNASeq, immunoblotting, and qPCR were performed. Confirmatory tissue qPCR studies were performed in a rodent model of advanced nephropathy, Akita(*Ins2c96y*)-ReninTg (Akita-RenTg) mice and controls.

Results: Groups were well-matched and there was no statistical difference in age (ESRD 46.4±10.7; HTN 56.3±4.9; control 49.7±15.7 yrs, p=0.1) or sex (ESRD 60; HTN 64; control 58 % male, p=0.9). HTN patients had slightly higher BMI (HTN 31.5±6.6 vs ESRD 26.2±4. vs. 26.3±5.8 kg/m2, p=0.1). HTN and ESRD patients had significantly greater left ventricular wall thickness normalized to body surface area (p<0.0001). RNASeq of left ventricular tissue revealed that csrp3 is among the top 1000 genes dysregulated by ESRD. Immunoblotting for CSRP3 revealed increased LV CSRP3 in HTN patients (2.2-fold). ESRD patients had even greater levels (4.4-fold, p<0.0001) compared to controls; this was independent of LVH. These results were consistent with advanced nephropathy Akita-RenTg mice; cardiac CSRP3 mRNA was increased relative to controls (~14-fold).

Conclusions: We provide the first translational data demonstrating CSRP3 is greatly elevated in the hearts of humans with ESRD. Data from an experimental model of advanced nephropathy suggest that this cardiorenal crosstalk is conserved. We postulate that upregulation of CSRP3 may function as a stress signal in kidney failure and further studies are critically warranted to elucidate its role.

Funding: Veterans Affairs Support, Private Foundation Support

SA-PO775

Myocardiocyte Transcription Factor Cardiac LIM Protein (CSRP3) Mediates Renal Tubular Transcription

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Background: Cardiac LIM Protein (CSRP3, molecular weight 21 kD), is released from the heart into the systemic circulation after myocardial injury; we recently identified it as an endocrine cardiorenal connector. We hypothesized that modeled release of CSRP3 would alter tubular epithelial cell transcription of renal fibrosis-related genes in vivo and in vitro.

Methods: Cardiac arrest was induced with potassium chloride, and terminated with cardiopulmonary resuscitation (CA/CPR, a model of cardiac injury leading to acute cardiorenal syndrome). CA/CPR or sham procedure was performed in male, 8-12 week old male mice (WT mice). Mice were killed 10h, 24h, 72h, or 7 days later and plasma CSRP3 quantified by ELISA. Recombinant CSRP3 (rCSRP3) was purchased and 1 μg injected intravenously to WT mice. Mice were killed and plasma CSRP3 quantified by ELISA. Curves were fit to model pharmacokinetics. Following injection, mice were perfusion-fixed; the right kidney was snap-frozen and prepared for mRNA measurements and the left paraffin-embedded for immunofluorescence. qPCR for lef1 and tgfb1 mRNA, and CSRP3 immunofluorescence were performed on kidney tissue. Human kidney cells were exposed to 1 μM rCSRP3 or vehicle in translational relevance studies.

Results: CA/CPR resulted greatly increased plasma CSRP3 (max 20.3±3.3 *vs.* 1.4±0.2 in sham, ng/mL, p=0.04) and remained detectable in plasma at 7 days (5.6±1.6 ng/mL). The 7-day area-under the curve (AUC) was 65 ng/mL*day. The $t_{1/2}$ for injected rCSRP3, was 86 minutes, and the AUC for a single 1μg dose was 15 ng/mL*days. Immunofluorescence demonstrated CSRP3 within tubular epithelial cell nuclei following injection. Renal tissue mRNA for transforming growth factor beta (tgfb1) was 1.7-(±0.28-fold) increased 6h after rCSRP3 injection, while lef1 mRNA was not regulated. In human tubular epithelial cells, 16h exposure to 1 μM CSRP3 upregulated lef1 mRNA 1.8±0.15-fold compared to vehicle control (p=0.02).

Conclusions: CSRP3, highly specific to cardiomyocytes, is released into the circulation after cardiac injury, and mediates renal transcription of fibrosis-related genes *in vivo* and *in vitro*. We postulate this cardiomyocyte transcription factor may play a role in AKI-CKD transition following acute cardiac illness such as cardiac arrest or myocardial infarction.

Funding: Veterans Affairs Support

SA-PO776

Chronic, Combined Cardiac and Renal Dysfunction Exacerbates Renal Venous Pressure-Induced Suppression of Systemic Blood Pressure and Renal Function in Rats

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Background: Coexisting cardiac/renal dysfunction may be perpetuated by increased renal venous pressure (RVP) in this condition. We previously showed that acute RVP elevation depresses renal blood flow (RBF), GFR and induces renal vasoconstriction in the absence of changes in blood pressure in healthy rats. We established a rodent model of combined cardiac/renal dysfunction and tested whether an acute, superimposed RVP elevation would impair cardiovascular stability, baseline renal perfusion and exacerbate renal dysfunction.

Methods: Male rats were subjected to 5/6 renal mass resection (Nx or Sham) and 6% high salt diet to induce renal dysfunction followed 7 weeks later by ligation of the left anterior descending coronary artery (CL or Sham). Four experimental groups were as follows: CL+Nx (n=11); Sham CL+Nx (n=9); CL+ Sham Nx (n=3); Sham Control (n=4). 8 weeks post-recovery, rats were anesthetized and subjected to an acute experiment whereupon mean arterial pressure (MAP), heart rate (HR), RVP, RBF and GFR were measured at baseline and during partial left renal vein occlusion to increase RVP to 20-25 mmHg for 120 min.

Results: Baseline MAP, HR, RBF and renal vascular conductance (RVC) were comparable between all experimental groups. Baseline GFR was significantly depressed in CL+Nx and Sham CL+Nx groups compared to Sham Control and CL+Sham Nx groups. Upon RVP increase, an early, rapid and pronounced reduction in MAP occurred in CL+Nx, Sham CL+Nx and CL+Sham Nx compared to Sham Control (p<0.001); MAP fell to the same extent in all groups at the end of the recording period. HR fell gradually with the increase in RVP in all experimental groups to the same extent. RVP increase exacerbated the reduction in RBF in CL+Nx compared to Sham Control (p<0.001) with intermediate responses in Sham CL+Nx and CL+Sham Nx groups. Similarly, RVP increase virtually eliminated GFR in CL+Nx (-99%), Sham CL+Nx (-95%) and CL+Sham Nx (-100%) groups compared to Sham Control (-82% from baseline; p<0.001). Renal vascular conductance dropped significantly but comparably upon RVP increase in all experimental groups.

Conclusions: Combined cardiac/renal dysfunction impairs cardiovascular stability in response to elevated RVP; MAP instability impairs the ability to maintain RBF and GFR considering preserved intrarenal responses.

SA-PO777

Pericyte-Specific Manipulation of Hypoxia-Inducible Factors Regulates Erythropoiesis Without Aggravating Renal Fibrosis

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Background: Stabilizers of hypoxia-inducible factor (HIF) have been shown to be effective on treatment of anemia in patients with chronic kidney disease (CKD). Increased erythropoietin (EPO) production and enhanced erythropoiesis are known to be the major mechanisms responsible for the treatment effects. However, the effect of HIF stabilization on renal fibrosis is controversial. We created animal models characterized by CKD and pericyte-specific or non-selective stabilization of HIF to examine the effects of HIF on renal fibrosis and erythropoiesis.

Methods: *Gli1*$^{CreERT2/+}$*;Egln1*$^{F/F}$, *Gli1*$^{CreERT2/+}$*;Vhl*$^{F/F}$, and *Gli1*$^{CreERT2/+}$*;Hif1a*$^{F/F}$*;Hif2a*$^{F/F}$ mice were generated to study the effects of pericyte-specific overexpression or knockout of *Hif*. *Tg(UBC-CreERT2);Egln1*$^{F/F}$, *Tg(UBC-CreERT2);Vhl*$^{F/F}$, and *Tg(UBC-CreERT2);Vhl*$^{F/F}$*;Hif1a*$^{F/F}$*;Hif2a*$^{F/F}$ mice were generated to study the effects of non-selective stabilization of HIF. Unilateral ureteral obstruction (UUO) was used to induce CKD. The severity of fibrosis was determined by Picrosirius red stain and *Col1a1* mRNA level in the kidney.

Results: Pericyte-specific stabilization of HIF resulted in increased serum EPO level, augmented splenic erythropoiesis, and polycythemia, while the severity of renal fibrosis was not affected. In line with these findings, pericyte-specific knockout of *Hif1a* or *Hif2a* did not result in significant change of renal fibrosis. We further examined the role of HIF stabilization in mice with postnatal global stabilization of HIF. Surprisingly, unexpected mortality developed along with dramatically increased serum EPO levels in a HIF-dependent manner.

Conclusions: Our study endorses the neutral effects of pericyte-specific HIF stabilization on renal fibrosis. However, the possible risks of artificially increased serum EPO level warrant further study.

Funding: Government Support - Non-U.S.

SA-PO778

The Effect of Increased Blood MicroRNA on Apoptosis in Cardiac Cells and Cardiac Complications in CKD

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Background: Increased cardiovascular morbidity and mortality is the conundrum in chronic kidney disease (CKD). Although hemodynamic change has been blamed for the extremely high incidence of cardiovascular disease in CKD, the retention of uremic toxins might be directly associated with it, including decreased heart function and induction of serious arrhythmia. This study aimed to investigate the association between the cardiac fibrosis and uremic toxin in CKD. Furthermore, we will try to investigate the role of the alteration of blood microRNA (miRNA) levels like other uremic toxin on cardiac fibrosis.

Methods: We induced CKD in rats by 5/6-STNx. We investigated the changes in the renal function and the levels of blood miRNA by affymetrix miRNA array. Renal and cardiac fibrosis was evaluated by Masson's trichrome(MT) staining. We also isolated sinus nodal cells from cardiac atria of C57BL/6 mice, and treated a representative protein-bound uremic toxin, indoxyl sulfate (IS) and probenecid into the cells for 48 h, and evaluated the changes in the expression of fibrosis-related molecules.

Results: Serum creatinine(Cr) and blood urea nitrogen(BUN) were significantly higher in the 5/6-STNx than controls, while echocardiography were lower in the 5/6-STNx. The miRNA profiles of blood serum of 5/6-STNx were significantly different compared to controls. We focus on the significant decrease in the level of miRNA let-7 family for now. Additionally, MTstaining for the assessment of fibrosis showed the increased fibrosis in the heart and kidney of 5/6-STNx compared with controls. In vitro, protein expressions of fibronectin, phospho-p38 MAP kinase and Bax/bcl2 ratio after IS stimulation were significantly higher at 48 h, which was blocked by organic anion transporter inhibitor, probenecid.

Conclusions: These findings suggested that there was a direct effect of uremic toxin on the induction of fibrosis by MAPK activation in sinus nodal cells. The relationship between miRNA and cardiac fibrosis would be investigated down the road.

SA-PO779

Insignificant Renal Artery Stenosis Is Associated with a Decrease in Renal Perfusion and Function

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Background: Renal artery stenosis (RAS) exceeding 50% of vascular diameter is known as hemodynamically significant and can result in hypertension and deterioration of renal function, thus can require an invasive treatment. On the other hand, RAS < 50% of the diameter is thought to be safe. The study aimed to investigate whether renal artery narrowing < 50% of the diameter could influence renal perfusion and function.

Methods: Twenty-seven kidneys evaluated in an enhanced by contrast multidetector computed tomography (CE-MDCT; GE Discovery 750 HD) in 17 patients (6F, 11M; age 62.5 ±19.7 y) with hypertension and RAS 0-49% of the diameter were included to the study. Renal Parenchymal Perfusion (RPP), and renal function (eGFR) were evaluated.

Results: Mean eGFR was 52.4 ±26.1 mL/min/1.73m^2, and RPP 222.7 ±78.7 mL/s/100g. In twelve stenotic kidneys mean RAS was 30.0 ±8.8% of the diameter. Fifteen renal arteries were normal. The severity of RAS correlated significantly ($p<0.05$) with RPP ($r= -0.39$) and eGFR ($r= - 0,41$). In non-stenotic kidneys RPP and eGFR were significantly higher than in those having RAS (256.4 ±82.5 vs 189.5 ±49.9 mL/s/100g; $p=0.010$ and 62 ±27 vs 43 ±21 mL/min/1.73 m2; $p=0.045$, respectively).

Conclusions: Even mild renal artery stenosis can contribute to the decrease in renal perfusion and renal function. Due to the negative correlation of mild RAS with renal perfusion, the definition of significant RAS should be revised.

Funding: Government Support - Non-U.S.

SA-PO780

Patient Engagement in Knowledge Translation: A Collaborative Model for Moving Kidney Health Research into Practice

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Background: Effective knowledge translation is the process of moving research evidence into clinical practice. Can-SOLVE CKD is a pan-Canadian patient-oriented kidney research network with an established Knowledge User (KU) and Translation (KT) Committee that includes two patient partners. This committee provides guidance, expertise, and direction for all KT activities undertaken by research projects within the network and ensures KT approaches are patient-centered. This research defines key concepts related to KT, outlines the role of the KU/KT Committee in supporting kidney health research, and highlights the contributions of patient partners on this committee.

Methods: The KU/KT Committee provides core infrastructure support for 18 research projects within the Can-SOLVE CKD Network. Membership includes national representation of patients living with kidney disease, policymakers, health care professionals and researchers with KT expertise. In alignment with our strategic framework, we co-developed two KT reporting templates for research teams to complete, reviewed project KT plans, and discussed our KT assessments among the committee. The committee also provides ongoing support for stakeholder engagement and helps projects tailor their KT strategies for communicating, implementing and sustaining their findings in practice.

Results: As the main stakeholders in health research, there are opportunities for patients to participate in KT. Two patient partners act as full KU/KT committee members and maintain links with the Network's Patient Council and Indigenous Peoples' Engagement & Research Council (IPERC). Although all committee members share the responsibility of assessing project KT plans and identifying relevant KT strategies, the patient partners are uniquely positioned to understand real-world implications of the research findings. Continued acknowledgment of the patient voice in KT will help encourage ongoing relevant research, novel approaches to KT, and the translation of evidence into practice.

Conclusions: Our multi-stakeholder KU/KT Committee promotes patient-oriented research supporting the translation of kidney health research into practice. Patients can identify unique KT considerations, provide meaningful feedback to research teams, and encourage the generation and application of relevant research evidence.

Funding: Government Support - Non-U.S.

SA-PO781

Sleep Deprivation Induces Metabolic Reprogramming in Kidney

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Background: Sleep is critical to human being. Sleep deficiency, or sleep deprivation, is an increasingly important global issue of human health, and has been linked to obesity, diabetes, and cardiovascular disease. Many findings published has addressed the interaction between sleep and metabolism, and metabolic health relies strongly on sleep. Sleep deprivation is known to promote the development of chronic kidney disease. Individuals with shorter time of sleep were more likely to have proteinuria, and faster decline of glomerular filtration rate, yet little is known about the mechanism by which sleep deprivation deteriorate renal function.

Methods: Wild-type male C57BL/6J mice were housed in a 12:12 hr light/dark cycle (light on 8:00 A.M. to 8:00 P.M) at a constant temperature (22±1°C) with free access to food and water. For sleep deprivation, mice were placed in a chamber with a sweep bar moving along the bottom of the cage every 1 min for 20 hours (ZT0-8, ZT12-24) and shut-off for 4 hours. Control mice received no disruption during sleep were living with stationary sweep bars. Mice were sacrificed after the procedure of sleep deprivation lasts for 4 weeks at ZT0 and ZT12.

Results: Though body weight and food/water intake did not differ from SD group to control group, biochemical analysis revealed statistical differences in serum albumin, AST, SOD, STB, phosphorus ($p<0.05$) between SD mice and control. Oil Red O staining indicated larger lipid droplets in SD kidney. No difference in urinary albumin excretion was observed between the two groups, while a tendency towards higher urine albumin-creatinine ratio was seen in SD group. Transcription analysis identified altered gene expression most significantly involved in lipid metabolism and biosynthesis, insulin signaling pathway, and circadian rhythm. Protein expression confirmed by Western blot (CPT1α, ACADL, FASN, ADFP, CD36, PDK4, PDH) indicated depressed fatty acid oxidation, increased lipid accumulation and glycolysis.

Conclusions: Sufficient sleep is associated with kidney metabolic homeostasis. More lipid utilization might be occurred in kidney during sleep than waking state. Metabolism disorder caused by chronic sleep deprivation may be concerned in the progression renal function decline or proteinuria.

Funding: Government Support - Non-U.S.

SA-PO782

Apabetalone Downregulates Alkaline Phosphatase and Improves Cardiovascular Risk

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Background: Apabetalone is an inhibitor of BET proteins - epigenetic readers modulating gene expression. In phase 2 trials, apabetalone reduced major adverse cardiac events (MACE) in patients with cardiovascular disease (CVD) & improved eGFR in those with chronic kidney disease (CKD). Elevated serum alkaline phosphatase (ALP) is a risk factor for MACE, as it contributes to vascular calcification & endothelial dysfunction. We examined apabetalone-mediated effects on ALP in CVD patients post-hoc & determined apabetalone's impact on tissue non-specific ALP (TNAP) expression in cell culture systems.

Methods: Circulating ALP was measured in CVD patients receiving apabetalone in the 3-month (ASSERT) and 6-month (SUSTAIN & ASSURE) trials. Apabetalone's effect on expression of TNAP (gene symbol *ALPL*) was determined in cultured primary human hepatocytes (PHH), HepaRG, HepG2, calcifying vascular smooth muscle cells (VSMCs) & vascular endothelial cells. Protein abundance & ALP enzyme activity were also measured.

Results: In phase 2 trials, baseline serum ALP correlated with MACE ($R^2=0.87$). In ASSERT, apabetalone dose dependently reduced serum ALP ($p<0.001$ vs placebo). In ASSURE & SUSTAIN, patients on apabetalone (n=331) had greater reduction in serum ALP than placebo (n=166; median % change -3.2 vs -11; $p<0.001$), including those with CKD, i.e. eGFR<60 (apabetalone n=35 placebo n=13 median % change -6.3 vs -14; $p<0.02$). In vitro, apabetalone suppressed *ALPL* expression in PHH, HepaRG & HepG2 cells by 60-80%. Trans-differentiation of VSMCs to calcifying cells resulted in 2.5-fold increase in *ALPL* gene expression. Apabetalone countered calcium deposition & suppressed *ALPL*/TNAP gene expression, protein levels & enzyme activity. Apabetalone also downregulated *ALPL* in aortic endothelial cells, umbilical vein endothelial cells & brain microvascular endothelial cells 50-70%.

Conclusions: In phase 2 trials, apabetalone lowered serum ALP. Mechanistically, apabetalone downregulates *ALPL*/TNAP expression in multiple cell types, which may contribute to reductions in MACE observed in patients. The impact of apabetalone on biomarkers, renal function & CVD outcomes is being evaluated in the phase 3 BETonMACE trial.

Funding: Commercial Support - Resverlogix

SA-PO783

Short Time of Resistance Training Attenuates the Renal AKT Pathway; Improves Physical Capacity, Renal Function, and Glomerulosclerosis; and Decreases Mortality Rate in Rats with CKD

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Background: The aim of this study was to evaluate if 4 weeks of resistance training (RT) attenuates renal AKT Pathway, improves physical capacity (strength gain and VO_2 peak), renal function, glomerulosclerosis and mortality in rats with chronic kidney disease (CKD) by nephrectomy 5/6 (Nx5/6).

Methods: Adult Wistar rats were divided in four groups (n=8): Sedentary (S) Exercise (E), Nx 5/6 + Sedentary (NS), Nx 5/6 + Exercise (NE). We evaluated (by multiplex) renal AKT Pathway (IGF1R, TSC2, AKT, Mtor and PS706SK), creatinine clearance (CrCl), proteinuria (uProt), blood urea nitrogen (BUN), glomerulosclerosis, mean arterial pressure (MAP) as well mortality rate. Exercise periods were as follows: 6 to 12 climbs/day, 5 days a week, during 4 weeks, 40 to 60% of maximal load test (MLT). The physical capacity was performed with maximal load test (MLT), ergoespirometry test (Vo_2 peak) and maximal exercise test (MEtest).

Results: The Renal AKT Pathway was increased in NS vs all group in all protein analyzed (IGF1R, TSC2, AKT, Mtor and PS706SK), CrCl was improve in NE (43%) vs NS group, ($p<0.05$). Proteinuria was different in NS and NE vs S and E groups but not in NS vs NE. BUN was higher in NS and NE vs S and E. Glomerulosclerosis was different in NS vs NE ($p<0.05$). The MAP was lower in NE vs NS group ($p<0.05$). Physical Capacity (MLT, VO_2 peak and Mtest) was increased in NE vs NS. A higher mortality rate was observed in NS (30%). Results suggested that the 4 weeks of RT minimize the impact of 5/6Nx IN renal AKT pathway by increase in physical capacity (MLT, VO_2 peak and Mtest), reduce the impact on CrCl (43%) and improve in glomerulosclerosis (44%).

Conclusions: These parameters indicate that exercise could have a protective effect, especially under this experimental protocol. Thus, this study suggests that the exercise plays a preventive role in mortality and could be an additional strategy to be employed in CKD.

SA-PO784

CKD Is Associated with a Pro-Angiogenic and Inflammatory Profile Even in Post-Transplant CKD

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Background: Cardiovascular disease (CVD) is the most common cause of death in native and post-transplant chronic kidney disease (CKD). Circulating microparticles (MP) are increased in CKD and may reflect vascular injury and inflammation, important non-traditional risk factors for CVD. Here, we sought to identify novel biomarkers of vascular injury and inflammation common in both native and post-transplant CKD.

Methods: Proteomic analyses were conducted on plasma and MP of 9 healthy controls, 9 stage 3/4 native CKD patients, and 9 stage 3/4 post-transplant CKD patients. Somalogic SOMAscan assay, a highly sensitive assay that uses aptamers to quantify >1,300 proteins, was used. Ingenuity pathway analyses (IPA) were conducted.

Results: We identified 44 plasma proteins common to both native and post-transplant CKD vs healthy controls; the most significant being angiogenic proteins. IPA indicated Ephrin receptor signaling, serine biosynthesis, and transforming growth factor (TGF)-β as the top pathways activated in both CKD groups. The MP analyses indicated higher levels of 18 proteins common in both native and post-transplant CKD patients vs healthy controls. These proteins included cystatin C, β2-microglobulin, and renin precursor protein. Biomarkers of inflammation and fibrosis were most pronounced with IPA indicating acute phase response, insulin-like growth factor-1, tumor necrosis factor-α, and interleukin-6 signaling activation.

Conclusions: We have identified new putative pathways of vascular injury and inflammation in CKD. Pathways of angiogenesis and inflammation were significantly activated in CKD patients' plasma and MPs, respectively. Considering the high levels of MP renin precursor protein, the MPs most likely originated in the kidney. The activated pathways common in both native and post-transplant CKD suggest similar mechanisms of CVD in both groups of CKD.

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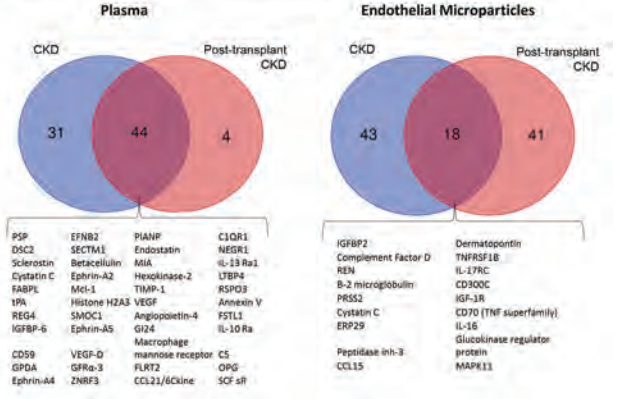
Figure: Venn diagrams illustrate the proteins that differed significantly in the plasma and MP of native CKD and post-transplant CKD (vs healthy controls) and the overlap between both CKD groups.



SA-PO785

Myokine SIRPα Causes Insulin Resistance Promoting Organ Cross-Talk in CKD

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Background: Signal regulatory protein alpha (SIRPα), a substrate for tyrosine phosphatases, promotes insulin resistance. SIRPα regulation in skeletal muscle and systemic responses to distant organs is largely unknown. Here we examine the influences of circulating SIRPα induced by chronic kidney disease (CKD) or hyperglycemia on disturbing insulin signaling pathways related to metabolism.

Methods: CKD was induced in muscle-specific and fat-specific SIRPα KO mice and compared to control mice and serum levels of SIRPα were evaluated. Next, acute hyperglycemia was induced in control and organ-specific SIRPα KO mice and serum levels of SIRPα were evaluated. Next, exogenous administration of recombinant SIRPα was utilized to treat control mice and skeletal muscle insulin signaling was determined. Finally, serum samples were obtained from CKD patients prior to peritoneal dialysis catheter placement and healthy control samples were obtained from blood donors.

Results: In control mice with CKD serum SIRPα levels were increased, while in muscle-specific SIRPα KO mice with CKD, we uncovered that serum SIRPα levels ($p<0.05$) were suppressed and associated with improved insulin signaling both in skeletal muscles and adipose tissue. However, in adipose-specific SIRPα KO mice with CKD, levels of serum SIRPα were increased over 2-fold ($p<0.05$) while muscle losses were minimally inhibited. Additionally, when acute hyperglycemia was induced in control mice and and organ-specific SIRPα KO mice, serum SIRPα levels were significantly increased in response to hyperglycemia in control and adipose-specific SIRPα KO, but not muscle-specific SIRPα KO mice. Next, recombinant SIRPα was injected into mice and skeletal muscle insulin signaling was significantly impaired by exogenous administration. Finally, SIRPα signaling is clinically relevant as suggested by our findings that include increased serum SIRPα expression in the serum of patients with CKD (2.4-fold, $p=0.000017$ vs. Healthy Controls).

Conclusions: SIRPα plays an important role as an anti-insulin myokine regulating insulin-mediated pathways. In muscle-specific KO mice with CKD, changes in serum SIRPα levels improve insulin signaling in muscle and adipose tissue, suggesting organ crosstalk. Therefore, targeting SIRPα may prevent metabolic dysregulation and insulin resistance in patients with CKD.

Funding: Veterans Affairs Support

SA-PO786

Nephrogenic Systemic Fibrosis (NSF) Is Induced in High-Phosphate-Diet CKD Rats Exposed to Gadolinium Gd^{3+}-Binding Contrast Agents: Role of Bone ASARM Peptides

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Background: High contrast Magnetic Resonance Imaging (MRI) requires the use of Gadolinium Binding Contrast Agents (GBCAs). Subsets of chronic kidney disease (CKD) patients exposed to GBCAs develop Nephrogenic Systemic Fibrosis (NSF), a progressive disease that leads to acute morbidity and death. Our previous work showed circulating ASARM-peptides bind to GBCAs and induce release of toxic Gd^{3+}. Bone-derived ASARM peptides induce hypophosphatemia and bone-mineralization abnormalities. We hypothesize increased levels of acidic ASARM-peptide exacerbates release of free Gd^{3+} resulting in an NSF pathology with reduced ectopic mineralization defects.

Methods: To test our hypothesis, we used a rat 5/6 Nephrectomy CKD disease model (NEPHREX). Male rats (16 wk, 250 gm) were fed a high phosphate diet (2% P, 200IU Vit D and 0.8% Ca; TEKLAD 170496). ASARM peptide was infused continuously for 4 weeks using subcutaneous implantation of osmotic pumps. As controls, co-implanted osmotic pumps were used to co-infuse SPR4 peptide - a peptide that neutralizes ASARM. Sera collections were taken at the beginning and end of the study. Three consecutive, daily bolus injections of Gd^{3+}-containing contrast agent (Omniscan™, gadodiamide) were given 3 days after pump implantation through surgically implanted jugular-vascular-catheters.

Results: NEPHREX rats treated with Omniscan™ and ASARM developed severe skin pathology, behavioral abnormalities, and joint abnormalities that were consistent with NSF. Computed tomography (CT) showed renal, brain, heart dermal metastatic calcifications and bone defects in Omniscan™ treated Rats. ASARM peptide treatment corrected the Omniscan™ induced skin, bone and soft tissue mineral abnormalities and corrected the hyperphosphatemia.

Conclusions: Our study shows CKD rats fed a high phosphate diet and treated with Omniscan™ develop severe NSF like pathology. ASARM infusion prevents Omniscan™ induced subdermal calcification, corrects mineral defects and hyperphosphatemia. In conclusion, ASARM peptides induce release of free Gd^{3+} from GBCAs but reduce mineralization pathology. These findings have clinical importance for GBCA use in inherited or acquired renal bone-mineral loss disorders with increased circulating ASARM-peptides.

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SA-PO787

Uremia Modulates the Action of Simvastatin on the ABCA1 (ATP-Binding Cassette Transporter-1) in Endothelial Cells

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Background: Ligands of the retinoid X receptor (RXR) and liver X receptor (LXR) activate ABCA1 in endothelial cells at levels of both promoter activation and mRNA induction. ABCA-1 has a broad specificity in cholesterol efflux in endothelial cell and is highly modulated by statins. Chronic kidney disease (CKD) drives an epidemic cardiovascular burden due to neurohumoral dysfunction related with uremic state. We investigated the role of sinvastatin on ABCA1 modulation by LXR-β/RXR-α pathway in HUVEC cells exposed to uremic serum of patients under regular hemodialysis.

Methods: Previously characterized HUVEC cells were pre-treated with statin and stimulated with uremic serum for the same period. TNF-α and IL-10 levels were measured in cell supernatant. The expression of ABCA-1, LXR-β and RXR-α was analyzed by real-time PCR. Transfection of HUVEC cells was performed for analysis of ABCA-1 and promoter activation mediated by LxR-β and RxR-α, evaluation was carried out by flow cytometry and Western blot.

Results: In HUVEC cells, uremic state reduced the expression of LXR-β and RXR-α receptors without changing ABCA-1 expression. Simvastatin reversed the decrease of LXR-β and RXR-α expression observed in HUVEC cells incubated with uremic serum leading to a significant increase in ABCA-1 expression. The 3-HMCoA reductase inhibitor

reversed the TNF-α increased secretion observed under uremic state without modifying IL-10. Sinvastatin-treated cells had a significant increase in transcription activation of LxR-β/RxR-α inducing ABCA-1 expression gene. Uremic state promoted a significant reduction in ABCA-1 transcription activation which was reversed by simvastatin.

Conclusions: We demonstrated that sinvastatin reduced inflammatory response of HUVEC cells exposed to uraemia by decreasing TNF-α secretion. We sugest that attenuation of inflammation observed by the 3-HMCoA reductase inhibitor is promoted through LxR-β/RxR-α pathway activation and consequent upregulation of ABCA-1 expression. Our study provides a potential role of statins on endothelial protection in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO788

Collaborative Peer-Review Model: Patient Partners as Equal and Contributing Voices in Patient-Oriented Research

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Background: Can-SOLVE CKD is a pan-Canadian network seeking solutions and innovations that will transform kidney health in Canada through 18 patient-centered projects. The Research Operations Committee (ROC) performs annual peer-review on all projects to provide guidance for successful implementation. The Patient-Oriented Research (POR) Collaborative Peer-Review Model employed by ROC and facilitators enables patient partners to participate as equal and contributing voices in the process.

Methods: Membership includes patients, Indigenous partners, experts on research methodology/clinical research. Reviewed aspects include design, feasibility of implementation plan, risk-mitigation, patient engagement, knowledge translation (KT) and Indigenous cultural safety and engagement. A review package includes a progress update by the project team, Knowledge Users and KT Committee review feedback, POR Training log, patient engagement check-in calls and survey report. A researcher is a primary reviewer, focusing on scientific methods, a patient partner is a secondary reviewer, focusing on patient engagement, and a reader contributes to the discussion. Reviewers complete an evaluation checklist and attend a session to agree on recommendations that are relayed back to the project team. Network supports may be dispatched to facilitate recommendations. Concerns require project teams to address and respond to ROC with possible interim reporting.

Results: The involvement of patient partners in the peer-review process is a new addition to what has traditionally been a highly technical, closed format. Patient partners play prominent roles in the review. Effective patient partner reviewers are 1) "comfortable with themselves" and not afraid to voice opinions, and 2) motivated and interested in the work. An environment that cultivates engagement includes respectful and inclusive facilitation at meetings, a forum for peer support to share learning and provide the opportunity to learn on the job.

Conclusions: The Collaborative Peer-Review Model ensures accountability of POR principles encouraging research outputs to have a high impact. This can be considered and adapted for other organizations for patient partners to have a prominent role in monitoring and governance of POR.

Funding: Government Support - Non-U.S.

SA-PO789

Association of Lower Dietary Potassium Intake with Higher Death Risk in a Prospective Hemodialysis Cohort

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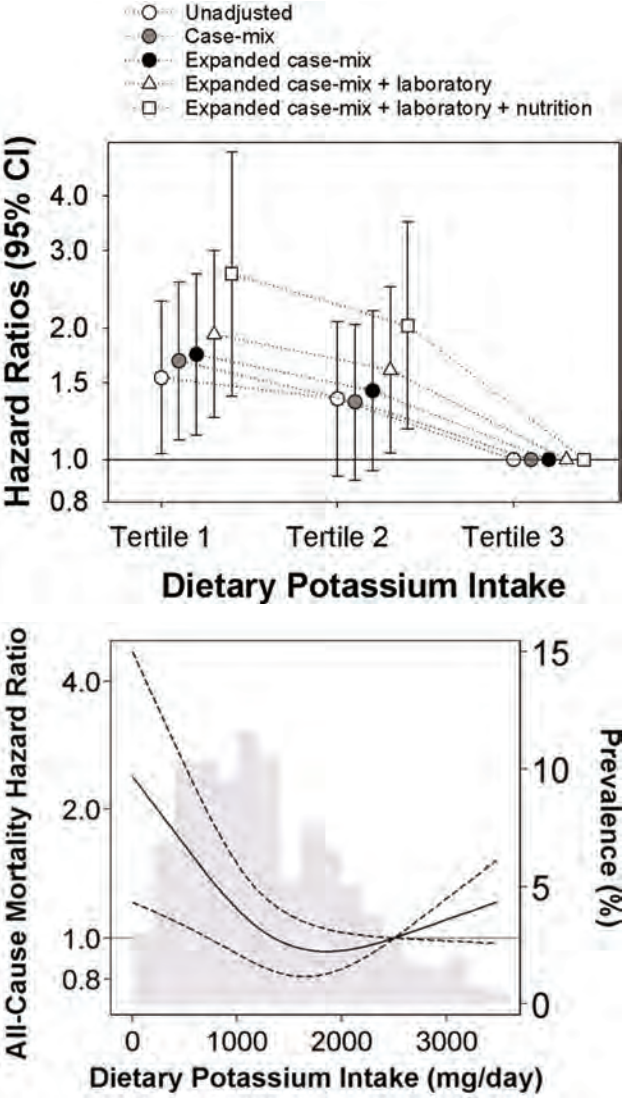
Background: Among hemodialysis patients, clinical practice guidelines recommend dietary potassium restriction given concerns about potential hyperkalemia leading to malignant arrhythmias and mortality. Yet there are sparse data informing recommendations for dietary potassium intake in this population. We thus sought to examine the relationship between dietary potassium intake and death risk in a prospective hemodialysis cohort.

Methods: Among 415 hemodialysis patients from the prospective "Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease" cohort recruited across 16 outpatient dialysis clinics, information regarding dietary potassium intake was obtained using Food Frequency Questionnaires (FFQ's) administered over 2011 to 2015. We first examined associations of baseline dietary potassium intake categorized as tertiles with mortality risk using Cox regression. We then examined clinical characteristics associated with low dietary potassium intake (defined as the lowest tertile) using logistic regression.

Results: In expanded case-mix Cox analyses, patients whose dietary potassium intake was in the lowest tertile had higher mortality (ref: highest tertile): adjusted HR (aHR) (95%CI) 1.74 (1.14, 2.66). These associations had even greater magnitude of risk following adjustment for laboratory and nutritional covariates: aHR (95%CI) 2.65 (1.40, 5.04). In expanded case-mix restricted cubic spline analyses, there was a monotonic increase in mortality risk with incrementally lower dietary potassium intake. In expanded case-mix logistic regression models, female sex; higher serum bicarbonate; and lower dietary energy, protein, and fiber intake were associated with low dietary potassium intake.

Conclusions: In a prospective cohort of hemodialysis patients, lower dietary potassium intake was associated with higher mortality risk. These findings suggest excessive dietary potassium restriction may be deleterious in hemodialysis patients, and further studies are needed to determine the optimal dietary potassium intake in this population.

Funding: NIDDK Support



SA-PO790

Proactive Identification and Nutritional Management of Hyperkalemia via Electronic Health Record Phenotyping

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Background: Hyperkalemia is common chronic kidney disease (CKD) patients and is often associated with adverse cardiac events. Patients with CKD are at increased risk of hyperkalemia due to impaired potassium homeostasis. CKD patients on long-term RAAS inhibitors and/or potassium-sparing diuretics are at increased risk of hyperkalemia, as are those with history of hyperkalemia who are not treated with potassium-binding agents. Targeted nutritional guidance is a low-cost, low-risk intervention for reducing hyperkalemic events.

Methods: Using longitudinal data of 110,998 patients from the Rogosin Institute, a rule-based cohorting criteria (Fig 1) was created using a custom web-based interface provided by pulseData to identify patients who are hyperkalemic or are at risk of hyperkalemia. A two-step workflow was developed: 1) EHR data-driven identification of patients at risk for hyperkalemia and 2) targeted delivery of a nutritional flyer to high-risk patients.

Results: 1) *Data-driven identification*: We developed a method to systematically identify high-risk patients and facilitate targeted delivery of the nutritional intervention. On retrospective review, this query identifies on average 10 patients each week. 2) *Nutritional Guidance*: A nutritional flyer was created to inform the identified patients on which high-potassium foods which should be avoided. Using a flyer is a less costly resource than an appointment with a nutritionist and can be brought with the patient to the grocery store.

Conclusions: A proactive, data-driven method was developed for delivery of nutritional guidance to high-risk patients to reduce future hyperkalemic events. This workflow will be implemented at The Rogosin Institute. Data will be collected on subsequent hyperkalemia events.

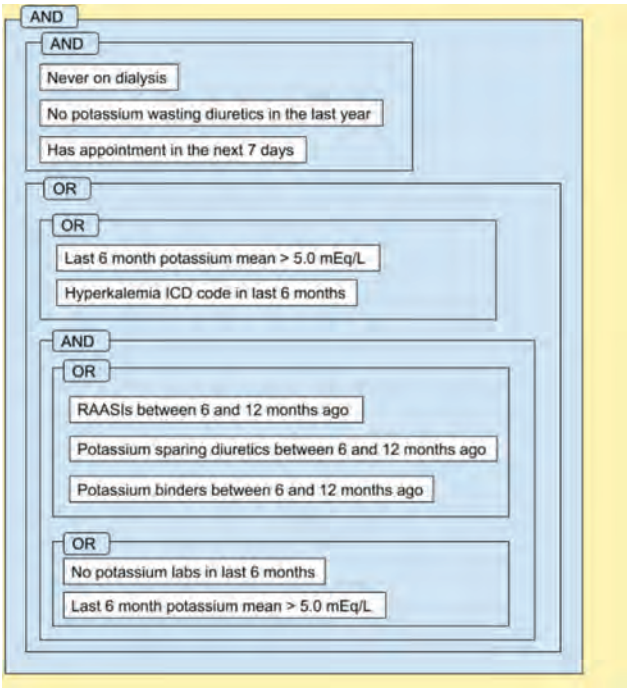

Figure 1

SA-PO791

Variability of Serum Phosphate and Markers of Malnutrition and Inflammation in Hemodialysis Patients

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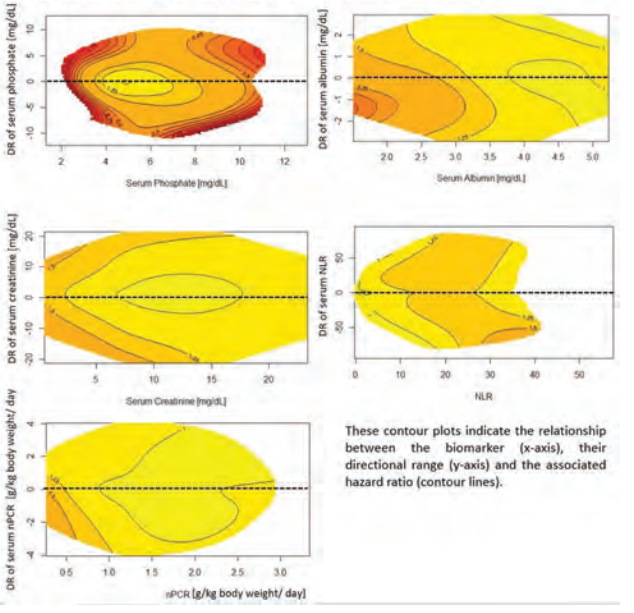
Background: Several biomarkers show significant short- and long-term variability. Here we assessed the variabilities of phosphate(P), albumin(alb), creatinine (creat), nPCR, and neutrophil-to-lymphocyte ratio(NLR) and their associations with outcome.

Methods: All incident in-center HD pts treated in Fresenius Medical Care North America clinics from 10/2010 to 10/2018 were enrolled. The 6-months (mo) baseline (mo 4 to 9) preceded a 12-mos follow-up (mos 10 to 21). Biomarker baseline variability was described by several metrics:(i) standard deviation (SD); (ii) average real variability (ARV = $1/(N-1) * \sum_{(i=1 \sim N-1)} | X_{i+1} - X_i|$; N is number of valid lab measurements); (iii) the directional range (DR), it is positive when the minimum antedates the maximum, otherwise negative. Cox proportional hazards models with spline terms were employed to investigate the association between these variables, their variability indicators, and all-cause mortality. ANOVA Cox proportional hazard models (adjusted for age, gender, race, diabetic, congestive heart failure) were built to study the interactions of these variables and their variability with outcome during follow-up.

Results: We enrolled 159703 patients, 17037 died during follow-up. Baseline P was 5.1 mg/dL, median serum P SD, ARV, and DR were 0.91, 0.95, -0.91 mg/dL, respectively. The relation between P variability and all-cause mortality was consistent across a wide range of P levels. For alb, nPCR and creat the highest mortality was observed in patients with low P levels and negative DR.

Conclusions: The direct relation between P variability and mortality is present across levels of nutrition and inflammation. A high P variability should prompt the search for underlying causes, such as poor nutrition and inflammation, and potential interventions.

Figure: Interaction of laboratory markers and their DR with all-cause mortality.



SA-PO792

Dietary Modification Improves FGF-23, KLOTHO, PTH, and Serum Phosphorous Levels in CKD Stages 1 and 2

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Background: Dietary phosphorus restriction is a potential therapy for improving cardiovascular outcomes. Aim: To examine effect of dietary counselling and dietary modifications on FGF-23, klotho, PTH levels and phosphorous in CKD Stage 1 and Stage 2 patients.

Methods: 100 subjects aged 35.37 ± 10.98 years with eGFR 83.55+16.53 ml/minute and BMI 24.74 ±2.18 were recruited in the study. 24 hour dietary recall was taken at baseline, Based on dietary phosphorous intake patients were divided into two groups. Group 1: low phosphorous diet and Group 2: high. phosphorous diet. Controls were 30 healthy subjects, aged 43.83±10.11 ml/min with eGFR 126.11+10.26 ml/min and BMI 24.06 ±2.09. FGF-23, soluble α-Klotho, iPTH were measured (ELISA)

Results: The independent t test showed that iPTH, serum creatinine, FGF-23, serum phosphorous, total cholesterol and VLDL were significantly higher in CKD patients compared to controls(p=0.000),. Hemoglobin (p=0.046), vitamin D(p=0.008), klotho (p=0.000) and HDL (p=0.000) were lower in CKD patients compared to controls (n=30). GFR showed a positive significant correlation with klotho (r=0.696, p=0.000) and a negative significant correlation with serum phosphorous (r=-0.494, p=0.000), iPTH (r=-0.751, p=0.000), FGF-23 (r=-0.638, p=0.000), urinary phosphorous (r=-0.476, p=0.000) and dietary phosphorous intake (r=-0.678, p=0.000). Urinary phosphorous showed a significant positive correlation with dietary phosphorous (r=0.488, p=0.000) After dietary counselling and diet modifications in group 2, dietary phosphorous decreased from 1384.74±117.32 to 1027.69±101.39 (p=0.008; serum phosphorus 3.89±0.57 to3.59±0.63 p **0.008**), FGF-23 (169.80±50.96 to 159.45±58.66; p **0.023**), klotho (351.77±134.88 to 316.83±167.25 p **0.037**) and iPTH decreased from 88.48±10.55 to 85.49±15.25; p **0.033**. There was decline in protein intake from 0.67±0.130.to 60±0.11g/kg/d p **0.010.** FGF-23 showed a strong significant negative correlation with klotho (r=0.754, p=0.000) i.e. as the levels of FGF-23 decreases, the levels of klotho increases after the diet modification in group 2 when they were advised to be strictly on a low phosphorous diet.

Conclusions: Both diet counselling and diet modification can bring down levels of FGF-23, Klotho, iPTH, serum phosphorous, urinary phosphorous which can be instrumental in slowing the progression of CKD and preventing cardiovascular disease.

SA-PO793

Hyperphosphatemia: Barriers to Treatment Adherence in Dialysis Patients

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Background: Hyperphosphatemia in end-stage renal disease is associated with increased morbidity and mortality. One important cause of hyperphosphatemia is non-compliance with low phosphate diet and phosphate binders. The primary objective of our study is to evaluate the adherence to prescribed treatment and barriers in accomplishing adherence.

Methods: We collected data from 2 dialysis units in Tucson. A questionnaire was designed to assess dialysis patient's access to nutritional resources, knowledge of medications as well as dietary restrictions and barriers to access appropriate care.

We included patient >18 years old who had phosphorus >5.5mg/dl in the preceding 3 months prior to screening. From the gathered information we identified the top 6 factors responsible for uncontrolled phosphorus and designed strategies to improve patient compliance and accessibility. Data were analyzed using SPSS.

Results: 38 patients were included in the final analysis. Mean age of participants was 52.9±16.3 year. Our cohort consisted of 63% male and 53% Hispanic population. 6 most common reasons are represented in figure 1. In 55% of subjects, budget affects the preference of food. 42%, 74% and 39% could not answer low phosphorus drink, snack and meal respectively. 74% suggested that the use of pamphlets for diet education could improve compliance. Reasons for noncompliance: education does not fit food habits, concern for own/family nutrition, fast food.74% not aware of the importance of phosphorus control. 74% not satisfied with doctor's explanation about phosphorus. 76% complained about phosphorus binders. Most common complaint about binders was size of the pill. Based on the findings, an intervention strategy was designed.

Conclusions: ESRD patients require a multidisciplinary approach to mobilize more local and national resources to achieve good phosphorus control. Diet changes, educational approach, reminder techniques, binder type should be tailored to the individual patient. Patients appreciate doctor's involvement in the management of phosphorus (it should not be completely left to the dietician.)

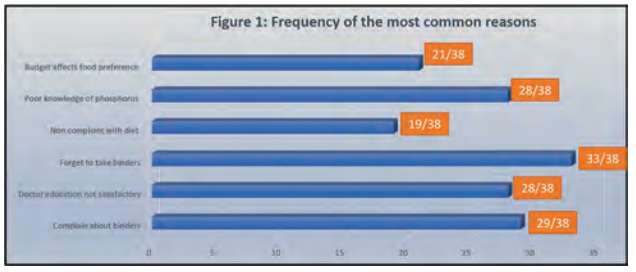

Figure 1

SA-PO794

Low Protein Intake Is Associated with Severe Fatigue in Stable Outpatient Renal Transplant Recipients

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Background: Severe fatigue is a frequent complaint in renal transplant recipients (RTR) that is often accompanied by functional impairment and poor quality of life. Low protein intake may lead to protein-energy malnutrition and thereby contribute to fatigue in RTR. We aimed to (1) compare the prevalence of severe fatigue between RTR and healthy controls, (2) investigate impact of severe fatigue on quality of life in RTR, and (3) investigate the association of protein intake with severe fatigue in RTR.

Methods: We included 601 stable RTR with a functioning graft >1 year and 237 prospective kidney donors from the TransplantLines Study. Overall fatigue was assessed using the Checklist Individual Strength (CIS) Questionnaire. A CIS-score >76 is commonly considered to indicate severe fatigue and was used as cut-off in this study. Quality of Life (QoL) was assessed with the RAND-36 Questionnaire. The Maroni formula was used to calculate protein intake from 24-hr urinary urea excretion. Chi-Square was used to test differences in prevalence of severe fatigue in RTR and donors. Mann-Whitney U was used to test differences in QoL of RTR with and without severe fatigue. Logistic regression was used to analyze the association between protein intake and presence of severe fatigue.

Results: RTR were 55 ± 13 years old, 347 (58%) were male and mean eGFR was 50 ± 18 ml/min/1.73m^2. Thirty-three percent of RTR were severely fatigued compared to 6% of kidney donors (P<0.001). QoL was significantly lower in RTR with compared to RTR without severe fatigue (median QoL-score 40 [30-60] *vs* 60 [50-75], P<0.001). Mean protein intake in RTR was 1.0 ± 0.3 g per kg bodyweight per day. Protein intake was inversely associated with severe fatigue in RTR (OR 0.17; 95%CI 0.07-0.40 per g/kg/d, P<0.001). This association remained materially unchanged after adjustment for potential confounders, including age, sex, eGFR, BMI, and anaemia (OR 0.20; 95%CI 0.08-0.51 per g/kg/d, P=0.001).

Conclusions: Severe fatigue is highly prevalent in RTR and a determinant of poor quality of life. Low protein intake is associated with higher risk of severe fatigue in RTR, independent of potential confounders, including age, sex, eGFR, BMI, and anaemia.

SA-PO795

Dietary Protein Intake, Kidney Function, and Mortality in a Nationally Representative Cohort

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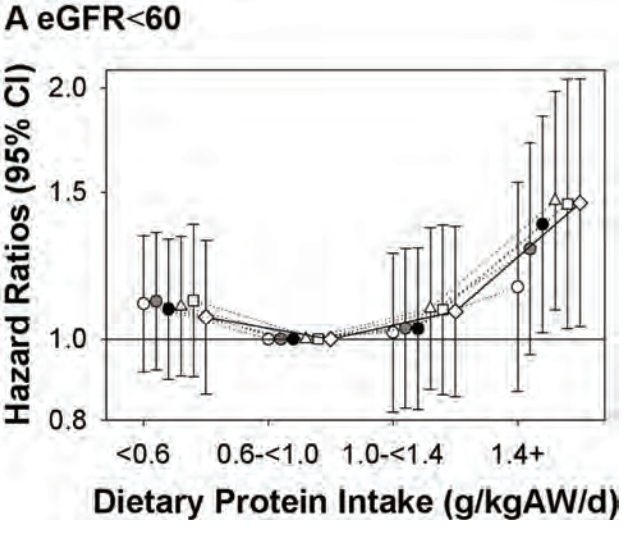
Background: In the general population, high protein diets (Paleo, Atkins, ketogenic) have gained popularity as a means to promote weight loss and avoid excess carbohydrate consumption. Yet in chronic kidney disease (CKD), evidence suggests low dietary protein intake (DPI) leads to attenuation of kidney function decline, although there remains concern about risk of protein-energy wasting. We thus sought to examine the association of DPI with mortality risk in a nationally representative cohort stratified by estimated glomerular filtration rate (eGFR).

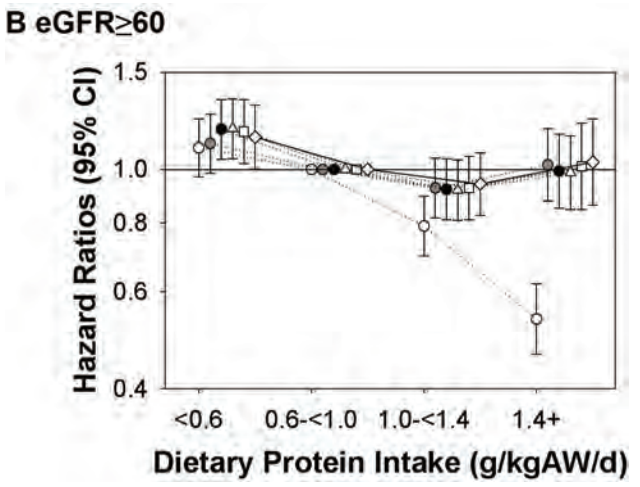
Methods: We examined the association of daily DPI normalized to actual body weight (g/kg actual weight [AW]/day) ascertained by 24-hour dietary recall, with all-cause mortality among 27,604 continuous NHANES adult participants (1999-2010) stratified by low vs. normal eGFR (<60 vs. ≥60ml/min/1.72m^2, respectively) in adjusted Cox models. We also examined the relationship between high biologic value (HBV) protein consumption with mortality.

Results: In participants with low eGFR (N=1999), high DPI ≥1.4g/kg AW/day was associated with higher death risk, while lower DPI levels were not associated with mortality (ref: 0.6-<1.0): HRs (95%CI): 1.09 (0.90, 1.32), 1.03 (0.82, 1.29), and 1.37 (1.02, 1.85) for DPI <0.6, 0.6-<1.0, 1.0-<1.4, and ≥1.4g/kg AW/day, respectively. Yet in those with normal eGFR (N=25,605), low DPI <0.6g/kg AW/day was associated with higher mortality, whereas higher DPI levels were not associated with death. In those with low eGFR, the highest two tertiles of HBV consumption were associated with higher death risk (ref: lowest tertile), whereas no association of HBV intake with mortality was observed with normal eGFR.

Conclusions: In participants with low eGFR, higher DPI and HBV consumption were associated with higher mortality, whereas lower DPI was associated with higher mortality in those with normal eGFR. Further studies are needed to elucidate the specific pathways between higher DPI and HBV consumption and mortality in those with CKD.

Funding: NIDDK Support





SA-PO796

Decline in Renal Function After Withdrawing Ketoanalogue Supplementation: A Randomized Clinical Trial

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Background: Studies have reported preservation of renal function and nutritional status in patients with a low protein diet supplemented by ketoanalogues. Our group reported preservation of renal function and nutritional status in patients who were supplemented with ketoanalogues. The aim of the study was to evaluate if the renal function is maintained after withdrawing ketoanalogue supplementation despite continuing on the same diet.

Methods: Forty CKD patients were randomized into two groups: Group 1 (Intervention) patients were supplemented with 6 tablets of ketoanalogue for 10 months. Patients were advised very low protein diet 0.4 g/kg/day. Group 2 (Control) patients were given conservative treatment with 0.6 g/kg/d protein restriction. Dietary assessment was done at visit 1 and at visit 2 (10 months). Nutritional assessment was evaluated with SGA score. GFR and serum albumin were evaluated at baseline and at 10 months. After 10 months ketoanalogue supplementation was stopped and patients were followed up for four years with same dietary intake.

Results: At baseline, the GFR was higher in controls (51.14±15.1 ml/minute). compared to supplemented group (47.79±13.2 ml/minute). After 10 months in control group, in GFR decline by 15.54 ml/min (51.14 to 35.5±7.94 ml/minute) and serum albumin decreased from 3.8±0.90 g/dL to 3.09±0.38 g d/l. In supplemented group the GFR and albumin remained stable at 47.79±13.2 ml/minute and 4.11±0.43 respectively. In ketoanalogue group patients did not comply to low protein diet, in stead they consumed normal protein diet 0.62±0.24 g/kg/d. In supplemented group serum creatinine decreased from 1.61±0.52 to 1.40±0.52 but increased to 2.2 mg% after stopping ketoanalgue. After stopping supplementation at 10 months patients were followed up for four years. Gradual decline was observed in GFR (47.79±13.2 to 28.0 ml/minute) and albumin (4.11±0.43 to 3.6 g/dL). Some patients progressed to ESRD. After stopping ketoanalogues, the dietary intake remained the same

Conclusions: Low protein diet supplemented with ketoanalogues preserves renal function and nutritional status in predialysis patients. However, a rapid decline in renal function is observed after stopping ketoanalogue supplemention.

Funding: Commercial Support - Panacea Biotech

SA-PO797

Urinary Proteomics in CKD Associated with Glomerular Endothelial Cell Injury

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Background: A number of studies have been conducted on the identification of urinary proteomics associated with the progression of chronic kidney disease (CKD). In the course of CKD, any injury to the glomerular structure is likely to affect the glomerular endothelial cell. In this study, we sought to identify proteomic markers that increase in CKD with endothelial cell injury.

Methods: Label-free quantitative proteomic analysis based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) was performed on urine samples obtained from 9, 11, and 10 patients in CKD stage 1, 3 and 5, respectively. Quantitative proteomic analysis based on Tandem mass tag (TMT) was also performed for primary cultured glomerular endothelial cells (GECs) before and after inducing hypoxia injury through maintenance in hypoxia chamber for 24 hours. Selection of differentially expressed proteins (DEPs) was based on false discovery rate-adjusted p-value <0.05.

Results: The mean estimated glomerular filtration rate of patients with CKD stages 1, 3, and 5 were 110.1 + 17.9, 43.2 + 12.5, and 10.5 + 3.0, respectively. We identified 65, 198, and 650 DEPs between CKD 1 and CKD 3, between CKD 3 and CKD 5, and between CKD 1 and CKD 5, respectively, when the urinary proteins were identified in these CKD patients. When comparing the proteins expressed before and after hypoxia injury in the GEC cell, we identified 4032 DEPs in the first experimental set and 3194 DEPs in the second set. Only 8 of these proteins showed significant results in both urine of CKD patients and endothelial cells. Among these 8, there were only 5 significant results between CKD 3 and 5 and between CKD 1 and 5, and there were no significant results between CKD 1 and 3. Among the significant proteins, IGFBP3, APOL1, and PROS1 increased more than 1.5 fold with hypoxia injury on GEC and increasing CKD stages, whereas HILPDA and MUC1 increased with GEC injury and decreased with increasing CKD stages.

Conclusions: We have identified specific urinary proteins that change with endothelial cell injury and CKD progression, and further analysis of the diagnostic value of these proteins for chronic renal failure and endothelial cell damage is needed.

SA-PO798

Metabolomics of Dietary Protein Sources and CKD Progression in Children

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Background: Recent evidence suggests that source of dietary protein may influence kidney disease risk. We aimed to characterize the plasma metabolome of plant and animal sources of protein and to determine whether dietary protein-related metabolites were associated with CKD progression in children.

Methods: Metabolites were measured using an untargeted platform (Metabolon) in baseline plasma specimens from 488 Chronic Kidney Disease in Children (CKiD) participants. We assessed the cross-sectional association between protein source (plant, animal) and metabolites using linear regression adjusted for age, sex, race, BMI, glomerular vs. non-glomerular diagnosis, and eGFR, and statistical significance was determined using a false discovery rate <0.05 to account for multiple comparisons. Metabolites that were significantly associated with protein were included in the prospective analysis with CKD progression (renal replacement therapy or ≥50% eGFR decline) after accounting for proteinuria, anemia, hypertension, and serum albumin in addition to the same covariates in the cross-sectional analysis.

Results: A total of 94 (9.9% of 949) known serum metabolites were significantly associated with animal protein and 45 (4.7% of 949) metabolites were significantly associated with plant protein. Only one metabolite was significantly associated with both animal and plant protein: phenylacetate. For the prospective analysis, 23 animal protein-related metabolites (24.5% of 94) and 8 plant protein-related metabolites (17.8% of 45) were associated with CKD progression, including 21 lipids, 3 amino acids, 3 cofactors and vitamins, 2 xenobiotics, 1 peptide, and 1 nucleotide (p<0.05; **Table**).

Conclusions: An untargeted metabolomic platform identified multiple blood metabolites that were associated with animal and plant protein consumption and CKD progression. These findings could inform more nuanced dietary recommendations for children with CKD regarding protein source.

Funding: NIDDK Support

Table. Plasma Known Metabolites Cross-sectionally Associated with Sources of Dietary Protein and Prospectively Associated with CKD Progression in the CKiD Study

			Cross-sectional analysis with dietary protein		Prospective analysis with CKD progression	
Compound	Super Pathway	Subpathway	β	Q value	β	P value
Metabolites Significantly Associated with Dietary Intake of Animal Protein						
N,N,N-trimethyl-5-aminovalerate	Amino Acid	Lysine Metabolism	-0.0021	0.03	0.4484	0.007
isovalerylglycine	Amino Acid	Leucine, Isoleucine and Valine Metabolism	0.0032	0.03	0.2382	0.04
adrenate (22:4n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	-0.0033	0.03	-0.6130	0.007
1-(1-enyl-palmitoyl)-2-oleoyl-GPE (P-16:0/18:1)*	Lipid	Plasmalogen	0.0013	0.05	0.5669	0.02
linolenate (18:3n6)	Lipid	Polyunsaturated Fatty Acid (n3 and n6)	-0.0034	0.05	-0.3032	0.02
1-(1-enyl-stearoyl)-2-oleoyl-GPE (P-18:0/18:1)	Lipid	Plasmalogen	0.0019	0.005	0.4036	0.03
3-hydroxyhexanoylcarnitine (1)	Lipid	Fatty Acid Metabolism(Acyl Carnitine)	-0.0028	0.04	0.5253	0.004
ceramide (d18:1/20:0, d16:1/22:0, d20:1/18:0)*	Lipid	Ceramides	0.0017	0.045	0.6765	0.004
ceramide (d18:1/24:1, d18:1/22:1)*	Lipid	Ceramides	0.0042	0.04	0.2748	0.03
1-stearoyl-GPC (18:0)*	Lipid	Lysophospholipid	0.0028	0.047	0.3480	0.003
1-palmitoyl-GPG (16:0)**	Lipid	Lysophospholipid	0.0019	0.02	0.5542	0.007
1-arachidonoyl-GPC* (20:4)*	Lipid	Lysophospholipid	0.0020	0.01	0.4304	0.01
1-palmitoleoyl-GPC* (16:1)*	Lipid	Lysophospholipid	0.0018	0.04	0.4203	0.02
sphingomyelin (d18:1/14:0, d16:1/16:0)*	Lipid	Sphingomyelins	0.0024	0.01	0.8899	0.002
sphingomyelin (d17:1/16:0, d18:1/15:0, d19:1/14:0)*	Lipid	Sphingomyelins	0.0016	0.03	0.8457	0.005
sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0)*	Lipid	Sphingomyelins	0.0015	0.01	0.5492	0.008
sphingomyelin (d17:1/14:0, d16:1/15:0)*	Lipid	Sphingomyelins	0.0024	0.04	0.2949	0.048
13-HODE + 9-HODE	Lipid	Fatty Acid, Monohydroxy	-0.0052	0.03	-0.2015	0.007
2-hydroxybutanoate	Lipid	Fatty Acid, Monohydroxy	-0.0031	0.048	-0.3553	0.03
myristoyl dihydrosphingomyelin (d18:0/14:0)*	Lipid	Dihydrosphingomyelins	0.0035	0.01	0.7722	0.002
phenylacetylcarnitine	Peptide	Acetylated Peptides	0.0052	0.02	0.2032	0.02
homostachydrine*	Xenobiotics	Food Component/Plant	0.0051	0.008	0.3683	0.002
dihydroferulate	Xenobiotics	Food Component/Plant	-0.0048	0.048	-0.3367	0.03
Metabolites Significantly Associated with Dietary Intake of Plant Protein						
tryptophan betaine	Amino Acid	Tryptophan Metabolism	0.0277	0.04	0.1795	0.004
zeaxanthin dicd (2)	Cofactors and Vitamins	Vitamin A Metabolism	0.0065	0.01	0.3653	0.02
carotene diol (1)	Cofactors and Vitamins	Vitamin A Metabolism	0.0071	0.007	0.2557	0.03
beta-cryptoxanthin	Cofactors and Vitamins	Vitamin A Metabolism	0.0108	0.03	0.3552	0.04
15-HETE	Lipid	Eicosanoid	-0.0113	0.05	-0.1506	0.03
1-arachidonoyl-GPA (20:4)	Lipid	Lysophospholipid	-0.0076	0.047	-0.1792	0.04
sphingomyelin (d18:2/24:2)*	Lipid	Sphingomyelins	-0.0027	0.02	-0.6678	0.03
orotate	Nucleotide	Pyrimidine Metabolism, Orotate-containing	-0.0038	0.05	-0.4156	0.03

SA-PO799

Dietary Results from the CKD Observational Database (CKDOD) in China

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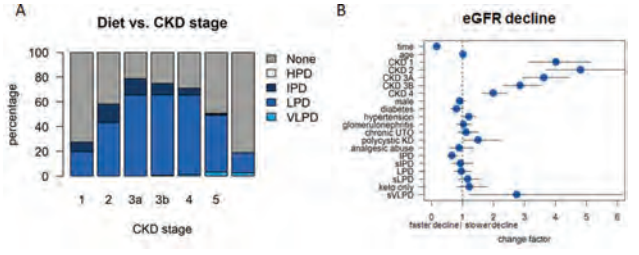
Background: Protein restricted diets (PRD) with or without ketoanalogue (KA) supplementation are an established dietary treatment option in chronic kidney disease (CKD). The aim of this study was the evaluation of specific types of protein restriction for management of CKD in China and assessment of associations between different nutritional protein interventions and estimated glomerular filtration rate (eGFR) changes over time.

Methods: 733 non-dialysis CKD patients were observed for median 1.1 year in this registry from routine care in China. Demographics and dietary prescriptions were analyzed descriptively. A mixed-effects model adjusting for demographics, CKD stage, and primary cause of CKD was used for longitudinal analysis of eGFR changes.

Results: Time since diagnosis of CKD was 1.1 [0.1; 3.1] years. 15% of patients were in stage 1-2, 35% stage 3, 20% stage 4, and 24% stage 5. PRD were mainly used in stages 3 and 4 (Figure 1A), with 90% of these patients receiving an advice for target of protein intake of 0.6-0.8 g/kg/d (LPD). Higher protein recommendations (0.8-1.0 g/kg/d, intermediate protein diet (IPD)) were more common in earlier CKD stages, e.g., in stage 2, 58% received recommendation for PRD with 25% of these for IPD. KA were prescribed more frequently with lower dietary protein intake (72% LPD, 38% IPD, p<0.001). Mixed effects regression suggested that lower protein intake is associated with slower eGFR decline compared to IPD or normal protein intake (Figure 1 B).

Conclusions: In this select Chinese population cohort, the use of protein restricted diets with or without KA supplementation in advanced stages of chronic kidney disease might be associated with a trend towards slower eGFR decline.

Funding: Commercial Support - Fresenius Kabi



SA-PO800

Low-Protein Diet for Patients Older Than 70 Years with CKD due to Benign Nephrosclerosis Is Effective in Suppressing Its Progression Without Causing Sarcopenia and Frailty

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Background: Restriction of protein intake delays or stops the progression of CKD. However, the effect of low-protein diet (LPD) in the elderly CKD patients is not well understood because of risk for malnutrition and other concerns. We studied the effect of LPD on them.

Methods: Patients with CKD stage 3-4 due to benign nephrosclerosis (BNS) were studied. All of them were 70 years old or older. Nutritional guidance of energy 30-35 Kcal/kgBW/day, protein intake 0.6-0.8 g/kgBW/day, salt intake 6g/day was given to patients. Protein intake was evaluated using the Maroni's formula by 24-hour urine sample. We studied for 3 years after the start of the LPD and also evaluated renal function and nutritional status.

Results: 50 patients were included in this study. Majority of patients were male (64%). The average age of patients is 75.5±5.39 years. 33 (LPD group) out of 50 patients were able to achieve less than 0.8g/kgBW/day (average: 0.60±0.10g/kgBW/day) of dietary protein in the evaluation of the Maroni's formula. 87.8% patients of the LPD group used low protein rice as a special low protein food. The LPD group showed significant improvement in eGFR, salt intake compared with the non-LPD group (n=17). The LPD group also did not have body weight loss, trouble climbing stairs, poor balance, weakness and not decrease walking speed, hemoglobin, albumin, T-cho and BMI (table 1). Four patients in the LPD group decreased eGFR. These four patients had significantly more amount of urine protein since the start of the study.

Conclusions: Even in the elderly, application of LPD is possible and effective in CKD stage 3-4 patients due to BNS. LPD in the elderly does not cause sarcopenia/frailty if it contains enough energy. Use of special protein-restriction foods is important in success of continuation of low protein diet.

Table 1

	Non-LPD group (>0.8g/kgBW/day, n=17)			LPD group (< 0.8kg/kgBW/day, n=33)		
	Baseline	End of the study (3-year)	P	Baseline	End of the study (3-year)	P
Protein intake (g/kgBW/day)	1.42±0.12	1.03±0.13	<0.05	1.35±0.10	0.60±0.10	<0.05
Salt intake (g/day)	10.2±1.8	7.4±1.7	<0.05	10.0±2.9	5.6±1.7	<0.05
BMI	24.2±2.1	23.8±1.9	N.S.	21.4±2.3	21.5±2.1	N.S.
Hb (g/dl)	12.4±1.4	12.0±1.7	N.S.	11.9±1.4	12.1±1.4	N.S.
Albumin (g/dl)	4.1±0.3	4.1±0.3	N.S.	4.0±0.4	4.0±0.4	N.S.
T-cho (mg/dl)	181.1±31.0	176.8±44.5	N.S.	193.4±27.3	189.1±18.1	N.S.
eGFR (ml/min/1.73m^2)	30.34±13.85	24.78±12.64	<0.05	28.49±10.91	30.11±12.58	<0.05
Usage of low protein rice (%)	23.5			87.8		

SA-PO801

Adherence to a Low-Protein Diet (LPD) Is Associated with Slower Rate of eGFR Decline in Patients with CKD

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Background: LPD is considered an effective strategy to defer transition to dialysis in patients with CKD through azotemia reduction. However, whether dietary protein intake impacts the rate of kidney function decline remains controversial.

Methods: We included 135 patients with an eGFR between 20 and 60 mL/min/1.73m^2 who started LPD (0.6-0.7g/kg/d) between 2015 and 2017 and retrospectively collected clinical history (diabetes status and RAASi therapy), serial eGFR (CKD-EPI), proteinuria, and urinary phosphorus. Dietary energy intake was >30Kcal/Kg/d. eGFR and 24h proteinuria were collected at the time of LPD initiation and at 6 and 12mo before and after LPD initiation. These time points were used to generate eGFR slopesbefore and after starting LPD. Adherence to LPD was estimated based on phosphaturia at 6mo after starting LPD. Patients on immunosuppressive therapy were excluded.

Results: There was a significant decrease in the rate of eGFR decline after LPD initiation (eGFR slopes: -0.35 ± 0.007 vs. -0.02 ± 0.003 ml/min/1.73m^2/month before vs. after LPD; p = 0.0007) (**Fig. 1**), though proteinuria did not significantly change. Univariate analyses showed that phosphaturia was the only variable significantly (p = 0.05) associated with rate of eGFR change, while diabetes status, RAASi therapy, and proteinuria at baseline were not. In a multivariate analyses, phosphaturia retained an independent association.

Conclusions: This retrospective, single center study shows that adherence to LPD is independently associated with ameliorated kidney function decline. These data support strategies to increase patient adherence to LPD. Further studies are needed to elucidate mechanisms by which LPD exerts renoprotection.

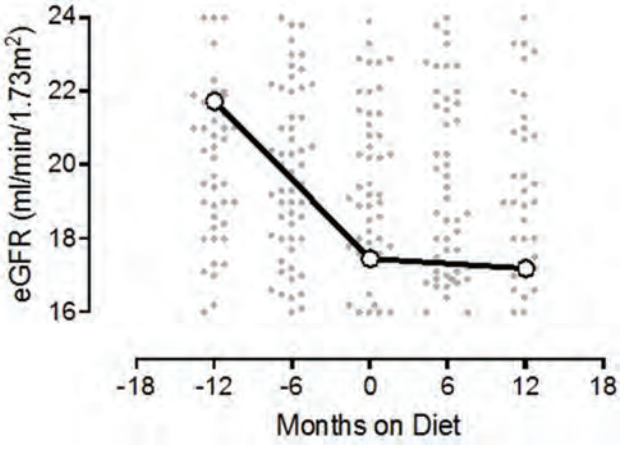

Fig. 1. Average eGFR at different time points before and after low-protein diet initiation. Grey dots represent single patients.

SA-PO802

High Plasma Branched-Chain Amino Acids Are Associated with Higher Risk of Post-Transplant Diabetes Mellitus in Renal Transplant Recipients

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Background: Post-transplant diabetes mellitus (PTDM) is a serious complication in renal transplant recipients (RTR). Branched-chain amino acids (BCAAs) are involved in the pathogenesis of insulin resistance and may predict new onset diabetes in the general population. Here, we prospectively determined the association of plasma BCAAs which comprise the amino acids valine, leucine, and isoleucine, with PTDM.

Methods: Adult RTR (≥ 18 y) recruited between November 2008 and May 2011 with a functioning graft for ≥1 year were eligible. Plasma BCAAs were measured in 518 RTR using nuclear magnetic resonance spectroscopy. We excluded RTR with a history of diabetes, leaving 368 non-diabetic RTR eligible for analyses. Cox proportional hazards analysis was used to assess the association of BCAAs with the development of PTDM.

Results: In 368 non-diabetic RTR (mean±SD age: 52.7±13.0 y, 53.7% men), fasting plasma BCAA was 377.6±82.5 μM. During median follow-up of 5.3 (IQR, 4.2-6.0) y, 38 (9.8%) RTR developed PTDM. RTR developed PTDM more frequently in the highest tertile of total BCAA (17.3%) when compared to the lowest two tertiles (8.0%; p=0.02). Total BCAAs were associated with a higher risk of developing PTDM (HR: 1.42, 95% CI 1.08-1.89) per SD change (p=0.01), independent of age and sex. Adjustment for other potential confounders did not significantly change these associations.

Conclusions: High concentrations of plasma BCAAs are associated with developing PTDM in RTR.

SA-PO803

High Circulating Concentrations of Very-Long-Chain Saturated Fatty Acids Are Associated with Low Risk of Premature Mortality in Renal Transplant Recipients

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Background: Recent epidemiological studies indicate that high exposure to very long chain saturated fatty acids (VL-SFA), present in peanuts and canola oil, is associated with positive health effects. Despite successful transplantation, health of renal transplant recipients (RTR) remains fragile, resulting in high risk of premature mortality. We hypothesized that high circulation concentrations of VL-SFA in RTR are associated with low risk of premature mortality in RTR.

Methods: We included 680 stable RTR with a functioning graft >1 year. Plasma behenic acid (C22:0) and lignoceric acid (C24:0) were measured by Agilent gas chromatography with flame ionization detector. Dietary data were collected using a Food Frequency Questionnaire. Correlations between dietary intake and C22:0 and C24:0 were analyzed by Spearman's Rho. Cox regression was used to analyze the association of VL-SFA on mortality and to estimate mortality risk across tertiles of VL-SFA concentrations.

Results: Age was 53±13 years, 57% were male and eGFR 52±20 ml/min/1.73m^2. Plasma concentrations of C22:0 and C24:0 were 73.7±17.7 and 62.5±16.3 nmol/L, respectively. C22:0 and C24:0 concentrations were correlated with intake of peanuts (r=0.13; *P*=0.001 and R=0.16, *P*<0.001, resp.) and peanutbutter (r=0.11, *P*=0.008 and R=0.11, *P*=0.005, resp.). During median follow-up of 5.4 years, 146 (22%) RTR died. Plasma C22:0 and C24:0 were inversely associated with mortality, independent of potential confounders, including age, sex and eGFR (HR 0.84 [95%CI 0.76-0.93], *P*=0.001 and HR 0.82 [95%CI 0.74-0.92], *P*=0.001, reps.). Moreover, RTR in the 3rd tertile of plasma C22:0 and C24:0 had significantly better survival compared to RTR in the 1st tertile (Table1).

Conclusions: Plasma VL-SFA is inversely associated with mortality in RTR. Increasing intake of foods containing VL-SFA, such as peanuts, may improve patient survival in RTR.

Mortality risk according to tertiles of C22:0 and C24:0

	C22:0		C24:0	
	Hazard Ratio (95%CI)	P-value	Hazard Ratio (95%CI)	P-value
Tertile 1	Reference	n/a	Reference	n/a
Tertile 2	1.07 (0.74-1.55)	0.74	0.76 (0.52-1.10)	0.15
Tertile 3	0.51 (0.33-0.80)	0.003	0.41 (0.27-0.64)	< 0.001

SA-PO804

Lipoatrophy and Metabolic Disturbance in Mice with Adipose-Specific Deletion of Kindlin 2

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Background: Kindlin-2 regulates the integrin-mediated cell adhesion and migration on the extracellular matrix. Our recent studies demonstrate important roles of Kindlin-2 in regulation of mesenchymal stem cell differentiation and skeletal development.

Methods: In this study we generated adipose tissue-specific conditional knock-out Kindlin-2 mice by using the Adipoq-Cre BAC transgenic mice. We used GTT to assess the glucose tolerance and ITT to assess insulin sensitivity.

Results: The results showed that deleting Kindlin-2 expression in adipocytes in mice caused a severe lipodystrophy with drastically reduced adipose tissue mass. Kindlin-2 ablation elevated the levels of blood nonesterified fatty acids (NEFA) and triglyceride, resulting in massive fatty livers in the mutant mice fed with high fat diet (HFD). Furthermore, HFD-fed mutant mice displayed type II diabetes-like phenotypes, including elevated levels of fasting blood glucose, glucose intolerance, and peripheral insulin resistance. Kindlin-2 loss dramatically reduced the expression levels of multiple key factors, including PPARg, mTOR, AKT, and b-catenin proteins, and suppressed adipocyte gene expression and differentiation. Finally, Kindlin-2 loss drastically reduced leptin production and caused a high bone mass phenotype.

Conclusions: Our study established a critical role of Kindlin-2 in control of adipogenesis and lipid metabolism as well as bone homeostasis.

Funding: Government Support - Non-U.S.

SA-PO805

Lipoprotein Abnormalities Are Associated with Mitochondrial Function and Intermuscular Adipose Tissue in Patients with CKD

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Background: Dyslipidemia such as increased LDL cholesterol and triglycerides levels, and decreased HDL levels frequently occurs in patients with CKD. There are limited data regarding the changes in lipoprotein composition and lipoprotein subfractions (based on density and size) in patients with CKD. Mitochondrial dysfunction may contribute to dyslipidemia and dyslipoproteinemia in patients with CKD including ectopic fat in skeletal muscle, i.e. intermuscular adipose tissue (IMAT). We now tested wheter lipoprotein abnormalities are associated with mitochondrial function and IMAT in patients with CKD.

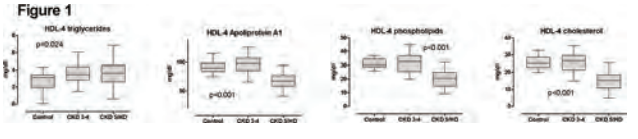
Methods: In a cross-sectional study, we evaluated 63 patients (20 with CKD 3-4, 22 with CKD 5 on hemodialysis (HD), and 21 matched controls). Composition of lipoprotein subfractions was determined in plasma from proton nuclear magnetic resonance spectra (NMR). Mitochondrial function was evaluated by ^{31} phosphorus magnetic resonance spectroscopy (^{31} P-MRS). IMAT was evaluated in the quadriceps muscle using magnetic resonance images.

Results: Groups were matched by gender, body mass index, and history of diabetes and hypertension. We identified changes in lipoprotein composition in patients with CKD, particularly in the mature (the smallest and most dense) HDL subfraction 4 (HDL-4) including increased triglyceride content, loss of apolipoproteins (AI and AII), and a decrease in cholesterol (free and esterified) and phospholipids (**Figure 1**). Mitochondrial dysfunction was associated with HDL triglycerides content (ρ=0.47, p<0.001) and HDL-4 Apolipoprotein AII (ρ=-0.43, p=0.001). IMAT accumulation was associated with HDL triglycerides content (ρ=0.65, p<0.001) and HDL-4 phospholipids (ρ=-0.36, p=0.009).

Conclusions: HDL composition is altered in patients with CKD and it is associated with mitochondrial dysfunction and IMAT accumulation. Dysfunctional HDL is unable to efficiently remove lipids from peripheral tissues and may contribute to IMAT accumulation. Likewise, changes in HDL apolipoproteins may affect mitochondrial function. Further studies should evaluate the interrelation among lipoproteins, mitochondrial function, and IMAT in patients with CKD.

Funding: NIDDK Support, Private Foundation Support

Figure 1



SA-PO806

High Circulating Concentrations of Marine-Derived N-3 Polyunsaturated Fatty Acids Are Associated with Low Risk of Premature Mortality in Stable Renal Transplant Recipients

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Background: Cardiovascular disease contributes significantly to high rates of premature mortality in renal transplant recipients (RTR). Plasma marine derived omega-3 poly-unsaturated fatty acids (N-3 PUFA) have been shown to have a positive effect on cardiovascular risk in the general population. The benefit of marine derived N-3 PUFA in RTR is unclear as most studies relied on intake derived from food frequency questionnaires rather than on plasma concentrations.

Methods: We included 680 stable RTR with a functioning graft >1 year. Plasma EPA and DPA were measured by Agilent gas chromatography with flame ionization detector. We used linear regression analyses to investigate the association of plasma EPA+DHA with log-transformed plasma concentrations of N-terminal Pro Brain Natriuretic Peptide (NT-proBNP). Cox regression analyses were used to analyze the prospective association of EPA+DHA on mortality.

Results: RTR were 53 ± 13 year old, 386 (57%) were male and mean eGFR was 52 ± 20 ml/min/1.73m^2. Mean plasma concentrations of EPA+DHA were 0.28 ± 0.12 µmol/L. Median NT-proBNP concentrations were 249 [IQR 105-625] ng/L. EPA+DHA was inversely associated with NT-proBNP, independent of potential confounders, including age, sex and eGFR (st.β -0.080, *P*=0.02). During 5.4 years of follow-up, 146 (22%) RTR died. In prospective analyses, we observed EPA+DHA was inversely associated with risk of premature mortality, independent of potential confounders (HR 0.24; 95%CI 0.06-0.98, *P*=0.047).

Conclusions: High circulating concentrations of marine derived N-3 PUFA (EPA+DHA) are associated with low circulating concentrations of NT-proBNP, consistent with beneficial effects on cardiovascular health and low risk of premature mortality in RTR. These results support advices for increased intake of N-3 PUFAs in RTR.

SA-PO807

The High Dietary Polyunsaturated Fatty Acid Level Is Associated with Lower Prevalence of CKD: A Population-Based Cohort Study

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Background: There have been steady interests in the effects of polyunsaturated fatty acid (PUFA) on health and several studies have proved PUFA is associated with lower risk of hypertension and diabetes. However, the effect of dietary PUFA on renal function in general population has been relatively unexplored, yet. Therefore, we aimed to evaluate the relationship between dietary PUFA intake and renal function in a nationwide nutritional survey.

Methods: Data were retrieved from the Korea National Health And Nutrition Examination Survey (KNHANES). Among 39,225 subjects collected from 2013 to 2017, 22,079 subjects were included in final analysis, after exclusion of those who were under 18 or whose baseline data were missing. FPF (fraction of PUFA among dietary fat intake) was defined as percentage of daily PUFA intake (g) relative to daily total fat intake (g). The subjects were categorized into quartiles according to the FPF. Primary outcome was defined as a prevalent chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) by Korean version of CKD-EPI < 60 mL/min/1.73 m^2 and composite outcome was eGFR < 60 mL/min/1.73 m^2 or the presence of proteinuria, defined as ≥ 1+ by dipstick urine test.

Results: The mean age and eGFR of the subject were 51.1 ± 16.4 years and 94.6 ± 18.8 mL/min/1.73 m^2, respectively. The mean FPF was 26.4 ± 10.0 %. Interestingly, the subjects in higher FPF group tended to be older and have slightly lower eGFR compared to those in lower FPF group. Moreover, they had lower daily fat intake and higher prevalence of HTN, DM and dyslipidemia. Total 899 subjects were found to have prevalent CKD and 1,106 subjects had composite outcomes. Multivariable logistic regression analyses revealed that the risk of CKD was lower in the group with the highest FPF compared to the lowest FPF group after adjustment for confounding factors [odds ratio (OR) 0.71, 95% confidence interval (CI) 0.58-0.88, P = 0.002]. This finding was consistent in terms of composite outcome (OR 0.75, 95% CI 0.62-0.90, P = 0.002).

Conclusions: The risk for CKD was lower in the subjects with the high dietary PUFA. Fraction of PUFA among dietary fat may affects renal function in healthy population.

SA-PO808

The Effects of Omega-3 Fatty Acids on Proteinuria Among Diabetic Patients: A Meta-Analysis of Randomized Controlled Trials

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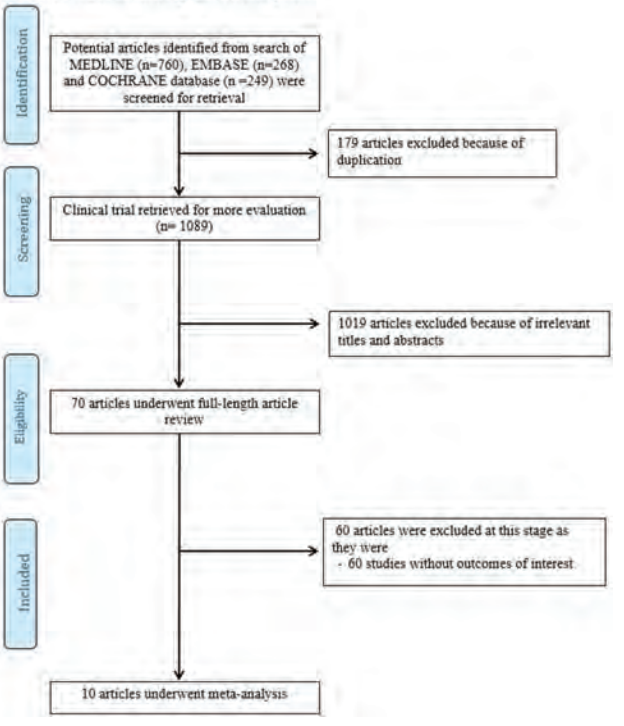
Background: Long-chain omega-3 fatty acids including eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA) have been the focus of experimental studies in humans. There are clinical trials studying in various types of kidney diseases including IgA nephropathy and lupus nephritis. However, the effects of omega-3 fatty acids on diabetic kidney disease have not been studied adequately.

Methods: We conducted electronic searches in Pubmed, Embase and Cochrane Central Register of Controlled Trials from January 1960 to April 2019 to identify RCTs, which examined the effects of omega-3 fatty acids on proteinuria, eGFR and metabolic biomarkers among diabetic patients.

Results: Ten RCTs with 344 participants were included in our meta-analysis. Omega-3 fatty acids reduced the progression of proteinuria among type 2 diabetes mellitus (type 2 DM) and type 1 diabetes mellitus (type 1 DM). This association was only significant among type 2 DM (SMD = -0.29 (95% CI: -0.54, -0.03; p = 0.03). Only studies with duration of intervention of 24 weeks or longer demonstrated a significant decline in proteinuria comparing omega-3 fatty acids to placebo group (SMD = -0.30 (95% CI: -0.58, -0.02; p = 0.04). There was a slower decline in eGFR for both type 1 and type 2 DM groups, however, the effect was not statistically significant. Regarding, serum LDL-cholesterol and HbA1C, there was no significant difference comparing omega-3 fatty acids to placebo group. There was a non-significant systolic blood pressure reduction in the omega-3 fatty acids supplementation group compared to placebo.

Conclusions: Omega-3 fatty acids could help diminish proteinuria among type 2 DM who received omega-3 supplementation for at least 24 weeks without adverse effects on HbA1C and serum LDL-cholesterol.

Figure 1 Search methodology and selection process



SA-PO809

Lipidomics of Feces in Hemodialysis Patients and Some Potential Biomarkers

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Background: Earlier studies have demonstrated that chronic kidney disease (CKD) results in profound changes in lipid. Serum lipid profile of CKD patients has been determinated at many studies, but few studies have measured fecal lipid profile of CKD patients. To gain an in-depth insight into the fecal lipid profile of CKD, we performed a fecal lipidomics study of patients receiving hemodialysis (HD).

Methods: Ultra-performance liquid chromatography/mass spectrometry was used to investigate the fecal lipid profiles of 16 healthy controls and 26 patients receiving regular hemodialysis. Principal component analysis (PCA) and orthogonal-partial least squares analysis (OPLS-DA) were used for multivariate statistical analysis to screen potential biomarkers related to diseases.

Results: A total of 478 lipid species were identified from positive and negative ion modes. Out of 478, 52 identified lipid species were significantly altered in patients with ESRD(all P<0.05). According to the VIP value of OPLS-DA model, 46 lipid molecules with VIP > 1 were screened. There were only 4 lipid molecules satisfying the condition of VIP > 1 and P < 0.05, including DG(18:0/18:3)+NH4, TG(18:1/18:1/22:0)+NH4, TG(20:1/18:1/18:1)+NH4 and TG(18:1/18:2/22:0)+NH4. They were all decreased compared with the healthy controls. TG(18:1/18:1/22:0)+NH4, TG(20:1/18:1/18:1)+NH4 and TG(18:1/18:2/22:0)+NH4 are all triglycerides which participate in pathways including fat digestion and absorption, vitamin digestion and absorption and regulation of lipolysis in adipocytes that could be searched at the KEGG website. DG (18:0/18:3) +NH4 is diglyceride involved in adipocytokine signaling pathway which is correlated with leptin production.

Conclusions: Fecal lipidomics uncovered the lipid metabolism disorder of HD patients, especially disturbances in the gut. The 4 lipid species could be potential biomarkers of ESRD. Aa reported, the incidence rate of cardiovascular and cerebrovascular diseases (CCDs) is now increasingly high in CKD patients and high cholesterol is closely related to CKD. Our study indicated that ESRD patients had lower triglycerides and diglycerides in feces than healthy controls and we considered that CKD patients may absorb more glycerides which promote to the development of CCDs. However, the exact mechanism still needs to be studied further.

SA-PO810

Diploid Gene Deletion of Transient Receptor Potential Canonical 1 (TRPC1) Channel Produces Metabolic Syndrome (MetS) but Prevents Further Liver Steatosis and Dyslipidemia Induced by a High-Fat Diet (HFD)

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Background: There is growing evidence for the role of TRPC1 in regulating glucose & lipid metabolism. Secretion of insulin, leptin & adiponectin is sensitive to cell free Ca. TRPC1 may mediate the effects of leptin in anorexigenic hypothalamic neurons. TRPC1 iwas found low in diabetes & we recently found hyperglycemia in null mice. We tested if TRPC1 deficiency produces MetS & if 45% HFD x 3 mon aggravates it.

Methods: In age-matched TRPC1 +/+. +/-, & -/- mice, we measured glucose & lipids using standard methods & insulin, leptin, & adiponectin by mouse ELISA. We did glucose tolerance test (GTT) by IP glucose (2 mg/kg) after 13 h fast.

Results: From 4-30 week, null mice ate & weighed more than +/- & wt. At 4 mon, HOMA-insulin resistance (IR) was up 60% & HOMA β down 40%. By 12 mon, HOMA-IR was up 8 fold. At 7 mon, by GTT, both TRPC1 +/- & -/- mice were diabetic. In null, adiponectin was down 11% but leptin up 77%. At 2 mon, total cholesterol was 85% hgher in null, their liver 36% heavier, & triglyceride content (TGC) 47% higher. Liver echogenicity was up by 50-150% at 7, 11, & 22 mon, confirmed by 140% higher liver TGC. At 12 mon, only null mice had hyperlipidemia (cholesterol up 30%, LDL up 60%, & TG up 200%). In +/- & wt, lipids, liver density at 12 & 19 mon, & liver TGC at 19 mon were all normal. Fasting glucose was high only in null from 1 through 16 mon). Thus on a normal fat diet (NFD), 1 wt allele prevented hyperphagia, obesity, MetS & hepatic steatosis. As expected, HFD vs NFD stimulated leptin & insulin, similarly in all 3 genotypes without altering adiponectin. Unlike NFD, HFD increased liver density in +/- & wt, but not in null. HFD induced the highest HOMA-IR in wt (3.1 vs 1.3 x in +/-) & the largest liver TGC hike in wt (3.3 vs 1.6 x in null). During GTT, AUC for glucose vs time was the highest in wt vs null.

Conclusions: 1. Diploid TRPC1 deletion produces hyperphagia, obesity & Met S, all resolvable by caloric restriction, implying hypothalamic resistance to leptin in null mice. 2. HFD raises the risks of dyslipidemia & hepatic steatosis, only in the presence of 1-2 wt alleles, as if deficiency would block the pathogenic Ca-CM-NFAT signaling pathway. 3. TRPC1 -/- is a good model to study MetS.

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

SA-PO811

Higher Fruit Intake Is Associated with Albuminuria in a Nested United Kingdom Biobank Case Control Cohort

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Background: Fruit and vegetable (F&V) consumption is associated with better renal function and lower risk of CKD. These associations may be explained by the protective effects of antioxidant vitamins and phytonutrients, nitric oxide precursors, and other active substances present in F&V. The potential negative consequences of increased fruit intake on renal health however have not been extensively studied. Fruit is an important dietary source of the monosaccharide fructose that has been implicated as an environmental toxin contributing to gout, acute kidney injury and chronic kidney disease. This study evaluated associations between F&V consumption and albuminuria in the United Kingdom Biobank (UKBB www.ukbiobank.ac.uk).

Methods: A nested case-control design included cases defined by urinary albumin to creatinine ratio (ACR) ≥ 3mg/mmol and controls with ACR < 3mg/mmol, matched for age, sex and ethnicity. Typical daily F&V intake was assessed by touch screen food frequency questionnaire. Associations between fruit, vegetable or F&V intake and ACR were tested using binary logistic regression adjusted for potential confounders age, sex, ethnicity, systolic blood pressure (SBP), diabetes, smoking, blood pressure medication, waist circumference and alcohol consumption.

Results: In a sample of 6998 participants (3499 case-control pairs), the mean age was 59 years (standard deviation [SD] 8), 53% were female, and 86% were white. SBP was 150 mmHg (SD 22) for cases and 144 mmHg (SD 20) for controls (24% of cases and 16% of controls used BP lowering medication). Twice as many cases (16%) had diabetes compared to controls. In adjusted models, no significant association was found between vegetable intake and ACR. Greater fruit, and combined F&V intake, were significantly associated with ACR ≥ 3mg/mmol (fruit: odds ratio [OR] = 1.03, 95% confidence intervals [CI]: 1.01, 1.05; P = 0.005; Combined F&V intake: OR = 1.02, CI: 1.00, 1.03; P = 0.01).

Conclusions: In the UKBB population, vegetable intake alone was not significantly associated with albuminuria. However, increased fruit intake was significantly associated with a greater risk of albuminuria. These findings are consistent with previous associations between fructose intake and renal damage.

Funding: Government Support - Non-U.S.

SA-PO812

Fewer Daily Fruit and Vegetable (FV) intake in Adults with CKD May Increase the Risk of ESRD

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Background: Previous studies have examined the overall FV intake and the effect on CKD progression. However, the association between the number of servings of FVs per day with kidney functional decline is relatively unexplored. We examined the relation between daily number of servings of FV and risk of ESRD in adults with CKD stage 3 and 4.

Methods: We analyzed a cohort of 1084 adults with CKD stage 3-4 (eGFR 15-59 ml/min/1.73m^2) aged≥ 20 years in the 1988-1994 National Health and Nutrition Examination Survey linked with the US Renal Data System, allowing for assessment for ESRD over a follow-up of 14 years. Daily FV servings were ascertained using a food frequency questionnaire. We examined the association between sex-specific quintiles for FV servings and incident ESRD using a Fine Gray competing risk model with age as time scale and cardiovascular mortality as the competing event. We adjusted for age, sex, socio-economic status (SES), total caloric intake, meat and fish intake, A1C, systolic BP, baseline eGFR, and urinary albumin–to-creatinine ratio (ACR).

Results: Mean age was 76.1 years; 47.8% were men. Those in quintile 1 (fewest servings of FV per day) were more likely to have lower SES; those in highest quintile (most servings of FV per day) were more likely to have DM and hypertension. 120 participants (11.1%) developed ESRD during follow-up. Compared to quintile 5, those in lowest quintiles had a greater risk of ESRD--for quintile 4: relative hazard [RH, 95% CI] = 1.07[0.84-1.40], for quintile 3: 1.11[0.89-1.36], for quintile 2: 1.56[1.18-1.98] and for quintile 1: 1.39[1.10-1.72]. Sex modified the estimated effect of FV quintile (p-interaction=0.03), the RH for the lowest vs highest quintile was (2.10[1.71-2.64]) for women and (1.24[0.90-1.57]) for men.

Conclusions: Fewer servings of FVs per day, with a threshold value corresponding to servings less than quintile 3 (<4.5 servings/day in men and women), is independently associated with a higher risk of ESRD. Since dietary restrictions in the setting of CKD result in a lower intake of FVs, a randomized trial to evaluate potential benefits and harms of higher FV servings may provide guidance for effective dietary recommendations.

Funding: Other U.S. Government Support

SA-PO813

Cycles of a Fasting Mimicking Diet Restore Renal Function in a Rat Model of PAN Nephrosis

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Background: A major hallmark of end-stage renal disease (ESRD) is the irreversible loss of the glomerular filtration barrier, the structure in charge of the blood ultrafiltration. The only treatment options for ESRD are dialysis or transplantation. To date, no cure is available to restore kidney function in ESRD patients. While dietary recommendations are currently given to patients with kidney disease to minimize the burden of the disease itself and slow down its progression, no diet has proven effective in restoring renal function. Animals have evolved adaptive mechanisms to fasting that are associated with stress resistance, reduced inflammation, longer lifespan. The fasting mimicking diet (FMD) was developed to induce similar metabolic changes as observed during fasting and FMD has been clinically proven to be extremely efficient in various human disease settings (including diabetes and cancer) by activating endogenous regenerative mechanisms.

Methods: We tested the potential of FMD to treat kidney disease. Sprague Dawley rats were injected with puromycin aminonucleoside (PAN) to induce chronic nephrosis. Multiple cycles of FMD have been applied to PAN-induced rats to determine their effect on renal function and structure. Rats were monitored for renal physiological parameters, histological and WB analysis of glomerular and tubular structures were performed.

Results: We observed amelioration of proteinuria and reduced levels of BUN in rats undergoing 6 cycles of FMD compared to the PAN group. The effect was sustained long term up to 6 weeks after the last dietary cycle. Histological characterization showed preservation of the renal structure including tubular and glomerular structures in rats treated with FMD in contrast to PAN-induced rats. Podocyte number in FMD treated rats was comparable with that of healthy animals, while a significant reduction was noted in the PAN group. WB also revealed mitochondrial function protection measured by the level of mtTFA protein expression (mitochondrial transcription factor A) associated with the post re-feeding time after only one cycle of diet.

Conclusions: These results support the application of multiple cycles of FMD to restore renal function and as a possible treatment of chronic kidney disease.

Funding: Private Foundation Support

SA-PO814

Skipping Breakfast and Dinner and Incidence of Proteinuria: A Retrospective Cohort Study

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Background: Chronic kidney disease (CKD) caracterized by proteinuria and low glomerular filtration rate (GFR), is one of the major risk factors of end-stage kidney disease, cardiovascular disease (CVD), and mortality. Recent studies showed that skipping breakfast was associated with type 2 diabetes (T2D) and CVD. Regarding CKD, little information is available about a clinical impact of skipping breakfast on CKD. The aim of the present study was to assess an association between breakfast frequency and incidence of proteinuria in a retrospective cohort study, along with lunch and dinner frequency.

Methods: The present study included 7,881 employees of Osaka University, one of the largest national university in Japan, who underwent their annual health checkups between April 2004 and March 2013, and had nagative or trace result of dipstick urinary protein and estimated GFR (eGFR) ≧60 ml/min/1.73m^2 at their baseline visit. Main exposure of interest was self-reported frequency of breakfast, lunch and dinner at their baseline visit: almost every day vs. irregularly. The associations of irregular breakfast, lunch, and dinner with the incidence of proteinuria defined as 1+ or more of dipstick urinary protein, using a Cox proportional hazards model adjusting for clinically relevant factors.

Results: Baseline clinical characteristics of 7,881 employees: age, mean 35 ± SD 9 years; body mass index, 21.6 ± 3.2 kg/m^2; eGFR 92 ± 15 ml/min/1.73m^2; current treatment for hypertension and CVD, 6.5% and 0.2%, respectively. During median 4.8 (interquartile range 2.1-7.7) years of the observational period, 582 (13.2%) males and 446 (12.9%) females developed proteinuria. In females, irregular breakfast and dinner was significantly associated with the incidence of proteinuria in a multivariable-adjusted model, whereas not irregular lunch (adjusted incident rate ratio of irregular breakfast, lunch, and dinner: 1.49 [1.22-1.81], 1.21 [0.82-1.79], and 1.41 [1.01-1.97], respectively). In contrast, no association was observed in males (0.95 [0.75-1.21], 1.00 [0.69-1.46], and 0.88 [0.50-1.56]).

Conclusions: Skipping breakfast and dinner were risk factors of proteinuria in females, not males.

SA-PO815

Dietary Oxalate Ingestion, Urinary Oxalate Levels, and Response to Reloxaliase in Three Phase 2 Studies

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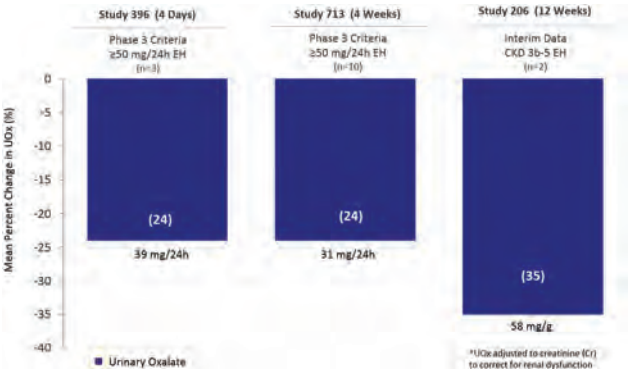
Background: Over-absorption of oxalate from dietary oxalate can lead to hyperoxaluria (HOx) in patients with malabsorptive gastrointestinal (GI) conditions {enteric HOx (EH)}. Reloxaliase is an oral enzyme that degrades oxalate within the GI tract, resulting in less oxalate absorbed and lower urinary oxalate (UOx) excretion. We hypothesized that patients with greater baseline levels of UOx may show increased responsiveness to a therapy that degrades dietary Ox. Data on patients with EH in three phase II trials were analyzed to examine this hypothesis.

Methods: A composite analysis of data from three Phase 2 studies of reloxaliase was performed to include: an uncontrolled study with 5 EH subjects treated for 4d (NCT02289755), an RCT with 11 EH subjects treated for 28d (NCT02547805) and an ongoing open label study in EH patients with advanced CKD (NCT03391804). Ox intake was assessed via dietary recall in studies 396 and 713. UOx levels were assessed serially as part of the respective protocols.

Results: There was a consistent effect seen in EH subjects with higher UOx levels across three Phase 2 clinical trials. All EH patients demonstrated an average reduction of at least >20 mg/d across all three studies. On average, patients who had a >50 mg/24h baseline UOx, demonstrated a >30 mg/d or ≥24% reduction in UOx across all studies. The results of these Phase 2 studies support the design of the ongoing Phase 3 program for UOx in EH.

Conclusions: Consistent with the mechanism of action of reloxaliase, patients with higher baseline UOx appear to benefit from a therapy that degrades oxalate in the GI tract before systemic absorption.

Funding: Commercial Support - Allena Pharmaceuticals Inc



SA-PO816

Association Between Probiotic Intake and Inflammation in CKD Patients

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Background: Little is known about the effect of probiotics on inflammation in chronic kidney disease (CKD) and results are inconsistent. Our study aims to investigate the association between probiotic intake and inflammation in patients with CKD.

Methods: This study is based on 900 patients with moderate or advanced CKD from the French CKD-REIN cohort. The intake of both dietary supplements and yoghurts was assessed from a food frequency questionnaire, and divided in 3 classes: probiotics (yoghurts or dietary supplement), regular yoghurts (which contains 2 regulated bacteria strains), and none. Inflammation was defined as CRP>5mg/l. Multivariable logistic regression was performed to assess the cross-sectional association between probiotic intake and inflammation.

Results: Patients' median (IQR) age was 70(63-78) years, eGFR, 31.1(22.8-40.7) ml/min/1.73m^2, CRP, 3.0(1.6-7.2) mg/L and 34% had inflammation. 30% consumed probiotics, 58% regular yoghurts and 12% none. Compared to non-consumers, patients consuming probiotics or regular yoghurts were less likely to have inflammation, although it did not reach significance [OR (95% CI): 0.64 (0.40;1.01), P = 0.05, and 0.75(0.49;1.15), P = 0.2, respectively]. After adjustment for co-morbidities, socio-demographics and nutrients intake, probiotic intake was associated with a significant decrease in the risk of inflammation [0.57 (0.35;0.94); P = 0.03], while the association was weaker and non-significant for regular yoghurts [0.67(0.43;1.04); P = 0.08].

Conclusions: Probiotic intake, but not regular yoghurts, was found to be associated with lower odds of inflammation.

SA-PO817

Dietary Fiber Intake Is Associated with Indoxyl Sulphate in Hemodialysis Patients

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Background: Gut microbiota imbalance is a common complication in chronic kidney disease (CKD) patients. This dysbiosis is linked to increased gut-derived uremic toxins production such as indoxyl sulphate (IS), involved with inflammation and oxidative stress in these patients. Lifestyle modifications may have significant favorable effects on reduction of uremic toxins from the gut microbiota, as increased dietary fiber intake which seems to be associated with gut microbiota modulation and reduction on uremic toxins production. The aim of this study was to verify a possible relationship between fiber intake and IS plasma levels in hemodialysis (HD) patients.

Methods: In this cross-sectional study, 50 HD patients were evaluated. Indoxyl sulphate plasma levels were measured by Reversed-Phase High-Performance Liquid Chromatography (HPLC) and, the food intake was assessed using a 3-day 24-hour dietary recall.

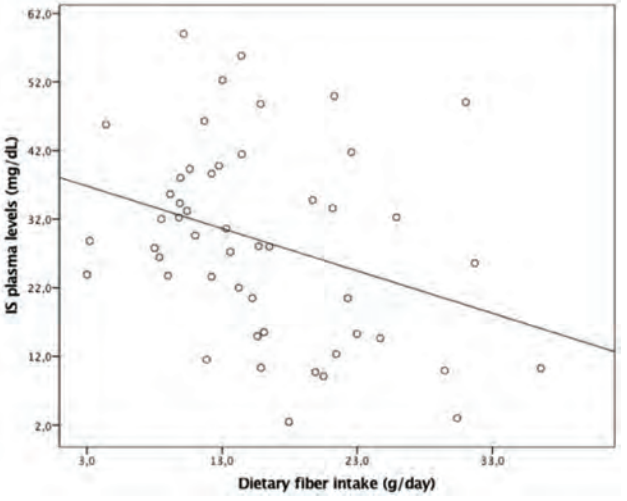
Results: Table 1 shows the characteristics and food intake parameters of the HD patients evaluated. The IS plasma levels were negatively correlated with fiber intake (r = - 0.32, p = 0.02, Figure 1).

Conclusions: Our results suggest that increasing dietary fiber intake the IS plasma levels can be reduced in hemodialysis patients, probably due the gut microbiota modulation.

Funding: Government Support - Non-U.S.

Table 1. Characteristics and food intake parameters of the HD patients.

Parameters	Results
Age (years)	54.1 ± 10.4
BMI (kg/m2)	26.2 ± 4.8
Time on HD (months)	47 (28 -78)
Kt/V	1.4 ± 0.3
Energy Intake (Kcal/Kg/day)	19.0 ± 8.0
Protein Intake (g/Kg/day)	1.0 ± 0.3
Fiber Intake (g/day)	16.0 ± 7.6
Indoxyl sulfate (mg/dL)	28.0 ± 14.2



SA-PO818

Resistant Starch Supplementation Attenuates Inflammation in Hemodialysis Patients

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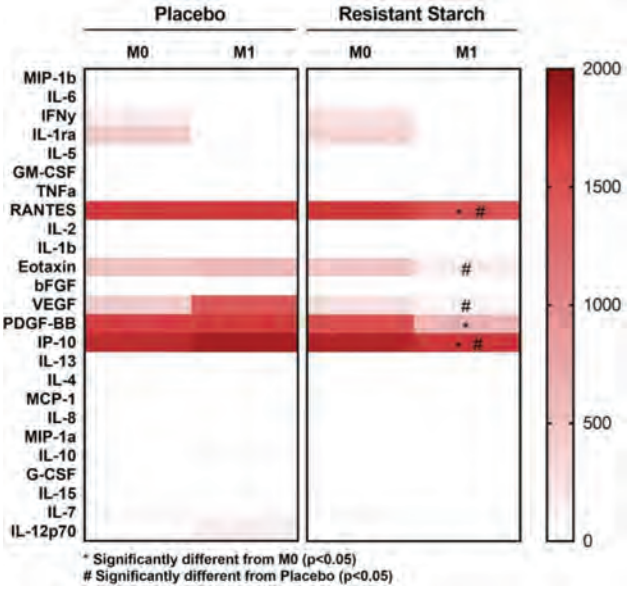
Background: Dysbiosis in chronic kidney disease (CKD) is linked to oxidative stress and inflammatory response. Researchers have investigated strategies capable of reestablishing the symbiosis of the gut microbiota in CKD, and suggested that resistant starch (RS) can promotes many benefits, including immunomodulatory effects. The aim of the study was to evaluate the impact of RS supplementation on levels of some inflammatory markers in hemodialysis (HD) patients.

Methods: A double-blind, placebo-controlled, randomized trial was conducted with sixteen HD patients [55.3 ± 10.0 years, BMI, 25.9 ± 5.42 kg/m^2, 56% men, time on dialysis 38.9 ± 29.2 months] that were equally divided in RS (16 g of RS HI-MAIZE 260, Ingredion®) or placebo (manioc flour) groups, to receive alternately 9 cookies/day (dialysis days) and 1 sachet/day (non-dialysis days) for 4 weeks. Cytokines and growth factors plasma levels were evaluated by XMap-labeled magnetic microspheres based multiparametric immunoassay (LuminexCorp, USA), before and after supplementation.

Results: After RS supplementation there was a reduction of Normal T Cell Expressed and Secreted (RANTES) (p<0.001), Platelet-derived growth factor two B subunits (PDGF-BB) (p=0.014) and Interferon-inducible protein 10 (IP-10) (p=0.027) (Fig 1). The other parameters did not change significantly.

Conclusions: The results of this randomized study suggested that supplementation with prebiotic, specifically RS, was able to minimize the inflammation in CKD patients on HD. These findings support the hypothesis that the use of prebiotics can be an effective non-pharmacological intervention in reducing the inflammatory state in CKD patients.

Funding: Government Support - Non-U.S.



SA-PO819

Effects of Anti-Inflammatory and Insulin Sensitizing Agents on Markers of Inflammation and Protein Turnover in Maintenance Hemodialysis (MHD) Patients

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Background: Systemic inflammation and insulin resistance are associated with increased protein catabolism leading to protein energy wasting in MHD patients.

Methods: We studied the metabolic effects of a PPAR-gamma agonist (pioglitazone-TZD 30 mg daily, N=9) and an Interleukin-1 receptor antagonist (anakinra subcutaneous injections 3 times weekly during hemodialysis, N=7) versus placebo (n=8) over 3 months in MHD patients through a randomized placebo-controlled trial. Whole body and skeletal muscle protein turnover, inflammatory markers and body composition were measured at baseline and 12 weeks after intervention in all patients (Total N = 24). The primary outcome was change in whole-body protein balance (WBPB) measured by stable isotope technique. Inflammatory markers and lean body mass (LBM) were secondary outcomes.

Results: There were no significant demographic or clinical differences at baseline between groups. There were no statistically significant differences in whole-body protein balance between groups over 3 months (Table 1). Patients in the pioglitazone group demonstrated a significant decline in HsCRP concentrations compared to placebo (p= 0.03), but there were no statistically difference in changes in IL-6 for either group. There were no statistically significant differences between groups regarding changes in lean body mass or fat mass in any of the study groups.

Conclusions: In this pilot mechanistic trial, we were not able to demonstrate a significant change in whole body protein balance and lean body mass with 3-month administration of anakinra or pioglitazone in MHD patients. While these results indicate a lack of efficacy of the anti-inflammatory and insulin sensitizing interventions tested in this study, our analyses could be limited by relatively small number of subjects and duration of intervention.

Funding: NIDDK Support, Veterans Affairs Support

Variable	IL1ra (A) N = 9	TZD (b) N = 7	Placebo (C) N = 8	P A vs C	P B vs C
hsCRP Baseline	2 (1.8, 6.1)	6.3 (3.1, 46.4)	6.7 (1.8, 9.8)		
hsCRP wk 12	1.5 (1.0, 3.2)	2.0 (1.5, 6.5)	4.7 (4.0, 11.5)		
Delta hs CRP	**-0.4 (-5.4, 1.2)**	**-3.0 (-42.3, 0)**	**1.35 (-0.7, 5.3)**	**0.16**	**0.03**
IL6 baseline	0.6 (0.1, 1.2)	2.5 (1.3, 7.7)	1.9 (0.9, 2.6)		
IL6 wk 12	0.62 (0.1, 1.07)	1.84 (1.34, 8.34)	4.26, (1.3, 10.2)		
Delta IL6	**0.0 (-0.58, 0.09)**	**-0.4 (-1.23, 0.24)**	**0.88 (0.02, 3.07)**	**0.11**	**0.19**
WBPB Baseline	4.2 (3.8, 5.0)	3.9 (3.4, 4.5)	4.0 (4.0, 4.1)		
WBPB wk 12	4.2 (4.1, 4.5)	4.4 (3.6, 4.6)	4.4 (4.2, 4.7)		
WBPB delta	**-0.08 (-0.69, 0.40)**	**0.36 (0.35, 0.54)**	**0.28 (0.09, 0.64)**	**0.12**	**0.91**
LBM Baseline	51.6 (42.8, 57.1)	55.6 (49.8, 60.3)	50.1 (48.5, 52.2)		
LBM wk 12	51.3 (43.7, 59.0)	55.8 (46.6, 59.1)	52.7 (48, 55.6)		
LBM Delta	**0.77 (-0.3, 1.9)**	**1.5 (-0.5, 2.1)**	**0.6 (-0.4, 2.8)**	**0.12**	**0.91**

Median and IQR values for baseline and after 8 weeks of intervention.

SA-PO820

Low Dietary Fiber Consumption Contributes to Gut Dysbiosis with Increased Fecal Indole and Circulating Indoxyl Sulfate in CKD Patients

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Background: Recent advances in the understanding of the role of gut microbiota and its function and composition in health and disease have revealed previously unappreciated effects of CKD-associated colonic pathology on the development of uremic complications. We aim to investigate the relationship between dietary content, gut microbiota, fecal bacterial metabolites, and circulating gut-derived uremic toxins in CKD patients.

Methods: We obtained dietary frequency questionnaires, blood, and stool samples for patients in CKD stage 5, and healthy controls. We examined and analyzed their gut microbiome by 16S rRNA sequencing and fecal indole amount. Also, we successfully developed a method for quantification of the indole level in human fecal samples.

Results: We enrolled 62 patients, among which 40 patients were CKD stage 5. Compared to healthy controls (n = 22), and we found a distinct gut microbiome between groups. Next, we stratified study subjects into age-matched subgroups, and we found that though the most dominant phylum was *Bacteroides* within each group, its relative abundance in the CKD group was much higher than the other two control groups. Second, three genera *Fusobacterium, Shewanella*, and *Erwinia* were present in the CKD group, but not in the others (Fig. 1). Besides, in contrast to the sum of relative abundance of the common top 10 genera in the control groups and the top 10 genera within individuals, the microbial composition of the fecal community were much diverse in a CKD patient than in the controls (Fig. 2). Furthermore, we also found that dietary fiber consumption is less, and fecal indole is higher in CKD patients (Fig. 3). Interesting, through combining FFQ and nutrient quantification, we identified that the circulating levels of total p-cresol sulfate negatively correlated with fiber-rich and ascorbic acid-rich diet intake.

Conclusions: Vegetables and fruits are enriched with dietary fibers but were instructed to be restricted in patients with advanced CKD to avoid hyperkalemia. Our data proved that such fiber-restricted diet creates an intestinal environment which is unfriendly for beneficial microbial flora with subsequent local and systemic inflammation as evidenced by increased fecal indole and increased the circulating level of indoxyl sulfate.

Funding: Government Support - Non-U.S.

SA-PO821

Effect of Cranberry Extract (Vaccinium macrocarpon) on Inflammation, Oxidative Stress, and Uremic Toxins in CKD Patients

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Background: Chronic kidney disease (CKD) patients present many complications that potentially could be linked to increased cardiovascular risk such as inflammation, oxidative stress and high levels of uremic toxins from gut microbiota. Bioactive compounds from food may reduce these complications, such as polyphenols present in fruits like cranberry, which have antioxidant, anti-inflammatory and prebiotics properties.

Methods: In this randomized, double-blind, placebo-controlled study, 30 non-dialysis CKD patients were randomized to receive cranberry dry extract (1000 mg/day containing 72mg of proanthocyanidins) or placebo (1000mg/day of corn starch) for 2 months. Blood samples were collected at baseline and after intervention. The mRNA expression of factor erythroid 2-related factor 2 (Nrf2) and nuclear factor-kappa B (NF- κB) was evaluated by real-time PCR. Uremic toxins plasma levels [indoxyl sulfate (IS), p-cresyl sulfate (PCS), and indole-3-acetic acid (IAA)] were obtained by Reversed-Phase HPLC and, the analysis of thiobarbituric acid reactive substances (TBARS) were also performed.

Results: Twenty-seven patients concluded the study: 13 patients in the cranberry group (55.7 ± 7.5 years, 5 males) and 14 in the placebo group (57.7 ± 5.7 years, 4 men). Treatment adherence was above 96% in both groups. There was no significant difference in NF-κB or Nrf2 mRNA expression after cranberry supplementation [0.91 (0.62 – 1.19) to 1.20 (0.75 – 1.80), p=0.21 and 1.31 (0.59 – 2.95) to 0.99 (0.61 – 1.25), p=0.57), respectively]. TBARS levels did not change after cranberry supplementation. The uremic toxins plasma levels also did not change [IS: 2.97 (1,28 – 4.42) mg/L to 2.86 (1.32 – 4.14) mg/dL, p=0.53; PCS: 14.94 mg/L (7.12 – 23.53) to 17.63 (5.74 – 23.50)mg/L, p=0.48; IAA: 758.99 (608.5 – 1237.4) μg/L to 664.5 (500.5 – 1592.3) μg/L, p=0.58). There were no significant differences in the placebo group.

Conclusions: Short-term cranberry dry extract supplementation does not appear to influence inflammation, oxidative stress and uremic toxins in non-dialysis CKD patients. Long-term studies with different doses are needed to determine whether cranberry dry extract may affect these markers in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO822

Effect of the Dietary Antioxidant Supplement Alpha Lipoic Acid on Nuclear Reduced Glutathione Levels in Kidney Cortex and Medulla from Young Rats

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Background: Supplementation with antioxidants, such as alpha lipoic acid, are thought to be beneficial since they can increase the level of reduced glutathione (GSH) inside cells. GSH is the major antioxidant inside cells and provides protection against damage by free radicals produced as a consequence of oxidative metabolism. Previous studies have reported that GSH levels in mitochondria from kidney, liver and heart are significantly increased with alpha lipoic acid supplementation in old rats, but not in young rats. This suggest that dietary antioxidant supplementation may not always be beneficial in young rats. The purpose of this study was to determine whether the nucleus in kidneys from young rats does respond to alpha lipoic acid supplementation with an increase in GSH levels.

Methods: Young female Experimental Lewis rats (3 months of age; n=7) received alpha lipoic acid (100 mg/Kg) via i.p injection for one week. Age-matched Control rats (n=4) did not receive any supplementation. The kidneys were harvested from anesthetized rats, and the cortex and medulla were separated and homogenized. The nuclear fractions were isolated using differential centrifugation. The GSH and total glutathione (Tot GLUT; GSH plus oxidized GSH) were measured with a spectrophotometric assay. The GSSG (oxidized GSH) levels were determined from the difference between Tot GLUT and GSH levels, and then divided by 2. Comparisons were done using a Student's T Test.

Results: There was a significant increase in nuclear GSH levels in the kidney cortex and medulla with dietary supplementation with alpha lipoic acid. This was accompanied by a significant decrease in nuclear GSSG levels. Nuclear Tot GLUT levels did not change or were decreased following supplementation.

Conclusions: The nucleus in kidney cells from young rats does respond to alpha lipoic acid supplementation with an increase in GSH levels.

Effect of Alpha Lipoic Acid on Nuclear GSH Levels in Young Rat Kidney

	GSH-nmol/g kid wet wt		GSSG-nmol/g kid wet wt		Tot GLUT-nmol/g kid wet wt	
	Control	Experimental	Control	Experimental	Control	Experimental
Cortex	182 ± 21	265 ± 21*	108 ± 25	35 ± 5*	322 ± 46	328 ± 25
Medulla	180 ± 17	231 ± 9*	122 ± 15	46 ± 15*	513 ± 38	315 ± 40*

All data shown as X +/- SEM. * Significantly different from Control at $p<0.05$.

SA-PO823

Changes in Metabolic Syndrome Components Affect the Incidence of ESRD in the General Population: A Nationwide Cohort Study

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Background: Few studies have investigated the impact of a change in metabolic syndrome (MetS) components on clinical renal outcomes in the general population.

Methods: Using nationally representative data from the Korean National Health Insurance System, 13,310,924 subjects without chronic kidney disease who underwent two health examinations over 2 years and were free from end-stage renal disease (ESRD) from 2009 to 2012 were followed to the end of 2016. The subjects were divided into four groups according to the change in MetS components between the two visits over 2 years: no MetS (–/–), post-MetS (–/+), pre-MetS (+/–), and both MetS (+/+).

Results: The proportion of patients in the no-MetS (–/–), post-MetS (–/+), pre-MetS (+/–), and both-MetS (+/+) groups was 61.3%, 10.8%, 8.3%, and 19.5%, respectively. After a median follow up of 5.11 years, 18,582 incident ESRD cases were identified. In the multivariate adjusted model, the hazard ratio (HR) and 95% confidence interval (CI) for the development of ESRD in the both-MetS (+/+) group compared with the no-MetS (–/–) group was 5.65 (95% CI, 5.42–5.89), which was independent of age, sex, and baseline estimated glomerular filtration rate. Additionally, the HR for the pre-MetS (+/-) group versus the no-MetS (–/–) group was 2.28 (2.15–2.42). In subgroup analysis according to renal function, the impact of a change in MetS on the incidence of ESRD was more pronounced in individuals with advanced renal dysfunction.

Conclusions: Subjects with resolved MetS components had a decreased risk of ESRD, but not as low as those that never had MetS components. This provides evidence supporting the strategy of modulating MetS in the general population to prevent the development of ESRD.

Funding: Government Support - Non-U.S.

SA-PO824

Abdominal Fat, Physical Function, and Their Associations with Insulin Resistance, Inflammation, and Adipokines in CKD

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Background: Adiposity and physical inactivity are major drivers of cardiometabolic risk, and may confer differential metabolic risk profile in CKD. We examined the associations of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and physical function with inflammation, insulin resistance, adipokines in those with CKD.

Methods: We obtained MRI of the abdomen and pelvis, and 400m walk test to assess the VAT, SAT volume and physical function among 419 CRIC study participants using a standardized protocol. We also measured markers of inflammation (IL-beta, IL-6, TNF-R1, and TNF-R2), insulin resistance (HOMA-IR), and adipokines (adiponectin- total and HMW, resistin, and leptin). We evaluated the associations between VAT, SATvolume and physical function, and individual markers (log-transformed values) adjusting for relevant confounders.

Results: Mean age of the study population (n=419) was 64.3 years; 40% were females, and the mean eGFR was 55.7 (+/- 18.4) ml/min/1.73 m^2. Over 85% of them were overweight or obese, and 39% were diabetics. Each SD higher VAT and SAT were associated with lower levels of total and HMW adiponectin, and higher levels of leptin and insulin resistance [Figure]. However, higher 400m walk time was associated only with higher levels of plasma IL-6 and TNFR-1 [Figure].

Conclusions: The observations that greater adiposity is associated with altered adipokine profile and insulin resistance, while lower levels of physical function are related to enhanced inflammation in CKD are intriguing. A deeper understanding of the reasons for these differential associations may lead to new approaches to management of patients with CKD.

Funding: NIDDK Support

Outcome	Regression coefficient	Standard Error	P-value
VAT (per 1-SD increase)			
Total Adiponectin	-0.31	0.04	<0.001
HMW Adiponectin	-0.30	0.04	<0.001
Leptin	0.47	0.06	<0.001
Resistin	0.05	0.03	0.10
HOMA IR	0.21	0.05	<0.001
HS-IL6	0.04	0.05	0.35
TNFAR1	-0.01	0.01	0.68
TNFAR2	0.002	0.02	0.92
SAT (per 1-SD increase)			
Total Adiponectin	-0.22	0.04	<0.001
HMW Adiponectin	-0.22	0.04	<0.001
Leptin	0.61	0.05	<0.001
Resistin	0.03	0.03	0.28
HOMA IR	0.18	0.05	<0.001
HS-IL6	0.08	0.04	0.06
TNFAR1	0.001	0.01	0.91
TNFAR2	-0.01	0.02	0.73
Time taken to complete 400 m walk test (per 1-SD increase)			
Total Adiponectin	0.10	0.05	0.04
HMW Adiponectin	0.04	0.05	0.39
Leptin	0.09	0.05	0.07
Resistin	0.05	0.03	0.09
HOMA IR	-0.09	0.05	0.07
HS-IL6	0.16	0.04	0.001
TNFAR1	0.0	0.02	<0.001
TNFAR2	0.03	0.02	0.34

SA-PO825

Associations Between Visceral Obesity and Renal Impairment in Medical Checkup Participants

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Background: Obesity has been reported to be a risk factor for chronic kidney disease, which is now considered one of the most important public health issues worldwide. We aimed to evaluate the relationships between obesity indicators (visceral fat area [VFA], body mass index [BMI], waist circumference, waist-to-height ratio, and visceral-to-subcutaneous fat ratio [VSR]) and changes in kidney function and the risk of proteinuria, and to determine the most sensitive obesity indicator to predict a decline in kidney function and new-onset proteinuria.

Methods: Design: Retrospective cohort study. **Setting:** Routine medical check-up program at two Japanese hospitals. **Participants:** Subjects who underwent VFA measurements during medical checkups in 2012 at Takeda Hospital Group Medical Examination Centers were included. The follow-up period was from April 2012 to March 2018. **Exposures:** Obesity was defined using a separate baseline value of each indicator: VFA (≥100 cm^2), BMI (≥25 kg/m^2), waist circumference (≥85 cm for men and ≥90 cm for women), waist-to-height ratio (≥0.5), and VSR (≥0.4). **Main outcomes measures:** Changes in estimated glomerular filtration rate ($eGFR_{cr}$) and time to new-onset proteinuria were measured. **Statistical analysis:** The relationships between obesity indicators and $eGFR_{cr}$ were evaluated using a linear mixed effects model. The relationships between obesity indicators and new-onset proteinuria were evaluated using Poisson regression analysis.

Results: Analysis was performed on 2,753 subjects (mean age 50.3 years [standard deviation 10.0], 1,419 men, 1,334 women). The VFA ≥100 cm^2 group exhibited a significantly larger difference in the annual change in $eGFR_{cr}$ (-0.24 mL/min/1.73 m^2, p=0.03) than the <100 cm^2 group. Furthermore, there was a significant difference in the proteinuria incidence ratio, which was 1.54 times higher in the VFA ≥100 cm^2 group (95% confidence interval: 1.01 to 2.35). Significant correlations were not observed with any of the other obesity indicators.

Conclusions: VFA ≥100 cm^2 was significantly associated with a greater annual decline in $eGFR_{cr}$ and the higher incidence of new-onset proteinuria. VFA is suggested as the most sensitive obesity indicator for the decline in kidney function and new-onset proteinuria.

Funding: Government Support - Non-U.S.

SA-PO826

The Effect of Bilateral Nephrectomy on Gene Expression of Hypothalamic Neuropeptides Regulating Feeding Behaviors

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Background: Anorexia is one of the most widespread eating disorders that appears to contribute to malnutrition in patients with advanced kidney dysfunction. Previously, many neuropeptides synthesized in the hypothalamus have been shown to regulate feeding behavior. While several mechanisms underlying uremic anorexia have been proposed, the hypothalamic neuropeptides that regulate feeding in the hypothalamus of patients with kidney dysfunction are poorly understood.

Methods: The gene expressions of hypothalamic neuropeptides controlling feeding behaviors were evaluated after bilateral nephrectomy, which is a model of acute kidney dysfunction, by *in situ* hybridization histochemistry. Adult male rats received bilateral nephrectomy or a sham operation under anesthesia. The rats were decapitated at 6, 12, and 24 h after treatment. The gene expression of corticotrophin-releasing hormone (CRH) in the paraventricular nucleus (PVN); proopiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART), neuropeptide Y (NPY), agouti-related peptide (AgRP) in the arcuate nucleus; and melanin-concentrating hormone (MCH) and orexin in the lateral hypothalamic area, were quantified by *in situ* hybridization histochemistry. After treatment, cumulative food intake, water intake, and body weight were measured.

Results: Food consumption decreased markedly in bilateral nephrectomized rats. The mRNA levels of *CRH*, *POMC*, *CART*, which suppress feeding behavior, were significantly higher in bilateral nephrectomized rats than in sham-operated rats. On the other hand, the mRNA levels of *NPY*, *AgRP*, *MCH*, and orexin, which promote feeding behavior, were significantly lower in bilateral nephrectomized rats than in sham-operated rats.

Conclusions: The results suggest that hypothalamic neuropeptides regulating feeding behaviors may be involved in the development of anorexia in bilateral nephrectomized rats. This report is the first step to elucidating the physiological mechanisms of anorexia in patients with kidney dysfunction.

SA-PO827

Obestatin Response to a Meal and Association with Subsequent Appetite Sensations in Maintenance Hemodialysis Patients

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Background: Obestatin, a physiological opponent of acylated ghrelin, linked to the regulation of appetite reducing food intake in mice but its anorexigenic property in human is controversial. We aimed to investigate a potential role of obestatin in dietary intake regulation by examining response to a meal in maintenance hemodialysis (MHD) patients.

Methods: In this case-control study we have investigated the response of obestatin around a fixed calorie meal (500 kcal) in 21 MHD patients (age 69.2±13.1 years, 10 women, with body mass index 27.2±5.5 kg/m^2). Parallel changes in serum obestatin and insulin levels and subjective scores of appetite (visual analogue scales for hunger, satiety, fullness and prospective food consumption) were recorded on fasting and 30, 60 and 120 min after meal.

Results: In a linear mixed effects model controlling for baseline demographics and clinical parameters including serum insulin concentrations, postprandial levels of obestatin did not change significantly from baseline in response to the meal. The response was the same in MHD patients treated with high or low flux dialyzers. However, postprandial obestatin levels were associated with the rate of change in sensation of fullness (linear estimate: 11.60 (95% confidence interval 0.17 to 23.04, P<0.05). The remained sensations of appetite did not correlate with postprandial obestatin levels in time.

Conclusions: Obestatin levels do not change acutely with food administration in MHD patients, but associate with the changes in sensation of fullness. This supports the possible role of obestatin in the long-term regulation of appetite in MHD population.

SA-PO828

Protective Effect of Leuconostoc in Renal Damage Induced by Obesity

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Background: There is enough evidence showing that obesity promotes kidney damage. Probiotics might help in improving several diseases. Mexican honey water contains bacteria known as *Leuconostoc* that have anti-obesity activity. However, its role in prevention of renal injury induced by obesity still unknown.

Methods: Forty three C57BL6 male mice were divided into four groups: control diet, 3.41 Kcal/g (n=10), probiotic control, $2x10^9$ CFU, IG, (n=10), hypercaloric diet, 4.9 Kcal/g, (n=11), and hypercaloric diet+probiotic (n=12). The groups were studied for 3 months and a half. Weekly measurements of weight and caloric intake were made. At the end of the follow-up, the determination of body fat and water was carried out using nuclear magnetic resonance (NMR). Urine was collected to analyze renal function and biomarkers. Tissue was stored for molecular analysis and the other kidney was fixed for histopathological analysis.

Results: At the end of the study, the hypercaloric diet induced a significant increase by 52.1% in body weight (BW) and by 3-fold in body fat (BF), with a reduction in lean mass by 27.4%. Also renal damage was observed that was characterized by a significant increase in: albuminuria, oxidative stress and KIM-1 levels, as well as, kidney inflammation, and TGF-b up-regulation. *Leuconostoc* administration significantly reduced the increase in BW and BF by 14.2% and 42.8%, respectively, with the same food intake. *Interestingly, albuminuria, oxidative stress, and KIM-1 levels in the hypercaloric+probiotic group were similar to control groups. Effects that were accompanied by restoration of IL-6, TNFa, and TGF-b mRNA levels.*

Conclusions: These results show that hypercaloric diet induced metabolic and renal alterations. While, *Leuconostoc* was efficient in preventing weight gain, renal injury, and oxidative stress, as well as, profibrotic and inflammatory pathways activation. Therefore, this probiotic seems to be a feasible and useful tool for the treatment of renal injury induced by obesity; however, controlled clinical studies are required to prove this hypothesis.

Funding: Government Support - Non-U.S.

SA-PO829

Noninvasive Measures of Visceral Adiposity and Risk of Kidney Function Decline

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Background: Measures of visceral obesity are better markers of adverse outcomes than body mass index (BMI) and waist circumference (WC). Lipid accumulation product (LAP) and visceral adiposity index (VAI) are novel, non-imaging markers of visceral adiposity calculated by using BMI, WC and serum lipids. We hypothesized that LAP and VAI will be associated with adverse kidney outcomes independent of traditional risk factors.

Methods: Using data from Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, we evaluated the association of LAP, VAI, BMI and WC with (a) 1127 cases of incident CKD, defined as reaching an eGFR <60ml/min/1.73m^2 with at least 25% decline between visit 1 and 2; (b) 1452 cases of >30% eGFR decline using logistic regression; and (c) 353 cases of incident ESRD using Cox regression.

Results: Mean age was 65 years, 54% were women, and 41% were African American. The median time between visit 1 and 2 was 9.4 years. After adjusting for confounders, the top quartiles of VAI, LAP, BMI and WC were associated with higher odds of incident CKD and progressive eGFR decline compared to bottom quartiles. VAI and LAP were associated with an increased risk of ESRD after demographic and risk factor adjustment (HR 1.94; 95% CI, 1.37 to 2.76) but this association was no longer significant after adjusting for baseline eGFR and albuminuria.

Conclusions: Adiposity assessed by measures of generalized and visceral obesity is associated with higher risk of incident CKD and eGFR decline. VAI and LAP are not more strongly associated with CKD and eGFR decline compared to BMI and WC. However, for incident ESRD, VAI and LAP may be valuable for providing useful information beyond BMI and WC (in the models that do not include eGFR/ACR).

Table. 1 Association of adiposity measures with kidney outcomes

	Exposure type	Incident CKD OR (95% CI)*	Progression of eGFR decline OR (95% CI)	Incident ESRD HR (95% CI)
VAI*	Q4 vs. Q1 ≥ 5.92 vs. ≤ 2.31	1.26 (1.02, 1.55)	1.20 (1.00, 1.44)	0.72 (0.50, 1.03)
	Continuous model (per doubling)	1.12 (1.04, 1.20)	1.11 (1.04, 1.18)	0.93 (0.82, 1.04)
LAP**	Q4 vs. Q1 ≥ 339.58 vs. ≤ 124.89	1.51 (1.22, 1.87)	1.36 (1.13, 1.63)	0.82 (0.56, 1.20)
	Continuous model (per doubling)	1.21 (1.13, 1.29)	1.18 (1.11, 1.26)	0.89 (0.81, 0.99)
BMI	Q4 vs. Q1 ≥ 40.0 vs. 18.5 - 24.9	1.74 (1.26, 2.41)	1.45 (1.09, 1.92)	0.58 (0.40, 0.82)
	Continuous model (per doubling)	1.23 (1.14, 1.33)	1.16 (1.09, 1.24)	0.85 (0.76, 0.95)
WC	Q4 vs. Q1 ≥108 (w); ≥122 (m) vs. <80(w); <94 (m)	2.16 (1.68, 2.77)	1.68 (1.36, 2.10)	0.55 (0.39, 0.78)
	Continuous model (per doubling)	1.22 (1.14, 1.32)	1.18 (1.10, 1.25)	0.81 (0.72, 0.91)

* VAI: M= WC/[39.68 + (1.88×BMI)]×TG/1.03×1.31/HDL
F= WC/[36.58 + (1.89×BMI)]×TG/0.81×1.52/HDL
** LAP: M= (WC-65) x TG
F= (WC-58) x TG
+ Adjusted for age, sex, race, CAD, stroke, HTN, DM, smoking, eGFR, UACR

SA-PO830

Comparative Study on the Prognostic Value of Body Composition Parameters in Hospitalized Patients with Dialysis

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Background: Body composition is essential to the prognosis of dialysis patients, but comparison of prognostic value of different nutritional and fluid load parameters in the hospitalized patients with dialysis are limited.

Methods: We conducted a prospectively observational study to assess the association of different parameters in body composition with all-cause mortality in dialysis inpatients. The body composition was measured by bioelectrical impedance within the first 3 days after admission and hemodialysis patients should be measured before dialysis session. The parameters in fluid volume included overhydration (OH), the ratio of OH to extracellular water (OH/ECW), the ratio of extracellular water to body cell mass (ECW/BCM), the ratio of extracellular water to intracellular water (ECW/ICW); the parameters in nutritional status included fat tissue index (FTI), lean tissue index (LTI) and body cell mass index (BCMI).

Results: Of the 832 study patients, 191 (23.0%) died during a median follow-up of 31 months. In multivariable adjusted Cox models, higher ECW/BCM (adjusted hazard ratio per 1-SD, 1.30; 95% CI, 1.09 to 1.54) were associated with a significantly greater risk of death, as were lower LTI (adjusted odds ratio per 1-SD, 0.70; 95% CI, 0.59 to 0.83) and BCMI (adjusted hazard ratio per 1-SD, 0.72; 95% CI, 0.62 to 0.84). BMI, FTI and BCM/weight were also associated with death, but the magnitude of the association was greatest for ECW/BCM, LTI and BCMI. When ECW/BCM, LTI and BCMI were added to the fully adjusted model, only LTI improved the predictability for all-cause mortality (net reclassification index =0.15, P=0.04; integrated discrimination improvement =0.02, P=0.01).

Conclusions: ECW/BCM was the most relevant to mortality in fluid volume indices, and LTI and BCMI were most two relevant to mortality in nutritional status indices. Higher LTI was significantly associated with a lower risk of death and exhibited a stronger association with mortality than ECW/BCM, BCMI and other body composition parameters in dialysis inpatients.

SA-PO831

Effect of Age and Gender on the Relation Between Body Fat Area and Kidney Outcomes in Patients with CKD

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Background: Increase in body fat area has been noted as a risk factor for progression of chronic kidney disease (CKD) as well as cardiovascular disease and death. Similarly, obesity has been shown to be associated with CKD progression, but this association might be interacted with patient's characteristics. Here, we examined obesity assessed by body fat area is related to kidney outcomes in patients with CKD with possible interaction by age and gender.

Methods: We included 367 patients who completed CKD educational program between January 2011 and February 2017. Patients were classified into four groups: male patients under 75yo, (n=164), female patients under 75yo(n=52), male patients 75yo or older(n=98), and female patients 75yo or older(n=53). Body fat area was measured at the level of the umbilicus using an CT-image analysis system. Kidney outcomes was defined as initiation of renal replacement therapy or incidence of 50% reduction in estimated glomerular filtration rate.

Results: The overall mean age of the patients was 73.0 (65.0-78.0) years old, of whom 262 patients (71.4%) were male, and the median estimated glomerular filtration rate based on plasma cystatin C (eGFRcys) was 26.9 mL / min / 1.73 m^2. During the observation period [median 1.7 year (0.7-3.5)], 187 patients reached kidney outcomes. In both univariate and multivariate Cox regression analysis, VFA and SFA were not associated with increased kidney outcome in overall population. However, in males under 75yo, multivariate Cox regression analysis showed SFA but not VFA as significant risk for kidney outcomes (SFA: HR 1.06, 95% CI: 1.02-1.11). In turn, VFA but not SFA was significantly associated with decreased kidney risk in female under 75 yo (VFA: HR 0.83, 95% CI: 0.71-0.97). Moreover, in patients 75yo or older in both sex, multivariate Cox regression analysis failed to show the significant association with kidney outcomes in both VFA and SFA.

Conclusions: Obesity as assessed by body fat area was not a significant risk for CKD progression in very old patients with CKD. In younger patients with CKD, high SFA in males was a significant risk factor for CKD progression, whereas high VFA in females was a significant renoprotective factor. When we consider obesity as a potential risk for CKD progression, we need to consider age and gender.

SA-PO832

Change in Glomerular Filtration Rate After Bariatric Surgery Varies by Baseline Kidney Function

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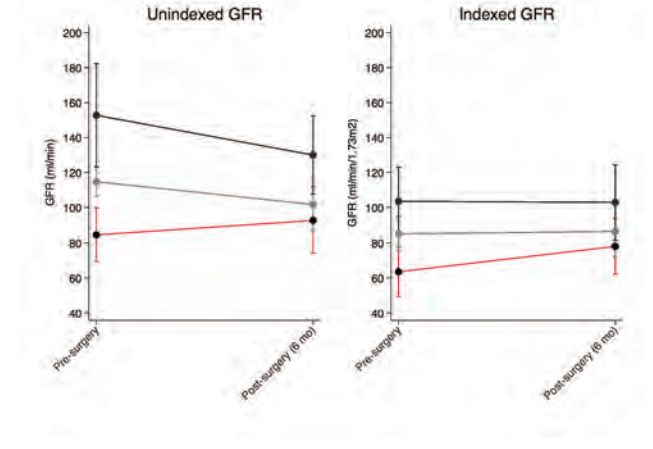
Background: It is unclear whether GFR decreases after bariatric surgery in individuals with lower baseline GFR who may lack renal functional reserve.

Methods: GFR was measured by plasma iohexol clearance in 27 adults at multiple research visits before and after bariatric surgery (twice pre-surgery, ~6 and 12 months post-surgery). We examined whether changes in GFR after bariatric surgery varied by pre-surgery GFR using generalized estimating equations, clustered by individuals.

Results: Pre-surgery, mean values of body mass index (BMI) and body surface area (BSA) were 49.4 kg/m^2 and 2.42 m^2. Mean unindexed and indexed GFR were 117.3 ml/min (range 57.4 to 206.0) and 84.1 ml/min/1.73m^2 (range 44.3 to 138.0), respectively. Six months after surgery, BMI decreased by 13.9 kg/m^2 (95% CI: -15.9, -11.8) and BSA decreased by 0.30 m^2 (95% CI: -0.34, -0.27). Post-surgery changes in GFR varied by pre-surgery GFR ($p<0.001$ for interaction). Those in the middle and upper tertiles of pre-surgery GFR had declines in unindexed GFR at 6 months post-surgery (upper tertile: -22.6 ml/min, -36.0, -9.2; middle tertile: -12.74, -23.1, -2.4). By contrast, individuals in the lowest tertile (GFR <100 ml/min) did not have a decline in unindexed GFR (8.9 ml/min, -2.2, 20.0). Indexed GFR was unchanged 6 months after surgery in the upper 2 tertiles whereas indexed GFR increased by 15.3 ml/min/1.73m^2(95% CI: 6.4, 24.3) in the lowest tertile. Overall, albuminuria tended to decrease (-41%, 95% CI: -67%, 4%). Findings were consistent in additional analyses accounting for regression to the mean, using GFR measurements from the other visits.

Conclusions: GFR did not decrease after bariatric surgery in severely obese individuals with GFR < 100 ml/min. This may reflect less capacity for physiologic changes in GFR, though we lack the ability to discern physiologic from pathologic decline in GFR.

Funding: NIDDK Support



Changes in GFR after Bariatric Surgery, by Baseline Tertile of GFR

SA-PO833

Dietary Zinc Amount Is Associated with Incident CKD in General Population

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Background: Previous study suggests that zinc is associated with diabetes. No studies have undergone the association of incident chronic renal disease (CKD) and zinc consumption amount in a preserved renal function population. Data from the Korean Genome and Epidemiology Study, a prospective community-based cohort study were used to assess the between zinc consumption amount and incident CKD.

Methods: Zinc consumption amount was calculated by a 24-h dietary recall Food Frequency Questionnaire and converted into relative zinc consumption amount with energy-adjust method. A. total 7821 participants were analyzed with a primary of incident CKD that defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2.

Results: The mean age was 52.1 ± 8.8 years, 47.5% were male, and mean eGFR was eGFR was 92.1 ± 16.1 ml/min/1.73m^2. The mean daily zinc consumption amount was 8.6 ± 3.4 mg. During a median follow up of 11.5 (1.6 – 13.0) years and 71417 person-year observation, CKD developed in 1428 (18.3%) participants. When the participants were categorized into quartiles according to energy-adjusted zinc intake, the lowest quartile was significantly associated with the development of incident CKD compared to third lowest quartile group in multivariable cox hazard analysis (Hazard ratio; 1.19; 95% Confidence Interval 1.02 – 1.39; P = 0.027) and this finding was consistent after further adjustment. The U shaped hazard association was noted between zinc consumption and incident CKD in restricted cubic spline analysis.

Conclusions: Thus, low zinc consumption was associated with the increased risk for CKD.

SA-PO834

Low Serum Zinc Concentration Is Associated with Infection Events in CKD Patients

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Background: Zinc plays an important role in immune function. Several studies reported the association between zinc deficiency and infection. Infectious disease is one of major complications in CKD patients. We investigated whether serum zinc concentration is associated with infection risk in stage 5 CKD patients.

Methods: We retrospectively analyzed 232 patients in whom serum zinc concentration was measured to evaluate renal anemia between January 2013 and December 2016. Of the 232 patients, 9 patients receiving zinc supplementation at the time of measurement were excluded. We followed up the remaining participants after enrollment. The endpoint was infection-related hospitalization. The length of infection-related hospitalization was also analyzed. Participants were divided into two groups according to the median of serum zinc concentration, categorized as low or high (Zn ≤ 50 and > 50 μg/dl, respectively). Data were analyzed using the Kaplan-Meier method and Cox hazards models.

Results: The median follow-up period was 36 months. During follow-up, 40 patients were hospitalized due to infection. Low serum zinc concentration was associated with a higher rate of infection-related hospitalization (low vs. high: 23.3% vs. 12.6%; p=0.042), and also associated with long-term hospitalization (more than 20 days) due to infection (low vs. high: 17.9% vs. 7.2%; p=0.016). After adjustment in Cox hazards models, low serum zinc concentration remains an independent risk factor for infection-related hospitalization (HR 2.11, 95% CI 1.06–4.21, p < 0.034).

Conclusions: Patients with low serum zinc concentration are at high risk of infection-related hospitalization, which also causes long-term hospitalization.

SA-PO835

Impact of Sodium Bicarbonate ($NaHCO_3$) on Systemic and Urine Metabolites in Patients with and Without CKD

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Background: Net acid excretion (NAE) falls in early stages of CKD, yet systemic metabolic acidosis (MA) occurs in late CKD. Homeostasis may be maintained by compensatory decrease in acid production. As conjugate bases of endogenously produced acids, organic anions (OAs) lost in the urine are markers of acid production. Modulation of OA excretion may defend against MA and alkalosis. Here we explore changes in urine OAs and potential consequences for systemic metabolism after alkali in a cross-over trial.

Methods: The Acid-Base Compensation in CKD Study was a cross-over trial evaluating 7-days of $NaHCO_3$ vs. 7-days of NaCl supplementation in the setting of fixed diet in adult, non-diabetic patients with (n=8) and without CKD (n=6). 24h urine, and fasting and 90-minute postprandial plasma were collected at the end of each period. We used nontargeted GC/MS metabolomics to explore the excretion of urine OAs and systemic metabolism in plasma. Linear mixed-effects models and discriminant analyses (sparse PLS-DA) were used to identify metabolites that vary with $NaHCO_3$ treatment independently in CKD and non-CKD subjects and overall.

Results: We found 15 urine metabolites higher with $NaHCO_3$ at a nominal p-value <0.05 in CKD participants and 13 lowered in non-CKD. Rise in 3-indoleacetic acid, citric

acid/isocitric acid, and glutaric acid in CKD participants were the only significant changes after false discovery rate (FDR) correction (each p=0.01). These changes were not detected in those without CKD. There were no changes in plasma metabolites overall or in any group after FDR correction. A primary component including higher fatty acids and lower leucine, asparagine, serine and lysine, among others, was identified by sparse PLS-DA in fasting plasma samples from the CKD group after $NaHCO_3$. A component loading directly on fructose, phosphate, urea, valine, leucine and aminomalonic acid, among others, was higher in post-prandial samples overall after $NaHCO_3$.

Conclusions: Several urine OAs were increased by alkali in CKD suggesting possible increased acid production. Changes in sugars, mineral ions, and protein metabolites in the fed state suggest concurrent changes in nutrient metabolism which could represent an additional response to acid-base manipulation.

Funding: NIDDK Support

SA-PO836

Metabolic Acidosis Is Associated with Failure to Thrive and Fractures and Falls in Patients with CKD

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Background: Metabolic acidosis causes muscle-wasting and bone loss in experimental animal and human studies. However, its association with clinical outcomes in epidemiological studies is unknown. Here we assess the role of metabolic acidosis as an independent predictor of adverse muscle, bone and functional outcomes in patients with non-dialysis CKD.

Methods: De-identified electronic medical records (Optum® EMR), 2007–2017 were queried to identify non-dialysis CKD patients with ≥2 consistent serum bicarbonate test values 28–365 days apart, ≥3 eGFR values >10 and <60 mL/min/1.73m^2 and ≥2 years of post-index data or until death. Patients were followed for 2 years for adverse outcomes using ICD codes: failure to thrive (muscle/functional outcome); composite of hip, spine, pathological fractures or falls (bone outcome). Metabolic acidosis and normal serum bicarbonate groups were defined by two serum bicarbonate values between 12 and <22 mEq/L and 22-29 mEq/L, respectively. Logistic regression was used to examine serum bicarbonate as an independent predictor of 2-year outcomes and possible demographic and comorbidity confounding factors.

Results: 51,558 patients qualified for this longitudinal observational study. The incidence of adverse outcomes was significantly higher in patients with metabolic acidosis during the 2-year follow-up compared to patients with normal serum bicarbonate: muscle outcomes: 6.5% vs. 1.9%, p<0.0001; bone outcomes: 17.3% vs. 11.6%, p<0.0001, respectively. Serum bicarbonate was a significant predictor of both types of outcomes; odds ratios for failure to thrive, 0.883, CI: 0.869-0.898, and for fracture/fall, 0.948; CI: 0.939-0.956, independent of age, sex, race, eGFR, diabetes, hypertension, heart failure, coronary artery disease, peripheral vascular disease, hemoglobin and serum albumin. Each 1 mEq/L increase in serum bicarbonate was associated with a 12% decrease in failure to thrive and a 5% decrease in fracture/fall risk.

Conclusions: In this analysis of > 51,000 non-dialysis CKD patients followed for 2 years, metabolic acidosis was independently associated with increased incidence of failure to thrive and the composite endpoint of fractures (hip, spine, or pathological) and falls.

Funding: Commercial Support - Tricida, Inc.

SA-PO837

Impact of a Virtual Multidisciplinary Care Management Program for Advanced CKD on Patient Knowledge, Dialysis Modality Choice, and Planned Dialysis Start

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Background: Among persons with advanced chronic kidney disease (CKD), education and preparation for renal replacement therapy (RRT) remain suboptimal. We conducted a pilot study to evaluate the impact of a virtual multidisciplinary care program including a nurse, dietitian, pharmacist, and peer mentors for patient education, monitoring, and managing transitions to RRT.

Methods: We invited adults with eGFR <30 ml/min/1.73m^2 not on RRT from a community-based nephrology clinic into Cricket Health's online multidisciplinary care program. We compared CKD knowledge, confidence in disease self-management, and first choice of RRT modality before and after education. Then, in a matched prospective cohort design, we evaluated the association of program participation with planned RRT initiation (in-hospital vs. outpatient planned) after 9 months using conditional logistic regression. For each participant, we identified 1 to 2 controls from the same clinic, matched on age, gender, baseline eGFR, diabetes, and heart failure status.

Results: Among 50 invited, 37 (74%) enrolled, with average age 66 (SD=13), eGFR 19 ml/min/1.73m^2 (SD=6), 68% female, and 53% diabetic. 36 participants (97%) completed a pre-program survey, and 23 (62%) completed a post-education survey. After education, the average percent correct on a 7-item CKD knowledge assessment increased from 52% to 89%, p<0.001. The percent reporting confidence in self-care dialysis was 83% after education, compared with 64% prior, p=0.22. Before education, 50% were unable to choose a RRT modality. After education, 91% of respondents made a choice, of whom 76% preferred a home RRT modality. At 9 months, 5 program participants and 5 controls started RRT. A total of 4 of 5 program participants (80%) started RRT as outpatients with planned starts, compared with 1 of 5 controls (20%) (OR=6.3, 95% CI=0.7-57, p=0.06).

Conclusions: A virtual multidisciplinary care program for persons with advanced CKD improves patient CKD knowledge, confidence in self-care, and interest in home RRT. Our findings also suggest this virtual multidisciplinary care program may increase the likelihood of planned RRT initiation.

SA-PO838

Validation of a Smartphone-Based Proteinuria Testing Solution

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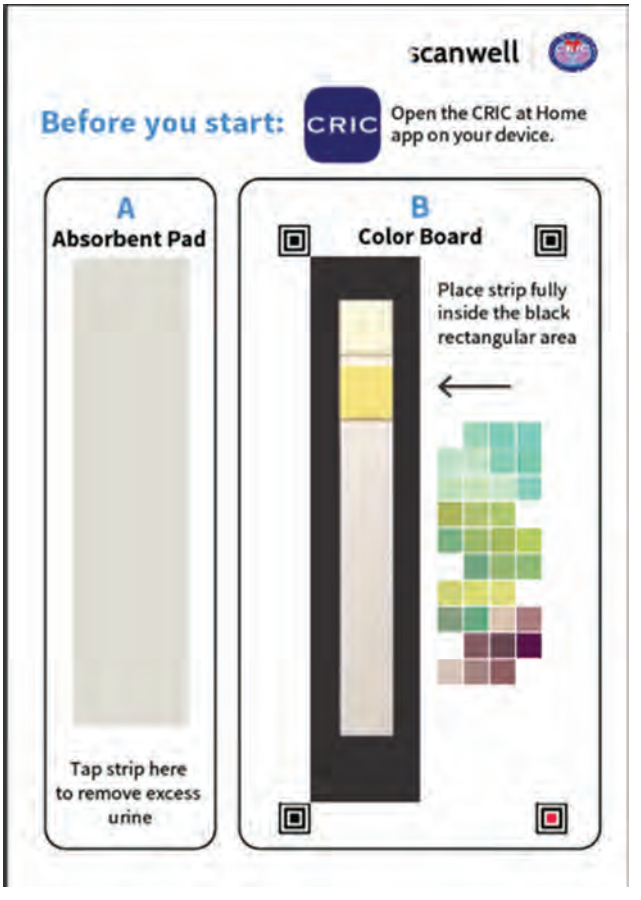
Background: Proteinuria is a potent risk factor for ESRD. Guidelines recommend screening and monitoring for urinary protein in those with or at high-risk for CKD, but this involves lab or clinic procedures that contribute to undertesting. A valid smartphone-based testing solution could facilitate widespread testing.

Methods: We prospectively evaluated the feasibility and accuracy of a smartphone-based urinary protein testing platform in a sample of adults with CKD not receiving dialysis enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study at Kaiser Permanente Northern California/UCSF. The urinary protein testing solution involves a smartphone-based app combined with a color-calibration card and urinalysis dipstick (Scanwell Health, Inc.)(**Figure**). Participants provided a urine sample that was tested using (1) the smartphone-based testing platform and (2) Clinitek urine dipstick analyzer. Test results were reported as negative, trace, 1+, 2+ or >=3+ proteinuria.

Results: Eighty-seven participants were enrolled, with mean (SD) age 70 (9) years, 53% women, 31% black, 8% Asian, 5% Hispanic, 24% with diabetes and mean (SD) eGFR 57 (17) ml/min/1.73 m^2. Based on results from the clinical Clinitek analyzer, 32 (37%) had evidence of proteinuria. The smartphone-based testing solution exactly matched the categorical result in 61% of patients, while 82% were within one category level of proteinuria compared with the Clinitek analyzer result.

Conclusions: We found a high level of concordance for a semi-quantitative smartphone-based proteinuria testing platform compared with a clinical standard within a diverse sample of adults with CKD. Our study supports the utility of a smartphone-based testing solution to expand proteinuria screening and monitoring.

Funding: NIDDK Support, Commercial Support - Scanwell Health



Smartphone-based urinary protein testing solution

SA-PO839

Evaluation, Classification, and Identification of CKD Progression in Rhesus Macaques

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Background: Chronic kidney disease (CKD) is characterized by progressive reduction in kidney function, and with accelerated cardiovascular disease and increased mortality. The goal of the present study was to characterize naturally occurring CKD in rhesus monkeys in comparison to the CKD of humans, to explore the relationship between CKD and CVD, and to evaluate the response of rhesus monkeys with combined CKD-CVD to the angiotensin receptor blocker, Valsartan.

Methods: Plasma biomarkers (Creatinine (Cr), Cystatin-C (CYSC), and Blood Urea Nitrogen (BUN)) were measured in 1198 adult rhesus monkeys (*Macaca mulatta*, 7-22 yrs). Four hr urine collections were obtained from 100 of these monkeys in order to measure urine albumin and urine creatinine for calculation of the urine albumin/creatinine ratio (UACR). Monkeys with eGFR (CKD-EPI) 30-59 ml/min/1.73m^2 and/or UACR≥10mg/g were defined as having CKD (Grade G3a-3b). Blood pressure and cardiac function were measured, monkeys with LVEF<50%, e'<8 cm/s and E/e'>10 were defined as having CVD. A colony of 37 adult male monkeys received medical examinations and direct GFR measurements (Iohexol clearance). Eight monkeys with combined CKD-CVD were enrolled in the validation study and divided into the Valsartan group (n=4)(3 mg/kg, Bid) and the vehicle group (n=4). Cardiac function, blood pressure and UACR were measured before and after 8 weeks treatment. Cr, CYSC, BUN and eGFR were measured every 2 weeks.

Results: Among the 1198 adult rhesus monkeys studied, 52 monkeys (4.3%) had eGFR 30-59 ml/min/1.73m^2 and/or UACR≥10mg/g. Among the 52 monkeys with CKD, 30 monkeys had confirmed CVD. With Valsartan treatment, average eGFR increased by 23.31%; average UACR decreased by 76.45%; and average SBP decreased by 14.40%. All of these biomarkers differed significantly compared to the vehicle group (p's<0.05). The cardiac ultrasound parameters remained stable.

Conclusions: The 4.3% incidence of CKD in adult rhesus monkeys was similar to that in adult humans, and 58% of those with CKD also had CVD as in patients. Valsartan increased eGFR, and also decreased UACR and BP in monkeys. The extent of change in rhesus monkeys was similar to that observed in clinical trials. These monkey models, therefore, provide important new opportunities to understand the pathogenesis of CKD and predict the human response to new therapeutic agents.

SA-PO840

Use of Kidney Disease Progression Model Care Planning Report Associates with Lower Dialysis Catheter Rates at the Initiation of Hemodialysis

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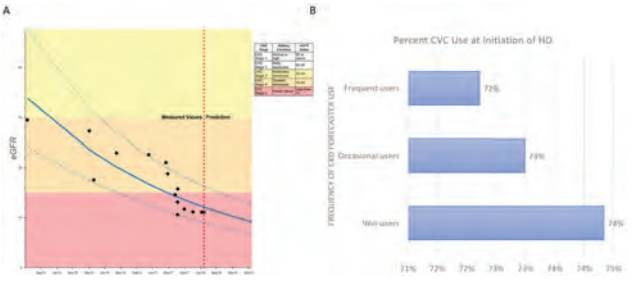
Background: Approximately 80% of end stage kidney disease (ESKD) patients use a central venous catheter (CVC) at the initiation of hemodialysis (HD) (USRDS 2018). A healthcare organization developed a CKD Forecaster Tool for nephrologists to use for prognostic clinical decision support and patient education in care planning for the transition from CKD to ESKD. We assessed CVC rates at the initiation of HD based on the nephrologists' level of utilization of the CKD Forecaster Tool.

Methods: We used data from CKD patients treated by nephrology practices using Acumen Electronic Health Record system who progressed to ESKD during April 2018 to October 2019. The CKD Forecaster Tool uses an artificial intelligence modelling of historic eGFR values to predict the trajectory of eGFR values in the future. We assessed CVC rates at HD initiation in patients who progressed to ESKD stratified by the frequency of their nephrologist accessing the CKD Forecaster Tool. Only nephrologists with ≥15 CKD patients who transitioned to ESKD were used for the analysis. Frequent users accessed the tool on >1% of their CKD patients, occasional users accessed the tool on >0-1% of their CKD patients, and non-users did not use the tool.

Results: Among a population of 106,915 CKD patients treated by 309 nephrologists, we analyzed data on 6,917 patients who progressed from CKD to ESKD (this includes only nephrologists with ≥15 CKD patients who transitioned to ESKD). A total of 30 nephrologists were frequent users of the CKD Forecaster Tool, 39 were occasional users, and 240 were non-users. Patients treated by nephrologists who used the CKD Forecaster Tool exhibited 1% to 2% lower CVC rates at HD initiation (Figure 1).

Conclusions: Nephrologists who used the CKD Forecaster Tool had slightly less patients transitioning to HD with a CVC. Further assessments are needed to determine if greater adoption and consistent use of the CKD Forecaster Tool over time is associated with larger improvements.

Funding: Commercial Support - Fresenius Medical Care North America



SA-PO841

Added Value of Census Tract Measures of Socioeconomic Status to Identify Patients at High Risk of CKD in the Twin Cities Metro Area

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Background: CKD is associated with low socioeconomic status (SES); however, guidelines do not recommend screening low SES patients for CKD. Our objective was to assess whether adding census tract level SES status to the traditional CKD screening approach improves our ability to detect patients with CKD.

Methods: Electronic health records of 256,212 patients with outpatient serum creatinine available who received primary care at a health system serving the 7 county Minneapolis/St Paul metro area. CKD was defined as having an estimated glomerular filtration rate <60 ml/min/1.73m^2 or proteinuria. We compared 3 screening approaches: Approach 1(traditional), screening patients with diabetes(DM) or hypertension(HTN); Approach 2A, DM, HTN, or low census tract SES-housing (quartile 1 of the median value of owner occupied housing units); Approach 2B, DM, HTN, or low census tract SES-education (quartile 1 of percent of residents >= 25 years with complete college education); Approach 3A, screening patients with low census tract SES-housing; Approach 3B: screening patients with low census tract SES-education.

Results: In our cohort, 34,489 patients had CKD. Adding low census tract SES (Approach 2A and 2B), significantly increases the sensitivity of detecting CKD (Table1). Number needed to screen to detect 1 CKD case was 4, 5, 5, 8, and 7 for Approaches 1, 2A, 2B, 3A, and 3B, respectively.

Conclusions: Adding an individuals' residence SES status to traditional risk factors improved our ability to detect individuals at risk of CKD who may benefit from interventions to reduce risk of cardiovascular disease and progression of CKD.

Table 1. The sensitivity, specificity, positive predictive and negative predictive value of the screening approaches for detecting CKD.

	Number of CKD cases detected	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Approach 1	17,117	50	77	25	91
Approach 2A	18,769	54	69	22	91
Approach 2B	19,192	56	68	21	91
Approach 3A	3,439	10	90	13	87
Approach 3B	4,303	13	88	14	87

SA-PO842

Outcomes from Development of a Unique Statewide Platform to Improve CKD Care

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Background: The division of Nephrology at University of Arkansas for Medical Sciences (UAMS) and Arkansas health department faculty co-investigated a pilot project identifying barriers to chronic kidney disease (CKD) awareness in the State of Arkansas (AR). These included a lack of infrastructure and patient and provider education. To address these barriers, our core investigators reached out to potential stakeholders. We invited a multidisciplinary team of health-care professionals to partner with non-profit organizations and CKD patients, creating the platform of the Arkansas State CKD Advisory Committee (ARCKDAC), with a mission to increase CKD awareness, detection and education through community engagement activities. We also provided baseline AR data to improve systems of care and generate data for future research.

Methods: ARCKDAC focused on 4 projects: 1) Analysis of end-stage renal disease (ESRD) incident data provided by ESRD Network-13 identifying regional differences. 2) Compile a cost/saving analysis of health-care dollars spent on CKD in AR 3) Develop model continuous quality improvement (CQI) projects based on Healthy People 2020 CKD objectives, clinical indicators and targets 4) Improve patient, provider and public education.

Results: Result highlights by projects include: 1) There was a 2% decrease in incident ESRD patients in 2017and an increase from 13.6% to 18.9% incident peritoneal dialysis in the central region which has dedicated CKD education programs. 2) Costs for transplantation and dialysis are lower in AR than national averages. AR spends $7K less per patient/per year for transplants and $10K less for dialysis. 3) Two CQI models were developed for future use: CKD detection by ICD10 codes and Targeted education of providers assessing practice improvement using claims data. 4) Compiled resources for patients and increased provider education by live and web-based education, published articles in the state physician and nursing magazines and development of a "Know-Your-Kidney-Number"

campaign. A white paper detailing data, resources, and recommendations for each project is available electronically to all providers and stakeholders.

Conclusions: From our knowledge, this unique statewide approach to CKD care is the first of its kind in the country and can serve as a model targeting efforts for improving CKD outcomes.

Funding: Commercial Support - Baxter Healthcare

SA-PO843

The Relationship Between County-Level Contextual Determinants and Risk of CKD

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Background: Multiple studies described geographic variation in the burden of chronic kidney disease (CKD) in the United States, and evidence suggests that this variation cannot be fully explained by individual level risk factors. We aimed to examine the relationship between county level contextual determinants and individual risk of incident eGFR<60 ml/min/1.73 m^2.

Methods: We built a cohort of 2,456,853 US veterans with eGFR>60 ml/min/1.73 m^2 and followed for up to five years. Contextual determinants were curated from County Health Ranking databases. High dimensional propensity score method was used to estimate prognostic score for CKD based on individual level risk factors. Logistic regression analyses were conducted to examine the association between contextual determinants and incident eGFR<60 ml/min/1.73 m^2, controlling for individual risk factors.

Results: Within 38 contextual determinants, the top 5 determinants which have strongest univariate association with incident eGFR<60 ml/min/1.73 m^2 included physical inactivity, injury deaths, some college or above degree, health care costs and median household income. After controlling for sumarized pronostic score, physical inactivity, injury deaths, health care cost and median household income associated with eGFR<60 ml/min/1.73 m^2 independent of individual risk factors (table). Interaction analyses suggested that association between individual risk factors and incident eGFR<60 ml/min/1.73 m^2 was modified by county level contextual determinants including physical inactivity, health care costs and median household income.

Conclusions: Contextual determinants are associated risk of eGFR<60 ml/min/1.73 m^2 independent of individual risk factor. In addition, they could modify the relationship between individual risk factors and eGFR<60 ml/min/1.73 m^2. Contextual determinants may play important role in burden of CKD; their role should be reflected in the national discussion about reducing CKD burden.

Funding: Veterans Affairs Support

Association between contextual determinats and incident eGFR<60 ml/min/1.73 m2

Contextual determinants	Unit	Univariate OR	OR controlling for individual risk factor	Interaction between contextual determinants and individual risk factors
Physical inactivity	5%	1.08 (1.08, 1.08)	1.05 (1.04, 1.05)	P<0.001
Injury deaths	Per 100 in 100,000	1.31 (1.29, 1.33)	1.16 (1.14, 1.17)	P=0.16
Some college or above	5%	0.97 (0.97, 0.97)	0.99 (0.99, 0.99)	P=0.65
Health care costs	Per $10000	1.50 (1.47, 1.53)	1.36 (1.33, 1.40)	P<0.001
Median household income	Per $10000	0.96 (0.96, 0.96)	0.96 (0.96, 0.96)	P<0.001

SA-PO844

Housing Insecurity and Healthcare Engagement Among People with CKD

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Background: Housing insecurity is characterized by high housing costs or unsafe living conditions. Among persons with CKD, we examined whether housing insecurity was associated with postponing medical care.

Methods: We performed a cross-sectional analysis of data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study (Baltimore, MD) during study visit 4. We used multivariable log binomial and Poisson regression with robust estimate of variance clustered on neighborhood to quantify associations between housing insecurity (self-report of inability to afford a suitable home or difficulty paying rent/mortgage payments) and self-report of postponing medical care that was felt to be needed among individuals with CKD (eGFR <60 ml/min/1.73m^2 or albumin-to-creatinine ratio ≥30 mg/g).

Results: Among 355 HANDLS participants with CKD, 135 (38%) reported housing insecurity. Individuals with housing insecurity were younger (mean [SD] age 57.8 [9.1] years versus 61.1 [8.3] years), more likely to be male (48.9% versus 38.6%), less likely to have a high school degree (60.5% versus 72.3%) and more likely to lack health insurance (6.7% versus 4.1%) than stably housed persons. Overall, 85 (23.9%) participants reported postponing medical care that was felt to be needed. Housing insecurity was associated with increased risk of postponing medical care even after adjusting for demographics, clinical variables, health insurance status, CKD awareness, food insecurity and education level (**Table**).

Conclusions: Individuals with CKD experiencing housing insecurity may be more likely to postpone medical care, which could increase their risk of poor clinical outcomes.

Funding: Other NIH Support - National Institute on Aging, National Institute of Health

Association Between Housing Insecurity and Postponement of Medical Care Among People with CKD

Regression Model	Incidence Rate Ratio (95% CI)
Unadjusted	1.92 (1.44 – 2.56)
Model 1	1.73 (1.34 – 2.23)
Model 2	1.69 (1.34 – 2.15)
Model 3	1.59 (1.20 – 2.10)

Model 1: adjusted for demographics (age, race, sex, and poverty level).

Model 2: adjusted demographics and clinical variables (baseline eGFR, urine albumin-creatinine ratio, blood pressure, and diabetes).

Model 3: adjusted for demographics, clinical variables, health insurance, CKD awareness, food insecurity and education level.

SA-PO845

Documenting CKD in the Primary Care Electronic Health Record

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Background: The KDOQI guidelines recommend 2 measurements of glomerular filtration rate (GFR) <60 mL/min/1.73m^2 or evidence of kidney damage at 3 months intervals or more to establish the diagnosis of chronic kidney disease (CKD). We examined whether the diagnosis of CKD in an outpatient primary care setting was documented in the Electronic Health Record (EHR) according to the GFR-based KDOQI criteria.

Methods: We used the CKD-Epi equation to assess GFR from the serum creatinine records of patients seen in a network of primary care offices from 2011 to 2015. Our study population was defined as patients 18+ with at least one GFR<60 and at least one followup visit. We excluded patients with an initial GFR<15, those in renal replacement therapy and those with a known CKD diagnosis. Followup began at the time of the first GFR<60. We calculated the time interval between the first GFR<60 and the second GFR and stratified patients into 3 categories according to their first GFR (GFR 15-<30; 30-<45; 45-<60). We used the Systematized Nomenclature of Medicine (SNOMED) codes to ascertain documentation of CKD.

Results: Our final study population included 7098 patients. Of those, 37% were male, 84% white, 15% black; 3%, 18%, and 78% had a first GFR 15-<30, 30-<45 and 45-<60 respectively. Mean age was 70. Overall 63% had a second GFR<60. A total of 4669 patients did not have a CKD diagnosis during followup. Of those, 65% met the KDOQI criteria and CKD should have been documented in the EHR. Of the 2429 patients assigned a CKD code, 41% met the KDOQI criteria, 12% had a second GFR≥60, 27% were given the diagnosis prior to the second GFR measurement, 20% had a second GFR measured within 3 months. Of our study population (n=7098), 43% met the KDOQI criteria but did not receive a documented diagnosis and 20% had a documented diagnosis but did not meet KDOQI criteria.

Conclusions: CKD diagnosis was not appropriately documented in a large number of patients. Algorithms used to identify CKD patients for population health management should not rely only on diagnosis codes but also include measurements of GFR. More resources should be developed to assist primary care physicians to enter the appropriate code in the EHR. The lack of albuminuria information in our dataset limits the interpretation of the apparent over CKD coding of those who did not meet the GFR-based KDOQI guidelines.

Funding: Other NIH Support - NIGMS- U54-GM104941

SA-PO846

Kidney Disease Knowledge, Health Literacy, and Self-Care in CKD

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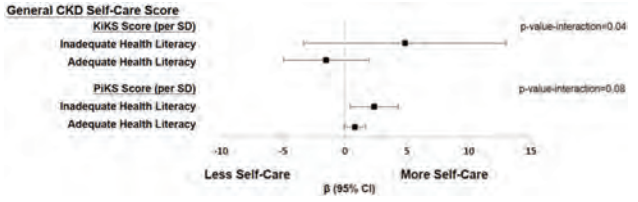
Background: Research is needed to better understand the links between health literacy and kidney disease knowledge on patient self-care behaviors in order to guide interventions to improve self-care in chronic kidney disease (CKD).

Methods: Among study participants with CKD stage 1-5, validated surveys assessed level of health literacy (Rapid Estimate of Adult Literacy in Medicine [REALM]), perceived kidney disease knowledge (Perceived Kidney Knowledge Survey [PiKS]), objective kidney disease knowledge (Kidney Disease Knowledge Survey [KiKS]), and self-care behaviors (modified Summary of Diabetes Self-Care Activities Assessment [SDSCA]). A summary score of self-care was constructed utilizing the SDSCA scoring system. Multivariable adjusted linear regression estimated the association of self-care scores with health literacy (inadequate vs. adequate, determined by REALM score ≤59 vs. >59, respectively) and PiKS and KiKS scores (per SD). Health literacy was also explored as a potential effect modifier.

Results: Of the 401 participants: mean age was 57 years; 47% female, 38% diabetes; 77% CKD stage 3-5. The prevalence of inadequate health literacy was 18%. The median KiKS score (range 0-1) was 0.7 (interquartile range [IQR] 0.6-0.8), and median PiKS score (range 0-4) was 2.6 (IQR 2.1-3.0). After full adjustment, a PiKS score was positively associated with self-care scores (β=1.0, 95% confidence interval: 0.3-1.7). Health literacy and KiKS scores were not associated with self-care. There was evidence of effect modification by health literacy; a KiKS score appeared to positively associate with self-care scores only among those with inadequate literacy, but this did not reach statistical significance (**Figure**).

Conclusions: Objective kidney knowledge is likely necessary, but not sufficient for self-care, and may be particularly helpful to those with inadequate health literacy. Perceived kidney knowledge has a strong positive association with self-care, offering a novel target to support self-care among patients with non-dialysis dependent CKD.

Funding: NIDDK Support



Association of Knowledge and Self-Care by Health Literacy Level.

SA-PO847

A Tale of Two Neighborhoods: Association of Neighborhood-Level Social and Environmental Contexts with High CKD Prevalence

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Background: Although CKD risk has been linked to neighborhood income, its association with other neighborhood contexts is less clear.

Methods: We estimated the 2017 prevalence of KDIGO CKD 3-5 among adults age 30 and older living in 153 Durham County census block groups (i.e. 'neighborhoods'). Data were derived from the Durham Neighborhood Compass, a publicly available platform which integrates local electronic health record data with social and environmental data from 153 neighborhoods in Durham County, North Carolina-- a diverse US county of 295,373 residents. We characterized differences in neighborhood contexts reflecting social cohesion, economic stability, safety, transportation and the built environment among neighborhoods with 'high' CKD prevalence (above median county CKD prevalence among residents age 30-64 and age 65+) vs. 'low' CKD prevalence. In logistic regression models, we quantified the association of specific contexts with 'high' (vs. 'low') neighborhood CKD prevalence while adjusting for neighborhood median age and % black population.

Results: Among all 153 neighborhoods, the mean (SD) prevalence of CKD 3-5 was 2 (1.1)% and 11.7 (4.3)% among those age 30-64 and 65+, respectively. Nearly a quarter (22%) of neighborhoods (27,619 residents) had 'high' CKD prevalence. Contexts of 'high' and 'low' CKD prevalence neighborhoods varied substantially. After adjustment, neighborhoods with above median violent crimes, evictions, and impervious areas had greater odds of 'high' (vs. 'low') CKD prevalence; neighborhoods with above median household income and primary election participation had lower odds of 'high' (vs. 'low') CKD prevalence.

Conclusions: Durham neighborhoods with high and low CKD prevalence had substantially different social and environmental contexts. Further study of the influence of these factors on CKD risk is warranted.

Funding: NIDDK Support, Other NIH Support - Duke CTSI UL1TR002553

Table
Social and Environmental Contexts in Durham Neighborhoods with 'high' and 'low' CKD prevalence

Determinant of Health	Neighborhoods with 'high' CKD prevalence N=34	Neighborhoods with 'low' CKD prevalence N=119	p	Adjusted* Odds Ratio [95% CI] for 'high' versus 'low' CKD prevalence**	p
Violent crimes per square mile, Median [IQR]	125.9 [60.6-194.2]	12.6 [4.3-47.8]	<0.01	12.7 [3.21-50.0]	<0.01
Evictions per square mile, Median [IQR]	177.1 [74.0-363.1]	29.1 [4.41-127.5]	<0.01	6.04 [1.70-21.5]	<0.01
% impervious areas, Median [IQR]	32.5 [26-41]	26.0 [17-31]	<0.01	2.70 [1.05-6.97]	0.04
% of population with long commute times	32.5 [21-41]	25 [17-34]	0.08	2.14 [0.897-5.135]	0.09
% primary election participation, Median [IQR]	26 [21-33]	45[35-50]	<0.01	0.087 [0.02-0.38]	<0.01
Median household income ($), Median [IQR]	30,025 [22,105-40,897]	60,879 [42,533-75,191]	<0.01	0.086 [0.022-0.335]	<0.01
% African American population, Median [IQR]	65.1 [54.7-76.3]	25.1 [12.0-39.6]	<0.01	6.33 [2.51-16.0]	<0.01
Median age, Median [IQR]	32.0 [30.3-36.3]	36.0 [32-42.7]	0.03	0.94 [0.893-1.009]	0.10

*Each determinant adjusted for neighborhood median % African Americans and neighborhood median age
**Odds of 'high' versus 'low' CKD prevalence in neighborhoods with above versus below median threshold for determinant of health

SA-PO848

Predicted Risk of Renal Replacement Therapy at Time of Referral for Arteriovenous Fistula Placement in CKD

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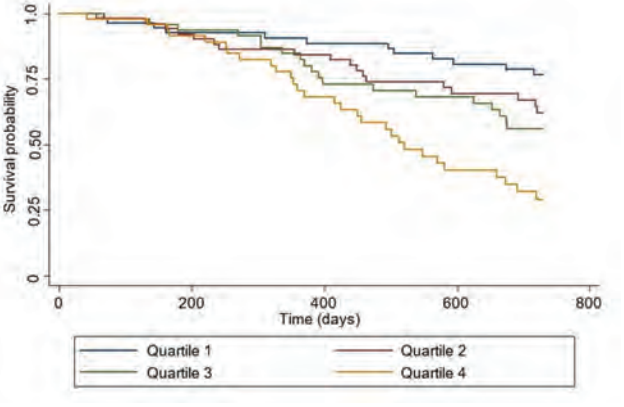
Background: The complexity in predicting which and when patients with chronic kidney disease (CKD) will progress to renal replacement therapy (RRT) contributes to 80% of patients starting hemodialysis without a functioning permanent access. This has been associated with higher mortality, morbidity, and cost. A prediction model developed at Kaiser Permanente Northwest may help guide timing of AVF placement.

Methods: 398 CKD stage 4 patients followed by nephrology were classified into AVF referral group (n = 199) and non AVF referral group (n = 199). The non-referral group was randomly selected and matched 1:1 on age, gender, and eGFR. Patients were followed for up to two years and censored if they died or discontinued coverage. Survival analyses were performed for overall hemodialysis initiation.

Results: The average age was 68.5 years in the AVF referral group and 68.1 years in the non AVF referral group. The mean eGFR among the AVF referral group was 16.8 mL/min and 17.2 ml/min in the non AVF referral group. The average 2-year predicted risk of progression to RRT was 47.7% in the AVF referral patients and 44.1% in the matched controls. Hemodialysis initiation occurred at a significantly higher rate in the AVF referral group than in the non AVF referral group (43.7% vs. 23.6%, HR = 1.9, $p < 0.001$). The AVF referral group was stratified into quartiles based on predicted risk of progression to RRT. The lowest quartile (average risk 17.6%) had a 78% lower risk of hemodialysis initiation than the highest quartile (average risk 84.3%); HR = 0.22, $p < 0.001$.

Conclusions: In patients with CKD stage 4, a computer-generated risk score identified a subgroup of AVF referred patients with a low predicted risk to RRT that may have been referred too early.



Kaplan-Meier curve of dialysis free survival by 2 years risk for renal replacement therapy divided into quartiles

SA-PO849

Association of Educational Attainment with Incidence of CKD: Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Background: Chronic kidney disease (CKD) is a major public health challenge that is greatly impacted by social determinants of health, including education. There are limited data on relationship of low educational attainment with incidence of CKD in young adults.

Methods: We evaluated the association of education with incident CKD and with change in estimated glomerular filtration rate (eGFR) over 20 years in 3140 participants of the Coronary Artery Risk Development in Young Adults (CARDIA) Study. We categorized education into low (high school and below), medium (college), and high (masters and professional studies) groups. Incident CKD was defined as new development of estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2, or urine albumin to creatinine ratio (ACR) ≥ 30 mg/g.

Results: At baseline (year-10 study visit), mean age was 35 ± 3.6 years, mean eGFR was 110.2 ± 16.0 ml/min/1.73m^2, and median ACR was 3.9 (interquartile range, 2.7 – 5.9) mg/g. Participants with lower educational attainment were less likely to have health care access and engage in healthy lifestyle, and had more comorbidities. Over 20 years, 407 participants (13%) developed CKD. Compared to individuals with low educational attainment, those with medium educational attainment had an unadjusted hazard ratio (HR) for CKD of 0.79 (95% confidence intervals [CI] 0.65 – 0.97) and those with high

educational attainment had a HR of 0.44 (95%CI 0.30 – 0.63). This association was no longer significant after adjusting for health care access, lifestyle, and comorbid conditions. Low educational attainment remained significantly associated with change in eGFR, although the relationship was attenuated with adjustment for covariates.

Conclusions: Health care access, lifestyle, and comorbid conditions likely help explain the association between low educational attainment and incident CKD in young adults.

SA-PO850

Developing a Clinical Decision Support Software to Monitor and Tailor Treatment of CKD Patients

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Background: CKD is a complex disease with several therapeutic challenges: silent onset; different: etiopathologies, progression patterns, prognosis and comorbidities; polypharmacy. Clinical decision support (CDS) software may improve CKD management.

Methods: Within the German Chronic Kidney Disease (GCKD) study, a multi-center, prospective, observational CKD stage 3 cohort study, demographic, phenotypic, and clinical parameters of 5,217 Caucasian patients have been collected. We will model these data and variable dependencies by state-of-the-art machine learning methods to predict the risk of adverse endpoints, to interpret the results in the context of current biomedical knowledge, and to use the estimated models as a backbone for a CDS software, which will be provided as a user-friendly app to nephrologists (CKDNapp).

Results: CKDNapp, based on mathematical models and enriched by state-of-the-art literature (**Fig 1** (1)), will assess patient parameters in one consistent framework, schematically represented by a network (**Fig 1** (2)). Only the mathematical models will enter the app (**Fig 1** (3)) ensuring data security. Nephrologists will be able to use CKDNapp as a CDS system (**Fig 1** (4)), entering patient data like clinical parameters and disease history. CKDNapp will integrate all provided patient information and return personalized adverse event / disease progression prediction, support medication management, and offer in silico modification of patient parameters exploring effects of future treatment strategies.

Conclusions: The overall goal of CKDNapp is to facilitate personalized CKD patient treatment. First results will be available for presentation at ASN Kidney Week 2019.

Funding: Government Support - Non-U.S.

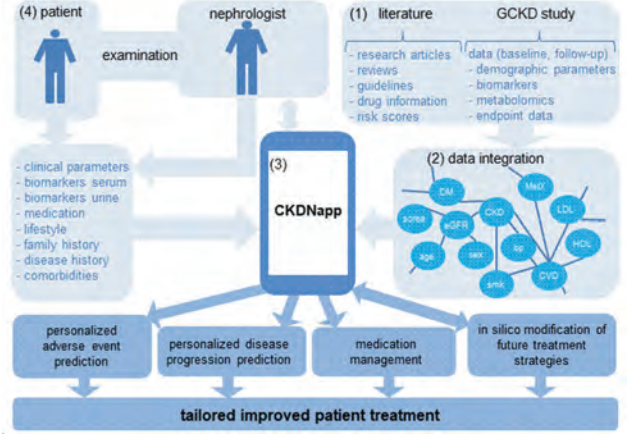

Figure 1 Schematic workflow of the development and application of CKDNapp.

SA-PO851

The Keeping Kidneys Program: Baseline Results from a New Model of Care for Community Kidney Health

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Background: Intervention in early-stage CKD slows rate of progression. First contact healthcare providers like general practitioners (GPs) are at the forefront of detection and management of the early stages of CKD. Keeping Kidneys (KK) was implemented in 2018 to augment kidney care skills of GPs in a less-privileged socio-economic area of Queensland, Australia, where access to specialized kidney care was not available. Here we describe the characteristics of patients referred to this program.

Methods: Two GPs were recruited and trained in a specific subset of CKD skills. Training included didactic knowledge acquisition and clinical detailing by a nephrologist. Demographic and clinical data were extracted from electronic medical records; patient-reported outcomes (CKD knowledge and self-management) were completed at KK entry. Data were analysed descriptively (frequency distributions and mean/median as appropriate).

Results: 140 patients were referred to KK in the first 8 months. Median age was 76 years (67-81). Most patients were in CKD stage 3B (54%) or 3A (22%). Hypertension and diabetes were the leading CKD causes but 33% had no aetiological diagnosis at entry. Most patients had low-average scores for CKD knowledge (13±14/28) and CKD self-management (46±6/116). Median Charlson comorbidity score was 7, predicting survival of <10 years. Mean haemoglobin (Hb) was 12.6±2 g/dL and 5% of patients had Hb<10g/dL. Mean parathyroid hormone, calcium (Ca^{++}) and phosphate (PO^4) were respectively 94±81 pg/mL, 9.6±0.5 and 3.4±0.5 mg/dL. Prevalence of hypoCa^{++} and hyperPO_4 were respectively 1% and 2%. Median urine albumin:creatinine ratio was 38 (12-75) mg/g. One patient was referred for renal biopsy and one for bone marrow biopsy. Patients travelled, on average, 25 minutes less for their appointments, with 72% seen within 15 km of their homes.

Conclusions: KK focuses on the interface between patients, GPs and specialists. Trained GPs were capable of staging severity of kidney disease, initiating the work up of the cause/s of the kidney disease and screening for complications. They managed a cohort of patients with CKD that were elderly, had intermediately advanced CKD and complex co-morbidities in their communities.

Funding: Other U.S. Government Support

SA-PO852

Improving Care by Targeting High-Risk Communities in North Carolina (NC)

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Background: Nearly one million in NC have chronic kidney disease (CKD), not including end-stage kidney disease. A goal of the UNC Kidney Center's Kidney Education and Outreach Program (KEOP) is to understand potential healthcare barriers faced by rural communities. The objective of this study was to describe characteristics of screening participants and their access to physician care.

Methods: The KEOP conducted 206 screenings, predominantly in rural communities, collecting urinalysis and surveys (10/2005-11/2015). This exploratory data analysis compared participants who had seen their regular doctor in the past year to those without a regular doctor or who had not seen one in over a year. Characteristics examined included, age, gender, race, diabetes (DM), hypertension (HTN), income status and others. Proteinuria was assessed by dipstick (negative, trace, 1+, 2+, and 3+).

Results: 5512 were screened; 53% were Black, 55% and 26% had HTN and DM, respectively. 8% had > trace proteinuria, among whom 92% were unaware of a kidney problem, and 50% fell below the NC poverty line. 18% reported not having a regular physician or not seeing a provider for >1 year (Figure); and although younger, reported a worrisome presence of DM (13%) and HTN (30%), with 45% reporting no health insurance and 20% Hispanic.

Conclusions: NC is the 9th largest state; 40% rural. It is abysmal that nearly 1-in-5 screened reported no regular medical care despite having common CKD risk factors. Community medical resources in rural NC were unavailable or under-utilized. Obviating financial and language barriers is critical to connect this high-risk group to chronic disease care.

Figure

Characteristics % or as noted	No Regular physician or Last visit > 1 year (N=929) (18%) *	Saw Regular physician in < 1 year (N=4298) (82%) *
Mean Age (SD)	47 (15.2)	59 (15.5)
Race/Ethnicity**		
Black	49%	55%
Hispanic	20%	3%
Female gender	59%	76%
Less than high school education	25%	16%
Income (<40,000 annually)	78%	65%
DM	13%	30%
HTN	30%	62%
History of kidney disease	3%	4%
> Trace proteinuria	7%	8%
BMI (Mean, Std Dev.)	29.4 (7)	30.8 (7)
Smoked 100 cigarettes	37%	37%
No Health Insurance	45%	10%

*<5% missing except for income (6%); table excludes missing values; **mutually exclusive groups with the remaining participants predominantly White non-Hispanics.

Figure

SA-PO853

Physician Practice Characteristics Associated with Quality of CKD Care

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Background: Improving the quality of CKD care has important implications for delaying disease progression and preventing ESKD. Understanding physician practice characteristics associated with high quality CKD care is critical to provide insight into effective care delivery for CKD.

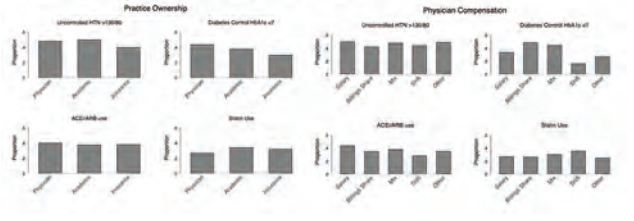
Methods: We performed a serial cross-sectional study of visits to office-based ambulatory care practices for adults with diagnosed CKD using National Ambulatory Medical Care Survey data. Our predictors were physician practice characteristics: geographic region, metropolitan area, solo practice, type of specialty, practice ownership, employment status, and physician compensation. Outcomes were quality indicators: 1) uncontrolled hypertension; 2) uncontrolled diabetes; 3) ACEi/ARB use; and 4) statin use if age ≥50. Using multivariable logistic regression, we determined the association of physician practice characteristics with quality indicators, adjusting for patient age, sex, race, and comorbidities (hypertension, diabetes, congestive heart failure, and coronary artery disease).

Results: In 2006-2014, there were 9554 unweighted visits for CKD patients representing 232,899,670 weighted visits. Patients seen in medical specialty vs. primary care had nearly 2-fold odds of uncontrolled diabetes (95% CI: 1.11–2.86). Patients in metropolitan vs. non-metropolitan areas had higher use of ACEi/ARBs (41% vs. 33%, p=0.021), but there was no statistically significant association in adjusted analyses. CKD patients aged ≥50 seen in non-solo vs. solo practice had lower odds of statin use (aOR=0.81; 95% CI 0.66–0.99). Those seen in practices owned by insurance companies or health plans had 1.5-fold odds of statin use (95% CI 1.03–2.08), compared with practices with other ownership. Practice characteristics were otherwise not associated with CKD quality indicators.

Conclusions: In a nationally representative subset of outpatient visits for patients with diagnosed CKD, we found that few physician practice characteristics were associated with CKD quality indicators. Further studies are needed to determine optimal care delivery models based on practice-level characteristics.

Funding: NIDDK Support

Figure 1. CKD Quality Indicator Performance by Select Physician Practice Characteristics (unadjusted).



SA-PO854

Utilising Mobile and Web-Based Technology for Capturing Patient-Specific Information: Methods from the DISCOVER CKD Program

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Background: Chronic kidney disease (CKD) is a global health problem associated with cardiovascular complications, impaired health-related quality of life (HRQoL) and high mortality. New ways of capturing patient experiences and burden of disease in settings outside of the clinic through mobile or web-based technology are becoming more widely used, but not within CKD real-world data.

Methods: DISCOVER CKD is an enriched hybrid observational study utilising a novel cloud-based IT platform to integrate retrospective and prospective data from patients with estimated glomerular filtration rate (eGFR) <75 ml/min/1.73 m² through to end stage kidney disease from the UK, US, Italy, Denmark, Sweden, China and Japan. Prospective data will be captured over a 3-year period from >1,000 CKD patients. Data collected by validated instruments including HRQoL (SF-36), physical activity (RAPA), work productivity (WPAI), diet (food diary), and other patient-reported outcomes will be captured in a bespoke mobile/web-based application to be completed by the patient before, during or after their routine clinical visit. The application will be available, validated and user-tested in multiple languages.

Results: Capturing patient-reported information outside of the clinic setting provides an innovative patient-centric approach for understanding the burden and journey of CKD from a patients' perspective. Initial results are anticipated in 2020.

Conclusions: Utilising mobile/web-based technology to collect patient experiences has the potential to increase the understanding of a disease, with easier communication, minimising burden of data collection in the clinic from a patient, physician and eCRF perspective while improving the consistency and validity of data that patients enter.

Funding: Commercial Support - AstraZeneca

SA-PO855

Where Patients Get Their CKD Information: Perceptions Vary by Individual Demographics

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Background: Patient education is a critical first step in the pathway to improved outcomes. Little data is available about sources of CKD information that patients perceive as most useful, and whether perceptions vary with patient characteristics.

Methods: Adults with CKD Stages 1-5 were enrolled in a cross-sectional survey. Eleven questions assessed patient ratings (1=not at all helpful to 5=extremely helpful) of specific sources of kidney information (e.g. healthcare providers, peer mentors, internet). Patients also answered questions about their perceptions of communication by providers and how well they thought providers communicate with each other (0=do not communicate at all to 4=outstanding communication). Associations between patient demographics and summarized patient ratings were examined using linear regression.

Results: 245 patients enrolled with a mean age of 60 years, mean eGFR of 34 mL/min/1.73m², 49% were men, 80% White, 15% African American, 5% other and/or multiple races. Summarized patient ratings for each source of kidney information were: Kidney doctors (mean 4.7, SD 0.9), PCPs (3.4, 1.5), nurses (2.8, 1.9), dieticians (2.6, 2.1), Internet (2.2, 1.8), handouts/brochures (1.8, 1.6), social workers (1.6, 1.9), family/friends (1.2, 1.7), classes (1.1, 1.7), news (0.9, 1.2), peer mentoring (0.7, 1.3). Most patients reported it was NOT difficult to talk with their doctors about CKD (213, 92%), and rated overall communication fair (mean 2.9, SD 1.1). In analyses adjusted for age, sex, race, education, income, and eGFR the following were significantly associated with summarized patient ratings: 1. Women rated kidney doctors higher compared to men (β 0.26, p=0.03), higher eGFR predicted lower ratings for dieticians (-0.02, 0.01), higher income predicted lower ratings for social workers (-0.20, 0.01), Nonwhite race predicted higher ratings for family/friends (0.78, <0.01) for brochures/handouts (0.36, 0.02) and a trend for peer mentors (0.26, 0.07), older age predicted lower ratings (-0.03, <0.01) and more education higher ratings (0.20, 0.03) for Internet.

Conclusions: Patient perceptions about the usefulness of kidney information from different sources vary significantly by patient demographics. More work is needed to explore reasons for, and interventions to improve, disparities in these perceptions.

Funding: NIDDK Support

SA-PO856

No Independent Relationship Between Socioeconomic Status and CKD Progression in South Korea: Results from the KNOW-CKD Cohort

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Background: Socioeconomic status (SES) has long been conjectured to be associated with the incidence and progression of chronic kidney disease (CKD). However, prospective studies from Asian data for impact of SES on renal progression were less. We revealed the association between SES and renal progression in CKD patients especially in South Korea where medical insurance is well established.

Methods: Data were collected from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD, NCT01630486 at http://www.clinicaltrials.gov). SES was characterized based on monthly income which was divided into three strata; ≥$4,500, $1,500-4,000, <$1,500. Patients who underwent baseline tests but did not have follow-up visits thereafter or who did not respond to questionnaires regarding SES were excluded. The outcome was a composite of estimated glomerular filtration rate (eGFR) halving or the onset of end-stage renal disease (ESRD). ESRD was defined as the initiation of maintenance dialysis or kidney transplantation. Cox or time-dependent cox regression analysis were conducted as appropriate. Age, sex, cause of CKD, baseline eGFR by CKD-EPI (cr) equation, hemoglobin, albumin, uric acid, calcium, phosphorus, mean blood pressure, 24hr sodium intake calculated by 24hr urine sodium was included as covariates in multivariable analysis.

Results: Total 1,732 patients were enrolled in this study. Mean age was 52.9 ± 12.0 years and 61.5% were men. Higher monthly income was associated with higher educational attainment (*P* for trend <0.001). There is an incremental tendency of CKD progression according to lower monthly income level ($1,500 to $4,500, adjusted hazard ratio [HR] 1.55, 95% confidence interval [CI] 0.86-2.77, *P*=0.144; <$1,500, adjusted HR 1.75, 95%

CI 0.93-3.29, *P*=0.080; ≥$4,500 group as reference), but the statistical significance was not observed, event after the subgroup analysis according to age ≥ 50 years or below.

Conclusions: In the Korean CKD population, there is no definite association between SES classified by monthly income level and renal progression. We speculate that this is because health care accessibility is high regardless of the SES in Korea due to Korean National Health Insurance Service. Further studies are needed to confirm this phenomenon.

Funding: Government Support - Non-U.S.

SA-PO857

Development and Initial Analysis of a Nationwide Multicenter Electronic Health Record Database of CKD in Japan (J-CKD-DB)

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Background: Chronic kidney disease (CKD) is not only a precursor of end stage renal disease but also a strong risk factor for various adverse outcomes like cardiovascular disease and dementia. To collect clinical data from CKD patients in Japan, the Japanese Society of Nephrology in collaboration with the Japan Association for Medical Informatics has embarked on the Japan Chronic Kidney Disease Database (J-CKD-DB) project.

Methods: J-CKD-DB is a large-scale, nation-wide registry based on electronic health record (EHR) data from university hospitals in Japan. Using a standardized exchangeable information storage (the Standardized Structured Medical Information eXchange 2), J-CKD-DB succeeded to efficiently compile clinical data of CKD patients across hospitals despite their different EHR systems. CKD was defined as dipstick proteinuria ≥1+ and/or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 based on both out- and inpatient laboratory data.

Results: As an initial analysis, we analyzed 40,409 CKD outpatients from 7 university hospitals and observed that majority of them were older than 65 years old, with the most prevalent age category 70-79 years in both sexes. Median age was 71 years (IQI 62–79), 54.8% were men, median eGFR was 50.2 mL/min/1.73 m^2 (42.6–57.5). The number of patients with a CKD stage G1, G2, G3a, G3b, G4 and G5 were 929 (2.3%), 3,972 (9.8%), 23,333 (57.7%), 8,357 (20.7%), 2,710 (6.7%) and 1,108 (2.7%), respectively. Although proteinuria data were available in 19,725 cases (48.8%) of all patients, the number of patients with a CKD stage A1 [dipstick proteinuria (-)], A2 [dipstick proteinuria (±)], and A3 [dipstick proteinuria ≥1+] were 10,360 (52.5%), 3,049 (15.5%) and 6,316 (32.0%), respectively. Younger CKD patients in J-CKD-DB tended to be at more advanced stages than older patients.

Conclusions: In the present study, we have constructed the J-CKD-DB which is a comprehensive nationwide CKD database. This registry will be a platform for a number of analyses, for example, mortality and morbidity risk, by clinical diagnoses, lab data, or medication data and may be able to fill important knowledge gaps surrounding CKD care.

Funding: Government Support - Non-U.S.

SA-PO858

Detecting Lifestyle Risk Factors for CKD with Comorbidities: An Association Rule-Mining Analysis

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Background: The rise in the number of patients with chronic kidney disease (CKD) and consequent end-stage renal disease (ESRD) necessitating renal replacement therapy has placed significant strain upon healthcare. The burden of CKD is substantial. According to WHO global health estimates, 864,226 deaths (or 1.5% of deaths worldwide) were attributable to this condition in 2012. The rate of progression of CKD is influenced by both modifiable and unmodifiable risk factors. Identification of modifiable risk factors such as lifestyle choices has been vital in informing strategies towards renoprotection as modification of unhealthy lifestyle choices lessens the risk of CKD progression and associated comorbidities. However, the lifestyle risk factors and modification strategies may vary due to different comorbidities and studies on suitable lifestyle interventions for CKD patients with comorbidities are sparse.

Methods: We applied ARM to identify lifestyle risk factors for CKD progression with comorbidities using questionnaire data for 450,000 participants collected from the Behavioral Risk Factor Surveillance System (BRFSS) 2017, a web-based resource, including demographic information, chronic health conditions, fruit and vegetable consumption, sugar or salt-related behavior, among others. To enrich the BRFSS questionnaire, the Semantic Medline Database (SemMedDB) was also mined to identify lifestyle risk factors.

Results: The results suggest that the lifestyle modification of CKD varies among different comorbidities. For example, the lifestyle modification of CKD with cardiovascular disease (CVD) needs to focus on increasing aerobic capacity by improving muscle strength or functional ability. For CKD patients with chronic pulmonary disease (CPD) or rheumatoid arthritis (RA), lifestyle modification should be high dietary fiber intake and participation in moderate-intensity exercise. Meanwhile, the management of CKD patients with diabetes focuses on exercise and weight loss predominantly.

Conclusions: We have demonstrated the use of ARM to identify lifestyle risk factors for CKD with common comorbid chronic conditions using data from BRFSS 2017. Our methods can be generalized to advance chronic disease management with more focused and optimized lifestyle modification of NCDs.

Funding: Government Support - Non-U.S.

SA-PO859

Quality of CKD Management in the Canadian Primary Care System

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Background: Although patients with chronic kidney disease (CKD) in Canada are routinely managed in primary care settings, no nationally representative study has assessed the quality of CKD care received by these patients. We evaluated the current state of CKD management in Canadian primary care practices leveraging guideline-concordant quality of metrics.

Methods: This cross-sectional study leveraged electronic medical record data from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) from 2010–2015. We examined the proportion of CKD patients meeting a set of 12 quality indicators in six domains: (a) detection and recognition of CKD, (b) testing and monitoring of kidney function, (c) use of recommended medications, (d) appropriate monitoring after initiation of ACEIs/ARBs, (e) management of blood pressure, and (e) glycemic control in patients with CKD. We also analyzed predictors of divergence from these quality indicators.

Results: The baseline cohort comprised 46,162 patients with CKD Stages 3–5 (defined as those with at least two eGFR measurements < 60mL/min/1.73m^2 within a period of at least three months, but not more than 18 months apart). Results show that only four out of 12 quality indicators were met by ≥ 75% of the study cohort: one in the testing and monitoring of kidney function domain (i.e., follow-up serum creatinine measurements), two in the blood pressure management domain, and one in the glycemic control domain. Indicators in the domains of detection and recognition of CKD, testing and monitoring of kidney function (specifically, urine albumin creatinine ratio [UACR] testing), use of recommended medications, and appropriate monitoring after initiation of ACEIs/ARBs were not met. Only 18.4% of patients with CKD received a urine albumin test within six months of their qualifying eGFR measurement and 39.4% had a second measurement within six months of an abnormal baseline urine test (UACR > 2.5mg/mmol).

Conclusions: Management of CKD in primary care settings varies according to quality indicator. Over 75% of patients with CKD received quality-concordant (or guideline concordant) testing and monitoring of kidney function, and achieved blood pressure and glycemic control. Prevalence of albuminuria detection and use of recommendation medications were much lower. These findings reveal priority areas for quality improvement initiatives in primary care.

SA-PO860

An Innovative, Community-Based Screening Strategy Identifies High Rates of Advanced CKD in Asymptomatic Individuals Living in a Low-Income, Largely African-American Community

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Background: The USRDS most recently (2018) reported a statistically significant increasing prevalence of more advanced stages (3-5) of chronic kidney disease (CKD). Individuals with early CKD are generally asymptomatic and so remain largely unidentified until presenting to health systems with symptomatic, far advanced, CKD at which time kidney-protective interventions offer limited benefit to delay progression to end-stage kidney disease. Reducing prevalence of advanced CKD must include proactive screening to identify asymptomatic individuals with early CKD while in their routine living environments.

Methods: As part of a grant (R21DK113440) we tested an innovative screening strategy to identify asymptomatic individuals with CKD through community-level screening in settings trusted by community members including churches, community-based organizations, and community events in low-income, largely African American communities that studies show to be at high CKD risk. We met with these community-based organizations to describe our study testing the effectiveness of education regarding preparation of provided fruits and vegetables compared to providing the fruits and vegetables alone. We then dispatched the screening team to those that agreed to allow dipstick measurements of urine albumin concentration (Ualb).

Results: To date, we screened 282 participants, finding 83% (N= 234) with albumin > 30 mg/l, the level designated as "positive". The first 55 individuals who completed measures had mean (SD) age of 55.4 (11.1) years, 30.9% were male, and had mean eGFR (CKD-EPI creatinine-based) of 50.3 (13.2) ml/min/1.73m^2 with 0% CKD 1, 20% CKD 2, 76% CKD 3a/b, and 2% CKD 4. This proportion of measured participants with CKD stage 3 was much higher than anticipated based on NHANES 2001 – 2016 data (~47%).

Conclusions: This innovative screening strategy found high rates of both albuminuria and subnormal eGFR in asymptomatic individuals living in communities at high CKD risk through leveraging trusted community organizations. The strategy should be explored further to identify asymptomatic individuals with early CKD who are candidates for kidney protective interventions designed to reduce the increasing prevalence of advanced stages of CKD.

Funding: NIDDK Support

SA-PO861

Urine Testing of Community Residents in a Region of Nicaragua with a High Burden of Mesoamerican Nephropathy Reveals That Background Systemic Inflammatory Signs Rapidly Increase in Younger Ages

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Background: A large and ongoing epidemic of kidney disease of unknown etiology affects the rural poor from Mexico to Panama and has resulted in greater than 50,000 deaths. Mesoamerican nephropathy (MeN) is a devastating and rapidly progressing disease that affects primarily young agriculture workers who are otherwise healthy and lack traditional risk factors for kidney disease. Very little is known about renal function in the community-at-large, especially among children.

Methods: Urine specimens were collected from individuals of all ages at health fairs in 4 rural, agricultural communities in the Pacific lowland areas of Nicaragua, a region heavily affected by MeN and where morbidity and mortality due to the epidemic has more than quadrupled since its emergence. Semi-quantitative dipstick and microscopic analysis were performed on fresh specimens. We generated descriptive statistics and tested for differences by age and community by Chi-squared and ANOVA in Stata 15.

Results: Urine from 471 community residents, ages 3 months to 89 years (median 21 years) were analyzed. Almost all individuals (99%) were shedding leukocytes, many (21%) with >5 per field. Renal cell shedding (11%), hematuria (13.4%) were also noted. Proteinuria was rare (3.2%). Hematuria and leukocyturia varied by locale ($p<0.05$). Leukocyturia was more common in adults than children ($p<0.05$). Leukocyturia increased with age, which was driven by the age group 12-33 years.

Conclusions: In this community-based sample, clinical urine specimens indicate an underlying prevalence of markers of impaired renal function. These markers increase in adolescence and young adulthood. Further investigations into MeN should target populations other than agricultural workers and should specifically look at renal function in children. Geographic differences in clinical indicators may also point to the highest risk communities.

SA-PO862

CKD Detection Might Benefit from an Ethnic-Specific Screening Approach: Results from the HELIUS Study

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Background: Screening for chronic kidney disease (CKD) is currently recommended for patients with a history of diabetes mellitus, hypertension or cardiovascular disease (CVD). This approach may not identify all individuals with CKD. Ethnicity, age and socio-economic status (SES) have been described to affect CKD risk and these factors may influence CKD detection in the general population. We studied whether the addition of criteria for age and socio-economic status may improve CKD detection in a multiethnic population.

Methods: Baseline data from the HELIUS study, a multiethnic cohort study conducted in the city of Amsterdam, were used. Analyses were conducted among 21,617 partcipants (mean age 44 years, 43% male) of Dutch (n=4564), South-Asian Surinamese (n=3043), African Surinamese (n=4151), Ghanaian (n=2339), Moroccan (n=3614) and Turkish (n=3906) ethnic origin. Detection success of three screening approaches was investigated in each ethnic group. Respectively, approaches I, II and III consisted of the traditional approach (i.e, screening when a history of diabetes mellitus, hypertension or CVD was present); the traditional approach combined with age >50 yr; and the traditional approach combined with low SES (i.e, none or elementary schooling only). We defined CKD as eGFR (CKD-EPI formula, < 60ml/min/1.73m^2) or albuminuria (A2/A3).

Results: In our cohort, 2284 (10.6%) participants had CKD. Overall, compared to approach I, approach II increased detection success with 6.7% and approach III with 6.3%. Detection success of approach I among the ethnic groups varied from 38.8 to 70.3%. Detection improvement by using approach II and III showed ethnic specific differences. In participants of Dutch origin, approach II significantly increased the detection rate with 15.1%, while in participants of Turkish and Moroccan origin approach III significantly increased detection rates (8.9 and 14.1%, respectively).

Conclusions: Addition of age and SES criteria to the currently advised screening approach results in higher CKD detection. This improvement varies among ethnic groups. Addition of an age criteria improved detection in Dutch participants, while adding a SES criterium improved detection in Turkish and Moroccan participants. Our results may prompt for development of a different set of CKD screening criteria in a multiethnic population.

SA-PO863

The Association of Physical Activity with Poor Health Outcomes in Patients with Advanced CKD

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Background: Chronic kidney disease (CKD) disproportionately affects older adults, and is known to be associated with low physical activity levels. In the general population, low physical activity level is associated with an increased risk of all-cause mortality and other adverse outcomes. This association also exists in patients with moderate CKD and those on dialysis; however this has yet to be explored in patients with advanced CKD (G4-G5). The primary aims of this study were to determine the association of physical activity level with all-cause mortality, as well as the assocation with progression to dialysis and future fall risk in patients with advanced CKD.

Methods: Individuals with advanced CKD (G4-G5) were identified from the CanFIT cohort, a multicenter, prospective study of frailty, between October 2012 and July 2018 (n=592). Self-reported physical activity was assessed at baseline by the Physical Activity Scale for the Elderly (PASE). PASE scores were stratified by tertiles (0-40 (Low Activity); 41-90 (Light Activity); >90 (Moderate-High activity). Baseline clinical characteristics and comorbidities were obtained through chart review. Our primary outcome of all-cause mortality and secondary outcome of progression to dialysis were analyzed using Cox proportional hazard models. Logistic regression was performed for our secondary outcome of future fall risk.

Results: We had 121 participants die during the study (mean follow-up 1193 days) and 215 participants progressed to dialysis (mean follow-up 896 days). Compared with low physical activity level, higher levels of physical activity were associated with a reduction in all-cause mortality (HR 0.56 [95% CI: 0.33-0.94]) when adjusted for age, sex, and comorbidities. Of 472 participants with follow-up assessing falls, 131 (28%) had a fall event. Level of baseline physical activity did not predict progression to dialysis or future falls.

Conclusions: In advanced CKD, higher levels of physical activity were associated with a 50% reduction in all-cause mortality. Although progression to dailysis and future fall risk were not associated with baseline physical activity level, the impact in the change of physical activity level on these outcomes requires further investigation.

SA-PO864

Automated Urinary Albumin Creatinine Testing in Stage 3 CKD and Effect on Prescriptions of ACE Inhibitors and ARBs

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Background: Kidney Disease Improving Global Outcomes recommends assessing for albuminuria annually in patients with chronic kidney disease (CKD). Despite this recommendation, many patients with CKD do not undergo annual testing for albuminuria. We were interested in whether automated testing in CKD for annual urinary albumin creatine (ACR) testing improved ACR testing and prescribing of ACE inhibitors and ARBs.

Methods: We defined a CKD 3 cohort registry in April 2018 in Kaiser Permanente Northwest. We compared ACR testing and filled ACE inhibitor and ARB prescriptions in the year before and after April 2018 after implementing a quality improvement project targeting patients with stage 3 CKD based on eGFR criteria or ICD-10 codes. A web-based tool examined the registry and ordered an ACR in those patients that did not have an ACR checked within the past year. In those patients not on an ACE inhibitor or ARB who had a renal indication, primary care providers received an alert in the electronic health record (EHR) which recommended initiation. Renal indications for an ACE inhibitor or ARB were hypertension and an ACR > 30 mg/g with diabetes mellitus (DM) or an ACR > 300 mg/g without DM.

Results: There were 11,229 patients in the initial CKD registry with index date of April 2018. Average age was 72.7 years, 37.4% had DM, 79.4% had hypertension, and mean eGFR was 46.8 ml/min. One year after implementation of annual ACR testing, the registry decreased to 10,934. Average age was 73 years, 37.1% had DM, 79.4% had hypertension, and mean eGFR was 47.4 ml/min. One year after implementation of ACR testing, rate of ACR testing increased from 25.1% to 83% ($p < 0.001$). In patients with renal indication, ACE inhibitor or ARB use increased from 77.4% to 80.2% but was not significant ($p = 0.07$). Maximum dose ACE inhibitors or ARB use increased from 26.8% to 32.1% ($p = 0.02$) in patients with A3 grade albuminuria and hypertension.

Conclusions: In patients with stage 3 CKD, a population-based tool that automated testing of ACR linked with EHR alerts resulted in a significant increase in ACR testing but did not result in a significant increase in ACE inhibitor or ARB prescriptions in patients who had a renal indication. However, prescribing of maximum dose ACE inhibitors or ARBs did increase in patients with A3 grade albuminuria and hypertension.

SA-PO865

The Effects of a Participatory Structured Group Educational Program on the Development of CKD: A Population-Based Study

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Background: The type of lifestyle guidance that is effective for preventing development of chronic kidney disease (CKD) is unknown. Here, we aim to investigate the effects of a participatory structured group education (SGE) program on the development of CKD in a population-based study.

Methods: We retrospectively analyzed 1,060 adult special health check-up examinees with CKD. Examinees with an estimated glomerular filtration rate (eGFR) from 50 to 60 mL/min/1.73 m^2 and/or proteinuria 1+ were encouraged to attend an SGE program.

The SGE program included participatory small group discussions on the attendees' remaining risk factors. The primary outcome of this study was the change in eGFR per year.

Results: The changes in eGFR in examinees who attended the SGE program (n = 209, +2.9 mL/min/1.73 m^2/year [95% confidence interval (CI) +1.9–+3.9]) significantly improved compared with control (n = 383, +1.2 mL/min/1.73 m^2/year [95%CI +0.5–+1.9], p = 0.006). Attending an SGE program was independently and positively related to the changes in eGFR at 1 year after attendance, after adjusting for classical covariates (β = 1.55 [95%CI 0.37–2.73], p = 0.01). In subgroup analysis, attending an SGE program was effective for the examinees with a lower eGFR compared with those with only proteinuria.

Conclusions: Our SGE program showed the beneficial effects of preventing the development of CKD, independent of classical factors. The type of SGE program that is more effective for preventing development of CKD should be investigated in a long-term analysis.

SA-PO866

CKD Awareness Among US Adults by Future Risk of ESKD, 1999-2016

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Background: Individuals with chronic kidney disease (CKD) are often unaware of their disease. Efforts to improve CKD awareness would have the most benefit if focused on individuals at highest risk of progression to end-stage kidney disease (ESKD). Therefore, we examined CKD awareness by future risk of ESKD in a representative sample of US adults.

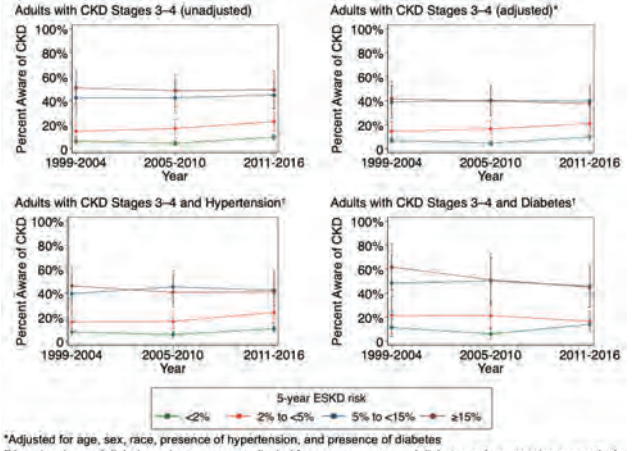
Methods: We assessed the prevalence of CKD awareness among non-pregnant adults (≥ 20 years) with CKD stages 3-4 who participated in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2016 (n=3,668). CKD awareness was defined by a "yes" answer to the question, "Have you ever been told by a doctor or other health professional that you had weak or failing kidneys?". The 5-year probability for ESKD was estimated by the 4-variable Kidney Failure Risk Equation. ESKD risk was categorized as minimal (<2%), low (2% to <5%), intermediate (5% to <15%), or high (≥15%). Unadjusted and adjusted trends in prevalence of CKD awareness by ESKD risk group were computed using logistic regression with complex sample survey methods.

Results: Unadjusted CKD awareness was less than 10% among adults with minimal risk and was higher in the intermediate and high ESKD risk groups (approximately 45% and 50%, respectively). CKD awareness within each risk group was stable over time. Similar results were obtained when adjusted for age, sex, race, hypertension status, and diabetes status, and when analysis was limited to the subgroup with hypertension (Figure). Among adults with diabetes, awareness within each risk group was greater but was also stable over time.

Conclusions: Among adults with CKD stages 3–4 with over 15% 5-year risk of ESKD, approximately half were unaware of having kidney disease. CKD awareness was stable over time, demonstrating the need for intensified efforts to increase CKD awareness.

Funding: NIDDK Support, Other U.S. Government Support

Figure: CKD awareness among adults with CKD stages 3-4 by 5-year ESKD risk



*Adjusted for age, sex, race, presence of hypertension, and presence of diabetes
†Hypertension and diabetes subgroups were adjusted for age, sex, race, and diabetes or hypertension respectively.
CKD = chronic kidney disease; ESKD = end-stage kidney disease

SA-PO867

Technology Use, Interest in Mobile Health Technology, and eHealth Literacy in CKD

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Background: Mobile health (mHealth) technologies improve patient-provider communication and increase information accessibility. eHealth literacy is needed to effectively find and appraise health information from electronic sources. Using a mixed methods approach, we assessed technology use, mHealth interest, and eHealth literacy among those with CKD.

Methods: We utilized data from Chronic Renal Insufficiency Cohort Study participants who completed a technology survey (N=424) and an eHealth Literacy Scale (eHEALS) (N=633). We report technology use (Internet/email/smartphone), interest in mHealth (Internet/email/ smartphones/mHealth applications [apps]), and level of eHealth literacy, determined by the eHEALS score. We examined the association of participant characteristics with technology use, mHealth interest, and eHealth literacy by estimating prevalence ratios (PRs) and 95% confidence intervals (CI). We conducted a thematic content analysis of open-ended survey responses to augment the quantitative findings.

Results: Study participants (N=932): mean age 68 years, 59% male, mean eGFR 54 ml/min/1.73^2. About 70% currently use Internet/email/smartphones; only 27% had adequate eHealth literacy (eHEALS score ≥32). Participants <65 years (vs. older), of White (vs. non-White) race, and with high school education (vs. lower) had more Internet/ email use. Those of non-White (vs. White) race had more interest in mHealth apps (see **Table** for more results). Three themes emerged from the content analysis: opposing views on using mHealth, concerns about losing the patient-provider face-to-face interaction, and barriers to mHealth use.

Conclusions: Many people with CKD currently use and are interested in mHealth, but few have adequate eHealth literacy. Leveraging mHealth represents a potential opportunity to engage individuals with CKD, especially minorities since they had more interest in mHealth apps, compared to non-minorities.

Funding: NIDDK Support

Patient Characteristics and Technology Use, Interest, and eHealth Literacy. Prevalence ratios (PR) and 95% CI reported.

	Internet/Email Current Use	Smartphone Current Use	Interest in Internet/Email/Smartphone Use	Interest in mHealth application Use	Adequate eHealth Literacy
Age ≥65 vs <65 years	0.68 (0.64-0.72)	0.61 (0.57-0.65)	0.74 (0.69-0.79)	0.95 (0.87-1.03)	0.56 (0.69-0.79)
White vs. Non-White race	1.28 (1.19-1.38)	0.99 (0.91-1.07)	1.16 (1.06-1.28)	0.82 (0.75-0.90)	1.25 (0.97-1.62)
High school or more vs. Less than	2.69 (2.09-3.45)	1.60 (1.33-1.92)	1.96 (1.43-2.69)	1.02 (0.92-1.14)	4.11 (2.16-7.79)

SA-PO868

The Role of Renal Pharmacists in the Management of Patients with Renal Conditions

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Background: The review of the renal pharmacist role in assisting in the management of CKD is not clear. Our review is the first evaluation in the United States that tests the renal pharmacist as part of the interdisciplinary team in the management of patients with renal conditions.

Methods: This retrospective study assessed the clinical outcomes after the intervention of our renal pharmacist in the Nephrology clinic at the Miami VA Medical Center. The patients were initially evaluated in the outpatient clinic by the nephrologist and the renal pharmacist; medications were changed to decrease the progression of CKD, for the management of hypertension (HTN), immunosuppression and CKD complications. The renal pharmacist followed the patients according to the changes in medical care.

Results: Fifty-six patients were assigned to the renal pharmacist in a 3-month period. Fifty patients (89%) were male; six patients (11%) were female. In 20 patients (35.7%) that had CKD III, HTN, and proteinuria, ACEIs or ARBs were started with close monitoring of the renal function, electrolytes, and proteinuria. In 10 patients (17.9%) that had uncontrolled HTN and CKD, BP medications were added and adjusted. In 9 patients (16.1%) that had a kidney transplant, tacrolimus dosages needed modification to achieve levels. In 15 patients (26.7%) that had CKD IV and V with anemia, erythropoietin stimulating agent dose was adjusted to reach appropriate hemoglobin (HB) levels. In 2 patients (3.6%) that had hypomagnesemia, magnesium supplements and amiloride were added to their medication regimen with close follow up of electrolytes and renal function. The interventions that were made in the 56 patients were successful (Proteinuria decreased, BP was controlled, tacrolimus levels achieved goal, HB levels reached goal), and patient adherence increased

Conclusions: The intervention from renal pharmacists has improved the quality of care in our patients not just by close monitoring of potential adverse effects from therapies, but also by improving BP goals, electrolyte management, and medication adherence. These changes may reduce the progression of CKD, improve cardiovascular outcomes, lower hospital admissions, and decrease the risk of death.

SA-PO869

Screening and Recognition of CKD in Primary Care Clinics in the VA Health Care System and Its Impact on Delivery of Care

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Background: The successful implementation of interventions targeted to improve kidney disease outcomes requires early identification of CKD. Early identification involves screening at-risk population as well as recognizing CKD. We determined CKD screening and recognition rate in at-risk veterans enrolled in Vertically Integrated Service Network (VISN) 17, and evaluated the impact of CKD awareness on processes of care.

Methods: We interrogated VISN 17 corporate Data Warehouse for Veterans seen at least twice in primary clinics with ICD-9 codes for hypertension (HTN) and diabetes (DM). The final cohort of 220,229 subjects (55.6% HTN, 6% diabetes and 38.4% both) was examined for serum creatinine/eGFR reported at least twice 90 days apart, urine protein and ICD-9 for CKD. Presence of CKD was defined as eGFR <60ml/min at least twice 90 days apart and/or urine albumin creatinine ratio (uACR) of >30 mg/g. BP readings from last two visits were averaged to evaluate HTN control. Prescription rate for statins and non-steroidal anti-inflammatory agents (NSAIDs) were assessed.

Results: Overall, 173,966 (79%) patients had one or other screening procedure done. Patients with isolated hypertension were less likely to have any screening procedure (72.8%) as compared to DM (81.1%) or both conditions (87.6%). Only 40.3% of total patients had urine protein in the chart, worse in HTN (18.3%) compared to DM (62.6%) or both (68.5%). Of 173,966 patients, 73,965 (42.5%) had lab evidence of CKD. However, only 19,317 (26.1%) did have a documented ICD-9 CKD diagnosis. Many of these unrecognized CKD patients (30.5%) had CKD based on uACR criteria. There was no clinically significant difference between recognized vs. unrecognized CKD groups in terms of age, sex and race. Moreover, blood pressure control and statin prescription rate were also not different. Of note, patients with BP >140/90 mmHg consistently had high rates of uACR >300 mg/g irrespective of CKD documentation. Diuretics prescription was higher (66.7% vs 58%) and NSAIDs was lower (11.4% vs. 22.9%) in documented vs undocumented CKD groups.

Conclusions: While overall CKD screening rate was 79%, identification of albuminuria was suboptimal and despite screening procedures the recognition of CKD was low in VISN 17 population with HTN and DM. Early awareness of CKD may improve processes of care.

Funding: Veterans Affairs Support

SA-PO870

Renal, Cardiac, and Safety-Related Events with Alpha Blockers in Patients with CKD

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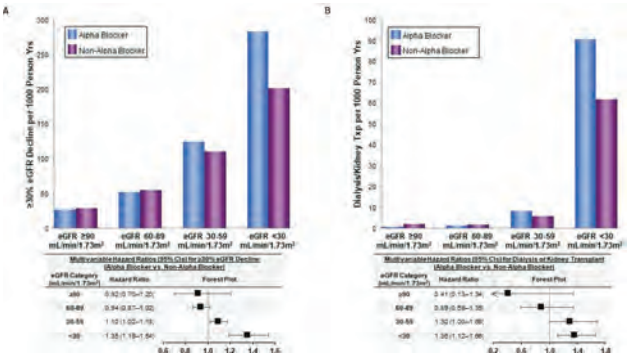
Background: Alpha-blockers (ABs) are commonly prescribed as add-on therapy for blood pressure (BP) control in patients with and without chronic kidney disease (CKD). However, the association between AB use and renal, cardiac, mortality, and safety-related outcomes by CKD stage remains unknown.

Methods: Population-based, retrospective cohort study of Ontario (Canada) residents ≥66 years old with a diagnosis of hypertension from 2007 to 2015. Patients newly prescribed an AB (doxazosin, terazosin, prazosin) were matched to patients newly prescribed a non-AB BP-lowering medication using a high dimensional propensity score. Cox proportional hazards models examined the association of AB use with renal (≥30% eGFR decline, need for renal replacement therapy [RRT]), cardiac, mortality, and safety (hypotension, syncope, falls, fractures) outcomes compared to AB non-use by baseline eGFR categories (≥90, 60-89, 30-59, <30 mL/min/1.73m^2).

Results: From 329,799 eligible patients, 18,460 were dispensed ABs and matched 1:1 to non-AB users. Among patients with CKD, AB use was associated with a higher risk of the following adverse renal outcomes compared with non-AB use: (**See Figure**) ≥30% eGFR Decline: eGFR 30-59 mL/min/1.73m^2: HR 1.10 [95%CI 1.02-1.18] eGFR <30 mL/min/1.73m^2: HR 1.35 [95%CI 1.19-1.54]; p-interaction <0.001 RRT: eGFR 30-59 mL/min/1.73m^2: HR 1.30 [95%CI 1.00-1.68] eGFR <30 mL/min/1.73m^2: HR 1.36 [95%CI 1.12-1.66] There were no significant differences in cardiac, mortality, or safety-related events between AB users and non-users by CKD stage.

Conclusions: ABs are associated with a higher risk of adverse renal outcomes in patients with CKD compared with other BP-lowering medications.



Adverse Kidney Outcomes in Alpha-Blocker Users vs. Non-Users

SA-PO871

Nephrotoxin Exposure After Hospital Discharge Predicts Development of CKD Among AKI Survivors

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Background: Survivors of acute kidney injury (AKI) are at high risk of progression to chronic kidney disease (CKD). A potentially modifiable risk factor for subsequent CKD is exposure to drugs with potential nephrotoxicity. The objective of this study was to evaluate the association between the prescription of potentially nephrotoxic medications in AKI survivors at hospital discharge and the subsequent risk of new or worsening CKD, readmission with AKI or death.

Methods: We conducted a population-based cohort study of adult Olmsted County, MN residents who developed AKI while hospitalized between 1/1/2006 and 12/31/2014 using data from the Rochester Epidemiology Project (REP). The REP links medical records across care providers in Olmsted County, making population-based studies possible. The cohort included those with a hospitalization complicated by AKI who survived to discharge. Discharge medication lists, prescription records, and clinical notes were queried for prescription of potentially nephrotoxic medications over the 3 years after discharge. New or worsening CKD was identified by both diagnosis codes and calculated estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2. Cox proportional hazards models were fit to evaluate the association between exposure to potentially nephrotoxic medications and the study outcomes. A validated CKD risk prediction score was used to adjust the Cox models for the baseline risk of CKD following AKI.

Results: Among 2,894 AKI survivors, 2143 (74%) received a potentially nephrotoxic medication at discharge. Those that received these drugs experienced a significantly higher risk of new or worsening CKD during 3-years of follow-up (cumulative incidence 71% vs. 57%; HR 1.44: 95% CI 1.28, 1.63). Patients prescribed potentially nephrotoxic medications after discharge also experienced a significantly greater risk of the composite endpoint of CKD, AKI readmission, or death within 3 years of discharge (HR 1.32: 95% CI 1.20, 1.46).

Conclusions: In this population-based cohort study, we observed that AKI survivors prescribed potentially nephrotoxic medications at hospital discharge were at significantly greater risk for CKD development, AKI readmission, and death in the 3 years following hospitalization.

Funding: Private Foundation Support

SA-PO872

Baclofen and the Risk of Encephalopathy in Older Adults with CKD: A Population-Based Cohort Study

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Background: Importance: Baclofen, a popular muscle relaxant, undergoes renal clearance and can accumulate in patients with low kidney function. Over 30 case reports link baclofen use to encephalopathy in patients with chronic kidney disease (CKD). Objectives: The primary objective was to compare the 30-day risk of encephalopathy in patients with CKD newly prescribed a high vs low dose of baclofen (≥20 vs <20 mg/day). The secondary objective was to compare the risk in baclofen users vs non-users.

Methods: Design: Population-based cohort study using linked healthcare data. Setting: Ontario, Canada (2007–2018). Participants: Older adults with CKD (defined as an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 but not on dialysis). The primary cohort was restricted to new baclofen users; the secondary cohort included both new users and non-users. Exposure: Oral baclofen (≥20 mg/day vs <20 mg/day). Main Outcome and Measure: Hospital admission with encephalopathy, defined as a main diagnosis of delirium, disorientation, transient cerebral ischemic attack, alteration of awareness, or dementia. Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health. Weighted risk ratios (wRR) were obtained using modified Poisson regression and weighted risk differences (wRD) using binomial regression.

Results: The primary cohort included 15,942 patients with CKD (61% women; median age 77); 9707 (61%) patients started baclofen at ≥20 mg/day and 6235 (39%) at <20 mg/day. The primary outcome, hospital admission with encephalopathy, occurred in 108 (1.11%) patients in the high-dose group and in 26 (0.42%) patients in the low-dose group. The wRR was 3.54 (95% CI, 2.24–5.59) and the wRD was 0.80% (95% CI, 0.55%–1.04%). In subgroup analysis, the absolute risk increased progressively as eGFR declined. In patients with eGFR<30 mL/min/1.73 m^2, the wRR was 4.26 (95% CI, 1.77–10.25) and the wRD was 2.90% (95% CI, 1.30%–4.49%). In the secondary comparison with 284,263 non-users, both low-dose and high-dose users had a higher risk of encephalopathy: wRR, 5.90 (95% CI, 3.59–9.70) and 19.8 (95% CI, 14.0–28.0), respectively.

Conclusions: Baclofen should be used cautiously or avoided in patients with CKD.

Funding: Government Support - Non-U.S.

SA-PO873

Immunosuppressive Agents for Treating IgA Nephropathy: An Updated Cochrane Review

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Background: IgA nephropathy (IgAN) is the most common glomerular disease worldwide. High certainty evidence for effective interventions has been impeded because due to the rarity of patient-centred endpoints such as end-stage kidney disease (ESKD) and heterogeneity in clinical progression and disease severity. As several recent trials have reported, we updated the Cochrane review evaluating the benefits and harms of immunosuppression for the treatment of IgAN.

Methods: A Cochrane systematic review with meta-analysis was updated to include randomized controlled trials in which adult and children with biopsy-proven IgA nephropathy were randomly allocated to immunosuppressive agent versus placebo, no treatment/standard care, or other non-immunosuppressive agent. Treatment effects were estimated by random-effects meta-analysis. Evidence certainty was adjudicated using GRADE methodology.

Results: 54 studies (3730 patients) were included. Median follow-up was 24 months. Risk of bias was generally high or unclear. Steroid treatment probably prevents progression to ESKD (RR 0.41, 95% CI 0.26-0.65; moderate certainty evidence) and annual GFR loss (MD -5.40 ml/min/1.73m2, 95% CI -2.25 to -8.55; moderate certainty evidence), and may induce complete remission (RR 1.76, 95% CI 1.03-3.01; low certainty evidence). The addition of cytotoxic therapy to steroids had uncertain effects as did regimens containing mycophenolate mofetil (MMF), or calcineurin inhibitors as monotherapy on background steroid treatment. Adverse effects of treatment, especially infections, were uncertain due to a lack of data and heterogenous results in studies.

Conclusions: Steroid therapy probably prevents progression of ESKD and annual GFR loss and may induce complete remission. The effects of other treatments for treating IgA nephropathy were very uncertain and adverse events are poorly understood.

SA-PO874

Inpatient Admissions Account for the High Medical Costs of CKD

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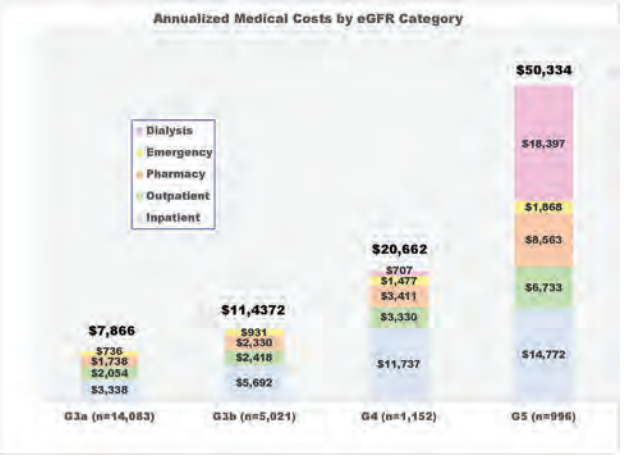
Background: Chronic kidney disease (CKD) results in high medical costs typically attributed to renal dialysis but excess costs begin to accumulate in earlier CKD stages. Better understanding of medical costs and its determinants may help to optimize patient care in resource-constrained settings. We evaluated annual medical costs in patients with CKD across types of care and in subgroups of patients with and without diabetes, cardiovascular disease, and heart failure.

Methods: We used the electronic medical records of Kaiser Permanente Northwest to identify 21,252 patients with CKD in 2016 or 2017 and examined non-mutually exclusive groups according to presence of comorbidities. We used 1 year of follow-up data to calculate the annual outpatient, inpatient, emergency, pharmaceutical, dialysis, and total medical care costs by KDIGO-defined stages of CKD adjusted for age, sex, non-white race, and within subgroups of patients with selected comorbidities.

Results: Inpatient costs accounted for 42%, 50%, 57% and 29% of total costs for stages G3a, G3b, G4, and G5, respectively (figure). Nearly 30% of all hospitalizations were CVD-related. Patients with CKD and 1 or more comorbidities incurred 2.4 to 4-fold greater medical costs than those with no comorbidities. Inpatient costs accounted for 35%-66% of the total in stages G3a, G3b and G4, and 23%-37% in stage G5.

Conclusions: Inpatient costs consistently accounted for over 40% of the total costs of care for CKD patients prior to reaching end-stage kidney disease regardless of the presence of comorbidities. Considering the significant economic burden evident in early CKD stages, development and implementation of effective measures to reduce the need for inpatient care is critical.

Funding: Commercial Support - Boehringer Ingelheim



SA-PO875

Predictors of Hyperkalemia in Patients with Advanced CKD

Ankur A. Dashputre,[1] Keiichi Sumida,[1] Praveen Kumar Potukuchi,[1] Oguz Akbilgic,[1] Suryatapa Kar,[1] Yoshitsugu Obi,[2] Fridtjof Thomas,[1] Miklos Z. Molnar,[1] Elani Streja,[3] Kamyar Kalantar-Zadeh,[4] Csaba P. Kovesdy.[1] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]University of California Irvine, Irvine, CA; [3]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [4]University of California Irvine, School of Medicine, Orange, CA.*

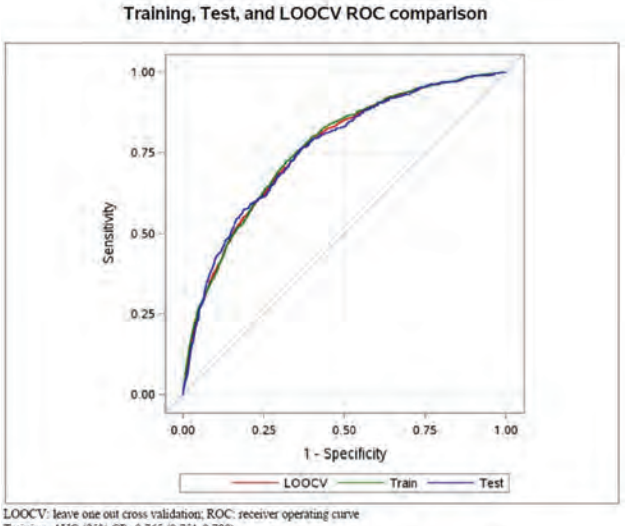
Background: Identifying predictors of hyperkalemia will help clinicians in managing patients with advanced CKD at a greater risk for future hyperkalemia events.

Methods: In 20,657 US Veterans with eGFR <30 ml/min/1.73m^2 and with ≥1 year of follow-up prior to dialysis initiation, we identified predictors of plasma potassium [K^+] >6.0 mEq/l using multivariable logistic regression models with backward-selection based on Akaike's information criterion, adjusted for demographics, comorbidities, vital signs, laboratory tests and medications. The sample was split (70%:30%) into training set (n=14,461) and test set (n=6,196). We conducted model cross validation using the leave one out cross validation method (LOOCV). We assessed model predictive discrimination using the area under the receiver-operator curve (AUC).

Results: The mean (SD) age of the patients was 67 (10) years; 98% were male, 29% were African American, with a mean (SD) baseline K^+ of 4.6 (0.6) mEq/l, and baseline eGFR of 23.6 (4.7) ml/min/1.73m^2. At least one event of [K^+] >6.0 mEq/l was experienced by 7.4% of the patients. Our final model included 16 predictor variables. The AUC (95% CI) estimates for training, test, and LOOCV were 0.765 (0.751-0.780), 0.761 (0.738-0.784), and 0.762 (0.749-0.774), respectively (Figure). Baseline K^+ (OR [95%CI], 3.09 [2.83-3.39]), baseline Na polystyrene sulphonate use (2.51 [2.16-2.93]), and age (0.97 [0.96-0.98]) were the strongest predictors of hyperkalemia.

Conclusions: We developed and tested a prediction model with good discrimination ability to identify future hyperkalemia in patients with advanced CKD. Accurate prediction of future hyperkalemia could help implement preventive measures and may have a beneficial impact on outcomes.

Funding: NIDDK Support



LOOCV: leave one out cross validation; ROC: receiver operating curve
Training, AUC (95% CI): 0.765 (0.751-0.780)
Test, AUC (95% CI): 0.761 (0.738-0.784)
LOOCV, AUC (95% CI): 0.762 (0.749-0.774)

SA-PO876

Plasma Potassium Trajectories and Associated Post-Transition Mortality in Patients with Advanced CKD Transitioning to ESRD

Ankur A. Dashputre,[1] Keiichi Sumida,[1] Praveen Kumar Potukuchi,[1] Suryatapa Kar,[1] Yoshitsugu Obi,[2] Fridtjof Thomas,[1] Miklos Z. Molnar,[1] Elani Streja,[3] Kamyar Kalantar-Zadeh,[4] Csaba P. Kovesdy.[1] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]University of California Irvine, Irvine, CA; [3]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [4]University of California Irvine, School of Medicine, Orange, CA.*

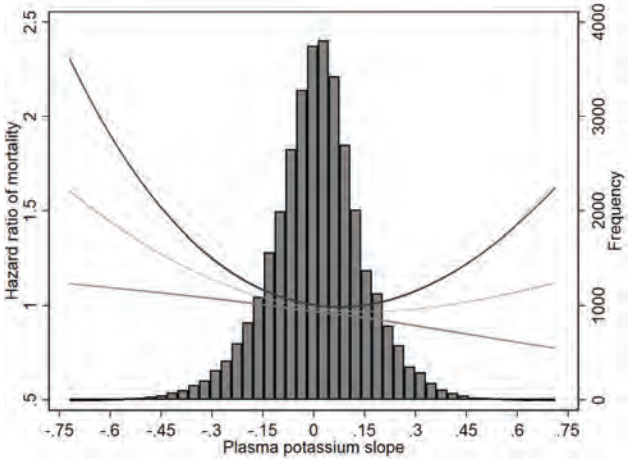
Background: Potassium (K^+) homeostasis is impacted by reduced kidney function, but the pre-ESRD trajectory of plasma K^+ concentration and the associated post-ESRD mortality is unknown.

Methods: In 34,167 US Veterans who transitioned to dialysis between 2007-2014 and had ≥1 K^+ measurement in each year over the last three years prior to dialysis initiation, we examined K^+ trajectory (slope) for both the entire three-year and for each of the three one-year pre-ESRD periods, using linear mixed effects models adjusted for fixed (age, sex, race, diabetes and congestive heart failure) and time-varying (RAAS inhibitor, sodium-polystyrene sulphonate, loop diuretics and mineralocorticoid receptor antagonist use, and eGFR) covariates with patient as the random effect. Quadratic spline and Cox regression models were used to assess the multivariable adjusted association between K^+ slope and all-cause mortality within 6 months of dialysis initiation.

Results: The mean (SD) age of the cohort was 67 (11) years; 98% were male, 29% were African American, and 77% were diabetic. The unadjusted mean (95% CI) K^+ slope was 0.008 (0.006, 0.011) mEq/l/year, which reversed after multivariable adjustment, especially for eGFR levels (adjusted mean [95% CI] K^+ slope, -0.10 [-0.13, -0.07] mEq/l/year). Most of the change over time in plasma K^+ was observed in the last year prior to dialysis. A reverse J-shaped association was observed between K^+ slope and mortality (Figure).

Conclusions: The average intraindividual plasma K^+ trajectory is remarkably stable in patients nearing ESRD, likely as a result of physiologic mechanisms and therapeutic interventions which counteract the progressively limited ability of the failing kidneys to excrete K^+. A declining slope, but not an increasing slope, is associated with higher mortality risk.

Funding: NIDDK Support



SA-PO877

Higher Discharge Serum Creatinine Is Associated with CKD Among Survivors of AKI

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Background: Despite many studies showing patients have higher risk of developing chronic kidney disease (CKD) after a hospitalization with acute kidney injury (AKI), data on the prognostic value of discharge serum creatinine (SCr) are limited. The aim of this study is to explore the association between discharge SCr and CKD risk among survivors of AKI.

Methods: From January 2011 through December 2011, patients hospitalized with AKI in the First Affiliated Hospital, College of Medicine, Zhejiang University without known CKD were screened. The primary endpoint was CKD progression within 5 years. The association between discharge SCr and CKD was assessed by multivariate logistic regression. The net reclassification improvement(NRI) and integrated discrimination improvement (IDI) statistics were applied in statistical analysis.

Results: 673 patients was enrolled and 526 (78.1%) progressed to CKD in 5 years' follow-up. After adjusting for age, gender, stage of AKI, diabetes, hypertension, coronary heart disease, proteinuria and baseline SCr, the odds ratio(OR) rose with the increase of discharge SCr. Multivariable model showed prognostic significance, with the area under the receiver operating characteristic curve (AUC) of 0.77. The addition of discharge SCr to established risk factors improved risk prediction of CKD (AUC of 0.841; NRI of 18.18%; IDI of 10.12%, all P < 0.01).

Conclusions: Higher levels of discharge SCr were associated with increased risk of CKD among survivors of AKI, indicating that discharge SCr could be a predictor independent of established conventional risk factors.

Table 1. Discharge SCr concentrations prediction of CKD with AUC.

	AUC					
Endpoint	Discharge SCr	Risk factors	Risk factors with discharge SCr	Incremental area (P)	NRI (P)	IDI (P)
CKD	0.763	0.77	0.841	0.071 (P < 0.01)	0.182 (P < 0.01)	0.101 (P < 0.01)

Established risk factors including age, gender, stage of AKI, diabetes, coronary artery disease, hypertension, proteinuria and baseline SCr.

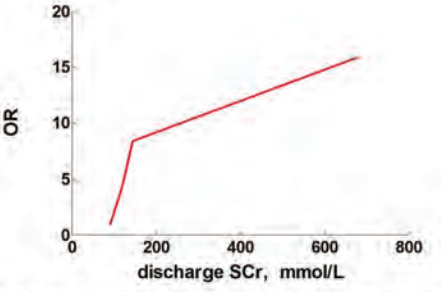

Figure 1. Adjusted OR of CKD according to discharge SCr concentrations.

ORs were adjusted for age, gender, stage of AKI, diabetes, hypertension, coronary artery disease, proteinuria and baseline serum creatinine.

SA-PO878

Pre-Operative Biomarkers and Risk for CKD After Cardiac Surgery

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Background: The associations between various biomarkers and long-term kidney outcomes after cardiac surgery are unknown.

Methods: In patients undergoing cardiac surgery who were enrolled in the TRIBE-AKI study, we assessed the associations of 32 plasma and 8 urine biomarkers measured pre-operatively with the composite kidney endpoint of incident CKD or progression of existing CKD. The cohort was separated into exploration (Canada, n=613) and replication (USA, n=310) cohorts due to differences in outcome ascertainment and lack of data integration of the two cohorts. In the exploration cohort, top biomarkers were identified from the 40 candidate biomarkers. Results were confirmed in the replication cohort, thereby reducing resubstitution and model selection biases. Estimates were pooled for biomarkers that were statistically significant in both the derivation and replication cohorts. Cox proportional hazard regression models adjusted for age, sex, AKI stage, pre-op albuminuria, pre-op SCr, discharge SCr estimated the relationship of the biomarkers with the CKD outcome.

Results: After a median (IQR) follow-up of 5.6 (4.3-5.8) years, a total of 172 (28%) patients experienced the CKD endpoint. 7 plasma and 0 urine biomarkers were independently associated with the CKD endpoint in the exploration cohort, of which 4 biomarkers retained statistical significance in the replication cohort and upon pooling. The pooled HRs (95% CI) per natural log increase were as follows: TNFR1 2.3 (1.6, 3.2), TNFR2 1.7 (1.2, 2.3), KIM1 1.8 (1.3, 2.4), NT-proBNP 1.2 (1.1, 1.4) (**Table**).

Conclusions: Pre-operative plasma TNFR1, TNFR2, KIM-1 and NT-proBNP were associated with incidence and progression of CKD several years after cardiac surgery. As in other clinical settings, these biomarkers may provide prognostic value for long-term kidney outcomes after cardiac surgery.

Funding: Other NIH Support - NHLBI

Table: Risk of CKD Incidence or Progression by Pre-operative Biomarker Level

Biomarkers (log-transformed)	Hazard Ratio (95% CI)			
	Unadjusted HR, Exploration Cohort	Adjusted HR, Exploration Cohort‡	Adjusted HR, Replication Cohort‡	Pooled HR‡
Plasma Biomarkers				
TNFR1	1.8 (1.3, 2.7)	2.5 (1.5, 4.2)	2.1 (1.3, 3.4)	2.3 (1.6, 3.2)*
TNFR2	1.5 (1.1-2.2)	1.9 (1.2, 3.1)	1.5 (1.0, 2.3)	1.7 (1.2, 2.3)*
KIM-1	1.7 (1.3, 2.2)	1.7 (1.1, 2.5)	2.0 (1.2, 3.4)	1.8 (1.3, 2.4)*
NT-proBNP	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	1.4 (1.1, 1.7)	1.2 (1.1, 1.4)**
hsTnT	1.2 (1.0, 1.4)	1.2 (1.0, 1.5)	1.1 (0.9, 1.4)	
ST2	1.8 (1.3, 2.6)	1.6 (1.1, 2.4)	1.0 (0.6, 1.5)	
IL-10	1.3 (1.0, 1.5)	1.2 (1.0, 1.5)	0.9 (0.7, 1.3)	
YKL-40	1.3 (1.1, 1.6)	1.2 (0.9, 1.5)		
VEGFd	1.5 (1.0, 2.1)	1.4 (0.9, 2.0)		
Urine Biomarkers				
UACR	1.2 (1.0, 1.3)	1.0 (0.7, 1.4)		

*I^2= 0%; **I^2 = 27%
Exploration cohort= Canada; Replication Cohort= US
‡Adjusted for age, sex, AKI stage, pre-op albuminuria, pre-op SCr, discharge SCr.
Other biomarkers that were not statistically significant:
Plasma: bFGF, CK-MB, EGF, Galectin-3, h-FABP, interferon, IL-1, IL-12, IL-4, IL-6, IL-8, IL-12, IL-13, IL-18, MCP-1, NGAL, PlGF, TIE2, TNF-alpha, Troponin I, VEGF, VEGFc, VEGFr1
Urine: albumin, creatinine, Cystatin C, IL-18, KIM-1, L-FABP, NGAL

SA-PO879

Plasma Potassium Variability and Associated Post-Transition Mortality in Patients with Advanced CKD Transitioning to ESRD

Ankur A. Dashputre,[1] Praveen Kumar Potukuchi,[1] Keiichi Sumida,[1] Suryatapa Kar,[1] Yoshitsugu Obi,[2] Fridtjof Thomas,[1] Miklos Z. Molnar,[1] Elani Streja,[3] Kamyar Kalantar-Zadeh,[4] Csaba P. Kovesdy.[1] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]University of California Irvine, Irvine, CA; [3]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [4]University of California Irvine, School of Medicine, Orange, CA.*

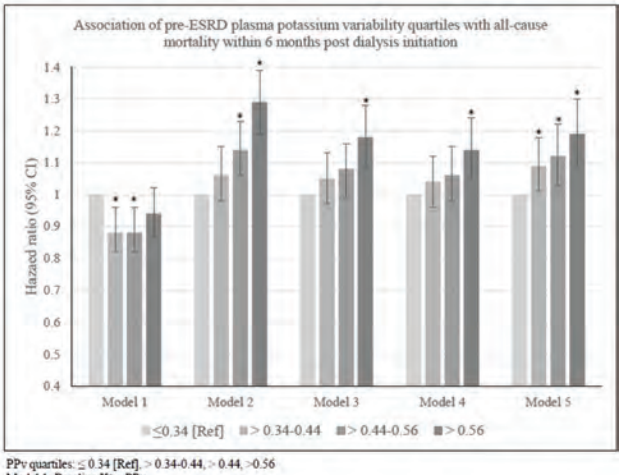
Background: Both higher and lower plasma potassium (K^+) levels are associated with increased mortality, but it is unclear if a propensity for higher plasma K^+ variability (i.e. more frequent or extreme deviations in plasma K^+) prior to dialysis initiation is associated with post-ESRD adverse outcomes independent of baseline K^+ levels.

Methods: In 34,167 US Veterans who transitioned to dialysis between 2007-2014 and had ≥1 plasma K^+ measurement in each year over the last three years prior to dialysis initiation, we examined the association of plasma K^+ variability (PPv, defined as the standard deviation of intra-individual K^+ values over the three-year study period and expressed as quartiles) with all-cause mortality within 6-months after dialysis initiation, using Cox proportional hazard models with adjustment for baseline K^+, demographics, comorbidities, cumulative length of hospital stay, medications, and average eGFR and number of K^+ measurements (median [IQR]: 19 [8-35]) over the three-year study period.

Results: The mean (SD) age of the cohort was 67 (11) years; 98% were male, 29% were African American, and 77% were diabetic. After adjusting for potential confounders, higher PPv quartiles were consistently associated with increased risk of all-cause mortality within 6 months of dialysis initiation (adjusted HRs [95% CI] for quartiles 2-4 [vs. quartile 1], 1.09 [1.01-1.18], 1.12 [1.03-1.22], and 1.19 [1.09-1.30] in model 5; Figure)

Conclusions: Greater pre-ESRD PPv is associated with higher all-cause mortality within 6 months of dialysis initiation. Clinical trials are needed to determine if measures used to stabilize plasma K^+ can improve patient outcomes.

Funding: NIDDK Support



PPv quartiles: ≤ 0.34 [Ref], > 0.34-0.44, > 0.44, >0.56
Model 1: Baseline K^+ + PPv
Model 2: Model 1 + demographics
Model 3: Model 2 + comorbidities + cumulative length of hospital stay
Model 4: Model 3 + medications
Model 5: Model 4 + eGFR + baseline K^+ counts

SA-PO880

Impact of ACE Inhibitor/ARB Discontinuation After an Episode of Hyperkalemia in Patients with CKD

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Background: Angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) are recommended in diabetic and proteinuric nondiabetic chronic kidney disease (CKD). However, therapy with ACEi/ARBs is also associated with an increased risk of hyperkalemia (HK+) that ranges from mild to life-threatening. After an acute episode of hyperkalemia is treated, physicians are faced with the important clinical decision of whether to discontinue ACEi/ARBs. With this study we aim to evaluate the effect of discontinuation of ACEi/ARBs after an episode of HK+ in patients with CKD.

Methods: We performed a retrospective cohort study using administrative health data from Manitoba, Canada. We included all adults (≥ 18 years) with an episode of de novo HK+ (defined as serum potassium ≥ 5.5 mmol/L) between January 1st, 2007 and December 31, 2016. We identified a subgroup of patients with CKD who were current ACEi/ARB users at the time of their HK+ episode. Discontinuation was defined as the absence of a new prescription for an ACEi/ARB within 90 days of the index date among surviving patients. Cox proportional hazards were used to examine the association of ACEi/ARB discontinuation and all-cause and cardiovascular mortality, and initiation of dialysis.

Results: In our cohort, 37,633 episodes of hyperkalemia were identified. Among those, 10,273 had CKD and were current ACEi/ARB users at the time of the hyperkalemia episode. Ninety days after the episode of hyperkalemia, 7,699 surviving patients were included for analysis. A total of 1,707 (22.3%) patients discontinued the ACEi/ARB. ACEi/ARB discontinuation was associated with a more than 2-fold higher risk of all-cause and cardiovascular mortality [hazard ratio (HR) 2.15, 95% CI: 1.99-2.32] for all-cause mortality and [HR 2.04, 95% CI 1.81-2.31] for cardiovascular mortality. Discontinuation of ACEi/ARB was not associated with initiation of dialysis [HR 0.76, 95% CI: 0.49-1.18].

Conclusions: ACEi/ARB discontinuation was associated with a more than 2-fold higher rate of all-cause mortality compared with those who continued ACEi/ARB. Newer therapies for hyperkalemia may be better tolerated and can allow patients to stay on ACEi/ARB therapy.

Funding: Commercial Support - Astra Zeneca

SA-PO881

The Impact of Prevalent Stroke at Critical Junctures in the Care for Patients with Kidney Disease

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Background: Chronic kidney disease is an independent risk factor for stroke in the general population. The impact of a prior stroke on important outcomes for CKD patients is less well characterised. We examined associations between prior stroke and clinical outcomes in a large UK CKD cohort at study recruitment and at time of dialysis commencement

Methods: 3060 participants of the Salford Kidney Study (a large UK CKD longitudinal epidemiological cohort study recruiting since October 2002) were included in the analysis. Multivariable cox regression survival analyses, adjusted for competing risks, was performed to examine the effects of prevalent stroke on endpoints of death, end stage renal disease (ESRD) and non-fatal cardiovascular events (NFCVE). Similar methodology was used to examine the impact of prior stroke on survival in patients who commenced dialysis

Results: Of 3060 study recruits 227 had suffered a stroke prior to recruitment (table 1). Stroke was independently associated with mortality (HR 1.20 95%CI 1.0-1.43, p=0.05), reaching ESRD (HR 1.34 95%CI 1.06-1.69, p=0.02) and future NFCVE (HR 1.54 95%CI 1.12-2.11, p=0.01) after adjustment for age, gender, eGFR, diabetes, hypertension, myocardial infarction, heart failure, atrial fibrillation, smoking history and peripheral vascular disease. 579 patients reached ESRD and commenced dialysis. Stroke prior to dialysis commencement (N=48) was significantly associated with mortality (HR 1.47 (95%CI 1.01-2.14 P=0.05) after adjustment for the same factors (except eGFR) over median 25 months follow up.

Conclusions: Sroke prior to study recruitment was independently associated with mortality, ESRD and future NFCVE. Similarly, stroke was independently associated with mortality in patients who commenced dialysis. This large observational study indicates that stroke alters cardiovascular risk in CKD patients and emphasises the importance of kidney brain crosstalk.

Comparison between patient outcomes (Prevalent stroke v no prevalent stroke)

Outcome	No Stroke at Recruitment N=2833	Stroke at Rectuitment N=227	
Stroke	81 (2.9%)	20 (8.8%)	<0.001
Myocardial Infarction	154 (5.4%)	24 (10.6%)	0.001
End Stage Renal Disease	887 (31.3%)	92 (40.5%)	0.004
All cause mortality	1275 (45%)	157 (69.2%)	<0.000
Death from cardiovascular disease	174 (43.5%)	31 (57.5%)	<0.001

Between group comparisons made using chi square test

SA-PO882

Association of Laxative Use with Change in eGFR in Patients with Advanced CKD

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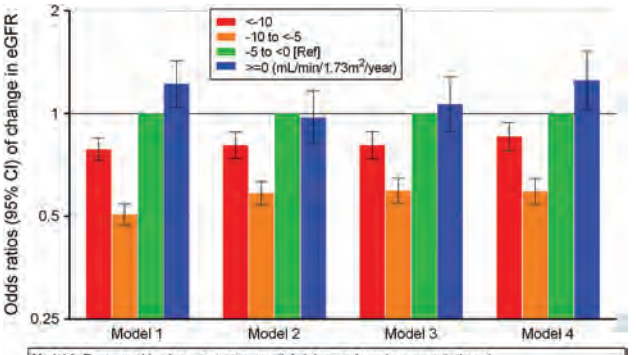
Background: Constipation is highly prevalent in advanced CKD and is associated with adverse kidney outcomes potentially through altered gut microbiota. Laxatives are typically used for constipation management; however, little is known about the effect of laxatives on kidney function in advanced CKD patients.

Methods: We examined the association of laxative use with change in eGFR (slope) over the last two years before dialysis initiation in 25,140 US veterans transitioning to dialysis from 2007-2014. Laxative use was defined as having ≥2 prescriptions of laxatives of ≥30-day supply each during the two-year prelude period. eGFR slopes were estimated by linear mixed effects models using all available outpatient eGFR measurements in the same period. Associations were examined in multinomial logistic regression models with adjustment for demographics, comorbidities, medications, nephrology care, cumulative length of hospital stay, vascular access type, and clinical variables.

Results: The mean (SD) age of the cohort was 70 (11) years; 98% were male; 26% were African American; and 75% were diabetic. Patients with (vs. without) pre-ESRD laxative use were at lower risk of experiencing more progressive eGFR decline and also had higher risk of increasing eGFR even after accounting for various potential confounders (fully adjusted multinomial odds ratios [95% CI] for eGFR slope <-10, -10-<-5, and ≥0, vs. -5-<0 mL/min/1.73 m^2/year, 0.86 [0.78-0.94], 0.59 [0.54-0.65], and 1.26 [1.03-1.52], respectively; Figure).

Conclusions: The use of laxatives may have potential renoprotective benefits in advanced CKD patients, in whom the gut gains importance in the acid-base and mineral homeostasis and the disposal of nitrogenous waste products. Further studies are needed to elucidate the underlying mechanisms and to evaluate its clinical effectiveness.

Funding: NIDDK Support



SA-PO883

Patterns of Care for Lipid Management in CKD Stage 3-5 Patients: Results from CKDopps

Daniel G. Muenz,[1] Stephanie R. Reading,[2] Keith McCullough,[1] Viviane Calice-Silva,[4] Paul Dluzniewski,[2] Ziad Massy,[3] Kiran Philip,[2] Helmut Reichel,[5] Bruce M. Robinson,[1] Roberto Pecoits-Filho.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Amgen, Los Angeles, CA; [3]Ambroise Pare University Hospital and Inserm U1018 Eq5, Boulogne Billancourt/ Paris cedex, France; [4]Pro-Kidney Foundation, Joinville, Brazil; [5]Nephrological Center Villingen-Schwenningen, Villingen-Schwenningen, Germany.*

Background: Current KDIGO guidelines recommend conducting a lipid profile upon diagnosis for chronic kidney disease (CKD) and treating patients ≥50 years with a statin +/- ezetimibe. However, these guidelines do not provide target lipid levels for treatment. Thus, we aimed to evaluate current nephrologist care practice patterns for lipid management, including perceptions of target levels of LDL-cholesterol (LDL-C), statin/ezetimibe prescription, and achieved LDL-C using the CKD Outcomes and Practice Patterns Study (CKDopps).

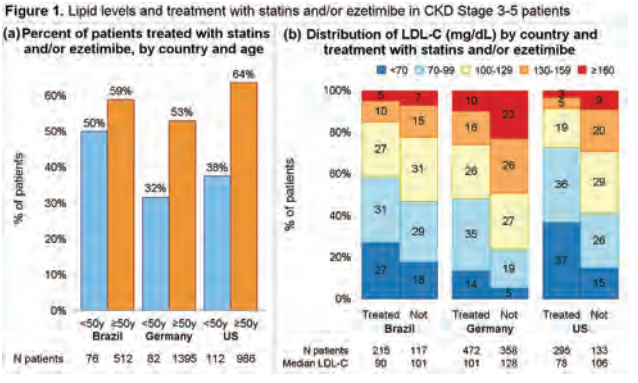
Methods: We analyzed patient-level treatment and LDL-C levels and nephrologist-specified target LDL-C upper limits from CKDopps clinics in Brazil, Germany, and the United States (2013-2018). Patients were ≥18 years old with eGFR <60ml/min at enrollment. P-values were obtained from a logistic model of the prevalence of treatment with statins +/- ezetimibe by age (< or ≥50), country, and CKD stage; and a linear model of mean LDL-C by treatment, country, and CKD stage. Both models used generalized estimating equations to account for patient clustering by clinic.

Results: Statin/ezetimibe treatment was more prevalent among CKD patients ≥50 years-old (p<0.0001) and differed significantly by country (p=0.001; Figure 1a). LDL-C was lower among treated patients (p<0.0001) and differed significantly by country (p<0.0001; Figure 1b). Neither patient-level outcome varied significantly by CKD stage (p≥0.2). Between 7-23% of untreated patients in each country had LDL-C ≥160 mg/dL. Only 7-17% of nephrologists believed that LDL-C should be <70 mg/dL.

Conclusions: There is substantial variation in practice patterns regarding lipid-lowering therapies across countries, but not across CKD stages. Treated patients appear to benefit with regard to LDL-C lowering, yet a significant proportion of hyperlipidemia patients are not receiving treatment.

Funding: NIDDK Support, Commercial Support - This analysis was supported by Amgen. The DOPPS Program is supported by Amgen (since 1996, founding sponsor), Kyowa Hakko Kirin (since 1999 for Japan DOPPS), and Baxter Healthcare Corp. Additional support for specific projects and countries is provided by Akebia Therapeutics, AstraZeneca, European Renal Association-European Dialysis & Transplant Association (ERA-EDTA), Fibrogen, Fresenius Medical Care Asia-Pacific Ltd, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGfN), Italian Society of Nephrology (SIN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Otsuka America, Proteon Therapeutics, the Association of German Nephrology Centres, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Belgian Federal Public Service of Public Health in Belgium, Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN) in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN), and Kidney Research UK (KRUK) in the United Kingdom, and the Agency for Healthcare Research and Quality (AHRQ) and National Institutes of Health (NIH) in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health and not to Dr. Muenz directly., Private Foundation Support, Government Support - Non-U.S.

Figure 1. Lipid levels and treatment with statins and/or ezetimibe in CKD Stage 3-5 patients



SA-PO884

Treatment Preferences of Patients with CKD in Acute Coronary Syndrome: A Discrete Choice Experiment

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Background: Chronic kidney disease (CKD) is associated with a high incidence of acute coronary syndrome (ACS) and related morbidity and mortality. Treatment choices for patients with CKD involve tradeoffs in potential benefits and harms of invasive management options.

Methods: To design, pilot and field a discrete choice experiment (DCE) to quantify preferences of patients with CKD towards invasive heart procedures. Attributes of invasive versus conservative treatment for ACS were identified through semi-structured qualitative interviews. Levels for each attribute were determined from CKD subgroup analyses of early invasive versus conservative management clinical trials and cohort studies. The DCE was co-developed with physicians and patient input. Eligible patients for the study included those with CKD over 18 years of age, recruited from two multidisciplinary CKD clinics in Calgary, Alberta. Patients were recruited for the pilot study from September to November 2018 and the full study commenced in January 2019. Average importances for treatment attributes were quantified using Hierarchical Bayes estimation, and scaled on a 0-100 scale to reflect their relative importance.

Results: Among 64 patients who provided consent to participate in this full study, 59 (92%) completed the survey. Participants had an average age of 67 years, with 41% female, and mean eGFR 18mL/in/1.73m^2. The most important attributes were risk of death within one-year (32.0, 95% CI [28,6, 35.4]) and end stage renal disease (20.5, 95% CI [17.3, 23.7]). The attributes AKI requiring dialysis, risk of another heart attack within one year and invasive procedures (versus conservative management) were of lesser importance (17.2, 95% CI (14.8, 19.7); 15.8, 95% CI (14.2, 17.5); and 14.5 95% CI (11.0, 18.0), respectively).

Conclusions: These results demonstrate the feasibility of conducting a DCE to quantify preferences of patients with CKD. Preliminary findings suggest patients with CKD are most risk averse towards death, however, end-stage kidney disease is a strong consideration. Measurement of these patient preferences can be used to inform the strength of clinical guideline recommendations and to improve shared-decision making approaches for cardiovascular disease for patients with CKD.

Funding: Private Foundation Support

SA-PO885

Statin Prescription in CKD Patients Aged ≥50 Years Without Prevalent Coronary Heart Disease

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Background: According to the 2013 Kidney Disease Improving Global Outcomes (KDIGO) guideline, statins are recommended in adults aged ≥50 years with chronic kidney disease (CKD) stages 3-5, not on dialysis. Our objective was to examine whether there was a change in prescription prevalence after publication of the KDIGO guideline in November 2013 in two real-world populations.

Methods: We created one-year period prevalence cohorts for each year in the Geisinger Health System (2004-2016) and Johns Hopkins Medicine (2013-2016), including patients with CKD stages 3-4 (to be conservative so as not to inadvertently include end-stage kidney disease), age ≥50 years, and without prevalent coronary heart disease (another indication for statin use that could confound interpretation).

Results: At Geisinger (N=54,788, mean age 72 years, 65% female, 99% white, mean eGFR 50 ml/min/1.73 m^2), statin prescription increased from 28% to 41% from 2004 to 2007 (p<0.001), but then remained relatively stable (**Figure**). There was no significant change in statin prescription after the KDIGO guideline was published; prevalence of statin prescription in 2016 was 47%. At Hopkins (N=19,682, mean age 70 years, 61% female, 67% white, mean eGFR 50 ml/min/1.73 m^2), statin prescription did not change after the KDIGO guideline; prevalence of prescription in 2016 was 52%.

Conclusions: Despite the 2013 KDIGO's recommendation that all adults with CKD aged ≥50 years should be prescribed statins, nearly half of the patients were not prescribed for statin in 2016 in two real-world settings. We need to understand better why adherence to KDIGO guideline on statin use is low in this high-risk population.

Funding: NIDDK Support

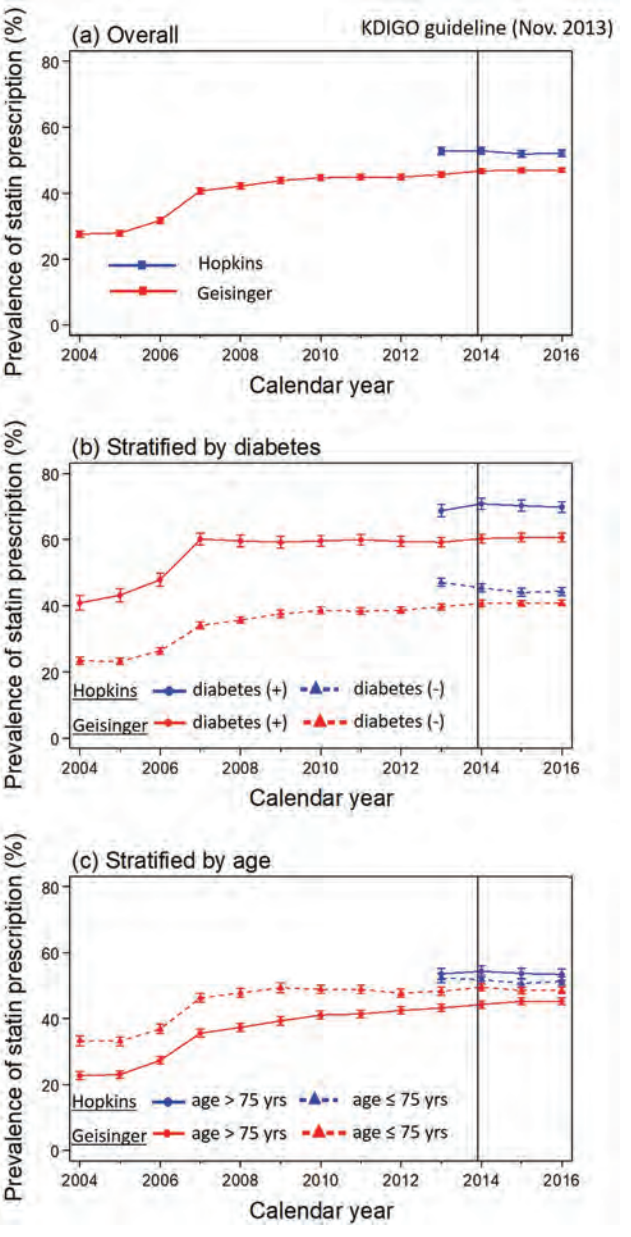

Figure. Prevalence of statin prescription in CKD G3-4 patients aged ≥ 50 years without prevalent coronary heart disease

SA-PO886

Hospitalization with Major Infection and Incidence of ESRD: The Atherosclerosis Risk in Communities (ARIC) Study

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Background: Animal studies have suggested deleterious impacts of infection on the kidney. Whether incidence of infection increases long-term risk of incident ESRD has not been systematically evaluated in the general population.

Methods: In 10,293 participants of the ARIC Study who attended visit 4 (1996-1998), we evaluated the association of incident hospitalization with major infection (pneumonia, urinary tract infection, bloodstream infection, and cellulitis/osteomyelitis) with subsequent risk of ESRD. Hospitalization with major infection was entered into multivariable Cox models as a time-varying exposure to estimate the HRs.

Results: The mean age was 63 years, 56% were female, 22% were black, and 7% had eGFR < 60 ml/min/1.73m^2. During a median follow-up of 17.4 years, there were 2,910 incident hospitalizations with major infection and 279 cases of ESRD (209 cases

after hospitalizations with major infection). The risk of ESRD was higher following major infection compared to while free of major infection (crude incidence rate, 5.0 vs. 0.6 per 1,000 person-years) (Table). In multivariable time-varying Cox analysis, hospitalization with major infection was associated with 3.4-fold increased risk of ESRD (HR, 3.41 [95%CI, 2.61-4.46]) (Table). The association was similar across pneumonia, urinary tract infection, bloodstream infection, and cellulitis/osteomyelitis and stronger among participants with a concurrent diagnosis of acute kidney injury (HR, 4.30 [95%CI, 3.00-6.18]) compared to those without (HR, 2.06 [1.57-2.72]).

Conclusions: Hospitalization with major infection was independently and robustly associated with subsequent risk of ESRD. Whether preventive approaches of infection have beneficial impacts on kidney outcomes may deserve future investigations.

Funding: NIDDK Support, Other U.S. Government Support

The hazard ratios for incident ESRD

	All major infection (2,910 events)	Pneumonia (1,499 events	Urinary tract infection (1,422 events)	Bloodstream infection (910 events)	Cellulitis and osteomyelitis (602 events)
IR per 1,000 person-years while free of hospitalization	0.6 (0.5-0.8)	1.1 (0.9-1.3)	1.3 (1.1-1.5)	1.2 (1.1-1.4)	1.4 (1.3-1.6)
IR per 1,000 person-years following hospitalization	5.0 (4.3-5.7)	6.0 (5.0-7.1)	4.6 (3.7-5.6)	7.5 (6.2-9.2)	6.8 (5.3-8.8)
Hazard ratio (95%CI)					
Model 1	5.20 (4.03-6.72)	4.31 (3.21-5.78)	4.05 (3.01-5.45)	4.72 (3.26-6.83)	3.69 (2.57-5.28)
Model 2	3.41 (2.61-4.46)	2.84 (2.11-3.83)	2.61 (1.92-3.54)	3.11 (2.15-4.51)	2.37 (1.64-3.44)

Model 1 adjusted for age, sex, race, BMI, smoking, ever drink, education, sBP, anti-HTN, DM, eGFR, ACR, CRP, CVD, COPD and cancer. Model 2 additionally adjusted for incident CVD.

SA-PO887

Proton Pump Inhibitor Use in Ambulatory Care Setting in Patients with CKD: A Patient Safety Project

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Background: Proton pump inhibitors (PPI) are widely prescribed medications, and recent observational studies suggest that PPI exposure increases the risk of adverse renal outcomes including acute kidney injury (AKI), chronic kidney disease (CKD), and progression to end-stage renal disease (ESRD). Timely cessation of PPI therapy may improve patient safety and health care costs. **Objective:**To assess PPI use in the absence of indications, the missed opportunities to deprescribe, and to develop strategies for sustainable quality improvement (QI).

Methods: As a requirement of the clinical QI program during nephrology fellowship training, we performed an audit of records spanning September 1, 2018 to May 31, 2019 in an academic outpatient Nephrology clinic. We selected patients with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 and used FDA recommendations and American College of Gastroenterology (ACG) consensus derived guideline for PPI indications. We counted the total number of outpatient clinic visits that patients attended during the study period. Comparisons between groups were tested using Wilcoxon tests to get two-tailed p-values.

Results: 116 consecutive clinic patients with eGFR<60 were audited .99% were Male, 23% Black, mean age was 72(standard deviation/SD 9). Mean eGFR was 39(SD 11) ml/min/1.73 m^2 and mean BMI was 31(SD 5.6). 53% of patients were diabetic, 91% were hypertensive and 53% had proteinuria. 38% (44/116) patients were on PPI. Of those on PPI, 68% did not have an indication to be on it. Average duration of PPI prescription was 434(SD 145) days in the indicated group compared to 482 (SD 266) days in the non-indicated group (p=.6). PPI were prescribed by PCPs for 77% of patients, with other providers prescribing for 23%. PPI users averaged 8 outpatient clinic visits during the time audited; for indicated patients the average was 8.3, while for non-indicated patients the average was 7.9 visits, which were considered as missed opportunities for PPI deprescription.

Conclusions: Knowing the adverse outcomes associated with PPI use, 68% CKD patients were on PPI despite lack of a clear indication. There were several subsequent missed opportunities to de-prescribe these non-indicated medications. A concerted multidisciplinary program to de-prescribe PPI in high-risk CKD patients can improve patient safety and outcomes.

SA-PO888

Association Between Proton-Pump Inhibitors and CKD in Japanese Patients

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Background: Proton-pump inhibitor (PPI) use has been reported to be a risk factor for chronic kidney disease (CKD), potentially mediated by recurrent acute kidney injury (AKI). We aimed to estimate the progress rate of renal dysfunction in patients taking PPI in real clinical settings and to compare the results with those of patients taking histamine-2 receptor antagonist (H2RA) and those taking neither PPI nor H2RA.

Methods: We retrospectively reviewed patients' data collected from Kochi Medical School Hospital's information system between 2001 and 2017. Patients were classified into the PPI, H2RA, and CONT (control patients without PPI/H2RA use) groups, and their data were compared. Survival time was defined as the time between drug administration date (zero hour) and a 30% decrease in estimated glomerular filtration rate (eGFR; primary endpoint).

Results: We initially evaluated 92,585 Japanese individuals. According to the study protocol, the final analysis evaluated data of 5,849 patients, including 3,211 patients in the PPI group and 2,638 patients in the H2RA group. The mean age was 58±18.5, 67.4±14.1, and 63.8±15.8 years for the CONT, PPI, and H2RA groups, respectively. On survival analysis, the PPI and H2RA groups had a significantly higher survival rate ($p<0.001$) than the CONT group, whereas no significant difference was found between the PPI and H2RA groups. When the CONT group was set as a reference, PPI use, or H2RA use were associated with high HRs at 1.2861, and 1.5437, respectively. Frequencies of male sex, older age, CKD (G3a, G3b, G4), and diabetes mellitus (DM) were significantly higher in the PPI group, followed by the H2RA group, then the CONT group. Our cohort had higher frequencies of male sex, older age, DM, and AKI history, associated with high HRs at 1.1015, 1.025, 1.219, or 12.7142, respectively.

Conclusions: PPI or H2RA use was significantly associated with an increased risk of CKD development. H2RA use was associated with CKD development. PPI or H2RA users may include patients with CKD risk factors. Given that CKD risk was not different between Japanese PPI and H2RA users, PPIs may not be more involved in CKD development than H2RAs.

SA-PO889

Characteristics and Symptom Severity of Patients Reporting CKD in the PatientsLikeMe Online Health Community

Elisabeth Nyman, Glen James, Jonatan Hedberg, Cathy E. Emmas. *AstraZeneca, Cambridge, United Kingdom.*

Background: Online health communities and research networks such as PatientsLikeMe (PLM) may provide important insight into understanding the real-world experiences of patients with chronic diseases, including chronic kidney disease (CKD).

Methods: Retrospective cross-sectional observational study using the PLM online health network database. Inclusion criteria were registration with PLM between 2011-2018, aged ≥18 years at registration, with self-reported CKD within 30 days of registration and not receiving dialysis. Information reported by patients within 30 days of registration was used to assess demographics, clinical history, comorbidities, treatments and patient reported symptoms, both general (prompted for all PLM patients) and other symptoms.

Results: 1848 patients met the inclusion criteria. The median age at registration was 56 years (IQR 45-64), most patients were female (66%), and US residents (87%). The 1496 patients who recorded race were predominately Caucasian (80%) and African-American (9%). Median age at diagnosis was 47 years (IQR 33-56, N=578) and the median age of first symptom onset was 43 years (IQR 28-54, N=378). Most patients (74%, N=1374) reported at least one comorbidity (median 3 (IQR 0-4)), the most common being type 2 diabetes (57%), hypertension (48%), hypercholesterolemia (32%) and diabetic neuropathy (27%). Less than half of patients (41%) entered any symptom within 30 days of registration. General symptoms were reported by 487 patients and rated as moderate or severe by 72% for fatigue, 58% for pain, 48% for insomnia, 41% for anxious mood, and 41% for depressed mood. Additional symptoms reported by more than 15% of patients and rated moderate or severe by >30% were problems concentrating, nerve pain, and feet tingling (N=315-338). Treatments were reported by 1369 (74%) patients, the most common were for diabetes (51%) and hypertension (27%).

Conclusions: Characteristics of CKD patients in the PLM community are broadly consistent with the general US CKD population, although the percentage of females is slightly higher. PLM provides a unique source of real-world information on the patient experience beyond the clinical environment that can be utilized to improve understanding of the patient-level impact of CKD.

Funding: Commercial Support - AstraZeneca

SA-PO890

Identification of Symptom Clusters and Their Association with Clinical Characteristics and Quality of Life Outcomes in CKD: A Multicenter Study

Thomas J. Wilkinson, Daniel Nixon, Alice C. Smith. Leicester Kidney Lifestyle Team *University of Leicester, Leicester, United Kingdom.*

Background: Renal patients suffer from an overwhelming symptom burden including fatigue, dyspnea, sleep problems and depression. Research into symptom *clusters* (co-occurrence of symptoms) is emerging although primarily limited to end stage renal disease. Whilst individual symptoms are established contributors to poor quality of life (QoL), no research has investigated the role of symptom *clusters* on these outcomes.

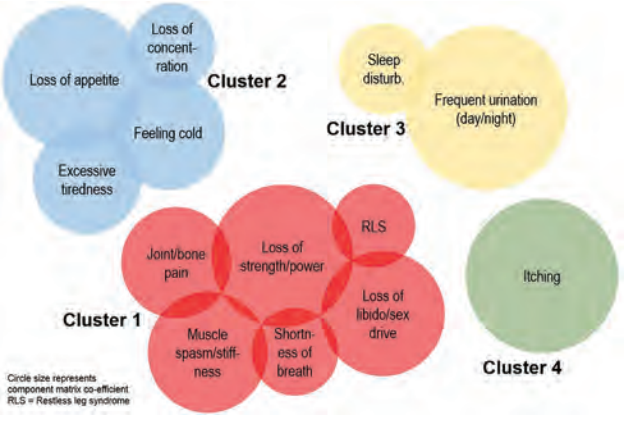
Methods: Self-reported symptoms of 876 CKD pre-dialysis patients (44% females, age 67±16 years, eGFR 40±25ml/min) were assessed using the Kidney Symptom Questionnaire. Clusters were derived based on the frequency of the 13 symptoms using Principle Component Analysis (minimum factor loading 0.4, KMO=.925). Associations between clusters, QoL (EQ5D), and physical function (Duke Activity Status Index) was analysed using generalized regression modeling (age and sex used as co-variants).

Results: Symptom clusters based are shown in Figure 1. Cluster 1-type patients were older (β=.297, P<.001) whilst cluster 2 patients were younger (β=-.211, P<.001). Sex had no effect on symptom clustering. Symptom cluster 1 was the *greatest* predictor of reduced

QoL (using the EQ5D index; β=-.465, P<.001) and physical function (β=-.407, P<.001). Cluster 3 was *least* predictive of poor QoL (β=-.108, P=.044) and cluster 4 least predictive of physical function (β=-.079, P=.015), although both significant. Worsening of eGFR was associated with cluster 2 symptoms only (β=-.142, P=.001). Higher inflammation (CRP) was associated with cluster 1 symptoms (β=.181, P=.040).

Conclusions: We identified 4 unique symptom clusters in patients with non-dialysis dependent CKD. QoL was primarily affected by physiological symptoms relating to muscle and joint pain, dynapenia and dyspnea. Routine clinical assessment and management strategies targeted at cluster level could have synergistic effects in reducing the burden of CKD symptoms.

Funding: Private Foundation Support



SA-PO891

Disability and Its Association with Chronic Diseases, Especially Early CKD

Dong-Young Lee, Hyeonjeong Kim. *VHS Medical Center, Seoul, Republic of Korea.*

Background: In older people muscle weakness, defects in the organs of the body are common, and in severe cases help is needed for daily life. In addition, vision, hearing are reduced, walking disorders occur, and in this condition, they are called disabled. People with disabilities need continued support from family and community people, and people with disabilities have a higher mortality rate. Disabilities are known to occur and worsen when accompanied by chronic diseases such as stroke, ischemic heart disease, arthritis, diabetes and hypertension. Plantinga et al reported that disability is also associated with chronic kidney disease (CKD) and it can be induced from early CKD. We evaluated the association between disability and various chronic diseases, especially CKD, in older Koreans.

Methods: The subjects of this study were 3rd KNHANES participants who were over 65 years old. 3rd KNHANES did not conduct a microalbuminuria test, so the definition of CKD was defined as estimated glomerular function rate<60 ml/min/1.73 m2 regardless of urine test, and the CKD stage followed the KDIGO. Disabilities included abnormal activity of daily living (ADL), instrumental ADL and vision, hearing, walking impairment.

Results: The prevalence of abnormal ADL in CKD stage 3a, stroke, arthritis, DM and hypertension were 52.2%, 42.6%, 20.1%, 25.3% and 18.7%, respectively (Table 1). The prevalence of CKD stage 3a for vision, hearing and walking impairment was significantly higher and as high as that of other chronic diseases. In multivariate logistic regression analysis, abnormal ADL is significantly associated with CKD 3a (Odds ratio, 1.78 [95% confidence interval, 1.03-3.09]).

Conclusions: CKD was associated with the disorder from the early state, and was as frequent as the previously known chronic diseases.

Prevalence of disabilities between CKD and other comorbidities

	Abnormal ADL (%)	Abnormal IADL (%)	Visual impairment (%)	Hearing impairment (%)	Walking impairment (%)
DM	25.3†	43.2	60.4†	32.9	51.7
Hypertension	18.7†	39.2	52.6	29.1	49.8†
Arthritis	20.1†	46.8	58.2†	39.8†	63.4†
Cancer	8.9	37.8	46.7	31.1	60.0
Stroke	42.6†	62.3†	57.4	37.7	78.7†
IHD	17.9	44.6	64.3	33.9	75.0†
CKD 3a	52.2†	47.3†	59.8†	34.3†	52.0†

† p<0.005

SA-PO892

Efficacy and Safety of Direct-Acting Antiviral Based Treatment in HCV-Infected Patients with Chronic Renal Function Impairment: Updated Systemic Review and Meta-Analysis

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Background: To further determine the efficacy and safety of direct acting antiviral (DAA) -based treatments in hepatitis C virus (HCV) infected patients with renal function impairment.

Methods: MEDLINE, EMBASE, and the Cochrane Library were searched for relevant studies. All studies assessing the efficacy and safety of DAA -based treatments against HCV infection in patients with renal impairment and HCV infection were eligible for inclusion. Outcomes assessed included efficacy outcomes and safety outcomes. Summary estimates were obtained using an inverse-variance weighted random effect model and Freeman-Tukey double arcsine transformation.

Results: 27 studies (n= 1048 participants) were included. The majority of included studies were of fair quality with Newcastle–Ottawa scale scores between 4-6. The pooled virologic response rates at the end of treatment or 4, 12, 24 weeks after treatment (i.e. EOTR, SVR4, SVR12 and SVR24 rates) were 97.0% (95% CI, 94.0%-99.0%), 80.9% (95% CI, 49.3%-98.7%), 94.1% (95% CI, 91.6%-96.3%), and 89.6% (95% CI, 75.5%-98.1%), respectively. The pooled relapse rate was 6.4% (95% CI, 3.4%-10.4%). The pooled incidence of adverse events and severe adverse events leading to discontinuation were 47.6% (95% CI, 35.0%-60.4%) and 2.9% (95% CI, 1.4%-5.0%), respectively. High heterogeneity among studies exist for SVR4 and SVR24 rates. Formal statistical testing did not identify the presence of publication bias for all measured outcomes except the relapse rate.

Conclusions: The results support the efficacy and safety of DAA -based treatments in this population. Future studies with better design, larger sample size and longer follow up will be the next step.

Funding: Government Support - Non-U.S.

SA-PO893

The Prevalence of Subtypes of Substance Use Disorder in Patients with Advanced Kidney Disease

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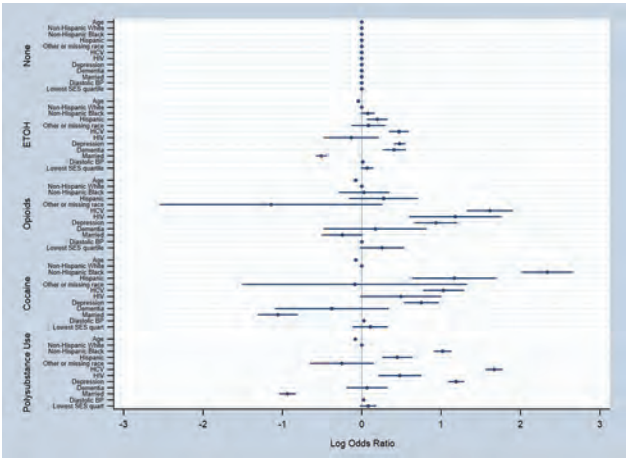
Background: Previous studies have shown that illicit drug use in patients on hemodialysis is associated with poor outcomes. The prevalence and characteristics of different types of substance use disorder (SUD) have not been well-described in patients with advanced chronic kidney disease (CKD).

Methods: Diagnostic codes were used to characterize the prevalence of different types of SUD in a national cohort of veterans with incident stage 4 CKD from 2003 to 2014. Subtypes of SUD were grouped as alcohol, opioid, cocaine, or polysubstance use disorders. Their clinical and demographic characteristics were compared to those among veterans without SUD using multinomial logistic regression.

Results: Among 57,874 veterans with incident stage 4 CKD, the prevalence of alcohol use disorder was 7.0%, opioid use disorder 0.4%, cocaine use disorder 0.6%, and polysubstance use disorder 4%. See Figure for adjusted relative differences in demographic and clinical characteristics by subtype of SUD (with no SUD as the reference group). The prevalence of non-Hispanic black race and Hispanic ethnicity were higher with cocaine (aOR 10.38, 95% CI 7.51-14.35 and aOR 3.21, 95% CI 1.89-5.46, respectively) and polysubstance (aOR 2.78, 95% CI 2.48-3.10 and aOR 1.56, 95% CI 1.30-1.89, respectively) use disorders.

Conclusions: Demographic and clinical characteristics vary significantly across different subtypes of SUD in veterans with stage 4 CKD. Future research is needed to evaluate the differential association of these SUD subtypes with CKD progression and mortality.



Baseline Characteristics, Grouped by SUD Subtype, Among Veterans with Stage 4 CKD

SA-PO894

Cannabis Use and Its Association with Incidence of Ischemic Stroke in Advanced CKD Patients Transitioning to ESRD

Praveen Kumar Potukuchi,[1] Keiichi Sumida,[1] Miklos Z. Molnar,[1] Abduzhappar Gaipov,[2] Frank Park,[7] Cameron M. Kaplan,[1] Hamid Moradi,[3] Fridtjof Thomas,[1] Justin Gatwood,[1] Ankur A. Dashputre,[1] Yoshitsugu Obi,[4] Elani Streja,[5] Kamyar Kalantar-Zadeh,[6] Csaba P. Kovesdy.[1] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]National Scientific Medical Center, Astana, Kazakhstan; [3]University of California, Irvine, Orange, CA; [4]University of California Irvine, Irvine, CA; [5]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [6]University of California Irvine, School of Medicine, Orange, CA; [7]University of Tennessee Health Sciences Center, Memphis, TN.*

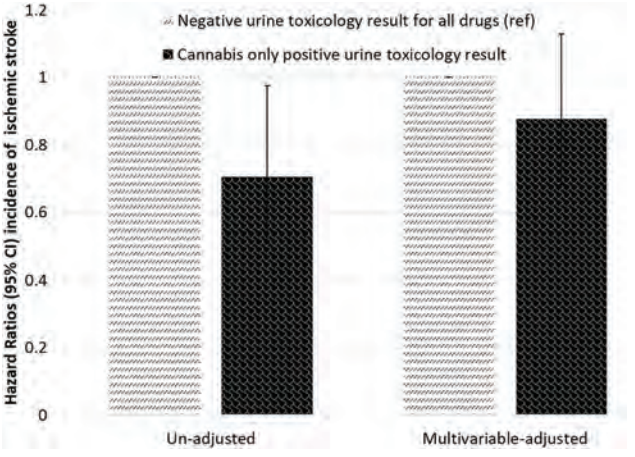
Background: The risk of stroke is especially high in patients with CKD/ESRD. The effects of cannabis use on incidence of stroke in patients with advanced CKD are unclear.

Methods: We examined 3,615 US veterans who transitioned to dialysis during 2007-2014 and had undergone urine toxicology tests up to one year prior to dialysis. We compared patients whose toxicology tests were positive for cannabis alone (N=202) with those whose tests were negative for all drugs (N=3,413). We examined the association of cannabis use with incident ischemic strokes (defined using ICD-9-CM codes) using Cox proportional hazards model adjusted for sociodemographics, comorbidities, medications, vital signs and time dependent dialysis initiation. We applied conditional repeated measures in Cox regression (modeling the full time-course of the recurrent events) to handle the occurrence of multiple strokes in the same patient.

Results: The mean (SD) age of the cohort was 61.4 (10.3) years; 97% were male, 41% were African American, and 73% had diabetes. Ischemic stroke occurred in 18% of the cohort (N=661) with a median (IQR) follow up time of 2 (1-4) years (one stroke event N=311 and ≥ 2 stroke events N=350). Cannabis use was associated with lower risk of stroke in unadjusted analysis [Figure]. However, the protective effect of cannabis use was attenuated in multivariable adjusted models [hazard ratio (95%CI): 0.88 (0.68-1.13)].

Conclusions: Cannabis use in advanced CKD patients is not significantly associated with the incidence of ischemic strokes.

Funding: NIDDK Support



SA-PO895

Association Between Pre-ESRD Opioid Use and Post-ESRD Mortality

Praveen Kumar Potukuchi,[1] Keiichi Sumida,[1] Christina A. Spivey,[1] Ankur A. Dashputre,[1] Abduzhappar Gaipov,[2] Suryatapa Kar,[1] Fridtjof Thomas,[1] Justin Gatwood,[1] Yoshitsugu Obi,[3] Miklos Z. Molnar,[1] Elani Streja,[4] Kamyar Kalantar-Zadeh,[5] Marie Chisholm-Burns,[6] Csaba P. Kovesdy.[1] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]National Scientific Medical Center, Astana, Kazakhstan; [3]University of California Irvine, Irvine, CA; [4]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [5]University of California Irvine, School of Medicine, Orange, CA; [6]University of Tennessee Health Science Center College of Pharmacy, Memphis, TN.*

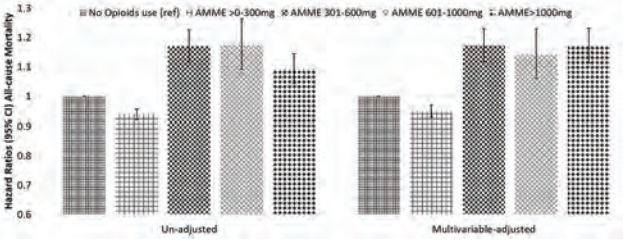
Background: Opioids are frequently used for chronic pain management in patients with advanced CKD. The relationship between pre-ESRD opioid use and post-ESRD mortality is unclear.

Methods: In a national cohort of 69,765 US veterans who transitioned to dialysis during 2007-2014 we assessed the association between pre-ESRD opioid use and post-ESRD all-cause mortality. Opioid use was defined as receiving opioids within a year prior to dialysis initiation (N=31,472) and divided into four groups based on the cumulative received dose, expressed as annual morphine milligram equivalent (AMME): >0-300 mg (N=25,282), 301-600 mg (N=2,499), 601-1000 mg (N=993) and >1000mg (N=2,698). Associations were examined using Cox proportional hazards models adjusted for demographics, smoking status, comorbidities, nephrology care, number of outpatient visits, and cumulative length of hospitalizations.

Results: The mean (SD) age of the cohort was 71 (12) years, 93% were male, 24% were African American, and 64% had diabetes. Opioid users (AMME >300 mg) displayed significantly higher mortality compared to non-users [Figure]. The multivariable adjusted hazard ratios (95%CI) associated with the four incrementally higher AMME categories (vs. no opioid use) were 0.95 (0.93-0.97), 1.17 (1.12-1.23), 1.14 (1.06-1.23), and 1.17 (1.11-1.23), respectively.

Conclusions: Pre-ESRD opioid use was associated with higher post-ESRD mortality in patients with AMME >300 mg. Further studies are needed to determine whether this association is confounded by indication or whether part of the increased risk can be mitigated.

Funding: NIDDK Support



SA-PO896

Extended and High-Dose Nonsteroidal Anti-Inflammatory Drug Use Is a Risk Factor for CKD Incidence

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Background: The use of non-steroidal anti-inflammatory drugs (NSAIDS) and its risk for CKD progression is well known. However, risks for onset of CKD have not been definitively established. This study examined the extended use of NSAIDS and the extended use of high-dose NSAIDS among patients from a third-party insurer for risk of CKD development.

Methods: Serial observations from 2007 through 2017 were examined. Patients with valid serum creatinine measurements and complete supporting data, including other lab values (albumin, bilirubuin, calcium, sodium, potassium, hemoglobin, glucose, chloride, and carbon dioxide), medication use (NSAIDS, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, proton pump inhibitors, hydralazine, and antihistamines), and comorbid conditions (diabetes, hypertension, cardiovascular diseases, congestive heart failure, proteinuria) were included for analysis. In addition to chi-squared tests of association between NSAIDS use and CKD development, Kaplan-Meier survival analysis of time to CKD onset was stratified by NSAIDS use and log-rank tests were performed on the full sample and 1:1 matched samples of patients with 1) NSAIDS use in over 50% (NSAIDS-50) of their prescription history matched to similar controls; and 2) evidence of high-dose oral NSAIDs usage (NSAIDS-H) matched to similar NSAIDS-50 controls.

Results: 80,619 patients qualified for the full data analysis, with 4,185 patients developing CKD, and 4,086 NSAIDS-50 patients (chi-sq p-value < 0.0001). In the NSAIDS-50 matched analysis, 514 of 8,172 patients develped CKD, 282 of which were NSAIDS-50 patients (chi-sq p-value = 0.0255). 755 patients were identified as NSAIDS-H patients with 54 developing CKD, while 34 of 755 controls developed CKD (chi-sq p-value = 0.0363). The full sample showed differences in log-rank tests of survival curves between NSAIDS and non-NSAIDS groups (p < 0.0001), as in the matched NSAIDS-50/non-NSAIDS-50 sample (p = 0.0033) and the matched NSAIDS-H/non-NSAIDS-H sample (p = 0.0167).

Conclusions: While establishing firm dosing and exposure guidelines requires further research, this study suggests that extended and/or high-dose usage of NSAIDS carries an increased risk of CKD onset. Additional multivariate analysis to confirm the reliability and extent of these findings is underway and will be presented.

Funding: Other U.S. Government Support

SA-PO897

Emergency Department Utilization by Patients with Advanced CKD and Dialysis

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Background: Chronic Kidney Disease (CKD) is a potent risk factor for kidney failure, cardiovascular events and all cause hospitalizations. In addition to higher outpatient resource use, patients with CKD may present more frequently to the emergency department (ED) and may be more likely to be admitted for hospitalization. In Manitoba, we previously demonstrated an 8-fold increase in the frequency of ED presentations by patients on dialysis as compared to a non-dialysis population. Comparable data on ED visits remain sparse for patients with CKD G3-G5, not on dialysis. Here, we aim to describe the frequency of ED visits and highlight differences in reasons for visit in patients with CKD stages G3-G5 and Those on dialysis when compared to a non-CKD population.

Methods: We performed a retrospective cohort study using administrative health data from the Winnipeg Regional Health Authority, Canada. We included all adults (≥ 18 years) with CKD stages G3-G5 and patients undergoing dialysis between January 1st, 2010 and December 31, 2014. Secular trends in the in the rates of ED visits were calculated for those with CKD, those on dialysis and in the non-CKD population.

Results: Over the study period, patients undergoing dialysis had the highest incidence of ED visits, followed by patients with CKD and those with normal kidney function (150 vs 106 vs 34 per 100 persons per year respectively). These rates were stable over the period studied. Among the non-CKD population, the most common reasons for an ED visit were musculoskeletal complaints (25.6%), followed by gastrointestinal (11.04%) and cardiovascular complaints (10.26%). In the CKD and dialysis cohort, ED visits were more commonly secondary to cardiovascular complaints (21.54% and 18.99% respectively), followed by respiratory and gastrointestinal complaints. Admission to hospital was higher in CKD and dialysis populations than in the non-CKD population (29.56%, 26.07% vs 10.61%, respectively).

Conclusions: Patients with CKD present frequently to the ED, and are often admitted after presentation. Cardiovascular and respiratory complaints are more common in the CKD population.

SA-PO898

Associations of Opiate Use and Mortality Risk by Estimated Glomerular Filtration Rate in the NHANES Cohort

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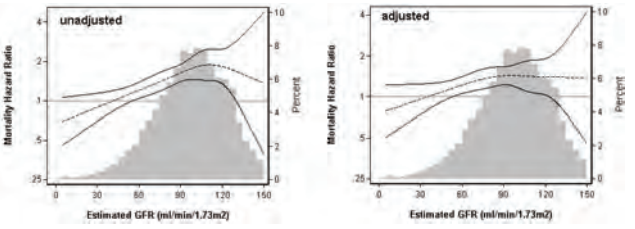
Background: A previous study from the National Health and Nutrition Examination Survey (NHANES) cohort revealed that adults with chronic kidney disease (CKD) had a higher likelihood of having an active prescription for opioid medication. Although it is known that opioids are associated with a higher mortality risk, it is unknown if that risk differs according to estimated glomerular filtration rate (eGFR) or CKD stage. We sought to examine the association of opioid use with mortality risk across eGFR in the NHANES cohort.

Methods: We examined associations of opioid use with mortality risk in 42,041 NHANES adult participants between 1999-2014 using Cox proportional hazards models with adjustment for demographics, body mass index, serum albumin and indicators of comorbid conditions such as cancer, diabetes, and hypertension. eGFR was estimated from serum creatinine using the CKD-EPI equation. Data on mortality up to year 2015 were downloaded from the corresponding CDC website. Effect modification by continuous eGFR using restricted cubic splines were modeled.

Results: The mean±SD age of the cohort was 47±19 years and was comprised of 52% females and 21% non-Hispanic black patients. Patients reporting opioid use were slightly older and were more likely to have a lower eGFR or eGFR<60 mL/min/1.73m^2. Overall opioid use was associated with a 27% higher risk of mortality in fully adjusted models (HR: 1.27, 95%CI: 1.13, 1.32). Hazard Ratios for eGFR 90+, 60-<90, and <60 were [HR:1.47, 95%CI: 1.20, 1.81; HR:1.32, 95%CI: 1.11, 1.58; HR: 1.06, 95%CI: 0.87, 1.29], respectively in fully adjusted models (p-for interaction eGFR-category and opioid use: p=0.067). In both unadjusted and adjusted models, restricted cubic splines show that the risk estimates of opioid use with mortality risk decline with lower GFR [figure].

Conclusions: In the NHANES cohort, mortality risk with opioid use appears to decline with lower eGFR or worsening CKD. Further studies should investigate these relationships in larger CKD cohorts with the ability to address potential confounding by indication, and impact of opioid dose, and opioid type.



SA-PO899

Laxative Use in Patients with Advanced CKD Transitioning to Dialysis

Keiichi Sumida,[1] Ankur A. Dashputre,[1] Praveen Kumar Potukuchi,[1] Suryatapa Kar,[1] Fridtjof Thomas,[1] Yoshitsugu Obi,[2] Miklos Z. Molnar,[1] Elani Streja,[3] Kamyar Kalantar-Zadeh,[4] Csaba P. Kovesdy.[1] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]University of California Irvine, Irvine, CA; [3]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [4]University of California Irvine, School of Medicine, Orange, CA.*

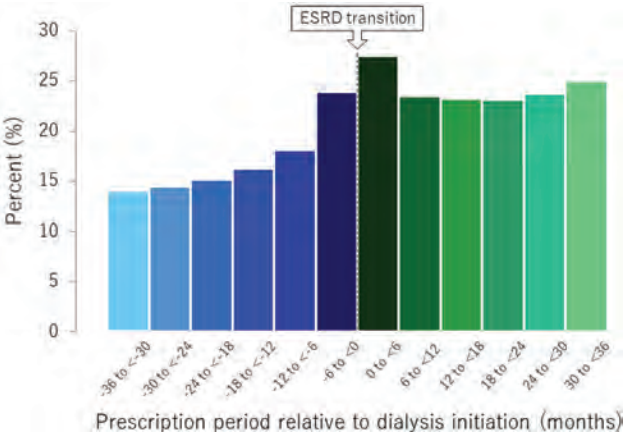
Background: Constipation, typically managed by laxatives, is one of the most prevalent conditions in primary care settings and associated with poor quality of life and adverse outcomes. Constipation is highly prevalent in dialysis patients; however, little is known about laxative use in patients with advanced CKD transitioning to dialysis.

Methods: In 67,377 US veterans transitioning to dialysis from 10/2007-3/2014, we examined the proportion of patients who filled a prescription for any type of laxatives within each 6-month time period over 36 months pre- and post-transition to ESRD. Prescribed laxatives were ascertained using both inpatient and outpatient prescriptions sourced from CMS Medicare Part D and VA pharmacy dispensation records. We also identified factors associated with pre-ESRD laxative use by multivariable logistic regression.

Results: The proportion of patients prescribed laxatives was 14% in -36 to <-30 months pre-transition to ESRD and gradually increased as patients progressed to ESRD. Laxative use markedly increased immediately prior to ESRD transition and reached the highest proportion (28%) in the first 6 months post-transition. The proportion remained relatively stable at ~23% throughout the rest of the post-transition period (Figure). The use of antihistamines (OR [95%CI], 3.12 [2.89-3.37]), antacids (2.06 [1.96-2.17]), and K-lowering agents (1.73 [1.65-1.82]) were the strongest factors associated with pre-ESRD laxative use after multivariable adjustment.

Conclusions: Laxative use increased considerably and peaked at 28% as patients neared transition to ESRD and remained fairly stable thereafter, likely mirroring the increasing burden of drug-induced constipation during the transition period. Further studies are needed to elucidate the underlying causes of this trend and the clinical implication of constipation management in advanced stages of CKD.

Funding: NIDDK Support



SA-PO900

Trends in Use of Antidiabetic Drugs Among Diabetic Patients with and Without CKD in the United States (2006-2016)

Yun Han,[1] Brenda W. Gillespie,[2] Nilka Rios Burrows,[3] Stephen R. Benoit,[3] Delphine S. Tuot,[4] Neil R. Powe,[5] William H. Herman,[1] Rajiv Saran.[1] *[1]University of Michigan, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI; [3]Centers for Disease Control and Prevention, Atlanta, GA; [4]University of California, San Francisco, San Francisco, CA; [5]Priscilla Chan and Mark Zuckerberg San Francisco Gen Hosp & UCSF, San Francisco, CA.*

Background: Since 2006, several new antidiabetic drugs have been introduced and shown to be safe in patients with chronic kidney disease (CKD) and metformin's use among CKD patients has been expanded. How these have changed the prescription of diabetes therapy plans is not clear. Our study compares trends in the use of ten different classes of antidiabetic drugs among diabetic (DM) patients with and without CKD in the US.

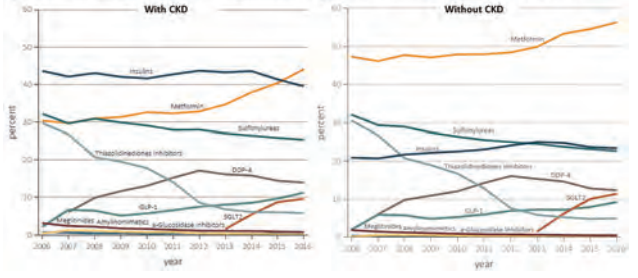
Methods: Analysis included 4,281,223 commercially insured members from Optum Clinformatics™ aged 20-64 years from 2006 to 2016. ICD-CM diagnosis codes were used to identify DM and CKD. Antidiabetic drug use by year was measured as the proportion of patients prescribed the specified medications. OLS model is used to compare changes in antidiabetic therapy between DM patients with and without CKD.

Results: Newer antidiabetic drugs, including SGLT2 inhibitors and two incretin-based therapies (DDP-4 inhibitors and GLP-1 agonists) are increasingly being used for DM patients regardless of kidney function (Fig.1, all p<0.001). There was a notable decline in the use of thiazolidinediones and sulfonylureas in both populations over the same time period (all p<0.001). The decrease in use of sulfonylureas was greater among those without CKD (p<0.05). From 2006-16 metformin use increased considerably from 30% to 44% among individuals with CKD and from 47% to 56% among individuals without CKD. In 2016, metformin became the most common therapy for both populations, followed by insulins. Insulin use slightly decreased after 2014, from 44% to 40% among those with CKD and 25% to 23% in those without CKD (p<0.01).

Conclusions: Use of SGLT2 inhibitors, incretin-based therapies, and metformin increased among individuals with and without CKD, suggesting that safety data has driven evidence-based practice. Nevertheless, substantial treatment differences exist in diabetes therapy among those with and without CKD suggesting that other strategies may be needed to accelerate translation of evidence to practice.

Funding: Other U.S. Government Support

Figure 1: Utilization rate of the 10 different classes of antidiabetic drugs in diabetic patients with or without CKD from 2006-2016



SA-PO901

The Effects of Testosterone Replacement Therapy (TRT) in Patients' Established CKD

Aditi Gupta,[1] Peter S. Wiegmann,[2] Virginia J. Savin,[3] Mukut Sharma,[4] Archana Goel,[4] Mariana Garcia-Touza,[6] Thomas Wiegmann.[5] *[1]University of Kansas Medical Center, Kansas City, KS; [2]Midwest Biomedical Research Foundation, Kansas City, MO; [3]KC VA Medical Center, Kansas City, KS; [4]KCVA Medical Center, Kansas City, MO; [5]VA Medical Center, Kansas City, KS; [6]Kansas City VA, Kansas City, MO.*

Background: We have previously shown that TRT provides significant survival benefits and reduces CKD progression in hypogonadic men. Testosterone deficiency is common in CKD but the benefits of TRT are disputed. Here we examined if TRT slows CKD progression, cardiovascular disease and all cause mortality in patients with established CKD.

Methods: Data from a large cohort of veterans diagnosed with low total testosterone (n=57,985) were used to determine the effect of TRT on the CKD progression, cardiovascular diseases and all-cause mortality in patients with CKD. Data were extracted using the Veterans Administration Informatics and Computing Infrastructure (VINCI), and analyzed using SAS. Propensity score matching was used to adjust for age, vascular disease and follow up time. Results were compared by means tests, frequency tables, odds ratio and p values (p=<0.01).

Results: Of the 3,627 patients with CKD, 2,469 received TRT, and of the 54,358 controls without CKD 41,965 received TRT. Mean baseline serum creatinine was 1.97 mg/dl in CKD and 0.98 mg/dl in controls. TRT reduced new cardiovascular accident (CVA) in CKD (OR 0.86, 95% CI 0.76-0.98), and in controls (OR 0.86, 95% CI 0.77-0.94), and reduced all-cause mortality in CKD (OR 0.749, 95% CI 0.66-0.85) and controls (OR 0.71, 95% CI 0.68-0.74). New myocardial infarction (MI) in CKD were higher with TRT (OR 1.37) and lower in controls (OR 0.79). Prior cardiovascular disease was more common with CKD (% difference CKD/Control), coronary artery disease (130), congestive heart failure (284), CVA (111), hypertension (92), MI (162), peripheral artery disease (265). Average follow up was 6.1 years.

Conclusions: The protective effect of TRT on CKD progression in hypogonadic men appears to taper off in patients with established CKD. CKD is associated with a higher burden of cardiovascular disease. TRT reduces all-cause mortality in established CKD (and controls) but the beneficial effect on cardiovascular events is blunted in CKD, underscoring importance of early TRT.

Funding: Other NIH Support - NIA

SA-PO902

Opioid Utilization for Pain Management Among Medicare Fee-for-Service Beneficiaries with ESRD in 2016

Matthew L. Maciejewski,[1,2] Lindsay Zepel,[5] Virginia Wang,[3,2] Clarissa J. Diamantidis,[4] Serene Olin,[8] Jacquelyn Blaz,[7] Shondelle Wilson-Frederick,[6] Valerie A. Smith.[5,1] *[1]VA HSR&D, Durham, NC; [2]Population Health Sciences, Duke University, Durham, NC; [3]Durham VA Health Care System, Duke University, Durham, NC; [4]Duke University School of Medicine, Durham, NC; [5]Duke University, Durham, NC; [6]CMS, Baltimore, MD; [7]National Committee for Quality Assurance, Washington, DC; [8]NCQA, Washington, DC.*

Background: Opioid misuse has raised concerns about opioid utilization under the Part D drug prescription benefit for Medicare beneficiaries. It is important to understand whether Medicare Fee-for-Service (FFS) beneficiaries with end-stage renal disease (ESRD) are more likely to utilize opioids compared to other beneficiaries.

Methods: We assembled a 100% Medicare FFS sample (n=20,880,490) with 12-month Part A, B, and D coverage between 1/1/2016-12/31/2016 to examine patient factors associated with 2 opioid utilization outcomes. We used a two-part model to estimate the probability of opioid utilization in 2016 via logistic regression and the level of average daily dose (ADD)≥120 morphine milligram equivalents (MME) via a generalized linear model with a gamma distribution and identity link in those with >1 opioid prescription. Beneficiary characteristics (age, disability, ESRD, dual eligibility, race and ethnicity, rurality, 16 chronic conditions) were adjusted.

Results: 35% of FFS beneficiaries had 1 or more opioid prescription fills in 2016 and 1.5% had ADDs≥120 MME. Compared to age-eligible beneficiaries without ESRD, beneficiaries were more likely to fill opioids if they were disabled with ESRD (odds ratio (OR)=2.57, 95% confidence interval (CI): 2.53, 2.61) or without ESRD (OR=1.43, 95% CI: 1.42, 1.43), age eligible with ESRD (OR=1.99, 95% CI: 1.96, 2.02), or eligible due to ESRD alone (OR=2.31, 95% CI: 2.25, 2.37). Beneficiaries who were disabled without ESRD (OR=2.99, 95% CI: 2.95, 3.03) or with ESRD (OR=1.34, 95% CI: 1.29, 1.40) had higher odds of having ADDs≥120 MME, while beneficiaries who were age-eligible with ESRD (OR=0.71, 95% CI: 0.66, 0.76) had lower odds compared to those age-eligible without ESRD.

Conclusions: Beneficiaries who are vulnerable due to ESRD filled opioid prescriptions at higher rates than other beneficiaries and at ADDs ≥120 MME. Based on recently endorsed opioid-related quality metrics and more restricted policies on opioid dispensing, these beneficiaries should be prioritized for opioid optimization strategies to balance pain management and adverse event risk.

Funding: Veterans Affairs Support, Other U.S. Government Support

SA-PO903

Acceptance Measured as Psychological Flexibility Protecting Against Depression Among Different Severities of CKD

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Background: Depression is associated with poor survival among chronic kidney disease (CKD) patients. Psychological flexibility (PF) is conceptualized as "the ability to contact the present moment more fully (i.e., accept any physical or emotional experiences without controlling them) and to change, or persist in, behaviors to pursue identified values." Although PF is often measured as acceptance in clinical settings and its reduction by behavioral therapy is associated with reduced depression in the general population, this concept has not been examined in CKD patients.

Methods: This multicenter cohort study included five hospitals in Japan and patients with non-dialysis stage 3-5 CKD or stage 5D CKD receiving hemodialysis or peritoneal dialysis. The main exposure was PF measured by a 7-item Acceptance and Action Questionnaire (AAQ-II). The inverse mean of its summation score was used (ranging from 1 [low PF] to 7 [high PF]). The outcome was depression defined as a Center for Epidemiologic Studies Depression (CES-D) questionnaire score of 16 points or higher. The association between PF and presence of depression among all CKD patients, and between PF and incidence of depression after one year among CKD patients without baseline depression were analyzed by logistic regression models, with adjustment for age, sex, performance status, primary renal disease, treatment modality, presence of family, work status, and comorbidities.

Results: The cross-sectional and longitudinal analyses included 433 and 195 patients, respectively. The means (standard deviations) of age, PF, and CES-D were 67.2 (13.8) years, 5.64 (1.14) points, and 13.4 (8.6) points, respectively. Higher PF was associated with lower likelihood of depression (per 1 point increase, adjusted odds ratio [AOR] 0.44, 95% confidence interval [95%CI] 0.35-0.55) and lower likelihood of developing depression (per 1 point increase, AOR 0.50, 95%CI 0.33-0.75) after one year.

Conclusions: PF measured by the AAQ-II was associated with lower prevalence and incidence of depression. Nonpharmacological interventions to improve PF, such as acceptance and commitment therapy, could be useful for preventing depression in patients with different severities of CKD.

SA-PO904

Cognitive Impairment, Vascular Dysfunction, and Sedentary Behavior Differ Between Older Adults with and Without CKD

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Background: Chronic kidney disease (CKD) is common in older adults and is associated with numerous complications, including cognitive impairment and vascular dysfunction. Additionally, older adults have lifestyle factors that can negatively influence health, including being sedentary- a phenomenon associated with cognitive impairment, vascular dysfunction, and mortality in the general population. The objective of this study was to determine if there are differences in cognitive impairment, vascular dysfunction, and sedentary behavior between older adults with and without CKD. We hypothesized that older adults with CKD would exhibit cognitive and vascular impairment and be more sedentary, compared to those without CKD.

Methods: Utilizing a cross-sectional approach, 48 older adults (24 with CKD, age 68.4(5.6), eGFR 43.9(11.6)ml/min; 24 without CKD, age 68.5(5.5), eGFR 82.7(12.3) ml/min) were evaluated for performance on a test of global cognition and executive function (Montreal Cognitive Assessment (MoCA)), vascular function via carotid-femoral pulse wave velocity (cfPWV)) and ultrasound (carotid compliance, flow mediated vasodilation), and sedentary behavior via actigraphy. Data was analyzed utilizing t-tests and OLS regression.

Results: Older adults with CKD had higher levels of cognitive impairment and vascular dysfunction and higher sedentary time. In regressions including CKD and the covariates of age, years of education, history of smoking, and gender, the variance was significantly explained for total MoCA score, MoCA executive function score, cfPWV, indicators of carotid compliance, and sedentary time per day.

Conclusions: Cognitive impairment, vascular function, and sedentary behavior in older adults with CKD are different compared to those without CKD. This represents a possible unique phenotypic presentation in this at-risk population.

Funding: Private Foundation Support

	Non-CKD	CKD	t	p	R^2	p
	n=24	n=24				
MoCA	26.79 (2.69)	23.04 (2.93)	4.62	<.05	.3468	.0003
Executive Function	4.46 (.78)	3.29 (.95)	4.64	<.05	.3708	.0001
cfPWV	7.45 (.96)	8.66 (1.65)	-3.02	.0042	.2189	.0148
Distensibility Coefficient	.0028 (.00075)	.002 (.001)	3.04	.0038	.1774	.0337
Young's Modulus	888.77 (324.32)	1286.6 (489.0)	-3.32	.0018	.2089	.0153
Elastic Modulus	13017.5 (4059.1)	17983.5 (7289.4)	-2.92	.0055	.1720	.0384
Sedentary min/day	654.17 (106.3)	707.64 (107.3)	-1.72	.0931	.2329	.0092

SA-PO905

Central Systolic and Pulse Pressures as Predictors of Cardiovascular Events: A Prospective Study

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Background: Central blood pressure (BP) is proposed as a better predictor of cardiovascular (CV) burden than peripheral BP. Nevertheless, its clinical value remains to be determined. This study aims to characterize the role of central BP in CV risk stratification.

Methods: We included 15,923 CARTaGENE participants with available central BP (SphygmoCor Px; type I device) and prospective data from an administrative healthcare database. Major adverse CV events (MACE) included myocardial infarction, stroke, heart failure with hospitalization and CV death. The associations between of brachial and central BP parameters with MACE were assessed using Cox regressions adjusting for: age, sex, BMI, smoking, diabetes, known CV disease, HbA1c, LDL-c, eGFR, uric acid, heart rate, use of beta-blockers, renin-angiotensin system blockers, calcium channel blockers, diuretics, aspirin, clopidogrel and anticoagulants. Restricted cubic splines were performed to account for nonlinear associations.

Results: 1,399 MACE occurred over a median follow-up of 70 months. Significant associations between central and brachial systolic and pulse pressures (PP) and MACE were found (Figure 1). Increments of 5 mmHg in brachial and central systolic BP were both associated with increased risk [HR 1.04 (95%CI 1.01-1.06), p<0.005, for both], which was significant at BPs greater than 130 mmHg and 140 mmHg respectively. HRs remained similar at higher values of systolic BP and PP.

Conclusions: There is a significant association between MACE and both central and brachial systolic BP and PP. There appears to be a similar relationship between central and brachial BP parameters and CV risk but with different thresholds. In this regard, central BP alone estimated with SphygmoCor may not provide an added benefit in CV risk stratification compared to brachial BP.

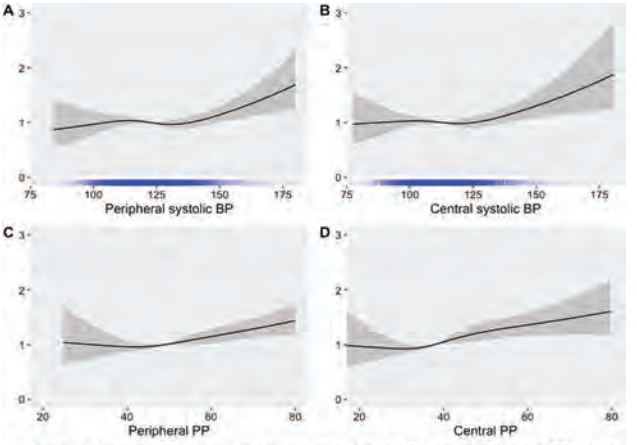

Figure 1. Relationship between central and brachial BP parameters and MACE for A) Brachial systolic BP, B) Central systolic BP, C) Brachial PP and D) Central PP. Hazard ratios with 95% confidence intervals. Marginal rug on X axis representing the distribution of systolic BP. BP; blood pressure, PP; pulse pressure.

SA-PO906

Iohexol Renal Measurement In Uro-Oncological Patients: Ready to Quit Pandora's Box?

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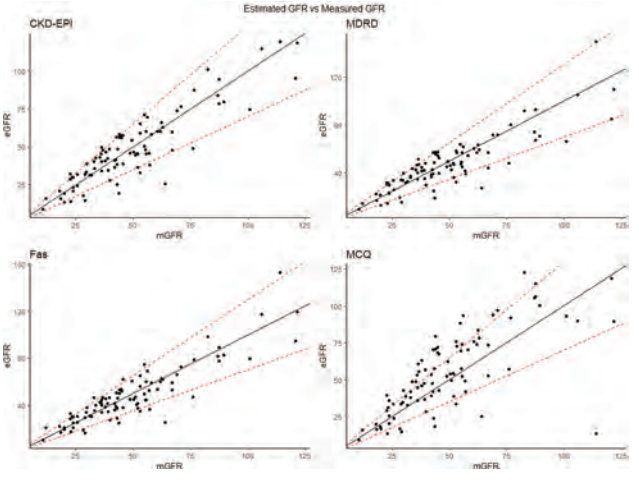
Background: An accurate assessment of renal function in urological and oncological patients should be mandatory to define the most appropriate urological surgery technique (nephron sparing vs radical nephrectomy) and to decide the correct dose for each type of chemo-immuno therapy. Unfortunately, the most used method to measure GFR in clinical practice is represented by the estimated glomerular filtration rate (eGFR) which harbours error in comparison to gold standards methods (mGFR). The objective of this study is to determine the extent of the error of eGFR in the oncological and urological pts category.

Methods: A prospectively consecutive cohort of 91 pts affected by uro-oncological neoplasm was collected comparing eGFR with mGFR using iohexol renal measurement. Four estimated GFR formulas were used for this study: CKD-EPI, MDRD, MCQ, FAS. The agreement them was evaluated taking in account Bias, expressed as median of percent difference between mGFR and eGFR and overall accuracy as P_{30} representing the percent of estimates within 30% of measured GFR.

Results: The agreement between formulas and mGFR was poor. The Bias for MDRD was -1%, for CKD-EPI was 0%, for FAS was 1% and for MCQ was -19% indicating that, except for the latter, those formulas don't harbour systematic errors. Different information was provided by the accuracy parameter: the P_{30} was 81% for CKD-EPI, 76% for MDRD, 82% for FAS and 58% for MCQ.

Conclusions: In our cohort study we observed that formulas equally over or underestimate mGFR resulting in unbiased methods; however the magnitude of the over/underestimations is not negligible, at least ± 20 mL/min/1.73 m^2, and could led to errors in clinical management.



eGFR formulas vs mGFR: Black line represents identity; red dotted lines represent P_{30} boudaries

SA-PO907

Association Between Kidney Function and the Risk of Cancer: Results from the China Health and Retirement Longitudinal Study (CHARLS)

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Background: Increased cancer risk after dialysis or transplantation has been recognized, but studies of cancer in pre-dialysis chronic kidney disease are extremely limited. Therefore, we aim to investigate the risk of cancer in individuals with reduced kidney function.

Methods: Our study was based on a nationally representative sample of population aged 45 years or older from China Health and Retirement Longitudinal Study (CHARLS) conducted between June 2011 and March 2015. Altogether 17,708 participants were randomly chosen using a multistage sampling scheme. For the current analyses, 11,508 eligible individuals with measurement of kidney function and without cancer at baseline were included. Then, 104 participants without follow-up and 392 died of causes unrelated to cancer during follow up were excluded. Estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiological Collaboration equation. Reduced kidney function was defined as eGFR <60 ml/min/1.73m^2. Incident cancer cases diagnosed by doctors were documented in the biennial questionnaire of CHARLS. Poisson regression was used to examine the association between kidney function and the risk of cancer.

Results: Altogether 11,012 participants with an average of 58.6 years were included. Participants with eGFR≥90, 60 to 89, and <60 ml/min/1.73m^2 accounted for 63.4%, 33.4% and 3.2%, respectively. During 43,854 person-years of follow-up, 217 new cases of cancer were recorded. Compared to participants with eGFR ≥90 ml/min/1.73m^2, those with eGFR <60 ml/min/1.73m^2 was associated with the increased risk of cancer, with fully adjusted relative risk of 2.04 (95% confidence interval 1.20 to 3.46).

Conclusions: Reduced kidney function is associated with a higher risk of cancer and therefore should be integrated into the risk-stratification of cancer management.

RRs and 95% CIs for cancer risk in different eGFR groups.

eGFR, ml/min/1.73m^2	Number	No. of case	Incidence rate, Per 10,0000 person-year	RR (95% CI)[a]	RR (95% CI)[b]	RR (95% CI)[c]
≥90	6979	117	421	1 [reference]	1 [reference]	1 [reference]
59 to 89	3677	79	540	1.28 (0.96, 1.70)	1.04 (0.76, 1.43)	1.01 (0.73, 1.38)
<60	356	21	1489	3.52 (2.21, 5.60)	2.41 (1.43, 4.07)	2.04 (1.20, 3.46)

a. Unadjusted;

b. Adjusted for age, sex and smoking;

c. Adjusted for age, sex, smoking, education, PCE, BMI, drinking, diabetes, hypertension, dyslipidemia and micro-inflammation.

SA-PO908

Effect of Statins on Cardiovascular Complications in CKD Patients: A Network Meta-Analysis

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Background: It is well known that cardiovascular mortality and morbidity increase in advanced chronic kidney disease **(**CKD), and that mild to moderate CKD is also associated with an increase in cardiovascular events. Statins have been shown to reduce cardiovascular events, and in this study we investigated the lipid-lowering effect of different statins in CKD patients.

Methods: We searched CENTRAL, MEDLINE, Embase, and Science Citation Index Expanded databases from 1970 until February 2019 to identify cardiac events, cardiac mortality, and all-cause mortality affect in CKD patients according to statin types and doses. We performed direct and indirect network meta-analysis in Bayesian models and generated rankings of the different lipid-lowering agents via generation mixed treatment comparison.

Results: We analyzed the network meta-analysis of 19 studies (N = 45,863) for commonly used statins. Compared with placebos, pravastatin 40 mg groups showed a statistically significant decrease in patient mortality(odds ratio0.66 [95% confidence interval, 0.46 to0.91]). In reducing cardiac events, atorvastatin 80 mg, fluvastatin 40 mg, lovastatin 20 mg, pravastatin 40 mg, and simvastatin 40 mg showed statistically significant effects. In rank probability, pravastatin was ranked first in all-cause mortality rate. In cardiac events, lovastatin, fluvastatin, and pravastatin ranked first, second, and third, respectively.

Conclusions: We found that pravastatin 40mg reduced mortality and cardiovascular events CKD patients receiving statin therapy of hyperlipidemia. In addition, drugs that reduce cardiovascular events appeared effective in the order, lovastatin 20 mg, fluvastatin 40 mg, and pravastatin 40 mg.

SA-PO909

Continuous System Improvements to Reinstate Kidney Patients Lost to Follow-Up

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Background: In chronic disease clinics, reducing the number of patients who are lost to recommended follow-up (LTFU) may improve outcomes. We designed a method to identify LTFU patients and trigger a procedure to schedule appointments. Using this system at our nephrology clinic, we reduced the number of LTFU patients from 24% to 3.8% in one year. MDs activated an electronic medical record (EMR) trigger indicating follow-up (FU) time frame for 77% of visits. We sought to explore reasons for incomplete MD EMR triggers use and persistent LTFU patients.

Methods: We generated a monthly LTFU report that identifies patients who did not return to clinic in the recommended FU time frame. Clinical staff called these patients and classified them into three groups: "scheduled" (appointment made successfully); "no need to return" (patients transitioned to dialysis, transferred to another nephrologist, declined appointment, or died); or "active" (i.e. actively trying to reconnect). We aimed to increase MD use of the EMR trigger by faculty meeting reminders and administrative assistant prompts. Lastly, we identified explanation categories for patients persisted on the "active" list.

Results: We had 5730 patient visits from 1/31/2018 to 3/31/2019. MDs successfully used the EMR trigger on 3598 (62.8%) of the visits. The most common barriers for using the EMR trigger were: rotating trainees not familiar with this system; MDs running behind on charting; and MDs short on time during clinic. We identified 460 (12.8% of total visits) LTFU patients among whom 252 (54.8%) were "scheduled,"114 (24.8%) were designated "no need to return," and 94 (20.4%) as "actively trying to reconnect." Among the 94 patients, reasons we were unable to reach patients included homelessness; inaccurate contact information; and having multiple stressors at home causing postponement of routine care.

Conclusions: Retention in care is associated with improved outcomes. Our team has identified a method by which patients LTFU were identified and reconnected. A future goal may be to make MD trigger activation mandatory via EMR validation point. For the difficult to reconnect patients who may be the most vulnerable, a team approach with case management may improve the chances of reconnection. Limitations of our study are that we lack outcome data on patients who were LTFU and the development and implementation of the system is time-intensive.

SA-PO910

Resistance Exercise Training in CKD: A Randomized Pilot Trial

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Background: Resistance exercise training has been shown to improve vascular function and cardiovascular risk factors in healthy individuals, but studies in patients with chronic kidney disease (CKD) are lacking.

Methods: We randomly assigned adults with mild-to-moderate CKD to a 12-week resistance exercise training intervention (45-minutes sessions, twice per week) or to control (educational material regarding the benefits of physical activity). The primary outcomes were aortic pulse-wave velocity (PWV), carotid artery stiffness and systolic blood pressure (BP), measured at baseline, 6 weeks and 12 weeks. Intention-to-treat analyses with repeated measures ANOVA were used.

Results: Of the 32 individuals included in the analyses (15 randomized to the intervention group and 17 to the control group), mean (SD) age was 57 (1.8) years, 47% were male, 94% African American, and 27% had diabetes; mean (SD) eGFR was 42 (14) ml/min/1.73m^2. Of those randomized to the resistance exercise intervention, 67% completed at least half of the training sessions. No adverse effects were observed with the intervention. There was a decrease in PWV, carotid stiffness and systolic BP among participants randomized to resistance exercise training, but these changes were not statistically significant when compared with controls (Table).

Conclusions: Resistance exercise training is feasible and safe among patients with CKD, and has the potential of improving vascular function in this population.

Funding: NIDDK Support

Outcome Measures Mean (SD)	Baseline	Week 6	Week 12	p-value
PWV, m/s				
Intervention	9.5 (2.9)	7.9 (1.6)	8.3 (2.0)	0.2
Control	9.1 (2.9)	9.1 (2.5)	8.5 (2.9)	
Carotid ß stiffness				
Intervention	10.1 (3.8)	8.8 (2.5)	8.5 (3.6)	0.5
Control	10.6 (4.7)	10.0 (4.0)	10.1 (4.5)	
Systolic BP, mmHg				
Intervention	141 (19)	127 (14)	133 (19)	0.9
Control	131 (19)	134 (18)	129 (21)	

SA-PO911

Effect of Sodium Bicarbonate on Acid Excretion and BP in Patients with and Without CKD: The Acid-Base Compensation in CKD (ABC) Study

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Background: As kidney function worsens, net acid excretion (NAE) diminishes resulting in subclinical, then overt, metabolic acidosis (MA). Treatment with alkali may improve outcomes in CKD even when overt MA is not present. Our goal was threefold: 1) evaluate NAE and response to alkali in the setting of controlled diet acid load; 2) compare response in those with and without CKD; and 3) evaluate change in 24h BP as a potential mechanism of benefit.

Methods: We enrolled 14 non-diabetic adults in a random order, cross-over feeding study; 8 had CKD and 6 did not. After a 3-day run-in, participants consumed a 7-day controlled acid load diet supplemented with $NaHCO_3$ tablets (alkali; 31 or 39 mEq/day based on weight) and an identical 7-day diet supplemented with NaCl as table salt (control), in random order. We assessed NAE and other acidification markers from two 24h urines, and measured 24h ambulatory BP at the end of each period. We estimated the alkali effect using mixed models adjusted for CKD status, study period, and intervention order, and tested for interaction between alkali and CKD.

Results: Mean age was 68, 64% were women, and 57% were white. In the control period, mean NAE and urine citrate were lower for those with CKD (29.6±7.7 mEq/d and 388.4±213.5 mg/d) vs. non-CKD (40.4±18.6 mEq/d and 687.5±218.6 mg/d) on identical diets. Overall, alkali lowered NAE and urine ammonium and increased urine pH, HCO_3 and citrate. Response in urine pH and citrate to alkali differed by CKD status. Alkali increased urine pH more in patients with vs. without CKD (p-int=0.17), whereas urine citrate increased only among those with CKD (p-int=0.05). Alkali had no effect on 24h BP (**Table**).

Conclusions: Despite identical diets, NAE and urine citrate are lower in CKD vs. non-CKD suggesting that NAE in CKD has non-diet determinants. $NaHCO_3$ decreases NAE; however, it increases, thereby restoring, lower urine citrate in CKD. Urine citrate may be a useful marker of early, subclinical acidosis in CKD that responds to therapy.

Funding: NIDDK Support

	β (95% CI)
Urine studies	
Δ NAE, mEq/d	-20.7 (-29.9, -11.5)*
Δ Ammonium, mEq/d	-7.0 (-12.2, -1.8)*
Δ Bicarbonate, mEq/d	7.0 (4.0, 10.1)*
Δ Citrate, mg/d	25.5 (-65.5, 116.4) Non-CKD; 131.5 (52.7, 210.2)* CKD
Δ pH	0.6 (0.2, 1.0)* Non-CKD; 0.9 (0.6, 1.3)* CKD
24-hour mean BP	
Δ Mean 24-hour SBP, mm Hg	-2.1 (-6.0, 1.8)
Δ Mean 24-hour DBP, mm Hg	-0.3 (-2.8, 2.1)

For outcomes without a treatment-by-CKD effect at p>0.20, main alkali effects are displayed adjusted for CKD status, period, and intervention order. For outcomes with a treatment-by-CKD effect at p≤0.20, simple alkali effects are displayed adjusted for CKD status, period, intervention order, and alkali-by-CKD interaction. Overall N = 14, CKD N = 8, Non-CKD N = 6. Δ represents value at end of intervention period minus value at end of control period, irrespective of randomization order.

SA-PO912

Nitrite, Isoquercetin, and Endothelial Dysfunction Trial (NICE trial): Design and Preliminary Data

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Background: Endothelial dysfunction may be an early etiology for chronic kidney disease (CKD) and cardiovascular disease in CKD. We studied the safety and efficacy of combination treatment with sodium nitrite and isoqercetin on endothelial dysfunction, inflammation and oxidative stress in CKD patients.

Methods: This double blind, randomized, placebo-controlled trial enrolled 70 CKD patients. 35 patients were randomly assigned to oral combination of immediate-release sodium nitrite (40 mg twice daily) and isoquercetin (225 mg, once daily) or placebo for 3 months. The primary endpoint was changes in flow-mediated dilation (FMD) from baseline. The secondary endpoints were changes in biomarkers of endothelial function, inflammation, oxidative stress, eGFR, and urine albumin. The follow-up rate was 97%. Mixed-effects models were used to assess the treatment effects.

Results: Baseline characteristics were similar between groups. FMD increased by 1.13% (95% confidence interval [CI], -0.07 to 2.32) vs. 0.34% (95% CI, -0.86 to 1.53) in treatment vs. placebo group (p=0.35). The level of von Willebrand factor (vWF) decreased by 695 pg/mL (95% CI, -3793 to 2403) vs. increased by 2768 pg/mL (95% CI, -300 to 5838) in treatment vs. placebo group (p=0.047). There were statistically insignificant reductions between treatment and placebo groups in other biomarkers of endothelial dysfunction (intercellular adhesion molecule-1, vascular adhesion molecule-1, E-selectin, and Endothelin-1), oxidative stress (oxidized low-density lipoprotein and nitrotyrosine), and urine albumin. Additionally, there were no differences in changes of inflammatory biomarkers (C-reactive protein, tumor necrosis factor-α, interleukin [IL]-6, and monocyte chemoattractant protein-1) except IL-17 (1.35 [95% CI, 0.87 to 1.82] vs. 1.98 [95% CI, 1.50 to 2.45] in treatment vs. placebo group, p=0.05). There was no significant change in eGFR between groups. Methemoglobin and side effects were not different between groups.

Conclusions: The combination treatment significantly reduces vWF and IL-17 and may potentially improve endothelial dysfunction, inflammation, oxidative stress, and proteinuria. Larger trial is warranted to confirm those findings.

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SA-PO913

Correspondence of Ankle-Brachial Index and Doppler Ultrasound Findings in Patients with CKD

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Background: Ankle-brachial index (ABI) is used to diagnose peripheral artery disease (PAD). ABI may be artificially high among patients with chronic kidney disease (CKD) due to increased arterial calcification and stiffness. It is not well studied how ABI and toe-brachial index (TBI) are correlated with more accurate diagnostic measures of doppler ultrasound in evaluating PAD in CKD.

Methods: We conducted retrospective chart review among pre-dialysis CKD patients in Tulane Hospital in New Orleans, Louisiana. Total of 251 were included in the study. De-identified demographic information, clinical measures, ABI, TBI, and doppler ultrasound findings were extracted into the study forms. The correlations of ABI, TBI, doppler waveforms, and peak systolic velocity (PSV) were analyzed. PSV is calculated as percentage change of measured PSV from normal value.

Results: Among patients with ABI ≤ 0.9, 73% had normal US waveform, 24% had biphasic waveform, and 3 % had monophasic waveform; 54% had TBI ≤ 0.7. Among those with ABI > 1.4, 77% had normal waveform, 23% had biphasic waveform, and 0% had monophasic waveform; 0% had TBI≤ 0.7. Among those with TBI ≤ 0.7, 50% had normal waveform, 43% had biphasic waveform, and 7% had monophasic waveform. In addition, ABI ≤ 0.9 or >1.4 and TBI ≤ 0.7 were poorly corelated with a ≥30%- <100% or ≥ 100% increase in PSV.

Conclusions: These data indicate that the ABI and TBI diagnostic criteria for PAD needs to be further evaluated in CKD. Larger study is warranted to confirm these study findings.

SA-PO914

Correlation of Raised NT proBNP Levels and Left Ventricular Filling Pressure in CKD Patients with Acute Decompensated Heart Failure (ADHF)

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Background: Left ventricular filling pressures (LVFP) and N-Terminal pro brain natriuretic peptide (NT-proBNP), both of which are well known indicators of poor prognosis, are elevated in ADHF. The relationship of NT pro-BNP with LVFP in CKD patients is not well documented. Therefore, the aim of our study is to find integrative utility of measuring NT-pro BNP levels with LVFP in patients with acute dyspnea enabling their utilization as diagnostic and prognostic markers in the management of CKD patients with ADHF.

Methods: From 1st May, 2018 through 30th April, 2019, 450 patients who presented in Emergency department of Doctors Hospital Lahore with acute dyspnea and potential fluid overload were assessed. Out of these, 85 patients who underwent simultaneous echocardiography and NT Pro BNP measurement were included in the study. Charts were analysed by a nephrologist and cardiologist. Both CKD(66) and non CKD(19) patients with reduced LV ejection fraction (LV EF <40%:HFrEF), Midrange (LV EF:40-50%: HFmrEF) and preserved ejection fraction(LV EF >50%:HFpEF) were included. eGFR was measured using the CKD-EPI(Chronic kidney disease Epidemiology collaboration) equation. Data was analysed using SPSS version 25.

Results: Echo parameters were compared with different NT pro-BNP levels in this study group. The mean value of NT pro BNP was much higher(1895.74±10.57 pmol/L) in CKD patients with ADHF as compared to non CKD patients(550.66 pmol/L). As shown in the image, in patients with eGFR<60ml/min with ADHF and NT Pro- BNP > 1000, 51.8% had EF less than 40%(14/27)(p-value :0.014) 74% of patients had increased LVFP(20/27) (p-value:0.028), 85.1% had PCWP more than 15 mmHg (23/27)(p-value:0.031), and 76.9% had Grade II/III Diastolic dysfunction (20/26)(p-value:0.051).

Conclusions: NT pro-BNP is a rapid and reliable marker for accurate and early diagnosis of ADHF since it has a significant correlation with LVEF and LVFP in CKD patients with ADHF.

NT pro-BNP Levels(pmol/L)			<100	100-500	500-1000	>1000	p-value
eGFR < 60ml/min	EF(%)	<40	1	5	0	14	0.014
		40-49	0	2	2	4	
		≥50	8	16	5	9	
	LVFP	Normal	7	13	3	7	0.028
		Increased	2	10	4	20	
	PCWP(mm Hg)	<15	6	7	2	4	0.031
		>15	3	16	5	23	
	Diastolic Dysfunction	Grade I	3	7	0	6	0.051
		Grade II-III	2	11	4	20	

SA-PO915

Effects of a 16-Week Physical Training on Mortality, Quality of Life, and CKD Progression: NEPHROS Post-Trial Follow-Up

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Background: The NEPHROS is a randomized controlled trial which applied a 16-week aerobic and resistance training to patients with chronic kidney disease (CKD) and high blood pressure and found an improvement in functional capacity, inflammatory status and metabolic profile, compared with usual care. The current report describes a long-term post-trial observational follow-up study, comparing survival, health-related quality of life (HRQoL) and estimated glomerular filtration rate (eGFR) change between the intervention and control groups, and according to in-trial cardiovascular (CV) risk factors. Clinicaltrials.gov NCT01935297.

Methods: After three years of the original trial, the NEPHROS participants were revaluated. Cox proportional hazards was used to compare survival time and linear regression to compare the change in eGFR and physical and mental HRQoL summary scores, between intervention and control groups, and according to age, sex, and in-trial eGFR, hs-CRP, fasting plasma glucose, lipids, ankle-brachial index (ABI), functional capacity and blood pressure (BP).

Results: Of the 150 participants of NEPHROS, 128 individuals were included in the long-term analysis. There were 13 deaths, no patient needing renal replacement therapy, and none reported maintaining regular exercise. No effect of the previous exercise training on survival, eGFR or HRQoL change was observed. Baseline in-trial eGFR (HR 0.95; 95% CI 0.92 to 0.98) and ABI (HR 0.03; 95% CI 0.002 to 0.43) were positive independent predictors for survival. Lower ABI (coef. 9.00; 95% CI 0.43 to 17.5) and higher systolic blood pressure (coef. -0.13; 95% CI -0.24 to -0.03) were independent predictors for eGFR decline.

Conclusions: We conclude that **l**ower eGFR and ABI, and higher systolic BP were associated with poorer prognosis among CKD patients. A sixteen-week exercise program had no long-term effect on survival, quality of life or glomerular filtration change in patients with CKD stages 2 to 4. This finding highlights the scant usefulness of short-lasting structured exercise interventions if not associated with long-term lifestyle changes.

SA-PO916

What Is the Best Predictable Subfraction for Cardiovascular Outcomes in Patients with CKD?

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Background: Dyslipidemia is an important parameter for prediction of cardiovascular disease (CVD). We aimed to investigate the most valuable subfraction of lipid for predicting CVD in patients with chronic kidney disease (CKD).

Methods: We retrospectively reviewed the National Health Insurance Service (NHIS) database for a people who received nationwide health check-up in 2009. The population was divided as control, early CKD (eGFR 45-60 ml/min/m^2), and advanced CKD (eGFR <45 ml/min/m^2) by estimated glomerular filtration rate. Each subfraction of lipid profile including LDL, TG, HDL, and TG/HDL was categorized by decile, and the reference was the fifth decile. The end-point of the study was major adverse cardiovascular events (MACCE) such as fatal, non-fatal myocardial infarction, revascularization, acute ischemic stroke, and heart failure. The hazard ration (HR) of MACCE was calculated using Cox regression models after adjustment of multiple covariates.

Results: A total of 3,634,915 examiners were included in this study with 66,810 (1.8%) and 404,315 (11.1%) in advanced and early CKD, respectively. For all populations, LDL, TG, and TG/HDL showed a linear relationship to MACCE, the tenth decile for each subfraction showed highest adjusted HR: 1.45 (1.42-1.49) in LDL; 1.25 (1.22-1.28) in TG; 1.30 (1.27-1.33) in TG/HDL. Moreover, HDL showed inversed relation with lowest HR 0.88 (0.85-0.90) in the tenth decile. In the subgroup analysis for LDL and TG/HDL, control and early CKD showed similar patterns for HR with significantly increasing from the sixth decile. In advance CKD, TG/HDL showed significant HR in the tenth decile as 1.19 (1.05-1.34). However, there was no significance of LDL for MACCE in advanced CKD.

Conclusions: The pattern and significance of lipid subfraction were different according to the grade of renal function. Thus, TG/HDL should be additionally considered with LDL as a target variable in patients with advanced CKD.

SA-PO917

Outcomes in Patients with Renal Impairment and Myocardial Infarction Identified by High-Sensitivity Cardiac Troponin Testing: A Prespecified Analysis of the High-STEACS Trial

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Background: Patients with renal impairment are at increased risk of myocardial infarction (MI), but the interpretation of cardiac troponin in this context is challenging. Using a high-sensitivity cardiac troponin I (hs-cTnI) assay that has been widely adopted into clinical practice, we describe the diagnosis and outcomes of patients with MI, stratified by renal function.

Methods: In a pre-specified secondary analysis of a stepped-wedge cluster-randomised controlled trial, consecutive patients with suspected acute coronary syndrome (ACS), a hs-cTnI concentration greater than the sex-specific 99th centile and renal impairment (defined as an estimated glomerular filtration rate [eGFR] of <60 mL/min/1.73m^2) were identified between June 2013 and March 2016. Diagnoses of type 1 or type 2 MI were adjudicated and classified according to the 4th Universal Definition of Myocardial Infarction. The primary outcome of type 1 MI or cardiovascular death was compared in patients with and without renal impairment at 1 year.

Results: eGFR was available in 46,927 (97.1%) patients. 38,994 (83.1%) patients had an eGFR ≥60, 6,627 (14.1%) had an eGFR 30-59 and 1,306 (2.8%) had an eGFR <30. Plasma hs-cTnI concentrations were raised in 47.9% of patients with and 16.2% without renal impairment. Patients with renal impairment were less likely to be diagnosed with type 1 MI (35.2% [1,336/3,800] *vs* 56.3% [3,556/6,311]) but more likely to be diagnosed with type 2 MI (12.6% [480/3,800] *vs* 9.8% [619/6,311]; P<0.001 for both) than patients with normal renal function. In patients with hs-cTnI concentrations >99th centile, the risk of subsequent MI or cardiovascular death at 1 year was significantly increased in patients with renal impairment compared to those without it (24.9% [945/3,800] *vs* 12.0% [757/6,311]; adjusted hazard ratio [aHR] 1.56, 95% CI 1.34 to 1.82; P<0.001). This risk increased as eGFR declined: 30-59 mL/min/1.73m^2 (23.2% [674/2,905]; aHR 1.51, 95% CI 1.28-1.78); <30 mL/min/1.73m^2 (30.3% [271/895]; aHR 1.74, 95% CI 1.39-2.19) (P<0.001 for both).

Conclusions: Almost half of all patients with suspected ACS and renal impairment had a hs-cTnI greater than the sex-specific 99th centile. This was associated with a poorer prognosis, especially in those with an eGFR <30mL/min/1.73m^2.

SA-PO918

A Cardiovascular Risk Mitigation Strategy on the Safety of Bardoxolone Methyl Post-BEACON

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Background: Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes (BEACON) was a multinational, randomized, double-blind, placebo-controlled Phase 3 trial that enrolled patients with type 2 diabetes (T2D) and stage 4 CKD. The BEACON trial was terminated due to a significant increase in the risk of heart failure occurring within the first four weeks of treatment with bardoxolone methyl (Bard). Post-hoc analyses identified a history of heart failure and elevated baseline serum concentrations of B-type natriuretic peptide (BNP) as risk factors for these events. Four subsequent clinical trials in other disease states have excluded patients with these clinical characteristics. Additionally, BNP and NT-proBNP were measured as safety parameters over the course of these trials. Safety data from these trials will be presented.

Methods: Data from four studies were included: a 48-week, open-label Phase 2 study in patients with Alport syndrome (CARDINAL; NCT03019185); a 12-week, open-label Phase 2 study in patients with autosomal dominant polycystic kidney disease, IgA nephropathy, focal segmental glomerulosclerosis, or type 1 diabetes CKD (PHOENIX; NCT03366337); a 16-week, randomized, placebo-controlled, double-blind Phase 2 study patients with T2D and CKD in Japan (TSUBAKI; NCT02316821); and a 16-week, randomized, placebo-controlled, double-blind, global Phase 2 study of pulmonary hypertension (PH) (LARIAT; NCT02036970).

Results: A total of 423 patients were enrolled in four studies that were initiated after the termination of BEACON. There were no fluid overload-related serious adverse events in any patients treated with Bard in any of these studies. Treatment with Bard was not associated with increases in mean blood pressure in any of these studies. Mean decreases in body weight were apparent by Week 12 of treatment with Bard and were more pronounced in patients with higher baseline BMI.

Conclusions: In four clinical studies that enrolled over 400 patients without elevated BNP or a history of heart failure, Bard did not result in an increased differential risk of heart failure, other signs of overt fluid overload or subclinical measures of fluid retention (increases in blood pressure or weight).

Funding: Commercial Support - Trial sponsored by Reata Pharmaceuticals Inc.

SA-PO919

Increased Heart Rate Reflects Intrarenal Renin-Angiotensin System Activation in CKD Patients but Not in Subjects Without CKD

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Background: A higher heart rate is one of the risk factors for heart failure and cardiovascular disease as well as accelerated glomerular filtration rate (GFR) decline. Activation of the intrarenal renin-angiotensin system (RAS) plays an important role in the development of hypertension and renal damage. However, the association between heart rate and intrarenal RAS activation is unclear.

Methods: We investigated the relationship between heart rate and urinary angiotensinogen (AGT) excretion, a surrogate marker for intrarenal RAS activity, in 10 subjects without chronic kidney disease (CKD) [age 50.1 ± 6.4 years, 4 men and 6 women, serum creatinine (sCr) 0.71 ± 0.13 mg/dL, urinary protein excretion 35.6 ± 15.3 mg/day, and urinary AGT excretion 7.22 ± 4.69 μg/day] and 72 CKD patients who were not taking medications that influence heart rate and RAS blockers [age 50.0 ± 17.4 years, 27 men and 45 women, sCr 1.85 ± 2.71 mg/dL, urinary protein excretion 1.27 ± 2.63 g/day, and and urinary AGT excretion 747.4 ± 2714.6 μg/day]

Results: As heart rate is influenced by behavior and emotion, we divided it into daytime and nighttime. Heart rate had a significant positive association with sCr levels during daytime and nighttime in CKD patients but not in non-CKD subjects. Moreover, although heart rate was not associated with urinary AGT excretion levels in non-CKD subjects during daytime ($r = 0.39$ and $p = 0.28$) and nighttime ($r = 0.34$ and $p=0.38$), it was associated with urinary AGT excretion levels during daytime ($r = 0.23$ and $p = 0.047$) and nighttime ($r = 0.45$ and $p < 0.01$) in CKD patients. Multiple linear regression analysis revealed that heart rate had a significant positive association with the urinary AGT excretion levels during nighttime, but not daytime, after adjustments for age, sex, body mass index, and sCr in CKD patients ($\beta = 0.31$ and $p = 0.034$).

Conclusions: Heart rate is associated with urinary AGT excretion levels, especially during the nighttime, in CKD patients but not in non-CKD subjects. Heart rate measurement may be a convenient surrogate marker for intrarenal RAS activation in CKD patients.

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SA-PO920

Comparison of Heart-Type Fatty Acid Binding Protein with Troponin T for Prediction of Cardiovascular Events in the German CKD Study

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Background: Measurement of heart-type fatty acid binding protein (H-FABP) is more sensitive than high-sensitive troponin T (hs-TNT) in the early detection of myocardial injury. H-FABP also improves prediction of long-term cardiovascular (CV) outcomes in patients with acute coronary syndrome. We have investigated the ability of H-FABP in comparison with hs-TNT to predict all-cause mortality and long-term CV outcomes in patients with CKD.

Methods: H-FABP (ELISA, Hycult biotech) and hs-TNT (Cobas system) levels were measured from baseline samples of patients enrolled into the German Chronic Kidney Disease (GCKD) study (n=5127). The associations of H-FABP and hs-TNT with all-cause death, CV death, combined major adverse cardiovascular events (MACE) and hospitalization for heart failure were evaluated by cox regression analyses adjusted for demographics, estimated glomerular filtration rate, urinary albumin excretion rate, CV risk factors, use of statins and renin angiotensin inhibitors. Cardiac structure was examined by magnetic resonance imaging (MRI) in a subgroup of 290 patients.

Results: Both H-FABP and hs-TNT levels were inversely related with renal function. Over a follow-up period of 4 years, there were 345 deaths, 117 CV deaths, 329 MACE and 224 patients were admitted for heart failure. The hazard ratios (HRs) for prediction of these events were greater with hs-TNT than with H-FABP. When both markers were entered simultaneously, only hs-TNT remained a significant predictor in each of the models (e.g. HR for CV death for 1SD increase on the log10 scale: 1.96 (CI 95% 1.54-2.40) for hs-TNT and 0.88 (CI 95% 0.65-1.20) for H-FABP). In the subgroup with MRI measurements, only hs-TNT was related with left ventricular hypertrophy and concentricity (both $P<0.001$).

Conclusions: In this large prospective cohort of CKD patients, hs-TNT clearly outperformed H-FABP in the prediction of all-cause mortality and CV outcomes. As a potential explanation for these findings, only hs-TNT was associated with altered cardiac structure in a deep-phenotyped subgroup of CKD patients.

Funding: Commercial Support - Roche

SA-PO921

Peak Oxygen Consumption Is Reduced at All Levels of CKD in Chronic Heart Failure Patients

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Background: There is an increasing body of literature showing reduced Cardiorespiratory Fitness (CRF) in CKD. This is mainly proven in CKD stages 4 and 5, but increasing knowledge suggests that this is the case in earlier stages as well. Chronic heart failure (CHF) is characterized by the hearts inability to meet tissues blood demands, mainly during exercise. We wanted to see if CKD affected peak oxygen consumption (VO_{2peak}) in CHF.

Methods: Participants were enrolled from two regional CHF clinics with similar access for all phenotypes of HF and all levels of renal insufficiency without any upper age limit. Echocardiography was performed at inclusion. Left ventricular and left atrial volumes and ejection fraction (EF) were measured in 4- and 2-chamber view. HF phenotype was classified according to the 2016 European Society of Cardiology Guidelines. All participants underwent testing for VO_{2peak} on a treadmill. Hemoglobin (Hb) was analyzed with a photometric method whereas creatinine was measured enzymatically. Analysis were performed in hospital routines. Estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. For statistical analysis we used multiple linear regression.

Results: 59 participants (10 female) had valid test results for Hb (mean 13.3, SD 1.8), VO_{2peak} (mean 17.9, SD 4.6) and eGFR (mean 57.6, SD 24.2). In a multiple regression analysis, VO_{2peak} showed a strong association with eGFR after correcting for Hb of -0.078 ml/min/kg per 1 ml/min/1.73 m^2 drop in eGFR (95% CI -0.031 - -0.123, p=0.001).

Conclusions: Lower eGFR is a major predictor of poor cardiorespiratory fitness even in a chronic heart failure population where VO_{2peak} is already severely reduced. This relation holds for eGFR ranging from ESRD to normal renal function. Whether reduced renal function is caused by the severity of the heart failure and thereby lower VO_{2peak}, or reduced renal function leads to worsening heart failure with lower VO_{2peak} is not known from our cross-sectional design.

Funding: Government Support - Non-U.S.

SA-PO922

The Association of Diastolic Dysfunction with CKD in Patients with Heart Failure

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Background: Chronic Kidney Disease (CKD) is tightly connected to cardiac disease, including Chronic Heart Failure (CHF) through different Cardiorenal Syndromes (CRS). CHF caused by hypertension and CKD often presents with left ventricular hypertrophy, stiffening and increasing filling pressures depicted as Chronic Renocardial Syndrome, whereas CHF caused by primary myocardial disease display dilation of left ventricle with venous congestion leading to reduced renal perfusion in the Chronic Cardiorenal Syndrome. This heterogeneity in CRS complicates the study of its pathophysiology, and studies comparing echocardiographic features of diastolic function in CHF between CKD and non-CKD patients are scarce.

Methods: Patients from two regional heart failure clinics were included if they had stable CHF and were medically optimized. Echocardiographic recordings, analyses and estimation of filling pressure and grade of diastolic dysfunction were based on latest recommendations. Estimated glomerular filtration rate (eGFR) was calculated based on creatinine, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Results: Mean age of the 67 participants was 68 (65.6-71.1) years (82 % male). eGFR⟨60 ml/min/1,73m^2 was present in 46 %. Three patients were in dialysis and 1 had a renal transplant. NYHA class II and III was present in 77 % and 23%, respectively. Patients with elevated filling pressure had lower eGFR than patients with normal filling pressure (-14.8 ml/min/1.73m^2, $p = 0.03$). Indexed left atrial end-systolic volume was significantly larger in HF patients with eGFR⟨60 ml/min/1.73m^2 compared to those with better renal function (11 ml/m^2, $p = 0.02$). Patients with grade I diastolic dysfunction had a higher eGFR compared to grade II (18 ml/min/1.73m^2, $p = 0.01$). The differences between grade I and III, and II and III diastolic dysfunction did not reach statistical significance.

Conclusions: Reduced renal function was associated with increased filling pressures and larger left atrial volumes in a general heart failure population. This shows a common trait in CKD-patients with CHF despite the otherwise heterogeneity in clinical presentation.

Funding: Government Support - Non-U.S.

SA-PO923

Intraventricular Septum Thickness (IVST) Increases Depending on the Decline of eGFR in AL Renal Amyloidosis

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Background: In advanced AL amyloidosis, cardiac walls show thickening and cardiac functions reveal deterioration. It is unclear whether renal dysfunction and hypertension affect cardiac walls and functions in AL amyloidosis. We aimed to study the relationship between CKD progression and the ultrasound cardiac parameters in patients with AL amyloidosis.

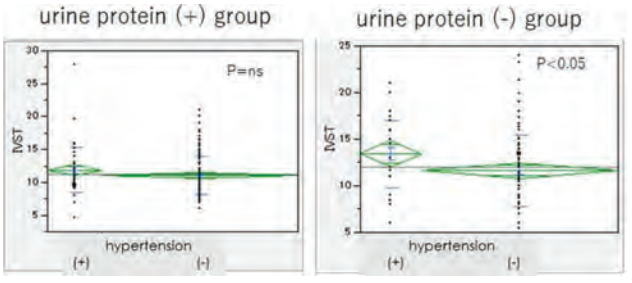
Methods: The Amyloidosis Research Group, supported by funds from the Ministry of Health, Labour and Welfare in Japan surveyed the patients with AL amyloidosis in 2015. We could collected clinical data concerning renal and cardiac functions from 353 cases.

Two hundred forty patients had positive urine protein and 113 patients had negative urine protein.

Results: In urine protein positive group, eGFR showed a significant negative correlation with IVST and LVPWT (p<0.05), while did not with LAD, EF, and E/e'. The cardiac ultrasound parameters showed no significant differences between hypertension positive and negative groups. Multiple linear regression analysis showed IVST and LVPWT showed independently significant relationship with eGFR but not with hypertension. In urine protein negative group, eGFR showed no significant relationship with IVST and LVPWT. IVST and LVPWT showed significant differences between hypertension positive and negative group. The both parameters were significantly thicker in hypertension positive group (p<0.05).

Conclusions: In AL amyloidosis with urine protein, IVST and LVPWT became significantly thick according to the decline of renal function but the thickening of cardiac walls had no relationship with hypertension. In urine protein negative group, these results were up and down. From the present data, we suspected the cardiac amyloid deposition might begin from the appearance of urine protein in AL amyloidosis. The progression of cardiac wall thickening might not depend on hypertension in AL renal amyloidosis.

Funding: Government Support - Non-U.S.



SA-PO924

Right Coronary Artery (RCA) Dominant Distribution of Coronary Artery Lesions in the Development of CKD Stage

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Background: It is reported that a more proximal lesions in RCA was observed in CKD patients compared with non-CKD patients (Kidney International (2009) 75, 80–87). CKD may affect the location and/or distribution of coronary atherosclerosis. The characteristics of coronary artery disease in CKD patients, however, have not entirely been clarified. We elucidate the relationship between the progression of CKD and the distribution of coronary artery stenosis diagnosed by coronary artery angiography.

Methods: Among the 13391 cases of coronary artery angiography performed in our hospital from 2003 to 2017, we characterized coronary artery lesions in predialytic phase of CKD patients. The inclusion criteria was the patients who had been treated with the first elective PCI. The patients with previous revascularization, acute myocardial infarction, unstable angina pectoris, coronary artery bypass imaging after coronary artery bypass grafting, or hemodialysis or unknown renal function were excluded in this study. Finally, 3268 CKD patients were enrolled into this study.

Results: The average age was 71 (64-77) years, and average eGFR was 65 (53-77) ml/min. A single lesion was observed in 2168 cases and multiple lesions were observed in 1085 cases. location of the lesion was the right coronary artery (RCA) in 914 cases, left main trunk in 101 cases, left anterior descending artery (LAD) in 1832 cases, and left circumflex artery in 733 cases. The prevalence of RCA lesion significantly increases in parallel with the development of CKD stage, however this phenomenon disappeared in LAD and LCX lesion. In multivariate logistic regression analysis, odds ratios of RCA for stage 4 and 5 were 1.79 (C.I. 1.10 to 2.94, p=0.019) and 4.21 (C.I. 1.90 to 9.29, p<0.001) respectively compared with the reference of CKD1. After adjusting for age, male, diabetes, hypertension, and dyslipidemia, this strong association remained statistically significant.

Conclusions: It is still unclear the mechanism, it is possibility that progression pattern is different between three major coronary arteries. The deterioration of renal function may affect the progression of atherosclerosis more in RCA than LAD or LCX.

SA-PO925

Maximisation of Renin-Angiotensin-Aldosterone System Inhibition (RAASi) in CKD Patients with Heart Failure (HF): Experience from a CKD-HF Clinic

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Background: CKD-HF patients suffer from high hospitalisation and mortality rates, which may improve with maximum RAASi- often avoided by physicians due to fear of worsening renal function and hyperkalaemia. This study reports impact of a novel multidisciplinary cardiology-nephrology clinic for RAASi maximisation in CKD-HF patients.

Methods: Clinical, biochemical data and medications were obtained from electronic patient records and clinical letters on 97 patients seen and followed up in CKD-HF clinic from 23/03/17 to 11/04/19. Daily doses of each medication were classified into None, Low, Medium (≥50% maximum dose) and Maximum dose. Medication dose groups and blood test results were compared between the first and last clinic visit.

Results: Patient characteristics were: median age 78.5 years (IQR 66.8-84.3 years), male 71.1%, diabetes mellitus 53.6%, mean ejection fraction (EF) 38.6±13.7%, HFrEF 48.5% and CKD stages 3 (56.7%), 4&5 (43.3%). Median follow up time was 302 days (IQR 178-479 days). 15 patients died during follow up. At the end of follow up: 78.4% patients remained same or milder CKD group. There was a difference in the number of RAASi patients were on, between first and last visit (p=0.02): none (41.2% vs 29.9%), one (45.4% vs 50.5%), both ACEi/ARB and MRA (13.4% vs 19.6%). ACEi/ARB dose was increased in 33.0% patients and MRA dose in 17.5% of patients. Proportion of patients on each dose category between first and last visit for ACEi/ARB was not different (p=0.11): none (45.4% vs 39.2%), low dose (26.8% vs 26.8%), medium dose (16.5% vs 20.6%), maximum dose (11.3% vs 13.4%); for MRAs, it was different (p=0.02): none (82.5% vs 71.1%), low dose (7.2% vs 13.4%), medium dose (10.3% vs 12.4%), maximum dose (0% vs 3.1%). There was no change in serum Na, K, creatinine in patients with ACEi/ARB or MRA dose increase between first and last visit. The change of eGFR was significant in patients with MRA dose increase (p=0.03), however, it was small (34.5 vs 32.1 ml/min/1.73m2). There was no significant correlation between RAASi dose increase and the likelihood of patients having CKD progression (p=0.64 for ACEi/ARB; p=0.66 for MRA).

Conclusions: A combined CKD-HF clinic was effective in maximising RAAS inhibition in a high-risk group of patients without clinically significant hyperkalaemia or deterioration in renal function.

SA-PO926

The Influence of Vascular Endothelial Dysfunction on the Prognosis of CKD and Its Possible Related Influencing Factors

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Background: Vascular endothelial dysfunction may be involved in progression of renal fibrosis in CKD patients. Asymmetric dimethylarginine(ADMA) is an endogenous nitric oxide synthase(NOS) inhibitor, which plays an important role in the pathophysiological process of endothelial dysfunction. Elevated circulating ADMA level is one of the primary biomarkers of endothelial dysfunction. This study will explore the associated factors leading to endothelial injury in CKD patients and the relationship between vascular endothelial dysfunction and CKD prognosis.

Methods: 77 adults in CKD stage 1–5 were enrolled. Baseline demographic data including age, gender and etiology of kidney disease were all recorded. Serum ADMA, α-klotho and phosphorus levels were measured and immunohistochemical staining was carried out. Patients were divided into two groups by the median serum ADMA level and were followed up for 6 years. The primary outcome was initiation of renal replacement therapy.

Results: The mean serum ADMA level of all patients was 64.3±34.6ng/mL. Serum ADMA level increased with declining renal function(r=–0.267, p=0.020). It was negatively correlated with serum α-klotho(r=0.–233, p=0.042) and positively correlated with phosphorus(r=0.243, p=0.037) levels. The expression of α-klotho in renal perforation tissues of CKD patients was decreased by immunofluorescence staining. The expression of sodium-phosphorus synergistic transporter(NaPi) in renal tubules, which promoted phosphorus reabsorption and the expression of dimethylarginine-dimethylamine hydrolase(DDAH), which regulated ADMA level, were significantly decreased, consistent with the clinical results. Kaplan-Meier analyses showed that the incidence of renal replacement therapy initiation in high ADMA group was significantly higher than that in low ADMA group(35.9%vs13.2%, p=0.029, log rank test).

Conclusions: Serum ADMA level increased with deterioration of renal function and increase of CKD stage. Low serum α-klotho and high phosphorus levels are associated with increased circulating ADMA levels, which implies that they may be involved in the pathogenesis of endothelial dysfunction in CKD patients. High serum ADMA level predicts the occurrence of end-stage renal failure. Alleviating endothelial injury and improving endothelial dysfunction in patients with CKD may delay the progress of CKD.

SA-PO927

Incidence of Cardiovascular Events and Mortality in Korean Patients with CKD: Results from KNOW-CKD Cohort

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Background: There are lack of studies regarding the incidence of major adverse cardiovascular events (MACE) in Asian pre-dialysis population. This study was conducted to analyze the incidences of MACE and death in Korean chronic kidney disease (CKD) population, using the data from a multicenter prospective cohort.

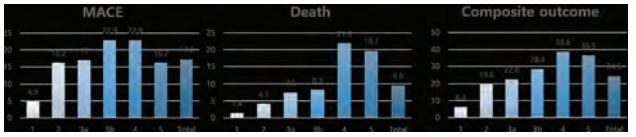
Methods: This is a longitudinal analysis from a multicenter prospective cohort study, entitled KNOW-CKD. Among a total 2,238 patients enrolled, 59 patients without follow-up data were excluded and, finally, 2,179 patients were included. MACE was defined as any of the cardiovascular events occurred during the follow-up. The composite outcome was defined as MACE and all-cause death.

Results: Mean age was 53.6±12.2 years and 38.7% were female. At enrollment, mean eGFR was 53.2±30.7 ml/min/1.73m² and the prevalence of cardiovascular disease and diabetes were 6.0% and 33.4%, respectively. During median 4.1 years of follow-up, the incidences of MACE, death and composite outcome were 17.2, 9.6 and 24.5 per 1,000 patient-year (PY). All outcome incidences were higher in diabetic patients compared

to non-diabetics (p<0.001). The incidence rate increased as CKD stages advanced, for MACE (p=0.001), death (p<0.001) and composite outcomes (p<0.001). In the multivaraite regression model, CKD stage G4 and G5 showed increased HR of 2.5 and 3.2 for MACE compared to G1 adjustment for age and sex. However when other confounding factors were adjusted, the significance disappeared. For the composite outcome, CKD stage G4 and G5 showed significant increased HR of 2.9 and 4.3 over G1, even after other confounding factors were adjusted. When the incidence rate of composite outcome was compared to general population using National Health Insurance service – National, sample cohort, this CKD population had increased HR of 1.5 (CI 1.31-1.72, p<0.001) compared to general population.

Conclusions: The incidence rate of MACE, death and composite outcome in Korean non-dialysis CKD patients were 17.2, 9.6 and 24.5 per 1,000 PY, respectively, which were similar to Japan cohort data but lower than western cohorts data.

Funding: Government Support - Non-U.S.



Incidence of outcomes according to CKD stages

SA-PO928

Effect of Blood Pressure Variability and Arterial Stiffness for Renal Outcome in Patients with CKD Stage 3 or 4

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Background: Previous studies have reported that higher visit-to-visit blood pressure (BP) variability is higher risk of decreased renal function in hypertensive individuals. Arterial stiffness is associated with decline of renal function. We examined the association between BP variability and renal outcome in patients with chronic kidney disease (CKD) stage 3 or 4, and whether theses renal outcomes were associated with arterial stiffness.

Methods: Among 2238 CKD patients in Korea in 2011 through 2017, 1241 patients who had CKD stage 3 or 4, and measured BP more than 3 times during follow-up period were included. BP variability was defined as standard deviation (SD) of systolic BP across 3 to 8 visits. SD was divided into quintiles. Composite renal outcome included ≥ 50% reduction of eGFR, dialysis or transplantation. Arterial stiffness was measured with brachial-ankle pulse wave velocity (baPWV). We calculated adjusted hazard ratio (AHR) for composite renal outcome across SD quintile and analyzed the effect of baPWV.

Results: Mean age was 53.6±11.1 years, 37% was women, and mean estimated glomerular filtration rate was 36.9±12.2 ml/min/1.73m^2. Median follow-up was 3.0 years and 391 outcomes occurred. The AHR for composite renal outcome were 1.10 (95% confidence interval [95% CI]: 0.77-1.58), 1.19 (95% CI: 0.84-1.68), 1.30 (95% CI: 0.92-1.83), and 1.62 (95% CI: 1.15-2.28) for second through fifth versus the first quintile of SD. baPWV >15 m/s was significantly higher risk for renal outcomes in fifth compared to the first quintile (AHR: 1.75, 95% CI: 1.08-2.80).

Conclusions: Higher visit-to-visit BP variability are associated with rapid deterioration of renal function. Furthermore, there are different association between BP variability and renal outcome depending on arterial stiffness such that higher BP variability has a strong association with CKD progression among patients with high arterial stiffness.

SA-PO929

Short-Term Systolic Blood Pressure Variability Predicts Renal Events in CKD: Results from the C-STRIDE Study

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Background: Whether short-term blood pressure variability (BPV) correlates with renal and cardiovascular (CV) events is controversial in patients with chronic kidney disease (CKD).

Methods: A total of 1421 CKD stage 1-4 patients with ambulatory BP (ABP) data from the Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE) were enrolled in the present study. Short-term BPV was evaluated by calculating 24-hour standard deviation (SD) andthe weighted SD (w-SD) of systolic BP (SBP). The association of short-term BPV with CKD outcomes, including initiation of renal replacement therapy and CV events, was evaluated by Cox regression model. The adjustment included age, gender, smoking, diabetes, anti-hypertensive treatment, body mass index, serum albumin, estimated glomerular filtration rate, logarithm transformed low-density lipoprotein cholesterol and logarithm transformed urine protein.

Results: The mean age of the cohort was 49.4±13.7 years with 56% males. The average value of 24-hour SBP SD and w-SD were 13.9±4.8mmHg and 12.6±4.4mmHg, respectively. During a median follow-up of 4.8 years, 236 renal events and 93 CV events occurred, respectively. Both 24-hour BP SD (hazard ratio [HR]: 1.04, 95% confidence interval [CI]: 1.01-1.06) and w-SD (HR: 1.05, 95%CI: 1.02-1.08) showed a greater hazard for renal events in fully adjusted model. Compared with the bottom tertile group, the risk for renal events was significantly increased in top tertile group for both 24-hour SBP SD (HR:1.58, 95%CI:1.11-2.24) and w-SD (HR:1.48, 95%CI: 1.07-2.06), respectively. Neither 24-hour SBP SD nor w-SD showed a significant relationship with CV events when expressed as a continuous variable (HR: 1.04, 95% CI: 0.99–1.08 and HR: 1.03, 95% CI: 0.99–1.08, respectively). Similar findings were found with tertiled 24-hour SBP SD and w-SD.

Conclusions: In CKD patients, short-term systolic blood pressure variability increases the risk for renal events independently.

SA-PO930

Clinical Burden of Complications Associated with CKD: A Novel Cardio-Renal Risk Tool

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Background: The prevalence of chronic kidney disease (CKD) is growing worldwide. CKD affects approximately 15% of Americans. CKD patients are a complex and comorbid population. Complications are frequent in people with CKD and represent an important component of the associated disease burden. This study aimed to synthesize evidence reporting associations between two common complications of CKD, hyperkalemia (HK) and anemia, and risk of adverse outcomes including death and cardiovascular (CV) events in a novel risk tool to encourage a holistic approach to evaluating the associated disease burden.

Methods: Systematic literature reviews were conducted to identify studies reporting risk of either HK or anemia in people with CKD including those receiving dialysis, and studies associating the incidence of HK or anemia with clinical outcomes including mortality, hospitalization and CV events. Reported evidence was then incorporated in a Cardio-Renal Risk Awareness and Impact Tool developed in Excel to characterize the risks of HK, anemia and associated adverse outcomes in people with CKD.

Results: A total of 314 studies were identified that reported the risk of HK (n=123) or anemia (n=191), or the association between each complication and patient outcomes. For male patients aged 65 years with CKD stage 3b, the estimated 5-year risk of a HK event (potassium>5.5mmol/L) was 11.9%. Separately, the prevalence of anemia (Hb<11g/dL) was 35.0%. For a patient with HK the estimated relative risks (RR) of death, hospitalization and CV events were 1.50, 1.20 and 1.08, respectively. For a patient with anemia corresponding RRs were 1.13, 1.47 and 1.12. Furthermore, estimated RRs increased with the severity of each complication; RRs of death, hospitalization and CV events increased to 2.19, 1.73 and 1.14 for a patient with potassium>6.0mmol/L and to 1.13, 1.72 and 1.24 for a patient with Hb<10g/dL, respectively.

Conclusions: HK and anemia are both consistently and independently associated with increased risk of adverse outcomes in CKD patients. This study uniquely synthesizes the growing body of evidence on the epidemiology and impact of complications such as HK and anemia in CKD patients. This novel risk tool can be used to communicate the importance of timely diagnosis and management of these conditions to reduce the burden of disease in this population.

Funding: Commercial Support - AstraZeneca

SA-PO931

Osteoprotegerin Is Associated with Development of Coronary Artery Calcification but Not Severity and Progression in Non-Dialysis CKD: Results from the KNOW CKD Study

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Background: Coronary artery calcifications (CAC) are recognized as a predictor of all-cause and cardiovascular mortality in chronic kidney disease (CKD). Osteoprotegerin (OPG) could be a marker of vascular calcification presence and extent. The purpose of this study was to evaluate relationships between OPG levels and presence/severity/progression of CAC score in non-dialyzed CKD patients.

Methods: We prospectively enrolled 1974 CKD patients (1180 male/794 female, mean age: 53.2 years) who had OPG and electron beam computed tomography (CT) or multi-detector CT for CAC scoring at baseline. A CAC score of > 400 Agatston unit (AU) s was used to define severe CAC. In term of definition for CAC progression: among those with no baseline CAC, incidence was defined as an annual increase in CAC score ≥ 5 AUs. Among those with baseline CAC, progression was defined as 15% annual increase.

Results: Mean serum concentrations of OPG amounted to 6.79 ± 3.53 pmol/L. Among 1974 patients, 1011 (51.2 %) had CAC score >0 and 209 (10.6 %) had scores > 400. Higher OPG levels were associated with the present CAC but not severe CAC at baseline. [LnOPG, presence: OR =2.033, P = 0.001; severe CAC: OR =1.700, P =0.070]. Among 827 patients with 4-year follow up CAC scores, 22 (4.9%) participants without CAC at baseline had incident CAC and 243 (63.8%) participants with CAC at baseline had CAC progression. Among subjects without CAC at baseline, higher OPG levels were associated with incident CAC (LnOPG, OR = 5.045. P = 0.042). However, OPG were not associated with CAC progression among participants with CAC at baseline or in total.

Conclusions: Our results indicated that higher serum OPG levels are associated with the presence and development of CAC non-dialyzed CKD patients. However, OPG does not seem to be involved in severity and progression of CAC.

Funding: Government Support - Non-U.S.

SA-PO932

Marijuana Use and CKD in an Urban Population

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Background: Marijuana is the most commonly used illicit drug in the US. Little is known about the relation of marijuana with kidney outcomes. We examined the association of marijuana use and CKD among a cohort of African American and white adults in Baltimore, Maryland.

Methods: We examined baseline data from the Healthy Aging in Neighborhoods of Diversity across the Life Span study. Marijuana use was self-reported and defined as never, former or current. CKD outcomes were prevalent reduced kidney function (eGFR <60 ml/min/1.73m^2) or prevalent albuminuria (urine albumin-to-creatinine ratio (ACR) >=30 mg/g). The association of marijuana use with CKD outcome was examined using multivariable logistic regression.

Results: Among 2352 participants, there were 56% never, 30% former and 14% current marijuana users. Current marijuana users were younger, with fewer yrs of education, and were more likely to be male, African American and use cigarettes, opiates and/or cocaine than never or former marijuana users; but were less likely to have hypertension or diabetes. Overall prevalence of reduced kidney function was 5.3%, with 6.1% of never, 4.6% of former and 3.4% of current marijuana users having reduced kidney function. Overall prevalence of albuminuria was 11.5%, with 12.2% of never, 10.9% of former and 9.7% of current marijuana users having albuminuria. There was no independent association of marijuana use with reduced kidney function or albuminuria.

Conclusions: Marijuana use was prevalent among this urban population. We found no independent association of marijuana use with prevalent CKD. The effects of marijuana use on long term renal outcomes warrants further study.

Logistic regression models of reduced kidney function by marijuana use status

Model	Marijuana Use	Odds Ratio (95% CI)
1: unadjusted	Never	Ref
	Former	0.8(0.5,1.2)
	Current	0.6(0.3,1.0)
2: adjusted for age, sex, race, education, poverty status	Never	Ref
	Former	1.0(0.6,1.6)
	Current	0.8(0.5,1.4)
3: model2+ hypertension, diabetes	Never	Ref
	Former	1.0(0.6,1.7)
	Current	0.9(0.5,1.6)
4: model3+cigarette, opiate, cocaine use	Never	Ref
	Former	0.8(0.4,1.6)
	Current	0.7(0.4,1.3)

SA-PO933

Effect of -55C/T Polymorphism of Uncoupling Protein 3 Gene on Risk for New-Onset Diabetes in Chinese Peritoneal Dialysis Patients: A Prospective Cohort Study

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Background: Patients who have no history of glucose intolerance could develop diabetes mellitus after the initiation of PD therapy due to a high glucose load. Different genetic background may result in risk modulation. However, it has been rarely explored among PD patients. Uncoupling protein 3 (UCP3) belongs to a family of mitochondrial transporters and is associated with energy homeostasis. The aim of our study was to investigate the effect of polymorphism of the UCP3 promoter (–55C/T) on the risk of new-onset diabetes mellitus (NODM) in PD patients.

Methods: Non-diabetic patients newly started on PD therapy between May 2005 and March 2018 were recruited (n=150). The -55C/T polymorphism of UCP3 was genotyped in all participants at baseline. Patients were divided into two groups based on the genotypic difference. The cohort was followed for up to 165 months (median: 60.1 months; interquartile range: 34.1 months). Cox regression models were used to analyze the impact of -55C/T polymorphism on risks of NODM. Association between glucose intolerance and genotypes were further ascertained in a second cohort of HOMA-IR low and high subjects.

Results: 62 patients (41.3%) had the genotype -55CC (wild group), whereas 88 patients (58.7%) were T carriers (mutant group). During the follow-up, 14 NODM occurred in the mutant group while only 4 occurred in the wild group. Patients in the mutant group experienced significantly higher morbidity (HR: 3.324; 95% CI: 1.088 to 10.151; p = 0.035). Even after adjustments for age, body mass index, total cholesterol, triglycerides, and HOMA-IR, genotypes with T allele remained an independent predictor of NOMD morbidity (HR: 5.804; 95% CI: 1.739 to 19.375; p = 0.004). In the mutant group, HOMA-IR values were higher. Frequencies of the T allele were 27.7% in the HOMA-IR low group compared with 42.1% (p=0.009) in the HOMA-IR high group. The variant of T allele was significantly associated with a higher HOMA-IR value (OR: 2,287; 95% CI:1.177-4.445; p=0.015).

Conclusions: The variant of T allele of UCP3 -55C/T polymorphism was associated with high insulin resistance and was an independent predictor of NODM in PD patients. Early identification of the genotype may provide scientific basis for clinic management of PD patients, improving the surveillance and prevention of diabetes.

Funding: Other NIH Support - National Natural Science Foundation of China (NSFC)

SA-PO934

GLP-1 Analogue Ameliorates Progression of Not Only Left Ventricular Hypertrophy But Also Atrial Volume in Patients with Type 2 Diabetes Mellitus on Peritoneal Dialysis

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Background: Diabetes mellitus (DM) is a progressive multifactorial disease associated with cardiovascular complications. Patients undergoing peritoneal dialysis also experience an increased incidence of cardiovascular disease. To prevent progression of systemic cardiovascular complications in DM patients, glycemic control is important. Moreover, left ventricular mass index (LVMI) or left atrial volume index (LAVI) were known to be the predictive factors for mortality in dialysis patients. In this study, we examined the efficacy and safety of the glucagon-like peptide analogue (GLP-1) to treat type 2 diabetes patients undergoing peritoneal dialysis.

Methods: Thirty-four type 2 diabetes patients who underwent peritoneal dialysis were enrolled. Participants were divided in two groups (Group A; n=24, liraglutide 0.9mg daily, Group B; n=10, duraglutide 0.75mg once a week). Prior to GLP-1 therapy, 16 patients used insulin, 8 used oral antidiabetic agents, and 3 used diet therapy. After liraglutide initiation, biochemical examination and echocardiography was examined at baseline and every 12 months for 36 months.

Results: In Group A, there were no differences in glycemic control before and after initiation of liraglutide. Nevertheless, medical adherence was improved after liraglutide use. After liraglutide use, brain natriuretic peptide (BNP) and human atrial natriuretic peptide (HANP) were significantly decreased. Moreover, echocardiographic finding showed LVMI and LAVI were significantly ameliorated instead of unchanged left ventricular ejection fraction or E/e'. Similar findings were shown after duraglutide use in Group B. (Table)

Conclusions: These findings suggest that GLP-1 analogue for type 2 diabetes patients undergoing peritoneal dialysis improved medical adherence and was effective for ameliorating left ventricular function. Moreover, it may ameliorate progression of diastolic function including E/e' and LVAI.

Funding: NIDDK Support

Table. Clinical data change

	Liraglutide 0.9mg / day (n = 24)				Duraglutide 0.75mg / once a week (n = 10)			
	at baseline	after 12 months	after 24 months	after 36 months	at baseline	after 12 months	after 24 months	after 36 months
daily oral tablets (n)	17.4 ± 5.2	14.1 ± 4.4*	14.5 ± 4.3*	14.8 ± 4.8*	15.7 ± 5.1	12.2 ± 5.4*	11.0 ± 6.4*	11.9 ± 5.5*
HbA 1c (%)	6.27 ± 0.80	6.01 ± 0.68	5.91 ± 0.70	5.96 ± 0.57	6.28 ± 0.66	6.06 ± 0.57	6.02 ± 0.59	6.10 ± 0.35
Ejection Fraction (%)	59.1 ± 12.9	64.9 ± 9.6**	63.4 ± 7.9**	61.8 ± 11.6	60.7 ± 7.8	69.4 ± 8.8**	70.1 ± 4.9**	66.4 ± 9.8
E/e'	17.1 ± 4.9	15.3 ± 5.3	14.2 ± 5.6	14.5 ± 5.5	16.4 ± 3.5	15.0 ± 1.9	15.0 ± 1.9	17.3 ± 6.0
LVMI (g/m^2)	171.2 ± 23.4	146.6 ± 21.2*	150.9 ± 24.7*	143.1 ± 20.1*	164.3 ± 13.8	132.2 ± 16.9*	140.8 ± 25.8**	148.1 ± 42.0
LAVI(mL/m^2)	44.0 ± 10.2	37.2 ± 9.8	35.8 ± 8.6**	34.6 ± 9.2**	38.2 ± 9.7	33.3 ± 9.8	34.7 ± 8.3	35.4 ± 9.5

*:p<0.01,**:p<0.05 vs at baseline

SA-PO935

Higher Neutrophil to Lymphocyte Ratio (NLR) Associates with Poor Clinical Outcome Independent of Traditional Factors in Peritoneal Dialysis Patients

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Background: Neutrophil to lymphocyte ratio (NLR) is an inexpensive and widely available biomarker of inflammation that predicts clinical outcomes in dialysis patients. However, the association between NLR and mortality among patients treated with peritoneal dialysis (PD) is not fully explored.

Methods: In 767 incident PD patients (median age 50 years, 57 % males, 15% diabetes and 6% cardiovascular disease, CVD), baseline NLR andother metabolic biomarkers potentially linked to CVD were analysedin relation to mortality during follow up period of up to 60 months. All-cause and cardiovascular mortality risk associated with NLRwere analyzed with competing-risk regression models with transplantation as competing risk, adjusting for all investigated covariates.

Results: Patients with highest tertile of NLR were older, had higher creatinine and BMI and low serum albumin and parathyroid hormone (iPTH). In univariate analysis, NLR associated with white blood cell count (rho=-0.33, p=0.001), age (rho=0.10, p=0.01), calcium (rho=-0.10, p=0.01), iPTH (rho=0.09, p=0.01) and C-reactive protein (n=644; rho=0.10, p=0.01). Highest tertile of NLR associated with high all-cause mortality risk compared with low + middle tertiles, sub-hazard ratio (sHR) of 1.79 (95% CI, 1.18-2.73; p=0.006), and high CVD mortality risk, sHR 1.55 (95% CI, 0.85-2.85; p=0.01)

after adjusting for Framingham's score, presence of CVD, circulating levels of uric acid, creatinine, calcium, phosphate, Hb, iPTH, alkaline phosphatase, ALAT and ASAT, and calendar year of recruitment.

Conclusions: In patients undergoing PD, higher NLR was associated with increased all-cause mortality risk, independently of Framingham's risk score and additional confounders, suggesting that this biomarker of inflammation is a useful prognostic tool in PD patients.

SA-PO936

TH1 and TH2 Immune Response to External Stimuli in Patients on Peritoneal Dialysis

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Background: Infections remain leading complication in patients undergoing peritoneal dialysis (PD). Peripheral blood mononuclear cells (PBMCs) provide first-line defense against invading pathogens. Cytokines are central host molecules involved in modulating the host environment during inflammatory conditions. Though few studies have demonstrated expression of cytokines from stimulated PBMCs in hemodialysis patients, no study has systematically looked at their function among patients on PD. We evaluated cytokines expression in PBMCs stimulated by various external stimuli in patients on peritoneal dialysis (PD group), patients having chronic kidney disease stage 5 not on dialysis (CKD group) and compared it with those of healthy controls.

Methods: PBMCs were isolated as per standard procedure and were seeded in tissue culture plates in a concentration of 1 × 106 cells/well. They were stimulated with phytohaemagglutinin (PHA, a potent T- and B-cell mitogen), peritoneal dialysate effluent (DE) and fresh peritoneal dialysis fluid (PDF; Baxter, India). To evaluate the cytokine productions by stimulated PBMCs, ELISA was performed.

Results: In CAPD patients the expression of TH1 (IL- 1β, TNFα, IFNg), TH2(IL-10, IL-4)cytokines from PBMCs stimulated by dialysis effluent was significantly lower, compared with CKD5 (*P*=.001, *P*=.001, *P*=.001, *P*=.001, and*P*=.001*P*=.004, respectively) and healthy controls (*P*=.001, *P*=.001, *P*=.001, *P*=.001, and *P*=.001, *P*=.001, respectively). Th1 (TNF-α, IFN-g, IL-1β,), Th2 (IL-4) and regulatory (IL-10) cytokines were significantly lower in PD patients when compared with healthy controls stimulated by dialysis effluent. PBMCs of PD patients stimulated by fresh fluid expressed reduced Th1 cytokines than those dialysis effluents. Cytokine immune response was significantly reduced when stimulated with PHA and dialysis effluent in PD patients as compared CKD5 patients and controls. Cytokines values were significantly more with PHA followed by DE and PDF respectively in each group.

Conclusions: Polarization of helper T-cells in response to mitogenic stimulation was blunted in CAPD patients compared with controls and CKD 5 resulting in a significant decrease in both Th1 cells and Th2 cells. These studies suggest that the clinical presentation of the dialysis was influenced by the type of cytokine (Th1 and Th2) production.

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SA-PO937

T Regulatory Cells in Uremia: Effect of the First Peritoneal or Hemodialysis Treatment

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Background: A major challenge for the immune system is to preserve tolerance to self while maintaining the ability to fight foreign pathogens and infectious agents. This function is largely performed by the $FOXP3^+$ T-regulatory (Treg) cells. In the literature, contrasting results have been reported about the influence of dialysis on Treg cells, in chronic kidney disease stage G5 (CKD G5) patients that show activated but impaired immune system. The aim of this study is to evaluate the changes in Treg cells numbers before and after the first dialysis treatment.

Methods: Peripheral blood samples for this pilot study were obtained from 21 CKD G5 patients not yet on dialysis (CKD G5): 8 started hemodialysis (HD, N = 8), 13 started peritoneal dialysis (PD, N = 13). Treg were studied by flow cytometry using CD3-PerCP; CD4-FITC; CD25-PECy7; CD127-PE and FOXP3-APC antibodies. Time point: T0 (before the first dialysis treatment); T1 (after 1 month). We performed Wilcoxon test for dependent samples to compare the mean percentage difference between T0 and T1 (Δ %): (100*(T1-T0)/T0).

Results: The total cohort (8HD and 13PD, n = 21) included 88.9% and 77% males in HD and PD groups respectively. Mean age was 68 in HD group and 67 in PD group. The proportion of lymphocytes and T lymphocytes did not change before and after the first dialysis treatment (as evaluated 1 month after the start of dialysis) in PD and HD patients. Treg cells (considered either as $CD25^+$ $FOXP3^+$, $Foxp3^+$ or $CD25^+$ $CD127^+$) analyzed as percentage of lymphocytes showed a statistically significant increase post-PD (median=35.92; p=0.0425 for $CD25^+$ $FOXP3^+$; median=30.85; p=0.0479 for $FOXP3^+$ and median=23.71; p=0.0215 for $CD25^+$ $CD127^-$); The same populations did not change after the first HD session (median=0.07; p=0.843 for $CD25^+$ $FOXP3^+$; median=2.32; p=0.945 for $FOXP3^+$ and median=6.69; p=0,742 for $CD25^+$ $CD127^-$).

Conclusions: Our study is the first to evaluated the effect of PD or HD treatment on the status of T-regulatory cells to understand their role in immune homeostasis. PD was more effective in increasing Tregs levels when analyzed at one month post dialysis and may contribute to improvement of inflammatory status. Thus, PD may contribute to better outcomes for patients with renal dysfunction by not only restricting inflammation, but also maintaining homeostasis of peritoneal and renal tissues.

Funding: Private Foundation Support

SA-PO938

Implication of Inflammasome Activation in the Progression of Peritoneal Fibrosis in Mice

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Background: During peritoneal dialysis, the peritoneum is exposed to bioincompatible dialysate, which causes tissue fibrosis, which then limit the long-term effectiveness of peritoneal dialysis. Peritoneal fibrosis is the end result of chronic inflammation reactions induced by a variety of stimuli including peritonitis, allergic responses. Thus, understanding the molecular events that drive fibroproliferation and matrix deposition has been a favored area of investigation. However, the detailed mechanisms underlying peritoneal fibrosis process have not been elucidated. Considering that activation of inflammasome triggers chronic inflammation, which ultimately causes fibrosis. We investigated whether inflammasome activation causes peritoneal fibrosis.

Methods: We used ASC-deficient mice (ASCKO) to investigate the role of inflammasome, which ASC are critical components of the inflammasome. C57Bl/6 mice (WT) were used for control. Peritoneal fibrosis was induced by chlorhexidine gluconate (CG) into the peritoneal cavity of mice every other day for 4 weeks. VX-765 (100 mg/kg/day), an inhibitor of caspase-1 activity, was administered by gavage for 2 weeks. The mice were divided into the following groups; (1) WT-vehicle, (2) WT-CG, (3) ASCKO-vehicle, (4) ASKO-CG, and (5) WT-CG/VX-765.

Results: After exposure to CG, WT-CG mice showed the progression of peritoneal fibrosis evaluated by Masson's trichrome stain, and also been observed to enhance mRNA expression of TGF-β in peritoneal tissue. Increased expressions of inflammasome components, NLRP-3 and ASC, were demonstrated in WT-CG. Increased Caspase-1 activity and concomitant overproduction of IL-1β and IL-18 were also demonstrated in the WT-CG. These changes were suppressed in the ASCKO-CG and VX-765 injected mice. Furthermore, ASC-positive cells were merged with the immunofluorescent staining for the macrophage marker F4/80. Therefore, inflammasomes were mainly activated in the infiltrating macrophages.

Conclusions: Our results suggest that inflammasome activation plays a pivotal role in the development of peritoneal fibrosis in infiltrated macrophages. Thus, inflammasome activation in macrophages could be a new therapeutic target for chronic inflammation-induced peritoneal fibrosis.

SA-PO939

Innate Immunity Dysfunction: A Prospective Study on Peritoneal Dialysis and Hemodialysis

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Background: The immunological disorder associated with chronic kidney disease is complex since there is a coexistence of a proinflammatory state and immunological deficiency, both contributing to patients' morbidity and mortality. The immune dysfunction on end-stage renal disease covers both innate and adaptive immunity, although disturbances in the innate branch are far less described in the literature. The aim of the present work is to study the innate immune system changes in patients undergoing hemodialysis and peritoneal dialysis, and if significant residual renal function influences innate immunity.

Methods: A prospective, case-control study was performed using peripheral blood samples from 21 patients undergoing PD, 20 patients undergoing HD and 12 healthy patients. Whole blood cells were analyzed and quantification of leukocyte subpopulations and surface molecules was made by flow cytometry using different fluorescent antibody conjugates.

Results: There was a significant decrease in monocytes and dendritic total cell counts in dialysis patients compared to healthy controls. Natural killer cells in hemodialysis patients, compared to peritoneal dialysis and controls, had enhanced expression of the receptors NKp30, NKp44, CD94/NKG2C, and IFNg, indicating enhanced cytokine production, and increased expression of CD57. Hemodialysis patients also presented more pro-inflammatory markers in iNKT and gdT cells than peritoneal dialysis patients.

Conclusions: Our study suggests an innate immunity dysfunction in dialysis patients, more evident in hemodialysis patients that express a proinflammatory profile and chronic activation of the innate immunity system.

SA-PO940

Mean Corpuscular Volume Associates with Clinical Outcome in Incident Peritoneal Dialysis Patients

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Background: Mean corpuscular volume (MCV), a measure of the average size of circulating erythrocytes, is used for differential diagnosis of anemia and for monitoring macrocytosis. While several studies revealed that MCV is associated with mortality in various clinical settings, it is unclear whether this association applies to PD patients. We investigated the relationship of MCV with all-cause and cardiovascular mortality in incident PD patients.

Methods: In 767 incident PD patients (median age 50 years, 57 % males, 15% diabetes, DM, and 6% cardiovascular disease, CVD), MCV andother metabolic biomarkers potentially linked to CVD were analysedat baseline. We investigated factors associated (Spearman correlations) with MCV at baseline and during follow up period of up to 60 monthswe analysed the association of MCV with mortality risk using competing-risk regression models with transplantation as competing risk and adjusting for covariates.

Results: In univariate analysis, MCV associated with white blood cell count (rho=-0.12, p=0.001), age (rho=0.15, p<0.001), BMI (rho=-0.15, p<0.001), gender (rho=-0.14, p=0.002), uric acid (rho=-0.15, p<0.001), HDL cholesterol (rho=0.10, p=0.005), parathyroid hormone (rho=0.12, p=0.001), ASAT (rho=0.12, p=0.001) and DM (rho=-0.09, p=0.01). Compared with middle+ high tertiles, the lowest tertile of MCV associated with decreased all-cause mortality risk, sub-hazard ratio (sHR) of 0.61 (95% CI, 0.42-0.89; p=0.01), and with decreased CVD mortality risk, sHR 0.50 (95% CI, 0.29-0.87; p=0.01) after adjusting for age, gender, DM, CVD and calendar year of recruitment.

Conclusions: In incident PD patients, after adjusting for age, sex, and presence of CVD and diabetes, low MCV was independently associated with decreased all-cause and CVD mortality risk. These results suggest that monitoring of MCV may provide useful prognostic information in patients treated with PD.

SA-PO941

Genetic or Pharmacologic Blockade of Enhancer of Zeste Homolog 2 Inhibits the Progression of Peritoneal Fibrosis

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Background: Dysregulation of histone methyltransferase enhancer of zeste homolog 2 (EZH2) has been implicated in many cancers. However, the role of EZH2 in peritoneal fibrosis remains unknown.

Methods: We investigated EZH2 expression in peritoneal dialysis (PD) patients and assessed its role in peritoneal fibrosis induced by chlorhexidine gluconate (CG) or high glucose peritoneal dialysis fluid (PDF) in mice by using 3-deazaneplanocin A (3-DZNeP), and EZH2 conditional knockout mice in fibroblasts.

Results: An abundance of EZH2 was detected in the peritoneum of patients with PD associated peritonitis and the dialysis effluent of long-term PD patients. EZH2 was also highly expressed in the peritoneum of mice after injury by CG or PDF, and treatment with 3-DZNeP attenuated peritoneal fibrosis and inhibited activation of several pro-fibrotic mechanisms. Moreover, delayed administration of 3-DZNeP inhibited peritoneal fibrosis progression, reversed established peritoneal fibrosis and reduced matrix metalloproteinases-2 (MMP-2) and MMP-9 expression. Finally, EZH2-KO mice exhibited less peritoneal fibrosis compared with EZH2-WT mice. In cultured peritoneal mesothelial cells, EZH2 inhibition resulted in suppression of α-SMA and Collagen I and preservation of E-cadherin.

Conclusions: These results indicate that EZH2 is a key epigenetic regulator that promotes peritoneal fibrosis. Targeting EZH2 may have the potential to prevent and treat peritoneal fibrosis.

SA-PO942

Nuclear Factor of Activated T Cells 5 (NFAT5) Mediates Peritoneal Fibrosis via Modulation of Nod-Like Receptor-3 (NLRP3) Inflammasome

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Background: NLRP3 inflammasome is a multiprotein oligomer that promotes the maturation of IL-1β and IL-18. NFAT5 is an essential transcription factor regulating cellular homeostasis to hypertonicity-induced osmotic stress, and recently reported as pro-inflammatory and pro-fibrotic mediator. We investigated whether NFAT5 played a role in peritoneal fibrosis and epithelial-to-mesenchymal transition (EMT) via a modulation of NLRP3 inflammasome

Methods: The expressions of NFAT5 and components of NLRP3 inflammasome (NLRP3, ASC, and procaspase-1) were evaluated in human peritoneal mesothelial cells (HPMCs) and animal model of peritoneal fibrosis. Effects of siNFAT5, siNLRP3, siASC or NLRP3 inflammasome inhibitor (MCC950) on EMT of HPMCs were evaluated. Peritoneal EMT and fibrosis were compared in adenoviral vector of TGFβ (ad-TGFβ)-injected NFAT5 +/+ and +/- mice

Results: TGFβ increased NFAT5 expression and its nuclear translocation in HPMCs. TGFβ-induced EMT was associated with an up-regulation of NLRP3, ASC, procaspase-1 and an increased production of IL-1β/IL-18. siNFAT5 ameliorated TGFβ-induced NLRP3 inflammasome pathway and EMT with an increase in E-cadherin promotor activity as well as a decrease in snail expression and nuclear translocation of β-catenin. siNLRP3, siASC, and MCC950 also alleviated TGFβ-induced EMT. In NFAT5$^{+/-}$ mice, ad-TGFβ induced peritoneal fibrosis were ameliorated with a reduction in peritoneal thickness compared to wild-type NFAT5 $^{+/+}$ mice

Conclusions: This data suggest NFAT5 plays a key role in peritoneal fibrosis via tonicity-independent mechanism by either an inhibition of E-cadherin transcription and activation of NLRP3 inflammasome. Modulation of NFAT5 and NLRP3 inflammasome in peritoneum could be a novel approach to protect peritoneal fibrosis in PD patients

SA-PO943

Crucial Role of NLRP3 Inflammasome in the Development of Peritoneal Dialysis-Related Peritoneal Fibrosis

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Background: Long-term peritoneal dialysis (PD) therapy leads to peritoneal inflammation and fibrosis. However, the mechanism underlying PD-related peritoneal inflammation and fibrosis remains unclear. Recent evidence indicates that sterile inflammation triggered by danger signals is mediated through a multiprotein complex called the NLRP3 inflammasome. In the present study, we investigated the role of NLRP3 inflammasome in the pathophysiology of peritoneal fibrosis using a mouse model of methylglyoxal (MGO)-induced PF.

Methods: C57BL/6J (wild-type [WT]) and ASC-deficient mice were mainly used throughout the study. PF was induced by intraperitoneal injection of peritoneal dialysis fluid (PDF) (100 mL/kg) containing 40 mM MGO solution for 3 weeks, 5 consecutive days per week. The control group received the same volume of PDF. In in vitro experiments, human umbilical vein endothelial cells (HUVEC) and primary mouse lung vascular endothelial cells (MLVEC), were stimulated with MGO.

Results: Inflammasome-related molecules were upregulated in the peritoneum of MGO-treated mice. MGO induced parietal and visceral peritoneal fibrosis in wild-type mice, which was significantly attenuated in mice deficient in NLRP3, ASC and interleukin-1β. ASC deficiency reduced the expression of inflammatory cytokines and fibrotic factors, and the infiltration of macrophages. However, myeloid cell-specific ASC deficiency (ASC$^{f/f}$; LysM$^{cre/+}$) failed to inhibit MGO-induced peritoneal fibrosis. MGO caused hemorrhagic ascites, fibrin deposition, and plasminogen activator inhibitor-1 upregulation, but all of these manifestations were inhibited by ASC deficiency. Furthermore, in vitro experiments showed that MGO induced cell death via the generation of reactive oxygen species in vascular endothelial cells, which was inhibited by ASC deficiency.

Conclusions: Our results showed that endothelial NLRP3 inflammasome contributes to PD-related peritoneal inflammation and fibrosis, and provide new insights into the mechanisms underlying the pathogenesis of this disorder.

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SA-PO944

A Novel Device Allows Simplicity and Independence to Peritoneal Dialysis (PD) Patients

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Background: Although peritoneal dialysis is considered a simple method of renal replacement therapy accesible to almost every one, it is still underutilized worldwide. The barriers could be difficulties in fine motor skills, decreased vision, insecurity of performing a precise method alone, time consumption and more. liberDi's portable PD system (PPDS™) is a newly developed small automatic device intended for PD exchange. It uses a small electric battery operated pump for inflow/outflow mechanism to drain and fill the dialysate at a controllable rate. The device makes the exchange after automatic disinfection of the connectors. The PPDS™ also enables monitoring of effluent dialysate (stream flow, fluid clarity, temperature) and transmits the data to the PD center. This first-in-human open single arm, multicenter clinical trial was performed in 2 different PD units- Carmel Medical Center and Meir Medical Center in Israel. The goal of the study was to verify safety of the liberDi's PPDS™ as primary endpoint toward evaluating its usability and feasibility.

Methods: The trial includes 10 stable chronic adult CAPD patients, treated more than 3 months, used to do at least 3 exchanges daily. During the trial a single exchange was

performed in the PD clinic via the liberDi's PPDS™ under supervision of the PD team, followed by a one-month clinical follow-up.

Results: Average drainage time was 10.7±2.3 min, filling time 8±2.6 min. Three patients noted mild abdominal discomfort at the end of the draining and start of filling (not unusual for them), while one patient showed slow drainage and shifted to a regular manual exchange. None of the patients developed peritonitis during the follow- up period. One patient died due to acute ST elevation myocardial infarction 5 days after the trial procedure, which was considered as unrelated to the procedure itself.

Conclusions: This first-in-human study showed the safety of liberDi's PPDS device demostrating its feasibility in a single automatic PD exchange. Its use seems to be convenient, easy and safe.

Funding: Commercial Support - liberDi

SA-PO945

The Significance of Mini-PET and Fibrosis-Related Factors in Effluents in Peritoneal Function

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Background: Peritoneal dysfunction characterized by peritoneal fibrosis is the problem of long-term peritoneal dialysis. Recent studies have reported that sodium sieving (ΔNa) in mini-PET has the correlation with free water transport (FWT) and peritoneal fibrosis. We previously reported that lysophosphatidic acid (LPA) signaling-dependent connective tissue growth factor (CTGF) was significant to peritoneal fibrosis. Therefore, we examined the association of mini-PET markers with fibrosis-related factors in effluents.

Methods: We performed mini-PET (1hr-dwell) for 43 patients (60 samples) and assessed peritoneal function-related factors such as ΔNa and FWT. ΔNa was determined by the difference of sodium concentration in dialysate between 1hr and 0hr, and FWT by ultrafiltration volume except for the influence of sodium removal. In addition, we measured autotaxin (ATX), which is the enzyme of LPA production pathway, and CTGF concentrations as the fibrosis-related factors. We also performed standard-PET (4hrs-dwell) to assess D/P Cr and D/D0, and estimated the association of these values with mini-PET markers as well as the fibrosis-related factors.

Results: ΔNa had the correlation with FWT (r=0.86, p<0.01), D/P Cr (r=-0.28, p<0.05), D/D0 (r=0.40, p<0.01). In cases observed over the years (n=16), ΔNa at 1st year had the correlation with FWT (r=0.82, p<0.01) and D/P Cr (r=-0.65, p<0.01) at 2nd year. The changes of ΔNa had the correlation with the change of ultrafiltration (r=0.61, p<0.05). Moreover, ΔNa had the correlation with ATX (r=-0.80, p<0.01) and CTGF (r=-0.75, p<0.01).

Conclusions: ΔNa and fibrosis-related factors in effluents have the possibility to be the predictive factors of peritoneal function.

SA-PO946

Nintedanib Attenuates the Development and Progression of Peritoneal Fibrosis

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Background: Nintedanib, a FDA approved triple tyrosine kinase inhibitor, has antifibrotic effects in idiopathic pulmonary fibrosis and renal fibrosis. Here, we examined the effect of nintedanib on the development and progression of peritoneal fibrosis.

Methods: Daily intraperitoneal injections of chlorhexidine gluconate (CG) induced peritoneal fibrosis in mouse and TGF-β1 was used to induce fibrotic changes in cultured human peritoneal mesothelial cells. The effects of nintedanib were determined by histochemical and immunofluorescent staining, immunoblot and ELISA analysis.

Results: Administration of nintedanib immediately after injury prevented the onset of peritoneal fibrosis and delayed administration of nintedanib (3 days after the onset of peritoneal fibrosis) halted fibrosis progression. Nintedanib treatment abrogated the increased phosphorylation of PDGFR, FGFR, VEGFR, Src, decreased the expression of extracellular matrix(ECM) protein (Fibronectin and type I Collagen), inhibited the expression if marker proteins of mesenchymal phenotype (α-SMA,β-Vimentin) and transcription factors(Snail and Twist), increased expression E-Cadherin, blocked the phosphorylation of Smad3, STAT3, and NF-κB during peritoneal fibrosis; it also inhibited the accompanying overproduction of proinflammatory cytokines (MCP-1, TNF-α, IL-1β, and IL-6) and the infiltration of macrophages (CD68-positive) to the injured peritoneum, and reduced the peritoneal increase of CD31-positive blood vessels after injury. Moreover, delayed administration of nintedanib significantly induced MMP-2 expression and inhibited TIMP-2 expression. Finally, nintedanib abrogated TGF-β1–induced the epithelial-to-mesenchymal transition, ECM protein overproduction and phosphorylation of aforementioned cell signaling molecules in cultured human peritoneal mesothelial cells.

Conclusions: These results demonstrate that nintedanib may inhibit epithelial-to-mesenchymal transition, extracellular matrix overproduction inflammation and angiogenesis, and improved extracellular matrix degradation, possibly through its blockade of RTKs and Src simultaneously. It suggests that nintedanib may have therapeutic potential in attenuating onset and progression of peritoneal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO947

Deletion of Matrix Metalloproteinase 10 Ameliorates Peritoneal Fibrosis

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Background: Peritoneal fibrosis is one of major characteristics of peritoneal membrane damage. Our group previously reported highly upregulated genes in the peritoneal membrane from chlorhexidine gluconate (CG)-treated peritoneal fibrosis mice compared with control in microarray analysis, one of which was matrix metalloproteinase-10 (MMP-10). MMP-10 was a proteinase protein degrading components of extracellular matrix (ECM) and was known to be associated with arteriosclerosis or tissue repair. Although deletion of MMP-2 and MMP-9, which were called gelatinases, ameliorated peritoneal fibrosis, the role of MMP-10 has not been elucidated in peritoneal fibrosis yet.

Methods: To investigate the role of MMP-10 in peritoneal fibrosis, we induced peritoneal fibrosis by intraperitoneal injection of chlorhexidine gluconate in wild-type (WT) and MMP-10 knockout (KO) mice. We administrated 0.01 mL/gBW of 0.1% CG in 15% ethanol and 85% phosphate-buffered saline (PBS) 3 times per week for 4 weeks. Control mice received intraperitoneal injection of PBS. Peritoneal sections were stained with Masson's trichrome and were analyzed by immunohistochemical study.

Results: We identified upregulation of MMP-10 by 8.6-times in the peritoneum from CG-treated WT mice by a microarray analysis. There were no histological changes in the peritoneum between PBS-treated WT mice and PBS-treated MMP-10 KO mice. CG-treated WT mice had a remarkable thickening of peritoneum, an increased number of αSMA-, F4/80-positive cells in the peritoneum, and upregulation of MMP-10 mainly within the mesothelial cells and fibroblasts in the submesothelial area of the peritoneum. In contrast, CG-treated MMP-10 KO mice showed reduction of peritoneal thickness and accumulation of αSMA-, F4/80-positive cells in the peritoneum. Furthermore, the peritoneal enhanced expression of Tgfb1, Col1a1, Ctgf, and Ccl2 (MCP1) in WT mice was remarkably reduced in MMP-10 KO mice.

Conclusions: These results indicate that MMP-10 is upregulated in mesothelial cells and fibroblasts in peritoneal injury and can aggravate peritoneal fibrosis. Therefore, inhibition of MMP-10 could become a therapeutic strategy in peritoneal fibrosis.

SA-PO948

Valsartan Ameliorates High Glucose-Induced Peritoneal Fibrosis by Blocking mTORC1 Signaling

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Background: Increasing evidences suggest that angiotensin II type 1 receptor (AT1R) blockers prevent peritoneal fibrosis (PF) under high glucose (HG) conditions. The study aimed to investigate the undefined mechanisms by which AT1R blocker valsartan on HG induced PF.

Methods: We used HG peritoneal dialysis solution (PDS) in a mouse peritoneal dialysis model to induce *in vivo* PF and HG in human peritoneal mesothelial cells (HPMCs) *in vitro* to stimulate extracellular matrix (ECM) accumulation.

Results: After the injection of 4.25% PDS for 4 weeks, mice showed typical features of PF, including markedly increased peritoneal thickness, excessive matrix deposition, increased peritoneal permeability, and higher expressions of ECM markers, such as α-smooth muscle actin (α-SMA) and collagen I. Valsartan significantly ameliorated these pathological changes at either week 6 or 8. These effects of valsartan were closely correlated with a decrease in the activation of mammalian target of rapamycin complex 1 (mTORC1) pathway, which was mediated through the down-regulation of protein expressions of phosphorylated-mTOR (p-mTOR), p-eukaryotic initiation factor 4E-binding protein 1 (p-4EBP1), and P-p70 S6 kinase (p-S6K1). Further analysis showed the protein expression of p-mTOR, p-4EBP1, p-S6K1 was positively correlated with the expression of either α-SMA or collagen I in the peritoneum. *In vitro*, HG increased the protein expressions of α-SMA and collagen I in a dose dependent manner, while valsartan significantly inhibited HG-induced ECM accumulation in HPMCs. The effect was also accompanied by a decrease in the activation of mTORC1 pathway. Furthermore, mTOR agonist-MHY1485 could reverse the downregulation of ECM components in HPMCs, even in the presence of valsartan.

Conclusions: We conclude that valsartan shows a protective effect on HG-induced PF by inhibiting the activity of mTORC1 pathway.

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SA-PO949

Pasp Deletion Mutation Reduced the Virulence and Pathogenic Ability of Pseudomonas aeruginosa

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Background: Pseudomonas aeruginosa is a very important conditional pathogen commonly existing in the environment, and it is the main pathogen of catheter-related infection in peritoneal dialysis. The formation of intraductal biofilm is an important reason, and the expression of PasP protein is increased in Pseudomonas aeruginosa, which is easy to form biofilm. It is intended to further explore the effect of PasP protein on the virulence of Pseudomonas aeruginosa.

Methods: the pasP gene of Pseudomonas aeruginosa PAO1 was knocked out by homologous recombination method, and the PAO1::pasP strain was constructed. The following parameters of parental bacteria and homologous recombinant bacteria were observed: colony morphology, biofilm forming ability, minimum bactericidal concentration of common antibiotics to bacteria, tolerance of bacteria to temperature, determination of bacterial virulence (pyocyanin, protease, elastase). Difference analysis of protein spectrum were performed;

Results: the pasP gene of Pseudomonas aeruginosa PAO1 was successfully deleted, PAO1::pasP was successfully constructed by homologous recombination. The relative virulence of PAO1::pasP was weaker than that of parent bacteria, including the weakening of biofilm formation ability and the decreasing tolerance to temperature. the production of pyocyanin, protease, elastase were all decreased. The expressions of two-component reaction regulator, two-component sensor, ATP binding protein of ABC transporter, bacteriophage protein, purine binding protein, and the two-component reaction regulator, two-component sensor, ATP binding protein, bacteriophage protein and purine binding protein of PTX transporter decreased, Aer2 protein, type IV flagellin Flp and rhamnose glycosyltransferase subunit A were significantly lower than in PAO1::pasP strain than in parental bacteria.

Conclusions: Pseudomonas aeruginosa pasP gene is involved in the biofilm formation and QS sensing system, and pasP gene deficient strains show weaker bacterial virulence and pathogenic ability.

SA-PO950

Effluent DcR2 Is a Novel Biomarker for Peritoneal Fibrosis in Peritoneal Dialysis Patients

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Background: Peritoneal fibrosis is the most severe complication of peritoneal dialysis (PD), but lack of noninvasive biomarkers for monitoring the rate of progression of peritoneal fibrosis. Decoy receptor 2(DcR2), a marker of senescence, has been used to evaluate the degree of differentiation of tumors. The aim of this study is to determine whether peritoneal effluent DcR2 could serve as a novel specific and sensitive biomarker for assessing peritoneal fibrosis.

Methods: 149 PD patients (PD duration>6 months) were enrolled in our unit from 2008 to 2018, free from acute infection and recent peritonitis. The fibrosis of peritoneal biopsy tissues were detected by Masson trichrome staining. Effluent and serum DcR2 levels were measured by ELISA and effluent appearance rate (AR) were calculated. The association of DcR2-AR with clinical parameters were analyzed. Receiver operating characteristics (ROC) curve analyzed area under the curve (AUC) of AR DcR2 for assessing peritoneal fibrosis. Double staining was undertaken for DcR2 with peritoneal mesothelial cells and fibroblast marker vimentin and fibrotic markers α-SMA and FN.

Results: There were 75 patients with peritoneal fibrosis and 74 without. Effluent and serum DcR2 levels had no statistical difference between two groups, but DcR2-AR levels were higher in patients with peritoneal fibrosis compared with normal peritoneum. Effluent DcR2-AR levels were associated with Duration of PD, total glucose exposure, past peritonitis (%) and 4h D/P. The area of under curve was 0.74 for peritoneal fibrosis, with a sensitivity of 73% and specificity of 76%, respectively. DcR2 was co-expressed with vimentin and colocalized with α-SMA and FN in peritoneal tissue.

Conclusions: Effluent DcR2 can could potentially serve as a novel biomarker for peritoneal fibrosis and may reflect senescence of fibroblasts in PD patients.

Funding: Government Support - Non-U.S.

SA-PO951

Hepcidin, Iron Status, and Mineral Metabolism in Peritoneal Dialysis Patients

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Background: Few studies have examined the association between hepcidin, iron status, and bone mineral metabolism in peritoneal dialysis (PD) patients. The present study aimed to investigate the association of hepcidin with iron status and bone mineral metabolism in PD patients.

Methods: Patients who started PD at Seoul National University Hospital from January, 2010 to August, 2018 and who had not received renal replacement therapy before and whose baseline serum samples were available were enrolled. Serum hepcidin levels were measured by enzyme-linked immunosorbent assay (ELISA) using Hepcidin 25 (bioactive) HS ELISA kits (DRG Diagnostics, Marburg, Germany), according to the manufacturer's protocol. Multivariable linear regression analysis was used to identify the association of hepcidin with iron status and bone mineral metabolism.

Results: A total of 162 incident PD patients were analyzed. The patients were 45.4±13.6 years old and 78 (48.1%) were male. The median serum hepcidin level was 50.67 ng/mL (interquartile range, 25.34-83.61 ng/mL). Mean hemoglobin level was 10.4±1.3 g/dL. The prevalence of hemoglobin <10 and <11 g/dL were 40.1% and 67.9%, respectively. Hemoglobin (Pearson correlation, -0.19; P = 0.014) and ferritin (Pearson correlation, 0.59; P< 0.001) were associated with hepcidin in unadjusted analysis. In multivariable linear regression analysis with adjustment for multiple confounders, hepcidin was positively associated with ferritin (β=0.66; 95% confidence interval, 0.50-0.81; P< 0.001). There were not significant associations between hepcidin and markers of mineral metabolism: calcium (Pearson correlation, -0.01; P = 0.161), phosphorous (Pearson correlation, -0.05; P = 0.538), LogPTH (Pearson correlation, 0.05; P = 0.554), 25(OH)VitD (Pearson correlation, 0.04; P = 0.683). Hepcidin levels were not significantly different according to use of iron therapy, erythropoiesis stimulating agents or phosphate binders.

Conclusions: Hepcidin was positively associated with ferritin. There were not significant associations between hepcidin and markers of mineral metabolism in our PD patients.

SA-PO952

Prognostic Value of Serum and Dialysate APX-501 in Chronic Dialysis

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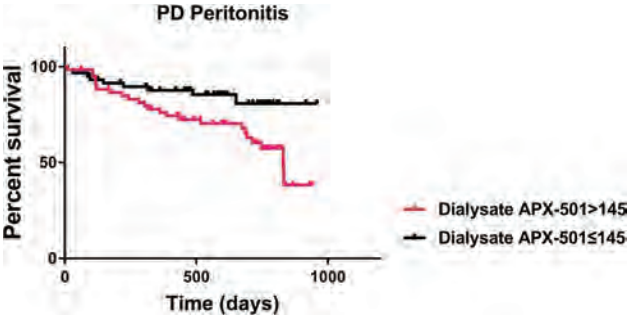
Background: Patients on chronic dialysis are known to be in a chronic inflammation associated with increased oxidative injury, which results in increased morbidity and mortality. Recently APX-501 protein was identified to have regulatory role on oxidative stress. In the present study, we examined the clinical utility of APX-501 levels in serum and dialysate in chronic dialysis patients.

Methods: This study was a multicenter, prospective study that examined the level of serum and dialysate APX-501 in patients on chronic dialysis. Patients on dialysis (both peritoneal (PD) and hemodialysis(HD)) were enrolled between January 2016 to February 2018. Serum APX-501 level was measured using ELISA method. Time to overall mortality was recorded as the primary endpoint. For secondary endpoint, admission for major adverse cardiac events (MACE) and admission due to infection were recorded.

Results: Of 216 patients, patient on PD consisted of 136 patients. 37.5% of PD patients were enrolled initiating PD as the first dialysis modality (defined as new PD). During follow up period of 625±172.8 days, 15 patients died (6.9%), 27 experienced MACE (12.5%), 64 admitted to the hospital due to infection from any cause (29.6%). PD peritonitis event was reported in 35 patients (25.7% of PD group), of which 17(48.6%) patients were who initiated PD for the first time. Serum APX-501 did not predict overall mortality, MACE or acute infection event during the follow up period. In PD patients, dialysate APX-501 level was increased in patients who were initiating PD, and those with increased level of baseline dialysate APX-501 were at an increased risk of incidence for infection including PD peritonitis.

Conclusions: Dialysate APX-501 level may help to predict the risk of infection, especially the risk of PD peritonitis. Whether it can predict imminent PD peritonitis should be studied.

Funding: Commercial Support - Fresenius Medical Care



SA-PO953

Systems Biology Analysis of Lithium-Mediated Cytoprotection in PD

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Background: Peritoneal dialysis fluids (PDF) harm peritoneal cells, leading to transdifferentiation and cell death. Lithium chloride (LiCl), a clinically applicable kinase inhibitor, improved survival of immortalized mesothelial cells. Due to its availability and well-characterized pharmacological profile, LiCl could be a promising molecule to be used as local cytoprotective additive to PDF. The pleiotropic effects of LiCl on mesothelial cells, have not yet been investigated.

Methods: Here, we analyzed the protective potential of LiCl added to PDF in a systems biology approach which combined transcriptomics and proteomics analyses followed by validation in human samples and a chronic mouse model.

Results: PDF with LiCl caused significantly lower cell injury of primary human mesothelial cells in a dose dependent manner. PD-induced cell injury was associated with significantly differential expression of 478 genes and 92 proteins compared to control, LiCl in PDF altered 749 genes and 102 proteins. Pathway over-representation and molecular process enrichment tests showed a strong regulation of angiogenesis related pathways in response to PDF. Analysis of transcripts and proteins that were counter-regulated in PDF with LiCl compared to PDF alone, yielded candidates associated with the LiCl effect, with the small heat shock protein αB-crystallin as most strongly regulated candidate. αB-crystallin was significantly upregulated by PDF but close to control level with LiCl in the omics and targeted analyses. Modulated expression of αB-crystallin, which has been described as regulator of VEGF-mediated angiogenesis, confirmed its regulatory involvement in PD-induced pathomechanisms. Uremic as well as non-uremic mice showed significantly reduced peritoneal membrane thickening and transdifferentiation with LiCl. PDF-induced increased VEGF and αB-crystallin levels in peritoneal membranes were reduced with LiCl. The relevance was confirmed in significantly upregulated abundances of mesothelial αB-crystallin in biopsies from children treated with PD, compared to age-matched healthy controls or with CKD5.

Conclusions: The beneficial effects of LiCl in PDF may be explained by counter-regulation of the PD-induced angiogenesis via the novel target αB-crystallin. Reduction of cell damage and fibrosis suggests therapeutic potential of this intervention.

SA-PO954

Probiotics Decreased Concentrations of Indoxylsulphate in PD Patients

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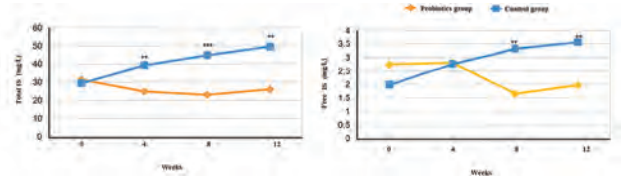
Background: Clearance of protein-bound uremic toxins (PBUTs) by dialysis is a challenge in the treatment of uremic patients. P-cresylsulphate (PCS) and indoxylsulphate (IS) are protein-bound uremic toxins which produced in the intestine by certain intestinal bacteria, and the productions of them are affected by various intestinal environmental factors. Quantitative and qualitative alterations in gut microbiome are noted in patients with end-stage renal disease (ESRD). The indol- and p-cresol-forming bacterial families were found more abundant while the formation of short-chain fatty acidswas diminished. These changes in intestinal microbial metabolism may contribute to increased IS and PCS production. Treatment with probiotics may reduce serum/plasma PCS and IS levels, but there have been no randomised controlled trials to test the effects of probiotics on the serum PCS and IS levels in peritoneal dialysis(PD) patients.

Methods: We conducted a randomized controlled trial to evaluate the effects of probiotics on serum IS and PCS. Participants were randomized to probiotics or control group. Probiotics group received Bifid Triple Viable Capsules 0.42g orally 3 times daily for 12 weeks, IS and PCS concentrations were determined by HPLC/MS/MS and blood biochemical parameters were assessed during the study. Patients were followed up to observe the long terms clinical outcomes.

Results: A total of 60 patients were included in the clinical trial. Total IS level was significantly lower in probiotics group than in control group at week 4, 8, and 12. Free IS in probiotics group was also lower than in control group at week 8 and 12. However, there were no difference of total and free PCS between two groups during 12 weeks. After 10.20±4.48 months follow up, it showed that the incidence of peritonitis in the treatment group was significantly lower than that in the control group(log rank *P*=0.038). However, there were no significant difference in the incidence of PD failure, cardiovascular mortality and all-caused mortality.

Conclusions: Administration of probiotics decreased serum IS level effectively in PD patients. Benefits of PD patients' outcomes from IS reduction by probiotics awaits further large size and long duration clinical trials to verify.

Funding: Government Support - Non-U.S.



SA-PO955

Contribution of Proximal Tubular Solute Clearance in Residual Kidney Function

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Background: Residual kidney function (RKF) is associated with better health outcomes in end-stage kidney disease (ESKD). Current assessment of RKF relies on creatinine and urea clearance to estimate the glomerular filtration rate. Proximal tubular secretion is an essential intrinsic kidney function that is rarely measured in ESKD. We measured the kidney and peritoneal clearances of tubular secretory solutes in a primary cohort of incident peritoneal dialysis (PD) patients and determined association with uremic symptoms.

Methods: We enrolled 29 incident PD patients with RKF. We used liquid chromatography-mass spectrometry to quantify plasma, 24-hour urine, and dialysate concentrations of ten tubular secretory solutes. We calculated the kidney and peritoneal dialysis clearances of secretory solutes, creatinine, and urea standardized to 1.73m^2. We created a composite secretory clearance score as the average of each solute clearance. We assessed symptom severity using the Dialysis Symptom Index.

Results: The mean age of our cohort was 55 years, mean dialysis duration was 4 months, and mean $GFR_{urea+Cr}$ was 7.8 mL/min/1.73m^2. The kidney clearances of secretory solutes ranged from 1.3 ml/min/1.73m^2 for p-cresol sulfate to 94.6 ml/min/1.73m^2 for hippurate (**Table**). The residual kidney clearance of each secretory solute was substantially higher than peritoneal dialysis clearance. Worse dialysis symptom severity was correlated with a lower composite secretory clearance score (r= -0.46; p=0.01) and, to a lesser extent, lower $GFR_{urea+Cr}$ (r= -0.35; p=0.06).

Conclusions: Among incident PD patients, tubular secretory solutes are more avidly cleared by residual kidney function than peritoneal clearance. Secretory solute clearance correlates more strongly with the severity of uremic symptoms compared with $GFR_{urea+Cr}$.

Funding: NIDDK Support

Table: Residual kidney and peritoneal dialysis solute clearance

	Clearance (ml/min/1.73m^2)		
Solutes	Kidney	Peritoneal	Kidney/Peritoneal
Filtration			
Urea	6.5 [5.0, 14.4]	7.5 [6.2, 10.1]	0.9 [0.5, 1.8]
Creatinine	7.6 [3.4, 12.7]	2.7 [1.9, 3.3]	3.3 [1.1, 4.9]
Secretion			
Cinnamoylglycine	9.5 [6.7, 12.2]	0.5 [0.3, 0.7]	22.4 [7.2, 55.6]
Dimethyluric acid	57.2 [31.7, 82.7]	3.4 [2.2, 4.5]	17.4 [4.3, 28.6]
Hippurate	94.6 [67.3, 121.9]	9.6 [5.5, 13.7]	15.6 [5.1, 30.2]
Indoxyl sulfate	6.6 [5.0, 8.2]	1.1 [0.5, 1.7]	9.9 [3.3, 19.9]
Isovalerylglycine	29.3 [21.1, 37.6]	3.8 [3.1, 4.5]	8.4 [2.4, 13.3]
Kynurenic acid	18.7 [14.0, 23.4]	0.9 [0.6, 1.2]	23.0 [7.8, 42.9]
P-cresol sulfate	1.3 [1.0, 1.6]	0.3 [0.2, 0.4]	5.4 [1.7, 9.5]
Pyridoxic acid	48.7 [34.3, 63.2]	4.1 [2.7, 5.5]	12.9 [3.8, 22.2]
Tiglylglycine	21.5 [14.8, 28.3]	2.1 [1.5, 2.7]	10.8 [3.5, 16.3]
Xanthosine	9.1 [5.8, 12.3]	1.6 [1.1, 2.0]	6.3 [2.2, 14.8]

Values expressed as median [interquartile range]

SA-PO956

L-Carnitine Supplementation Preserves Residual Renal Function in Patients Undergoing Peritoneal Dialysis

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Background: Residual renal function (RRF) is the most important factor to maintain well-being and quality of life in patients undergoing peritoneal dialysis (PD). Carnitine plays a central role in fatty acid b-oxidation and energy production by transporting long-chain fatty acids from the cytoplasm to the mitochondria. Furthermore, carnitine was reported to inhibit oxidative stress. We recently reported that serum carnitine levels were significantly decreased in patients undergoing PD. Therefore, we investigated the impact of L-carnitine supplementation on peritoneal function and RRF in these patients.

Methods: Total 24 PD patients with a mean age of 62.6 ± 9.5 years and a mean PD duration of 515.1 ± 382.5 days were randomly assigned to the L-carnitine (750 mg/day, n = 12) or control (n = 12) group and followed for 6 months. Serum free carnitine (FC) and acyl-carnitine (AC) levels were determined by enzyme cycling method. Additionally, the following parameters were measured before and after the treatment period: clinical chemistry, peritoneal function, RRF, urine volume, urinary L-FABP, serum LPO, and serum MDA.

Results: Both serum FC and AC levels, which did not differ at baseline between the two groups, significantly increased in the L-carnitine group after treatment (4.7 ± 9.2, 128.2 ± 29.9 and 12.8 ± 3.3, 50.9 ± 16.6 μmol/L, respectively). Both the Δrenal Kt/V and Δurinary volume, which decreased after 6 months in the control group, were preserved in the L-carnitine group (–0.26 ± 0.32 vs –0.02 ± 0.22, p = 0.043; –367.1 ± 473.3 vs 99.2 ± 316.2 mL, p = 0.010, respectively). The Δserum LPO levels were significantly lower in the

L-carnitine group (0.33 ± 0.81 vs –0.58 ± 0.67 nmol/mL, p = 0.007), whereas the Δurinary L-FABP and Δserum MDA levels tended to decrease by L-carnitine treatment (19.5 ± 53.7 vs –24.1 ± 65.0 ng/mL, p = 0.087, -0.02 ± 0.04 vs 0.08 ± 0.06 ng/mL, p = 0.177). Furthermore, there was an inverse correlation between Δurinary volume and ΔL-FABP (r^2 = 0.585, p = 0.004) in the L-carnitine group.

Conclusions: L-carnitine supplementation is a promising therapeutic strategy for maintaining RRF by alleviating oxidative stress in L-carnitine-deficient patients undergoing PD.

SA-PO957

Protective Effect of COMP-Angiopoietin 1 on Peritoneal Vascular Permeability and Peritoneal Transport Function in Uremic Peritoneal Dialysis Rats

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Background: The angiopoietin-1 (Ang-1)/Tie-2 signaling pathway plays a crucial role in the maintenance of vascular stabilization and permeability.

Methods: Thirty-six male Sprague-Dawley rats were randomly assigned to the sham operation group, uremia group or uremia+PD group (each n=12). Then, COMP-Ang-1 adenovirus or vehicle adenovirus was injected into twenty other uremic PD rats via the tail vein (each n=10). A peritoneal equilibration test (PET) was performed to evaluate peritoneal transport function before the rats were euthanized. Peritoneal vascular permeability was assessed by measuring FITC-dextran (4 kDa) and FITC-BSA (69 kDa) leakage. The pericyte coverage rate was quantified by anti-CD31 and anti-Desmin immunofluorescence staining. Expression of endothelial junction proteins and Ang-1/Tie-2 signaling were examined by western blotting. The levels of proinflammatory adhesion molecules and cytokines in the peritoneum were measured by real-time quantitative polymerase chain reaction (PCR).

Results: Compared to the sham controls, uremic rats were characterized by decreased pericyte coverage, downregulated endothelial junction protein expression and increased FITC-BSA and FITC-dextran leakage, accompanied by increased levels of proinflammatory adhesion molecules and cytokines, increased D/Pcr and decreased ultrafiltration. After infusion of PDF for 4 weeks, more marked changes were noted. Peritoneal Ang-1 protein expression and Tie-2 phosphorylation were significantly lower in uremic rats than in control rats and were further significantly reduced in uremia+PD rats. After COMP-Ang-1 administration, phosphorylation of the Tie-2 receptor was significantly increased. Treatment with COMP-Ang-1 also significantly enhanced pericyte coverage, upregulated endothelial junctions expression and inhibited the leakage of FITC-BSA and FITC-dextran from the peritoneal vasculature induced during PD therapy; these changes were accompanied by reduced peritoneal tissue levels of proinflammatory adhesion molecules and cytokines, decreased D/Pcr and increased ultrafiltration.

Conclusions: COMP-Ang-1 exerts a protective effect against damage-induced peritoneal vascular permeability and inflammation at least in part by enhancing pericyte coverage and endothelial junction protein expression, which subsequently significantly improves peritoneal transport function.

SA-PO958

Cross-Omics Analysis of Transcriptome, Proteome, and Metabolome Dynamics During Peritoneal Dialysis

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Background: Peritoneal dialysis effluent (PDE) represents a rich but underexplored source of molecular markers for the prediction of clinical outcome, therapy monitoring and investigation of deregulated molecular and cellular processes during PD. Novel PD-fluids (PDF) may enable patient-tailored interventions, such as peritoneal immunomodulation. Alanyl-glutamine (AlaGln) has recently been shown to have beneficial effects in experimental and clinical PD. Modern high performance methods allow monitoring of hundreds of analytes in parallel. In this study, we investigate the transcriptome, proteome and metabolome of PDE samples with or without AlaGln-addition to PDF.

Methods: Samples from a cross-over RCT, investigating AlaGln supplementation of PDF, were analyzed in a cross-omics analysis of effluent cells (RNAseq), soluble proteins (LC-MS) and metabolites in the PDE and plasma (targeted MS) to investigate the effect of AlaGln on the interplay of peritoneal cell populations and fluid transport. Peritoneal immune-competence was analyzed by functional ex-vivo stimulated cytokine release of effluent cells. From each PD dwell, PDE was analyzed at multiple time-points. Bioinformatic analysis results and pathway analysis results from the different datasets were conjoined to reveal novel insights into the "PD-effluentome".

Results: We were able to quantify ~10,000 cellular transcripts, and 2,700 proteins and 300 metabolites in the PDE. Changes in the proteome could in part be explained by co-regulated biological processes observed on the transcript level. The remaining effects on the proteome are likely due to changes in transport characteristics, supported by clinical findings in patients treated with AlaGln. These results correlated with restoration of suppressed peritoneal immune responses by AlaGln. Bioinformatic analysis of proteome-metabolome interference was employed to discriminate local and systemic regulation and transport.

Conclusions: This combined investigation of proteomic and metabolomic properties of PDE represents the first cross-omics analysis of poorly understood molecular processes during PD and the obtained results enable a further step to unravel the beneficial effects of AlaGln-supplementation. Our data also suggest feasibility of multi-omics approaches to investigate pathomechanisms and interventions relevant in PD.

SA-PO959

Markers of Oxidative Stress, Inflammation, and Endothelial Dysfunction in Diabetic and Non-Diabetic CKD Patients on Peritoneal Dialysis

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Background: Oxidative stress, inflammation and endothelial dysfunction represents the key triad for development and progression of atherosclerosis. In this study we assessed the markers of oxidative stress, inflammation and endothelial dysfunction in diabetic and non-diabetic chronic kidney disease (CKD) patients on peritoneal dialysis (PD).

Methods: This is a Cross-sectional study in 100 patients on PD among which 52 patients were non-diabetic and 48 diabetic. Blood samples were measured for oxidative stress markers- Malondialdehyde (MDA), Ferric Reducing Ability of Plasma (FRAP), Inflammatory markers - Interleukin-6, hsC-Reactive Protein (hs CRP), Fibrinogen and markers of endothelial dysfunction-Nitric Oxide (NO). Carotid Intimal Medial Thickness (CIMT) and number of plaques was measured by imaging studies. Comparisons between the two groups for continuous variables were assessed with the Student's unpaired *t*-test and for categorical variables with χ2-test.

Results: MDA is found to be elevated in both group of patients on PD though there was no significant difference (p- 0.279). FRAP was decreased in both diabetic and non-diabetic patients on PD (p- 0.850). The markers of inflammation-interleukin 6, hs CRP were found to be significantly higher in diabetics when compared to non-diabetics (p- 0.001). Serum fibrinogen was found to be elevated in diabetic compared to non-diabetics though not significant (p- 0.181). The markers of endothelial dysfunction- nitric oxide, carotid intimal medial thickness, lipid profile and atherogenic indices was found to be significantly higher in diabetics compared to non-diabetics (p- 0.001). The number of plaques found were significantly higher in diabetic compared to non-diabetics (p- 0.05).

Conclusions: Our study showed presence of increased markers of inflammation and endothelial dysfunction in diabetics compared to non diabetic CKD patients on PD. Markers for oxidative stress were found to be elevated in both subset of patients on PD. These findings will have clinical implications regarding the progression of atherosclerosis in diabetic compared to non-diabetic CKD patients on PD and need to be reconfirmed in a larger sample size.

SA-PO960

Alanyl-Glutamine Decreases Cellular Injury and Enhances Cytoprotective Responses in Endothelial Cells During PD-Fluid Exposure

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Background: Vasculopathy, hypervascularization, and diabetes-like damage of vessels are important factors limiting peritoneal dialysis (PD). The composition of all currently available PD fluids (PDF) leads to morphological and functional changes in the peritoneal membrane in adults and infants. During PDF exposure, relevant cellular pathomechanisms might be similar to those in hyperglycaemic diabetic conditions. This study focuses on omics-based characterization of endothelial cell injury and stress responses with or without addition of alanyl-glutamine (AlaGln).

Methods: Protein profiles of primary human umbilical vein endothelial cells (HUVEC) exposed to medium-diluted conventional PDF with or without 8mM AlaGln were analysed by gel-based proteomics. Cell damage was assessed by quantification of lactate-dehydrogenase (LDH) release. Microdissected omental arterioles of children treated with conventional PDFs and healthy controls were analysed with quantitative multiplex mass spectrometry. In-vitro findings were related to PD-induced arteriolar changes based on abundance profiles of proteins identified in both proteomic analyses.

Results: Marked cellular injury of HUVEC after PDF exposure was associated with a molecular landscape of the enriched biological process clusters 'glucose catabolic process', 'cell redox homeostasis', 'RNA metabolic process', 'protein folding', 'regulation of cell death', and 'actin cytoskeleton reorganization' that characterize PDF cytotoxicity and counteracting cellular repair process respectively. Addition of AlaGln to PDF preserved endothelial cell integrity shown by significantly decreased LDH-release and by restored control levels of proteins in PDF perturbed processes, especially enhancing protein folding capacity and response to stress. Comparison to human arterioles confirmed overlapping protein regulation between endothelial cells in-vitro and in-vivo, proving harmful effects of PDFs on endothelial cells leading to drastic changes of the cellular process landscape. Cellular damage and proteome changes in HUVEC were counteracted by AlaGln in-vitro.

Conclusions: In summary, this study elucidates potential mechanisms by which AlaGln exerts cytoprotective effects in PD-induced endothelial cell damage, offering therapeutic targets to reduce side effects of PD.

SA-PO961

Ionic Conductivity Uses on Evaluation of Peritoneal Transporter Type

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Background: Peritoneal equilibrium test (PET) was developed to evaluate peritoneal transport rate on peritoneal dialysis users, being the gold standard. Based on test results, peritoneal transport can be classified as: high, medium high, medium low and low. This classification has clear implications, since it allows making particular recommendations and patients individualized treatment. PET carries long realization time, given this, studies on ionic conductivity show good correlation with creatinine concentration ratio between dialysis product and plasma (D/PCreat), making it novelty on peritoneal function evaluation

Methods: An analytic transversal study was made on 200 patients diagnosed with chronic kidney disease (CKD) on ambulatory continuous peritoneal dialysis (ACPD) from nephrology department at Unidad Medica de Alta Especialidad (UMAE) 1 of Instituto Mexicano del Seguro Social (IMSS) at Leon, Guanajuato. A modified PET was made, following standardized steps and classifying peritoneal transport, then cut point value of ionic conductivity was determined by under-the-curve analysis (UTC).

Results: Sensible cut values were found, which may allow using ionic conductivity as a suitable test to classify peritoneal transport as low, medium high and high, not so for medium low

Conclusions: Ionic conductivity test shows moderate accuracy to classify peritoneal transport.

Table 1. Clinical and biochemical characteristics of each peritoneal transport type

	Low transport (n=67)	Medium low transport (n=39)	Medium high transport (n=39)	High transport(n=55)	Significance
Time*(years)	2.11±2.08	2.18±1.94	2.84±1.86	2.57±1.82	p= 0.243
D/Pcreat	0.32±0.22	0.58±0.04	0.72±0.04	1.55±1.45	p= 0.001[a]
Cd (mS/cm)	7.52±1.37	8.07±2.04	9.51±2.39	9.19±2.15	p= 0.001[a]
ΔDNa 240	3.22±6.20	4.92±10.30	3.20±6.55	2.49±10.30	p= 0.587
UF (ml)	273.13±152.33	391.03±296.22	430.13±330.47	342.73±192.06	p= 0.006[a]
UFSP	201.36±180.73	280.91±271.58	352.56±260.87	270.15±198.59	p= 0.010[a]
Na D240	123.76±6.73	125.54±8.49	127.79±5.49	126.426±9.08	p= 0.053
Na R	27.70±24.78	39.05±37.52	48.53±35.04	38.06±26.69	p= 0.008[a]
CreatS120	12.86±5.52	9.27±5.01	6.87±2.92	6.30±3.43	p= 0.001[a]
CreatD240	3.89±1.89	5.35±2.87	4.96±2.09	8.42±5.41	p= 0.001[a]
Na S240	137.71±5.01	138.94±5.70	139.15±5.45	139.63±10.55	p= 0.496

*Years in peritoneal dialysis
[a]Mark the significant difference between all groups
The data, unless indicated otherwise, are presented as mean and standard deviation
Ratio for creatinine between dialyzed fluid and plasma (D/Pcreat); ionic conductivity (Cd); difference between the Na concentration in the fresh PD solution and dialysate after a dwell time of 240 min (ΔDNa 240); Ultrafiltration (UF); ultrafiltration through small pore (UFSP); dialysate Na at 240 minutes (Na D240); Na removal in the first hour of the test (Na R); Serum creatinine at 120 minutes (CreatS120); dialysate creatinine at 240 minutes (CreatD240); serum Na at 240 minutes (NA S240)

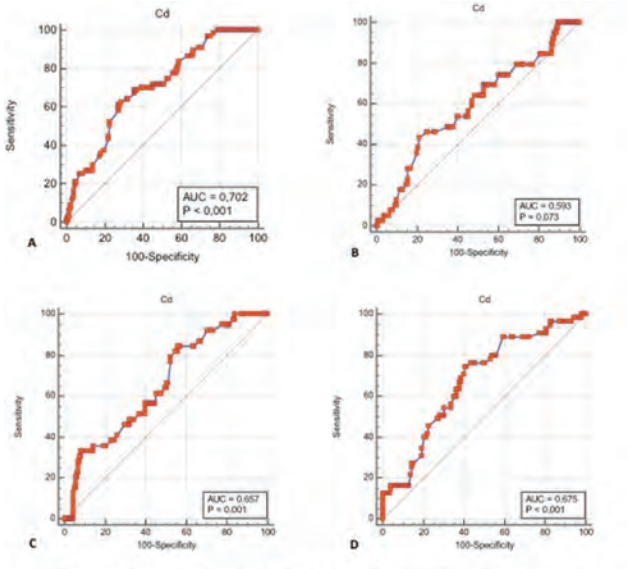

Figure 1. ROC curves for each type of peritoneal transporter. Panel A: low peritoneal transporter; Panel B: low intermediate peritoneal transporter; Panel C: high intermediate peritoneal transporter; Panel D: high peritoneal transporter

SA-PO962

Uric Acid Clearance in Peritoneal Dialysis Patients

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Background: There's a paucity of systematic study focus on the clearance of UA in peritoneal dialysis (PD). The aim of this study was to investigate the peritoneal UA transport and its influence factors in PD patients.

Methods: This was a cross-sectional study. The patients who performed peritoneal equilibration test (PET) and Kt/V from April 1, 2018 to April 31, 2019 were enrolled. The demographic data, clinical and laboratory parameters including the UA levels in the dialysate, blood and urine samples were collected.

Results: Totally 122 prevalent PD patients(male 55.7%) were enrolled in this study, with a mean age of 46.2±13.1 years and a mean peritoneal UA clearance (pUACL) of 40.1±6.9 L/week/1.73 m^2. The average mass transfer of UA between 0-4h dwell with 2L of 2.5% dextrose solution was 22.2±5.2 mg/h. Compared with the normal serum UA group, the hyperuricemia group showed significantly lower pUACL (38.0±5.7 vs.41.8±7.3L/week/1.73m^2, p=0.003). The bivariable correlation analysis revealed that the serum UA levels was positively correlated with the UA mass transfer (r=0.715, p<0.001) but negatively correlated with pUACL (r=-0.310, p=0.001). Furthermore, the higher (high or high-average) transporters showed greater pUACL than the lower (low or low-average) transporters (42.0±7.1vs.36.7±4.9L/week/1.73 m^2, p<0.001). The 4 hours dialysate to plasm (4h D/P) ratios of UA correlated fairly well with the ratios of creatinine (r=0.933, p<0.001). And the correlation between the pUACL and 4h D/P UA (r=0.446, p<0.001) or creatinine (r=0.428, p<0.001) were similar. Among the widely used solute removal evaluation indicators, the peritoneal creatinine clearance performed best to predict higher pUACL in the ROC analysis (area under curve AUC 0.951,95%CI0.908-0.993). On multivariable logistic regression, each 1kg/m^2 decrease of BMI [odd ratios (OR) 0.761, 95% CI0.634-0.913], each 1mL increase of the dialysis dose (OR1.001,95%CI1.000-1.002), each 0.1% increase of the average glucose concentration of dialysate (OR1.400,95%CI1.017-1.927), female sex (OR5.170,95%CI1.819-14.695) and higher transporters (OR5.749,95%CI 1.795-18.406) were independently associated with higher pUACL.

Conclusions: The clearance of UA in PD were similar to that of creatinine. Increasing dialysis dose or glucose concentration of the solution may help to control the hyperuricemia in lower transporters.

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SA-PO963

Impact of Renal Replacement Therapies over Quality of Life of ESRD Patients

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Background: Renal transplant is generally considered as the ideal renal replacement therapy (RRT). Nonetheless, at the moment, hemodialysis and peritoneal dialysis remain as the main alternative treatment options for patients with end stage renal disease (ESRD). The negative impact of ESRD on the quality of life (QoL) has already been well described, and improvement of QoL could actually be translated into lower mortality.

Methods: Transversal, cohort, observational study, evaluating ESRD patients subjected to renal transplant (RT), undergoing hemodiafiltration (HDF) or automated peritoneal dialysis (APD). QoL was assessed using the Kidney Disease Quality of Life Questionnaire (KDQOL-SF), as well as Becks inventories for anxiety and depression. Additional factors like dialysis quality, body composition, and muscle strength were also assessed.

Results: 82 patients met the inclusion criteria: 32 RT patients, 26 on APD and 24 on HDF. 43% of them were in the age range between 31- 50 years. Lower phase angles and muscular strengths were measured in the HDF and APD groups when compared to RT patients (p=0.005) (p=0.0003). As for QoL, RT patients obtained better scores when compared to the other groups, however, statistically significant differences were only observed in five of the categories, which ultimately emphasized the importance of disease burden (p=0.0006) and effects of disease (p=0.0001). The HDF group had a slight tendency towards better QoL results than the APD group, without reaching statistical significance. Hydration status measured with bioelectrical impedance analysis revealed greater levels of overhydration in the HDF group, as expected, since measurement was performed pre HDF treatment (p=0.14). Higher levels of anxiety and depression were observed in the HDF group.

Conclusions: QoL of RT patients is superior to that of patients remaining on dialysis, yet on most of the categories assessed in the KDQOL-SF, no statistical significance was observed, suggesting QoL is acceptable, or even satisfactory, in patients on HDF and APD. As for these two dialysis modalities, there was no significant difference of QoL in our study group.

SA-PO964

Using Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA) on Pancreatic Lesions in Peritoneal Dialysis (PD) Patients

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Introduction: Any invasive procedure involving the abdominal or pelvic regions in a PD patient raises concerns for infection, bleeding, and peritoneal fluid leakage. EUS-FNA is a well-established minimally invasive GI procedure to diagnose and stage cancers of the pancreas, upper GI tract, and mediastinum. We report the pre-procedure preparation, peri-procedure precautions, and outcomes of 2 PD patients who underwent EUS-FNA for suspicious pancreatic lesions. These cases are the first to be reported in the literature.

Case Description: Patients performed the following to avoid complications and ensure the best outcome: 1-Performed additional dialysis daily for 3 days pre-procedure to optimize volume, electrolyte, and acid-base status as well as remove uremic toxins to improve platelet function. 2-Stopped any medications that would interfere with coagulation. 3-Reported to EUS-FNA with minimal PD fluid and received IV prophylactic antibiotics (ampicillin 1 gm and gentamicin 1 mg/kg) within 1 hr pre-procedure to minimize peritonitis risk. 4-Delayed restarting PD for 48 hrs to reduce peritonitis, bleeding and PD fluid leakage risks. 5-Monitored for abdominal pain, low blood pressure, fever, and GI symptoms such as nausea, vomiting, or diarrhea. During the EUS-FNA procedure, an endoscope with high frequency ultrasound capability examined the entire pancreas and the cystic lesion in the pancreas was sampled using a 22-gauge FNA needle. Samples were sent for pathologic evaluation. Patient-1's findings were consistent with pancreatic pseudocyst. Patient-2's findings were consistent with mucinous cyst, either side-branch intraductal papillary mucinous neoplasm or mucinous cystic neoplasm. PD risks (peritonitis and PD fluid leakage) and EUS-FNA risks (perforation, infection, iatrogenic pancreatitis, bile peritonitis, fistulization, and malignancy seeding) were not appreciated. Patient-2 noted bloody PD fluid on a manual exchange without hemodynamic compromise. PD fluid cleared after another rapid exchange.

Discussion: Take away lessons: EUS-FNA can be performed safely in PD patients with minimal short term complications. Appropriate measure should be taken to ensure peritonitis, bleeding, and PD fluid leakage risks are minimized (see points 1-5 above) EUS-FNA can be used to evaluate pancreatic lesions and malignancies for diagnosis and staging.

SA-PO965

Elevated WBC Count in the Peritoneal Fluid After Transcatheter Arterial Chemoembolization and Microwave Ablation of Hepatocellular Carcinoma in a Peritoneal Dialysis Patient: A Case Report

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Introduction: Hepatitis C is a risk factor for hepatocellular carcinoma (HCC). The prevalence of Hepatitis C is high among end stage renal disease (ESRD) patients, and these patients are at high risk for developing HCC. In the past decade, transcatheter arterial chemoembolization (TACE) combined with microwave ablation (MA) have emerged as an effective therapy for HCC. These therapies can decrease the tumor burden while patients are on the liver transplant wait-list. Here we present an ESRD patient on peritoneal dialysis who developed a high white blood cell count in the peritoneal fluid following the TACE and MA procedure

Case Description: A 63-year old male with ESRD on Peritoneal Dialysis (PD), and cirrhosis due to Hepatitis C was diagnosed with HCC. At the time of the HCC diagnosis, the patient was listed for a combined liver-kidney transplant. The patient underwent TACE and MA, but immediately following the procedure he developed fever (101°F) which subsided within 24 hours. As part of the fever workup, the peritoneal fluid was sent for white blood cell (WBC), gram stain and culture. The peritoneal fluid WBC was found to be elevated: 1131 (57% PMN, 19% lymphocytes), remaining elevated for more than a month. Notably, it was not accompanied by any associated signs or symptoms such as abdominal pain or cloudy peritoneal fluid. The peritoneal fluid gram stain and culture remained negative, and the patient was able to continue PD without any problems

Discussion: TACE induces ischemic necrosis through arterial chemoembolization, and MA induces coagulative necrosis through thermal ablation. The most common complications of these therapies include fever and abdominal pain likely related to underlying tumor necrosis. It is important for Nephrologists to be aware of the complications related to these therapies, as was seen in our patient who developed an elevated WBC count in the peritoneal fluid. However, this persistent WBC elevation was not accompanied by abdominal pain, cloudy fluid, infection, and did not warrant PD catheter removal or cessation of PD. To the best of our knowledge, this is the first reported case of elevated WBC in peritoneal fluid in a PD patient following the TACE and MA procedure

SA-PO966

A Quality Improvement Program to Reduce Avoidable Hospital Stays for Dialysis Patients Presenting to the Emergency Department

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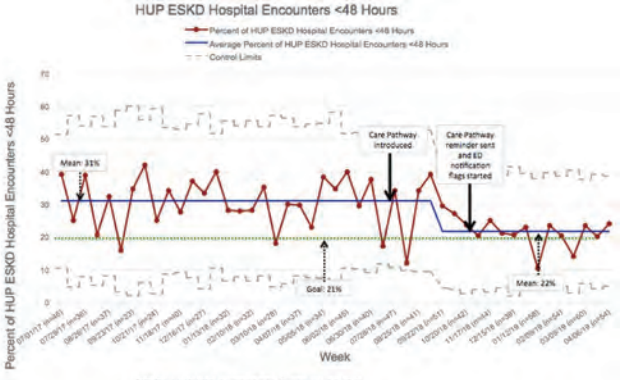
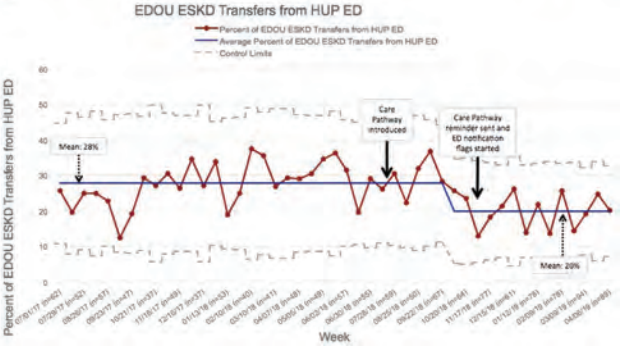
Background: When an End Stage Kidney Disease (ESKD) patient presents to the ED, if he/she requires dialysis, this may result in a costly hospital stay. In Fiscal Year 2017 at the Hospital of University of Pennsylvania, 70% of ESKD patients who presented to the ED were admitted to an inpatient service or transferred to the ED observation unit (EDOU) and 31% of these hospital stays were <48 hours. We believe hospital stays <48 hours can be potentially avoidable.

Methods: A multidisciplinary team was formed with members from the departments of nephrology and emergency medicine (EM). We used Voice of the Customer to survey key stakeholders (RNs, advanced practitioners, residents, attendings, social workers, clinical resource coordinators, and representatives from large dialysis organizations). We performed a root cause analysis using the Ishikawa fishbone model. As a countermeasure, we developed a care pathway to standardize management of patients' dialysis needs, with dialysis provided in the hospital before discharge or as an outpatient (introduced July 2018). A second plan-study-do-act cycle was performed in November 2018. New countermeasures included an alert identifying the patient as a dialysis patient with specific dialysis unit information and working with the hospitalist superutilizer program to identify additional dialysis patients appropriate for the program.

Results: After introduction of the care pathway, hospital stays <48 hours decreased from 31% to 22% and transfers from the ED to EDOU from 28% to 20%.

Conclusions: By utilizing QI tools and developing a care pathway as a countermeasure, we were able to decrease the percent of hospital stays <48 hours, which we believe represent potentially avoidable hospital stays.





SA-PO967

Reducing Hospitalizations with Artificial Intelligence and Clinical Decision Support: Lessons Learned

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Background: Artificial intelligence has the potential to improve healthcare. Previously, we created a model to predict which patients with kidney failure treated in outpatient dialysis clinics were at risk for all cause hospital admission in the next week. This model has an area under the receiver operating characteristic curve (AUROC) of 0.78 with a sensitivity of 69% and specificity 72%. Here we discuss lessons learned from integrating this model in a telephonic intervention.

Methods: Starting in December 2018, our analytics team partnered with a team of nurses who perform chart reviews and telephonic outreach to manage a large population of patients distributed across the United States. The goal of the outreach is to reduce the

number of hospitalizations. The workflow consists of pulling patients from a worklist, reviewing a chart, documenting any needs identified, and then calling the patient if warranted. Through the last few months, we have utilized agile techniques to iteratively improve each step of this process using observations, surveys, and data analytics.

Results: We deployed the predictive model as a worklist ranked by risk score through an excel sheet format. Initial review demonstrated that 1) excel sheets are difficult to use to display individual patient data, and 2) significant time was spent digging through electronic charts. To help mitigate these issues, we built a dashboard that showed the prediction-based prioritization worklist as well as an integrated patient view. Testing of the dashboard with 3 nurses increased the number of chart reviews by over 50%. We believe this is likely due to aggregating information from multiple electronic health records, reducing the time spent searching for information. Further, nearly every nurse who uses this new system has reported an increase in job satisfaction. To date, the existing workflow results in 70% increase in chart reviews per day with 250% increase in calls per day. Investigation of hospitalization rate is still underway.

Conclusions: Building healthcare predictive models is only part of the story for artificial intelligence to improve healthcare. Additional work must be conducted to understand how to fully integrate predictive models into existing and newly designed clinical workflows.

Funding: Commercial Support - Fresenius Medical Care North America

SA-PO968

Impact of In-House Dialysis Schedule Change on Hospital Readmission Rate in Hemodialysis Patients

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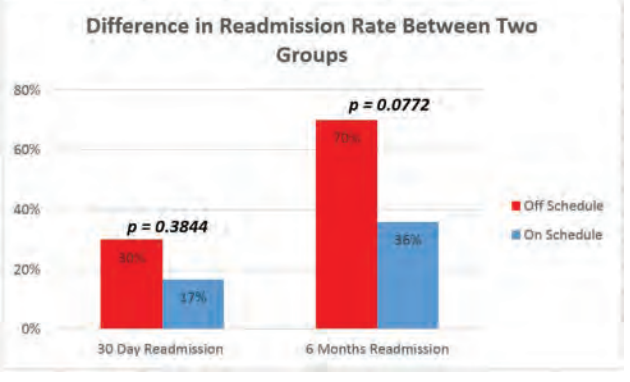
Background: ESRD patients on Hemodialysis (HD) have high frequency of hospitalization and readmissions for multiple reasons. Once inpatient, they may not get HD treatments on their designated days (MWF or TThS) due to various reasons, including nursing availability and patient condition. We hypothesized that changing HD schedule could impact readmission rate due to care coordination factors

Methods: Data was collected from EMR at Stony Brook University Hospital for adult HD patients admitted from January 2019 to October 2019. First admission was taken as index admission, and dialysis days on index admission were noted as on or off-schedule. Patients who received ≥2 HD treatments on days other than their outpatient schedule were labelled as "off-schedule". The readmission rate within 30 days and 6 months and baseline demographics was compared using Fisher's exact test. Continuous variables were compared with t-test

Results: In total, 46 patients were reviewed, of them 10 were labeled as "off-schedule" and 36 as "on-schedule". Mean age of all patients was 60.8±18.6 years, 61.1% were male and 47% Caucasian, with no differences between groups. Both diabetes as cause of ESRD (70% vs. 44.4%), and history of CHF (80% vs. 50%) were more frequent among the off-schedule. Dialysis access between groups was not different. The 30-day readmission rate was not statistically significant (30% vs. 16.7%, p-value 0.3844) between two groups. However, six month readmission rate showed a trend towards significance in off-schedule vs on-schedule group (70% vs. 36%, p-value 0.0772, OR 4.128, 95% CI 0.9315-16.14). There were no deaths in either group at 6 month follow up

Conclusions: Off-schedule inpatient dialysis had no effect on 30 day readmission rate. A trend towards increased rate of readmission within 6 months was observed. Future studies involving more patients and longer follow up are necessary to see the impact of on schedule HD for hospitalized patients



SA-PO969

Patterns of Emergency Department Visits Among American Dialysis Patients

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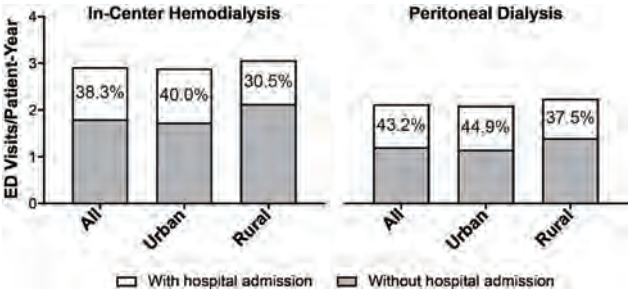
Background: Dialysis patients are at risk for medical events requiring immediate intervention in the Emergency Department (ED). Despite this, patterns of ED visits among the contemporary dialysis population have not been described.

Methods: Data were derived from the 2016 Centers for Medicare and Medicaid Services 100% claims sample. Included patients were those who, in a given calendar month and for the preceding 3 months, were Medicare A & B eligible, diagnosed with ESRD, and treated with either in-center hemodialysis (ICHD) or peritoneal dialysis (PD). Core-based statistical areas were designated as urban; other regions were considered rural. Causes of ED visits and hospital admissions were ascribed based on the associated ICD-10 code and grouped using Clinical Classification Software categories. Outcomes were described as rates, counts, and percentages; no statistical comparisons were performed.

Results: Patients treated with ICHD (N=321,934) had 2.9 ED visits/patient-year; with 38.3% of visits resulting in hospital admission. PD patients (N=35,720) had 2.1 ED visits/patient-year, with 43.2% of visits resulting in admission. For both modalities, the majority of all hospital admissions initiated in the ED: 80.1% for ICHD and 74.8% for PD. ICHD patients residing in rural areas had a higher rate of ED visits compared to urban areas (3.1 vs 2.9/patient-year), although a smaller percentage of those ED visits resulted in hospital admission (30.5% vs 40.0%), corresponding to a lower overall hospitalization rate among rural patients (1.3 vs 1.4 admissions/patient-year). Similar trends were observed for PD. Across modalities, ED visits attributed to Diseases of the Circulatory System and Injury and Poisoning were common and likely to result in hospital admission; ED visits attributed to Infectious and Parasitic Diseases almost invariably resulted in admission.

Conclusions: ED visits are common among dialysis patients and precede the majority of hospitalizations. Understanding causes and patterns of ED visits may facilitate interventions to reduce the frequency of ED visits and subsequent admissions.



SA-PO970

Predictors of Need for Recurrent Emergency Medical Service Transport to an Emergency Department After Dialysis Initiation

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Background: Dialysis patients are frequently transported to the emergency department (ED) by Emergency Medical Services (EMS) due to acute illness. However, little is known about the predictors of recurrent transport to the ED (EMS-ED), based on characteristics at the time of dialysis initiation.

Methods: We analyzed a cohort of adult (≥18 years) patients affiliated with a large quaternary care center who initiated chronic dialysis from 2009-2013 (last follow-up: 2015). Data on patient characteristics at the time of dialysis initiation was linked to regional EMS data. Candidate predictors of recurrent EMS-ED transport included comorbid conditions, dialysis characteristics and frailty severity (using the first version of the clinical frailty scale score; CFS). Time to recurrent EMS-ED was analyzed using the Anderson-Gill counting approach, accounting for competing risks of death and transplant.

Results: A total of 455 patients were included in the study, 246 (54%) had one or more EMS-ED events, 90 (20%) never required an EMS-ED at last follow-up, and 15% and 12% experienced transplant or death as their first event, respectively. The mean age of the cohort was 62 ± 15 years, 89% were Caucasian, and 34% were of female sex. Patients were highly comorbid (48% had diabetes, 30% had coronary artery disease and 17% had peripheral vascular disease) and 97/381 with available data on frailty severity had a CFS score of ≥5 corresponding to "mildly to severely frail". After adjustment, increasing CFS score (subdistribution hazard ratio (SHR) 2.41, 95% confidence interval (CI) 1.48-3.95 for CFS 3-4; and SHR 3.05, 95% CI 1.73-5.38 for CFS ≥5 relative to a CFS 1-2), rheumatologic disease (SHR 1.54, 95% CI 1.04-2.29), end-stage renal disease (ESRD) secondary to polycystic kidney disease (SHR 2.00, 95% CI 1.11-3.59 relative to glomerulonephritis as cause of ESRD) and > 3 months of nephrology follow-up prior to dialysis initiation (SHR 1.52, 95% CI 1.10-2.08) predicted recurrent EMS-ED.

Conclusions: Patients are at a high risk of EMS-ED after dialysis initiation. Frailty severity (at the time of dialysis initiation) is the strongest predictor of recurrent EMS-ED and this may be important to guide informed decision making and resource planning for dialysis patients.

SA-PO971

High-Frequency, Distinctive Staffing and Outcomes: Improving the Dialysis Experience

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Background: Frequent dialysis has consistently improved patient outcomes. Professional staffing of dialysis affects patient care quality and safety. Requirements for physician presence during dialysis and for nursing staff levels are highly variable worldwide. We have set up a 24-stations in-center short daily hemodialysis (SDHD) program whose all day long care is provided by two on-site nephrologists, certified nurses, renal dietitians and psycologists with fulltime dedication. This report outlines the impact of 10 years of combining daily hemodialysis with selected clinical staffing on patient outcomes.

Methods: Nephrologist schedule, patient to staff ratios, adverse events rates (hypotension, medication errors, patient falls), vascular access profile (type, infection rates), patient compliance (missed treatment rate), hospitalization (days per patient-year [pp-y]), cumulative survival and kidney transplantation rates were assessed in 200 private-insured patients (122M/78F; mean age 58.0±18.5yrs, 18-96) receiving in-center SDHD (6-7 x/wk; lasting 115.4±11.2min, 90-180; ultrapure dialysate and single-use high-flux dialyzer).

Results: From June 2009 to May 2019 four out 5 nephrologists shared equitable schedule 7 days/wk, each one prescribing up to 24 patients in 2 parallel and 2 sequential 6-hour workday. In 2009 we stopped hiring technicians and moved to 100% nurses staffing, reaching 21 fulltime certified nurses (up to 3:1 ratio). Additionaly, 2 dietitians and 2 psycologists assist 80 current patients (40:1 ratios). In 2018 symptomatic hypotension occurred in 3% of 20,035 treatments, medication errors in 17 occasions (none critical) and no patients fell in the unit. Over the 10-year study period, arteriovenous fistula was used in 53% and tunneled catheter in 47% of prevalent patients, with bacteremia rate of 0.27 and 0.50 events per 1,000 days. Missed treatment rate was 1.49% or 4.6 days pp-y. Hospital length of stay was 2.9 days pp-y, 5-year survival was 64% and average kidney transplantation rate was 7.5%. Duplicating nephrologist presence and replacing technicians with certified nurses doubled labor costs, largely offset by higher productivity (five 2-hour shifts/day) and longer dialysis vintage.

Conclusions: This intensive dialysis modality delivered by a first-rate clinical staffing represents an unparalleled approach toward an optimal treatment.

SA-PO972

Improvements in Quality of Care of Incident Hemodialysis Patients: An International Multicenter Study

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Background: The transition from predialysis care to initiation of hemodialysis (HD) has received increased attention, as this period is one of exceptionally high vulnerability. This analysis focuses on improvements in quality of HD care during the first 6 months.

Methods: We included 3462 patients (mean age 65.9, 41% females) on HD (incident <90 days, n=603, prevalent >90 days, mean 55 months, n=2859) from 56 DaVita centers in Poland and Portugal. We compared all incident to all prevalent patients (t-test and Chi-2) and analyzed improvements in quality of dialysis care in a subgroup of patients (n=258) who were followed prospectively for 6 months (paired t-test and McNemar analysis). Linear and logistic regression was used to identify features associated improvements in care.

Results: Incident (<90 days) vs all prevalent (>90 days) patients: Compared with all prevalent patients, incident patients had lower Kt/V: 1.4 vs 1.7 ***; lower Hb: 9.9 vs 11.0 g/dL ***; lower TSAT: 26% vs 31% ***; lower ferritin: 305 vs 541 ng/ml ***; lower albumin: 37 vs 40 g/dL ***; lower UF vol/HD session: 1687 vs 2260 mL ***, similar Charlson comorbidity index (CCI): 6.9 vs 6.9 (p=NS); more use of central dialysis catheters (CDC) 68% vs 26% ***; less use of AV fistulae (AVF) 34% vs 70% ***. Incident patients <90 days on HD vs the same patients after 6 months of dialysis (n=258): Treatment time increased from 679 to 715 min/week ***; dialysis blood flow increased from 294-329 mL/min ***. Linear and logistic regression including age, gender, Kt/V, albumin, diabetes and CCI showed that improvements in Kt/V at 6 months and a shift from CDC to AVF was associated with female gender, HR 0.27 (CI 0.13-0.34; ***) and HR 0.48 (CI 0.24-0.98; **), respectively. **p<0.01, ***p<0.001, NS=not significant

Conclusions: This large European multicenter analysis of incident hemodialysis patients indicates that the use of medical protocols and medical targets assures significant improvements in quality of care and a shift from CDC to AVF, which may correspond to better outcomes.

Paired statistical analysis of quality of dialysis care over 6 months

	Kt/V	Hb	TSAT	Ferrit	Alb	Phos	PTH	CDC	AVF	MAP	UF
<90 days	1.4	9.8	26	332	37	4.8	389	68	35	96	1611
>6 months	1.5	10.7	30	462	42	5	340	47	55	95	1946
p	***	***	***	***	**	NS	**	***	***	NS	***

SA-PO973

Pre-ESKD Nephrology Care and Employment at the Start of Dialysis

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Background: Employment is associated with improved sense of well-being in general population and higher quality of life in patients with kidney disease. Patients who receive nephrology care prior to onset of End-Stage Kidney Disease (ESKD) experience better health outcomes, perhaps due to smoother transitions to ESKD. We examine whether pre-ESKD nephrology care can also help patients to remain employed when starting dialysis.

Methods: We used a national ESKD registry to identify all patients in the United States between the ages of 18 and 54 who initiated dialysis from January 1st, 2006 to December 31st, 2014 and who were employed 6 months prior to ESKD. Using a multivariable (Modified Poisson) regression model, we examined the independent association between ≥ 6 months of pre-ESKD nephrology care and employment at the start of dialysis. Additionally, we measured geographic variation in pre-ESKD nephrology care by county-level population quintiles among patients who were excluded from the primary cohort due to age or pre-ESKD employment status. We then examined whether geographic variation in pre-ESKD care is associated with employment at dialysis initiation.

Results: Of the 75,700 patients included in study cohort, 36,940 (49%) reported receiving pre-ESKD care for ≥ 6 months. At the individual patient level, ≥6 months of pre-ESKD care was associated with a 21 % increase in the relative risk (RR) of remaining employed at dialysis initiation (95% CI: 20% to 23%). While geographic variation in pre-ESKD care was strongly correlated with a patient's likelihood of receiving pre-ESKD care, there was no association between geographic measures of pre-ESKD care and the likelihood of employment at initiation of dialysis

Conclusions: Despite there is a strong association between pre-ESKD care of ≥ 6 months and employment at the time of dialysis onset, geographic variation in pre-ESKD care is not associated with the likelihood of remaining employed. This suggests that while pre-ESKD care may be necessary for some patients to remain employed, it may not, by itself, be sufficient to foster employment.

Funding: Private Foundation Support

SA-PO974

Andon System in Hemodialysis

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Background: Maintenance hemodialysis is a treatment that imposes clinical challenges and expenses to the health care system. Patients with end stage renal disease (ESRD) require disproportionately high use of health care in the USA, with <1% of the population using about 7% of the Medicare resource. Similar data have been reported in the other countries. The health care system have unchanged cost trajectories over the past 20 years, often neglecting one of the essential elements of successful innovation: a disciplined approach to meeting consumers' needs. Evolving to new service models on hemodialysis (e.g. encouraging automation of process) may be important. Currently the dialysis service is organized in shifts counting on own teams (doctors, nurses, and cleaning staff). Waiting time between shifts is often long, resulting in an excessive number of working hours for the staff and poor quality of life for patients. Our aim was to minimize "waiting time" for patients on in-center HD, in southern Brazil through the Andon System, method pioneered in the Toyota Production System and part of the Lean approach.

Methods: This incenter HD takes care of about 130 ESRD patients, performing more than two thousand HD session/month. An external totem attached to an inward video monitor was installed to record the patient arrival and to allocate it in the queue. The patient is identified by the system through a barcode card printed by the hospital. The admission process is done using the Andon method. The order of arrival is arranged on the computer screen from the hemodialysis room, sparing the staff work of calling the patient.

Results: Before implantation, the Lead time was one hour and thirty minutes. After the automation, the minimum transition time between HD sessions has been reduced to 30 minutes. Currently the unit starts working at 6 a.m., with the closing time around 9 p.m. (before the intervention it was 11 p.m.). Around one thousand and six hundred hours/year was spared, with an estimated savings of almost $ 80,000.

Conclusions: Examining the patient needs rather than the available delivery-system resources, can lead to the exploration of more efficient and effective ways of provide the services. The wages of health-care professionals are a key contributor to the high cost of in-center HD. Turning the dialysis service into a continuous flow mapping can be a true innovation agenda in hemodialysis care.

SA-PO975

Impact of National Payment Contracts on VA Spending and Access to Outpatient Community Dialysis

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Background: End-stage kidney disease (ESKD) is common among Veterans. VA's limited capacity to deliver dialysis care means that VA relies heavily on community providers, making chronic dialysis the largest VA expenditure for outpatient community care. In the past, VA paid for non-VA dialysis on a local, ad hoc basis, with some payments exceeding Medicare rates. In 2011 the VA began implementing payment policies to standardize the process of pricing non-VA dialysis care, including use of the Medicare fee schedule and national dialysis contracts. This study examined the effect of VA's standardized pricing policies on VA costs and patient outcomes.

Methods: We used an interrupted time series design and 2006-2016 VA, Medicare, and the US Renal Data System data to identify Veterans receiving VA-financed dialysis in the community from non-VA providers. Changes in price over time for non-VA dialysis were ascertained from >7M VA-paid community dialysis claims. We performed multivariable regression analyses, using differential trend and intercept shift models, to examine the effects of VA pricing policies on: VA treatment prices for non-VA dialysis, access to non-VA dialysis care (number of non-VA dialysis facilities, patient distance to non-VA dialysis care), and 1-year mortality, controlling for patient and facility fixed effects.

Results: The cohort comprised 24,130 Veterans who received ≥1 VA-finaned community-based chronic dialysis treatment in 2006-2016. Before implementation of national contracts, treatment prices for non-VA dialysis care varied widely across VA facilities from $61 to $1,575 per treatment. After implementation of national contracts, there was much less variation in the cost of treatment across individuals ($73.40 to $663.37) and the average price per dialysis session dropped by 40% (p<0.001). Over the same time period, the average number of dialysis facilities providing VA-paid dialysis care grew from 19 to 37 and there were no changes in patient distance to non-VA dialysis facilities (p=0.81) or 1-year mortality (12% vs. 11%, p=0.98).

Conclusions: VA's policy to standardize national dialysis contracts resulted in a substantial increase in the value of VA-financed community dialysis care by reducing spending with no adverse effect on Veterans' access to care nor on mortality.

Funding: Veterans Affairs Support

SA-PO976

ESRD Quality Incentive Program Payment Reductions, Mortality, Utilization, and Cost

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Background: The ESRD Quality Incentive Program (QIP) adjusts Medicare payments to dialysis facilities based on their performance on a set of quality measures. We assessed whether the magnitude of ESRD QIP payment reductions was associated with several important patient outcomes that are largely not an intrinsic part of the QIP measure set.

Methods: We compared mortality, utilization of healthcare services and Medicare payments per patient-year during 2015-2017 for facilities in each ESRD QIP payment reduction category corresponding to their QIP performance for the same year. The patient cohort consisted of Medicare fee-for-service beneficiaries receiving chronic dialysis for ESRD on the first day of each year. Patients were attributed to the first facility that provided treatment during the year. The data sources include Medicare claims and enrollment files. Descriptive findings were confirmed with regression models that adjusted for patient factors (age, sex, race, ethnicity, diabetes, duration of ESRD and dual eligibility).

Results: Most patients were treated in facilities that did not receive an ESRD QIP payment reduction (Table). There was a stepwise increase in rates of mortality, hospitalization, hospital days and Medicare payments per year in facilities with successively larger payment reductions. The increase in Medicare payments was largely for inpatient services. All findings were statistically significant in adjusted regression models.

Conclusions: Mortality, utilization and Medicare payments were substantially higher for patients treated in facilities whose contemporaneous performance on ESRD QIP measures resulted in a payment reduction. Moreover, these outcome measures increased stepwise with the magnitude of facility payment reductions. The findings are consistent with the hypothesis that the ESRD QIP measures and scoring system capture meaningful determinants of healthcare quality and value.

Funding: Other U.S. Government Support

Patient Outcomes vs. Facility QIP Payment Reduction

		ESRD QIP Payment Reduction				
		0%	0.5%	1.0%	1.5%	2.0%
Patient Years		763,902	163,635	42,808	9,437	2,949
Mortality (%/Yr)		15.6%	16.3%	17.3%	21.2%	24.5%
Utilization (per Pt-Yr)	Hospitalizations	1.63	1.93	2.04	2.34	2.44
	Hospital Days	10.85	13.10	14.36	17.96	20.91
Payments (per Pt-Yr)	Total	$75,285	$79,729	$82,090	$94,446	$99,810
	Inpatient	$24,761	$28,678	$30,701	$37,560	$40,881

SA-PO977

Dialysis Facilities with Recurring Payment Reductions Under the ESRD Quality Incentive Program (QIP)

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Background: The ESRD QIP is designed to promote quality of care through financial incentives that reward improvement. It is not known whether a lack of improvement in certain aspects of quality may lead some facilities to consistently receive payment reductions under the ESRD QIP. We assessed the extent to which there are facilities continuing to receive payment reductions over time, whether this is more common among certain facility types, and whether this results from lower performance on certain ESRD QIP measures.

Methods: We studied 6,135 dialysis facilities eligible for the ESRD QIP in each payment year (PY) from 2017-19. Data sources include Medicare claims and CROWNWeb. We compared ESRD QIP measure scores among facilities with a payment reduction for 0, 1, 2, or 3 PYs. We used descriptive analyses and Poisson regression to examine factors associated with the number of PYs with a payment reduction.

Results: Among ESRD QIP eligible facilities during 2017-19, 60.5% had no payment reductions, 23.9% had a payment reduction in 1 PY, 10.6% had a payment reduction in 2 PYs, and 5.0% had a payment reduction in all 3 PYs. Payment reductions in all 3 PYs were more common among facilities that are independent (17.5%) or hospital-based (14.3%), treat ≥100 patients (6.1%), and in ESRD Networks 2 or 7 (13.8% and 11.2%). These findings were statistically significant based on Poisson regression. Facilities with recurring payment reductions had lower average scores for all clinical ESRD QIP measures (Table).

Conclusions: Dialysis facilities that receive recurring payment reductions under the ESRD QIP have lower performance across a range of quality measures. It is important to assess both opportunities and potential challenges for improvement among facilities with recurring payment reductions.

Funding: Other U.S. Government Support

Average facility measure score, ESRD QIP PYs 2017-19

ESRD QIP Measure or Measure Topic	No. of years with a payment reduction, 2017-19			
	0	1	2	3
Kt/V	8.3	7.2	6.0	4.3
Vascular access type				
Catheter	6.2	4.7	3.9	2.7
Fistula	6.0	4.3	3.3	2.4
Hypercalcemia	8.3	7.7	7.1	6.3
National Healthcare Safety Network Bloodstream Infection	5.8	5.1	4.5	3.5
Standardized Readmission Ratio	5.5	4.1	3.5	3.0
Standardized Transfusion Ratio	6.1	4.6	3.9	3.2
In-center Hemodialysis Consumer Assessment of Healthcare Providers and Systems	5.8	4.3	3.2	2.7

SA-PO978

Expansion of the ESRD Payment Bundle and Dialysis Facility Closures in the United States

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Background: The inclusion of formerly separately billable injectable medications into the ESRD payment bundle in 2011 led to concerns that some facilities facing higher costs would close, disrupting care delivery and limiting access to care for some patients. We examined whether patients were more likely to be affected by dialysis facility closures after the 2011 payment reform, and whether factors that influence closures changed following te payment reform.

Methods: We identified all patients receiving in-center hemodialysis in the United States between 2005 and 2015 and tracked dialysis facility closures throughout this time period. We used an interrupted time-series regression model to examine immediate and longer-term changes in the odds of being at a facility that closed following enactment of the expanded ESRD payment bundle. We then included interaction terms in a series of logistic regression models to examine whether the associations among selected patient, dialysis facility, and geographic characteristics and facility closures changed after 2011.

Results: Dialysis facility closures were relatively uncommon throughout the study period, ranging from 92 facilities (2.0%) affecting 3,725 patients in 2005 to 32 facilities (0.2%) affecting 797 patients in 2014. In a model where we adjusted for changes over time in patient, geographic, and dialysis facility characteristics, the odds of being affected by a dialysis facility closure did not change significantly immediately after enactment of the expanded ESRD payment bundle. Over time, the odds of being affected by a dialysis facility closure decreased by 18% (OR 0.82; 95% CI 0.81 to 0.84) each year after 2011. Patients who were black and those in rural areas and hospital-based facilities experienced a relative *increase* in the likelihood of being affected by closures after 2011, while patients who were Hispanic, dual-eligible and at smaller dialysis facilities experienced a relative *decrease* in the likelihood of being affected by closures after 2011.

Conclusions: We did not find evidence that the 2011 expanded ESRD payment bundle was associated with an increased impact of facility closures on patients receiving outpatient dialysis. However, the likelihood of being affected by facility closures changed for some potentially high risk patient groups.

Funding: NIDDK Support

SA-PO979

Associations Between Mortality and Payment Reductions Under the Centers for Medicare & Medicaid Services (CMS) ESRD Quality Incentive Program (ESRD QIP)

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Background: The implementation of CMS' ESRD QIP in 2010 introduced financial incentives for certified dialysis facilities to provide high/adequate levels of care. Under the QIP, underperforming dialysis facilities receive a Medicare payment reduction of up to two percent. This study assesses how QIP penalties are associated with 1-year mortality during performance years (PY) and the likelihood of death in the years after each quality assessment.

Methods: We used Medicare claims, enrollment, and CROWNWeb data to examine mortality among outpatient dialysis patients enrolled in Medicare fee-for-service between 2010 and 2017. We used a Cox Proportional-hazards model to measure survival by payment reduction percentage and a difference-in-differences (DD) model to evaluate whether the gap in mortality between penalized and non-penalized facilities changed over time. We adjusted both models using facility and patient characteristics.

Results: Compared to facilities that received no penalty based on 2017 performance, 2017 mortality at penalized facilities was 9% higher (1.091 hazard ratio; $p < 0.001$). Mortality rates were also higher for facilities that received higher reductions: for PY2017, mortality at a facility with a 2% reduction was about 21% higher than at a facility with no reduction and 7% higher at a facility that received a 0.5% reduction (1.209 and 1.069 hazard ratios, respectively; $p < 0.001$). Results were similar for PY2010–2016. The difference in probability of death among patients at penalized facilities compared to non-penalized facilities decreased slightly after the performance year by up to 1 percentage point. DD model estimates varied in size and statistical significance across years and amount of time elapsed after each performance year.

Conclusions: Receiving an ESRD QIP payment reduction is correlated with same-year mortality among Medicare fee-for-service dialysis patients, and higher reduction amounts are associated with higher mortality rates. The differences in mortality between penalized and non-penalized facilities persisted after each performance year, though these differences decreased modestly in subsequent years.

Funding: Other U.S. Government Support

SA-PO980

Comprehensive Kt/V Measurement in the Medicare ESRD Quality Incentive Program: Including More Facilities and Recent Improvements in Pediatric and Home Dialysis

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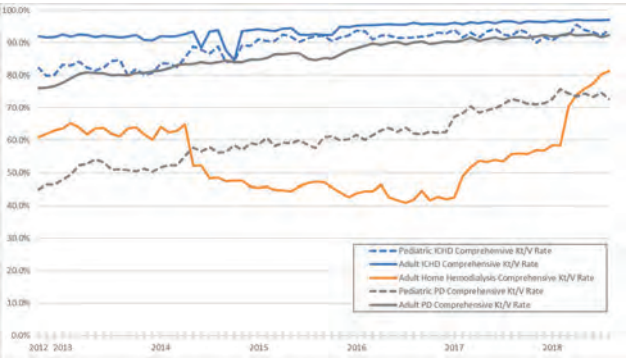
Background: In prior Payment Years (PY), facilities primarily treating pediatric patients were often excluded from QIP dialysis adequacy measures for not treating 11 or more eligible patients. In the PY19 QIP, to include more facilities treating pediatric patients, CMS introduced a Comprehensive Kt/V measure combining age groups and modalities.

Methods: Trends in Comprehensive Kt/V were retrospectively assessed using Medicare claims and CROWNWeb data from 2012-2018. Comparisons of Kt/V QIP scores among facilities eligible for the measure in PY19 to those eligible in the prior year used publicly available Performance Score Summary Reports. Pediatric facilities were defined as having more than 50% of period prevalent patients <18 years old; home dialysis facilities were defined as having more than 50% of period prevalent patients on home HD or PD.

Results: The national average Kt/V QIP score in PY19 was 8.0, an increase of 0.6 points over PY18. However, the average Kt/V score was lower for facilities newly eligible for the measure in PY19 compared to facilities eligible in both PY19 and PY18 (5.8 vs. 8.2). For pediatric facilities, the average score in PY19 was 4.0 (N=47), compared to 7.6 (N=8) in PY18. For home dialysis facilities, the average PY19 score was 5.6 (N=409), compared to 6.9 (N=287) in PY18. Performance rates for Comprehensive Kt/V were lowest among pediatric patients, but improved since initial data collection in July 2012 (Figure).

Conclusions: The change to the Comprehensive Kt/V measure in PY19 resulted in the inclusion of more pediatric and home dialysis facilities and lower Kt/V scores for these subgroups. Increases in Comprehensive Kt/V performance rates improved among pediatric PD and home dialysis patients in 2017 and 2018.

Funding: Other U.S. Government Support



Comprehensive Kt/V rates over time by age and modality

SA-PO981

Clinical Quality Outcomes in Dialysis Facilities Performing Clinical Research

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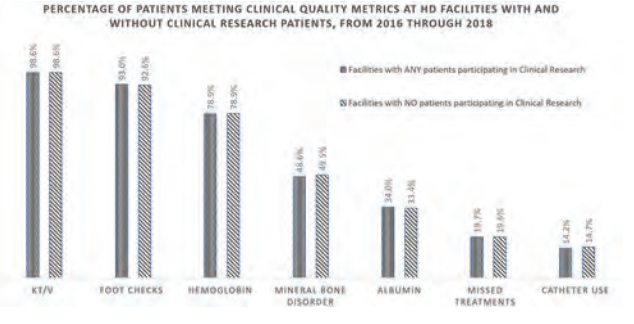
Background: Clinical research trials in kidney disease are underperformed compared to most chronic or acute disease states (Giovanni F, et al. JASN 2004). Barriers between stakeholders in clinical trials further impedes its advancement. Uncertainty regarding the impact of clinical trials on quality scores, star ratings, and related reimbursements might be contributing to such hurdles. We compared the profiles of clinical quality scores at a large dialysis organization (LDO) between clinics performing research trials vs those that did not.

Methods: We analyzed data from in-center hemodialysis (HD) patients treated at the LDO from 2016 to 2018. We performed a pooled analysis of the percent of patients achieving targets for the clinical quality measures for: albumin (≥4g/dL), mineral bone disorder (calcium ≤10.0mg/dL, phosphate 3.0-5.5mg/dL, and iPTH 150-600pg/dL), hemoglobin (10-11g/dL), adequacy (kt/V>1.2), diabetic foot checks, missed HD treatments, and catheter use.

Results: We included data from 252 and 2201 facilities with and without clinical research, respectively. We observed no remarkable differences in clinical quality scores for clinics that performed research trials, versus clinics without research (Figure 1).

Conclusions: Findings indicate there are no meaningful differences in clinical quality scores in dialysis facilities conducting research or not. These results are of importance to clinicians and providers considering involvement in clinical research, to advance care paradigms and the state of the art in nephrology.

Funding: Commercial Support - Fresenius Medical Care North America



SA-PO982

How to Reduce the Costs of Hemodialysis Treatment in Low-Income Countries

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Background: We aimed to design a low-cost (~5000 €) dialysis monitor (LCDM) to increase access to hemodialysis (HD) in low-income countries.

Methods: LCDM is a hermetic tank with a volume of 64 l. The dialysate circulates in a closed circuit and in a single pass without mixing between the fresh dialysate and the spent dialysate. The experimental simulation setup was: 4-hour HD session; 70 kg body weight; variable dialysate flow rates (QD); blood flow rate (QB) of 300 ml/min; FX 100® dialyser; dialysate as a solution of NaCl at 155 mmol/l; "blood" as a solution of NaCl + 30 mmol/ urea l , 996 µmol/l creatinine; ultrafiltrate flow (UF) controlled by a 1% resolution pump. Samples from the inputs and outputs of the dialyzer were taken simultaneously by two operators.

Results: Table 1 shows the quality of the removal of urea and creatinine with a QB of 300 ml/min and a QD of 250 ml/min for twelve sessions of 4 hours. Table 2 shows the result of several ultrafiltration tests and the significant absence of deviation between the prescribed volume and that obtained. LCDM device meets dialysis standards and UF control equivalent to the performance of conventional HD monitors, and also reduces water consumption by around 50%.

Conclusions: LCDM is an original low cost HD monitor which paves the way to an industrial prototype. This device, along with the reuse of dialyzers/extracorporeal lines, and lactate dialysates, would drastically reduce the cost of HD in low income countries

Table 1

	UREA	CREATININE
Instantaneous clearances (ml/min)	207-210	187-212
Reduction (%)	71.2-73.2	69.6-71.8
Mass Conservation Index	0.94-1.05	0.92-1.02

Table 2

UF Volume (ml)	Deviation (%)	Uncertainty (ml/h)
Prescribed Obtained		
2600-2760 2590-2730	0.4-1.2	2.5-7.5

SA-PO983

The Nephrology Association of Karnataka (NAK) Multicentric Dialysis Practice Pattern: A Cross-Sectional Pilot Study in Karnataka, India

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Background: The rising prevalence of chronic kidney disease (CKD) in India poses a major challenge due to absence of a national registry and validated data capture systems. Policy makers as well as treating physicians face dilemmas due to absence of evidence. Karnataka, a State in South India, with over 200 dialysis centers, lacks systems and processes to ensure comprehensive data capture. The present cross sectional study, is part of NAK's initial attempt to develop and validate norms and systems for a comprehensive statewide dialysis registry in India.

Methods: Nephrologists from various dialysis centers across Karnataka state were invited to participate. Data was captured from consenting centers, after ethics board clearance. Cloud based electronic repository (Amazon Web Space) with online platform (Renalyx NIS) was used. Only confirmed prevalent CKD-V pts on maintenance hemodialysis (HD) or peritoneal dialysis (PD) were included. Unlinked, anonymized demographics and clinical details were analyzed using SPSS, Version 16.0.

Results: 2050 patients (70% male) from 32 hospitals were recruited. Mean age was 53.49 (±14.09) years. Mean BMI was 23.68. 1909 (93.1%) were on HD. Nearly 70% had dialysis vintage >1 year. Etiology wise, 801 patients (39.1%) had Diabetic Kidney Disease, 506 (24.7%) Hypertensive Nephrosclerosis, 272 (13.3%) Chronic glomerulonephritis and 92 (4.5%) chronic interstitial nephritis. At initiation of HD, 1378 (67%) had temporary catheters & 466 (22.7%) had arteriovenous fistulae (AVF). However 1691 (82.5%) prevalent pts had an AVF as current vascular access. While 56.4% were on 3/week HD, 33.2% were on 2/week HD. 121 patients (5.9%) were hepatitis C positive & 31 (1.5%) were hepatitis B positive. 8.7% pts were not on any blood pressure medications, 27.6% of pts were on 1 med, 27.7% were on 2 meds, 23.1% were on 3 or more meds. Of 104 patients (4.7%) on CAPD, 57.6% had percutaneous PD catheter insertion and 40.4 % had it surgically inserted. 81.7% were on 4 exchanges/day with 94% CAPD being manual.

Conclusions: This study highlights wide differences in dialysis practices within the state of Karnataka in South India. The vast majority of the patients were on HD. Fistula first initiative needs greater focus. Granular data capture would provide more knowledge for improvement and policy.

Funding: Private Foundation Support

SA-PO984

Characteristics and Effectiveness of Dedicated Care Programs for Patients Starting Dialysis: A Systematic Review

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Background: The transition period during dialysis initiation is associated with increased morbidity and mortality. Transitional care units are increasingly being used to reduce the risk of complications during this vulnerable period. The objectives of our systematic review were to determine the characteristics of existing transitional care programs and their effect on clinical outcomes.

Methods: We used a search strategy to search Embase, Ovid Medline, Web of Science, Cochrane Central and CINAHL for English-language studies that evaluated dedicated programs for management for incident dialysis patients; our timeline included studies published from start of database to date. Any study design was eligible, but we required the presence of a control group and patient-relevant outcomes (e.g. mortality, central venous catheter use, and quality of life). We extracted data describing the intervention, participant demographics, comorbidities, type of renal replacement therapy, and follow-up period. We assessed study quality using the Newcastle-Ottawa Quality Assessment Scale (NOQAS).

Results: The search strategy yielded 8557 studies; 62 full texts were evaluated and 9 studies with 13,033 patients were included. 6 studies evaluated in-center hemodialysis and 3 evaluated peritoneal dialysis. All included studies were observational. 5 studies were rated as high quality, with scores of 8-9 on the NOQAS evaluated programs that provided patient education, structured patient monitoring and a structured vascular access program. Three high quality studies that were similarly structured to provide intensive education and patient monitoring at the start of dialysis suggested a trend towards reduction of mortality and use of central venous catheters. However, study heterogeneity precluded meta-analysis. No studies evaluated for an effect on home dialysis or transplant uptake, and few collected feedback from patients and staff on their sustainability.

Conclusions: Few high-quality studies have evaluated dedicated programs for patients new to dialysis, and most only measure for an effect on mortality and vascular access. Further research is needed to design and evaluate these models of cares before widespread implementation, with an emphasis on patient-relevant outcomes, such as home dialysis uptake, transplant, and quality of life.

SA-PO985

Is Initiation of Twice-Weekly Maintenance Hemodialysis an Acceptable Option?

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Background: Twice weekly maintenance hemodialysis (HD) is not an acceptable form of renal replacement therapy primarily because there are not enough studies to prove its sustainability. However with the concept of incremental dialysis and residual renal function gaining ground this can definitely prove to be a good option for initiation of hemodialysis. The benefits of twice weekly hemodialysis at initiation are significant with respect to economic issues, patient quality of life, access longevity and preservation of residual renal function. We present a three year follow up of patients on twice weekly HD and outcomes.

Methods: This was a three year observational folllow up of 88 patients initiated on twice weekly HD. Children, pregnant ladies, and patients being worked up for renal transplant were excluded from the study. Adequacy and basic cost effective hematologial and biochemical parameters were studied monthly in each patient. In case of complications develoing in the form of recurrent fluid overload, uncontrolled hypertension, refractory anaemia, hyperphosphatemia and features of malnutrition, the patient was shifted to thrice weekly HD.

Results: 16406 sessions of HD were studied analysing adequacy, residual renal function, cardiovascular outcomes, mineral bone status and socioeconomic factors and vascular access. Majority of the patients had a urine output of 1176 ml at initaion with a RRF of 3.1ml/min. BP was controlled in 93.19% of patients and left ventricular hypertrophy was seen in 37.2%. SpKt/v was 1.75, eKt/V was 1.38 and Std Kt/V was 2.8. IDWG was 1.91 Kgs with a mean ultrafiltration of 2600ml. There were 27.2% deaths during this period the commonest cause being cardiovascular causes and emergency HD was required in 0.24% of sessions.

Conclusions: Twice weekly HD at initiation is a favourable option with increments, in case of requirement, as majority of patients had a good urine output and RRF at commencement. It also preserves the residual renal function, reduces cost and improves the quality of life. Lack of vascular access is a major cause of morbidity and mortality as seen and more focus is required at this end. Adequacy parameters are fallaciously high as they are dependent on ultrafiltration volumes and body weight. A prime factor favouring twice wekly HD is economic and social factors in the form of cost of travel and distance/ time to reach dialysis centre.

Funding: Government Support - Non-U.S.

SA-PO986

Planned Incremental Hemodialysis (PIHD) Is a Cost-Effective and Patient-Centered Renal Replacement Therapy (RRT)

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Background: Hemodialysis (HD) in Japan is the highest quality of RRT in the world, but its cost is increasing continuously. The conventional thrice-weekly regimen is a common way to introduce HD but not Incremental hemodialysis (IHD) in Japan. When HD patients' conditions are sufficiently managed by once-/twice-weekly HD with good adherence to their diet, its cost reduction effect can be expected.

Methods: We selected 26 CKDG5 outpatients with good-adhered of diet, we initiated PIHD considered residual renal function individually and careful follow-ups from 2013 to 2018. The average age was 63.7 (36 to 90), and 69.2% was men. Their causes of ESRD include chronic glomerulonephritis (38.5%), diabetic kidney disease (26.9%), nephrosclerosis (23.1%), and others (11.5%; polycystic kidney disease, chronic interstitial nephritis, Hypoplastic kidney). We also examined the cost of IHD.

Results: Initiation of HD was performed as follows: 11 patients were treated with once-weekly HD, and their mean eGFR was 4.49 and mean urine volume was 1510 mL/ day. 15 patients were treated with twice-weekly HD, and their mean eGFR was 2.97 and mean urine volume was 1278 mL/day. At the end of 2018, six patients, who had been treated once-weekly for 8 months on average, were transited to twice-weekly HD. Five patients, who had been treated twice-weekly for 15.6 months on average, were transited to thrice-weekly HD. Three patients have continued once-weekly HD for 3 to 11 months. 13 patients have continued twice-weekly HD for 16.4 months on average. The overall 1-year survival rate of PIHD was 91.8%, and the 5-year survival rate was 88.3%. On January 2019, we have 27 (24.5%) once-/twice weekly and 87 thrice-weekly HD patients(total 110 maintenance HD) in our clinic. The monthly costs of dialysis in January 2019 were as follows: 146,000 yen for once-weekly, 254,500 yen for twice-weekly, and 396,200 yen for thrice-weekly HD. The calculated one-year cost of 110 patients was reduced by 10.02% as

compared with the cost for all patients receiving the conventional thrice-weekly HD (4.28 vs 4.76 million yen/year, respectively.) Limitation: The cost of January 2019 is based on the current Japanese medical insurance system. Selection bias cannot be avoided.

Conclusions: PIHD is a patient-centered RRT that provides cost-effective and sustainable treatment for ESRD patients.

SA-PO987

Hepatitis B Virus Vaccine Immune Response in Dialysis Patients and Mortality: A Meta-Analysis

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Background: Despite the effectiveness of the hepatitis B virus (HBV) vaccine in the general population, dialysis patients frequently do not develop a protective immune response. We performed a systematic review and meta-analysis to identify patient- and dialysis-related factors that are associated with HBV vaccine immune response in dialysis patients, and the association between the immune response to the HBV vaccine and mortality.

Methods: Electronic databases were searched for studies of dialysis patients that compared the characteristics of HBV vaccine responders and non-responders. Mortality was analyzed according to the vaccine immune response[NC1]. Random-effects meta-analyses were performed to compute a weighted mean difference (WMD), a pooled odds ratio (OR), and a pooled risk ratio (RR) between groups.

Results: We identified 63 studies (57 cohort studies and 6 clinical trials) with a total of 6,867 dialysis patients receiving the HBV vaccine, resulting in 4,764 (69%) responders and 2,103 (31%) non-responders. By meta-analysis, relative to non-responders, HBV vaccine responders were younger (WMD -4.6 years, P<0.001) and less likely to have diabetes mellitus (pooled OR 0.65, P<0.001), and they were less likely to carry the human leukocyte antigen (HLA) DR3 (pooled OR 0.38, P=0.01). HBV vaccine responders also had a higher serum albumin (WMD 0.12 gm/dL, P<0.001), a higher normalized protein catabolic rate (WMD 0.12 gm/kg/day, P<0.001), a higher hemoglobin (WMD 0.14 gm/dL, P=0.048), a higher parathyroid hormone level (WMD 44 pg/mL, P=0.004), and a higher Kt/V (WMD 0.10, P<0.001). Compared to non-responders, HBV vaccine responders had a 36% lower risk for all-cause mortality (pooled RR 0.64, P<0.001), a 26% lower risk for cardiovascular-related mortality (pooled RR 0.74, P=0.01), and a 24% lower risk for infection-related mortality (pooled RR 0.76, P=0.29).

Conclusions: In dialysis patients, the lack of immune response to the HBV vaccine is associated with older age, diabetes mellitus, HLA-DR3 status, lower nutritional status, lower hemoglobin, lower PTH level, and lower dialysis adequacy. Tackling some of these modifiable factors (e.g., nutritional status and dialysis adequacy) might improve the HBV vaccine immune response.

SA-PO988

Immune Response to Influenza Vaccination in Dialysis Patients: Analysis of Four Consecutive Seasons

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Background: Hemodialysis (HD) is associated with the state of immune dysfunction. In our previous study we identified low antibody response to influenza vaccine as an independent predictor of mortality in HD population. In the present study we tried to determine the factors influencing the immune response to influenza vaccination.

Methods: We analyzed data of a total of 46 HD patients who were vaccinated against influenza in four consecutive seasons from 2015/16 to 2018/19 and completed the 4-year follow-up. Their pre- and post-vaccine hemagglutination-inhibition antibody titres (HIA), iron status, C-reactive protein (CRP), albumin, parathyroid hormone and 25-OH vitamin D were measured each year at the time of vaccination. Post-vaccination seroprotection rates in consecutive seasons were compared using Cochran's Q test with multiple comparisons. To identify variables associated with the immune response to vaccine, analyses were performed using Spearman's correlation among post-vaccine rise in HIA, demographic data and the above mentioned biomarkers.

Results: Seroprotection rates changed during the 4-year follow-up, but >70% of seroprotection against all vaccine strains was achieved in all 4 years except H1N1 strain in a 2018/19 season. Results are summarized in table 1. We did not prove significant correlations among intensity of immune response to influenza vaccine and iron status, CRP, albumin, iPTH and 25-OH vitamin D.

Conclusions: The immune response to influenza vaccine varies from year to year in the HD population, but the percentage of seroprotection, with rare exceptions, is very high. We did not find a significant association between the potential factors of immunodeficiency (markers of inflammation / malnutrition, bone metabolism or iron status) and the level of seroprotection in HD patients.

Funding: Government Support - Non-U.S.

Vaccine strain / season	2015/16	2016/17	2017/18	2018/19
A H1N1 SPpost (%)	94	94	80	58 [a]
A H3N2 SPpost (%)	80	94	82	71 [b]
B strain 1 SPpost (%)	89	76	83	98 [b]
B strain 2 SPpost (%)	N/A	N/A	78	98

Statistical analysis using Cochran's Q test with multiple comparisons; a = p<0.01 (2018/19 vesus all other years), b = p<0.05 (2018/19 versus 2016/17); N/A = not applicable

SA-PO989

Pneumococcal Vaccination Status and Mortality Risk in a National Dialysis Cohort

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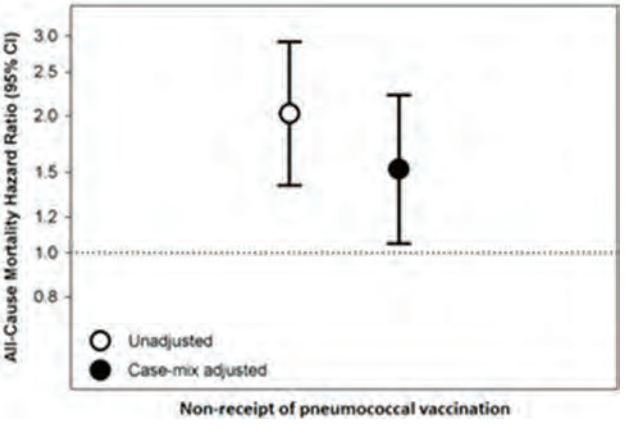
Background: Infection-related deaths are the second most common cause of mortality in end-stage renal disease (ESRD) patients, with pulmonary sources as the second dominant contributor following bacteremia/sepsis. While clinical practice guidelines recommend that ESRD patients undergo pneumococcal vaccination, large population-based studies suggest that non-vaccination is common, particularly in the setting of patient decline or contraindication. We thus sought to examine the relationship between pneumococcal vaccination status and mortality risk in a national dialysis cohort.

Methods: Among 976 ESRD patients from the national Biospecimen Registry Grant Program (BioReG) receiving dialysis treatment over the period of 1/2008-12/2014, we examined the relationship between pneumococcal vaccination status and all-cause mortality risk using unadjusted and multivariable Cox models adjusted for socio-demographic characteristics (e.g., age, sex, race, and ethnicity).

Results: In the overall cohort, mean ± SD age was 59 ± 14 years; 47% were female; 39% were Black; and 18% were of Hispanic ethnicity. During the follow-up period, 89.5% vs. 10.5% of received vs. did not receive pneumococcal vaccination. In unadjusted analyses, non-vaccination status was associated with a two-fold higher death risk: HR (95% CI) 2.02 (1.41-2.91), p<0.001. Following adjustment for socio-demographic characteristics, associations between non-vaccination status and higher mortality risk persisted: adjusted HR (95% CI) 1.53 (1.05-2.22), p=0.03.

Conclusions: In a national dialysis cohort, non-receipt of pneumococcal vaccination was associated with higher mortality risk. Further studies are needed to identify management strategies and develop clinical tools that augment vaccination rates in the ESRD population.

Funding: NIDDK Support



SA-PO990

HCV Eradication Campaign in a Dialysis Clinic in Argentina: Nephrologists' Role in Patient Safety

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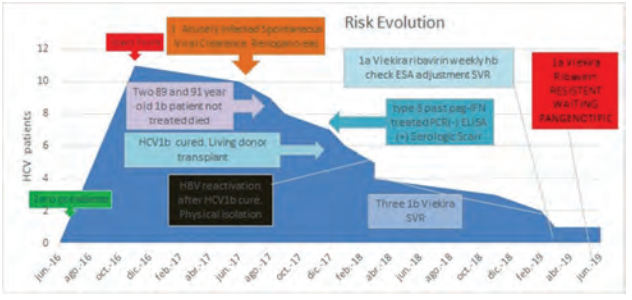
Introduction: Hepatitis C (HCV) increases mortality in dialysis patients and carries a worse prognosis for transplant. Still outbreaks continue to be reported. Direct antiviral agents (DAA) open the door to HCV free units with individual benefits and overall patient security.

Case Description: In 2016 eleven HCV patients were transferred to our zero prevalence clinic. As Infection risk rises with the number of positive patients and DAA were recently available, medical decision was to start the fight against HCV. Whole staff participation was of key impact. Remote hepathologist advice was enough except for complex cases. ELISA III was used for screening. PCR and posterior genotiping were done as no pangenotypic was available. Seven PCR + patientes were genotype 1b and two 1a. Spontaneous viral clearence occured in one of three 1b acutely infected patients. Three 1b patients were not treated due to their short life expectancy. One patient had Hepatitis B (HBV) and HCV 1b coinfection requiring hepathologic surveillance. Cirrhosis did not developed but HBV activation ocurred after HCV sustained virologic response (SVR). All Four HCV 1b patients were effectively treated with 90 day Viekira Pak Abbvie (Ombi/Pari/Rit/Dasa). Two HCV 1a patients were treated with Viekira Pak + Ribavirin needing ESA adjustment and weekly Hb check. Only one HCV 1a patient did not achieve response despite supervised compliance. Re-genotyping was done and pangenotypic scheduled. No patient had cirrhosis nor was IV drug user. Functional isolation was applied while viremic,

general when SVR and "N2 functional isolation" while no viremic but waiting SVR. No side effects but great relief was reported when SVR obtained.

Discussion: HCV eradication in the dialysis setting is an achievable goal even in 2019 Argentina. Preventing harming our patients, lowering their mortality and even curing some part of their chronicity is becoming possible. A clear north heading and a tight biosecurity are essential for a safe trip for our patients on care.



SA-PO991

Efficacy and Tolerability of Sofosbuvir and Daclatasvir for Treatment of Hepatitis C Genotype 3 in Patients Undergoing Maintenance Hemodialysis

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Background: There is paucity of data using direct anti-virals agents (DAA) in patients on maintenance hemodialysis infected with HCV-genotype 3. Sofosbuvir (SOF) based therapy leads to high rates of SVR with few side effects (18), however its use is restricted to patients with an eGFR of ≥ 30 ml/min per 1.73 m^2. The aim of this study is to evaluate DAA therapy in patients infected with HCV-genotype 3 on maintenance hemodialysis (MHD)

Methods: In this prospective open label, parallel, non-randomized interventiona trial, group1 received 400 mg daily sofosbuvir/ 60 mg daily daclatasvir; while group 2 received thrice a week 400 mg sofosbuvir/ daily 60 mg daclatasvir for 12 weeks. Patients with compensated cirrhosis received therapy for 24 weeks. Patients were classified as having compensated cirrhosis based on clinical data, Child-Pugh score and abdominal imaging. Fibro Scan and EGD were performed when indicated. Baseline data were obtained before, during and after therapy. HCV viral load was assessed at week 4, 8, at end of therapy and 12 weeks after treatment. The primary end point was acheivment of SVR. SVR was defined as undetectable viral load 12 weeks after completion of therapy.

Results: Eighteen patients were enrolled in each group. Mean age was 47.22±14.17 in group 1 and 53.89±14.11 in group 2. Mean duration of known infection was 4.61±1.84 years in group 1 and 3.55±1.92 years in group 2. Four (22.2%) patients in group 1, while six (33.3%) in group 2 had cirrhosis. Genotype 3 was most common with 12 (66.6%) in group 1, and 11 (61.1%) in group 2. Three patients (16.6%) had prior HCV treatment in group 1, while 02 (11.1%) in group 2. Three patients in group 1 left treatment (non-compliance) while one left in group 2 (adverse effects = skin rash). All patients in both groups achieved undetectable viral load at 12th week. Overall 29/32 (90.62%) patients achieved SVR (group 1= 15/15 or 100%; group 2= 14/17 or 82.35%). Three patients in group 2 who did not achieved SVR were all infected by genotype 1 and two of them had previously received treatment with interferon.

Conclusions: DAA therapy using sofosbuvir and declatsavir is highly effective and tolerable in patients with HCV genotype 3 undergoing maintenance hemodialysis, especially when given daily. Decreasing the dose or frequency of SOF may lead to decreased SVR or higher relapses.

SA-PO992

Viral Hepatitis Infections in Hemodialysis Facilities in a Non-Government Controlled Area in Syria

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Background: The prevalence of hepatitis C infections in the Syrian end stage renal disease (ESRD) population has been reported to be around 15% or less in both goverment controlled areas and host countries of Syrian refugees. The prevalence of this condition in non-government controlled areas, known to have limited resources for healthcare delivery and quality control, is unknown.

Methods: In January of 2019 we conducted a cross sectional survey of all dialysis facilities operating in a non-government controlled area in Northwestern Syria. Collected information included sources of funding of operations, available resources, patients demographics and testing of patients and staff for hepatitis C and HIV antibodies, hepatitis B surface antigen (Hep B SAg), and recent history of blood transfusion. The study was conducted by the WHO and non-government organizations (NGO's)

Results: All 20 dialysis facilities identified in the area participated in the study. Funds for operation were provided by 11 different charitable NGO's for 17 of these centers, the other three were funded by a local health directorate (n= 2) and the Turkish goverment (n=1). The area had two nephrologists and most facilities were covered by internists. Two facilites had no physician coverage. Some facilities had telenephrology care from US nephrologists. There was no regulatory body to supervise the operation of the facilities. Among 598 patients hepatitis C virus antibodies were present in 300 (50%) varying between 5 and 84% per facility. Hep B SAg was + in 32 patients (5%). One patient was HIV +. Among 148 staff members the prevalence of hepatitis C antibody was 3% and hepatitis B surface antigen 5%. The median time on dialysis for the hepatitis C positive patients was 3 years versus 2 years for the hepatitis C negative patients (P < .01). No funding is currently available to confirm the diagnosis by nucleic acid testing or for treatment.

Conclusions: Hepatitis C prevalence in this non-government area of Syria seems to be much higher compared to published data on patients in the government areas and countries hosting Syrian refugees. Limited resources and inadequate regulatory environment are contributing to this problem. Educating staff about infection control methods, and their reinforcement are of high priority. NGO's and renal societies should collaborate on this effort.

Funding: Private Foundation Support

SA-PO993

Polymorphism rs368234815 of Interferon-λ4 Gene and Development of Antibodies to Surface Antigen of Hepatitis B Virus in Hemodialysis Patients

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Background: The rs368234815 (TT/ΔG) polymorphism of interferon-λ4 gene (*IFNL4*) alone or in combination with other genes may be involved in hepatitis B virus (HBV) surface antigen (HBsAg) clearance in non-uremic subjects infected with HBV. We investigated whether *IFNL4* rs368234815 is associated with the development of HBsAg antibodies (anti-HBs) in response to HBV vaccination or infection, and HBsAg loss after HBV infection in uremic patients treated with hemodialysis (HD).

Methods: To evaluate the association between anti-HBs and rs368234815, non-responders to HBV vaccination (n=122) were compared with responders (n=121), and HBsAg positive patients not able to develop anti-HBs (n=35) were compared with HBsAg negative subjects who generated anti-HBs (n=65) after HBV infection. All anti-HBs negative subjects (n=189) were also compared with all anti-HBs positive patients (n=190). To evaluate the association between HBsAg loss after HBV infection and rs368234815, all HBsAg positive patients (n=39) were compared with all subjects who eliminated HBsAg (n=97). Patients were genotyped for *IFNL4* rs368234815 polymorphism by a polymerase chain reaction-restriction fragment length polymorphism method.

Results: Rs368234815 genotypes were distributed in accordance with Hardy-Weinberg equilibrium. The tested polymorphism was not associated with anti-HBs development either after HBV infection or HBV vaccination as well as with HBsAg loss (analyzes in models of inheritance and differences in variant allele frequencies yielded P>0.05). Adjustment for age at renal replacement therapy (RRT) onset, RRT duration, and positive antibodies to hepatitis C virus revealed that patients harboring the ΔG allele had 1.59-fold (0.98-2.56, P=0.057) higher risk for remaining anti-HBs negative after HBV vaccination or infection compared with the TT/TT subjects.

Conclusions: *IFNL4* rs368234815 is not associated with anti-HBs development in HD patients. Therefore, this polymorphism alone cannot be useful as a predictor either of responsiveness to HBV vaccination or HBsAg seroclearance in HBV infection. However, due to the relatively small number of the examined patients and borderline associations, further studies exploring this subject are reasonable.

SA-PO994

Exploring the History and Outcomes of Hepatitis B Core Antibody-Positive Hemodialysis Patients Focusing on Occult Hepatitis B

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Background: Occult HepatitisB (OHB) is defined as hepatitisB core antibody (HBcAb) positivity(pos) in the absence of surface antibody (HBsAb) or surface antigen (HBsAg). The reported incidence in hemodialysis (HD) patients (pts) is 0.3% - 58%. Our study is among the first in the US to examine the history of OHB. This work is of interest in HD pts to estimate HepatitisB transmission risk.

Methods: A retrospective study of 352 HBcAb pos HD pts at a medium sized dialysis organization was performed from 2010 to 2017. Primary outcomes were the development of HBsAb pos(considered protective) or development of HBsAg pos or new HepatitisB viremia(adverse events). Univariate and multivariate regression analysis was used to study pertinent risk factors for the outcomes comparing OHB and NonOHBpts.

Results: In our study 98 (27%) pts had OHB. Each group had similar baseline demographics, while OHB pts had a higher ALT, proportion of drug use and HepatitisC compared to nonOHB pts (Tab1). There were 15 adverse events (10 viremias) in the nonOHB group. Only 1 adverse event (viremia 19 copies/mL) was seen in the OHB group (Tab2). Conversely, OHB status was a statistically significant predictor of protective HBsAb development in follow up, occurring at a 7 fold increase compared to nonOHB pts. Univariate analysis showed that history of liver disease, HepatitisC and drug use predicted HBsAb development (Tab3). History of liver disease raises risk of adverse events in an unadjusted models (P<0.05) (Tab4).

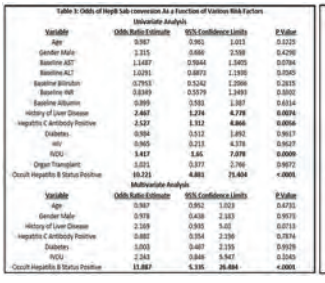
Conclusions: OHB pts at our center tend to develop protective HBsAb titers over time rather than develop viremia/antigenemia in contrast to nonOHBpts. Our study finds that OHB confers minimal risk of potential transmission of HepatitisB among HDpts.

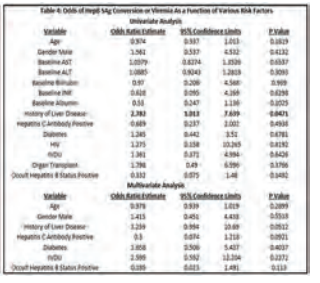
Table 1: Hepatitis B Core Antibody Positive Patients at HFHS and Greenfield Dialysis Centers, SE Michigan. 2011-2018.
Total N = 352

Demographics	Non-Occult Hepatitis B (N = 254)		Occult Hepatitis B (N=98)		P Value
Age in Years (Mean, SD)	68.57	12.8	68.65	10.10	0.9472
Gender (N Male, %)	152.00	59.8	63.00	64.30	0.4435
Baseline AST (Mean, SD)	25.45	18.11	33.82	43.59	0.0689
Baseline ALT (Mean, SD)	19.21	15.21	30.72	48.10	**0.0236**
Baseline Bilirubin (Mean, SD)	0.50	0.34	0.53	0.39	0.6246
Baseline INR (Mean, SD)	1.29	0.55	1.22	0.28	0.2167
Baseline Albumin (Mean, SD)	3.42	0.62	3.57	2.37	0.556
History of Liver Disease (N, %)	66.00	26.0	29.00	29.6	0.3989
History of Hepatitis C (N, %)	81.00	31.9	48.00	49.0	**0.0017**
Diabetes (N,%)	140.00	55.1	52.00	53.1	0.8262
HIV (N,%)	12.00	4.7	5.00	5.1	0.7878
IVDU (N,%)	29.00	11.4	24.00	24.5	**0.0014**
Organ Transplant (N, %)	34.00	13.4	7.00	7.1	0.0972

Table 2: Outcomes Examined - Clinical Endpoints

Endpoint	Non Occult Hepatitis B Patients N=254		Occult Hepatitis B patients N=98		P-Value
Acute Viremic Patients, N, %	10	3.9	1	1.0	0.3026
Total Conversions of Serum Antibody - N, %	13	5.1	32	32.7	**<.0001**
Total Conversions of Serum Antigen - N, %	11	4.3	1	1.0	0.191
Maximum Viremia level (Mean, SD)	4002748	62750171.0	0.1939	1.9	0.3103
Received Hep B Treatment - N, %	11	4.3	0	0.0	0.0677
Adverse Outcome (Ag Conversion or Viremia) N,%	15	5.91	1	1.0	0.1295
Protective Outcome (Ab Conversion Alone) N,%	11.00	4.3	31.00	31.6	**<.0001**





SA-PO995

A Study on Prevalence of Hepatitis C Virus Infection and Its Genotype Distribution Among Chronic Renal Failure Patients on Maintenance Hemodialysis: A Single-Center Experience

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Background: Hepatitis c virus (HCV) infection is a very common infection in chronic renal failure (CRF) patients on maintenance hemodialysis (HD). Genotype detection is crucial for management of chronic hepatitis c patients, prediction of prognosis, epidemiological study and also for vaccine preparation. Based on the sequence divergence, till date HCV strains are divided into 7 main genotypes and multiple subtypes (67 confirmed, 20 provisional).

Methods: The aim of this study was to find out single centre prevalence and distribution of HCV genotypes in CRF patients on maintenance haemodialysis (MHD). Genotyping was performed by nested reverse transcriptase PCR. Isolation of HCV RNA, reverse transcription and nucleic acid amplification of 5' UR was carried out. Biotinylated oligonucleotide primers were used to generate amplified product and reversely hybridized to type-specific probes on nitro-cellulose strips. Conjugate and substrate were added post-hybridization to observe the generated bands which were then matched with control bands. The genotypes studied were 1a to1c, 2a to 2d, 3a to 3f, 4a to 4k, 5a and 6a.

Results: Out of 2550, 210 patients (12.14%) (Male: 166, Females: 44) were HCV positive. Genotype 1 was found in 179 (85.2%) and genotype 3 in 31(14.8%) patients. Amongst genotype 1, subtype 1a, 1b, 1ba and undetermined comprised 71.4%, 24.6%, 0.6% and 3.4% respectively. Amongst genotype 3, subtypes 3a, 3b and undetermined comprised 70.9%, 9.7% and 19.4% respectively. No other genotypes were found.

Conclusions: HCV infection was found in 12.14 % CRF patients on MHD with genotype 1 (85.2%) being predominant followed by genotype 3 (14.8%) in our study.

SA-PO996

Impaired T Cell Functionality in ESRD Is Not Reversed by Immune Checkpoint Blockade

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Background: Polyfunctional T cells are critical for maintaining protection against pathogens. Patients with end-stage renal disease (ESRD) are at increased risks for infection but their pathogen-specific T cell function is not well understood.

Methods: 32 healthy individuals and 57 patients on maintenance hemodialysis were enrolled in this study. All the donors were seropositive for CMV. In addition to PMA/ionomycin, CMV peptide pools (IE1 and pp65) were used to stimulate PBMCs and four effector functions were measured by multicolor flow cytometry (IL-2, TNFα, IFNγ and CD107a) to identify polyfunctional T cells (cells capable of all four functions). The statistical comparisons were performed using the Kruskal-Wallis equality-of-populations rank test.

Results: The age of the two groups was similar (mean, 60 years old). ESRD patients showed increased levels of T cell differentiation, including the decrease in CD4+ and CD8+ T_N cells and the increase in the CD4+ and CD8+ T_{EM} and T_{EMRA} cells. T cells from ESRD patients exhibited significant impairment in their effector functions in response to PMA/ionomycin, and such impairment is independent from differentiation status. While the cellular frequency of virus-reactive CD4+ and CD8+ T cells were similar, polyfunctional T cell response were dramatically reduced in the ESRD. The CD8+ CMV-pp65-reactive polyfunctional cell frequencies showed the most dramatic reduction, 12.4% in healthy donors versus 0.8% in ESRD patients ($p<0.001$). We further identified that immune checkpoint molecules PD-1 and TIM-3 are upregulated on T cells from ESRD patients; nevertheless, immune checkpoint blockade therapy and regulatory T cell depletion did not reverse the dysfunction phenotype. Transcriptome analysis demonstrated pathway enrichment of advanced T cell differentiation in ESRD but did not demonstrate the enrichment of exhaustion related genes in T cells from ESRD patients.

Conclusions: Renal failure patients are characterized by a dramatic loss of polyfunctional T cells and impairment in T cell effector functions, which might explain the increased risk for infection and cancer. Although inhibitory receptors such as PD-1 are upregulated, such phenomenon is distinct from T cell exhaustion.

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SA-PO997

Pre-ESRD Infection Event and Post-ESRD Mortality in Patients with Advanced CKD Transitioning to Dialysis

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Background: Accumulating evidence indicates that infection is a frequent event in patients with non-dialysis advanced chroinc kidney disease (CKD) and that reduced estimated glomerular filtration rate(eGFR) is associated with a higher risk of subsequent short-term mortality. However, It remains unclear whether infection events before entering dialysis have a long-term negative impact on patients with advanced CKD who survive to permanent dialysis.

Methods: Using Taiwan National Health Insurance Research Database, we enrolled 62,872 patients with advanced CKD who transitioned to maintenance dialysis between January 1, 2004 and December 31, 2013. We identified 20,566 (32.7%) patients who had at least one infection episode during the pre-dialysis advanced CKD period. We used multivariable Cox models to determine the association of pre-dialysis infection exposure with all-cause mortality after starting dialysis. Furthermore, we analyzed the risk of post-ESRD mortality according to four quartiles based on the annual number of infection episodes during pre-dialysis advanced CKD.

Results: Compared with no infection during advanced CKD, the presence of infection exposure during that period was independently associated with a higher risk of first-year mortality (hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.35–1.50) and the increased risk still exits during entire follow-up period (HR 1.22, 95% CI 1.19–1.25). The risks also increased incrementally with higher annual number of infections during advanced CKD (P for trend< 0.001).

Conclusions: Pre-ESRD infection events are associated with increased risk of ealy and late post-ESRD moratlity in patients with advanced CKD transitioning to dialysis.

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

All-cause mortality in patients with and without infection history during pre-dialysis advanced CKD

	No. of events (%)			Infection vs. non-infection			
	All	Infection	Non-infection	Univariate		Multivariate	
All-cause mortality	(n = 62872)	(n = 20,566)	(n = 42,306)	HR (95% CI)	P value	HR (95% CI)	P value
1-year follow-up	5,637 (9.0)	2,681 (13.0)	2,956 (7.0)	1.94 (1.84, 2.04)	<0.001	1.42 (1.35, 1.50)	<0.001
At the end of follow-up	25,475 (40.5)	9,556 (46.5)	15,919 (37.6)	1.49 (1.46, 1.53)	<0.001	1.22 (1.19, 1.25)	<0.001

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

SA-PO998

Implementation of Antibiotic Stewardship (AS) in a Large Dialysis Organization

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Background: Fresenius Kidney Care (FKC) implemented an antibiotic stewardship (AS) program to ensure blood cultures were drawn prior to antibiotic administration and to optimize the selection of empiric antibiotic therapy, timing of de-escalation of broad-spectrum antibiotics, and the duration of antibiotic therapy.

Methods: The FKC AS program consisted of the following: 1) a care pathway for catheter-related blood stream infection (BSI); 2) implementation of a software platform that allowed for real-time monitoring of blood cultures, prescription of IV antibiotics, and blood culture (BC) and sensitivity results; 3) a pharmacist to monitor BC results and IV antibiotic treatment; and 4) educational programs. Starting in 2018, a targeted deployment of the AS program was undertaken sequentially in four regions. To examine the effect of AS on BSI rates, we identified hemodialysis (HD) patients in FKC facilities between January 1, 2016, and March 31, 2019 and ascertained vascular access (VA) type in use during each HD session and positive BC results. To estimate effects of the intervention,

we fit a series of Poisson regression models of BSI incidence, adjusted for region, VA type, secular trend, seasonality, and region-specific timing of the launch of the intervention.

Results: The cohort included 42,535 HD patients; 696,106 patient-months (80% with fistula/graft, 20% with catheter); and 3,747 BSIs (39% with fistula/graft, 61% with catheter). Among all 4 regions, the adjusted secular trend during the study era was 7% lower BSI incidence per year. After accounting for this trend and seasonality, the adjusted relative rate (ARR) of BSI incidence after the launch of AS was 0.58 (95% CI 0.48-0.70), relative to expected incidence in the absence of the intervention. The ARR was 0.78 with fistula/graft and 0.48 with catheter; ARR varied among the regions (Table).

Conclusions: Implementation of AS was associated with a reduction in BSI incidence relative to modeled trends. However, outcomes differed by access type and region.

Funding: Commercial Support - Fresenius Medical Care North America

	Fistula/Graft		Catheter	
	ARR	95% CI	ARR	95% CI
All Regions	**0.78**	**0.58-1.04**	**0.48**	**0.39-0.60**
Region 1	0.51	0.27-0.97	0.33	0.24-0.45
Region 2	0.62	0.36-1.08	1.02	0.59-1.76
Region 3	1.44	0.72-2.89	0.73	0.41-1.28
Region 4	1.03	0.62-1.71	1.12	0.68-1.85

SA-PO999

Bloodstream Infections in Relation to Environmental Cultures in 12 Dialysis Units in New York City

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Background: Infections are an important complication of end-stage renal disease (ESRD) and represent a significant contribution to morbidity and mortality rates. Central venous catheters (CVC) contribute to bloodstream infections (BSI). We examine environmental cultures in 12 units of a small dialysis organization (SDO) in New York City in comparison to bloodstream infection surveillance data to discern whether a potential association exists.

Methods: Direct and non-direct care staff members and the dialysis unit environment (dialysis chair, dialysis machine, laptop, television remote, doorknobs, countertops, etc.) were cultured. Jewelry worn and method of hand hygiene were noted. Cultures that grew normal flora, or airborne contaminate were considered negative. This data was compared with the number of bloodstream infections in 2018 and standardized infection ratio (SIR) of CVC BSI.

Results: A total of 560 environmental cultures were collected: 349 from the dialysis environment and 211 from staff. Of the total cultures, 25% were positive, while 18.5% of staff cultures were positive. 56% of staff performed hand hygiene immediately prior to culture: 6.2% with alcohol-based sanitizer, 49.2% with soap and water, and 0.5% with both. 18.5% of staff also wore jewelry, namely non-direct care personnel. Table 1 displays the percentage of all positive cultures and positive direct-care staff cultures in each unit, as well as their associated number of BSIs and SIR.

Conclusions: The 12 units of this SDO have BSI rates that are lower than predicted. Additionally, environmental cultures are in large majority negative. This suggests that these dialysis units are following infection protocol and reducing the spread of BSIs. Infections that do arise may be stemming from other environmental sources, which include the home environment and other healthcare settings. Staff is not following the latest CDC guidelines regarding using hand sanitizer preferentially over hand washing, which is an opportunity for education and improvement

Table 1: Environmental culture growth compared to BSI and SIR in 12 units of an SDO in New York City

	1	2	3	4	5	6	7	8	9	10	11	12	Total
+All Cx (%)	24	27	29	8	43	10	10	30	46	55	6	24	139
+Direct-care staff Cx (%)	9	17	17	0	0	13	14	23	5	40	0	0	16
BSIs	2	6	4	3	2	3	4	14	1	15	3	3	66
SIR	0.19	0.58	0.24	0.31	0.2	0.32	0.48	1.25	0.05	0.6	0.37	0.32	0.4
Total patients	177	194	197	115	92	158	164	187	196	287	155	127	2049

SA-PO1000

Analysis of Dual-State Antibiotic Prescription Practices in the ESRD Population

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Background: We previously analyzed outpatient oral antibiotic prescriptions (ABP) for end-stage renal disease patients on hemodialysis (ESRD) in New York State (NYS). Nearly 50% of ABPs had no associated infectious diagnosis. Here, we compare ABPs between NYS and South Carolina (SC).

Methods: 2018 NYS and SC Medicare part B and D data were collected and linked to ICD-10 diagnosis (DX) codes. Patients under 18 years of age, on peritoneal dialysis, or who had chronic kidney disease were excluded. ICD-10 codes were classified into 14 DXs. Chi-square analysis was used to compare data between NYS and SC.

Results: Table 1 presents the top 5 infection DXs. Incidence of ABPs was 619.9/1000 patients in NYS compared with 597.3/1000 patients in SC. In both states nearly 40% of ABP were categorized as nonspecific symptoms or had no DX. The top 10 ABPs were also similar between states (Table 2). Trimethoprim-sulfamethoxazole was prescribed often in both states despite not being recommended in ESRD.

Conclusions: Antibiotic selection and sources of infection were similar in both states, and indications are often not clear. This suggests that antibiotic guidelines in ESRD is a national problem. The number of skin infections may reflect access complications.

Table 1: Top 5 Infectious Diagnosis			
	NYS	SC	P
Respiratory	19.48%	19.96%	0.39
Nonspecific symptoms	19.11%	17.40%	< 0.05
No diagnosis	18.48%	21.79%	< 0.05
Skin	17.74%	17.79%	0.95
GU	6.81%	8.72%	< 0.05
Other	18.38%	14.34%	
Table 2: Top 10 Antibiotics			
	NYS	SC	P
Levofloxacin	11.50%	11.02%	0.29
Azithromycin	11.45%	10.74%	0.12
Amoxicillin-Clavulanate	10.93%	8.82%	< 0.05
Doxycycline	10.27%	12.44%	< 0.05
Cephalexin	9.69%	11.81%	< 0.05
Ciprofloxacin	9.33%	10.70%	< 0.05
Sulfamethoxazole-Trimethoprim	7.04%	7.36%	0.39
Amoxicillin	6.97%	6.72%	0.51
Metronidazole	4.48%	4.98%	0.10
Clindamycin	3.66%	5.34%	< 0.05
Other	14.68%	10.07%	

SA-PO1001

Microbiome in Tunneled Catheters of Patients Receiving Maintenance Hemodialysis

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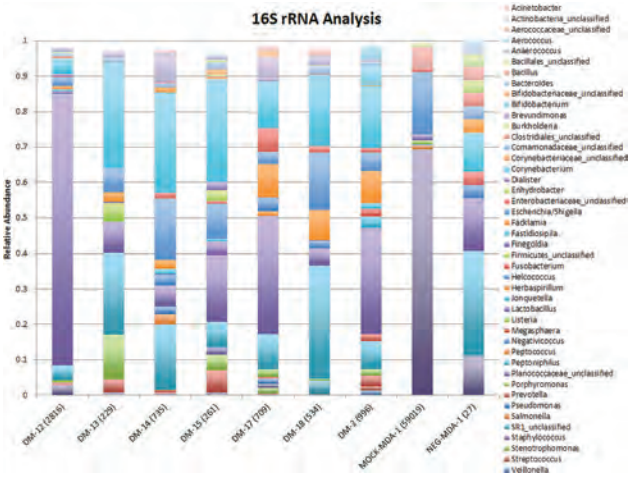
Background: Sepsis is one of the leading causes of morbidity and mortality in patients receiving maintenance hemodialysis via catheter. Bacteremia in dialysis patients generally results from contamination of the catheter lumen (biofilm). Dialysis catheter lumen is instilled with sterile heparin solution at the end of dialysis treatment and discarded prior to next treatment. The aim of our pilot study was to identify the presence and characteristics of microbiome in heparin fluid in tunneled catheters.

Methods: For 20 hemodialysis patients with catheters, 3 ml samples of heparin (mixed with blood) in catheter lumen was collected. Bacterial DNA was isolated and amplified using multiple displacement amplification; 16S rRNA sequence analysis was used to identify and characterize the microbiome. Sample diversity of the sequence positive composition was quantified using the inverse Simpson, and Chao indices.

Results: Among the 20 patients with a tunneled hemodialysis catheter, median age was 54 (range 20-80 years), 50% were male, and race was African American in 50% and white in 20% and rest were Hispanic or Asian. Median catheter days was 127 (range 42 to 347 days). Seven of the 20 catheter fluid samples had greater than 200 reads. One specimen was dominated (greater than 50%reads) by the genera Lactobacillus. This patient with dominance of Lactobacillus species in the catheter microbiome was a young female with catheter duration of 344 days. The other 6 showed no dominant species and showed high diversity with inverse Simpson Index 6.25 (95% CI 4.34, 11.11) and Chao index of 35.22 (95% CI 27.42, 43.02).

Conclusions: The microbiome of heparinized fluid in tunneled dialysis catheters does not appear to be sterile. Information on the catheter biome may be used to predict future blood stream infections and/or to develop protocols for infection prevention.



SA-PO1002

Change in the Incidence and Pattern of Staphylococcus aureus Bacteraemias in Haemodialysis Patients: 12-Year Single-Centre Experience

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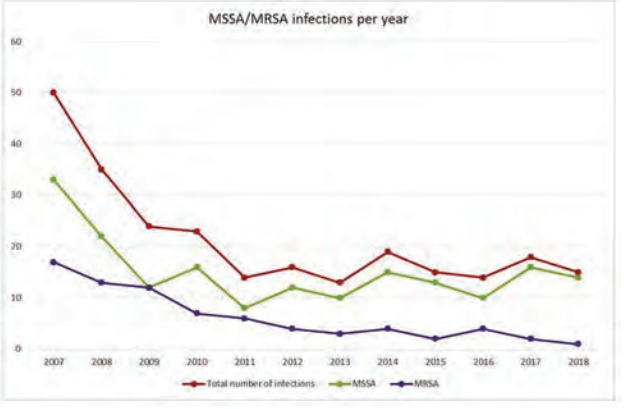
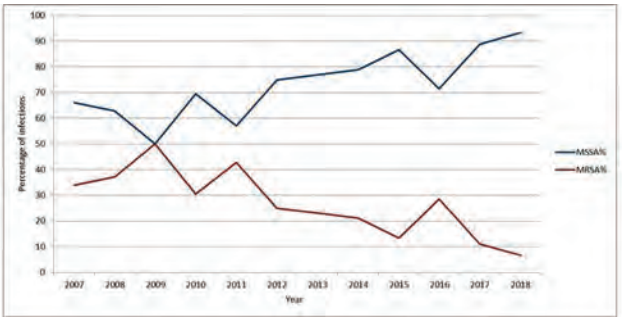
Background: Patients on haemodialysis (HD) are greater risk of infection if they dialyse through lines, than with via arteriovenous fistulae or grafts. The most commonly implicated organism is *Staphylococcus aureus* (SA), which can cause metastatic infections e.g endocarditis, osteomyelitis. There has been a focus on reducing the incidence of infections, especially methicillin resistant SA (MRSA). We looked at the incidence of methicillin sensitive SA (MSSA) and MRSA in HD patients with SA bacteraemia at our centre over the last 12 years.

Methods: Data were collected from the hospital's microbiology database of all the SA bacteraemias in HD patients between 2007 and 2018.

Results: There were 261 bacteraemias in 1361 patients, from a total of 32,000 dialysis episodes. 62.8% were male. Median age was 67 years (range 18-96). Blood cultures grew MSSA - 71%, MRSA - 29%. 78% occurred in patients dialysing via lines. The incidence of infections fell from 50 in 2007 to 15 in 2018. The proportion of MSSA infections increased however.

Conclusions: There was a significant reduction in SA bacteraemias, but an increase in the proportion of MSSA bacteraemias. It is important not to allow the reduction in numbers (in particular of MRSA) to lead to complacency in the efforts to reduce the numbers of MSSA and other infections in this particularly vulnerable group of patients.





SA-PO1003

A Clinical Nomogram for the Prediction of Early Mortality in Elderly Patients Initiating Dialysis for ESRD

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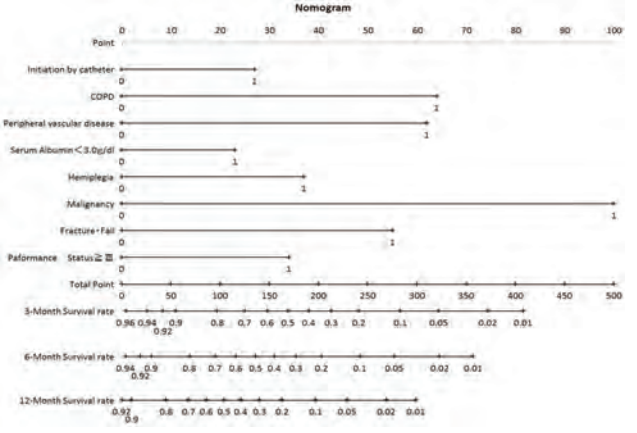
Background: The number of elderly patients (>80 years) with end-stage renal disease is rapidly increasing. The initiation of dialysis extends the duration of survival; however, the rate of early mortality—mortality within the first few months after the initiation of dialysis—is reportedly higher than the rate of late mortality.

Methods: We retrospectively studied a cohort of 300 patients, aged 80 years or older, in whom dialysis was initiated between January 1, 2010 and December 31, 2017. The rate of early mortality was assessed using the Kaplan-Meier method and the equivalence of survival curves was tested using log-rank tests. The univariate and multivariate analyses were performed using the Cox proportional-hazards model. To evaluate nomogram performance, we assessed both the discrimination and calibration of these models. Two hundred bootstrap resamples were used for internal validation of the accuracy estimates to reduce over-fit bias and to determine 95% confidence intervals

Results: The nomogram was built from eight predictors of initiation of dialysis by the temporary catheter (Hazard Ratio[HR] : 1.58, P=0.025), COPD (HR : 2.93, P=0.008), Peripheral vascular disease (HR : 2.82, P=0.019), Hemiplegia (HR : 1.87, P=0.011), Malignancy (HR : 5.37, P<0.001), Serum Albumin<3.0g/dl (HR : 1.48, P=0.061), Bone fracture by the fall within one year (HR : 2.52, P=0.010) and Performance status≧3(HR : 1.77, P=0.025). Nomogram to predict 3-, 6- and 12-month survival using eight easily available clinical characteristics. To use the nomogram, locate patient's variable on the corresponding axis; draw a line to the points axis, sum the points, and draw a line from the total points axis to the 3-, 6- and 12-month survival rate axis.

Conclusions: We developed and validated a nomogram that predict early mortality in elderly patients starting dialysis for end-stage renal disease. Nomogram might help nephrologists make a shared decision with patients and families regarding the initiation of dialysis.



SA-PO1004

Measurement of Dialysate Sodium: Beware of Assay Artifact

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Background: Dialysate sodium is traditionally set at a constant in the range of 136 to 140 mmol/L. However, increasing dialysate sodium, either as a constant, or using sodium ramping, modelling, or using biofeedback systems, can decrease intradialytic hypotension, and symptoms. An individualised dialysate sodium prescription may decrease thirst, interdialytic weight gain and blood pressure. There are some reports that the measured dialysate sodium concentration may vary from the the ordered sodium. This quality assurance study was conducted to measure the bias between machine reported conductivity and the actual delivered dialysate sodium and determine the factors associated with the bias.

Methods: We conducted analyses on 3 different dialysis machines by running patient-free dialysis sessions with varying combinations of sodium and potassium baths. With the different permutations of the 3 machines, sodium and potassium baths. The conductivity meters of the machines were validated prior to each run using a calibrated external handheld conductivity meter. Dialysate samples were sent for measurement of sodium (indirect ion selective [ISE] method) using the Siemens Vista 1500 analyzer in an accredited clinical laboratory, using serum and urine modes. Samples were obtained from the arterial dialyser port. The primary outcome was quantification of the bias between ordered and measured dialysate sodium, defined as the mean difference between the two. The secondary outcome was to measure the variation of the bias based on certain prespecified covariates.

Results: Overall data are available as 230 measurements from 85 sessions. Overall, there was a significant difference between ordered sodium level and measured sodum (mean +5.6, standard deviation [SD] 1.8 mmol/L), with the delivered sodium being higher. There was no significant difference between the different machines, differing sodium ordered (135 or 140), K bath (2 or 3K), time (0, 1, 2, 4 hours). However, there was a marked difference between using serum mode (+ 6.0 SD 1.6) and urine mode (mean 1.5, SD 2.9).

Conclusions: Since serum plasma is composed of 7% solids, the serum measurement has a correction factor that should not be applied when measuring samples with lower amouont of proteins. In the case of the dialysate, using urine mode for measurement of electrolytes corrects the apparent bias in delivered sodium.

SA-PO1005

Impact of the Serum Sodium and Chloride Difference on All-Cause Mortality in Japanese Hemodialysis Patients: The Miyazaki Dialysis Cohort Study

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Background: Few studies have examined the relationship between the acid-base balance and mortality in hemodialysis patients. In actual clinical settings, the regular collection of blood gas data is rarely conducted. In theory, the serum sodium and chloride difference (SCD) is equal to the anion gap plus bicarbonate, and we herein investigated whether SCD as a simple acid-base balance index affected the risk of mortality in maintenance hemodialysis patients.

Methods: Study design: Cohort study. Setting, Participants: Data from the Miyazaki Dialysis Cohort study, including 1113 hemodialysis patients aged ≥18 years, dialysate sodium 140 mEq/L, with SCD pre- and post-dialysis. Predictors: Pre-dialysis SCD, <33, 33 to 35, 35 to 37, ≥37 (reference), and post-dialysis SCD <36, 36 to 37, 37 to 39, ≥39 (reference) according to quartiles. Outcomes: All-cause mortality during a 2-year follow-up. Measurements: The crude mortality rate in each group was assessed using a Kaplan–Meier analysis with the Log-rank test. Hazard ratios (HRs) were estimated using Cox's model for the relationships between SCD categories and mortality, and adjusted for potential confounders. Patients in the higher group were set as our reference category.

Results: Among the 1113 patients in this cohort study (median age [interquartile range], age 69 [59-77] years, dialysis vintage 72 [34-141] months, and females 42.7%), 154 patients died during the follow-up. The Kaplan-Meier analysis showed that the survival rate was significantly lower in patients in the lowest SCD (<36) group post-dialysis than in those in the other groups (Log-rank test, P<0.01), whereas no significant differences were observed pre-dialysis (Log-rank test, P=0.26). Cox's regression analysis showed that the lowest SCD (<36) group post-dialysis was independently associated with an increased risk of mortality (adjusted HR [95% CI] 2.01 [1.25-3.23]). No relationship was observed between pre-dialysis SCD levels and all-cause mortality.

Conclusions: Among Japanese maintenance hemodialysis patients, low SCD levels post-dialysis, but not pre-dialysis, increased the risk of mortality. The present results suggest that SCD post-dialysis is a predictor of mortality.

SA-PO1006

Anion Gap Predicts Early Mortality After Starting Dialysis in the Elderly

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Background: The kidney has the principal role in the maintenance of acid-base balance. Metabolic acidosis develops due to reduced renal function and excretion of the daily acid load. It is well known that uremia causes an increase in the serum anion gap (AG). However, it is not known whether changes in AG is associated with mortality after starting dialysis. Therefore, we investigated the association between AG and early mortality after starting dialysis in elderly patients with end-stage renal disease (ESRD).

Methods: We conducted a retrospective cohort study to investigate the association between AG and early mortality after starting dialysis in the elderly. The cohort consisted of patients aged 75 years old or older who started dialysis for ESRD at the National Center for Global Health and Medicine from 2010 to 2017 and at Yokosuka Kyosai Hospital from 2007 to 2011. They were stratified into three groups (G1-3) based on delta AG (ΔAG). ΔAG was calculated using a following equation, ΔAG = serum sodium level - (serum chloride level + serum bicarbonate level) - 12. The primary outcome was death within a year of the start of dialysis. Data were analyzed using Cox proportional hazard models with adjustments for baseline characteristics.

Results: We enrolled 254 patients (males, 59%). Median ΔAG was 2.6 (G1, >3, n=111; G2, 0-3, n=103; G3, <0, n=40). During a mean follow-up of 320 days, the primary outcome was observed in 43 patients. G1 and G3 had significantly higher hazard ratios (HR) for the primary outcome than G2 (G1, HR 2.47, 95% confidence interval 1.13-5.37; G3, HR 3.86, 95% confidence interval 1.62-9.16). After adjusting for baseline characteristics, G1 had significantly higher adjusted hazard ratio (aHR) for the primary outcome than G2 (G1, aHR 3.63, 95% confidence interval 1.56-8.45; G3, aHR 2.33, 95% confidence interval 0.88-6.19).

Conclusions: It is noteworthy that there is an obvious J-curve phenomenon between AG and early mortality after starting dialysis in the elderly.

SA-PO1007

Comparing the Prognostic Value of eGFR and Residual Urine Volume in New Dialysis Patients

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Background: Residual renal function (RRF) is a pivotal predictor for long-time outcome of maintenance dialysis patients that can be assessed by simply measuring residual urine volume (RUV) or calculating estimated glomerular filtration rate (eGFR) at the start of dialysis. However, it remains unknown which one is better for prognostic evaluation as the substitution of RRF in new dialysis patients.

Methods: This is a multiple-center, retroperspective cohort study. Patients who started dialysis between January1, 2008 and December 31, 2017 at the third affiliated hospital of Sun-Yat Sen University were eligible for the study with follow-up through June 30, 2018. The data was collected at the start of dialysis. All eGFR was calculated by eGFR-EPI equation. Main endpoint was all-cause mortality. The predictive accuracy and discriminative ability of the nomogram were determined by a concordance index (C-index) and calibration curve and were compared with eGFR-EPI and RUV. The results were validated with data from dialysis patients at the other two institution enrolled from 2008 to 2017.

Results: 612 patients were included in the primary cohort, while 236 patients were enrolled in the validation cohort. Compared with eGFR, RUV showed a better prognostic value for dialysis patients both in the primary and validation cohort either by K-M method or cox regression analysis. Independent risk factors derived from multivariable analysis of the primary cohort to predict mortality were age, diabetes mellitus, mean blood pressure, albumin, uric acid which were all assembled into the nomogram with RUV (nomogram B) or with eGFR (nomogram A). The calibration curve for the probability of mortality showed that the nomogram B (RUV) predictions were in better agreement with actual observations. The C-index of nomogram B (RUV) for predicting mortality was 0.680 (P =0.004), which was statistically higher than the C-index values of nomogram A (0.570). The results were confirmed in the validation cohort.

Conclusions: Our results show that higher residual urine volume at the beginning of dialysis was associated with lower risk of mortality, that indicates the RUV has a better prognostic value than eGFR at the beginning of dialysis for maintenance dialysis patients.

SA-PO1008

Impaired Secretory Clearance in the Residual Kidney of Hemodialysis Patients

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Background: Residual kidney function is associated with survival and better control of fluid and inorganic solutes in patients on hemodialysis (HD). This study assessed the extent to which the residual kidney maintains the ability to clear organic solutes by tubular secretion.

Methods: Plasma and timed urine were collected to measure kidney clearances for the secreted solutes hippurate (HIPP), indoxyl sulfate (IS), and p-cresol sulfate (PCS) in 10 patients on twice weekly HD with residual kidney function and in 10 control subjects. Clearances were expressed in terms of the free, unbound solute levels. Clearances were normalized to the GFR (fractional clearances) to assess the degree to which solutes were secreted. GFR was calculated as the mean of the creatinine and urea kidney clearances.

Results: As expected, the GFR was much lower in the HD patients than control subjects (4.0±2.0 vs. 97±18 ml/min/1.73m^2, p<0.001). Kidney clearances of HIPP, IS, and PCS were also much lower in the HD patients. The fractional clearances of these solutes remained greater than 1 in the HD patients, confirming that they were cleared by secretion. The degrees to which secretory clearances of these solutes were maintained relative to GFR in the residual kidney, however, varied greatly. Fractional HIPP clearance was preserved in the HD patients as compared to control subjects (15±10 vs. 19±5, p 0.35). Secretion of IS and PCS, however, declined to a greater degree than the GFR in the residual kidney of HD patients, so that their fractional clearances were markedly lower than the control subjects (IS: 9.2±6.1 vs. 31±18, p<0.001; PCS: 4.4±2.7 vs. 12±3, p<0.001).

Conclusions: Secretory clearances of organic solutes are variably impaired in the residual kidney of HD patients. Residual secretory function cannot therefore be assessed by measurement of a single solute. Further studies will be required to assess the residual kidney's contribution to removal of medications and uremic solutes which are cleared by secretion and guide adjustment of medication doses and dialysis prescriptions.

Funding: Veterans Affairs Support

Solute	Clearance (ml/min/1.73m2)		Fractional Clearance	
	HD	Control	HD	Control
GFR	4.0 ± 2.0 *	97 ± 18	-	-
HIPP	67 ± 67 *	1921 ± 783	15 ± 10	19 ± 5
IS	38 ± 39 *	3032 ± 506	9.2 ± 6.1 *	31 ± 8
PCS	18 ± 17 *	1229 ± 249	4.4 ± 2.7 *	12 ± 3

* p < 0.001, HD versus Control

SA-PO1009

Non-GFR Determinants of Endogenous Filtration Markers in Dialysis Patients

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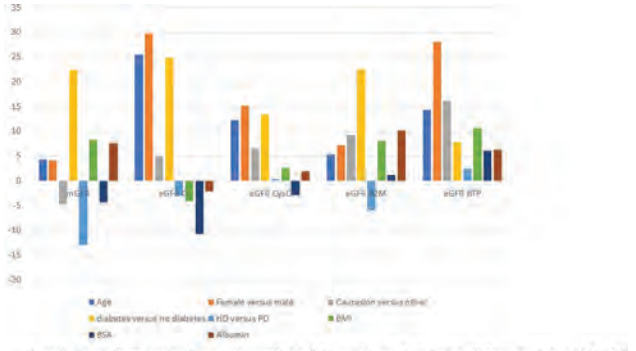
Background: When kidney function declines, measurement of residual kidney function (RKF) becomes challenging, while the importance of precise measurement rises. We sought to understand the non-GFR determinants of endogenous filtration markers (Beta-2-microglobulin (B2M), Beta-Trace Protein (BTP), and cystatin C) in dialysis patients.

Methods: We measured GFR (mGFR; average of urinary urea and creatinine clearance) and estimated GFR (eGFR) from endogenous markers in patients from the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD) cohort. We used stacked generalized estimating equation (GEE) models to estimated associations of several factors with eGFR, including mGFR.

Results: 1107 patients were eligible for inclusion, of whom 224 without RKF. Mean age was 61 (± 15) years, and mean mGFR was 4,4 (± 32,1) ml/min/1.73m2. In those with RKF. BTM, BTP and Cystatin C were all associated with age. Only BTP was associated with race. All associations became smaller after accounting for mGFR. Compared to creatinine, the effect of age was significantly smaller for B2M and the effect of sex was significantly smaller for B2M and Cystatin C After adjustment for age, sex and race associations dialysis modality was significantly less strong associated with BTP than with mGFR. Additional adjustment for mGFR resulted in a smaller associations for diabetes with cystatine C when compared to creatinine. However, diabetes was stronger associated with BTP than creatinine.

Conclusions: In dialysis patients, BTP, B2M, and cystatin C were mainly influenced by mGFR, but additionally by age sex and race. Furthermore, diabetes and dialysis modality also influenced these results. Use of these makers for GFR estimation should account for these influences.

Funding: Government Support - Non-U.S.



Associations of age, sex and race are unadjusted. Associations of diabetes, dialysis modality, BMI, BSA and albumin (g/dL) are adjusted for age, sex and race

SA-PO1010

Eliminating Routine Post-Dialysis Serum Urea Nitrogen Measurements in Hemodialysis: Testing a Proposed Method Using Conductivity Dialyzer Clearance to Determine Protein Catabolic Rate

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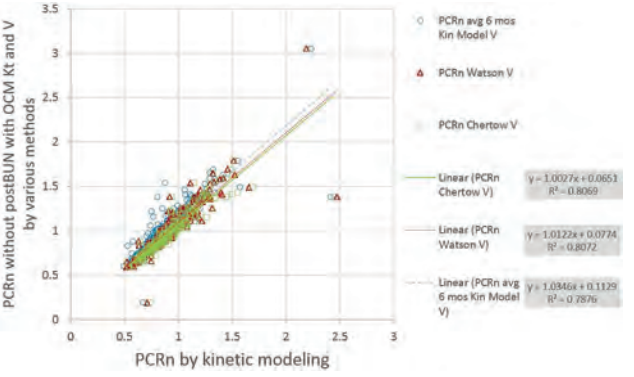
Background: Traditionally, pre and post-HD BUN measurements are used to determine Kt/V and normalized protein catabolic rate (PCRn). Timing and care of post-HD BUN sampling is critical for results to be accurate. A method of estimating PCRn without the post-HD BUN, utilizing conductivity clearance and only a pre-HD BUN, has recently been proposed. We tested this method in a cohort of patients in which online conductivity clearance monitoring (OCM) and clearance by usual formal kinetic modeling were measured.

Methods: We used a retrospective cohort of 39 patients totaling 271 HD treatments during which OCM and routine monthly laboratory tests with formal kinetic modeling for Kt/V and PCRn were performed. Data (including residual renal function) were entered into the Solute-Solver® version 2.11 online 2-pool kinetic modeling program. For volume of distribution of urea (V), we tested 3 values for each treatment: 1) average of 6 months prior kinetic model V; 2) Watson formula estimated V; and 3) Chertow formula estimated V. Output data of interest included the estimated post-HD BUN, spKt/V and PCRn based on these estimated values.

Results: The spKt/V by OCM underestimated that of formal kinetic modeling with a mean difference of 0.40, primarily driven by difference in V. The overall correlation of spKt/V was modest. Using pre-HD BUN with OCM to estimate PCRn as proposed by Daugirdas, we found a good correlation between PCRn by kinetic modeling and OCM method (Fig 1).

Conclusions: In this retrospective evaluation, the method using OCM without a post-HD BUN, as proposed by Daugirdas, appears to adequately estimate PCRn. The post-HD blood draw, subject to inaccuracies due to improper sampling technique, is potentially problematic in traditional determinations of HD adequacy and calculation of PCRn. OCM based calculations of Kt/V and PCRn remove this potential source of error. This process has practical applications and should be further validated.

Funding: Clinical Revenue Support



SA-PO1011

Relationship Between Phosphate Binder Type and Gut Microbiome-Derived Uremic Toxin Levels in Hemodialysis Patients

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Background: Phosphate binder choice may differentially affect gastrointestinal physiology (e.g. colonic transit time and gut microbiota composition). Interestingly, patients on sucroferric oxyhydroxide (SFO; Velphoro®) have lower rates of constipation than those taking sevelamer carbonate (SEV; Renvela®). We hypothesized that phosphate binder choice may affect serum levels of gut microbiome-derived uremic toxins (UTOX). We examined the relationship between the type of prescribed phosphate binder and gut microbiome-derived UTOX levels in hemodialysis (HD) patients treated with either SFO or SEV.

Methods: Weekly blood samples and bowel movement diaries were collected from 16 HD patients during six consecutive weeks per subject. Stool types were categorized according to the Bristol Stool Chart. Nine substances including eight UTOX (7 gut microbiome-derived; 1 mammalian-derived) and tryptophan (TRP) were quantified in serum using liquid chromatography–mass spectrometry. For each substance, we calculated the median concentration per subject, then the median across all subjects. We also report the differences in median serum concentrations between the treatment groups and their respective 95% confidence intervals.

Results: Subject characteristics are shown in Table 1. The SEV group reported a 3.3-fold higher frequency of stool types 1 and 2 (constipation), while stool types 5 to 7 (diarrhea and urgency), indicating reduced colonic transit time, were 1.5-fold more frequent in the SFO group. Most gut microbiome-derived UTOX, including three protein-bound UTOX, showed a trend towards lower serum levels in the SFO group, while one mammalian-derived UTOX and TRP were higher in the SFO group (Table 2).

Conclusions: Compared to SEV, SFO may lower the serum levels of gut microbiome-derived uremic toxins, putatively by decreasing colonic transit time.

Funding: Commercial Support - Fresenius Medical Care

Table 1. Hemodialysis patient characteristics. All patients on thrice-weekly dialysis regimen.

Characteristics	Total (n=16)	SEV (n=8)	SFO (n=8)
Female / Male	5 / 11	3 / 5	2 / 6
Age [years]	55.1 ± 13.7	58.3 ± 13.5	51.9 ± 14.0
BMI [kg/m²]	27.5 ± 5.9	27.1 ± 7.1	27.9 ± 4.9
Dialysis Vintage [years]	4.8 ± 3.8	5.1 ± 4.6	4.4 ± 3.2

Values are mean ± SD. BMI: Body Mass Index, SEV: sevelamer carbonate (Renvela®), SFO: sucroferric oxyhydroxide (Velphoro®)

Table 2. Serum UTOX and TRP levels.

	Gut Microbiome-derived							Mammalian-derived	Nutritional Marker
Substance	TMAO	IG	PAG	IS	CMPFA	PCS	HA*	KYNA	TRP
SFO	31.5	0.8	92.2	98.5	1.8	87.0	160.8	1.3	21.0
SEV	39.8	1.9	111.6	88.8	1.8	88.8	375.2	1.0	18.6
Δ Median (CI)	-8.3 (-23.1;8.9)	-1.1 (-2.4;1.4)	-19.4 (-86.1;43.2)	9.6 (-55.9;46.9)	0.0 (-1.0;0.7)	-1.8 (-51.7;49.2)	-14.4 (-84.8;96.5)	0.3 (-0.3;0.6)	2.6 (-2.3;9.0)

Values are median serum concentrations in µmol/L and analyzed by Wilcoxon rank sum test. CI: Confidence Interval, SEV: sevelamer carbonate (Renvela®), SFO: sucroferric oxyhydroxide (Velphoro®), TMAO: trimethylamine-N-oxide, IG: indoxylglucuronide, PAG: phenylacetylglutamine, IS: indoxylsulfate, CMPFA: 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid, PCS: p-cresylsulfate, HA: hippuric acid, KYNA: kynurenic acid, TRP: tryptophan. *HA is derived from both the gut microbiome and mammalian sources.

SA-PO1012

Comparison of Actual Dietary Intakes in Hemodialysis Patients: A Prospective Observational Study

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Background: Although appropriate dietary adjustments in hemodialysis (HD) patients are important, most HD patients have difficulty adhering to dietary therapy due to the stress of a restricted-food diet or loss of appetite, which eventually leads to malnutrition and other complications. The actual dietary intakes among HD patients stratified by nutritional status have not yet been studied.

Methods: In total, 111 HD patients from five dialysis centers were stratified into 2 groups based on subjective global assessment (SGA): the well-nourished group vs. the poorly-nourished group. The 7-day dietary intakes and food behaviors of the two groups were compared. Logistic regression analysis was performed to reveal the factors associated with the poorly-nourished status.

Results: The enrolled HD patients consumed an average of 23.44 kcal/kg/day and 0.92 g/kg/day of protein. However, they also consumed an average of 3285 mg/day of sodium, 1856.91 mg/day of potassium, and 760.61 mg/day of phosphorus. The poorly-nourished group ate out and ate fried food significantly more frequently than the well-nourished group. More frequent eating out, more frequent fried food consumption, and lower serum albumin level were significantly associated with the poorly-nourished status.

Conclusions: These findings demonstrate the differences in actual dietary intake patterns and food behaviors of well- and poorly-nourished HD patients. However, further research should be performed on HD patients to design customized nutritional education, consultations, and dietary management.

Table 1. 7-day dietary research between the two groups stratified by the nutritional status

	Total N=111(100%)	Nutritional status: Well-nourished group N=81(72.9%)	Nutritional status: Poorly-nourished group N=30(27.0%)	*P-value*
Total Energy, Kcal/kg/day	14.37±10.73	16.94±10.45	7.41±8.18	<0.001
Major nutrient components				
Carbohydrates, g/kg/day	2.21±1.60	2.61±1.56	1.14±1.13	<0.001
Lipids, g/kg/day	0.74±0.36	0.71±0.37	0.82±0.31	0.131
Proteins, g/kg/day	0.61±0.42	0.69±0.41	0.38±0.38	<0.001
Fluid and Mineral components				
Total fiber, g/kg/day	4.48±5.47	3.22±5.05	7.89±5.17	<0.001
Water, mL/kg/day	10.02±5.39	10.22±5.83	9.49±3.96	0.531
Calcium, mmol/kg/day	8.88±5.01	8.13±5.00	10.91±4.52	0.009
Phosphate, mmol/kg/day	31.11±26.84	25.61±24.37	45.96±27.98	<0.001
Sodium, mmol/kg/day	33.45±30.70	40.77±30.54	13.70±21.20	<0.001
Potassium, mmol/kg/day	17.66±16.91	21.65±16.56	6.89±12.78	<0.001
Magnesium, mmol/kg/day	0.61±0.50	0.71±0.50	0.35±0.37	<0.001
Iron, mmol/kg/day	0.16±0.06	0.17±0.06	0.13±0.05	0.019

Data are expressed as mean (with standard deviation)

Table 2. Comparison of the food behavior according to the nutritional status evaluated by SGA

Dietary habits or behaviors*	Nutritional status: Well-nourished group N=81(72.9%)	Nutritional status: Poorly-nourished group N=30(27.0%)	*P-value*
How many times in a week?			
No. of eating three meals/day	1.35±0.80	1.23±0.75	0.463
No. of eating various nutrients	1.21±0.66	0.96±0.62	0.078
No. of eating fruits/day	1.02±0.79	1.06±0.70	0.800
No. of drinking milk/day	0.37±0.56	0.41±0.64	0.751
No. of behavior to reduce potassium	1.04±0.83	1.15±0.81	0.571
No. of salted or processed foods	1.80±0.45	1.61±0.58	0.111
No. of eating more than two protein-rich meals/day	1.19±0.74	0.93±0.75	0.110
No. of eating sweet food	0.85±0.69	0.80±0.63	0.721
No. of fried food	0.51±0.71	0.85±0.70	0.029
No. of remembering how much of water per day	1.34±0.75	1.33±0.64	0.968
No. of eating out	0.66±0.75	1.05±0.83	0.023

*Several questions in Supplementary table 2 were surveyed two times at the initiation of the study and the end of the study. Moreover, we presented the average of the two points in the Table 3.

SA-PO1013

Dietary Advanced Glycation End Products Restriction Effects on Intestinal Bacterial Flora and Microinflammation State in Maintenance Hemodialysis Patients

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Background: It had been found that dietary AGEs was related to markers of inflammation and oxidative stress in a population of end stage renal disease (ESRD) patients undergoing dialysis. This study was to explore the effects of dietary advanced glycation end products(AGEs) restriction on microinflammation state and intestinal bacterial flora in maintenance hemodialysis(MHD) patients.

Methods: Patients were randomized to normal group(n=10) continuing the same diet, and intervention group taking a dietary AGE restriction for one month(n=10). Blood and stool samples were collected before and after intervention. Highsensitive C-reactive protein and interleukin-6 were detected. The alteration of gut microbiomes were analyzed by bacterial 16S rDNA amplification and DNA pyrosequencing to determine the presence of bacteria.

Results: Plasma High-sensitive C-reactive protein and interleukin-6 levels were significantly reduced in dietary AGEs restriction group($p<0.05$). The number of Bifidobacterium and Lactobaeillus decreased whereas the number of E. coli and Enterococcus faecalis increased $p<0.05$) in intervention group.

Conclusions: This study showed significant microbiota differences between two groups in MHD patients, might provide evidence for reducing uremic toxin from the view of gut microbiota, and play a role in improving life quality of patient. More research is needed.

SA-PO1014

Comparison of Three Nutritional Screening Tools for Predicting Mortality in Maintenance Hemodialysis Patients

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Background: There has been a great consensus that the key first step in the evaluation of nutritional status is to identify "at risk" status by using the validated nutritional screening tools. However, an effective and simple nutrition screening tool has not been identified in maintenance hemodialysis (MHD) patients. To the best of our knowledge, the comparison of mortality predictability between the objective score of nutrition on dialysis (OSND) and the malnutrition-inflammation score (MIS) or the geriatric nutritional risk index (GNRI) has not been conducted in previous studies.

Methods: A cohort of 1,025 MHD patients were enrolled from 8 hospitals. The MIS, OSND, and GNRI were measured at baseline. All-cause mortality and cardiovascular (CV) mortality were the major study outcomes. Harrell's C statistics were derived to examine the discrimination between three tools and mortality.

Results: The median follow-up duration was 28.1 months. The MIS (per standard deviation (SD) increase, HR =1.35, 95% CI: 1.18–1.55), the OSND (per SD decrease, HR =1.24, 95% CI: 1.09–1.42), and the GNRI (per SD decrease, HR =1.26, 95% CI: 1.10–1.43) were all significantly associated with the risk of all-cause mortality. More importantly, the mortality predictability of the MIS appears similar to the GNRI ($P=0.182$) and greater than the OSND (MIS *vs.* OSND: $P=0.001$; GNRI *vs.* OSND: $P=0.045$). Similar results were found for CV mortality.

Conclusions: Each of the three nutritional screening tools was significantly associated with an increased risk of all-causes and CV mortality. The mortality predictability of the MIS was similar to the GNRI and greater than the OSND.

Results of Harrell's C Statistic

Variables	Harrell's C Statistic (95%CI)	P-value	
All-cause mortality			
MIS	0.62 (0.58, 0.66)	Ref.	0.001
OSND	0.56 (0.52, 0.60)	0.001	Ref.
GNRI	0.6 (0.56, 0.64)	0.182	0.045
CV mortality			
MIS	0.62 (0.58, 0.67)	Ref.	0.001
OSND	0.55 (0.50, 0.60)	0.001	Ref.
GNRI	0.6 (0.55, 0.65)	0.226	0.035

SA-PO1015

The Efficacy of Probiotic, Prebiotic, and Synbiotic Supplementation in Modulating Gut-Derived Circulatory Particles Associated with Mortality in Dialysis Patients: Systematic Review and Meta-Analysis

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Background: There is accumulating evidence that modification of the microbiota through prebiotic, probiotic or synbiotic supplementation in individuals with end-stage renal disease receiving dialysis may be efficacious in reducing circulating levels of toxic metabolites. This systematic review and meta-analyses provides an up to date synthesis on the effects of supplementation on circulating levels of toxic metabolites, markers of uremia and inflammation, blood lipids and other clinical outcomes.

Methods: Seventeen databases were searched, supplemented with internet and hand searching. Randomised controlled trials of adult end stage renal-disease individuals receiving either haemodialysis or peritoneal dialysis were eligible. Trials were restricted to those which had administered a prebiotic, probiotic or synbiotic as an oral supplement. Primary outcomes were measures of circulating endotoxin, indoxyl-sulphate and p-cresyl sulphate.

Results: Twenty-one trials were eligible (1152 randomised participants) of which 19 trials were considered to have a high risk of bias. The number of trials available for meta-analysis varied for each primary outcome. Synthesised data indicated that supplementation significantly reduced circulating levels of endotoxin (standardised mean difference -0.61, 95% confidence interval -1.03 to -0.20, P=0.004, I2=0%), indoxyl-sulphate (-0.34, -0.64 to -0.04, P=0.02, I2=0%) and p-cresyl sulphate (-0.34, -0.61 to -0.07, P=0.01, I2=0%). For secondary outcomes supplementation significantly reduced gastrointestinal symptoms (-0.54, -1.02 to -0.07, P=0.02, I2=0%). There were no significant effects on any secondary outcome measure.

Conclusions: Supplementation reduces toxic metabolites associated with cardiovascular disease and mortality in individuals receiving dialysis. However, the majority of trials included were low in quality.

SA-PO1016

Association of Race/Ethnicity and Pre-ESKD Disease Duration with Subsequent Dialysis Mortality in US Veterans with ESKD

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Background: The mortality rate of patients undergoing dialysis is exceptionally high. The role of disease duration before end-stage kidney disease (ESKD) on subsequent dialysis mortality is not clear due to lack of data on the accurate time of CKD onset. Using a national incident CKD cohort we recently constructed, we examined the association between disease duration prior to ESKD and dialysis mortality by race/ethnicity.

Methods: We first identified all subjects with new onset CKD (stage 3-5) in the U.S. Veteran Affairs database since 4/1/2002. CKD onset was determined by two eGFRs (based on CKD-EPI equation) <60 mL/min/1.73 m^2 at >90 days apart. We then extracted the subset of patients who started dialysis with at least one year of follow-up until 5/1/2016. Disease duration was determined as time from the date of CKD onset to the date of first dialysis. Hazard ratios for death were examined for duration of <1 year, 1-3 years, and 3-5 years as compared to duration of ≥5 years for each race/ethnicity, adjusted for covariates including age at ESKD onset, gender, last eGFR prior to first dialysis, and major comorbid conditions such as diabetes, hypertension, and cardiovascular diseases.

Results: Of 28,129 incident dialysis patients included, 8,874 were Black, 1,892 Hispanic, and 17,363 White. The median duration from CKD onset to ESKD onset was 2.7 years for Blacks, 2.8 for Hispanics, and 3.3 for Whites. More than half of Blacks (55%) and Hispanics (53%) developed ESKD within 3 years of CKD onset, compared to 46% of Whites. After adjustments, shorter disease duration before ESKD was significantly associated with greater mortality on dialysis for Blacks, but not for Whites and Hispanics (Table). P value for testing the differential associations across three racial/ethnic groups was 0.003.

Conclusions: Our findings suggest the association of disease duration before ESKD and dialysis mortality differed by race/ethnicity, prompting the need to delineate the factors responsible for these differential associations.

Funding: NIDDK Support

Adjusted hazard ratios (HR) by race/ethnicity

	Black			Hispanic			White		
Pre-ESKD duration (years)	% patients	HR (95% CI)	P value	% patients	HR (95% CI)	P value	% patients	HR (95% CI)	P value
<1	19.6	1.32 (1.19-1.46)	<0.001	20.3	1.05 (0.86-1.27)	0.64	15.7	1.01 (0.95-1.07)	0.78
1-3	34.9	1.15 (1.04-1.25)	0.004	32.9	1.01 (0.85-1.19)	0.93	30.1	0.96 (0.92-1.01)	0.15
3-5	23.2	1.15 (1.04-1.26)	0.006	22.0	0.93 (0.77-1.11)	0.42	24.2	0.99 (0.94-1.04)	0.58
≥5	22.3	1		24.8	1		30.0		

SA-PO1017

Does Erythrocyte Stimulating Agent (ESA) Exposure Contribute to the Obesity Paradox?

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Background: Epidemiologic and retrospective data document a survival advantage for obese (BMI > 30 kg/m^2) patients treated by maintenance hemodialysis (HD). Prospective data suggest that higher ESA doses are associated with adverse clinical outcomes.

Methods: Our quality program reviews the proportion of patients with hemoglobin (hgb) between 10-11.5 g/dL and ESA dosing and costs. We sought to understand variations by comparing ESA requirements based on BMI.

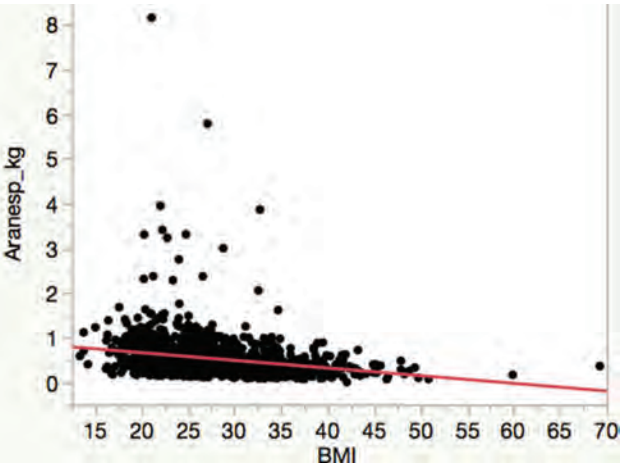
Results: The facility with the lowest average patient weight has the lowest average ESA cost (See table). ESA exposure decreased as BMI increased (p<0.0001). Hgb levels did not vary with BMI. (See figures.) There is a trend towards longer survival among obese patients.

Conclusions: ESA exposure varies with BMI in our patient population; hgb does not. ESA costs and doses vary with BMI. We hypothesize that lower ESA exposure contributes to improved survival among obese patients with CKD treated by HD.

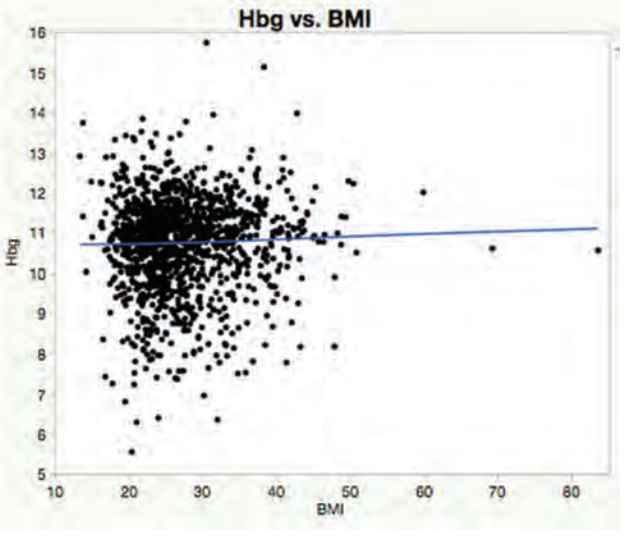
Funding: Clinical Revenue Support

Impact of Weight on ESA Cost per Treatment Q1 2019

Facility	ESA Cost/Treatment ($)	Average Patient Weight (kg)	ESA Cost/Treatment/kg ($/kg)
1	17.47	72.5	0.24
2	18.30	75.3	0.24
3	27.28	80.0	0.34
4	22.72	75.3	0.30
5	23.86	77.8	0.31
6	20.37	79.4	0.26
7	19.68	79.3	0.25
Average	21.38	77.1	0.28



ESA exposure by BMI



hgb by BMI

SA-PO1018

Efficacy and Safety of CKD-11101 (Darbepoetin-Alfa Proposed Biosimilar) Compared with Darbepoetin Alfa in Patient on Hemodialysis

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Background: Anemia is critical problem which is caused by deficiency of endogenous erythropoietin (EPO) synthesis in patient on dialysis. Darbepoetin-alfa is a useful EPO with long elimination half-life. Herein, we aim to evaluate the efficacy and safety of intravenous CKD-11101 (biosimilar darbepoetin-alfa) compared with darbepoetin-alfa in patients undergoing hemodialysis.

Methods: The study group composed with 24 different institutes was divided by randomized, double-blinded, and prospectively. Follow-up duration was 24 weeks which was consisted with 20 weeks of maintenance and 4 weeks of evaluation period. All patients underwent the stabilization period to achieve target baseline hemoglobin (Hb) as 10-12 g/dL before randomization. After randomization, patients received EPO by weekly or biweekly with adjusted dose following the permitted rule of darbepoetin alfa. First, we compared the efficacy of CKD-11101 to darbepoetin-alfa. Secondly, we investigated the safety of CKD-11101.

Results: A total of 403 patients were randomized to two different groups during June 2015 and June 2017. Among randomized populations, 78 (19.35%) were dropped-out with major infraction or side effect, 325 (80.65%) patients completed the investigation. The average administered dose of EPO was not different in both groups; 74.90 ± 56.85 mcg and 61.96 ± 43.51 mcg in CKD-11101 and darbepoetin-alfa, respectively. During the study period, the percentage of patients with targeted Hb was 19.44% (28/144), and 20.95% (31/148) with CKD-11101 and darbepoetin-alfa, respectively (p = 0.750). There was no difference in rate of patients need to be changed the dose; 95.83% (138/144) and 93.24% (138/148) with CKD-11101 and darbepoetin-alfa (p = 0.331). There was only one patient who needed to be transfused in each group.

Conclusions: The difference in change of the level of Hb, dose of EPO, and achievement rate to target Hb during study period was comparable between two groups. CKD-11101 has an equivalent therapeutic efficacy compared with the darbepoetin-alfa in patient undergoing hemodialysis.

Funding: Commercial Support - Chong Kun Dang Pharm.

SA-PO1019

Vitamin E Polysulfone Dialyzer Improves Erythropoietin Hyporesponsiveness in CKD Patients on Dialysis with Low-Grade Inflammation

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Background: This work aimed at evaluating vitamin E-coated polysulfone (PS) membrane (VItabranE®, VIE) effect on erythropoietin hyporesponsiveness through two prospective multicenter studies, one controlled randomized study (*Study-1*) and one observational study *(Study-2)* in chronic kidney disease patients on dialysis with low grade inflammation after a 12-month period.

Methods: *Study-1*. 60 dialysis patients with CRP level in the range [5-20] mg/L were randomly assigned in a 1:1 ratio to either PS control 'C' group (n=30) or 'VIE' group (n=30). *Study-2*. 148 eligible dialysis patients out of a total of 244 included, with mean baseline CRP level at 11±12 mg/L and with EPO overconsumption were dialysed with VIE. Administered EPO dose was recorded and blood samples withdrawn at inclusion and after 3, 6, 9 and 12 months of treatment in both studies.

Results: After a 12-month treatment, VIE use was associated to a reduction in EPO doses in both studies. In *Study-1*, we observed a ΔEPO dose at -2710.5±3983.7 IU (p=0.011) corresponding to a 24% reduction when comparing M12 and M0 in VIE group vs -1074.5±5151.4 IU (p=NS) in C group. No improvement in inflammatory markers (CRP, IL-6, TNF-alpha and fibrinogen) or impairement of nutritional parameters (albumin and transthyretin) were observed over the period. In *Study-2*, a 28% EPO reduction (p=0.001) was reported when comparing M12 and M0, associated to a 31% iron dose reduction (p=0.002) and stable hemoglobin and serum iron levels. Here again, no improvement in CRP level was obtained.

Conclusions: Both multicenter prospective studies confirm that vitamin E-coated PS membrane can improve EPO efficacy in dialysis patients with low grade inflammation. Such positive effect appears independent of inflammation and nutritional parameters but associated with an improvement of iron metabolism.

Funding: Commercial Support - Hemotech SAS

SA-PO1020

The Effect of Supplementation with Zinc Acetate Hydrate for Hypozincemia on Renal Anemia

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Background: Whether zinc supplementation with zinc acetate hydrate for hypozincemia improved renal anemia in hemodialysis patients was examined.

Methods: Study participants included 21 hemodialysis patients who presented with a serum zinc level of less than 60 mg/dL and who were administered zinc acetate hydrate at 50 mg (the dose was reduced to 25 mg, as appropriate) for 6 months. Patients having a hemorrhagic lesion, acute phase diseases (pneumonia or cardiac failure) or hematologic disease, and those whose treatment was switched from peritoneal dialysis to hemodialysis were excluded. The change in the erythropoietin resistance index (ERI) before and after the administration of zinc acetate hydrate, was examined; ERI was defined as the dose of erythropoiesis-stimulating agent (ESA; IU/week/body weight [kg]/hemoglobin content [g/dL]). The difference between the two groups was analyzed using a Wilcoxon signed rank sum test and a difference with $p < 0.05$ was considered statistically significant.

Results: The study patients consisted of 19 males and 2 females aged between 41 and 95 years (mean ± standard deviation [SD]; 67.1 ± 13.6). Changes in values of measured parameters, before and after the administration of zinc acetate hydrate, were as follows: blood hemoglobin content did not change significantly from 10.0 – 13.6 g/dL (11.5 ± 1.0 g/dL) to 10.2 – 12.4 g/dL (11.4 ± 0.7 g/dL); the serum zinc concentration significantly increased from 33 – 59 mg/dL (52.4 ± 7.6 mg/dL) to 57 – 124 mg/dL (84.1 ± 16.3 mg/dL; $p < 0.01$); the dose of ESA significantly decreased from 0 – 12,000 IU/week (5,630 ± 3,351 IU/week) to 0 – 9,000 IU/week (4,428 ± 2779; $p = 0.04$); and the ERI was significantly reduced from 0 – 18.2 (8.1 ± 5.1) to 0 –16.0 (6.3 ± 4.3; $p = 0.04$).

Conclusions: Zinc supplementation in patients with hypozincemia increased the serum zinc concentration and significantly reduced the ESA dose and ERI, suggesting that a correction of hypozincemia contributes to an improvement in patients' renal anemia.

SA-PO1021

Wearable Device for Continuous, Noninvasive Monitoring of Blood Hemoglobin Levels in Hemodialysis Patients

David J. Kuraguntla, Samit K. Gupta, Forrest Miller. *GraftWorx, South San Francisco, CA*.

Background: Maintenance of euvolemia is a major challenge for hemodialysis patients, who account for a combined 6.5M annual hospital days. Clinical outcomes could be improved, and healthcare costs lowered, by preventing fluid overload. This study presents a novel wearable device that enables remote monitoring of multiple key fluid status metrics in dialysis patients. This device, SmartPatch, incorporates multi-wavelength photoplethysmography (PPG) and acoustic, thermal and mechanical sensors to measure blood hemoglobin concentration (Hb), hematocrit (Hct), oxygen saturation and volumetric flow rate. The SmartPatch system also comprises an end-to-end data path that facilitates secure data transmission and analysis and generates actionable alerts. The aim of this study was to evaluate the system's ability to accurately and precisely measure Hb and Hct, critical markers for anemia that dictate dialysis treatment.

Methods: 29 hemodialysis patients with arteriovenous fistulas currently undergoing hemodialysis were recruited across three clinical sites. Each of these patients had a SmartPatch device placed on the skin over their fistula. A total of 257 sets of multi-channel PPG data were recorded and analyzed using the GraftWorx data hub and software backend. A subset of 76 reads was used to train an Hb quantitation algorithm, with reference values obtained from a HemoCue Hb 201+ device. This algorithm was then tested on the remaining 181 reads to determine the accuracy and precision of the SmartPatch when measuring Hb and Hct.

Results: The SmartPatch system measured Hb and Hct with respective root-mean-square error (RMSE) of 0.863 g/dL and 2.585 Hct compared to reference values obtained from the HemoCue device, whose accuracy has been reported to be between 0.3 and 1.6 g/dL (0.9 to 4.8 Hct). The standard deviations for each read on the same patient–with the same device–were computed and averaged, weighted by group size, as a measure of precision. These precision metrics were computed to be 0.283 g/dL and 0.85 Hct for Hgb and Hct, respectively.

Conclusions: The results of this study illustrate the ability of the wearable SmartPatch system to non-invasively measure blood Hb and Hct in hemodialysis patients with AV fistulas, to a degree of accuracy comparable to available methods. This study also demonstrated the efficacy of the end-to-end GraftWorx data path.

SA-PO1022

Clinical Significance of Red Cell Distribution Width (RDW) in ESRD Initiated with Hemodialysis (HD)

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Background: RDW is routinely measured in complete blood count indicating the variation of erythrocyte volume. RDW is affected by nutritional and inflammatory status. Recently worse survival of high RDW patients has been reported in coronary disease, chronic kidney disease, HD and peritoneal dialysis. To evaluate the clinical significance of RDW in ESRD, we studied 1) correlation of clinical data with RDW, 2) influence of HD and 3) prognostic value in survival.

Methods: Subjects were 873 patients in 17 centers participating in Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) from 2011 to 2013. Subjects were divided into two categories (RDW Low< 15.5, High ≥ 15.5%). RDW and clinical parameters obtained at the initiation of hemodialysis (RDW-1) including laboratory data and comorbidities were analyzed statistically. RDW after stable hemodialysis was established (RDW-2) was compared with RDW-1 and categorized in four groups High-High (H-H) 43.4%, High-Low (H-L) 6.5%, Low-High (L-H) 9.0%, Low-Low (L-L) 41.0%. Factors affecting these changes were studied. Correlation in each category with mortality was analyzed using Kaplan-Meier method. All-cause, CVD, infection and malignancy mortality were compared using multivariate Cox proportional hazard analysis.

Results: RDW-1 was correlated with high CRP (p=0.003) and low total cholesterol (p=0.027) but not with other parameters. 84% was remained in the same category after initiation of HD, and H-H group showed highest mortality, L-H next, and L-L was lower and interestingly H-L was lowest (Log rank test: P<0.001). Characteristics of this small group was that brain natriuretic peptide was higher than other group (p<0.033) while ejection fraction was similar suggesting the complication of uremic cardiopathy which was recovered by HD. During a median follow-up duration of 1,297 days, 228 subjects died. All-cause (HR 1.41: 95%CI 1.07-1.86), CVD (1.65: 1.07-2.61) and infection (2.72: 1.44-5.60) mortality were higher in High RDW. No correlation with malignancy was noted. (HR1.09: 95%CI 0.58-2.11).

Conclusions: In ESRD patients, RDW is influenced by inflammation and nutrition. In HD patients, low RDW at baseline and lowered RDW after HD suggests better prognosis. In HD patients with high RDW, infection and CVD are statistically higher as a cause of death.

SA-PO1023

Coagulation and Circulating Heparin Profile in Patients with ESRD Undergoing Maintenance Hemodialysis

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Background: Unfractionated heparin is widely used as an anticoagulant for maintenance hemodialysis in end-stage renal disease (ESRD) patients. Since these patients are administered with heparin repeatedly throughout treatment, it is hypothesized that detectable circulating levels of heparin may be present in their blood 48 hours post-dialysis session. The profiling of these parameters may provide the hemostatic status of patients in reference to circulating residual heparin in the pre-dialysis blood samples.

Methods: This study included 95 patients with ESRD undergoing maintenance hemodialysis, which was administered 3 times per week in 48-hour intervals. Plasma samples were analyzed utilizing clot-based methods including activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT). Employing a chromogenic assay, the circulating levels of heparin in each patient were measured. All of these samples were also analyzed for thrombin generation capacity using calibrated automated thrombogram (CAT, Diagnostica Stago. Paris, France).

Results: In the clotting assays, prothrombin time was elevated (16.4±20.3 sec.) in comparison to the normal control (11.1±2.1 sec.;p<0.05). Activated partial thromboplastin time was also prolonged (43.09±43.1 sec.) when compared to normal human plasma (32.3±4.2sec.;p<0.05). The thrombin time values were markedly higher (44.6±83.1 sec.) in comparison to normal (11.2 ±2 sec.;p<0.001). Circulating heparin levels, measured by anti-Xa methods, were found to be 0.11± 0.21 U/ml and anti-IIa levels being 0.25±0.27 U/ml;(p<0.05). In the thrombin generation assay, the ESRD samples showed wide variation and a lowered thrombin generation value (107±55.2 nM) in comparison to normal control (185±16.5 nM;p<0.05).

Conclusions: These results suggest patients undergoing maintenance hemodialysis exhibit a mild hypo-coagulable state as determined by PT and aPTT methods. The circulating levels of heparin were lower in anti-Xa compared to anti-IIa, suggesting the presence of higher molecular weight components of circulating heparin. These studies suggest that ESRD patients on maintenance hemodialysis exhibit a hypocoagulable state in which circulating residual heparin may contribute to the overall hemostatic deficit.

SA-PO1024

Measurement and Characterization of Circulating Heparin in Heparin-Naive ESRD Patients on Maintenance Hemodialysis

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Background: In a cohort of 95 ESRD patients undergoing maintenance hemodialysis, 30 patients did not receive any exogenous heparin during their routine dialysis sessions. However, these patients showed an increase in their PTT, anti-Xa, and anti-IIa assays which were neutralized upon heparinase treatment indicating the presence of endogenous heparin. The objective of this study is to quantify and characterize the heparin in this cohort of the ESRD patients.

Methods: Thirty heparin-naïve patients were identified through a chart review. Pre-dialysis blood samples collected from these patients were centrifuged to obtain plasma which was frozen at -70°C. These samples were thawed in batches and each sample was divided into two equal volumes; one sample was supplemented with saline while the other was mixed with a heparin digesting enzyme (Heparinase-1). These samples were analyzed for aPTT using a clot-based assay, amidolytic anti-Xa, and anti-IIa assays using specific chromogenic substrates. The test results were compiled as group mean +/- 1SD.

Results: The results collected from these patients showed an average PTT in the pre-Heparinase sample of 36.5 +/- 24.8, which decreased to 30.9 +/- 5.5 in the post-Heparinase samples (P=0.224). Anti-Xa and Anti-IIa are markers used in the study to demonstrate Heparin activities – a decrease upon Heparinase treatment in these activities confirms the presence of circulating Heparin. The average Anti-Xa in pre and post-Heparinase were 0.08 +/- 0.15 and 0.02 +/- 0.07 (P<0.05), whereas the average Anti-IIa in pre and post-Heparinase were 0.24 +/- 0.30 and 0.13 +/- 0.12, (P<0.05). These results indicate there was heparin activity present in the pre-Heparinase samples, but that activity was reduced in the post-Heparinase samples.

Conclusions: These findings demonstrate that there is endogenous heparin present in these heparin naïve patients. It has been hypothesized that endogenous heparin in these patients may have originated from endothelial sites. The shedding of heparin from endothelium may reflect endothelial dysfunction which has been reported in ESRD patients and may be correlated the severity of the pathogenesis of ESRD.

SA-PO1025

Persistence of Circulating Residual Heparin in ESRD Patients Undergoing Maintenance Hemodialysis

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Background: ESRD patients who receive routine maintenance hemodialysis are administered with unfractionated heparin to prevent thrombotic complications. The hemostatic dysregulation along with detectable levels of circulating heparin may cause them to be in a hypocoagulable state. The purpose of this study is to determine the circulating levels of heparin in ESRD patients and its characterization using heparinase digestion methods.

Methods: Blood plasma samples collected at routine pre-dialysis sessions from 95 ESRD patients undergoing maintenance hemodialysis were analyzed for the presence of residual heparin utilizing standard laboratory methods such as aPTT, Anti-Xa and Anti-IIa activities On a centrifugal analyzer (ACL-Elite: Instrumentation Laboratory, Bedford, MA). The levels of heparin were calculated in terms of units per ml relative to the USP reference standard. Heparinase digestion was used to confirm the presence of heparin.

Results: Wide intra individual variations were noted in the different tests carried out on these samples. The pre-heparinase aPTT was 43.1 ± 49.8 seconds whereas the post-heparinase clotting time was 31.1 ± 10.2 seconds (P<0.0002). The mean anti-Xa activity pre-heparinase was 0.11 ± 0.21 U/ml whereas the post-heparinase anti-Xa activity was 0.04 ± 0.14 U/ml (P<0.0001). The mean anti-IIa activity for the pre-heparinase samples was 0.25 ± 0.27 U/ml whereas the post-heparinase samples had a mean of 0.14 ± .15 U/ml (P<0.0007).

Conclusions: The presence of residual heparin was demonstrated by both clot- based and amidolytic assays in the plasma samples collected from ESRD patients prior to their next-dialysis session. Since these samples were obtained 3 days following the last dialysis session the presence of significant levels of heparin was surprising. Upon heparinase treatment of these samples, the aPTT and the anti-Xa and IIa tests were restored to near normal levels. Our studies confirm the presence of residual heparin in pre-dialysis plasma samples obtained from ESRD patients. The Anti-IIa activity was greater pre-heparinase and it was not decreased to the same extent as Anti-Xa after heparinase digestion. These results suggest that heparin found in ESRD patients plasma is of high molecular weight origin with delayed clearance.

SA-PO1026

Heparin-Free Dialysis: A Phase 2 Pilot Study Using Asymmetric Cellulose Triacetate (ATA) Dialyzers

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Background: Not all dialysis patients tolerate heparin anticoagulation. Heparin should be avoided in patients at high risk of bleeding. Strategies include saline infusion, citrate-containing dialysate, regional citrate anticoagulation and heparin-coated membranes. We recently studied the combination of a heparin-coated membrane and citrate-containing dialysate, with a success rate of 94%. Although this combination resulted in low rates of clotting, heparin-coated membranes are not ubiquitously available. The quest for easy to perform, safe and affordable heparin-free dialysis is on. Asymmetric cellulose triacetate (ATA) dialyzers have a low degree of platelet contact activation and might be an alternative to heparin-coated dialyzers.

Methods: We performed a phase II pilot study in maintenance dialysis patients. The 'Strategies for Asymmetrical Triacetate dialyzer heparin-Free Effective hemodialysis (SAFE study)' was a two-arm open-label cross-over study. In Arm 1, patients were dialyzed using a 1.9 m2 ATA membrane (Solacea™-19H, Nipro Corp., Japan) in combination with citrate (1 mM) containing dialysate. In Arm 2, patients were dialyzed with the same 1.9 m2 ATA membrane, in combination with high volume predilution hemodiafiltration. The primary endpoint was the success rate to complete 4 hours of hemodialysis without preterm clotting.

Results: We scheduled 240 dialysis sessions (120 per arm) in twenty patients. Ten patients were randomized to start in Arm 1, the others to Arm 2. All patients crossed to the other arm halfway the study. 232 (96.7%) study treatments were delivered. Overall, 23 clotting events occurred, 7 in Arm 1 and 16 in Arm 2. Success rate in Arm 1 (ATA + citrate containing dialysate) was 90.8 / 94.0 % (intention to treat/ as treated). Success rate in Arm 2 (ATA + predilution HDF) was 83.3 / 86.2 % (intention to treat/ as treated). Therapy survival was borderline significantly better in Arm 1(Mantel-Cox log rank $P = 0.05$).

Conclusions: Asymmetric cellulose triacetate (ATA) dialyzers have a low clotting propensity. In combination with citrate-containing dialysate, asymmetric cellulose triacetate (ATA) may be a suitable alternative to heparin-coated membranes for systemic heparin-free hemodialysis.

Funding: Commercial Support - Nipro restricted grant

SA-PO1027

Hemodialysis with a Citrate Containing Ca- and Mg-Free Dialysis Fluid: Exit Heparin?

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Background: Hemodialysis (HD) with heparin increases mortality of bleeding. Regional anticoagulation with citrate (C) HD (infusion of C before dialyzer, Ca-, Mg-free dialysis fluid and Ca/Mg substitution after dialyzer) may decrease this risk, but is laborious. This study describes the effect of adding C to the Ca-, Mg-free dialysis fluid.

Methods: In 12 HD patients on anticoagulants (6 vit. K antagonist; 6 acetylsalicylic acid), 2 HD sessions with dalteparin (D) and 2 with C were performed. During D dialysis fluid contained Ca 1.5 and Mg 0.5 mmol/l. During C, a Ca-, Mg-free, 0.8 mmol/l C containing dialysis fluid was used. Ca 540/ Mg 240 mmol/l substitution was 35 ml/h. Before, during and after HD, urea, ionized Ca (iCa), Mg were tested and clotting tests (APTT, NATEM full blood CT (ROTEM Delta, Tem-innovations Munich) were done. Clotting phenomena in venous airtrap and dialyzer were graded by visual inspection (grade 0-2 respectively 0-3). Data were analyzed using linear mixed models to account for repeated measurements.

Results: No HD was stopped prematurely. During C, clotting tests remained unaltered (APTT 31 vs 32 vs 32 sec; NATEM CT: 1079 vs 1052 vs 1048 sec). At D, clotting tests became significantly abnormal (APTT: 32 vs 42 vs 35 sec; NATEM CT: 1132 vs 2892 vs 1913 sec; p<0.001). Small clots in the venous airtrap were seen in 3/46 sessions (2C and 1D). There were significant more clotting phenomena in the dialyzer after C vs D (mean (95% CI) score 1.8 (1.6-2.1) vs 1.0 (0.7-1.2), p<0.001). spKt/V was slightly but significantly lower after C than after D (mean (95% CI) score 1.53 (1.37-1.69) vs 1.61 (1.45-1.76), p=0.045). iCa was stable during C but increased during D (C: 1.18 vs 1.15 vs 1.19; D: 1.16 vs 1.24 vs 1.25 mmol/l). In C, iCa after the dialyzer showed adequate anticoagulation (iCa 0.18 mmol/l). Mg increased slightly in C and decreased in D with a significant difference (p<0.001) during and after HD (C: 1.04 vs 1.06 vs 1.09; D: 1.00 vs 0.86 vs 0.84 mmol/l).

Conclusions: HD with a 0.8 mmol/l citrate, calcium- and magnesium-free dialysis fluid was slightly but clinically irrelevant inferior to HD with dalteparin without changing clotting tests in patients. Thus, citrate HD probably may prevent the increased risk of bleeding in patients already on maintenance anticoagulants.

Funding: Commercial Support - Werfen Benelux, Breda, The Netherlands

SA-PO1028

Effect of Taurolidine Citrate and Unfractionated Heparin Combination on Inflammatory Response and Dialysis Adequacy in Hemodialysis Patients

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Background: In hemodialysis (HD) patients, Catheter-related infections and dysfunction are a major health problem. In Egypt, recent data show that 6.6% of HD patients use catheters, of which short term catheters represent 59.6% and 40.4% with long-term catheters. In this study, we **aim** to assess the effect of using Taurolidine citrate and unfractionated heparin combination, as a lock solution for temporary dialysis catheters, on inflammatory markers, incidence of catheter related infections (CRIs) and dialysis adequacy in HD patients.

Methods: A randomized controlled clinical trial included 60 stable HD patients from Ain-Shams University hospitals at the time of catheter insertion. Patients were randomized into 2 groups: **Group 1**: 30 Patients received *taurolidine citrate (4%) and 500 i.u of heparin* as a catheter lock after HD session. **Group 2**: 30 Patients received *unfractionated heparin (heparin sodium 5000i.u/ml)* as a catheter lock after HD session. Both groups were followed up for 1 month period and monitored for signs of CRbsI. Also, Urea reduction ratio (URR) were measured weekly. Highly sensitive CRP & Interleukin 6 (IL-6) were measured at baseline and 1 month after using the lock solutions. Blood cultures were withdrawn in patients who developed signs of CRIs.

Results: Group 1 (mean age 39.5 ± 14, 46.7% males), **Group 2** (mean age 39.3 ± 14, 60% males). As regard *inflammatory markers*, a significant difference was noted between the 2 groups one month after catheter insertion (***P***: 0.001 and 0.018 for hsCRP and IL6 respectively), with the higher levels of inflammatory markers showed in group 2. *Catheter performance* determined by URR and blood flow rate between the 2 groups by the 4th weeks was significantly different in favor of group**1**, suggesting better performance of the catheter (***P*** :0.007 and 0.001 respectively). *CRIs* were demonstrated in **9** patients group **2** (30%) in contrast to **1** patient only in group **1**(3.3%) (***P*** 0.006).

Conclusions: We may conclude that using Taurolidine citrate and unfractionated heparin combination as a lock solution for temporary dialysis catheters was associated with lower levels of inflammatory markers and lower incidence of CRIs when compared to the standard unfractionated heparin lock. Its use also was associated with better catheter performance.

SA-PO1029

Anticoagulation for People Receiving Long-Term Hemodialysis: A Cochrane Review and Meta-Analysis

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Background: Hemodialysis requires safe and effective anticoagulation to prevent clot formation during the procedure. Low molecular weight heparins (LMWH) may provide more predictable anticoagulant effects and be simpler to administer than unfractionated heparin (UFH) but may increase risks of bleeding. This Cochrane review evaluates the benefits and harms of anticoagulation strategies for long-term hemodialysis.

Methods: We searched the Cochrane Kidney and Transplant Register of Studies for randomized controlled trials evaluating anticoagulant agents administered for hemodialysis treatment in adults with end-stage kidney disease (ESKD). Two authors independently screened citations for eligibility, extracted data, and assessed risk of bias using the Cochrane tool. Evidence certainty was evaluated using GRADE.

Results: Eighty-seven studies (3548 participants) were eligible. Median trial duration was 0.75 months (range 1 week to 24 months). Median trial age was 58.2 years (range 10.93 to 74 years). Methodological risks of bias were high or incomplete for most studies. Forty-three studies (2066 participants) compared LMWH with UFH. The certainty of the evidence was very low or low for all outcomes. Two of 43 studies reported the outcome for extracorporeal dialysis circuit thrombosis, with one study reporting one or more events. LMWH had very uncertain effects on dialysis circuit thrombosis compared to UFH (very low certainty evidence). Four studies reported zero major bleeding events (very low certainty evidence). No study reported time to achieve dialysis vascular access hemostasis. LMWH had uncertain effects on all-cause mortality (relative risk [RR] 2.41, 95% CI 0.62, 9.33; low certainty evidence). A single study reported the effect of LMWH on dialysis adequacy, measured as KT/V, such that meta-analysis could not be performed. Treatment effects of other anticoagulants were very uncertain.

Conclusions: Evidence for different forms of anticoagulation for hemodialysis is of very low certainty due to methodological limitations in existing trials and paucity of trial data. This review suggests the need for a head-to-head trial of LMWH versus UFH that is sufficiently powered to assess critical clinical outcomes such as bleeding, dialysis adequacy, mortality or cardiovascular events, or complications related to dialysis vascular access.

SA-PO1030

Real-World Effectiveness of Sucroferric Oxyhydroxide in European Hemodialysis (HD) Patients: A 1-Year Retrospective Study

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Background: Retrospective analysis evaluated the effectiveness of the phosphate binder (PB), sucroferric oxyhydroxide (SO), for serum phosphorus (sP) control among European HD pts in routine practice.

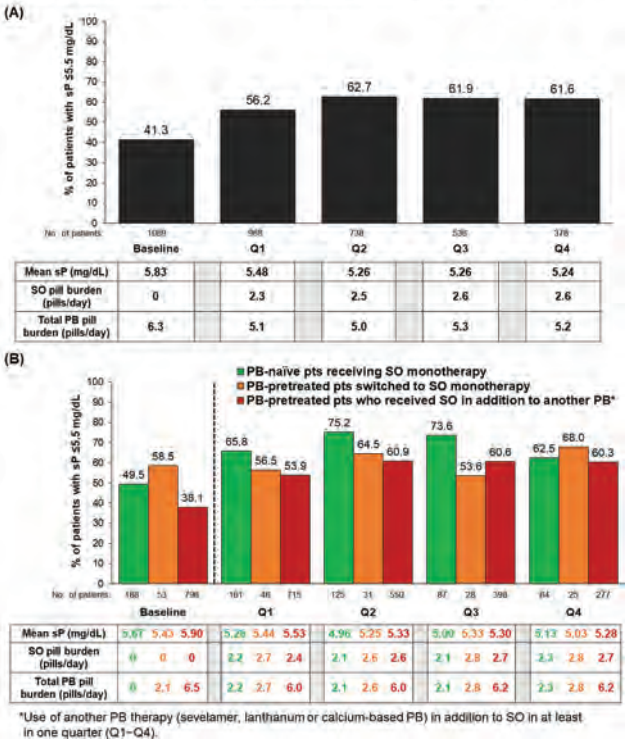
Methods: De-identified data were extracted from a clinical database (EuCliD5) for adult HD pts (France, Italy, Spain, Portugal, Russia) newly prescribed SO between Jan 2015–Jan 2019 for up to 1 year. PB pill burden and sP were compared between baseline (BL; 3-month period prior to SO prescription) and 4 consecutive quarters of SO therapy (Q1–Q4) for the overall cohort and 3 subgroups: PB-naïve pts treated with SO monotherapy (mSO), and PB pre-treated pts either switched to SO monotherapy (PB→mSO), or who added SO to another PB (PB+SO).

Results: The overall cohort comprised 1096 pts (mean age: 60.6 years; 65.8% male) including 796, 188 and 53 pts in the PB+SO, mSO, and PB→mSO groups. Comparing BL and Q1–Q4 for the overall cohort, SO provided consistent reductions in mean sP, and increased the % pts achieving sP target (≤5.5 mg/dL) (**Fig.A**). Of the 3 subgroups analyzed, mean BL sP levels were highest among PB+SO pts (5.9 mg/dL) and lowest among PB→mSO pts (5.43 mg/dL) (**Fig.B**). % of pts achieving sP target increased in all 3 subgroups during Q1–Q4, but to the greatest extent in the mSO and PB+SO groups. For PB+SO pts, sP improvements were achieved with a similar number of PB pills prescribed at BL prior to SO (6.5 vs. 6.2 pills/day at Q4). SO pill burden was low across all 3 subgroups (2.1–2.8 pills/day).

Conclusions: This real-world analysis suggests SO can improve sP control among HD pts either administered as monotherapy or add-on therapy to another PB, without increasing pill burden.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma

Figure: sP control and PB pill burden during baseline and SO follow-up (Q1–Q4)



	Baseline	Q1	Q2	Q3	Q4
Mean sP (mg/dL)	5.83	5.48	5.26	5.26	5.24
SO pill burden (pills/day)	0	2.3	2.5	2.6	2.6
Total PB pill burden (pills/day)	6.3	5.1	5.0	5.3	5.2

	Baseline			Q1			Q2			Q3			Q4		
Mean sP (mg/dL)	5.67	5.43	5.90	5.28	5.44	5.53	4.96	5.25	5.33	5.00	5.33	5.30	5.13	5.03	5.28
SO pill burden (pills/day)	0	0	0	2.2	2.7	2.4	2.1	2.6	2.6	2.1	2.8	2.7	2.3	2.8	2.7
Total PB pill burden (pills/day)	0	2.1	6.5	2.2	2.7	6.0	2.1	2.6	6.0	2.1	2.8	6.2	2.3	2.8	6.2

*Use of another PB therapy (sevelamer, lanthanum or calcium-based PB) in addition to SO in at least in one quarter (Q1–Q4).

SA-PO1031

Impact of Hyperphosphatemia Severity on Serum Phosphorus Reduction with Sucroferric Oxyhydroxide: A Subgroup Analysis of the VERIFIE Study

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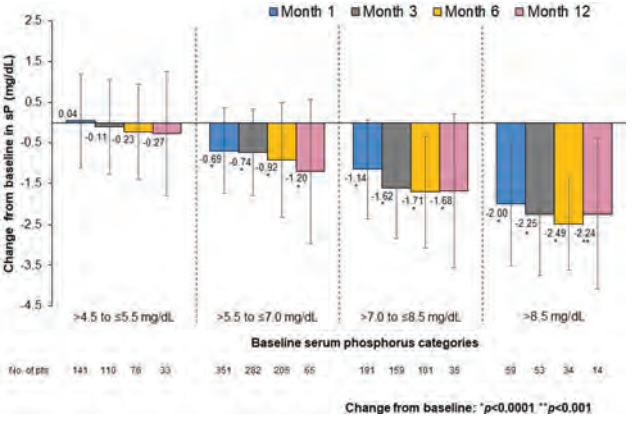
Background: Sucroferric oxyhydroxide (SFOH) is an iron-based phosphate binder indicated for the treatment of hyperphosphatemia in dialysis patients.

Methods: VERIFIE is a non-interventional, prospective, multicenter, European cohort study evaluating the real-world safety and effectiveness of SFOH in dialysis patients with hyperphosphatemia. This interim analysis, performed 24 months after study initiation, evaluated serum phosphorus (sP) changes during SFOH treatment in 4 subgroups of patients stratified according to their sP levels at baseline (>4.5 to ≤5.5 mg/dL; >5.5 to ≤7.0 mg/dL; >7.0 to ≤8.5 mg/dL; >8.0 mg/dL).

Results: In total, 874 patients who received ≥1 dose of SFOH and had effectiveness follow-up data available, were included in the subgroup analysis, which evaluated sP changes during the first 12 months of treatment. Approximately 40% of patients received concomitant phosphate binders (in addition to SFOH) during the study. Statistically significant ($p<0.001$) reductions in sP from baseline through Month 12 were observed among patients with baseline sP >5.5 to ≤7.0 mg/dL, >7.0 to ≤8.5 mg/dL or >8.5 mg/dL. Smaller reductions in sP were observed in the >4.5 to ≤5.5 mg/dL subgroup (**Figure**). Overall, reductions from baseline in mean sP were greater among patients with higher baseline sP levels.

Conclusions: This subgroup analysis demonstrated that treatment with SFOH can lower sP in real-world dialysis patients with hyperphosphatemia, regardless of their baseline sP levels, and these reductions were sustained over 12 months.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma



SA-PO1032

Association of White Blood Cell Count and Cause-Specific Mortality in Incident Hemodialysis Patients

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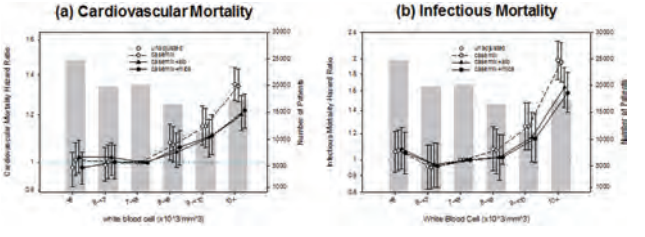
Background: Previous studies have shown higher white blood cell (WBC) counts to be strongly and independently associated with all-cause mortality in incident maintenance hemodialysis (HD) patients. However, the association between WBC count and cause-specific mortality in incident HD patients is unknown.

Methods: In a retrospective observational cohort study of 109,767 HD patients from a large US dialysis organization (2007-2011), we examined cardiovascular (CV) and infectious mortality associations with baseline WBC. Using Cox models, we examined the associations with three hierarchical adjustments for case-mix variables, albumin, and additional laboratory markers of malnutrition and inflammation (MICS).

Results: Mean patient age of the cohort was 63 ± 15 years; 44% of patients were female, 32% were African American, and 58% were diabetic. Patients with higher WBC levels (≥8.0 $x10^3/mm^3$) had a higher CV and infectious mortality risk compared to the reference group (7-<8.0 $x10^3/mm^3$) in baseline models, and across all levels of adjustment. In the fully adjusted models, compared to the reference, patients with WBC ≥10.0 $x10^3/mm^3$ had a 22% higher risk of CV mortality (hazard ratio [HR]: 1.22, 95% CI: 1.14, 1.30) and a 58% higher risk of infectious mortality (HR: 1.58, 95%CI: 1.38, 1.82) [Figure].

Conclusions: Among incident HD patients, higher WBC count is associated with higher CV and infectious mortality risk, independent of other markers of malnutrition and inflammation, including albumin. These data suggest that higher WBC may be indicative of stronger risk of infectious mortality outcomes but further studies are needed to ascertain its use as a predictive marker in HD patients.

Funding: NIDDK Support



SA-PO1033

Hypersegmented Neutrophils in Hemodialysis Patients and Cobalamin (B12) Requirements

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Background: Estimation of Nuclear Hypersegmentation of Neutrophils (HN) has been widely used as an indicator of Vitamin B12 (B12) or Folate (FO) deficiency. We chose to monitor the above as an indicator of functional deficiency of B12, since B12 supplementation, either for reducing the level of homocysteine (HC) or as factor decreasing erythropoietin (EPO) resistance in hemodialysis (HD) patients (pts), still remains a controversial issue.

Methods: Serum B12 levels were calculated from 57 HD pts prior to HD, after having received weekly intramuscular B12 injections (1000 μg Cyanocobalamine) for the past

6 months. All pts had smears of their peripheral blood examined to assess percentage of cells with HN, finding consistent with B12 deficiency. Hgb, MCV, FO, HC, PTH levels, Kt/V and EPO requirements were also recorded. Testing was repeated 6 months after discontinuation of B12 supplementation and 6 months after re-challenging with B12. FO supplements were administered throughout the study. Ferritin levels were kept > 200 ng/mL.

Results: Nuclear Hypersegmentation of Neutrophils was found in 55% of our patients to exceed the accepted level of 5% and reached 100% after stopping B12 supplementation along with a significant increase in EPO requirements, though B12 levels were well above the upper normal limit. EPO needs returned to previous levels after re-challenge with B12. HC and FO levels were unaffected. No difference in other parameters were observed.

Conclusions: In this study maintaining FO levels stable, we have demonstrated that despite high B12 blood levels, there is a functional deficiency which is reversed by B12 supplementation. HN seems to be a sensitive indicator of this process. The elevated percentage of HN in these pts (55%) has not been elucidated in the literature. When B12 was discontinued, 100% of the neutrophils nuclei were rendered hypersegmented but responded to B12, 6 months later, lowering overall EPO requirements. In spite of this beneficial effect, the optimal frequency and supplemental dose remain to be clarified.

Results

	HN %	B12 pg/mL	FO ng/mL	HC µm/L	EPO U/Hgb/L
T0	55*	4275.6*	19.87	20.1	403.05*
T6	100*	821*	19.05	20.08	531.13*
T12	63*	3407.5*	20.03	18.92	407.95
p	< 0.05	< 0.05	ns	ns	< 0.05

SA-PO1034

Effect of Interleukin-6 on All-Cause Mortality in Renal Dialysis Patients: A Systematic Review

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Background: In patients post myocardial infarction, there is strong evidence from a large randomized controlled trial of an anti-inflammatory that the association between chronic inflammation and mortality is causal. We aimed to assess how consistent with a causal interpretation is the evidence linking chronic inflammation and mortality in end stage kidney disease. We undertook a systematic review of the association between Interleukin-6 levels and mortality in patients undergoing dialysis.

Methods: MEDLINE, Embase, PsychInfo and Cochrane databases were searched for prospective cohort studies and randomised controlled trials published up until December 2018. Two independent reviewers selected papers reporting relationships between all-cause mortality and systemic inflammation as defined by IL-6, in adult dialysis patients. Demographics, all-cause mortality, and cardiovascular mortality data were extracted and reviewed in a descriptive fashion.

Results: Of the 1,324 papers initially identified, 28 were selected for the review with a total of 7,490 participants (range 50 to 959). Despite significant heterogeneity in analytical approach, higher levels of IL-6 were associated with worse all-cause mortality in 26 of the papers. In 18 of the 26 studies results were from multivariable survival analyses adjusting for age (65%), gender (58%), diabetes (46%), dialysis duration (35%), albumin (46%), smoking (27%), and CRP (27%). All 6 of the 25 studies assessing cardiovascular mortality, all of which reported multivariable analysis, found that IL-6 levels were predictive. The remaining two studies reported all-cause mortality in relation to variants in the -174G/C IL-6 polymorphism. Both studies found that the CC variant was associated with increased mortality compared to the GG variant (hazard ratio 1.71 [95%CI 0.98-1.78] and 3.58 [1.41-9.07, p<0.01]), although the relationship between the polymorphism and levels of IL-6 is less clear.

Conclusions: Systemic inflammation, assessed by plasma IL-6 concentration, is consistently associated with increased all-cause and cardiovascular mortality in adult dialysis patients. This is consistent with, but not proof of, a causal association.

SA-PO1035

An Exploratory Clinical Trial on the Efficacy and Safety of the GLP-1 Receptor Agonist Dulaglutide in Patients with Type 2 Diabetes Mellitus on Maintenance Hemodialysis

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Background: Dulaglutide is a once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes mellitus (T2DM). However, the efficacy and safety of dulaglutide remain unclear in insulin-treated patients with T2DM on maintenance hemodialysis (HD).

Methods: Fourteen insulin-treated T2DM patients on maintenance HD were enrolled. Dulaglutide treatment was initiated and the insulin dose was adjusted as needed. Primary outcomes were changes in the mean and standard deviation (SD) of blood glucose (BG) levels evaluated by continuous glucose monitoring (CGM) for 6 days, and glycoalbumin (GA), HbA1c, and mean daily total insulin dose from baseline over 24 weeks. Secondary outcomes were changes in treatment satisfaction levels from baseline, measured using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Diabetes Therapy-Related Quality of Life questionnaire (DTR-QOL) scores. Changes in body composition, including body mass index (BMI), fat mass (FM), skeletal muscle mass (SMM), and rate of interdialytic weight gain (IDWG), were also assessed.

Results: Two patients discontinued the study because of severe nausea or protocol deviation. In the full analysis set, the mean GA change was -3.1% (p = 0.008). Although the mean and SD values of BG and HbA1c levels did not change significantly, mean daily total insulin dose decreased significantly by -16.3 U/day (p = 0.001). Moreover, no significant changes were observed in area over the glucose curve <70 mg/dL per 24 h (AOC<70) in CGM. Six cases of gastrointestinal disorders were reported; however, both the DTSQ treatment satisfaction score (p = 0.029) and DTR-QOL total score (p = 0.014) improved significantly. BMI and FM changes were -0.6 kg/m^2 (p = 0.001) and -2.6 kg (p = 0.029), respectively. SMM and IDWG did not significantly change.

Conclusions: Dulaglutide may help improve glycemic control, body composition, and QOL without increasing hypoglycemia in insulin-treated patients with T2DM on maintenance HD.

SA-PO1036

Impact of Diabetic Nephropathy on Morbidity and Mortality in a Large Cohort of Hemodialysis Patients in Saudi Arabia

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Background: The aim of this study was to evaluate the impact of diabetes as a cause of ESRD on morbidity and mortality in a large cohort of Saudi hemodialysis patients.

Methods: All patients referred to Davita-Saudi Arabia clinics to continue ESRD treatment with hemodialysis from October 2014 to December 2018 were included in this analysis. The study population was divided in Group 1, corresponding to patients referred with the diagnosis of diabetes as a cause of ESRD and, Group 2, in whom ESRD was attributed to other causes with or without diabetes as a comorbidity. Mortality and hospitalization rates were calculated by dividing the number of events by the cumulative period of follow-up. Logistic regression was used to identify parameters that were independently associated with mortality and hospitalization.

Results: The cohort included 3508 patients (54% men). Patients with diabetic nephropathy represented 40.3% of included patients (G1), their mean age was of 58.1 ± 14.5 years vs. 48.7 ± 17.4 in Group 2 (p<0.0001). There was a slight male predominance in both groups with a sex ratio of 1.20 in G1 vs. 1.16 in G2 (NS). The proportion of patients who were hospitalized was of 31.7% in G1 vs. 22.3% in G2 (p<0.0001), corresponding to a rate of 38.8 per 100 patient-years (CI, 95%: [36.15-41.46]) in G1 vs. 21.8 per 100 patient-years (CI, 95%: [20.20-23.31]) in G2. Mean duration of hospital stay was of 4.8 days per patient in G1 (CI, 95%: [4.8-4.9]) vs 2.5 days in G2 (CI, 95%: [1.4-2.5]). The mortality rate was of 10.5 per 100 patient-years in G1 (CI, 95%: [9.10-11.86]) vs. 5.1 in G2 (CI, 95%: [4.33-5.83]). After adjustment for age, gender, type of vascular access and, time on HD, hospitalization, and mortality risks were of 1.61 (CI, 95%: [1.33-2.11]) and 1.47 (CI, 95%: [1.24-1.73]) in G1 compared to G2.

Conclusions: Saudi patients hemodialyzed for ESRD related to diabetic nephropathy, are with a higher risk for the number of hospitalization, hospital length stay and, mortality in comparison to those hemodialyzed for other causes.

SA-PO1037

The Impact of Antidiabetic Drugs on Morality in Diabetic Patients Undergoing Hemodialysis

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Background: Diabetes mellitus (DM) is associated with an increased risk of morbidity and mortality in patients undergoing hemodialysis (HD). Insulin and other oral antidiabetic drugs (OAD) are usually long-term given for glycemic control. However, there has been little research that have analyzed the long-term effect of antidiabetic drugs to mortality rate. The aim of this study is to evaluate the impact of use of antidiabetic drugs on the risk of mortality in such patients.

Methods: In this retrospective cohort study, we identified 212 diabetic HD patients who continued using at least one kind of antidiabetic drugs for more than 6 months in Chang Gung Memorial Hospital between November 1, 2009 and November 31, 2016. We excluded patients that had dialysis duration less than 6 months (N=60) and follow-up time less than 6 months (N=9). The final cohort comprised a total of 143 patients. Primary outcome was all-cause mortality. Hazard ratios (HR) were calculated by Cox proportional hazard regression models which were used to adjust for age, gender, laboratory data and different antidiabetic drugs use.

Results: In all 143 patients, mean age was 60.9 ± 12.2 years; 43.4% of patients was male and mean dialytic duration was 45.1 months. 71 patients (49.7%) used insulin for glycemic control, 54 (37.8%) used Sulfonylurea, and 25 (17.5%) used Dipeptidyl peptidase-4 inhibitors. After a median follow-up duration of 39.0 months, 60 patients died. Cox-multivariate analysis revealed only age (HR = 1.04, p =0.001), serum albumin (HR = 0.206, p <0.001), and insulin users (HR = 2.39, p= 0.011) to be independent

predictors of mortality. The finding persisted after adjusting for hemoglobin A1c level being treated as both a categorical variable or a continuous variable.

Conclusions: This study demonstrated that compared with non-insulin users, insulin users were associated with a higher risk of mortality in diabetic HD patients, independent of glycemic control.

Cox-multivariate analysis for all-cause mortality

	Hazard ratio(HR)	95% Confidence interval(CI)	p value
Age	1.040	1.015-1.065	0.001
Albumin	0.206	0.093-0.461	<0.001
Insulin	2.389	1.223-4.669	0.011

Multivariate adjustments were made for gender, dialysis duration, hemoglobin, triglycerides, use of Sulfonylurea, Dipeptidyl peptidase-4 inhibitors, and Hemoglobin A1c level.

SA-PO1038

Standardized Clinical Foot Examination in Prevalent Diabetic Hemodialysis Patients: Association with Mortality and Hospitalization

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Background: Atherosclerosis, neuropathy and SHPT contribute to increased risk of peripheral vascular disease (PVD) and adverse outcomes (eg, ulcers, limb amputation, hospitalizations and mortality) in diabetic patients on HD. Both the ACC/AHA and KDIGO guidelines recommend screening of individuals at risk. This study analyzed the frequency of foot complications following implementation of a standardized foot examination in 345 prevalent diabetic HD patients in 12 DaVita centers in Poland (n=177 pts) and Portugal (n=168 pts). Hospitalizations and cause-specific mortality were documented during 24 months follow up.

Methods: The protocol includes: history of the patient (ulcers, amputation), inspection of feet (skin, nails) and examination of the pedal pulses (a dorsalis pedis and a tibialis posterior) Foot complications were classified according to Wagner (grade 0-5) and PVD was classified by pulse measurement (normal vs weak or missing). We analyzed risks associated with hospitalization and mortality using Cox proportional hazard models.

Results: Mean age of patients (58% men) was 70.4 (SD 14) yrs. A normal pulse in L and R a dorsalis pedis and in L and R a tibialis post was found in 17% and 10% of patients, respectively. All other patients had weak or absent pulses. The Wagner score was 0 or 1 in 88% of patients, 2-3 in 6%, and 4-5 in 5%. All-cause mortality was 31% during the 2 year follow up. 71% of patients had at least one hospital stay. Cardio-cerebrovascular disease, PVD, and infection accounted for 76% of all mortality. In unadjusted analyses presence of weak or absent pulses in a dorsalis pedis was significantly associated with all-cause mortality RR 2.1 (CI 1.1-4.3; p<0.05). In adjusted models including age, sex, Hb, albumin, Kt/V, vascular access, phosphorus, PTH and Charlson score, only albumin was associated with mortality (RR 0.89, CI 0.84-0.94; p<0.001) and risk of hospitalization (RR 0.92, CI 0.89-0.96; p<0.001).

Conclusions: Implementation of a standardized foot examination protocol in diabetic patients on HD showed a high prevalence of clinically significant complications that warrant close attention. This clinical tool is suitable to identify patients at high risk of future complications and could be the basis of a program to improve overall health outcomes.

SA-PO1039

Epidemiology of Pericardial Effusions in Patients with ESRD on Hemodialysis

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Background: Cardiovascular disease, including pericardial disease, remains a prominent cause of morbidity and mortality in patients with end-stage renal disease (ESRD). The prevalence, clinical and prognostic significance of pericardial effusions (PE) in ESRD patients has not been well established. This study examines the epidemiology of PE in patients on chronic hemodialysis (HD).

Methods: This was an observational, retrospective study of chronic HD patients (> 2 months on HD) from Stony Brook University Hospital Kidney Center from January 1, 2010 to November 31, 2017 with analysis of transthoracic echocardiograms (TTE) along with corresponding clinical and demographic data. Effusions were classified by size: trivial (< 5 mm), small (5-10 mm), moderate (10-20 mm), or large (≥ 20 mm) echo-free space in end-diastole, as per European Society of Cardiology guidelines. Statistical analysis was conducted in SAS v9.4 using parametric and non-parametric tests as appropriate.

Results: A total of 185 TTEs from 82 patients on HD were analyzed. Twenty-nine (35.4%) patients had some degree of PE. Sixteen (19.5%) patients had trivial, thirteen (15.9%) had small, five (6%) had moderate and two (2.4%) had large (including one with tamponade physiology requiring pericardiocentesis) PE. Eighteen patients had multiple TTEs during the study period and were found to have varying degrees of PE (ranging from none to moderate). Patients with PE had a significantly lower median age compared to those who did not have PE (54 years old vs. 65 years old), with the moderate/large effusions primarily observed in relatively younger patients (median age of 46). Patients with lower serum albumin levels had significantly higher numbers of PEs, with the most severe PEs seen in the groups with the lowest albumin levels (3.2 g/dL). Patients with PE also had a lower mean hematocrit level compared to those without PE (29.6% vs. 32.7%). No significant association was found between the presence of PE and gender, ethnicity, cardiac ejection fraction, change in weight compared to dry weight, urea reduction ratio, or kt/v.

Conclusions: Approximately one-third of patients on chronic HD therapy had some degree of PE. In this study, relatively younger age, lower levels of serum albumin and lower hematocrit were independently associated with increased prevalence of PE.

SA-PO1040

The Association of Dialysis Adequacy, Body Mass Index, and Mortality Among Hemodialysis Patients

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Background: We examined the relationship between adequacy of hemodialysis (HD) and mortality in HD patients according to body mass index (BMI).

Methods: We retrospectively reviewed patient data from the Korean Society of Nephrology registry, a nationwide database of medical records of HD patients, from January 2001 to June 2017. We included patients who were ≥18 years old and receiving maintenance HD. Patients were categorized into three groups according to baseline BMI (<20 (low), 20 to <23 (normal), and ≥23 (high) kg/m^2). Baseline spKt/V was divided into six categories.

Results: Among 18,242 patients on HD, the median follow-up duration was 5.2 (IQR, 1.9–8.9) years. Cox regression analysis showed that, compared to the reference (spKt/V 1.2–1.4), lower and higher baseline spKt/V were associated with greater and lower risks for all-cause mortality, respectively. However, among patients with high BMI (n=5,588), the association between higher spKt/V and lower all-cause mortality was attenuated in all adjusted models ($P_{interaction}$<0.001). Compared to patients with normal BMI and spKt/V within the target range (1.2–1.4), those with low BMI had a higher risk for all-cause mortality at all spKt/V range. However, the gap in mortality risk became narrower for higher values of spKt/V. Compared to patients with normal BMI and spKt/V in the target range, those with high BMI and spKt/V <1.2 were not at increased risk for mortality despite low dialysis adequacy.

Conclusions: The association between spKt/V and mortality in HD patients may be modified by BMI.

SA-PO1041

Survival of Hemodialysis Patients in Saudi Arabia: A Large 4-Year Observational Analysis

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Background: The aim of this study was to analyze survival rates in a large cohort of patients receiving hemodialysis in 22 outpatient clinics all over Saudi Arabia (KSA) and also to identify factors influencing the risk of mortality.

Methods: We included all patients referred to DaVita-KSA clinics to continue renal replacement with hemodialysis from October 2014 to December 2018 (n=3508). Survival rates were calculated according to the actuarial method and the Cox proportional model was used to identify factors influencing mortality.

Results: Altogether 3508 patients on hemodialysis were included (54% men, 46% women) with a mean age of 52.5 ± 16.9 years. Diabetic nephropathy (40.3%) and hypertensive nephropathy (35.7%) accounted together for 75.8% of all causes of ESRD. Only 38.2% of patients had available autogenous /graft fistulae ready for use at the date of their transfer to Davita clinics vs. 65% at the last follow-up (p<0.0001). During the study period, 462 patients (13%) had been transferred to other dialysis facilities, 245 (7%) had been transplanted and 398 (11%) were deceased, representing an annual mortality rate 7.1% patients. Cardiovascular and cerebrovascular complications accounted for 49.0% of known causes of death and 14.3% were attributed to infections, while 40.4% of death causes remained unknown. Survival rates were of 98.0, 93.9, 87.7 and 73.3% at 3, 6, 24 and 48 months, respectively. The predictors of mortality identified by multivariate regression analysis were: Older age category (RR: 3.5, 95% CI: 2.4-4.9); p< 0.0001), dialysis duration before joining Davita-KSA clinics <3 months (RR: 1.4, 95% CI: 1.1-1.7) diabetes as a cause of ESRD (RR: 1.5, 95% CI: 1.2-1.8)), and catheter as vascular access (RR: 1.4, 95% CI: 1.1-1.8).

Conclusions: Survival at 2 and 4 years was high (88% and 73%) despite a high percentage of diabetics, that the annual mortality was of 7.1% and that cardio-cerebrovascular causes accounted for about the half of known causes of deaths. Use of a central dialysis catheter was identified as a modifiable predictor of mortality. Efforts should be increased toward an early creation of, and a timely shift to, an AV fistula.

SA-PO1042

Dialysis Outcomes at 12 Months Among Patients Starting Hemodialysis in India

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Background: Hemodialysis (HD) is the dominant renal replacement therapy (RRT) in India. Despite a national free dialysis programme since 2016, outcomes in dialysis have received limited attention. 1000 incident HD patients were followed up to evaluate the determinants of outcomes. We describe the baseline socio-demographic and clinical characteristics associated with 12-month survival on HD.

Methods: 1000 participants were recruited from 2016 to 2018 at 16 dialysis facilities across 9 Indian states. Demographic, clinical, socioeconomic and quality of life parameters were collected through a secure online data collection platform. We examined the association of survival with age, gender, education, family income, OoP expenditure, insurance coverage, vascular access, hemoglobin and intradialytic weight gain. Chi-square and Fishers T tests were used to test for associations and a p value of <0.05 was deemed significant.

Results: The median age (IQR) was 58 (18) years, and 29% were female. 20% of the participants had education beyond school. 80% of the females worked within the home, while 44% of the males were retired or not working. Of those who had a job, 9% changed their occupation. Median monthly family income was US$ 500 (586). Median distance traveled for dialysis was 10 (15) kms. 75% funded dialysis out of pocket (OoP), 19% had government or an employer-based, while 6% had private insurance. The median monthly OoP expenditure was US$ 360±220 for uninsured participants and US$ 180±140 for insured participants. At 12 months, 53.4% remain on HD, 18.5% had died, 14.9% withdrew from dialysis, 7.5% received a transplant, 2.9% switched to PD, and 2.8% were lost to follow-up. Survivors had shorter travel distance, higher family income, hemoglobin and lower interdialytic weight gain. In the QoL analysis, the highest decline of function was observed in the domain of self-care(16%) followed by mobility(15%).

Conclusions: In this national HD cohort, 64% continued on RRT at 12 months. Availing dialysis closer to home, adequate financial risk protection was associated with continuing on dialysis. Hemoglobin levels more than 10 g/dL and low Inter dialytic weight gain were strongly associated with survival. Monitoring outcomes in dialysis provides an opportunity to identify modifiable factors to improve quality and inform policy.

Funding: Commercial Support - Baxter International

SA-PO1043

Survival in Patients Who Return to Dialysis with Kidney Allograft Failure: The Argentinian Dialysis Registry Study

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Background: The number of patients (Pts) who return to dialysis (Dx) after Kidney allograft failure (KAF) is increasing. The outcome of these Pts remain unclear. Some studies showed lower survival rates in KAF Pts than transplant naïve incidents dialysis (TNID) Pts. Our aim was to compare outcome of KAF versus Pts on waiting list (WL) and those with a kidney transplant contraindication (KTC)

Methods: We performed a retrospective observational study using data from the Argentinian Dialysis Registry between 2005 and 2016. We recorded demographics, laboratory markers and vascular access at entry. To compare mortality between the 3 groups Kaplan Meier, log rank test and Cox regression were used

Results: This study included 75722 Pts of which 2734 (3.6 %) were KAF Pts. The TNID (n=72988) Pts were significantly older, included higher percentages of males, diabetic and hypertensive when compared with Pts who started Dx after KAF. Regarding Dx modality, 5.8 % of Pts initiated PD in KAF group vs 3.9 % in TNID group (p<0.0001). There was a high percentage of Pts starting HD with transient catheters, being 66.1% and 65.5 % in KAF and TNID group respectively. Overall mortality was 54.6 % during follow up. Death probability between the 3 cohorts (KAF(n=2734) vs WL (n=14630) vs KTC(n=58358) revealed a significant difference (log-rank test: 10734.5; P< 0.0001) indicating worse survival for KTC incident Dx Pts cohort and best survival for WL. We also performed a survival curve adjusting for covariates that were statistically significant for mortality in Cox multivariate analysis. We found that KAF Pts had as poor outcome as KTC Pts. Multivariate Cox analysis showed that age >65 years: HR: 1.845 (1.79-1.89) P < 0.0001**,** transient catheter: HR: 1.303 (1.26-1.34) P < 0.0001, male sex: HR: 1.043 (1.01-1.07) P < 0.0002, diabetic: HR: 1.273 (1.22-1.31) P < 0.0001, hemodialysis modality: HR: 1.168 (1.07-1.27) P < 0.0004, hepatitis C: HR: 1.303 (1.26-1.34) P < 0.0001 and Albumin: HR: 1.247 (1.21-1.28) P < 0.0001 were strongly associated with mortality, while being on waiting list: HR: 0.285 (0.23-0.35) P < 0.0001 was found to be protective

Conclusions: Patients who return to Dx after KAF have higher mortality than WL patients and similar to KTC patients

SA-PO1044

A Comparison of Death Records Between the USRDS and a Large Health Care System

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Background: The accuracy of mortality data is important when determining the mortality rates for the end stage renal disease (ESRD) population and assessing interventions to improve survivability or quality of life. Little research has been done to examine the completeness and accuracy of the USRDS mortality reports. The purpose of this study is to compare mortality records from a large integrated health system with the USRDS registry.

Methods: A retrospective cohort study (1/1/2007-12/31/2016) of ESRD patients within Kaiser Permanente Southern California (KPSC), an integrated health system, was performed. Patients were linked to the USRDS death records and evaluated. KPSC mortality data are obtained from several sources, but primarily from California state death certificates. USRDS mortality data are similarly obtained from several sources, but primarily from CMS form 2746.

Results: A total of 4827 death records were found between 2007 and 2016. There were 4189 death records found in both KPSC and USRDS databases, 609 found only at KPSC and 29 found only at USRDS. An average of 12.7% of death records per year were captured at KPSC but missing from the USRDS database. Of the 4189 death records, 86.92% of KPSC death records had consistent dates of death (DOD) with the USRDS. A few death records had a DOD that differed by more than a week (1.03%) to more than a year (0.07%).

Conclusions: These data suggest that mortality information from the USRDS could be systematically under-ascertained. Researchers should use caution when using USRDS mortality data because of the potential for incompleteness of the data as currently collected. The use of additional sources of information may supplement and help overcome these challenges.

Funding: Government Support - Non-U.S.

Difference in Days	N	%
No difference	3641	86.92
1-7	502	11.98
8-15	22	0.53
16-31	15	0.36
32-91	5	0.12
184-365	1	0.02
365+	3	0.07

SA-PO1045

Sex-Specific Survival Advantage In Patients Undergoing Hemodialysis: Ten-Year Outcomes of the Q-Cohort Study

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Background: The survival advantage of females is observed in the general population. However, there is a controversy on the survival benefits of being females compared to males in patients undergoing hemodialysis. The aim of the study was to compare the risk for infection-related and all-cause mortality between males and females in patients undergoing hemodialysis.

Methods: A total of 3,504 Japanese hemodialysis patients aged ≥18 years were prospectively followed for 10 years. The primary outcomes were infection-related and all-cause deaths. Multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) of these outcomes were calculated using a Cox proportional hazards model.

Results: During the median follow-up period of 5.3 years, 448 died of infection and 1736 patients died of any cause. Compared with males, the multivariable-adjusted HRs (95%CIs) for infection-related and all-cause deaths in females were 0.47 (0.41–0.55) and 0.34 (0.25–0.44), respectively. This relationship was remained significant even when propensity score matching or inverse probability of treatment weighting (IPTW) adjustment methods were employed. Furthermore, even when the competing events of non-infection-related deaths were taken into account, the infection-related mortality rate in females was significantly lower than that in males.

Conclusions: The current study showed that the female advantage in survival is observed in patients undergoing hemodialysis. Further studied are necessary to confirm the survival benefit of females and its underlying mechanism in patients receiving hemodialysis.

SA-PO1046

Rural vs. Urban Residence and Survival on Chronic Maintenance Dialysis in US Veterans

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Background: Most of the VA dialysis centers are urban. Veterans receiving maintenance hemodialysis (MHD) care in non-VA rural facilities may have ↑ mortality. Hence, rural and urban disparities might explain the better survival of veterans initiating MHD within the VA.

Methods: We examined a national cohort of veterans who initiated MHD from May 2012 to May 2016 by combining United States Renal Data System data obtained from VA Information Resource Center and VA Corporate Data Warehouse data obtained via VA Informatics and Computing Infrastructure. We defined rural and urban residence by zip codes. We used USRDS data to define VA and non-VA dialysis facilities, dialysis quality metrics and time to death.

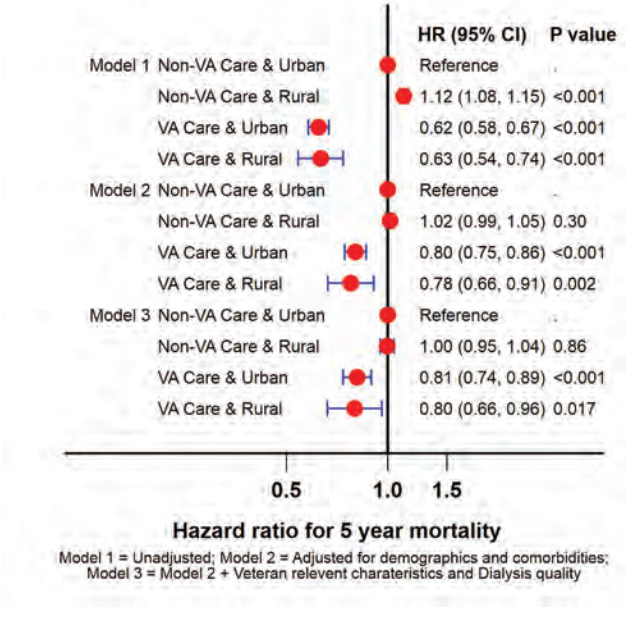
Results: 46,470 veterans were included. VA veterans were younger, less likely to be white, had lower income and higher prevalence of traumatic brain injury and PTSD. However, irrespective of rural or urban residence, veterans who received dialysis care within the VA had better 5-year survival than veterans who received care outside the VA (Fig).

Conclusions: Veterans who received dialysis care within the VA had better survival compared to those who received care outside of the VA regardless of rural or urban residence.

Funding: Veterans Affairs Support

Baseline Characteristics

	Non-VA-care (N=43,900)		VA-care (N=2,570)	
	Urban (N=33,784)	Rural (N=10,116)	Urban (N=2,150)	Rural (N=420)
Age (yr)	70 ±12	71±11	65±11	65±10
Male (%)	91	93	96	97
White (%)	69	82	54	62
Atherosclerosis (%)	19	23	20	18
ESRD due to DM (%)	36	38	44	40
Means Tested Status (%)	18	21	25	27.2
Traumatic Brain Injury (%)	1.2	1.3	2.5	2.4
PTSD (%)	11.0	10.9	17.0	17.5



Residence, VA care and 5 year mortality

SA-PO1047

Impact of Altitude on Dialysis Patient Characteristics and Outcomes

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Background: Barometric pressure, oxygen pressure as well as ultraviolet radiation are environmental factors that variate by altitude and have the potential to impact outcomes. Patients undergoing hemodialysis (HD) tend to suffer from several chronic conditions and could vary depending on the elevation they reside in. We aimed to define the characteristics and outcomes of the HD population at a large dialysis provider (LDO) by the altitude of residence.

Methods: We used data from HD patients treated at the LDO in 2018. Patients were stratified by the average elevation of the state of residence extracted from the US Geological Survey. Average state elevations were defined as: high (>4000 feet), mid (1000 to 4000 feet), and low (<1000 feet). We defined patient demographics, comorbidities, clinical characteristics and outcomes in the different elevations.

Results: Among a population of 244720 HD patients, 59% resided at low elevation, 35% at mid elevation, and 6% lived at high elevation. The percentage of females varied from 41-43% in the three elevations, and age ranged from 63-64 years old. Low elevations had the lowest percentage of white and Hispanic patients (whites: 44% vs 55% and 68% at low, mid and high elevations respectively; Hispanics: 5%). Low elevations had the smallest percentage of patients with diabetes (66%, 69% and 70% at low, mid and high elevations), while it had the highest number of patients with heart diseases (congestive heart failure: 21% vs 19% and 13% at low, mid and high elevations; ischemic heart disease: 21% vs 19% and 12% for low, mid and high elevations; hypertension 66% vs 67% and 70%, at low, mid and high elevation). Patients more commonly received an extra HD treatment in higher elevations (7% vs 8% and 9% at low, mid and high elevation). Low elevation also had the highest hospitalization rates (1.9 vs 1.8 and 1.7 at low, mid and high elevation).

Conclusions: HD patient characteristics and outcomes vary by elevation. In low elevations heart diseases were more prevalent, patients more often received an extra HD treatment, and patients had higher hospital admission rates. Diabetes was more prevalent in higher elevations in HD patients. Further adjusted analysis are needed to identify the influences of altitude on practice patterns and outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

SA-PO1048

Racial Differences Among Recipients of Staff-Initiated CPR in Outpatient Dialysis Clinics

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Background: Sudden cardiac arrest is the leading cause of death among hemodialysis patients. Despite practice guidelines recommending basic life support training for all hemodialysis clinic staff, rates of staff-initiated CPR are sub-optimal. Little is known about whether patient and clinic characteristics are associated with lower rates of dialysis staff-initiated CPR.

Methods: We examined data in the Cardiac Arrest Registry to Enhance Survival, a national surveillance registry with data submitted from 23 statewide registries and 70 additional communities, along with dialysis clinic data from the Centers for Medicare & Medicaid Services to identify cardiac arrests in outpatient hemodialysis clinics as well as characteristics of the rescue response between 2013 and 2017. Using multivariable logistic regression, we examined the likelihood of receiving dialysis staff-initiated CPR based on patient and dialysis clinic characteristics.

Results: Of the 1,581 patients who experienced cardiac arrest in hemodialysis clinics, 88.0% received staff-initiated CPR. 91.1% of White and 84.8% of Black patients received staff-initiated CPR (p=0.009). After accounting for patient age and sex, clinic characteristics, dialysis clinic neighborhood characteristics, and U.S. region (see Table), Black patients remained significantly less likely to receive staff-initiated CPR than White patients (aOR 0.45, 95% CI, 0.28 to 0.73). There was no relationship between patient race and dialysis staff automated external defibrillator application.

Conclusions: Black patients are significantly less likely than White patients to receive staff-initiated CPR during cardiac arrest in dialysis clinics across the US. Further understanding of resuscitation practices in dialysis clinics is necessary to address this finding.

Funding: NIDDK Support

Table: Multivariable Predictors of Dialysis Staff-Initiated CPR

Variable	Adjusted Odds Ratio (95% Confidence Interval)	*p* Value
Patient Characteristics		
Age (per year increase)	1.00 (0.98-1.01)	0.465
Sex		
Female	1.00 (ref)	
Male	1.26 (0.91-1.75)	0.161
Race		
White	1.00 (ref)	
Black	0.45 (0.28-0.73)	0.001
Other/Unknown	0.73 (0.47-1.14)	0.171
Cardiac Arrest Characteristics		
Witnessed Status		
Unwitnessed	1.00 (ref)	
Witnessed	1.92 (1.30-2.84)	0.001
Clinic Characteristics		
Facility Type		
Other (non-profit, non-chain)	1.00 (ref)	
For-profit, chain-based clinic	1.14 (0.71-1.82)	0.595
Number of Dialysis Stations (per station increase)	1.02 (1.00-1.04)	0.081
Medicare Star Quality Indicator		
4-5	1.00 (ref)	
3	1.00 (0.71-1.42)	0.991
1-2	1.02 (0.53-1.96)	0.954
Region (U.S. Census Bureau)		
South	1.00 (ref)	
Northeast	0.75 (0.43-1.29)	0.294
Midwest	1.04 (0.66-1.65)	0.863
West	0.99 (0.61-1.59)	0.952
Dialysis Clinic Neighborhood/ Census-Tract Characteristics		
Population Density (natural log)	0.85 (0.73-0.99)	0.036
Proportion Black	1.40 (0.66-2.99)	0.386
Median Household Income (per $10,000 increase)	0.93 (0.87-0.99)	0.030

SA-PO1049

Racial Disparities in Advance Care Planning in Patients Receiving Maintenance Dialysis

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Background: There is a paucity of literature on racial differences in completion of advance care planning (ACP) documents among maintenance dialysis patients. We studied differences in the presence of advance care planning (ACP) documents in patients receiving maintenance dialysis.

Methods: A forty-one item questionnaire was administered to adult patients receiving maintenance dialysis in seven dialysis units located in the city of Cleveland, Ohio, and its suburbs. Of the 450 patients who were asked to participate in the study, 423 (94%) agreed. Of those who responded, 285 were African Americans, and 114 were Caucasians The questionnaire Items assessed patients' knowledge of their kidney disease, attitudes toward chronic kidney disease (CKD) treatment, and preference for end-of-life (EoL) care. A single question was used to assess completion of advance care planning documents "Have you completed any of the following?: (a) Living will (b) Personal directive/Medical Order for Life-Sustaining Treatment (MOLST) form (c) Healthcare proxy document (d) Enduring power of attorney (e) None of the above/Don't know." All responses about power of attorney were excluded from the current analyses. We used logistic regression to identify predictors of completion of any ACP document. Candidate predictors were patient demographics, attitudes toward CKD treatment, and EoL care preferences.

Results: African American race (OR 0.56, CI 0.35, 0.92, p=0.02) and lack of prognostic discussions (OR 0.48, CI 0.27, 0.87, p=0.02) were associated with a lower odds of having any advance care planning document. Age >65 years (OR 2.1, CI 1.35, 3.26, p=0.001) and religiosity (OR 3.76, CI 1.52, 9.27, p=0.003) were associated with higher odds of completion of ACP documents.

Conclusions: Racial disparities exist in completion of ACP documents. Factors associated with lower odds of advance care planning include African American race and the absence of prognostic discussions. Future interventions are needed to mitigate racial disparities in completion of ACP and encourage prognostic discussion with dialysis patients.

SA-PO1050

Mortality and Morbidity Among African American Patients with Sickle Cell Disease and ESRD Initiating Dialysis

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Background: High rates of mortality have been described in sickle cell disease patients with end-stage renal disease (SCD-ESRD), however, risk factors for mortality and associated morbidity have not been elucidated. We examined vascular access failure (VAF), hospitalization and mortality among a cohort of adults with SCD-ESRD.

Methods: We identified adult, black patients with SCD who initiated peritoneal or in-center hemodialysis (PD or ICHD) dialysis in Fresenius Kidney Care clinics between 2000-2014 with up to 10 years of follow up. Patients with SCD were matched 1:3 to a reference population of black patients receiving PD or ICHD without SCD or sickle cell trait using age, sex, year of dialysis initiation and end-stage renal disease (ESRD) network. Multivariable Cox proportional hazards models were used to examine time to first VAF, first hospitalization, and 10-year mortality. Unadjusted mortality rate differences were estimated between vintage categories 2000-2004 and 2010-2014.

Results: We identified 504 SCD-ESRD patients and 1,425 matched reference patients. The mean age was 47±14 years, 49% were female, 95% were receiving ICHD and median follow up was 2 (IQR 1-4) years. SCD-ESRD was associated with a higher risk of VAF (adjusted HR 1.23; 95% CI 1.03-1.48), hospitalization (adjusted HR 1.60; 95% CI 1.42-1.80) and 10-year mortality (adjusted HR 1.58; 95% CI 1.31-1.96). Univariate analysis produced similar results. Hemoglobin < 8g/dl, higher weekly epoetin doses, higher ultrafiltration rates, dialysis catheter use, and low serum albumin were associated with higher mortality in SCD-ESRD. Changes in 10-year mortality rates in SCD-ESRD were non-significant between 2000-2004 and 2010-2014 (203 to 145/1,000 person-years, p=0.06) in contrast to a downward trend in mortality in the reference in the same period (109 to 57/1,000 person-years, p<0.01).

Conclusions: SCD-ESRD was associated with a higher risk of VAF, hospitalization and mortality. Although mortality rates decreased in the SCD-ESRD population during the timeframe of observation, rates did not decline to the same extent observed in the reference population. Prospective studies are needed to better characterize risk factors for mortality and address target parameters to improve outcomes in SCD-ESRD.

SA-PO1051

Global Kidney Health Atlas 2019: Current Status of ESKD Care in World Countries and Regions

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Background: Although substantial literature describes the costs and consequences of end-stage kidney disease (ESKD), limited data are available on the capacity to deliver kidney replacement therapy (KRT) and conservative kidney management (CKM) across the world. We aimed to collect information on current global capacity (availability, accessibility, quality and affordability) to deliver KRT (dialysis and transplantation) and CKM.

Methods: A cross-sectional survey conducted from July to September 2018 by the International Society of Nephrology (ISN) across 182 countries using a purposive sample of key stakeholders identified by ISN's national and regional leaders.

Results: Responses were received from 160 of 182 countries (87.9%), including 317 of 460 individuals (68.9%, 2–4 respondents per country), representing 98.6% (7338.5 million of 7441.5 million) of the world's population. Results showed wide variation in capacity and structures for KRT and CKM, funding mechanisms, health workforce, service delivery and available technologies. Information on the prevalence of treated ESKD was available in 42% (n = 91) of countries worldwide, with estimates varying >800-fold from 4 to 3392 per million population (pmp). While there was at least some reported availability of hemodialysis, peritoneal dialysis, and kidney transplantation in 100%, 76%, and 74% of countries, respectively, dialysis and kidney transplantation were accessible to >50% of patients in only 70% and 29% of countries that offer the services, respectively. CKM was available in 124 (81%) countries. Worldwide, the median rate of nephrologists was 9.96 pmp, and this varied with income level.

Conclusions: The analysis demonstrates significant variability worldwide in both the burden of ESKD as well as the current capacity for KRT and CKM. This includes important gaps in services and workforce. These findings have implications for policy and advocacy efforts aimed at promoting universal, equitable access to the full spectrum of ESKD care.

SA-PO1052

Characteristics and Outcomes of Hemodialysis Patients by Population Density

Hao Han, Sheetal Chaudhuri, Brian S. Ash, Janice D. Lindsay, Marta Reviriego-Mendoza, John W. Larkin, Len A. Usvyat, Jeffrey L. Hymes, Robert J. Kossmann, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Population density associates with distinct profiles of health in the general population. Patients undergoing hemodialysis (HD) could be affected by the urbanicity level of their residence. We classified the characteristics and outcomes of HD patients at a large dialysis organization (LDO) by population density.

Methods: We analyzed 2018 data from HD patients. They were classified according to the county level population density defined by the Rural Institute, University of Montana: i) Metropolitan: ≥50,000 residents with integration to adjacent counties; ii) Micropolitan: ≥10,000-50,000 residents with integration to neighboring counties; iii) Rural: <10,000 residents. Median income data was obtained from the US Census database. We defined the profiles of demographics, clinical characteristics, and outcomes by level of population density.

Results: We analyzed data on 254322 HD patients. Of those, 84% resided in a metropolitan county, 10% lived in a micropolitan county, and 6% resided in a rural county. Average age was 64 years old in all population densities. More females lived in an urban county (44% vs 42% and 42% in metropolitan, micropolitan and rural counties, respectively). White race varied from 49%-52% and was the highest in micropolitan and lowest in metropolitan counties. Metropolitan areas had the highest proportion of Hispanics (13% vs 7% and 5% in metropolitan, micropolitan and rural counties). Median income was the highest in metropolitan areas ($54883 vs $43060 and $39630 in metropolitan, micropolitan and rural). In metropolitan to rural counties, the prevalence of comorbid conditions varied from 67-69% for diabetes, 19-22% for congestive heart failure, and 19-23% ischemic heart disease. In rural counties, patients less commonly received an extra HD treatment each week (7%, 7%, and 5% in metropolitan, micropolitan and rural). Hospital admission rates were higher in metropolitan areas (1.8 vs 1.7 and 1.7 admissions per patient year in metropolitan, micropolitan and rural).

Conclusions: Our findings suggest the characteristics and outcomes of HD patients vary by the population density of their residence. Further analyses are needed to understand the influence of practice patterns, access to health care, and distinctions in demographics on patient outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

SA-PO1053

Association Among Primary Care Involvement, Death, and Hospitalizations for Patients Newly Started on Dialysis: A Population-Based Study from Ontario, Canada

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Background: The transition to dialysis is a vulnerable time, where patients may benefit from nephrology and primary care support. However, the role of primary care for patients on dialysis is poorly defined. We sought to determine whether primary care physician (PCP) involvement during the transition to dialysis improves outcomes.

Methods: Using linked administrative databases in Ontario, Canada, we conducted a population-based study of patients who initiated chronic dialysis between 2005-2014 and survived at least 90 days. We defined persistent PCP involvement as both 1) high usual provider of care index in the 2 years before dialysis, an established measure of PCP continuity and 2) ≥1 visit with the usual provider in the 90-days after dialysis initiation. We used propensity scores to match patients 1:1 based on indicators of baseline health. The primary outcome was all-cause mortality and secondary outcomes included all-cause and disease-specific hospitalizations.

Results: We identified 19,099 patients who survived for >90 days. There were 6612 patients (35%) with persistent PCP involvement who were matched 1:1 to 6391 patients without persistent PCP involvement. Persistent PCP involvement was not associated with a lower risk of mortality 2 years after cohort entry (14.5 deaths per 100 person-years vs 15.2 deaths per 100 person-years; hazard ratio [HR] 0.96, 95% CI 0.89-1.02). There was no difference in the rate of all-cause hospitalizations (HR 0.96, 95% CI 0.92-1.01), and persistent PCP involvement was not associated with a lower risk of any disease-specific hospitalization except for diabetes (HR 0.88, 95% CI 0.80-0.97).

Conclusions: Persistent PCP involvement during the transition to dialysis was not associated with a lower risk of mortality or all-cause hospitalization. These additional visits have opportunity costs for patients and economic costs for the healthcare system, suggesting primary care redesign may be needed to better support patients during this vulnerable period.

SA-PO1054

Trends in Outcomes for Patients Receiving Renal Replacement Therapy in Canada

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Background: Alternate renal replacement therapy (RRT) modalities offer different survival and quality-of-life outcomes for patients. Recent technological and process advances in dialysis treatments and transplantation offer the opportunity for better survival outcomes for patients. Longitudinal data from the Canadian Organ Replacement Register (CORR) for patients receiving RRT in Canada allows for national-level tracking of patient outcomes over time. We analysed patient data from the CORR to investigate the near-, mid- and longer-term survival outcomes for patients receiving RRTs including hemodialysis (in-centre and home), peritoneal dialysis and kidney transplantation (living and deceased donors).

Methods: The dataset comprised 74,108 patients registered in the CORR between 2003 and 2017 for all provinces excluding Quebec. We calculated graft and patient survival rates at 3 months, 1-, 3-, 5- and 10-years after start of dialysis and after transplantation. We calculated Kaplan–Meier survival rates for 10 years after start of dialysis and after transplantation, and we adjusted rates based on a direct-adjusted Cox model controlling for patient age, sex and primary diagnosis of renal disease.

Results: Crude 5-year patient survival rates was highest in the living-donor transplant group (94.6%), followed by the deceased-donor transplant group (88.3%), PD treatment group (51.3%) and HD treatment group (40.9%). Between 2003 and 2012, crude 5-year survival rates for dialysis patients have increased by 6.6 and 7.0 percentage points for HD and PD patients, respectively. Graft survival rates improved over the 10 years by 0.9 and 4.6 percentage points for those who received a donation from a living or deceased donor, respectively.

Conclusions: Crude survival rates have generally increased over time across all RRT modalities, with similar rank order of survival between modalities as previously reported. Improvements in survival rates may reflect improvements in technology, technique, and patient education and characteristics, and process improvements within dialysis and transplant programs in Canada. CORR national data allow measurement and reporting of this important outcome as a performance measure.

SA-PO1055

Inverse Relationship Between Waist Circumference and Body Mass Index on Risk for All-Cause Mortality in Hemodialysis Patients: A Nationwide Population-Based Cohort Study

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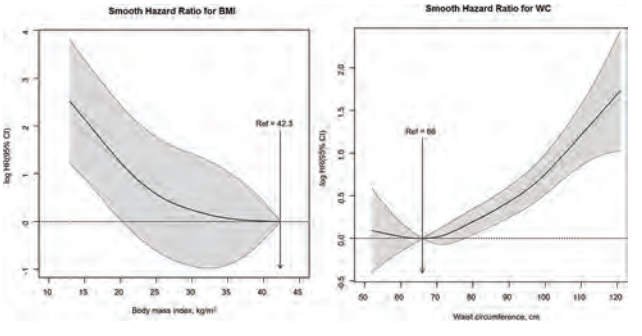
Background: Obesity underlies a high risk of all-cause and cardiovascular mortality in patients with end-stage renal disease. We investigated that the association between waist circumference and body mass index (BMI) and mortality in patients undergoing hemodialysis through a nationwide large population-based study.

Methods: Using nationally representative data from the Korean National Health Insurance System, 6,823,298 participants aged over 40 years with information for waist circumference and BMI were followed up during 4.5 years.

Results: The mortality rate is greater in hemodialysis patients with highest waist circumference category than those with lowest waist circumference category (5.67 per 100 person-years, ≥ 100 cm in men and ≥ 95 cm in women; 4.09 per 100 person-years, < 80 in men and < 75 in women). However, participants with higher BMI showed lower mortality rate than those with lower BMI (3.83 per 100 person-years in ≥ 30 kg/m^2 and 6.87 in < 18.5 kg/m^2). Multivariable Cox regression analysis found that participants with highest waist circumference category had higher risk of all-cause mortality than those with waist circumference 85 to 90 in men and 80 to 85 in women (reference group) [adjusted hazard ratio (HR), 1.280; 95% confidence interval (CI), 1.057–1.550], while those with lowest waist circumference category showed significantly lower risk of mortality compared to reference group (adjusted HR, 0.819; 95% CI, 1.410–1.929). Inversely, BMI categories ≥ 23 kg/m^2 were associated with significantly lower risk for mortality compared to the reference group (18.5 to 23 kg/m^2), with adjusted HR of 0.734 for BMI of 23 to 25 kg/m^2, 0.591 for BMI of 25 to 30 kg/m^2 and 0.530 for BMI ≥ 30 kg/m^2.

Conclusions: Central obesity measured by waist circumference is associated with all-cause mortality in hemodialysis patients, whereas body volume measured by BMI is an inverse relationship with this outcome.



SA-PO1056

Effect of Serum Uric Acid Level on Mortality Risk in Maintenance Hemodialysis Patients

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Background: There is still much controversy about the relationship between serum uric acid level and all-cause or cardiovascular mortality in hemodialysis patients.

Methods: A retrospective cohort study was conducted to enroll 201 MHD patients in the Third Affiliated Hospital of Sun Yat-sen University. The baseline data of clinical and laboratory examinations were compared. The correlation between serum uric acid level and clinical variables was analyzed by Pearson correlation coefficient. Kaplan-Meier and Cox proportional hazard regression model was used to examine the association between serum uric acid and all-cause and cardiovascular mortality in HD patients.

Results: The average age of patients was 56.9 ± 16.7 years, and the average baseline serum uric acid level was 531.1 ± 137.9 umol/L. With 442 umol/L, 523 umol/L and 620 umol/L as the boundary points, the patients were divided into four groups according to the level of serum uric acid. The lowest quartile group was older and had more diabetes mellitus than the highest quartile group ($P< 0.05$). Compared to the highest quartile group, the serum albumin, serum phosphorus and serum creatinine were lower in the lowest quartile group, while the hypersensitive C-reactive protein were higher($P < 0.05$). Pearson correlation coefficient showed that uric acid level was positively correlated with albumin, serum phosphorus and serum creatinine. After a median follow-up of 49.8 months, 66 (32.8%) all-cause deaths and 37 (18.4%) cardiovascular deaths were recorded. Kaplan Meier method showed that with the decrease of serum uric acid, all-cause mortality (Log Rank = 23.63, P = 0.000)and cardiovascular mortality(Log Rank =23.10,P=0.000) increased. Cox proportional hazard model was used to correct age, sex, complications. It was found that for every 100 umol/L increase in baseline serum uric acid level, the risk of all-cause mortality decreased by 24.1% [HR 0.759 (0.595-0.968), P=0.026]. Compared to the highest group, all-cause mortality [HR 0.287 (0.118-0.696), P=0.006] and cardiovascular mortality [HR 0.147 (0.032-0.677), P=0.014] were higher in the lowest serum uric acid quartile group.

Conclusions: Low serum uric acid level increases the risk of all-cause mortality and cardiovascular mortality in MHD patients.

Funding: Government Support - Non-U.S.

SA-PO1057

Lactate Rising: The "Unconventional" Use of Continuous Renal Replacement Therapy in Metformin-Associated Lactic Acidosis

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Introduction: Metformin is considered first-line therapy for many patients with type II diabetes mellitus (DM2). Metformin toxicity is a rare, yet potentially fatal complication of chronic metformin use with an incidence of ~4.2 cases per 100,000 patient years and a mortality rate between 30-50%. Extracorporeal treatment with intermittent hemodialysis (iHD) remains the modality of choice for severe metformin poisoining. However, patients with metformin-associated lactic acidosis (MALA) often present similarly to patients with septic or cardiogenic shock with severe hemodynamic instability making iHD treatment less desirable. I present a case of severe metformin toxicity treated successfully with continuous venovenous hemofiltration (CVVH).

Case Description: A 75 year old male with history of hypertension, DM2, and chronic kidney disease presented with altered mental status, nausea, vomiting, hypoglycemia and dyspnea. His home medications included metformin 1 gm twice daily and Lisinopril. The patient was intubated and found to have an initial arterial pH of 6.82, serum bicarbonate of 4 mmol/L, potassium of 6.3 mmol/L, SCr of 8.1 mg/dL, white blood cell count of 23.3 x10^9/L and lactate of 20.5 mmol/L. He required maximal doses of both norepinephrine and vasopressin for hemodynamic support. An EKG demonstrated peaked T-waves; therefore, a temporary femoral dialysis catheter was placed and CVVH was initiated. Initial concern was for ischemic bowel versus septic shock, however, MALA was also considered. Lactate levels decreased over the subsequent 24 hours to <2.0 mmol/L and arterial pH increased to >7.4, and the patient was discharged from the hospital six days later. One week after discharge, the metformin level returned at 37 mg/L confirming the diagnosis of metformin toxicity.

Discussion: Metformin toxicity is a rare, but treatable condition that poses unique challenges to clinicians given its similar presentation to more frequently observed clinical ailments. Although iHD has been the preferred modality for treatment of MALA, this case demonstrates that not only is CVVH an acceptable alternative, but may be the safest modality given the diagnostic uncertainty initially present. More studies evaluating the utility of CVVH in MALA may be beneficial to determine the optimal modality of extracorporeal therapy in patients with this rare but fatal condition.

SA-PO1058

Presence of Bisphenol S in Haemodialysis Patients: Environmental and Dialysis-Associated Exposure

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Background: In recent years, many studies demonstrated the effects xenobiotic of BPA, as results of these evidences; the industries are replacing BPA for different analogues such as Bisphenol S, it is a structural analogue, where in central quaternary carbon has been replaced by a sulfone. Due to of this similitude structural between BPA and BPS further studies promote to investigate the bioavailability and toxicities of BPS, and especially in the renal patient because of neither there is no literature about this group. In this study, our objective is to determine the plasmatic levels of BPS in comparison with BPA in the terminal renal patient and the influence of dialysis membrane.

Methods: The concentration of total BPS, BPA and hippuric acid (free, conjugated with sulphate or glucuronate, or bound to proteins) was determined by single reaction monitoring mass spectrometry (SRM-MS).

Results: BPA and BPS were measured in two groups: one of 10 healthy subjects (blood donors) and the other of 14 patients in hemodialysis (hemodiafiltration) which they were previously dialyzed for a week with cellulose triacetate (CTA) membranes. BPS in healthy controls were in almost all cases below LOD of 0.05 ng/mL, while in hemodialysis patients regardless of the membrane used was 0.32 ± 0.52 ng/mL. BPA in healthy controls range from 0.8 ± 0.7 ng/mL and 16.96 ± 58.57 ng/mL in renal patients. When membranes are compared, we found an increase of both after one dialysis session with polynephron (BPA: 45.63 ± 54.58 ng/mL at pre-dialysis vs 49.41±44.67 ng/mL at post-dialysis; BPS: 0.42±0.35 ng/mL at pre-dialysis vs 0.56 ± 0.36 at post-dialysis). On the other hand, with the polysulphone membrane exist there is a greater increase in the accumulation of BPA compared with BPS (BPA 51.4 ± 60.31 ng/ml at pre-dialysis vs 62.86 ± 77.39 ng/mL at post-dialysis; BPS: 0.59 ± 0.82 ng/mL at pre-dialysis vs 0.58 ± 0.47 at post-dialysis).

Conclusions: Similar to BPA, BPS accumulates in the renal patient as a result of the excretion problems of these patients along with the contribution of the dialysis membranes itself. However, the quantities measured are an order of magnitude lower than those measured for BPA both in a single dialysis session as well as in long-term dialysis (3 months or more).

Funding: Government Support - Non-U.S.

SA-PO1059

Exposure to Wildfire Smoke Increases Mortality in US Hemodialysis Patients

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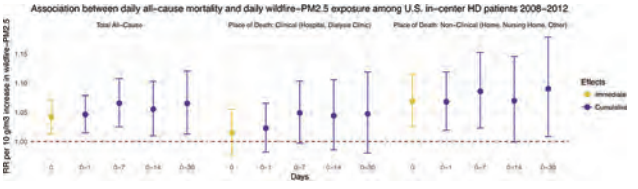
Background: Wildfires are a significant source of fine particulate matter ($PM_{2.5}$) that is causally related to mortality. Our objective is to assess the effect of wildfire-$PM_{2.5}$ on daily mortality among patients receiving chronic in-center hemodialysis (HD) in the US.

Methods: From the United States Renal Data System (USRDS), we identified patients who 1) had Medicare as primary payer, 2) survived first 3 months of dialysis, and 3) visited dialysis clinics within the 627 counties impacted by at least one large wildfire between 2008-2012. Outcomes were daily all-cause mortality and all-cause mortality by place of death (clinical and nonclinical). Exposure was county-level daily wildfire-$PM_{2.5}$ concentrations. We tested the association of wildfire-PM2.5 exposure to daily mortality using time series analysis, while controlling for time-dependent factors (temperature, etc.) and by design for time-independent characteristics (demographics and comorbidities). The immediate (same day) effect and the cumulative effect of 1, 7, 14, and 30 days of the exposure to wildfire-$PM_{2.5}$ on mortality were expressed as adjusted rate ratios (RR) per 10 mg/m^3 increase in $PM_{2.5}$.

Results: Among 48,454 deaths, the RR of the same day effect on all-cause mortality was 1.04 (95%CI: 1.01-1.07) and the cumulative effects of 1, 7, 14, and 30 days following the exposure were 1.05 (1.02-1.08), 1.07 (1.03-1.11), 1.06 (1.01-1.10), and 1.07 (1.01-1.12), respectively. For all-cause death occurring in non-clinical settings, the RR of the same day effect was 1.07 (95%CI: 1.02, 1.12), and the respective RRs of cumulative effect were 1.07 (95%CI: 1.02, 1.12), 1.09 (95%CI: 1.02, 1.15), 1.07 (95%CI: 1.00, 1.15), and 1.09 (95%CI: 1.01, 1.18).

Conclusions: Wildfire-$PM_{2.5}$ exposure was associated with a ~5% increase in daily all-cause mortality rate among HD patients. These deaths occurred in non-clinical settings such as homes, where exposure to $PM_{2.5}$ may be exacerbated. The first of its kind study highlights the impact of environmental exposures on a fragile population, and the need for additional research. This abstract does not reflect EPA policy.

Funding: Other U.S. Government Support



SA-PO1060

Long-Term Effect of Particulate Matter on Mortality Risk of Patients with ESRD

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Background: Aerodynamic particulate matter (PM) significantly worsens morbidity and mortality in various diseases, especially in cardiovascular and pulmonary diseases. However, little is known for relationship between PM and mortality of end-stage renal disease (ESRD).

Methods: 5041 patients who began dialysis from August 2008 to February 2015 were prospectively enrolled in the Clinical Research Center for End-Stage Renal Disease cohort study. We assigned daily mean concentration of PM < 10 μm in aerodynamic diameter (PM_{10}) to each participants for provincial-level divisions (si-do) by the location of station. Time-varying Cox proportional hazard models were used to investigate the relationship between PM_{10} and mortality of ESRD patients who have received dialysis. Stratified analysis was also conducted by potential confounders such as age, sex, smoking status, education, insurance, marital status, and social and familial support.

Results: During the follow-up period (mean 4.18 years), 1475 deaths occurred among 5041 participants. We found non-linear relationship between PM_{10} and mortality. Based on a threshold level at 44.15μg/m^3, although lower PM_{10} group had higher HRs for mortality with decrease in PM_{10} (HR 0.71, CI 0.69-0.74), higher PM_{10} group had higher HRs with increase in PM_{10} (HR 1.25, CI 1.22-1.28). Those who married and highly educated were at high risk in both groups, but opposite tendency was shown in each groups when stratified by population density, family and social support and the number of hospitals.

Conclusions: We found that the mortality of ESRD patients has contrary effects based on a threshold level of PM_{10}. It may be caused by toxicity of PM and characteristics of behavior at the region with relatively low concentration of PM_{10}.

SA-PO1061

The Effect of Dialysis on Aryl Hydrocarbon Receptor Binding Activities in Patients with CKD

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Background: Persistent organic pollutants (POPs) are well-known endocrine disrupting chemicals reported to be associated with various metabolic diseases. We hypothesized that POPs levels are increased in patients with chronic kidney disease or undergoing dialysis, thus further complicating the disease course. In this study, we measured serum POPs levels using a highly sensitive cell-based arylhydrocarbon receptor (AhR) dependent luciferase activity (CALA) assay in end stage renal disease (ESRD) patients undergoing dialysis or not, and compared differences between patients.

Methods: Patients undergoing peritoneal dialysis(22), hemodialysis(38) for at least 36 months, and and intracellular ATP levels were measured and compared according to treatment modality. We performed a correlation analysis between AhR binding activities and ATP levels and various clinical parameters.

Results: AhR binding activities differed significantly between groups, AhR binding activity was higher in non-dialysis CKD patients, compared to patients undergoing dialysis, and higher in patients undergoing hemodialysis compared to peritoneal dialysis. AhR binding activities decreased after hemodialysis treatment in HD patients. ATP level was the higher in healthy controls, compared to pre-dialysis CKD patients, and patients with peritoneal dialysis and hemodialysis. AhR binding activities and intracellular ATP levels showed significant correlations with multiple clinical parameters associated with cardiovascular risk factors.

Conclusions: POPs were associated with chronic kidney disease, and ESRD, while dialysis treatment reduced POPs levels. Further studies are mandated to specify the AhR binding activities and to evaluate the exact role in patients with chronic kidney disease

SA-PO1062

Cancer in Hemodialysis Patients

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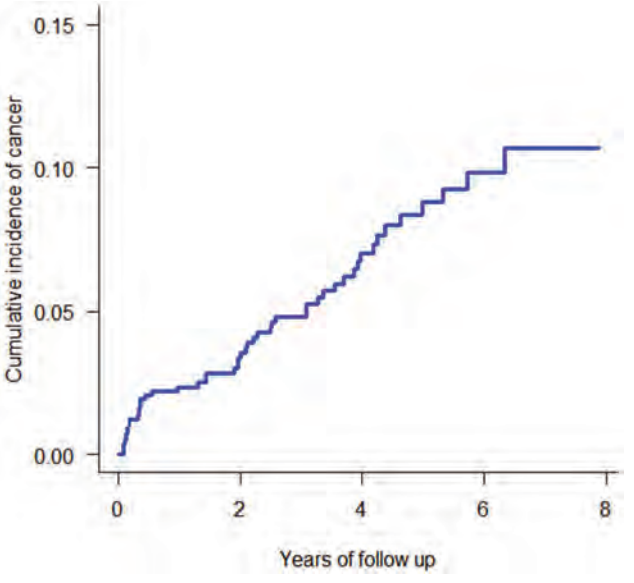
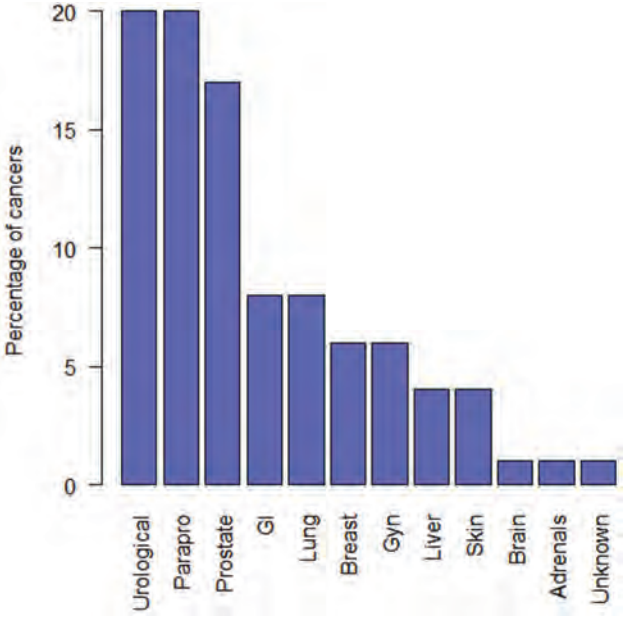
Background: Describe the incidence of cancer in hemodialysis patients. Describe the most common types of cancer in hemodialysis patients.

Methods: Incident hemodialysis patients enrolled in the Emory Dialysis program form 1/2011 to 12/2015 were followed until the diagnosis of cancer, death or censoring up to 12/31/2018. Time from inititation of dialysis to diagnosis of cancer and type of cancer was recorded.

Results: 902 patients were enrrolled in the hemodialysis program. 25 (2.8%) patients with prior cancer were excluded from the analysis as well as 51 patients followed less than a month. The remaining 826 patients are the base of this report. 51 patients (6.2%) developed a new cancer. Cancer patients were older (65 vs 57). The cumulative risk of cancer is presented in figure 1 (11%). The most common cancers were urological (20%), paraproteinemia (20%), prostate (17%), gastrointestinal (8%), lung (8%), breast (6%), gynecological (6%), liver (4%), skin (4%) and brain, adrenals and unknown primary with 1% (Figure 2)

Conclusions: The cumulative risk of cancer was 11% over 8 years. Cancer patients were older and had a lower hemoglobin. Urological, paraproteinemias and other solid organ cancers represent the majority of cancer diagnosed and this information could be used to delineate strategies for early detection of cancer in hemodialysis patients.





SA-PO1063

Concomitant Prescription of Gabapentinoids and Opioids Predicts Mortality and Morbidity Among US Dialysis Patients

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Background: The opioid epidemic is a public health emergency and appropriate prescription of medications for pain symptom management remains a challenge. Increasingly, providers prescribe gabapentenoids (gabapentin and pregabalin) for pain despite limited evidence to support their off-label use and reports of abuse in combination with opioids. We sought to estimate the prevalence of concomitant gabapentenoid and opioid prescriptions and evaluate the effect of concomitant prescriptions on morbidity and mortality among end-stage renal disease (ESRD) patients in the US.

Methods: We used the United States Renal Data System to identify ESRD patients who were continuously treated with dialysis and had part A, B, and D coverage for all of 2010. Part D filled prescription claims were used to identify whether each patient had filled a prescription for opioids, gabapentin, and pregabalin in 2010. Patients were followed for all-cause death, discontinuation of dialysis, and hospitalizations.

Results: The study population included 153,758 ESRD patients who met inclusion criteria. Concomitant prescription of an opioid and gabapentin (15%) was more common than concomitant prescription of an opioid and pregabalin (4%). In adjusted analyses

using Cox models, concomitant prescription of an opioid and gabapentin was associated with increased risk of death (HR=1.16, 95% CI= 1.12, 1.19), dialysis discontinuation (HR=1.14, 95% CI= 1.03, 1.27), and hospitalization (HR=1.33, 95% CI= 1.41, 1.53). Similarly, concomitant prescription of an opioid and pregabalin was associated with increased mortality (HR=1.22, 95% CI= 1.16, 1.28) and hospitalization (HR=1.37, 95% CI= 1.33, 1.41), but not dialysis discontinuation (HR=1.13, 95% CI= 0.95, 1.35).

Conclusions: Concomitant prescription of opioids and gabapentenoids among US dialysis patients is common and is associated with worse outcomes. We were unable to identify the reasons why drugs were prescribed. The mechanisms underlying adverse effects are unclear, but prescription of gabapentenoids may be a marker for a sicker patient. Future research should investigate the potential harms of concomitant use of these drugs prospectively and identify safe alternatives for pain symptom management.

SA-PO1064

Geographic Variation of Increasing Mortality Risk in Black Dialysis Patients with Medicare Fee-for-Service Coverage

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Background: We recently reported that the weekly risk of death in black dialysis patients with Medicare fee-for-service coverage increased between 2014 and 2017, from 25.2 deaths per 10,000 patients per week to 27.1 deaths per 10,000 patients per week (*Am J Nephrol*, 2019). We aimed to assess whether this increase was homogeneous across US Census Divisions.

Methods: Using Medicare Limited Data Sets, we identified all black patients with Medicare Part B claims documenting outpatient dialysis from January 2014 to December 2017. For each calendar week (Monday to Sunday), we identified patients who had at least one outpatient dialysis session and who were alive at the end of the week; we calculated the proportion of patients who died during the subsequent calendar week. From the time series of weekly death rates in each US Census Division, we fit an autoregressive integrated moving average model to assess secular trend.

Results: The cohort included 208,768 unique patients; 23,685,808 patient-weeks; and 62,200 deaths. Mean age was 59.2 ± 14.0 years, 53% were female, and 54% of patients were concurrently enrolled in Medicare and Medicaid. Weekly mortality rates among all black patients were 25.1, 26.3, 26.5, and 27.1 deaths per 10,000 patients per week in 2014, 2015, 2016, and 2017, respectively. Death rates per 10,000 patients per week, by Census Division, are displayed in the table. Weekly mortality rates increased both monotonically and significantly ($P < 0.05$) in the South Atlantic and East South Central regions, an area that stretches from the Mississippi and Ohio Rivers to the Atlantic Ocean.

Conclusions: Increasing mortality among black dialysis patients with Medicare fee-for-service coverage appears to be a unique feature of the southeastern part of the United States. The extent to which this trend reflects dialytic factors versus broader health and socioeconomic trends is unclear, but merits detailed investigation.

	2014	2015	2016	2017	*P* for trend
New England	24.5	21.6	27.5	22.9	0.68
Middle Atlantic	26.5	27.4	27.1	26.5	0.98
East North Central	26.2	26.9	28.1	27.7	0.42
West North Central	24.4	24.7	22.9	26.2	0.57
South Atlantic	24.6	26.0	26.2	27.3	<0.01
East South Central	23.6	26.0	26.4	27.0	0.04
West South Central	26.3	26.2	26.3	27.5	0.35
Mountain	19.9	20.9	24.5	24.3	0.31
Pacific	24.8	28.6	26.8	28.2	0.23

SA-PO1065

Effect of Probiotic Supplementation on Regulatory T Cells and Inflammatory Monocytes in Patients Undergoing Hemodialysis

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Background: Emerging evidence suggests that intestinal dysbiosis might contribute to systemic inflammation and cardiovascular diseases in dialysis patients. This study investigated the effects of probiotics supplementation on various inflammatory parameters in hemodialysis (HD) patients.

Methods: This study included 22 patients undergoing maintenance HD (IRB No. 2018AN0346). Patients received probiotics twice daily for 3 months (Zigunduk Bifidus Premium from BIFIDO Co, total 10 billion CFU of *Bifidobacterium bifidum* BGN4, *Bifidobacterium longum* BORI, *Lactobacillus acidophilus* AD031, and *Enterococcus facium* BH06). The percentages of CD14+CD16+ proinflammatory monocytes and CD4+CD25+ regulatory T cells (Treg) were determined by flow cytometry. Serum levels of calprotectin and zonulin (novel biomarkers of intestinal inflammation), and cytokine response to lipopolysaccharide (LPS) challenge, as well as various clinical parameters were compared before and after probiotics supplementation.

Results: The percentage of Treg showed a significant increase after 3 months of probiotic supplementation compared with baseline levels (8.6% vs. 3.5%, p<0.001), and the event count of CD14+CD16+ proinflammatory monocytes decreased significantly over baseline counts (194 vs. 310 cell numbers, p<0.05). LPS stimulation-induced interleukin (IL)-10 and IL-6 levels increased significantly (1159 vs. 517 pg/mL, and 37431 vs. 27663 pg/mL, respectively, p<0.05). Serum levels of calprotectin but not zonulin significantly decreased after probiotic supplementation.

Conclusions: These preliminary data suggest that probiotic supplementation may modulate systemic inflammation via expansion of Treg, suppression of proinflammatory monocytes, as well as reduction of gut inflammation in patients undergoing HD. Thus, targeting intestinal dysbiosis might be a new therapeutic strategy.

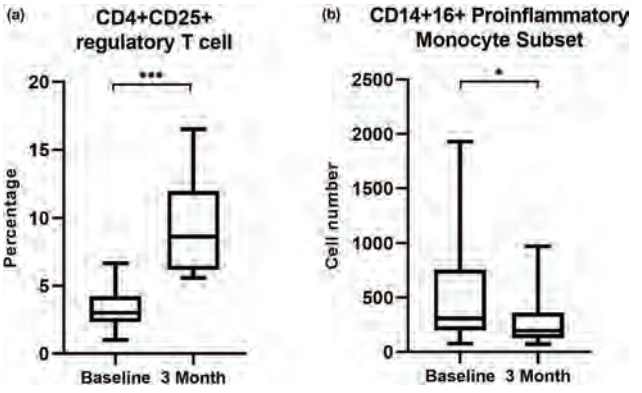

Figure 1 (a) CD4+CD25+ Treg percentage (b) Actual event count of CD14+CD16+ proinflammatory monocyte subset * p<0.05, *** p<0.001

SA-PO1066

Metabolic Changes in Peripheral Blood Mononuclear Cells Isolated from Dialysis Patients with Vascular Access Dysfunction

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Background: As numerous complex pathologies can stem from cellular energy dysfunction, we aimed to elucidate whether mitochondrial dysfunction contributes to arteriovenous fistula (AVF) and arteriovenous graft (AVG) failure in a cohort of dialysis patients. We used peripheral blood mononuclear cells (PBMCs) as the model system of disease monitoring for bioenergetic analyses.

Methods: The bioenergetics study was conducted using PBMCs and serum from dialysis patients with AVF or AVG (re)stenosis. PBMCs and serum are isolated from whole blood through the use of a density gradient centrifugation, aliquoted and frozen at -80°C until analysis. On the day of analysis, PBMCs from healthy controls and patients were thawed, diluted and counted before being seeded into Seahorse XF24 assay plate to detect changes in mitochondrial respiration. The bioenergetics analysis was performed in the presence of Seahorse XF medium (free of bicarbonate, pH 7.4) using mitochondrial stress test kit and Seahorse flux analyzer. In order to test the metabolic changes caused by patient serum, we used commercially available control PBMCs and treated those with 10% serum from healthy controls and patients in 6-well plates. After 24 hours, cells were harvested and loaded to Seahorse XF24 assay plates for the bioenergetic analysis.

Results: We developed a technique to measure mitochondrial oxygen consumption in PBMCs isolated from dialysis patients with AVF or AVG (re)stenosis and control PBMCs fed with patient's serum for 24 h. In PBMCs of patients, we found a reduction in each of fundamental parameters of mitochondrial function such as basal respiration, ATP turnover, proton leak, maximal respiration and spare respiratory capacity. A similar trend was observed when the control PBMCs were cultured in the presence of 10% serum from patients for 24 h.

Conclusions: Our data demonstrates a correlation between mitochondrial oxygen consumption of PBMCs and end-stage renal disease (ESRD) in a case-control study of 30 patients. We propose a link between mitochondrial dysfunction and vascular access failure since PBMCs are exposed to metabolic and hemodynamic stimuli in the vasculature. Our findings and the methodology may help identify individuals at risk for hemodialysis vascular access dysfunction.

Funding: NIDDK Support

SA-PO1067

Evaluation of NATEM (ROTEM Delta) in Whole, Non-Citrated Blood in Hemodialysis Patients During Citrate and Dalteparin Anticoagulation

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Background: Standard clotting tests are performed in citrated blood. To investigate clotting in a study comparing citrate vs dalteparin anticoagulation during hemodialysis (HD), a NATEM in whole blood was developed using non-citrated blood. This study evaluates this NATEM.

Methods: 12 HD patients on anticoagulants (6 vit. K antagonist; 6 acetylsalicylic acid), underwent 2 standard HD sessions with dalteparin and 2 sessions using a Ca/Mg-free, 0.8 mmol/l citrate containing dialysis fluid with Ca/Mg substitution at the venous needle. Before, during and after HD, blood was taken for NATEM (ROTEM Delta, Tem-innovations Munich) in non-citrated (NC-) and citrated tubes (NC+). Clotting time (CT) is the time from starting the measurement until clot formation starts. Clot formation time (CFT) is the time from CT until a clot firmness of 20 mm is reached. Alpha is the angle of tangent between 0 mm and the curve when the clot firmness is 20 mm. A10 and A20

describe the clot firmness after 10 and 20 minutes. Maximum clot firmness (MCF) is the greatest vertical amplitude. NC+ within 10 minutes of NC- were considered to be simultaneous measurements. Data were analyzed using linear mixed models to account for repeated measurements and using linear regression to assess bias between methods. Median (M) and interquartile range (IQR) are reported.

Results: NC- CT (n=130; M 1116, IQR 942 – 1455 sec) and NC+ CT (n= 126; M 937, IQR 747 – 1281 sec) were correlated (Spearman rho 0.71; p<0.001). There was a constant and a proportional bias with NC- CT giving higher values than NC+ CT. After 45-60 minutes 2 duplicate NC+ were performed. The mean of these CT values (n= 43; M 546, IQR 448 – 776 sec) showed a significant constant bias towards the initial NC+ indicating a decrease of CT in time. Spearman rho correlations between NC- and NC+ were for CFT 0.44, alpha 0.53, A10 0.52, A20 0.58 and MCF 0.63 (p < 0.001).

Conclusions: (Anti)coagulation in citrate HD can be measured with NATEM in whole, citrated blood (NC+), NATEM (NC-) in whole, non-citrated blood can be done but is not necessary. However; results in NC+ change over time. This dictates that NC+ should be performed at a set time after sample collection.

Funding: Commercial Support - Werfen Benelux, Breda, The Netherlands

SA-PO1068

Hospitalization Patterns in a Large Saudi Hemodialysis Population

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Background: Our aim was to analyze patterns and risks of hospitalizations in a large cohort of hemodialysis patients treated in 22 outpatient clinics all over Saudi Arabia (KSA).

Methods: The study included all patients admitted at Davita-KSA clinics to continue hemodialysis treatment during the period from October 2014 to December 2018. Overall and cause-specific hospitalization rates were calculated by dividing the number of hospitalizations by the cumulative period of follow-up. Logistic regression was performed to identify factors predisposing to hospitalization.

Results: 3508 patients were included (1897 males, 1611 females) with a mean age of 52.5 ± 16.9 years. During a cumulative follow-up period of 5584 years, 1576 hospitalizations were recorded in 26.1% of included patients, 38.7% of them had repeated admissions. Infectious causes, including those related to vascular access, accounted for 34.1% of all recorded hospital admissions vs. 18.8% for cardiovascular complications. The overall hospitalization rate was of 28.2 % patient-years with an annual duration of 3.4 days per patient. Infectious complications, not related to vascular access, accounted for the highest cause with an annual rate of 6.73 % vs. 5.32% for cardiovascular causes and 4.83% for hospitalizations attributed to vascular access creation and complications. The median length of hospital stays 11.5 days (range: 2-244 days) with an annual rate of 3.39 days per patient. This rate ranged from 0.05 for hospitalizations related to vascular access to 0.70 and 0. for infectious causes. Predictors of hospitalization were: Female gender (RR: 1.34, 95%; CI: 1.15-1.56), Age ≥ 65 years (RR: 1.32, 95% CI: 1.11-1.58); time on dialysis (RR: 1.44 per year, 95% CI: 1.34-1.55) diabetic nephropathy (RR: 1.61, 95% CI: 1.38-1.89), and Catheter as vascular access (RR: 1.38, 95% CI: 1.17-1.63)). Among all these factors, Diabetic nephropathy predisposed to a prolonged hospital stay.

Conclusions: Infectious complications were the leading cause of hospitalization among our hemodialysis patients and resulted in the longest hospital stay. Female gender, Age ≥ 65 years, Diabetic nephropathy, Catheter as vascular access and, time on dialysis were found as predisposing to hospitalization but only diabetic nephropathy is associated with prolonged hospitalization.

SA-PO1069

Profiles of Dialysis Recovery Time in Incident Home and In-Center Hemodialysis

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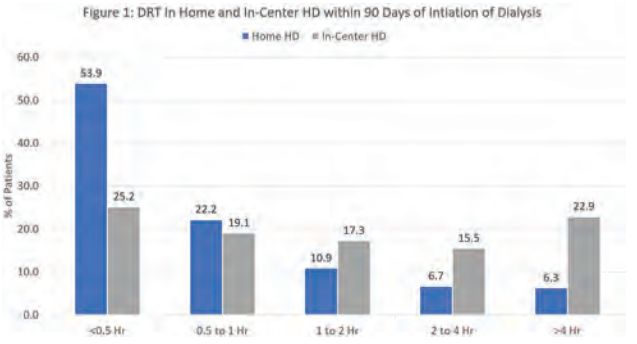
Background: Home hemodialysis (HHD) includes frequent treatments typically 4-6 times per week and yields a higher adequacy and fluid removal. HHD associates to reductions in dialysis recovery time (DRT) compared to in-center HD (ICHD) in prevalent patients who switch to the modality. DRT is a measure of the perceived time after HD a patient feels they can return to performing normal daily activities. We characterized the profiles of DRT in incident patients treated with HHD and ICHD.

Methods: We used data from adult incident HD patients treated at a large dialysis provider who completed a DRT survey ≤180 days from the first date of dialysis (FDD) during 2014 to 2017. DRT survey is administered with the annual KDQOL questionnaire and asks: "How long does it take you to be able to return to your normal activities after your dialysis treatment?" Categorical answers include: <0.5, 0.5-1, 1-2, 2-4, >4 hours. We calculated the percentage of patients in DRT categories for the HHD and ICHD groups.

Results: We analyzed data from 1091 HHD and 98616 ICHD patients who completed the DRT survey ≤180 days from FDD. A lower proportion of HHD patients reported DRT >1 hour compared to ICHD (Figure 1). About half of HHD patients (53.9%) and a quarter (25.2%) of ICHD patients reported a DRT <0.5 hour.

Conclusions: Incident HD patients treated by HHD appear to experience a shorter DRT compared to ICHD. These findings show consistent signals with the Frequent Hemodialysis Network trial results in prevalent HD (Garg Kidney Int. 2017). Patients who chose HHD modality may be younger and have distinct clinical presentations and adjusted analysis are needed to substantiate these findings.

Funding: Commercial Support - Fresenius Medical Care North America



SA-PO1070

Provision of Outpatient Backup Dialysis in a Home Hemodialysis Unit

Claire Kennedy,[1,2] Bourne L. Auguste,[1,2] Michael Y. Girsberger,[1,2] Thatsaphan Srithongkul,[1,2] Rose Faratro,[4] Christopher T. Chan.[3,2] *[1]Nephrology, Toronto General Hospital, Toronto, ON, Canada; [2]Medicine, University of Toronto, Toronto, ON, Canada; [3]Toronto General Hospital, Toronto, ON, Canada; [4]University Health Network, Toronto, ON, Canada*.

Background: Patients doing home hemodialysis (HHD) require support from the parent unit when medical, dialysis-related and psychosocial issues arise at home. It is important that each HHD program makes provision for timely clinical assessment and back-up hemodialysis (HD), although this need has not been well quantified previously.

Methods: This was a retrospective, single-center cohort study of a HHD unit with an open-door policy in terms of clinical assessment and back-up HD during weekday office hours. Back-up HD in the incenter HD unit was organized for outpatient situations that arose outside of these hours. Emergency situations were directed to the emergency department (ED). The HHD unit electronic and paper medical records were reviewed for a twelve-month period. The uptake of outpatient back-up HD was established and reasons for this need were summarized.

Results: There were 104 to 107 prevalent patients in the HHD program during the twelve-month period. 79 outpatients attended for back-up HD (167 separate issues requiring 254 back-up HD sessions). Back-up dialysis was performed most commonly for medical reasons; followed by vascular access issues, technical issues, respite HD and post-operative/post-procedure HD (Figure). The majority of these issues necessitated one back-up HD session, facilitated in the HHD unit during weekday office hours. Respite HD for psychosocial reasons accounted for a small proportion of provided back-up HD.

Conclusions: One to two staffed dialysis stations were required each weekday for back-up HD in this HHD program of 100+ patients. Prompt access to clinical assessment and back-up HD in the parent HHD unit may relieve pressure on the incenter HD unit, ED and inpatient ward, and may facilitate ongoing HHD technique survival.

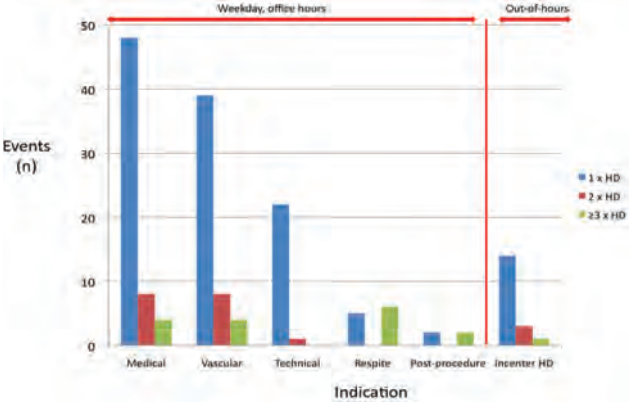


Figure: The number of separate events necessitating back-up outpatient HD that arose in a twelve-month period, and the number of back-up HHD sessions each issue required.

SA-PO1071

Barriers to Home Hemodialysis in Saskatchewan Canada: Results from a Provincial Survey

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Background: Home hemodialysis (HHD) offers similar, and perhaps even superior clinical outcomes to in-center hemodialysis (HD) at a fraction of the cost. HHD remains underutilized as remote HD patients in Saskatchewan often relocate or travel hundreds of kilometers weekly in order to receive dialysis related care. The purpose of this study was to determine the barriers to receiving HHD in our province.

Methods: We conducted a cross sectional survey of in center HD patients across the province of Saskatchewan. 740 in center HD patients (two academic sites, 7 satellite units) were approached by study coordinators. 421 patients (n=268 in the main units and n=153 in the satellite units) agreed to participate in the study. A five-point Likert scale survey was created to identify barriers to HHD with questions addressing HHD awareness and knowledge, accessibility, home constraints, impact on family members, and risks/ fears/beliefs surrounding HHD. Responses were anonymous and tabulated using a data collection tool.

Results: Only 76% of patients were aware of HHD. 46% of patients felt they had no understanding of the benefits or risks of HHD. Despite only 8% of patients being told they were unsuitable for HHD by their nephrologist, only 28% had ever considered it as a treatment option. Other prominent barriers to HHD were: satisfaction with in center HD (76%), medical supervision during HD (76%), opportunity to socialize with in center HD patients (73%), increase in utility payments (54%), and fear of having a major health event at home (51%). Other home constraints (space, inability to make modifications to the home) also figured prominently (35%).

Conclusions: In this study, we identified patient specific barriers to HHD in a prevalent cohort of HD patients. Several barriers were identified with a few consistent themes being identified, including deficiencies in knowledge and awareness, home constraints, and perceived benefits of in center care (satisfaction with current care, socializing with patients and staff, and fear of a catastrophic event at home). The most frequently reported knowledge barrier was a lack of understanding of the benefits and risks of HHD. While the study does not reflect views of all the patients, this information will be valuable in designing an educational program to improve adoption of HHD within our province.

SA-PO1072

Differences in Perceptions of Home-Based Dialysis Therapies Among the Renal Multidisciplinary Team

Krishna Poinen,[1] Mark Canney,[1] Lee Er,[2] Michael A. Copland.[1] *[1]University of British Columbia, Vancouver, BC, Canada; [2]BC Renal, Vancouver, BC, Canada*.

Background: Patients with end stage renal disease are encouraged to pursue home-based dialysis therapy (HDT) with the aims of improving quality of life, increasing patient autonomy and reducing the cost to the health care system. In the multidisciplinary setting, patients have exposure to nurses, clinicians and allied health staff, all of whom may influence a patient's modality choice. We aimed to evaluate the perceptions of HDT amongst multidisciplinary team members and identify avenues for further education

Methods: An electronic survey was distributed over a 6-week period to 695 non-transplant multidisciplinary team members across multiple renal centers in British Columbia, Canada. The survey contained questions about work environment, patient/ system factors in choosing HDT, perceived knowledge of HDT and the need for further education. Results were stratified by 5 categories of respondent: nephrologists, nurses in 3 clinical areas (facility hemodialysis, HDT, pre-dialysis), and allied health (pharmacists, social workers, dieticians)

Results: A total of 334 respondents were included (48% response rate). The majority of respondents in all categories stated that they would choose HDT if they were ever to require dialysis. The majority also recommended that a higher proportion of patients should receive HDT, especially patients who work or study. Facility nurses were believed to have the least impact on a patient's choice of modality, yet they also perceived themselves as key patient educators. Facility and HDT nurses favored in-center dialysis and HDT respectively for patients with lower socioeconomic status, lower education or a language barrier. All respondents acknowledged the benefits of HDT for cost-savings and improved patient survival. The majority of nurses and allied health staff felt the need for further education in HDT, favoring practical over knowledge-based educational opportunities

Conclusions: The majority of the renal multidisciplinary team members would welcome increased uptake of HDT due to benefits on the patient and healthcare system level. Nurses differed substantially in their perceptions of modifiable barriers to HDT depending on their primary area of work. Further HDT education has the potential to bridge these gaps and help patients make informed decisions about their dialysis modality

SA-PO1074

Clinical and Biological Comparison Between Nurse-Assisted Home Hemodialysis (NAHHD) and In-Center Hemodialysis (CHD) in Home-Bound and Multicomorbid Hemodialysis Patients: One-Year Results

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Background: Home hemodialysis (HHD) is a renal replacement modality used to treat active, autonomous, and relatively, healthy dialysis patients. The steady increase in the number of dialysis patients, with multi-comorbidities and limited mobility is creating a significant burden on the active hospital beds, and on the outpatient dialysis units. The clinical and biological outcome, of treating those highly comorbid and disabled dialysis patients with nurse assisted home hemodialysis (NAHHD) at home compared to in-center HD, is unknown. We are reporting the results of one year on NAHHD, compared to one year in CHD.

Methods: The data of 19 patients, treated in center hemodialysis (CHD) for average period of 12 months (4-14), was compared retrospectively, to average period of 12 months (4-25), on (NAHHD) for the same set of patients. All patients were dialyzed by Fresenius 5008 machine in center and by NxStage System One Cycler at home. Reasons for shifting patients to NAHHD program were: bed-confinement/ limited mobility in 12 (63%), morbid obesity in 3 (16%), psychiatric disorder/ mental retardation in 3 (16%), and others 1(5%).

Results: The mean age of the patients was 69.33 ± 12.08 (42-90) years. Etiology of ESKD was DM in 15(79%), HTN in 3(16%) and others 1(5%). The average number of comorbidities was 9.6 ± 3.07 (6-16). Vascular Access type: AVF 9(48%), AVG 1(5%), PC 7(37%), and AVG/PC/AVF 2(10%). The comparison between the results while in CHD and during NAHHD are illustrated in the Table.

Conclusions: In home bound and multi comorbid hemodialysis patients; NAHHD by using NxStage System One cycler, is safe, efficient, with better clinical and biological outcome, compared to in center HD.

Average Comparison of clinical and biological parameters in 19 patients

Parameter	NAHHD	In-center HD	P-Value	Decision
Albumin g/L	39	33	0.04	S
Ca mmol/L	2.2	2.2	0.14	NS
PO4 mmol/L	1.4	1.7	0.04	S
PTH pg/mL	331	594	0.000	S
Hb g/L	111	106	0.03	S
ESA monthly dose mcg	80.3	111.3	0.003	S
Iron monthly dose mg	171	177	0.04	S
Std Kt/V	2.21	2.16	0.12	NS
UF Weight Gain (L)	1.8	2.2	0.01	S
Dialysate volume L/session	26	120	0.000	S
Dialysis Frequency (sessions/week)	4	3	0.04	S
Dialysis Time (minutes/session)	216	230	0.04	S

S: = Significant: NS = Not Significant

SA-PO1075

Profiles of Demographics, Nutrition, and Outcomes in Home and In-Center Hemodialysis

John Danziger,[2] Sheetal Chaudhuri,[3] Joanna Willetts,[3] Marta Reviriego-Mendoza,[3] John W. Larkin,[3] Len A. Usvyat,[3] Joseph E. Turk,[3] Jeffrey L. Hymes,[3] Robert J. Kossmann,[3] Franklin W. Maddux.[1] *[1]Fresenius Medical Care, Waltham, MA; [2]Harvard Medical School, Brookline, MA; [3]Fresenius Medical Care North America, Waltham, MA.*

Background: Home hemodialysis (HHD) may have favorable attributes related to the provision of better adequacy and fluid removal with more frequent treatments. HHD has been associated with improved blood pressure control and lower all-cause/cardiovascular event rates. We characterized the demographics, nutritional status, and outcomes among patients undergoing HHD and in-center hemodialysis (ICHD) at a large dialysis organization (LDO).

Methods: We used data from HHD and ICHD patients treated at the LDO in November 2018 to January 2019. We profiled the average proportion of HHD and ICHD patients achieving target goals for i) albumin ≥4mg/dL, ii) mineral bone disorder (MBD)

with calcium ≤10.0mg/dL, phosphate ≥3.0-≤5.5mg/dL, and intact parathyroid hormone (iPTH) ≥150-≤600pg/mL, and iii) central venous catheter (CVC) <90 days. We also calculated the unadjusted hospital admission rates per patient per year (ppy) for the groups.

Results: We included data on 171,712 patients (HHD n=4141, ICHD n=167571). A larger proportion of HHD patients were younger (HHD=55.5, ICHD=63.5 years), male (HHD=63%, ICHD=57%), and white race (HHD=55%, ICHD=47%). A greater proportion of HHD patients achieved target albumin levels (HHD=51%, ICHD=37%), yet a slightly lower proportion of HHD patients achieved MBD goals (HHD=46%, ICHD=49%). The proportion of patients with catheter exposure >90 days was relatively consistent between groups (HHD=13%, ICHD=15%). Patients treated with HHD exhibited lower hospital admission rates (HHD=1.07, ICHD=1.55 admits ppy).

Conclusions: Patients treated with HHD more commonly achieved nutritional goals for albumin compared to those treated with ICHD. HHD patients may have unique eating habits with more protein and dietary phosphate intake that may be leading to lower MBD goal achievement compared to ICHD. HHD patients tended to have less hospital admissions compared to ICHD, yet an adjusted analysis is needed to validate this observation in a population group with distinct demographics.

Funding: Commercial Support - Fresenius Medical Care North America

SA-PO1076

Enhancement of Solute Clearance Using an Experimental Pulsatile Push Pull Dialysate Flow Mode for the Quanta SC+: A Novel Clinic-to-Home Hemodialysis System

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Background: The SC+ hemodialysis system is a small, easy to use dialysis system designed to improve patient access to self care and home hemodialysis. A prototype of the SC+ device with a pulsatile push pull dialysate flow was developed for evaluation purposes.

Methods: The pumping action of the prototype SC+ system was modified by altering software algorithms controlling the sequencing and timings of the valves and pumps associated with the flow balancing chambers that push and pull dialysis fluid to and from the dialyzer; no additional modifications to the hardware or consumables were required. Solute clearance performance was assessed in the prototype SC+ system across a range of molecular weights in two related series of laboratory bench studies. The first measured dialysis fluid moving across the dialyzer membrane using ultrasonic flowmeters to establish the validity of the approach; solute clearance was subsequently measured using fluorescently tagged dextran molecules as surrogates for uremic toxins. The second study used human blood doped with uremic toxins. In both, the performance of the SC+ prototype was assessed alongside reference devices operating in HD and pre-dilution hemodiafiltration (HDF) modes.

Results: Initial testing with fluorescein-tagged dextran molecules (0.3 kDa, 4 kDa, 10 kDa and 20 kDa) established the validity of the experimental pulsatile push-pull operation in the prototype SC+ system to enhance clearance and demonstrated a 10 to 15% improvement above the current HD mode used in clinic today. Additional testing using human blood indicated a comparable performance to pre-dilution HDF.

Conclusions: The observed enhancement of solute transport is attributed to the disruption of the boundary layers at the fluid-membrane interface which, when used with blood, minimizes protein fouling and maintains the surface area available for mass and fluid transport. In contrast with current HDF technologies, this improvement in performance has been achieved without the introduction of any additional complexity to the device hardware or fluidic circuit consumable sets maintaining ease of use of the SC+ system.

Funding: Commercial Support - Quanta Dialysis Technologies

SA-PO1077

Convective Daily Home Dialysis Program Development: Preliminary Outcomes

Philippe Nicoud. *Centre de Néphrologie du Mont Blanc, Sallanches, France.*

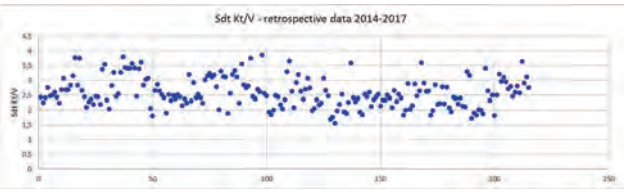
Background: Since 2014, 370 ESRD French patients entered a new short daily home dialysis program based on a convective therapy. We present here the primary clinical and biological outcomes of the first 140 patients treated.

Methods: The epidemiological and clinical characteristics of these 140 patients treated with this technique were analyzed after retrospective data collection. Weekly dialysis performance was evaluated according to the standardized Kt/V (SDT) using the Gotch method. Data were collected during the in-center training periods of each patient prior to their final home installation.

Results: The anonymized data of 140 patients in the technique (age: 53 ± 7 y, weight: 74.2 ± 16.5 kg) were collected. Sex ratio: Male 74%; Female 26%. 123 patients (88%), were diabetes type II free and 80 patients (57%) have kept a residual kidney function. 98 patients (70%) had full time job. 228 home daily dialysis sessions were performed between 2014 and 2017, average time 124 ± 12 min per session, 5.8 ± 0.4 sessions per week. Average blood flow was 284 ± 19 mL/min, dialysate flow 181 ± 6 mL/min. Average Convection volume excluding weight loss was 3.040 ± 1.059 mL per session. The urea Kt/V SDT, was greater than 2.1 in 184/215 (86%) sessions (figure) and the average ultrafiltration rate was 8.5 ± 5, 1mL/h/kg.

Conclusions: This work illustrates the clinical and biological profile of the first patients treated with a short daily home dialysis convective technic. It gives the level of performance in terms of urea RR, convective volume achieved and ultrafiltration rate. These results have to be confirmed and refined by a broader multicentric retrospective study, RECAP, currently underway, which include all the ESRD patients entering this technique between January 2014 and June 2018.

Funding: Commercial Support - PHYSIDIA



SA-PO1078

Daily Home Hemodialysis (DHHD) in Large Patients: Observation and Data from the Knowledge to Improve Home Dialysis Network in Europe (KIHDNEy) Cohort

Hafedh Fessi. *Hopital Tenon, Paris, France.*

Introduction: Obesity is steadily increasing among HD patients (15–26% in W.Europe), responsible for high morbidity and mortality due to multiple metabolic abnormalities and cardiovascular risk factors: insulin resistance, infections, hypertension, sleep apnea… and for reduced mobility. Kt/V target is poorly evaluated as usual formulas overestimate V.

Case Description: A male patient aged 34, 200kg weight, BMI 54.2kg/m2, presents CKD5 due to segmental and focal hyalinosis, is dialyzed incenter 3x5h=15h/week for 3 years, complains of severe fatigue and joint pain reducing his mobility, and of restless leg syndrome disrupting his sleep, stops working but agrees to train on SystemOne. Prescription is 6x150mn=15h/week, same duration as incenter. Dialysate and blood flow rates are 200 and 450ml/min. Restless leg syndrome disappeared and he complains less of fatigue at 4 weeks. Mobility improved and he returns to work after 2 months. Joint pain decreased at 6 months. Biological parameters improve as early as week 4: decrease in pre-dialysis urea 23 vs 38mmol/l and b2m 15.3 vs 21.4mg/l. Albuminemia increases from 35.9 to 45.6 g/l. Phosphoremia is stable, phosphorus chelators unchanged. Fistula used daily for 2 years (buttonhole) doesn't present complication.

Discussion: The retrospective Cohort Study KIHDNEy involved 219 patients on DHHD in 5 European countries. 101 patients (46.8%) had a normal BMIn, avg 21.8kg/m2, 47 patients (21.8%) had a high BMIh, avg 36.3kg/m2 (30.1–53.7). 68.1% of BMIh patients were male, aged 51.7±11.4. 66.0% of BMIh dialyzed ≥6x/week, cumulative time was 16.6±3.1h/w vs 14.0±3.6 for BMIn. Ultrafiltration rate was low, 4.6±3.5 ml/kg/h vs. 7.4±5.0. Dialysate volume was greater: 38.3% used ≤25 L/session vs. 75.2%. Mean stdKt/V 2.5 at 6 and 12 months did not vary and was equivalent to BMIn, 2.6(p=0.91). Baseline phosphoremia did not change at 6 and 12 months (1.70, 1.73, 1.63mmol/l, p=0.44). PO4 chelators decreased by 17% (3.07, 2.92, 2.53 tablets, p=0.04). Antihypertensives decreased by 37% (1.44, 1.03, 0.91, p<0.01). Conclusion: Evaluation of V with bioimpedance is recommended to customize prescription for obese and very large patients. Thus DHHD is adequate, with high clearance and low ultrafiltration. It improves clinical outcomes and quality of life, which are as good as normal size patients, and addresses the mobility challenge.

SA-PO1079

A Study to Evaluate a New Hemodialysis Device in the Home

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Background: The Tablo® Hemodialysis system is an automated, sensor-based system that simplifies operation and produces on demand dialysate without the need for separate water treatment. It is currently indicated for use in acute and chronic care settings. The purpose of this study was to describe the patient population enrolled in a home study and the rate of adherence to the dialysis frequency protocol requirement.

Methods: A prospective multicenter, open-label, non-randomized, cross-over study was completed to evaluate Tablo in the home by subjects with end stage renal disease (ESRD) who are on stable dialysis regimens. The FDA-approved study required an In-Center arm with 32 treatments, a transition period of 8-16 treatments, and an In-Home arm with 32 treatments. Dialysis frequency was 4 times per week. The primary efficacy endpoint was a weekly standardized Kt/V of ≥ 2.1, and the primary safety endpoint was the mean number of adverse events from a pre-specified list. The secondary endpoint was ultrafiltration (UF) rate within 10% of the prescribed UF goal.

Results: Thirty patients from 8 dialysis units in the US were enrolled, and 28 per-protocol patients completed 1742 treatments. Compliance to the protocol dialysis frequency in the per-protocol group was 97%. Preliminary analysis suggests the study met all safety and efficacy endpoints.

Conclusions: Patients in the study were representative of the overall dialysis population. Protocol compliance was high and preliminary data indicates study objectives were achieved.

Funding: Commercial Support - Outset Medical

Baseline Clinical Data

Demographics Variable	Category	Overall (N=30)
Gender	Male	19 (63.3%)
Age	Mean	52
	Range	26-71
BMI	Mean	31.8
	Range	22.2-40.5
Race/Ethnicity	White	9 (30.0%)
	Hispanic	8 (26.7%)
	Black or African American	13 (43.3%)
Access Type	Fistula	23 (76.7%)
	Catheter	4 (13.3%)
	Graft	3 (10.0%)
Primary Cause of ESRD	Diabetes	14 (46.7%)
	Hypertension	3 (10.0%)
	Failed Transplant	3 (10.0%)
	PCKD	2 (6.7%)
	Glomerulonephritis	1 (3.3%)
	Other	7 (23.3%)
Pre-dialysis Systolic BP (mmHg)	Mean	153.4
	Range	109-188
Pre-study modality	In-center dialysis	16 (53%)

SA-PO1080

Validation of Revisions to the NxStage Dosing Calculator

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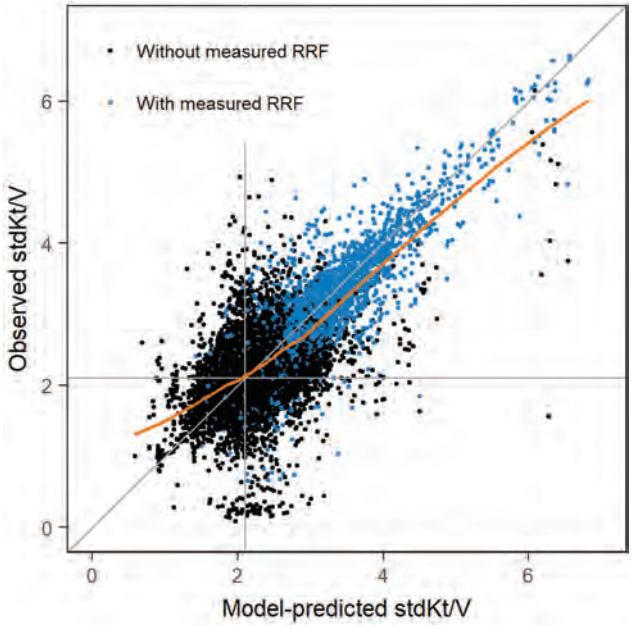
Background: The NxStage Dosing Calculator (DC) is an online tool that can be used to identify hemodialysis prescriptions that achieve a specified standardized *Kt/V* on the NxStage System One (NSO) platform. The DC has recently been revised to align with formulae in *Kidney Disease Outcomes Quality Initiative* guidelines and to permit incorporation of residual renal function (RRF). We used home hemodialysis (HHD) patient data from a large dialysis organization to validate DC revisions.

Methods: We identified adult patients who initiated HHD with NxStage equipment in Fresenius Kidney Care (FKC) clinics between March 1, 2016, and December 1, 2018. Patients were followed from completion of HHD training to discontinuation of HHD with NxStage equipment at FKC. We collected patient-days with pre- and post-dialysis blood urea nitrogen (BUN) measurements and retained those with exact adherence to prescribed treatment frequency during the preceding 7 days. We derived model-predicted standardized (std) *Kt/V* from the HHD prescription, and observed std *Kt/V* from BUN measurements, before and after DC revisions.

Results: The cohort included 3427 patients and 23,408 patient-days with BUN measurements. Over 91% of patient-days were accompanied by 4 or 5 weekly treatments, and RRF was measured in 19%. Model-predicted and observed std *Kt/V*, given DC revisions, are displayed in the figure, with a smoothed trend in orange. DC revisions increased the proportion of variation in observed std *Kt/V* that was explained by model-predicted std *Kt/V* from 26% to 58%.

Conclusions: Revisions to the NxStage DC have improved concordance of predicted and observed std *Kt/V* in HHD patients, especially near guideline targets. RRF is influential on forecasted *Kt/V*, so continued reliance on RRF in HHD patients requires accurate, timely data about RRF.



SA-PO1081

The Ambiguous Identity of Home Hemodialysis in Medicare Claims

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Background: Home hemodialysis (HHD) is performed in a home, which may be a private residence or a skilled nursing facility (SNF). Although the Centers for Medicare & Medicaid Services issued a condition code in 2005 for dialysis in a SNF, the code is rarely used. Epidemiologic and actuarial analysis of HHD in Medicare claims is thus compromised by an uncertain mix of two very different care settings. We analyzed Medicare expenditures among contemporary HHD patients, stratified by probable status of the HHD program as a SNF-oriented provider.

Methods: Using 2016 Medicare Limited Data Sets, including 100% of institutional claims and 5% of physician/supplier claims, we tallied Medicare Parts A and B expenditures, excluding those for outpatient dialysis, for HHD patients. We used public use files to remove wage indices from all expenditures. We stratified patients according to one facility-level factor: the percentage of patients in the facility on December 31, 2015, who had resided in a SNF during any part of 2015, as shown in the Dialysis Facility Report. For simplicity, we stratified HHD patients according to whether this facility-level factor was <40% versus ≥40%. Within each stratum, we calculated expenditures per patient-year (PY).

Results: Total Medicare Parts A and B expenditures, excluding those for dialysis, were $52,678 and $191,242 per PY among HHD patients in facilities with <40% and ≥40% prior-year prevalence of SNF residency. This factor was associated with large relative rates in inpatient facility, skilled nursing facility, and ambulance transport expenditures, as shown in the table. Analysis of individual facilities with HHD patients and the highest values of prior-year prevalence of SNF residency routinely revealed providers that deliver on-site hemodialysis in the SNF setting.

Conclusions: HHD in Medicare claims clearly reflects two phenotypes. CMS must address this inherent ambiguity to facilitate meaningful evaluation of outcomes on HHD.

	Prior-year prevalence of SNF residency	
	<40%	≥40%
Inpatient facility	$28,542	$108,080
Skilled nursing facility	$2,182	$51,356
Home health agency	$1,250	$612
Outpatient facility (excluding OP dialysis)	$7,108	$7,738
Ambulance transport	$574	$2,856
Nephrology MCP	$1,930	$1,727
All other physician claims	$11,093	$18,874

SA-PO1082

Surfacer Inside-Out Access Procedure for Effective and Quick Placement of Venous Catheters in Patients with Thoracic Central Venous Obstruction

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Background: Thoracic central venous obstruction (TCVO) associated with repeated insertion or prolonged use of central venous catheters (CVCs) is common in hemodialysis populations. The ***S**urfacer System to Facilitate **A**ccess in **V**enous Occlusions* (SAVE) Registry was designed to evaluate the performance of the Surfacer, a novel inside-out procedure for patients with limited or diminishing upper body venous access or pathology impeding standard access methods. During this prospective, single-arm, multicenter, international registry, the Surfacer System was integrated during routine clinical care to facilitate right-sided placement of CVCs in patients with TCVO.

Methods: Five sites enrolled 30 patients in the SAVE Registry. Enrollment occurred between February 2017 and September 2018. Patient demographics, medical history and type of TCVO based on Dolmatch et al (*J Vasc Interv Radiol*. 2018;29:454-460) were collected at enrollment. Twenty-nine of the 30 patients with TCVO required CVCs for hemodialysis and 1 for chronic apheresis. Surfacer performance (success rate of CVC placement, procedural and fluoroscopy time), device-related adverse events, catheter malpositionings and postprocedural complications were documented during the procedure and upon hospital discharge.

Results: Baseline venography revealed 30% of patients had Type 4 occlusions, 26.7% had Type 3, 16.7% has Type 2, and 26.7% had Type 1. Successful CVC placement was achieved in 29 patients (96.7%). Mean completion time was 24 ±14.9 minutes, mean fluoroscopy time was 6.8 ± 4.5 minutes and mean contract volume use was 29.7 ± 22.2. The procedure was discontinued in 1 patient (3.3%) due to significant vascular anatomical tortuosity. There were no adverse events or complications.

Conclusions: The Surfacer Inside-Out access procedure enables effective, safe and quick placement of right-sided venous catheters in patients with thoracic central venous obstructions.

SA-PO1083

Effect of Early Cannulation with Plastic Cannula on Patency of Arteriovenous Fistula for Hemodialysis

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Background: Plastic cannulas for hemodialysis have been used in Japan for many years; however, effect of early cannulation with plastic cannulas on arteriovenous fistula (AVF) patency is unknown. We studied if early cannulation with plastic cannulas would affect AVF patency.

Methods: ESRD patients who underwent primary AVF operations were divided into an early cannulation group with first cannulation time (FCT) within<10 days and a late cannulation group with FCT≥10 days. The Kaplan-Meier method and multivariable Cox regression models were used to investigate AVF patency.

Results: 122 patients were enrolled in the study (mean age, 72.5 yr;64.8%male;52%diabetes mellitus;89%RCAVFs), median FCT was 6 days. Kaplan-Meier analysis showed that there was no statistically significant between-group difference in primary or secondary patency rates. Early cannulation was not found significantly associated with primary patency or secondary patency after age, gender, the presence of diabetes mellitus, hypertention and being on hemodialysis were adjusted.

Conclusions: Early cannulation with plastic cannulas might not affect AVF patency, maybe we can cannulate AVFs earlier than 10 days after AVF creation to avoid the use of central venous catheters.

Table 1. Hazard ratios for primary patency of arteriovenous fistulas according to first cannulation time (n=122)

	FCT<10 days	FCT≥10 days	
	HR (95% CI)		*P*-value
Cases, n (%)	88 (72.1)	34 (27.9)	
Model 0[a]	1.11(0.70–1.77)	1.00 (reference)	0.651
Model 1[b]	1.13(0.71–1.80)	1.00 (reference)	0.595
Model 2[c]	1.21(0.71–2.05)	1.00 (reference)	0.477

Table 2. Hazard ratios for secondary patency of arteriovenous fistulas according to first cannulation time (n=122)

	FCT<10 days	FCT≥10 days	
	HR (95% CI)		*P*-value
Cases, n (%)	88 (72.1)	34 (27.9)	
Model 0[a]	0.57(0.13–2.55)	1.00 (reference)	0.459
Model 1[b]	0.44(0.10–2.00)	1.00 (reference)	0.288
Model 2[c]	0.46(0.08–2.77)	1.00 (reference)	0.399

[a]Model 0 single-factor analysis, [b]model 1 adjusted for age and sex, [c]model 2 additionally adjusted for diabetes mellitus, hypertension, and being on hemodialysis. CI, confidence interval; FCT, first cannulation time; HR, hazard ratio

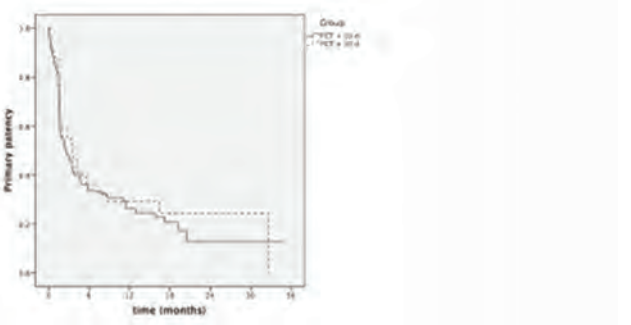

Figure 1. Primary patency of AVFs which were first cannulated within 10 days and more than 10 days after AVFs creation (*P*=0.643).

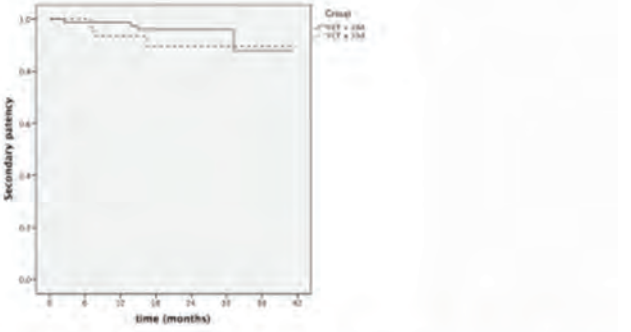

Figure 2. Secondary patency of AVFs which were first cannulated within 10 days and more than 10 days after AVFs creation (*P*=0.453).

SA-PO1084

Assessment of Arteriovenous Fistula Maturation Using Central-Venous Oxygen Saturation and Estimated Upper-Body Blood Flow

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Background: Arterio-venous fistula (AVF) is the optimal vascular access in most hemodialysis (HD) patients. However, AVF maturation is difficult to assess. Central-venous oxygen saturation ($ScvO_2$) and upper-body blood flow (UBBF) increase during AVF maturation. We followed AVF maturation using $ScvO_2$ and estimated UBBF (eUBBF).

Methods: We studied 19 patients from an ongoing AVF quality improvement project. $ScvO_2$ and hematocrit were measured with Crit-Line (FMC, Waltham, MA) between minutes 5 and 20 into HD, and eUBBF was computed as recently described (Rosales, Blood Purif, 2019).

Results: Following AVF creation, $ScvO_2$ and eUBBF increased in 9 patients with unassisted AVF maturation and in 4 un-cannulated patients with good clinical AVF function (1 transplanted, 1 transferred, 2 awaiting cannulation) (**Table 1**). These indicators increased less in 5 patients requiring assisted AVF maturation and in one patient who succumbed to sudden cardiac death with a clinically matured AVF.

Conclusions: Our preliminary results indicate that $ScvO_2$ and eUBBF provide point-of-care bio-signals that report AVF maturation and hemodynamic adaptation to the AVF. Advantages of this method are low costs, operator-independence, and scalability.

ScvO2 and eUBBF before and after AVF creation.

	Before AVF creation		Week 1 after AVF creation		Change between week 1 and pre AVF creation [%]		Week 4 after AVF creation		Change between week 4 and pre AVF creation [%]	
	ScvO2 [%]	eUBBF [L/min]	ScvO2 [%]	eUBBF [L/min]	ScvO2	eUBBF	ScvO2 [%]	eUBBF [L/min]	ScvO2	eUBBF
Successful unassisted maturation and CV adaptation (N= 9)	62.8 [60.5;63.5]	1.5 [1.2; 1.5]	76.4 [72.3;77.8]	2.8 [1.9; 3.0]	19.5 [15.9; 27.4]	75.0 [54.8; 87.1]	76.0 [74.6;80.9]	2.0 [1.9;3.1]	22.6 [15.4; 25.9]	57.7 [32.0;138.5]
"Clinical" maturation and CV adaptation (N=4)	61.9 [56.3;66.8]	1.1 [0.9; 1.3]	72.9 [69.5;74.7]	1.9 [1.3; 2.0]	9.7 [3.6; 30.4]	47.9 [6.9; 108.4]	66.2 [65.6;77.9]	1.5 [1.3;2.4]	19.9 [-2.1; 36.0]	57.7 [10.0;160.5]
Assisted maturation and CV adaptation (N=5)	62.2 [62.2;64.9]	1.2 [1.0; 1.3]	72.3 [70.7;74.0]	1.5 [1.4; 1.9]	13.9 [13.6; 16.2]	39.5 [32.3; 45.1]	71.2 [66.9;73.5]	1.7 [1.3;1.7]	9.6 [1.7; 44.2]	26.1 [21.3;41.8]
Failed CV adaptation (N=1)	71.2	2.3	76.9	3.0	8.0	27.6	72.6	1.8	2.0	-23.8

Values represent median, 25th and 75th percentiles. CV, cardiovascular; ScvO2, central-venous oxygen saturation; eUBBF, estimated upper-body blood flow.

SA-PO1085

The Importance of Monitoring Blood Flow in the Maintenance of Vascular Access in Patients Under Hemodialysis

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Background: The usefulness of blood flow monitoring (QA) in arteriovenous fistula (AVF) of patients with End Stage Renal Disease (ESRD) under hemodialysis (HD) patients is a current controversy in the international literature. Although all of the clinical guidelines for vascular access include monitoring protocols to prevent thrombosis (VA), randomized clinical trials (RCTs) have failed to consistently demonstrate the benefits of QA-based surveillance protocols. We present our experience of evaluating the usefulness of QA measurement using Doppler (DU) ultrasound in patients under HD.

Methods: 168 patients from two HD centers were under follow up for 3 years. The classic QA tracking method was applied to all once a year and moretimes on clinical indications. The episodes of thrombosis in vascular access that occurred acutely (group 1) and the interventions episodes made on the basis of DU findings (group 2) were recorded.

Results: During the 3-year follow-up period, 24 interventions were required to restore the functioning of vascular access. Of these, 8 were made after an acute event (group 1) and 16 after a finding derived from a DU control (group 2). Of the 8 acute cases of AVF or graft thrombosis, 5 ended up with a central venous catheter. Of the 16 cases requiring intervention after an ultrasound finding 12 events maintained the type of vascular access they had and 4 ended up with a central venous catheter. Group 1 required hospitalization of more than one day in 3 cases, which did not occur in any of Group 2 incidents.

Conclusions: Periodic QA measurement using DU significantly helps maintain vascular access of patients, limiting their days of hospitalization and significantly contributing to their better quality of life.

SA-PO1086

Global Home Dialysis Therapy Perceptions and Practices: An International Survey

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Background: Home hemodialysis (HHD) and peritoneal dialysis (PD) prevalence varies throughout the world. Home dialysis policies and clinician knowledge affect home dialysis prevalence. The goal of this study was to identify international policies and perceptions exploring: reimbursement of patient costs; telehealth; staff home visits; solo dialysis and patient training.

Methods: A 13 item web-based questionnaire was distributed to home therapy program clinicians in the 30 highest home dialysis prevalent nations worldwide. Questions explored patient reimbursement, telehealth, patient training, solo dialysis, home and clinic visit frequency. IRB approved surveys were independently translated into 9 languages with translation validation by an external translation service.

Results: 395 respondents from 30 nations using 7 different languages responded. 64% were aligned with combined HHD and PD programs, 29% PD only and 7% HHD only. 29% of programs had less than 20 patients, 30% had 20 to 50 patients, 22% had 51 to 100 patients and 19% had greater than 100 patients. 31% of all programs reported patient costs reimbursement, with non-US programs much more likely to report reimbursement than US programs (US 11%, non-US programs 59%, $\chi 2=93.6$, $p<0.0001$). Telehealth use was low throughout the world (23% prevalence), contrasting with 83% of respondents agreeing telehealth would improve home dialysis care. 31% of all programs enabled flexible training out of work hours. 72% of US clinicians agreed that monthly clinic visits were needed in comparison to 44% of non-US clinicians ($\chi 2 = 83.7$, $p<0.0001$). 31% of respondents agreed that dialysis partners are always required for home dialysis.

Conclusions: Global variation in home therapy protocols, knowledge and attitudes exist. Telehealth, cost reimbursement, training flexibility and acceptance of solo dialysis is low. Addressing these hurdles to home dialysis may increase home dialysis growth.

SA-PO1087

Costs of Hemodialysis in Survivors During the Incident Year by Vascular Access Type

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Background: Estimated cost of care of hemodialysis (HD) access types vary and infrequently account for survival. We identified benchmarks for Medicare expenditures in patients in an End Stage Renal Disease Seamless Care Organization (ESCO) who had an arteriovenous fistula/graft (AVF/AVG) implanted, or had only a central venous catheter (CVC), and survived various follow-up periods. The statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of the Centers for Medicare & Medicaid Services (CMS). The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Methods: We used data from adults at a large dialysis organization (LDO) who: 1) had Medicare as payor, 2) were treated at an ESCO by HD, 2) had an AVF/AVG implanted ≤90 days from first date of dialysis (FDD) or exclusively had a CVC, and 3) survived a 6, 9, or 12-month follow-up from FDD. We compared mean Medicare expenditures per member per month (PMPM) in AVF/AVG versus CVC patients who survived each follow-up period, as well as the entire incident year.

Results: Survivors with an AVF/AVG implanted ≤90 days of FDD had a lower Medicare expenditures PMPM from 90 days after FDD to the 6-month (AVF/AVG=$7,157±6,457 [n=1566]; CVC=$8,290±8,585 [n=723]; $p<0.001$), 9-month (AVF/AVG=$6,636±4,919 [n=1211]; CVC=$7,539±6,917 [n=483]; $p<0.01$), and 12-month (AVF/AVG=$6,424±4,333 [n=839]; CVC=$7,133±6,379 [n=309]; $p=0.03$) follow-up, as compared to CVC patients. Among survivors of the entire incident year, AVF/AVG patients consistently had a lower cost at the 9- and 12-month follow-up (both $p<0.05$) versus CVC patients, yet only favorable trends were seen at the 6-month follow-up ($p<0.19$).

Conclusions: Implantation of an AVF/AVG in the first 90 days of HD was associated with lower costs during the incident year of HD compared to CVC patients without a permanent access placed. Findings represent a sub-group who survived each defined period, or the overall incident year, yielding unadjusted comparisons with equivalent exposure times between access types. However, distinctions in survival between AVF/AVG versus CVC patients should be considered.

Funding: Commercial Support - Fresenius Medical Care North America

SA-PO1088

Percutaneous Transhepatic Venous Access for Hemodialysis: A 25-Year Experience

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Background: Vascular access is vital for hemodialysis (HD) patients, and some of them exhibit occlusions in the most common sites of catheter insertion. In such dramatic situations, percutaneous transhepatic (PT) placement of HD catheters can provide alternate vascular access for HD. Our objectives were to retrospectively evaluate survival, safety and complications associated with PT catheters in a HD center at a tertiary hospital in Brazil.

Methods: All PT catheters were placed in patients who had exhausted other vascular access sites, by an experienced interventional vascular team. The following outcomes were evaluated: catheter removal due to low flux, infection or catheter rupture. Additionally, death or kidney transplantation with functioning catheter were also noted. Data is expressed as median (25;75) percentiles, and crosstabulated in chi-square tests.

Results: During a 25-year period, 24 PT catheters were placed in 7 patients (one woman and six men). Median age at catheter insertion was 51 (33; 54) years and dialysis vintage of 197 (40; 522) months. Median PT catheter survival was 277 (24; 537) days. Catheter removal for low flux, infection and rupture was observed in 46%, 21% and 13% of patients, respectively. Removal for low-flux rate was 1.3/1000 patients-day and for infection, 0.59/1000 patients-day. Two patients died with functioning catheter and one underwent kidney transplantation. Two patients are currently dialyzing with PT catheters and no complications were observed. Reasons for TP catheter removal when comparing first *vs* non-first insertions were different (chi-square 9.24, $p=0.01$), as catheter rupture was more frequently observed in first insertion and low-flux in non-first insertions (table 1).

Conclusions: Using TP catheters in patients with multiple access failure is a feasible procedure, as overall infection and thrombosis rates are similar to other sites of catheter insertions. Patients should be advised about catheter-related care, especially in first insertion, in order to avoid catheter rupture.

Table 1. Outcomes according to catheter insertion

Event	First Catheter		p
	Yes	No	
Rupture	0	3	0.021
Low-flux	10	1	0.041
Infection	3	2	1.0

SA-PO1089

Where Should the Non-Tunneled Catheter Tip Be Placed for Hemodialysis? Fourth vs. Second Intercostal Space

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Background: Non-tunneled catheters (NTC) for hemodialysis are an indispensable vascular access and very common in patients in need of hemodialysis, especially urgently. The insertion method used for the placement of NTC can reduce serious complications.

Methods: Randomized clinical trial with adult patients at the University Hospital, Autonomous University of Nuevo Leon, Monterrey, Mexico, who required emergency hemodialysis by NTC. The NTC were inserted percutaneously with the ultrasound-guided modified Seldinger technique. Patients were randomized to NTC tip placement on the fourth intercostal space (4IS) and to the second intercostal space (2IS). The main outcome are to number of dysfunction, repositioning and relocation episodes due to NTC placement.

Results: The study included 115 patients who were placed on NTC for hemodialysis, with an average age of 51 years, 55% were female, the mean height was 163 cm, no difference between the groups. The incidence of catheter dysfunction and catheter relocation were not different. Catheter repositioning was presented in 50 and 16% for the 4IS insertion and 2IS groups, respectively (p 0.001).

Conclusions: The placement of the hemodialysis NTC tip on the 2IS decreases the incidence of repositioning, without affecting the incidence of dysfunction or repositioning when compared to 4IS. The search for new methods of catheter placement to reduce the potential complications of invasive treatments on renal replacement therapy is still pending.

Table 1. Primary outcome in classic and intervention group.

	Classic Group (4IS)	Intervention Group (2IS)	p
Disfunction, n(%)	4 (8%)	2 (4%)	0.39
Repositioning, n (%)	25 (50%)	8 (16%)	0.001
Relocation, n (%)	0 (0%)	1 (2%)	0.13

4IS, fourth intercostal space; 2IS, second intercostal space.

SA-PO1090

Ultrasound-Guided Protocol Safely Eliminates Chest Radiography After Non-Tunneled Catheter Placement in Urgent Hemodialysis

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Background: Despite its morbidity and mortality, the Non-tunneled catheter (NTC) continues to be an indispensable vascular access when imminent need for Hemodialysis. The confirmation of the proper NTC placement and complications detection are a real concern to optimize patient safety.

Methods: Prospective, comparative study. Included patients aged >17 years with life-threatening complications (uremic syndrome, potasssium >6.5 mmol/L, acidosis pH <7.2 with high anion gap and HCO3 <15 mmol/L and pulmonary edema) all resistant to management and urgent Hemodialysis need. After NTC placement with ultrasound (US) guided Seldinger technique in the right internal jugular vein; investigators performed a saline flush test and performed thorax evaluation for pleural sliding and pleural point with US and chest x-ray (CXR). Objetive is to compare successful venous placement and immediate detection of complications derived from NTC placement with US and CXR.

Results: 113 patients were involved, 60% in the emergency room. Their mean age was 50 years, 62% were male. The main causes of NTHC placement were uremic syndrome (41%) and fluid overload (28%). The mean blood urea nitrogen was 111 mg/dL. The correct NTC placement was documented in all patients when the US and CXR were used. The agreement between US-guided protocol and CXR protocol is good (Kappa= 1). Only 1 pneumothorax developed, correctly detected in the US-guided protocol, with a high NPV (100%). The median evaluation time for US and CXR were 3 and 37 minutes, respectively; median difference of 34 minutes (p <0.0001).

Conclusions: The US is an effective tool for the assesemnt of adequate NTC placement and immediate complications detection in patients with urgent need of hemodialysis when compared to CXR.

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SA-PO1091

A Rare Complication of a Permanent Haemodialysis Line

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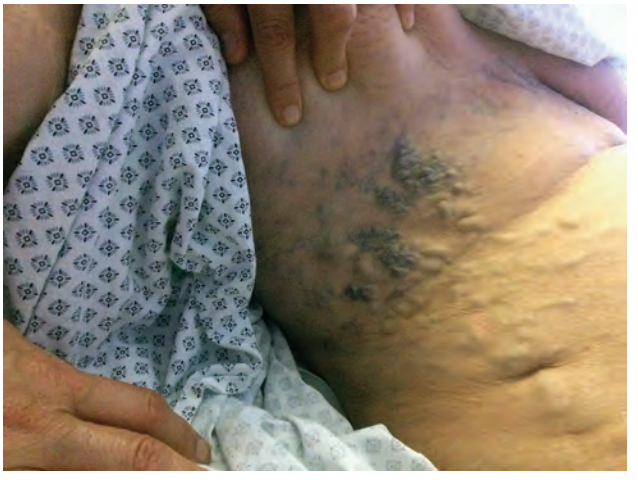
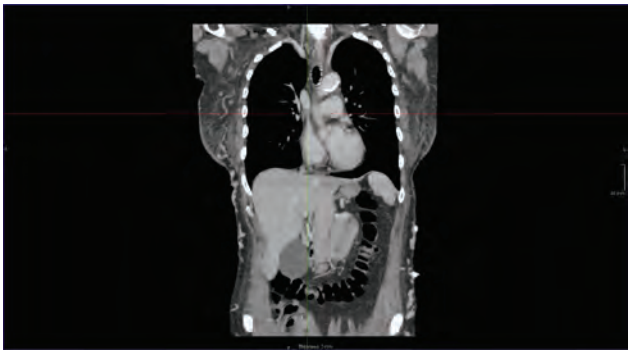
Introduction: Starting haemodialysis via an IJ permanent line is sometimes unavoidable in late presenters. Grievious complications can sometimes happen including this rare case report.

Case Description: A 67 years old female started HD via a permanent IJV line in Sep 2013 for 18 months untill a left sided AV fistula (AVF) was created, which then went to require multiple fistuloplasties. Eventually a right sided AVF was fashioned, while the left AVF was still in place. In May 2018, she presented with extensive trunkal varicose veins. 4 weeks later, she was admitted with large-volume hematemesis and hypovolemic shock requiring Critical care admission. Emergency endoscopy showed extensive esophageal varices. A CT scan showed an SVC stenosis and a thrombus extending and involving the left AVF. There was no evidence of liver cirrhosis. This was believed to be caused by previous IJ line. Intervention was deemed unsafe because of the risk of fatal bleeding. She was then anticoagulated and dialysis resumed via a femoral permanent line.

Discussion: Central venous thrombosis is not an uncommon complication among haemodialysis population starting dialysis via permanent IJ lines. However, it is very rarely reported to cause bleeding oesophageal varices. In the case we are presenting, the additional presence of two functioning fistulae had led to extensive venous drainage into her blocked SVC and encouraged the formation of extensive collaterals, the oesophageal varices are one of them. It was technically difficult to treat the SVC stenosis but the fact that her fistulae clotted relieved some of the back pressure on the varices and reduced future bleeding risk.





SA-PO1092

A Tragic Missed Opportunity: Leadless Cardiac Devices in Hemodialysis Patients

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Background: There is a frequent need for placement of cardiac implantable electronic devices (CIEDs) in hemodialysis patients. Placement of a CIED is associated with central vein stenosis, infections and access failure. Cardiac electrotherapy has advanced significantly with the availability of s-ICDs and Leadless pacemakers. The goal of this study is to assess the effectiveness of these devices in patients.

Methods: We conducted a retrospective study of adult ESRD patients who underwent leadless cardiac device placement between January 2014 - September 2018.

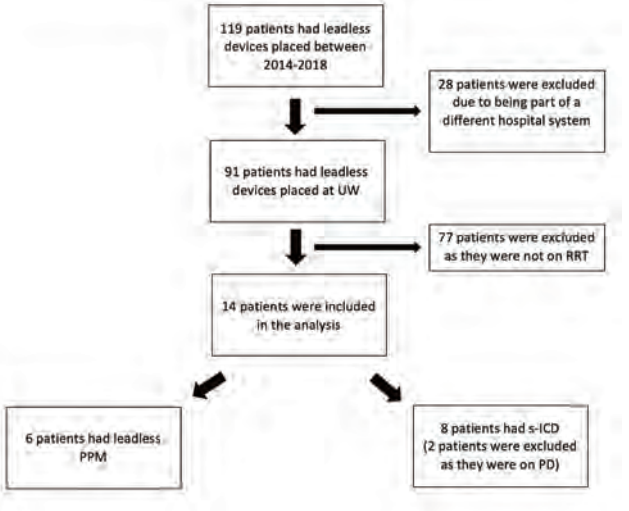
Results: Among patients who underwent leadless device placement, 14 patients were on renal replacement therapy (15.38%). Mortality among these patients after leadless device placement was 33.3%. There were no episodes of bacteremia requiring long term antibiotics or extended hospitalization post device placement. Patients with AVF required interventions due to stenosis of their peripheral veins, however the access remained patent until the end of the follow-up period.

Conclusions: A small minority of patients on dialysis underwent leadless device placement. Theses devices are associated with lesser incidence of catheter related bacteremia and sustained access patency in patients. Consideration should be given to the placement of such devices in patients on or close to needing renal replacement therapy.

Access characteristics in patients pre and post leadless device implantation

Venous Access for Hemodialysis	Tunneled Dialysis Catheter	Arterio-venous Fistula	Arterio-Venous Graft
At the time of Device placement	58.33% (7)	33.33% (4)	8.33% (1)
Bacteremia prior to device placement requiring prolonged antibiotics and lead removal	25% (42.85%)	8.33% (25%)	8.33% (100%)
Incidence of Central Venous stenosis	8.33% (14.28%)	8.33% (25%)	0
Need for intervention after device implantation	0	33.33% (100%)	0
Bacteremia post leadless device placement	0	16.67% (50%)	0
Access patency post device implantation	58.33% (7)	33.33 % (4)	8.33% (1)
Mortality	25% (42.85%)	8.33% (25%)	0

Figure 1: Patients included for analysis



SA-PO1093

Reducing Early Catheter-Related Bloodstream Infection in Hemodialysis Patients

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Background: Dialysis catheter-related blood stream infection (CRBSI) is a leading complication in hemodialysis (HD) patients, and is associated with increased risk of mortality, invasive procedures, extra hospitalization and/or increase in length of stay. Poor tunneled dialysis catheter (TDC) care by patient, inadequate skin preparation before TDC insertion and lack of prophylactic antibiotics during TDC insertion may contribute to early CRBSI. We examined the role of bundled interventions to reduce early CRBSI in HD patients with newly inserted TDC.

Methods: Between April to September 2017, we instituted a bundle of measures to reduce CRBSI in patients from two designated wards (intervention group); patients in other wards received usual care (control group). In the intervention group, daily chlorhexidine bath was administered for all patients prior to TDC insertion and nasal decolonization was performed for methicillin-resistant Staphylococcus Aureus carriers. In this group, prophylactic intravenous antibiotics was also administered at TDC insertion and topical antibiotics were applied to the exit site post-insertion. Patients were educated on TDC care and this was reinforced prior to discharge. Early CRBSI was defined as any new bacteremia occurring within 30 days of TDC insertion, and the rate of CRBSI was compared between the intervention and control groups.

Results: 308 TDC insertions or exchanges were performed during the study period (153 in intervention group and 155 in control group), of which there were 18 (5.8%) episodes of early CRBSI. Microbiological profile includes gram positive (8 episodes, 44.4%), gram negative (7 episodes, 38.9%), polymicrobial (2 episodes, 11.1%) and fungal (1 episode, 5.6%) organisms. In the intervention group, early CRBSI occurred in 5 (3.3%) TDC insertions while early CRBSI occurred in 13 (8.4%) TDC insertions in the control group, with a trend towards significance ($p = 0.056$). The interventions were well tolerated and cost effective, with the project resulted in significant healthcare cost savings.

Conclusions: The frequency of early CRBSI was successfully decreased, with a trend towards significance, using a comprehensive bundle of interventions. Further follow-up with regards to CRBSI frequency and analysis on the effectiveness of individual interventions would be helpful in assessing the utility of these measures.

SA-PO1094

Long-Term Outcomes of Catheter-Related Bloodstream Infections

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Background: Catheter-related bloodstream infections (CRBSIs) are common in patients receiving hemodialysis through a central venous catheter. In addition to antibiotics, treatment may include replacement of the catheter, exchange over a guide wire, or the catheter maybe left unchanged (salvage therapy). While these modalities are equally efficacious in the short run, the effect on long term infectious complications like endocarditis and epidural abscesses is not known. The purpose of our study was to determine the long-term complications of CRBSI and determine if catheter salvage or exchange is associated with an increased risk of long-term complications.

Methods: We retrospectively studied 100 randomly selected adult patients on hemodialysis admitted to a 1000 bed academic university hospital between May 1st, 2010 and April 30th, 2017 with CRBSI. Baseline demographics and clinical characteristics were stratified by line disposition. Multivariable logistic regression models were used to analyze the association between line disposition and long-term complications, adjusted for age, intensive care unit admission, and isolated organism.

Results: The mean age was 59.6 ± 15.7 years with 36% males and 64% females. Methicillin-resistant *Staphylococcus aureus* (MRSA) was the most common organism isolated (26%). 45% of catheters were replaced, 43% were exchanged, and 12%were salvaged. After excluding those who died and had catheter discontinued, 28% of the 75 patients developed long term complications. The long-term complications rates were 40% for catheter salvage, 32% for replacement and 21% for exchange ($p=0.383$). In univariate analysis there was no difference between groups. However, when adjusted for age, organism and ICU stay, patients with catheter exchange were less likely to develop long term complications compared to those with salvage therapy (adjusted OR: 0.14; 95%CI: 0.02-0.83). There was no statistically significant difference between the other groups.

Conclusions: Our results showed that there is a high incidence of long-term complications in patients admitted with CRBSI. The incidence was highest in those with catheter salvage. These results suggest the need for caution with catheter salvage and an adequately powered randomized controlled trial to determine the long-term safety of catheter salvage in patients with CRBSI.

SA-PO1095

Epidemiology and Clinical Outcomes of Staphylococcus aureus Bacteraemias in Haemodialysis Patients; 12-Year Single-Centre Experience

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Background: Patients on haemodialysis are at risk of access associated infections. The risk is greater in patients dialysed through lines, than those dialysing via arteriovenous fistulae (AVF) or grafts (AVG). Studies have shown that the most commonly implicated organism is *Staphylococcus aureus* (SA), which has a tendency to cause metastatic infections e.g endocarditis, osteomyelitis. We decided to look at the incidence and clinical outcomes in haemodialysis (HD) patients with SA bacteraemia in patients at our centre over the last 12 years.

Methods: Data were collected from the hospital's microbiology database of all the confirmed bacteraemias in HD patients between 2007 and 2018. We looked at the demography, type of dialysis access, and the outcomes following the bacteraemias.

Results: There were 261 bacteraemias in 1361 patients who had a cumulative total of 32,000 dialysis episodes over the 12 year period. Of the patients with bacteraemias, 164 (62.8%) were male. The median age was 67 years (range 18-96). The dialysis access at the time of the bacteraemia was as follows: AVF/AVG 57(22%), dual access - AVF or graft + line - 50 (20%), dialysis line 147 (56%), not documented 7 (3%). The blood cultures grew methicillin sensitive SA (MSSA) in 71% and methicillin resistant SA in 29% of cases. 204 (77%) cases occurred in patients dialysing through lines. Details about complications were available in 199 patients and are shown in Table 1.

Conclusions: Our data show that the bacteraemias and complications were most common in patients dialysing with lines, and emphasise the importance of trying to achieve dialysis through AVFs or grafts as soon as is possible.

Table 1 – Complications following SA bacteraemias

COMPLICATION	NUMBER (%)	LINES	AVF/GRAFTS
Discitis	5	4	1
Endocarditis	13	9	4
Septic arthritis	4	3	1
Death	26	21	5
Total	48	37 (77%)	11 (23%)

SA-PO1096

Reduction in Number of Hospital-Acquired Methicillin-Resistant Staphylococcus aureus Dialysis Catheter Related Bloodstream Infections: Role of Nasal Mupirocin and Chlorhexidine Body Wash

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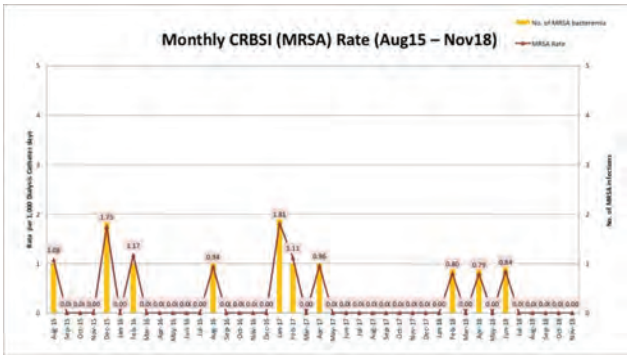
Background: Central Venous Catheter-Related Bloodstream Infections (CRBSI) are an important cause of hospital acquired infection associated with morbidity, mortality and cost. Patients undergoing haemodialysis using a catheter are at significant risk for developing CRBSI, especially with Methicillin-resistant Staphylococcus aureus (MRSA), resulting in serious complications. In our 1000-bed regional hospital, the average CRBSI(MRSA) rate was 0.56 per 1,000catheter days. A quality improvement project was initiated with an aim to reduce the rate by 50%.

Methods: Following the formation of a multidisciplinary team, the catheter insertion protocols and catheter care protocols were harmonised throughout the hospital. A decolonization protocol with Mupirocin 2% nasal cream along with Chlorhexidine bodywash for 5days, was initiated prior to dialysis catheter insertion. Monthly data on prescription and delivery of nasal and skin decolonisation protocol was collected. The CRBSI (MRSA) rates were collected monthly by averaging the number of infections per 1000 catheter days.

Results: Analysis of the data from July 17 – November 2018 showed a significant improvement in the CRBSI rates, after the robust implementation of nasal and skin decolonization protocol (>95%). The average CRBSI (MRSA) rate has improved to 0.14 per 1,000 catheter days from a baseline of 0.56 per 1,000 catheter days (Figure 1). Even though the improvement in CRBSI (MRSA) is believed to be due to introduction of the decolonization protocol, the outcome may have been influenced by other interventions.

Conclusions: The causes of CRBSI can be multifactorial and a multidisciplinary approach is required to reduce the infection rates. With nasal and skin decolonization prior to dialysis catheter insertions, the CRBSI rates, especially related to MRSA can be reduced significantly, as shown in our experience.



SA-PO1097

Use of Gentamicin-Citrate Lock Reduced Catheter-Related Bloodstream Infection Rates in Hemodialysis Patients: Results of a Natural Experiment

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Background: Use of central venous catheters (CVC) is a major risk factor for infections, a leading cause of morbidity and mortality in hemodialysis (HD) patients. Use of gentamicin 320 μg/mL in 4% sodium citrate lock (GCL) was previously shown to reduce the rate of CVC-related bloodstream infection (BSI). We report on the change of CVC-related BSI rates in four centers experiencing high BSI rates while using heparin catheter lock (period 1 [P1]) after switching to GCL (period 2 [P2]).

Methods: Retrospective observational study. Patient characteristics at time of switch to GCL were obtained from the provider's EHR. CVC patient-months and reported events of CVC-related BSI were obtained from the NHSN database. The rate ratio for pooled rates for P2:P1 was calculated and tested for significance.

Results: There were 684 and 896 CVC patient-months in P1 and P2 respectively. Mean patient age was 64 ± 14 years, and 48% were female. Monthly CVC-related BSI rates are shown in Figure 1. Pooled CVC-related BSI rates were 2.8 and 0.6 per 100 patient-months for P1 and P2 respectively, representing an 80% reduction in the rate of BSI (rate ratio 0.20, 95% Confidence interval 0.08 – 0.54, p = 0.0004).

Conclusions: These results are consistent with results from a previous trial, but in real-practice setting. Use of the gentamicin-citrate lock significantly reduces CVC-related BSI.

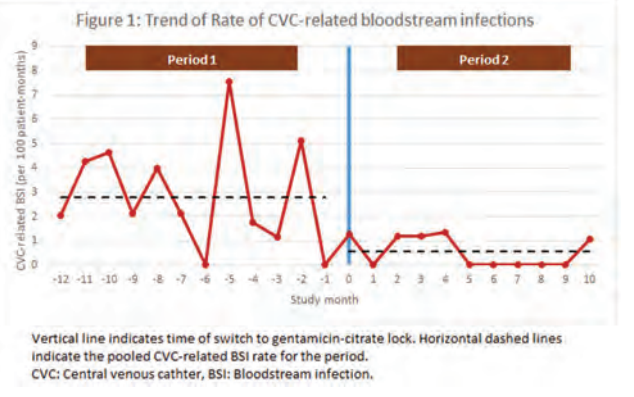

Figure 1

SA-PO1098

Prevalence and Conversion Rates of Central Venous Catheters in Hemodialysis: A Comparative Study of Public US and Mexican Dialysis Providers

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Background: Central venous catheter (CVC) as vascular access in hemodialysis (HD) associates with adverse outcomes. Early CVC-to-fistula conversion has been associated with improved outcomes. While socioeconomic disparities between the U.S. and Mexico exist, not much is known about how CVC prevalence and conversion rates compare

Methods: We retrospectively studied incident HD patients at the Hospital Civil de Guadalajara Fray Antonio Alcalde (HC) and the U.S. Renal Research Institute clinics (RRI) between 2014-2018. We compared CVC rates at HD initiation and conversion rates between months 1 and 6 between HC and RRI. Data were presented as mean±SD and count(%), rates were compared using χ^2 tests. A logistic regression model was built to identify factors associated with continued CVC status

Results: Patient characteristics and CVC conversion rates are shown in Table 1. During the observation period 174 and 824 patients started HD in HC and RRI, respectively. At HD initiation CVC prevalence was 97% at HC and 69% at RRI, respectively. The CVC conversion rate between months 1 and 6 was 10.6% in HC and 28.1% in RRI, respectively (p=0.0004). Albumin was the only significant variable associated with continuous CVC status in the RRI group (OR 0.52, CI 95% 0.37-0.44). An association was observed, although not significant between diabetes and the persistence of the catheter in HC patients (OR 0.5, CI 95% 0.13-4.19)

Conclusions: CVC prevalence and conversion rates differ between RRI and HC. Higher CVC prevalence in HC patients at HD initiation is likely due to more frequent "crashing" into HD, less pre-dialysis care, and socioeconomic disparities, reflecting the realities of an urban public hospital providing HD to a largely uninsured population. The presence of diabetes in HC seems to contribute as a barrier to CVC conversion, perhaps due to the economic cost that it entails. The impact of CVC conversion rates on patient outcomes warrants future studies

Variable	Overall		CVC_Unchanged		CVC_to_NONCVC	
	RRI	Hospital Civil	RRI	Hospital Civil	RRI	Hospital Civil
N	571	169	410	151	161	18
Age	63.54 ± 16.54	43.75± 19.47	64.58	43.58 ± 19.58	60.89	45.22 ± 19.04
Gender [%]						
Female	224 [39.2]	69 [41]	163 [39.8]	62 [41.1]	61 [37.9]	7 [38.9]
Male	347 [60.8]	100 [59]	274 [60.2]	89 [58.9]	100 [62.1]	11 [61.1]
Diabetic [%]						
Yes	372 [65.1]	11 [7]	266 [64.9]	9 [6]	106 [65.8]	2 [11.1]
No	199 [34.9]	158 [93]	144 [35.1]	142 [94]	55 [34.2]	16 [88.9]
Obesity						
Yes	176 [30.8]	17 [10]	122 [29.8]	16 [10.6]	54 [33.5]	1 [5.6]
No	395 [69.2]	152 [90]	288 [70.2]	135 [89.4]	107 [66.5]	17 [94.4]
Albumin	3.72 ± 0.44	4.05± 0.38	3.69± 0.44	4.04 ± 0.39	3.77 ± 0.43	4.08 ± 0.36

SA-PO1099

Outcomes of Upper Limb Arteriovenous Fistula After Insertion of Ipsilateral vs. Contralateral Tunnelled Vascular Catheters: A Single-Centre Experience

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Background: Observational data suggest that the use of central venous dialysis catheters is associated with reduced subsequent Arteriovenous Fistula (AVF) maturation and survival, but it's unclear if catheters directly affect AVF function. Catheter related central vein stenosis could affect flow and maturation of a subsequent AVF on the same side. To explore this further we aim to compare the outcomes of AVF created ipsilateral or contralateral to previous Tunnelled Vascular Catheters (TVC).

Methods: We retrospectively examined our vascular access database and electronic medical records of all patients who started dialysis at all units linked to Sydney Southwest Local Health District. We identified 142 patients who started dialysis with a TVC and subsequently had their first AVF created between Jan 2013 and Dec 2017. For patients with multiple AVFs only the first was included. All fistulas were monitored as per local policy. Successful fistula use (cannulated with two needles for ≥ 2 consecutive weeks) was analysed at 6 and 12 months after initial creation. We used Chi-Square test and logistic regression to analyse outcomes.

Results: 40 AVFs (12 upper arm, 33 right arm) were created ipsilateral to previous TVC insertion side and 102 AVFs (31 upper arm, 5 right arm) were contralateral. Median age (68 years, range=28-84; 66 years, range=25-87; p=0.38), the proportion of males (77.5% and 68.6%, p=0.29), and prevalence of diabetes (60.0% and 63.7%, p=0.70) were similar between ipsilateral and contralateral groups respectively. At 6 months, 40.0% of ipsilateral AVFs were functioning compared to 59.6% of contralateral AVFs (OR=0.45, CI=0.21-0.99, p<0.05). After adjusting for other factors (age, sex, diabetes, and hypertension) using a backwards conditional regression, non-smokers (p=0.005) and contralateral AVF placement (p=0.021) were associated with a greater AVF function at 6 months. There was no difference in functioning AVFs at 12 months (57.6% ipsilateral versus 65.9% contralateral, OR=0.70, CI=0.31-1.61, p=0.41).

Conclusions: Successful use of AVF was lower at 6 months in patients with AVF created ipsilateral to prior TVC insertion. Careful planning of prior TVC and future AVF locations should be guide management of long term vascular access.

SA-PO1100

The Diagnostic Value of Multi-Detector CT Venography for Catheter-Related Central Venous Stenosis in Hemodialysis Patients

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Background: Central venous stenosis (CVS) is a common complication in hemodialysis patients, especially those who are dialyzed through a catheter. The objective of our study was to assess the diagnostic value of Multi-detector CT venography (MDCTV) for catheter related-CVS compared with conventional digital subtraction angiography (DSA) in hemodialysis patients.

Methods: Between October 1, 2012 and September 30, 2018, hemodialysis patients admitted to our center for suspected catheter related-CVS who received both MDCTV and DSA were retrospectively enrolled. We compared the sensitivity, specificity, Cohen's kappa coefficient (κ) of MDCTV compared to DSA.

Results: A total of 1533 vascular segments in 219 patients were analyzed. Among the 280 lesions identified by DSA, 156 were correctly identified by MDCTV. MDCTV had a high specificity (96.73%) but a low sensitivity (55.71%), with a moderate inter-test agreement (κ=0.5930). In stratified analyses of vascular segments, the specificities of MDCTV were 89.93% (superior vena cava), 98.95% (left innominate vein), 95.33% (right innominate vein), 99.53% (left subclavian vein), 97.61% (right subclavian vein), 97.13% (left internal jugular vein), and 95.86% (right internal jugular vein), while the sensitivities were 90.00%, 65.52%, 66.67%, 87.50%, 40.00%, 20.00% and 8.11%, respectively (Figure 1).

Conclusions: MDCTV was a reliable imaging technique with high specificity in being able to diagnose catheter related-CVS in hemodialysis. However, the low sensitivity in some vascular segments diminished its value as a screening test. MDCTV seemed to have better diagnostic value for centrally localized CVS in superior vena cava and innominate veins.

Funding: Government Support - Non-U.S.

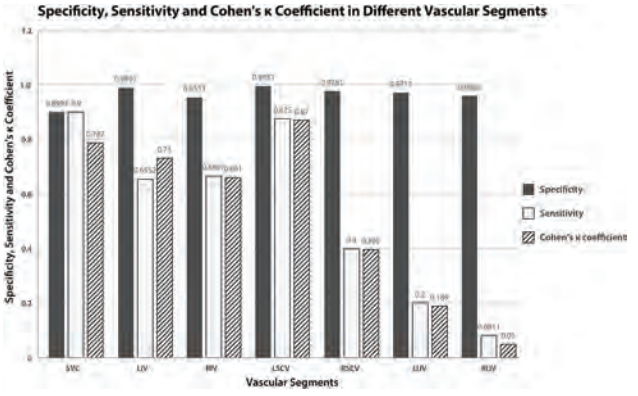

Figure 1. Specificity, sensitivity, cohen's κ coefficient by vascular segments. SVC: superior vena cava. LIV: left innominate veins. RIV: right innominate vein. LSCV: left subclavian vein. RSCV: right subclavian vein. LIJV: left internal jugular vein. RIJV: right internal jugular vein.

SA-PO1101

Kidney Disease Education: Marker or Effector of Improved Vascular Access Outcomes

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Background: Despite 2 large systemwide initiatives, vascular access outcomes for US incident end-stage renal disease (ESRD) patients continue to be suboptimal. Pre-ESRD renal care is the strongest predictor of vascular access readiness. Studies have shown that Kidney Disease Education (KDE) improves the quality of pre-ESRD care

Methods: We examined the impact of KDE on the incident vascular access rates among US adult ESRD Medicare beneficiaries since the implementation of CMS-KDE policy (2010-2014). Co-primary outcomes were incident fistula (AVF) rates and composite of incident fistula and/or graft rates (AVF±AVG). Secondary outcomes were composite maturing AVF±AVG, and any form of non-catheter vascular access (AVF±AVG in use or maturing). Multivariate analyses were performed in 4 progressive models (model1: KDE, model2: model1+socio-demographic adjustments, model3: model2+comorbidity and functional status adjustments, and model4: model3+adjustments for pre-ESRD renal care)

Results: Of the 309743 patients with their first dialysis as hemodialysis between 2010-14, 2916 (<1%) had at least one KDE during pre-ESRD (KDE cohort) whereas 306827 had no KDE (non-KDE cohort). All primary and secondary vascular access outcomes were significantly superior among the KDE cohort and the effect was maintained across all progressive multivariate models (Table). Stratified analyses further confirmed that the positive associations of KDE to vascular access did not dissipate even after accounting for pre-ESRD renal care, which has the strongest association with the vascular access outcomes (Table 2)

Conclusions: Pre-ESRD KDE is associated with improved quality of CKD care as judged by the incident vascular access outcomes. The positive effects of KDE is maintained across all baseline socio-demographic, comorbidity, and functional status variables, and is additive to the pre-ESRD renal care. Wider use of pre-ESRD KDE across advanced CKD patients may improve incident vascular access outcomes among US ESRD patients

Incident Vascular Access Outcomes among the Study Cohorts

Outcomes N (%)	KDE Cohort (N = 2,916)	Non-KDE Cohort (N = 306, 827)	Impact of KDE on the Odds of Achieving the Incident Vascular Access Outcomes in progressive multivariate models			
			Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
AVF Used at Incident ESRD	864 (29.63)	44,511 (14.51)	2.59 (2.39-2.81)	2.59 (2.39-2.81)	2.46 (2.26-2.68)	1.79 (1.64-1.96)
AVF ± AVG used at Incident ESRD	1,014 (34.77)	52,708 (17.18)	2.57 (2.38-2.78)	2.53 (2.34-2.73)	2.41 (2.23-2.62)	1.78 (1.64-1.94)
CVC used, AVF ± AVG Maturing at Incident ESRD	724 (24.83)	57,841 (18.85)	2.09 (1.90-2.29)	2.18 (1.98-2.39)	2.10 (1.91 2.32)	1.76 (1.59-1.94)
Any form of Vascular Access present, AVF ± AVG used or maturing present	1,738 (59.6)	110,548 (36.03)	2.62 (2.43-2.82)	2.68 (2.48-2.88)	2.59 (2.39-2.80)	2.01 (1.85-2.18)

OR: Odds Ratio, CI: confidence interval

SA-PO1102

Patient Values Toward Vascular Access Across Differing Age Groups

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Background: Current guidance strongly supports the arteriovenous fistula over a catheter in all patients regardless of age. However, an increasing proportion of the prevalent haemodialysis population is now made up of older and comorbid patients who may require a greater healthcare burden to achieve a fistula. It has been demonstrated in other areas of healthcare that this patient group have distinct healthcare values, defined as fixed general preferences regarding treatment goals, when compared to younger patients. The role of values in vascular access preference has not been studied.

Methods: Structured interviews were conducted in a group of prevalent haemodialysis patients, all unaware of the purpose of the study. Questionnaires described a set of non-renal healthcare scenarios, with patients asked to make a trade-off decision for each. Priority scores for four treatment goals were determined by weighted analysis of the decisions. The treatment goals were: longevity, comfort, aesthetics and convenience.

Results: From 106 patients enrolled across 4 dialysis satellites, 104 patients (aged 16-94, 56% male) completed interviews for analysis. Questionnaires revealed the most important values in order of descending priority score (mean+/-se): convenience 3.7+/-0.8, comfort 2.6+/-0.7, aesthetics -1.2+/-0.7, and longevity -5.0+/-0.8. Compared to those under 55, older patients (over 70) unconsciously assigned higher priority scores to convenience (7.9 vs -1.3, p<0.001) and comfort (6.5 vs -2.9, p<0.001), and lower priority scores to aesthetics (-5.2 vs 4.6, p<0.001) and longevity (-9.2 vs -0.4, p<0.001). Access choices similarly predicted priorities: compared to those with a fistula, patients dialysing via catheter assigned higher priority scores to convenience (4.8 vs -0.3, p=0.007) and comfort (4.6 vs -4.2, p<0.001), and lower priority scores to aesthetics (-2.7 vs 3.7, p<0.001) and longevity (-6.7 vs -0.8, p<0.001). In a matched group analysis, the effect of age and access on healthcare priorities were independent.

Conclusions: Unconsciously assigned priorities show that amongst older patients, convenience and comfort are more important than longevity and aesthetics, and access choices appear to depend on similar values. Healthcare values should be understood when making access decisions with patients, particularly in older age groups.

SA-PO1103

Timely Creation of Peripheral Vascular Access for Planned Initiation of Hemodialysis

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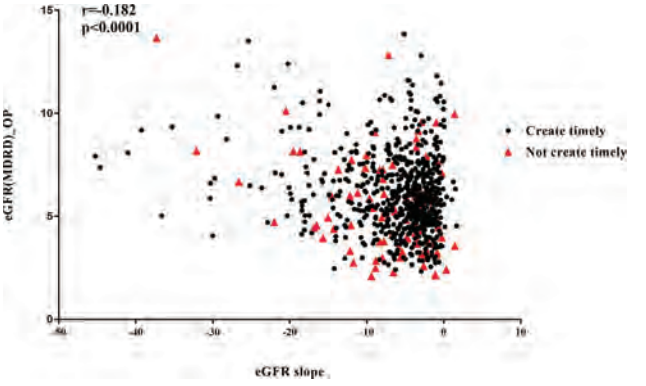
Background: Factor associated with timely creation of peripheral vascular access (VA) for planned initiation of hemodialysis is not clear.

Methods: From 2003 through 2016, every patient enrolled in integrated CKD program for more than 6 months and closed with the status of HD were included. The eGFR slope was counted between CKD program enrollment and VA creation or starting HD, which came first. We defined VA created timely as using VA when starting HD.

Results: Total 998 ESKD patients were included. (Age 65±12 y/o, Male 53%, DM 50%) The portion of VA created timely, created not timely and not created were 69%, 9% and 22%, respectively. By calendar year, created timely had the percentage increasing and around 74% in the last 6 years. Compared with not created, VA created timely had shallower eGFR slope (-4.2(-7.4, -2.3) *vs* -5.6(-10.8, -3.1), ml/min/1.73m^2/yr; p<0.0001), lower eGFR on first HD (4.3(3.4, 5.4) *vs* 4.6(3.4, 6.0), ml/min/1.73m^2; p=0.011) and longer stay at CKD program (729(417, 1439) *vs* 504(309, 1077), days; p<0.0001). There was a negative association of eGFR at VA creation with eGFR slope among VA created before HD (figure 1, r=-0.182, p<0.0001). Compared with created not timely, VA created timely had longer duration after VA creation till HD (108(53, 237) *vs* 14(7, 28); p<0.0001), shallower eGFR slope (-4.2(-7.4, -2.3) *vs* -4.8(-9.7, -2.2); p<0.0001), higher eGFR at VA creation (5.9(4.8, 7.2) *vs* 5.1(3.8, 7.1); p<0.005) and longer stay at CKD program (729(417, 1439) *vs* 521(312, 1048); p<0.0001). In multivariable analysis, only higher eGFR at VA creation (p=0.004) and shallower eGFR slope (p=0.05) were significant with timely creation of VA.

Conclusions: We disclosure that the stay in CKD program and eGFR slope are associated with timely creation of peripheral VA for HD initiation, and may be helpful with determining the time of peripheral VA creation.



SA-PO1104

The Impact of Comorbidity Index on the Association Between Vascular Access Type and Clinical Outcomes Among Elderly Patients Undergoing Hemodialysis

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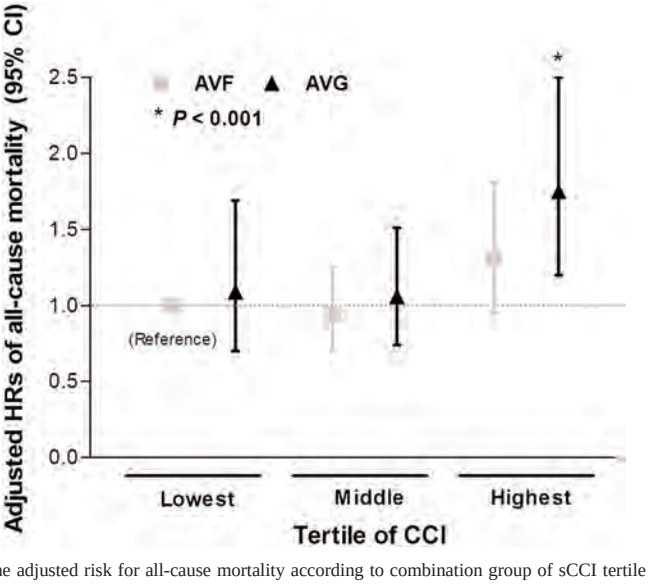
Background: The optimal type of vascular access for the elderly undergoing hemodialysis is controversial. We aimed to evaluate the impact of comorbidity burden on the association between vascular access type and mortality risk among elderly patients maintaining hemodialysis.

Methods: A total of 23,100 patients with ≥65 years undergoing hemodialysis were recruited from the Korean end-stage renal disease registry data (2001-2018). Study subjects were stratified into tertile according to simplified Charlson comorbidity index (CCI) and compared the survival and hospitalization rate among the type of vascular access.

Results: Among all tertiles of sCCI, CVC use showed highest risk of mortality than AVF use. In the lowest to middle tertile, no difference was observed in survival rates between the use of AVF and AVG. However, in the highest tertile, AVG use showed higher risk of mortality than AVF use. When subjects were classified according to a combination of sCCI tertile and access type (AVF vs. AVG), patients with the highest CCI with AVG showed 1.75-folded increased risk of mortality than those with the lowest sCCI with AVF. Hospitalization rates due to access malfunction were highest in patients with CVC in all sCCI tertiles. In the highest tertile, patients with AVG showed increased rates of hospitalization compared to those with AVF due to access malfunction. However, hospitalization rates due to access infection were highest in patients with AVG in all tertiles.

Conclusions: The use of AVF may be of benefit and switching to AVF should be considered in elderly hemodialysis patients with a high burden of comorbidity.



The adjusted risk for all-cause mortality according to combination group of sCCI tertile and the type of vascular access (AVF vs. AVG)

SA-PO1105

The Impact of Vascular Access Type on the Survival and Quality of Life in Incident Hemodialysis Patients: Comparisons Among Arteriovenous Fistula, Graft, and Temporary Catheters

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Background: Arteriovenous fistula (AVF) is the preferred vascular access for haemodialysis (HD); however, the association between vascular access and quality of life (QOL) is not well-known. We investigate the relationships between HD vascular access and all-cause mortality, health-related quality of life (HRQOL) and depression in a large prospective cohort.

Methods: A total of 1461 patients for whom HD was newly initiated were prospectively enrolled. The initial vascular access types were classified as AVF, arteriovenous graft (AVG) and central venous catheter (CVC). The primary outcome was all-cause mortality and the secondary outcomes were HRQOL, depression and all-cause hospitalisation. Kidney Disease Quality of Life Short Form 36 and Beck's depression inventory scores were measured to assess HRQOL and depression, respectively.

Results: Of 1461 patients, 314 patients started HD via AVF, 76 via AVG, and 1071 via CVC. In the survival analysis, patients with AVF or AVG showed significantly better survival than those with CVC (*P*=0.015). The numbers of annual hospitalisation were not different among the groups. The AVF and AVG groups had a significantly higher Kidney Disease Quality of Life Short Form 36 score and a significantly lower Beck's depression inventory score than the CVC group at 3 months and 12 months after the initiation of dialysis.

Conclusions: Patients with AVF or AVG have a better survival and HRQOL score and are less depressed than those with CVC. These suggest that the choice of vascular access in incident HD patients is important in terms of mortality and quality of life.

SA-PO1106

Hemodialysis Costs by Vascular Access Type and Outcomes in the Incident Year

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Background: We profiled Medicare expenditures over time among incident hemodialysis (HD) patients in an End Stage Renal Disease Seamless Care Organization (ESCO), stratified by vascular access type. The statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of the Centers for Medicare & Medicaid Services (CMS). The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Methods: We identified adult HD patients in a large dialysis organization (LDO) who: 1) were treated in an ESCO clinic, 2) had Medicare as payer, 3) had arteriovenous fistula/graft (AVF/AVG) implanted ≤90 days from first date of dialysis (FDD) or exclusively had a central venous catheter (CVC) throughout follow-up. We compared average costs of care per member per month (PMPM) in AVF/AVG versus CVC patients from 90 days to 6, 9, or 12 months after FDD. We stratified those with outcomes and censored their data in subsequent periods.

Results: Patients with an AVF/AVG implanted had lower average Medicare expenditures from 90 days from FDD to the 6, 9, and 12-month follow-up compared to those treated exclusively with a CVC (Figure 1; all p<0.05). Costs did not differ in any follow-up period among AVF/AVG versus CVC patients who died, received a transplant, or transferred out of the facility. However, survival was 6, 4, and 1 percentage points higher in AVF/AVG versus CVC patients at the 6, 9, and 12-month follow-up periods, respectively.

Conclusions: Compared to incident HD patients with exclusive CVC, those with an AVF/AVG placed within 90 days of initiation had a lower cost of care over the first year of HD. Costs in those with outcomes during a follow-up period were not distinct between AVF/AVG versus CVC groups.

Funding: Commercial Support - Fresenius Medical Care North America

Figure 1: Cost of Care Over Time in Patients with a AVF/AVG Versus CVC

SA-PO1107

Vascular Access Type Was Not Associated with Mortality and the Risk for Cardiovascular Death in Elderly Chinese Hemodialysis Patients

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Background: The objective of this study was to examine the impact of VA type on cardiovascular and all-cause mortality as well as the predictors for outcome in elderly Chinese patients.

Methods: In the retrospective study, patients who initiated HD aged ≥ 70 years and received a primary VA creation were enrolled between January 2007 and October 2018. Clinical characteristics of VA, and outcomes were collected from the electronic medical record and the local Death Index. Kaplan-Meier analysis, and multivariate regression analysis were employed.

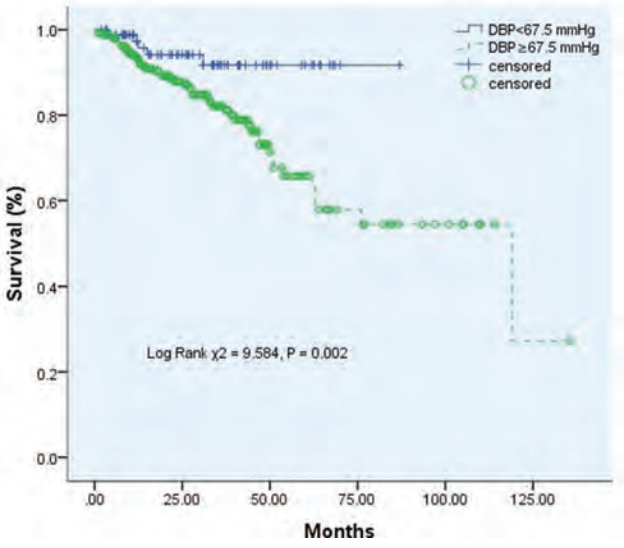
Results: A total of 358 elderly Chinese HD patients with median aged 74(72-78) years was analyzed. During the study period of 25.8 (12-43) months, 54 patients (15.1%) and 113 patients (15.1%) died of cardiovascular events and all-cause, respectively. The modality of VA type was not associated with mortality. Furthermore, CHF and DBP were the independent predictors for cardiovascular mortality (HR for CHF =3.462; HR for DBP per 1 mmHg elevated =1.033).

Conclusions: The modality of VA types showed insignificant effect on mortality in elderly Chinese population, while the presence of CHF and preoperative DBP might be used for the risk assessment of cardiovascular death.

Variable (per 1 unit increased) or (yes vs. no)	OR(a) cardiovascular death	95%CI	P	OR(b) all-cause death	95%CI	P
Male	1.492	0.754-2.953	0.250	0.878	0.526-1.464	0.617
Age (year)	1.031	0.981-1.107	0.393	1.044	0.987-1.104	0.130
Dialysis vintage (month)	0.994	0.976-1.013	0.542	0.987	0.973-1.002	0.79
DBP (mmHg)	1.049	1.020-1.079	0.001	1.028	1.007-1.050	0.10
Congestive heart failure	2.031	0.875-4.712	0.099	1.510	0.769-2.964	0.231
CVD with existing stent	2.035	0.520-7.966	0.307	2.219	0.709-6.948	0.171
Arrhythmia	1.188	0.412-3.427	0.750	0.760	0.313-1.846	0.545
Arrhythmia with a pacemaker	1.921	0.507-7.280	0.337	1.780	0.575-5.510	0.317
Previous stroke	1.842	0.774-4.383	0.167	1.351	0.660-2.766	0.411
Diabetes mellitus	0.665	0.336-1.317	0.242	0.855	0.512-1.426	0.547
Gout	0.348	0.072-1.688	0.190	-	-	-
Systemic vasculitis or lupus nephritis	0.802	0.160-4.013	0.789	1.178	0.377-3.676	0.778
Cancer	<0.001	-	0.998	0.825	0.238-2.862	0.762
VA types (contrasted by tcCVC)			0.467			0.125
AVF+tcCVC	0.657	0.239-1.808	0.416	0.847	0.392-1.831	0.672
AVF	0.575	0.201-1.644	0.302	0.451	0.210-0.971	0.042
Length of IJVC indwelling (month)	1.041	0.809-1.341	0.753	-	-	-
Length of FVC indwelling (month)	1.161	0.961-1.402	0.121	-	-	-
Total temporary CVC (number)	0.902	0.647-1.259	0.546	1.191	0.977-1.451	0.083
Total permanent VA (number)	1.209	0.753-1.940	0.433	0.897	0.619-1.302	0.568
Constant	<0.001	0.012		0.004		0.021

p for Hosmer-Lemeshow was 0.415, 0.958 and percentage correct was 70.1%, 85.5% in model a and b respectively.

baseline data of 358 elderly Chinese HD patients



cardiovascular mortality of survival curve

SA-PO1108

Hemodialysis Access in the Elderly and Survival

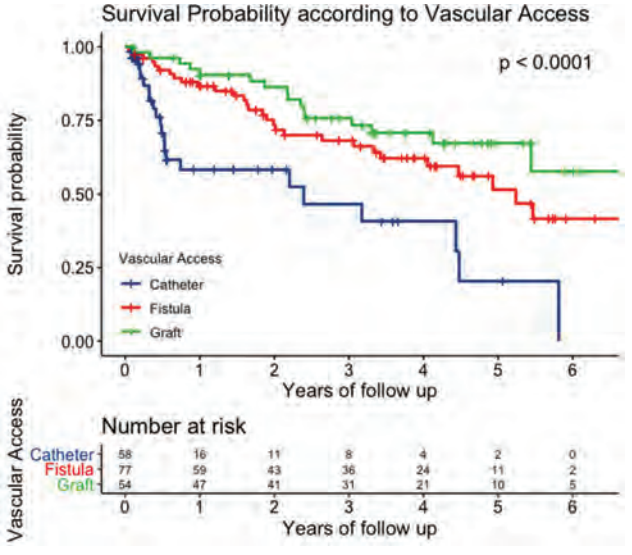
Jose E. Navarrete. *Emory University, Atlanta, GA.*

Background: To determine if achiveing the goal of having an AV fistula impacts survival in elderly dialysis patients.

Methods: Incident hemodialysis patients age 70 or older admitted to Emory Dialysis program form 1/2011 to 12/2015 were followed until death, transplant, or censoring up to 12/31/18. Demographic, laboratory and hemodialysis data were obtained. Patients were categorized as **C** if they only dialyzed with a catheter, **G** if they were able to dialyze with a graft and **F** if they used a fistula for dialysis.

Results: 189 patients were included. 30%, 29% and 41% of patiens used a **C**, **G** or **F** respectively. Demographics and comorbidities were similar among groups but diabetes was more common (65%) in **G** users than **C** or **F** (40 and 56%). Use of **C** was associated with lower survival compare to **G** or **F** (Figure 1). Patients using **C** were more likely to be hospitalized than those using **G** (RR 1.8, CI 1.1-3.1, p=0.005) or **F** (RR 2.6, CI 1.5-4.5, p<0.01). Hospitalization risk was higher in patients with **G** compared **F** (RR 1.4, CI 0.9-2.4, p=0.3) but the difference was not statistically significant. IV antibiotics use was more common in patients with C. 10.5%, 6.5% and 3.7% of patients used IV antibiotics in the catheter, graft and fistula groups respectively (p<0.05).

Conclusions: Elderly patients dialyzed with a catheter had lower survival than patients dialyzed with a graft or a fistula. There was no survival difference between patients using grafts or fistulas for dialysis. Patients using a dialysis catheter were significantly more likely to receive IV antibiotics and were hospitalized more often than patients using a fistula or a graft. There was no difference in hospitalization rate between **G** and **F.** These results underscore the importance of avoiding dialysis catheters as long term dialysis AV access and suggest that AV graft could be a reasonable dialysis access option in elderly patients.



SA-PO1109

Age and Arteriovenous Fistula Placement, Maturation, and Patency Loss in Elderly: A Competing Risk Analysis

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Background: Choosing the optimal vascular access for older hemodialysis (HD) patients is of primary importance. Our study aims to determine the association of age with arteriovenous fistula (AVF) placement, maturation, primary patency loss, and abandonment in the U.S. older HD patients.

Methods: We identified three national retrospective cohorts of incident HD patients aged 67 years and older who initiated dialysis (43,851), had an AVF placed (14,892), or had the placed AVF matured (7,528) from United States Renal Data System (USRDS). AVF maturation, primary patency loss, and abandonment were ascertained monthly. Cut-off value for age categorization was identified by restricted cubic splines (RCS). Cause-specific and subdistribution proportional hazards models were used with kidney transplantation, peritoneal dialysis, and death treated as competing events. We compared inverse probability weighted (IPW) cumulative incidence functions (CIFs) by Gray's test.

Results: Of 43,851 patients who initiated HD, 39.4% had an AVF placed. Among 14,892 patients with a placed AVF, 68.9% achieved maturation. In 7,528 matured AVFs, 75.2% had primary patency loss and 25.2% abandoned. Patients ≥77 years old had significantly lower probability for AVF placement (adjusted cHR 0.96, 95% CI 0.92-0.99; adjusted sHR 0.92, 95% CI 0.89-0.95; Gray's test p<.0001) and maturation (adjusted cHR 0.95, 95% CI 0.91-0.99; adjusted sHR 0.93, 95% CI 0.90-0.97; p<.0001) as compared to those 67-<77. However, age is not associated with AVF primary patency loss (adjusted cHR 1.05, 95% CI 1.00-1.11; adjusted sHR 1.04, 95% CI 0.99-1.09; p=0.091) or abandonment (adjusted cHR 1.05, 95% CI 0.95-1.15; adjusted sHR 1.03, 95% CI 0.94-1.13; p=0.613).

Conclusions: In conclusion, the chance of AVF maturation is the most important consideration for vascular access planning. AVF might not be the best vascular access for older HD patients approaching eighty years old.

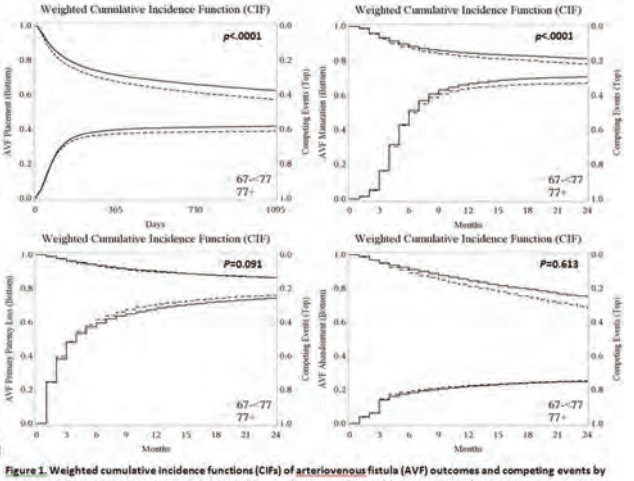

Figure 1. Weighted cumulative incidence functions (CIFs) of arteriovenous fistula (AVF) outcomes and competing events by age group in hemodialysis patients aged 67 and older. *P* values were obtained from Gray's test for equality of CIF. Bottoms lines: AVF outcomes; top lines: competing events including death, kidney transplant, and transfer to peritoneal dialysis.

SA-PO1110

Outcomes of ePTFE Grafts as Dialysis Access in Chinese Population: A Retrospective Analysis

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Background: With an increasing prevalence of end-stage renal disease and life expectancy of Chinese patients on renal replacement therapy, the quality and availability of superficial vessels can be limited and reduced with time. Arteriovenous access using ePTFE grafts have advantages compared with tunneled cuffed dialysis catheters. Guidelines suggest the usage of ePTFE grafts as access if native fistula is not possible. The aim of our study is to analysis the outcomes of AVGs that we have implanted in our patients.

Methods: We had retrospectively reviewed all the patients who had an AVG during October 2014 to June 2018 in our center. The demographic characteristics,duration of dialysis,laboratory tests, location and configuration of AVG, operation outcome,as well as the patency rate were collected and analyzed.

Results: A total of 262 patients were included in the investigation with the mean age of 60.1±13.8 years old. 56.5% of the study population was female gender. The most common comorbidities were hypertension (83.9%) and diabetes (47.7%). The range of follow-up period was from 10 to 54 months. The configurations of the grafts were 76.7% loop and 23.3% straight, and 62.6% of them were created on forearm. There was no operation-related mortality. Technical successful rate was 100%. However, 3 early failure were noted. The primary and secondary patency rates were 72.8% and 92.3%, 54.5% and 88.8%, 25.6% and 77.8%, 20.9% and 62.3%, 16.7% and 53.3%, at 6, 12, 24,

36, 48months, respectively. There was no difference between the primary and secondary patency of grafts on forearm and upper-arm (p-value: 0.337 and 0.812). The primary and secondary patency of straight grafts on upper-arm was better than loop grafts on upper-arm (p-value: 0.017 and 0.017). These patients required a mean 0.67 interventions per year and there is no difference between the location and configuration of AVGs.

Conclusions: Straight upper-arm AVGs has superiority of primary and secondary patency than loop. Arteriovenous access using ePTFE grafts seems to be an alternative in patients with poor superficial vessels.

Funding: Government Support - Non-U.S.

SA-PO1111

Evaluating Factors Predicting Outcomes of Secondary Patency of Arteriovenous Grafts for Hemodialysis

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Background: Our objective was to analyze outcomes in terms of secondary survival (CSS) and secondary patency rate (SPR) of AVG and to determine prognostic factors for these outcomes.

Methods: It was a retrospective, single-center analysis. Incident HD patients that received implantation of an AVG for angioaccess from January 2015 to December 2018 were included. Demographic factors, timing, type, and site of implanted AVG, as well as types of treatment of VA malfunction or failure, were recorded. Outcomes included CSS and SPR in 12, 24, 36 and 48 months. Kaplan-Meier survival analysis was conducted; univariate and multivariate analyses were used to evaluate prognostic factors.

Results: Data from 223 patients were analyzed. Those involved 119 proximal (arm) AVG, 101 loop (forearm) AVG, and 1 leg AVG, of which 147 were ePTFE grafts, 39 acute cannulation AVGs, and 37 biological vascular conduits. CSS was 49±4 months and SPR were 74%, 63%, 52%, 43% in 12, 24, 36 and 48 months, respectively. Multivariate analysis demonstrated that secondary patency was not associated with age, gender, duration in HD, graft position, stent deployment or use of cutting balloon angioplasty. Patency was negatively affected by graft type (acute cannulation HR, 3.09, 95% CI,1.66–5.75, p⟨0.005, biological HR, 0.70, 0.39–1.24, p=0.218), presence and number of successfully treated thrombotic events, with differences, noted depending on the type of treatment selected (Fogarty thrombectomy HR, 3.63, 1.89-6.98, p⟨0.005, Trerotola thrombolysis HR,3.14,1.53-6.43, p=0.002). A positive correlation was demonstrated between the increasing number of successful pre-emptive angioplasties and VA secondary patency (HR,0.90, 0.83-0.98, p=0.019). After 4.2±4.5 angioplasties per access, the association of CSS and stenosis proved to be weak (HR, 0.74, 0.32-1.70, p=0.474), a finding that requires further analysis.

Conclusions: Factors such as age, site or time on dialysis, traditionally thought to adversely affect access prognosis may not influence secondary outcomes of AVG. The use of new technology conduits, stenting or sophisticated endovascular catheters and declogging techniques may not contribute to prolonging access survival. Prompt stenosis recognition and pre-emptive correction could be a milestone in our continuous challenge for improving patency.

SA-PO1112

Comparing Outcomes of Forearm Loop and Arm Curved Configurations of Arteriovenous Grafts for Hemodialysis

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Background: We conducted a comparative analysis of outcomes of newly placed proximal upper arm straight grafts (pAVG) and distal forearm loop grafts (dAVG).

Methods: Retrospective, single-center analysis. Incident dialysis patients with newly placed AVGs involving the brachial or radial artery, pAVG or dAVG, were studied from 2015 to 2018. Primary survival (PS), primary assisted survival (APS) and secondary survival (ScS) (months) and patency rates for both conduit configurations were determined. Number of patency maintenance and access salvation interventions were recorded and compared.

Results: Data from 185 patients were analyzed, 108 patients received pAVG and 101 dAVG of loop configuration. PS was demonstrated to be 6.7±1.0 months for pAVG and 6.3±1.1months for dAVG (p=0.925), when APS was 21.7±4.0 for pAVG and 13.0±4.5 for dAVG (p=0.448). ScS was 48.3±5.4 for pAVG and 50.1±5.0 months for dAVG (p=0.829). An average of 3.03±3.76 angioplasty procedures was performed for patency maintenance in pAVG and 4.93±4.78 in dAVG, respectively (p=0.006). Moreover, 0.26±0.55 and 0.74±1.05 stents were deployed in pAVG and dAVG, respectively (p=0.001), with 20.3% of proximal grafts and 44.3% of distal conduits requiring stenting to maintain patency (p=0.002). In 28.6% of pAVGs and 41.9% of dAVGs no access salvation intervention was required, while in 71.4% of pAVGs and 58.1% dAVGs thrombectomy, transluminal thrombolysis or both were performed in order to restore patency, differences that were non-significant (p=0.355). Primary patency was 32% and 17% for pAVG and 28% and 18% for dAVG in 12 and 24 months, respectively. Assisted primary patency was 54%, 41%, 28% and 22% for pAVG and 46%, 35%, 25% and 19% for dAVG in 12, 24, 36 and 48 months, respectively. Secondary patency was 77%, 60%, 50% and 42% for pAVG and 70%, 64%, 52% and 42% for dAVG in 12, 24, 36 and 48 months, respectively.

Conclusions: Distal forearm grafts seem to perform similarly to proximal arm conduits since both configurations serve their respective purpose. Intensive follow-up, access surveillance, pre-emptive patency maintenance interventions are all essential for these outcomes, especially in the distal loop configuration. In order to preserve a maximal number of access sites, the forearm location should be advised to be considered first.

SA-PO1113

Prognosis of Vascular Access in Hemodialysis Patients with Autosomal Dominant Polycystic Kidney Disease

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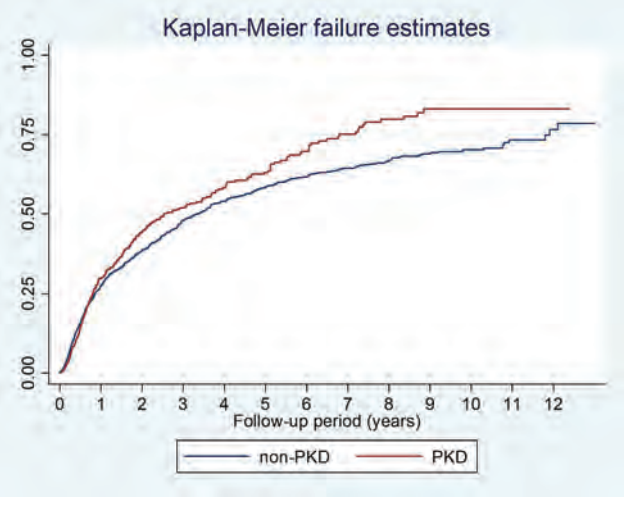
Background: Vascular diseases, including aneurysms of intracerebral arteries and abdominal aorta are commonly observed in patients with autosomal dominant polycystic kidney disease (ADPKD). We aimed to investigate the difference in the risk of malfunction of arteriovenous fistula or graft (AVF/AVG) between hemodialysis (HD) patients with and without ADPKD.

Methods: We enrolled 354 HD patients with ADPKD and 28264 HD patients without ADPKD in this study. Only 1062 propensity score-matched HD patients without ADPKD were included for analysis. The outcomes include the rate of AVF/AVG malfunction which is defined as the need for the first interventional procedure of either angioplasty, thrombectomy or creation of another AVF/AVG for all HD patients within 3 months, 1, 5 and 10 years respectively.

Results: The malfunction rate (per 100 person-years) of AVF/AVG for ADPKD and non-ADPKD was (1) 20.1 and 30.38 [HR=0.68, P=0.144] within 90 days, (2) 34.85 and 30.38 [HR=1.08, P=0.517] in first year, (3) 23.56 and 20.46 [HR=1.12, P=0.154] within 5 years, (4) 17.82 and 12.59 [HR=1.36, P=0.004] between 1st and 10th years, and (5) 22.6 and 17.52 [HR=1.21, P=0.015] at all period respectively.

Conclusions: In comparison with non-ADPKD patients, ADPKD patients had a trend of lower risk of AVF/AVG malfunction in the first 90 days but a significant higher risk after 1 year of AVF/AVG creation.

Funding: Government Support - Non-U.S.



Kaplan-Meier figure estimates show any new AVF cration or PTA representing AVF failure There is an overlapping of curves of the ADPKD and non-ADPKD group around 1-year follow-up period.

SA-PO1114

Resolution of High-Output Heart Failure, Recurrent Ascites, and AKI in a Renal Allograft After Ligation of the Arteriovenous Graft

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Introduction: A good vascular acces is crucial for effective dialysis. Arteriovenous graft (AVG) is an arteriovenous fistula (AVF) with a prosthetic interposition between the artery and vein. The complications can include infection, lymphedema, aneurysmal dilations, stenosis, high output heart failure (HOHF), steal syndrome and thrombosis. Ligation of the AVG should be considered in patients presenting with unexplained HOHF. Herein, we present a case of HOHF, recurrent ascites, AKI and slow graft function following a kidney transplant that resolved only with ligation of the AV graft.

Case Description: A 48-year-old Caucasian female with past medical history significant for end Stage Renal Disease (ESRD) secondary to congenital anomalies of the kidneys. She was on hemodialysis (HD) via right thigh AVG. Following AVG placement,

she experienced recurrent ascites (on and off) requiring multiple paracentesis. Extensive Gastrointestinal (GI) and cardiovascular (CVS) workup did not reveal any etiology and she was taken off the transplant list due to the ascites. Due to poor clearance through her AVG, she underwent right upper extremity AVF to continue dialysis. Eventually her ascites resolved without any intervention, following which she had a deceased donor kidney transplant (DDKT). It was complicated by volume overload and recurrent ascites resistant to diuretics and required multiple paracentesis. The creatinine did not come below 3.7 and was diagnosed with slow graft function. The sister donor kidney achieved a normal creatinine in two weeks after transplant. Echo was suggestive of normal EF, elevated left atrial pressures, severely dilated left atrium and moderate pulmonary hypertension ~ 57 mmHg. Serum Albumin Ascites Gradient (SAAG) was 1.5 g/dL and ascitic protein > 2.5 g/dL. A decision was made to ligate the old right femoral AVG and soon the Cr improved to 1.5 with complete resolution of ascites.

Discussion: Our case emphasizes the importance of hemodialysis access ligation to treat HOHF, a known complication of hemodialysis access. Our case is unique in that the patient is a kidney transplant patient who was taken off the transplant list due to unexplained ascites and who again developed recurrent ascites, slow graft function and AKI post-transplant that completely resolved with ligation of AVF.

SA-PO1115

De Novo ANCA-Associated Glomerulonephritis in Post-Transplant Kidney

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Introduction: De novo pauciimmune (ANCA-positive) GN in renal transplant is rare. Clinically, there is a rapid rise in serum creatinine level, accompanied by an active urine sediment, with or without symptoms of vasculitis involving others organs. The ANCA associated vasculitides can lead to segmental necrotizing or global necrotizing inflammation of the glomeruli, with the formation of crescents, an absence or paucity of glomerular immunoglobulins or complement, and ussualy rapidly progressive glomerulonephritis

Case Description: We report three cases of patients with living donor kidney transplant who had chronic kidney disease of undetermined cause, with a long time since the transplant. They developed graft dysfunction and proteinuria, so a renal biopsy was performed. Table 1

Discussion: Urinary abnormalities such as microhematuria and proteinuria are good indicators for the diagnosis of relapsing and de novo glomerulonephritis in kidney allograft in both cases. Combined with the urinary abnormalities, a confirmation of characteristic histological lesions to ANCA-V; necrotizing crescentic glomerulonephritis and/or small vessel vasculitis, by renal biopsy was required for the diagnosis of ANCA-V. The outcome of renal function is usually bad, with loss of renal function and fibrosis; In the case of the first patient, a second renal biopsy was performed with interstitial fibrosis III, and in the case of patient 2, she is currently under treatment.

Characteristics of patients

Case	Case 1	Case 2	Case 3
Age	59	34	46
Gender	Female	Female	Female
Race	Hispanic	Hispanic	Hispanic
Kidney disease etiology	Unknown	Unknown	Unknown
Allograft source	Living (brother)	Living (father)	Living (husband)
Time postransplantation, yr	23	15	9
Previous Treatment	Prednisone 5 mg/d Mofetil micofenolate 500 mg bid	Prednisone 5 mg/d Mofetil micofenolate 500 mg bid Cyclosporine 75 mg bid.	Prednisone 5 mg/d Mofetil micofenolate 500 mg bid Cyclosporine 125 mg bid.
sCr at biopsy, mg/dl	2.1	1.7	1.7
Proteinuria g/d	2.9	1.65	0.85
Treatment	Methylprednisolone 3 g. RTX 375 mg/m2	Methylprednisolone 3 g. RTX 375 mg/m2	Methylprednisolone 3 g. CFM 6 g
6 Mo Follow up	sCr 1.4, GFR 41 ml/min P/C 2g/g	In treatment.	sCr 1.4, GFR 41 ml/min P/C 0.2

SA-PO1116

A Case of De Novo Fibrillary Glomerulonephritis in Post-Kidney Transplantation

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Introduction: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease that results from deposition of Congo red-negative fibrils in glomerulus. Renal biopsy have shown that these fibrils, which consists of polymorphic IgG, are deposited mostly in mesangium and subendothelium areas. Recent studies show that DnaJ heat shock protein family member B9 (DNAJB9) has been associated with FGN. Patients usually present with nephrotic syndrome, hypertension, and hematuria. About 50% of the patients progress to end stage renal disease (ESRD). There are rarely reported cases of patients who present with de novo FGN post-kidney transplantation. Here we discuss a case of a patient with FGN post-kidney transplantation.

Case Description: This is a 61 year-old African American male with history of hypertension, ESRD on HD secondary to Diabetic Nephropathy, s/p Deceased Donor Renal transplant in March 2013, Hepatitis C, history of Banff 1A acute cell mediated rejection (August 2013), was evaluated for rise in creatinine to 3.1 from baseline of 2.0. in March 2019. He also had nephrotic-range proteinuria, hypertension without any other symptoms. He underwent transplant kidney biopsy, which showed Congo red-negative fibrillar deposits in glomeruli. Immunofluoroscence was consistent with FGN with lambda-chain restriction. He also had high Hepatitis C viral load of 273000 IU/ml. Immunofixation showed no monoclonal spike. FGN in this patient is presumed secondary to chronic Hepatitis C, thus was referred for Hepatitis C treatment and oncology referral for cancer screening.

Discussion: A retrospective study from University of North Carolina showed that among the FGN cases, Hepatitis C is most commonly reported in the African American population, and this is the group likely to transition to dialysis. Our patient was found to have high Hepatitis C viral load at the time of FGN diagnosis, thus supporting the hypothesis that Hepatitis C may be a causative factor of FGN. A case in 2013 reported a 56 year-old patient with a history of Hepatitis C who developed progressive renal graft failure due to FGN diagnosed 8 years after transplant. These studies indicate that Hepatitis C may be involved in developing fibrils in FGN, thus highlighting the importance of treating Hepatitis C virus for longer durability of renal allograft

SA-PO1117

BK Polyomavirus Nephropathy with Multiorgan Involvement: Whole-Genome Sequencing Data from a Killer Virus

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Introduction: Post kidney transplantation "organ limited" BK-polyomavirus (BKPyV) nephropathy (BKN) is a known complication. BKPyV infections with multi-organ involvement and severe morbidity are rare. 6/10 reported cases occurred in patients with lymphoproliferative disorders, with AIDS (3/10) and post renal transplantation (1/10). Whether severe immunosuppression, specific BKPyV strains, and/or viral gene mutations promote systemic viral spread is unknown. Here we report the first case of fatal BKN with multi-organ involvement from which detailed deep virus genome sequencing data are available.

Case Description: Patient: 24-year old woman with sickle cell anemia, status post CD34+ selected, T-cell depleted allogeneic peripheral blood stem cell transplantation (tx). Clinical data: Multiple post tx episodes of GVHD. Since post tx day 174 progressive BKPyViremia, very low CD3, CD4, CD8 counts, low immunoglobulin titers. Since day 459 progressive renal failure. Since day 631 respiratory distress; no hemorrhagic cystitis. Since day 651 pancreatitis. On day 696 patient death due to renal and respiratory failure. Autopsy findings: Productive PyV infection of both kidneys (PVN class 3), pancreas, and lungs with diffuse alveolar haemorrhage. Severe depletion of bone marrow and lymphoid organs. Whole Genome Sequencing data (from kidney, lung and pancreas): No diagnostic genomic mutations; systemic infection by episomal BKPyV strain Ib2. Viral mutations restricted to NCCR control domain with severe deletions, duplications and insertions in the "P,Q,R" NCCR sequences (largely sparing the "O" and "S" sequences). BKPyV-NCCR mutations more abundant and profound than those reported in BKN. No genetic evidence of mutant BKPyV 'metastatic' spread from one organ site to another.

Discussion: This is the first report identifying the common Ib2 strain of BKPyV in a case of multi-organ infection. Presumably profound immunosuppression allowed for evolution of mutated BKPyV strains. Severe rearrangement solely observed in the viral control region NCCR likely enhanced replication and pathogenicity with infection of uncommon organs such as pancreas and lung. Renal failure and multi-organ involvement due to mutated BKPyV should be considered in severely immuno-compromised patients.

SA-PO1118

Mystery Mass in an Asymptomatic Kidney Transplant Recipient

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Introduction: Malakoplakia is a rare inflammatory granulomatous mass comprised of partially digested bacteria due to the inability of macrophages to completely digest an infectious organism. It is most often seen in immunocompromised patients. Here we present a case of malakoplakia in a recent kidney transplant recipient with a complex urologic history who was otherwise asymptomatic.

Case Description: A 64-year-old male who received a living unrelated kidney transplant four months ago, complicated by slow graft function after transplant, and right femoral AV fistula ligation one month ago presents with two weeks of swelling in his right groin. He had bladder cancer with cystectomy and creation of an Indiana pouch with urinary diversion nineteen years ago, subsequent development of stomal stenosis and a ureteroenteric stricture causing obstructive nephropathy. The obstruction and chronic hypertension led to renal failure requiring hemodialysis. His creatinine improved after ligation of the right femoral AV fistula. Two "knots" in his right groin developed two weeks after fistula ligation and began draining purulent fluid. He admitted to intermittent cloudy urine draining from his urostomy but denied fevers, chills, allograft pain, weight loss, fatigue, malaise. A CT scan revealed a possible post-operative hematoma versus an indeterminate mass. Surgical exploration revealed scant seropurulent drainage, and organized inflammatory and necrotic tissue. Pathology was significant for PAS-diastase

and iron stains with numerous intracytoplasmic targetoid inclusions, consistent with pathognomonic Michaelis-Gutmann bodies. Cultures were positive for E. coli. The patient was treated with 4 weeks of ceftriaxone with subsequent resolution of his groin swelling.

Discussion: While malakoplakia is a rare diagnosis, this should be considered in the differential of any immunosuppressed patient with a mass. Tissue diagnosis, to confirm with specific request for PAS and von Kassa staining allows for identification of the pathognomonic Michaelis-Guttmann bodies. Cultures identify a causative organism and allow for targeted treatment. Most commonly, *E. coli* is the underlying pathogen, but *Klebsiella*, *Pseudomonas*, *Enterococcus*, and *Streptococcus* have been identified. Finally, careful evaluation of the immunosuppressive regimen should be undertaken if malakoplakia is identified.

SA-PO1119

An Interesting Case of Anti-HLA-C Antibody-Mediated Acute Humoral Rejection and Fabry-Like Zebra Bodies in a Renal Transplant Recipient

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Introduction: Detection of Donor Specific Anti-bodies (DSA) is essential in diagnosing Antibody-mediated renal allograft rejection (AMR). HLA-C antibodies testing is not part of routine DSA pre-transplant evaluation, but they have been reported to cause AMR. We present a case of AMR secondary to DSA against HLA-C, and incidental finding of ultrastructural zebra-bodies under Electron Microscopy (EM), raising suspicion for undiagnosed Fabry's disease, eventually determined to be of uncertain significance.

Case Description: A 39-year old African American male with ESRD due to hypertensive nephropathy underwent 2A/2B/2DR mismatched cadaveric transplant in 2014. Post-transplant Creatinine (Cr) was 1.4-1.6 mg/dl. Four years later, Cr was found to be elevated at 2.16 mg/dl. Allograft biopsy showed early chronic transplant glomerulopathy without evidence of acute cellular or humoral rejection. EM showed ultrastructural zebra-patterned lipid inclusions in podocytes (Fig 1), suspicious for donor-derived Fabry's disease, which turned out to be of unclear significance. Cr worsened and he developed nephrotic range proteinuria and hematuria. Repeat biopsy showed capillaritis and arteritis with focal fibrinoid necrosis (Fig 2), with weak and focal C4d deposits on IF. DSA were positive to Cw7 and Cw2. He was treated for acute AMR with pulse steroids, IV immunoglobulin, plasmapheresis and rituximab but his renal function worsened and he became dialysis-dependent.

Discussion: This case report emphasizes the role of HLA-C antibodies in causing AMR, and demonstrates the need for their recognition in the pre- and post-transplant period. In addition, the incidental presence of zebra-patterned lipid inclusions in podocytes in transplant renal biopsy doesn't necessarily indicate Fabry's disease.

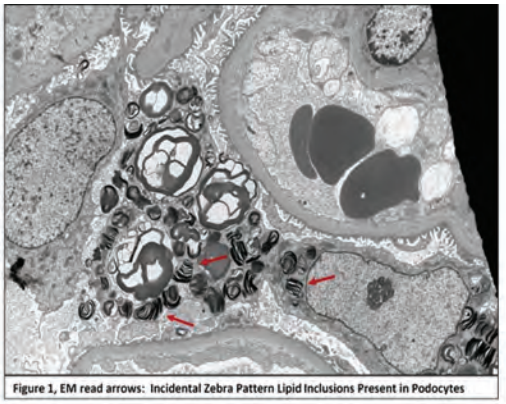

Figure 1, EM read arrows: Incidental Zebra Pattern Lipid Inclusions Present in Podocytes

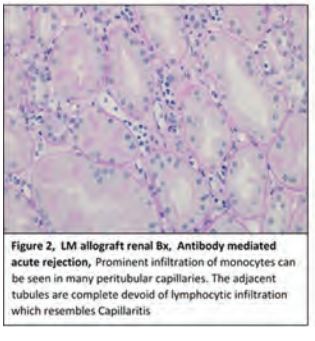

Figure 2, LM allograft renal Bx, Antibody mediated acute rejection, Prominent infiltration of monocytes can be seen in many peritubular capillaries. The adjacent tubules are complete devoid of lymphocytic infiltration which resembles Capillaritis

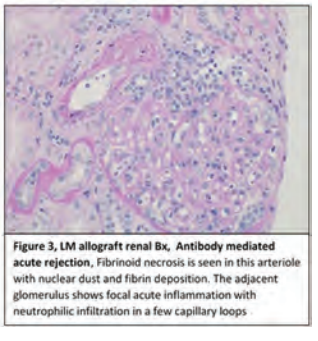

Figure 3, LM allograft renal Bx, Antibody mediated acute rejection, Fibrinoid necrosis is seen in this arteriole with nuclear dust and fibrin deposition. The adjacent glomerulus shows focal acute inflammation with neutrophilic infiltration in a few capillary loops

SA-PO1120

Metastatic Round Cell Sarcoma in a Renal Transplant Recipient

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Introduction: We present a rare case of metastatic round cell sarcoma in a renal transplant recepient. Our literature search shows this is a first reported case round cell sarcoma in this group of patients.

Case Description: 57-year-old male, end stage renal failure due to polycystic kidneys, underwent deceased donor renal transplantation. Patient received standard induction immunosuppression with basiliximab and maintainence immunosuppression of mycophenolate, tacrolimus and prednisone. 6 months post transplant patient noticed a lump about 4 cm in diameter on the medial side of the lower end of his thigh. Ultrasound showed that this mass was arising from the Sartorius muscle. He further underwent a biopsy of this mass, which showed un-differentiated round cell sarcoma. Staging CT scan did not show any evidence of metastatic disease. It was decided patient would have radiation therapy followed by surgical removal of sarcoma. A week prior to surgery, he presented with severe back pain and epistaxis. Blood test revealed thrombocytopenia with platelet count of 9* 10^9/litre. CT scan showed several metastatic lesions in lumbar spine and femur and lungs. Patient was deemed to unwell to tolerate chemotherapy. We did discuss with patient regarding stopping or reducing immunosuppression at the time of diagnosis of metastatic disease, as this might slow the progression of disease, however patient refused this. Patient was managed with platelet transfusion and analgesia with a plan to offer radiation therapy for pain. Patient was referred to Hospice for management of symptoms and end of life care and passed away 2 weeks later.

Discussion: Sarcomas are heterogeneous group of aggressive malignant tumors of mesenchymal origin that make up less than 1% of adult malignancies. Unlike Kaposis sarcoma, which is associated with immunosuppression, round cell sarcoma has never been reported in renal transplant recipient. Role of immunosuppression contributing to the genesis and progression of this tumor is unknown. Despite treatment with aggressive chemotherapy and radiation therapy, prognosis with metastatic round cell sarcoma is extremely poor. In our patient, sarcoma on intially testing was limited disease and thought to be curable. However within 1 months time, it progressed from solitary lesion to multiorgan metastasis. We think Immunosuppression might have contributed to accelerated progression.

SA-PO1121

Renal Aspergillosis After Liver Transplant

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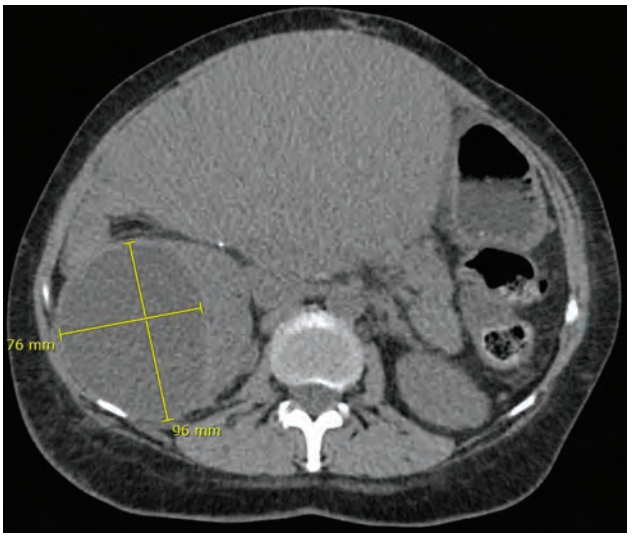
Introduction: Renal aspergillosis is a rare life-threatening disorder in liver transplant recipients. Only 3 cases have been reported in the literature to date. This dreaded complication usually occurs within 90 days of transplant but late onset has been reported. We hereby present a case of renal aspergillosis occurring one year after liver transplantation.

Case Description: A 40-year-old white female presented with right-sided abdominal pain and vomiting for two weeks. Her history was significant for cryptogenic cirrhosis for which she had a living donor liver transplant one year prior. Two months before admission, she was found to have a spontaneous right renal subcapsular hematoma and acute kidney injury with previously normal eGFR, which was managed conservatively. Immunosuppression on admission included tacrolimus and MMF. Work up showed WBC 30000/uL and a creatinine of 3.5 mg/dl. CT scan showed expansion of the right renal subcapsular hematoma, measuring 10 x 9.6 x 7.6 cm and compressing the renal parenchyma. She was urgently taken for exploration and was found to have a large abscess with nonviable kidney. As such, evacuation and nephrectomy was performed. Pathology showed acute pyelonephritis with abscess, necrosis, and necrotizing granulomas containing fungal organisms consistent with Aspergillus species. She was treated with antifungal therapy for three months. The kidney function continued to deteriorate following many subsequent ischemic insults. The patient eventually required dialysis.

Discussion: Renal aspergillosis in liver transplant recipients carries significant morbidity and mortality. Risk factor includes severe immunosuppression, kidney failure, prior urological procedures, CMV or HHV-6 infection, and fulminant hepatic failure as a cause for transplant. Although renal aspergillosis is uncommon, a high degree of suspicion is required in transplant recipients as early detection and treatment can be life-saving.



SA-PO1122

Collagenofibrotic Glomerulopathy in a Renal Transplant Patient

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Introduction: Collagenofibrotic glomerulopathy is a rare disease that can occur in childhood in an autosomal recessive inheritance pattern or sporadically in adults. It is non-immune mediated and is characterized by deposits of type III collagen in the mesangial and subendothelial areas of the glomeruli. Per prior case series, the average age of onset is 40 years. The rate of progression is variable and it sometimes results in end-stage renal disease.

Case Description: The patient is a 66 year old male with ESRD due to biopsy proven ANCA-negative pauci-immune crescentic glomerulonephritis, coronary artery disease, atrial fibrillation, and hypertension who underwent living unrelated renal transplant via paired exchange in December of 2016. His anti-rejection regimen was tacrolimus, everolimus, and prednisone. His post-transplant creatinine nadir was 1.5 -2.0 mg/dl but had slowly risen to 3.0 – 3.8 mg/dl in the months prior to evaluation. He had a negative DSA, low positive BK blood titers (peak of 244,000 copies/mL down to 838 copies/mL), and proteinuria of 500 – 1000 mg/g. His renal transplant biopsy demonstrated chronic changes with 30% interstitial fibrosis and tubular atrophy and arteriolar hyalinosis secondary to calcineurin inhibitor toxicity with no evidence of transplant rejection. The glomeruli exhibited focal accumulation of PAS pale material in the capillary lumina and in the mesangium. Immunofluorescence was negative. On electron microscopy, there were subendothelial and mesangial deposits of curvilinear collagen fibrils compatible with collagenofibrotic glomerulopathy. Unfortunately, additional tissue was not available for immunohistochemical staining. The patient's native renal biopsy was reviewed with no evidence of similar deposits. The donor's records were also reviewed showing serum creatinine of 0.93 mg/dl with no significant proteinuria. The patient was transitioned from tacrolimus to belatacept with improvement in his serum creatinine to 2.34 mg/dl.

Discussion: Collangenofibrotic glomerulopathy is an extremely rare disease and in this case it is unclear whether it was donor derived or developed de novo after renal transplant. Renal biopsy of the donor would be the definitive diagnostic test but was not indicated with normal donor kidney function.

SA-PO1123

Allograft Mucormycosis Presenting as AKI

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Introduction: Mucormycosis is a life-threatening complication of kidney transplantation associated with a 50% mortality rate. About 25 cases of renal involvement have been reported in the literature.

Case Description: A 62-year-old asymptomatic diabetic male was seen in the clinic 6 weeks after an uncomplicated 0 antigen mismatch living donor kidney transplant from his sister. He received basiliximab induction and standard immunosuppression. Labs showed an acute rise in creatinine (0.8 mg/dl to 1.5 mg/dl). Transplant ultrasound revealed hydronephrosis and creatinine worsened despite stent placement. Allograft biopsy was negative for rejection. His graft function worsened and dialysis was started on day 5. A nuclear scan showed decreased uptake in upper and middle poles. Intra-operative allograft exploration, biopsy and angiogram on day 7 revealed good perfusion but fungal hyphae were seen. A pulmonary nodule was seen on Chest X-ray ordered for worsening respiratory status on day 7. Whole body imaging revealed 3 scattered, cavitary pulmonary nodules suggesting disseminated fungal disease. Emergent transplant nephrectomy was performed and a repeat wedge biopsy revealed hyphae in the glomerular, tubular and vascular segments suggestive of allograft mucormycosis. Immunosuppression was stopped and Amphotericin was initiated.

Discussion: Risk factors in the post-transplant period include heightened immunosuppression (induction and anti-rejection therapy), diabetes, donor transmission, surgical contamination or presence of immunomodulating viruses (CMV and Hepatitis C). Being angioinvasive, mucor leads to thrombosis, ischemia or irreversible tissue necrosis. Histopathology is diagnostic and demonstrates ribbon-like, aseptate hyphae with wide angled branching. Blood and tissue cultures have a poor diagnostic yield. Management includes extensive surgical debridement, graft removal and antifungal agents. Amphotericin is the first line drug and posaconazole has been used as a step down or salvage therapy. Experimental therapies with iron chelation, hyperbaric chamber and cytokines (like G-CSF) have been tried with minimal benefits. Diagnostic challenges such as lack of serological tests, isolation difficulties and poor staining techniques delay recognition. A high index of clinical suspicion and prompt action with aggressive surgical resection and anti-fungal therapy is necessary for a favorable outcome.

SA-PO1124

Treatment of Valganciclovir-Resistant Cytomegalovirus with Letermovir

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Introduction: Cytomegalovirus (CMV) resistance to ganciclovir is an important concern post- kidney transplant. Resistance is often mediated by one of two mutations: UL97, which encodes a kinase responsible for phosphorylation and activation of ganciclovir; and UL54, which encodes the viral DNA polymerase targeted by ganciclovir (Vez et al, Clin K J 2014). Alternatives to ganciclovir include foscarnet and cidofivir, but their use can be limited by nephrotoxicity and marrow suppression. Letermovir is an anti-CMV agent approved by the FDA for prophylaxis against CMV infection post-transplant. It inhibits CMV replication by binding to the terminase complex not affected by the mutations seen in ganciclovir-resistant CMV, and has minimal myelosuppresive and nephrotoxic effects.

Case Description: This is a 73 year old woman with a history of ESRD due to anti-GBM disease who underwent deceased donor renal transplant in January 2019. She was considered high risk for CMV as a CMV IgG negative patient who received a kidney from a CMV IgG positive donor. In February 2019 she was found to have a detectable CMV viral load, rising throughout March and April despite increased doses of valgancyclovir. She was admitted in April 2019 for treatment with Foscarnet. CMV resistance genotyping showed a UL97 mutation predicting Ganciclovir resistance. CMV viral load peaked at 4.0 log 10 IU/ml and began to downtrend after 1 week of Foscarnet. She then developed AKI and pancytopenia with severe neutropenia which was likely Foscarnet-induced. In consultation with infectious disease we started oral letermovir 480mg twice for 7 days then converted to daily dosing until viral load becomes undetectable. Her viral load has downtrended to < 2.1 log 10 IU/ml on letermovir after 2 weeks of therapy. Neutropenia has recovered, and her AKI has improved.

Discussion: Letermovir is currently being studied for treatment of CMV resistant to ganciclovir (ID NCT03728426, phase 2 investigation). Here we present a case of an individual with proven UL97 mutation-driven ganciclovir-resistant CMV who developed severe side effects precluding further use of foscarnet and was started on Letermovir for treatment of CMV. CMV viral load improved to barely detectable levels on treatment with letermovir alone, without marrowsuppressive or nephrotoxic side effects.

SA-PO1125

Crystal Conundrum: Renal Allograft Failure from Recurrent 2,8 Dihydroxyadenine Nephropathy

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Introduction: Post transplant crystalline nephropathy, a rare occurrence, can significantly impact allograft outcomes. Here we present a case of adenine phosphoribosyltransferase (APRT) deficiency resulting in excess adenine and consequentially insoluble 2,8-dihydroxyadenine (2,8-DHA) crystals leading allograft failure.

Case Description: A 68-yo man with ESRD presumably due to hypertension presented for deceased donor renal transplant. Pre transplant evaluation was unremarkable. Imaging of native kidneys revealed multiple cysts without stones. He received a 2A1B1DR HLA mismatch kidney, crossmatch negative, PRA 89%, blood group identical kidney from a hypertensive, diabetic deceased donor with KDPI of 75%. Patient received thymoglobulin induction followed by maintenance immunosuppression with prednisone, tacrolimus and mycophenolate mofetil. The surgical procedure was uneventful. A zero-hour biopsy showed donor-derived disease consisting of mild arteriosclerosis, 9% global glomerulosclerosis, 10% interstitial fibrosis. Postoperative allograft function was delayed. Hemodialysis (HD) was started on postop day (POD) 3. Renal ultrasound was unremarkable. Immunologic assessment with DSA was negative. On POD 14, transplant biopsy was performed showing acute tubular epithelium injury with numerous birefringent crystals initially interpreted as calcium oxalate crystals, suspicious for hyperoxaluric condition. Daily HD and supplementation with pyridoxine and calcium acetate were initiated. Renal function did not improve. Closer inspection of the biopsy with special stains revealed features of the crystals suspicious for 2,8-DHA nephropathy consistent

with APRT deficiency. Patient was started on allopurinol, fluid infusion and low purine diet. HD was discontinued. Genetic testing revealed a homozygous pathogenic variant for the APRT sequence. Renal allograft function remained poor and progressed to primary nonfunction of the renal allograft.

Discussion: Although 2,8-DHA crystals, often misdiagnosed, resemble calcium oxalate crystals in being birefringent under cross-polarized light, crystals have a slightly yellow-brown coloration, and unlike oxalates, are argyrophilic with Jones silver stain. Timely diagnosis of 2,8-DHA nephropathy and aggressive management with xanthine dehydrogenase inhibitor and low purine diet may salvage the renal allograft.

SA-PO1126

West Nile Virus: A Peculiar Cause of Fever and Encephalopathy in a Transplant Patient

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Introduction: West Nile Virus (WNV) is an uncommon viral encephalitis. Here we describe an unusual presentation of WNV encephalitis in a kidney transplant recipient.

Case Description: 65 year old woman with ESKD due to fibrillary glomerulonephritis, recurrent UTIs, T2DM s/p living related donor kidney transplant with basiliximab induction, CMV -/+, EBV -/+, no PRA/DSA maintained on standard triple immunosuppression who presented with fever, dysuria. On presentation she was febrile, tachycardic, normotensive, and with normal mentation. She recently was treated for multi-drug resistant E. Coli UTI, but had persistent symptoms, positive UA and started on empiric pipercilin-tazobactam. Urine culture grew the same E. Coli. Blood cultures remained negative. She was narrowed to ceftriaxone. Despite appropriate coverage, she remained febrile, weak, and developed a dense hypoactive delirium. She developed dysarthria prompting Neurology consultation and head imaging, which were unremarkable. Over days, her mental status did not improve and exam changed with new spasticity/hyperreflexia. A lumbar puncture was performed, showing lymphocytosis and CSF WNV IgM positivity via ELISA testing with an index value of 9.73 (1.1 or greater suggestive of WNV). With this diagnosis, her immunosuppression was reduced to azathioprine/prednisone along with 1 dose of IVIG. Over days, her delirium resolved. She had a prolonged course of rehabilitation. Her graft function remained stable throughout her illness.

Discussion: West Nile Virus is a rare disease associated with marked neurological sequelae including weakness often lasting months. Diagnosis is often challenging, as manifestations can be non-specific and involve multiple organ systems. A high index of suspicion and thorough neurologic evaluation are key to diagnosis. CSF IgM is a useful test, specific for neuroinvasive WNV as IgM does not cross the blood brain barrier. Interpretation can be difficult as it usually takes 4-10 days to manifest. Interestingly, it can persist for 12 months i.e. may represent prior infection in some cases. Aside from insect repellent, no other preventative measures or directed therapies exist to quell this infection, which ultimately requires supportive care. West Nile Virus is a key differential diagnosis in the transplant patient with encephalopathy and its recognition is vital to guiding prognosis and management.

SA-PO1127

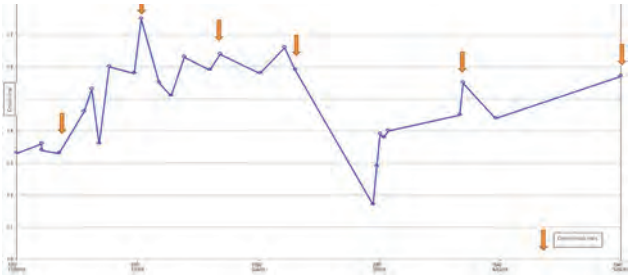
Contrary to Expectation: Preserved Renal Function After Using PD-1 Inhibitor Cemiplimab-rwlc in a Kidney Transplant Recipient

Muhannad Leghrouz, Svetomir N. Markovic, Aleksandra Kukla. *Mayo Clinic, Rochester, MN.*

Introduction: The use of the immune checkpoint inhibitors in transplant recipients with malignancy is associated with the risk of graft failure due to acute rejection. Here we present the first reported case of using Cemiplimab-rwlc (Libtayo), a recently approved programmed death receptor-1 (PD-1) blocking antibody for locally advanced and metastatic cutaneous squamous cell carcinoma (CSCC), in a kidney transplant recipient.

Case Description: 48 yo male with a history of ESRD secondary to ADPKD, received 5/6 ABDR HLA mismatch living donor kidney transplant in May of 2016. He had class II DSAs (DR4 with MFI 1975). He received Thymoglobulin induction and maintenance immunosuppression with Tacrolimus, MMF and Prednisone. Protocol allograft biopsy at 2 years post transplant showed Banff borderline acute cellular rejection. At 2 years post transplant, he was diagnosed with metastatic CSCC of head & neck, HPV positive. Tacrolimus and MMF were discontinued and patient was switched to Sirolimus. Treatment included Mohs procedure, chemotherapy (paclitaxel/carboplatin/cetuximab) for 4 cycles and radiation for 5 months. He had good response to the cervical lymph nodes metastasis but had minimal sustained response to skull metastasis. Subsequently, he was switched from intratumoral 5FU to intratumoral IL2 and started on immunotherapy with Cemiplimab (Libtayo). Prednisone was discontinued. He underwent excision of scalp lesion and right cortical mastoid metastatectomy while on the full dose of Sirolimus, which he tolerated well. His kidney function remained stable throughout over 5 months follow up period (Figure-1).

Discussion: Literature reports a substantial risk of rejection in kidney transplant recipients who are treated with immunotherapy. However, as our case shows, PD-1 inhibitor Cemiplimab (Libtayo) can be used with preserving allograft function on a Sirolimus-based immunosuppression regimen. More data is needed in to guide clinicians and to appropriately counsel patients regarding the risks and benefits of immunotherapy medications.



SA-PO1128

Sampling Site Matters: A Falsely Elevated Tacrolimus Level After Stopping IV Infusion in a Patient with Central Venous Catheters

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Introduction: Tacrolimus levels abnormalities constitute a major concern to transplant nephrologists. Based on these values; decisions are made to adjust Tacrolimus doses to achieve adequate immunosuppression. The recognition of pitfalls with these laboratory tests becomes crucial to better interpret the accuracy of these results, specifically when dealing with critically ill patients using intravenous Tacrolimus where a large subset of these patients have central venous catheters that are used for infusions and blood sampling. We are reporting a case of falsely elevated Tacrolimus levels after discontinuation of the medication.

Case Description: A 52-year-old male with history of gastroparesis and kidney transplantation in 2011, presented with sever nausea, vomiting and inability to tolerate oral intake including his oral tacrolimus for one day prior to admission. On presentation, his Tacrolimus level was 3.1 ng/mL. Intravenous continuous infusion of Tacrolimus was initiated via a PICC line. Two days later, his symptoms have resolved and subsequently transitioned back to oral Tacrolimus. Next day Tacrolimus trough (drawn from the PICC line after multiple flushes) came back at 38.9 ng/mL, repeated level confirmed to be more than 30 ng/mL. Immediately, his oral tacrolimus was held. Interestingly, he did not exhibit any signs or symptoms of tacrolimus toxicity and his renal function remained stable at baseline. Rechecked daily troughs for the next 3 days were 23, 17 and 19 ng/mL, despite holding tacrolimus. Simultaneous samples were drawn from both PICC line and peripheral vein showed great discrepancy with troughs of 39.0 ng/mL and less than 3.0 ng/mL respectively. Historically, a similar misinterpretation occurred which led to prolonged hospital stay with potential compromise to his immunosuppression.

Discussion: Falsely elevated Tacrolimus levels in samples drawn from central venous catheters have been reported to last several days despite rinsing the catheter. Studies have shown evidence of reversible adsorption of the drug from the inner walls of different catheters. Raising awareness to this misleading phenomenon helps avoiding dangerous dose reductions of the immunosuppressive drug and unnecessarily prolonged hospital stay. Sampling for Tacrolimus level should always be drawn from peripheral veins.

SA-PO1129

Angiotensin II Type I Receptor (AT1R) Antibody-Associated Collapsing FSGS in a Renal Allograft

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Introduction: Post renal transplant de novo collapsing FSGS could be associated with AT1R antibody.

Case Description: A 66-year-old man with type 2 diabetes mellitus underwent pre-emptive renal transplant for CKD of unproven etiology. He was HLA high risk with low level donor-specific DP1 antibodies and was induced with ATG and maintained on mycophenolate, tacrolimus and prednisone. Cytotoxic and flow cytometry cross matches were negative. Four weeks later he was noted to have proteinuria, which soon progressed to nephrotic range, while creatinine remained at baseline (1 mg/dl). Kidney biopsy was suggestive of acute humoral rejection with G1 glomerulitis, mild PTCitis and 60% C4d. HLA screen showed persistent low-level antibodies against DR52. Endothelial cell cross match was positive, indicating a non-HLA antibody mediated process. Treatment was initiated with pulse steroids, IVIG, plasmapheresis. AT1R antibody level was 14 units/ml (borderline) at 2 weeks and progressed to >40 units/ml at 4 weeks, following which he was started on Losartan and PLEX extended to 15 sessions. 3 months after the transplant, nephrotic range proteinuria persisted (10-12 g), however further escalation of immunosuppression was prevented by disseminated trichophyton infection and recurrent surgical site abscesses. Creatinine had increased to 2.4 mg/dl and a repeat biopsy showed diffuse collapsing glomerulopathy. C4d remained diffusely positive. Allograft function continued to decline and he returned to dialysis 8 months post-transplant.

Discussion: AT1R receptor is highly expressed on endothelial cells and podocytes and antibodies against it are known to cause acute humoral rejection. AT1R antibodies could potentially cause FSGS by enhancing the effects of AT II, which regulates matrix synthesis and cell proliferation. It also enhances the expression of transient receptor potential cation channel 6, which leads to FSGS in animal models. This report illustrates a case of AT1R antibody mediated humoral rejection with progression to an unusual clinical presentation (de novo collapsing FSGS), which was resistant to aggressive therapy.

SA-PO1130

A Unique Immunosuppression Strategy in a Patient with Atypical HUS Undergoing Kidney Transplant

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Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is a rare disease with estimated incidence of 1-2 per 1,000,000 caused by uncontrolled activation of alternative complement pathway due to genetic mutations mainly in complement inhibitor factors. Herein, we present a patient with atypical HUS who underwent deceased donor kidney transplant (DDKT) and successfully treated with a unique immunosuppressive strategy.

Case Description: A 23 year old female with no significant past medical history had a complicated pregnancy at age 18 with pre-eclampsia requiring emergent cesarean section. Post-partum, she developed acute kidney injury, anemia, thrombocytopenia and elevated LDH with normal ADAMTS-13 levels. Kidney biopsy showed acute thrombotic microangiopathy (TMA). Genetic testing revealed heterozygous missense mutations in complement factor H and complement factor H-related gene 5. She was diagnosed with atypical HUS and initiated on eculizumab but without renal recovery and was maintained on hemodialysis. Five years later patient was called in for DDKT with KDPI of 14%. Her PRA was high at 76%. She received a dose of eculizumab pre-operatively followed induction with by Thymoglobulin and methyl prednisolone. We chose maintenance immunosuppression with belatacept instead of tacrolimus along with mycophenolate mofetil (MMF). Eculizumab was continued. Her creatinine improved to 0.9mg/dl. Two months post-transplant, she developed acute T- cell mediated rejection type 1b successfully treated with methyl prednisolone followed by maintenance steroid therapy and increased dose of MMF. Serum creatinine remains at 1 mg/dl at 1 year follow up.

Discussion: Immunosuppressant management in aHUS patients with high PRA undergoing kidney transplant is challenging. Calcineurin inhibitors and DDKT itself are potential triggers for endothelial damage leading to TMA. Belatacept is a selective T-cell co-stimulation blocker which has not been reported to induce TMA. Our case demonstrates the safety and efficacy of Thymoglobulin induction followed by belatacept/MMF maintenance along with eculizumab in highly sensitized patient with aHUS.

SA-PO1131

Success of Intensive Immunosuppression to Prevent Post-Transplant Recurrence of C3 Glomerulonephritis in Children

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Introduction: C3 glomérulonephritis (C3GN) is characterized by the dysregulation of complement alternative pathway and is frequently associated with autoantibodies stabilizing the C3 or C5 convertase. There is currently no specific treatment and the renal prognosis is poor with a high risk of early recurrence post-transplant, leading to graft loss in more than 50% of cases, despite the use of Eculizumab.

Case Description: Two patients received a living donor transplant and one a deceased donor. Bi-nephrectomy was performed 5 +/-2 months before transplantation. Steroids (60mg/m^2/d) and MMF (1500mg/m^2/d) were started at least 1 month prior to transplant. Eculizumab was started 14 days before transplant in the 2 patients with a living donor and the 3rd patient was on long-term treatment. One session of immunoadsorption was performed 8h prior the renal graft for all. They received an induction by thymoglobulin or Basiliximab followed by Tacrolimus [T0 : 8-10 ng/ml], associated with MMF [AUC 50-60 µg.h.ml], steroids and Eculizumab. No early recurrence occurred. Protocolar renal biopsies at 3 months only showed C3 deposits in 1 patient without any inflammation. After a follow-up of 3, 6 and 15 months, none of the patients developed proteinuria or hematuria under Eculizumab. One patient developed a BK virus replication (4.8 log) at M4 that led us to decrease immunosuppression, this was complicated with acute cellular rejection (1B) at M5. eGFR at last follow-up was 55 ml/min/1,73m^2 in this patient and 80-86 ml/min/1,73m^2 in the two other patients.

Discussion: Intensive immunosuppression pre and post-transplant may prevent post-transplant recurrence of C3GN.

SA-PO1132

De Novo Cytomegalovirus-Triggered FSGS After Kidney Transplantation Associated with APOL1 Risk Allele

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Introduction: Recurrent and de novo glomerulonephritis (GN) account for 18% to 22% of death-censored kidney allograft failures. We report a case of de novo cytomegalovirus (CMV)-associated FSGS after kidney transplantation from an African American (AA) donor.

Case Description: A 52-yr-old White female (WF) with ESRD secondary to HTN underwent a 4-antigen mismatched, CMV D+/R-, deceased donor renal transplant from a 43-yr-old AA male in July 2018. Induction immunosuppression included methylprednisolone and Thymoglobulin followed by tacrolimus, mycophenolic acid (MMF) and prednisone. Serum creatinine (Cr) was 1 mg/dl at discharge. In Feb 2019, the patient presented with abdominal pain, diarrhea, and fever. Creatinine was 1.3 mg/dl, which worsened to 7.9 mg/dl over 5 days. Spot urine protein creatinine ratio (UPC) was 15. Infectious workup revealed CMV viremia (29,7460 IU/ml). Patient had discontinued valganciclovir (VGCV) 3 months after transplant. Allograft biopsy revealed podocyte effacement. Despite treatment for the CMV viremia (VGCV 900 mg po qd and discontinuation of MMF), Cr worsened and hemodialysis (HD) was initiated. VGCV was switched to IV ganciclovir 3 x wk with HD leading to clearance of viremia. Creatinine improved and HD was discontinued in April 2019. UPC improved to 7. Biopsy tissue sent for APOL1 risk variant genotyping revealed compound heterozygosity for G1/G2.

Discussion: Approximately 13% of AA carry two APOL1 risk variants. Increased risk of graft loss following kidney transplantation is associated with these alleles. However a second hit is required. Mechanisms for CMV-induced podocytopathy via injury to permeability barrier have been postulated. Our case exemplifies CMV as a second hit causing podocytopathy in a recipient with heterozygosity for APOL1 in an AA donor. Studies to better understand the mechanisms and predisposing factors for APOL1-associated kidney diseases are critical since recipients from donors with the risk alleles may warrant tailored management. Of note, the mate kidney was transplanted in a 48-yr-old WF who recently completed the 9-month CMV prophylaxis. Questions arise: 1) Should the duration of viral prophylaxis be extended in the second patient, 2) Should increased frequency of viremia screening be considered and, 3) Should aggressive antiviral strategies be considered at first identification of viremia?

SA-PO1133

Donor Derived Cell-Free DNA Positivity: Does It Always Denote Allograft Rejection?

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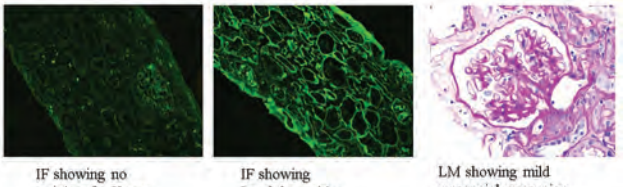
Introduction: Donor derived cell free DNA (dd-cfDNA) is a novel serum biomarker now available to predict acute rejection in renal allografts. Presence of dd-cfDNA > 1% suggests allograft injury; caused by acute rejection. We describe a rare form of post-transplant lymphoproliferative disorder (PTLD) presenting as positive dd-cfDNA.

Case Description: A 64 yo white male who underwent living related kidney transplant 3 years earlier with baseline serum creatinine(Cr) around 1.5 mg/dl presented with worsening allograft function. Serum Cr was 9mg/dl with 4.5 grams/day proteinuria. Elevated dd-cfDNA level at 2.5% prompted a renal allograft biopsy. Light microscopy showed mild mesangial matrix expansion, Immunofluorescence showed 3+ deposition of lambda light chain in a linear pattern along glomerular and tubular basement membrane suggestive of lambda light chain deposition disease(LCDD)-refer to figure 1. A subsequent bone marrow biopsy was consistent with lamda light chain restricted plasma cell dyscrasia. Patient was started on chemotherapy with cyclophosphamide, bortezomib, and dexamethasone along with plasmapheresis. Within a month, his renal allograft function improved with Cr of 1.6 mg/dl. After 6 months, he underwent autologous stem cell transplant(SCT)and currently remains in remission on Ixazomib. Repeat bone marrow biopsy and kidney biopsy have been normal. Cr remains at 1.3-1.5mg/dl one year post SCT. Repeat dd-cfdna levels remained <1%.

Discussion: This is the first reported case of lambda restriced LCDD, a rare form of PTLD in renal allograft presenting as positive dd-cfDNA. Elevated dd-cfDNA in our patient likely reflects allograft injury resulting from parenchymal infiltration with neoplastic cells along with light chain depostion. Our case highlights the need to include unusual causes of allograft injury in the differential diagnosis in patients presenting with renal allograft dysfunction and elevated dd-cfDNA. Allograft biopsy remains the gold standard in reaching a definite diagnosis.



IF showing no staining for Kappa | IF showing Lambda positive | LM showing mild mesangial expansion

SA-PO1134

Non-T Cell Depleting Induction Therapy Predisposes to Early Human Adenovirus Infection as Compared with T-Cell-Depleting Therapy: Case Report and Review of Literature

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Introduction: Human Adenovirus (HAdV) infections are increasingly recognized in post kidney transplant patients. We report a unique case of early post op HAdV infection presenting with a space occupying lesion in the allograft, evolving to bladder masses. We reviewed the literature to assess the effect of non T-cell depleting agents on frequency of early and late HAdV infection.

Case Description: A 38-year-old male, with end stage kidney disease (ESKD) due to IgA nephropathy underwent deceased donor renal transplant (DDRT). He received induction with Basiliximab. Post op course was uneventful. On post op day 8 he was admitted with fever (39.2 deg. C) and diarrhea of 2 days duration. Upon review of systems he had mild cough with mucoid sputum. On exam, he was tachycardiac with no allograft tenderness. Rest of the physical exam was unremarkable. Cellcept was held. The BioFire Film Array was positive for adenovirus. There was no viremia. He was lymphopenic and

serum creatinine rose from 0.9 to 1.2 mg/dL. Colonoscopic biopsy showed microscopic colitis. Ultrasound showed a space occupying lesion in the upper pole of the allograft and a mass in the bladder. Fever resolved on hospital day 8 without additional interventions. Cystoscopy revealed multiple masses in the bladder and in the ureter. Bladder biopsy was consistent with cystitis cystica glandularis.

Discussion: Non T-cell depleting agents prevent further T cell mediated immune responses while allowing other cell surface protein receptors such as CD48, CD80, and CTLA4, to be available for adenoviral entry. This causes the host to be vulnerable to viral entry in the early post-transplant period. Adenovirus integrates into the DNA, producing harmful proteins causing cellular injury and tumorogenesis. Literature review supports that early HAdV infections occur predominantly in patients who received non T-cell depleting induction therapy (Table 1.) Therefore, a high index of suspicion for HAdV infection should be maintained in febrile patients who receive non T-cell depleting induction therapy.

Table 1: Induction Therapy and Pattern of HAdV infection.

	Basiliximab / Daclizumab	T-cell Depleting Agents
Early Infections (4wks +/- 2 wks.)	13	3
Late Infections	1	9

P value = 0.00039;

Result is significant at P <0.05.

SA-PO1135

Simultaneous Acute Rejection and Recurrent Focal Segmental Glomerulosclerosis: A Match Made in Renal Transplantation

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Introduction: Simultaneous recurrent focal segmental glomerulosclerosis (FSGS) and acute rejection is extremely rare in kidney transplant recipients. In resistant FSGS cases failing conventional immunosuppression, addition of repository corticotropin injection (Acthar Gel®) may lead to proteinuria resolution.

Case Description: A 34-year-old man underwent deceased donor kidney transplantation for ESRD related to possible FSGS. Other medical history included hypertension and obesity. He had immediate allograft function with basiliximab induction. Maintenance regimen included tacrolimus, mycophenolate and prednisone. Eleven weeks after transplantation, he had sudden onset of nephrotic-range proteinuria (urine protein-creatinine ratio of 11.3 g/g from baseline of 0.5 g/g), generalized edema and acute kidney injury (serum creatinine 2.4 mg/dL from baseline 1.6 mg/dL). Kidney transplant biopsy was performed expecting histologic evidence of recurrent FSGS. Surprisingly, biopsy showed Banff II-B acute cellular rejection and segmental podocyte injury. He was treated for rejection and recurrent FSGS with anti-thymocyte globulin, solumedrol, plasmapheresis (TPE) and IVIg. Following TPE and immunosuppression intensification, his proteinuria improved briskly to 0.37 g/g with parallel decline in creatinine to baseline. Despite ongoing TPE and IVIg, his proteinuria recurred (8-10 g/g) with worsening creatinine. Repeat kidney biopsy showed complete resolution of rejection, but with 25% residual foot process effacement. With failure of two doses of rituximab and 40 TPE sessions to improve his proteinuria, he started corticotropin injections twice weekly. After 3 months of corticotropin, TPE was stopped, and corticotropin tapered off over another 3 months. He is now in complete remission of proteinuria with stable kidney function.

Discussion: Pre-transplant FSGS patients should be closely monitored in the post-transplant period for FSGS recurrence. Simultaneous presence of two diagnoses underscores the importance of performing kidney biopsy in those with proteinuria and acute kidney injury post-transplantation. Recurrent FSGS treatment in allografts resistant to conventional treatments may remit with corticotropin. Concurrent acute vascular rejection and recurrent FSGS is rare. In the era of significant organ shortage, all options should be tried to save the allograft.

SA-PO1136

Letermovir Therapy for Resistant Cytomegalovirus in a Kidney Transplant Recipient: Case Report

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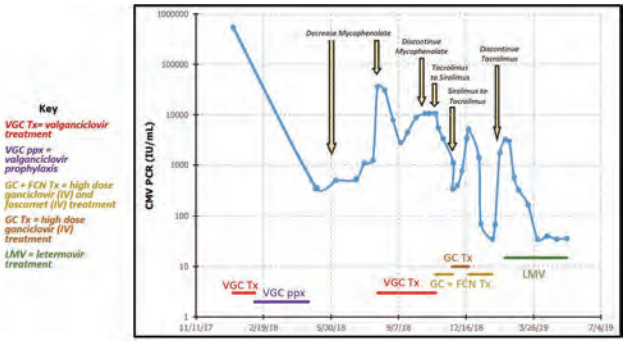
Introduction: Cytomegalovirus (CMV) infection is a leading cause of morbidity in kidney transplant recipients. Resistant CMV strains and medication toxicities complicate treatment. We describe a case of multidrug resistant CMV suppressed with letermovir after treatment with second line agents.

Case Description: 63 year old female with history of living donor kidney transplant (CMV donor + / recipient -) presented with severe diarrhea and leukopenia a month after stopping valganciclovir prophylaxis. CMV viral load was 544,002 copies/mL and she was given 3 weeks of treatment and 2 months of prophylaxis using valganciclovir. Low level viremia followed discontinuation of prophylaxis. After the viral load exceeded 30,000 copies/mL treatment was resumed without successful viral suppression. Genotyping revealed resistance to valganciclovir, foscarnet, and cidofovir. She was initiated on foscarnet and high dose ganciclovir. Upon therapy discontinuation, viral load increased again and oral letermovir 480 mg daily was started. Since introducing letermovir she maintained CMV suppression for 3 months. For treatment course please see figure 1.

Discussion: Resistance to agents for the treatment of CMV is increasing. Valganciclovir alternatives have significant toxicities and necessitate parenteral administration. Letermovir is a novel agent that inhibits the cleavage of CMV DNA concatemers by targeting the pUL56 subunit of the terminase enzyme complex. Letermovir is not myelosuppressive, it is available in an oral formulation, and does not require dose adjustments for renal function. Recently letermovir was approved for CMV prophylaxis in allogeneic hematopoietic stem cell transplant recipients, but use in solid organ transplant is being investigated. Letermovir for salvage therapy has been reported but widespread use has not been adopted due to the low barrier to resistance. Our unconventional approach using combination foscarnet and ganciclovir treatment then switching to letermovir presents a possible niche for agent's use to sustain suppression of a multidrug resistant CMV.



SA-PO1137

Fanconi Syndrome from Adenovirus Treatment in a Renal Transplant Patient: A Rare Complication from Novel Therapy with Brincidofovir

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Introduction: Brincidofovir is an oral pro-drug of cidofovir currently in Phase III clinical trials. In comparison to cidofovir, it displays lower nephrotoxic potential. We present a case of Fanconi syndrome within a week of therapy of brincidofovir for a patient with Adenovirus infection. This rare side effect has not been reported in the literature.

Case Description: We present a 62 year old woman with chronic kidney disease due to diabetes mellitus-2 and hypertension, who received a deceased donor kidney transplant. Induction therapy included alemtuzumab, solumedrol, and mycophenolate mofetil. Her baseline serum creatinine post-transplant was 0.7. Two months later her renal function began to worsen. A renal biopsy was performed which showed no evidence of acute cellular or antibody mediated rejection. However, BK virus as well as Adenovirus was found in both blood and urine. Immunosuppression medications were minimized; IVIG therapy for severe BK viremia and brincidofovir for Adenovirus viremia was initiated due to worsening viremia (656,000 copies/mL). She was readmitted to the hospital five days later due to acute graft dysfunction and a repeat biopsy revealed cellular IIA rejection. She completed the first course of brincidofovir but was readmitted for worsening renal function and brincidofovir was restarted due to reemergence of Adenovirus. Due to sepsis requiring ICU management, immunosuppression medications were stopped. On follow-up in the clinic, the patient was found to have glycosuria, phosphouria, hypomagnesemia and hypouricemia consistent with Fanconi syndrome. Aggressive electrolyte repletion was started and Brincidofovir stopped as this was determined to be most likely cause. Electrolyte imbalances gradually improved after stopping brincidofovir.

Discussion: Brincidofovir was utilized as therapy for Adenovirus infection due to its reported lower incidence of nephrotoxicity compared to standard therapy with Cidofovir. However, the side effect of Fanconi syndrome complicated the course of therapy. Fanconi syndrome is a known side effect of cidofovir, and due to brincidofovir's lower incidence of nephrotoxicity this side effect may not be anticipated. Patients receiving brincidofovir should be monitored for Fanconi syndrome by frequent follow-up, especially electrolytes in the serum and urine.

SA-PO1138

A Rare Case of Monoclonal Immunoglobulin Deposition Disease (MIDD) in a Transplant Recipient

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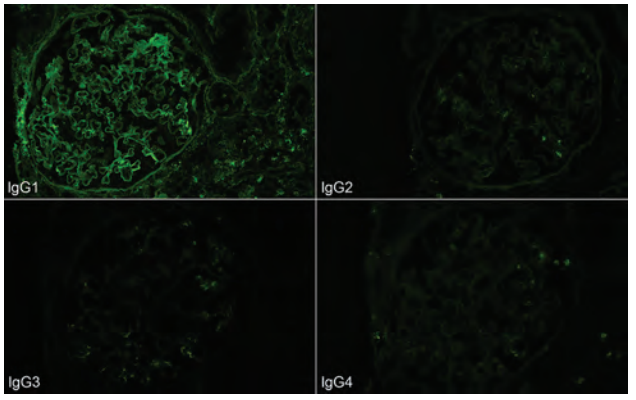
Introduction: A 36-year-old male with ESKD presumed secondary to Type-1-diabetes received a kidney-pancreas transplant on 09/19/2017, complicated with pancreatic-vein thrombosis (day two post-op), requiring pancreas re-transplant 10/24/2018. He received induction with ATG (cumulative-dose 5 mg/kg) and maintenance with tacrolimus (trough average 8), and everolimus.

Case Description: He had multiple admissions for nausea, vomiting, and prerenal AKI. His creatinine rose from a nadir post-transplant of 1.24mg/dl to a range of 2 mg/dl. At 18 months post-transplant, he developed anasarca with creatinine rise to 2.9mg/dl. Work up revealed nephrotic syndrome with UPC 10gm/gm and serum albumin 2.7g/dl. Urine amylase (44U/L), serum amylase (16 U/L), c-peptide (2.8ng/mL), and HbA1c (5.7). A transplant-kidney biopsy showed combined antibody and T-cell-mediated rejection grade 1B (Banff 2017). EM showed finely granular powdery subendothelial and mesangial electron-dense deposits. IF showed 2+ linear IgG1 heavy-chains along the GBM. Findings

were suggestive of MIDD. He was treated with steroids, and creatinine improved to 0.86mg/dL, though no improvement in pancreatic-function, leading to the resumption of insulin.

Discussion: The pancreas-kidney Donor was a 25-year old-white- healthy male with KDPI<20. Given the donor's age, donor-derived MIDD would be unlikely. The recipient SPEP, UPEP, and free-light-chain ratio were unremarkable. There was no pathological evidence of MIDD in his gastrointestinal and spleen biopsies. Whether the deposits are donor or recipient derived is unclear. We plan to closely monitor with yearly free light chains, and bone-marrow biopsy. Recurrence of MIDD is almost universal in kidney-allografts even without detectable paraprotein. The etiology for graft-failure remains elusive, though MIDD as a contributor is a theoretical possibility. Our case shows the importance of early transplant biopsy with the performance of IF and EM for all patients with suspected glomerular pathology.



SA-PO1139

De Novo Transthyretin Amyloidosis After Domino Liver Transplant Causing Kidney Graft Failure: A Case Report

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Introduction: Domino Liver Transplant (DLT) refers to a sequential transplant (Tx) where a recipient receives a liver from a donor who has usually Familial Amyloid Polyneuropathy (FAP). DLT increases the chance of getting a liver but poses the risk of the recipient manifesting amyloidosis years later. The current case describes a patient who received a kidney Tx 13 years after a DLT and developed *de novo* systemic amyloidosis with neuropathy.

Case Description: Male 69 yo, diagnosed with Hepatitis C and Hepatocellular Carcinoma, underwent a DLT transplant with a liver from a FAP donor. After 13 years of Tx he developed ESRD due to Cyclosporine toxicity and recurrent pyelonephritis. One year later he underwent a deceased donor kidney Tx under Basiliximab, Mycophenolate and Tacrolimus immunosuppression. Three years later, he presented progressive lower limbs paresthesia and weakness (electroneuromyography confirmed polineuropathy); anasarca, dyspnea and bilateral pleural effusion (echocardiography showed new diastolic dysfunction and myocardial hypertrophy) and progressive symptomatic hypotension episodes. Because of non-proteinuric subacute kidney graft dysfunction and dyspnea he was hospitalized and initiated hemodialysis. Kidney graft biopsy demonstrated acute tubular necrosis (ATN), light glomerulitis, C4d and Congo Red negative, and no signs of Tacrolimus toxicity. On the other hand, sural nerve biopsy stained Congo Red positive and confirmed Amyloid Neuropathy. Graft failure was attributed to ischemic injury, due to arterial hypotension secondary to autonomic neuropathy. Other features as neurogenic bladder with post-void retention and new myocardial hypertrophy without arterial hypertension were also attributed to amyloidosis. Dialysis ultrafiltration was progressively hindered by untreatable hypotension and he died 2 months later.

Discussion: This case illustrates the occurrence of Transthyretin Amyloidosis with severe manifestations in a recipient of DLT. We point out the differential diagnosis of kidney graft failure, here described as ATN as an indirect consequence of Amyloidosis.

SA-PO1140

De Novo Minimal Change Disease Immediately After Renal Transplantation

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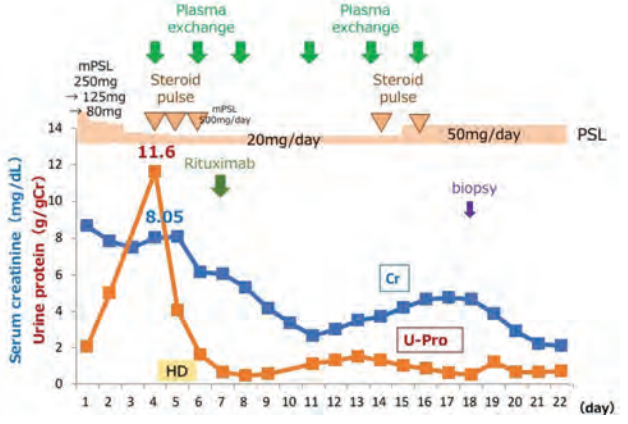
Introduction: De novo minimal change disease (MCD) is quite a rare cause of post-transplant nephrotic syndrome (NS). Only a few cases have been reported, partially due to the stringent criteria for this diagnosis. We report a challenging case of de novo MCD while the patient was on induction therapy immediately after transplantation.

Case Description: A 49-year-old male with end-stage kidney disease due to nephrosclerosis received ABO-compatible living kidney transplantation from his 47-year-old wife with four mismatches in HLA typing. Induction therapy included steroids, mycophenolate mofetil tacrolimus and basiliximab. At post-transplantation day 4, serum creatinine increased to 8.05 mg/dL with massive proteinuria (11.6 g/d). Although the flow cytometric crossmatch test for HLA came back negative, the patient received steroid pulse, plasma exchange and rituximab for possible recurrent focal segmental glomerulosclerosis (FSGS). Kidney function and proteinuria were improved soon after those treatments. The allograft biopsy taken on day 18 showed no specific glomerular changes under light microscopy; however, foot process effacement of podocytes was noted under the electron microscopy. De novo MCD was diagnosed. The patient has been achieved complete remission for one year since the transplant.

Discussion: De novo MCD after kidney transplantation is quite rare, but seems to have favorable prognosis. Nephrotic-range proteinuria usually develops immediately or shortly after transplantation, even when the patient is on induction therapy. Due to indistinguishable clinical course as well as similar histology of FSGS and MCD, it is possible that patients labeled as FSGS who respond readily to steroids or plasmapheresis may have MCD rather than FSGS. Therefore, the diagnosis of de novo MCD should be always considered even when induction therapy is given, especially if minimal light microscopic findings are detected.



SA-PO1141

Not a Classic Chickenpox Infection: Retinal Necrosis in a Renal Transplant Patient

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Introduction: Viruses are common opportunistic infection among kidney transplant patients. Varicella-zoster virus (VZV) is often reactivated at 6 to 12 months after transplant as Herpes Zoster (HZ). Primary VZV infection is less common and is more severe. We present the case of a kidney transplant recipient with a severe complication of primary VZV infection.

Case Description: A 42-year-old-woman with hypothyroidism, post-transplant diabetes mellitus, end stage kidney disease due to renal agenesis status post kidney transplant (2006) on Tacrolimus 2mg in the morning and 1.5 mg in the evening, mycophenolic acid 360 mg thrice daily, levothyroxine and insulin regimen was admitted to our institution after ophthalmology evaluation. Four weeks prior to admission she was hospitalized at another institution due to primary VZV infection, reported relative with HZ and no prior VZV vaccination, she was treated with intravenous (IV) acyclovir and discharged home with oral (PO) acyclovir after no new skin lesions occurred. Two weeks after initial onset she developed a rash at the dorsum of the hands and left eye blurry vision. She was evaluated by ophthalmology and was admitted with left acute retinal necrosis due to HZV. Evaluation was significant for no fever, no visible vesicular skin lesions but impaired left pupillary reflex and left facial nerve palsy. Laboratory results showed leukocytosis, creatinine level on baseline, 1.8 mg/dL, and hyperglycemia. She was started on acyclovir 1 gram IV every 8 hours, IV hydration and mycophenolic acid was discontinued. She received intravitreal ganciclovir every 48 hours for two weeks. After the second dose of gancylovir she noticed improvement of blurry vision and resolution of symptoms after first week of treatment. She was discharged home with PO acyclovir 800 mg every 4 hours and decreased mycophenolic acid dose to 180 mg twice daily.

Discussion: Our patient developed a rare complication of primary VZV infection, acute retinal necrosis, 13 years after kidney transplant. Recent studies show incidence of VZV after kidney transplant is less than 1%. This case emphasizes the importance of VZV vaccination in the pre-transplant period and vaccination of close contacts. Early and prompt intervention is needed in those patients with visual complications since they are at risk of vision loss.

SA-PO1142

Utility of Donor-Derived Cell-Free DNA for Detecting Allograft Rejection with PD-L1 Checkpoint Inhibitor Use

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Introduction: Donor derived cell free DNA (dd-cfDNA) is a useful biomarker that originates from allograft cells undergoing injury. Levels <1% have strongly correlated with absence of active rejection. We describe a case where serial dd-cfDNA monitoring allowed the use of immune checkpoint inhibitor therapy in a renal transplant recipient.

Case Description: A 72 year old man with ESRD from ADPKD underwent living unrelated kidney transplant in Dec 2010. His immunosuppression regimen included tacrolimus 2mg bid, mycophenolate 500mg bid and prednisone 5mg daily. In July 2017, he was diagnosed with metastatic squamous cell cancer. He underwent radiation therapy followed by chemotherapy with Cetuximab. However, in the setting of disease progression, PD-L1 inhibitor was considered. A baseline dd-cfDNA was 0.23%. PD-L1 inhibitor, Pembrolizumab, was initiated in Nov 2017 with serial dd-cfDNA monitoring (weekly x 8 weeks, followed by monthly). Despite serum creatinine fluctuations (Fig 1), the relative change in dd-cfDNA of <65% and overall <1% (Fig 2) reassured of a low likelihood of active rejection, allowing the continuation of therapy. Pembrolizumab was used for about 1 year; however, subsequent imaging was concerning for local disease progression and Pembrolizumab was discontinued in Nov 2018. Thereafter, his dd-cfDNA returned to baseline with excellent allograft function, suggesting that the initial elevation may have been from tumor death.

Discussion: Dd-cfDNA is a helpful noninvasive marker for diagnosing graft rejection with checkpoint inhibitor use. Future investigations into sequencing the dd-cfDNA will help determine whether it is of tumor vs allograft origin.

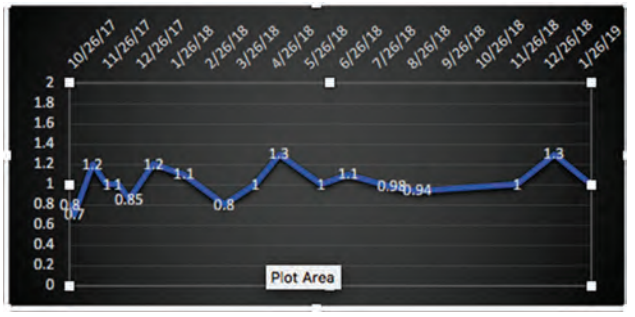

Fig 1

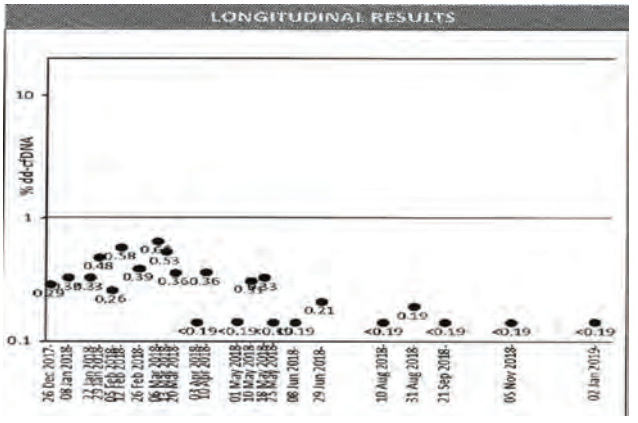

Fig 2

SA-PO1143

Francisella novicida: An Exceedingly Rare Cause of Pneumonia in a Kidney Transplant Recipient

Enrique Acosta,[1] Jose A. Castillo-Lugo,[2] Roberto L. Collazo-Maldonado,[2] Edward A. Dominguez.[3] *[1]Methodist Dallas Medical Center, Dallas, TX; [2]Dallas Nephrology Associates, Dallas, TX; [3]Methodist Transplant Physicians, Dallas, TX.*

Introduction: *Francisella novicida* is a gram negative coccobacilli that very rarely causes human illness. Its close relative *F. tularensisis* is well known for causing tularemia. Unlike *F. tularensis*, there have been no documented cases of *F. novicida* transmission to humans by through arthropod bites. All documented cases are associated with patients who are immunocompromised. Common clinical symptoms include fever, myalgias, lymphadenopathy, and pneumonia. *F. novicida* infection in humans is exceedingly rare and therefore often difficult to diagnose accurately. Only 11 cases of infection in humans have been documented.

Case Description: A 63-year-old AA woman with history of hypothyroidism and End Stage Kidney Disease on hemodialysis secondary to hypertension was admitted to the hospital for an elective kidney transplant. She underwent an en blocpediatric kidney transplant and received thymoglobulin induction due to the presence of a high cPRA of 91%. On post-op day 3 she developed hypoxemia with increased oxygen requirements and high-grade fever on post-op day 5. Chest CT showed diffuse bilateral patchy pulmonary infiltrates. Initial suspicion was volume overload or capillary leak syndrome due to thymoglobulin. However, oxygen requirements did not improve with ultrafiltration. Bronchoscopy with broncho alveolar lavage (BAL) was performed on post-op day 7. Initial blood cultures revealed gram negative coccobacilli. She was started on empiric meropenem, micafungin, and vancomycin which did not improve clinical status and Infectious Disease service added empiric fluoroquinolones. *Francisella novicida* was isolated in 2 sets of blood cultures and in BAL specimens. Final identification was performed at Centers for Disease Control and Prevention in Fort Collins, Colorado. The patient completed 14 days of fluoroquinolones and symptoms subsided. Kidney function improved and she is no longer on dialysis.

Discussion: Per our literature review, this is the first time that this bacteria has been isolated in a specimen other than blood or lymph node. Notably, there was an outbreak of *F. novicida* in a correctional facility in the patient's hometown in 2011. This case illustrates the value of a thorough history, the importance of interdisciplinary management, and the crucial role of early recognition of sepsis in solid organ transplant patients.

SA-PO1144

A Unique Case of Persistent Hypoxia in a Post-Kidney Transplant Patient due to Occlusion from Hemodialysis Reliable Outflow Graft Causing Right to Left Shunt

Michael Connery, Samer Kareem, Savneek S. Chugh. *Westchester Medical Center, White Plains, NY.*

Introduction: The Hemodialysis Reliable Outflow (HeRO) vascular access graft is a method of vascular access able to bypass a central venous occlusion. Cannulas within the superior vena cava (SVC) can lead to occlusion and syndromes such as SVC syndrome, subclavian steal and esophageal varices. We report a unique case of a chronically occluded HeRO graft in a renal transplant patient causing SVC occlusion leading to right to left shunting and hypoxia.

Case Description: A 56 year-old woman presented with worsening shortness of breath and documented hypoxia. She also had left arm weakness without swelling. She had a history of ESRD with HeRO graft which connected her left brachial artery to the left internal jugular vein and emptied into the IVC. It had not been used for 10 years since her first kidney transplant. The graft had occluded. A TTE with bubble study revealed bubbles in the left heart when injected in the left arm after Valsalva concerning for right to left shunt. Her HeRO graft was obstructing the SVC, left brachiocephalic vein (BCV), and left subclavian vein and she was found to have a persistent vein of Marshall with Cardinal vein extending from the mid portion of the BCV to the left superior pulmonary vein. The proximal section of the HeRO graft was removed and endarterectomy with patch angioplasty were performed on the BCV and SVC and the cardinal vein was ligated. After surgery her hypoxia had resolved.

Discussion: This is a case of a complication of long-term unused vascular access in a renal transplant recipient. Vascular occlusion is a common complication of indwelling catheters but can produce atypical symptoms. We have not been able to find any similar case studies of central occlusion induced hypoxia. This was a result of a shunt from abnormal vasculature that worsened with progressive obstruction of the left brachiocephalic vein. Removal of the offending catheter and ligation of the shunt cured the patient of her presenting symptoms. Detailed coordination between cardiology, vascular surgery, cardiothoracic surgery, and renal teams was vital for diagnosis and management.

SA-PO1145

Angiotensin II Type 1 Receptor Antibody (AT1-R Ab) Mediated Rejection in HLA-Incompatible Kidney Transplant Recipient

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Introduction: Donor-specific antibodies (DSAs) create an immunologic barrier to transplantation. The IgG degrading enzyme derived from Streptococcus pyogenes (IdeS), an endopeptidase, cleaves human IgG into F(ab')2 and Fc fragments inhibiting complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity. We report unique case of non-HLA antibody mediated rejection in IdeS recipient

Case Description: A 40 years old male with history of ESRD due to IgA nephropathy who received IdeS as part of a phase 2 IRB approved trial in preparation for positive flow crossmatch deceased donor kidney transplant. Immediately post IdeS his crossmatch became negative. Patient also received IV alemtuzumab and rituximab for induction as part of the study protocol. One-week post-transplant, HLA-DSA rose to the cytotoxicity positive level and he was empirically treated for antibody mediated rejection with 11 sessions of plasmapheresis and intravenous immunoglobulin (IVIg). His HLA-DSA became flow negative. Maintenance immunosuppression included prednisone 5 mg daily, tacrolimus, and mycophenolate mofetil 1-gram BID. Six months later, laboratory data revealed an increase in serum Cr from 1.0 to 1.4 mg/dL and HLA-DSA remained flow negative. Further histocompatibility testing showed increase in pre-transplant level of AT1-R Ab from 14 units/ml to > 40 units/ml (positive:>17 units/ml). Kidney pathology detected chronic active antibody mediated rejection. Patient was immediately started on IV solumedrol and losartan 50 mg daily, he also finished 5 sessions of plasmapheresis and IVIg. One week later, serum Cr trended down to 1.0 mg/dL and AT1-R Ab level dramatically improved to 10 units/ml.

Discussion: Although reduction of HLA-DSA with therapies such IdeS has allowed successful transplantation in highly sensitized patients, screening and surveillance for non-HLA antibodies such as AT1-R antibodies may be required in this high-risk population to prevent antibody mediated rejection

SA-PO1146

AT_1R and ETAR Antibodies, Proteinuria, and Renal Dysfunction in Pediatric Kidney Transplantation

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Background: Activating autoantibodies to Angiotensin II Type 1 Receptor (AT_1R) and Endothelin type A receptor (ETAR) are non-HLA antibodies which have been associated with poor kidney allograft outcomes. However, the association of these antibodies with proteinuria and renal dysfunction is unknown. We aimed to determine the association of AT_1R and ETAR antibodies (Ab) with proteinuria and renal allograft function in pediatric kidney recipients (KTRs).

Methods: 65 pediatric KTRs were monitored for 2 years after transplantation. ETAR-Ab and AT_1R-Ab (ELISA) were measured at 6 months (m), 12m, and 24m post-transplant and during episodes of rejection. Based on a receiver operating curve analysis, > 10 and >17 units/ml was considered positive for ETAR-Ab and AT_1R-Ab respectively. Renal function (updated Schwartz Equation) and proteinuria were also assessed at the above noted time points. Proteinuria was defined as ≥1+ (30-100 mg/dl) on urinalysis. Samples were excluded for factors that may result in false positives including high specific gravity ≥1.030, alkaline PH (≥8.5) and gross hematuria (n=3).

Results: AT_1R-Ab and ETAR-Ab were positive in 38 (58%) and 24 (37%) of patients during the first 24m post-transplant respectively. Proteinuria was present in 84 of 323 urinalysis samples (26%) with 44 patients (68%) positive during the first 24m post-transplant. We found that patients with both AT_1R -Ab and proteinuria had greater declines in renal function than patients with either predictor alone (p=0.004, Figure 1a). This relationship was also observed in patients with ETAR-Ab and proteinuria (p =0.018, Figure 1b).

Conclusions: Pediatric KTRs with AT_1R-Ab, ETAR-Ab, and proteinuria have greater declines in kidney function in the first 24m post-transplantation. This association highlights the potential detrimental effects of non-HLA antibodies on the renal allograft in the pediatric population.

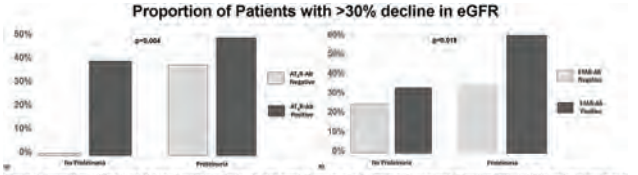

Figure 1: Proportion of Pediatric Kidney Transplant Patients with >30% Decrease in Estimated Glomerular Filtration Rate (eGFR) by Proteinuria and Non-HLA Antibody Status. In patients both with and without proteinuria, patients with AT1R-Ab (a) and ETAR-Ab (b) had greater declines in eGFR measured from their baseline from discharge to their lowest over the 24 month follow up period than patients without non-HLA antibodies.

SA-PO1147

Impact of Persistent and Transient Donor-Specific Antibodies Within First Year After Kidney Transplantation

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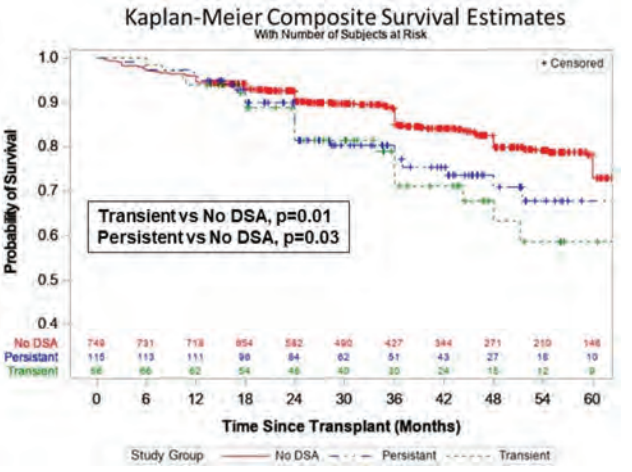
Background: The importance of Donor Specific Antibody (DSA) surveillance within 1st year (yr) post kidney transplant remains unclear. We studied the impact of DSA pattern during the 1st yr post-txp on clinical outcomes.

Methods: 931 patients (pts) from 2013-17 were enrolled (HLA Compatible, Flow xmatch negative). Pts were grouped into Transient DSA (T-DSA, n=66; 1 positive test, Class I/II), Persistent DSA (P-DSA, n=115, >1 positive test, Class I/II), and No DSA (N-DSA, n=750) within 1st yr post-txp. DSA testing was done @ 1,3,6,9, & 12 mos. Biopsies (protocol 3&12 mos, & indication) were included. Surrogate marker for this study included incidences of TCMR and ABMR. Outcomes measured were pt survival, graft survival and composite of pt loss, graft loss and eGFR <20ml/min at last follow-up.

Results: During the 1st yr, DSA was detected in 19% of pts (7% T-DSA vs 12% P-DSA). There were no differences in baseline or txp characteristics, other than increased sensitization (cPRA>20%) in P-DSA pts (67% vs 47%, p=0.001). P-DSA pts developed DSA earlier for Class I (75±136 vs 121±132 days, p=0.03) and II (83±141 vs 192±185 days, p<0.001), when compared to T-DSA pts. After 1 yr, DSA detection was far less in N-DSA pts (Class I/II 4/8%) than in T-DSA (Class I/II 53/62%, p<0.001) or P-DSA (Class I/II 64/69%, p<0.001) pts. P-DSA pts experienced more clinical TCMR (14 vs 8%, p=0.04), ABMR (12 vs 0.8%, p<0.001), & less normal biopsies (4 vs 11%, p=0.02) than N-DSA pts, and more ABMR than T-DSA pts (12 vs 0%, p=0.003). There were no differences in sub-clinical TCMR/inflammation, tacrolimus levels, renal function, pt survival, or death censored graft survival among all groups. However, lower composite outcome was noted with T & P-DSA pts (Figure 1).

Conclusions: Persistent and Transient DSA within 1 yr had similar outcomes and lower composite outcome when compared to No DSA pts. Thus, detection of DSA within 1 yr, whether Persistent or Transient, is detrimental to renal allograft.



SA-PO1148

Impact of Treatment of Borderline Rejection on Subsequent T Cell-Mediated Rejection in Kidney Transplant Recipients

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Background: The optimal management of borderline rejection (BR) seen in the early post-transplant period is unclear. Studies have shown that BR is associated with higher Subclinical or Clinical T-Cell Mediated Rejection (TCMR) within 1 year post-transplant. However, the role of steroids in attenuating this risk is unclear. We performed this study to evaluate the impact of treating BR with steroids on subsequent development of TCMR.

Methods: Adult kidney transplant recipients (N=183) with Subclinical or Clinical BR in the first 3 months post-transplant based on Banff 2005 criteria were divided into two groups: (i) No treatment group (N=143), and (ii) Steroid treatment group (N=40). We excluded prior TCMR, Antibody mediated rejection (AMR) and BK virus nephritis. All the patients with BR had their maintenance immunosuppression (MIS) optimized. All patients were induced with thymoglobulin (97%) or basiliximab (3%) and a rapid steroid taper over 5 days per protocol. Standard MIS was with tacrolimus and mycophenolate mofetil. Recipient, donor and transplant variables were similar between the groups. The subsequent development of subclinical and clinical TCMR over the course of the first year was followed.

Results: Refer to Results Table

Conclusions: Treatment of BR in early post-transplant period with steroids was not associated with lower rates of TCMR at 1-year post transplant. However, steroid dose varied in our study from 1 to 3 doses of methyprednisolone. Further studies with uniform dosing of steroids are required to establish definite treatment strategies for BR.

Results

	T Cell Mediated Rejection (Clinical or Sub Clinical)		Total	p-value
Treatment with Steroids	Yes	No		
Yes	10	29	39	0.52
No	30	114	144	
Total	40	143	183	

SA-PO1149

Phenotype of CD8 T Cells in Determining Risk of Acute Rejection in Kidney Transplant on Belatacept Regimen

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Background: Belatacept is a costimulatory blocker that is used as de novo maintenance immunosuppression in kidney transplantation. However, patients maintained on belatacept, mycophenolate, and corticosteroids have been noted to have more frequent and severe acute rejection than in calcineurin inhibitors. Experimental studies have shown synergy between costimulatory blockade and mTOR inhibitors. We investigated pretransplant recipient immune profiles to determine which subset of lymphocytes can predict acute rejection in patient on belatacept-based regimen.

Methods: We prospectively enrolled 65 kidney transplant recipients (31 deceased; 34 living donors) at our center to receive denovo belatacept from September 2012 to June 2018. PBMCs were collected prior to transplantation and at the time of biopsies. All patients received thymoglobulin for induction (3mg/kg divided into 2 doses) with belatacept 10mg/kg administered on POD 1, 4, 14, 28, 56, and 84. Monthly maintenance dose of 5mg/kg was given starting week 16. Patients were started initially on MPA but were converted to everolimus after 1 month, and all patients were maintained on prednisone.

Results: 16.9% developed acute rejection within the first year post transplant: 2 with ACR 1a, 1 with ACR 2a, 6 with ACR 2b, 1 with AMR, and 1 with simultaneous ACR 1a and AMR. All 11 rejections occurred in those who were on MPA and not on

mTORi. 12 patients were found to have borderline rejection on protocol biopsies (7 on mTORi, 5 on MPA). 42 patients did not have any inflammation on biopsies. 57 patients remained on belatacept, and 8 were converted to tacrolimus. Patients who had biopsy-proven rejection or borderline changes had significantly higher %$CD8^+$ $CD28^-$ T cells, and those who had rejection with low %CD8+CD28- were found to have high $CD2^{hi}$ $CD28^{hi}$ in CD8+CD45RO+ T cells. Belatacept patients receiving everolimus had more stable TIGIT expression on regulatory T cells.

Conclusions: This trial of combining belatacept with mTORi shows that it is possible to reduce the rate of acute rejection in belatacept-based regimens. The synergy between mTORi and belatacept may be related to mTORi's inhibitory effect on memory CD8+CD28-CD38+ cells that are refractory to costimulatory blockade. Pretransplant immunotyping to identify those with low percentage of CD8+CD28- & $CD2^{hi}$ $CD28^{hi}$ in CD8+CD45RO+ may reduce the risk of rejection on belatacept.

SA-PO1150

Use of Antithymocyte Globulins (ATG) to Treat Rejection in Kidney Transplantation Is Associated with Increased Risk of Viral Infections and with Increased Risk of Death in Older Patients

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Background: ATG is used to treat steroid-resistant T-cellular mediated rejection, vascular rejection and mixed rejection in kidney transplant recipients. Most of the studies which examined the efficacy and the safety of ATG did not include patients on modern immunosuppression regimes. In addition, they did not examine in detail the side effects of this potent treatment.

Methods: We studied the long-term efficacy and side effects of ATG in renal transplant recipients, who were treated with ATG between 2011-2018. We analysed the demographics, the types and rates of infection and cancer, the readmissions, the graft and patient survival.

Results: 87 (56 males) patients were treated with ATG in the study period. The mean age was 45 ± 13.5 years. The follow-up was 50.4 ± 36 months. The ATG was effective in treating rejection in 57 patients (66%). However, 49 patients (56%) developed bacterial and viral infections after ATG use with 20 (23%) patients developing severe infections (including 3 fungal infections and 1 mycobacterium infection). 40 patients (46%) were readmitted at least once for complications related to ATG. 5 (6%) patients developed cancer and 13 patients died during the study period. The patients who died were older when treated with ATG (p=0.34). In logistic regression, death was associated with age at treatment (p=0.042) but not with the ATG dose, the gender or history of previous transplant. There was no difference between the age (p=0.58) and the dose of ATG (p=0.09) among patients who were readmitted for ATG related complications and those who did not. The total dose of ATG was associated with increased risk of viral infections (p=0.027). This remained significant in logistic regression (p=0.033)

Conclusions: ATG is an effective treatment for rejection in kidney transplantation. However, it seems that it is associated with an increased risk of viral infections. In our cohort, older patients treated with ATG were at higher risk of death. This asssociation will be investigated further.

SA-PO1151

Preformed Donor-Specific Antibodies in Complement-Dependent Cytotoxic Cross Match Negative Living Unrelated Male-to-Female Spousal Kidney Transplantations Are Associated with an Increased Risk of Acute Antibody-Mediated Rejection

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Background: Shortage of deceased donor kidneys has led to increased numbers of living unrelated kidney, in particular spousal, donors. Female recipients of a spousal kidney have an increased risk for pre-immunization and acute antibody-mediated rejection (ABMR). The aim of this study is to assess the incidence of ABMR and preformed donor specific antibodies (pDSA) in living unrelated donors (LURD) and to identify risk factors for acute ABMR.

Methods: We identified all 349 ABO compatible, CDC-crossmatch negative, LURD transplants performed at our transplant center between 1997 and 2015. All for-cause biopsies were classified according to the BANFF 2017 classification. All patients with ABMR were retrospectively tested for the presence of pDSA with multiplex and single antigen tests (Luminexâ). Risk factors for immunization were extracted from personal health records and questionnaires.

Results: The overall incidence of biopsy-proven acute rejection in the first 6 months was 20% (TCMR: 85%; ABMR: 15%); median time to onset of ABMR was 8 days (range 5-75 days). Outcome was poor in ABMR as compared with patients with TCMR or those w/o rejection (graft loss or eGFR <30ml/min at month-6: 36%, 12% and 2% respectively). Eight patients with ABMR were female (73%) and six of these (75%) were recipients of a spousal kidney. Of these spouses four had given birth to a child of their kidney donor and 2 received blood transfusions prior to transplantation. Retrospectively 80% of spousal recipients with ABMR had pDSA in the multiplex or single antigen test.

Conclusions: Female spousal kidney recipients have a relatively high risk of ABMR. Traditional methods for detecting pDSA are not sensitive enough to rule out pDSA. Multiplex and single antigen should be included in the standard work-up of potential female spousal kidney transplant recipients to prevent ABMR and guide the option of indirect (cross-over) donation.

SA-PO1152

Clinical Significance of Pretransplant Donor-Specific HLA Antibodies in Kidney Transplant Recipients of Hispanic Population

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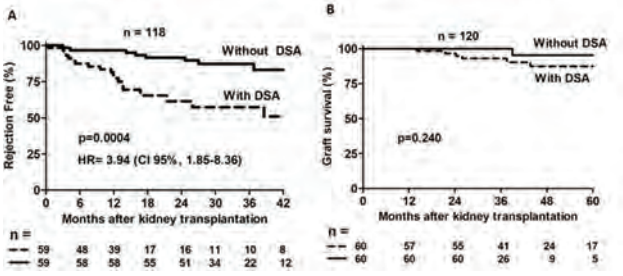
Background: Donor-specific HLA antibodies (DSA) before kidney transplantation (KT) is one of the major risk factors for humoral rejection and lower graft survival. In order to identify prognostic factors and develop follow up strategies in this high risk population, it is required for transplant center to share their outcome data.

Methods: Retrospective cohort and comparative study in KT recipients with pretransplant DSA measured by solid phase assays (Luminex), negative AHG-CDC-XM (living and deceased donor) and negative flow cross match (living donor). Our main objective was to determine graft survival and describe the incidence of acute rejection (AR) and renal function (eGFR by CKD-EPI).

Results: We identified 60 patients with pretransplant DSA and paired them based on donor type, induction therapy and maintenance immunosuppression to 60 KT recipients that did not have pretransplant DSA. The incidence of AR was higher in the pretransplant DSA group (35.5% vs. 15.2%, p=0.011) and the median time between KT and AR episodes was shorter in the pretransplant DSA group [12.8 (8.3-23.6) *vs* 32.1 (25.9-40.6) months, (p<0.0001)]. After 37.4 (range 29.2-52.3) months of follow up, eGFR was similar between groups [65.0 ± 22.0 vs 69.8 ± 21.4 ml/min/1.73m^2 (p=0.19)] and there was no difference in graft survival (87.7% vs 96.7% p=0.240) between groups with and without pretransplant DSA, respectively.

Conclusions: Although there is a higher incidence of rejection, KT recipients with pretransplant DSA had similar eGFR and graft survival. Therefore, this group of higher immunological risk could still be considered candidates for KT. One limitation of this study is the small sample size and short follow-up time. However, we propose that induction therapy with lymphocyte depleting agents and powerful maintenance immunosuppression, combined with follow-up strategies as protocol biopsies with early treatment of subclinical rejection could provide similar graft survival in KT recipients with and without pretransplant DSA.

Figure 1 Acute Rejection Free Survival (A) and Graft Survival (B) between KT recipients with pretransplant DSA and KT recipients without pretransplant DSA



SA-PO1153

Absence of Histologic Improvement Despite Reduction of Donor-Specific Antibodies with IVIG Treatment of Kidney Transplant Recipients

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Background: Donor-specific antibodies to donor HLA (DSA) are associated with higher incidence of antibody-mediated rejection and graft loss. Intravenous immunoglobulin (IVIG) exerts immunomodulatory effects in both humoral and cellular pathways. We examined the impact of IVIG therapy on circulating DSA, graft histology, and graft function.

Methods: 18 kidney transplant recipients with DSA maximum fluorescence intensity (MFI) ≥1000 treated with IVIG 1g/kg every 2 weeks x 6 months and a control cohort of 13 recipients with DSA managed as per physician preference were analyzed. In the IVIG-treated cohort, responders were defined by ≥50% reduction in DSA MFI-Sum at 18 months after start of IVIG. Baseline characteristics and graft function were compared between IVIG and control cohort.

Results: While there was no significant difference in baseline eGFR between groups, there was a significant decrease in eGFR in the control group at 18 months (Figure 1), and 23% of the control group had graft loss, compared to 0% in the treatment group. Ten recipients in the IVIG cohort met the definition of "responder." There were no significant differences in graft function between responders and non-responders at start of IVIG or at 18 months post-treatment (Table 1). There was no change in pre- and post-IVIG histologic Banff scores in both responders and non-responders (Figure 2a and 2b).

Conclusions: IVIG therapy is associated with DSA reduction and stabilization of renal allograft function in some patients. However, despite significant reduction in DSA,

there was no change in histologic parameters after IVIG therapy. Prospective randomized controlled trials with longer-term follow-up are needed to evaluate the beneficial impact of IVIG.

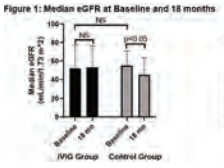
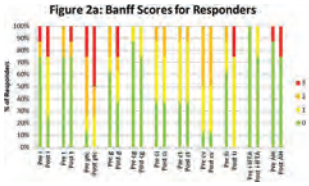
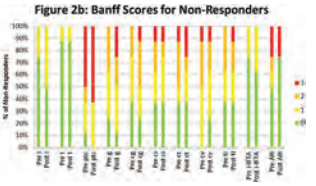


Table 1: Clinical Parameters of Responders and Non-Responders

	Responders (n=10)	Non-Responders (n=8)	p-value
Creatinine at start of IVIG, median (IQR)	1.18 (0.87-1.53)	1.70 (1.04-2.09)	0.24
Creatinine at 18 months post-IVIG, median (IQR)	1.16 (0.88-1.63)	1.92 (1.05-2.22)	0.35
eGFR at start of IVIG, median (IQR)	57.5 (47.3-79.7)	48.0 (38.4-74.6)	0.41
eGFR at 18 months post-IVIG, median (IQR)	53.7 (43.7-82.1)	52.4 (33.8-72.9)	0.51
MALIS/Cr at start of IVIG, median (IQR)	97.4 (8.4-340.7)	75.5 (10.1-80.4)	0.50
MALIS/Cr at 18 months post-IVIG, median (IQR)	102.8 (3.7-324.7)	48.9 (37.2-68.4)	0.64





SA-PO1154

Quantitative Assessment of Active and Chronic Lesions in Renal Allograft Biopsies to Improve Reproducibility, Clinical Correlations, and Outcome Prediction

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Background: Banff classification system is based on recognition and scoring of descriptive lesions allowing for pathogenetic classification of rejection. Although expert pathologists readily recognize these lesions, the routine semi-quantitative Banff scoring can be poorly reproducible. Specific immunohistochemical (IHC) stains and new imaging techniques can allow for more precise quantification of tubulitis, interstitial fibrosis (IF) and microvascular inflammation (MVI) (Delsante,TI,2018).

Methods: Tubulitis: we included 12 transplant biopsies of CMR, borderline and no rejection from Parma Hospital (Italy). Analysis of whole slide images of CD3+PAS IHC stained sections allowed for continuous scoring of tubulitis, and results were correlated with urinary CXCL9 levels (a biomarker of cell-mediated rejection). IF: Measuring second harmonic generation (SHG) signal on FFPE unstained kidney section, we assessed collagen deposition in 57 kidney transplant biopsies (Johns Hopkins Hospital-JHH). MVI was quantified in 75 biopsies from JHH using a dual IHC stain (CD34-endothelium and CD45-leukocytes); quantitative scores of peritubular capillaritis and glomerulitis were correlated with donor specific antibodies (DSA) levels and graft outcome

Results: Tubulitis quantitative scores showed significant correlation with urinary CXCL9 levels in patients with histological diagnosis of CMR, borderline lesions or no significant tubular inflammation: mean CD3+ cell per tubule (r2 0.75), tubulitis ratio (r2 0.66) and CD3+ cells is most inflamed tubule (r2 0.70). Measurement of interstitial collagen deposition using SHG outperformed standard Banff score in predicting graft failure hazard(increase 3.87 times per 2SD unit increase of SHG density, 95%CI 1.06-14.16). The use of CD34-CD45 dual stain increased interobserver reproducibility of Banff ptc score and significantly correlated with serum DSA levels and risk of graft loss. In the same cohort, glomerulitis scores showed no correlation with DSA/allograft outcome.

Conclusions: For selected Banff lesions (ptc, t and ci/ct) quantitative measurements can increase clinical correlation compared to semi-quantitative scoring. Quantitative methods are being studied in larger cohorts to confirm clinical and prognostic significance.

SA-PO1155

Significance of Revised Diagnosis for Chronic Active T Cell-Mediated Rejection in 2017 Banff Criteria: Surveillance of 1-Year Screening Biopsy in Kidney Transplantation

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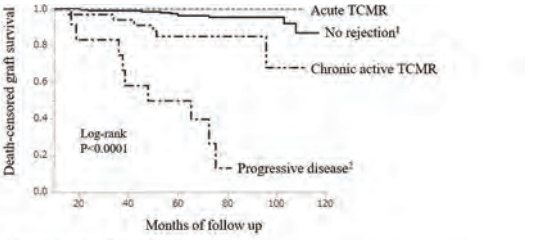
Background: The diagnosis criteria of chronic active T-cell mediated rejection (TCMR) was revised in Banff 2017 consensus, but the association between the diagnosis of chronic active TCMR at 1-year screening biopsy (SB) and long-term graft prognosis of kidney transplantation has not been reported.

Methods: In this single-center retrospective study, we extracted kidney transplant recipients from 2009 to 2013 who underwent 1-year SB. All the 1-year SB were re-evaluated according to the Banff classification revised in 2017. The primary endpoint was defined as a doubling of creatinine based on values at 1-year after kidney transplantation or graft loss. Death with graft function was censored. The impact of the diagnosis of chronic active TCMR was examined using a Cox regression model.

Results: Among a total of 258 patients who underwent 1-year SB (male of 58% and median age [interquartile range] of 46 [35-56]), 32 patients were re-classified to chronic active TCMR. They were previously diagnosed as normal (n=3), acute TCMR (n=17), and borderline changes (n=12). During the median follow-up period of 6.4 years, 25 patients, including six patients with chronic active TCMR, reached the endpoint. In the multivariate analysis, chronic active TCMR was associated with a higher risk of graft failure compared with no rejection (hazard ratio 2.93; 95% confidence interval, 1.02-8.41: P=0.045).

Conclusions: The chronic active TCMR diagnosis revised in Banff 2017 consensus may be useful for prognostic prediction and may help detect unfortunate prognosis cases in kidney transplant patients who underwent 1-year SB.



[1]No rejection included normal and borderline changes.
[2]Progressive disease included antibody-mediated rejection, glomerulonephritis, and BK virus-associated nephropathy.

Figure. Kaplan-Meier survival curve for death-censored graft failure stratified by the 1-year screening biopsy diagnosis of Banff classification revised in 2017

SA-PO1156

Treatment of C3 Glomerulopathy in Kidney Transplant Recipients: A Meta-Analysis

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Background: C3 glomerulopathy (C3G), a rare glomerular disease mediated by alternative complement pathway dysregulation, is associated with a high rate of recurrence and graft loss after kidney transplantation (KTx). We aimed to assess the efficacy of different treatments for C3G recurrence after KTx.

Methods: Databases (MEDLINE, EMBASE, and Cochrane Database) were searched from inception through 05/03/2019. Studies that reported outcomes of adult KTx recipients with C3G were included. Effect estimates from individual studies were extracted and combined using random-effects. Protocol for this meta-analysis was registered with PROSPERO (no. CRD42019125718).

Results: Twelve studies (7 cohort studies and 5 case series) consisting of 122 KTx patients with C3G (73 C3GN and 49 DDD) were included. The pooled estimated rates of allograft loss among KTx patients with C3G were 33% (95%CI: 12%-57%) after eculizumab, 42% (95%CI: 2%-89%) after therapeutic plasma exchange (TPE), and 81% (95%CI: 50%-100%) after rituximab. Subgroup analysis based on type of C3G was performed. Pooled estimated rates of allograft loss in C3GN KTx patients were 22% (95%CI: 5%-46%) after eculizumab, 56% (95%CI: 6%-100%) after TPE, and 70% (95%CI: 24%-100%) after rituximab. Data on allograft loss in DDD KTx patients after different treatment modalities were limited (1 cohort and 1 case series, 4/6 (67%) after eculizumab, TPE (1 case series, 0/2 (0%) at 6 months) and rituximab (1 cohort, 3/3 (100%) allograft loss). Among 66 patients (38 C3GN, 28 DDD) who receive no treatment (likely due to stable allograft function at presentation and/or clinical judgment of physicians), pooled estimated rates of allograft loss were 32% (95%CI: 7%-64%) and 53% (95%CI: 28%-77%) for C3GN and DDD, respectively. Among treated C3G patients, data on sMAC were limited to patients treated with eculizumab. 80% patients with elevated sMAC before eculizumab responded to treatment. In addition, all patients who responded to eculizumab had normal sMAC level after post-eculizumab.

Conclusions: Our study suggests that KTX patients with C3G treated with eculizumab had the lowest incidence of allograft loss (33%) when compared to those treated with TPE or rituximab. Among those who received no treatment for C3G due to stable allograft function, there is an incidence of allograft loss of 33% in C3GN and 53% in DDD.

SA-PO1157

Recurrence of Focal Segmental Glomerulosclerosis After Kidney Transplantation in an International, Multicenter Cohort from the TANGO Study

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Background: Focal segmental glomerulosclerosis (FSGS) recurrence after kidney transplantation is a major risk factor for graft loss. However, the natural history, clinical predictors, and response to treatment remain unclear due to small sample sizes and poor generalizability of single center studies, and disease misclassification in registry-based studies.

Methods: As part of The Post-Transplant Glomerular Disease (TANGO) project, we performed a multicenter, international, retrospective observational study to determine the incidence, predictors and treatment response of recurrent FSGS.

Results: Amongst 11,742 kidney transplant recipients screened for FSGS between 2005-2015, 176 had idiopathic FSGS. FSGS recurred in 57 patients (32%, 95%CI: 25-39%) and 39% of them lost their graft over a median (IQR) of 5 (3.0-8.1) years (Figure 1). Multivariate Cox-regression revealed an increased risk for recurrence with older age at native kidney disease onset (HR 1.37 per decade, 95%CI: 1.09-1.56). Other predictors were white race (HR 2.14, 95%CI: 1.08-4.22), BMI at transplant

(HR 0.89 per Kg/m^2, 95%CI: 0.83-0.95), and native kidney nephrectomies (HR 2.76, 95%CI: 1.16-6.57). Loss of prior allografts due to FSGS increased the chances of a subsequent recurrence with 45% in a second graft and 100% in a third graft. Plasmapheresis and rituximab were the most frequent treatments (81%). Partial or complete remission occurred in 57% of patients and was associated with better graft survival.

Conclusions: Idiopathic FSGS recurs post-transplant in one-third of cases, increasing by 5-fold the risk of graft loss. Response to treatment significantly improves outcomes but is achieved in only half of cases. Multicenter collaborative efforts such as TANGO allow for the identification of novel risk factors for FSGS recurrence as well as for more precise estimates of recurrence incidence and outcomes.

Funding: Private Foundation Support

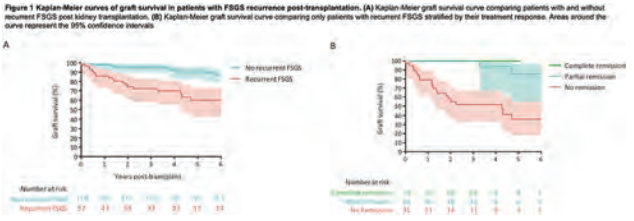

Figure 1 Kaplan-Meier curves of graft survival in patients with FSGS recurrence post-transplantation. (A) Kaplan-Meier graft survival curve comparing patients with and without recurrent FSGS post kidney transplantation. (B) Kaplan-Meier graft survival curve comparing only patients with recurrent FSGS stratified by their treatment response. Areas around the curve represent the 95% confidence intervals

SA-PO1158

Precise Clinicopathologic Findings May Increase the Detection Rate of Gene Mutations in Pediatric Kidney Transplant Recipients with Focal Segmental Glomerulosclerosis

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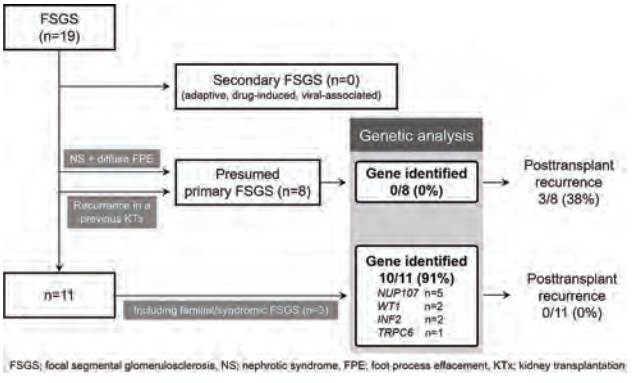
Background: Whole exome sequencing (WES) has enabled precision medicine in kidney transplant recipients with focal segmental glomerulosclerosis (FSGS), because individuals with a monogenic cause have a very low expectancy of posttransplant recurrence. However, it remains unknown whether all recipients with FSGS should undergo genetic testing. Here, we investigated the likelihood of detecting pathogenic mutations in recipients with FSGS divided into subgroups based on clinicopathologic findings.

Methods: Nineteen pediatric transplant recipients with FSGS were recruited and classified based on their clinical and pathologic findings. Adaptive, drug-induced and virus-associated FSGS were classified as secondary FSGS. Patients with family history of FSGS or extrarenal manifestations were classified as familial/syndromic FSGS. Patients who showed nephrotic syndrome (NS) and diffuse foot process effacement (FPE) in their native kidneys or had a history of recurrence in a previous transplantation were classified as presumed primary FSGS. We performed WES and examined a subset of 114 genes associated with FSGS in all patients.

Results: The results of classification and genetic testing are shown in Figure. WES revealed that 0 (0%) of 8 patients with presumed primary FSGS and 10 (91%) of the other 11 patients carried gene mutations known to cause FSGS. Three of 8 (38%) patients with presumed primary FSGS had posttransplant recurrence, while no recurrence was observed in the other patients.

Conclusions: The detection rate of pathogenic mutations known to cause FSGS was very high in the kidney transplant recipients after excluding individuals with secondary and presumed primary forms based on our precise clinicopathologic findings such as family history, extrarenal manifestations, NS and diffuse FPE.

Funding: Government Support - Non-U.S.



The results of classification and genetic analysis

SA-PO1159

Attitudes to Clinical Pig Kidney Xenotransplantation Among Medical Providers and Patients

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Background: In addition to governmental regulation and scientific expertise, the World Health Organization requires an extensive review of local opinions and attitudes prior to xenotransplantation (XTx) clinical trials. The current work will report the initial-phase of a multi-level public data collection process in preparation for clinical trials.

Methods: After university Institutional Review Board (IRB) approval, an anonymous online survey was emailed about attitudes towards XTx to medical center nephrologists, transplant surgeons, and nurses ("providers"). Pre and post-kidney transplant patients were randomly approached in the transplant clinic ("patients"). Both groups were requested to complete a 16-item likert scale survey with identical content. A total of 40 providers (51%; 40/78) and 163 patients (85%; 163/192) participated. Data were analyzed via SAS software.

Results: Eighty percent (32/40) of providers and 69% (113/163) of patients were agreeable to clinical XTx. Kidney providers rated the influence of religious beliefs (45%vs15%) and genetic engineering (43%vs25%) as being more important than patients ($p<0.05$). If risks and results were likely to be similar to kidney allotransplantation, providers were more supportive of XTx than patients (80%vs69%; $p<0.05$). If the results were likely to be less beneficial, patients were more likely to accept XTx as a bridge to allotransplantation (41%vs30%; NS). Both groups included <15% who identified concerns about (i) potential change in personality, (ii) how others would interact, (iii) a perception of being 'less human', or (iv) moral or ethical concerns. Logistic regression found that the odds of patients accepting XTx are 25 times greater if there are no religious concerns, and 82% more likely if it is a bridge to allotransplantation.

Conclusions: (i) There was strong support for XTx among both health providers and patients; (ii) providers over-estimated the influence of religious beliefs and genetic engineering on patient decisions, although religious beliefs still influenced patient attitudes; (iii) patient acceptance of XTx was not associated with likely medical outcome, per se; and (iv) there were few psychosocial concerns for either group. Overall, our findings would suggest that there is support for future clinical trials of XTx.

SA-PO1160

Outcome of ABO Incompatible Kidney Transplantation: With and Without Anti-CD20 Antibody Use

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Background: ABO-incompatible (ABOi) kidney transplants help in crossing an important immunological barrier against kidney transplantation. The study was conducted to assess the feasibility of performing ABOi kidney transplants without the use of Anti CD20 antibody and comparison of their outcomes with ABOi kidney transplants using Anti CD20 antibody.

Methods: The study, conducted between April 2014 and March 2019, included 54 live donor ABOi transplant recipients. They were divided into two groups based on using rituximab ABOiR$^+$ (n=21) or without rituximab ABOiR$^-$ (n=33). All Patients were started on Tacrolimus, Mycophenolate mofetil and Prednisolone 10 days prior to tentative date of transplant. In addition, ABOiR$^+$ group received Injection Rituximab 200 mg. Plasmapheresis was done and low dose intravenous immunoglobulin (100 mg/kg) given until an acceptable isoagglutinin titer (1:4) was obtained on the date of transplantation. All patients received induction immunosuppression: Thymoglobulin (1 mg/kg/day for 3 days). **Main Outcome Measures:** Patient and allograft survival; 1-, 3-, 6-, 12-, and 18-month renal function; infectious complications; and incidence of rejection.

Results: 19.04% of the ABOiR$^+$ recipients and 30.3% of ABOiR$^-$ recipients were females. Median isoagglutinin titer at start was 1:32 (1:1 to 1:256) in ABOiR$^-$ group and 1:8 (1:1 to 1:256) in ABOiR$^+$ group. Mean number of plasmapheresis required were 3 in ABOiR$^-$ group and 2 in ABOiR$^+$ group. There was no significant difference between the post transplant serum creatinine in the two groups. In the ABOiR$^-$ group, there were 6 episodes of biopsy proven acute antibody mediated rejection (AMR) and 1 patient had acute cellular rejection (ACR). 1 episode each of AMR and ACR was observed in the ABOiR$^+$ group. Two patients succumbed to fungal sepsis in the ABOiR$^-$ group while three patients died of pneumonia in ABOiR$^+$ group.

Conclusions: This study suggests that with the use of Anti-CD20 treatment, successful ABOi transplantation is possible with lower incidence of AMR but is associated with increased incidence of sepsis.

Table 1: Patient characteristics of ABO incompatible transplant with rituximab use (ABOiR+) and without rituximab use (ABOiR-) groups

		ABOiR+ (n=21)	ABOiR- (n= 33)
Donor	Age (Mean ± SD) in years	49.23±8.48	47.12±12.15
	Females	76.19%	51.51%
Recipient	Age (Mean ± SD) in years	49.23±12.63	42.93±11.71
	Females	19.04%	30.30%
Serum Creatinine (Mean ± SD) in mg%	At discharge	1.18±0.29	1.39±0.59
	At 1 month	1.13±0.30	1.37±0.41
	At 3 months	1.16±0.36	1.27±0.33
	At 6 months	1.22±0.41	1.29±0.36
	At 9 months	1.26±0.51	1.29±0.34
	At 12 months	1.23±0.61	1.29±0.31
	At 18 months	1.31±0.88	1.30±0.36
Graft survival at 1 year		78.57% (n=14)	84.84% (n=33)
Patient survival at 1 year		78.57% (n=14)	84.84% (n=33)
Rejection episodes	AMR	4.76%	18.18%
	ACR	4.76%	3.03%
Infections	UTI in first 12 weeks	4.76%	3.03%
	Fungal septicemia	4.76%	6.06%
	Pneumonia	14.28%	0%

SA-PO1161

Outcomes of Different Induction Therapies in ABO-Incompatible Renal Transplant Recipients in the Tacrolimus Era

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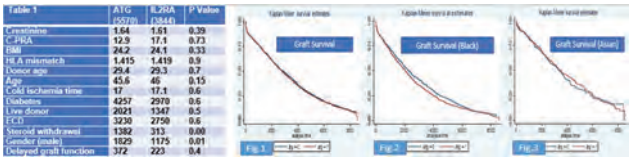
Background: ABO-incompatible renal transplantation is emerging as a safe and potentially acceptable routine procedure; however, outcomes of different induction therapies in ABO-incompatible renal transplant recipients (RTRs) remain insufficiently explored in the tacrolimus era.

Methods: Using data from organ procurement and transplantation network, all ABO-incompatible RTRs maintained on tacrolimus based immunotherapy between 2000 and 2017 were retrospectively reviewed. Data including age, sex, gender, ethnicity, functional status, diabetes, body mass index, cold ischemia time, number of previous transplants, panel reactive antibodies, donor type, donor age, HLA-mismatches, number of acute rejection episodes, induction therapies, maintenance immunotherapy, recipients and graft survival were collected (Table 1). Based on induction therapies administered, RTRs were divided into 2 groups; anti-thymocyte globulin (ATG) or interleukin-2 receptor antagonist (IL-2RA). Inverse probability weights were used to adjust confounders among different groups using propensity score analysis. Cox hazard regression analysis for adjusted data and treatment effects model were used to assess outcomes.

Results: Out of 14,414 RTRs, 8844 received IL2-RA while 5570 received ATG for induction. There were no significant differences between the IL2-RA and ATG groups in terms of early post-operative acute rejection episodes (95% CI ranges from -0.007 to 1.008, P=0.8), overall acute rejection episodes (CI ranges from -32.5 to 3.1, P=0.107) or graft survival (CI ranges from -169.6 to 199.3, P=0.87). Mean graft survivals were similar (7.8 vs 7.5 years, p=0.8), as well (Figure 1,2,3).

Conclusions: In the tacrolimus era, ATG as compared to IL2-RA induction therapy does not have a favourable graft or survival outcomes in ABO-incompatible RTRs.



SA-PO1162

Comparison of Clinical Outcomes Between High Anti-A/B Antibody Titer vs. Low Titer in ABO-Compatible Kidney Transplantation

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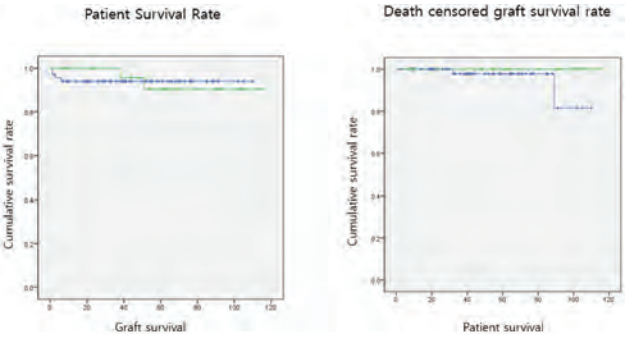
Background: ABO incompatible(ABOi) kidney transplantation(KTP) reduces the waiting time of deceased donor KTP and extends the pool of living donor KTP. In recent data, ABOi KTP is known to have no significant difference in long term outcome compared to ABO compatible. However, high A/B antibody titer is still a challenge to overcome in ABOi KTP. In this study, high anti A/B antibody and low titer Ab were compared in ABOi KTP

Methods: We retrospectively evaluated 95 cases of ABOi KTP recipients from 2009 to 2018 in Bong Seng Memorial Hospital, BUSAN, South KOREA. High-titer isohaemagglutinin patients were defined by IgG anti A/B titres ≥1:256. There were 28 patients with high titer and 67 patients with low titer group. Primary outcome was patient survival and graft survival. The secondary outcome was bleeding tendency, biopsy proven rejection, plasmapheresis number, cost of treatment

Results: There was no statistical difference in the baseline characteristics between high and low titer group. Patient survival rate in the high titer group was not statistically significant compared to the low titer group. There was no significant difference in graft survival rate(Figure 1). There were no differences in complications such as bleeding tendency and number of blood transfusions. However, the anti-A / B antibody titer(49 ± 37 vs. 502 ± 384)(p=0.00) and the number of plasmapheresis(3.8 ± 1.7 vs. 7.2 ± 2.5)(p=0.00) were significantly lower in the low titer group. There was no difference in complications such as PTDM, angina, and myocardial infarction after transplantation. There were no significant differences in infection and rejection

Conclusions: High A/B antibody titer ABOi KTP showed no inferiority in clinical outcome compared to low titer. The authors suggested that the high Anti A/B antibody titer lower the medical alert thresholds from contraindication to high risk



SA-PO1163

Reuse of Immunoabsorption Columns in ABO-Incompatible(ABOi) Kidney Transplantation: A Single-Center Experience

Anil Bhalla,[1] Priti Meena,[1] Devinder S. Rana,[1] Ashwani Gupta,[1] Manish Malik,[2] Anurag Gupta,[3] Vinant Bhargava,[1] Vaibhav Tiwari,[1] Yogeshman Anand.[1] *[1]Sir Ganga Ram Hospital, New Delhi, India; [2]Sir Ganga Ram Hospital and GRIPMER, New Delhi, India; [3]Synegy Hospital, Uttarakhand, India.*

Background: ABO-incompatible (ABOi) Kidney Transplantation has results comparable to ABO compatible transplantation. This is because patients are desensitized at the pre-transplant stage using apheresis & Rituximab therapy with tacrolimus (TAC) based immunosuppression. In some patients, baseline titers are very high and repeated plasma exchange sessions also fail to bring titer to the desired level. Immunoadsorption (IA) technique is very effective in reducing titers in such cases. But, IA therapy is quite expensive, hence we have tried to reuse the filter to see the effectiveness.

Methods: 190 ABOi transplants have been performed at our center since 2012. Patients received Rituximab and triple immunosuppression. Baseline IgG & IgM were tested with gel method and it ranged from 1: 2 to 1: 1024. The antigen-specific IA technique was used in 64 patients. Two types of IA filters were used Glycorex – glycosorb & Adsopak. IA columns were reused after regeneration. No. of column reuse, adverse events, and Anti A / Anti B antibody titers were assessed. Glycosorb filter was processed by rising with 1000ml saline and sterilized with Ethylene trioxide(ETO). Adsopac column was reused by different regeneration technique using saline wash, acidic solution followed by buffer and alkaline solution and regeneration solution(sodium azide):The column was placed at 2° to 8°C. Antibody titers were estimated in the blood taken 10 minutes before the end of the procedure from the line immediately after the Column. Negative or low antibody titer indicated efficient antibody removal at the end of treatment &despite reuse of the columns. Columns were used maximally for 3 times.

Results: 64 ABOi patients underwent antigen-specific IA and could be transplanted. In 4 patients, the titers did not come to target levels and these had to subject to therapeutic plasma exchange to achieve the target levels. Incidence of hypotension, fever with rigors & failure to bring down the titer was significantly higher in adsopak filter as compared to Glycorex filter. Column reuse resulted in a cost saving of 5000 to 10,000 USD per patient.

Conclusions: Although IA technique is very effective, it is expensive and the cost of treatment increases considerably. Reuse sessions were tolerated well and titer could be reduced to target levels.

SA-PO1164

Kinetic Characteristics and Validation of a Patient-Based Model for Therapeutic Plasma Exchange in Transplant Patients

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Background: Therapeutic plasma exchange (TPE) has become an important tool in kidney transplantation. The American Society of Apheresis gives TPE a category 1 indication for antibody mediated rejection (AMR). Understanding the kinetics of macromolecule removal is fundamental for rational prescription, optimization, and recognizing limitations of the TPE.

Methods: We evaluated 12 patients with biopsy confirmed AMR, who had indication for TPE. Each patient received 5 treatments every other day with 1.5 plasma exchanges, and all treatments where replaced with 5% albumin solution. Considering that Luminex is not a quantitative assay, we measured immunoglobulins (IgG, IgA, IgM) by immunoturbidimetry, and LDL cholesterol before and after each treatment. By knowing the initial value of macromolecules, their intravascular distribution, and the reduction ratio, we calculated the intravascular refill between treatments. Refill was independent of time, and constant for each patient through all treatments. We also identified three refill patterns. With this information we developed a predictive model for macromolecule kinetics during TPE, and conducted an internal validation of the model.

Results: We evaluated distribution prediction of the model and we obtained good correlation: IgG (r=0.94, 95%CI=0.91-0.96, R^2=0.88, P <0.001), IgA (r=0.89, 95%CI=0.84-0.92, R^2=0.8, P <0.0001), IgM (r =0.89, 95%CI=0.85-0.93, R^2=0.80 P <0.0001), LDL (r =0.94, 95% CI= (0.92-0.96), R^2=0.89 P <0.0001). The Bland Altman plots to evaluate agreement: IgG (Bias= 0.3, SD of Bias 23.45,95% Limits of agreement (-45–46)), IgA (Bias= -8.4, SD of Bias 13.95, 95% Limits of agreement (-35 to 19)), IgM (Bias= -0.13, SD of Bias 29.4, 95% Limits of agreement (-58 to 58)), and LDL (Bias= -17, SD of Bias 31.47,95% Limits of agreement (-78 to 44)).

Conclusions: The model predicted accurately the distribution of macromolecules after multiple treatments. The correlation and agreement was especially good for IgG, and IgA. Although the correlation was good for LDL, concordance was not, this can be explained by the intravascular distribution and the short half-life of this molecule. The model was programmed in an app format for IOS to make it practical. A validation cohort is being conducted.

SA-PO1165

Outcomes and Complications Following ABO-Incompatible Kidney Transplantation Performed After Desensitization by Antigen-Unspecific Immunoadsorption Devices

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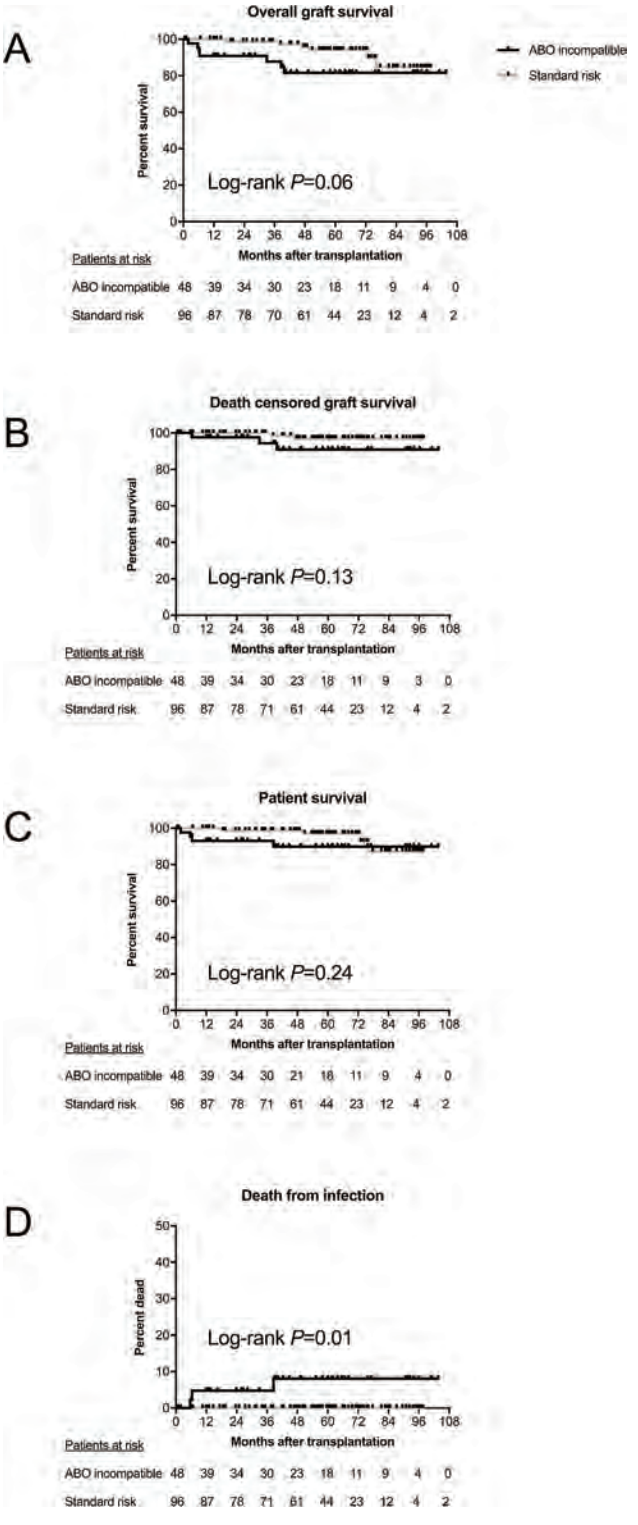
Background: Due to the current organ shortage, ABO incompatible (ABOi) transplantations have been increasingly performed in recent years. The results seem comparable to those of compatible transplantations, but there have also been reports of increased side effects possibly due to the desensitization therapy.

Methods: To address an increase in severe infectious complications, we compared the outcomes of 48 ABOi transplant recipients to outcomes of 96 matched ABO compatible (ABOc) controls transplanted at Heidelberg University Hospital from 2005 to 2018. In addition, we conducted a subanalysis of high-titer (≥1:256) recipients compared to low-titer (<1:256) recipients.

Results: Over a follow-up period of 8 years, ABOi transplant recipients had comparable graft and patient survival as well as graft function compared to ABOc patients. T cell-mediated and antibody-mediated rejections were not different between groups. In ABOi transplant recipients, urosepsis (23% vs. 9%; p=0.019) and pneumonia with opportunistic pathogens (8% vs. 1%, p=0.025) appeared more frequently. As a consequence, a significantly higher number of deaths from infection have been observed after ABOi transplantations (6% vs. 0%, p=0.010). High-titer recipients (isoagglutinin titer of ≥1:256) showed a higher incidence of BK virus replication and postoperative bleeding complications.

Conclusions: ABOi kidney transplant recipients may be safely transplanted, even when they have a high anti-A/B antibody titer before surgery. However, particular attention has to be paid to severe infectious complications. Especially pneumonia causes an increased frequency of deaths from infections in ABOi kidney transplant recipients during early follow-up.



SA-PO1166

Recipient ABO Blood Group May Be Associated with Increased Mortality Risk Among Patients with Kidney Transplants

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Background: Blood groups A and B have been associated with increased risks of cardiovascular disease, infection and cancers. To date, the effect of recipient ABO blood group on patient survival has not been studied in ABO-matched solid organ transplantation.

Methods: All Australian and New Zealand transplant recipients who received ABO-compatible primary kidney transplant between 1995-2016 were analysed using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. The exposure was recipients' ABO blood group, with the primary analysis being O / non-O and secondary analysis Individual blood groups. Outcome was patient survival. Recipient age, gender, ethnicity, body mass index, smoking status, comorbidities, primary kidney disease; donor type, age and gender; and transplant era were included in the multivariate model as confounders.

Results: On analysis of 15,523 kidney transplant recipients, blood group O was not associated with patient survival (hazard ratio (HR) 0.97, 95% confidence interval (CI) 0.91-1.05) compared to non-blood group O recipients. Blood group A was associated with reduced patient survival compared to non-blood group A recipients (HR 1.10, 95% CI 1.02-1.18).

Conclusions: This analysis suggests that blood group A recipients may have reduced patient survival compared to non-A recipients. Further research is required to confirm these findings and determine the source of this difference – be it biological or unmeasured confounders.

SA-PO1167

Mythbusters: Is Your ABO Titer Method Safe for Patients?

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Background: As transplantation of group A2 kidneys to group B patients becomes increasingly common, so does the practice of sending titers to reference labs, some of whom may not be performing their titers in a way that promises optimum patient safety and outcomes. ABO titer cutoff for transplant eligibility differs widely between institutions, largely due to differences in titration methods. Our study sought to refute the notion that a DTT-treated titer read at immediate spin (IS) is an accurate assessment of IgG titer and to suggest widespread adoption of more appropriate, traditional titer testing methods.

Methods: A method comparison study was performed by testing Anti-A titers of 10 group B kidney transplant candidates at immediate spin (IS), traditional tube method (tube AHG), DTT-treated IS (IS DTT), and DTT-treated tube method (AHG DTT). Dilution controls were performed for each patient.

Results: All IS and 9 of 10 AHG titers were reduced by DTT treatment. The amount of reduction varied, as shown in Table 1, suggesting that the proportion of ABO titer which is IgM vs. IgG varies individually. The highest AHG tube titer (256) was reduced down to an IS DTT titer of only 4. In this instance a patient with a high titer Anti-A would have been eligible to receive an A2 transplant at many institutions which use IS DTT titers.

Conclusions: Traditional titer methods which measure IgM and IgG provide a more comprehensive and clinically valuable view than DTT-treated titers. The practice of performing IS DTT-treated titers and reporting as IgG titer is misleading, with possibly harmful implications for patients. Titer performance must be standardized to prioritize patient outcome. Clinicians who refer ABO titers to reference labs should thoroughly assess the method being used to perform these titers and demand a method which ensures patient safety.

Table 1

Patient	IS Tube	AHG Tube	IS DTT	AHG DTT	Δ IS (# of tubes)	Δ AHG (# of tubes)
1	32	32	4	16	-3	-1
2	64	256	4	64	-4	-4
3	32	32	8	32	-3	0
4	32	16	2	2	-4	-3
5	32	128	2	4	-4	-5
6	32	64	8	32	-2	-1
7	32	128	2	1	-4	-7
8	32	128	1	64	-5	-1
9	64	64	4	4	-4	-4
10	32	64	8	32	-2	-1

SA-PO1168

Graft Survival and Patient Outcomes in ABO-Incompatible Kidney Transplant with Baseline High and Low Isohemagglutinin Titers Compared with ABO-Compatible Transplant

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Background: ABO incompatible kidney transplantation (ABOiKT) helps to increase donor pool. No study till date has compared outcomes in high & low baseline isohemagglutinin titers to that in ABO compatible transplants (ABOcKT). This study attempts to evaluate correlation of baseline anti-A & anti- B isoagglutinin titres on graft survival and patient outcome in ABOiKT as compared to ABOcKT.

Methods: This was a retro-prospective observational study evaluating 954 renal transplant recipients. Of these, 873 patients underwent ABOcKT. Of 81 patients who underwent an ABOiKT, 67 belonged to low titer group (baseline IgG ≤1:64) and 14 belonged to high titer group(baseline IgG≥1:128). Patients were followed up for 1 year. Graft survival, rejection episodes, patient survival & infections were assessed.

Results: Mean age of patients who underwent ABOcKT, ABOi-high titer group and ABOi-low titer group was 40.47±12.19,38.79±16.21& 40.37±12yrs respectively. Mean donor age was 45.08±10.26,49±11.42 & 45.91±10.15 yrs respectively. Majority of donors were females-68.8%,78.6% & 79.1% respectively. Chronic glomerulonephritis was most common cause of ESRD. HLA mismatches were lower in the ABOcKT group. Death censored graft survival was lower in high titer group (92.3%) compared to ABOcKT group (98.8%), p=0.231. Graft survival in low titer group (96.8%) was comparable to ABOc group(96.8%, p=0.328). Proportion of patients with biopsy proven rejections was lower in ABOcKT groups (6.5%) when compared to ABOi high (21.4%) & low titer groups (13.4%) respectively(p=0.063 and 0.033). Antibody mediated rejections were significantly fewer in ABOcKT group(1.8%) vs high titer(21.4%) & low titer group(11.9%) (p=0.003 and p<0.001). Patient survival was better in ABOcKT group(97.9%) compared to high (92.9%) and low titer (94.0%) groups. Most deaths were attributed to infections. Low titer group fared better than high titer group in having lesser infection episodes, though difference was insignificant(p=0.532).

Conclusions: High baseline isoagglutinin titers are associated with poor graft survival in ABOi grafts compared to ABOc grafts, even though the difference was not significant. High baseline antibody titers are associated with significantly greater number of rejections & infections

SA-PO1169

Association Between Post-Transplant Donor-Specific Antibodies and Recipient Outcomes in Simultaneous Liver-Kidney Transplant Recipients

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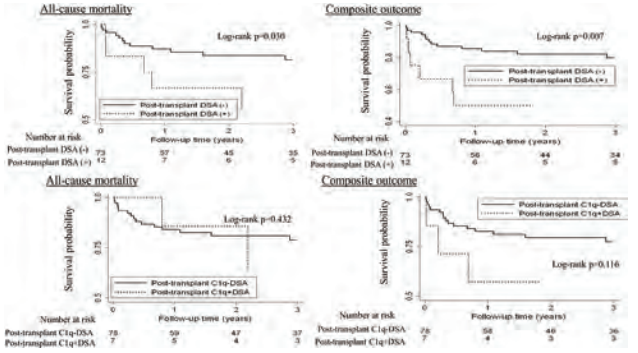
Background: There is a dearth of published data regarding the presence of post-transplant Donor Specific Antibodies (DSA), especially C1q binding DSA (C1q+DSA), and patient and kidney allograft outcomes in simultaneous liver-kidney transplant (SLKT) recipients.

Methods: We investigated 85 consecutive patients who underwent SLKT between 2009-2018 in our center. Associations between presence of post-transplant DSA [persistent and/or newly developed (de novo)] and C1q+DSA, and all-cause mortality and the composite outcome (mortality, allograft kidney loss, and antibody-mediated rejection) were examined using unadjusted and age and sex-adjusted Cox proportional hazards regression models.

Results: The mean age at transplantation was 56 years. Sixty and 26% of the patients were male and African-American, respectively. Twelve patients (14%) had post-transplant DSA and 7 (8%) patients had C1q+DSA. The presence of post-transplant DSA was significantly associated with increased risk of mortality (unadjusted model: Hazard Ratio (HR)=2.72, 95%Confidence Interval (CI): 1.06-6.98 and adjusted model: HR=3.20, 95%CI: 1.11-9.22) and the composite outcome (unadjusted model: HR=3.18, 95%CI: 1.31-7.68 and adjusted model: HR=3.93, 95%CI: 1.39-11.10) compared to the DSA negative group (Figure). There was no significant association between the presence of C1q+DSA and outcomes (adjusted model: HR=1.67, 95%CI: 0.43-6.45 for mortality, and HR=2.61, 95%CI: 0.70-9.75 for the composite outcome).

Conclusions: The presence of post-transplant DSA was significantly associated with increased risk of all-cause mortality and composite outcome including kidney allograft loss and ABMR. The presence of post-transplant DSA should not be ignored in routine patient care after SLKT even though pre-transplant sensitized status is usually neglected at the time of SLKT.



SA-PO1170

Renal Microvascular Autoregulation in an Ischemia-Reperfusion-Induced Model of Acute Kidney Injury

Bailey McEachen. *The University of Alabama at Birmingham, Birmingham, AL*

Background: Autoregulation alters renal vascular resistance (RVR) to keep glomerular filtration rate (GFR) stable during arterial pressure fluctuations. Ischemia-reperfusion-(IR)-induced acute kidney injury exhibits increased RVR and decreased GFR. Our previous study revealed that autoregulation was impaired in IR, but improved with acute treatment of ROS-scavenger and NADPH-oxidase-inhibitor. Therefore, we hypothesize that chronic antioxidant treatment (Tempol) preserves autoregulation by reducing oxidative stress and inflammation in IR rats.

Methods: Rats underwent 60 minute bilateral renal arterial occlusion, with or without Tempol (2mM, drinking water; 7 days), or sham surgery. Afferent arteriole (AA) autoregulatory behavior was assessed in blood-perfused juxtamedullary nephrons. Glomerular function was assessed by plasma creatinine, GFR using FITC-sinistrin, and proteinuria/albuminuria.

Results: SBP was normal across groups: 126-145mmHg (P>0.05) over 7 days. Plasma creatinine increased with IR (1.68±0.18 vs. 0.98±0.04mg/dL in shams, P<0.05), but remained normal in IR+Tempol rats (1.05±0.12mg/dL). Sham rats (n=3) exhibited pressure-dependent vasoconstriction. Control AA diameter averaged 12.2±0.9μm and decreased 32±3% from 65 to 170mmHg. In contrast, IR rats (n=2) lost autoregulatory capacity. AA diameter passively increased by 25% over 65-170mmHg, whereas IR+Tempol rats (n=2) maintained pressure-dependent vasoconstriction. GFR for shams remained constant (0.9-1.3mL/min/100g), while Tempol improved GFR to 0.5 compared to 0.0mL/min/100g in IR. Tempol treatment significantly reduced albuminuria (Day 3: Sham 0.5±0.1mg, IR 14.3±6.6mg, IR+Tempol 2.5±0.5mg) and proteinuria (Day 3: 12±1mg, 58±10mg, and 28±7mg respectively). mRNA expression of inflammatory markers MCP-1/TGF-β increased significantly in IR rats (6.7±1.5/4.0±0.5 vs. 1.1±0.2/1.0±0.1 in sham) and reduced in IR+Tempol rats (3.5±0.4/2.4±0.3).

Conclusions: Ultimately, antioxidant treatment preserved autoregulatory and kidney function in IR rats.

SA-PO1171

Endothelin-1 Promotes Renal Iron Deposition in Murine Models of Iron Overload

Rachel Meek. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Recent observations show that renal iron deposition correlates with plasma endothelin-1 (ET-1) in sickle cell disease (SCD). Iron accumulation in humanized SCD mice kidneys is ameliorated by a selective endothelin A receptor (ETA) antagonist, ambrisentan. Thus, we hypothesized that endothelial-derived ET-1 regulates iron trafficking in the kidney.

Methods: Vascular endothelial cell ET-1 knockout (VEET KO) male mice aged 12 weeks were injected with phenylhydrazine (40 mg/kg, IP) for two consecutive days to induce hemolysis and consequent iron overload. Heme oxygenase-1 knockout (HO-1 KO) mice, a model of iron overloading, aged 20 weeks were given ambrisentan (10 mg/kg/day, p.o.) for 4 weeks.

Results: VEET KO mice exhibited a higher survival rate relative to littermate control mice (66.7% vs 20% survival, n=9 and 5, respectively). Moreover, VEET KO mice with induced hemolysis have less renal iron deposition when compared with control mice (Prussian blue staining, 41.1 ± 5.1 vs 79.3 ± 0 Mpixel/μm, respectively). At baseline, iron trafficking mediators (TRF-1, DMT-1, FtH, FPN-1) assessed by RT-PCR were not upregulated in VEET KO mice when compared with control mice. HO-1 KO mice exhibited elevated plasma ET-1 (2.59 ± 0.78 vs 0.45 ± 0.09 pg/mL), cortical ET-1 mRNA expression (2-fold increase), and renal iron content (87.2 ± 27.5 vs 0.24 ± 0.2 Mpixel/μm) when compared with control mice; all were significantly reduced by ambrisentan. No significant changes in expression of iron uptake and storage mediators in KO mice. Ferroportin-1, an iron exporter, was significantly increased by ambrisentan.

Conclusions: These data suggest ET-1 contributes to renal iron overload.

SA-PO1172

The $SGLT_2$ Inhibitor Canagliflozin Reverts Hyperglycemia-Induced Metabolic Changes in Mouse Kidney Sections

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Background: Diabetes is associated with high rates of renal tubular glucose reabsorption, high kidney glycolytic activity and higher production of kidney injury markers. Canagliflozin is an SGLT2 inhibitor, used for type 2 diabetes and considered to have beneficial effects on the progression of diabetic kidney disease. This study tested the effects of Canagliflozin on renal metabolism in mouse kidney slices.

Methods: Kidneys were harvested from C57Bl/6 WT mice, sliced to 150 μM thick sections and incubated in media containing 7.2 mM glucose (NG) or 25 mM glucose (HG), without or with canagliflozin (1, 10 and 100 μM). Conditioned media was collected after 24h of incubation and metabolites were measured using YSI bioanalyzer and gas chromatography-mass spectroscopy. Additionally, kidney injury marker (KIM1) was measured by ELISA. Kidney tissues were frozen, sectioned to 10 μm sections using cryostat for mass spectrometry imaging (MSI) to identify spatial changes in glucose.

Results: In conditioned media, significant reduction in glucose ($p<0.0001$), and succinate and significant lactate ($p<0.001$) increase was noted in, HG compared to NG. MSI depicted increase in glucose in tissue sections treated with HG suggesting increased glucose uptake. Canagliflozin reduced the glucose uptake in both NG and HG treated tissue sections ($p<0.0001$ for HG and $p<0.01$ for NG groups). Likewise, 100 μM canagliflozin significantly reduced lactate in both glucose conditions. High glucose induced succinate and KIM1 were also reduced by canagliflozin.

Conclusions: Above results support the hypothesis that SGLT2 inhibitors, by blocking glucose uptake, can revert the metabolic changes induced by hyperglycemia and protect against tissue injury.

SA-PO1173

Missense Mutations in PKD1 Lead to Reduced Surface Localization of the Polycystins in ADPKD

Sanjna Girdhar. *Mayo Clinic, Rochester, MN.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD), characterized by the development of fluid filled cysts, is the fourth leading cause of renal failure in the US and is mainly caused by mutations in the genes PKD1 or PKD2 encoding the proteins Polycystin1 (PC1) and Polycystin2 (PC2) respectively. Localization of PC1 and PC2 to the cell surface is important for their function in cells, with a positive correlation between reduced surface protein levels to disease severity. The objective of this project was to quantify surface localization of a number of missense variant PC1 proteins, and combination of variants.

Methods: The single PC1 variants (p.Arg3277Cys, p.Met3346Leu, and p.Thr3270Met) were created by site directed mutagenesis and introduced into the full length PC1 tagged construct. In addition, variant combinations were similarly generated (p.Thr3270Met/p.Arg3277Cys, p.Met3346Leu/p.Thr3270Met, and p.Arg3277Cys/p.Met3346Leu/p.Thr3270Met), mimicking a variant combination detected in three ADPKD families. Epithelial cells from the kidney were transfected with constructs containing these single and combination variants. Immunofluorescence staining of the transfected cells was used to visualize the surface localized proteins.

Results: The intensity of the immunofluorescence signal, as determined by flow cytometry, indicated the amount of protein properly localizing to the cell membrane. The single variants were found to have reduced surface localization compared to wild type, with the surface localization further lowered as the number of significant variants increased.

Conclusions: Therefore an in cis combination of missense variants can significantly reduce PC1 surface localization, showing that a combination of hypomorphic alleles can result in a fully inactivating allele.

SA-PO1174

Electrogenic Transport Function of Low Temperature Rescued CLC-5: R345W Mutation and Towards Dent Disease Novel Therapies

Meihui Zhang. *Mayo Clinic, Rochester, MN.*

Background: Dent Disease type 1 (DD1) is an X-linked disorder characterized by low-molecularweight proteinuria, hypercalciuria, nephrocalcinosis, and kidney stones. DD1 has no effective therapy or treatment, although it is known to be caused by mutations in the *CLCN5* gene encoding ClC-5, a voltage-gated nCl-/H^+ exchanger found at the apical membrane of the proximal tubule and within endosomal membranes. Our previous studies revealed that functional defects of two novel *CLCN5* mutations (R345W, Q629X) were due to abnormal ClC-5 trafficking to the plasma membrane. Interestingly, R345W surface expression in cells could be rescued by lowering the incubation temperature from 37 to 30°C after transfection. However, the transport function of the rescued R345W has not been investigated.

Methods: Thus, we used whole cell patch-clamp electrophysiology to measure transport functions of transiently transfected renal proximal tubule cells (LLC-PK1) expressing wild type (WT) or R345W mutated ClC-5 incubated at 37 or 27°C.

Results: Cells expressing WT exhibited strongly outward rectifying current at positive holding voltages whereas R345W expressing cells incubated at 37°C demonstrated reduced current. Intriguingly, R345W expressing cells incubated at 27°C demonstrated significantly increased transport function compared to R345W expressing cells incubated at 37°C. We have also successfully established LLC-PK1 cell lines that stably express eGFP/HA double-tagged WT and mutant ClC-5. Using Western blot analysis, we documented that ClC-5 expression levels were sufficient to use these cells to screen candidate chaperones.

Conclusions: These results establish a rationale and the tools to explore the effect of pharmacological chaperones to facilitate proper protein folding and maturation of DD1 mutations, including R345W. Results could suggest new therapies for some populations of DD1 patients who currently have no specific therapy available.

SA-PO1175

Recessive Mutations in TLN1 Are a Potential Novel Cause of Nephrotic Syndrome in Humans

Roxanna Fouladi. *Harvard University, Cambridge, MA.*

Background: Nephrotic syndrome (NS) is characterized by a significant loss of protein in the urine causing hypoalbuminemia and edema. NS is categorized into steroid sensitive (SSNS) and steroid resistant nephrotic syndrome (SRNS). Steroid resistant nephrotic syndrome is the second most common cause of chronic kidney disease in the first three decades of life. Mutations in over 59 genes provide a monogenic cause in up to 29.5% of NS cases (*JASN* 26:1279, 2015). This implies that novel genetic and mechanistic causes of NS may explain some of the currently undiagnosed ~70% of cases. The mechanisms of steroid action in SSNS are still unknown and treatment options for SRNS are limited.

Methods: To identify additional monogenic causes of NS we performed whole exome sequencing in >2,000 individuals with NS. We identified a homozygous *TLN1* mutation in B3328-21 (c.5964_5966del, I1989del). We screened an additional cohort of 605 patients with NS with a Fluidigm Access ArrayTM for *TLN1* mutations and identified a compound heterozygous mutation in patient A3788-21 with SSNS (c.235A>G, M79V and c.3491G>C, S1164T).

Results: *TLN1* encodes a protein that binds to and activates integrins, coupling them to the actin cytoskeleton (*FEBS* Letters; 592:2108, 2018). Podocytespecific *Tln1* knock out mice have been described to develop an altered podocyte cytoskeleton structure, proteinuria, focal segmental glomerulosclerosis, and die at the age of 10 weeks likely due to renal failure (*JCI* 124:1098, 2014).

Conclusions: In conclusion, we have identified mutations of *TLN1* as a potential novel cause of nephrotic syndrome.

SA-PO1176

Plasma Fibroblast Growth Factor 23 (FGF23) and Protein Alpha-1-Microglobulin/Bikunin Precursor (AMBP) as Predictors of Cardiovascular Disease (CVD) Endpoints in The Boston Kidney Biopsy Cohort (BKBC)

Debbie Adam. *Harvard University, Cambridge, MA.*

Background: Chronic Kidney Disease (CKD) is a risk factor for the development of Cardiovascular Disease (CVD). Research into nontraditional risk factors could help to provide more information as to why this complex relationship exists. Specifically, fibroblast growth factor 23 (FGF23) and protein α1-microglobulin/bikunin precursor (AMBP) have both shown promise as renal failure biomarkers in CVD-related clinical trials. From this knowledge, we hypothesized that elevated levels of plasma FGF23 and AMBP in CKD patients would demonstrate an accelerated time to CVD endpoint.

Methods: The population of interest were patients enrolled for a native kidney biopsy date between 2006 and 2018 at Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH). Biological specimens were collected on all consented patients over the age of 18. Plasma FGF23 and protein AMBP were measured using multiplex immunoassay (inter-assay CV <10% for blind replicate samples). Univariate and multivariate regression models were generated to assess if plasma FGF23 and AMBP were predictors of CVD outcomes in CKD patients.

Results: Patients with the highest levels of plasma FGF23 had a 3.136 risk of reaching the composite CVD endpoint relative to patients with lower levels of plasma FGF23 (HR=3.136 (1.098-8.959), p<.05). Patients with mid-levels of plasma protein AMBP had a .312 risk of reaching the CVD endpoint(s) relative to patients with lower levels of plasma protein AMBP (HR=.312 (.122-.798), p<.05).

Conclusions: It can be inferred from our findings that plasma FGF23 can be used to predict cardiovascular outcomes in CKD patients, while the same cannot be said categorically for plasma protein AMBP.

SA-PO1177

IL-6 Mediated Activation of the Mineralocorticoid Receptor via Rac1

Oishi Paul. *Emory University, Atlanta, GA.*

Background: Hypertension (HTN) is characterized by excessive sodium (Na+) reabsorption and increased cytokine production, including interleukin 6 (IL-6). Aldosterone (Aldo) is the primary ligand for the mineralocorticoid receptor (MR) and studies suggest MR inhibition lowers blood pressure. However, Aldo levels are not always increased in HTN, suggesting alternate MR activation. Data from our laboratory have shown that IL-6 can activate the MR *in vitro*, and that Rac inhibition reduces mineralocorticoid response element (MRE) transcription. We hypothesize that IL-6 activates the MR via Rac1 in the late distal convoluted tubule (DCT), increasing activity of epithelial sodium channel (ENaC), a primary Na+ transporter in the late DCT (DCT2).

Methods: Using a voltohmmeter, we measured transepithelial resistance and voltage to calculate current in our cell culture model for DCT2 (mDCT15 cells). Cells were transfected with Rac1 expression vectors and treated (IL-6 [100ng/mL]).

Results: While IL-6 increased ENaC activity, Rac1 knockdown inhibited IL-6 induced ENaC (-1.16-fold change/baseline) activity. Since we observed that IL-6 induces nuclear MR translocation, we investigated whether Rac1 affects IL-6 mediated MR translocation. We cotransfected MR-eGFP tagged constructs and Rac1 expression vectors into mDCT15 cells. Cells were treated with IL-6 and visualized with confocal microscopy. Following IL-6 treatment, MR nuclear translocation was observed; however, with Rac1 knockdown, decreased MR translocation was observed.

Conclusions: We are the first to demonstrate cytokine-mediated ENaC activation in the DCT2. Additionally, these data suggest that Rac1 is crucial for IL-6 mediated ENaC activation and MR translocation, providing an alternate mechanism for increased ENaC Na+ transport during HTN.

SA-PO1178

Inhibition of Lymphangiogenesis Exacerbates Cisplatin Nephrotoxicity

Elisa Farrell. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: The lymphatic system is a complex network of channels responsible for lipid transport, fluid homeostasis, and immune response. The creation of new lymphatic vessels, or lymphangiogenesis, occurs primarily in development, though studies show that vascular endothelial growth factor C or D (VEGF-C or -D) stimulate *de novo* lymphangiogenesis in disease through interaction with their receptor, VEGFR-3. We have previously shown this process to occur following acute kidney injury (AKI). However, no previous studies have evaluated whether lymphangiogenesis is beneficial or harmful in AKI.

Methods: This study utilized MAZ51 [10 mg/kg bodyweight in DMSO intraperitoneally (i.p.)], a VEGFR-3 kinase inhibitor, to block lymphangiogenesis in a model of cisplatin nephrotoxicity (20 mg/kg bodyweight in saline i.p.). Mice were harvested 3 days post-cisplatin injection. Biomarkers of renal function, injury, inflammation, and lymphangiogenesis were measured.

Results: We report that inhibition of lymphangiogenesis exacerbates cisplatin nephrotoxicity. MAZ51 treated mice experienced significantly worsened kidney function, measured by elevated serum creatinine (1.1 ± 0.3 vs. 0.31 ± 0.05 mg/dL), decreased glomerular filtration rate (11.9 ± 3.9 vs. 80.6 ± 20.6 μl/min), and increased serum cystatin C. MAZ51 mice also experienced significantly increased expression of intrarenal KIM-1, compared with cisplatin alone treated mice. We also observed a significant rise in intrarenal inflammatory markers (*Csf1*, *Ccl2*, *Tnfα*) and heme oxygenase-1 (*Hmox1*), as well as increased cell death, compared with cisplatin alone controls.

Conclusions: Taken together, our study describes a novel role for lymphangiogenesis as an adaptive response following cisplatin AKI and may be a promising target for therapeutic intervention.

SA-PO1179

Role of Histone Deacetylase-1 in Interstitial Fibrosis

Kaitlyn Aldaz. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Acute kidney injury can lead to chronic kidney disease through myofibroblast secretion of extracellular matrix (ECM) leading to interstitial fibrosis and a loss of kidney function. We reported that following ischemia-reperfusion-injury (IRI), the transcriptional regulator, histone deacetylase-1 (HDAC1) is increased in the kidney. Inhibition of HDAC1 reduced IRI-mediated interstitial fibrosis. We hypothesized that fibroblast HDAC1 was profibrotic and developed an inducible HDAC1 fibroblast knockout (KO) mouse.

Methods: Fibroblast HDAC1 was deleted in adulthood, and the male mice underwent sham or bilateral IRI (2-weeks of reperfusion) surgeries.

Results: Plasma creatinine was significantly elevated in control IRI mice (0.20 ± 0.02 mg/dl) compared to sham (0.12 ± 0.001) or KO mice (sham = 0.13 ± 0.009, IRI = 0.14 ± 0.02, $P_{Genotype}$ = 0.2, $P_{Surgery}$ = 0.02, $P_{interaction}$ = 0.03) suggesting that the KOs had better kidney function. Interstitial sirius red staining, α–smooth muscle actin (αsma), and fibronectin expression was increased in the control IRI mice compared to shams or KO mice. Next, Normal Rat Kidney 49 Fibroblast cells transfected with human HDAC1 or empty vectors. Injury was simulated by treatment of cells with TGF-β1, a master regulator of myofibroblast activation. Overexpression of HDAC1 did not significantly affect myofibroblast markers (αsma, fibronectin). TGF-β1 treatment led to myofibroblast activation, regardless of HDAC1 level. Interestingly, HDAC1 was found to suppress p53 expression, a master regulator of the cell cycle.

Conclusions: Together, our data suggest that fibroblast HDAC1 is profibrotic, but it may be through regulation of myofibroblast cell cycle, rather than direct effects on ECM secretion.

PUB001

Cystatin C Utilization for Kidney Assessment in Acute Care

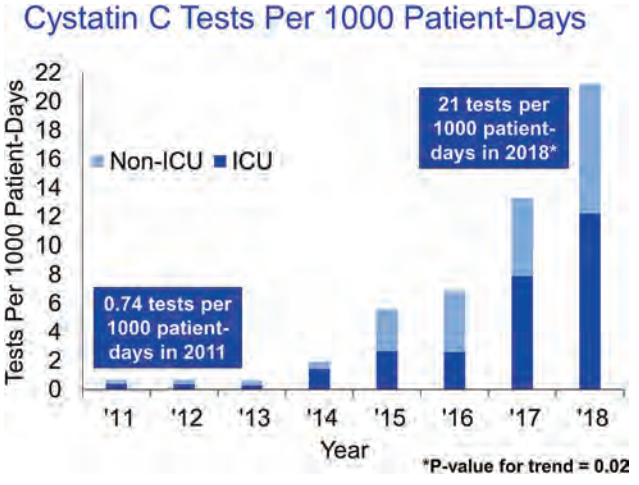
Hilary Teaford,[2] Diana J. Schreier,[1] Kristin C. Mara,[1] Andrew D. Rule,[1] John C. Lieske,[1] Kianoush Kashani,[1] Erin F. Barreto.[1] *[1]Mayo Clinic, Rochester, MN; [2]Mayo Clinic Hospital, Rochester, MN.*

Background: Serum cystatin C (CysC) is a kidney biomarker used most extensively for staging chronic kidney disease. Recently the potential role for CysC in acute care has been recognized; however, settings where it is clearly useful remain to be defined. Our objective was to retrospectively evaluate trends and patterns of inpatient use of CysC in a tertiary hospital where the test was readily available.

Methods: This was a single-center, observational study of adults hospitalized at Mayo Clinic with ≥1 CysC result between 2011–2018. CysC testing was available in house, with a turnaround time of ≤3 hours, and per provider discretion with 1 exception. During 2 years of the 7-year study period, a vancomycin QI project using CysC was conducted in 3 ICUs. Analyses of CysC ordering trends over time used Poisson regression. Descriptive statistics characterized the context for use.

Results: Over 7-years, 8168 CysC levels were obtained, during 4890 inpatient admissions, for 4337 patients. We found a 28-fold increase in CysC use over time (2011: 0.74 tests per 1000 patient-days, 2018: 21 tests per 1000 patient-days; *P*=0.02; Figure). Nephrology was consulted in 40% of cases. The majority (72%) of patients underwent CysC testing during 1 of 3 scenarios: 1) AKI, 2) expected alterations in muscle mass, and 3) vancomycin dosing in the ICU QI project. Non-GFR determinants of CysC were identified with 47% of tests, most frequently corticosteroid use.

Conclusions: In this cohort of inpatients with ready access to CysC testing, CysC utilization significantly increased over the last 7-years. Themes for use included renal-dosing of drugs, AKI monitoring, and to assess GFR in patients with altered muscle mass. Non-GFR determinants frequently occurred, exposing opportunities for misinterpretation. Additional studies are warranted to define the optimal role for CysC in the inpatient setting.



PUB002

Urinary Urea Excretion as a Potential Early Biomarker of AKI

David G. Morais, Mirela Santinho, Talita R. Sanches, Victor F. Seabra, Leandro U. Taniguchi, Lucia Andrade, Camila E. Rodrigues. *São Paulo University, São Paulo, Brazil.*

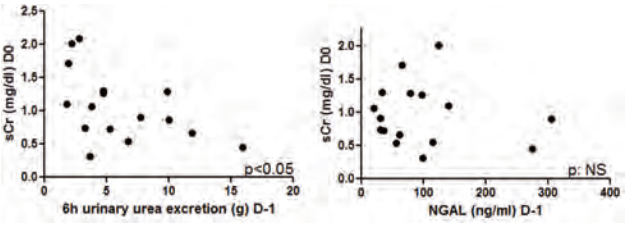
Background: The diagnosis of AKI is based on reduced urine output or elevated serum creatinine (sCr), neither of which provide reliable, timely information. Current AKI biomarkers are costly and not widely used. Urinary urea excretion (UUE) is impaired early in chronic kidney disease (CKD), and increased UUE suggests renal recovery in hemodialysis weaning. In renal ischemia or sepsis, reabsorption of water and urea can increase, and fractional excretion of urea (FEU) is reduced during AKI. Little is known about the period before changes in diuresis or sCr. We hypothesized that low UUE would be a timely marker of AKI.

Methods: We evaluated critically ill adults with a clinical AKI score. In high-risk patients, urinary/serum urea and creatinine were measured daily for 7 days or until ICU discharge. The day before AKI diagnosis (D–1) was compared with the day of ICU admission of AKI-free patients (D1), in terms of UUE and urinary neutrophil gelatinase-associated lipocalin (NGAL). Baseline exclusion criteria were CKD, AKI, kidney transplantation, and a body mass index < 19 kg/m^2. AKI diagnoses were based on KDIGO criteria. Results are mean±SD.

Results: We included 41 patients (age, 53.9±16.5 years). The Simplified Acute Physiology Score 3 was 48.7±14.1, and sCr was 0.66±0.26 mg/dl. AKI was classified as septic/ischemic or nephrotoxic. As AKI progressed, the FEU decreased (40.8±9.1% on D–2, 26.1±7.4% on D–1 and 22.1±11.2% on D0; p < 0.05). UUE on D–1 correlated negatively with sCr on D0 (Figure 1). On D–1, FEU was lower in patients with septic/ischemic AKI than in those with nephrotoxic AKI (No-AKI: 30.2 ±11.2% vs Septic/ischemic AKI: 25.4±9.9% vs Nephrotoxic AKI: 42.6±14.2%, p< 0.05).

Conclusions: UUE could be a timely, inexpensive biomarker of AKI, especially septic/ischemic AKI. Supported by FAPESP.

Funding: Government Support - Non-U.S.



PUB003

Epidemiology and Outcome of Kidney Failure due to Snake Bites: Twenty-Three Years of Experience from South Batinah Region, Oman

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Background: Snakebite is a significant global burden with high rate of mortalityand morbidity including Kidney Failure. Literature on renal failure among snake-bite patients of Middle East Gulf region is limited. A retrospective study of patients of renal failure in snake bites patients in South Batinah region of Oman during June 1995 to 31st March 2019 was undertaken.

Methods: As per policy all patients of snake bites in the region of South Batinah of Oman are referred to secondary care Rustaq Hospital. Paper and electronic Records of snake bite patients who developed acute renal failure requiring haemodialysis or managed conservatively during the period of study were studied retrospectively for demography, clincal characteristic & outcome.

Results: Incidence of snake bites in the region was 70 to 93 yearly with male preponderance. Renal failure occured in a minority (0-3 patients per year). While Male: Female ratio of snake bite was 3.46:1, female gender appeared to be at risk factor of developing renal failure (M/F: 0.4:1). Age of patients with renal failure varied from 21 to 78 years with majority between 37 to 55 years of age. 26 patients developed renal failure. There was significant drop in renal failure since 2010 while snake bite incidence remained unchanged. It might be possibly due to change in the policy of antivenom administration. Dialysis was required in 16 (61.5%) of patient of renal failure. Four patients progressed to ESRD. 13 patients lost follow up.9 patients are on follow up. Two among these 9 patients have CKD stage 3 and one has CKD stage 4 (eGFR 43, 55 & 23.6 ml/minute).

Conclusions: 1. South Batinah Region of Oman has high rate of snake Bites with male preponderance but the female gender appeared to be a risk factor of developing renal failure. **2.** There is decrease in incidence of renal failure among snake bite patients. possibly early administration of anti-venom may have a ptrotective effect against renal failure which is suggested by a definite recent trend of decrease in number of AKI due to snake bite after the policy of antivenom administration was modified in 2010 in favour of its administration at Primary health centre before referral to Regional Hospital. **3.** Acute renal failure due to snake bite may be a risk factor for progressive CKD. These patients must be followed up.

PUB004

Analysis of Cardiac Surgery Patients with AKI

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Background: To observe the incidence, clinical characteristics and risk factors of acute kidney injury (AKI) after cardiac surgery in our hospital, and provide evidence for better understanding and early intervention.

Methods: Retrospective analysis of patients with cardiac surgery from July 2017 to June 2018 in the First Affiliated Hospital of Xi'an Jiaotong University, screening patients with AKI and non-AKI recording their clinical data and analyzing risk factors.

Results: 1.575 patients were involved, AKI developed in 177 (31.78%) patients, whereas 4.17% of them received renal replacement therapy. Patients with AKI had significant higher mortality than patients without AKI (10.17%VS 0.5%, P<0.001). 2. The incidence of AKI stage 1, 2, and 3 was 19.13%(110/575), 5.22%(30/575), and 6.43%(37/575) respectively, and the mortality was 2.72%(3/110), 10%(3/30) and 32.43%(12/37). There was a statistically significant difference in mortality between three groups(P<0.001). 3. Multivariate logistic regression analysis showed that cardiopulmonary bypass (OR=1.436, 95%CI1.168-1.765), advanced age(OR=1.623,95%CI 1.311-2.009), previous cardiac surgery (OR=1.623,95%CI 1.311-2.009), high level of preoperative blood cystatinC (OR=1.623, 95%CI 1.311-2.009), perioperative infection (OR=1.436, 95%CI1.168-1.765) and intraoperative cardiopulmonary bypass time (OR=1.457, 95%CI1.077-1.971)were the independent risk factors of AKI after cardiac surgery. 4. The occurrence of AKI after cardiac surgery was mainly within 24 hours after surgery, accounting for 80.23% of AKI patients.

Conclusions: AKI can occur early after cardiac surgery. AKI has a significantly increased mortality compared with non-AKI patients. It should be alert to its risk factors and early intervention.

Funding: Government Support - Non-U.S.

PUB005

Kidney and Patient Outcomes After AKI in a Dialysis Centre in Sokolov from January 2017 to July 2018

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Background: The incidence of acute kidney injury (AKI) is increasing. Epidemiological studies can not reliably clarify this phenomenon. Since January 2017 to July 2018 were treated 66 patients with hemodialysis due to AKI on dialysis centre in Sokolov. In our lecture we want to show the effect AKI on their renal function and mortality. We also want to present our usual procedures for the treatment of AKI.

Methods: We evaluated dates of group of acutely dialysed patient on our dialysis centre by retrospektive analysis. Our attention was focused on mortality and irreversible decline in kidney function of patients overall and in relation to age, gender and pre-existing chronic kidney disease (CKD).

Results: Patients with acute kidney injury had a maintenance phase that typically lasted between 7 and 21 days. The duration was dependent upon the length and severity of the initial ischemic episode; whether or not recurrent ischemia occured or exposure to nephrotoxins was ongoing. An irreversible decline in kidney function after recovery was more likely in patients over age 65 years, in male sex and those with pre-existing chronic kidney disease and with heart failure. AKI during hospitalization is associated with high in-hospital mortality. In our patient group this mortality was up to 48 %.

Conclusions: From our short-term follow-up of a relatively small group of patients have been produced conclusions similar to those from multicentre reputable studies. Patients who develop AKI should be evaluated because of the risk of new onset or worsening of pre-existing CKD.

PUB006

Observational Analysis of Patients with Liver Cirrhosis Receiving Continuous Renal Replacement Therapy: A Single-Center Experience in Korea

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Background: To date, there was few data about liver cirrhosis (LC) patients undergoing continuous renal replacement therapy (CRRT) despite of a high mortality rate. The aims of this study are to observe the prognosis of patients with LC undergoing CRRT and identify factors related to prognosis.

Methods: A total of 155 LC patients who initiated CRRT in intensive care unit (ICU) were enrolled and finally analyzed 142 patients retrospectively excluding 13 patients with liver transplantation from January 2013 to December 2018.

Results: The enrolled patients were admitted to the ICU for the following reasons: infection (25.4%), other LC-related complications (23.2%), gastrointestinal (GI) bleeding (16.2%), acute kidney injury (AKI) (9.2%), cardiovascular events (5.6%) and others (20.4%). The most common cause of starting CRRT was AKI with shock (76.1%) mostly associated with GI bleeding (31.7%) and sepsis (26.1%). In-hospital mortality was 67.6% and the most common cause of death was other LC-related complications (36.5%). Compared with survivor group, use of vasopressor(%) and SOFA, APACHE II, MELD and MELD-Na were significantly higher in non-survivor group (81.3 vs.58.7, P=0.004; 13.86±4.05 vs. 10.57±3.92, p=0.000; 27.52±7.53 vs. 23.90±5.91, P=0.007; 33.68±7.98 vs. 29.85±7.14, P=0.006; 33.18±5.53 vs. 30.65±6.13, P=0.015) whereas 6hr urine output before CRRT is lower in non-survivor group (91.78±123.64 vs. 214.78±263.91, P=0.004). In laboratory values, white blood cell count and prothrombin time INR were significantly higher (15.20±11.91 vs. 11.94±6.52, P=0.037; 2.69±1.98 vs. 1.93±0.92, P=0.002) in non-survivors, whereas total protein and pH were significantly lower in non-survivors than survivors (5.23±1.09 vs. 5.73±1.36, P=0.021; 7.25±0.15 vs. 7.31±0.14, P=0.036). In multivariable analysis, SOFA score (odds ratio[OR] 1.200, 95% confidence interval[CI] 1.073-1.343, P =0.001), log 6hr urine output before CRRT (OR 0.809, 95% CI 0.6555-0.998, P = 0.048) and albumin (OR 0.435, 95% CI 0.231-0.818, P = 0.001) were associated with mortality.

Conclusions: In-hospital mortality of cirrhotic patients received CRRT was much higher than that of all patients received CRRT, which was previously reported as 53.7%. SOFA score, 6hr urine output before CRRT and albumin were associated with mortality.

PUB007

New Oral Anticoagulants and the Risk of Post-Contrast AKI After Computed Tomography with Intravenous Contrast Medium

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Background: Post-contrast acute kidney injury (PC-AKI) is a great concern in relation to worse renal outcome. However, the relationship between the use of new oral anticoagulants (NOACs) and the risk of PC-AKI remains unresolved.

Methods: A total of 2,158 patients who received prophylactic hydration with normal saline and N-acetylcysteine before and after computed tomography with intravenous contrast medium were reviewed. Among them, NOAC and warfarin were used in 34 and 65 patients, respectively. The risk of PC-AKI was compared between patients with and without these agents. Additionally, a propensity score matching was performed in a 1:4 block for variables such as age, sex, weight, contrast volume, blood pressure, comorbidities, and baseline serum creatinine. PC-AKI was defined as an increase in serum creatinine by ≥ 0.3 mg/dl or ≥ 1.5 times above baseline within 96 hours. The risk of end-stage renal disease or all-cause mortality was also evaluated.

Results: The events of PC-AKI occurred in 141 patients (6.5%). The risk of PC-AKI in the NOAC group was not higher than in the warfarin or non-agent group: odds ratios were 1.5 (0.72–2.96) and 2.0 (0.68–5.61), respectively. The risks of end-stage renal disease and mortality after contrast media use did not differ between the groups. These trends remained consistent irrespective of multivariable adjustment. When a propensity score matching was applied, the NOAC group had a similar risk of PC-AKI to the non-use group with an odds ratio of 1.2 (0.32–4.11).

Conclusions: The use of NOAC does not increase the risk of PC-AKI in patients who undergo computed tomography with contrast medium.

PUB008

Renal Damage Associated with Intravitreal Administration of Anti-VEGF Drugs

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Background: Vascular endothelial growth factor inhibitors (anti-VEGF) have been shown to be effective in the treatment of macular degeneration and diabetic macular edema. It is known that systemic administration of these drugs can produce adverse renal effects, such as decreased glomerular filtration rate (eFGR), proteinuria, hypertension or thrombotic microangiopathy. However, there is little information about it when the administration is intravitreal.

Methods: We analyzed the effect of anti-VEGF drugs with intravitreal administration on eFGR and proteinuria in diabetic patients, with and without chronic kidney disease (CKD), between 2017 and 2018.

Results: We included 40 diabetic patients (58% males) with a mean age of 74 ± 11.93 years, 92.7% being hypertensive and presenting 65.9% of the cases with CKD. 58.5% received bevazicumab, while the remaining 41.5% received ranibizumab. The evolution of eFGR and proteinuria are described in Table 1, where it stands out the increase in albuminuria and the decrease in eFGR in patients without previous CKD. Regarding the drug type, there were no differences but it is noteworthy that bevazicumab brushed the statistical significance (p 0.066) for the increase in albuminuria with respect to ranibizumab. On the other hand, within the CKD group, one patient presented two episodes of decompensation of heart failure after administration of an anti-VEGF drug, and two required the initiation of renal replacement therapy.

Conclusions: Based on the results of our cohort, we believe that it would be advisable to establish a closer monitoring in diabetic patients who are administered an intravitreal anti-VEGF drug, with determination of renal function as well as proteinuria to establish an early diagnosis of possible complications.

Table 1. Evolution of glomerular filtration rate (eFGR) and albuminuria, 6 months after administration of the anti-VEGF drug.

	No CKD (n = 14)	CKD (n =26)	Statistical significance (p)
Initial eFGR (*ml/min*) (X ± DS)	78.18 ± 11.05	34.17 ± 13.67	0.017
Initial albuminuria (*mg/g*) (X ± DS)	125.32 ± 228.88	739.34 ± 789.33	0.001
eFGR slope (%) (X ± DS)	8.31 ± 9.03	5.67 ± 23.82	0.025
Albuminuria (*mg/g*) (X ± DS)	1935.32 ± 6157.78	86.23 ± 215.90	0.07

PUB009

Comparison of Renal Function and Clinical Variables Between Patients With Sepsis And Cardiac Insufficiency

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Background: Heart failure (HF) is associated with large number of comorbidities that contribute to unfavorable outcomes, including acute renal failure (ARF). Sepsis is the leading cause of ARF in the critically ill patient.

Methods: We analyzed the medical records of 77 critically ill patients hospitalized at the Intensive Care Unit (ICU) of Hospital Israelita Albert Einstein. Patients hospitalized with decompensated HF and patients with a diagnosis of sepsis were compared. We compared demographic data, blood count parameters, renal function, liver enzymes, blood pressure and need for blood transfusion between HF and sepsis groups. KDIGO classification for acute renal injury. We performed t-test of student and chi-square to perform comparisons.

Results: Respiratory infection was the main cause of sepsis followed by gastrointestinal and bloodstream infections. KDIGO 2 was the most commonly found in all patients. Main finding was lower ejection fraction is associated with blood transfusion. Red Cell Distribution Width was higher in patients with decompensated HF when compared to septic patients (16.1 ± 2.1, 14.7 + -1.8, p = 0.02). Mean corpuscular

hemoglobin concentration values were higher in sepsis group (33.4±1.14, 32.3±1.19; p=0.04). Serum creatinine (3.9±0.8, 2.7±0.5, p=0.02), serum sodium concentration (140.5 ±5.8, 136.7±2.9; p=0.01), alkaline phosphatase (376.5±103.1, 120.5±18.5; p=0.03) and transaminases (AST [9328±4508, 159±98, p <0.001] and ALT [1967±888, 95.8±27.6; p=0.04] were higher in HF group, and diastolic pressure was lower in HF group (8.5±0,4; 9.6±0.3 mmHg; p=0.03). There were 9 patients in the sepsis group and 2 patients in HF group who required blood transfusion (p=0.01).

Conclusions: The results show that serum creatinine, Red Cell Distribution Width, serum sodium and liver enzymes were higher in severely ill patients with HF when compared to patients with sepsis.

PUB010

NephroCheck Meaning in Mild to Severe CKD: Single-Center Evaluation

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Background: The Nephrocheck (NC) is an emerging marker in the diagnosis of kidney damage, especially in ill critical patients. Chronic kidney disease (CKD) could be a confounding factor in its clinical use. The aim of our study is to assess NC performance in the prediction of acute kidney disease (AKI) or the need of continuous renal replacement therapy (CRRT) in CKD patients.

Methods: We followed a group of 692 patients hospitalized in intensive care between 6/2017 and 9/2018. Demographic parameters, comorbidities, BMI, SOFA score, NC, Procalcitonin, lactate and serum Creatinine (S-Cr) levels were collected. Mild to severe CKD was defined by an eGFR of 15 and 60 ml / min, while AKI was defined by an increase of S-Cr≥ 0.3 mg / dl in 48 hours, or by an increase of 50% values of basal S-Cr or diuresis ≤ 0.5 ml / kg in 6 hours. All continuous parametric variables were presented as mean and standard deviation, while continuous nonparametric variable were reported as median values with interquartile range (IQR). All categorical variables were reported as percentage. T Student, Kruskal Wallis, and Pearson's chi-square tests were used to compare continuous and categorical variables, as appropriate. Finally, we evaluated the AKI predictors and the predictor of CRRT need by logistic regression. All tests were performed with the SPSS version 20 package.

Results: 14% of patients had an eGFR <60 ml / min. CKD Patients presented a higher prevalence of AKI (61% vs 23% p <0.001) and higher need of CRRT (14.4% vs 2.6% p <0.001), if compared to patients with eGFR ≥60 ml / min. Moreover, in CKD patients NC value showed a good ability to predict CRRT needs (OR1.08 p = 0.018) but it failed to predict the development of AKI (OR 1.03 p = 0.31).

Conclusions: By our preliminary results, the levels of NC in mild to severe CKD patients seems able to predict the need for CRRT.

Funding: Private Foundation Support

PUB011

Incidence of AKI in Intensive Care Units in Brazil: a Cohort Study

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Background: Acute kidney injury (AKI) in Intensive Care Units (ICU) is common and it is a major problem to nephrologists and intensivists management. Little is known about associated factors and its incidence in low and middle-income countries, such as Brazil, where there is no reliable data available. Thus, the aim of this study was to investigate the incidence of AKI in ICU in Brazil.

Methods: A retrospective observational study in 3 ICUs from Brasília, Brazil. Data were collected in patients admitted in the ICUs from September 2017 to September 2018. Patients with end-stage renal disease on chronic dialysis were excluded. Demographic, clinical and laboratory data were recorded. Demographic data included age, gender, timing of hospital and ICU admission, comorbidity disease and primary diagnosis at ICU admission. Clinical data included Simplified Acute Physiology Score III, fluid balance status, the use of mechanical ventilator, vasopressor use and renal replacement therapy. Laboratory data included serum creatinine level. The primary outcome was AKI. The diagnosis of AKI was determined by KDIGO criteria. For the baseline serum creatinine, we used the most recent available serum creatinine before hospital admission. If the patients had no available data for baseline serum creatinine, then we estimated baseline serum creatinine using the lowest value between the serum creatinine at the time of hospital admission.

Results: This cohort study included 4453 patients from 3 ICUs, enrolled between September 2017 and September 2018. The average age of patients was 65.3 years and 50.0% were male. Based on the KDIGO criteria, 936 ICU patients (21.0%) were diagnosed with AKI during hospitalization. We had 275 patients (6.2%) who received RRT. Intermittent hemodialysis was the most common modality of RRT in our study (202 patients, 73.5%) followed by continuous RRT (34 patients, 12.4%).

Conclusions: This cohort study of the epidemiology of AKI in 3 ICUs in Brasília showed that AKI occurred in 936 patients (21.0%) during the time of ICU hospitalization.

Clinical data

	All Patients	Male	Female
Number of patients	4453 (100%)	2225 (50.0%)	2228 (50.0%)
AKI incidence	936 (21.0%)	472 (21.2%)	464 (20.8%)
Renal replacement therapy	275 (6.2%)	159 (7.1%)	116 (10.4%)
Mortality	474 (10.6%)	242 (10.9%)	232 (10.4%)

PUB012

A Brief Evaluation of Clinical Characteristics, Behavior, and Possible Causes of Acute Presentation of CKD of Undetermined Etiology (AIN) in Sri Lanka

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Background: Acute symptomatic presentation of CKDu has been reported from India, Nikaraguwa and Sri Lanka. Socio demographic features of patients with acute symptoms are almost identical to those already described CKDu. The response of the kidney in these cases could be due to toxic exposure precipitated by behavior in an adverse environment. Such injury could be directly causative or indirectly contributing to the development and progression of CKDu.

Methods: 49 suspected AIN patients were recruited from May 2017 to May 2019. Histological assessment confirmed varying degree of inflammation in the background of chronic changes.

Results: All were reported from CKDu endemic areas of the country.98% were symptomatic and presented, in the Maha season (From September to March in following year). Average temperature during that period was 28^{0}C with a peak of 35^{0}C during April to May. Relative humidity was 60% and maximum of 90% reported in May. Majority of patients were males. 86% were either farmers or engaged in heavy manual work. The retrospective study findings through an interviewer administered questionnaire have revealed that 74% of patients had evidence of dehydration prior to the acute symptoms. Among them 32% and 68% of patients had symptoms of mild and moderate dehydration respectively. 78% of patients had recent unprotected exposure to agrochemicals. Drinking water source of most patients were protected dug well (51%). Betel chewing (73%), alcohol consumption (55%) and smoking (45%)were common among patients.

Conclusions: Acute symptoms in CKDu is found predominantly in male farmers who had evidence of dehydration and exposure to agrochemicals under hot humid conditions.

Funding: Government Support - Non-U.S.

PUB013

Age as a Protective Factor from Mortality due to AKI

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Background: We aimed to study if **clinical features** can be used **to evaluate prognosis** in AKI.

Methods: This is a **retrospective, observational study**. **Inclusion Criteria**: Adult Pts, SCR increase >20%. **Cohort**: 2746 hospitalized patients (Mean age: 63; SD: 14; Sex: 71%males). **Studied parameters**: Age (using subgroups of <65vs≥65; <65vs65-85vs≥85), SCR (basal-with previous measurement- and initial-at the diagnosis of AKI-), acute/chronic health status (*Individual Severity Index* -ISI and *Karnofsky*-KPS), treatment type (IHD,CRRT or both) and in-hospital mortality.

Results: We performed a **multivariate logistic regression analysis of mortality risk due to AKI** including age, sex, initial and basal SCR, standardised ISI and KPS prognostic indexes and type of AKI treatment received. **AKI in the elderly** (≥65yo) was more functional (49%vs34%) and required less RRT (25%vs29%). Mean ISI was higher and mean KPS was lower in ≥65; however, we stratified them and found the elderly were less likely to present with high ISI and low KPS (ISI>0.5 18%vs19%; KPS≥60 92%vs89%). We found **RRT, high ISI and low KPS to be predictors of mortality**. **Mortality was lower in elderly patients** (overall mortality rate: 473pts-17%; <65: 257pts - 9%; ≥65: 216pts–8%). **Age's association with mortality was inverse** (OR=0.98, 95%CI=0.96-0.99); **being ≥65 and the association with lower mortality had a greater magnitude** (Table 1); the association with being 65-85 remained similar, but the ≥85 group-mortality association was not statistically significant.

Conclusions: Age is inversely associated with mortality due to AKI in our sample, this association being statistically significant when evaluated on its own, and also when comparing rates between <65yo and ≥65yo. **Age is not an adverse prognostic factor of in-hospital mortality due to AKI**. The association between being ≥65yo and mortality suggests **age is a protective factor from mortality due to AKI**.

Table 1

Mortality		OR	P value	95% CI	Mortality	OR	P value	95% CI
Age	≥65 y.o.	0.57	0.000	0.42-0.77	65-85 y.o.	0.57	0.000	0.42-0.78
					≥85 y.o.	0.56	0.130	0.27-1.18
Sex	Male	0.92	0.656	0.67-1.28	Male	0.92	0.656	0.67-1.28
Initial SCR		0.78	0.002	0.68-0.91	Initial SCR	0.78	0.002	0.68-0.91
Basal SCR		1.40	0.000	1.18-1.66	Basal SCR	1.40	0.000	1.18-1.66
ISI		2.45	0.000	2.01-2.98	ISI	2.45	0.000	2.01-2.98
KPS		0.61	0.000	0.53-0.70	KPS	0.61	0.000	0.53-0.70
RRT	IHD	4.70	0.000	2.55-8.65	IHD	4.70	0.000	2.55-8.65
	CRRT	2.35	0.000	1.56-3.52	CRRT	2.35	0.000	1.56-3.52
	Both	1.80	0.040	1.02-3.15	Both	1.80	0.041	1.02-3.15
_cons		0.12	0.000	0.08-0.17	_cons	0.12	0.000	0.08-0.17

PUB014

Dual Plasma Molecular Adsorption System Combined with Plasma Exchange and CVVH Improve Acute Liver Failure and Acute Renal Failure After Cardiopulmonary Bypass

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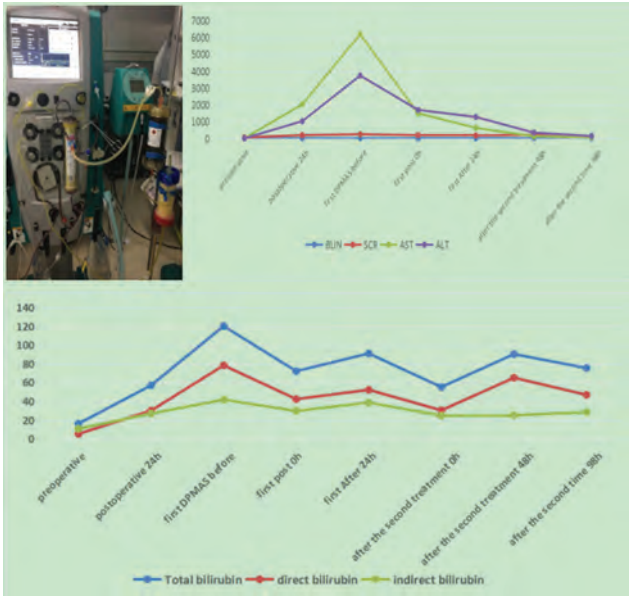
Background: Cardiovascular surgery patients use hypothermia cardiopulmonary bypass, may cause important organ ischemic injury, for example postoperative acute renal failure and acute liver failure, dual plasma molecular adsorption system (DPMAS) combined with plasma exchange, continuous CVVH can effectively improve liver function and renal function.

Methods: December 2018 - February 2019, Department of Cardiology, the First Affiliated Hospital of Xi'an Jiaotong University, underwent extracorporeal circulation, ascending aortic replacement, Bentall+ total arch replacement, elephant trunk or mitral valve replacement + tricuspid valvuloplasty, 3 patients, oliguria and AKI after 48 hours after operation was treated with CVVH and PE 1000 mL, followed by HA330-II tandem BS330 replacement plasma total volume 4500-5500 mL.

Results: One of the 3 patients underwent 3 times of PE+DPMAS, one case performed 2 times of PE+DPMAS, and one case performed PE+BS330. Total bilirubin: preoperative 16.26±6.91umol/L, first post 0h 72.23±13.95umol/L, first After 24h 91.1±11.18umol/L, after the second treatment 0h 55.35±8.41umol/L, after the third treatment 192h 86.3umol/L; creatinine: before operation 65±15.13umol/L, the first before 251.7±49.1umol / L, after the first treatment 0h 202±165.463umol/L, after the first treatment 24h 182.67±112.5umol/L, after the second treatment 0h 188±151.32umol /L, after the second time 98h 107.5±63.35umol/L

Conclusions: 24h after treatment compared with before treatment: total bilirubin decreased 24%, direct bilirubin decreased 33%, indirect bilirubin decreased 40%, AST decreased 89%, ALT decreased 66%, as DPMAS treatment mode can directly and effectively remove various kinds of patients Toxic substances, toxins, significantly shorten the course of disease.

Funding: Government Support - Non-U.S.



PUB015

Anuric AKI with Rapid Recovery Secondary to Vancomycin and Aminoglycoside Nephrotoxicity

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Introduction: The increasing use of higher vancomycin doses has been associated with an increased incidence of vancomycin induced AKI, although the precise mechanisms remain unclear. We report a rare case of anuric AKI secondary to concomitant use of high doses of vancomycin and an aminoglycoside, which resolved completely after discontinuing these antibiotics and serial dialysis sessions using high flux membranes.

Case Description: A 22 year old woman with cystic fibrosis-associated bronchiectasis developed fever, dyspnea and a productive cough, consistent with a cystic fibrosis exacerbation. Her baseline kidney function was normal (serum creatinine 0.8 mg/dl). She was started on empiric antibiotics, including vancomycin 1 gm IV TID and tobramycin 180 mg IV daily. One week later she presented to the emergency department with a 5-day history of lower extremity edema, anorexia, profound nausea, and anuria (80 ml daily). She was afebrile, and her vital signs were stable. Pertinent labs included: serum creatinine of 12.6 mg/dl, random vancomycin level 200 mcg/ml, random tobramycin level 18 mcg/ml. Urinalysis revealed muddy-brown granular casts suggestive of ATN. Renal ultrasound was unremarkable. She was suspected as having anuric AKI due to vancomycin and gentamicin toxicity. The antibiotics were stopped, and she underwent 7 sessions of intermittent hemodialysis using high-flux membranes over the ensuing 2 weeks, with serum vancomycin and tobramycin reduced into the therapeutic range. Her urine output improved dramatically, and her renal function returned to normal.

Discussion: Vancomycin nephrotoxicity is on the rise, coinciding with the increase in recommended therapeutic vancomycin trough levels. The rapid rise in serum creatinine levels reflects both the AKI itself, as well as the competition of vancomycin and creatinine secretion by the same organic cation transporter in the proximal tubule. Synergistic use of vancomycin with an aminoglycoside may lead to worsening nephrotoxicity and can be mitigated by monitoring their plasma levels and subsequent withdrawal as necessary. Temporary hemodialysis using high flux membranes may hasten renal recovery by rapidly lowering the serum antibiotic levels.

PUB016

Relationship Between the Presence of Infectious Disease and Clinical Outcomes of Patients with Cardiorenal Syndrome Type 1

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Background: Cardiorenal Syndrome type 1 (CRS-1) can be triggered by an infection. The pathophysiological basis is vascular congestion, which is why it has been treated with different strategies of diuretics, but in the presence of infection, where the inflammatory, neurohormonal and hemodynamic effects can compromise the efficacy of the diuretic therapy and potentially worsen clinical evolution. Here we compare the clinical evolution during the hospitalization of CRS-1 patients with and without infection.

Methods: This is a retrospective cohort study conducted in the Hospital Civil of Guadalajara "Fray Antonio Alcalde", from January 2015 to September 2018. Conducted in CRS-1 patients, we showed the clinical evolution and treatment strategies analyzed according to the presence or absence of infection. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Results: We identified 63 patients classified as having CRS-1, 28 (44.4%) were classified as having an infectious disease, the mean age in the group of infection was 62 years (±14.6) and 58 (±12.4) in no infection group. There were no statistically significant differences between the clinical outcomes of both groups, we found that in the infection group, the median length of hospital stay was 8 days and 7 days in the no infection group (p=0.065). Three patients (10.7%) of the group with infection received renal replacement therapy and 1 (2.9%) of the group without infection (p=0.315). In the group with infection 2 patients died (7.1%), while none in the uninfected group (p=0.194). sCr values trend to diminish in a similar manner trough the both groups. Serum **sodium** trend to increase thought the hospitalization but there was no significant difference between groups. During hospitalization we found that all patients received furosemide at least the first days of hospital stay, in addition the strategy of diuretics chosen for the treatment was similar between groups

Conclusions: Here we show that the clinical evolution of patients with CRS-1 is similar in the presence or absence of infection. We anticipate that this study may be a reason to expand knowledge in patients with CRS-1 and the presence of infection

PUB017

Before Crystalluria: High-Dose Amoxicillin Infusion Leads to Intracellular Amoxicillin-Induced Osmotic Nephrosis

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Background: Amoxicillin (AMX) is one of the most commonly prescribed antibiotics. Its renal toxicity is poorly described. The presence of urinary AMX crystals during acute kidney injury (AKI) has been proposed as a mechanism of intra-tubular precipitation. To date, deposition of AMX crystals within the kidney has not been reported.

Methods: We describe two cases of AMX-associated AKI and analysis of their renal biopsies using Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). We then injected escalating doses of AMX (200-3000mg/kg/day intraperitoneally) for 2 days into rats and for up to 9 days in mice. Crystallization, renal function and histology of rodents were analyzed at sacrifice.

Results: Two patients of 58 and 68 years old were hospitalized for bacterial meningitis and developed ARF following high-dose AMX injection. They received 12g/day and 25g/day intravenously respectively. Optical microscopy analysis of their renal biopsies revealed in both cases severe tubulopathy with unexplained osmotic nephrosis(ON) lesions (Fig 1A). In one case, the FTIR analysis combined with the SEM showed an intracellular-tubular AMX deposit (Fig. 1B and C). Crystalluria was not observed in these two cases. Experimentally, injection of high dose AMX in rodents resulted in ARF with acute tubular necrosis and conspicuous ON lesions. No intraparenchymal AMX crystals or crystalluria were observed.

Conclusions: Our study suggests that in both humans and rodents, high dose AMX infusion leads to a yet unsuspected tubular toxicity. Renal lesions are featured by tubular ON surrounding intracellular-tubular deposits of AMX.

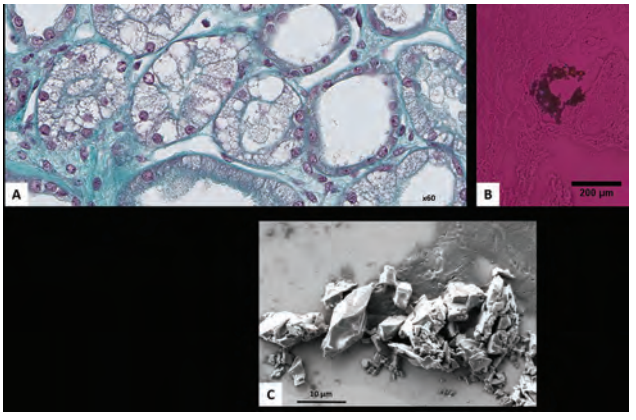

Figure 1. Histological features of AMX-associated nephropathy. A. Osmotic nephrosis and acute tubular necrosis. Masson's Trichrome. Magnification x60. B. Intra-tubular deposition of AMX. Magnification x10. C. Intra-tubular deposition of AMX under a scanning electron microscope. Magnification x6000.

PUB018

Granulomatous Interstitial Nephritis (GIN) in a Patient with B-Cell Lymphoma

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Introduction: GIN is a rare disease, seen in less than 1 % of renal biopsies. The commonest causes are infections, drug reactions, and sarcoidosis. We present a case of GIN in an elderly patient who presented with acute kidney injury (AKI) in the setting of recurrent B-cell lymphoma (BCL).

Case Description: A 67-year old Caucasian gentleman with history of large BCL in complete remission (2009), admitted with a relapse in November 2018, with weight loss, high grade fever of unknown cause and non-oliguric AKI requiring hemodialysis (HD). Physical examination showed no pertinent findings. Past Medical history included hypertension, with no prior history of kidney disease, liver disease or diabetes. Imaging showed bilateral enlarged kidneys (14 cm each). PET scan showed increased activity in both kidneys, liver and cervical lymph nodes, consistent with relapse of BCL. No mediastinal or abdominopelvic lymphadenopathy were noted. MRI of brain and bone marrow biopsy were unremarkable. Patient received multiple courses of antipyretics, antibiotics (Zosyn, Vancomycin) and 3 rounds of salvage chemotherapy with R-GCP followed by DHAC, with no significant improvement in renal function

Discussion: Labs revealed anemia (Hb 10.4) and elevated serum creatinine (Cr) 5.8 mg/dL (Baseline Cr 1.0-1.1). No other electrolyte or liver function tests abnormality were noted. Urine exam showed 2 + protein, > 5 RBC and 0.9 g proteinuria, with no RBC casts or abnormal WBCs. Autoimmune profile, complement levels and infectious profile, were all unremarkable. Serum ACE level was 26 U/L (ref 8-53). Percutaneous renal biopsy revealed diffuse GIN with CD3 positive (+) T cells and macrophages, no CD 20 + B cells, providing evidence against lymphomatous infiltration. Special stains for fungi and AFB were negative. The patient was subsequently started on prednisone 60 mg/day and received HD for 2 months. Kidney function subsequently improved, HD was stopped, and prednisone was tapered off after 8 weeks of use. Following month, patient underwent autologous stem cell transplant with most recent Cr 1.6 mg/dl and no proteinuria. GIN in this case was related to antibiotics used for fever of unknown origin. Although uncommon, GIN should be considered in the differential diagnosis of AKI in the setting of lymphoma with renal enlargement. Timely diagnosis and optimal management ensure a good outcome.

PUB019

Multiple Myeloma with the Onset of Ankylosis and Arthralgia and Subsequent Hypercalcinemia and Acute Renal Injury: A Case Report

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Introduction: Ankylosis and arthralgia have rarely been reported as initial manifestations in multiple myeloma (MM).

Case Description: Here we reported a male patient with the onset of ankylosis and arthralgia, who had been seeing rheumatologists for one month without any conclusive diagnosis until admission due to hypercalcinemia and acute renal injury. MM was confirmed by bone marrow aspirate. Renal impairment due to cast nephropathy and nephrocalcinosis was confirmed by renal biopsy. He reported improvement of ankylosis and arthralgia in both knees after plasma exchange and hemodialysis and was then referred to Hematology Division, where he received three courses of dexamethasone and bortezomib chemotherapy. Renal function did not recover completely.

Discussion: Ankylosis and arthralgia are rare in MM and the mechanisms are not clear. Further immunological blotting might help to elucidate the pathogenesis.

PUB020

Clinical Profile and Outcome of Dialysis-Requiring AKI Among Elderly Patients in St. Luke's Medical Center-Quezon City from January 2014 to January 2019

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Background: The incidence rate of AKI is highest in the elderly. It is related to an increased rate of mortality, morbidity, and hospitalization, with the elderly population at high risk of developing dialysis-requiring AKI. It has been established that the temporal incidence of dialysis-requiring AKI and mortality has not yet been recently characterized, hence this study aims to determine the clinical profile and outcome of dialysis-requiring AKI among this population.

Methods: This is a descriptive, non-observational, retrospective, case series study. It includes elderly patients 65 years old and above, admitted at the center from January 2014 to January 2019 who were diagnosed to have dialysis-requiring AKI and underwent hemodialysis.

Results: Amon the 193 eligible patients, mean age was 77.08 ± 8.31, 55.44% males and 44.56% females. Most common co-morbidities identified were hypertension and diabetes. The most common encountered complication during hemodialysis was hypotension. The 30-day mortality rate is 61.66% and average length of hospital stay was 18 days. The average days from the day of hospitalization to initiation of hemodialysis was an 3 days. There is a significant change from baseline creatinine levels and eGFR to its measurements upon renal recovery.

Conclusions: Diagnosis of dialysis-requiring AKI in the elderly is associated with a poor outcome. It is related to an increased in-hospital stay. The most common complication observed during hemodialysis is still hypotension. Renal recovery can be expected when eGFR returns to baseline levels. There is a significant change from baseline creatinine levels and eGFR to its measurements upon renal recovery.

Table 1. Clinical profile of elderly patients with dialysis-requiring AKI (n=193)

	Frequency (%); Mean ± SD; Median (IQR)
Age	77.08 ± 8.31
Sex	
Male	107 (55.44)
Female	86 (44.56)
Co-morbidities	
Hypertension	147 (76.17)
Diabetes mellitus	102 (52.85)
Congestive Heart Failure	15 (7.77)
Chronic Obstructive Pulmonary Disease	21 (10.88)
Coronary Artery Disease	32 (16.58)
Chronic Kidney Disease	30 (15.54)
Cerebrovascular Disease	16 (8.29)
Malignancy	46 (23.83)
Others*	49 (25.39)
Complications	
Hypotension	106 (54.92)
Arrhythmia	27 (13.99)
Other complications‡	17 (8.81)
Status after 30 days of diagnosis of dialysis-requiring AKI	
Expired	119 (61.66)
Alive	74 (38.34)
With renal recovery	58 (30.05)
Expired prior to observing renal recovery	16 (8.30)
Length of hospital stay in days	18 (9 to 32)
Days from hospitalization to initiation of hemodialysis	3 (1 to 10)
Days on hemodialysis prior to renal recovery (n=58)	9 (4 to 20)

* Includes liver cirrhosis, thalassemia, cystic fibrosis, Parkinson's Disease, Alzhemier's, amyotrophic lateral sclerosis, rheumatic heart disease, abdominal aortic aneurysm, peripheral arterial occlusive disease, myelofibrosis, mental retardation, systemic lupus erythematosus, myelodysplastic syndrome, and hypothyroidism.
‡ Includes desaturation, bradycardia, BP elevation, seizure, dyspnea and cardiopulmonary arrest.

Table 2. Comparison of Creatinine and eGFR from baseline, diagnosis of dialysis-requiring AKI, and renal recovery

	Baseline	On diagnosis of dialysis requiring AKI	On renal recovery	P-value
	Median (IQR)			
Creatinine (mg/dL)	2.19 (1.26 to 4.28)	3.43 (2.37 to 5.04)	2.33 (1.65 to 3.09)	<0.001
eGFR (mL/min/1.73 m^2)	26 (11 to 46)	15 (9 to 22)	26 (18 to 38)	<0.001

PUB021

Complications Associated with CRRT in a Community Hospital

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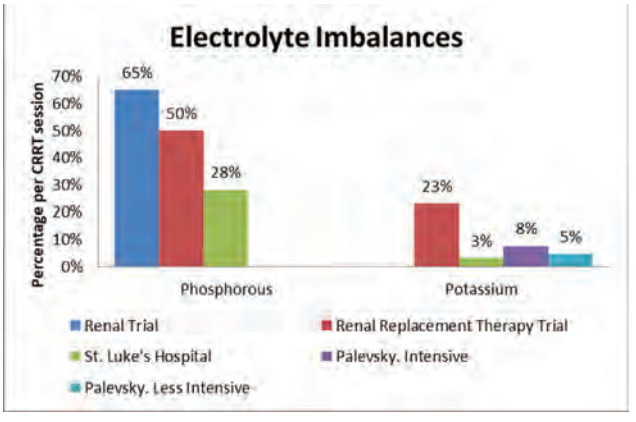
Background: Continuous renal replacement therapy (CRRT) is used for the treatment of critically ill patients with acute kidney injury, who are unable to tolerate intermittent hemodialysis due to hemodynamic instability. Complications of CRRT are the result of vascular access, bleeding, and electrolyte imbalances. In February 2016, CRRT became available in our community hospital in Chesterfield, Missouri. We investigated our initial complications associated with CRRT in our hospital and compared to complication rates reported in the literature.

Methods: We conducted a retrospective study of adult patients initiated on CRRT at St. Luke's Hospital in Chesterfield, MO between February 2016 and May 2018. The data was collected via Cerner Powerchart EMR.

Results: Among 52 qualified patients, there were a total of 162 dialysis sessions. Complications as number per dialysis session were as follows: 0/162 infections, 69/162 electrolyte imbalances, 3/162 arrhythmias, 7/162 bleeding, and 13/162 access problems. Out of the 69 electrolyte imbalances, 46 sessions had hypophosphatemia and 5 sessions had hypokalemia.

Conclusions: In a community hospital setting, within our first two years of implementing CRRT, we saw expected electrolyte imbalances in our patients (hypophosphatemia and hypokalemia); however, our incidence was less than in the literature. Infection, arrhythmias, and access related complications were also comparable to or lower than those in the literature. We attribute this to a common EMR orderset, limited CRRT utlization to our medical and surgical ICUs, and initiation of CRRT limited to nephrology.



PUB022

AKI due to Anticoagulant Related Nephropathy (ARN) and Thin Basement Membrane Disease (TBMD): Old Entities with a New Twist

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Introduction: ARN is a significant but under recognized complication of anticoagulation that is also associated with increased renal morbidity and all-cause mortality. It is defined as AKI without any other obvious etiology in the setting of INR>3, in patients on warfarin. TBMD is a relatively common cause of micro and less often macroscopic hematuria in adults.

Case Description: 66 year old male with hypertension, rheumatic heart disease with mechanical aortic and mitral valve replacement in 1995, on chronic warfarin therapy was admitted with AKI with serum creatinine 4.1mg/dL (baseline 1.3 mg/dL a month ago), anemia and brown colored urine for a week. His INR on admission was 2.8. All other pertinent history was negative. Physical exam and renal ultrasound were unremarkable. Urinalysis showed dysmorphic red blood cells. Work up including ANA, anti-GBM, HIV, Hepatitis panel, ANCA, Complements, SPEP, UPEP were negative. His warfarin was held and he was started on heparin infusion for renal biopsy. Renal biopsy showed acute tubular injury with recent and remote intratubular hemorrhages mostly in distal tubule. The intratubular granules stained positive for Gomori's stain, all consistent with ARN. Electron microscopy showed TBMD. With limited data on alternative anticoagulation options for mechanical heart valves, warfarin was restated at lower therapeutic goal, with subsequent improvement of renal function.

Discussion: ARN is known to most likely develop within 6-8 weeks of initiation of therapy, in the background of over anticoagulation. TBMD was most likely an additional risk factor that made our patient vulnerable to ARN. Although our patient was within therapeutic INR goal for his disease, it was higher than 3 few times in past. The dilemma is that although he had lived with these conditions, what triggered him to have an event now? We postulate that there may be a plausible third trigger that unmasked his underlying pathology. The other unsolved puzzle is management of patients who need warfarin and traditionally warrant higher INR goal. Our case is therefore unique with respect to timelines of presentation, and ARN diagnosis with no clear evidence of over anticoagulation for his clinical condition.

PUB023

Association of Continuous Renal Replacement Therapy Duration and the Outcome of Patients in Intensive Care Units

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Background: Acute kidney injury (AKI) is a common clinical problem and one of causes of high mortality rate in Intensive Care Units(ICU). Many severe AKI patients have received renal replacement therapy. Among them with hemodynamic instability need to the continuous renal replacement therapy (CRRT). Some patients keep the CRRT longer duration, on the other hands, others keep it shorter. We studied if the difference in these periods affected the survival rate.

Methods: Retrospectively, we designed this study consist of adult patients who received CRRT were in ICU of our hospital from January 1, 2016 to December 31, 2016. They were divided two groups; less than 2 days (L group) and more than 2 days (M group). The clinical manifestation associated with each groups were analyzed. The value was expressed by median (range).

Results: All patients who received CRRT in the intensive care units(ICU) of our hospital from January 1, 2016 through December 31, 2016 were initially screened. (n=186). We excluded patients under 18 years, End stage renal disease, not agreed to access the data and 6-hour urine less than 300cc. We excluded 77 patients according to exclusion criteria. A total of 102 patients were included in the analyses. 41 patients in L group and 68 patients in M group. The median age of patients was 72(36-89) year-old in L group and 68.5(18-90) year-old in M group. Septic shock was the main cause of CRRT in both group. [26(63.40%) vs. 53(77.90%), P=0.123]. 28-day mortality rate was higher in L group than M group. [36(87.80%) vs. 44(64.70%), P=0.013]. Also lactic acid level was higher in L group than M group [9.4mmol/L(1.63-38.53) vs. 3.4mmol/L(0.7-18.72), p=0.001]. Other laboratory results and baseline disease were similar except for the presence of chronic liver disease(CLD). Interestingly, underline CLD was much higher in L group than M group. [17 (68.00%) vs. 8 (32.00%), p=0.001]

Conclusions: CRRT duration which AKI patients received in ICU was affected the mortality rate. Especially, on this study, patients with chronic liver disease have shorter dialysis durations and higher mortality rate when CRRT was performed due to AKI.

PUB024

Effects of 5-HT3A Antiemetic Drugs on Cisplatin-Induced Nephrotoxicity

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Background: Cisplatin is an important component of chemotherapy for patients with lung, head and neck, and cervical cancer that induces cellular apoptosis by forming intrastrand DNA crosslinks that prevent DNA transcription. While desirable for malignant cells, cisplatin cytotoxicity in renal cortex leads to AKI. Tubular epithelial cell exposure to cisplatin is determined by its transport via organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1). MATE1 is inhibited by 5-hydroxytryptamine-3 receptor antagonists (5-HT3 RA) commonly used as antiemetics in oncology. Our data indicates that ondansetron use in mice results in greater GFR loss relative to other 5-HT3 RA. We sought to examine the association of 5-HT3 RA use in patients receiving cisplatin with AKI.

Methods: In retrospective chart review, we identified 7,094 patients who received cisplatin, of which 3,997 (56.3%) were treated with a 5-HT3 RA that included either granisetron, ondansetron or palonosetron. Fisher's exact test tested for univariable associations between categorical variables. Multivariable associations with AKI were analyzed using logistic regression.

Results: Ondansetron accounted for 27% of overall 5-HT3 RA use. AKI was observed in 1,737 or 24.5% of patients receiving cisplatin. 5-HT3 RA use was independently associated with lower risk of AKI (OR 0.38; 95% CI, 0.23-0.65, p< 0.001). Other significant multivariable associations with AKI are found in Table.

Conclusions: Protective effect of 5-HT3 RA use in humans, contrary to our animal model, is likely accounted for by lesser inhibition of MATE1 by the most commonly used palonosetron. Increased risk of cisplatin-induced tubular toxicity in this scenario is likely further offset by the lower risk of pre-renal AKI from vomiting and anorexia, incited by cisplatin. Effects of the individual 5-HT3 RA on renal outcomes are the subject of active investigation.

	OR (95% CI)	p-value
Age	1.02 (1.01 - 1.02)	<.001
Male gender	1.46 (1.29 - 1.66)	<.001
Black race	3 (2.19 - 4.09)	<.001
White race	1.72 (1.34 - 2.2)	<.001
5-HT3 RA use	0.38 (0.23 - 0.65)	<.001

PUB025

Bioimpedance in AKI: Corporal and Cardiothoracic Role in Evaluating Risk of Mortality and Renal Replacement Therapy Requirement

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Background: Evaluate application of Bioimpedance in AKI prognosis.

Methods: Observational. Creatinine increment >20%. Corporal bioimpedance (BIAC) study: Cohort of 205 patients (médium 67, male 73 %). Evaluate bioelectrical parameter:s phase angle (PA), Extracellular/intracellular water ratio (ECW/ICW), muscle mass (MM) and celular mass idex (CMI), and clinical parameters and prognostic index (individual severity index –ISI-), analytical renal, inflammatory and nutritional (days without optimal caloric intake 0, 1-3, 4-7 or > 7) and chronic health index (Karnofsky –K-, and ECOG). Cardiothoracic bioimpedance (BIAHEM) study: Cohort of 90 patients (médium 71 years, male 76.9%). Evaluate impedance (Z), cardiac output (CO), ventricular work index (VWI), systolic volumen (SV) and systemic vascular resistance index (SVRI) and Thoracic fluid volumen (TFV) Thoracic fluid volumen index (TFVI), and systolic volumen (SV) with clinical index prognosis (severity individual index –ISI), and metabolic, inflammatory and volemic parameters.

Results: BIAC study ISI was associated with PA (r=-0.244, p=0.003) ECW/ICW ratio (r=0.239, p=0.001). Peak CPR (c-reactive protein) with PA (r=-0.223, p =0.007) ECW/ICW (r=0.247, p <0.001), PA with lower Albumin (r=0.447, p<0.001). ECOG with PA (r=-0.369, p <0.001) and ECW/ICW (r=0.356, p<0.001). K with PA (r=-0.419, p<0.001) ECW/ICW (r=-0.356, p<0.001). MM with inspiratory volume (r=0.285, p=0.097). CMI was associated with inspiratory volume (r=0.338, p=0.098). Insufficient caloric intake with CMI (p=0.013) ECW/ICW (p<0.001) Exitus 8.9%. PA was independently associated with mortality risk (OR 0.391, p=0.039). ROC area 0.775, p=0.001,. PA lower than 3.8 indicates higher exitus risk. BIAHEM study: ISI was associated with SVRI (r=-0.249, p =0.020)-BNF (brain natriuretic factor) with CO (r=-0.292, p=0.013), VWI (r=-0.294, p=0.012), SVRI (r=0.337, p=0.004) SV (r=-0.333, p=0.004). Calcium with CO (r=-0.340, p=0.053) VWI (r=-0.351, p =0.042), Z with K (r=0.373, p=0.003) and ECOG (r=-0.260, p=0.043). TFV associated with respiratory failure (p=0.038) and SVRI with cardiovascular failure (p=0.037). Exitus 10.3%.

Conclusions: We can evaluate AKI prognosis with bioimpedance. Is associated with volemic and hemodynamic status evaluate with bioimpedance. We can use these to make a triage in AKI patient.

PUB026

Incidence of Contrast-Induced Nephropathy in Intermediate- to Very High-Risk Groups from a Single Center

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Background: Contrast induced nephropathy (CIN) is defined as an elevation of serum creatinine (Scr) of more than 25% or ≥0.5 mg/dl from baseline within 48-72 hours in the absence of alternate causes of acute kidney injury. Incidence of CIN in patients has been heterogeneously reported to be as low as 2% and as high as 50% depending upon the setting and population under scrutiny. It is an area of active clinical research and much controversy. There is no placebo controlled randomized controlled trials that establishes causation in CIN. Recently many studies have mushroomed that suggested that the risk of CIN is perhaps overestimated. Considering the international debate and the local scenario, we conducted this study to estimate the incidence of CIN in our center.

Methods: This prospective study was conducted between January and December 2018. It was approved by the ethical review committee and informed consent was taken from all patients. The patients in nephrology service with contrast media exposure and having Crcl between 20ml/min/m^2 and 60ml/min/m^2 were included in the study. As per CIN risk scoring system, only patients with intermediate to very high risk scores for CIN were included. Baseline creatinine was measured and post exposure RFTs were recorded at 24, 48 and 72 hours.

Results: Age of the patients ranged between 24 and 75 years (Mean 57 years) and 66% were of them were males. 80% of the patients underwent coronary angiography and 20% received contrast for computerized tomographic scans. Patients were equally distributed in the categories of intermediate, high and very high risk for CIN. 80% were hydrated per protocol prior to contrast exposure. Mean Scr of the cohort at baseline and after 72 hours were 2.12mg/dl and 2.10mg/dl respectively. Only 1 patient out of 30 patients, from the very high risk group, developed CIN.

Conclusions: The incidence of CIN in our small but high risk cohort was 3.3%. Among subgroup of the coronary artery disease patients that underwent angiography, majority benefited from life-saving interventions that were initially withheld for the overhyped fear of CIN. National level studies should document the local incidence so that informed decisions could be formulated tilting the risk benefit ratio of contrast exposure maximally in favor of the patients.

PUB027

Can a Patient Develop Rapidly Progressive End-Stage Pyelonephritis?

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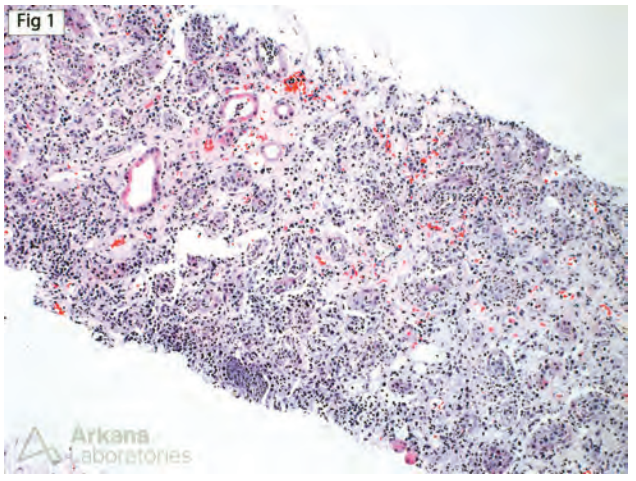
Introduction: Certain diagnoses can be inferred based on a kidney biopsy specimen alone. Pyelonephritis is one of these diagnoses, with a neutrophil-rich interstitial infiltrate, neutrophilic rimming of tubules with nutrophilic tubulitis, and neutrophilic casts. These findings are in contrast to acute interstitial nephritis which would demonstrate lymphocyte-rich inflammation. While AIN can progress rapidly and lead to dialysis-dependence, often improving with high dose steroids, acute pyelonephritis has not been described to lead to sudden onset renal failure with long-term dialysis dependence.

Case Description: A 57 year old male with history of chronic lymphaedema presented with a creatinine of 22 from baseline 0.8 several years prior. There was no evidence for UTI or obstruction. Urine studies revealed trace blood, moderate LE, 11 WBC and 2 RBC per HPF, with spot urine P/Cr of 4.5 grams/gram. Serologies and renal ultrasound were unrevealing except for large kidneys. Hemodialysis was initiated the day after admission for uremia and kidney biopsy revealed findings consistent with acute pyelonephritis. EM findings of patchy foot-process effacement suggested a possible unsampled focal segmental glomerulosclerosis. The patient remained dialysis-dependent despite a course of high-dose steroids, and rebiopsy was recommended but refused by the patient.

Discussion: Clinical context is crucial for interpretation of a pathology specimen but certain conditions such as acute pyelonephritis demonstrate pathognomonic findings. In this case, the biopsy findings were unexpected, especially the progression to presumed end-stage renal disease. When faced with diagnostic dilemmas, the clinician must consider whether alternative treatments exist to reverse the kidney damage, and alternative diagnoses must also be considered, with possible benefit to repeat kidney biopsy.



PUB028

Atg5 Overexpression in Proangiogenic Cells Significantly Improves Cell-Mediated AKI Protection

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Background: Acute Kidney Injury (AKI) significantly worsens the prognosis of hospitalized patients. Cell-based strategies have been established as reliable option for improving AKI outcomes in experimental AKI. Own studies performed in recent years utilized Proangiogenic Cells (PACs). Autophagy (AP) is commonly regarded as process of endogenous self-defense. The AP cascade, which may be stimulated by either substrate deprivation or certain exogenous / endogenous stressors, involves the activation of numerous proteins, the so-called Autophagy-related proteins (Atg proteins). Among these, Atg5 has been suggested to play a key role in augmenting AP. The current study evaluated whether selective Atg5 activation in syngeneic murine PACs may result in improved cell-mediated AKI protection.

Methods: Cultured murine PACs were selectively transfected for Atg5. Successful transfection was verified by detecting red fluorescing cells. AKI was induced in male C57/Bl6N mice (8-12 weeks) by bilateral renal ischemia (IRI - 40 minutes). Transfected cells were i.v. injected post-ischemia. Mice were analyzed 48 hours and 6 weeks later.

Results: IRI induced significant kidney excretory dysfunction as reflected by higher serum cystatin C levels (48 hours and 6 weeks). Cell administration (either native or after transfection) did not improve AKI outcomes at 48 hours. At 6 weeks, injection of native cells resulted in lower serum cystatin C, this effect was even more pronounced if transcfected cells were applied.

Conclusions: Together, our data show that selective Atg5 overexpression in murine PACs substantially augments cell-mediated AKI protection in the long-term. Thus, a new strategy for improving AKI protective effects of PACs has been identified.

PUB029

Validation of Transcutaneous Fluorescence for Monitoring Gut Permeability

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Background: At the gastrointestinal mucosa billions of microbes are in close contact with the host immune system. The maintenance of this barrier is vital for health and its compromise has been implicated in a variety of acute and chronic illnesses, including sepsis and chronic kidney disease. We have previously used transcutaneous fluorescence to measure the glomerular filtration rate using a fluorescent, inert i.v.-injected marker. We hypothesize that the transcutaneous fluorescence method can be adapted to measure intestinal permeability following oral gavage of a suitable marker.

Methods: Intestinal permeability was studied in the context of sepsis caused by the cecal ligation and puncture (CLP) surgical procedure. We compared 40 kDa FITC-Dextran and FITC-Ficoll as fluorescent markers. They were administered by oral gavage 3 hours prior to CLP to enable loading of the intestines. A transcutaneous fluorometer was attached to the skin (covering the spine) of each mouse, enabling the appearance of the fluorophore in the circulation to be detected. The stability of the fluorophores was evaluated in the blood and urine using ultrafiltration.

Results: Using the FITC-Dextran, post-mortem examination revealed significant fluorescence in the bladder despite the 40 kDa size of the parent molecule. After ultrafiltration of the urine, the fluorescence was able to pass through a 10 kDa filter indicating degradation, probably in the GI tract. In contrast, fluorescence from the injected FITC-Ficoll was not found in the urine. Following CLP, an increase in transcutaneous fluorescence was detected at ~3 hours that was absent in the sham.

Conclusions: This technique is a viable new approach for the measurement of intestinal permeability that avoids the need for blood collection. FITC-Dextran is degraded and can be filtered by the kidney. Using FITC-Ficoll should prevent underestimation of gut permeability due to glomerular filtration of fluorophore. Consistent with hemodynamic abnormalities and renal dysfunction, intestinal permeability can be detected ~3 hours after the induction of sepsis. We propose that gut permeability should be added to conventional multi-organ failure scores.

Funding: NIDDK Support

PUB030

Biomarker-Based Differentiation of Hemodynamic and Intrinsic AKI Agrees with Clinical Adjudication by Nephrologists

Sherry Mansour,[1] Nadeen J. Khoury,[5] Ravi Kodali,[2] Sarthak Virmani,[1] Isaac E. Hall,[4] Peter P. Reese,[6] Francis P. Wilson,[1] Dennis G. Moledina,[1] Jason H. Greenberg,[2] Yu Yamamoto,[2] Yaqi Jia,[3] Heather Thiessen Philbrook,[3] Chirag R. Parikh.[3] DDS consortium *[1]Yale School of Medicine, New Haven, CT; [2]Yale University, Woodbridge, CT; [3]Johns Hopkins University, Newton, MA; [4]University of Utah, Salt Lake City, UT; [5]Henry Ford Health, Detroit, MI; [6]University of Pennsylvania, Ardmore, PA.*

Background: We aimed to determine if clinical adjudication by nephrologists agrees with the biomarker-based differentiation of AKI by urine biomarkers.

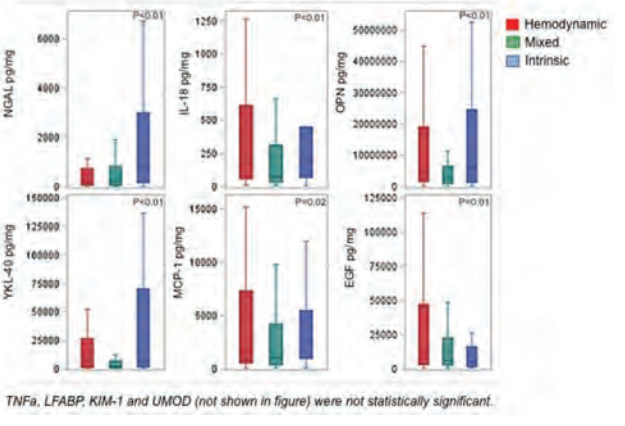
Methods: We abstracted and created graphical trends of longitudinal variables from 430 deceased donors charts. AKI was defined as a 0.3 mg/dL or 50% increase from the lowest recorded creatinine value. Three nephrologists independently reviewed AKI cases to adjudicate into hemodynamic, intrinsic or mixed subtypes; final diagnosis was determined by majority adjudication. If all three nephrologists disagreed, the phenotype was designated as mixed. We measured urine biomarkers at organ procurement and evaluated differences among AKI subtypes. Our secondary analysis assessed the association between subtypes and recipient delayed graft function (DGF) and 1-year eGFR.

Results: Of 430 donors, 68% had AKI; 36% were adjudicated as hemodynamic, 29% intrinsic, and 35% mixed. Stages 2 and 3 AKI, central venous pressure (CVP), and ventilator oxygen requirement were significantly higher in intrinsic AKI. There were no differences in vasopressor use or fluid balance. Biomarkers were significantly different in intrinsic AKI compared to other subtypes (**Figure)**. In secondary analysis, intrinsic AKI was independently associated with higher odds of DGF [aOR (95%CI); 2.52 (1.30, 4.88)] and lower 1-year eGFR [B coefficient (95% CI); -8 (-14, -2)] as compared to hemodynamic AKI after adjusting for donor and recipient characteristics. Results were similar when comparing intrinsic AKI to the mixed subtype.

Conclusions: Clinically adjudicated hemodynamic and intrinsic AKI were shown to be biologically different by urine biomarkers and were associated with different recipient outcomes.

Funding: Private Foundation Support

Distribution of Urine Biomarkers Among AKI Subtypes



TNFa, LFABP, KIM-1 and UMOD (not shown in figure) were not statistically significant.

PUB031

Kidneys Progressing from AKI to CKD Gradually Lose Their Inherent Potential to Recover

Lies Moonen,[4] Cristina Cuesta,[1] Francisco J. Lopez-hernandez,[2] Carlos Martinez-salgado,[3] Patrick C. D'Haese,[4] Benjamin A. Vervaet.[4] *[1]Institute for Biomedical Research of Salamanca (IBSAL), Salamanca, Spain; [2]IECSCYL - Instituto de Investigacion Biomedica de Salamanca, Salamanca, Spain; [3]Universidad de Salamanca, Salamanca, Spain; [4]University Antwerp, Edegem, Belgium.*

Background: It is increasingly clear that AKI can result in the development of CKD in humans. Murine renal unilateral ischemia-reperfusion injury (without contralateral nephrectomy; UIRI) models this AKI-CKD progression in the injured kidney (Le Clef et al, Plos One 2016). In mice, we and others demonstrated that contralateral nephrectomy (Nx), when performed shortly after UIRI (i.e. 3 days), is able to nearly completely attenuate the progression to CKD. Although non-translatable, Nx can be considered an experimental therapeutic intervention that incites inherent physiological repair/recovery

mechanisms in the kidney. Here, we investigate in rats to what extent contralateral Nx is able to attenuate or revert CKD progression when performed well beyond the acute injury phase, i.e. increased Nx delay time after UIRI.

Methods: AKI was induced in male Wister rats by left UIRI (60 min, 35°C body temp) after which contralateral Nx was performed 3, 10 or 20 days later. Renal function was assessed by serum/urine creatinine and transcutaneous GFR measurement 24h and 72h after Nx and weekly thereafter. In controls no Nx was performed until 24h before euthanization at week 11 to allow renal function assessment at that time. Rats were euthanized 11 weeks after Nx. Renal histology was evaluated by light microscopy.

Results: When no Nx was performed, renal function of the injured kidney decreased 44% compared to sham at week 11. Nx at day 3 induced full functional recovery from week 5 after Nx on, whereas Nx at day 10 and 20 led to a persistent 20% loss of renal function from week 1 after Nx on ($p<0.05$). Nx at day 3 was able to attenuate renal atrophy and tubulointerstitial expansion. Nx at day 10 and 20 were less efficient and led to 1.6 ($p>0.05$) and 2.6 ($p<0.05$) fold increase of tubulointerstitial area compared to sham. There was no difference in renal function outcome between Nx at day 10 and 20.

Conclusions: Early contralateral Nx after UIRI rescues renal function and morphology, whereas delayed Nx does not allow full recovery of the injured kidney. These results imply that a damaged kidney loses its intrinsic (compensatory) recovery potential over time and that an early intervention is more efficient in averting CKD outcome. The contribution of compensatory hypertrophy versus epithelial repair needs to be investigated.

PUB032

Role of Endothelial KLF4 in Determining the Severity of Cisplatin-Induced AKI in Mice

Wilfred Lieberthal,[2,1] Meiyi Tang,[2] Evgenii Boriushkin,[2] Sandeep K. Mallipattu.[2]
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Background: Cisplatin is a common cause of AKI in humans. The role played by the Kruppel-like Transcription-factor 4 (KLF4) in the pathogenesis of cisplatin-induced AKI is not known. This study had two objectives: i) to develop a novel model of cisplatin-induced AKI in mice and ii) to use this model to determine whether KLF4, expressed in endothelial cells (EC KLF4), contributes to determining the severity of this form of renal failure.

Methods: Cisplatin-induced AKI was induced by giving 3 daily doses of cisplatin (15mg/kg) (or its vehicle) to mice by intraperitoneal injection. Blood samples were obtained on Day 0 (immediately before the first dose of cisplatin/vehicle), and again on Days 4, 8 and 12.

Results: In wild type (WT) mice, the creatinines on Day 0 were comparable in the vehicle- and cisplatin-treated mice (0.098±0.005 and 0.112±0.004mg/dl respectively). On Day 4, the creatinines in vehicle- and cisplatin-treated mice were no different from those on Day 0. However, on Day 8, the creatinine in the cisplatin-treated group increased to 0.414±0.127mg/dl, and was higher than the creatinine in the vehicle-treated mice (0.122±0.007mg/dl) ($p<0.001$). On Day 12, the creatinine in the cisplatin-treated mice fell to 0.201±0.005mg/dl ($p<0.01$ vs day 8), and was comparable to the creatinine in the vehicle-treated mice (0.112±0.01mg/dl). We next compared the effects of cisplatin-induced injury in EC KLF4 KO mice and their Cre controls. The creatinines in the vehicle- and cisplatin-treated Cre and KO mice on Day 0 were comparable. On Day 4, all the KO mice (but none of the Cre mice) died after blood samples were obtained. The creatinine in cisplatin-treated KO mice on Day 4 was considerably higher (1.061±0.351mg/dl) than in the vehicle-treated KO mice (0.110±0.007mg/dl) ($p<0.001$). In the Cre mice, the creatinines in the vehicle- and cisplatin-treated mice on Day 4 were comparable to each other and to the creatinines on Day 0.

Conclusions: We have developed a model of cisplatin-induced AKI which is characterized by a developmental phase followed by a recovery phase. This pattern is similar to that observed in humans with AKI. We also show that EC KLF4 plays a major role in protecting endothelial cells from injury, and in reducing the severity of renal failure caused by cisplatin

Funding: Private Foundation Support

PUB033

Interaction of Properdin and Macrophages in Renal Ischemia-Reperfusion Injury and Its Related Models

Wenting Li,[1] Yuanyuan Wu,[2] Yufang Zhang,[1] Hui Wang,[3] Weiwei Chen,[1] Bin Yang.[4,1] *[1]Nantong University, Nantong, China; [2]University of Nantong, Nantong, China; [3]Yancheng First People's Hospital, YanCheng, China; [4]University of Leicester, Leicester, United Kingdom.*

Background: Properdin, the only positive regulator of complement alternative pathway, may also act as a pattern-recognition molecule. Macrophages play critical roles in renal ischemia-reperfusion injury (IRI). However, the interaction of properdin and macrophages in renal IRI, and upon which the impact of erythropoiesis derived helix B surface peptide (HBSP) and cyclic HBSP (CHBP), are not well defined.

Methods: This study used a mouse model subjected to bilateral renal ischemia for 30 min, and followed by reperfusion for 6, 12, 24, 48, 72 h and 1 week, and with or without CHBP treatment at 48 h. In addition, RAW 264.7 macrophages were stimulated by H_2O_2 of 50, 100, 200 and 400 μmol/L for 24 h; or 200 μmol/L H_2O_2 for 6, 12, 24 and 36 h. Moreover, macrophages were pretreated with 30 nM of HBSP or 20 nmol/L of siRNA target properdin to validate the effect of properdin on IR related injury. Properdin, inflammation and apoptosis-related caspase-3 and HMGB-1, and apoptosis were detected.

Results: Properdin protein and infiltrated macrophages were increased in the IRI kidneys started at 24 h, peaked at 72 h, and fell at 1 week. With increased H_2O_2 concentration or incubation time in macrophages, properdin was increased first and then decreased, with highest levels at 200 μmol/L or 12 h, and positively correlated with HMGB-1 and cleaved caspase-3 in Macrophages. CHBP inhibited properdin in mouse kidneys at the early stage of IRI, while HBSP pretreatment also inhibited properdin increased by H_2O_2 in macrophages, with decreased HMGB-1, caspase-3 and apoptotic cells. However, Properdin siRNA reduced properdin mRNA, but increased HMGB-1 and cleaved caspase-3 protein compared to negative siRNA, with raised apoptotic cells.

Conclusions: The dynamic change of properdin was shown in IRI kidneys and H_2O_2 stimulated macrophages, associated with the mediators of inflammation and apoptosis. Inhibiting properdin by CHBP/HBSP in mice or macrophages is protective against early injury, whereas silencing properdin in macrophages with compromised clearance of apoptosis and inflammation may be detrimental. The differential roles between HBSP and properdin siRNA, and their underlying mechanisms are worthy to be further explored.

Funding: Government Support - Non-U.S.

PUB034

Escherichia coli-Associated Hemolytic Uremic Syndrome (HUS) Treated with Eculizumab

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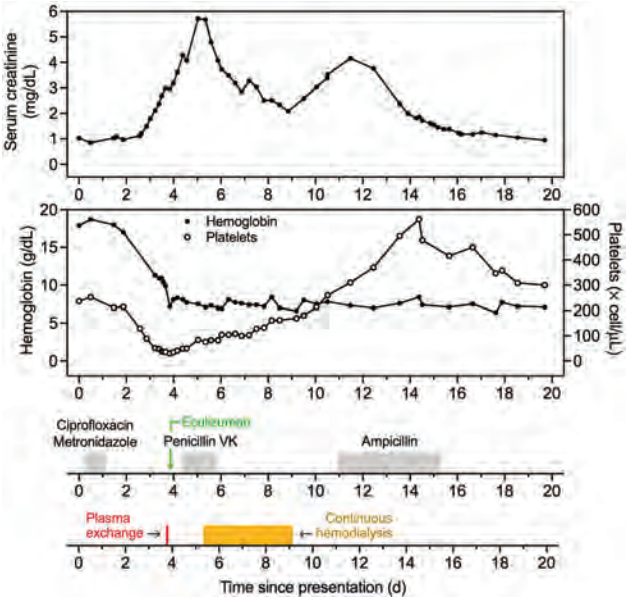
Introduction: Eculizumab, a terminal complement inhibitor, is enjoying use in a number of complement-disregulatory disease. A major use of eculizumab is treatment of atypical hemolytic–uremic syndrome (aHUS). Since Shiga toxin–associated HUS (STAHUS) are driven by toxic complement dysregulation, it stands to reason that eculizumab might provide therapeutic benefit in STAHUS.

Case Description: A 41-year old white male presented with a 2-day history of abdominal pain and frankly blood diarrhea. The only antecedent event of note was consumption of sushi. Initial exam showed normal vital signs and bilateral lower abdominal tenderness without signs of peritonitis. He received empiric antibiotics (ciprofloxacin and metronidazole) along with supportive care. Over 24 h he developed hypoactive encephalopathy, severe azotemia with oliguria, and a sharp drop in hemoglobin and platelet count. After 96 h his stool culture disclosed *E. coli* O157:H7, thus prompting the diagnosis of *E. coli* O157:H7–associated hemorrhagic enterocolitis with probable neurologically significant HUS. He underwent one session of plasma exchange followed by a single 900-mg dose of eculizumab. Continuous hemodialysis was ultimately initiated for oliguric AKI. After almost 3 weeks in-hospital he enjoyed a near-total recovery and was discharged to a rehabilitation facility prior to return home. The chronology of key clinical events and laboratory parameters is shown in the figure.

Discussion: We demonstrate here the favorable clinical course of Shiga toxin–associated hemolytic–uremic syndrome (STAHUS) following a single dose of the terminal complement inhibitor eculizumab in an otherwise healthy adult patient. Successful cases like this add to the base of evidence that eculizumab is useful in treating multiple diseases driven by complement system dysregulation.



PUB035

Protection Afforded by Angiotensin II Receptor Activation Against AKI Is Associated with Upregulation of Tubular Autophagy

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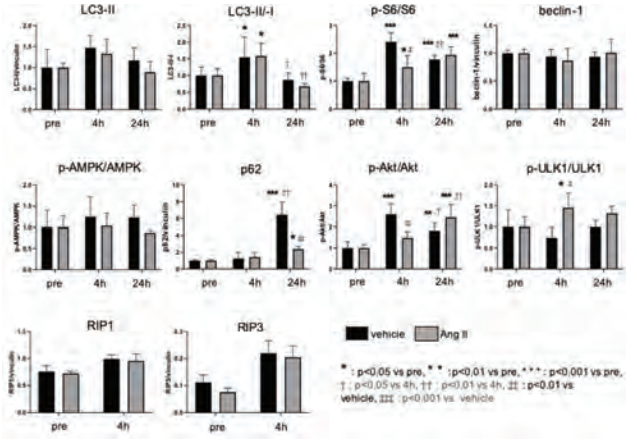
Background: Autophagy reportedly plays a protective role in acute kidney injury (AKI), and there is in vitro evidence to indicate autophagy upregulation by the renin-angiotensin system. Here we examined whether activation of the angiotensin II (Ang II)

receptor protects the kidney from ischemia-reperfusion (I/R) injury by upregulation of autophagy or modulation of necroptosis in vivo.

Methods: In Study 1, Sprague-Dawley rats were assigned into treatments with vehicle (Veh) or Ang II (200 ng/kg/min). Each drug was subcutaneously infused for 72 hrs. At the end of the infusion, kidneys were removed for assessment of autophagy. In Study 2, rats received treatments with Veh or Ang II and then underwent 30-min renal artery occlusion/reperfusion or sham surgery. Blood and kidneys were collected for assessment of renal damages and autophagy at 0.5, 4, or 24 hrs after the surgery.

Results: In Study 1, autophagosomes were increased in proximal tubular cells in the Ang II group than in the Veh group (0.88 vs. 0.29 a.u.; P=0.002). In Study 2, autophagosomes were increased at 4 hrs after I/R in the Veh group. BUN and ATN score were significantly lower in the Ang II group than in the Veh group at 24 hrs after I/R (99.2 vs. 123.3 mg/dl; P=0.004, 4.0 vs. 4.6; P=0.011, respectively). The number of autophagosomes was larger in the Ang II group than in the Veh group at baseline and 4 hrs after I/R (0.54 vs. 4.68; P<0.0001, 1.39 vs. 4.88 a.u.; P<0.0001, respectively). Akt phosphorylation was suppressed and ULK1-Ser555 phosphorylation was increased in the Ang II group at 4 hrs after I/R. RIP1 and RIP3 levels at baseline and after I/R were not affected by Ang II (Fig).

Conclusions: Short term infusion of Ang II increases autophagosomes in the renal tubular cells and alleviates I/R kidney injury. The renoprotective effect of Ang II may be associated with upregulation of autophagy but not with inhibition of necroptosis.



PUB036

Muscle-Renal Syndrome

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Introduction: Pathophysiology of non-traumatic rhabdomyolysis caused by viral infection has been poorly understood. We present a case of Adenovirus infection causing severe rhabdomyolysis and AKI that required dialysis for 2 weeks before complete clinical renal recovery.

Case Description: 29-year-old African American female with hypertension presented with flu like symptoms and decreased urine output. She had body aches, sore throat, loss of appetite, fevers/chills, and bilateral lower extremity weakness for four days. Denied herbal supplements or over the counter medications. Admission labs; sodium 127mmol/L, bicarbonate 17mmol/L, BUN 31mg/dl, creatinine 4.9mg/dl, phosphorous 7.6mg/dl, AST 920 U/L, ALT 256 U/L, Creatine Kinase (CK) >100,000 U/L. Urine analysis with moderate leukocytes, protein, moderate blood and positive myoglobin. Proteinuria 500 mg/24hr. Sputum culture was positive for adenovirus and plasma PCR levels were 29,000 copies/ml. CMV, EBV, HIV, Hepatitis, Influenza, Corona virus, Para influenza, Streptococcus, Legionella, LDH, Haptoglobin, Schistocytes, ANA, anti Jo, La, SSA, SSB, myomarker panel, toxic alcohols, acetaminophen and salicylates levels have been negative. Adenovirus was thought to be responsible for rhabdomyolysis leading to acute kidney injury. CK persistently remained elevated and her oliguria persisted despite aggressive fluids. She required dialysis for 2 weeks before renal recovery. Adenovirus PCR levels were undetectable and CK levels trended down by the day of discharge.

Discussion: Adenovirus is a non-enveloped dsDNA virus. There are 7 Human Adenovirus species and up to 57 serotypes that could induce different clinical manifestations. The mechanism of rhabdomyolysis and renal involvement has been described in multiple review papers, involves fluid sequestration and subsequent activation of neuro humoral response, tubular damage induced by renal vasoconstriction, oxidative stress and obstruction. Relevant areas of further investigation is to have a better understanding in the pathophysiology of rhabdomyolysis at the muscular level induced by virus (direct damage vs induced by cytokines) and if early use of antivirals may arrest the sequence of events.

PUB037

Cyclo(His-Pro) Protects Against Cisplatin-Induced AKI Through Inhibiting the p53-Mediated Apoptotic Pathway

Jong joo Moon,[4] Yong Chul Kim,[4] Jinseon Jeong,[4] Ji Eun Kim,[4] Sunhwa Lee,[4] Jae Wook Lee,[3] Mi-yeon Yu,[4] Dong Ki Kim,[4] Yon Su Kim,[2,1] Seung Hee Yang.[1] *[1]Kidney Research Institute, Seoul National University, Seoul, Republic of Korea; [2]Seoul National University College of Medicine, Seoul, Republic of Korea; [3]National Cancer Center, Seoul, Republic of Korea; [4]Seoul National University Hospital, Seoul, Republic of Korea.*

Background: Cyclo(His-Pro) (CHP) is an endogenous cyclic dipeptide that exerts cellular protective effects against anti-oxidative damages. However, the role and mechanisms for CHP in preventing cisplatin-induced nephrotoxicity remains largely unknown. In this study, we sought to investigate whether and how cyclo(His-Pro) prevents in cisplatin-induced acute kidney injury (AKI) mouse model.

Methods: In this study, a single intraperitoneal injection of cisplatin (10 mg/kg) was employed to induce AKI in ICR mice. To determine the role of CHP on cisplatin-induced AKI, the mice were pretreated with at different dosage CHP (1, 3 mg/kg) orally for 7 days before cisplatin injection. To explore the cell protective effect of CHP, in vitro study was also performed with primary cultured human tubular epithelial cells (hTECs). ROS assay was tested to measure antioxidant effect of CHP.

Results: The mice developed severe acute kidney dysfunction exhibited as elevated BUN and creatinine level at day 2 after cisplatin injection. Mice with pretreatment of CHP showed markedly attenuated cisplatin-induced acute kidney injury. Additionally, pretreatment of CHP improved the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) which are the enzymes to defense against oxidative stress. Comparable findings were observed in the protein expression of p53, Bax, caspase-3, and c-Jun which is associated with apoptosis, especially intrinsic apoptotic pathway. In cultured hTECs, which is a human kidney epithelial cells, CHP showed a protective effect against oxidative stress that induced by H_2O_2. Additionally, live cell frequency was increased with CHP dose dependent manners. This study demonstrated that CHP may protect against cisplatin-induced tubular cell apoptosis and AKI through suppression of p53 and up-regulation of antioxidant defense.

Conclusions: Together, this study demonstrated that CHP may protect cisplatin-induced AKI through inhibiting apoptosis. Considering the effects of CHP, it can be applied to the AKI protection.

PUB038

Isoliquiritigenin Attenuates Lipopolysaccharide-Induced AKI Through Suppression of the HMGB1 Pathway Against Ferritinophagy

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Background: Septic acute kidney injury (AKI) mainly results in life-threatening renal dysfunction involving renal tubular injury to bring heavy burden to patients in intensive care unit (ICU). However, there is still a lack of therapy to prevent septic AKI effectively and inexpensive.

Methods: To observe the role and novel mechanism of isoliquiritigenin (ISL) which isolated from the roots of licorice in septic AKI, we used LPS to induce renal tubular injury upon septic AKI both in vitro and in vivo. 50mg/kg ISL was once given to the mice orally one hour before 1 mg/kg LPS i.p injection. 50 μM and 100 μM ISL respectively pre-treat the human renal tubular cells 5 hrs before 2 μg/ml LPS stimulation.

Results: ISL pretreatment apparently reversed LPS-induced renal dysfunction and ameliorated murine renal tubular injury. Furthermore, we observed that LPS induced autophagy and ferroptosis in renal tubular, whereas ISL pretreatment significantly suppress autophagy and ferroptosis of renal tubular both in vitro and in vivo. Mechanically, autophagy activated ferroptosis via NCOA4-mediated ferritinophagy. Moreover, HMGB1 is required for ferritinophagy in renal tubular. ISL treatment inhibited the expression of HMGB1.

Conclusions: These results suggest that ISL protects LPS-induced acute kidney injury through suppression of HMGB1 pathway in renal tubular against ferritinophagy.

Funding: Government Support - Non-U.S.

PUB039

Cysteinyl-tRNA Synthetase Alleviates Renal Ischemia Reperfusion Injury Through Its Anti-Pyroptosis Role in Tubular Epithelial Cells

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Background: Acute kidney injury (AKI) is a common yet poorly treated entity, characterized by high mortality and significant risk of developing chronic kidney diseases. The pathophysiological mechanism of AKI remains underinvestigated.

Methods: To further elucidate the mechanism of AKI, we performed a detailed molecular characterization of ischemia reperfusion injury(IRI) model both *in vitro* and *in vivo*.

Results: The data comprising label free proteomics analysis in renal tubular epithelial cells, histological studies of renal tissue from IRI rat model, and molecular characterization of targeted gene activity provided a comprehensive profile of injury and repair responses in kidney due to IRI. Label free proteomics analysis and renal histological studies highlighted cysteinyl-tRNA synthetase (CysRS) was associated with renal tubular atrophy following IRI. CysRS was shown to alleviate IRI both *in vitro* and *in vivo* through its suppression of NLRP3 inflammasome assembly, thus reducing the renal tubular epithelium damage mediated by caspase-1 dependent cellular pyroptosis.

Conclusions: Our current study identified CysRs could alleviate renal IRI damage through its anti-pyroptosis role in tubular epithelium. The findings might provide valuable evidence for investigating potential underlying pathophysiological mechanisms and novel therapeutic targets for AKI. Feng Yunlin, Li Yi should be addressed as corresponding authors and these two authors contributed equally to this study.

Funding: Government Support - Non-U.S.

PUB040

Label-Free Identification of the Potential Association Between RPS7 and SRP14 in HK_2 Cells upon Ischemia-Reperfusion Injury

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Background: Renal ischemia/reperfusion injury (IRI) is one of the main reasons for acute kidney injury (AKI), which is associated with high mortality and end-stage renal disease (ESRD). However, we do not completely understand the mechanism of renal damage induced by IRI and renal failure with effective early diagnosis and treatment.

Methods: We performed LFQ Proteomic analysis and bioinformatics analysis of HK_2 renal tubular epithelial cells after ischemia for 45 min and reperfusion for 24 hrs. Then we identified the subsequent finding of LFQ and bioinformatics by RT-PCR and immunohistochemistryin renal IRI mouse model. To verify whether RSP7 and SRP14 interact, we validated by IP and cellular immunofluorescence.

Results: In current study, LFQ Proteomic analysis detected 28 proteins up-regulated by fold change>1.2 ($p<0.05$) and 45 proteins down-regulated by fold change<5/6 ($p<0.05$). The results of GO analysis showed these differentially expressed proteins could participate in biological processes, cellular components and molecular functions, mainly including multi-organism cellular process, interaction with host, intracellular organelle, protein binding, RNA binding and so on. KEGG systematically analysis revealed that the pathways involved in differential proteins include alanine, aspartate and glutamate metabolism, endocytosis, 2-Oxocarboxylic metabolism, TCA cycle and so on. In the network map, PPI analysis found an interaction between SRP14 and RPS7 in HK_2 renal tubular cells after IRI. Consistently with the results of PPI analysis, the RT-PCR and immunohistochemistry showed that the expression of SRP14 significantly increased and the expression of RPS7 significantly increased in murine renal tissue after IRI. The IP and cellular immunofluorescence confirmed that SRP14 and RPS7 are interacting.

Conclusions: Our data revealed increased expression of RPS7 and SRP14 *in vitro and in vivo*after renal IRI. And these results possible suggested the association of RPS7 and SRP14 in renal tubular epithelial cells after IRI. This finding might set base to further study of novel biomarkers and therapeutic targets for AKI caused by renal IRI. Li Wang and Yi Li should be addressed as corresponding authors and these two authors contributed equally to this study.

Funding: Government Support - Non-U.S.

PUB041

Cisplatin Induces Inflammation and Secretion of AKI Biomarkers in Kidney Organoids

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Background: The clinical use of the chemotherapeutic drug cisplatin is limited by its severe nephrotoxic side effects. The development of reno-protective therapies for cisplatin-induced acute kidney injury (AKI) is hampered by a lack of understanding of cisplatin-mediated nephrotoxicity. In recent years, kidney organoids derived from human pluripotent stem cells have been proposed as a platform to study AKI. Here, we describe a comprehensive approach to test the applicability of kidney organoids to model cisplatin-induced AKI.

Methods: Different doses of cisplatin were added to the culture medium of induced pluripotent stem cell-derived kidney organoids. Cisplatin-treated organoids along with controls were analysed for injury and inflammation markers by quantitative PCR, immunohistochemistry and antibody array.

Results: We found that organoids treated with cisplatin display increased levels of the kidney injury marker KIM1, DNA damage and cell death in a dose-dependent manner. Co-localization of the DNA double-strand break marker yH2AX with the different cell types in the organoids revealed that cisplatin predominantly affects proliferating cells suggesting a general cytotoxic effect reminiscent of the drug's impact on tumour cells. This result is contrary to cisplatin specifically damaging the proximal tubule *in vivo*. We measured low-level expression of proximal tubule-specific cisplatin transporters in organoids, providing one explanation for this observation. We further detected several AKI biomarkers and cytokines in the culture medium of cisplatin-treated organoids, consistent with the induction of an AKI-like inflammatory response. Notably, we observed peritubular accumulation of the injury biomarker Growth differentiation factor (GDF) 15 in cisplatin-treated organoids, and a worsening of cisplatin-induced injury when the organoids were co-treated with recombinant GDF15.

Conclusions: Our work validates the use of kidney organoids for modelling the inflammatory aspects of cisplatin-induced AKI and supports the potential of this human cell-based system for developing improved reno-protective therapies.

PUB042

Role of Necroptosis in Contrast-Induced Nephropathy in a Rat Model of CKD and Its Modification by Tolvaptan

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Background: Risk of contrast-induced nephropathy (CIN) is high in patients with chronic kidney disease (CKD). However, there is no specific preventive measures for CIN in CKD. In this study, we examine role of necroptosis in the mechanism of CIN in CKD and its possible modification by tolvaptan and saline infusion.

Methods: Using male SD rats, CKD was induced by subnephrectomy (5/6 nephrectomy, SNx), and CIN was induced by administration of indomethacin (10mg/kg), L-NAME (10mg/kg) and contrast medium (1600 mg I/kg). First, rats were divided into sham (n=6), SNx (n=17), and SNx+CIN (n=17). Forty eight hours after induction of CIN, serum creatinine (sCr), blood urea nitrogen (BUN), urinary albumin creatinine ratio (ACR) were measured and protein expressions in the kidney were examined by western blot. Next, we assessed the effect of necrostatin-1 (Nec-1, 1.65 mg/kg), a necroptosis inhibitor, injected just before and 24 hours after induction of CIN on renal function. Finally, to examine the effect of Tol (10 mg/kg) combined with saline infusion on CIN in CKD, we compared SNx (n=7), SNx+CIN (n=11) and SNx+CIN+Tol (n=8).

Results: SNx+CIN increased in sCr, BUN and log ACR compared with other groups, and also increased in caspase 3, cleaved caspase 3, caspase 8, RIP1, RIP3 (Fig.1), suggesting that renal damage in CIN was associated with activation of apoptosis/necroptosis signals. sCr (0.69 vs 0.56 mg/dl, $P<0.01$), BUN (37.2 vs 28.6 mg/dl, $P<0.01$) and log ACR (5.9 vs 4.5, $P<0.01$) were lower in Nec-1-treated SNx+CIN than in vehicle-treated SNx+CIN. Tol partially improved BUN and ACR and suppressed elevation of RIP1 and RIP3 levels in SNx+CIN (Fig.2).

Conclusions: Necroptosis contributes to CIN in CKD and its detrimental effect may be suppressed by tolvaptan.

Funding: Commercial Support - Otsuka Pharmaceutical Co.

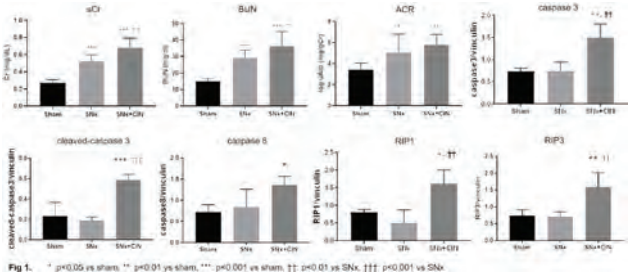

Fig 1. * p<0.05 vs sham, ** p<0.01 vs sham, *** p<0.001 vs sham, †† p<0.01 vs SNx, ††† p<0.001 vs SNx

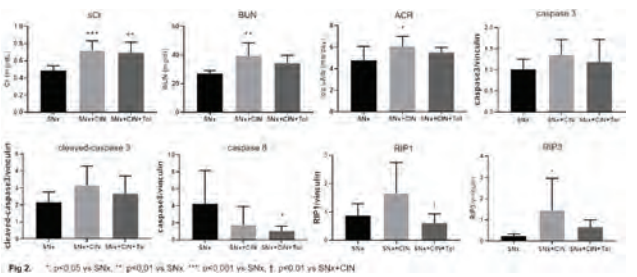

Fig 2. * p<0.05 vs SNx, ** p<0.01 vs SNx, *** p<0.001 vs SNx, † p<0.01 vs SNx+CIN

PUB043

Uncovering a Functional Loop Between Renal Tubular Epithelial Cells and Double Negative T Cells

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Background: Renal epithelium is a major tissue in kidney. Renal epithelial cells play an important role in inducing defensive mechanism and fully participate in renal innate immune responses. On the other hand, CD4-CD8- double-negative (DN) T cells, a rare population in periphery are preferentially localized into renal epithelial tissues and spontaneously proliferate in the steady state and protect against AKI. However, the functional relationship between renal epithelial cells and kidney DN T cells are unknown. We hypothesize that renal epithelial and kidney DN T cells regulate each other homeostasis and function.

Methods: To test this hypothesis, we used B6 wild type and MHC knockout mice, T cell functional assays and *in-vitro* co-culture system. Renal tubular epithelial cells and lymphocytes from both kidney and lymph node were isolated, cultured and analyzed by flow cytometry.

Results: Our data demonstrate that renal tubular epithelial cells (RTE) induce significant expansion of DN T cells in cultures. Addition of DN T cells with RTE significantly increased the frequency (DN; 1.2 ± 0.6 vs RTE+DN; 13.8 ± 3.5, p≤0.0001) and absolute cell number (DN; 0.2 ± 0.1x10^4 vs RTE+DN; 2.9 ± 0.9 x10^4, p≤0.0001) of DN T cells in *in-vitro*. The increased DN T cell number is due to increased activation and proliferation of DN T cells. Further, the activation and proliferation is TCR-independent, as RTE from class-I and II MHC KO mice can also induce proliferation of DN T cells. *In-vitro* experiments show that IL-7, a product of epithelial cells, significantly increases DN T cell proliferation (DN; 30.1% ± 4.2 vs DN+IL-7; 76.2%± 3.3, p≤0.0001) with decreased apoptosis (DN; 60.5% ± 10.5 vs DN+IL-7; 36.3 ± 2.5, p≤0.0001). In addition, the IL-7 dependent expansion of DN T cells is limited to PD-1+ DN T cell subsets. Transwell experiments show that cell-mediated interaction is necessary for enhanced DN T-cell proliferation in co-culture. Reciprocally, DN T cells also increased the survival of kidney epithelial cells *in-vitro*. However, the underline mechanism are unknown and investigated further.

Conclusions: These findings demonstrate a previously unknown mechanism and functional relationship between RTE and DN T cells, and its role in maintaining each other homeostasis and function. Ongoing studies are evaluating these responses during AKI and repair.

Funding: NIDDK Support

PUB044

The Effect of Nintedanib on Renal Interstitial Fibrosis

Donghyuk Kang,[2] Yun Jae Kwon,[2] Hyung Duk Kim,[2,1] Eun Nim Kim,[1] Yongjie Jin,[1] Ji Hee Lim,[1] Yaeni Kim,[2,1] Cheol Whee Park,[2,1] Bumsoon Choi.[3,1] *[1]The Catholic University of Korea, Seoul, Republic of Korea; [2]Seoul St. Mary's Hosp, Catholic Univ of Korea, Seoul, Seoul, Republic of Korea; [3]Division of Nephrology, Department of Internal Medicine, Seoul, Republic of Korea.*

Background: Pericyte is known as the main source of myofibroblast in renal interstitial fibrosis. However, the mechanism of mediating pericyte-myofibroblast transitions is unclear. In this study, we examined the effect of nintedanib, a triple kinase inhibitor of platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptors (FGFR) and vascular endothelial growth factor receptor (VEGFR) on renal fibrosis to identify the main factor inducing pericyte changes.

Methods: Surgically created unilateral ureteral obstruction (UUO) mouse model was used to generate progressive renal fibrosis. 3 groups were assigned; control group (sham operation), UUO 10 days and UUO 14 days. Nintendanib was given by gavage after ureteral ligation. Pericyte was confirmed by PDGFR-beta and NG2 double stain.

Results: In UUO (D10) group, decrease of pericyte and vascular density, and increase of interstitial fibrosis were observed. These findings were more noticeable in the UUO (D14) group. Compared with the UUO (D10) group, interstitial fibrosis was attenuated in the nintedanib treated UUO (D10) group, and pericyte was increased. In the nintedanib treated UUO (D14) group, the fibrosis progressed more than nintedanib treated UUO (D10) group. But they showed ameliorated interstitial fibrosis and increased number of pericytes compared to the UUO (D14) group.

Conclusions: Nintedanib treatment resulted in attenuation of renal interstitial fibrosis in UUO mouse model. And nintedanib decreased pericyte-myofibroblast transition. This is thought to be due to VEGFR inhibition.

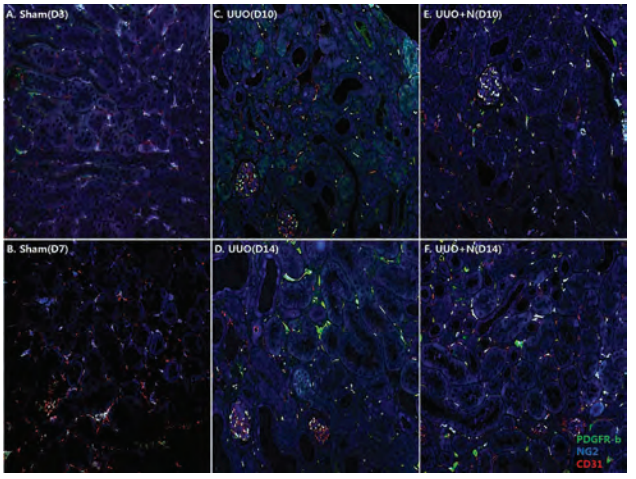

Figure 1. Chages of Pericytes in UUO Model

PUB045

Paradigm Shift: Sepsis-Induced AKI Not due to Hypotension

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Introduction: The patient is a 65 y/o man with a history of CKD 4 (eGFR 20- 25 ml/min), diabetes, stable chronic heart failure without recent exacerbation and hypertension. He was diagnosed with sepsis-associated acute renal failure (AKI) but in the absence of hypotension related etiology as to suggest acute tubular necrosis. We subsequently hypothize that sepsis-induced AKI may be the sequele of an adaptive to maladaptive inflammatory response rather than a purely hemodynamic phenomena.

Case Description: On presentation he was lethargic, hypothermic at 35.1 deg C, heart rate up to 107, eGFR 18 ml/min, peripheral leucocytosis 25 K/cmm, however his blood pressure (BP) was stable. The mean arterial blood pressure was significantly higher than 75 mmHg (94/65 mmHg) throughout hospital course and he did not require vasopressors or have shock. He was diagnosed with sepsis from ascending urinary tract infection due to Enterobacter Cloaca, as the source and was initially treated with Cefepime which was later changed to Levofloxacin in response to sensitivity report. Blood cultures, serology for HSV I/II PCR were negative. The patient however sustained AKI and given his comorbidities and previous CKD, he sustained inexorable decline in renal function and ended up needing to start dialysis due to uremic symptoms, with a new clinical designation as end-stage renal disease.

Discussion: We wish to point out that practicing clinicians are increasingly recognizing a concept we call "sepsis-induced AKI". It has been known that sepsis, major surgery, heart failure and hypovolemic shock are all associated with AKI & traditionally was taught to be due to ischemia on the basis of macro hemodynamic changes. However we document that AKI can occur in the absence of global hypoperfusion. In a paper published by Hermando Gomez et al. published in Shock. 2014 Jan; 41(1): 3-11 they attempted to put forward a theory for AKI in the absence of shock (or hypotension) involving DAMPs/PAMPs, abnormal signaling and oxidative stress response. Circulating factors from burn patients with sepsis-induced AKI can induce tubular and glomerular alterations in septic patients who do not have AKI (Crit Care. 2008; 12(2): R42.). We propose that it is time for a new paradigm for sepsis-induced AKI should lead to larger studies in translational medicine and randomized clinical trials.

PUB046

Mechanistic Insight for Increased Susceptibility to Cisplatin Nephrotoxicity with NHERF1 Loss

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Background: Acute kidney injury (AKI) develops in 30% of patients who receive cisplatin (CIS), a widely used chemotherapeutic agent. We have previously shown NHERF1 loss results in increased susceptibility to CIS nephrotoxicity. We hypothesize that NHERF1 loss leads to an altered renal oxidative state resulting in increased susceptibility to CIS toxicity.

Methods: We treated 3-4 month old male wild-type (WT) C57BL/6 and NHERF1 knock out (KO) mice with vehicle or CIS (20 mg/kg dose IP) for 72 hours. Plasma, liver and kidney cortex were collected for measurement by HPLC of the reduced and oxidized forms of small molecular weight thiols (glutathione (GSH), glutathione disulfide (GSSG), cysteine (Cys) and cystine (CySS), the mixed disulfide between the two, cysteine-glutathione disulfide (CySSG); for measurement of lipid peroxidation by Thiobarbituric Acid Reactive Substances (TBARS); for γ-glutamyl transferase (GGTase) activity; and immunohistochemistry (IHC) for 4-hydroxynonenal (4-HNE) was performed in kidney tissue slices.

Results: In vehicle-treated mice, the only significant differences observed were a decrease in plasma CySS and an increase in liver GSSG in KO mice relative to WT. In response to CIS, plasma CySS and GSH decreased, while both Cys and CySS increased in the kidney in both genotypes. CIS had no effect on the kidney levels of any of the forms of GSH, but in the liver, all 3 forms (GSH, GSSG and CySSG) were decreased in CIS WT and KO mice, corresponding to a 6.5 mV oxidation of the GSH/GSSG redox couple in the liver of both genotypes. No significant differences were found in TBARS or GGTase activity with either treatment or genotype. IHC for 4-HNE showed no differences between genotypes for vehicle-treated kidneys, while CIS resulted in an increase in 4-HNE staining within the cortex and juxtamedullary (JM) region of both genotypes, more marked in the CIS KO kidneys, especially in the JM regions.

Conclusions: We conclude that loss of NHERF1 does not lead to changes in kidney GSH metabolism but does so in liver. CIS results in more pronounced expression of the 4-HNE adducts in the KO vs WT mouse kidneys. Therefore, the increased susceptibility of KO mice to CIS nephrotoxicity may be related to increased sensitivity to CIS itself.

Funding: Veterans Affairs Support

PUB047

Suppression of Nrf2 Activity by HIF-1α Promotes Fibrosis After AKI

Corry D. Bondi, Brittney M. Rush, Mohammad M. Al-bataineh, Roderick J. Tan. *University of Pittsburgh, Pittsburgh, PA.*

Background: Acute kidney injury (AKI) is a rapid reduction in renal function due to damage to tubular epithelia and can occur after ischemia/reperfusion injury (IRI). Ischemic injury results in both impaired oxygen and nutrient delivery to the kidney. Kidney tubular epithelial cells are particularly vulnerable to ischemic injury. To offer protection, cellular mechanisms have evolved to mitigate the damage of IRI while attempting to restore cellular homeostasis. Specifically, two notable cellular pathways are activated including nuclear factor erythroid 2 like 2 (Nrf2) and hypoxia inducible factor 1α (HIF-1α).

Methods: C57BL/6 mice were subjected to IRI. Ischemia times were titrated to induce mild to severe injury and kidneys were harvested at various acute and chronic time points post-reperfusion. To simulate mild and severe injury conditions *in vitro*, proximal tubular HK-2 cells were exposed to either nutrient replete or nutrient deficient conditions, respectively, in the presence of HIF activation with cobalt chloride ($CoCl_2$). Immunoblotting, co-immunoprecipitation, qPCR, and RNA interference were used.

Results: The protective Nrf2 activity is activated by mild ischemia but is suppressed by severe ischemia *in vivo*. Mimicking these results, HIF-1α activation in nutrient replete conditions *in vitro* enhances Nrf2 nuclear localization and activity, while HIF-1α activation in nutrient deficient conditions suppressed Nrf2 activity. Localization and activity of Nrf2 were restored upon siRNA-mediated knockdown of HIF-1α. These effects were not due to direct interaction between HIF-1α and Nrf2, since these proteins did not co-immunoprecipitate *in vitro*.

Conclusions: Our data confirm that severe AKI leads to a maladaptive reduction in Nrf2 activity and ultimately to renal fibrosis. This may be due to Nrf2 inhibition by HIF-1α under severe ischemia conditions. We propose that the capacity to recover from an ischemic insult can be attributed to regulation of the Nrf2 pathway by HIF-1α.

Funding: NIDDK Support, Other NIH Support - NIH P30 DK079307; NIH T32 DK061296, Private Foundation Support

PUB048

Metabolic Alterations in a Mouse Model of Cisplatin-Induced AKI

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Background: Cisplatin-induced acute kidney injury (AKI) occurs in 1/3 of cisplatin-treated patients. Cisplatin-AKI is diagnosed by elevated serum creatinine (SCr), but nephrotoxicity develops before measurable changes to SCr. Novel diagnostic/predictive markers of AKI may explain why only certain cisplatin-treated patients get AKI. FVB/N mice are more susceptible to cisplatin-AKI than C57BL/6. These two strains were used to model the interindividual variability of cisplatin nephrotoxicity. We aim to: 1) Measure expression of renal transporters/enzymes involved in cisplatin disposition; 2) Investigate metabolic differences between FVB/N and C57BL/6 mice using metabolomics; 3) Determine the effects of pharmacological inhibition of Oct2 and Oat1/3 (cisplatin uptake transporters in proximal tubule) with inhibitors cimetidine and probenecid.

Methods: Mice were treated with 15 mg/kg cisplatin or saline by intraperitoneal injection and sacrificed 1,3, and 4 days post-treatment. A subset of mice were pre-treated with a combination of cimetidine+probenecid, 15 mg/kg and 200mg/kg respectively, 1 hour prior to cisplatin treatment. A repeat dose of cimetidine was given 6 hours after cisplatin injection. AKI severity was assessed by plasma creatinine quantification and histological analysis. Gene expression was assessed using RT-PCR. LC-MS was used for untargeted metabolomics.

Results: Renal mRNA expression of transporters Oct2 and Oat1, and metabolizing enzyme Ggt1 were higher (+20%,+38%,+45%;$p<0.05$) in untreated FVB/N mice compared to C57BL/6. Principal component analysis (PCA) of untreated plasma samples showed separation based on strain. PCA of day 4 plasma samples separated cisplatin and saline groups for both strains. LysoPC(16:0), taurine, indoxyl sulfate, phenyl sulfate and p-cresyl sulfate were metabolites altered in cisplatin-AKI. Pharmacological inhibition of Oct2 and Oat1/3 resulted in a non-significant reduction of SCr compared to cisplatin treatment alone.

Conclusions: FVB/N mice exhibited higher expression of various renal transporters/enzymes involved in cisplatin disposition compared to C57BL/6. PCA clustering of plasma samples from untreated mice indicates metabolic differences between strains; separation by treatment suggests that cisplatin alters the metabolic profiles of the mice. Future work will study the metabolic changes upon Oct2 and Oat1/3 inhibition.

Funding: Government Support - Non-U.S.

PUB049

In Vitro Models of AKI Reveal Cell Type-Specific Cytokine Responses

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Background: The nature and severity of the renal injury determine the progression from AKI to CKD. Renal tubule interstitial fibrosis is the final common pathway in end-stage renal disease and is characterized by abnormal deposition of extracellular matrix (ECM) produced by myofibroblasts. The role of TGFβ and MCP-1 in renal fibrosis is well known but there is also evidence for a role of different cytokines such as IL-18 and IL-15. However there is no significant data about these mediators in acute kidney injury. We reproduced three different in vitro model of AKI (septic, Ischaemia-reperfusion and toxicity drug related) with the aim to observe the response of these mediators to an acute insult that potentially could be considered as markers of AKI.

Methods: Primary human proximal tubular cells phenotypically expressing GGT were cultured in collagen, plasma and cellular fibronectin and harvested the supernatant of culture medium. We reproduced an in vitro model of AKI with NaN3 for ischaemia reperfusion, gentamicin as toxic drug and LPS (Lipopolysaccharides) as septic model. The treatment lasted for 18 hours followed by RNA extraction and PCR. Collagen and plasma-cellular fibronectin samples were tested for IL-18, IL-15, TGF β and MCP-1. We also analysed the NAG secreted by tubular cells in cell culture medium and we compare NAG with NGAL.

Results: Significantly higher NAG activity was detected in NaN3, LPS and gentamicin models of AKI compared to control (p= 0.0014, 0.0125 and 0.0028). NGAL results were below the level of detection. Results from the LPS model tended to be extreemly variable with no obvious patern despite relatively consistent NAG results. There was no significant change in TGFβ expression in any of the models. Gentamycin and NaN3 induced distinctly different cytokine resposnes. Gentamycin iinduced MCP1 and IL15 while reducing IL18 expression. NaN3 tended to increase MCP1 but to a lesser degree and did not alter the IL15/IL18 ratio. Unexpectedly culturing cell on cellular fibronectin without treatment altered MCP1 expression.

Conclusions: Our pilot data indicates that the cytokine responses of renal epithelial cells to AKI varies significantly depending on the nature and not the severity of the injury. The relative expression of key opposing mediators such as IL15 and IL18 may influence the nature of the renal recovery

PUB050

Anemia and Kidney Function Decline Among the Middle-Aged and Elderly in China: Results from the China Health and Retirement Longitudinal Study (CHARLS)

Chao Yang,[1] Qinqin Meng,[4] Yafeng Wang,[4] Zaiming Su,[2] Guilan Kong,[2] Luxia Zhang,[1,2] Yaohui Zhao.[3] China Kidney Disease Network (CK-NET) Work Group *[1]Renal Division, Department of Medicine, Peking University First Hospital, Beijing, China; [2]National Institute of Health Data Science at Peking University, Beijing, China; [3]National School of Development, Peking University, Beijing, China; [4]Institute of Social Science Survey, Peking University, Beijing, China.*

Background: Chronic kidney disease (CKD) is a public health burden worldwide. Anemia is common among patients with CKD and closely associated with kidney function progression. However, less is known regarding the longitudinal association between anemia and kidney function decline among the middle-aged and elderly population in China.

Methods: The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative longitudinal study starting from 2011. Participants without creatinine and demographic data in 2011 and 2015 were excluded. Anemia was defined according to WHO standards and rapid decline in kidney function was defined as a ≥16.9% (Quartile 3) decline in estimated Glomerular Filtration Rate (eGFR) calculated using the CKD-EPI equation during two visits. Multivariate logistic regression model was used to investigate their association.

Results: Altogether 7210 eligible participants were included in the final analysis, with a mean age of 58.6 ± 8.8 years. Rapid decline in kidney function occurred among 1802 (25.0%) participants. Those with rapid decline were more likely to be male, older, and to have lower eGFRs, anemia and hypertension. Anemia was significantly associated with rapid kidney function decline after adjusting for potential confounding factors (OR=1.64, 95% CI=1.32-2.04). The model using the continuous variable of hemoglobin (per 10 g/L) confirmed this positive association (OR=0.90, 95% CI=0.87-0.94) (Table 1).

Conclusions: Anemia is an important risk factor for the progression of CKD among the middle-aged and the elderly in China. Effective interventions targeting anemia could help reduce the risk of kidney failure.

Funding: Government Support - Non-U.S.

Association of anemia with rapid decline in kidney function in CHARLS, 2011-2015

Variable	OR	95% CI	P value
Anemia*	1.64	1.32-2.04	<0.001
Hemoglobin (per 10 g/L)*	0.90	0.87-0.94	<0.001

*Adjusted for age, gender, residence, education, medical insurance, personal consumption expenditures, cardiovascular disease, diabetes, hypertension, hyperuricemia, high sensitivity C-reactive protein, body mass index, central obesity, smoking, drinking, and baseline eGFR.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; OR, odds ratio.

PUB051

Cumulative Intravenous Iron in Incident Hemodialysis Patients and Spikes of Serum Alanine Aminotransferase

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Background: Use of intravenous iron (IV Fe) is vital in the management of anemia in hemodialysis (HD) patients. In the general population, elevated alanine aminotransferase (ALT) is associated with increased serum iron parameters, possibly exhibiting evidence of liver injury. We aimed to determine the association of cumulative IV Fe and other known liver risks with spikes in monthly ALT lab levels in incident HD patients.

Methods: This retrospective quality study examined incident HD patients over 14 years. Baseline demographic and clinical characteristics included age, dialysis vintage, sex, race, ethnicity, weight, cumulative IV iron given, statin use, viral hepatitis status, diabetes mellitus, laboratory results (albumin, ferritin and TSat%) and recent hospitalization. Analysis included general estimation equations for assessment of spikes in monthly ALT (defined as >56 U/L, the upper end of normal of the lab) as the dependent outcome.

Results: The cohort included 585 incident HD patients: mean age at ESRD=57.2±16.1 years; 40.2% female; 27.1% non-Hispanic White and 30.9% Black; 48.5% DM; and 12.5% Hep C antibody positive. 155 (26.5%) patients experienced at least one spike of ALT. General estimation equations suggested that cumulative IV Fe by itself was *inversely* associated with spike in ALT. However, the interaction term of Ferritin*cumulative IV Fe was *positively* associated with spikes of ALT; we found other factors associated with spikes in ALT (see Table 1 for significant factors). Other factors analyzed but *not* associated with a spike in ALT included: vintage, serum albumin, gender, race, ethnicity, DM and recent hospitalization.

Conclusions: Cumulative IV Fe by itself was not positively associated with spikes in ALT, whereas serum Ferritin was strongly associated. Since IV Fe is often withheld from patients with high Ferritin levels, we included the interaction term of Ferritin with IV Fe in the analysis; we found this combined factor was positively associated with ALT spikes. In the full analysis, other factors positively associated with ALT spikes included: younger age, lower body weight, higher TSat%, on statin therapy, and positive Hepatitis C status.

Funding: Clinical Revenue Support

Table 1

Parameter	Estimate	SE	95% Confidence Limits		Z	P
Age ESRD	-0.0258	0.0083	-0.042	-0.0095	-3.11	0.0019
Weight (avg post HD)	-0.0202	0.0081	-0.0361	-0.0044	-2.5	0.0123
Ferritin	0.5864	0.1438	0.3045	0.8683	4.08	<.0001
TSat	0.0131	0.0042	0.0049	0.0213	3.12	0.0018
Cumulative IV Fe (mg)	-0.5678	0.1936	-0.9472	-0.1883	-2.93	0.0034
on_STATIN	0.5164	0.2067	0.1113	0.9214	2.5	0.0125
Hep C AB positive	0.9437	0.2923	0.3708	1.5165	3.23	0.0012
Ferritin*cumulative IV Fe	0.4615	0.1509	0.1656	0.7573	3.06	0.0022

PUB052

Comparative Study Between Darbepoetin vs. Metoxi Polietilen Glycol-Epoetin Beta (CERA), in the Treatment of Anemia in Patients with Chronic Hemodialysis: Randomized Clinical Trial

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Background: At present, we have differents erithropoyesis stimulating agents (ESA) for the treatment of anemia in chronic hemodialysis. In the last ten years, news ESA have been improved as Darbepoyetin (DA) and methoxy polyethylene glycol epoetin beta (CERA), theses ESA have better pharmacologyc efficacy and less frequency of administration. We did a randomized clinical trial between DA and CERA in the treatment of anemia in hemodialysis.

Methods: 160 adults patients in chronic hemodialysis with anemia (Hb 8 g/dl, Hto 24%)) were included, patients with malnutrition, cancer, multiorganic failure and older than 75 years were excluded. Patients were randomized in two groups, DA (n=80) received 40 mg every 5 days, subcutaneous route and CERA group (n=80)) received 75 mcg, every 10 days, subcutaneous route. The medications were taken in a double blind way. Hb and Hto were taken at the beginning of the study and monthly during 4 months. Ferrum profile was taken at the beginning and at the end of the study. ANOVA was used for the comparison of values the Hb and Hto in the differents measures. P values less 0.05 were considered significant.

Results: The basal values of Hb and hto in the DA group were: 9±1 g/dl and 27±2%, in the M group were: 8.9±1 g/dl and hto 28±1% (p > 0.05), at the end of study in the DA group Hb 12±1 g/dl and hto 36±2% in the M group Hb 11.9±1 g/dl and hto 35±1 % (p > 0.05). Ferritin and transferrin saturation were similar in both groups at the beginning and at the end of the study (p >0.05).

Conclusions: Darbopoyetin and Mircera had the same efficacy in the treatment of anemia in chronic hemodialysis, there were not differences. Both options are useful for the treatment in patients in hemodialysis.

Funding: Government Support - Non-U.S.

PUB053

Novel Probe to Detect Autophagy Flux in Proximal Tubular Cells

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Background: Autophagy is a pathway to degrade or recycle damaged organelle and macromolecules. In autophagy, autophagosome including part of cytosol and waste fuses with lysosome and the content is degraded by hydrolytic enzymes. As autophagosome forms, microtubule-associated protein light chain 3 (LC3-I) is conjugated with phosphatidylethanolamine to become LC3-II. Many of present methods to measure autophagy utilize LC3 as a marker, such as GFP-LC3 or western blotting (WB) to detect the conversion of LC3-I to -II. The existing methods have several limitations, such as the static evaluation of autophagy instead of flux evaluation or their reliability. In this study, we applied a novel probe, GFP-LC3-RFP-LC3ΔG to measure autophagy flux developed by Kaizuka, Morishita and his colleagues to proximal tubular cell line, HK2. Endogenous ATG4 cleaves the probe into equimolar GFP-LC3 and RFP-LC3ΔG. While GFP-LC3 is degraded as autophagy proceeds, RFP-LC3ΔG stays intact and serves as internal control. Thus 1-GFP/RFP reflects the amount of autophagy flux. We used HK2 cells transfected with the probe to evaluate autophagy flux in hypoxia or hypoxia inducible factor (HIF) stabilizer, enarodustat.

Methods: We transfected HK2 cells with pMRX-GFP-LC3-RFP-LC3ΔG, using lipofectamine 3000 (Thermo Fisher Scientific, USA). After selecting the cells with puromycin, single cell cloning was performed to pick up colonies without homologous recombination. Autophagy flux was evaluated using flow cytometry (BD biosciences, USA), and 1-GFP/RFP was calculated. We exposed the cells to amino acid depletion, a major autophagy inducer, for 4 hours and compared the results of the probe with existing LC3 WB. We also measured the autophagy flux in HK2 cells in 1% O2 for 0-48 hours and HIF stabilizer, 10 mM enarodustat for 0-48 hours.

Results: With amino acid depletion, autophagy flux was increased compared to normal medium, which was comparative to the result of WB. Under 1% hypoxia, autophagy was also increased over time, reaching almost 100% by 48 hours. Enarodustat increased autophagy more slowly.

Conclusions: We established HK2 cells stably transfected with autophagy probe for flux evaluation. After validating the cells using amino acid depletion, we evaluated the autophagy flux in hypoxia and HIF stabilizer and found that it was increased in both settings.

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PUB054

Inhibition of Angiotensin-Converting Enzyme 2 by Fibroblast Growth Factor 23 Through FGFR1

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Background: Fibroblast growth factor 23 (FGF-23) is a protein which is responsible for phosphate and vitamin D metabolism in humans. Renin angiotensin-aldosterone system (RAAS) activation leads to phosphate retention and FGF-23 elevation in chronic kidney disease. This study was designed to investigate the unclear influence and mechanism of FGF-23 on angiotensin-converting enzyme 2 (ACE-2) of RAAS.

Methods: Rat renal tubular epithelial cells (NRK-52E) were treated with 0, 10, 25 and 100 ng/mL FGF-23 for 24h, respectively. Then renal epithelial cells were treated with 100 ng/mL of FGF-23 for 6, 12 and 24h, respectively. ACE-2 expression was detected by RT-PCR and western blotting. Angiotensin 2 (Ang-2) in cell supernatant was detected by enzyme linked immunosorbent assay (ELISA). Immunofluorescence was used to detect the localization and expression of ACE-2. FGF receptor 1 (FGFR1) was inhibited using FGFR1 inhibitor (PD173074).

Results: 100 ng/mL FGF-23 significantly inhibited mRNA and protein levels of ACE-2 in renal epithelial cells compared with 0, 10, and 25 ng/mL FGF-23 groups respectively. FGF-23 inhibited ACE-2 expression in a time-dependent manner, which was most significant at 24h. 100 ng/mL FGF-23 increased Ang-2 expression in the supernatant of renal epithelial cells compared with the control group by ELISA. Moreover, immunofluorescence found that the granular fluorescence of ACE-2 expressed mainly in the cell membrane and cytoplasm, and the fluorescence intensity of ACE-2 decreased after the treatment of 100 ng/mL FGF-23 compared with the control group. Treatment of FGFR1 inhibitor PD173074 (25nmol/mL) blocked the inhibiting effect of FGF-23 on ACE-2 in renal epithelial cells.

Conclusions: FGF-23 could inhibit the expression of ACE-2 through FGFR1 in renal tubular epithelial cells. The cross-talk between FGF-23 and RAAS is complex and needs future studies to investigate.

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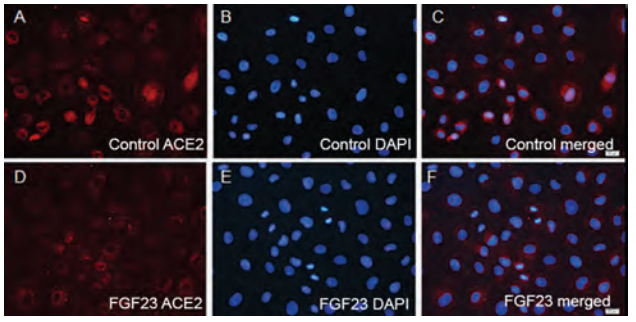

PUB055

High-Dose Denosumab for the Management of Immobilization-Related Hypercalcemia in a Patient on Maintenance Hemodialysis: A Case Report

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Introduction: Immobilization-related hypercalcemia arises due to a higher rate of osteoblastic bone formation compared to osteoclastic bone resorption. Renal impairment increases the risk of immobilization-related hypercalcemia. There is limited evidence about the safety and efficacy of denosumab in the management of immobilization-related hypercalcemia in hemodialysis (HD) patients.

Case Description: We report a case of successful treatment of immobilization-related hypercalcemia with denosumab 120 mg. A 55-year-old woman admitted to the ICU with suspected catheter-related bacteremia that led to septic shock. After 13 days of admission, the patient's corrected serum calcium rose to 3.39 mmol/l from a baseline of 2.52 mmol/l despite calcium carbonate and alfacalcidol discontinuation. Cinacalcet 60 mg once daily for 10 days, subcutaneous Calcitonin 250 mcg/dose for 6 days, a single dose of intravenous Zoledronic acid 4 mg, and a single dose of subcutaneous denosumab 60 mg were sequentially administered without response. Thus, subcutaneous denosumab 120 mg was administered and resulted in a gradual decline of the corrected calcium level from 4.18 mmol/l to 2.45 mmol/l over 3 weeks. Corrected calcium level was maintained below 2.8 mmol/l for 2 months later without notable adverse reactions. The patient's serum phosphorus level and PTH were within the normal ranges during the whole admission period.

Discussion: The management of immobilization related hypercalcemia in ESRD patients include withholding calcium and vitamin D, HD using a low-calcium dialysate (not available in our setting), Bisphosphonates, Cinacalcet, Calcitonin, and Denosumab. In our case, all management options were not effective except high dose denosumab. Cinacalcet has poor tolerability due to its common gastrointestinal side effects. Bisphosphonates lack of efficacy was possibly due to their limited antiresorptive action. Moreover, Bisphosphonates safety in ESRD patients is not well established and they are not recommended in this population for non-malignancy uses. Unlike Bisphosphonates, Denosumab lacks the need for renal dose adjustment. Besides, Denosumab has a rapid onset and extended duration of action. Our case showed that High-dose denosumab could be effective and safe for the management of immobilization-related hypercalcemia in HD patients.

PUB056

Associations of Body Composition, Bone Mineral Density, Serum Phosphate, and Magnesium Levels in Hemodialysis Patients

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Background: Sarcopenia, osteoporosis, hyperphosphatemia, and hypomagnesemia are reportedly associated with mortality in hemodialysis patients. This study aimed to assess the associations of body composition, bone mineral density (BMD), serum phosphate (P) and magnesium (Mg) levels in maintenance hemodialysis (MHD) patients.

Methods: Pre-dialysis laboratory data, post-dialysis body composition parameters by the Body Composition Monitor (Fresenius), and radius, lumbar spine, and femoral bone mineral density (BMD) using dual energy X-ray absorptiometry were assessed in MHD patients. Body composition, BMD, and clinical data were compared based on serum P and Mg levels. Multiple regression analyses for body cell mass index (BCMI): fat-free mass without extracellular water, and overhydration/extracellular water (OH/ECW) were performed, respectively.

Results: Among 264 patients (male: 65%, diabetes: 42%), mean age was 65±12 years and the median dialysis vintage was 79 (39–144) months. Serum P tertiles (T1–T3) were <4.5, 4.5–5.5, and <5.5 mg/dl. The low (T1) serum P group exhibited significantly (P<0.05) lower normalized protein nitrogen appearance (nPNA), intact parathyroid hormone (iPTH), lean tissue index, BCMI (6.5±1.8, 6.9±1.8, and 7.2±2.0 kg/m^2), intracellular water and significantly higher OH/ECW (9.2±10.0, 8.9±9.8, and 6.4±8.9, P<0.05) than other groups; BMD and coronary artery calcification score (CACS) did not differ. Serum Mg tertiles were <2.3, 2.4–2.5, and <2.5 mg/dl. Compared with other groups, the low (T1) serum Mg group showed lower nPNA and iPTH (P<0.05), but no significant differences in body composition parameters, BMD, or CACS. BCMI was significantly (P<0.05) associated with age (β:-0.30), presence of diabetes (β:-0.16), serum albumin (β:0.13), serum P (β:0.12), femoral BMD (β:0.23) [or radius BMD (β:0.41)], but not serum Mg or lumbar spine BMD. OH/ECW was significantly (P<0.05) associated with the presence of diabetes (β:0.21), serum P (β:-0.13), and femoral BMD (β:-0.19) but not age, serum albumin, Mg, or radius or lumbar spine BMD.

Conclusions: In MHD patients, associations among serum P levels (but not serum Mg levels), body composition parameters (BCMI, OH/ECW) and BMD were observed; serum P <4.5 mg/dl may indicate worse body composition and lower BMD.

Funding: Private Foundation Support

PUB057

Hip Fracture and CKD: Eighteen Years of a Temporary Perspective in a Spanish Hospital

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Background: Hip fracture (HF) is a frequent cause of morbidity and mortality in the elderly, who have a high incidence of chronic kidney disease (CKD). The recent concept of "uremic osteoporosis" shows that uremic toxins favor the loss of bone mass, increasing the rate of HF. However, CKD is not included in HF risk prediction tools, as FRAX. We study the characteristics of patients with CKD and HF, in order to determine if the impairment of renal function influences it prognosis to establish a risk profile of HF in CKD and to design intervention protocols. We compared patients with advanced CKD (GFR <20 ml / min) with the rest of patients with CKD (GFR <60 ml / min).

Methods: We have performed an observational, descriptive and transversal study of the characteristics of hospitalized patients with HF and ERC, from January 2000 to December 2018. The quantitative variables are expressed as median and interquartile range and qualitative ones are expressed as percentages. The comparisons were made with T of Student and Chi2, with a level of significance of p <0.05.

Results: In this period, 291 patients with CKD, were hospitalized for HF, 105 male (36.1%) and 186 female (63.9%). The rest of the variables are expressed in the following tables.

Conclusions: - CKD worsens the prognosis of HF: it makes surgical treatment difficult and increases the time of hospitalization and risk of death. - The increase in markers of bone mineral disease in advanced CKD favors the development of uremic osteoporosis, which is possibly responsible for this unfavorable profile of HF. - Patients with advanced CKD, heart failure and elevation of markers of the bone mineral disease, suffer a high risk of poor FC prognosis, needing special vigilance.

VARIABLE	PERCENTAGE
ERC TYPE	
ERC WITHOUT DIALYSIS	94,8
HD	4,1
DP	0,3
TRASPLANT	0,7
STEROID TREATMENT	6,5
TYPE OF FRACTURE:	
SUBCAPITAL	41
PERTROCHANTERIC	59
SURGERY (PROSTHESIS / NAIL)	82,3
DEATH DURING INCOME	16,4
DEATH CAUSE	
MULTI-REGIONAL FAILURE	53,8
SEPSIS	10,3
RESPIRATORY INFECTION	15,4
DIGESTIVE HEMORRHAGE BECAUSE OF HYPOTENSION	7,7
UNREGISTERED CAUSE	5,1
SECONDARY HYPERPARATHYROIDISM (REFLECTED DIAGNOSIS)	18,6%
DEMENTIA	33,7%
VASCULAR CALCIFICATION	79,4
MINERAL BONE DENSITY	1,4
PREVIOUS DIAGNOSIS OF OSTEOPOROSIS	41,2
BIFOSPHONATES	3,8
CALCIUM SUPPLEMENTS	9,2
SUPPLEMENTS OF VITAMIN D	13,4
PRIOR HIP FRACTURE	9,7
TRIGGERING FALL	97,6
OBESITY	7,9
DISLIPEMIA	39,9
DIABETES	37,4
ARTERIAL HYPERTENSION	86,9
HEPATIC CIRRHOSIS	3,5
VIRAL HEPATITIS	2,1
PULMONARY OBSTRUCTIVE CHRONIC DISEASE	13,9
CONGESTIVE CARDIAC INSUFFICIENCY	21,1
ISCHEMIC HEART DISEASE	16
CKD<20 ML/MIN	18,2

VARIABLE	RESULT
Age (years)	87 (83-91)
Creatinine clearance (ml/min)	30,7 (23,0-39,7)
Average length of hospital stay (days)	11 (7,25-15,0)
Albuminemia (g/dl)	3,2 (2,7-3,7)
PTH (pg/ml)	147,5 (87,3-276,7)
Ca (mg/dl)	9,1 (8,6-9,5)
P (mg/dl)	3,5 (3,1-4,1)
CaxP	32,2 (27,5-37,8)
Vit D3 (ng/ml)	10,0 (6,2-15,2)
Alkaline phosphatase (U/L)	102,0 (78,0-149,5)

PARAMETER	AVERAGE VARIATION, OR AND CI
AVERAGE LENGTH OF HOSPITAL STAY	↑ 3,002 days (0,516-5,488)
ALBUMINEMIA	↓ 0,226 g/dL (0,019-0,433)
PTH	↑ 160,301 pg/m· (18,424-302,179)
PHOSPHORUS	↑ 0,677 mg/dL (0,319-1,034)
CaXP	↑ 6,474 (3,073-9,875)
ALKALINE PHOSPHATASE	↑ 34,656 U/L (8,855-60,456)
POSSIBILITY OF SURGERY	↓ OR 1,982 (0,978-4,015)
RISK DEATH	↑ OR 0,391 (0,193-0,792)
SECONDARY HYPERPARATHYROIDISM RISK	↑ OR 0,097 (0,012-0,796)
DEMENTIA RISK	↑ OR 2,033 (1,011-4,089)
VITAMIN D SUPPLEMENTS	↑ OR 0,229 (0,110-0,479)
CONGESTIVE HEART FAILURE RISK	↑ OR 0,488 (0,251-0,947)

PUB058

Thyroid Function Changes in Dialysis Patients with Severe Secondary-Hyperparathyroidism

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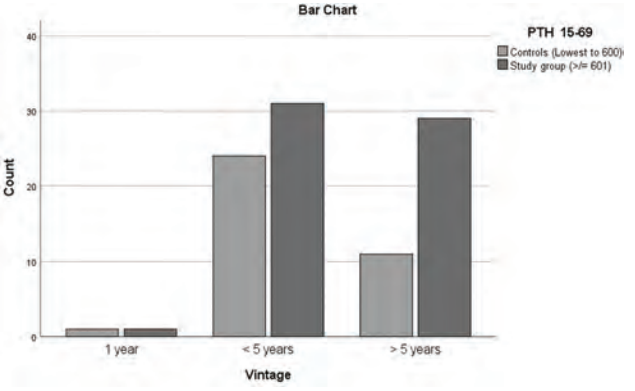
Background: Common complication of advanced Chronic Kidney Disease is secondary-hyperparathyroidism, which is associated with increased cardiovascular morbidity and mortality. While kidney-failure causes a wide array of thyroid abnormalities, little is known about whether uncontrolled hyperparathyroidism in dialysis patients is associated with thyroid-dysfunction and if this association has a relation to dialysis vintage and adverse cardiovascular outcomes

Methods: Parathyroid hormone(PTH) levels were dichotomized into groups of <600(controls: n=36) and ≥600(study group:n=62). Serum levels of PTH, thyroid function tests were obtained and statistically analyzed during two different times within a month-period. Using chart review, cardiovascular events, defined as coronary artery disease, heart-failure, and/or sudden cardiac death, that occurred over the past 5years were retrieved from the electronic medical records. In addition, dialysis vintage defined as short[<5years] and long defined as[≥ 5 years] was obtained. A Spearman's Rho correlation, Mann Whitney U test, and Fisher's Exact test were performed to determine the relationships between PTH, TSH, and FT4.

Results: There was no relationship between the thyroid and PTH levels as was TSH by PTH group was non-significant(p=0.98), as was the FT4 by PTH group(p=0.98). Controls arm had a higher % of shorter vintage(68.6%) compared to the study-group(51.7%), which was non-significant(p=0.134). Conversely, those in the study arm had a higher proportion of those in longer vintage arm(48.3%) than the control arm(31.4%)Fig1. A higher proportion of those with CVD(83.3%) were found in the control arm(83.3%) than those in the PTH study group(74.0%); p=0.41, which was non-significant.

Conclusions: No correlation was found between the severity of 2HPT and development of thyroid dysfunction and no statistically significant difference between two groups in CV outcomes. However, dialysis vintage was longer in study vs.control arm.



PUB059

Healthcare Cost of a Voracious "Hungry Bone Syndrome": How Far Can It Go?

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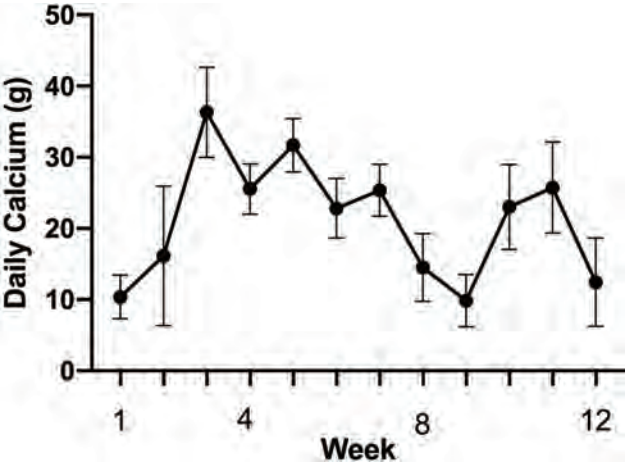
Introduction: Protracted 'Hungry Bone Syndrome(HBS)' post parathyroidectomy(PTX) in haemodialysis(HD) may last upto 4 wk. We report a lengthiest case-81 days-and calculated for the first time healthcare cost and total therapy

Case Description: A 50yr F, HD for 7yr had Cinacalcet refractory symptomatic HPT (iPTH 4267 pg/ml) underwent total PTX with auto-transplantation(AT). HBS developed a wk later, demanding massive doses of calcium(Ca) -PO, IV bolus and infusion- and active vitamin D for 11.5 wk. Additional Ca required- pre, mid, end HD. Poor AT function at 3 wk(iPTH 12 pg/ml) compelled unlicensed rhPTH(Teriparatide) use to control HBS. Data on total therapy (salt/elemental) collected from medication and HD charts. Treatments listed in Tab1. Blood test(n) retrieved. Hospital stay verified. Procurement/finance provided unit prices. HBS lasted 81 days, needing large doses of remineralisation therapy (Tab.1). Mean daily ca.dose 21.3±9.5g/d (5.8 – 46.8 g) with highest in 3rd wk(Fig.1). Huge hospital cost($56686) was due to teriparatide followed by bed cost, Ca. and blood tests(n=154)

Discussion: HBS in sustained severe HPT require sizable remineralisation therapy with increasing risk factors, as this case– age, postmenopausal, female, SHPT+ vintage, high PTH 4267, high ALP 1550, large adenomas and low VitD. AT may not function as expected. HBS can be challenging for patients, clinicians, pharmacy(exhausted Ca. stock), nurses(dialysate modified to low bicarbonate 28 mmol-to keep ionized Ca. high) and managers. Substantial healthcare burden of HBS could be minimized by focussed prior assessment of severity risks, adequate preparation/timing and ensuring sufficient stocks of remineralisation therapies

	Daily (salt/elemental) g	Total (g)	Cost ($)
Calcium PO	4.6±2.0 (4±1.5)	383	67
IV	16.7±9.6 (4.6±1.7)	1388	1496
Alfacalcidol(mcg)	6.1±2.5	494	288
Cholecalciferol(U)		200000	3.3
Phosphate PO	1.6±0.4	128	161
IV		12	389
Magnesium		37	5
Teriparatide(mcg)	20	1320	33316
Hospital days (n)		81	20459
Lab tests (n)	2	154	503
TOTAL			56,689



Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PUB060

Correlation of Phosphate Levels with Homeostatic Model Assessment of Insulin Resistance in Non-Diabetic Non-Dialysis Stage 3-5 CKD Patients

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Background: CKD is associated with insulin resistance which plays an important role in the pathogenesis of cardiovascular disease. In other hand, hyperphosphatemia that appeared in metabolic-bone disease, also associated with cardiovascular morbidity and mortality. The association between these two cardiovascular risk factors in CKD has not been determined yet.

Methods: This study was an observational analytic study with cross-sectional design, involving non-diabetic, predialysis CKD patients stage 3-5 from a tertiary referral hospital outpatient centre in Surabaya. Insulin resistance is described by using Homeostasis Model Assessment - Insulin Resistance (HOMA-IR). Analysis of relationship between phosphate levels and HOMA-IR is done by Spearman correlation test. P value is significant if <0.05. SPSS 23.0 software is used for data collection, recording and calculation.

Results: There were 40 patients. Mean of HOMA-IR levels in patients in stage 3A was 1.34 (±SD 0,16), stage 3B 1.84 (±SD 0,58), stage 4 3.01 (±SD 1,23), and stage 5 1.89 (±SD 1,14), and from overall results were 2.13 (±SD 1,15). Mean of phosphate level in CKD stage 3A was 3.45 (±SD 0,5), stage 3B 3.70 (±SD 0,77), stage 4 4.42 (±SD 1,57), and stage 5 4.99 (±SD 0,44), and from overall results were 4.51 (±SD 1,04). There was no correlation between HOMA-IR and phosphate level in CKD.

Conclusions: There was no correlation between phosphate levels and HOMA-IR in CKD stage 3-5 non-diabetic predialysis patients

PUB061

An Unexpected and Atypical Evolution Under Etelcalcide

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Introduction: Cinacalcet increases the sensitivity of the calcium membrane receptor (CaSR) to extracellular ionized Ca leading to decreased secretion of PTH. Etelcalcide can activate the CaSR even under calcium free conditions indicating its additional function as direct CaSR agonist. Etelcalcide have a higher biological efficiency (decrease of PTH) than Cinacalcet.

Case Description: A 60 years-old men, with obesity, diabetes-2, hypertension, ischemic cardiopathy, and polyvascular disease, is treated for ESRD with chronic hemodialysis since October 2011. Hyperparathyroidism (sHPT) has been treated by subtotal parathyroidectomy in April 2016. Recurrence of sHPT occured in 2018. Parathyroid MIBI scan (11/2018) identified an ectopic adenoma in the antero-lateral side of the medio-lobar region of the left thyroid lobe. Treatment by Etelcalcide, along with the use of calcium enriched dialysis fluid (1.75 mmol/L) has been started in January 2018. Etelcalcide is administrated at the end of dialysis sessions, with a gradual increase in dosage. PTH remained very high for 13 months, followed by a collapse in February 2019 and a moderate rebound in April 2019 (Table). Alkaline Phosphatase, Bone Alkaline Phosphatase, Vit-D, Magnesium and Albumin are normal in april 2019.

Discussion: Similarly to Cinacalcet, Etelcalcide is expected to cause rapid and dose-dependent decrease of PTH. Here, the response is very delayed with almost no detectable effects of the calcimimetic during the first 13 months of treatment. Then suddenly, severe hypocalcemia developed associated with a collapse in PTH level indicating hypoparathyroidism. Surprisingly, while PTH secretion increased after withdrawal of Etelcalcide hypocalcemia persisted indicating peripheral (bone) resistance to PTH. This state resembles to acquired pseudo-hypoparathyrodism despite the absence of hypomagnesemia or major vitamin D deficiency. In conclusion, this case suggests that Etelcalcide can cause hypocalcemia not only by depressing PTH secretion but also might alter signaling pathways downstream to PTH receptor.

Evolution of results following Etelcalcetide treatment

	01/04/2018	03/01/2018	05/03/2018	08/02/2018	11/08/2018	01/03/2019	02/07/2019	04/04/2019
Etacalcetide mg/Week	7.5	15	30	30	30	30	30 / 0	0
PTH (pg/ml)	1 709	1 617	1 500	2 031	1 611	1 597	72	385
% PTH Reduction	-	- 5%	- 12%	+ 19%	- 6%	- 7%	- 96%	- 77%
Total Ca (mmol/L)	2.33	2.32	2.35	1.99	1.97	2.09	1.35	1.37
P (mmol/L)	2.06	1.34	1.54	2.15	1.91	2.24	0.95	1.21

PUB062

Unilateral Nephrocalcinosis and Isolated Hypocitraturia: A Curious Combination or Mere Coincidence?

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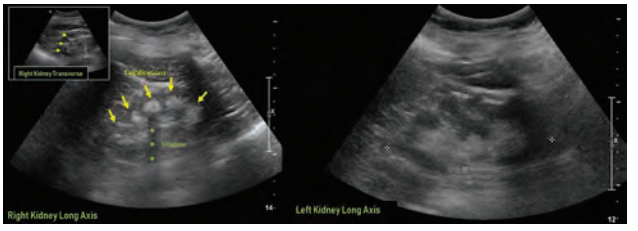
Introduction: Nephrocalcinosis is characterized by the deposition of calcium oxalate or phosphate in the kidney. A variety of inherited and acquired diseases have been associated with nephrocalcinosis and the most common metabolic cause is hypercalciuria with or without hypercalcemia followed by hyperphosphaturia. It is expected to be bilateral because of systemic origin, though unilateral cases have been reported. Herein, we present a unique case of unilateral nephrocalcinosis in a patient with hypocitraturia but no associated hypercalciuria or hyperphosphaturia.

Case Description: A 56-year-old Hispanic woman with a history of hypertension was seen for evaluation of chronic kidney disease. Serum creatinine was ~1.3 mg/dL, which was relatively stable compared to 4 months prior. A renal sonogram was obtained, which demonstrated findings suggestive of medullary nephrocalcinosis on the right [Figure]. Patient denied any history of nephrolithiasis in the past. Laboratory data did not demonstrate hypercalcemia, hypokalemia, metabolic acidosis or hyperparathyroidism. Vitamin D level was low-normal. Urine stone risk profile revealed normal 24-hour excretion of calcium (127 mg), phosphorus (310 mg) and oxalate (28 mg) but hypocitraturia was noted with a value of 71 mg/day [320-1240] as well as high sodium excretion of 329 mmol/day [<90 for hypertensives]. Medication history did not reveal any drugs implicated in hypocitraturia. She was treated with citrate supplementation and advised to restrict dietary sodium and increase consumption of fruits and vegetables.

Discussion: Hypocitraturia, a well-known known risk factor for nephrolithiasis and less commonly nephrocalcinosis is considered to be a systemic disorder. However, our case in addition to previously published small observational studies suggests that other local factors may play a role in the development of unilateral nephrocalcinosis. It is also not clear whether isolated hypocitraturia itself resulted in nephrocalcinosis or there was transient hypercalciuria in the past in our patient. It is of note that Once nephrocalcinosis is detected radiographically, it is unlikely to be reversed.



PUB063

Calcium Regulatory and Bone Turnover Biomarker Levels Do Not Indicate Presence of Osteoporosis and Osteopenia in ESRD

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Background: Concomitant BMD disorders like osteoporosis and osteopenia are often observed in ESRD patients. The criteria for diagnosis of a BMD disorder is through the evaluation of BMD by dual x-ray absorptiometry (DXA). This study aims to profile six biomarkers related to calcium regulation, bone turnover, and osteoblastic/osteoclastic activity in ESRD patients to determine if plasma levels of any markers were predictive of concomitant diagnosis of osteoporosis/osteopenia.

Methods: Plasma levels of osteopontin (OPN), bone morphogenic protein 7 (BMP-7), C-terminal collagen telopeptide I (CTX-I), IL-6, myeloperoxidase (MPO) and 25-hydroxyvitamin D2 and D3 (25(OH)D) were measured via commercially available enzyme linked immunosorbent assays in ESRD patients (n=92) and 50 normal healthy control samples. The ESRD cohort was further stratified into two groups: those with additional diagnosis of osteopenia or osteoporosis (n=23) and those without a BMD disorder diagnosis (n=69). The biomarker levels in these groups were compared to each other and to the normal population via Dunn's multiple comparisons test. Diagnosis of a BMD disorder was based upon T score reports of those who underwent a DXA bone scan. T scores between -1.5 and -2.5 indicated osteopenia, while a T score less than -2.5 indicated osteoporosis.

Results: In ESRD patients (n=92), OPN, IL-6, and MPO were significantly elevated compared to normal plasma samples (n=24-50; $p < 0.0001$, $p = 0.0146$, $p < 0.0001$). CTX-I was significantly decreased in ESRD patients compared to normal plasma samples (n=27; $p < 0.0001$). There was no statistically significant difference in 25(OH)D levels or BMP-7 levels between the ESRD cohort and normal plasma samples ($p > 0.05$). For all biomarkers evaluated, there was no statistically significant difference between ESRD patients with osteopenia/osteoporosis versus ESRD patients who did not have concomitant BMD disorder ($p > 0.05$).

Conclusions: Overall, there were significant differences in biomarkers related to bone turnover and osteoclastic/osteoblastic activity in ESRD patients compared to the normal population. These findings support the hypothesis that bone metabolism is significantly affected in patients with ESRD.

PUB064

Reducing Pill Burden of Phosphate Binders Has the Potential to Improve Patient Adherence

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Background: Pill burden and medication intolerance are important factors that influence phosphate binder adherence for managing hyperphosphatemia. The number and size of pills are key factors contributing to pill burden. We compared the pill burden of currently approved phosphate binders with lanthanum dioxycarbonate (RenaZorb), second-generation, lanthanum-based drug in development to evaluate its potential for improving patient adherence.

Methods: A literature analysis of phosphate-binding medications were examined to assess the impact of pill size and pill number on non-adherence in hemodialysis patients. We also compared their equivalent doses relative to the phosphorus binding capacity of 1 g calcium carbonate (PBED) in table 1.

Results: Amongst approved phosphate binders lanthanum carbonate and sucroferric oxyhydroxide have lower pill burden than other phosphate binders but higher discontinuation rates than some due to patient intolerance. Phase 1 data for lanthanum dioxycarbonate[1], suggest comparable urinary excretion of phosphate to published data for lanthanum carbonate.

Conclusions: Lanthanum dioxycarbonate has the potential to significantly improve patient compliance by offering a lower-in-class pill burden and smaller sized tablets to achieve similar therapeutic benefit as other phosphate binders. Reference: [1]Finn WF, DenupCiocca CJ, Joy MS et al. Double-Blind Dose-Ranging Study of Lanthanum Dioxycarbonate (Renazorb) in Healthy Volunteers Shows High Phosphorous Binding Capacity. Kidney Week 2013, Atlanta, GA, Nov 5-10

Funding: Commercial Support - Unicycive Therapeutics Inc., Private Foundation Support

Dosages of selected phosphate binders required to reach a phosphorous binder equivalent dose (PBED). Table is modified from St. Peter[2]

Phosphate binder	Tablet strength (mg)	Tablet Size (mm)	Dose of binder needed to reach a PBED of 6 g/day [a]	Approximate number of tablets to reach PBED of 6 g day	Grams of calcium in 6 g PBED dose
Calcium carbonate	648	11	6	8	2.4
Calcium acetate	667	13	6	9	1.5
Lanthanum Carbonate	500 [b]	18	3	6	0
Sevelamer carbonate	800	19-21	8	10	0
Sucroferric oxyhydroxide	500	20	1.5	3.75	0
Ferric citrate	210	19	2	9	0
Lanthanum dioxycarbonate	500	11	2.1	4	0

[a] In US dialysis patients, PBED averages around 6 g/day. This means that patients require 6 g/day of calcium carbonate to control their serum phosphorous. [b] Tablets are sold by weight of lanthanum and not of lanthanum carbonate. 2 WL. St Peter, LD Wazny, E Weinhandl et al. Drugs, 2017, 77:1155-1186

PUB065

High Fructose Diet-Induced Hypertension and Renal Damages Are Exacerbated in Dahl Salt-Sensitive Rats via Renal Renin-Angiotensin System

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Background: High-fructose diet (HFr) was reported to induce metabolic syndrome, salt-sensitive hypertension and multiple organ damages. However, it has been unknown whether the HFr-induced hypertension and renal damages exaggerate in subjects with salt sensitivity. Thus, we tested impacts of HFr on blood pressure, renal damages and expression of renal renin-angiotensin system(RAS) components in Dahl salt-sensitive (DS) and salt-resistant (DR) rats in a normal-salt intake condition.

Methods: Six-week old, male DS rats and DR rats were fed a control diet or a HFr (60% fructose) with a normal-salt content (1.25%) for 12 weeks. Systolic blood pressure (SBP) and urinary albumin excretion were measured every 2 weeks. After 12 weeks, plasma biochemical parameters and renal histology were examined. Furthermore, we tested effects of enalapril (10mg/kg/day) and candesartan (1mg/kg/day) in DS rats fed the HFr diet.

Results: Compared with the control diet, HFr significantly elevated SBP in DS rats (166±5 vs 115±2 mmHg) but not in DR rats (95±4 vs 90±2 mmHg). HFr induced albuminuria in both DS and DR rats (DS: 16.5±2.0 vs 3.9±0.4 mg/day; DR: 10.5±1.4 vs 5.0±0.7 mg/day). HFr significantly increased plasma triglyceride, uric acid and urea nitrogen in both DS and DR rats. However, HFr significantly increased creatinine clearance in DS rats but not changed in DR rats. HFr-induced glomerulosclerosis, podocyte injury and tubulointerstitial fibrosis exaggerated in DS rats compared with DR rats. HFr significantly increased the renal expression of renin, (pro)renin receptor ((P)RR), angiotensin converting enzyme (ACE), angiotensin II type 1 receptor (AT1-R) in DS rats. In contrast to DS rats, HFr significantly decreased the renin and AT1-R expressions without changing the (P)RR or ACE expression in DR rats. Both enalapril and candesartan attenuated the HFr-induced hypertension, albuminuria, and renal damages in DS rats.

Conclusions: Even in the normal-salt intake condition, HFr-induced hypertension and renal damages are exacerbated in DS rats compared with DR rats via renal RA system. HFr may have a higher risk to develop hypertension and renal damages in human with salt sensitivity, and RAS inhibitors are effective against the HFr-induced renal damages.

Funding: Government Support - Non-U.S.

PUB066

Cordyceps militaris Preserves Nephrin Expression on Podocyte Under TGF-β1 and Hyperglycemia Stimulation

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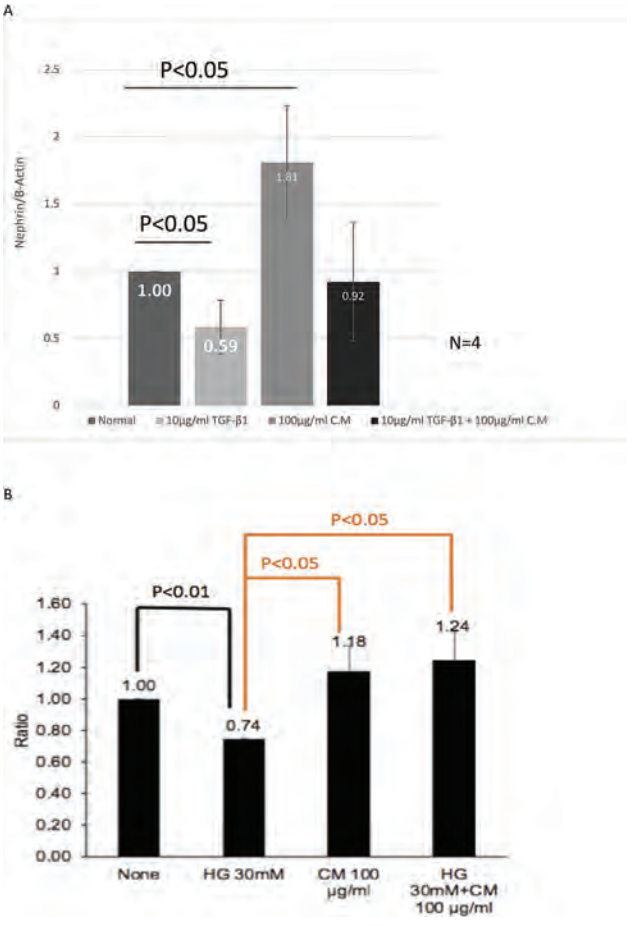
Background: Cordyceps militaris (CM) is a kind of fungus used as herbal medicine for multiple purposes. The study aim is to know the effect of CM on nephrin expression under the TGF-β1 and hyperglycemic stimulation.

Methods: Experiment 1: Cultured podocytes were divided into four groups treated with Group 1 Control, Group 2 TGF-β1 10ng/ml, Group 3 CM100ug/ml and Group 4 both CM and TGF-β1. Experiment 2: Podocytes were cultured in different mediums: Group 1 normal, Group 2 High glucose (HG; 30mM), Group 3 CM100ug/ml, in normal medium, Group 4 CM100ug/ml in HG medium. Protein was extracted on day 6 for nephrin analysis.

Results: The nephrin expression was significantly lower in the TGF-β1 group and higher in the CM group than it was in the control group. When podocytes were treated with CM and TGF-β1 simultaneously, the CM could restore the nephrin expression as compared to TGF-β1 group (Figure 1A). Hyperglycemia suppressed the nephrin expression and CM significantly attenuated this effect (Figure 1B)

Conclusions: CM might not only enhance the nephrin expression of podocytes but also attenuate the nephrin suppression from TGF-β1 and hyperglycemia.

Funding: Commercial Support - Phytomed Bio-Tech co., Ltd.Taiwan.



Nephrin expression on Day 6 after stimulation of (A) TGF-β1 and (B) hyperglycemia

PUB067

Irisin-Regulated miR-29 Expression in db/db Mice

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Background: In mice, it has been demonstrated that irisin plays a key role in metabolic regulation, energy expenditure. Both animal and in vitro studies have suggested that irisin exerts anti-inflammatory effects modulating the production of cytokines as IL-6, IL-1β and TNF-a. Inflammation and its consequent fibrosis are two main features of diabetic nephropathy. miR-29b is a novel therapeutic agent capable of inhibiting progressive renal inflammation and fibrosis. However, the function of irisin and miR-29b for regulation for diabetic nephropathy remain unexplored.

Methods: Male db/db mice and their normal littermates (db/m) at the age of week 12 were purchased from Laboratory Animal Services Centre, the Nanjing University of China. Groups of four mice were used, groups of db/m or db/db mice were treated with/without irisin or empty vector control from the age of week 12 and sacrificed at week 20, then to detecte the expression miR–29 of renal tissue.

Results: In groups of db/m or db/db mice were treated with/without irisin, miR–29a-3p, miR–29a-1-5p miR–29c-3p, and miR–29c-5p were no significant change(***P***>0.05). miR-29b was significant change(***P***<0.05), the group of db/db mice were treated with irisin had higher level of miR-29b, lower body weight and blood sugar Compared with db/db mice without irisin treatment.

Conclusions: The irisin may regulate miR-29b level, and improved metabolic regulation, energy expenditure, and inflammation state.

PUB068

MicroRNA Profile as a Therapeutic Target for Diabetic Nephropathy

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Background: Diabetic nephropathy is a leading cause of chronic kidney disease in diabetic patients requiring renal replacement therapy. Chronic low-grade systemic inflammation coupled with impaired microvascular function, podocyte apoptosis, epithelial to mesangial transformation and fibrosis are the critical hallmarks for the pathogenesis of Diabetic Nephropathy. MicroRNAs (miRNAs) regulate the function of various downstream molecular pathways involved in Diabetic nephropathy pathophysiology.

Methods: This review focuses on the recent developments and identification of therapeutic potential of various miRNAs on the prevention and treatment of Diabetic Nephropathy. An in-depth systematic review of full-text original articles published in English in a period between 2008 and 2019 and indexed in PubMed, Ovid Medline or Embase was conducted.

Results: Stimulation of miRNAs that are commonly downregulated and inhibition of miRNAs that are upregulated or modulation of an intermediary target for miRNAs were found to be renoprotective and reduce albuminuria, decrease mesangial cell proliferation, decrease epithelial to mesenchymal transition, reduce podocyte foot process effacement and apoptosis & inhibit glomerular or tubulointerstitial fibrosis.

Conclusions: Therapeutic agents targeting the miRNAs have the potential in the prevention of diabetic nephropathy as well as early treatment and prevention of progression.

PUB069

Renal Function Decline in Type 2 Diabetes: Post Hoc Analysis of LEADER

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Background: Diabetic kidney disease (DKD) is a frequent complication in type 2 diabetes (T2D). Identifying patients at risk of fast DKD progression is key for early care. This LEADER post-hoc analysis describes patients with varying renal function decline.

Methods: LEADER (NCT01179048) was a randomized double-blind cardiovascular (CV) outcomes trial of liraglutide (≤1.8 mg/day) vs placebo, both added to standard care, in 9340 patients with T2D and high CV risk (median follow-up 3.8 years). Renal function decline (average decline in estimated glomerular filtration rate [eGFR] from month 6 to month 24 or later) was classified from patient-specific slopes estimated via linear regression. Disregarding treatment arms, patients were categorized according to annual eGFR decline (mL/min/1.73m²): ≤5 (77% of patients), >5 to ≤10 (17%), >10 to ≤15 (4%) or >15 (2%) and differences in baseline characteristics were investigated using 2-sided trend tests (Jonckheere-Terpstra for continuous, Cochran-Armitage for binary and Goodman and Kruskal's Gamma for ordinal parameters).

Results: Overall mean (standard deviation) eGFR decline was 2.2 (5.7) mL/min/1.73m2/year. Largest average eGFR decline was associated with longer T2D duration (P=0.02), higher baseline A1C (P<0.001), urinary albumin-to-creatinine ratio (UACR; P<0.0001), systolic (P<0.0001) and diastolic blood pressure (BP; P<0.01), total cholesterol (P=0.02), being a current smoker (P=0.04) and insulin use (P<0.01; Table). Patients with the largest eGFR decline tended to have higher eGFR at baseline (P<0.0001).

Conclusions: This post-hoc analysis confirmed the importance of glycemic levels, systolic BP levels and smoking status for the risk of fast annual eGFR decline (>5mL/min/1.73m2). Fast annual eGFR decline was associated with high baseline eGFR.

Funding: Commercial Support - Novo Nordisk

Table. Renal decline according to baseline characteristics

Baseline characteristic	Renal decline (mL/min/1.73m²/year)			
	≤5 N=6099	>5 to ≤10 N=1366	>10 to ≤15 N=312	>15 N=147
Age, years	64.4 (7.2)	63.8 (6.8)	62.6 (6.6)	63.5 (7.4)
Male sex, n (%)	3939 (64.9)	854 (62.5)	201 (64.4)	88 (59.9)
Body mass index, kg/m²	32.5 (6.1)	32.5 (6.3)	32.6 (7.2)	31.6 (6.4)
Diabetes duration, years	12.6 (8.0)	13.0 (7.7)	12.5 (7.4)	13.1 (8.0)
A1C, %	8.6 (1.4)	8.9 (1.6)	9.1 (1.7)	9.2 (1.9)
eGFR, mL/min/1.73m²	79.0 (25.8)	85.6 (27.7)	94.0 (28.6)	101.5 (33.5)
UACR, mg/g*	16.0 (462.3)	33.0 (860.9)	40.2 (808.1)	50.3 (1198.8)
Systolic BP, mmHg	135.3 (17.4)	138.0 (17.7)	138.1 (19.1)	138.5 (18.8)
Diastolic BP, mmHg	77.0 (10.1)	77.5 (10.2)	78.8 (10.8)	78.5 (10.2)
Smoking status, n (%)				
Current	667 (10.9)	192 (14.1)	42 (13.5)	30 (20.4)
Previous	2874 (47.1)	605 (44.3)	149 (47.8)	58 (39.5)
Never	2558 (41.9)	569 (41.7)	121 (38.8)	59 (40.1)
History of ischemic heart disease, n (%)	3359 (55.1)	701 (51.3)	164 (53.0)	66 (44.9)
LDL cholesterol, mg/dL	89.9 (35.6)	89.3 (35.8)	94.7 (36.6)	97.2 (39.4)
Total cholesterol, mg/dL	169.0 (43.9)	169.6 (44.4)	178.0 (54.8)	175.0 (48.6)
Insulin treatment, n (%)	2679 (43.9)	637 (46.6)	143 (45.8)	83 (56.5)
Lipid-lowering therapy, n (%)	4702 (77.1)	1020 (74.7)	221 (70.8)	97 (66.0)
RAAS blocking therapy, n (%)	4903 (80.4)	1118 (81.8)	247 (79.2)	120 (81.6)

Unless stated otherwise, data are mean (standard deviation). *Geometric mean (coefficient of variation)
A1C, glycated hemoglobin; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system

PUB070

Clinicopathological Findings and Renal Outcome of Diabetic Nephropathy in Type 2 Diabetes: A Single-Center Study in Japan

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Background: Besides conventional clinical factors such as CKD stage, pathological findings have become important in diabetic nephropathy (DN) due to their usefulness to predict prognosis. In 2015, Japan Renal Pathology Society (JRPS) developed a new pathological classification of DN, describing the detailed glomerular changes compared to that Tervaert *et al*. had reported (J Am Soc Nephrol 21: 556-563, 2010). Recently, Hoshino *et al*. have created J-score, a novel DN pathological scoring system with the JRPS classification (Plos One 13: e0190923, 2018). They proved the J-score to be a significant predictor of renal outcome. Here, we investigated the association of pathological findings with renal prognosis in DN by utilizing the J-score.

Methods: We analyzed 13 followable Japanese patients who underwent renal biopsy and were diagnosed with DN in our department from Dec. 2006 to Aug. 2015. We evaluated their pathological findings based on the J-score and studied their associations to renal outcome (dialysis initiation, doubling serum creatinine level, or 50% eGFR decline) at three years after the biopsy.

Results: All patients had type 2 diabetes with the mean duration of 9.8 ± 8.8 years. Diabetic retinopathy was observed in 9 patients. At the time of renal biopsy, the mean values of age, serum creatinine level, eGFR, urinary protein level, HbA1c level, and systolic blood pressure were 55.0 ± 7.2 years, 1.4 ± 0.6 mg/dl, 47.7 ± 23.2 ml/min/1.73 m², 5.2 ± 4.0 g/gCre, 6.9 ± 1.8%, and 148 ± 22.7 mmHg, respectively. Renal biopsy findings included diffuse lesions in 11 patients, exudative lesions in 11 patients, nodular lesions in 9 patients, and mesangiolysis in 7 patients. According to the previous report, we divided patients into four groups (grades 1 to 4), those with the J-score 0-5 (grade 1), 6-10 (grade 2), 11-15 (grade 3), and 16-19 (grade 4), respectively. The detailed numbers of the patients in each group were as follows: one in grade 1, five in grade 3, and seven in grade 4. Renal events were found to be zero (0%) in grade 1, two (40%) in grade 3, and five (71%) in grade 4.

Conclusions: In our single-center study, we observed the trend of worsening renal prognosis as the grade of the J-score increased. This finding suggests the potential of the scoring system for prognostic prediction of DN.

PUB071

Individual Effects of Liraglutide on Cardiorenal Risk Markers: Results from the LEADER Trial

Frederik Persson,[1] Emilie Hein Zobel,[2] Tine Hansen,[3] Soren Rasmussen,[4] Bernt Johan Von Scholten,[4] Benjamin Wolthers,[5] Peter Rossing.[1,6] *[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [2]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [3]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [4]Novo Nordisk A/S, Søborg, Denmark; [5]Novo Nordisk A/S, Søborg, Denmark; [6]University of Copenhagen, Copenhagen, Denmark.*

Background: Liraglutide has pleiotropic effects improving cardiorenal risk markers and beneficial effects on cardiac and renal outcomes. This LEADER post-hoc analysis investigated cross-dependency in the individual treatment response to liraglutide in 6 cardiorenal risk markers.

Methods: LEADER (NCT01179048) randomized patients (n=9340) to liraglutide or placebo (1:1) in addition to standard of care. We interrogated 6 markers at baseline and after 1 year of therapy: glycated hemoglobin (A1C), body weight, systolic blood pressure (SBP), urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR) and low-density lipoprotein (LDL) cholesterol. In the liraglutide group, 'good responders' in a specific marker were defined as those with a change from baseline

(A1C, weight, SBP: observed difference; UACR, eGFR, LDL: observed ratio) within the best quartile (Q4); the remaining were classified as 'low responders'.

Results: Treatment difference (liraglutide-placebo) after 1 year: weight -2.4 (95% CI: -2.6;-2.2) kg; A1C -0.70 (-0.75;-0.65) %; SBP -1.9 (-2.6;-1.3) mmHg; treatment ratio (liraglutide/placebo): UACR 0.77 (0.73;0.81), eGFR 0.99 (0.99;1.0) and LDL 0.98 (0.97;0.99). In general, we observed statistically significant but not clinically relevant associations in risk marker response. Thus, for good vs low responders in A1C, the difference in weight change was -2.8 (5.5) vs -2.6 (5.0) kg (P=0.44); SBP -0.99 (18.0) vs -2.3 (17.5) mmHg (P=0.04), UACR 0.77 [2.0] vs 0.88 [1.7] (P=0.001), eGFR 0.94 [0.19] vs 0.97 [0.17] (P<0.001) and LDL 0.99 [0.34] vs 1.00 [0.33] (P=0.14) (Table).

Conclusions: Good response in 1 cardiorenal risk marker was not in general associated with a clinically relevant response in other markers. The substantial heterogeneity in individual risk marker response is important when effect of liraglutide is evaluated in the clinic.

Funding: Commercial Support - Novo Nordisk

Table. Good versus low responders in 6 cardiorenal risk markers for the liraglutide-treated group

Variable	A1C Q4	A1C Q1-Q3	P	Weight Q4	Weight Q1-Q3	P	SBP Q4	SBP Q1-Q3	P	UACR Q4	UACR Q1-Q3	P	eGFR Q4	eGFR Q1-Q3	P	LDL Q4	LDL Q1-Q3	P
A1C (%)	**-3.2 (1.4)**	**-0.77 (0.92)**	*	-1.5 (1.3)	-1.3 (1.4)	*	-1.3 (1.3)	-1.4 (1.5)		-1.6 (1.5)	-1.3 (1.4)	*	-1.2 (1.2)	-1.4 (1.4)	*	-1.3 (1.4)	-1.4 (1.4)	*
Weight (kg)	-2.8 (5.5)	-2.6 (5.0)		**-9.0 (5.0)**	**-0.49 (2.9)**	*	-3.5 (5.5)	-2.3 (5.0)	*	-3.2 (5.5)	-2.5 (5.0)	*	-3.3 (5.4)	-2.4 (5.0)	*	-2.6 (5.0)	-2.6 (5.2)	
SBP (mmHg)	-0.99 (18.0)	-2.3 (17.5)	*	-5.2 (17.7)	-0.86 (17.4)	*	**-23.2 (10.1)**	**-5.4 (13.2)**	*	-5.9 (17.5)	-0.66 (17.4)	*	-1.2 (18.0)	-2.9 (17.5)	*	-2.8 (17.8)	-1.4 (17.5)	*
UACR ratio	0.77 [1.9]	0.88 [1.7]	*	0.75 [1.8]	0.89 [1.7]	*	0.68 [1.7]	0.92 [1.7]	*	**0.20 [0.99]**	**1.4 [0.99]**	*	1.1 [1.9]	0.80 [1.7]	*	0.78 [1.7]	0.88 [1.7]	*
eGFR ratio	0.94 [0.19]	0.97 [0.17]	*	0.97 [0.17]	0.98 [0.17]	*	0.94 [0.18]	0.97 [0.17]	*	0.93 [0.18]	0.97 [0.17]	*	**1.2 [0.14]**	**0.91 [0.14]**	*	0.96 [0.16]	0.97 [0.17]	
LDL ratio	0.99 [0.34]	1.0 [0.33]		0.99 [0.33]	1.0 [0.33]		0.99 [0.33]	1.00 [0.34]		0.97 [0.34]	1.0 [0.33]	*	1.0 [0.34]	1.0 [0.33]		**0.88 [0.34]**	**1.1 [0.25]**	*

Comparison of the change in the 5 other risk markers for 'good' compared to 'low' responders in one specific risk marker. Liraglutide-treated participants. Good responders had a change in a specific risk marker within the best quartile. Mean (standard deviation), geometric mean [coefficient of variation]. P: two-sample t-test using Satterthwaite approximation. *P<0.05

PUB072

Prevalence of Triglyceride Deposit Cardiomyovasculopathy in CKD Patients

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Background: Triglyceride deposit cardiomyovasculopathy (TGCV) had been recently described (Hirano K, et al. N Engl J Med 2008; 359(22): 2396) from heart transplantation patient. Primary TGCV is caused by genetic Adipose triglyceride lipase (ATGL)mutation. The lack of ATGL caused disorder of triglyceride metabolism resulting in the accumulation of triglyceride in many kinds of cells. Idiopathic TGCV is caused by decrease of activity of ATGL in spite of gene mutation from unknown reason. Idiopathic TGCV had been observed in diabetes patients (Ikeda Y, et al. Pathol Int 2014;64:325.). Washout ratio in BMIPP (123I-beta-methyl-P-iodophenyl-pentadecanoic acid) scintigraphy, which can evaluate the triglyceride metabolism in heart, manifested marked decrease. Jordan body, which is some kind of lipid vesicles, can be observed in white blood cells. Heart failure occurs because the metabolism in heart usually required triglyceride. As the prevalence of idiopathic TGCV remained unknown, we evaluate the prevalence of TGCV in CKD patients with heart failure from unknown origin.

Methods: Diabetes patients with chronic kidney disease and heart failure from unknown origin were evaluated by BMIPP scintigraphy, Wash out rate in BMIPP scintigraphy less than 5% was treated as positive for TGCV. All patients gave the written informed consent.

Results: Ten candidate patients were evaluated by BMIPP scintigraphy. Average of age was 51.4 years old. Average of creatinine was 6.1+-2.9mg/dl. Four patients (40%) had positive BMIPP study (Washout rate less than 5%), who were diagnosed as idiopathic TGCV. TGCV patients were significantly younger than non-TGCV patients (40.5+-1.1 years old vs 58.7+- 12 years old, P=0.0188). TGCV patients had worse heart failure (Ejection Fraction) than non-TGCV patients (33+-12% vs 47+-13%). There was no change of septum thickness (10.7+-2.2mm vs 9.6+-0.9mm). Coronary lesions had been overserved more frequently in TGCV patients than non-TGCV patients (100% vs 66%). Diabetic retinopathy had been overserved more frequently in TGCV patients than non-TGCV patients (75% vs 33%). It remained unclear the reason why TGCV was highly associated with diabetes CKD patients.

Conclusions: Prevalence of idiopathic TGCV patients was 40% in diabetes patients with chronic kidney disease and heart failure from unknown origins.

PUB073

Risk Factors of Cardiovascular Disease in Diabetic Hemodialysis Patients with Smoking Is Extremely High: Smoking Cessation Is Important to Their Prognosis

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Background: Prevention of the development of CVD, which is the major cause of death, is key to improving prognosis. We had investigated factors associated with CVD mortality risk in maintenance dialysis patients. In this study, an additional analysis was performed on data in hemodialysis patients with diabetic nephropathy compared with those having other underlying diseases. And furthermore, we investigated factors that influence CVD mortality risk in hemodialysis patients with diabetic nephropathy.

Methods: This retrospective study was conducted with 201 outpatients with hemodialysis at our Blood Purification Therapy Center and our other related hemodialysis facilities (57 diabetic nephropathy and 144 others). Logistic regression analysis was conducted with outcome- measured as CVD death. Hemoglobin levels and blood pressure values before and after dialysis were summed up at 3, 6, and 12 months. A curve was obtained by changes in blood pressure per month and the area under the blood pressure curve (AUC) was calculated.

Results: Diabetic nephropathy was the highest mortality risk among underlying disease groups. A comparison with other underlying diseases revealed that significant differences were found for the variables older age ($p<0.001$) and a shorter history of hemodialysis ($p<0.001$) in patients with diabetic nephropathy. There was no significant difference in anemia control between two groups. Poor blood pressure control and higher dose of erythropoietin were found in patients with diabetic nephropathy. The multivariate analysis of risk factors for mortality in patients with diabetic nephropathy showed that smoking (odds ratio(OR): 4.71 [95%CI: 1.97~11.26, p<0.001], history of ischemic heart disease (OR: 2.56 [95%CI: 0.95~6.85, p=0.061], age (OR: 1.07 [95%CI: 1.03~1.13, p=0.002], and a history of dialysis therapy (OR: 0.78 [95%CI: 0.69~0.87, p<0.001] were risk factors.

Conclusions: Introduction to hemodialysis for patients with diabetic nephropathy, given higher CVD mortality risk, it is important to actively prevent the development of CVD shortly after hemodialysis. Furthermore, higher smoking rates with higher CVD mortality risk associated with smoking among patients with diabetic nephropathy suggested that smoking cessation is important for patients with diabetic nephropathy to improve their prognosis.

PUB074

Pentoxifylline in Diabetic Kidney Disease: The VA Pentoxifylline in Diabetic Kidney Disease PTXRx Study

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Background: Diabetic kidney disease (DKD) is the most frequent cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the U.S. The recent CREDENCE trial demonstrated that the sodium-glucose cotransporter 2 (SGLT2) inhibitor canagliflozin reduced ESRD and cardiovascular events in DKD patients with an estimated glomerular filtration rate (eGFR) of 30 to <90 mL/min/1.73m^2 and a urinary albumin to creatinine ratio (UACR) of >300 to 5000 mg/g. This trial excluded patients with eGFR < 30 or lesser degrees of proteinuria. Recent experimental and clinical data suggest that the phosphodiesterase inhibitor pentoxifylline (PTX) may also decrease progression of DKD to ESRD. Putative mechanisms of action of PTX include an increase in intracellular cyclic AMP, inhibition of inflammatory cytokines, and reduced oxidative stress.

Methods: VA PTXRx is a randomized, controlled multicenter Veterans Affairs (VA) Cooperative Study to test the hypothesis that PTX, when added to usual care, leads to a reduction in the incidence of ESRD and death in type 2 diabetic patients with DKD when compared to usual care plus placebo. Secondary endpoints will be: (1) quality of life (2) time until doubling of serum creatinine, (3) hospitalization for congestive heart failure, (4) a three-point MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), (5) peripheral vascular disease, (6) percentage of participants with ≥ 50% reduction in UACR from baseline, (7) Rate of change in eGFR per year during the study period. The key statistical assumption is that the primary endpoint will occur in 26.6% of the placebo group at six years with a risk reduction of 19% for PTX compared with the placebo group. The study aims to randomize 2510 participants to either PTX or placebo. Inclusion criteria are based on risk of ESRD from the KDIGO "heat map"; participants must be in one of the following categories: eGFR 15 to <30; eGFR 30 to <45 and UACR > 30 mg/g; eGFR 45 to <60 and UACR > 300 mg/g.

Results: N/A

Conclusions: If PTX is found to reduce the incidence of ESRD and/or death, this will provide another effective treatment for DKD which could extend to patient groups not currently candidates for SGLT2 inhibitors.

Funding: Veterans Affairs Support

PUB075

Effect on Major Renal Outcome of Continuous Metformin Use in Patients with Type 2 Diabetes and Advanced Kidney Disease: A Retrospective, Propensity Score-Matched, Common Data Model-Based Cohort Study

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Background: Metformin is an effective, inexpensive and widely used drug for type 2 diabetes (T2DM) patients. However, use of metformin is contraindicated in patients with advanced CKD owing to risk of lactic acidosis. Although several studies have revealed metformin-associated lactic acidosis has rare incidence rate, study for metformin effectiveness in those patients is hard to conduct because of established contraindication. This study aimed to generate real-world evidence for effect of metformin on renal outcome in a T2DM patients with CKD.

Methods: We performed a retrospective, propensity score matched, observational cohort study by using The Observational Medical Outcomes Partnership common data model version 5. We used medical data of 1.82 million patients in a tertiary hospital in Korea from 2003 to 2017. Study participants were identified by drugs, diagnosis codes and laboratory test values in combination with event time. More than six months ongoing of metformin treatment after each index time of EPI-CKD eGFR< 60 ml/min/1.73m^2 were considered as treatment group. Never use of metformin after three months since index time were considered as comparative group. Composite renal outcome was defined as receiving renal replacement therapy, having EPI-CKD creatinine-based eGFR< 15 ml/min/1.73m^2 or in-hospital death. After 1:1 propensity score-based matching (PSM), Cox proportional hazards model was used to analyze hazard ratio for the renal outcome.

Results: An 894 of metformin using patients and a 236 of non-metformin using patients were identified. After 1:1 PSM, we matched each of 154 patients in both groups. Mean follow-up time were 7.2 and 5.4 years, respectively. Baseline age, sex distribution, EPI-CKD eGFR, HbA1c level and spot urine albumin-to-creatinine ratio were not significantly different between groups. Continuous metformin use was associated lower outcome risk (HR=0.29, 95% CI [0.10-0.81], p=0.008).

Conclusions: Continuous use of metformin was associated with lower incident rate of composite renal outcome in T2DM patients with reduced renal function equivalent to advanced CKD. This longitudinal real-world study may support benefit of metformin in T2DM patients having reduced renal function for major renal outcome.

PUB076

Implementation of Routine Foot Checks Among Dialysis Patients at an Outpatient Dialysis Clinic

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Background: Diabetes is the leading cause of lower limb amputations and renal failure in the United States. The risk of amputation is increased in people with long standing diabetes, poor glucose control, retinal or renal complications. The burden of diabetic foot disease on dialysis patients is huge as evidenced by high morbidity and mortality associated with it. Sadly, foot care is not an integral part of care provided in our clinics. Early recognition and management of risk factors for foot ulcers can delay the onset of adverse outcomes. Timely referral to a foot care specialist is critical in the care of these patients. We aimed to introduce foot examination as part of routine dialysis clinic care in order to identify patients at risk and refer for proper evaluation.

Methods: Patients with End Stage Renal Disease (ESRD) who had diabetes were identified by chart review. A total of 81 patients were identified. A foot check list was developed and distributed at the clinic. Foot exams were done by the nurses while patients were receiving scheduled hemodialysis. It was focused on physical examination, including checking for intact skin, corns and calluses, toe nail and checking for poor circulation. Foot education was provided at the end of the exam

Results: 81(52%) out of a total of 156 patients who were receiving dialysis care at the pilot site had diabetes. 79 (98%) of patients who had diabetes participated in the foot checks. About half of the patients had abnormal findings. The most notable finding was in-growing toe nails which was found in about 81% of the patients. Corns or Calluses were present in 32% of the patients. Non intact skin and abnormal color was found in 24% and 28% of the patients respectively. These patients with abnormal findings were referred to podiatry for further evaluation and care

Conclusions: Patents with abnormal foot exam were appropriately identified and referred to podiatry for further evaluation and treatment. We believe that regular foot exams for patients with ESRD who have diabetes is critical to their care. Our target is to implement routine foot care across all Emory dialysis clinics

PUB077

Analysis of 416 Non-Dialysis Inpatients with Diabetic Kidney Disease: A Retrospective Cohort Study

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Background: Diabetic kidney disease (DKD) has become one of the major causes of end-stage renal disease worldwide. In China, there is an obviously increasing trend of hospitalization rate with DKD. We aim to explore the survival of hospitalized patients with DKD through a single-center retrospective analysis.

Methods: Patients in hospital during 2011/01/01 to 2016/12/31 diagnosed with DKD but without commencing renal replacement therapy (RRT) at the time of diagnosis were included, excluding patients whose interval between the time of diagnosis and the time of receiving RRT less than 3 months or only with baseline follow-up data. Taking death or receiving RRT as a composite endpoint, survival time was compared after dividing patients into different groups according to whether angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) was used or not and whether hemeturia occurred or not. Cox regression was used to analize the influence of ACEIs, ARBs and hemeturia on the prognosis of DKD.

Results: 416 patients were enrolled, of which 155 received RRT, 31 died, 176 survived and 54 were lost to follow-up. The median survival time for the whole with composite endpoint was 27.53 months. The median survival time of patients in 3 or 4 stage chronic kidney disease (CKD) was 33.03 months while it's 11.47 months in 5 stage CKD (P < 0.001). The median survival time of patients using ACEIs of ARBs was longer than that without using (43.03 months vs 17.60 months, P < 0.001). The use of ACEIs or ARBs had a lower risk of death or entering RRT when adjustment for case mix (gender, age, BMI, duration of diabetes, history of hypertension and use of diuretics) (HR, 0.390; 95% CI, 0.279-0.545; P < 0.001). The median survival time of patients without hemeturia was 39.30 months while those with hemeturia was 20.30 months (P = 0.002), and it's risk of composite endpoint was higher compared with patients without hemeturia after adjusting for gender, age, BMI, duration of diabetes, history of hypertension and use of diuretics (HR, 1.483; 95% CI, 1.040-2.115; P = 0.029).

Conclusions: The use of ACEIs or ARBs is considerably beneficial to the prognosis of DKD. Hemeturia is not conducive to the survival of patients with DKD, which needs further researches.

PUB078

Patterns of Hospitalisation in Individuals with and Without Diabetes: Results from a Large Australian Linked Cohort Study (EXTEND45)

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Background: Diabetes is a risk factor for cardiovascular and renal complications. We sought to compare hospitalisation rates in individuals with and without diabetes, and additionally examine the hospitalisations for cardiovascular disease (CVD) and end-stage renal disease (ESRD) in these groups.

Methods: The EXTEND45 Study (2005-2014) is a linked dataset that combines baseline questionnaire responses (2006-2009) with data from community pathology providers, medical services and prescription medication data (the Medicare Benefits Schedule [MBS] and Pharmaceutical Benefits Scheme [PBS]; provided by the Department of Human Services) and for participants of the population-based 45 and Up Study (n = 267,153). MBS and PBS data was linked by the Sax Institute and all other data sources by the Centre for Health Record Linkage. Individuals with diabetes were identified using pre-specified criteria. All hospitalisations between January 2006 and June 2014 were identified and the proportion and mean LOS of hospitalisations calculated.

Results: Amongst 151,760 individuals with linked pathology data, 24,400 met the criteria for diabetes. Of these, 17,293 (70.9%) received glucose-lowering pharmacotherapy at any time during the study period. The annual mean number of overnight hospitalisations per individual was 0.33 for those without diabetes, 0.62 for those with diabetes but not receiving pharmacotherapy and 0.66 for those with diabetes and receiving pharmacotherapy. The diabetes cohorts had a higher proportion of hospitalisations due to CVD (7.6-8.9%) and ESRD (0.8%) than individuals without diabetes (6.0% and 0.3%, respectively). Mean LOS for CVD-related hospitalisations for those receiving pharmacotherapy, for those with diabetes and not receiving pharmacotherapy, and for those without diabetes was 6.13 (SD 8.12), 6.02 (SD 6.80) and 5.41 (SD 6.58) days, respectively. The corresponding mean LOS for ESRD-related hospitalisations was 15.4 (SD 18.0), 13.0 (SD 19.4) and 14.5 days (SD 17.6) days respectively. Limitations include sampling biases in the opt-in design of the 45 and Up Study.

Conclusions: Differences in the patterns of hospitalisation between individuals with and without diabetes were observed. Factors driving this warrant further investigation.

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PUB079

Noninvasive Method of Differentiating Diabetic Nephropathy and Nondiabetic Renal Disease Using Serum Bone Morphogenetic Protein 7 and TGF-Beta1 Levels

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Background: The current evidence for clinical benefits from the administration of BMP-7 in diabetic nephropathy remains limited, and mainly derived from animal models. In this context, this study is taken up with an aim to assess the circulating levels of serum TGF β1 and BMP 7 in patients of type 2 Diabetes mellitus and to assess the correlation between IFTA and serum BMP 7, TGF β1 levels.

Methods: This is a prospective observational study done from December 2014 to December 2016 in Department of Nephrology, Gandhi hospital, Hyderabad in 100 patients of type 2 Diabetes mellitus patients presenting with symptoms and signs of renal disease. **Selection Criteria: Inclusion Criteria:** Patients with Type 2 Diabetes mellitus presenting with clinical features of renal disease in the form of urinary abnormalities with or without rise in serum creatinine. **Exclusion Criteria** Diabetes mellitus with acute kidney injury DM with pregnancy Type 1 diabetes mellitus Type 2 diabetes mellitus without renal insufficiency and proteinuria

Results: Mean BMP 7 levels in histopathological class DN II was 28 ng/ml, DN III was 18±7.13 ng/ml, DN IV was 15.15±9 ng/ml. Over all Serum BMP 7 levels are lower in DN and the levels progressively decreased with increasing histopathological class of DN (P = 0.47). Over all serum TGF β1 levels are higher in patients with DN and the values progressively increased with increasing histopathological class of DN (P = 0.07). Mean BMP 7 levels in patients with IFTA < 25% in NDRD was 474.89 ± 58 ng/ml, in biopsy proven DN was 12 ± 5.8ng/ml, and the difference is statistically significant (P< 0.0001). Mean BMP 7 levels in patients with IFTA 25% to 50 % in NDRD was 460 ng/ml, in biopsy proven DN was 21.7 ± 12.8ng/ml and the difference is statistically significant (P = 0.02).

Conclusions: (1)Low serum BMP 7 and high TGF beta 1 levels may be used as screening markers to differentiate diabetic nephropathy and non diabetic renal disease, instead of subjecting the patients to an invasive procedure like renal biopsy. (2) Low serum BMP 7 and high TGF beta 1 levels have a strong correlation with increasing severity of histopathological class of diabetic nephropathy.

PUB080

How Important Is Glucose Nephrotoxicity in Type 2 Diabetes Mellitus-Associated Cardiovascular Risk?

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Background: Diabetes mellitus is frequently associated with different macro and microvascular lesions, widely accepted as responsible for the high cardiovascular morbidity and mortality associated with this pathology. It is also accepted that diabetic nephropathy is part of this spectrum of vascular involvement. Recently several multicenter clinical trials have digged into this association between diabetes and cardiovascular damage. The first one, EMPAREG, showed that the inhibition of SGLT2 in the proximal tubule reduced cardiovascular mortality, mortality from any cause, hospitalization due to chronic heart failure (CHF) and the progression of the renal lesion, but had little or no effect on non-lethal acute myocardial infarction (AMI) or non-lethal stroke. The studies on iSGLT2 that followed, CANVAS and DECLARE, have shown apparently discordant effects, with significant effects in some cardiovascular outcomes, but not in others. Although various explanations have been proposed, none justifies the heterogeneity between the studies. So, discussion about the existence or not of a class effect persists.

Methods: In this study, we perform a meta-regression of the three studies comparing the prevalence of any single or composite variable in the control group against the reduction in the risk obtained with every iSGLT2. And we compared the results with those of the HOPE study.

Results: Meta-regression shows that SGLT2 blockade reduces in a risk-dependent manner cardiovascular mortality, hospitalization due to CHF and the progression of nephropathy, but not the risk of stroke or AMI. The results are exactly as expected according to the HOPE study if the primary mechanism of cardiovascular protection in diabetes mellitus type 2 treated with iSGLT2 is the reduction in kidney damage.

Conclusions: We discuss the evidences of this interaction between iSGLT2 and renal tubular damage of different etiologies, the mediating role of the inflammasome activated by the renal tubular lesion on vascular and cardiac damage and propose an explanation for the absence of effects at the central nervous system level.

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PUB081

Lipoprotein(a) and Decline in Renal Function, Incidence of Cardiovascular Disease, and Mortality in Individuals with Type 2 Diabetes and Microalbuminuria

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Background: Lipoprotein(a) (Lp(a)) has emerged as an independent risk marker for cardiovascular disease (CVD) in both general populations and populations with existing CVD. We investigated associations between Lp(a) concentrations and decline in renal function, incidence of CVD and all-cause mortality in individuals with type 2 diabetes, microalbuminuria and no history or symptoms of coronary artery disease.

Methods: Prospective cohort of 198 individuals with type 2 diabetes and microalbuminuria (moderately increased urinary albumin excretion rate (UAER) 30-300 mg/24 hours). All-cause mortality and CVD (fatal and non-fatal) events were tracked from national registries. Yearly p-creatinine was measured after baseline in 176 of the participants. The renal endpoint was defined as eGFR-decline of >30% from baseline. Cox regression analyses were applied both unadjusted and adjusted for traditional risk factors (sex, age, systolic blood pressure, LDL-cholesterol, smoking, HbA_{1c}, creatinine and UAER).

Results: Baseline mean (SD) age was 58.7 (8.6) years, eGFR 89.1 (17.4) ml/min/1.73m2, 77% were male, and median [IQR] UAER was 103 [38-242] mg/24-h. Median Lp(a) was 8.04 [3.42-32.3] mg/dL. Median follow-up was 6.1 years; 38 CVD events, 26 deaths and 43 renal events were recorded. For each doubling of baseline Lp(a), the following hazard ratios (95% confidence intervals) were found before and after adjustment respectively: 0.98 (0.84-1.15) and 1.01 (0.87-1.18) for a decline in eGFR>30%, 0.96 (0.81-1.13) and 0.99 (0.82-1.18) for cardiovascular events, 1.04 (0.85-1.27) and 1.06 (0.87-1.30) for all-cause mortality.

Conclusions: In this cohort of individuals with type 2 diabetes and microalbuminuria, the baseline concentration of Lp(a) was not a risk factor for decline in renal function, CVD events or all-cause mortality.

PUB082

Diabetic Fibrillosis: The Resurgence of an Entity of Unknown Significance

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Background: Diabetic Fibrillosis(DF) is a rare glomerular abnormality detected in association with diabetic kidney disease(DKD). It is seen as random nonbranching fibrillary deposits in mesangium under electrone microscopy. First described by Zohar et alin 1970, only few case reports are available on this entity and we report the largest case series till date.

Methods: We reviewed all the cases of DKD who underwent renal biopsy for various indicationsin last two years (April 2017 to march 2019). Cases which were reported as DF in electron microscopywere collected. Clinical course, investigation reports and biopsy findings were analysed.

Results: DF was reported in 10(4.03 %) out of 248 cases of DKD. The mean age was 57.6±.6years (44-67). All were diabetic with mean duration 13±3.1years. The mean creatinine was 7.2±3.1mg/dl and nephrotic range proteinuria seen in 40%. Autoimmune and myeloma workup was negative. Light microscopy showed diabetic nephropathy class IVin all 10 cases. TheImmunofluorescence andcongo red stain was negative in all. GBM was thickened (range432 to 885 nm)in all cases along with random non branching fibrillary in mesangium. No spherular microparticles ortubuloreticular inclusions were seen.

Conclusions: DF is not an uncommon entity with a prevalence of 4.03 % in our case series. The clinical significance of this entity is yet to be determined. Larger prospective studies are needed to evaluate the correlation with long term renal outcomes.

PUB083

The Effects of Testosterone Replacement Therapy (TRT) in Patients with Established Dementia

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Background: We have previously shown that TRT provides significant survival benefits and that patients with dementia have a faster progression of chronic kidney disease (CKD). Testosterone deficiency is common in both CKD and dementia. Here we examined if TRT slows CKD progression, cardiovascular disease and mortality in patients with dementia.

Methods: Data from a large cohort of veterans with low total testosterone were used to determine the effect of TRT on progression of CKD, cardiovascular diseases and all-cause mortality in patients with dementia (ICD9). Increase in serum creatinine > 1.5 mg/dl was taken as a measure of progression of CKD. Data were extracted using the Veterans Administration Informatics and Computing Infrastructure (VINCI), and analyzed using SAS. Propensity matching for age, followup time and prior vascular disease was used to adjust groups. Results were compared by means tests, frequency tables, odds ratio and p values (p=<0.01).

Results: Of 57,985 patients with testosterone deficiency, 1,317 with dementia diagnosis (Dx) had treatment (Dx_TRT) and 475 had none (Dx_No_TRT), compared to controls (Ctrl_TRT, N=44,434, Ctrl_No_TRT, N=13,551). Followup was shorter with DX (Ctrl vs Dx: 5.5 vs 4.4 yrs). Baseline age and creatinine were similar (59.3 vs 60.2 yrs; creatinine 1.03 vs 1.03 mg/dl). TRT provided significant reduction in all-cause mortality in both groups, (Odds Dx 0.61, 95% CI 0.49-0.75) vs (Odds Ctrl 0.85, 95% CI 0.84-0.87). TRT reduced the progression of CKD (Odds Dx 0.63, 95% CI 0.51-0.79 vs Odds Ctrl 0.89, 95% CI 0.88-0.91). TRT reduced CVA (Odds Dx 0.57,95% CI 0.41-0.79 vs Odds Ctrl 0.88, 95% CI 0.81-0.95). The effect on new MI was significant in Control only (Odds 7.6, 95% CI 0.67-0.85). TRT reduction of new diagnosis of retinopathy and nephropathy was not significant. Prior cardiovascular disease was more common with dementia (% difference Dx/Ctrl), e.g. CAD (117), CHF (92), CVA (496), HTN (67), MI (140), PAD (129).

Conclusions: TRT is associated with significant reductions in progression of early CKD[AG1], all-cause mortality and new cardiovascular diagnoses in patients with dementia even while dementia is associated with increased prior cardiovascular disease. [AG1]How are we defining early CKD?

Funding: Veterans Affairs Support

PUB084

Worsening of Dental Caries Is Associated with Arteriosclerosis Among Patients on Hemodialysis

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Background: Patients on hemodialysis (HD) must undergo HD therapy three times weekly and might be unable to visit a dentist. Dentists may hesitate to provide routine oral care to patients with HD, as they are medicated with anticoagulants and are thus particularly susceptible to bacterial infections; they might also experience unusual drug reactions. Patients on HD possibly have worse oral status than healthy people; this might predispose such patients to systemic complications.

Methods: The dental caries and periodontitis statuses of 80 patients on HD and 76 healthy individuals (controls) were compared using the decayed, missing or filled teeth

(DMFT) index and the *community periodontal* index (CPI), respectively. In addition, the clinical data of included patients and controls were analyzed after they provided written informed consent to participate in the study.

Results: All values for C4 level of dental caries, missing teeth index, and DMFT index score > 24 were significantly higher in patients on HD than in controls ($p < 0.05$). Pulse pressure and the prevalence of a history of heart disease, such as angina pectoris and acute myocardial infarction, were higher in patients with higher (> 24) DMFT index scores, compared with patients with low (< 24) DMFT index scores ($p < 0.05$). In contrast, CPI scores did not significantly differ between these two groups.

Conclusions: Prior reports have indicated that arteriosclerosis progresses concomitantly with increases in pulse pressure difference; progression of arteriosclerosis is associated with cardiovascular disease. Worsening of dental caries status may be associated with progression of arteriosclerosis among patients on HD.

Funding: Government Support - Non-U.S.

PUB085

Expansion of Monocytic Myeloid-Derived Suppressor Cells in Patients Under Hemodialysis May Lead to Cardiovascular Disease and Death

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Background: The specific mechanism of cardiovascular vasculopathy in the context of end stage renal disease was not clear. In the present study, we investigated the clinical impact of myeloid-derived suppressor cell on hemodialysis patients and the mechanism.

Methods: Myeloid-derived suppressor cell was tested among hemodialysis patients under hemodialysis and their association with overall survival and cardiovascular disease was determined by survival analysis.

Results: Hemodialysis patients presented with a significantly higher level of monocytic myeloid-derived suppressor cells compared with healthy controls. Monocytic myeloid-derived suppressor cell was an independent prognostic factor for overall survival, heart failure and stroke illustrated by multivariate Cox regression, which indicated that monocytic myeloid-derived suppressor cell hazard overall survival of hemodialysis patients by inducing cardiovascular diseases. Monocytic myeloid-derived suppressor cell positively correlated to circulation monocyte counts and share the same surface marker with monocytes. T cell proliferations were significantly abrogated by the addition of hemodialysis related M-MDSCs in a dose-dependent manner which confirmed that monocytic myeloid-derived suppressor cell, instead of monocyte, contributed to cardiovascular disease. Besides, monocytic myeloid-derived suppressor cell presented higher level of CXCR4 and VLA-4 compared with monocytes, which indicated their enhanced capability to be recruited to atherosclerotic lesions. The expression of arginase I and activity of arginase also significantly raised in hemodialysis related monocytic myeloid-derived suppressor cells which indicated that they accelerated atherosclerosis by exhausting local L-arginine.

Conclusions: Above all, monocytic myeloid-derived suppressor cells was elevated in hemodialysis patients and an independent prognostic factor for overall survival and cardiovascular diseases. They might contribute atherosclerosis by enhanced recruitment to vascular lesions and exhausting local L-arginine.

PUB086

Uremic Toxins Nexus with Nutritional Profiles

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Background: High protein intake is associated with increased levels of albumin-bound uremic solutes in hemodialysis (HD) patients (p). We analyze the patterns of the prototypic uremic toxins Indoxyl Sulfate (IS) and β2microglobulin (β2M) relationship with protein metabolism and inflammation.

Methods: Study of 60 chronic HD p. 60.8±1.8 (mean±SE) years. 32 M/28 F. 34 standard HD / 26 postdilutional hemodiafiltration (HDF). 54 p residual diuresis <500 ml/24 h. Dialyzer: 54 polynephron, 4 cellulosic. HD time 244±2.5 min. QB 357.5±6.6 ml/min. Q_D 500-800 ml/min. Pre/postHD serum IS total by HPLC. Pre/post (post in HDF p) serum β2M by nephelometry. UKM by Solute Solver. Midweek sessions. T-test or ANOVA for IS and β2M as dependent v, and as categorical factors: 1) Albumin (Alb) ≥ (25 p) or < (35 p) to 38 g/L; 2) C Reactive Protein (CRP) ≥ (22 p) or < (38 p) to 10 mg/L; 3) double pool normalized Protein Catabolic Ratio (dp nPCR) ≥ 1 (31 p) or < 1 (29 p) g/kg/day; 4) dp nPCR categorized by levels (<0.6 / 5 p 8.3%, 0.6-0.79 / 11 p 18.3%, 0.8-0.99 / 14 p 23.3%, 1-1.19 / 17 p 28.3%, >1.2 / 13 p 21.6%); 5) "nutritional profiles": catabolic (alb < 38 g/L and dp nCRP ≥ 1 g/kg/day) 12 p 20%, low intake (Alb < 38 and dp nPCR <1) 21 p 35%, high intake (Alb ≥ 38 and dp nPCR ≥ 1) 19 p 31.6%, anabolic (Alb ≥ 38 and dp nPCR < 1) 8 p 13.3%.

Results: PreHD uremic toxins (mean±SE): IS total 18,9±1.6 mg/L, β2M 35.6±1.9 mg/L. IS higher in the high vs the low dp nPCR group: 22.8 (18-27.6) vs 14.4 (10.6-18.8) mg/L (means and CI 95%) (p=0.0006). β2M higher in the low vs high Alb group: 40.9 (35.6-46.1) vs 29.4 (24.7-34.2) mg/L (p=0.002). IS higher in the high vs low dp nPCR group: 22.8 (18-27.6) vs 14.14 (10.6-18.8) (p=0.01). IS relationship with dp nPCR: <0.6 g/kg/day=12.9 mg/L, 0.6-0.79=16.9, 0.8-0.99=17.7, 1-1.19=23.4, >1.2=21.7. High intake (23.5 mg/L) and catabolic p (21.1 mg/L) had the mean highest levels of IS and anabolic (17.2 mg/L) and low intake (16.2 mg/L) the lowest. Catabolic (41.8 mg/L) and low intake p (38.5 mg/L) had the mean highest levels of β2M, and high intake (32.4 mg/L) and anabolic p (26. mg/L) the lowest.

Conclusions: IS concentrations had direct correlation to nPCR determined by protein intake. β2M had inverse correlation to albumin level and direct correlation with CRP. Catabolic p showed both IS and β2M highest levels.

Funding: Government Support - Non-U.S.

PUB087

Ultrafiltration Volume During Hemodialysis and Its Correlation with Central Pressure Parameters

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Background: Determination of the ultrafiltration volume during hemodialysis (HD) is crucial for ESRD patients. It is challenging during HD to maintain a balance between excess fluid removal and hypoperfusion. Noninvasive central pressure measurement was utilized to identify the independent variables related to the ultrafiltration volume (UFV).

Methods: A cross-sectional study was performed to monitor the central blood pressure, using Mobil-O-Graph device, with peripheral brachial cuff for 10 hemodialysis sessions among 10 patients. The Central BP, Cardiac output (COP), Peripheral vascular resistance (PVR), Pulse Wave velocity (PWV), and Augmentation index (AUI) were continuously monitored during the whole hemodialysis sessions. Age, gender, BMI and cardiovascular risk were recorded from the medical files. The total and hourly ultrafiltration volume were calculated from the patients Pre, Post dialysis weight and the dialysis machines. Significant univariate correlations were selected to generate a multivariate linear regression equation to test all the independent variables.

Results: The mean age for the patients was 55 years (SD 8.6), BMI 27.7 kg/m^2 (SD 4.7). Five of the patients were males. Mean number of CV risks were 2 in each patient, not counting ESRD. We recorded 136 measurements of central pressure, COP, PWV, PVR and AUI over 10 Hemodialysis sessions. Mean COP was 5L (SD 0.9), mean AUI 28% (SD12), mean PWV 9m/s (SD 2), mean PVR 1858 dyn.s/cm^5 (SD 379), mean central pulse pressure 45mmHg (SD 16), mean central MAP 110mmHg (SD 12). The total and the hourly ultrafiltration volumes were recorded from the patients pre, post dialysis weight and the machines. The mean total UFV was 1891ml (SD 972) and the mean hourly UFV was 658ml (SD286). The total and the hourly UF volume were significantly correlated with age, gender, BMI, CV risk, COP, PWV, TVR, PVR, and central pulse pressure. However, the AUI and Central MAP were not significantly correlated. The UFV was determined by the age, gender, BMI, CV risk, COP, PWV, PVR, and central pulse pressure in a multivariate regression with an R^2 of 0.8.

Conclusions: Demographic factors, CV risk and Central pressure measurement, including pulse wave velocity, Central pulse pressure, cardiac output and peripheral vascular resistance were independent variables that determined the ultrafiltration volume during dialysis with an accuracy of 80%.

PUB088

Early Initiation of Hemodialysis in Advanced CKD with Severe Heart Failure Improves Survival and Quality of Life (QOL)

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Introduction: The survival benefits of early initiation of hemodialysis [HD] in patients with chronic kidney disease [CKD] has recently been called into question. Also the presence of heart failure [HF] at HD initiation is a strong predictor of high mortality. We present a case series of 3 non-diabetic patients with CKD stage 4 [CKD 4] and severe non-ischemic cardiomyopathy [NICM] in whom HD was initiated early as a result of recurrent hospitalizations for volume overload and diuretic resistance.

Case Description: The patients were elderly with history of hypertensive CKD, severe heart failure secondary to NICM and low ejection fraction. All were on standard HF therapy which included: angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta blockers, combination therapy with fixed dose Hydralazine with Isosorbide dinitrate and two diuretic agents [a loop and a distal tubule acting agent]. Each patient also had an Implantable Cardioverter-Defibrillator [ICD]. They were adherent with their medications but had recurrent hospitalization 2-3 times each month for worsening HF. As a result of these hospitalizations, it was decided that chronic HD should be initiated even though their mean estimated glomerular filtration rate at HD initiation was over 15 ml/min. They have been followed for a mean duration of 40 months since initiation of maintenance HD. The table provides a comparison of their clinical characteristics before and after HD initiation over 3 yrs. of follow up.

Discussion: The median survival of elderly HD patients with HF is less than 30 months but all the patients in this report were alive 40 months post HD initiation. Contrary to recent reports, early initiation of HD in select patients with advanced CKD and severe HF may improve QOL and survival. This should ultimately translate into reduced healthcare costs.

	Pre -HD	1 yr, on HD	2 yr. on HD	3 yr. on HD	p value
Age (mean yr.)	70 ± 2	-	-	-	-
eGFR (ml/min/1.73m2)	20 ± 2	-	-	-	-
EF %	12 ± 3	20	18	28 ± 3	0.04
NYHA Class	4	-	3	2	-
Hospitalization Rate (per pt/yr.)	18 ± 6	6 ± 2	2	-	0.01
MLHFQ	90 ± 10	40 ± 10	34	17 ± 6	0.01

EF= Ejection Fraction; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association; MLHFQ = Minnesota Living with Heart Failure Questionnaire

PUB089

Results from the First Use of High Flux Dialysis in Algeria

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Background: Traditional low-flux dialysis is the only treatment currently available in Algeria, while high-flux dialysis can improve renal disease patient's health related quality of life, Water treatment remain one of the major obstacles to prevent this method from developing in our country. The aim of the study was to compare for the first time the effect of permeability of LF versus HF dialysis membranes on metabolic abnormalities control, Inflammation and body composition by bioimpedance spectroscopy.

Methods: Six prevalent patients on regular hemodialysis were enrolled in a prospective study, from M'sila hospital in Algeria, Chronic LF polysulfone membranes were used, all patients were switched to HF Polyethersulfone during one year. Predialysis samples were taken from the arteriovenous fistula while Postdialysis samples were taken from the arterial blood tubing after the dialyzer blood flow rate had been reduced to 80ml/min. Standard biochemical parameters, Albuminemia, C-reactive protein, Vitamin B12 and intact parathyroid hormone concentration were analyzed with standard laboratory techniques, β2microglobuline (β2M) by Chemiluminescence. The dialysis time and schedule, blood and dialysate flows, and the anticoagulation protocol were kept constant during the study period. Bacteriology water and Endotoxin assessment were performed each three months.

Results: We observed a significant decrease of pre-dialysis levels of β2M 44,27±5,47mg/l, 25,49±2,15mg/l respectively (p = 0.0002) and significant increase in Vitamin B12 between pre-HF and post HF dialysis (P= 0,011). However, we noticed no significant differences of the other parameters (Albumin, CRP, PTH), Hemoglobin mean levels remained stable with reduced erythropoietin doses. An increase in Lean tissue index and decrease in Fat occurred 6 months after the beginning of the trial (P= 0,564 and 0,113). On the other hand, we should state that the removal of small toxins was similar with HF and LF.

Conclusions: HF dialysis membranes seems to be more efficient in terms of metabolic abnormalities control for chronic hemodialysis patients than low-flux membranes. Reduction of β2M and improvement of nutritional parameters are encouraging us to use HF in our setting. Our greatest pleasure was when HF proved its tolerance without evidence of major adverse side effects. HF dialysis is feasible in our context with limited resources, so we look forward to spread it in all of Algeria hospitals.

Funding: Government Support - Non-U.S.

PUB090

Enhancing Volume Management in Hemodialysis Through Integration of Point-of-Care Ultrasonography

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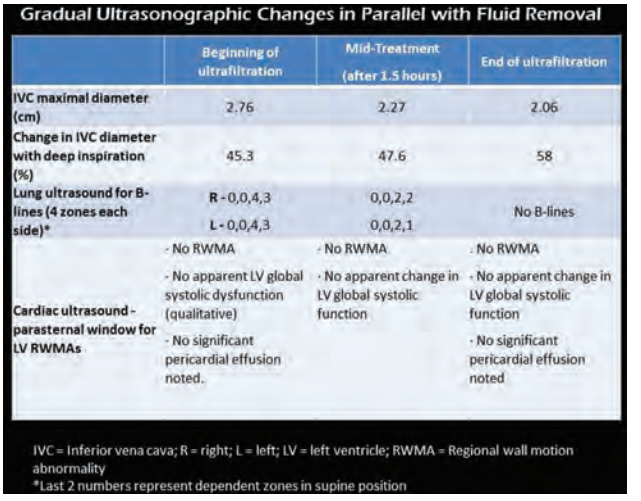
Introduction: Volume overload is associated with increased morbidity and mortality in patients with end-stage renal disease (ESRD). In routine practice, physical examination is commonly used to estimate volume status and guide ultrafiltration (UF) in hemodialysis (HD) patients. Herein, we describe a case in which point of care ultrasonography (POCUS) uncovered volume overload in an apparently euvolemic patient and changed the management strategy.

Case Description: A 68–year-old woman with a history of ESRD on maintenance HD presented with severe dyspnea. On physical examination, blood pressure was 260/110 mmHg, lungs were clear to auscultation, and there was no pedal edema. The last HD treatment was 2 days prior and the patient was at her estimated dry weight at the end of therapy. Nitroglycerin infusion resulted in improvement in BP and complete resolution of dyspnea over the next few hours. Since there was an unexplained significant discrepancy between her presentation and physical exam, POCUS was performed to more objectively assess volume status. Despite her apparent clinical euvolemia, focused sonography of the inferior vena cava, lung, and the heart revealed presence of significant fluid excess implying the need for aggressive UF. We were able to perform POCUS-guided UF to achieve an impressive 6.8% reduction in weight within 3 hours with no adverse event. Sonographic findings [**Figure**] and BP showed progressive improvement throughout the UF session.

Discussion: This case highlights the capability of POCUS to enhance patient care in ESRD, not only through uncovering of concealed hypervolemia, but also by guiding the UF process. In addition, limited cardiac POCUS can provide insights into patient's cardiac tolerance as transient changes in ventricular function and regional wall motion abnormalities are known to occur during HD. Future longitudinal studies need to explore whether these salutatory effects translate into improved outcomes.



PUB091

Effects of Ultrafiltration Rate (UFR) on Hemodialysis Patient Survival

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Background: Increasing levels of UFR have been associated with higher mortality. We attempt to examine the effect of increasing levels of UFR on mortality of incident hemodialysis patients.

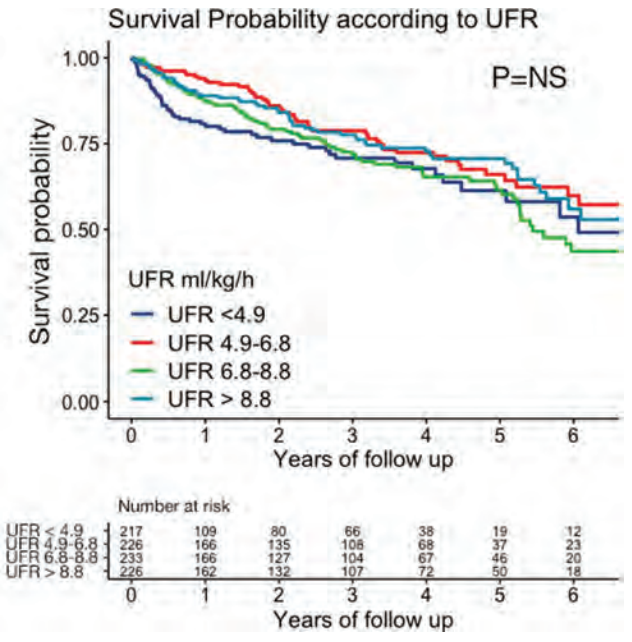
Methods: Incident hemodialysis patients admitted to Emory University Dialysis program form 1/1/11 to 12/31/15 were followed until death, transplant, or censoring up to 12/31/18. Demographic, laboratory and hemodialysis data including UFR and changes in blood pressure were obtained. Hospitalizations and common complications were extracted from the medical record. Patients were divided in 4 groups according to quartiles of UFR distribution (<4.9, 4.9-6.8, 6.8-8.8 and >8.8 ml/kg/h) and will be referred as Groups A, B, C and D.

Results: 903 incident patients were included. The average age of the cohort was 57.2 years, with a weight of 82kg and UFR of 7mL/kg/h. The differences between groups are presented in table 1. The survival probability was similar for all groups and is represented in Figure 1, The cumulative incidence of admissions was similar among groups.

Conclusions: We found no association between different quartiles of UFR on hemodialysis patient survival. Higher UFR was associated with younger age, lower weight and lower incidence of hypotension during dialysis. Incidence rate of admissions was similar among UFR groups.

	GROUP A n=229	GROUP B n=214	GROUP C n=223	GROUP D n=236	P
Wt (kg)	87.5±26.3	85.3±21.3	82.9±20.1	73.8±17.0	<0.005
Age (years)	59.4±14.2	59.6±14.8	57.7±14.2	52.3±15.7	<0.005
Gender (M/F), %	52, 48	56,44	64,36	56, 44	0.056
UFR (ml/k/h)	3.4±1.4	5.9±0.5	7.7±0.5	11.0±2.2	<0.005
Access (C,G,F), %	44,10, 46	26, 25, 49	25, 21, 54	20, 21, 59	<0.05
Diabetes %	38	49	49	39	<0.05
MAPpre (mmHg)	123.8±16.8	126.5±14.8	129.4±15.6	134.2±16.1	<0.005
MAPpost (mmHg)	118.9±15.1	119.2±12.0	120.4±12.5	124.1±13.9	<0.005
Change in MAP	25.1±11.6	26.3±10.4	26.9±12.4	25.9±10.1	NS
% HD with MAP<60	2.9±9.1	2.4±5.2	1.7±4.8	1.4±4.7	<0.005
Kt/V	1.4±0.3	1.4±0.2	1.4±0.3	1.4±0.3	NS
Albumin (g/dL)	3.5±0.6	3.7±0.5	3.6±0.5	3.7±0.5	<0.005
Hemoglobin (g/dL)	10.1±1.3	10.3±1.1	10.3±1.1	10.1±1.2	NS
PTHi (pg/mL)	499±403	468±289	514±344	595±401	<0.005
PO4 (mg/dL)	4.7±1.1	5.1±1.2	5.2±1.2	5.6±1.3	<0.005

Table 1. Demographic, dialysis and laboratory data. Values represent mean±SD



PUB092

Blood Pressure Elevation Just Before Cerebral Hemorrhage in Patients Undergoing Hemodialysis

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Background: Pre-symptomatic blood pressure elevation is known to be associated with intracerebral hemorrhage; however, only a few studies have reported this association. Cerebral hemorrhage is an important complication in patients undergoing hemodialysis, and it is possible to evaluate the pre-symptomatic situation from patients' dialysis charts. We investigated the association between blood pressure elevation and the onset of cerebral hemorrhage.

Methods: This study included patients undergoing hemodialysis who were treated for cerebral hemorrhage at our hospital between 2008 and 2016 (case group) and patients treated at Nagasaki Renal Center between 2011 and 2012 (control group). Data regarding participants' backgrounds were obtained from medical records and 3 consecutive dialysis charts just before the onset of cerebral hemorrhage (case group) and participants' birthdays (control group).

Results: The case group included 99 patients (mean age 65 years, median dialysis vintage 87 months, 67% men), and the control group included 339 patients (mean age 67 years, median dialysis vintage 56 months, 57% men). Compared with the control group, the case group showed a significant increase in systolic blood pressure (approximately 6 mmHg) during the last among 3 dialysis sessions (P=0.02). After adjusting for age, sex, dialysis vintage, history of diabetes and cerebrovascular disease, serum hemoglobin, calcium, and phosphate levels, antiplatelet drug use, and fluid removal rate, logistic regression analysis showed that blood pressure elevation over baseline levels was significantly associated with cerebral hemorrhage (odds ratio 1.02 per/mmHg, P<0.001). Multiple regression analysis showed that in the case group, blood pressure elevation was significantly associated with a history of diabetes (P=0.03) and lower serum calcium levels (P=0.01) but not with weight gain between dialysis sessions.

Conclusions: Blood pressure elevation over baseline levels, which may reflect failure of vascular system autoregulation, was associated with cerebral hemorrhage. The tendency of blood pressure elevation may depend on a patient's background.

Funding: Government Support - Non-U.S.

PUB093

Percutaneous Left Atrial Appendage Closure: A Safe Alternative to Anticoagulation for Patients with Non-Valvular Atrial Fibrillation and ESRD on Hemodialysis

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Background: The prevalence of non-valvular atrial fibrillation (NVAF) in patients with end-stage renal disease (ESRD) on hemodialysis is 13 to 27%. There is little evidence on the effectiveness and safety of vitamin K antagonists (VKAs) in them since their potential benefit have shown conflicting results. Moreover, direct oral anticoagulants are not recommended by current cardiology guidelines in patients on hemodialysis. Percutaneous left atrial appendage occlusion (LAAO) has demonstrated to be an alternative therapeutic option to anticoagulation for stroke prevention in NVAF. However, the evidence of its use in patients on hemodialysis is scarce. The aim of this study is to present our single-center experience of LAAO in ESRD patients on hemodialysis.

Methods: Retrospective chart review of clinical records, demographics, LAAO procedure and devices, complications, post-procedure therapy and oucomes of patients with ESRD on hemodialysis and NVAF who underwent a percutaneous LAAO in our center between January 2017 and January 2019.

Results: Eight patients (six males) with ESRD on hemodialysis underwent a percutaneous LAAO in our center. The mean age was 67.5 years (range 56–81; SD±7.2). All patients had permanent NVAF. The mean dialysis duration was 8.49 years (range 0.83-14.8; SD±6.2). The mean CHA2DS2-VASc and HAS-BLED scores were high [4.75 (SD±1.16) and 4.62 (SD±0.91), respectively]. All patients had history of a major hemorrhagic event (BARC Score ≥3). Contraindications for anticoagulation were gastrointestinal hemorrhage (n=3), repeated bleeding from the dialysis vascular access (n=3), intracranial hemorrhage (n=1) and massive epistaxis (n=1). All devices (5 Amplatzer-Amulet, 2 Watchmann and 1 LAmbre) were implanted successfully. Post-procedural antithrombotic regimen was based on antiplatelet therapy during 3.1±1.24 months. No deaths, cardioembolic events, device thrombosis or peri-device leaks, major adverse efects according to VARC criteria, or major bleeding were reported during a mean follow-up of 14.24 months (SD±9.44).

Conclusions: Percutaneous LAAO could be a safe and an effective alternative to anticoagulation in patients with NVAF and CKD in hemodialysis. Further studies will be necessary to confirm this hypothesis.

PUB094

Prefilter Hemodiafiltration with Heparin-Dose Minimization: A Safe and Effective Technique

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Background: Unfractionated heparin (UFH) administered during hemodialysis (HD) has cumulative adverse effects; hence the importance of using the lowest possible dose and avoid overdosing.

Methods: We analyzed 30 patients with chronic hemodiafiltración (HDF) treatment divided in 3 groups: pos filter HDF with heparin standard impregnation dose (27±6.5 IU / kg), HDF pos filter with impregnation low dose (15±4.2 IU / kg); in both groups, heparin impregnation and maintenance were given, and a third group HDF pre-dilution only with heparin impregnation dose (27±12.8 IU / kg). We measured partial thromboplastin time (aPTT) and serum heparin levels at 30 and 190 min.

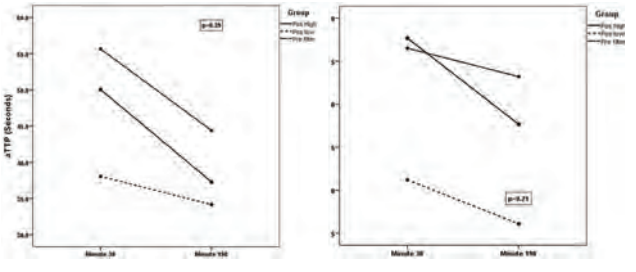
Results: HDF pre-dilution group received a significantly lower total dose than the other 2 groups; 1750 vs 2650/3444 UI/Kg (p <0.001), maintaining 30 min aPTT target (55,6±43.4) as aPTT 190 min (44,4±30.3), as well as effectiveness of the treatment (substitution volume of 51.4±11.8 L, Ktv 1.38±0.3). The other two groups reached aPTT 30 min target, but decreased towards the end of HDF sessions (aPTT 190 min). HDF pre-dilution did not increase clot formation (p <0.678). There were no major coagulation or bleeding events.

Conclusions: Pre dilution HDF with only impregnation heparin is a safe and effective method; after the amplification and reproduction of our results, it could represent an alternative treatment that minimizes UFH doses in order to reduce the associated adverse events.

Table 2. Paraclinical values according to the study group.

	Pos Filter Standard Dose N=10	Pos Filter Low dose N=10	Pre Filter Low Dose N=10	*p=
Total Dose Administered (IU)	3444±836	2650±502	1750±790	<0.001
aTTP 30 min (s)	50±19.7	38±5.8	55.6±43.4	0.372
aTTP 190 min (s)	37.2±7.1	34.6±6.4	44.4±30.3	0.465
Heparin levels 30 min (IU/mL)	0.27±0.23	0.11±0.12	0.26±0.31	0.226
Heparin levels 190 min (IU/mL)	0.17±0.1	.06±0	0.2±0.4	<0.241
Basal Hemoglobin (Hbi)	7.6±0.9	7.6±1.2	9.1±1.0	.007
Final Hemoglobin (Hbf)	9.64±2.1	9.4±2.2	11.5±1.5	.044
Gap Hb (Hbf-Hbi)	2±1,48	1.7±1.5	2.4±1.18	0.55
Coagulation score	1.86±0.6	1.88±0.3	1.73±0.2	0.678
HDF Total time (min)	188±8.5	187±4.5	185 ±11.3	0.625

* Anova



PUB095

The NLRP3 Inflammasome Plays an Important Role in IL-1β Secretion in Hemodialysis Patients

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Background: Inflammasomes have been elucidated as an important inflammatory agent in several diseases, including chronic kidney disease (CKD). These molecules are multimeric protein complexes that act as activators of the inflammatory process and can also be induced by other inflammatory mediators considered agonist, for example, the Nuclear Factor-κB (NF-kB). The most studied inflammasome is NLR pyrin domain-containing protein 3 (NLRP3) that cleaves pro-Interleukin 1β (IL-1β) to IL-1β mature, which is involved with activation of acute phase response proteins in the liver such as C-reactive protein, leading to systemic inflammation. Therefore, the aim of the present study was to evaluate the possible involvement between gene expression of NLRP3 and IL-1 β in hemodialysis (HD) patients.

Methods: Eleven HD patients [63.6% female, 50.9 ± 17.9 years, 49.0 (23 – 193) months on HD] were included in this study. Blood samples were drawn after 12h fasting, and the peripheral blood mononuclear cells (PBMC) were isolated. Quantitative Real-Time PCR analysis was performed using *7500 Real-Time PCR* System (*Applied Biosystems)* to evaluate the mRNA expression encoding NLRP3, IL-1β and NK-kB. High sensitive C-reactive protein (hs-CRP) plasma levels were analyzed using Bioclin® kit by automatic biochemical analyzer.

Results: NLRP3 mRNA expression was 0.83 ± 0.35, IL-1β was 2.1 ± 1.6 and NF-kB was 0.91 ± 0.32. The plasma levels of CRP were 4.3 (2.5 – 10.7) mg/dL. There was a positive correlation between the expression of the inflammatory factor NLPR3 and IL-1β (r = 0.73, p-value = 0.02) and between NLPR3 and hs-CRP (r = 0.75, p-value = 0.03).

Conclusions: The NLPR3 gene expression may lead to increased IL-1β gene expression and increased plasma hs-CRP levels. Then, the inflammasome-IL-1β axis should be more explored in CKD patients and therefore, as the NLRP3 inflammasome has been shown to be an important inflammatory marker, it may be a new target for alternative therapies in CKD patients on HD.

Funding: Government Support - Non-U.S.

PUB096

Evaluation of the Efficacy of a Very High Permeability Dialyzer and Comparison with Other High-Flux Dialyzer in Online Hemodiafiltration

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Background: Online hemodiafiltration (OL-HDF) techniques that combine diffusive and convective transport have been introduced in the last years, resulting in better outcomes in terms of cardiovascular mortality in hemodialysis patients. "Super high flux" dialyzers are now commercially available with the purpose of removing a large amount of larger middle solutes by achieving higher convective volumes. One of these high performance dialyzers, called Xevonta HI 23®Braun, with very high water permeability (*in vitro* ultrafiltration coefficient (Kuf) of 124 ml/h/mmHg), has been recently introduced, but there is still a lack of evidence on its use. The main objective of the present study is to evaluate the efficacy of this very high permeability (VHP) dialyzer and to compare it to other high flux (HF) dialyzer in OL-HDF.

Methods: In this crossover study, 14 prevalent OL-HDF patients were studied in two consecutive mid-week dialysis treatments, first with the VHP dialyzer and second with the HF dialyzer. Convective volumes, reduction ratios (RR) of different-sized molecules and other dialysis parameters were collected for the different dialyzers.

Results: Mean total convective volume per session was significantly higher with the VHP dialyzer than with the HF dialyzer (33.5±5.4 vs 30.9±4.6 litres/session; p 0.013). There were no differences in the reduction ratios of small or middle size molecules nor in *in vivo* Kuf, transmembrane pressures or albumin losses between the two dialyzers (Table 1).

Conclusions: VHP dialyzer achieves significantly higher convective volumes compared to the HF dialyzer and it is not inferior in the removal of small and middle molecules.

Comparison of dialysis parameters between dialyzers

DIALYSIS PARAMETERS	VHP dialyzer	HF dialyzer	p
Mean total convective volume (L/session)	33.5±5.4	30.9±4.6	0.01
Minimum TMP (ml/h/mmHg)	155.9±53.7	157.8±34.6	0.68
Maximum TMP (ml/h/mmHg)	244.85±41.1	230.7±38.1	0.09
Medium TMP (ml/h/mmHg)	213.6±47.2	205.5±32	0.28
Mean Kt/V per session	1.8±0.4	1.9±0.6	0.31
Mean ionic dialisance per session (ml/min)	287±25	284±40	0.27
In vivo Kuf (ml/h/mmHg)	40.9±10.8	38.2±6.1	0.3

Mean±SD

VHP: Very High Permeability, HF: High Flux, TMP: transmembrane pressure, Kuf: ultrafiltration coefficient

PUB097

Observational Study of Individualised Dialysate Sodium Prescription to Manage Intradialytic Hypertension

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Background: Intradialytic hypertension (IDH) associates with higher mortality risk but optimal treatment is uncertain. Increasing antihypertensives or reducing post dialysis target weight may lower intradialytic BP but increases the risk of hypotension. Standard dialysate [Na] at our unit had been 140 mmol/L, despite patient plasma [Na] often being lower or, rarely, higher than this. We thought that positive Na flux during dialysis likely contributed to BP rises during dialysis and introduced a clinical protocol to guide changes in dialysate [Na]. The protocol aimed to reduce net Na diffusion during dialysis.

Methods: IDH was defined as ≥10mmHg BP rise in >50% of 7 consecutive sessions. Patients identified with IDH had target weight and medications adjusted and were then re-assessed for IDH 3 months later. Those that still had IDH were offered an iterative adjustment of dialysate [Na] to target an equal blood inlet and outlet [Na]. The range of allowable dialysate [Na] was 135 to 145mmol/L. Thirst was assessed on a visual analogue scale from 0 to 100mm (100mm represents severe thirst), measured before, and 5 months after, dialysate [Na] modification. Target weight and medications continued to be adjusted as clinically required by attending physicians throughout the observation period.

Results: IDH was identified in 14 patients. After 3 months' medication/weight adjustment IDH was still present in 10. Of these, 8 consented to dialysate [Na] adjustment and 7 completed 5 months' follow-up (1 transferred out of area). Median age of consenting patients was 71 and mean dialysis vintage was 3.5 years. Median dialysate [Na] post adjustment was 136mmol/L (range 135 to 141). In those completing 5 months' follow-up; mean thirst scores improved from 33.3 to 23.6mm (p=0.07), mean pre-dialysis plasma [Na] fell from 138.1, to 135.3 mmol/L (p=0.05) and IDH was present in only 3 of the 7 patients at 5 months. No adverse events attributable to changes in dialysate sodium were recorded, but in 1 patient, dialysate [Na] was increased from 135 to 140 mmol/L during an admission for diarrhoea.

Conclusions: Due to the small and uncontrolled nature of this observational study, it is uncertain if individualising dialysate sodium by attempting to equalise the blood inlet and outlet sodium concentrations improves IDH. However, such changes appear to be safe.

PUB098

Effectiveness of Sacubitril-Valsartan in the Treatment of Heart Failure in ESKD Patients on Maintenance Hemodialysis

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Background: Sacubitril-Valsartan (SV) has been used well in the treatment of heart failure with excellent results. However data regarding its effectiveness in End Stage Kidney Disease (ESKD) patients with heart failure is lacking

Methods: Twenty patients who were undergoing regular maintenence hemodialysis and who had at least two hospitalisations due to heart failure over the preceeding 6 months were included in the study. Patients were started on SV at a dose of 50 mg per day which was increased to a maximum tolerated dose of upto 200 mg per day. All had reduced ejection fraction. They were then followed up for a period of 6 months.

Results: There were 11 males and 9 females. The average age was 62.15 ± 9.02 years. There were 15 diabetics and 19 hypertensives. The average duration on hemodialysis was 14.9 months. The average number of hospitalisations before starting SV was 2.2 and average ejection fraction (EF) was 36.05 ± 10.55 percent. All were started with a SV dose of 50 mg per day and the maximum dose achieved was 115 ± 46.16 mg per day. Hyperkalemia was noted in 15 patents which was managed with diet and a reduction in dose. 2 patients expired - one at 2 months and the other at 5 months both unrelated to heart failure. There was a marked reduction in hospitalisations after starting SV. The mean hospitalisation number was 0.16 (p=0.012) post starting SV and the ejection fraction improved to 48.8±10.76 percent (p=not significant).

Conclusions: Sacubitril -Valsartan has been found to be very much useful in the management of heart failure in the general poupulation. Our study in ESKD patients undergoing hemodialysis has shown it is very much useful in this group also and its use has resulted in much less hospitalisations (statistically significant) and improved ejection fraction (not statistically significant). However there is the problem of hyperkalemia which needs to be closely monitored. Our experience has shown SV is beneficial in ESKD patients on hemodialysis with recurrent heart failure. But we need studies with a large number of patients to validate these findings.

PUB099

Information Technology Platform for Expanded Comprehensive ESRD Care

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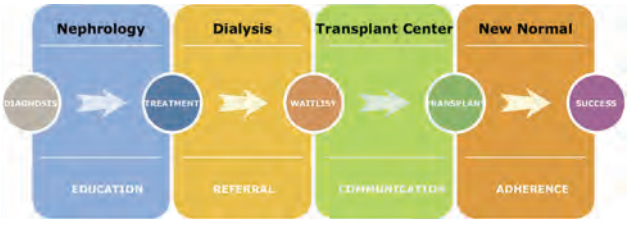
Introduction: We are proposing an information technology (IT) platform that permits data informing pertinent quality metrics to be gathered, collated and tracked for all end-users. The most recent iteration of Centers for Medicare and Medicaid Services (CMS) Conditions for Coverage includes a transplant-based metric applicable to dialysis facilities, the Percentage of Prevalent Patients Waitlisted (PPPW). The IT platform will allow facilities to track their PPPW rates in real time. In addition to the PPPW, the IT

platform will offer a novel tool dialysis facilities can use to design and implement quality improvement projects around all steps of transplantation. Transplant centers can also make use of the IT platform to inform quality improvement projects around waitlist criteria and waitlist management. Nephrology practices can make use of the IT platform to actualize population-health level tracking the transplant education, referral, evaluation and listing of prevalent patients with advanced chronic kidney disease (CKD) and/or end-stage renal disease (ESRD).

Case Description: Technical Requirements: 1. Active on the federally certified Health IT product list 2. Linked to a patient record with unique patient identifier (UPI) 3. Facilitates instant and bi-directional communication capabilities among the patients, payers, providers, and other Health IT systems: a. Videos/Pictures/Files/Medical Imaging b. Recorded audio and video calls c. Text messaging d. Customizable Notifications e. Delivered/Read receipts f. Acknowledgment emojis g. Patient record data fields

Discussion: This proposal includes organ transplant with metrics and IT infrastructure/ platform to support the communication and coordination of the patients and providers in the network. The OmniLife platform provides the infrastructure supporting all technical requirements above, including an upcoming interface with BlueButton 2.0. OmniLife leverages existing IT systems to accelerate implementation throughout the provider network. Aim 1: implement the IT platform among an ESRD care provider network. Aim 2: reduce the cost of care for the patient population through better coordination of patients among providers.



PUB100

Vascular Access Transition and Hemodialysis Adequacy in Hemodialysis Patients

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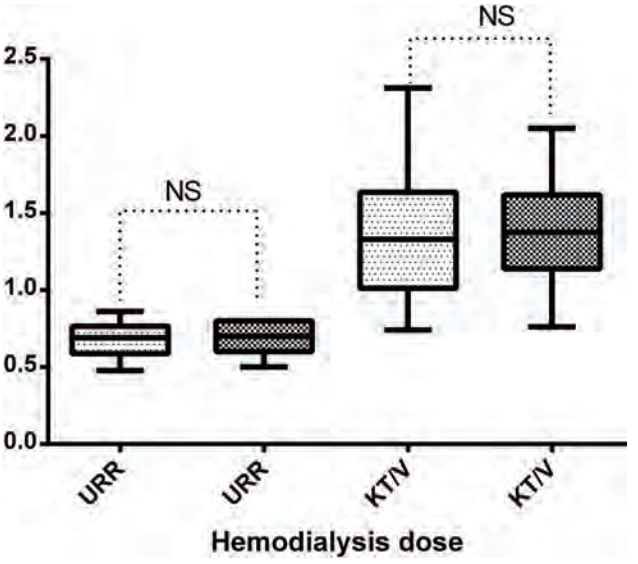
Background: Fistulas are regarded as the best choice for vascular access in hemodialysis (HD) patients because they are associated with improve survival, and less infectious complications specially in incident patients. However, in Mexico, more than 90% of patients who start on HD with a non-tunneled central venous catheter (CVC), and the transition to a permanent vascular access is delayed for months or years. The Instituto Mexicano del Seguro Social (IMSS) is the largest health institution in Mexico who provide HD service. Due to the high incidence of end stage renal disease, this institute subrograte HD treatments from private ambulatory units, and the patients selected for this service are receiving HD sessions usually for two to three years. Our objective was to test if the change from non-tunneled CVC to fistulas or tunneled CVC were associated with better adequacy in chronic HD patients.

Methods: During March 2018 to April 2019 as part of a continuous improvement program, we changed all non-tunneled catheters to fistulas or tunneled catheters. We measured urea reduction ratio (URR), standard KT/V as well as hemoglobin and erythropoietin dose, serum calcium and phosphates before and after the vascular access change.

Results: A total of 50 (32.1%) patients changed their vascular access. The median time elapsed before the vascular replacement was 18 months (QR 6.7-32.6). 22 (44%) were male and 28 (56%) female. The median age was 49.4 years (QR 29.3-62.7). There were no differences between URR, KT/V, hemoglobin levels, erythropoietin dose or phosphate before and after the vascular change, however, there was a lower serum calcium after the change.

Conclusions: Change of vascular access to a fistula is not associated with better adequacy in terms of urea, anemia or calcium and phosphates.



Dose of dialysis before and after vascular change

PUB101

Use of XGBoost Machine Learning Model to Forecast the Changes in Dry Weights of Hemodialysis Patients

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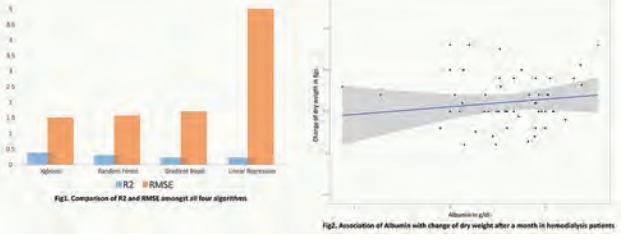
Background: Making a clinical estimation of dry weights in the hemodialysis (HD) patients is a routine among renal physicians. The objective of this study was to develop a machine learning app to estimate dry weight of HD patients alongside the conventional clinical methods.

Methods: This was a prospective cohort study carried out from Jul to Dec 2018, at a tertiary care hospital in Pakistan. All the consenting patients (by non-probability convenience sampling) who had received HD for at least 3 months were included. A total of 78 patients were enrolled. An MBBS qualified physician administered a proforma to the patients at the start of a one-month observational period recording predictors like age, sex, income, HD related variables etc. Dry weight as an outcome was estimated clinically by the in-charge renal consultant at the start and end of this observational period. We used R statistical software version 3.5.2 for the analysis.

Results: The study population included 53% (42/78) males and a median age of 58 years. We divided the data into training and testing sets and built four models from the training set; Linear regression (R2=0.24, RMSE=9.71), Gradient Boost (R2=0.24, RMSE=1.72), Random forest (R2=0.31, RMSE=1.58) and Xgboost (R2=0.39, RMSE=1.52). The best performing model Xgboost which was able to explain about 39% variance in the dependent variable. A mobile app was later developed which takes in the predictors from last month and can estimate dry weight change expected in a given patient. There are plans to increase the sample size thus improving the accuracy of the model and to perform a cost-benefit analysis in terms of work-hours saved per week down the line.

Conclusions: We were able to develop a predictive model using Xgboost machine learning algorithm which could estimate a change in dry weight in a given HD patient one month from the start of the enrollment. This model was then implemented in the form of a mobile app which can be used by clinicians around the world to get a better estimate of dry weight changes in their HD patients. Future plans are to increase the sample size to further improve the accuracy.



PUB102

Malnourished CKD Patients: Screening Malnutrition Using a Short Nutritional Assessment Questionnaire and Body Mass Index

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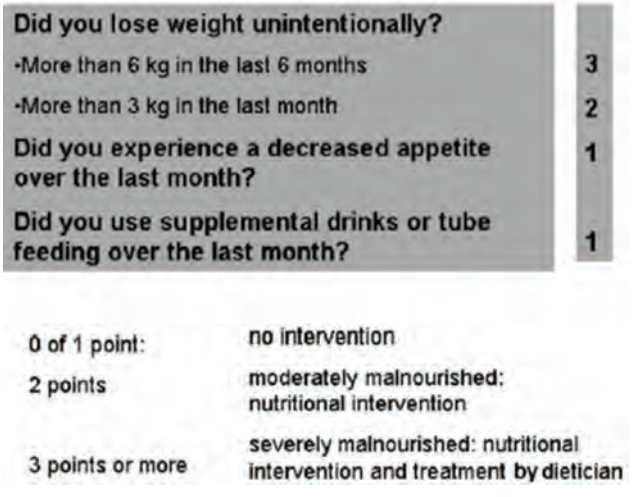
Background: Malnutrition is prevalent among hemodialysis patients. Its diagnosis and treatment is important because of its adverse consequences. However, an ideal and comprehensive nutrition assessment is time-consuming and expensive. A valid, quick and easy screening tool is therefore essential to its recognition and subsequent management. Short Nutritional Assessment Questionnaire is a 3 item screening tool developed by statistical analysis of 26 questions to determine 3 questions most predictive of nutrition status- unintentional weight loss, decreased appetite and use of supplemental drinks or tube feeding. It is >75% sensitive and 83% specific. Patients with SNAQ score ≥2 points are considered malnourished.

Methods: This cross-sectional correlational study determined malnutrition prevalence among hemodialysis patients at University of Santo Tomas Hospital using SNAQ and body mass index and their association. Nutritional status of 94 patients was evaluated by completion of SNAQ and BMI measurements.

Results: Subjects consisted of 50 women and 44 men, with mean age of 58 years. Based on SNAQ scores, 10% was moderately malnourished and 14% was severely malnourished. Based on Asia-Pacific BMI Classification, 11.7% was underweight and 47% was overweight-obese. Using Spearman R, there is a statistically significant moderate negative correlation between SNAQ scores and BMI (inverse relationship). This supports that SNAQ can be used to predict malnutrition but since the correlation is only moderate at best, it cannot be used to exclude the diagnosis.

Conclusions: Undernutrition among hemodialysis patients is not as prevalent as expected however, increasing prevalence of overweight/obesity is an emerging concern. SNAQ can be used to aide in recognition of malnutirition and as such, its use among hemodialysis patients should be encouraged.



Short Nutritional Assessment Questionnaire

PUB103

Centre-Level Factors Independently Affect Survival in Hemodialysis Patients: Findings from a Multicentre Cohort in India

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Background: Mortality of patients on dialysis in India is higher than that reported from western countries. Clinical and socioeconomic factors play an important role in determining survival of these patients, as do differences between dialysis centres. We examined differences in survival across dialysis centres in a large Indian dialysis network, accounting for patients' characteristics.

Methods: We analyse data from 12,640 patients who received dialysis at 129 centres managed by NephroPlus, India's largest dialysis provider between January 2014 and December 2017. The outcome is the time since the patient comes to the dialysis centre until death or end of follow-up. We use a mixed effects Cox proportional hazard model to examine the differences in mortality between dialysis centres, after accounting for the patient characteristics.

Results: Of the 12,640 patients, 3060 (24%) died during the follow-up period (median of 342 days). 4090 (32%) patients were lost to follow up. The 129 dialysis centres were distributed across cities in urban (33%), semi-urban (26%) and rural (41%) areas of India. 64% were setup under PPP programs (Public Private Partnership). About 54% were visited by a nephrologist at least once a week. The overall unadjusted mortality rate was 21.3 per 100 patient years. The individual-level variables that were associated with the outcome were age, having temporary dialysis catheter, history of heart attack or heart failure and lower income and less education. There was substantial variation in mortality between dialysis centres after accounting for the individual-level variables – with centre effects ranging between less than half to over 2.26 times the average risk, and an estimated variance of 0.18. Dialysis centres with high patient volume performed better than low-volume centres. Also, dialysis centres in the rural areas fared worse than the ones in urban areas.

Conclusions: There exist differences in survival between dialysis centres that are not explained by patients' individual characteristics. Of the various centre-level characteristics that we explored, patient volume was found to be associated with patient survival. Future research should explore other possible explanations for observed variation in patient survival across dialysis centres – differences in care practices and other patient characteristics.

PUB104

It Is Not Just Care: Haemodialysis Patients Free from HCV Infection in Qatar - A Multidisciplinary Approach

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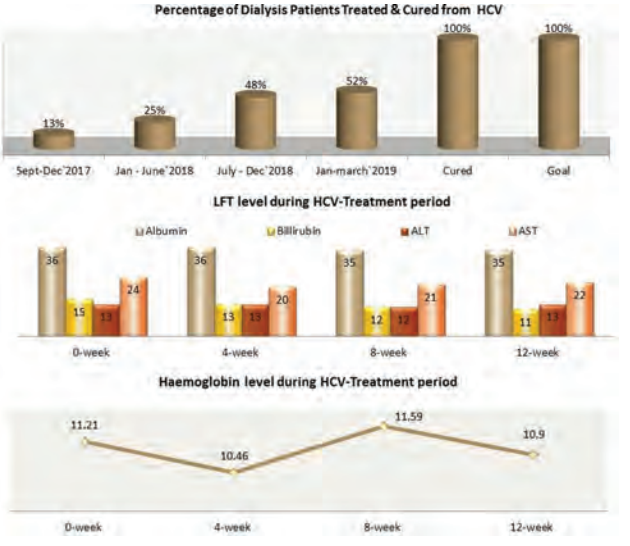
Background: Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV). Chronic hepatitis C develops in most people infected with HCV and can cause serious complications, such as end-stage liver disease. Although no vaccine is available to protect against hepatitis C, interventions can prevent HCV transmission. HCV infection can be treated with antiviral drugs and, in most cases, successfully cured, reducing the risk of morbidity/mortality and theoretically risk for transmission. Qatar National Plan for HCV control by 2020 was launched in December 2014, elaborated by a group of stakeholders from the Qatar ministry of Public Health and Hamad Medical Corporation. Then Approved and adopted by the Qatar Government (MOPH). In 2017, WHO accepted to support the development and implementation of national multispectral policies and strategies for hepatitis C prevention and control in Qatar, based on local epidemiological context of HCV. The prevalence of HCV in Haemodialysis patients in Qatar is 8.4%.

Methods: Non-Interventional, single-Center cohort study, including retrospective collection of real world data on 64 Hemodialysis patients infected with HCV, 33 of them completed the 12 weeks treatment and 12 weeks follow up period. Using of Ombitasvir, Paritaprevir, and Ritonavir (Viekirax) has been accepted as a treatment option in this group of patients.

Results: from 64 HCV positive Patients we initiate the treatment for 33 patients for 12 weeks and 100% of them cured, during the treatment biochemical values was within normal limits.

Conclusions: The outcome of first phase treatment of Hepatitis C in patients on HD is highly effective, it was 100 %. Successful HCV antiviral treatment will decrease the risk for infection transmission within dialysis units, and reduce the occurrence of complications occurring after kidney transplantation.



PUB105

Evaluation of a Mobile Digital Health Intervention (patientMpower) to Capture Patient-Reported Data and Symptoms and Optimise Fluid Management in Hemodialysis

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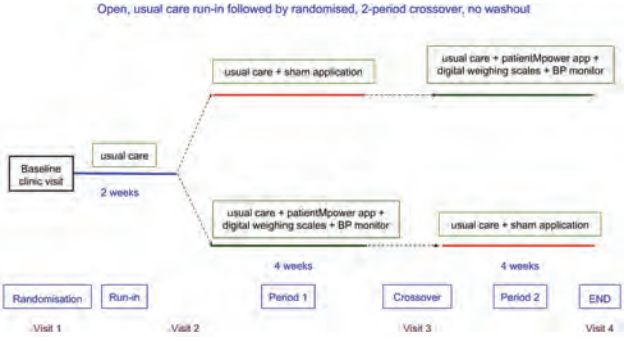
Background: Digital health tools to capture relevant patient-reported health data are available for many chronic conditions but few are available for hemodialysis patients. patientMpower is a mobile digital health intervention which connects wirelessly to measurement devices [e.g. blood pressure (BP) meter, digital weighing scales] enabling patients to have real-time access to relevant health data and encourage greater participation in managing their condition.

Methods: We designed a prospective, pilot-scale, open-label, randomised, 2 x 28-day crossover, sham-controlled protocol to evaluate patientMpower in optimising fluid management (NCT03403491). After a 2-week run-in, ambulatory hemodialysis patients were randomly allocated to patientMpower app+weighing scales+BP meter [patientMpower intervention (pMp)] or to a sham version of the app [sham intervention] for 28 days and then crossed over to the alternative intervention for 28 days with no washout. (See Figure.) The planned sample was 50 patients. There was no change to patients' usual care. Patients were asked to record weight, BP, symptoms, fluid intake & medicines adherence daily during the pMp period. pMp calculated and displayed weight gain relative to individualised target (dry) weight to each patient. pMp delivered tailored feedback messages (dependent on actual weight gain) to optimise fluid intake between dialysis sessions. Sham intervention did not enable patients to record any data and did not provide feedback.

Results: Primary endpoint was patient engagement (usage metrics & patient questionnaire). Secondary endpoints were comparison of pMp vs. sham on clinic-observed interdialytic weight gain (IDWG), ultrafiltration volumes and BP. Patient-recorded and clinic-observed IDWG and BP were also compared.

Conclusions: This design allows evaluation of engagement with a mobile digital approach to feedback relevant information to hemodialysis patients. It can provide data on the impact of active self-monitoring on hemodialysis parameters.

Funding: Commercial Support - patientMpower Ltd, Government Support - Non-U.S.



PUB106

Association of Religious Affiliation with Hospitalization Rates in the Dialysis Population

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Background: People reporting spirituality tend to have better physical and mental health, especially for low income, chronically ill patients. (Koeing, 2015. Adv. Mind Body Med). We investigated if belonging to a spiritual congregation is associated with improvements in hospitalization in hemodialysis (HD) patients from a large dialysis organization (LDO) in the United States.

Methods: We used data from adult HD patients who had a comprehensive social work assessment completed in 2017. We analysed responses to the questions: "Is spirituality an important part of a patient's life" and "If yes, are they a member of a spiritual community?" Information on congregation number and adherents per county was obtained from the 2010 US Religion Census. A Poisson regression analysis was utilized for comparisons of hospital admissions and day rates. We adjusted for age, sex, race, albumin and vintage. The association between belonging to a religious congregation and hospital days and hospitalization rates was investigated.

Results: We analyzed data on 186026 patients. A total of 75% patients reported being part of a spiritual community. Over the 1-year follow-up after social work assessment was completed, the hospital admission rates for patients not belonging to a congregation was higher than for patients who belong to a spiritual congregation (1.65 ppy vs 1.59 ppy). The hospital days for patients not belonging to a congregation was higher as compared with patients who participate in a spiritual congregation (11.37 vs 11.02 ppy). An adjusted regression model showed significantly higher rate of hospital admissions [relative rate (RR) = 1.04; p-value = 0.0035] and hospital days (RR =1.02; p-value = 0.1198) in patients not belonging to a congregation, as compared with patients belonging to a spiritual congregation.

Conclusions: Our analysis shows that belonging to a religious congregation is associated with lower hospitalization rates. Being part of a congregation may increase the patient's exposure to a community environment, resulting in better selfcare. Further investigation is warranted to elucidate whether spirituality/community environment affects dialysis patients' outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

PUB107

Mental Health and Perspectives on Death in Patients with CKD and Their Family Caregivers: A Prospective Study

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Background: The treatment of chronic kidney disease (CKD) generates overload in the health of patients and caregivers. Objective: To assess the physical and mental health and perspectives about the death of patients and their family caregivers.

Methods: Prospective cohort study in a four-year follow-up. Evaluation by questionnaires (Socio-economic, Short Form-36, ILSS (Inventory of Lipp Stress Symptoms), HADS (Hospital Anxiety and Depression Scale), SSPS (Social Suppot Perception Scale), Fatigue Pictogram and Brief Perspective on Death Scales). Analysis performed in SPSS 17.0.

Results: At the initial time 21 patients and 21 caregivers participated, in the second evaluation 14 patients and 21 caregivers. Patients had a mean age of 57.28 years (± 16.29). The caregivers had a mean age of 55.35 years (± 15.61). Over time, levels of anxiety and depression tend to decline in patients ($p = 0.028$) and caregivers ($p = 0.017$). In patients the stress level tended to decline ($p = 0.082$) including the psychological symptoms of stress ($p = 0.001$). It should be emphasized that initially there is a difference in the evaluation of psychological symptoms of stress among patients and caregivers ($p = 0.071$), at which time the lowest Functional Capacity in the patient ($p = 0.010$) is also observed. Patients tend to be more physically limited ($p = 0.013$) with an increase in the large physical domain ($p = 0.005$) and increase social aspects over time ($p = 0.080$). As for caregivers, they tended to increase vitality ($p = 0.093$), as well as to increase levels of emotional social support ($p = 0.087$) together with a decrease in physical stress symptoms ($p = 0.051$). Regarding beliefs about death, most interviewees presented the death perspective as unknown (27.90 ± 5.49), followed by the prospect of post-death reward (27.48 ± 7.87) and death as natural phenomenon (22.38 ± 4.05). It is observed that the belief about death as a natural phenomenon is less frequent among patients (21.00) when compared to caregivers. There was no impact of the psychological variables of patients and caregivers at the beginning of follow-up on mortality.

Conclusions: Caregiver overload is remarkable. Because it is a disease with high mortality, it is fundamental to approach beliefs about death in patients and family caregivers.

PUB108

Adductome of Serum Albumin from Hemodialysis Patients: An Exploratory Study

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Background: Chronic kidney disease (CKD) is associated with an increased cardiovascular (CV) morbidity/mortality and post-translational modifications (PTM) of proteins could participate to this burden. PTM of serum albumin (SA) and especially carbamoylation have been linked with an increase CV mortality among HD patients. We aimed to describe the adductome of SA from hemodialysis patients.

Methods: Plasma of 3 hemodialysis and 1 healthy control patients were analyzed using an nano-RSLC (high performance liquid chromatography) coupled on line with a Q-Orbitrap mass spectrometer. Oxidation, acetylation, carbonylation (with 4-HNE), carbamoylation, guanidinylation, chlorination, nitration and nitrosylation were set as potiential mass excesses on histidine (H), lysine (K) and tyrosine (Y) of SA.

Results: Among 102 post-translational modifications found on HD SA or control SA, 49 were only found onto peptides of SA from HD patients. The main specific PTM were glycation (27%), carbamylation (24%), carbonylation by 4-HNE (14%), nitrosylation (14%), nitration (10%) and guanidylation (10%) while chlorination was not found. These PTM were located in all the domains of SA and especially hit lysines (K), histidines (H) and tyrosine (Y) from domain I of SA. Y150 and K199, two main amino-acids from Sudlow site I (warfarine biding site) were found to be modified in HD SA only.

Conclusions: Serum albumin from HD patients presented several unique post-translational modifications of their proteins compared to control. As key-amino-acids were found adductable, PTM of SA could contribute the dysfunction of SA in HD patients. Further analysis should be conducted to investigate the role of such PTM in the key functions of SA.

Funding: Commercial Support - Baxter SA

PUB109

Comparison of Cognitive Impairment by Montreal Cognitive Assessment (MoCA) with Sarcopenia in Hemodialysis Patients

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Background: Sarcopenia has been implicated in the increased risk for cognitive impairment. Hemodialysis patients are at increased risk for sarcopenia. In this cross-sectional study, we investigated the relationship of sarcopenia with cognitive impairment in hemodialysis patients.

Methods: Total 118 hemodialysis patients, 64 men and 54 women, aged 40 years or older were included in the study. The Montreal cognitive assessment (MoCA) was used to assess cognitive performance. The MoCA consists of seven separate items (visuospatial/executive, naming, attention, language, abstraction, delayed recall, orientation).

Demographics, body composition, and history of cardiovascular diseases were assessed as covariates. The cut-off of the MoCA score of the diagnosis of cognitive impairment was 22 points. The European Working Group on Sarcopenia in Older People (EWGOP) diagnostic criteria were applied to diagnose sarcopenia. The muscle mass was measured using Bioimpedance analysis and muscle strength was measured using handgrip strength.

Results: Of the patients included, 55 (women 36.4 %) were diagnosed with sarcopenia (46.6 %). The incidence of sarcopenia was higher in older patients (67.0 vs 70.0, p=0.046), but there was no difference in other variables. There was significant difference in the cognitive impairment ratio according to the presence or absence of sarcopenia (31 (56.3%) vs 28 (44.4%), p=0.046). Odd ratio (OR) and 95% confidence interval (95% CI) of cognitive impairment was calculated sarcopenia status. Compared to non-sarcopenic, sarcopenic hemodialysis patients had the ORs of 1.09 (95% CI of 1.05-1.15, p=0.030) for cognitive impairment.

Conclusions: Sarcopenia was significantly associated with cognitive impairment in hemodialysis patients. Cognitive impairment reduces the quality of life of hemodialysis patients. Therefore, it is important to prevent sarcopenia, which can cause cognitive impairment in hemodialysis patients.

PUB110

Prevalence and Risk Factors of Anemia in 1161 Patients on Maintenance Hemodialysis

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Background: Management of anemia is a remarkable issue in hemodialysis. Studies on prevalence and risk factors of anemia, especially the dialysis related factors in patients undergoing hemodialysis are limited.

Methods: A multi-center cohort study enrolled 1161 patients on maintenance hemodialysis from ten medical centers in South Guangdong, China from July 2016 to September 2016 for research on prevalence and risk factors of anemia.

Results: There were 1161 patients enrolled in the cross-sectional study, among whom, 250 patients presented with anemia (Hb<90g/L), with the rate of 21.5%; 524 patients presented with hemoglobin concentration of 100-120g/L, with the rate of 45.1%. Comparing to the normal hemoglobin group (NHb group, 110≤Hb<130g/L), patients in anemia group presented with shorter duration of dialysis (26(10,53)months vs. 35(16,68) months in NHb group, p=0.003), less use of arteriovenous fistulas as dialysis access, less use of low molecular heparin for anticoagulation, fewer times of hemodiafiltration and hemoperfusion therapy, with the rates of 78%, 82%, 39.2% and 9.2% (vs. 89.2%, 91.6%, 57.3%, 16.6% in NHb group, p<0.001, 0.003, <0.001, 0.020), respectively. And they showed lower serum creatinine (933.2±291.3μmol/L vs. 1065.1±308.5μmol/L in NHb group, p<0.001), albumin (35.39±4.89g/L vs. 38.62±3.96g/L in NHb group, p<0.001), triglyceride (1.30±0.86mmol/L vs. 1.79±1.72mmol/L in NHb group, p<0.001), calcium level (2.10±0.26mmol/L vs. 2.19±0.29mmol/L in NHb group, p<0.001). Adjusting Logistic regression analysis indicated that frequency of dialysis ≤twice weekly (OR=1.721, 95%CI 1.201-2.466, p=0.003), use of unfractionated heparin for anticoagulation (OR=1.822, 95% CI 1.104-3.006, p=0.019) and hypoalbuminemia (OR=2.112, 95% CI 1.463-3.049, p<0.001) were independent risk factors of anemia in hemodialysis patients.

Conclusions: 21.5% patients on hemodialysis in South Guangdong presented with anemia (Hb<90g/L); 45.1% patients presented with hemoglobin concentration of 100-120g/L. The risk factors of anemia contained dialysis ≤twice weekly, use of unfractionated heparin for anticoagulation and hypoalbuminemia.

PUB111

Behavior of High-Sensitivity Cardiac Troponin I Levels in Asymptomatic Hemodialysis Patients

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Background: Troponins are biomarkers of choice for the diagnosis of myocardial injury. The interpretation of high-sensitivity troponin I levels in the context of hemodialysis (HD) patients is not clear, and there is no reported evidence of its behavior during HD treatment. The objective of the study was to explore kinetics of the hsTnI levels in HD patients.

Methods: Prospective cohort of 33 prevalent asymptomatic HD patients. Venous blood samples were taken to measure the Troponin I levels, during 5 different time periods, to evaluate the kinetics of this biomarker during HD: before the start HD (T0), at 2 hours after starting HD (T1), 60 min before the end (T2), 1 hour after disconnection (T3), and the last sample at the start of the next HD session (T4). The Troponin I levels are expressed in median with minimum and maximum. Non-parametric statistics were used.

Results: The mean age of the population was 41.5 years, 60.6% were female, 36.3% had diabetes, 72.2% systemic arterial hypertension, dialysis vintage was 25.6 months, mean Kt/ V was 1.65, and the average residual urinary volume was 580 ml. The median TnI levels were: T0: 7.4 ng/L (1.3-62.4), T1: 7.1 ng/L (1.2-64.1), T2: 7.2 ng/L (1.6-69.3), T3: 5.9 ng/L (1.6-59.5), and T4: 6.7 ng/L (1.3-63.2). Women had significantly lower TnI levels than men (p=0.03) in all sample times. Eighteen patients had history of cardiovascular disease (CVD), in them all the determinations were higher than in patients who had no history of CVD (p:0.009). Five patients (15.2%) had TnI levels grater than the normal range (16 ng/L), 80% with history of CVD.

Conclusions: The measurements of hsTnI levels during the HD remained stable with slight decrease in the different time tests, which suggest that the troponin I is not dialyzable due to its molecular weight. Troponin I levels were higher than the general population (16 ng/ml) in 15% of the cases. Patients with a history of CVD had higher levels of hsTnI in all measurements. The analysis of Echocardiographic changes and their relation to changes in troponins is still pending in order to have a better correlation of the biomarker with the dynamics of the heart.

F (0), M (1)	Age	T0	T1	T2	T3	T4	History of Cardiovascular Disease
1	47	62.4	64.1	69.3	59.5	63.2	0
1	85	52.9	51.9	49.5	37.3	32.4	1
1	22	26.8	22	21.5	22.7	20.4	1
0	27	21.7	6.7	6.8	5	11.4	1
1	61	17.4	20.2	17	19.1	16.6	1

PUB112

More Frequent In-Center Dialysis Associated with Decreased Hospitalization Length of Stay

Maggie Meier, Lalit Kalvala, Pablo D. Dayer. *St. Luke's hospital, Chesterfield, MO*.

Background: According to the United States Renal Data System (USRDS) as of 2017, ESRD patients on average are admitted to the hospital nearly twice a year and about 35% ESRD discharged have a readmission within 30 days. Approximately 33% total Medicare expenditures for dialysis patients are from hospitalizations, representing a significant financial burden. In 2014, Nxstage Dialysis Center in St. Louis, MO started doing more frequent in-center hemodialysis. We investigated the effect more frequent in-center hemodialysis on our patient's hospital days per year.

Methods: We conducted a retrospective study of adult patients undergoing more frequent hemodialysis at Nxstage Dialysis Center in St. Louis, MO between July 2014-May 2019. The data was collected via Clarity EMR.

Results: Between July 2014 and May 2019, a total of 14 patients were treated with more frequent hemodialysis. Of the 14 patients, 11 patients were hospitalized. In 2016, the hospital readmission rate was 16%. [Figure 1]

Conclusions: We found our patient population with more frequent in-center hemodialysis had clearly lower hospital days per patient year and readmission rates when compared with the national average as reported by USRDS. In 2016, our average hospital day per patient year was 6.41 days compared to 11.3 days. The 30-day readmission rate for hemodialysis patients in 2016 was 37% versus our more frequent in-center rate of 16%. One limitation of our study was our small sample size. However, more frequent in-center hemodialysis was associated with a decreased length of stay and readmission rates.

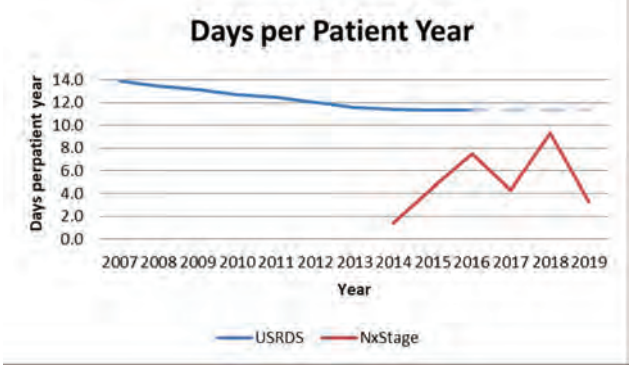

Figure 1.

PUB113

Hepatitis B Virus (HBV) Conversion in a Patient with HBV Antibodies, CKD, and HIV

Rachael DiRienzo-Lawless,[1] Minna Park,[2] Diane Morris,[1] Gail N. Frumkin,[3] Migdalia Barekzei,[5] Barbara A. Casazza,[4] Jeffrey I. Silberzweig.[1] *[1]The Rogosin Institute, New York, NY; [2]Rogosin institute, Woodside, NY; [3]Frumkin Nephrology Associates, Forest Hills, NY; [4]Rogosin Institute Queens Dialysis Center, Woodside, NY; [5]Rogosin Institute Queens, Woodside, NY*.

Introduction: Hepatitis B serologies may be difficult to interpret in patients with CKD and HIV. Assumptions about serologies in the general population may not apply to patients with CKD especially those with concurrent HIV infection.

Case Description: A 59-year-old man became infected with HIV in 1983 then developed HIVAN and CKD. He began a course of maintenance hemodialysis in 2005. He was variably compliant with antiretroviral therapy; his HIV viral load was 48 IU/mL in February 2019. His serologies at that time demonstrated no hepatitis B surface antigens (HBsAg) or core antibodies (HBcAb); he had antibodies to hepatitis B surface antigen (HBsAb). His most recent hepatitis B (HBV) vaccination booster was in 2008. His last admitted IV drug use was in 2017 and he denied sexual activity since 2009.

He was hospitalized on October 3, 2018 because of hematemesis. He received transfusion of one unit of platelets which were leukocyte-reduced and irradiated; he was intubated and underwent bronchoscopy but required no red blood cell transfusions. Over the next two months, he was hospitalized twice for endocarditis and once for a dental procedure but he received no transfusions. Routine testing on April 2, 2019 revealed the presence of HBsAg, HBsAb and HBeAb but no HBcAb. Ten days later, the HBsAg result was negative; HBsAb and HBeAg were positive; HBcAb and HBeAb were negative; his HBV viral load was 1149 IU/ml Three weeks later, his antigen and antibody results were unchanged; HBV viral load decreased to 211 IU/mL.

Discussion: This case points out the difficulty in identifying new HBV infection in patients with HIV infection and CKD. In this case, the source of exposure is unclear. The only documented opportunity for exposure occurred during a hospital admission six months prior to detectable HBsAg serologies. The only documented transfusion was platelets which are not common carriers of viral infections. It also points out the difficulty in identifying the true virilogic status of such patients. Our patient has had HBsAb for almost 15 years so should not be susceptible to new infection yet serologies indicate a change in his antigen status and the presence of viral DNA in his blood. The role of his HIV infection is unclear as is its influence on his hepatitis serologies.

PUB114

Prevalence of Metabolic and Cardiometabolic Syndrome in Patients on Hemodialysis Program

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Background: The prevalence of metabolic syndrome (MS) and cardiometabolic syndrome (CMS) in hemodialysis (HD) patients is not well studied. The aim of this study was establish the prevalence of those syndromes in patients on hemodialysis program.

Methods: Cross-sectional study done in the HD unit. The MS was defined by ATP3 and harmonization criteria. To determine CMS, we included hyperuricemia and high LDL-c. We used descriptive statistic, absolute and relatives frequencies.

Results: Sixty seven patients were evaluated with mean age 40.16±16.12 years. Thirty-six were women (54%). Mean of dry weight was 56.11±9.66 kg; BMI 22.16±3.2 kg/m^2; mean of systolic blood pressure 134.24±21.93 mmHg and diastolic of 76.04±15.24 mmHg. Cholesterol 139.39±31.9 mg/dL; triglycerides 139.69±74.14 mg/dL; LDL-c 70.02±28.11 mg/dL; HDL-c 41.48±9.18; glucose 112.85±41.34 mg/dL; albumin 3.95±0.6 g/dL; and uric acid (UA) of 6.98±2.15 mg/dL. Nine patients (13%) had underweight; 73% (49) normal weight and 13% (9) overweight and obesity (Figure 1A). With ATP3 criteria, we identified MS in 36% (24) of patients and with harmonization criteria 40.4% (27) (Figure 1B); CMS, was identified in 54% (36) patients (Figure 1C)

Conclusions: The prevalence of MS and CMS in HD patients was common; however, the diagnostic criteria for those syndromes should be validated in patients with ESRD. HD by itself, increases the risk of death 20-fold high than general population, the presence of MS concurrent with ESRD could be increasing substantially the risk for cardiovascular diseases.

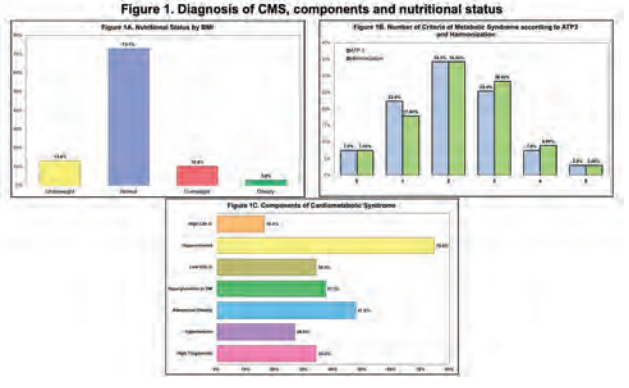

Figure 1. Diagnosis of CMS, components, and nutritional status

PUB115

Database Construction for Hemodialysis Patients in Sichuan Province

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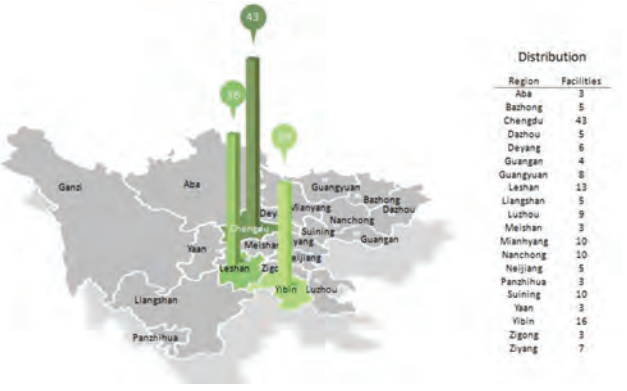
Background: The incidence of hemodialysis(HD) is escalating dramatically in recent years, which brings about great challenge and also opportunities for Sichuan Quality Control Center of Renal Disease. In order to acquire general information, patient distribution, medical staff, medical equipments and the principle clinical indexes of HD patients, basing on previous experience in software designing, we initiated a provincial renal database, providing free HD software for the whole province.

Methods: The provincial database was a web-based database, which was set up with free connections to the HD software. In order to help dialysis center in Sichuan. We provided a free software (Jiangsu Huibang Information Technology Co., Ltd.), which could pack the data and upload to the provincial database. We also provide a connection protocol for other HD software that was already installed in HD facilities. The provincial database did not open manually input function in order to reduce the tasks for HD staff. The database was set up in May 2018. The free HD software was open for application from May 2018. Survey and visit interview was carried out to help setting up the database.

Results: There were 171 HD centers (around 1/2 of HD centers in Sichuan Province) completing the installation of free HD software by April 2019, among which, 77 HD centers begun to upload data to provincial database. There were 11583 HD patients in the database, accounting for about 1/3 of the HD patients in the whole province. The mean age was 55 years for the reported patients with a female proportion of 41.46%. The proportion of HD patients within treatment target for hemoglobin, serum calcium level, serum phosphorus level and serum albumin was 37%, 52% and 58% and 84% in year 2018.

Conclusions: A new strategy for setting up a provincial database from providing software in dialysis centers is an efficient way, which is not only good for dialysis quality control, but also is important for registry based studies.

Funding: Government Support - Non-U.S.



The distribution of facilities in Sichuan Province

PUB116

Assessment of Quality of Life in Patients Undergoing Hemodialysis: A Single-Center Study

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Background: The purpose of this study was to investigate the relation between selected demographic and clinical characteristics and Quality of Life (QOL) scores in patients with end-stage renal disease (ESRD) who receive dialysis.

Methods: The study was conducted at one hemodialysis unit in Bahrain from May 2018 to July 2018. We used standard QOL Index score instrument Arabic form. This study included 100 patients (66 men and 34 women), aged 22-80 years treated with maintenance hemodialysis for 4-190 months. Inclusion criteria included dialysis for at least 3 months and age more than 18 years with no severe morbidities or psychological diseases.

Results: Following QOL scores were recorded: The health and functioning domain (64.8±15.3), the social and economic domain (65.6±14.1), the psychological/spiritual domain (74.9±14.3), and the family subscale domain (75.9±14.5). The male patients had none-statistically significantly reduced QOL and younger patients had better QOL scores. The QOL scores revealed a decreasing trend with decreasing level of education and they were higher among keep house patients. Also, the family subclass scores were significantly higher among the married patients. Correlations between the demographic characteristics and QOL scores showed that there was a significant negative correlation between family domain and educational level and marital status while there was a significant positive correlation between residence and psychological domain.

Conclusions: Age, gender, marital status, residence, ethnicity, education level, employment status, income, and duration on hemodialysis non-significantly affected one or more domains of QOL Index scores in such patients. Adequate management of these factors could influence patient outcomes.

PUB117

A New Approach to Assess Patient-Reported Outcomes of Patients with ESKD in an International Randomized Clinical Trial

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Background: The CONVINCE trial is an outcome-based RCT comparing high-dose hemodiafiltration (HDF) versus conventional high-flux hemodialysis (HD) in nine European countries. Primary objective is the comparison of all-cause mortality, one of the secondary objectives is the comparison of the experienced health status of patients. The aim of the CONVINCE Consortium was to develop a toolbox to assess the patient health status with a particular focus on constructs related to pathophysiological changes following implementation of the two dialysis modalities, which is applied in the CONVINCE trial.

Methods: We applied a state-of-the-art approach to develop the conceptual framework for the toolbox. Health aspects and constructs relevant for ESKD patients were identified in due consideration of international initiatives such as the SONG Initiative and ICHOM, a thorough literature review and interviews/focus groups with patients and experts. Psychometrically advanced instruments in combination with new measurement approaches were incorporated in the toolbox and applied in the CONVINCE trial.

Results: Out of 11 identified health domains and 41 ESKD-specific symptoms and health problems, we included 9 health domains and 20 symptoms/health problems in the toolbox according to the conceptual model of the CONVINCE trial. The compilation of the PRO assessments balanced comprehensiveness, respondent burden, and goal of measurement. Items to assess the proximal outcome *recovery time* and *treatment-related fatigue* were developed using state-of the art methods. Generic outcomes, e.g. physical function, depression and fatigue are measured by use of the psychometrically advanced tools of the PROMIS® initiative. Data collection started in Nov 2018 aiming to include 1,800 patients, which should be followed up for 24 moths including approx. 16 measurement points. First results of the baseline assessment will be presented.

Conclusions: The application of the toolbox using psychometrically advanced tools, instead of an off-the shelf PRO measure, facilitates the assessment according to a specific research objective. Thus, the impact of ESKD and treatment on patients can be accurately evaluated.

Funding: Government Support - Non-U.S.

PUB118

Scheduled vs. Emergency Dialysis in Undocumented Migrants with ESRD as Exemplified in France: Medical, Social, and Economic Issues

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Background: Compared to scheduled chronic dialysis, emergency dialysis is associated with higher mortality, worsened quality of life, and additional medical expenses. Scheduled dialysis is struggling to emerge as the primary care approach for undocumented migrants with end-stage renal disease.

Methods: We analyzed the data of the undocumented migrants treated with dialysis in our intensive care unit (ICU) in Paris between April and May 2019

Results: A total of 18 undocumented migrants were managed in our nephrology ICU at Tenon Hospital in Paris, France. The majority (61 %) was not dialysed in their country of origin. Out of the 7 patients already dialysed, 71% had previously received dialysis treatment from another center in Europe. 40% of them left their country due to the laxk of kidney transplantation resources in their country of origin. 13 patients (72%) were scheduled for regular chronic dialysis treatment directly after their first admission in the ICU. Admission to chronic dialysis was delayed for three patients, with different waiting times before receiving scheduled dialysis: 11 days (resulting in 2 admissions for dialysis), 26 days (5 admissions for dialysis) and 77 days (11 admissions for dialysis). Two patients were never scheduled for chronic dialysis: one was in transit in France, the other was lost to follow up after being admitted in the ICU 6 times over 28 days. The total cost for these acute-care treatments was 242 770 USD, with a mean of 13 487 USD per patient, which is the equivalent of 45 dialysis per patient.

Conclusions: In France, despite that virtually all healthcare expenditure are funded by a national agencies system, there is a lack of standardization pertaining to the management of dialysis of undocumented migrants across the country. Each centre edicts its own policy based on physician's belief and local resources. In our center, despite an overall willingness for an expeditious scheduling of those patients in chronic dialysis, there remains a discrepancy in patients' care, mainly due to logistical issues. We believe that the benefits of scheduled chronic dialysis for undocumented migrants are threefold (for the patient, the physician and the society) thus legitimising it as the universal standard of care for this vulnerable population in our developed health resources countries.

PUB119

Neutrophil-to-Lymphocyte Ratio May Replace C-Reactive Protein in Predicting Prognosis of Patients on Maintenance Hemodialysis: A Longitudinal Study

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Background: The Neutrophil - to - Lymphocyte ratio (NLR) is a readily available marker closely associated with survival in maintenance hemodialysis (MHD) patients. Our purpose was to examine the cross-sectional and longitudinal relationships between NLR and C-reactive protein (CRP) levels and consequent associations with adverse clinical outcomes in this population.

Methods: A retrospective, longitudinal cohort study was conducted using a clinical database which included 554 patients (mean age of 67.6±14.2; 34% women) in a single center receiving MHD from November 2007 to July 2018. NLR, CRP and nutritional parameters were recorded at 0, 6, 12, 18, 24, 30, and 36 months followed by 58 additional months of clinical observations.

Results: In a linear mixed effects model adjusted for baseline demographics and clinical parameters including white blood cell count, NLR was associated with CRP levels at any given time-point of longitudinal observation (linear estimate : 1.53 (95% CI: 0.11 to 2.95, P=0.04) regardless of baseline NLR (NLR x Time interactions were insignificant). Longitudinal changes in NLR were inversely associated with serum albumin, creatinine, triglycerides and hemoglobin changes over time. For each 1.0 unit increase in NLR over time, the fully-adjusted all–cause mortality hazard ratio using Cox models with the time-varying risk effect was 1.04 (95% CI: 1.01 to 1.07, P=0.006). However, when CRP was included in this model, the relationship was no longer significant.

Conclusions: Longitudinal changes in NLR appear to be reliable in detecting changes in CRP over time and in predicting of all-cause mortality risk in MHD patients.

PUB120

Incident Dialysis Patients in a Country with High Prevalence of CKD

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Background: In our country with a population around 10,000,000 inhabitants, by the end of 2018, 13,000 patients(pts) were treated with dialysis, 2607 of which incident pts. The majority started hemodialysis(HD), only 8,7% peritoneal dialysis(PD). Our aim was to compare characteristics and outcomes of both modalities in a single-center hospital serving a population of around 450,000 inhabitants.

Methods: A retrospective cohort study with 652 incident pts on renal replacement therapy between January 2013 and December 2017 in a single-center with follow-up until December 2018. Charlson Comorbidity Index(CCI) was calculated and pts divided into modality. Kaplan-Meier survival curves were estimated for subgroups defined by age (<65 *vs* >65) and a Cox proportional hazards regression used to estimate relative mortality risk, adjusting for CCI.

Results: 556(85,2%) started HD and 96(14,8%) PD. On HD 61.2%(n=340) were male *vs* 69.8%(n= 67) on PD; median(IQR) age 73(64-81) *vs* 57.5(41-70), 27% *vs*69.8% were <65 and 30.6% *vs*5.2% <80. Comorbidities concerned, 84.9%(n=472) *vs* 92.7%(n=89) had hypertension, 48.9%(n=272)*vs*37.5%(n=36) diabetes. The median(IQR) CCI was 8(6-10) *vs* 5(3-8),(p<0,001). Younger pts had 1-year survival rate of 89.1% on HD *vs*95.2% on PD; 3-year 77.9% *vs*86.6% and 5-year 76.2% *vs*74.9%. In older pts 1-year 70.5% *vs*86.2%; 3-year 47.1% *vs*74.3% and 5-year 34.6% *vs*74.3%. A Kaplan-Meier analysis showed a better survival for PD(*p*=0.004) in older pts while no difference was found in younger pts (*p*= 0.096). In a multivariable analysis, we found that pts being educated about dialysis was predictor of choosing PD(p<0.001). A multivariate analysis showed that CCI(OR 4,16, CI 95% 1,96-8,82; p<0,001) and HD(OR 2,87, CI 95% 1,35-6,10; p= 0,006) were independent predictors of mortality in older pts, while in younger pts the modality had no influence but CCI was an independent predictor of mortality(OR 5,19, CI 95% 2,51-10,72; p<0,001).

Conclusions: A higher percentage of PD incident pts compared to the national average was found, and in pts eligible for both modalities, previous education about RRT modalities was a predictor of choosing DP. Our cohort shows better survival for PD compared to HD in older pts and that higher CCI is associated with worst outcomes regardless of age.

PUB121

Assessment of Primary Cognitive Deterioration in Patients with Chronic Renal Disease in Hemodialysis

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Background: Patients with Chronic Kidney Disease (CKD) often present a variety of disorders in the Central and Peripheral Nervous System that have been widely described in the medical literature. However, its approach is only carried out when the signs

and symptoms that are evident, this causes that the intervention is only palliative. The Objective was to establish the degree of primary cognitive deterioration (PCD) in patients with chronic kidney disease on dialysis therapy.

Methods: A multicenter (3 IPS), cross-sectional study was conducted. The patients were given the Montreal Cognitive Assessment (MoCA) questionnaire with prior informed consent, and the latest paraclinical data (Hemoglobin, Sodium, BUN, Serum Creatinine), KtV, Date of the first dialysis were recorded. base disease and comorbidities. To establish a possible structure of dependence between the FAD and the Factors enunciated, the correlation coefficient was calculated, for which a generalized multivariate linear model (GML-M) was used. This was constructed using the own values of each Factor, through the technique of adding Factors.

Results: A total of 62 patients on dialysis were evaluated. 58.5% were men. The overall average age was 53 ± 16 years (women: 47 ± 16 years | men: 58 ± 15 years). The time on dialysis was 7.5 ± 5 years (women: 7 ± 5 years | men: 8 ± 5 years). Associated comorbidities were Hypertension (68%), Diabetes Mellitus (32%), Urinary Tract Infections (3%). Only two patients (3.5%) obtained not to classify them with primary cognitive impairment. A correlation of mixed effect between Age and Time on dialysis, however the value of R^2 is moderately weak (31.2%) although the significance value indicates that these are very significant (p-value <0.05), these results indicate the need to include the dose values in the model of dialysis as well as laboratory parameters, as well as co-morbidities and other relevant clinical data.

Conclusions: According to the Coef. Determination and Correlation is determined by the ratio of serum creatinine, phosphorus and total cholesterol, being a multivalued model dependent on the inverse interaction with the patient's age.

PUB122

Allergic Reactions Associated with Bicarbonate Bath During Hemodialysis

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Introduction: Allergic reactions during hemodialysis (HD) treatment have been well explained in the past. Most common causative factors implicated are secondary to dialyzers with synthetic or cellulose membranes. Other agents like latex, intravenous iron supplements, heparin and formaldehyde have also been reported. We report a case of end stage renal disease (ESRD) patient on HD with severe allergic reaction secondary to bicarbonate bath.

Case Description: We report a case of 49-year old gentleman with ESRD on HD secondary to diabetes and Hypertension, on HD for the last 5 years. Patient has been complaining of allergic reactions including rash and hives within half an hour to one hour after initiation of hemodialysis. His HD session was terminated earlier on few occasions in the setting of hypotension, contributed by anaphylactic reaction, in addition to hemodynamic changes. He was thoroughly investigated for any possible cause of allergic reaction and extreme caution was used in terms of changing the dialyzer types, latex exposure and any commonly implicated solution or medication, with no success. He was prescribed anti allergic medications and emollients with limited response. Allergic reactions usually subsided soon after HD session. After close observation and exclusion of any possible causative factor, he was found to be allergic to standard powdered bicarbonate cartridge by Gambro. He was switched to liquid bicarbonate solution and his allergic reaction completely resolved on following HD sessions.

Discussion: Allergic reactions due to variety of substances have been reported during HD sessions. As per literature review, the allergic reactions secondary to bicarbonate bath have not been reported in the past. Nephrologists and dialysis center staff should be vigilant to identify this rare cause of anaphylactic reaction.

PUB123

Impact of Cinacalcet on Secondary Hyperparathyroidism (SHPTH)

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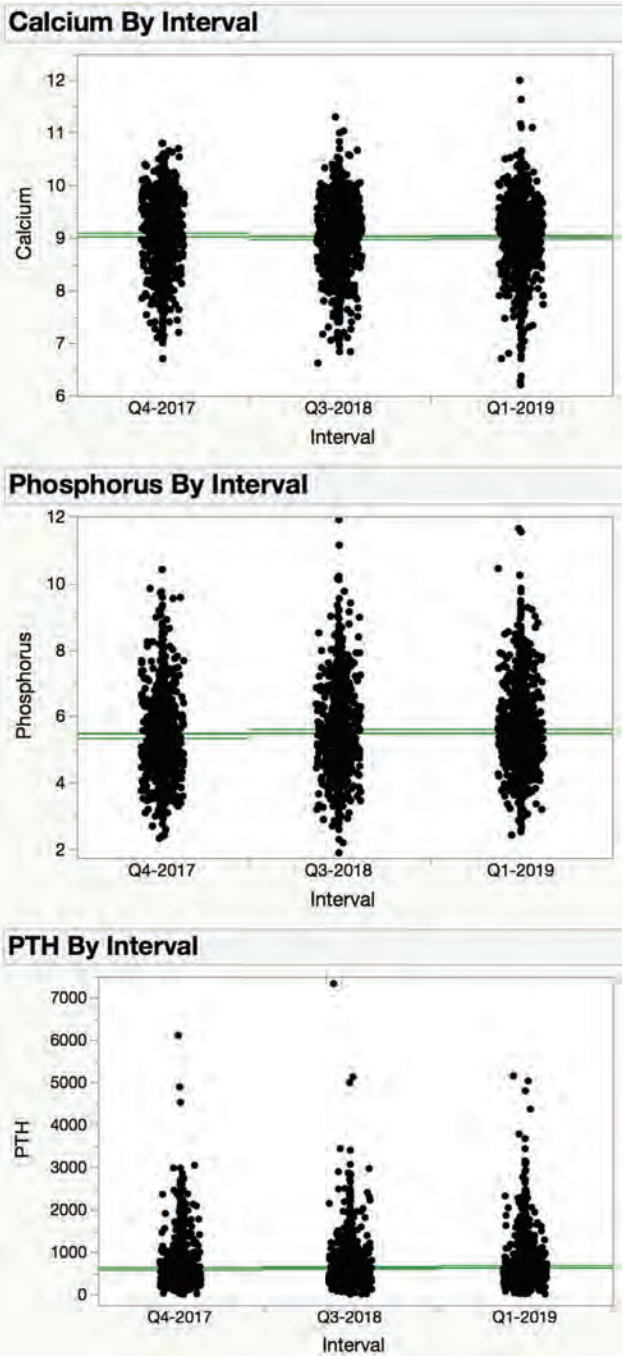
Background: SHPTH is caused by reduced phosphate (P) excretion and hydroxylation of vitamin D (vitD) leading to decreased calcium (Ca) levels and stimulation of parathyroid hormone (PTH) secretion. Clinical findings include decreased bone mineralization and increased rates fractures, cardiovascular disease and mortality. SHPTH is treated with P binders, vitD analgogues (analogues) and calcimimetics (CM) like cinacalcet which suppresses PTH secretion via the calcium-sensing receptor. CM were added to the prospecitve payment system in January 2018; analogue use increased while CM use decreased.

Methods: Our QAPI program monitors levels of Ca, P and PTH with a goal of maintaining >98.5% of patients with Ca 8.5-10.2 mg/dL, 57% with P 3.5-5.5 mg/dL and >90% with PTH 100-750 pg/mL. Here, we evaluate the cost and effectiveness of CM using an intention-to-treat approach.

Results: Results from the 4th quarter of 2017 (baseline) were compared to the 3rd quarter of 2018 and the 1st quarter of 2019 for 996 patients present at all three time points. Ca showed no significant change; there were statistically significant increases in P and PTH. (See figures.)

Conclusions: CMs have not improved management of SHPTH in our real world analysis. Based on our average cinacalcet cost of $17.32 per treatment and the apparent lack of benefit, our analysis argues against use of cinacalcet for treatment of SHPTH.

Funding: Clinical Revenue Support



Calcium, phosphorous, and PTH levels over time

PUB124

Atypical Dialyzer Membrane Reaction: A Mask Behind the Curtain

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Introduction: Prior to the advent of the polysulfone dialyzer membrane, dialyzer reaction was common with cellulose dialyzers and easily identified. In this report, we present a case of atypical dialyzer reaction manifesting as only difficulty in achieving ultrafiltration without eliciting the other classical dialyzer reaction symptoms. Our case is unique in the atypical pattern and feature of presentation of this dialyzer.

Case Description: A 56 yr old male with history of HTN, DM, and slowly progressive chronic kidney disease with nephrotic range proteinuria initiated on hemodialysis (HD) for acute renal failure with oliguria in setting of left foot cellulitis. Clinical examination reveals fluid overload with bilateral lung crepitations and 3 + bilateral pedal edema. His dialysis orders were Polysulphone high flux dialyzer F180 dialyzer. He had gradual increasing duration of HD from 2.5 hrs to 4 hrs on the third session with increasing blood. His Pre-Hemodialysis blood pressure (BP) was 140-160s systolic range. His BP meds were typically held pre-HD with last dose over 12 hrs pre HD. Patient repeatedly had

drops in his systolic BP to the 80s with symptoms of fatigue and dizziness requiring IVF boluses during dialysis. His post dialysis weight continue to be higher than his predialysis. Daily HD and increasing adjustment of blood flow as well low temp bath did not yield any changes. Dialyzer change on his 3rd session to F250 also did not make any difference. He did not describe any rash or fever with negative cultures and absence eosinophilia. Echocardiogram was normal. A suspected dialyzer reaction was elicited and dialyzer switched from the F series to the cellulose triacetate high flux. Patient on his 4th HD treatment and first with Ex 170 was able to tolerated HD well with no drop in BP and target UF of 2.3 L obtained successfully. Subsequent dialyses were uneventful despite advancement to the Ex 210 dialyzer use. **Outcome**-Patient's symptoms resolved after changing from the polysulphone series to a different one, a cellulose-based dialyzer membrane

Discussion: In this patient, the atypical pattern of presentation neither fit the classic type A nor Type B reaction. Episodic dialyzer reaction is rare at initiation in the absence of cardiac disease or pericardial tamponade. This case is atypical due to absence of these other causes of hypotension and resolution of the clinical symptoms with change of dialyzer membrane.

PUB125

Factors Associated with Achievement of a High Convective Volume Target on Post-Dilution Online Hemodiafiltration (HDF)

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Background: A higher convective volume (23 liters, 3x/week) has been associated with a lower risk of death in post-dilution online HDF. We aimed to identify factors associated with achieving a high weekly volume of convection

Methods: Retrospective analysis of all HDF patients at 13 dialysis units in Brazil in 2018. A convective volume of 69 L/week was considered the lowest adequate HDF dose.

Results: A total of 286 patients (67% men, 39% diabetics, 62±16 years-old, 33% with tunneled catheter, 43% on more frequent HDF [14% 4x/week, 29% on daily HDF] and 63% incident on HDF) underwent to 28,078 HDF sessions in the period. Weekly HDF time was 717±73 min (56.7% ≥720 min) and blood flow 347±45 mL/min. Weekly convective volume was 79.5 (IQR 69.0-87.6) L/week, with 75.7% reaching the target of 69 L/week. In the logistic regression model, having the target of 69 L/week as the dependent variable, female gender (P<0.0001), age (P=0.035), hemoglobin >12 g/dL (P<0.0001) and use of catheter (P<0.0001) were associated with the risk of not achieving the minimum dose, whereas blood flow ≥350 mL/min (P<0.0001), weekly HDF time ≥12 hours/week (P<0.0001) were independent factors positively associated with a high convective volume.

Conclusions: A high convective volume can be achieved by most of the unselected patients on HDF. The weekly HDF time is a modifiable variable that can be used to achieve the appropriate weekly convective volume.

PUB126

A Prospective Study on the Association Between Ultrafiltration Rate and Mortality in Hemodialysis Patients: The Effect Modification by Muscle Mass

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Background: The association between ultrafiltration rate (UFR) and mortality may be affected by muscle mass or volume status in maintenance hemodialysis (MHD) patients. However, there are no prospective data about those association in patients receiving MHD.

Methods: This was a prospective observational study on the patients (≥ 18 years old) who have been on MHD for at least three months and gave informed consent. A portable whole body bioimpedance spectroscopy device (BCM) was used for bioimpedance analysis measurement at baseline. Primary outcome was all-cause mortality.

Results: Among 169 patients, mean (SD) age was 62 ± 12 years and male were 59%. Mean (SD) UFR was 12.8 (11.1) mL/h/kg. Median (interquartile range, IQR) overhydration volume by BCM was 2.4 (1.4, 3.9) L. Median (IQR) lean tissue index (LTI) (calculated as lean tissue mass/height^2) was 12.4 (10.4, 14.6) kg/m^2. The median follow-up duration was 1.4 years. In an adjusted Cox regression analysis, greater mortality was associated with higher UFR. This association remained consistent even after adjusting for overhydration status. However, the association between UFR and mortality was modified by LTI ($P_{interaction}$=0.03); the association was only significant in patients with LTI of less than 12 kg/m^2.

Conclusions: Higher UFR was associated with increased all-cause mortality regardless of volume status in MHD patients. However, muscle mass may modify the association with higher UFR and increased mortality.

Funding: Government Support - Non-U.S.

PUB127

Hospitalisation and Mortality in Hemodialysis Patients in India: A Single-Center Prospective Study

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Background: In India over 2 lakh new cases develop end stage kidney failure every year but only 10-20% are able to continue long term dialysis. USRDS 2014 hemodialysis (HD) data shows that average number of hospitalization was 1.7/patient/yr & duration of stay was 10.9 days. There is paucity of data on hospitalization & mortality in HD population from India. We prospectively studied the hospitalization & mortality in HD patients at our center.

Methods: All patients who came to our center for HD from Nov 2016 to May 2019 were the subjects of this study. Patients who had HD for less than a month or were on immunosuppressives or having underlying malignancy were excluded. Details of all the hospitalizations/ mortality were recorded & their relation with age, sex, underlying DM & CAD was studied. Analysis was done using SPSS 23.

Results: 395 patients came to our multi-specialty center for HD during the study period. Of these, 70 patients had HD for less than a month and were excluded; remaining 325 formed the study group. There were 201 males. Mean age of the study group was 56.86±13.98 y (range 18-84) & mean duration of follow up was 11.66±5.96 mo (range 1-31). Of these 325 patients, 40 received renal transplant, 46 died & 80 left for other centers after a mean follow up of 6.35±5.96 mo, 11.46±5.90 mo & 9.98±5.14 mo respectively. 198 (60.9%) of these 325 patients had 348 hospitalizations (mean 1.07±1.32 hospitalization/ patient). Total days of hospitalization were 1736 days (mean 8.77±10.03). The underlying reason for hospitalization was Infections (33%), Cardiopulmonary (31%), Vascular access related (19%), CNS complications (7%), & other causes were 10%. Hospitalization was significantly higher in those with advanced (age>60 years) (p=0.044). Presence of diabetes, gender & CAD status didn't show any significant association. 46 patients died after a mean follow up of 11.46±5.90 months. Mean age of this group was 61.45±13.29 years. Causes of death were sepsis (50%), CV events including SCD (39.1%), CVA in 6.5 % & miscellaneous causes in 4.34%. Mortality was significantly higher in those with advanced age(p=0.026) DM(p=0.026) & CAD (p=0.043).

Conclusions: Our follow up study of 11.46 months shows, hospitalization rate of 1.07/patient with duration of hospitalization 8.77 days. Infections were the leading cause of hospitalization & death. Advanced age, DM & CAD were associated with bad outcome.

PUB128

Risk Factors for Mortality in the Short- and Long-Term in Patients with Chronic Renal Disease After Renal Replacement Therapy

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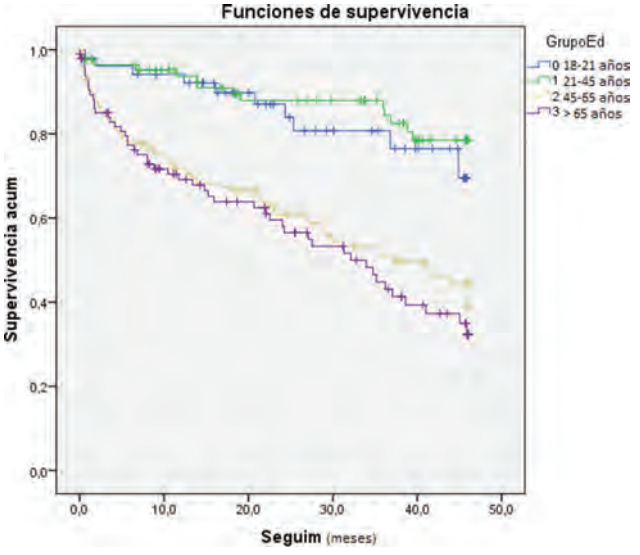
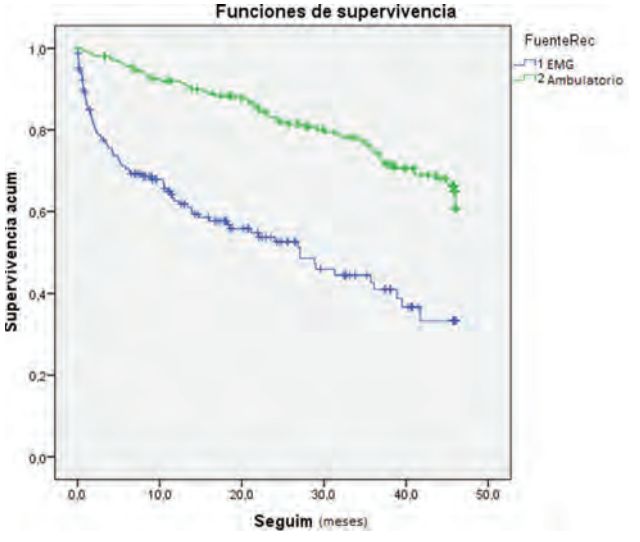
Background: Chronic Kidney Disease in Stage V (CKD5) and its need for Renal Replacement Therapy (RRT) has increased markedly in recent decades by the rise of chronic diseases and the opening of services to marginalized populations, generating relevant costs in health systems, the effect should be evaluated objectively to improve their efficiency. Objective: Evaluate the survival of patients with CKD5 in RRT from a population favored with a new financing system (SIS) in a General Hospital of MINSA, Lima-Peru, identifying the variables associated with poor prognosis.

Methods: Were studied patients benefit from the SIS with ERC5 incidents to the Emergency of the Hospital Cayetano Heredia (HCH) who entered TRR between September 2014 to December 2017 in whom survival was evaluated and analyzed factors associated with mortality. The evaluation was finalized in July 2018.

Results: 374 patients with CKD5 for RRT were studied, 169 were admitted for emergency and 205 on an outpatient basis. The variables found in this population were: age greater than 45 years (p = 0.000), female sex (p = 0.002) and admission to the program for emergency (p = 0.000).

Conclusions: Age (> 45 years), female sex and admission to the program for emergency were the conditions associated with higher mortality in patients benefiting from SIS to receive RRT.





PUB129

Prevalence of Obesity and Overweight in a Peripheral Dialysis Center and Its Association with Comorbidity Evaluated Through the Charlson Index

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Background: The obesity is accompanied by many comorbidities, it could be deduced that obese patients on hemodialysis (HD) follow the same pattern and therefore would be more prone to present cardiovascular complications. However, this hypothesis has not been proven yet. In fact, several studies have observed an inverse relationship between the Body Mass Index (BMI) and mortality, phenomenon called "paradoxical obesity. Objectives: To evaluate prevalence of obesity / overweight in a HD center and the body composition of HD patients by bioimpedance spectroscopy (BCM, Fresenius Medical Care), obtaining the fat tissue index (FTI) and the lean tissue index (LTI). Study the presence of different pathologies using the Charlson Comorbidity Index (CCI) and evaluate the relationship between the different diseases that make it up with obesity / overweight.

Methods: Cross-sectional descriptive study in January 2017 that included 73 patients. The BMI according to the WHO (World Health Organization) was analyzed and grouped the patients according to the FTI in tertiles: FTI ≤ 13.00; FTI = 13.01-19.00; FTI≥19.01. All the pathologies that make up the CCI, renal diagnosis, laboratory values and clinical parameters of HD were recorded.

Results: The prevalence of obesity was 28.77% and overweight was 32.88%. When studying the BMI with the different pathologies that make up the CCI, it turned out that the overweight patients presented a significantly higher percentage of diabetes with organic damage (P = 0.047). On the other hand, when relating the FTI with pathologies of the CCI, it was found that the percentage of patients with Congestive Heart Failure (CHF) was significantly higher as the tertile of the FTI was higher (P = 0.020). When finding these percentage differences by pathology, an ROC curve analysis was performed. This analysis revealed the FTI as a predictor of Congestive Heart Failure (AUC = 0.689, P = 0.028, CI 95% = 0.527-0.852), not being a predictor of this comorbidity the BMI (AUC = 0.645, P = 0.093, CI 95% = 0.455-0.806).

Conclusions: Over 60% of patients in the analyzed cohort were overweight or obese. Only diabetes with organic damage was associated with overweight, while Congestive Heart Failure with a higher FTI. Our results suggest that FTI determined by BCM can help predict better comorbidities than BMI, especially CHF

PUB130

Verification of Nutrition Maintaining Effects by Using Anti-Thrombotic PMMA Membrane (VENUS STUDY)

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Background: Nutritional status and QOL are the most important indicators for the prognosis of dialysis patients, and the dialysis prescription which enables to maintain the nutritional status and improve QOL should be needed. Polymethylmethacrylate (PMMA) is a synthetic dialysis membrane with protein adsorptive property and was reported that it had beneficial effects on nutritional status and QOL of dialysis patients. In VENOUS study the beneficial effects of newly introduced anti-thrombotic PMMA (NF membrane) on the nutritional status and QOL of older dialysis patients were evaluated.

Methods: This study is a randomized control trial which compared PMMA with polysulfone (PS) on the patients older than 70 years old. The 54 registered patients were randomly assigned to the NF group (28 patients) or PS group (26 patients) and followed for 12 months. The nutritional status was considered by Malnutrition Inflammation Score (MIS) as a primary outcome, normalized protein catabolic rate (nPCR), and creatinine generation rate (%CGR) as a secondary outcome every 3 months. Patients symptoms as a QOL indicator were also monitored as a secondary outcome every 3 months on arthralgia, skin itchiness, irritable sense, fatigue, headache, dialysis related hypotension, leg cramps, and post-dialytic bed-free time.

Results: 11 patients in the NF group and 10 patients in the PS group were dropped out from the study. Finally, 15 patients in NF and 14patients terminated the study, however, 2 patients with the data deficit in each group were excluded. The MIS was increased at 6-, 9-month but there was no difference between 0-month and 12-month in NF group. The MIS was also increased at 9-month but was no difference between 0-month and 12-month in PS group. There are no remarkable changes were observed in nPCR, %CGR in both groups. Patients' symptoms were not different between NF group and PS group through the study period. However, the symptom total score was gradually reduced in NF group, but that in the PS group did not change.

Conclusions: In the current study we did not admit the advantages of new PMMA compared with PS on the MIS as a primary outcome. However, we could clarify the beneficial effects on the parameters of QOL only in NF group and it suggested that new PMMA membrane could ameliorate QOL of dialysis patients.

Funding: Commercial Support - TORAY

PUB131

User Satisfaction and Cost Savings of a Novel Hemodialysis System in an ICU Setting

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Background: AKI requiring RRT is increasing in frequency in the ICU. Because of hemodynamic instability the treatment of choice is either CRRT or PIRRT. The former is relatively expensive due to the cost of fluids and the latter technically difficult for non-dialysis nurses because it uses a dialysis machine. Outset Medical's Tablo is an all-in- one system with a user-friendly touch screen interface that requires minimal training and produces AAMI quality dialysate using tap water and conventional dialysate concentrate. The purpose of this pilot project was to assess whether the Tablo system was both easy to use and provided cost savings.

Methods: 17 ICU patients with AKI requiring renal replacement were treated for 6-12 hours using the Tablo system. Tablo was set up and run by the ICU nurse. Dialysis prescription, duration and ultrafiltration rate were left to the discretion of the attending nephrologist. Cost savings were compared with CRRT, nursing satisfaction was assessed by a Likert scale questionnaire.

Results: Compared to NxStage the majority of nurses found it easier to use (average score 4.8/5); most nurses felt comfortable providing treatment with this system after completion of training (average score 4.3/5) and they were also satisfied with Tablo as a treatment option (average score 4.8/5). Several participants also reported that the system was easy to transport and required less space. Comparing a 12-hour Tablo treatment to a 24-hour CRRT treatment using NxStage fluid at an effluent rate of 25 ml/kg/h would generate a cost savings of $303/day.

Conclusions: In our study, we found the Tablo system to be a viable alternative to CRRT. The nursing staff were easy to train and found this system straightforward to operate. In addition, because of its compact size Tablo took up less space, which is advantageous in the limited ICU environment. Importantly, Tablo when compared to CRRT led to significant cost savings at this facility.

Funding: Commercial Support - Outset medical supplied the Tablo machines.

PUB132

Extracorporeal Therapy in Cefepime-Related Neurotoxicity

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Introduction: Cefepime is a fourth generation cephalosporin with broad spectrum antimicrobial activity and is primarily excreted by the kidneys. It may rarely be associated with neurological side effects.

Case Description: Patient is a 61 years old male, with a history of end stage renal disease and on peritoneal dialysis, who was admitted with a 5 day history of lightheadedness. Work up showed orthostatic hypotension. Patient developed a low grade fever, non-productive cough and shortness of breath during his stay. A CT scan of the chest was suggestive of bilateral pneumonia. Patient was started on intravenous Cefepime 2 grams every 8 hours. Approximately 36 hours later, patient was noted to be confused. On reevaluation, patient was noted to be hemodynamically stable and not hypoxic. Detailed neurological exam showed that patient was alert but not oriented to his surroundings. No focal deficits were noted. A repeat infectious workup was unremarkable. The degree of azotemia was stable. CT brain, electrocardiogram and arterial blood gas were unremarkable. Due to clinical concern for Cefepime neurotoxicity, IV Cefepime was discontinued. Cefepime levels were not checked as they are not available at our hospital. Given the low clearance of Cefepime with peritoneal dialysis, patient had a temporary hemodialysis catheter placed and was started on hemodialysis. He underwent 2 sessions of hemodialysis in 2 days, 4.5 hours each using a Fresinius Optiflux F200 dialyzer with a blood and dialysate flow rates of 450 ml/minute and 750 ml/minute respectively. There was a complete resolution of confusion after 2 sessions of hemodialysis.

Discussion: The primary route of elimination of Cefepime is renal, with more than 80% of the drug excreted unchanged in patients with normal renal function. Cefepime-related neurotoxicity occurs mostly with incorrect dosing especially in the setting of renal dysfunction as the half life of the drug is increased from 2 hours to nearly 22 hours. However, it may also be seen in patients with appropriate dosing. Extracorporeal drug removal with dialysis may be needed to facilitate drug removal and improvement in neurological status. Peritoneal dialysis is less efficient at clearance of cefepime compared to hemodialysis, with clearance only 9% of that reported with hemodialysis.

PUB133

Can Metolazone Help Control Interdialytic Weight Gain and Serum Phosphorus Levels in Hemodialysis Patients with Residual Renal Output?

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Background: Phosphorus is an important uremic toxin that is difficult to control in hemodialysis patients. Metolazone is a thiazide like diuretic that has been reported to increase urinary phosphate excretion through a carbonic anhydrase independent proximal tubular effect. Metolazone is frequently used in conjunction with furosemide to increase urine output in patients with advanced renal insufficiency from cardio renal syndrome, often as a last attempt to avoid repeated hospitalizations and dialysis, and is well tolerated in this population.

Methods: Here we summarize anecdotal clinical observations to see if the use of metolazone in conjunction with furosemide in hemodialysis patients with residual urine output might be beneficial to reduce high interdialytic weight gains and hyperphosphatemia.

Results: A medication and chart review reveals three ESRD patients with high interdialytic weight gains of >3-4 kg and a residual urine output of more than 500ml of urine a day who had metolazone 5mg daily added to furosemide treatment. All three patients had hyperphosphatemia in the 6.4-11mg/dl range. There was no effect on either interdialytic weight gain or serum phosphorus level and metolazone was stopped. A fourth patient had continued treatment with both metolazone and furosemide for several months since her renal transplant failed, and regardless, her dialysis treatments were complicated by constantly high serum phosphorus levels and high interdialytic weight gain.

Conclusions: In conclusion, these anecdotal observations suggests that the combination of a 5mg daily dose of metolazone with furosemide is no more effective to decrease interdialytic weight gain or decrease hyperphosphatemia in hemodialysis patients than furosemide alone.

PUB134

Kibow Multisite Hope Study Dialysis Randomized Clinical Trial Protocol: A Unique Double-Blind Placebo-Controlled Cross-Over Design Using Renadyl™ with Standard-Care Therapy (n=100, 5 Sites in the United States)

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Background: Hemo or peritoneal dialysis patients are fatigued after dialysis sessions, susceptible to infections, have poor quality of life due to the high blood levels of uremic toxins and, many are depressed. Outcomes like fatigue, pain, anxiety though major concerns and critically important to patients and clinicians may not be reported in clinical trials (Kid Int 2019; 95:1280-1283). The 2014 Standardized Outcomes in Nephrology (SONG) initiative established core outcome sets for nephrology trials (https://songinitiative.org/). An alternative regime to address some of these issues would benefit all dialysis patients. Renadyl™; a Pro/Prebiotic dietary supplement, is proven to reduce several uremic toxins in three pilot clinical trials with no reports of adverse outcomes. We propose to carry out large scale RCT to validate it as a Live Bio-Therapeutic (LBT) drug with needed IND and US FDA approval.

Methods: Six month RCT controlled cross over design in an outpatient setting. Renadyl™ will be orally given at 90 B CFU/day.

Results: Measured endpoints will be:1: Dialysis duration, Quality of Life (QOL). 2:Uremic metabolite panel, CBC, liver function test 3: Biomarkers including Indoles, p-Cresol, TMAO, KIM-1, NGAL, IL-6 and CRP.

Conclusions: This is the first-ever RCT proposed using Renadyl™ as a Live Bio-Therapeutic (LBT) drug for Dialysis patients. Being noninvasive the intervention avoids any possible infection. As a rare unconventional crossover design patients will be their own control for prudent data analysis. Secondly every patient gets the interventional product thus accelerating better patient recruitment. Significance of p-value alone does not help in the decision of the application of results to clinical care and its policy (Kid Int. 2019; 95:28-30). $P < 0.05$ and $P > 0.05$ can affect interpretation and lead to bias. Other parameters are also important. (Kor J Pain 2017; 30(4): 241-242). The addition of pro/prebiotics with standard care of therapy may possess excellent potential towards Dialysis applications worldwide. Seriously interested clinical PI's please contact: rangan@kibowbiotech.com

Funding: Commercial Support - Kibow Biotech Inc

PUB135

Experience with Directly Acting Antiviral Agents for Hepatitis C in Maintenance Hemodialysis Patients in a Single Center from Pakistan

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Background: The prevalence of Hepatitis C in Pakistan is around 6 % in general population. Prevalence of hepatitis C in manintenance HD paients is between 22 to 55%. Seroconversion rates are reportedly one of the highest in the world.

Methods: Patients on maintenance HD at our center were included in the study. All the patients recieved sofosbuvir with one of the other available oral antiviral agents. Pertinent data at baseline, 3 months, 6 months and 12 months.

Results: Total of 31 patients were included in the study with Mean age of 50.3 years with Standard Deviation of 16.8. Twenty patients were male (64.5%) and Eleven were Female (35.5%). Duration of Hemodialysis prior to starting treatment was 2 months to 150 months. Four different regimens were used depending upon the availability of Drugs all of them containing Sofosbuvir in dose of 400mg OD. Pre-treatment PCR was Positive in all patients. SVR at end of therapy that is 3 months was achieved in all patients that completed study period. One patient had relapsed after 15months of achieving SVR (previously treated with Sofosbuvir and ribazole). Successfully treated with sofosbuvir plus valpatasvir for 4 months and achieved SVR successfully. Only 4 patients experienced Anemia, all recieving ribazole.

Conclusions: DAA based therapy delivered expected and desired results of therapy without any major therapy related adverse events in our center.

PUB136

How ESRD Creates, Enhances, and Promotes Poverty for Patients in the United States

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Background: It is well documented that the treatment is both expensive and takes a physical and financial toll on the patient and their respective families. Depending on the treatment modality, many patients fall out of the workforce under the age of 65 and depend on disability to survive creating an additional expense for the government and the general economy through a lower utilization of the workforce. The question, which has been somewhat explored, is if the diagnosis of renal failure leads to inevitable poverty? Despite coverage ratios and access to care, it still seems to negate that undergoing such a treatment regime removes the economic impact to the patient as well as society in general in addition, in many cases, of a quality of life previously experienced. If indeed dialysis results in patients facing an economic burden that translates into poverty, are there treatments that unlike in-center hemodialysis, can maintain a patient's employment and financial viability?

Methods: Accumulated Journal Articles

Results: CKD and ESRD places a tremendous financial burden on a patient and their subsequent family.

Conclusions: For the United States to step forward, like many of our health care equals and partners in Europe, the community, partnerships, and governmental organizations needs to address the issue from both a patient care and the humanitarian perspective as well as an economic analysis methodology and the general view on quality of life. Dialysis will always be an expensive treatment, but the costs can be reduced with a higher quality of life for patients. But the treatment doesn't have to cost as much as it does if providers

are willing to promote other modalities outside of the standard in-center thrice a week treatment that Fresenius and DaVita promote given their large investment in free-standing clinics. It must also be noted that these two providers create more wealth for their investors via this treatment option.

PUB137

A Home Away from Home: Patients' Experiences of Community Hemodialysis: A Qualitative Interview Study

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Background: Community hemodialysis is a sub-modality of home hemodialysis that enables patients to perform hemodialysis independent of nursing or medical supervision in a shared community house. This study describes the perspectives and experiences of patients using community hemodialysis in New Zealand to explore ways in which this dialysis modality may support the wider delivery of independent hemodialysis care.

Methods: Qualitative, semi-structured, in-depth interview study of thirty patients who had experienced community hemodialysis. Participants were asked about why they chose community hemodialysis and their experiences and perspectives of this hemodialysis modality. Data was analysed using thematic analysis.

Results: Twenty-five patients were interviewed (14 men and 11 women, 31 to 65 years of age). Most were of Māori or Pacific ethnicity and in part-time or full-time employment. Over two-thirds dialyzed for 20 hours a week or more. We identified four themes that described patients' experiences and perspectives of choosing and using community hemodialysis: reducing burden on family (when home isn't an option; minimizing family exposure to dialysis; maintaining privacy and self-identity; reducing the costs of home hemodialysis; gaining a reprieve from home); offering flexibility and freedom (having a normal life; maintaining employment; facilitating travel); control of my health (building independence and self-efficacy; a place of wellness; avoiding institutionalization; creating a culture of extended hour dialysis); and community support (building social inclusion; supporting peers).

Conclusions: Community house hemodialysis is a dialysis modality that overcomes many of the socioeconomic barriers to home hemodialysis, is socially and culturally acceptable to Māori and Pacific people, supports extended hour hemodialysis and thereby promotes more equitable access to best practice services. It is therefore a significant addition to independent hemodialysis options available for patients.

PUB138

Omphalitis in Adult Peritoneal Dialysis Patients

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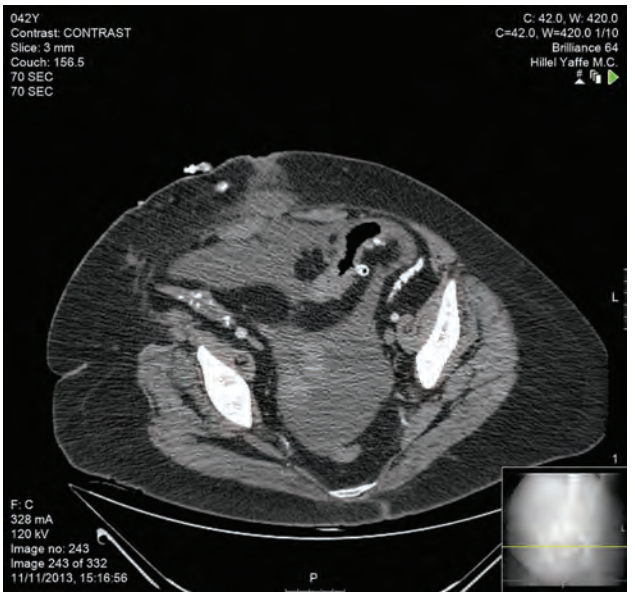
Introduction: There are very few literary reports related to omphalitis in peritoneal dialysis (PD) patients which described peritonitis after severe omphalitis. We describe 2 cases of omphalitis that occured in adult PD patients with CAPD-related peritonitis preceding the event of omphalitis.

Case Description: The first patient, 44-year old woman, was presented with abdominal pain, swelling and local pain in umbilical area. Peritoneal effluent was clear with elevation of WBC and PMN cells count, culture was negative. US of umbilical region revealed thickening, infiltration of subcutaneous fat and suspected fluid collection near the inner side of the abdominal wall. Abdominal CT demonstrated fluid collection in subcutaneous region and smaller collection extended to peritoneal cavity. The patient was treated like culture-negative peritonitis with recovery of clinical signs of omphalitis. 1.5 months before the patient experienced an episode of culture -positive peritonitis, was treated and recovered. Peritoneal culture was negative after the treatment. The second patient, 67 year women, was presented with abdominal pain, redness and local warmth in the umbilical region. Dialysate was clear with a little increase in WBC and PMN count, culture was negative. US of abdominal wall demonstrated thickening and infiltration of abdominal fat in umbilical and periumbilical area. Two small peritoneal lesions of unknown origin were seen. The patient was treated like culture-negative peritonitis and omphalitis recovered. One month before the patient was treated for culture - negative peritonitis and recovered.

Discussion: Our cases caused us to suggest that the omphalitis may be a complication of peritonitis in PD patients. Perhaps this patients had a predisposition like remnants of the umbilical cord and high abdominal pressure converts this rare problem from occult to obvious.



Abdominal CT of the first patient

PUB139

First Onset of Exit-Site Infection, but Not Peritonitis, Is Influenced by Body Mass Index in Newly Patients Started on Peritoneal Dialysis

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Background: Peritoneal dialysis (PD)-related infections such as exit-site infection (ESI) and peritonitis, are leading causes of technique failure in patients undergoing PD. However, the incidence rate of ESI and the clinical factors associated with ESI have not been well investigated.

Methods: The present study aimed to assess ESI and peritonitis in patients newly started on PD. The clinical records of 55 patients for whom PD was initiated between January 1, 2012 and December 31, 2018 at a single center were retrospectively reviewed. The baseline clinical factors influencing the time to the first onset of ESI and peritonitis events, and the relation between ESI and peritonitis were investigated.

Results: The following patient characteristics were as follows: age (median, interquartile range), 68.0 (55.0–78.0) years; body mass index (BMI), 22.6 (20.1–26.0) kg/m^2; diabetes, 30.9%; step-wise initiation of PD, 47.3%; bag exchange by caregivers, 32.7%; serum albumin level, 3.2 (2.7–3.6) g/dL; serum creatinine level, 8.3 (5.9–9.6) mg/dL; and dialysate-to-plasma creatinine concentration ratio (D/PCr), 0.64 (0.54–0.75). The total number of ESI evets was 162, and the incidence ratio was 1.22 per patient year. The total number of peritonitis events was 33, and the incidence ratio was 0.22 per patient year. The onset of ESI during the initial 60 days correlated with BMI (γ = 0.49; p = 0.001), with D/PCr (γ = –0.52, p = 0.000), and with incidence ratio of ESI (γ = 0.35, p = 0.017), but not with peritonitis incidence. Cox proportional hazards model revealed that the first onset of ESI was significantly affected by BMI [hazard ratio (HR), 1.19; 95% confidence interval (95% CI), 1.04–1.36; p = 0.009] but not by diabetes (HR, 0.69; 95% CI, 0.25–1.86) or D/PCr (HR, 0.79; 95% CI, 0.03–19.0), and that the first onset of peritonitis was not significantly affected by any of the factors including BMI, diabetes, and step-wise initiation of PD. The number of ESI events was correlated with the number of peritonitis events (p = 0.04), but the incidence ratio of ESI did not correlate with the incidence ratio of peritonitis (p = 0.11).

Conclusions: High BMI was associated with the first onset of ESI but not with peritonitis. The onsets of ESI and peritonitis over time were not closely related.

PUB140

Eligibility and Patient Barriers to Peritoneal Dialysis in Patients with Advanced CKD

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Background: The burden of chronic kidney disease is on the rise in Kenya and is a significant cause of morbidity and mortality. While definitive treatment is renal transplantation, many patients require renal replacement therapy in the form of hemodialysis or peritoneal dialysis. The predominant modality utilized in Kenya is hemodialysis despite peritoneal dialysis having similar survival outcomes with the potential benefit of cost-effectiveness. There is need therefore to explore why peritoneal dialysis remains underutilized and whether patient factors may be contributory to barriers that limit the uptake of peritoneal dialysis. The main objective of this study is to determine eligibility for peritoneal dialysis of patients considered potential candidates for the modality. In addition, barriers to the same were determined. Further, the impact of presence of support on PD eligibility was determined

Methods: This was a descriptive cross-sectional study where patients who were were potentially PD candidates were consecutively recruited. A mutidisciplinary team assessed these patients for PD eligibilty and this was done using a standardized tool. Contraindications and barriers to the modality were recorded as was the presence or absence of support for provision of self-care PD. Other demographic and clinical data were also recorded using a standardized questionnare. The impact of support on PD eligibility was also determined.

Results: In this study on eligibility of patients with advanced CKD for self-care PD we found 68.9% of the patients eligible for self-care PD. Surgery-related abdominal scarring was the most common contraindication. Barriers to self-care PD were identifed in 45.9% and physical barriers were more common than cognitive barriers. Presence of support was associated with a significant increase in PD eligibility (p<0.001%)

Conclusions: A significant proportion of the population studied was eligible for peritoneal dialysis as a treatment modality. The presence of support may be an important factor to explore in patients with barriers to self-care PD as it may be associated with an increase in PD eligibility.

PUB141

The Effects of Fatigue and Depression on Clinical Outcome Among Different Dialysis Modalities

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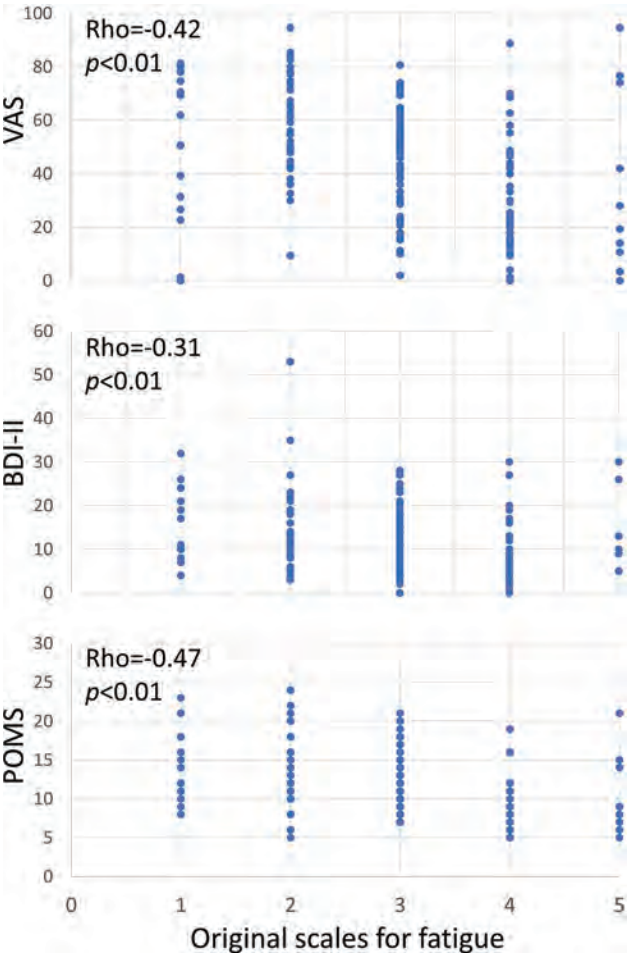
Background: It is well-known that both fatigue and depression are common manifestation among dialysis patients. Additionally, they were reported to be associated not only with quality of life but also patient mortality. There are several relative factors including mental factors, anemia, inflammation and dialysis-relater factors. However, the difference among different dialysis modalities is still unknown.

Methods: In the cross-sectional study, we recruited 194 dialysis patients (mean age, 61±11 years; 134 males). Fatigue was assessed using Profile of Mood States (POMS), Visual Analogue Scale (VAS) and our original scales for fatigue, whereas depression was assessed using the Beck Depression Inventory-second edition (BDI-II).

Results: Our original scales for fatigue was strongly correlated with VAS, BDI-II and POMS. There were no significant differences of the markers for fatigue and depression among patients receiving peritoneal dialysis (n=94), hemodialysis (HD, n=26) and online hemodiafiltration (OHDF, n=74). Among HD and OHDF patients, fatigue was pronounced on the day on dialysis as compared to the day not receiving dialysis.

Conclusions: Further investigations will be needed to clarify the effects of fatigue and depression on the clinical outcome among the different dialysis modalities.

Funding: Commercial Support - Baxter International, Inc.



PUB142

Subcutaneous Cuff Migration in Peritoneal Dialysis Patients: A Single-Center Observational Study

Yan-ru Chen, Wenbo Zhao, Zengchun Ye, Peizhi Wu, Canming Li, Hui Peng. *The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*.

Background: Cuff extrusion is an important reason of catheter-related infections in patients with maintenance peritoneal dialysis (PD). During the long-term follow-up, we found that subcutaneous cuff tends to slowly migrate to the exit-site of catheter in many PD patients. However, few study show the correlation between subcutaneous cuff migration and duration of PD, and seldom do they analyze the possible effect factors of cuff migration.

Methods: 124 patients who have been undergoing PD for more than 6 months were included in this one-year observational study at our Nephrology division from October 2017 to September 2018. The exposed length of PD catheter was measured with a soft ruler every three months. The exit-site of catheter, BMI, biochemical parameters, and dialysis adequacy indexes were monitored at the same time.

Results: The mean age of these PD patients were 53.1±12.0 yrs and the mean duration of PD was 50.0±24.9 ms. At the beginning of the follow-up, the exposed length of PD catheter was 9.5~16.5 cm (average13.9 ±1.4 cm) and 11.0~17.0 cm (average 14.2 ±1.3 cm) for one year later ($P < 0.001$). The average length of catheter exposure increased 0.28cm. BMI of these patients was 23.0 ±3.2 at baseline, and 23.2 ±3.2 for one year later ($P=0.11$). The length of catheter migration was negatively correlated with hemoglobin level (r = - 0.212, $P < 0.018$) and positively correlated with urea nitrogen level (r = 0.295, $P < 0.001$). There were no correlations between the length of catheter migration and serum albumin, immunoglobulin, pre-albumin, calcium, phosphorus, serum creatinine dialysis adequacy and exit-site infection. During the observational period, 1 patient developed shallow cuff extrusion. There was no exit-site infection during the observational period.

Conclusions: Based on our observation, subcutaneous cuff slowly migrates to the exit-site of catheter as the duration of PD increases in patients. It might be affected by hemoglobin level and urea nitrogen level in these patients. Preventing such cuff migration and extrusion need to be considered by peritoneal dialysis nurses.

PUB143

Outcome Measures for Life Participation in Peritoneal Dialysis: A Systematic Review

Karine E. Manera,[5,1] Wenjing Qiao,[5] Angela Ju,[5,1] Amanda Baumgart,[5,1] Yeoung Jee Cho,[2,3] Jenny I. Shen,[4] Jonathan C. Craig,[6] David W. Johnson,[2,3] Allison Tong.[5,1] *[1]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, Australia; [2]Department of Nephrology, Princess Alexandra Hospital, Brisbane, QLD, Australia; [3]Australian Kidney Trials Network, University of Queensland, Brisbane, QLD, Australia; [4]LaBiomed at Harbor-UCLA, Torrance, CA; [5]University of Sydney, Sydney NSW, NSW, Australia; [6]Flinders University, Adelaide, SA, Australia*.

Background: Patients receiving peritoneal dialysis (PD) require daily treatment and are at risk of potentially life-threatening complications, which can limit their ability to participate in activities of daily living. Despite being a prioritized outcome among patients and clinicians, it is infrequently and variably assessed in existing research. We aimed to identify the characteristics, content and psychometric properties of the measures used to assess life participation in PD research.

Methods: We searched MEDLINE, Embase, PsychINFO, and CINAHL from inception to March 2019 for all studies that reported life participation in patients on PD. The characteristics, dimensions of life participation and psychometric properties of these measures were extracted.

Results: In total, 78 studies were included (3 [4%] randomized trials and 75 [96%] observational studies). Across these studies, we identified 16 different measures that were used to report life participation. None of the measures specifically assessed life participation, but evaluated broader constructs (e.g. quality of life) that included questions on life participation. The 36-Item Short Form Survey (SF-36) and Kidney Disease Quality of Life Short Form (KDQOL-SF) were the most frequently used measurement tools, employed in 36 (46%) and 26 (33%) studies, respectively. Validation data to support the use of these measures in patients on PD were available for nine.

Conclusions: Life participation is inconsistently assessed across studies in PD, and some of the measures used have not been validated in the PD population. Establishing a standardized, validated measure of life participation will facilitate consistent and accurate assessment of this outcome, thereby enabling research to inform strategies which can help patients on PD better engage in their life activities.

PUB144

Single-Dose Prophylactic Antibiotic Did Not Significantly Reduce Peritonitis After Peritoneal Dialysis Catheter Insertion

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Background: It is recommended to use prophylactic antibiotics before the catheter insertion by ISPD guideline. Previously in our hospital, the physician who did the surgery would decide whether to use antibiotics according to patient's condition. To investigate the use of antibiotics around the Tenckhoff catheter insertion for continuous ambulatory peritoneal dialysis(CAPD) and its effect on the incidence of early peritonitis, we performed the retrospective study.

Methods: From Jan. 2012 to Mar. 2019, there were 642 patients underwent PD catheter insertion. Each patient's electronic medical record was reviewed to determine the use of antibiotics and the occurrence of peritonitis. Patients received catheter due to acute severe pancreatitis, retreated from PD or died within 14 days after the insertion were ruled out. The remaining patients fell to three groups: Systemic group(SG), due to lung, urinary tract, etc. infection, patients received antibiotics orally or intravenously(IV) for more than one dose (mostly more than three days) during the time from 3 days before to 14 days after the insertion; Prophylaxis group(PG), patients received a single dose Cephalosporin or Quinolone mostly IV before or in PD fluid after the insertion; Non-prophylaxis group(NPG), patients did not receive any antibiotics during the time frame set in SG. Peritonitis in 14 days after the insertion was recorded. Peritonitis rates were compared by Chi-square test.

Results: Out of total 642 patients, 28 were ruled out. The remaining 614 patients(318 men and 296 women) were as follow: 185 in SG, 164 in PG, and 265 in NPG. Peritonitis occurred in 5 patients(2.7%) in SG, 11(6.71%) in PG, and 32(12.08%) in NPG. The results of Chi-square test are as follow: SG *vs* PG, p=0.1215; SG *vs* NPG, p=0.0003; and surprisingly, PG *vs* NPG, p=0.0971. In terms of gender, peritonitis rates in men and women were 11% and 4.39% (p=0.0024). The differences among all groups in women were not significant (SG *vs* PG, p>0.9999; SG *vs* NPG, p=0.3541; PG *vs* NPG, p=0.3209), and in men were partial significant (SG *vs* PG, p=0.0282; SG *vs* NPG, p=0.0004; PG *vs* NPG, p=0.2468).

Conclusions: Our data suggest that single dose prophylactic antibiotic did not significantly reduce peritonitis following PD catheter insertion and male was more susceptible to early peritonitis after insertion.

Funding: Government Support - Non-U.S.

PUB145

Activation of Renin Angiotensin System Disrupts the LDLr Pathway: A Novel Mechanism for Extracellular Matrix Accumulation in Human Peritoneal Mesothelial Cells

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Background: Peritoneal fibrosis (PF) is characterized by progressive extracellular matrix (ECM) accumulation in human peritoneal mesothelial cells (HPMCs) under high glucose (HG) conditions. The aim of this study was to explore the potential mechanisms of HG-induced production of ECM in HPMCs.

Methods: HPMCs were stimulated by HG. The activity of renin angiotensin system (RAS) was inhibited by valsartan or angiotensin II (AngII) type 1 receptor (AT1R) siRNA. Morphological changes in the cells were observed under an inverted microscope. Oil red O, filipin staining and high-performance liquid chromatography were used to examine lipid accumulation. The expression of low-density lipoprotein receptor (LDLr) regulation, the RAS component and ECM-associated markers were assessed by real-time PCR and western blot analysis.

Results: The results showed that after treatment with HG, HPMCs showed notable elongation consistent with the morphology of myofibroblasts, and the expression of ECM proteins such as α-smooth muscle actin (α-SMA), fibroblast specific protein-1 (FSP-1) and collagen I was increased. In addition, there was a parallel increase in lipid accumulation, the effect of intracellular lipid deposits was closely correlated with dysregulation of LDLr, which was mediated through the upregulation of LDLr, sterol regulatory element-binding protein (SREBP) cleavage-activating protein (SCAP), SREBP-2 and through enhanced coexpression of the SCAP with the Golgin. Further analysis showed that HG enhanced the gene and protein expressions of RAS component, such as renin, angiotensinogen, angiotensin-converting enzyme, AngII and AT1R. Interestingly, blocking RAS activity reversed the dysregulation of LDLr, even in the stimulaltion of HG. These effects were also accompanied by a decrease in the expression of ECM components.

Conclusions: Our findings demonstrated that increased RAS activity exacerbated ECM formation in HPMCs by disrupting LDLr regulation, which contributed to lipid disorder-mediated PF.

Funding: Other NIH Support - the Nanjing Medical Science and Technique Development Foundation (No.QRX17120), and the Key Project supported by Medical Science and Technology Development Foundation,Nanjing Department of Health (No. YKK18068)

PUB146

Serum Ferritin as a Predictor of All-Cause and Cardiovascular Mortality Depends on Systemic Inflammation in Peritoneal Dialysis Patients

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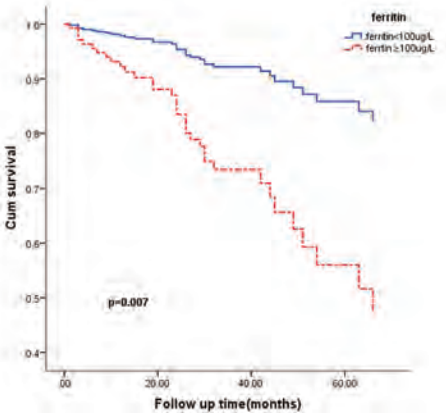
Background: It is proposed that inflammation may modify the association between serum ferritin and the adverse outcomes in hemodialysis patients. However, the optimal level of serum ferritin remains ambiguous at what level advantage outweighs the disadvantage in peritoneal dialysis patients when the inflammation taken into consideration. This study aimed to explore the optimal concentration of serum ferritin for the improving the outcome of peritoneal dialysis patients.

Methods: We classified 221 patients into two groups according to serum ferritin concentration (100ug/L) and followed up regularly from the date of catheterization to Dec 31th, 2016 at SunYat-Sen Memorial Hospital, China. Clinical and biochemical data were collected as baseline, and clinical outcomes such as all-cause, cardiovascular, infection -related mortality were assessed.

Results: The Kaplan–Meier survival revealed a significant worse survival accumulation in PD patients with higher serum ferritin under elevated hsCRP level (p=0.022). A multivariate cox regression analysis revealed that enhanced level of ferritin was independently associated with higher risk of all-cause and cardiovascular mortality in PD patients (HR=0.263, p=0.007 and HR=0.094, p=0.029) after adjustment for relevant confounding factors under the condition of hsCRP above 3mg/L. However, correlations were not statistically significant for serum ferritin and poor outcome within the normal range of hsCRP level.

Conclusions: Higher levels of serum ferritin were associated with increased risk of all-cause and cardiovascular mortality in patients undergoing PD only in the presence of elevated hsCRP level. The correlation of serum ferritin with poor outcome should take systemic inflammation into consideration.

Figure 2 Survival probability with respect to serum ferritin under elevated hsCRP levels by multivariate cox proportional hazards regression analysis with confounding factors adjusted.



PUB147

Hyperkalemia in Chronic Peritoneal Dialysis

Michael E. Ullian,[1,2] Andrew B. Elliott,[1] Karim M. Soliman.[1] *[1]Medical University of South Carolina, Charleston, SC; [2]Nephrology, Ralph H Johnson VA Hospital, Charleston, SC.*

Background: Since peritoneal dialysate contains no potassium, hypokalemia is expected in patients on chronic peritoneal dialysis (PD).

Methods: We explored retrospectively the incidence and potential mechanisms of hyperkalemia, not previously described, in 779 blood samples obtained monthly from 33 patients over 1 – 59 months of PD. Patients were dialyzed daily via cycler, usually 9 – 15 hours per day, with a "dry" period. Normal range of serum potassium concentrations was defined as the hospital standard: 3.5 - 5.1 meq/l.

Results: Although mean monthly serum potassium concentrations were in the normal range and stable over 59 months, we observed hypokalemia (< 3.5 meq/l) in 40 (5%) and hyperkalemia (> 5.1 meq/l) in 110 (14%) blood samples. The incidence of hyperkalemia did not change appreciably over Years 1 (15%), 2 (11%), 3 (19%), and 4 - 5 (22% [fewer samples]) of PD. Hyperkalemia was mostly modest: 5.2 – 5.4 (55%), 5.5 – 5.7 (21%), 5.8 – 6.0 (10%), > 6.0 (14%) (meq/l for each). Of the 33 patients, 39% displayed hyperkalemia only, 23% displayed hypokalemia only, and the remainder (38%) displayed both or neither. Comparing the hyperkalemia-only patients with the hypokalemia-only patients, we found no difference in use of potassium chloride therapy or medications that interrupt the renin-angiotensin system, small-molecule transport status, or renal urea clearance. We compared biochemical parameters from the hypokalemic and hyperkalemic blood samples and observed lower serum bicarbonate concentrations, higher serum creatinine concentrations, and higher blood urea nitrogen concentrations in the hyperkalemic samples ($p < 0.001$ for each), without difference in serum glucose concentrations.

Conclusions: In summary, our chronic PD patients exhibited hyperkalemia almost 3 times as frequently as hypokalemia. We wonder if high-potassium diet (patients are instructed to eat potassium-containing foods to prevent hypokalemia), non-compliance with therapy (evidence: more azotemia), increased muscle mass (evidence: higher serum creatinine concentration), cellular shifts of potassium (evidence: more metabolic acidosis), and/or the long period without PD each day contribute to the unexpected frequency of hyperkalemia in our population.

PUB148

Peritoneal Equilibration Test (PET) with Temporary Drainage at 60 Minutes: Utility to Identify Potential Risk of Severe Damage on Peritoneal Membrane

Mabel Alvarez quiroga, Martin E. Guinsburg, Rosanna V. Garofalo, Carolina V. Martinez, Adrian M. Guinsburg. *Fresenius Medical Care, Buenos Aires, Argentina*.

Background: Long term preservation of peritoneal membrane is key to maximize modality survival. Presence of ultrafiltration failure over time are commonly associated to fibrosis, inflammation and severe damage on peritoneal membrane. Several authors has postulated that measuring changes in sodium concentration (DipNa), and free water transport (FWT) could help to detect patients at risk of developing encapsulated peritoneal sclerosis (EPS). We aim to evaluate transport changes over time in our population.

Methods: We performed modified PET to peritoneal dialysis (PD) patients in Fresenius Medical Care Argentina between 06-2015 and 12-2018 and calculated FWT, small pore ultrafiltration, dipNa and d/p Cr h4 according to Bernardo et al.[1] Test results were correlated to time in PD to identify progressive damage. Patients with combination of DipNa < 5 mEq/l, FWT < 75 ml, total UF < 400 ml and d/p Cr h4 > 0.81 were classified at high risk for EPS. Pearson was used to evaluate correlation while Student t-test for mean comparisons.

Results: We included 549 incident and prevalent PD patients. Age 49.4±16.2 years, 48.2% male, diabetes 15.1%, time in PD 30.1±28.6 months. According to d/p Cr h4, transport type was 2.5% low, 13.9% low-average, 48.7% high-average and 32.3% high. Time in PD correlates negatively with DipNa (-0.214, p<0.001), FWT (-0.225, p<0.001) and total UF (-0.186, p<0.001) and positively with d/p Cr h4 (0.129, p 0.002). High risk for EPS was identified in 26 patients (4.7%) with significant greater time on PD (48.9± 32.5 vs 29.2±28.1 months) but no difference in age, gender, diabetes or peritonitis prevalence. Remarkable is that d/p Cr h1 showed a high correlation with d/p Cr h4 (0.793, p<0.0001).

Conclusions: Time in PD has a significant impact in transport changes of the peritoneal membrane. Performing modified PET test allowed to early identify membrane injury thus increasing detection of patients at potencial risk for EPS. High correlation between d/p Cr h1 and d/p Cr h4 may allow to shorten the test to just one hour long, mostly useful for patients with low tolerance to intraabdominal pressure increases. [1] Perit Dial Int. 2012 Sep-Oct; 32(5): 537–544.

PUB149

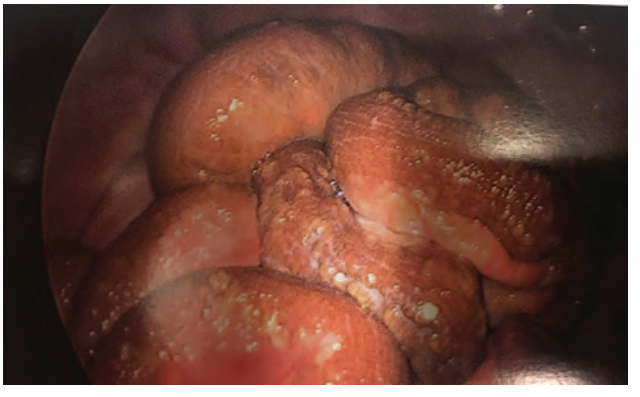
Encapsulating Peritoneal Sclerosis (EPS): Initial Presentation as Incidental Finding of Peritoneal Calcifications During Laparoscopic PD Catheter Placement

Zhi Xu, Moiz Dawood. *University of New Mexico Hospital, Albuquerque, NM.*

Introduction: EPS is a rare but devastating complication of longterm peritoneal dialysis (PD) characterized by inflammatory and fibrotic peritoneal capsule that entraps the bowel loops.

Case Description: A 64 year-old woman with end-stage kidney disease who had been on PD for 13 years was referred to a surgeon for a new PD catheter placement after temporary transfer to hemodialysis (HD) due to refractory peritonitis. During the laparoscopic procedure, the surgeon noticed many plaques of "sclerosing reactions" on her mesentery. No adhesions were observed. In light of the patient's long period of 13 years on PD, we were concerned about EPS and promptly transitioned her to HD. Up to this point, patient had done well on PD. She had effective ultrafiltration. She was a low transporter. Six months after her transition to HD, she was admitted to the hospital with anorexia and weight loss. She was found to have small bowel obstruction. She underwent lysis of adhesions and was noted to have dense fibrosis of the visceral peritoneum. She declined steadily and withdrew from care.

Discussion: As our case demonstrates, early diagnosis of EPS requires a high degree of vigilance. There are no specific tests to diagnose EPS. The early phase of EPS maybe indicated by appearance of ultrafiltration failure with change to high transporter status. Unfortunately EPS is usually diagnosed in the later progressive stage when intestinal obstruction becomes evident. As EPS becomes apparent, evidence supporting its diagnosis includes radiologic findings of loculated ascites and calcifications along the peritoneum and small bowel loops. Time on PD (> 5 years) is the only consistent predictor for the occurrence of EPS. The diagnosis of EPS mandates the immediate transition from PD to HD. There is no consensus regarding optimal treatment, which may include surgical lysis of intestinal adhesions, nutritional support, and immunosuppressive therapy with prednisolone and or tamoxifen.



PUB150

Comparison of Utilization of Peritoneal Dialysis (PD) Between a High-Volume PD Center (HVC) and a Low-Volume Center (LVC) in New York City (NYC)

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Background: NYC has one of the lowest PD utilization rates within the United States but within NYC itself there is segmental distribution of facilities that have high PD utility rates. Metropolitan neighborhoods are generally considered to have adequate infrastructure support to sustain home-based programs. We compared a HVC to a LVC to identify potential factors that lead to sustenance of home-based programs such as PD.

Methods: We reviewed selected factors that would sustain a PD program from the 2017-2018 data of a HVC (n = 80) and compared them to a LVC (n = 12) located in Manhattan and Brooklyn, respectively. Proportions and rates were either analyzed via chi square statistics or Poisson rate models.

Results: See Table

Conclusions: Amongst the factors analyzed above, the only factor that demonstrated statistical significance was the rate of new-start PD patients in the HVC. Rates of patient loss to hemodialysis or kidney transplant as well as provider-to-patient ratios did not show statistically significant difference between centers. Contrary to previous publications that demonstrated that the disparity in the economies of scale influenced the safety and rate of complications; such findings were not seen in this study. Health care providers or institutions that would like to grow their home-based programs need to look at strategies that enhance patient recruitment.

Comparison between a high-volume PD center (HVC) and low-volume center (LVC) in 2017-2018 within New York City.

	HVC	LVC	P
Proportion of new patients per year/N	38/80 (0.48)	2/12 (0.17)	0.04
Proportion of patients lost per year/N	37/80 (0.46)	4/12 (0.33)	0.40
Hemodialysis to PD transitions	9/80 (0.11)	2/12 (0.17)	0.63
PD to hemodialysis transitions	27/80 (0.34)	5/12 (0.42)	0.75
Kidney transplant per year/N	10/80 (0.13)	0/12 (0)	0.35
Nurse to patient ratio	5/80	1/12	0.75
Nephrologist to patient ratio	2/80	1/12	0.33
Peritonitis rate (per patient months)	1/36	1/19.4	0.66
Exit site infection rate (per patient months)	1/76	1/47.4	0.74

PUB151

Insight into the Mechanism of Electrolyte Management in Sorbent-Based Peritoneal Dialysis

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Background: Electrolytes play a key role in maintaining fluid balance, osmolarity, acid-base balance in healthy humans and hence the management of electrolytes is important to control the morbidity of CKD and ESKD patients. The positively charged electrolytes like sodium (Na^+), potassium (K^+), calcium (Ca^{2+}) and Magnesium ($Mg2^+$) together with negatively charged electrolytes like chloride (Cl^-), bicarbonate (HCO_3^-) and phosphate ($PO4^{3-}$) perform unique physiological functions and concentration above or below the normal range can affect homeostasis or specific organ function detrimentally.

Methods: The regulation of electrolyte balance in sorbent-based PD is managed by ion exchange mechanism, infusion and/or diet. Zirconium phosphate and zirconium oxide are used as cation and anion exchangers respectively. Certain electrolytes like sodium, bicarbonate and chloride are maintained by ion exchange processes while other ions like magnesium, calcium, potassium, phosphate are completely removed by the sorbent and managed by corresponding salt infusion and/or diet.

Results: The results of electrolyte management by AWAK sorbent cartridge, including follow up data, in one representative patient (P) who underwent nine AWAK therapies over a period of three days is shown below.

Conclusions: The specially formulated sorbent in AWAK PD device helps to regulate and maintain electrolyte concentration close to physiological levels and thus promising safe therapy.

Funding: Commercial Support - AWAK TECHNOLOGIES PTE LTD

Type	Electrolyte	Extracellular	Balance Mechanism in AWAK Sorbent Based PD	P (D1)	P [D2 to EOT]	FU (1W)	FU (1M)
Cation	Sodium	135-146	Sorbent	141	139-143	140	142
	Magnesium	1.5-2.5	Sorbent and Infusion	1.66	1.52-1.60	1.52	1.48
	Calcium	4.4-5.2	Sorbent and Infusion	4.52	4.82-5.52	5.04	4.3
	Potassium	3.5-5.5	Sorbent and Diet	5.2	4.5-5.3	4.3	4.4
Anion	Bicarbonate	22-26	Sorbent	27.3	21-24.5	24.5	25.6
	Phosphate	3.4-5.2	Sorbent and Diet	2.42	4.20-4.80	2.43	2.16
	Chloride	96-109	Sorbent and Infusion	97	99-100	94	94

P: Individual Subject; D1: Concentration of electrolyte before starting AWAK therapy; EOT: End of therapy; FU (1W): Follow up after one week; FU (1M): follow up after one month; numbers in mEq/L (serum)

PUB152

Regulation of Mesothelial Epithelial-to-Mesenchymal Transition by Vitamin D and Statins

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Background: Epithelial to mesenchymal transition (EMT) has been implicated in the pathogenesis of peritoneal sclerosis. The factors that regulate EMT in the peritoneum are incompletely understood. Data obtained in cell culture and in animal models of peritoneal dialysis indicate that active Vitamin D analogues and statins may attenuate the changes of EMT. We explored whether these compounds, at doses used in ordinary clinical practice, have effects on EMT in man. patients receiving PD.

Methods: Human peritoneal mesothelial cells (HPMCs) were obtained from peritoneal effluent. Patients included in the study had been on stable doses of the agent(s) of interest and devoid of peritonitis for at least 3 months. Patients were analyzed in four groups: Those using neither an active vitamin D compound nor a statin (N) (n=6) Patients using an active D compound but not a statin (D) (n=5) Patients using a statin but not an active D compound (S) (n=6) Patients using both an active D compound and a statin (B) (n=6) RNA was isolated from cell lysates and cDNA was generated using reverse transcriptase. Using quantitative real time polymerase chain reaction (qRT-PCR), transcript levels of E-cadherin (a marker of epithelial phenotype), smooth muscle alpha actin (EMT marker), Snail (EMT promoter), and IL-6 (pro-inflammatory cytokine) were measured. Results were normalized to transcript levels of GAPDH. Statistics were performed using ANOVA.

Results: The table shows relative levels of EMT transcripts normalized to GAPDH in all groups. Data is presented as mean (standard error). There were no statistically significant differences in transcript levels of E-cadherin, Snail, smooth muscle alpha actin, or IL-6 between the four treatment groups.

Conclusions: This data does not support the hypothesis that vitamin D or statins reduce EMT in patients on PD. However, the study does have several limitations, including possible heterogeneity in effluent cell mix and small sample size. Larger studies are needed to determine whether activated vitamin D or statins prevent EMT in patients receiving PD.

Table

	N	D	S	B
E-cadherin	0.72 (0.34)	0.56 (0.24)	0.53 (0.32)	1.1 (0.33)
Snail	0.56 (0.2)	0.73 (0.1)	0.73 (0.1)	0.52 (0.15)
SMA	2.6 (1.8)	1.17 (0.48)	0.92 (0.35)	1.5 (0.55)
IL-6	1.7 (0.79)	0.88 (0.38)	0.76 (.18)	0.74 (0.22)

PUB153

A Case of Catastrophic Calcific Uremic Arteriolopathy Involving Multiple Organ Systems in the Setting of ESRD

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Introduction: Calcific uremic arteriolopathy (CUA), or calciphylaxis, is a grave disease, associated with high morbidity/mortality, that presents with skin ischemia/necrosis and occurs, most commonly, in ESRD patients. Diagnosis is primarily a clinical one. Manifestations include painful, plaque-like subcutaneous nodules that progress to ischemic/necrotic ulcers with eschars. Although skin involvement is well known in diagnosing this disease, extra-cutaneous involvement has not been discussed extensively. We present a case of catastrophic CUA, involving multiple organ systems.

Case Description: 65 y/o woman with a PMH of ESRD, on CCPD, HTN, COPD, OSA, DM-2 and PAD p/w painful B/L LE ulcers, starting 2 weeks prior to admission with skin discoloration, progressing to painful ulcers with dark eschars. As there was high suspicion for CUA, patient was started on sodium thiosulfate and sensipar/sevelamer. Hospital course was complicated by aspiration pneumonia (s/p course of antibiotics), acute ischemic stroke (MRA) secondary to cardio-embolism (cardiac CT showing severe mitral annular calcification with areas of caseation necrosis). Anticoagulation was deferred due to her co-morbidities/risk of bleeding. Patient had persistent leukocytosis/bilateral submandibular swelling (concerning for parotitis), re-started on antibiotics; blood cultures and mumps titers were negative. She developed hematemesis, associated with abdominal pain and worsening hypoxia, conservatively managed with oxygen and PPI therapy. Subsequently, patient developed AMS with unresponsiveness. She was sedated, intubated and transferred to the ICU. CT Head showed a new large R temporal hematoma, midline shift and R uncal herniation, deemed not a surgical candidate. Family opted for comfort care. Shortly thereafter, patient was found to be in PEA arrest followed by asystole. She was later pronounced dead.

Discussion: This case highlights the multiple organ systems involved in this devastating disease process, which have been rarely emphasized in the literature. Treatment options are limited, and often do not attenuate its dismal prognosis. Six-month survival rate of patients with CUA is 50%. The advent of more awareness of the widespread involvement of CUA can help to diagnose this ominous condition early, and may help to mitigate its complications.

PUB154

A Case of Persistent Left Superior Vena Cava in a Hemodialysis Patient Detected During Left Upper Arm Arteriovenous Graft Thrombectomy

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Introduction: Persistent Left Superior Vena Cava (PLSVC) is the most common thoracic venous anomaly with a reported incidence of 0.3% - 0.5% in the general population though the incidence can be up to 6% in patients with congenital heart disease. The majority of the patients with PLSVC are asymptomatic, with the anomaly usually discovered incidentally during central venous catheter (CVC) or cardiac pace-maker placement. This is a case of PLSVC in a hemodialysis patient discovered during a left upper arm arteriovenous graft (AVG) thrombectomy procedure

Case Description: 63-year old male with end stage renal disease presented to the dialysis unit with a clotted left upper arm AVG. The AVG (brachial artery to axillary vein) was created 6 months prior and was being used for hemodialysis treatment for 4 months. The patient did not have a prior history of CVC placement. During the AVG thrombectomy, the patient was found have a PLSVC with no accompanying Right SVC. The thrombectomy was successful, and the patient did not have any adverse events during or after the procedure. However, at the end of the thrombectomy procedure it was unknown if the patient had an accompanying cardiac anomaly or a left to right shunt. A contrast echocardiogram was performed which did not reveal a left to right shunt or any other cardiac anomaly

Discussion: PLSVC is generally an asymptomatic condition. In most patients, the left sided SVC drains into the right atrium through the coronary sinus. However, in up to 8% patients, the left sided SVC drains into the left atrium creating a left to right shunt. In addition, cardiac anomalies such as ventricular and atrial septal defects can be present. It is well known that during the AVG thrombectomy there is dislodgement of the clot downstream into the venous circulation, resulting in pulmonary emboli. These pulmonary emboli are generally small, and usually asymptomatic. However, in the presence of a left to right shunt, the patient is at potential risk for paradoxical embolism which could result in an embolic stroke. It is therefore important to determine the presence of left to right shunt in the setting of PLSVC to assess the risk of systemic embolism during a dialysis AV access thrombectomy

PUB155

Risk Factors Associated with Early Vascular Catheter Dysfunction

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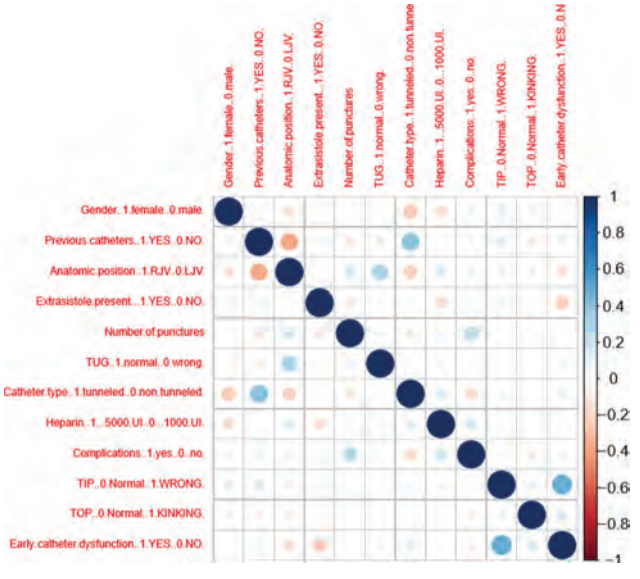
Background: In our center, the majority of vascular catheters (Cath) are placed urgently, either for AKI or CKD, so it is imperative to obtain adequate functionality of the Cath to stabilize the patient. Risk factors associated with EARLY vascular catheter dysfunction (EVCD) have not been clearly studied

Methods: 66 patients had jugular Cath placement from Feb-May 2019. Primary objective:Risk factors associated with EVDC, defined as blood flow <250 ml/min at the first HD session. The Cath were placed guided by US. We analyzed age, gender, height, previous Cath, lab tests, Glasgow, BP, anatomic position, extrasystoles (EXS), #punctures, JV collapsability, Cath TUG-TIP-TOP, Cath size and type, heparin, complications, neck circ., breastbone-chin DIST, skin-JV DIST, JV and carotid diam. and DIST between JV-Carotid. A correlation matrix and uni- and multivariable logistic regression model were performed. P <0.05 significant

Results: 66 vascular Cath placements were analyzed. The EVDC was presented in 4 patients (6.06%). The incorrect position of the Cath TIP was associated with EVDC (OR 1.35, 95% CI 1.13-1.62, P = 0.0018). The presence of EXS during the procedure was associated with a lower risk of EVDC (OR 0.81, 95% CI 0.69-0.95, P = 0.0185). No other variable was significant. Factors associated with complications during the procedure were performing>= 2 punctures (OR 1.21, 95% CI 1.02-1.42, P = 0.027) and carotid diameter>= 0.85 cm (OR 1.55, 95% CI 1.10-2.20, P = 0.017)

Conclusions: Avoiding EVDC is importance in patients with an emergency HD. Only the incorrect position of the Cath TIP was associated with EVDC (OR 1.35, 95% CI 1.13-1.62, P = 0.0018) while the presence of EXS during the procedure was associated with lower risk of EVDC (OR 0.81, 0.69-0.95, P = 0.0185). Larger sample is need it



PUB156

Is Basilic Vein Transposition an Alternative Option for Unsuitable Veins? An Indian Scenario

Vinant Bhargava,[1] Priti Meena,[1] Anurag Gupta,[1] Neha Jain,[2] Anil Bhalla,[1] Ashwani Gupta,[1] Krishna K. Agrawaal,[3] Devinder S. Rana,[1] Manish Malik.[4] *[1]Sir Ganga Ram Hospital, New Delhi, India; [2]UCONN Health, Hartford, CT; [3]Nepal Medical College and Teaching Hospital, Parasi-5, Nepal; [4]Sir Ganga Ram Hospital and GRIPMER, New Delhi, India.*

Background: According to the National Kidney Foundation's KDOQI, "radial-cephalic (RC) and brachial-cephalic (BC)" fistulae are the first choices for vascular access but in the absence of adequate veins or after failed RC/BC access, basilic vein transposition (BVT) provides an alternative autologous option for hemodialysis.

Methods: This is a prospective, observational study conducted in the Department of nephrology at Sir Ganga Ram Hospital, New Delhi. Forty five patients with end stage renal failure who underwent BVT during 1st January 2017 to December 2018 were included in the study. Patients were followed up for 1 year. All the complications including secondary interventions and patency rates were noted.

Results: Total number of patients included in the study was 45. The mean fistula maturation time was 40 ± 10 days. The mean age of patient was 49.98 years and 57% of the patients were male. The mean basilic vein diameter was 3 mm. Fistula thrombosis was the most common complication seen in 15.5% cases followed by limb edema in 10% and surgical site infection in 2 % of cases. 25 % patient required repeat interventions (fistula thrombectomy, balloon angioplasty etc.). The primary patency rate and secondary patency rate at 1 year of follow up were 80.5% and 89%, respectively.

Conclusions: BVT is the most viable and feasible surgical option for patients having unsuitable veins or failed radio-cephalic/ brachio-cephalic arteriovenous fistula for maintenance haemodialysis.

PUB157

Paclitaxel-Coated Balloon Angioplasty for Stenosis of Access in Patients Under Hemodialysis

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Background: The recording of the experience of the use of paclitaxel-coated balloons in patients with End Stage Renal Disease under hemodialysis (HD) exhibiting narrowing in arteriovenous fistulas (AVF).

Methods: 11 patients with ultrasonographically confirmed AVF dysfunction were subjected after angiographic screening to prosthesis with a simple angioplasty balloon, and then a balloon drug gradually released the drug paclitaxel. After the damage was restored, arteriovenous communication was used immediately. The degree of vascular stenosis, blood flow to it and kt / V before and after recovery were assessed by ultrasound. At the same time, the clinical course of the patient and the vestibule of the vessel were monitored for 6 months.

Results: In the 11 patients in the study after the damage was recovered, AVF was immediately treated without any problems. After angioplasty the degree of stenosis of the responsible vessel was statistically significantly reduced from 69.28% to 32.14% (p <0.05). Flow volume increased statistically significantly from 621.43 mils / min to 928.57 mils / min (p <0.05). The kt / v of patients improved from 1.25 to 1.6. During the 6-month follow-up, the clinical course of the patients was stable, no problems related to vascular access occurred. Restenosis occurred only to a patient.

Conclusions: Drug-releasing balloons can be a useful therapeutic option for patients with AVF stenosis due to accelerated endothelial hyperplasia. The use of paclitaxel-coated balloons helps reduce the risk of restenosis of arteriovenous anastomoses and is a safe and immediate solution to AVF management.

PUB158

Rethinking Access for Dialysis in Older People: Proposed Study Design

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Background: The arteriovenous fistula is widely regarded as the best long-term haemodialysis access, due to fewer complications and longer patency, whereas tunnelled catheters have traditionally provided temporary access when emergency dialysis is required, or when a fistula has not been successful. However, the dialysis access landscape has changed with older and more comorbid patients making up a greater proportion. These patients have both poorer fistula outcomes and shorter life expectancy, and whilst fistula formation is still desirable it may be less tolerable. Catheters are increasingly advocated as a long-term access option for some older and more comorbid patients. We propose a pilot randomised controlled trial comparing a fistula to a tunnelled dialysis catheter, which has never been carried out before, in older haemodialysis patients to determine the optimal study design.

Methods: By performing a pilot randomised controlled trial we aim to; 1. Establish the willingness of patients to participate and the protocol drop-out rates in the two treatment arms. 2. Determine the best validated questionnaires to measure differences in quality of life between the two treatment arms. 3. Assess staff acceptability This study is an open label randomised controlled trial with a 12-month follow up period intended to answer key design issues. We will include patients aged over 70, with declining kidney function

and expecting to start haemodialysis within 6 to 12 months. Patients will be randomised in a 1:1 ratio to the fistula or catheter treatment group; the fistula group will be referred for fistula formation after randomisation and the catheter group will have a line inserted when dialysis is required. We aim to recruit 52 patients, 26 in each treatment arm, over an 8-month period.

Results: Patients will be followed for a minimum of 12 months. Data collection will be performed using electronic patient records and clinical correspondence.

Conclusions: The primary outcomes will be the willingness of patients to be randomised to either a fistula or a catheter and the study drop-out rate as defined in the fistula group as failure to achieve a fistula attempt within 3 months of randomisation. The secondary outcomes to be observed in this study include mortality, unplanned admissions, quality of life measurements and dialysis initiation.

PUB159

Ultrasound Evaluation and Interventional Therapy for Dialysis of Peripheral Vascular Access Stenosis

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Background: To investigate the patency rate and restenosis after percutaneous transluminal angioplasty(PTA) for the treatment of arteriovenous fistula(AVF) and arteriovenous graft(AVG)stenosis.

Methods: The patients who were successfully treated by PTA for the first time in the blood purification center of our hospital from January 2016 to June 2017, including 71 cases of AVF in the forearm, 52 cases of AVF in the upper arm and 59 cases of AVG were recorded. The data of different stenosis parts were analyzed before and after treatment and followed up for 12 months. The initial patency rate and assisted-PTA patency rate were observed at 3 months, 6 months, 9 months, and 12 months after ultrasound interventional therapy, and the initial patency time for patients who need to reintervention among all types of pathways were recorded.

Results: The initial patency rates at 3 months, 6 months, 9 months and 12 months after ultrasound interventional therapy were forearm AVF(98.59%,90.14%,71.93%,54.93%), upper arm AVF(90.38%,65.38%,42.31%,32.69%), AVG(91.53%,32.20%,6.78%,1.69%), and the PTA-assisted patency rates were forearm AVF(98.59%,97.18%,95.77%,94.37%), upper arm AVF(92.31%,86.54%,84.62%,80.77%), AVG(100%,98.31%,96.61%,93.22%), while the initial patency time was forearm AVF(8.99±3.54) months, upper arm AVF(6.33±3.01) months, AVG(4.80±1.40) months.

Conclusions: Ultrasound can comprehensively evaluate the function of peripheral vascular access, guide PTA treatment, and evaluate treatment outcomes. Ultrasound intervention therapy is the best initial patency rate for forearm AVF stenosis, the prognosis of upper arm AVF stenosis PTA is relatively poor due to the easy cephalic stenosis, although AVG has a short interval of restenosis, it can achieve a better long-term patency rate through regular intervention with ultrasound intervention.

Funding: Government Support - Non-U.S.

PUB160

Arteriovenous Access Use Is Associated with Greater Interdialytic Weight Gains and Ultrafiltration Rates in Veteran Hemodialysis Patients

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Background: High interdialytic weight gain (IDWG) and ultrafiltration rate (UFR) associates with adverse cardiovascular outcomes, fluid overload related hospitalization and mortality in HD patients. We examined whether IDWG and UFR was influenced by type of hemodialysis vascular access.

Methods: We conducted a retrospective observational study of patients at a single, outpatient Veteran's Affairs (VA) HD unit. Arteriovenous fistula (AVF) or graft (AVG) users were combined into a single AV group and compared to tunneled catheter users. Analyzed outcomes were UFR, IDWG, single pool KT/V and normalized protein catabolic rate (nPCR). Data were averaged across months of observation per patient. Patients who used both AV and catheter accesses were self-paired for comparison between access types. Mean differences and 95% confidence intervals (CI) between AV and catheter groups were calculated using 2-sample or paired t-test.

Results: 163 Veterans (age 67.9 years, HD vintage 40 months, 96% male, 87% Black) dialyzed at an outpatient VA HD unit between 8/2013–3/2018. Access use was AVF (n=118), AVG (n=25), and catheter (n=67). 32 patients converted between AVF (n=29) or AVG (n=3) and a catheter. Compared to patients using a catheter, patients using AV access had greater IDWG (275 mL [28-522] p=0.029) and UFR (0.97 mL/kg/hr [0.19-1.76] p=0.016). KT/V was slightly higher in the AV group (0.12 [0.06-0.19] p<0.001); there was no difference in nPCR (0.045 g/kg/min [-0.01-0.10] p=0.10). Similar patterns in IDWG, UFR and nPCR existed in self-paired patients (n=32) between months using AV access (mean 21 months) or a catheter (mean 13 months). Paired comparisons showed significant increases in IDWG (406 mL [135-677] p=0.005) and UFR (1.2 mL/kg/hr [0.2-2.2] p=0.02), with no significant increase in KT/V (0.07 [-0.00-0.13] p=0.055) and minimal increase in nPCR (0.06 [0.00-0.11] p=0.03) in months using AV access.

Conclusions: AV access use associated with increased IDWG (and hence increased UFR), independent of clinically significant gains in nPCR. This effect existed in the broad patient population and for patients who were self-paired to compare outcomes while using AV or catheter access.

PUB161

A Multimodal Patient Education Approach to Catheter Care in a Hemodialysis Unit: Do It Daily

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Background: Central venous catheters are the leading cause of mortality and morbidity in the dialysis population. Existing educational material is difficult to access ad impractical to use for re-education. By collaborating with patient partners, we have developed novel and innovative multi-modal patient educational materials, to improve patient knowledge, skills and confidence in catheter care.

Methods: Patients were administered a pre-education survey to collect their baseline knowledge, attitudes and skill levels. Educational materials were developed in liaison with patient partners. The materials were based on practice guidelines, and best practice recommendations. Educational materials included: two short videos, posters, easy to understand pamphlets, and fridge magnets using the catchphrase **"Do it Daily".** Post education surveys were conducted to assess their knowledge and skill levels.

Results: Thirty-three patients completed baseline surveys, education program and post education surveys. There was no significant difference in Knowledge or Skill level pre- and post-education survey; however, there was a trend towards increase in patient confidence regarding catheter self-care. Eighty nine percent of patients found the educational material and training easy to understand.

Conclusions: Multi-modal catheter-care educational material did not demonstrate an improvement in knowledge or skill level but was found to be easy to understand. This educational material, which utilizes directed and simplified information, is focused, innovative, and easy to implement.

PUB162

Performance of Machine Learning Model Deployed Within Multidisciplinary Care to Increase Optimal Dialysis Starts in Patients with Advanced Renal Function Loss

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Background: In The Rogosin Institute's PEAK program, a multidisciplinary care team assists patients in making informed, optimal transitions to renal replacement therapy (RRT). The PEAK program educates patients about dialysis options and encourages home modalities and pre-emptive transplantation. In collaboration with a healthcare machine learning company pulseData, a machine learning (ML) model was deployed to systematically identify patients at high-risk of renal failure in the next 6 months and recommend enrollment into the PEAK program. The industry-standard Kidney Failure Risk Equation (KFRE) predicts kidney failure in the next two years, while the ML model predicts progression to eGFR < 10 mL/min/1.73m2 in the next six months. We compare the ML model against the KFRE by contrasting their performance in the Rogosin population.

Methods: Using longitudinal data from the EHR we created an ML algorithm using lab and diagnosis based features and then retrospectively calculated both the KFRE score and ML score as of November 1st 2018. We excluded patients without a recent eGFR value, patients with eGFR < 10, and patients on dialysis.

Results: There were 824 patients scored by the ML model and 644 scored by the KFRE. The patients whose KFRE score could not be calculated were given a KFRE score of 0. Of the 44 patient outcomes, the ML model correctly identified 39 in the top quartile of risk, while the KFRE only identified 28 at the same threshold, a dramatic improvement in sensitivity 89% vs. 64%.

Conclusions: The deployed ML model achieves 40% better precision and sensitivity than the benchmark KFRE. This improvement illustrates that incorporating ML models into clinical practice has greatly enhanced identification of the highest risk patients. Allowing the clinical team to focus on providing patients more access to education, the most important aspect of informed decision making for RRT.

Funding: Commercial Support - pulseData

PUB163

A New Idea for Longer Life of Arteriovenous Grafts Using Multidirectional Venous Outflow in Hemodialysis Patients

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Background: Although a new device has been developed one after another, the status of arteriovenous graft (AVG) survival are far from satisfaction at this moment. As one solution to escape from sudden graft deaths, we have implanted a graft intentionally on axillary vein having multiple branches. The aim of the present study was to prove that our method contributed to the long-term AVG survival.

Methods: Hemodialysis patients who had implanted AVG in upper limbs in our hospital from Feb 2015 to Mar 2019 were recruited. Tapered (4-6 or 4-7 mm in diameter) polytetrafluoroethylene grafts were used in all cases. Branches of the axillary vein were carefully prepared and reserved for second outflow channels as many as possible. The anastomosis size were fixed to almost 15 mm. Primary AVG patency was defined as the time to first intervention, and secondary patency as the time to creation of a subsequent vascular access (VA). The Kaplan-Meier method was used to calculate for each.

Results: Forty-nine ipsilateral axillary AVG operations were done in 42 patients. Mean age was 71 years, with 17 males and 25 females. The median hemodialysis duration was 104 months and the mean follow-up period after operations was 398 days. The average time until the first cannulation was 13 days. There were two early (<30 days) access thrombosis. Any other early accidents were not detected. Forty of the 49 grafts developed late (>30 days) complications: postanastomotic stenosis on the outflow vein in 24 grafts, graft occlusion in 12 grafts, central vein stenosis in 2 grafts, infection in 2 patients. There were radiological intervention in 36 cases and surgical intervention in 4 cases for graft salvage. The primary/secondary patency rate at 6, 12, 24 months were 39.8/82.9%, 14.2/82.5% and 9.5/75.6% respectively. Angiography revealed that reserved venous branches had been working as a substitute for main drainer in some cases with occlusion or severe stenosis on juxta-anastomosis.

Conclusions: In order to avoid complete graft loss, our surgical procedure might be useful to extend the life of the axillary AVG. However, longer-term VA survival required the assistance of radiological and surgical interventional therapies in most cases.

PUB164

Decline in Renal Function-Slow with Fistu "Low"

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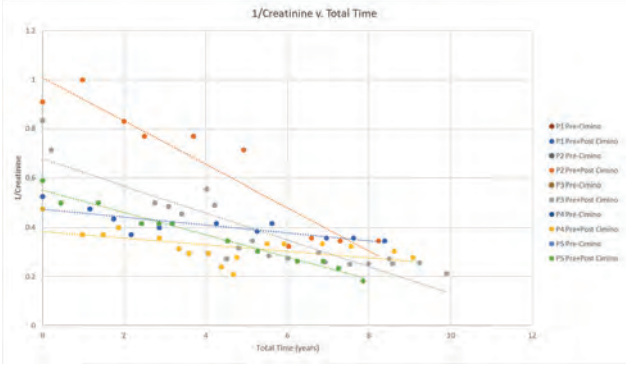
Background: We would like to report a small study of 5 male patients with CKD who had undergone preemptive AV fistula placement in preparation for hemodialysis. Patients were subsequently followed for an extended period of time. Our study found a previously little known advantage of AV fistula placement in slowing the rate of decline in renal function(1). Our finding suggests the possibility of a decline in the progression of eGFR in patients with AV fistula.

Methods: In our patients, we used the reciprocal creatinine plot with time after the patients had an AV fistula placed to determine whether the decline in renal function has slowed down and if there is any correlation with age. We studied 5 males who had AV graft establishment in anticipation for need for RRT at the time of placement of the vascular access.

Results: Based on our observation all our patients had a slower decline in their renal function.

Conclusions: Even though our sample size was very small and only male patients, we can establish a signal that the preemptive placement of access for hemodialysis can slow down the decline in renal function. Underlying mechanism is not clear, but improved circulatory hemodynamics is plausible (2). Further studies with a larger more diverse patient population is needed to determine if early fistula creation can indeed delay the onset of renal replacement therapy in patients with advanced CKD. References (1)Golper TA, Hartle PM, Bian A. Fistula creation may slow estimated glomerular filtration rate trajectory. Nephrol Dial Transplant 2015; 30: 2014–2018 (2)Korsheed S, Crowley LE, Fluck RJ et al. Creation of a fistula associated with significant acute local and systemic changes in microvascular function. Nephron Clin Pract 2013; 123: 173–179



PUB165

Integrating Engineering Principles in a Medical School Nephrology Curriculum

Jean L. Holley,[2,1] Hyunjoon Kong,[1,4] Eliot Bethke,[4] Kenneth R. Wilund,[3,4] Jennifer Amos.[4] *[1]University of Illinois Urbana-Champaign, Urbana, IL; [2]Internal Medicine, Carle Illinois College of Medicine, Urbana, IL; [3]University of Illinois, Urbana, IL; [4]Carle Illinois College of Medicine, Urbana, IL.*

Background: Nephrologists are concerned about the failure to attract young investigators and clinicians. An innovative curriculum may enhance nephrology's appeal. The Carle Illinois College of Medicine (CICOM) enrolled its first class of 31 students in 2018. CICOM integrates a traditional medical school curriculum with engineering, technology, innovation, ethics and humanities with the goal of developing physician innovators.

Methods: The entering class is 45% women, 71% engineering degree graduates with 39% having advanced degrees and a mean age of 26 yr. The 4 yr curriculum has 3 phases; phase 1 is 18 mo of problem-based learning (PBL) presenting the basic science medical areas by organ systems. The renal course was developed by a nephrologist, a basic scientist, and an engineer. The course is 5.5 weeks organized around 6 PBL cases (a living kidney donor and his brother with ESRD, cardiorenal AKI, rhabdomyolysis ATN, diabetic nephropathy, SIADH, and recurrent kidney stones). The engineering curriculum occurs simultaneously with the PBL cases: GFR and glomerular hemodynamics with the living donor case, mass transport and quantification with the AKI cases, flux and hemodialysis membranes with the ATN case, and crystallization kinetics with the kidney stone case. Engineering labs present boundary value problems from a clinical perspective to illustrate physiologic principles, e.g., estimating GFR with blood and osmotic pressures using Starling's law, determining maximum reabsorptions using the Michaelis-Menten equation, filtration using Darcy's law and dialysis membrane properties, and citrate modulation of kidney stone growth via kinetics and thermodynamics. Matlab and Simulink are used to study the physiology and chemistry of kidney filtration and realistic clearance responses to a variety of drugs and other solutes based on Huang's model (Pharmacometrics Syst. Pharmacol 2018;7:593-602).

Results: Weekly quizzes include basic and clinical science material as well as topics covered in the engineering labs. The mean score on the 5 weekly quizzes was 76±5% with a mean of 85%±26% on the engineering questions.

Conclusions: Engineering principles can be utilized to expand the approach and understanding of basic science learning topics in nephrology and may serve as a spark of curiosity for medical students to consider careers in nephrology.

PUB166

Active Learning and Clinical Integration to Promote Knowledge and Interest in Nephrology

Jean L. Holley,[1,2] Kenneth R. Wilund,[3] Hyunjoon Kong,[1] Eliot Bethke,[4] Jennifer Amos.[4] *[1]University of Illinois Urbana-Champaign, Urbana, IL; [2]Internal Medicine, Carle Illinois College of Medicine, Urbana, IL; [3]University of Illinois, Urbana, IL; [4]Carle Illinois College of Medicine, Urbana, IL.*

Background: Innovative strategies are suggested to promote interest in nephrology. Educators stress active learning as a way to create interest and knowledge retention. The 2018 opening of a new medical school (Carle Illinois College of Medicine, CICOM) integrating engineering, technology, innovation, ethics and humanities with early clinical exposure prompted us to design a 5.5 week nephrology course incorporating multiple forms of active learning into an organ system based curriculum.

Methods: Three course directors (a nephrologist, a basic scientist, and an engineer) developed the course. CICOM uses a problem-based curriculum (PBL) spanning 18 mo in which all traditional yr 1 and 2 medical school courses (with the addition of engineering and ethics/humanities) is covered. Five weekly quizzes and a comprehensive exam (n = 61 items) comprised of retired questions from Step 1 NBME exams were the evaluation tools. Six PBL cases, 1TBL (team-based learning on renal embryology), 3 engineering labs, 1 anatomy lab, and a patient interview (adolescent on CCPD) sessions were required. Optional sessions included: 3 physiology, 1 histopathology, 1 pathology, 11 clinical pathophysiology lectures, 7 short clinical case discussion sessions, and 1 journal club (tissue sodium). Clinical lecture topics were: U/A and kidney function*, urology, acid-base and K**, AKI*, disorders of Na*, measuring volume status, CKD*, GN*, stones, renal imaging, urinary tract infection, and renal nutrition (* indicates a session based on multiple short clinical cases on this topic also occurred).

Results: Student feedback was especially positive for the patient interview, short case discussions, the engineering lab on dialysis membranes, and the pathophysiology lectures which were attended by an average of 9-15/31 students. Class mean score on the comprehensive exam given after 7 mo of medical school was 74% with a mean of 77% by the NBME nationwide average (taken after 24 months of medical school). Class scaled score was 70 ±8 (SD).

Conclusions: Based on NBME scores, our students' knowledge after a 5.5 month course was comparable to the nationwide score obtained after 2 yrs of medical school. Students were positive about opportunities for active learning. It is hoped that early clinical exposure to nephrology via active learning sessions and engineering labs will enhance interest in the field.

PUB167

Virtual Reality and Education: A Framework to Guide Development and Integration

Georges Nakhoul,[1] Jonathan J. Taliercio,[2] Ali Mehdi,[3] Remy Daou,[4] John R. Sedor,[3] Joseph V. Nally,[3] John F. O'Toole,[3] S. beth Bierer,[3] Wendy M. Green.[5] *[1]Cleveland Clinic Foundation, Cleveland, OH; [2]Glickman Urological and Kidney Institute, Cleveland, OH; [3]Cleveland Clinic, Mayfield Hts, OH; [4]Saint Joseph University, Beirut, Lebanon; [5]Cleveland State University, Cleveland, OH.*

Background: Recent advances in technology have lead to the creation of innovative teaching tools such as immersive simulations. With funding from the American Society of Nephrology, we are building a Virtual Reality (VR) platform aimed at delivering renal physiology content to medical students, internal medicine residents, and nephrology fellow. The content will be adapted to the level of the learner. In order to guide our project, we elected to develop a framework that can serve as an example to other similar endeavors.

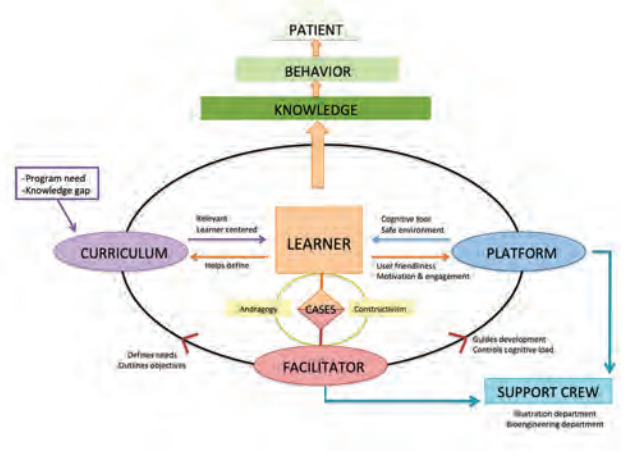
Methods: We performed a literature review in order to determine the different factors needed to successfully develop and integrate an educational curriculum onto a VR platform. We then organized them into a guiding framework that we summarize below.

Results: Our model is learner-centric and encourages the learner to contribute both to the development of the curriculum and to the testing of the VR platform. The curriculum stems from an identified need and is developed with the assistance of both the facilitator and the learner. The platform development requires technical support that can be offered by institutional departments such as bio-engineering and bio-illustration. The relation between the learner and the facilitator is collaborative. In our particular case, we elected

to use problem-based learning cases and grounded our instructional methods in andragogy and constructivism. This part can be adapted to the particular need of the program. The end-goal is to impact learner knowledge with the intention to lead to a change in learner behavior and ultimately patient outcomes (See figure 1).

Conclusions: We offer a framework to guide the development and integration of an educational curriculum into a Virtual Reality (VR) platform.

Funding: Private Foundation Support



PUB168

Can Twitter Help Shape the Future of Point-of-Care Ultrasonography in Nephrology?

Abhilash Koratala,[1,2] Deepti Bhattacharya,[3] Amir Kazory.[2] *[1]University of Texas Health, San Antonio, TX; [2]University of Florida, Gainesville, FL; [3]Reed Elsevier, San antonio, TX.*

Background: While there has been a renewed interest in the nephrologist-performed point of care ultrasonography (POCUS), standard guidelines for its practice (e.g. identification of the enablers and barriers) are lacking. Social media play an ever-increasing role in contemporary medical education; they can be powerful tools for shaping the future of emerging skills such as POCUS. Twitter provides a unique platform to gather opinions of health care professionals (HCP) from various specialties and geographic locations. We sought to explore whether Twitter polls can be used as a needs assessment tool to enhance data on the practice of POCUS.

Methods: We composed a series of 12 Twitter polls over a 36-day period (consisting of up to 4 options) accessible for 3 days each. The pre-planned questions were tweeted on a regular basis from a single handle with over 1000 followers. All questions contained the hashtag #POCUS to increase their dissemination and obtain responses from the intended HCP. The distribution of the responses was stored and analyzed after completion of the study.

Results: The median number of responses per poll was 83. Sixty-three percent of respondents opined that attending live workshops is the best way to start learning POCUS, and 49% preferred a 1-week hands-on supervised program to acquire confidence in scanning. Interestingly, half of the participants identified fear of missing pathology as the prime hurdle for nephrologists performing 'comprehensive' renal sonography. On a note of caution, 39% reported that they have personally seen a case of inadequate POCUS harming the patient. The abridged version of the questions and responses is presented in Figure 1.

Conclusions: This pilot study suggests that Twitter polls could efficiently provide valuable information regarding needs assessment and program development in emerging fields such as POCUS. Capture of an audience with a wide range of expertise at low or no cost is the advantage, while it does portend inherent limitations of survey-based research.

@NephroP POCUS

No.	Question	n	Option 1 (%)	Option 2 (%)	Option 3 (%)	Option 4 (%)
1	Best way to start learning POCUS	209	Workshops (63)	Colleague (16)	Other specialist (4)	Online resources (17)
2	Best way to acquire skills initially	57	Scan patients on own (30)	Observership (11)	1 week Hands-on (49)	Shadow EM doctor (10)
3	Willing to teach POCUS to other faculty	69	Yes (91)	No (7)	Other (2)	-
4	Minimum scan needed for competency	154	25 (39)	15 (8)	40 (40)	Other (13)
5	Preferred self-study resource	84	YouTube (39)	Twitter (36)	Blog posts (10)	Text books (15)
6	Ideal time for a POCUS-teaching video	87	<10 min (68)	Up to 20 (23)	Up to 30 (3)	Up to 1 hour (6)
7	How long it takes for volume assessment using POCUS	105	<5 min (50)	6-10 (34)	>10 (10)	Other (6)
8	How do you estimate LV ejection fraction on echo	82	Eye ball only (57)	Eye ball + Mitral M-mode (28)	Eye ball + fractional shortening (10)	Simpson method (5)
9	Do u routinely scan posterior lung zone	56	Yes (64)	No (32)	Other (4)	-
10	Major hurdle for doing 'comprehensive' renal ultrasound	58	Radiology push back (19)	Hospital privileges (7)	Missing pathology (50)	Time consuming (24)
11	Most worried consequence of nephrologist-performed POCUS	61	Poor image quality (10)	Wrong interpretation (59)	Not obtaining formal study when indicated (13)	Missing incidental findings (18)
12	Aware of any instances where inadequate/inappropriate POCUS harmed a patient	98	Yes (39%)	No (61%)	-	-

PUB169

A Healthcare Matrix Conference Enhances Nephrology Teaching of Interpersonal Communication, Professionalism, and Systems-Based Practice

Gregory L. Braden,[1] Amanda Duda,[1] Daniel L. Landry,[1] Reham Shaaban,[2] Anthony E. Poindexter.[1] *[1]University of Massachusetts Medical School-Baystate, Springfield, MA; [2]Baystate Medical Center, Springfield, MA.*

Background: A Healthcare Matrix was created to link the Institute of Medicine (IOM) aims assessment of patient care quality to the ACGME 6 core competencies (CC) of Patient Care (PC), Medical Knowledge (MK), Interpersonal and Communication Skills (ICS), Professionalism (PRO), Systems-Based Practice (SBP) and Practice Based Learning & Improvement (PBLI) (Jt Comm J Qual Patient Saf, 31:98, 2005).

Methods: Each patient case is evaluated in the presence of all patient care stakeholders, attendings, fellows and nurses. Using a spreadsheet, each CC is evaluated using IOM criteria as to whether the patient case is safe, timely, effective, efficient, equitable, & patient-centered.

Results: A summary of the number of quality issues per case with the number of interdisciplinary teams involved is presented in the table below. The number of teams averaged 3 per case. We found that a disagreement between teams on how best to manage the patients' primary nephrology disorder often lead to a breakdown in ICS, PRO and SBP in all patients' cases. The average teaching points per patient case was 2 for ICS & SBP and 1 for PRO. At the end, a consensus from all participating members created definitive PBLI guidelines for each patient's case.

Conclusions: The use of a Healthcare Matrix format for Nephrology M&M conferences creates significant learning opportunities for interdisciplinary discussions and for simultaneously teaching ICS, PRO and SBP not found in any other format for nephrology training.

Summary of Core Competency Teaching Points Per Case

Disorder	PC	MK	ICS	PRO	SBP	PBLI	# of teams
Pregnancy HUS	1	2	2	2	3	2	4
Renal infarct	1	2	2	2	2	1	3
ESRD options	1	1	2	1	1	2	3
CRRT timing	2	1	3	1	2	2	3
Myeloma kidney	1	2	2	1	2	2	3
Pontine myelinolysis	2	2	2	1	3	2	2
ECMO/LVAD/AKI	2	2	2	1	2	2	4
Lupus nephritis therapy	1	2	1	0	1	1	3
Dialysis withdrawal	1	0	2	1	1	1	3

PUB170

Continuing Education Improves Health Care Provider Knowledge and Competence in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Dana Ravyn,[1] Beth Goodwin,[1] Rob Lowney,[1] Arlene B. Chapman.[2] *[1]CMEology, W Hartford, CT; [2]University of Chicago, Chicago, IL.*

Background: Little is known about the familiarity, knowledge, and competence of nephrologists or other health care providers regarding management of patients with ADPKD. It is unclear what impact continuing education (CE) has on this topic.

Methods: Learners were invited to participate in a multimedia online certified CE activity launched in March 2018. Participants completed pre-activity and post-activity assessments. We measured commitment to change and confidence before and after the activity. Results were analyzed using the chi-square test and Cohen's *d*.

Results: There were 3,799 participants, of whom 954 completed posttests. Twenty percent were physicians, 61% were nurses or physician assistants, and the remainder were other types of providers; the most common specialties were family medicine/internal medicine, nephrology, surgery, and critical care/emergency medicine. On completion, participants had increased confidence in achieving the aims of the learning objectives. Confidence in ADPKD-related practices increased after the activity, including overcoming barriers, translating evidence into care, and improving outcomes (Cohen's d=0.319-0.374). Ten multiple-choice questions/vignettes evaluated learning in pathogenesis, genetics, imaging, diagnosis, and management. Educationally and statistically significant improvements (P<0.001) were seen for all questions. For all participants, the mean increase in score from pretest (n=1086) to posttest assessment (n=954) was 59.0% (SD=3.2; range 43-79); results for nephrology participants were not substantially different from others. Importantly, baseline scores were low in all participants and the nephrology group, suggesting suboptimal knowledge of ADPKD. Among nephrology and all participants, the mean baseline scores were 33.4% (SD=3.9) and 30.0% (SD=3.5), respectively, and the mean posttest scores for nephrology and all participants were 85.8% (SD=2.5) and 89.0% (SD=1.7), respectively.

Conclusions: A CE activity effectively improved confidence, knowledge, and competence among providers who diagnose and manage patients with ADPKD. Baseline scores were low for all participants, suggesting the need for further education and increased awareness of ADPKD, especially given the evolving role of risk assessment for disease progression and the availability of disease-modifying therapy.

Funding: Commercial Support - Otsuka America Pharmaceutical, Inc.

PUB171

Analysis of the Official ASN Hashtag #KidneyWk: How It Has Changed Outreach and Medical Education

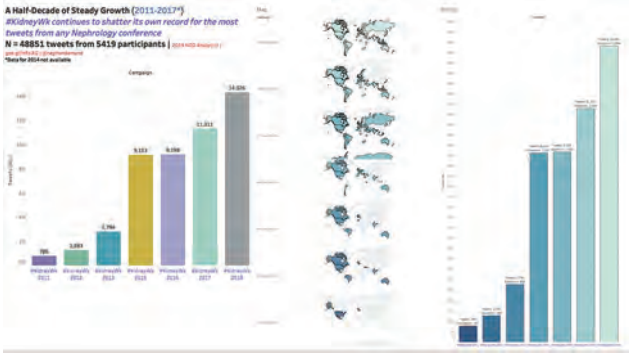
Hector M. Madariaga,[1] Edgar V. Lerma,[2] Tejas Desai.[3] [1]*Good Samaritan Medical Center, Brockton, MA;* [2]*Associates in Nephrology, SC, Berwyn, IL;* [3]*NOD Analytics, Charlotte, NC.*

Background: The official hashtag of the ASN is #KidneyWk. Since its inception in 2011, #KidneyWk has been an efficient channel for conference communications and an easy tool to use among attendees using social media (#SoMe) as an education tool. It has been a great connection for people who are unable to attend the live meeting.

Methods: Searching the @nephondemand database for tweets composed during #KidneyWk from 2011-2018, including total number of people tweeting, gender, location and total number of tweets.

Results: Since 2011, the number of social media (#SoMe) nephrology educators using the official #KidneyWk, has grown exponentially. Cumulatively, a total 5,419 #SoMe educators have tweeted 48,851 tweets. Each year #KidneyWk breaks its own previous record. #SoMe educators from Latin America and South Asia have increasingly contributed to the online learning in the last few years. In 2017, ASN made a policy change allowing attendees to take pictures during presentations, increasing engagement among attendees. Additionally, this change increased the number of multimedia tweets, thereby increasing the information density of each tweet. Female #SoMe educators were early adopters of #KidneyWk, but have not reached gender parity since that time.

Conclusions: #KidneyWk has been extensively used by ASN members attending Kidney Week. Since its creation the #SoMe community has increased in activity and has provided valuable educational material for learners globally. The #KidneyWk community of learners and educators is a great way to connect nephrologists around the world.



Global participation during Kidney Week. As seen in the figure, it has continued to grow since 2011

PUB172

Goal-Directed Protocol with Educational Approach Prolongs Continuous Renal Replacement Therapy (CRRT) Filter Life

Catherine C. Wells, Divya Monga, Neville R. Dossabhoy. University of Mississippi Medical Center Division of Nephrology *University of Mississippi Medical Center, Jackson, MS.*

Background: One of the biggest challenges faced in CRRT is sustaining the continuous extracorporeal circuit for the duration of therapy, in order to deliver the prescribed dose. There are many ways to prevent premature loss of the CRRT circuit (i.e. clotting and clogging). Our center has defined a CRRT protocol to deliver optimal CRRT while preventing premature loss of the circuit.

Methods: We collect and analyze Quality Assessment and Performance Improvement (QAPI) data on all CRRT treatments performed with the Baxter PrismaFlex ™ CRRT machine using Baxter TrueVue Analytics ™ QAPI outcome measures include average filter life, reasons for early loss of filter and delivered CRRT dose. Average filter life (the running hours per filter for every filter used averaged per month) is reviewed as a trend. Beginning October 2017, we observed a negative trend in above indices and hence we changed our education strategy for teaching and adherence to our protocol. We historically provided general education for all medical providers and nurses (dialysis, ICU) on CRRT concepts and the institutional protocol, annually. Starting October 2017, the education frequency was increased (every 1 to 2 months). In addition, QAPI outcomes data were included in the education, and education was added to the EMR ordersets in a format easily seen by ordering providers. Our last educational intervention was use of the new education-enhanced ordersets in August 2018.

Results: In 2017, we had noticed negative trends in our monthly average filter life. In 2018, after our final intervention, and strict adherence to our protocol, our average filter life trends improved. The average filter life for the quarter before the first intervention (April-June 2017) was **38.3 hours/filter**. The average filter life for the quarter after the last intervention (October - December 2018) rose to **53.7 hours/filter**. Throughout the intervention, average delivered dose of CRRT was 24-26 mL/kg/hour.

Conclusions: Implementing an educational strategy in response to QAPI outcomes, using a goal directed approach, improved CRRT filter life. Close monitoring of data trends, adaptable action plans and frequent education are the key elements to a successful QAPI program.

PUB173

Development of Tools Addressing Early CKD Management by Primary Care Providers

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Background: Of 400,000 Arkansans with Chronic Kidney Disease(CKD), only 10% are aware of it. Nephrologists can do a variety of things to improve chronic kidney disease (CKD) care, however, we see patients at late stages. Primary care providers (PCPs) offer the first line of defense against CKD and are pivotal in early diagnosis and management, including timely referrals. When addressed early, a fairly short list of measures could greatly improve outcomes for the patients. Our hypothesis is that PCPs could provide even higher quality care if given the tools to manage CKD easily. We aimed to develop a checklist of high-yield measures for CKD management which can be used by PCPs and their patients during an office visit. Making PCP's aware of the multiple ICD codes that can be used in the complex CKD care, along with the literature behind these recommendations would further enhance care.

Methods: A 10-point checklist of CKD management recommendations was designed by a core group of Nephrologists at UAMS. The list underwent content validation and revisions by a multidisciplinary group. This was pilot tested in a small group of PCPs. The checklist system includes : 1. Ten 'CKD talking points' for patients 2. A Ten point guideline-driven checklist for PCPs 3. Companion supporting explanations of each recommendation for PCPs. 4. ICD 10 codes with average reimbursement data for components of a primary care visit 5. Feedback forms

Results: The CKD Management Checklist system is an interactive platform designed for use during clinic visits with PCP's. The system addresses talking points with patients as well as guideline-based management recommendations for the providers. Initial feedback had been overwhelmingly positive, with additional comments about further needs of the primary providers.

Conclusions: A system of early CKD care and management tools using checklists has been developed to help provide guideline-based care in primary care settings. These are planned to be further tested and disseminated widely encouraging early care and closer collaborations between nephrologists and PCPs. Future plans include adding these to electronic medical health records and to provide continuing medical education credits to providers. CKD management checklist system has been developed to efficiently transfer evidence-based guidelines from nephrologists to PCPs and from PCPs to their patients.

PUB174

Teaching Point-of-Care Ultrasonography: Description of a Novel Curriculum for Faculty and Fellows

Daniel W. Ross,[1] Rushang Parikh,[1] Shamir Hasan,[2] Mala Sachdeva.[1] [1]*Zucker School of Medicine at Hofstra/Northwell, NY, Manhasset, NY;* [2]*Northwell Health, Port Washington, NY.*

Background: Ultrasound machines are becoming more portable and affordable. The increased availability of ultrasound machines has led many physicians to use point of care ultrasonography (POCUS) as an extension of physical examination. In Nephrology, POCUS has been used to image the kidneys and bladder and assess volume status. Here we describe a curriculum we used to orient faculty and fellows to an ultraportable ultrasound device.

Methods: We designed a three-hour curriculum for faculty and fellows. The course began with a review of ultrasound physics including discussion on frequency, reflection, attenuation. Next, knobology was discussed giving focus to the importance of depth and gain. Following these didactics, we performed a live demonstration using a hand-carried ultraportable ultrasound device. We demonstrated what we call the Renal Focused Ultrasound Exam (ReFUsE) which includes imaging of the kidneys, bladder, and lung. During the ReFUsE demonstration we reviewed optimal strategies for image acquisition and reviewed basics of image interpretation including how to identify hydronephrosis and how to interpret artifacts arising from the pleural line. Learners then had approximately one hour of hands on practice doing a ReFUsE on a standardized patient guided by an expert in POCUS. We maintained a 4 to 1 learner to expert ratio. The course concluded with an exercise where learners interpreted normal and abnormal images.

Results: Narrative feedback by learners was that the course was a good introduction but most felt that additional supervised practice would be required in order to attain proficiency in both image acquisition and interpretation.

Conclusions: POCUS is becoming more prevalent in nephrology practice. The optimal strategy for training faculty and fellows in POCUS is not clear and has yet to be defined. Here we described our introductory approach. Initial training should be followed up by continued direct observation by experts before proficiency can be achieved

PUB175

Trends in Twitter Coverage of Nephrology Conferences Through Novel Indices of Impact

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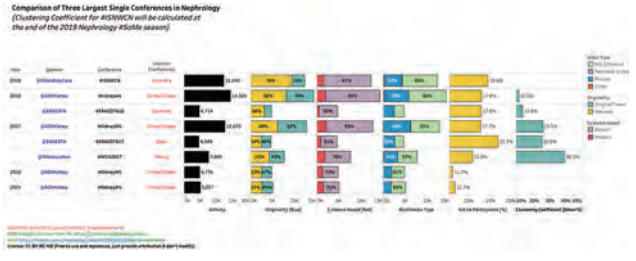
Background: Social Media (#SoMe) helps in real-time, worldwide interactive distribution of knowledge from medical conferences. While conventional analytics provide a simple view of the Twitter activity of a conference, novel analytics provide insight and a framework for the assessment of innovative #SoMe strategies.

Methods: Twitter metadata of Kidney Week (2015-2018), ISN WCN (2017-2019) and ERA EDTA (2017-2019) was analysed by NOD Analytics (& Symplur) for % of original tweets, evidence support (tweets with link to evidence), multimedia (tweets with images, videos, audio files), percentage of active participants (>1 tweet/day), clustering coefficient (measure of connection amongst tweeters), and global reach.

Results: Nephrology conference Twitter activity has seen significant growth in the last 5 years. Kidney week recorded the highest number of tweets in 2018. ISN WCN had the greatest growth in Twitter activity from 2015 to 2019 (266 to 12240). The proportion of original tweets improved, with ISN WCN leading at 76% in 2019. An increase in multimedia content was common, with ISN WCN leading in the proportion of novel content such as poster interviews (n=259 (2017), 662 (2019)) and live visual abstracts in 2019. The percentage of evidence supported tweets remained <30% for all. Active participation increased from 11% in 2015 to ~20% with ERA EDTA 2017 and ISNWCN 2019 at the forefront. The clustering coefficient was highest for ISN WCN at 39.1%, indicating excellent tweeter-interaction. ISNWCN reached out to >90 countries across all the continents.

Conclusions: In-depth analysis of Twitter metadata of nephrology conferences with novel metrics indicates a considerable growth in both quantity and quality of conference coverage. The ISN WCN, with a dedicated #SoMe team, organised approach, novel strategies, society's support and peer interaction, leads in several metrics and delivers significant global academic impact.



Twitter performance metrics of nephrology conferences

PUB176

Welsh Kidney Club: Trainee-Led Development of a National Online Renal Community

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Background: Renal Training in Wales is conducted across a single deanery with a strong national identity, but wide geographic spread can restrict opportunities to collaborate and network, leading to practice variation across centres and a diminished sense of community amongst trainees, which may negatively impact our ability to recruit new doctors.

Methods: We sought to create a trainee-led e-resource to promote inclusivity and equity of access to all training materials via: **A bespoke website - www.welshkidney.org** -"WKC Quick Guides" : Bullet-point guidance for daily encountered challenges (e.g. Management of IgAN) composed by individual trainees as Quality Improvement projects -Videos of renal simulation scenarios and interventional procedures performed by trainees -Renal diary of upcoming abstract deadlines/events -Research profiles demonstrating the breadth of available opportunities and promoting collaborative research ventures **Facebook** -Multidisciplinary "closed group" community where ideas and messages are shared **Twitter** -An international platform to showcase the work of the Welsh nephrology community and interact with the wider renal world Formal evaluation of the above web resources was conducted via electronic survey 6 months following initial launch.

Results: Google analytics showed >600 unique visitors to the website. The facebook group has 98 members, with excellent multi-disciplinary team (MDT) and multi-centric representation. @Welshkidneyclub twitter page has 215 followers, inclusive of renal institutions, charities and patient groups. 82% of the 60 survey respondents from across the renal MDT rated the website "very useful". Moreover, following a year with no nephrology applicants in Wales, 50% of our current junior doctors have expressed an interest in applying to nephrology training in Wales, 100% of whom have accessed the website to explore the opportunities presented.

Conclusions: The landscape of speciality training is rapidly evolving, with social networks increasingly accessed by trainees as channels for collaboration and learning. Using the tools presented here, we have empowered our MDT to establish the foundations of a national renal community, providing support to geographically isolated trainees. Outward presentation of a unified, inclusive training programme is essential to attract new trainees in the current global nephrology recruitment crisis.

PUB177

Enhancing Twitter's Educational Value for Point-of-Care Ultrasonography in Nephrology: A Reach Analysis

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Background: Point-of-care ultrasonography (POCUS) is an emerging field within nephrology; a novel educational tool may conceivably help its more widespread acquisition. While Twitter is an appealing platform to share POCUS-related material succinctly, the factors leading to higher engagement of the healthcare professionals with the tweets have yet to be identified. Using a twitter handle dedicated to POCUS (i.e. @NephroP), we sought to explore the impact of visual content [tweets with infographics vs. plain images], subtopic [renal POCUS vs. fluid volume assessment] and adding a well-known hashtag (#) in medical education (i.e. #FOAMed) to #POCUS on the reach of the tweets.

Methods: The potential reach of a tweet is estimated by the 'impressions' (I^o) and 'engagements' (E^o) defined as the number of times users saw the tweet and interacted with it respectively. One other helpful metric is the number of times a tweet has been reposted by another user, i.e., 'retweets' (R^o). We analyzed the 'top 15' tweets from the @NephroP handle over a 90-day period (February 20, 2019 to May 20, 2019) using built-in Twitter analytics.

Results: Interestingly, 100% of the top 15 tweets contained an image. The mean number of Io, E^o and R^o earned was 7823, 680.5 and 35.7 respectively. There was no difference in reach indicated by I^o (8362 vs. 6741, p= 0.35), E^o (785.2 vs. 471.2, p=0.17) or R^o (38.4 vs. 30.4, p= 0.35) between tweets containing infographics and those without. Tweets about urinary tract POCUS and those about volume assessment did not differ in Io (7788 vs. 8180, p=0.88), E^o (594.8 vs. 752.4, p=0.55) or R^o (36.2 vs. 37.1, p=0.91). Similarly, there was no difference between tweets with or without the hashtag #FOAMed in I^o (6969 vs 8798, p=0.26), E^o (557.4 vs 821.3, p=0.23) or R^o (32 vs 40, p=0.32).

Conclusions: Similar to reported data from general users, all top POCUS-related tweets contained an image. However, contrary to what would be expected for an image-based communication, presence of infographics or addition of an education-related hashtag does not seem to change the engagement of POCUS audience or dissemination of the content. The Twitter's built-in analytics represent a readily accessible means to enhance its educational value through identification of the factors that boost engagement of the audience in less well established fields such as POCUS.

PUB178

Point-of-Service Ultrasound in a Nephrology Clinic

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Background: Ultrasound is a versatile diagnostic tool but access and cost limit its use in Grenada. Technological advances have led to smaller, affordable probes that work with smart phones. We report our initial experience with point-of-service ultrasound as an aid to diagnosis and disease management in the setting of our busy public Nephrology Clinic at the Grenada General Hospital.

Methods: 17 random clinical encounters were evaluated in which patients underwent a medical history, physical examination, and urine dipstick testing, leading to a preliminary diagnosis. Point-of-service ultrasound using a Butterfly IQ probe attached to an iPhone 8 Plus was then performed to either confirm or alter the diagnosis.

Results: Ultrasound confirmed 12/17 diagnoses and led to 4/15 new diagnoses. One study was inconclusive (Table 1).

Conclusions: Point-of-service ultrasound is an effective diagnostic modality in the Nephrology Clinic. There is a steep learning curve associated with its use by ultrasound-naïve clinicians. With increased experience, the potential to improve diagnostic accuracy, and thus outcomes, is limitless.

Table 1. Results with Point-of-Service Ultrasound

Patient	Clinical Diagnosis	Ultrasound Findings
A	Nephrolithiasis with hydronephrosis	No stone seen
B	Metabolic syndrome	Hepatic steatosis
C	Metabolic syndrome	Hepatic steatosis
D	Metabolic syndrome	Hepatic steatosis
E	Enlarged thyroid	Diffusely enlarged thyroid; no cyst or mass
F	Metabolic syndrome	Hepatic steatosis
G	Acute on chronic kidney failure	Renal cyst; no hydronephrosis
H	CKD with suprapubic catheter	No hydronephrosis
I	Metabolic syndrome	No significant findings: normal liver
J	Renal cyst	Large benign renal cyst
K	Hypertensive cardiac and renal disease	Left ventricular hypertrophy, reduced ejection fraction
L	Metabolic syndrome	Hepatic steatosis
M	ESRD; right pleural effusion?	Large right pleural effusion
N	CKD 3; Rt. sided CHF	Right pleural effusion, enlarged RV
O	Ventral hernia	Inconclusive
P	PD catheter exit site/tunnel infection	Tunnel abscess
Q	Uremic pericarditis; calciphylaxis	Moderate pericardial effusion; cardiac calcification

PUB179

Nephrology Education and the Use of Social Media Among Irish Nephrologists

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Background: Recent advances in technology allow instantaneous access to online resources such as journal articles, social media (Facebook, Twitter), blogs, visual abstracts and videos. These can now be accessed by anyone with a desire to share information, learn, or to highlight recent advances in the field. The aim of this study was to evaluate the use of educational tools in the Irish nephrology community and the extent of the use and attitude towards social media as a learning modality.

Methods: We conducted an online survey of Irish nephrologists and nephrology fellows which was disseminated via e-mail with 25 questions. These included the delivery of teaching at institutional level, ranking of educational resources, use of Twitter to seek nephrology resources and the appeals and pitfalls of social media in education.

Results: The response rate was 60%. There were 52 respondents (28 female) 18 consultants, 29 SpRs/fellows on a training scheme and 5 in stand-alone posts. 36 were<40 years old. 92% used "UptoDate" and 90.4% accessed journal articles online. 45.2% ranked "UptoDate" as their top resource, 29% ranked online journals, 24% ranked Twitter as their top resource. 51% use handheld devices to access these resources and 98% accessed these from home. 77% have a Twitter account, and 60% use it as an educational resource.33% of these respondents use Twitter daily. 91% were familiar with NephJC (33% have participated in/reviewed NephJC) and 86% with NephMadness. 85% were attracted to social media as an educational resource based on educational benefit, 78% on the basis of up to date information and 73% for the breadth of international opinion. In terms of pitfalls, 54% felt it is too easy to get lost in the volume of information, 48% cited concerns about confidentiality and 40% felt information was unreliable.

Conclusions: The utilisation of online resources and FAOMed among Irish nephrologists who responded to this survey is common. There is a high level of engagement with the use of social media, particularly Twitter, across all age groups. Future steps to improve engagement can be done with Irish fellows through Twitter, engagement with the NSMC internship and the introduction of a "Staying Connected in Nephrology" installation at our national conference with a plan to re-survey respondents in the next year

PUB180

Can Empathy Be Taught? Assessing Training Received in Chronic Renal Failure Diagnosis Delivery

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Background: The announcement of chronic kidney disease has a major impact on patients. Yet, the delivery of this diagnosis is not formally taught or even discussed within our medical curriculum. To fill this training gap, we set up a training course of chronic renal failure diagnosis delivery for residents in 2016. In this study, we evaluate the impact of this training over the years.

Methods: We evaluated participants' satisfaction in the training as well as the impact of the training on their clinical practice. A satisfaction questionnaire was submitted to all participants immediately after the training and in spring 2019. Self-questionnaires were used to assess participants' empathy, based on the Jefferson scale of empathy (from 20 to 140) before the training and immediately after. During spring 2019, we submitted an online questionnaire to assess empathy levels in residents and senior nephrologists in the Paris area.

Results: 46 residents were trained over 6 sessions through role play. 52 residents of the Paris area filled out the empathy questionnaire online. Half of them had received the training 5 to 34 months before. The other half didn't attend the training. 66 senior nephrologists with different types of practises took part in the study. 97% of the respondents rated the formation as either essential or very useful for their clinical practice. 76% of respondents considered the training to have a long-lasting effect on their clinical practice. Empathy scores using the Jefferson scale were similar in untrained and pre-training residents. Post training, participants' empathy score significantly improved and was sustained several months afterwards. Average empathy score for senior nephrologists was in between the untrained/pre-training residents and the post-training residents, with no significant difference.

Conclusions: Patient-centred care requires willingness to listen, empathy and kindness. These skills are thought to be innate and instinctive, but they can be learned and should be taught within the medical curriculum. Role-play and simulation are easy and effective ways of teaching this. It helps participants take a step back from their day-to-day practice. Being invited to play the patient role may also help participants understand the patient's position, pain and concerns.

Funding: Government Support - Non-U.S.

PUB181

A Different Technique: Real-Time Ultrasound Guidance Percutaneous Renal Biopsy Using the Perpendicular Needle Trajectory in a Training and Reference Center

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Background: Recently, a variant of the classical technique has been proposed a perforated ultrasound probe is used to guide the needle along a perpendicular trajectory to the terminal section of the lower kidney pole offering to the needle a 3-4 cm thick cortical tissue front which allows to obtain a cortical tissue sample with a single needle pass and less frequent complications.

Methods: We perform from November 2018 to May 2019 in 76 consecutive patients a real time ultrasound guidance percutaneous renal biopsy using the perpendicular needle trajectory variant technique. Perform by nephrology fellow supervised by an interventional nephrologist. We revised number of glomeruli the histological sample and the presence of complications associated to the procedure.

Results: Table 1

Conclusions: Renal biopsy continues to be gold standard for the diagnosis of kidney diseases, in our center using the new technique its possible to get a biopsy of smaller kidney size with a sufficient histological sample and complication were minors than reported in the literature.

Results

Patients, n.	76
Age.(years)	41.6±16.2
Male/Female, n	29/47
Hemoglobin (g/dL)	11.8±2.3
Platelet count 10x3/L	273.9±97
Creatinine (mg/dL)	3.3±6.3
Urea Nitrogen (mg/dL)	36.5±26.3
Kidney Size	
Large (cm)	8±3.4
Wide (cm)	6.8±2.5
Kidney depth (cm)	4.1±1.5
Needle passes	1.5±0.5
Histological simple (#glomeruli)	15.8±8.2
Complications	10(13.1%)
Macrohematuria, n	2(2.6%)
Small non-significant hematomas, n.	4 (5.2%)
Large Hematomas, n	2(2.6%)
Hemoglobin fall ≥ 2 gr/dl after biopsy, n.	2 (2.6%)
Requirement of embolization	2 (2.6%)
Requirement of Nephrectomy	0
Death	0

PUB182

Gender Disparities in Faculty at ASN Kidney Week 2012-2019

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Background: Women remain underrepresented in academic medicine. To determine the proportions of female early program chairs, moderators and speakers at ASN Kidney Week (ASN-KW) from 2012 to 2019, we conducted this study.

Methods: The list of faculty names for 2012-2019 was accessed from the ASN-KW website and the genders of the early program chairs, moderators, and speakers was determined. Any undeterminable gender by name was checked twice with an internet search of their image or gender identifying information.

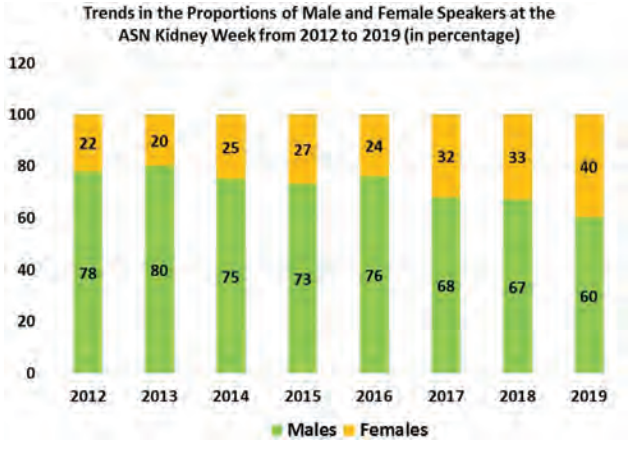
Results: In the years 2012-2016, there was a significant male predominance of early program chairs, moderators and speakers at ASN-KW. From 2017 onwards there was an uptrend in female moderators and speakers. From 2012-2016, the proportion of female speakers ranged from 20-27% of all speakers. The proportion of female speakers increased from 32% in 2017 to 40% in 2019. From 2012-2016 the female moderators ranged from 12 to 28% but increased to 49% in 2019. For early program chairs, female representation ranged from 18 to 38% from 2012-2019.

Conclusions: There is an increasing trend in the proportion of female moderators and speakers at ASN- KW since 2017. The uptrend in the recent 3 years could be related to the increase in female leadership within the ASN council. It is hopeful that this increasing

trend in proportion of female moderators and speakers at ASN KW continues. Other opportunities to enhance gender equality should also be considered by the nephrology communities and societies.

Gender disparities during ASN-KW 2012-2019

	Early Program Chairs				Moderators				Speakers			
	Male (N)	Male %	Female (N)	Female %	Male (N)	Male %	Female (N)	Female %	Male (N)	Male %	Female (N)	Female %
Year												
2012	28	78	8	22	237	75	79	25	550	78	159	22
2013	31	81.5	7	18.5	238	77	70	23	572	80	143	20
2014	23	70	10	30	241	77	72	23	470	75	158	25
2015	22	73	8	27	263	88	64	12	428	73	158	27
2016	18	82	4	18	210	72	81	28	430	76	136	24
2017	17	74	6	26	185	62	113	38	589	68	275	32
2018	13	81	3	19	174	55	140	45	604	67	291	33
2019	13	62	8	38	116	51	110	49	335	60	221	40



PUB183

Just in Time Teaching Tips (JITT Tips): A Tool to Efficiently Teach Learners and Team Members in the Clinical Setting

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Background: ACGME standards state that trainees must demonstrate communication skills that result in the effective exchange of information. It is imperative that training programs provide the proper tools to improve the learning environment for students who receive much of their instruction from resident/fellow supervisors who are themselves inexpert in teaching skills and conveying knowledge. Programs need to incorporate newer methods of teaching and communication to prepare trainees. Northwell Health GME leadership (NHGME) developed a new tool that provides a mechanism to electronically send content-specific clinical teaching tips just prior to educational opportunities. In a pilot study, NHGME collaborated with 7 required medical student clinical rotation leaders to develop relevant JITT infographics with evidence-based content and teaching cues. A series of 6 weekly JITT Tips were identified (generic and discipline specific) to be delivered to residents who engage with learners in the clinical environment via email or text. The targeted clinician educator received 1 JITT weekly in the early AM on a Monday for 6-8 weeks, at the start of the academic year and again at the 6-month mark.

Methods: Using this framework, the Division of Nephrology at Lenox Hill Hospital sought to create several renal focused JITT infographics. Renal faculty and fellows were assigned to the project. Fellows identified deficiencies in their knowledge, expertise and teaching skills, to guide initial discipline-specific topics to address with teachers and learners.

Results: Four topics were chosen that foremost reflect information that renal fellows should be able to teach to housestaff and medical students: acute kidney injury, acute glomerulonephritis, urinalysis and hyponatremia. Infographics templates were created providing both topic-specific content as well as key teaching phrases to engage and encourage the trainee.

Conclusions: JITT provides an innovative way to reinforce positive teaching behaviors and enhance the learning environment. This electronic communication is an adaptive learning system and is invaluable in connecting with early career physicians (residents and faculty) and medical students. An added bonus is engaging nephrology fellows in medical education in professional development as a medical educator in academic programs.

PUB184

Live Visual Abstracts: A Novel Method of Disseminating Scientific Information Live from a Conference

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Background: Medical conferences pack a large amount of information, which is consumed by the attendees, often predominantly from a local or national geographical area. While live-tweeting of information presented at a conference can help to disseminate the key messages, it often leads to significant clutter. Combining the idea of visual abstracts and live-tweeting led to the concept of 'Live Visual Abstracting'. Live visual abstracts help disseminate scientific data from the conference in a concise, pictorial format.

Methods: The visual abstracts were created live, during the session and were tweeted out with the hashtag #LiveVisualAbstract. Over a period of 1 and half days, 7 Live visual abstracts were created and tweeted out. The variables studied were (i) number of times the tweet was seen (impressions), (ii) Number of interactions received for each tweet (Engagements) which included (a) the number of times the tweet was shared (retweets), (b) No of replies/comments per tweet (c) number of interactions leading to profile visits. The results were compared with the most popular media tweets covering the session from the same handle to assess the impact of #LiveVisualAbstract

Results: The tweets with #livevisualabstract received significantly greater number of impressions with a median of 1820 (1059 - 7040) impressions compared to the most popular tweets from the same session - 891(241 - 1869), P - 0.013. The number of engagements [124 (86- 339) vs 24 (9-56); P - 0.002], retweets [7 (5 - 14) vs 4 (0 - 5), p - 0.005], likes [21 (17 - 38) vs 7 (3 - 12), p - 0.002] and profile visits [3 (1 - 16) vs 1 (0 - 4), p - 0.002], were all significantly greater with #livevisualabstract. The number of comments/ replies did not differ between the two groups.

Conclusions: Our analysis shows that visual abstracts are promising tools of disseminating information not just for journal articles but also for conferences. This will help in minimizing clutter, spread information and potentially generate discussion which is the key to success of free online access to medical education (FOAMed).

Serial No	Session name	Speaker	Impressions	Retweets	Engagements	Likes	Comments	Profile Visits
LVA1	Access simulation workshop - 1	Dr. Mathias Widmer	7040	14	339	38	13	16
LVA2	Access simulation workshop - 2	Dr. Mathias Widmer	1820	7	125	18	2	3
LVA3	Indian Data - CKD, Dialysis, Vasc Access	Dr. Chako Jacob	3710	8	166	29	6	10
LVA4	Ethical Issues in Vascular Access	Dr Tushar Vachharajani	1059	5	86	17	1	3
LVA5	Doppler for access monitoring	Dr Lalathaksha Kumar	1407	7	124	21	1	1
LVA6	Newer updates in vasc acess	Dr Bharat Sachdeva	1258	5	110	21	1	1
LVA7	Emergent Start PD	Dr K. S. Nayak	1935	8	152	19	0	4
Comparator Tweets								
Session 1	Access simulation workshop - 1	Dr. Mathias Widmer	1869	5	53	12	0	4
Session 2	Access simulation workshop - 2	Dr. Mathias Widmer	1041	5	24	8	1	0
Session 3	Indian Data - CKD, Dialysis, Vasc Access	Dr. Chako Jacob	830	4	53	7	3	2
Session 4	Ethical Issues in Vascular Access	Dr Tushar Vachharajani	344	2	9	3	1	0
Session 5	Doppler for access monitoring	Dr Lalathaksha Kumar	1093	2	28	5	2	1
Session 6	Newer updates in vasc acess	Dr Bharat Sachdeva	241	0	17	4	1	0
Session 7	Emergent Start PD	Dr K. S. Nayak	920	3	56	9	1	1

PUB185

Healthcare Transition in a Medical School Curriculum: Navigating the Transition Process of Chronically Ill Youth to Adult Healthcare

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Background: Increasingly pediatric patients with chronic conditions are surviving into adulthood. Successful transition from pediatric to adult healthcare reduces gaps and avoids poor health outcomes. Providers must attain the knowledge necessary to foster a successful process during their training. Within the undergraduate medical curriculum it is not apparent that any school has incorporated a non-discipline specific required healthcare transition course early into their curriculum particularly for early learners. We describe the implementation and evaluation of a healthcare transition course in our medical school curriculum.

Methods: A pre-course survey was distributed to 102 first-year medical students and 32 course facilitators within the Delivery of Clinical Care course (DoCC). The survey assessed knowledge, attitudes and practice surrounding healthcare transition. Results were used to design a healthcare transition course within the Adolescent portion of DoCC utilizing videos, reading and in-class case discussions with collaborative group problem solving. A similar post-course survey was emailed to students. Pre- and post-survey responses were compared using a two-sample t-Test assuming unequal variances.

Results: Pre-course survey response rates were 86.5% and 78.8% for medical students and course facilitators, respectively. Most students (95.5%) report no prior experience with healthcare transition as compared with 53.8% of facilitators. Only 5.6% of students and 11.5% of facilitators were able to correctly answer a question regarding the age to begin the patient transition process as recommended by the American College of Physicians. This increased to 59.2 % following the course. Students reported a more moderate level of comfort explaining (avg 3.43 on 1-5 scale, $p<0.001$) and participating in (avg 3.49 on 1-5 scale, $p<0.001$) healthcare transition after the course. Participants expressed preference for case-based learning (70% students, 96.1% facilitators) and group discussion (65.6% students, 69.2% facilitators) format.

Conclusions: The first-year medical student course on healthcare transition was well received by participating students. Early implementation of a healthcare transition course in undergraduate medical education can provide a pathway to mastering of the topic in clinical practice.

PUB186

What Fellows Want: A First Survey of Nephrology Fellowship Training in Korea

Kyung Don Yoo,[1] Sejoong Kim,[2] Ki Young Na.[2] On behalf of Committee of the Training and Education, Korean Society of Nephrology at 2018 *[1]Ulsan University Hospital, Ulsan, Republic of Korea; [2]Seoul National University Bundang Hospital, Seongnam, Republic of Korea.*

Background: The Korean Association of Internal Medicine (KAIM) introduced a shortening of the training period from the existing 4-year training system to a 3-year training program in 2017. In line with this, the demand for a full-time fellowship is expected to be different from that in the past in each sub-specialty. We, Korean Society of Nephrology (KSN), conducted a study surveying the full-time fellowship program for the first time.

Methods: From 2017 to 2018, physicians who were nephrology fellows were contacted. Through the cooperation of the KAIM, we secured an overall table of organization (T.O.) data in Korea. An anonymous questionnaire survey was conducted at each hospital without any compulsion.

Results: According to the data of the KAIM, specializing nephrologists showed modest growth from 47 to 58 people from 2007 to 2017. This was the third place, show 511 people in size subsequent to 1,849 people in majoring Gastroenterology & Hepatology, 563 people in Cardiology on 10 years from 2007. A total of 104 subjects were contacted and 93 questionnaires were obtained. There were 63 fellows in the first year (57.7%) and 24 in the second year (25.8%). Fifty-three (56.9%) were women, and 76% were married. The fellows who were respondents were engaging in 4.02 month on nighttime duty per year, and the mean number of night calls was 8.8 ± 11.7 per month. The hemodialysis unit training rounds worked an average of 7.8 ± 4.3 months per year. In the academic training program, seventy-five percent of nephrology fellows attended a conference together with a pathologist, and 71% of the fellows attended medical grand rounds. However, intervention nephrology training was scarce in spite of the need in this area with a rate as low as 13%. After the fellow training, they preferred to work in the hemodialysis unit rather than an academic position (61/93). The most critical issue regarding work-life balance for fellows in their training period was associated with the night-time duty, and salary.

Conclusions: This study was the first nation-wide questionnaire survey, and 89% of the overall nephrology fellows replied. We expect that it can be used as baseline data for the improvement of quality in full-time nephrology fellow training.

PUB187

Developing a Renal Fellow Curriculum in Telenephrology: Providing Nephrology Care to Underserved Rural Hospitals

Janice P. Lea,[1] Jason Cobb,[2] Jose E. Navarrete,[1] James L. Bailey,[2] Tahsin Masud,[1] Jerome S. Tannenbaum,[3] Jeff M. Sands.[4] Emory University *[1]Emory University, Atlanta, GA; [2]Emory University School of Medicine, Atlanta, GA; [3]Sanderling Healthcare, LLC, Nashville, TN; [4]Emory University Renal Division, Atlanta, GA.*

Background: Telemedicine has recently permeated into the nephrology space allowing patients in rural underserved areas to receive nephrology care in their local hospitals without transfer to larger healthcare systems. Due to the national shortage of nephrologists and to declining interest in the pursuit of renal fellowships, there is a need to train future nephrologists in telemedicine to build capacity of the renal workforce.

Methods: Our academic nephrologists at Emory University have been providing telemedicine services to both ESRD and non-ESRD patients (pts) in 3 rural hospitals in South Georgia (128 unique pts with 525 pt encounters) for the last 2 years and now will incorporate telenephrology training into our renal fellowship in the fall of 2019. Renal fellows will be trained during the second year clerkship for a period of at least 3 months. Fellows will be expected to perform at least 15 patient encounters along with a telenephrology attending. We currently average 25 encounters per month and thus have adequate volumes to reach this goal. Fellow competency will be evaluated after each rotation and feedback from fellows will be solicited in order to improve their training experience.

Results: Telenephrology curriculum will include fellow training on: 1) use of audio-video technology and electronic stethoscope to perform real-time history and physical exams remotely, 2) how to write hemodialysis (HD) orders and monitor dialysis sessions using non-traditional portable technology that supports electronic real-time data monitoring, 3) how to properly communicate and build rapport with referring physicians, and 4) develop and master process for remote urine microscopic examination using digital microscope adapters to electronically transmit images via secure web-based platforms.

Conclusions: The incorporation of a telenephrology curriculum into our renal fellowship program is innovative and will be a model for other training programs. Development of a method for remote urine microscopic examination will enhance the quality of telenephrology consults. The expansion of telenephrology services to more rural areas will help to build future nephrology workforce capacity and may increase medical resident interest in nephrology.

PUB188

Study on the Application of a Five-Star Teaching Model in Prevention and Control Health Education of Hemodialysis Patients with High Blood Phosphorus

Jin-mei Yin. *The Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, China.*

Background: Hyperphosphatemia is an independent risk factor for the mortality rate of patients with chronic kidney disease. The rate of blood phosphorus compliance in developed areas in China is only 37.6%, which is far lower than that of developed countries. Controlling hyperphosphatemia has become an important issue. The core idea of the Five-Star Teaching Method is that under the principle of "focusing on solving problems", teaching should have the principle of continuously repeating the activation of original knowledge, demonstrating new knowledge, trying to apply exercises, and integrating and mastering four stages of circulation. This teaching method is considered to be High-quality, efficient teaching that meets the learning process and the psychological development requirements of learners. In recent years, the five-star teaching model has been applied to medical teaching and doctor-patient communication, and has achieved good evaluation.

Methods: With the aim of focusing on solving problems, the application repeats the activation of the original knowledge, demonstrates the new knowledge, attempts to apply the practice, and integrates the five-stage teaching mode of the four stages of the cycle to carry out up to 6 366 cases of maintenance hemodialysis patients in our district. Month's prevention and control education on hyperphosphatemia, observing the changes in the knowledge of disease-related knowledge, social support, medication compliance and satisfaction before and after intervention, and statistically at 3 months and 6 months after intervention. Pre-blood phosphorus levels change.

Results: After the intervention of the five-star teaching model, the degree of knowledge, social support, medication compliance and satisfaction of patients with disease-related knowledge increased significantly before intervention. At the same time, the pre-existing blood phosphorus level decreased gradually from 1.92±0.51mmol/l before intervention to 1.68±0.37mmol/l, and the phosphorus compliance rate increased from 43.5% to 54.9%. The difference was statistically significant.

Conclusions: Applying the five-star teaching mode to the phosphorus-controlled knowledge of hemodialysis patients can effectively reduce the blood phosphorus level and increase the phosphorus compliance rate.

PUB189

Hemodialysis in Patients with Severe Metabolic Acidosis: Insights from a Physiology-Based Mathematical Model

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Background: Maintenance of acid-base homeostasis is one of the fundamental kidney functions. In patients with severe acute metabolic acidosis (MA), daily acid load production and intake overwhelm compensatory secondary responses. Severe MA can manifest itself in a multitude of pathologies and result in increased morbidity and mortality. In this study, we have developed a physiology-based model of acid-base regulation in order to investigate the use of hemodialysis (HD) to correct severe MA.

Methods: Our dynamic model of the HCO_3^-/CO_2 buffering system comprised Henderson-Hasselbalch mass-action kinetics, endogenous production of both CO_2 and H^+, loss due to non-bicarbonate buffering, ventilation, and renal regulation. Inducing several degrees of MA, we employed a dialyzer model to investigate the effectiveness of HD for correcting MA. Qualitative predictions of clinically observed post-HD acid-base status are demonstrated.

Results: We parameterized the model to induce severe MA steady-state conditions (pre-HD pH from 7.1-7.3) and showed the effect of different dialysate HCO_3^- concentrations (28-38 mM) on the acid-base status correction. We observed that pre-HD HCO_3^- increased (up to 2.03-fold change from the pre-HD values) to values below Gibbs-Donnan-corrected dialysate HCO_3^-, and pre-HD pCO_2 and pH increased only by up to 1.036 and 1.041-fold, respectively, at the end of HD. In addition, with less severe pre-HD MA, the change in pH over the course of HD increased to between 0.4% and 1.95%.

Conclusions: Our model qualitatively predicted serum HCO_3^-, pCO_2 and pH. Further clinical validations are needed to assess its predictive utility in clinical practice. Once validated, the model may be used to gain insights into the acid-base status and to individualize therapeutic interventions in patients with severe MA.

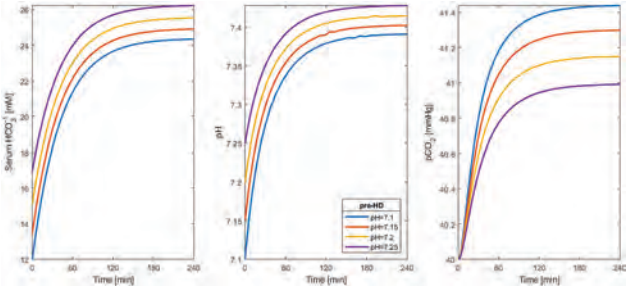

Figure 1: Intradialytic acid-base dynamics in a patient with severe metabolic acidosis (dialysate HCO_3^- of 32 mM)

PUB190

Hyperkalemia in Ill Renal Patients from Lactated Ringer

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Introduction: Balanced crystalloid solutions are touted to be superior to 0.9% saline. Our recent experiences call for caution with LR in older patients with advanced renal failure.

Case Description: **Patient #1**: An 83-yo man developed AKI following coronary angioplasty and stenting requiring hemodialysis (HD). While on 3x/week HD, he developed hyperkalamia following 750cc bolus of LR. (Figure 1). **Patient #2**: A 70-year old male with a solitary functional left kidney developed AKI from an obstructing stone. This was relieved by a JJ stent. Despite 2 liters of brisk of diuresis in one hour, he developed worsening hyperkalemia following 500cc of LR given in the OR (Figure 2).

Discussion: In the 2018 NEJM report on noncritically ill patients, the median baseline serum creatinine (MBSC) was 0.84 - 0.85 mg/dl in the balanced crystalloids and saline groups. Moreover, in the second NEJM report on critically ill patients, the MBSC was 0.89 mg/dl in both groups. Therefore, patients with more advanced renal failure may not tolerate these solutions as well. Furthermore, the median age of the noncritically ill cohort was 53-54 years, whereas the median age of the critically ill cohort was 58 years. Clearly, without prejudice to the touted advantages of balanced crystalloids, we would continue to argue for a more patient-centered approach to individualized patient care. One size does not fit all.

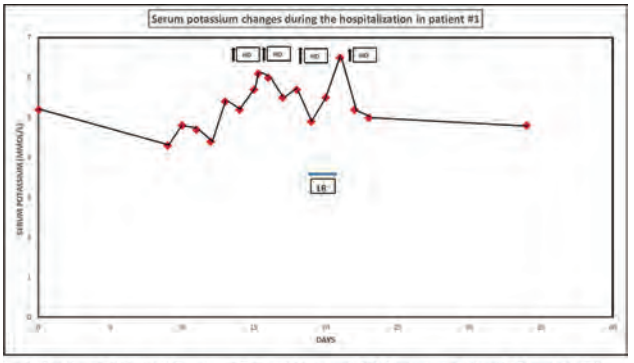

Figure 1: Hyperkalemia spike in patient #1 following Lactated Ringers (LR) Solution resuscitation for hypotension despite alternate daily hemodialysis (HD)

Hyperkalemia after LR despite alternate daily HD

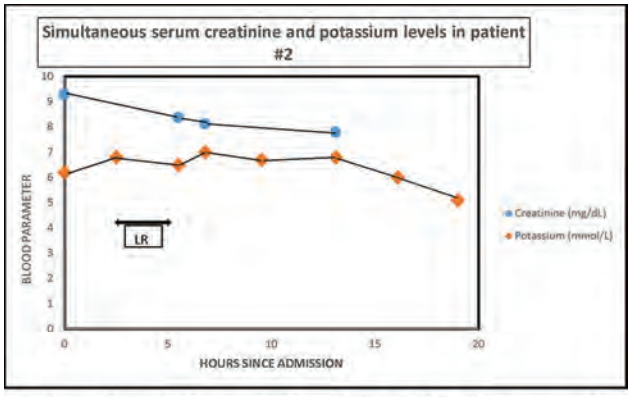

Figure 2: Hyperkalemia spike following Lactated Ringers (LR) in the OR despite falling creatinine and 2L of post-ureteric stent diuresis

Hyperkalemia despite diuresis after LR

PUB191

Positive Blood Alcohol (Al) Level in a Teetotaler

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Background: True hypotonic Hyponatremia (↓Na) despite a normal measured(M) serum(Se) osmolality(Osm) is common in patients with Al use. However, our case is unique that our patient(pt) whose asymptomatic(Asy) ↓Na warranted hospital admission various times and initially thought secondary to Al consumption vouched not having consumed Al entirely.

Methods: 49 year old male with cryptogenic end stage liver disease and CKD 4 secondary to HTN enlisted for dual liver kidney transplant, presented to vascular surgery suite for AVF creation. Initial workup revealed Asy ↓Na for which he was admitted. Physical exam was remarkable for 2+ lower extremity(LE) edema without ascites. His Se Na was 117meq/L with M Se Osm of 294mOsm/L. His BUN was 29mg/dL with calculated(C) Se Osm of 249mOsm/L and osmolar gap(Og) 44. When pt was asked about Al use, he mentioned that he is very aware of the potential consequences of consuming Al in his case. His toxin screen revealed blood Al level of 49mg/dL. Considering hypervolemic ↓Na with low urine Na < 20, this was suggestive of reduced effective circulatory volume. Pt was fluid restricted and his diuretics were resumed after which his Se Na improved to 127meq/L and was discharged. He was admitted after 3 months again for Asy ↓Na of 114meq/L with an Og of 47. His BUN was 25mg/dL. This time his blood Al level was 70mg/dL and his FeUr was 29%. His bilateral LE edema was less than before. He was again treated on the same lines. However this time, his nephrologist was informed about his blood Al level so that he can speak with the pt about updating transplant center. Further investigation into this matter finally revealed that pt was chewing tobacco containing Al.

Results: Hypervolemic ↓Na in the setting of liver cirrhosis is common but may raise concern for transplant candidacy when there is an Og. Our case is unique in describing the relation of chewing smokeless tobacco with high ethanol content;the same substance which breath analyzers have been programmed to detect. Usually, the amount of Al in smokeless tobacco may not be sufficient to keep one intoxicated but it can radically increase the rate of Al content in the breath usually termed as mouth Al which cannot be differentiated from the breath of Al intoxication. However, the quantity of chewing tobacco in our pt was so large that the blood Al level was positive.

Conclusions: Clinicians need to be aware of Al content in smokeless tobacco as a potential cause of high Se Og.

PUB192

Be Mindful of Effective Osmoles When Instituting Therapy for Re-Establishment of Eunatremia

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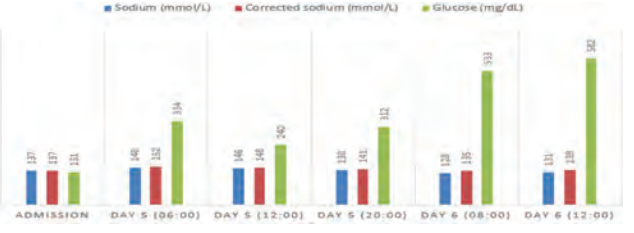
Introduction: Hyponatremia is commonly encountered in clinical practice. Here we present a case of chronic hypernatremia complicated by acute hyponatremia.

Case Description: A 67-year old woman with DM was admitted to the hospital for assessment and management of nausea, vomiting and decreased oral intake. Laboratory data on admission were remarkable for serum Na of 137 mmol/L and glucose of 131 mg/dL. Despite pharmacological attempts to control nausea, the patient's oral intake remained poor. Follow up laboratory data were remarkable for hyperglycemia (serum glucose of 334 mg/dL) and hypernatremia with a serum Na of 148 mmol/L (corrected Na of 152 mmol/L; serum osmolality of 337 mOsm/kg). Repeat laboratory data six hours later were still remarkable for hyperglycemia (serum glucose of 240 mg/dL) and hypertonic hypernatremia with a serum Na of 146 mmol/L (corrected Na of 148 mmol/L). Next set of laboratory data, now fourteen hours after the first, showed a serum glucose of 312 mg/dL and Na of 138 mmol/L (corrected Na of 141 mmol/L). The patient was started on D-amino D-arginine vasopressin (DDAVP) followed by D5W IV. Twelve hours later, serum glucose was 533 mg/dL and Na was 128 mmol/L (corrected Na of ~135-138 mmol/L). D5W was discontinued and the patient was started on 3% NaCl IV. Four hours later and after ~50 mL of 3% NaCl, serum Na was 131 mmol/L (corrected Na of 139 mmol/L). Hypertonic saline was discontinued. Symptomatic management of nausea was optimized and the patient's oral intake improved. Follow up measurements of serum Na showed an increase toward reference values and a delta Na value <6 mmol/L in any 24-hour period (see image).

Discussion: This case highlights the interplay between effective serum osmoles and the importance of frequent monitoring of serum Na when instituting therapy for re-establishment of eunatremia. Correction of this patient's hypernatremia resulted in acute hyponatremia. Identification of glucose as an effective osmole allowed correction of serum Na. Failure to discontinue hypotonic fluids and discontinue DDAVP would have resulted in chronic hyponatremia and further decrease of serum Na, which had already corrected by 17 mmol/L in 24 hours.



PUB193

Management of Patients with Acquired Distal Renal Tubular Acidosis Among US Nephrologists and Rheumatologists

Kamyar Kalantar-Zadeh,[2] Robbie Mccarthy.[1] [1]*Rare Insights LLC, Ardmore, PA;* [2]*University of California Irvine, School of Medicine, Orange, CA.*

Background: AdRTA, which is linked with Sjogren's disease, systemic lupus erythematosus (SLE), primary biliary cirrhosis (PBC) and autoimmune hepatitis, is often encountered by rheumatologists and nephrologists. To better understand the interdisciplinary management of AdRTA patients a quantitative market research study was undertaken in Q1 2019

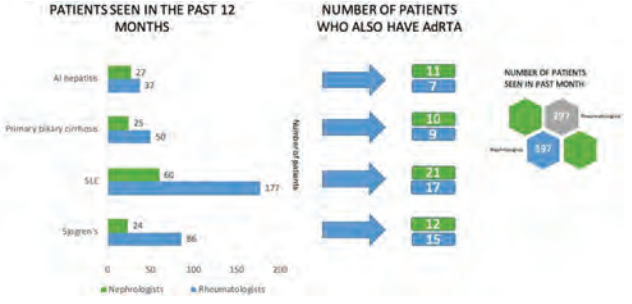
Methods: Between March 25th–April 15th, 2019, an online survey was conducted with 30 nephrologists and 20 rheumatologists in the USA on the subject of dRTA, with a focus on AdRTA. All screened respondents had direct clinical experience of AdRTA patients. The database was cleaned, and the collected data were analyzed by SPSS

Results: Rheumatologists reported larger SLE and Sjogren's caseloads than nephrologists, seeing an average of 177 cases of SLE patients in the past 12 months vs. 60 cases for nephrologists. Nephrologists saw similar numbers of patients with Sjogren's, PBC and AI Hepatitis in the past 12 months (27, 25, 24 respectively), vs. higher numbers

for rheumatologists (237, 50, 86 respectively). The number of AdRTA patients seen monthly was a relatively small percentage (approximately 1 in 100) of the overall number of patients seen by both specialists (see Figure). All nephrologists either agreed (20%) or strongly agreed (80%) with the statement *"In patients with autoimmune conditions in which AdRTA is co-morbid, such as Sjogren's and SLE, I take the lead in managing AdRTA*" compared to 20% of rheumatologists who disagreed, 20% who agreed and 60% who strongly agreed. One-third of nephrologists and 70% of rheumatologists agreed that AdRTA is underdiagnosed due to lack of knowledge and awareness in primary care [Figure]

Conclusions: Although patients with AdRTA are a small % of their patient caseloads, both nephrologists and rheumatologists have a role in managing AdRTA in patients with comorbid AI disease, with nephrologists more likely to consider themselves the lead physician than rheumatologists. The majority of physicians surveyed believe the AdRTA is underdiagnosed due to a lack of knowledge and awareness in primary care

Funding: Commercial Support - Advicenne S.A.



PUB194

The Temperature, Volume, and Calcium Concentration of the Water in the Lung Influences the Serum Calcium Concentration of a Drowned Person

Takahide Kimura,[1] Seiki Yamada,[1] Takeshi Yokoyama,[1] Hiroyuki Shirai,[1] Masayuki Tanemoto,[1] Naoki Washida.[2] *[1]Nephrology, International University of Health and Welfare Atami Hospital, Atami, Japan; [2]International University of Health and Welfare Medical School, Atami, Japan.*

Background: Electrolyte concentrations of the solution getting into the lung will change the serum electrolyte concentrations of a drowned person. Serum calcium concentration (Ca) of drowned persons was analyzed according to places of drowning.

Methods: From September 2014 to March 2019, 22 persons were referred to our hospital because of drowning in hot spring. The Ca in them was compared with those of drowned persons in either the sea (n = 8) or house bathtubs (n = 5). Blood ionized calcium concentration (iCa) was also compared between the groups. In the persons drowned in hot spring, the volume of the water in the lung (Vol) was estimated by using images of computed tomography, and correlations of Ca and iCa with Vol were further examined.

Results: The sea-side hot spring water contained calcium of 36 mg/dL (9 mmol/L). In the drowned persons of the hot spring, the sea, and bathtubs, Ca was 13.04 ± 3.70, 10.29 ± 1.94 and 9.04 ± 1.24 mg/dL, respectively (p= 0.037, p< 0.001), and iCa was 1.55 ± 0.48, 1.46 ± 0.25, and 1.21 ± 0.12 mmol/dL, respectively (p = 0.823, p = 0.047). In the hot-spring-drowned persons, Vol was 1253 ± 673 mL and its ratio to the whole lung volume (Vol-ratio) was 0.43 ± 0.19. The Vol-ratio correrated with iCa (r= 0.386, p= 0.47).

Conclusions: The Ca in the hot-spring-drowned persons was significantly higher than those in the sea-drowned and bathtub-drowned persons. It correlated with the relative volume of the hot-spring water in the lung. Since the calcium concentration of the hot spring water is slightly lower than that of the seawater, the temperature in addition to the volume and calcium concentration of the water in the lung could have influenced the amount of calcium absorbed from the lung into the serum.

PUB195

Referral Patterns for Patients with Acquired Distal Renal Tubular Acidosis (AdRTA)

Robbie Mccarthy,[1] Ludovic Robin,[2] Kamyar Kalantar-Zadeh.[3] *[1]Rare Insights LLC, Ardmore, PA; [2]Advicenne S.A., Paris, France; [3]University of California Irvine, School of Medicine, Orange, CA.*

Background: AdRTA, which is linked with Sjogren's disease, systemic lupus erythematosus, primary biliary cirrhosis and autoimmune hepatitis, is often encountered by rheumatologists and nephrologists. To better understand key referral routes and issues for AdRTA patients a quantitative market research study was undertaken

Methods: Between March 25th–April 15th, 2019, an online survey was conducted with 30 nephrologists and 20 rheumatologists in the USA on the subject of dRTA, with a focus on AdRTA. All screened respondents had direct clinical experience of AdRTA patients

Results: Most AdRTA patient referrals to nephrologists (Nphs) and rheumatologists (Rhms) are from primary care (Nphs 60% and Rhms 61% - of total AdRTA referrals). Internal medicine accounted for 23% of AdRTA patient referrals to Nphs and 17% to Rhms. In the most recent 12 months, referral patterns were consistent with the most common routes of referral, but with more of an even split between primary care and internal medicine for both Nephs (38 vs 31%) and Rhms (38% vs 21%). Both specialists indicate around 6% referral rate from urologists, with very small numbers from other specialists considered potential referrers of AdRTA patients (inc. pediatric nephrology, dermatology, audiology and opthalmology). Both Nphs and Rhms either Agree (33% vs. 30%) or Strongly agree (67% vs 70%) that AdRTA is underdiagnosed due to a lack of knowledge and awareness of the condition in primary care. Only 20% of the total number of referrals to nephrologists came from rheumatologists

Conclusions: Most AdRTA patient referrals to rheumatologists and nephrologists are from primary care, with only small numbers of patients referred from other specialist physician types considered potential referers due to known AdRTA co-morbidities. There is concern among nephrologists and and rheumatologists that poor knowledge and education around AdRTA in primary care is lacking resulting in the potential for *"Patient issues [to be] worsened because of late referral to nephrology"*. The low percentage of referrals from Rhms to Nephs was suprising, potentially indicating that Rhms manage patient's AdRTA without the involvement of nephrology

Funding: Commercial Support - Advicenne S.A.

PUB196

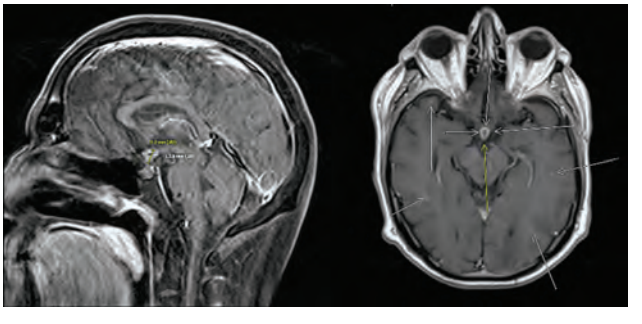
Stalking the Hypernatremia: A Case of Central Diabetes Insipidus due to Metastatic Small Cell Lung Cancer

Rupam Ruchi, Eddy J. De Jesus. *University of Florida, Gainesville, FL.*

Introduction: Symptoms from metastatic tumors in general are relatively rare, but when it involves the infundibular stalk, central diabetes insipidus (CDI) has remained the most common manifestation.

Case Description: A 70-year-old man with a 3-month history of small cell lung carcinoma, managed with Carboplatin, Etoposide, and Pegfilgrastim in an outside facility when diagnosed, transferred to our institution for Non-ST segment Elevation Myocardial Infarction. Initial labs showed hypernatremia of 146 mmol/L, urine specific gravity of 1.010, urine osmolality of 138 mOsm/Kg. As there were concerns for sepsis, he received 3 liters of normal saline that lead to the development of significant hypernatremia (156 mmol/L). His urine output was noted to be 12 L in the first 24 hours. On further questioning, he acknowledged feeling excessive thirst for the last 2 weeks. This was accompanied by polyuria and mild abdominal pain. Concern for possible carboplatin-induced partial nephrogenic diabetes insipidus (DI) vs central DI. With administration of 100 mcg desmopressin, urine output improved to 3 L and urine osmolality increased to 400. Upon holding desmopressin the next day, urine output again increased to 10 L accompanied by decrease in urine osmolality. This suggested Central DI. Magnetic Resonance Imaging (MRI) of the brain was done which showed diffuse innumerable sub-centimeter punctate metastases throughout the brain including 1 cm metastatic lesion to the hypothalamus/infundibulum/floor of the third ventricle with loss of normal spontaneous T1 hyperintensity of posterior pituitary gland

Discussion: In patients with DI and an intact thirst mechanism, hypernatremia develops due to increased excretion of free water and the lack of Antidiuretic Hormone (ADH). Metastasis to the pituitary stalk has been related to breast cancer as the primary source followed by lung cancer, prostate, and renal cell carcinoma respectively. At least 80% of vasopressin-synthesizing neurons must be destroyed before any clinical manifestations are evident. MRI remains the image diagnostic of choice for evaluation of the pituitary



PUB197

Hippurate Clearance Provides a Measure of Renal Plasma Flow

Kumar Rohit,[1] Avinash G. Adiga,[3] Aleksey Etinger,[1] Jerome Lowenstein.[2] *[1]New York University, Jersey City, NJ; [2]New York University Medical Center, New York, NY; [3]Texas Tech University Health Sciences Center, Lubbock, TX.*

Background: Prior to the introduction of eGFR in 1999, glomerular filtration rate and renal plasma flow were assessed by measuring the plasma clearances of inulin and para-amino hippurate. As this required constant infusion, timed urine collection and a

specialized laboratory, these measures were not widely available. Data available from the period identified a number of clinical disorders in which the ratio of GFR to renal plasma flow (Filtration Fraction) varied considerably. Filtration fraction was known to vary considerably in different clinical states. With the introduction of eGFR, renal plasma flow is no longer measured and renal function is judged solely by eGFR. With the recognition that endogenous hippurate was transported by OATs in the proximal tubule, we undertook studies to determine whether the clearance of hippurate would present a means of estimating renal plasma flow.

Methods: Studies were carried out in 5 subjects with hypertrophic cardiomyopathy under going right heart catheterization and 10 subjects undergoing electrophysiologic studies. Blood samples were obtained from the right renal vein and the IVC below the renal veins. A voided urine was collected 1-3 hours before blood sampling. Eight patients were receiving beta-blockers, two were receiving ACE inhibitors. Hippurate was measured utilizing MS-HPLC. Creatinine was measured by colorimetric technique.

Results: Among the 15 subjects, **extractionof hippurate**(IVC-RV/IVC) was .935 and .909 in two, from .739 to .58 in six. In the remaining seven subjects the findings suggested the RV catheter was not in the renal vein or the blood collected was an admixture of renal vein and IVC blood. The **clearance ratio**(**U/Phippurate**to **U/P creatinine**) was evaluated in 12 subjects; it ranged from 7.05 to 1.64 and exceeded 4 in five of the subjects studied.

Conclusions: The renal clearance of hippurate exceeded creatinine clearance in all subjects studied. Hippurate/creatinine clearance ratios greater than 4 suggests that hippurate clearance provides a measure of RPF. Ratios below 4.0 may reflect reduced renal plasma flow in some of the patients, who were studied during evaluation of either hypertrophic cardiomyopathy or cardiac arrhythmias. Reduced cardiac output or other medications may have reduced renal blood flow.

PUB198

Prevalence and Investigation into Community- and Hospital-Acquired Hypercalcemia

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Background: Hypercalcemia can be a presenting sign at hospital admission or may occur over the course of an admission. While workup and treatment protocols have been well-established, the prevalence of hypercalcemia and adherence to investigatory evaluation is largely unknown. We present data on the prevalence of hypercalcemia and seek to reclassify it in terms of community-acquired versus hospital-acquired hypercalcemia to further understand the nature and course of hypercalcemia.

Methods: We queried the enterprise EHR at 14 hospitals in a large integrated health system, for all admissions in 2018, with at least one serum calcium result greater than 10.5 mg/dL. We then defined two distinct patient cohorts: "community-acquired hypercalcemia" (CAH), where the first result is >10.5, and "hospital-acquired hypercalcemia" (HAH), where the initial result is normal and any subsequent result is >10.5. We performed data analysis on each cohort and assessed data on work-up of hypercalcemia.

Results: There were 202,109 admissions of which 2.2% of patients were admitted with hypercalcemia, and 0.6% of patients who developed at least 1 elevated calcium value during the hospitalization. Patients with CAH, had a mean age of 68 years (median 70 years). The mean length of stay was 170.2 hours with a median of 105 hours. Patients with HAH, had a mean age of 68.5 years (median 70 years). The mean length of stay for these patents was 381 hours with a median of 241.6 hours. The mean time to development of HAH was 7.5 days with a median of 4 days. We found that 82.3% of patients with CAH and 78.5% of patients with HAH had no work-up (including 25-Vitamin D, 1,25-Vitamin D, PTHrP, and PTH). Fewer than 2% of patients in either group had all 4 laboratory investigations performed.

Conclusions: With our distinction of community-acquired versus hospital-acquired hypercalcemia we find that there is a stark difference in the length of stay of these patients (170.2 hours vs. 380.9 hours). Furthermore, in both cohorts, most patients have incomplete or investigation performed for the cause of hypercalcemia, a major quality gap. Additional work is required to better understand the etiologies of these distinct hypercalcemic groups (e.g. hypercalcemia of malignancy, hyperparathyroidism, drug-induced hypercalcemia, or hypercalcemia of immobilization) as well as their outcomes.

PUB199

Pseudohyponatremia Caused by Severe Hypercholesterolemia

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Introduction: Pseudohyponatremia is a well-known phenomenon. Most commonly it is secondary to hyperproteinemia or hypertriglyceridemia. We present a case of pseudohyponatremia that was secondary to severe hypercholesterolemia.

Case Description: A 60-year-old woman who suffered from itraconazole-induce hepatitis was noted to have a serum sodium (Na) of 119 mmol/L (normal 133-143 mmol/L). She was initially admitted to a community hospital where she was treated with intravenous fluids and then fluid restriction with no change in her Na concentration. Ultimately, she was referred to our tertiary center where further workup revealed an elevated serum osmolality gap of 56 mOsm/kg (normal <10) with a mildly elevated serum osmolality of 307 mOsm/kg (normal 278-305 mOsm/kg). Serum glucose level was 131mg/dL (normal 70-99mg/dL). Total serum protein was low at 5.7 g/dL (normal 6.4-8.3 g/dL) with a mildly low serum albumin of 3.1 g/dL (normal 3.5-5 g/dL) ruling out the possibility of pseudohyponatremia secondary to hyperproteinemia. A lipid panel revealed elevated triglycerides at 350 mg/dL (normal <150 mg/dL), however, more surprisingly a cholesterol level of 2,730 mg/dL (normal <200mg/dL). Serum Na measured using a blood gas analyzer was 139mmol/L and thus the diagnosis of pseudohyponatremia was confirmed. Over the ensuing months, as her liver function improved, her cholesterol levels normalized and so did her Na levels on the chemistry panels.

Discussion: Pseudohyponatremia is a well-known phenomenon that is commonly associated with hypertriglyceridemia or hyperproteinemia. It has been reported in cases of hypercholesterolemia in the setting of obstructive jaundice. Our case is unique since the trigger was drug-induced hepatitis rather than an obstructive process. Clinicians should always have a high index of suspicion for pseudohyponatremia. Measuring the serum osmolality to rule-out an elevated osmolality gap must be one of the first steps in managing patients presenting with hyponatremia. Although uncommon, hypercholesterolemia can be an etiology for pseudohyponatremia, especially in liver disorders.

PUB200

Respiratory Failure as an Initial Presentation of Starvation Ketoacidosis

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Introduction: The incidence of ketonemia has been estimated to be approximately 5%, in a hospital setting post-operatively, however it usually doesn't affect the peri-operative management.

Case Description: A 64-year-old female with a history of type 2 diabetes mellitus, hypertension, dyslipidemia and sigmoid cancer (adenocarcinoma T1N4) status post-proctocolectomy followed by chemotherapy presented with decreased appetite, severe abdominal pain and obstipation of 5 days duration. A CT scan of the abdomen showed partial small bowel obstruction. The patient failed conservative measures and underwent adhesiolysis 4 days later under general anesthesia. The intraoperative and the immediate post-operative period were uneventful. Two days post-operatively, the patient started complaining of shortness of breath and was found to be tachypneic. She was transferred to the intensive care unit for further monitoring. An arterial blood gas showed severe anion gap metabolic acidosis with appropriate respiratory compensation (see table). Further investigations revealed ketones in the blood and urine with a normal blood glucose. The patient received parenteral nutrition and her respiratory status improved promptly.

Discussion: In clinical practice, fasting is seldom suspected to the cause of severe metabolic acidosis. However depletion of the glycogen stores by prolonged fasting, in addition to a state of relative insulin deficiency secondary to the diabetic state of the patient might have accounted for this dramatic presentation. In conclusion, starvation ketoacidosis is a potentially serious cause of severe morbidity post-operatively and should be screened for in patients at risk such as diabetic patients with a poor nutritional status.

Post-Op	Urea mg/dL	Creatinine mg/dL	Na mEq/L	K mEq/L	Cl mEq/L	CO2 mEq/L	Glucose mg/dL	Anion Gap	Delta Delta	pH	PaO2 mm Hg	PaCO2 mm Hg	HCO3 calculated mmol/L	Lactic Acid mmol/L	O2 Sat %
Day 2	19	0.5	142	3.7	106	14.6	151	21.4	1.24	7.38	63	22	12.6	0.6	96
Day 3	19	0.4	142	4	105	11.5	140	21.5	1.06	7.34	100	21	11	0.8	99
Day 4	27	0.4	142	3.2	107	15.8	175	19.2	1.18	7.43	85	27	17.7	1.1	98
Day 5	26	0.3	144	3.1	103	22.2	161	18.7		7.51	63	31	25	1	94

PUB201

Hospitalization in Patients with ESRD Secondary to Polycystic Kidney Disease: A Cohort Study

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Background: Patients with End-Stage Renal Disease (ESRD) secondary to Polycystic Kidney Disease (PKD) have been shown to have improved health outcomes compared to those with other ESRD diagnoses. Less is known about their comparative risk of hospitalization and time admitted in hospital following initiation of chronic dialysis. We compared the rate of hospitalization and days in hospital for patients with PKD versus other causes of ESRD.

Methods: We conducted a cohort study of all ESRD patients who initiated dialysis at a large quaternary centre between 1 Jan 2009 and 1 Jun 2015 (last follow-up 1 Jul 2016). Exposure was ESRD cause categorized as diabetes, ischemic/HTN, PKD, glomerulonephritis, unknown and other. Primary outcome was all-cause hospitalization rate (number hospitalizations/follow-up time) excluding transplant admissions. Follow-up commenced at the date of dialysis initiation or discharge date from hospital for those who started dialysis as inpatients. For the primary outcome, follow-up time was exclusive of time spent in hospital and concluded at the earliest of either death, admission for transplant or date of last follow-up. Secondary outcomes included the number of hospital days/total follow-up time. Comparisons between PKD and other ESRD causes were analyzed using negative binomial regression adjusting for demographics, dialysis access, comorbidities and laboratory values at dialysis initiation.

Results: The cohort consisted of 636 patients. 45 (7%) patients had ESRD due to PKD; the most common cause of ESRD was diabetes (35%). Patients with PKD were younger (56 ± 11 versus 62 ± 15 years), had a higher likelihood of PD access (44% versus 21%), more likely female (53% versus 36%), and had lower burden of comorbidity. A total of 24 PKD patients (53%) experienced 1 or more hospitalizations, but the rate was low (incidence rate 0.45/patient year), unadjusted incidence rate ratio of 0.55 (95% CI 0.41-0.72, P<0.001) compared with other causes. PKD patients spent 3.8 days in hospital/ patient year (IRR 0.36, 95% CI 0.33-0.39). In a multivariable adjusted model, the IRR for hospitalization remained low (0.54, 95% CI 0.39-0.74).

Conclusions: The risk of both hospitalization and time admitted were less for patients with ESRD secondary to PKD. These findings can help inform patient care decisions for those approaching chronic dialysis.

Funding: Commercial Support - Otsuka Canada Pharmaceutical Inc.

PUB202

Identification of Housekeeping Genes for MicroRNA Expression Analysis in Pkd1-Deficient Mouse Models

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Background: There are no reports of systematic validation of genes commonly used for normalization of gene expression by RT-qPCR in kidney tissues of mouse models orthologous to autosomal dominant polycystic kidney disease (ADPKD). The aim of this study was to identify the most suitable housekeeping genes for RT-qPCR analyses of kidney tissues in *Pkd1*-deficient mouse models from eight currently used candidates.

Methods: Eight different control genes for microRNA (miR) studies were investigated in kidney tissues of *Pkd1*-deficient mouse models and their corresponding controls by RT-qPCR. All lines were generated and maintained on a C57BL/6 background. The expression of the candidate housekeeping genes (*miR-20a*, *miR-25*, *miR-26a*, *miR-191*, *miR-423*, *miR-547-3p*, *miR-674-5p* and *U6*) and 2 target genes (*miR-21* and *let-7a*) was analyzed in the kidneys of 10-12-week-old cystic mice ($Pkd1^{flox/flox}$:$Nestin^{cre}$, CY,n=10), non-cystic controls ($Pkd1^{flox/flox}$, NC,n=10), *Pkd1*-haploinsufficient mice ($Pkd1^{+/-}$, HT,n=6), wild-type controls ($Pkd1^{+/+}$, WT,n=6) and 15-day-old severely cystic mice ($Pkd1^{V/V}$,SC,n=7) and wild-type controls (CO,n=5). The stability of the candidate genes was investigated using six software applications: NormFinder, GeNorm, BestKeeper, DataAssist, comparative ΔCt and RefFinder.

Results: As shown in the table below, our comprehensive analysis identified *miR-26a* as the most stable housekeeping gene, although the best one varied among the models. Our analyses revealed upregulation of *miR-21* upregulation in SC and HT kidneys and trends of *let-7a* downregulation in CY and HT kidneys when expression was normalized to the best housekeeping gene *miR-26a*.

Conclusions: We have established the best housekeeping, *miR-26a*, for RT-qPCR analyses in kidney tissues of *Pkd1*-deficient mouse models.

Funding: Government Support - Non-U.S.

Best individual and combination of housekeeping miRNAs for each group of samples.

	Best one	Best pair	Best trio
All groups	miR-26a	miR-20a+miR-26a	miR-20a+miR-25+miR-26a
CY	miR-20a	miR-20a+miR-25	miR-20a+miR-25+miR-26a
NC	miR-20a	miR-20a+miR-26a	miR-20a+miR-26a+miR-191
HT	miR-26a	miR-20a+miR-26a	miR-20a+miR-26a+miR-191
WT	miR-20a	miR-20a+miR-25	miR-20a+miR-25+miR-26a
SC	miR-25	miR-25+miR-191	miR-25+miR-191+miR-20a
CO	miR-26a	miR-20a+miR-26a	miR-20a+miR-25+miR-26a

PUB203

Pain in Autosomal Dominant Polycystic Kidney Disease: Results from the DRINK Randomised Phase 2 Trial

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Background: Pain affects 60% of the adult Autosomal Dominant Polycystic Kidney disease (ADPKD) population. Despite being an early and debilitating symptom, mechanisms of ADPKD-related pain (ACP) are poorly understood. We designed and administered an ADPKD-specific pain questionnaire to participants in the 'DRINK' Phase 2 study of water intake in ADPKD (NCT02933268), where 42 pre dialysis adult ADPKD patients were randomised to either high water (n=21) or ad libitum water (n=21) intake over 8 weeks follow up.

Methods: 'DRINK' participants completed the bespoke pain questionnaire on paper or via smartphone application. The questionnaire explored key domains including pain severity, quality, interference, frequency and location. Analgesic burden was also evaluated. Primary objectives were to describe the nature of ACP and develop a validated ADPKD-specific pain assessment tool.

Results: 39 participants completed 72 questionnaires during the study. 59% were Female, 90% White British with a mean±SD age 47±13 years. 69% had enlarged kidneys (bipolar length≥16.5cm), and median eGFR was 76 (47-111) ml/min/1.73m^2. 17% of respondents indicated pain frequency 0-1 times/week, 79% had pain 2-3 times/week and 4% had continuous pain. Pain severity was assessed using an 11-point numerical score further classified: 0-No pain, 1-3 Mild, 4-6 Moderate, >7 Severe. For overall pain, 36% had no pain, 38% had mild pain, 17% moderate pain, and 3% severe pain. In a multivariable regression model, pain severity was associated with increasing age, female gender, CKD stage 3 or worse and hypertension but not with kidney size.

Conclusions: In our cohort pain was common and severe. Despite the association between some markers of disease progression and pain severity, the poor correlation with kidney size suggests that there are mechanisms unrelated to renal anatomy that contribute to chronic pain in patients with ADPKD.

Funding: Government Support - Non-U.S.

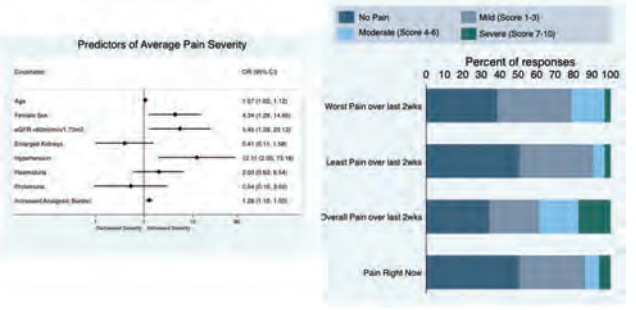

Figure: Predictors of overall pain severity (left), Frequency of pain severity categories (right)

PUB204

The Pathogenic AGTc.856+1G>T Mutation of a Patient with Multiple Renal Cysts and Hypertension

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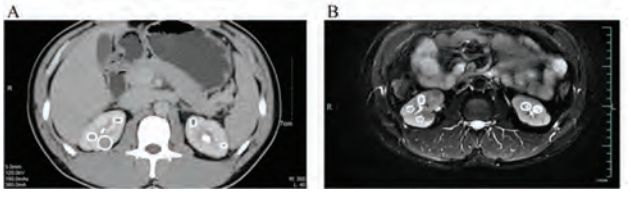
Introduction: Angiotensinogen (AGT) is an essential member of the renin-angiotensin system (RAS), this system regulates blood pressure and affectsphysiological function of the kidney. Here we report a 29-year-old male Chinese with essential hypertension and cystic kidney disease. Direct sequence analysis of the patient and his parents revealed a mutation in the splice donor site of intron 2 of the *AGT* gene, c.856+1G>T. This mutation was a heterozygous form and inherited from mother.

Case Description: Direct sequence analysis of the patient and his parents revealed a mutation in the splice donor site of intron 2 of the *AGT* gene, c.856+1G>T. This mutation was a heterozygous form and inherited from mother, and the mother was diagnosed with essential hypertension over 20 years. We tested the serum angiotensinogen concentration and found the patient and the mother hadlowerserum angiotensinogen levels than the father. Function prediction of c.856+1G>T mutation using online software showed this intron mutation may affect protein feature by destroying normal splice site. These findings suggest that this intron mutation of the *AGT* gene is related to the patient's essential hypertension and cystic kidney disease.

Discussion: Studies found that mutations of the human *AGT* gene areinvolved in diseases such as recessive renal tubular dysgenesis (RTD) and essential hypertension (EHT). We presented a case of a new intron mutation of *AGT* Gene in a 29-year-old male Chinese with multiple renal cysts and hypertension, it is a heterozygous mutation inherited from his mother. The patient's renal function impairment progressed slowly. His renal cystic lesion and hypertension seem to be due to the presence of heterozygous c.856+1G>T mutation in the*AGT* gene. Animal experiments and large sample studies are needed to confirm the relationship of c.856+1G>T mutation in the *AGT* gene of angiotensinogen expression and renal cyst formation and hypertension.



Typical renal cystic structures of the enhanced CT image of the patient's kidneys.

PUB205

AD(H)PKD: A Prospective Cohort Study on the Use of Tolvaptan in ADPKD

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Background: The approval of tolvaptan as the first targeted therapy of autosomal-dominant polycystic kidney disease significantly changed treatment of this disease and the counselling of patients. But which patients are actually treated and how is the therapy managed and tolerated in the real-life setting?

Methods: To answer these questions, we initiated the AD(H)PKD registry which enrolls ADPKD patients who present with the question whether tolvaptan would be a treatment option. The cohort contains data of patients on Tolvaptan and without targeted treatment. We collect information on a yearly basis including lab values, kidney volume, quality of life, adherence, genotype, extrarenal manifestations, comorbidity, side effects and complications.

Results: Since the start of the study at the end of 2015 until now more than 560 patients could be enrolled. Here, we present data on the first 500 patients. Of those, 54.4 % (n=272) are female. Mean age at enrolment was 43.9±11.9 years (female (f): 44.1±12.1, male(m):43.7±11.6). While women were diagnosed with a mean age of 25.7±13.0 years, males learned about their disease at the age of 28.4±12.8 years. As expected, the majority of patients (87.6%; n=438) reported a positive family history with regard to ADPKD. In 83.4% of the cohort (n=417) arterial hypertension was diagnosed, 42.2% (n=211) experienced elevated blood pressure before the age of 35. Mean GFR at baseline visit (CKD-EPI) was 68±44 ml/min. Kidney function in females was more preserved than in males (f:72±53 ml/min, m: 64 ±28 ml/min). In 393 participants, renal volume could be calculated via radiologic imaging. In line with the more advanced loss of kidney function, height adjusted total kidney volume was larger in male patients (htTKV, f:875±543ml m:1350±1168ml). 24.9% (n=98) of the cohort were classified as Mayo A or B, 75.1% (n=295) as Mayo class C to E.

Conclusions: The AD(H)PKD study continues successful enrolment and provides valuable data on patient characteristics, selection strategies for targeted treatment and tolerability of tolvaptan in a real-life setting. We expect analyses concerning outcome parameters on tolvaptan treatment with a sufficient amount of 3 year follow up data in 2020. These results will be very useful for guiding treatment strategies and patient counselling in the future.

Funding: Commercial Support - Otsuka

PUB206

Elderly-Onset Rapidly Progressive Renal Dysfunction with Renal Enlargement and Medullary Cystic Kidney Disease (MCKD) Might Be a New Disease Entity of Ciliopathy Unlike Traditional Hereditary MCKD

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Introduction: Recently there have been several reports of rapidly progressive renal dysfunction in elderly patients with renal enlargement and MCKD in Japan. Here we reported three cases who have undergone dialysis with rapid progression and performed analysis of gene panel for target sequence of inherited kidney disease. But neither mutation of known MUC1 or UMOD was detected.

Case Description: 1.84-year-old Japanese woman without family history of kidney diseases was noted to have renal dysfunction of unknown etiology 1 year prior to admission. She had developed progressive renal dysfunction (Cr 3.7mg/dL). Her abdominal CT revealed bilateral renal enlargement and histological findings revealed marked tubular dilatation with extensive fibrosis in the interstitium, consistent with MCKD. She was initiated dialysis 3 month after. 2.74-year-old woman was noted to have mild renal impairment (Cr 1.1mg/dL) 1 year prior to admission. She developed progressive renal dysfunction (Cr 3.6mg/dL). Her serial abdominal CT revealed no evidence of renal enlargement before admission and bilateral renal enlargement at admission. Her histological findings revealed consistent with MCKD. She was initiated dialysis 5 month after. 3. 80-year-old woman was noted to have renal dysfunction (Cr 1.9mg/dL) 1 year prior to admission. She had developed progressive renal dysfunction (Cr 3.3mg/dL). Her CT revealed bilateral renal enlargement and histological findings revealed consistent with MCKD. She developed progressive renal dysfunction just before dislysis initiation 1 year after.

Discussion: We reviewed the literature on 16 subjects (thirteen similar cases reported in Japan since 2007 and our three cases). The age at renal biopsy was 70 years. Before renal biopsy, a rate of Cr elevation was 0.6 mg / dL / month, and renal biopsy was performed at 4.1 mg / dL of Cr. Urine protein were positive in all cases, urine occult blood was positive in 9 cases. Renal enlargement was observed in 13 cases. Renal biopsy findings showed minor glomerular changes and marked dilated renal tubules and interstitial fibrosis. After renal biopsy, 13 cases reached ESRD in 3.9 months. Target gene sequence of inherited kidney disease were performed in 6 cases, and neither mutation of MUC1 or UMOD was detected.

PUB207

Comparative Effectiveness of Disease-Modifying Agents in Patients with ADPKD: A Systematic Review and Network Meta-Analysis

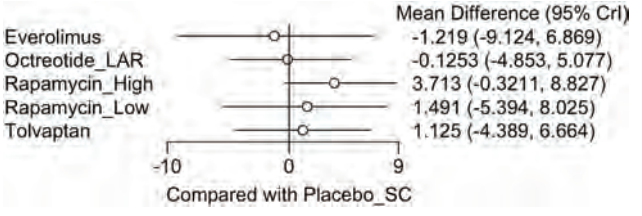
Nigar Sekercioglu,[1] Rui Fu,[2] Luciane C. Lopes,[3] Rosilene M. Elias,[4] Bryan M. Curtis.[5] ADPKD study *[1]Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]Uniso, Sorocaba, Brazil; [4]Universidade de Sao Paulo, Sao Paulo, Brazil; [5]Memorial University, St. John's, NL, Canada*.

Background: ADPKD is the most common hereditary kidney disease with about 1:500 frequency, 100% penetrance and multisystem involvement. The purpose of this study is to explore the effectiveness and safety of disease-modifying agents for ADPKD.

Methods: We conducted searches on the MEDLINE, EMBASE and CINAHL databases from the inception to May 2019 for RCTs with ≥ six-month follow-up. Teams of two reviewers, independently and in duplicate, screened titles and abstracts, completed full-text reviews, and abstracted data. Eligible trials enrolled patients with ADPKD, randomized to receive rapamycin, everolimus, octreotide, tolvaptan, standard care, or placebo, and reported effects on patient-important outcomes (e.g., all-cause mortality), total kidney volume (TKV), glomerular filtration rate (GFR), or medication-related adverse events. We excluded preclinical experiments, crossover trials, and conference proceedings. We performed network meta-analysis (NMA) and pooled treatment effects as mean differences (MD) and calculated 95% credible intervals (Crls) using random-effects models. We applied the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to rate the quality of evidence.

Results: Our search yielded 635 citations, of which 11 met the inclusion criteria and involved a total of 3703 adults with ADPKD, including 2106 (56%) patients receiving treatments and 1597 (44%) receiving placebo and/or standard care. The random-effects models suggested rapamycin leads to a reduced change of TKV at 12 months (NMA MD, -436 [95% Crl, -639 to -212]. Twenty-five comparisons failed to reach statistical significance in the network estimates for the GFR outcome. Patients treated with rapamycin at high target dose had a higher likelihood of slowing of GFR decline as compared to those treated with other treatment categories.

Conclusions: Our results suggest that rapamycin reduced changes in TKV at 12 months and in high doses attenuated the GFR decline.



Network meta-analysis results for GFR. Forest plot of effectiveness outcome for mean GFR reduction at the end of the study period.

PUB208

A Novel Genetic Model of Cystic Kidney Disease in the Mouse

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Background: Polycystic kidney disease is the most common genetic cause of chronic kidney disease and end stage renal disease. While mutations in PKD1 and PKD2 cause most cases of autosomal dominant PKD, other genetic factors are thought to act as modifiers.

Methods: Using an ENU mutagenesis screen, we have identified a cystic kidney mutant that is transmitted in an autosomal dominant manner. We have characterized the mutation using both whole genome sequencing and RNA sequencing.

Results: Mice heterozygous for the trait develop glomerular and tubular cysts all along the nephron, but otherwise appear healthy. Mice that are homozygous for the trait develop hypoplastic, cystic kidneys, and are perinatally lethal with pulmonary hemorrhage. We have performed whole genome sequencing and identified potentially causative gene mutations on mouse chromosome 6. We have also performed RNA sequencing on kidneys from affected mice and matched controls and have identified significant changes in gene expression.

Conclusions: We present a novel mouse model of cystic kidney disease, which we have genetically and phenotypically characterized. We propose that the differentially regulated genetic elements that we have identified may represent genetic modifiers of cystic kidney disease.

Funding: NIDDK Support

PUB209

Just a Sugar Pill: Trehalose in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Daniel Atwood. *University of Colorado Anschutz, Aurora, CO*.

Background: ADPKD has been described as a case of suppressed autophagy. Trehalose (TRE) is a non-reducing disaccharide and FDA-approved food sweetener. Trehalose has demonstrated utility *in vivo* and *in vitro* as an autophagy inducer. The goal

of the present study was to test the interventional effects of TRE on cyst growth, kidney function, and autophagy-associated proteins in a hypomorphic *Pkd1*$^{RC/RC}$ mouse model of ADPKD.

Methods: Wildtype (WT) and *Pkd1*$^{RC/RC}$ (PKD) mice were treated with either tap water (VEH) or 2% TRE from 50-120 days of age. Water intake was recorded as it is known to affect cyst burden. Autophagy-associated proteins were measured in kidney homogenates by immunoblot: pBeclin1 (Ser15) (marker of initial steps of autophagosome formation), ATG12/5 complex (lipidates and inserts LC3B into autophagosome membrane), LC3-II (marker of autophagosomes) and Ras-related protein 9a (Rab9a) (marker of late steps of autophagosome maturation). Statistical analysis was performed on relative densitometry units (RDU) obtained from immunoblots (Table).

Results: See Table. TRE, that is slightly sweet, did not affect water intake, nor did it change serum arginine vasopressin (AVP) or serum copeptin levels, which are sensitive to water intake. LC3-II was increased by TRE in WT but not PKD kidneys. Rab9a was decreased in PKD kidneys and not affected by TRE. pBeclin1 was increased in PKD kidneys and restored by TRE. ATG12/5 complex was decreased in PKD kidneys and not affected by TRE. TRE did not reduce cyst number or two kidney weight (2KW) to body weight (BW) ratios or improve kidney function in PKD vs. WT.

Conclusions: The most striking finding was suppressed ATG12/5 complex and decreased Rab9a suggesting defects in LC3B lipidation and insertion into autophagosome and autophagosome maturation, respectively, in *Pkd1*$^{RC/RC}$ mice. These defects were not rescued by TRE. TRE did not reduce cyst burden or improve kidney function.

Funding: Veterans Affairs Support, Other U.S. Government Support

Table 1

	WT	WT + TRE	PKD	PKD + TRE	P value
LC3-II	0.4	0.6	0.4	0.3	0.009
Rab9a	0.5	0.5	0.3	0.3	0.001
pBeclin1	0.3	0.3	0.8	0.3	0.008
ATG12/5 complex	0.4	1.0	0.03	0.02	<0.001
2KW/TBW (%)	1.2	1.2	2.7	3.0	<0.001
Cyst Number			321	321	NS
BUN (mg/dL)	16		23	23	0.001

PUB210

Autosomal Dominant Polycystic Kidney Disease (ADPKD): Optimization of the Evaluation of Total Kidney Volume

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD**)** is the most common inherited renal disorder. It is characterized by progressive development of renal cysts and increase in total kidney volume (TKV). TKV is a critical requisite to initiate tolvaptan therapy. Patients (pts) must have a TKV >750 ml. To be eligible to treatment. To date, the gold standard for the radiological technique to measure TKV remains undefined. Aim: Comparison between currently available radiological techniques to measure TKV evaluated for tolvaptan therapy focusing on precision in TKV measuring, reproducibility and costs of the radiological technique. Patients selection**:** Patient with a diagnosis of ADPKD, with Genetic positivity or Familiar history of ADPKD and ultrasound evaluation.

Methods: Thirty-nine patients were screened for potential therapy with tolvaptan (range of age 18-49 yrs). Twenty-nine patients were excluded because of either e-GFR values of >90 ml\min (18 pts) or e-GFR values <40 ml/min (4 pts), refusal of treatment (3 pts), linguistic problems (2 pts), liver disease (1 pt) or currently breast feeding. Ten patients (6 female mean age: 38 years, mean creatinine value 1.1mg/dl, mean e-GFR 63 ml/min) were enrolled and were examined by Magnetic Resonance Imaging (MRI), Ultrasound and Computer Tomography (CT). TKV values were measured using the ellipsoid formula applied in each technique a. It was combined to manual evaluation in the case of MRI and CT. The values were compared by linear regression analysis and Altman-Plot graphs.

Results: As compared to CT and MRI, ultrasound, especially at the higher TKV values, gave over-estimated TKV values, MRI and CT showed comparable accuracy and reproducibility, especially when data were manually processed (R2= 0,99).

Conclusions: Ultrasound proved to be not as reliable as MRI or CT when measuring TKV. Patients age, comorbidities, availability of instrumentations and costs may influence the choice between MRI and CT, which appear to be comparably effective in TKV evaluation.

PUB211

Vaptans, New-Generation Diuretics, Exert Their Aquaretic Effect Through Inhibition of Aquaporin 2 Trafficking in Renal Collecting Duct Cells

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Background: Selective vasopressin V2 receptor (V2R) antagonists (vaptans) are a new generation of diuretics. Compared with classical diuretics, vaptans promote the excretion of retained body water in disorders where plasma vasopressin concentrations are inappropriately high for any given plasma osmolality. Under these conditions an aquaretic drug would be preferable over a conventional diuretic. The clinical efficacy of vaptans is in principle due to impaired vasopressin-regulated water reabsorption *via* the water channel aquaporin-2 (AQP2).

Methods: Here, the effect of lixivaptan - a novel selective V2R antagonist - on the vasopressin-cAMP/PKA signaling cascade was investigated in mouse renal collecting duct cells expressing AQP2 (MCD4) and the human V2R. Compared to tolvaptan - a selective V2R antagonist indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia -, lixivaptan has been predicted to be less likely to cause liver injury.

Results: In MCD4 cells, immunofluorescence localization of AQP2 and analysis by confocal microscopy showed that clinically-relevant concentrations of lixivaptan (100nM for 1h) prevented dDAVP-induced AQP2 phosphorylation at ser-256 and AQP2 translocation to the plasma membrane. Consistent with this finding, real-time fluorescence kinetic measurements demonstrated that lixivaptan prevented dDAVP-induced increase in osmotic water permeability.

Conclusions: These data represent the first detailed demonstration of the central role of AQP2 blockade in the aquaretic effect of lixivaptan and suggest that lixivaptan has the potential to become a safe and effective therapy for the treatment of disorders characterized by high plasma vasopressin concentrations and water retention.

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PUB212

Medullary Sponge Kidney with Recurrent Nephrolithiasis: A Genetic Disease?

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Introduction: Medullary Sponge Kidney (MSK) is a malformation with tubular dilation of the collecting ducts and cystic dilation of the medullary pyramids of the kidney. It can manifest as nephrocalcinosis, nephrolithiasis, renal tubular acidification and concentration defects or rarely as frequent urinary tract infections. It can be seen in up to 20% of recurrent stone formers.

Case Description: A 62 year old woman with a history of nephrolithiasis for over 30 years, presented to the emergency department with dysuria and flank pain and was found to have recurrent kidney stones. The patient had undergone three extra corporeal shock wave lithotripsy (ESWL) procedures and numerous other urological procedures with stent placement for calcium oxalate and calcium phosphate stones. An ultrasound study done of the kidney showed images with uniform distribution of multiple stones, with distention of the medullary and papillary portions of the collecting ducts, suggestive of medullary sponge kidney. 24 hour urine studies were suggestive of hypercalciuria and hypocitraturia. Renal function remains normal, with no proteinuria or hematuria. Patient was encouraged a high fluid intake and normal calcium and low sodium diet. Thiazide was started with decrease in 24 hour calcium excretion.

Discussion: MSK is now thought to be a developmental disorder related to issues arising during renal morphogenesis. Problems with concomitant urteric bud and metanephric blastemal due to abnormal signaling of glial cell line derived neurotrophic factor (GDNF) and its receptor RET is speculated to play a role. Usually sporadic and asymptomatic, it can manifests in familial clusters. recurrent calcium nephrolithiasis and nephrocalcinosis are prominent features with hypercalciuria seen in almost 100% of MSK patients. Distal acidification defect seems to be a major player in pathogenesis. The clinical course varies from silent to indolent, to rarely progression of nephrocalcinosis. ESRD is seen in less than 10% of MSK patients. Diagnosis is radiographic with traditionally urography being the gold standard. Now Ultrasound, uro CT and MR urography are being used for diagnosis. Though there is no treatment for MSK, prophylactic therapy for stone prevention is crucial. Screening of family members should be considered as part of history taking.

PUB213

Association Between VDR Gene FokI Polymorphism and Renal Function in Patients with IgA Nephropathy

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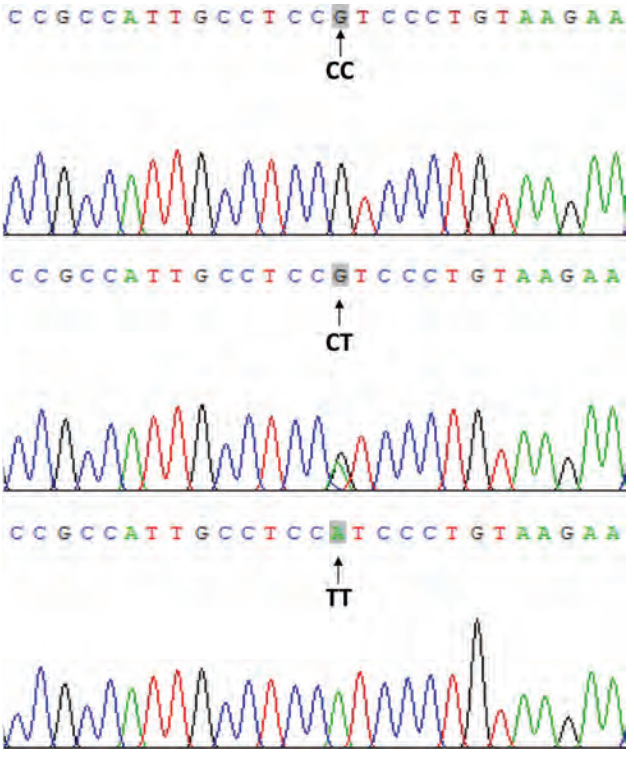
Background: To investigate the association between *VDR* gene *FokI* rs2228570 polymorphism IgA nephropathy (IgAN) and IgAN renal function and related clinical and pathological parameters, and to seek the genetic susceptibility genes for patients with renal dysfunction in IgAN.

Methods: Clinical and pathological data of 282 IgAN patients treated at the First Affiliated Hospital of Guangxi Medical University were collected, and *FokI* genotypes

were determined by PCR and direct sequencing. Patients were divided into the renal dysfunction group and normal renal function (control) group by estimated glomerular filtration rate (eGFR) and serum creatinine level.

Results: Among 282 patients with IgAN, 55.32% of patients had renal dysfunction (156/282). Frequencies of TT genotype and T allele in the renal dysfunction group were higher than those of the control group. Blood urea nitrogen, serum phosphorus (P), proportions of mesangial cell proliferation, interstitial fibrosis/tubular atrophy and crescents in T allele carriers were higher than those in non-T allele carriers, while eGFR and 25-Hydroxyvitamin D3 were lower in T allele carriers than non-T allele carriers. Multiple linear regression analysis showed that eGFR was affected by *FokI* genotypes in IgAN patients. Logistics regression analysis showed that middle and elderly age, elevated P, intact parathyroid hormone and TT genotype were independent risk factors for renal dysfunction in IgAN patients; the odds ratio of carrying the TT genotype was as high as 84.77 ($P<0.05$ for all).

Conclusions: Patients of IgAN carrying *VDR FokI* TT genotype have an increased risk of renal dysfunction. *VDR FokI* is closely related to renal function, calcium-phosphate metabolism and related pathological damage in IgAN patients.



Chromatograms of direct sequencing for *VDR FokI* rs2228570 polymorphism

PUB214

Tissue Is the Issue: When a Second Biopsy Reveals the True Diagnosis

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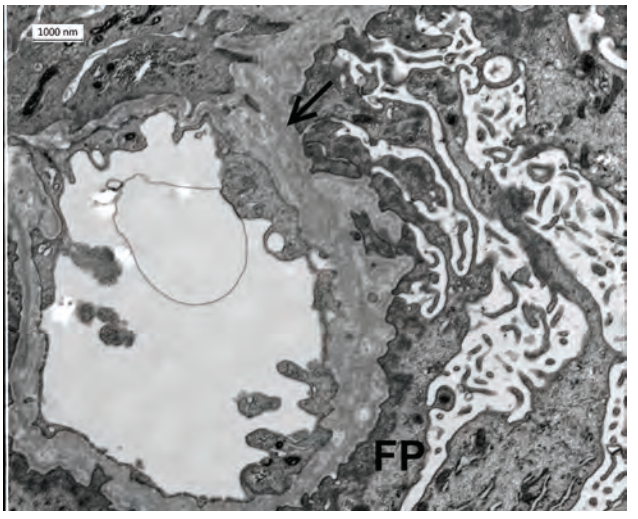
Introduction: We describe the case of a woman 41-years old, followed at our outpatient clinic with stable microscopic haematuria and mild proteinuria since 10 years. Underlying diagnosis of minimal glomerular changes was made after initial kidney biopsy.

Case Description: After several years of stable clinical and biochemical follow-up, progressive proteinuria was present since the end of 2017, upon nephrotic range of 3,5g/24h. Therefore a new kidney biopsy was planned, revealing focal segmental glomerulosclerosis (FSGS). Further differentiation by electron microscopy (EM) suggested an underlying genetic disorder. Next generation DNA sequencing was performed and showed that the patient was heterozygous for a pathogenic mutation in the *COL4A3* gene. This disorder shows considerable heterogeneity and is in our patient associated with late onset of FSGS that developed on top of the basement membrane nephropathy. Establishing a genetic cause of disease in this patient avoids exposure to immunosuppressive regimens, used to treat primary FSGS, as such treatment is ineffective in genetic FSGS and may pose considerably toxicity.

Discussion: By this case we want to stress the importance of re-biopsy when there is non-explained substantial increase in proteinuria on long term follow-up. Furthermore EM can be helpful for further differentiation and treatment decision. Genetic testing in all patients with adult onset FSGS that cannot be regularly categorized by clinic-pathologic assessment should be considered. Establishing a genetic cause of disease in this patient avoids exposure to immunosuppressive regimens, used to treat primary FSGS, as such treatment is ineffective in genetic FSGS and may pose considerably toxicity.



Ultrastructural alterations: Splitting of the lamina densa is observed (arrow), resulting in irregular thickening and contouring of the glomerular basement membrane. The foot processes (FP) are effaced (x 7000).

PUB215

Renal Functional Reserve Capacity Through Acute Protein Load in Patients with Gitelman Syndrome

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Background: Gitelman syndrome (GS) is a recessively inherited salt-losing tubulopathy caused by the disorder of sodium-chloride co-transporter (NCC). This pilot study aims to evaluate the renal functional reserve (RFR) in GS patients by acute protein load, and to figure out the effect of connecting tubule glomerular feedback (CTGF) secondary to NCC dysfunction.

Methods: We recruited 19 healthy controls and 4 GS patients, diagnosed by clinical examination and genotyping. Serum and urine were collected before and after oral protein load (1.2g/kg of body weight) at different timepoints (-1h, 0h, 1h, 2h, 3h and 4h). RFR was evaluated by eGFR changes, based on creatinine and serum cystatin C clearance. The urinary metabolite of prostaglandin E2 (PGEM), the signaling molecule of CTGF metabolite, was tested by ELISA through the process.

Results: The average age of healthy control group was 27.1±2.9 yr and 47.7% were male. Their baseline creatinine clearance was 140.9±31.5 ml/min/1.73m^2 and a significant difference between stress and basal creatinine clearance ($p<0.001$) was observed, with a mean RFR of 32.8±20.8 ml/min/1.73m^2. In GS patients with an average age of 27.0±7.0 yr and 50% male, both the baseline creatinine clearance and RFR showed no significant difference between the patients and controls ($p=0.091$), neither in cystatin C clearance. A good agreement between the creatinine clearance and cystatin C-based GFR was found by Bland-Altman plots. Higher level of urinary PGEM in GS patients than that of controls was observed. After protein load, the urinary PGEM levels were increased in both groups.

Conclusions: GS patients had normal RFR stimulated by acute protein load. It might be associated with the activating of CTGF, afferent arteriolar vasodilation and increased blood flow and GFR.

PUB216

Enzyme Replacement Therapy and Fabry Nephropathy

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Introduction: In Fabry nephropathy (FN), alpha-galactosidase deficiency leads to accumulation of glycosphingolipidis in all kidney cell types, proteinuria and progressive loss of kidney function. The aim of this study was to assess the clinical course of FN in two women with pathogenic mutations undergoing treatment with agalsidase beta (Fabrazyme®; Sanofi Genzyme, Cambridge, MA, USA) during a 6-year period.

Case Description: Case 1– AMSL, aged 61. Symptoms first appeared when the patient was aged 51, when she complained of myalgia, arthralgia, asthenia, dyspnea on exertion, tinnitus, abdominal pain and constipation. One year later, she was diagnosed with proteinuria and heart disease. She performed a kidney biopsy, which under light microscopy suggested deposit disease. No electron microscopy was performed. Genetic analysis demonstrated a mutation in exon 5 - p.K237X. At the time, she presented with creatinine (Cr) of 0.9 mg/dL and proteinuria of 1.2 g/day and an echocardiogram with a left ventricular mass (LV) of 392 g and LV mass index 238 g/m^2. In January 2012, she initiated enzyme replacement therapy (ERT) with agalsidase beta, 1.0 mg/Kg body weight once every 2 weeks, and conversion enzyme inhibitor. Currently, Cr is 1.0 mg/dL and proteinuria 0.3 g/day. During the follow-up period, there were no major cardiovascular

and/or central nervous system events. **Case 2**– DCBT, aged 60. The patient was diagnosed with cornea verticillata aged 13. Twelve years ago, she presented clinical signs of hypohidrosis, arthralgia, bradycardia and proteinuria. Genotyping revealed a C142R mutation. In 2012, after presenting a transient ischemic attack, she was commenced on ERT with agalsidase beta (1.0 mg/kg once every 2 weeks). At the time, she presented Cr 0.9 mg/dL and proteinuria 0.3 g/day. During the follow-up period, she presented three episodes of atrial fibrillation, which motivated treatment with propafenone and rivaroxaban. Currently, Cr is 0.8 mg/dL and proteinuria 0.17 g/day.

Discussion: This 6-year study has documented the effectiveness of agalsidase beta in patients with FN, despite delayed initiation of ERT.

PUB217

Mechanism of Mutation of AarF Domain-Containing-Kinase 4 (ADCK4) Glomerulopathy

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Background: AarF domain-containing-kinase 4 (ADCK4) is a mitochondrial resident protein kinase belonging to the UbiB protein kinase-like family. Comprised of a single N-terminal transmembrane helix and C-terminal kinase domain, ADCK4 is thought to facilitate the ATP dependent biosynthesis of coenzyme Q10 (CoQ10). Mutations in *ADCK4*, an inherited mitochondrial nephropathy, result in defects in CoQ10 production as well as in activities involved in mitochondrial respiration, manifesting as early-onset proteinuria, focal segmental glomerulosclerosis/nephrotic syndrome, followed by end-stage renal disease (ESRD). The regulation of ADCK4 in CoQ10 biosynthesis is not well understood, necessitating biochemical and structural investigations into its functions. Furthermore, characterization of ADCK4 protein will help to discover a targeted therapy for this type of glomerulopathy/nephrotic syndrome. This work started with genetic anaysis of an 18-year-old female who presented with proteinuria at age of 5 years and developed ESRD at 20 years of age. Her family was noted with proteinuria and structural anomalies of kidney.

Methods: Genetic analysis using whole exone sequencing for a family with proteinuria and structural anomalies of kidney and urinary tract revealed a novel compound heterozygous mutation in the *ADCK4*. We generated a computational model to understand the mechanism of action of 2 novel identified mutations: I346S in the C-lobe of the ADCK4 kinase domain, and a termination at W520 that leads to the truncation of the C-terminal a5 helix.

Results: The alterations of ADCK4 c.1560G>A and c.1037T>G are novel mutations. Our computational model suggests potential mechanisms for alterations in protein function through either destabilization of important allosteric interactions necessary for kinase activation and/or conformational changes that facilitate enzyme activity.

Conclusions: ADCK4 is promising therapeutic targets for patients with *ADCK4* glomerulopathy that need a rigorous biochemical characterization. ADCK4 protein is not well characterized at biochemical level. Computational model to understand the mechanism of mutation suggests potential mechanisms for alterations in protein function destabilization of important allosteric interactions and/or conformational changes that facilitate enzyme activity. Ongoing work to reveal the biochemical and functional analysis of ADCK4 protein.

PUB218

Challenges of Identifying Older Adults Initiating Hemodialysis

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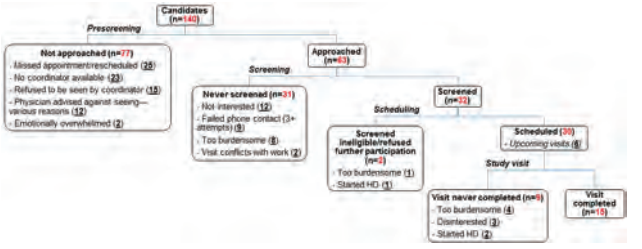
Background: Hemodialysis (HD) is a physical and psychological burden for older adults on maintenance HD. After HD initiation, while many do poorly, some older adults do quite well, recovering function with improved quality of life. Little is known about predictors of such resilience in CKD progression and transition to ESRD among older adults. We launched the Resiliency in Dialysis Initiation (ReDI) pilot study to identify short- and long-term physical resiliency indicators in older adults prior to, during and following HD initiation. Here we describe challenges in identifying participants for ReDI to inform future studies of similar design.

Methods: We aimed to recruit adults (age ≥55) with CKD who were expected to initiate HD within 8 wks. Eligible patients were prescreened in Nephrology clinic. Interested patients were formally screened by phone and those eligible were scheduled for a baseline visit. Recruited patients underwent testing including: ECG, echocardiogram, ACTH stimulation test, bioimpedance, spirometry, cognitive/physical function, psychosocial measures and accelerometry.

Results: We identified no patients expected to initiate HD within 8 wks. We then extended our inclusion criteria to eGFR ≤20mL/min/1.73m^2 and plans for future HD. Here (N=140), major barriers to prescreening (N=77) were missed clinic visits (32%) and patient refusal (19%). Barriers to screening (N=31) were disinterest (39%), failed phone contact (29%) and perceptions of study burden (26%). Barriers to baseline visit (N=9) were perceptions of burden (44%), disinterest (33%) and HD initiation prior to visit (22%). Over 5 mo, 15 (11%) eligible patients enrolled; 2 (13%) later initiated HD during hospitalization. (Figure)



Conclusions: Efforts to recruit older adults with CKD approaching dialysis in research studies should mitigate concerns of participant burden. Uncertainty surrounding which older adults with advanced CKD will initiate HD, and when, is a major factor limiting research in this area. Tools for short-term identification of older adults likely to initiate HD are needed.

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PUB219

Hyponatremia in Elderly Patients with CKD Stages 3-5

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Background: Elderly patients with chronic kidney disease (CKD) are at high risk to develop hyponatremia, which is associated with an increased risk of all-cause mortality. Our aim was to identify the frequency of hyponatremia and the associations with clinico-biological parameters in elderly patients with CKD stages 3-5.

Methods: We performed a retrospective observational study on 125 patients out of the 1739 hospitalized between 2015 and 2017 in our center. Inclusion criteria were: age ≥65 years, CKD stages 3-5 (not on dialysis). Volume status was measured by spectroscopic bioimpedance.

Results: The frequency of dysnatremia was 54.4%, including 50.4% hyponatremia and 4% hypernatremia. Regarding hyponatremia severity, 39 patients had mild, 15 moderate and 9 severe expression. Mean age was 73.6±6.5 years, 60% of patients had CKD stages 4-5 and the most frequent causes of CKD were hypertensive (31.2%) and diabetic nephropathy (30.4%). Mean BMI was 25.9±6.6 kg/m^2, 89.6% of patients were hypertensive, 41.6% diabetic, 37.6% had cardiac heart failure, 28.8% atrial fibrillation (AF), 40.8% ischemic heart disease (IHD), 14.4% peripheral artery disease, 16% history of stroke. Mean serum Na was 134±6.4 mmol/l, median overhydration status was 1L (-0.21- + 2.65) and 67.2% were diuretic users. Moderate and severe neurological symptoms were found in 12 and 6 patients, respectively. Patients with hyponatremia had more often AF (31.7% vs 25.8%), history of stroke (19% vs 12.9%), decreased levels of urea (85 vs 116 mg/dl) and no difference of eGFR. Moreover, there was a significantly decreased proportion of diuretic use (58.7% vs 75.8%, p=0.04), especially for loop diuretics (45.2% vs 54.8%, p=0.01), but a significant proportion of patients was treated with loop+aldosterone antagonist diuretic (15.9% vs 4.8%, p=0.03) in the hyponatremia subgroup. By multivariate logistic regression analysis, diuretic treatment reduced the risk of hyponatremia by 39% (OR=0.61; 95% CI 0.38-0.98; p=0.04) and the combination of loop and aldosterone antagonist therapy increased the risk 5.4 times (OR=5.43; 95% CI 1.35-2.89; p=0.01).

Conclusions: We showed that hyponatremia was frequent in elderly patients with CKD stages 3-5 and associated with cardiovascular comorbidities. Also, the diuretic treatment was an independent factor for hyponatremia.

PUB220

Epithelial Trophic Cytomegalovirus Causes Abortive Infection in Cultured Podocytes

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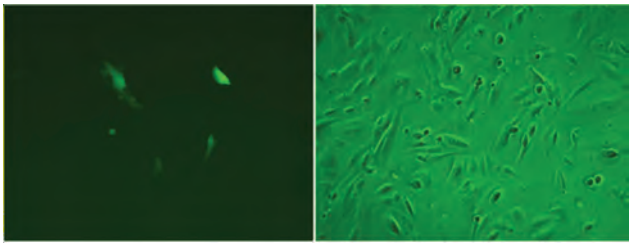
Background: Cytomegalovirus (CMV) is a herpesvirus with broad tropism, allowing for infection of virtually all tissues. Clinical manifestations include retinitis, hepatitis, and kidney dysfunction, particularly in renal allografts. In native kidneys, CMV is associated with collapsing focal segmental glomerulosclerosis (FSGS). We investigated CMV infection of podocytes due to their central role in glomerular function.

Methods: Human urine-derived podocytes were cultured in collagen type I-coated flasks. Immunocytochemistry confirmed the presence of podocyte cell markers including podocalyxin, following cell differentiation. Cells were exposed to two CMV laboratory strains, TB40 or Towne, both which were engineered to express green fluorescent protein (GFP). GFP expression was analyzed by flow cytometry. RT-PCR of the early CMV gene product UL123 was performed. In order to test for a productive infection, conditioned cell media was added to a retinal pigmented epithelial cell line (ARPE) that is highly susceptible to CMV infection.

Results: Cultured podocytes demonstrated the capacity of infection when exposed to an epithelial trophic strain of CMV (TB40) as seen by GFP expression in up to 3% of cells and by RT-PCR for CMV gene expression, but not when exposed to a fibroblast trophic strain (Towne). ARPE cells exposed to cell media from infected cultured podocytes did not become infected with CMV.

Conclusions: Cultured human podocytes are susceptible to infection by an epithelial trophic CMV strain *in vitro* and this process appears to be abortive, as the infection is not transmitted to other cells. Future studies will assess cytopathic effects following CMV infection including changes in podocyte function. Studies of CMV infection of podocytes may provide mechanistic information about CMV-mediated glomerular injury, including collapsing FSGS.

Funding: Private Foundation Support



Left: Green fluorescent protein (GFP) expression in cultured podocytes exposed to CMV (TB40 strain).*Right:* Cultured podocytes prior to GFP expression analysis

PUB221

Lyso-GL3-Mediated Podocyte Injury in Fabry Disease

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Background: Podocyte injury is an early feature of Fabry nephropathy. Fabry disease is a rare X-linked lysosomal glycosphingolipid storage disorder resulting in the deficiency of the α-galactosidase A enzyme, eventually leading to end-stage renal disease. Globotriaosylceramide (lyso-GL3) is a bioactive molecule that accumulates in Fabry disease. However, the association between molecular mechanisms of lyso-GL3 and kidney damage is not well known. Thus, we investigated a mechanism how lyso-GL3 induced podocyte injury.

Methods: Cultured podocytes were stimulated with lyso-GL3 to induce Fabry disease mimic condition. Intracellular reactive oxygen species (ROS) generation was analyzed using 2'-7' dicheloro fluorescenin diacetate (CM-H2DCF-DA). Lyso-GL3-induced podocyte injury was evaluated by western blot, immunofluorescence, and albumin permeability analysis.

Results: Synaptopodin protein was significantly decreased and ROS was increased after lyso-GL3 treatment. Lyso-GL3 induced actin cytoskeleton rearrangement in podocyte. Fibronectin was increased in dose-dependent manners by treatment with lyso-GL3. Furthermore, lyso-GL3 treated podocytes showed the increased albumin permeability.

Conclusions: These results suggest that lyso-GL3-induced ROS and cytoskeletal reorganization may induce podocyte dysfunction in Fabry disease.

PUB222

Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Positive Glomerulonephritis in Childhood: Description of a Single-Center Cohort

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Background: Renal vasculitis is a severe manifestation of a anti-neutrophil cytoplasmatic antibody (ANCA)-associated vasculitis and often presents as rapid-progessive glomerulonephritis (GN). In particular, elderly patients over 50 years are affected and data on pediatric patients are rare with shorter observation times.

Methods: We retrospectively analyzed all 14 pediatric patients in our center from 1999 to 2018 (12 female; mean age 13.2 years, mean observation time 7.2 years) with histologically confirmed ANCA-associated GN.

Results: 43% (6/14) of our patients developed end stage renal disease (ESRD), 4 patients at the time of diagnosis, 2 patients after 3 years and renal recovery could not be achieved despite laboratory remission. 4/6 ESRD patients were successfully transplanted after 2.3 years. Initially, 9/14 (64%) patients presented with extrarenal manifestations, primarily respiratory (7/14) and/or CNS (2/14) manifestations. Laboratory remission could be achieved in all patients with steroids and in addition, 5 patients received cyclophosphamide, 8 plasmapheresis and 9 patients rituximab. All 6 patients with ESRD at time of diagnosis were treated with steroids, plasmapheresis and rituximab. 7/14 patients presented with antibodies against myeloperoxidase (p-ANCA) and 7/14 against proteinase 3 (c-ANCA). All c-ANCA positive patients developed pulmonary symptoms but showed a better renal outcome (ESRD: 2/6 c-ANCA positive patients vs. 4/6 p-ANCA positive patients). On the contrary, 4/7 p-ANCA positive patients did not develop extrarenal manifestations. Renal recovery or occurence of extrarenal manifestations did not correlate with the antibody level, however, patients with ESRD showed a higher amount of affected glomeruli in renal biopsies. 2/14 patients (14%) developed a relapse of the disease 6 months and 16 years following transplantation which could be treated successfully with steroids and rituximab.

Conclusions: Several children with ANCA-positive vasculitis developed early ESRD without renal recovery after succesful antibody eliminiation. Extrarenal manifestations were frequently observed. The initial antibody level had no prognostic value for renal recovery or extrarenal mainfestations. However, patients with ESRD showed a higher amount of affected glomeruli in renal biopsies. Relapses were infrequently observed.

Funding: Clinical Revenue Support

PUB223

Thrombotic Microangiopathy vs. Class IV Lupus Nephritis in Systemic Lupus Erythematosus

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Background: The kidney is often involved in systemic lupus erythematosus (SLE). Lupus in the kidney manifests predominantly as lupus nephritis or as vascular involvement with the severest form being thrombotic microangiopathy (TMA). The objective of this study was to capture the clinical and prognostic characteristics of TMA compared to class IV lupus nephritis in SLE patients.

Methods: We conducted a retrospective analysis of kidney pathological reports and laboratory data in 89 SLE patients. Renal prognosis was determined as the need for dialysis. All data were collected at the time when the biopsy was taken. Quantitative data were reported as mean and standard deviation, while categorical data were reported as frequency and percentage.

Results: Among 89 SLE patients screened, 27 met the inclusion criteria. Eight had TMA without evidence of ISN/RPS lupus nephritis and 19 had class IV lupus nephritis. No significant difference between the two groups according to age, gender or race. Patients in TMA group had significantly higher lactate dehydrogenase levels (718±499vs. 264±107.7 U/L, P = .009), serum C3 (100.6±39.3 vs. 65.8±27 mg/dL, P = .049), white blood cell count (14743.8±7933.3 vs. 5807.9±2053.2 x10E3/uL, P = .0004), fasting glucose level (121.5±39.8 vs. 92.1±19.4 mg/dL, P = .02), and total bilirubin (0.8±0.5 vs. 0.3±0.1 mg/dL, P = .007). Patients in TMA group had significant lower platelet count (158.4±88.6 vs. 240.3±100.3 x10E3/uL, P = .03), haptoglobin (68.8±116.1 vs. 166.8±95.4 mg/dL, P = .03), subepithelial deposits (P = .001), intramembranous deposits (P = .001), mesangial deposits (P = .009), lambda deposits (P = .015) and albumin deposits (P = .002). All TMA patients had negative Anti-DNA antibody titers. After a median follow up time of 53 weeks, renal prognosis in TMA patients was worse (P = .002). Among the TMA patients, 3 were dialysis dependent (37.5%), compared with none in class IV lupus nephritis patients. Mortality occurred in 2 TMA patients during the period of follow up.

Conclusions: Renal prognosis in TMA-associated SLE is worse than in class IV lupus nephritis. Laboratory findings can be suggestive, but renal biopsy remains superior for discrimination between the two groups.

PUB224

Renal Biopsy Performed to Diagnose Sarcoidosis but Diagnosed IgA Nephropathy: A Case Report

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Introduction: Renal disorder attributed to sarcoidosis generally causes tubulointerstitial damage. We herein report a case in which renal biopsy was performed for sarcoidosis diagnosis but was diagnosed as IgA nephropathy.

Case Description: We encountered a 69-year-old female with persistent proteinuria and hematuria. Her history included facial palsy and neurosarcoidosis diagnosed by bronchoscopy (CD4/CD8 ratio: 7.22) and CT findings (hilar lymph node swelling) 5 years prior to visiting our hospital. She was treated with prednisolone (PSL) 50 mg and her symptoms improved. PSL was gradually tapered and discontinued. She had no proteinuria and no hematuria 2 years previously (Cr 0.68 mg/dL). She was diagnosed with renal disorder (Cr 0.92 mg/dL, proteinuria 1+, hematuria 3+) 1 year previously, and she subsequently visited our hospital. CT showed lung hilar region lymph node swelling and multiple mottled shadows in the liver. Laboratory findings included the following results: ACE 36.5 U/ml, 1,25$(OH)_2$-vitamin D 67.4 pg/mL, soluble IL-2 receptor 2230 U/ml, proteinuria 0.46 g/day, and urine β-2 MG 9450 μg/L. We suspected recurrence of sarcoidosis and renal biopsy was performed for diagnosis. Mild to moderate increase of mesangial cells and matrix was observed in most glomeruli. Although tubulointerstitial injury was partially observed, epithelioid cell granuloma, which is characteristic of sarcoidosis, was not observed. IgA and C3 deposition in mesangial areas was observed in immunofluorescent analysis. Based on these findings, we diagnosed the patient with IgA nephropathy, not sarcoidosis, for the kidney lesion. Hepatic biopsy was then performed for definitive diagnosis, which showed epithelioid cell granulomas. The patient was finally diagnosed with sarcoidosis. She was subsequently treated with PSL 30 mg and her renal function and urinary findings improved.

Discussion: We experienced an interesting case that suggested IgA nephropathy diagnosed by renal biopsy and sarcoidosis diagnosed by liver biopsy. It is very rare for sarcoidosis to accompany IgA nephropathy. We speculate that IgA nephropathy occurred secondary to immune abnormality caused by sarcoidosis.

PUB225

Purtscher-Like Retinopathy: A Cue for Underlying Thrombotic Microangiopathy

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Introduction: Purtscher-like retinopathy (PLR) is a retinal disorder characterized by acute visual loss and retinal findings including cotton-wool spots and intraretinal hemorrhages. PLR is a rare ophthalmological manifestation of systemic thrombotic

microangiopathy (TMA). We describe a patient who presented to the hospital with PLR and was subsequently diagnosed as having atypical hemolytic uremic syndrome (aHUS) with multiple organ involvement.

Case Description: A 36-year-old woman presented with a sudden onset of blurred vision, marked dyspnea, and decreased urine output. Vital signs were stable on admission. Fundoscopy revealed multiple bilateral peripapillary yellow-white patches like cotton wool spots, intraretinal hemorrhages, and macular edema suggestive of PLR. She was found to have worsening anemia (Hb 6.8 gm/dl), thrombocytopenia (platelet count 40,000/mm^3), and oliguric acute kidney injury (serum creatinine 8.3 mg/dl; unknown baseline renal function). Other pertinent labs included elevated LDH levels (1074 U/L), undetectable haptoglobin levels, normal coagulation profile, elevated D-Dimer (4303 ng/ml), and decreased fibrinogen levels (136 mg/dl). C3 levels were low (85 mg/dl), with normal C4 and CH50 levels. Autoimmune and infectious serologies were unremarkable. Serum vitamin B12 level was normal (628 pg/ml). A peripheral smear demonstrated numerous schistocytes. Stool shiga-toxin testing was negative. ADAMTS13 levels were normal (68%). Genetic testing panel for aHUS was unremarkable. A renal biopsy demonstrated TMA without segmental sclerosis, fibrinoid necrosis, karyorrhexis or crescents. No immune complex deposits were seen. She was treated with pulse dose steroids with slight improvement in her vision; and received 2 doses of Eculizumab. Renal function and hematological parameters failed to improve, and she was started on intermittent hemodialysis. Hospitalization was complicated by seizures secondary to posterior reversible encephalopathy syndrome because of systemic TMA. She later died owing to anoxic brain injury.

Discussion: aHUS is a subtype of TMA characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. It occurs owing to dysregulation of the alternative complement pathway leading to vascular endothelial damage. The presence of PLR should alert physicians to evaluate for an underlying TMA. Unfortunately, no effective treatment for PLR exists.

PUB226

Apol1 Non-Risk and Renal Risk Variants mRNAs Directly Interact with Vitamin D Receptor (VDR) Protein in Podocytes

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Background: The 3D structural bioinformatics approaches can provide useful insights into specific RNA recognition. The prediction of RNA structure helps understand the mapping of genotype (nucleotide sequence) and phenotype (secondary structure) in terms of computational modeling of evolutionary principles. RNAs adopt complex structures in the cellular environment, and RNA binding proteins bind to these complex secondary structures of the folded RNA and the exposed nucleic acid bases provide excellent recognition features for proteins and allow a much more vibrant ensemble for interactions.

Methods: The mRNA sequence of ApoL1 and its variants RNAs were retrieved by reverse transcribe and transcribing process, and the multiple sequence alignment (MSA) of mRNA sequences were performed by using R-COFFEE tool. The secondary and tertiary structures of ApoL1G0 and its variants ApoL1G1 and Apol1G2 were compared using mfold, RNAfold, RClick, and SETTER tools. After finding a VDR binding site in the ApoL1G0, G1 and G2 RNA tertiary structure, we docked VDR and PKR into the ApoL1G0, G1 and G2 RNA tertiary structures using NPDock tool that combines GRAMM program to perform a rigid body global search, ranking and scoring of best decoys using statistical potentials, clustering of best decoys and finally, a Monte Carlo Simulated Annealing procedure (with protein and nucleic acid molecules treated as rigid bodies) to optimize the protein-nucleic acid interactions in the representative clusters.

Results: The ApoL1G1 has two site-specific changes A1024G (Ser342Gly), and U1152G (Ile384Met) and the ApoL1G2 has deletions (A1162-U1167) of two codons AAC (N388) and UAU (Tyr389). These mutations correspond to the amino acid changes in ApoL1 variants ApoL1G1 and ApoL1G2 proteins. The ApoL1G0 RNA and VDR interaction are most robust in comparison to ApoL1G1 and G2 variants thermodynamically. However, in ApoL1G1 RNA-VDR complex, the number of essential hydrogen bonds are increased because of the mutated base G1152; as guanine substitution for an adenine increases essential hydrogen bonding interactions. However, ApoL1G2RNA and PKR complex formation is the most favored thermodynamically.

Conclusions: ApoL1 mRNA has a preference for protein binding and there may be a competition between VDR and Dicer or other miRISC complex protein.

Funding: NIDDK Support

PUB227

IgA Nephropathy: Role of Interleukin-17, a Novel Pilot Sequential Treatment

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Background: IgA Nephropathy (IgAN) is the most common glomerulonephritis; unfortunately, it is refractory(r-IgAN) to immunosuppressive and angiotensin aldosterone inhibitors in some cases. The new pathogenic data in particular interleukin-17(IL-17) opens a new field to explore more effective treatments. We design an MNL Therapy (multicytokine normalization levels therapy) to control sequentially the possible cells (Th1, Th17, Treg lymphocytes), cytokines (IL-17 inhibition) and liposomal actions involved in IgAN. **Objective:** To evaluate the efficacy of the sequential administration of the paricalcitol and secukinumab on the proteinuria and creatinine in patients with r-IgAN.

Methods: This is a trial pilot treatment report. Changes in proteinuria (24hours-collected), plasma creatinine and urine N-Acetyl-B-D-galactosaminidase (u-NAG) during 6 months of follow-up (induction phase: month 0 to1 and maintenance phase: month 2 to 6). Evolutions of the hematuria, peripheral blood Th17, Treg (% of CD4) cells were also evaluated.

Results: Four patients were included. As whole proteinuria decreased 28, 45 and 30% from baseline at month 1, 3 and 6 respectively, including one patient who increased proteinuria. Hematuria disappeared at month 3 in all patients. Creatinine did not change over time. Treg did not change, while Th17 decreased in all patients, showing a change in the Th17/Treg profile. The u-NAG increased in 3 patients during the induction phase y decreased in all during the maintenance phase.

Conclusions: The sequential MNL therapy seems to be effective in IgAN patients; this effect was associated with a change in the inflammatory and pro-inflammatory profile. The changes in u-NAG were associated with benefits in proteinuria, which suggest that the treatment influences lysosomes activity.

PUB228

The Efficacy and Safety of Bortezomib-Based Treatment in Patients with Monoclonal Gammopathy of Renal Significance: A Single-Center Case Series Study

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Background: Monoclonal gammopathy of renal significance (MGRS) is still an understudied disease. Bortezomib-based treatment has been shown to be effective in this population. However, the majority of relevant reports in China were single case reports. We presented our own experience on managing a series of MGRS patients by bortezomib-based treatment.

Methods: This retrospective study enrolled patients who had been diagnosed as MGRS and received bortezomib-based treatment in our division from January 2016 to January 2019. The diagnosis of MGRS was re-confirmed according to the updated International Kidney and Monoclonal Gammopathy Research Group consensus definition. Charts were retrospectively reviewed for demographic and clinical information. Serum creatinine and urinary protein were measured after each treatment to evaluate the renal outcome. Treatment-associated adverse events were also recorded. The outcomes were descriptively summarized individually.

Results: Nine patients (male/female=7/2) were included, with a median age of 68 (range, 49–73) years. All had been confirmed to have an abnormal plasma cell-originated pathologic clone by bone marrow flow cytometry. Median treatment duration was 5 (range, 1–7) weeks. The overall response rate of 33.3% (3/9), including one case of complete response and two cases of partial response. There were three episodes of severe infection, leading to an incidence of 7.3% (3/41).

Conclusions: Bortezomib-based treatment achieved a renal response of 33.3% in the treated nine MGRS patients. Incidence of adverse events was 7.3%, all being infection. A tailored and clone-targeted approach would be the core of future management.

Funding: Government Support - Non-U.S.

PUB229

A Prescribed Chinese Traditional Medicine, Shen Ping Decoction, Inhibits Multiple Protein Kinases Activated by PDGF in Human Mesangial Cells

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Background: A prescribed Chinese traditional medicine, Shen Ping decoction (SP), has been used in China to treat IgA nephropathy (IgAN) successfully for decades, reducing proteinuria and hematuria. Our previous work showed that SP inhibits mesangial-cell (MC) proliferation, phosphorylation of PDGFR-β, Axl and ERK1/2, induced by PDGF or pathogenic IgA1-containing immune complexes. Furthermore, SP inhibited phosphorylation of EGFR induced by angiotensin II. In this study, we used kinomic profiling to assess the effects of SP on tyrosine kinases in MC.

Methods: Primary human MCs were stimulated with 10 ng/ml PDGF for 15 min in the presence or absence of SP. Cell lysates were harvested and subjected to array-based profiling of protein-kinase activities against ~144 phosphorylatable peptide targets. These targets were mapped to upstream kinases that were then overlaid on network models.

Results: Global protein-tyrosine kinome profiling revealed that PDGF activated multiple kinases. Top 10 activated kinases were fms, RYK, Lyn, Flt3, TRKB, PDGFR, Txk, CCk4/PTK7, Ret, and Flt4. SP inhibited activation of multiple kinases that were induced by PDGF. Top 10 of those inhibited kinases were PDGFR-β, Ron, PDGFR, Flt4, Hck, ITK, RYK, CTK, Lmr1, and JAK1. Network-model analysis suggested that these kinases are mainly involved in signaling of PDGF/PDGFR pathway through STAT and NF-κB, cytoskeleton remodeling, TGF-β-mediated cellular proliferation, TGF-β-mediated transactivation of membrane receptor signaling, and MAPK-mediated cellular proliferation.

Conclusions: The inhibitory effects of the Chinese traditional medicine SP on multiple tyrosine-kinase activities activated by PDGF may provide a mechanistic explanation for SP activities in IgAN. Future studies are needed to identify active compounds in SP and then test them as targeted therapy of IgAN.

Funding: NIDDK Support, Private Foundation Support

PUB230

Production of Human Podocyte PLA2R Protein with Application of Anti-PLA2R ELISA in Patients with Membranous Nephropathy

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Background: Anti-phospholipase A2 receptor (PLA2R) autoantibodies could be found in 60~85% patients with idiopathic membranous nephropathy. It's believed that these autoantibodies attacking on the auto-antigens, membrane-form PLA2R upon the podocyte, form immune complex and then cause podocyte damage. To investigate the entities of these autoantibodies, we conduct a study to manufacture the recombinant human PLA2R protein with extracellular domain (soluble-form PLA2R).

Methods: The cDNA of extracellular PLA2R was cloned into specified vector, then transfected into Freestyle 293 system. After expression, protein is undergone purification with affinity chromatography. Recombinant protein was examined by Western blot, SDS-Page to confirm the protein properties. Finally, these recombinant proteins would be used as coating protein to detect plasma anti-PLA2R autoantibodies which are confirmed by commercial ELISA-kit (Euroimmune).

Results: According to the Western blot and SDS-Page, the recombinant proteins have accurate molecule weight. Recombinant human PLA2R protein can be used to detect plasma anti-PLA2R autoantibodies. Comparing to commercial ELISA-kit, the titers trends of autoantibodies are highly correlated (r=0.89).

Conclusions: We successfully manufactures recombinant human PLA2R protein. Entities of the protein was carefully examined. This recombinant protein could be applied as in-house anti-PLA2R ELSIA assay. Furthermore, the recombinant protein could help us to investigate the feature of anti-PLA2R autoantibodies from patient's sample in further studies.

PUB231

The Role of Secretary IgA in the Pathogenesis of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most frequent primary glomerulonephritis, characterized by glomerular deposition of IgA-containing immune complexes (IC). Dysregulation of mucosal immune system is recognized as a major cause of development of IgAN. Secretary IgA (SIgA), which is the dominant in external mucosal secretions, is characterized as the 'first line defense' of mucosal areas. Previous reports have shown that the serum level of SIgA is elevated in Dutch IgAN patients, and higher serum SIgA is associated with creatinine clearance and proteinuria. In addition, mesangial deposits of SIgA were detected in about 15% of IgAN patients, and observed a colocalization with IgA, MBL, and C4d. Currently, a strong evidence has demonstrated that galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1-containing IC are essential effector molecules in IgAN. In present study, we analyzed the association of SIgA and Gd-IgA1 in the pathogenesis of IgAN.

Methods: We measured serum SIgA in patients with IgAN (n=37), disease controls (n=5) and healthy controls (n=5) by ELISA. The associations between serum level of SIgA and serum Gd-IgA1, urine Gd-IgA1 and IgG-IgA IC in Japanese patients with IgAN were investigated. We also analyzed correlation between serum level of SIgA and clinical parameters (total serum IgA, eGFR, degree of hematuria and proteinuria) as well as the pathological findings (acute and chronic lesions).

Results: Serum levels of SIgA were not significantly different between patients with IgAN (2.443±0.81), disease controls (2.125±0.48) and healthy controls (2.318±0.74). There were no significant associations between serum level of SIgA and Gd-IgA1 or IgG-IgA1 immune complexes. Moreover, serum SIgA did not correlate with any clinical parameters and pathological phenotypes.

Conclusions: Serum level of SIgA was not elevated in Japanese patients with IgAN. Moreover, serum level of SIgA did not correlate with Gd-IgA1 and disease severity of IgAN. Thus, it is suggested that SIgA is not involved in the pathogenesis of IgAN.

Funding: Government Support - Non-U.S.

PUB232

The Pharmacogenomic Association of FCGR2B-232I/T with Response to Treatment in Lupus Nephritis

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Background: To determine FcγRIIB-I232T polymorphisms is relation to susceptibility, activityand treatment response to lupus nephritis (LN) of Chinese.

Methods: FcγRIIB-I232T genotype was determined by sequencing in LNpatients and 196healthy individuals from China. The disease activity index was calculated using theACR SLE Disease Activity Index (SLEDAI) and pathologicclassificationswere according toInternational Societyof Nephrology/Renal Pathology Society 2003 classification. Theassociationof FcγRIIB-I232Tpolymorphismwiththesusceptibility and activityin LNwere analyzed by Chi-square test. The correlations of FcγRIIB-I232Tpoly morphismwiththecompleteremission at 6 months were analyzed by logistic regression.

Results: The CC genotype wasassociated withincreased occurrence of LN(P=0. 022, odds ratio [OR] 2. 388 [95% confidence interval (95%CI) 1.111-5.132]. LN patients homozygous FcgRIIB-I232TCC variant showedhigherSLEDAI-2K (p = 0. 035), indicated by higher incidence of thrombocytopenia (p=0. 03), anemia (p=0. 02) and Class IV+V(p<0. 005), higher AI index (p=0. 042), lower level of C3 (p=0. 011). As toremission status between CC genotype and TT/CT genotype, the non-responder with CC genotype were much more than TT/CT genotype (p=0. 025, OR=3. 295, 95%CI 1.198-9.061). The patients who used the IV CYC therapy with CC genotype was more difficult to remiss (p= 0. 012, OR=19, 95%CI1.198-9.061).

Conclusions: The FcgRIIB-I232T polymorphism associated with susceptibility to lupus nephritis. Additionally, LN patients homozygous for FcgRIIB-I232T show more severe clinical manifestations. The finding that the homozygous FcgRIIB-I232T CC genotype was associated with non-complete response in the LN patients, especially the IV CYC therapy, implies that FcgRIIB-I232Tmay be broadly involved in disease pathogenesis and response to therapy.

PUB233

Clinical and Pathological Features and Renal Outcomes of Lupus Nephritis in Elderly Patients

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Background: Lupus nephritis (LN) is one of the most common and severe complications of systemic lupus erythematosus (SLE). Renal involvement is the second cause of death in patients with SLE. There are many risk factors associated with poor renal outcome, however, it has not been defined exclusivity. The retrospective analysis is to describe the clinical and pathological characteristics and renal outcomes of LN in elderly patients.

Methods: The clinical features of patients with LN from Jan 1,2012 to Dec 31,2017 in Center of Kidney Disease of 2nd Affiliated Hospital, Nanjing Medical University were collected and analyzed. SLE patients without renal biopsy were excluded. All LN patients were pathologically classified according to the 2003 International Society of Nephrology/ Renal Pathological Society (ISN/RPS) classification system.

Results: Among the 34 patients with biopsy-proven lupus nephritis, there were 32 (94%) females and 2 (6%) males, with an average onset age of (44.6±12.9) years old. Renal damage was the first symptom in 16(47%) patients and acute kidney injury (AKI) accured in 8(24%) patients. The incidence of blood system involvement, malar rash, pleurisy, arthritis and fever was 91%, 47%, 41%, 29% and 26% respectively. The highest positive rate of serum autoantibody was ANA(100%), and the following was Anti-Sm(59%) and Anti-dsDNA(53%). The incidence of low serum C3 was 91%. All patients were pathological classified based on ISN/RPS 2003 classification, only 4(12%) patients with class II and 1(3%) patient with class III, 29 (85%) patients with class IV, V, III+V or IV+V. 13(38%) patients with class IV, 3(9%) patients with class V, 5(15%) patients with class III+V and 8(23%) patients with class IV+V. These 34 patients with an average follow-up time of 1.2- 6 years (median duration was 4 years), 22 (64.7 %) patients were in completely remission, 9 (26.5%) patients were in partly remission, 3 (8.8%) patients relapsed.

Conclusions: The patients diagnosed with LN in our center have an older onset age. Proliferative lupus nephritis was the most common renal damage type in our center, and the renal outcome was favorable. In addition to the proven clinical risk factors and treatment regimens, compliance of patients and socioeconomic factors are also important factors affecting prognosis.

Funding: Government Support - Non-U.S.

PUB234

NSAID-Related Minimal Change Disease and Interstitial Nephritis with Tertiary Lymphoid Organ Formation

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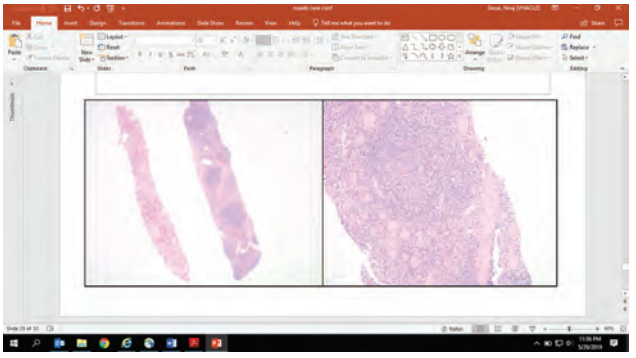
Introduction: Interstitial nephritis (AIN) and minimal change disease (MCD) are known complications of NSAID exposure. Intense inflammatory infiltrates occasionally lead to formation of tertiary lymphoid organs (TLOs) which are unencapsulated nodular aggregates consisting of a core of B-cells, surrounded by T-cells and neo-lymphatics. TLO's have been described in chronically rejected kidney allografts, IgA nephropathy and lupus nephritis. We report a case of TLO formation in NSAID induced AIN with MCD.

Case Description: A 69-year-old African American male was admitted with fatigue, anasarca and oliguria. Medical history was notable for remote right nephrectomy, prostate cancer, hypertension, and gout. The patient reported daily ibuprofen use (1200-1800mg/d) for 3 months prior to admission for shoulder pain. Admission blood work showed serum creatinine 11.4 mg/dL and serum albumin 1.8 g/dL. Urinalysis showed new 3+ proteinuria, 12 RBCs and 9 WBCs. A 24-hr urine collection measured 11.5 g protein. Serologic work up was negative. Renal ultrasound was normal. Kidney biopsy was performed. The histopathology sample revealed one core with normal glomeruli and mild focal interstitial infiltrate another core with near-total obliteration of renal architecture with a patchy dense lymphoid infiltrate with germinal centers separated by plasma cell rich infiltrate admixed with eosinophils. IF was negative. EM showed diffuse podocyte foot process effacement.

The patient was advised to avoid NSAIDS and was treated with oral prednisone 40mg/d for 6 weeks followed by a short taper. Serum creatinine improved to 1.3 mg/dL ('baseline') and proteinuria reduced to less than 30 mg/g following cessation of steroids.

Discussion: The above findings illustrate novel histopathology in NSAID induced nephrotoxicity and highlight the importance of chronic antigen stimulation in its pathogenesis. The functional significance of TLO's remains undefined, and it is unclear whether the presence of TLO's serve a pathologic or protective role.



PUB235

ANCA-Negative Necrotizing Crescentic Glomerulonephritis with C3 Deposits

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Introduction: Ten percent of pauci-immune and crescentic glomerulonephritis is ANCA-negative. Isolated C3 staining on immunofluorescence can be suggestive of C3 glomerulopathy or can be non-specific. Here we report a case of ANCA-negative crescentic and necrotizing glomerulonephritis with C3 staining which presented a diagnostic dilemma.

Case Description: A 27 year old white woman was referred for elevated creatinine detected incidentally on routine laboratory evaluation. She complained only of lower extremity edema. She had a history of birth weight of 3 pounds and prior tendon-release surgery as a child for cerebral palsy. History was otherwise unrevealing. Vital signs were normal except blood pressure 150/95 mmHg and body mass index 31 kg/m^2. Exam disclosed mild edema and was otherwise unremarkable. Laboratories revealed creatinine of 1.6 mg/dL rising from 1.4 mg/dL at initial evaluation 1 month prior. Mild anemia and leukocytosis were noted with normal platelets. Urinalysis showed 3+ protein 2+ blood. Dysmorphic RBCs and RBC casts were noted on urine sediment. Urine protein to creatinine ratio was 1. ANA, ANCAs, and anti-GBM serologies were negative. Complements were within normal limits. Blood cultures were negative. Ultrasound demonstrated normal bilateral kidneys. Kidney biopsy demostrated diffuse necrotizing and crescentic glomerulonephritis. 11 of 23 glomeruli were globally sclerotic and 8 of 12 remaining had densely cellular crescents. Immunofluoresence disclosed only 2+ granular mesangial C3. Pronase digestion did not unmask deposits. Moderate to severe interstitial inflammation was noted with moderate interstitial fibrosis with tubular atrophy. Electron microscopy failed to demonstrate deposits. The patient was started on pulse steroids and rituximab. She had a good response with creatinine stabilizing at 1.4 mg/dL and urine protein to creatinine ratio falling to 0.08 at 6 months. C3 functional panel was essentially normal with only mild hemolytic activity. Repeat biopsy at 6 months showed chronic changes with resolution of the dominant C3 staining. Repeat ANCA serologic testing was negative.

Discussion: The differential diagnosis included ANCA-negative renal vasculitis, C3 glomerulopathy, and infection-related glomerulonephritis. We excluded infection clinically and initiated empiric treatment promptly. Repeat biopsy and C3 functional panel were helpful in prioritizing the differenential diagnosis.

PUB236

Nonclinical Safety and PK/PD of BION-1301, a Fully Blocking Antibody Targeting A PRoliferation Inducing Ligand (APRIL) for the Treatment of IgA Nephropathy

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Background: IgA Nephropathy (IgAN) is a common form of glomerulonephritis and its pathogenesis is thought to consist of sequential pathogenic hits, including the critical production of galactose-deficient IgA1 (Gd-IgA1) and auto-antibody formation ultimately leading to immune complex deposition, inflammation and functional deterioration of the kidneys. Serum levels of APRIL (A PRoliferation Inducing Ligand, TNFSF13) and levels of Gd-IgA1 are correlated with severity of disease (Zhao et al, 2012). As a ligand for the receptors BCMA and TACI, APRIL is thought to regulate B cells and plasma cells. In nonclinical studies treatment with an anti-mouse APRIL antibody was reported to reduce serum IgA and halt proteinuria progression in the IgAN "grouped ddY" mouse model (Kim et al. 2015; Myette et al 2019). Here we describe the nonclinical safety assessment of BION-1301, a humanized anti-APRIL antibody, to support its clinical development for the treatment of IgA Nephropathy.

Methods: A 14wk repeat-dose safety and pharmacokinetic/pharmacodynamic (PK/PD) study in non-human primates (NHP) (Cynomolgus monkey) was performed by biweekly intravenous (i.v.) administration of BION-1301 at three different dose levels. To support a potential change in route of administration, a 4wk repeat-dose NHP bridging study was conducted with weekly subcutaneous (s.c.) administration of BION-1301 at three different dose levels.

Results: In both the 14wk i.v. study and the 4wk s.c. study, BION-1301 was evaluated for safety, PK and PD. For PK and PD, BION-1301 levels, uncomplexed APRIL levels and immunoglobulin levels (IgA, IgG, IgM) were quantified in serum. Immunophenotyping was performed on peripheral blood to assess the impact of BION-1301 on the B cell compartment.

Conclusions: Results of these extended nonclinical pharmacology and toxicology experiments add to the BION1301 safety, PK, PD assessments reported earlier (Dulos et al, ASN 2018) and inform the ongoing clinical program to develop BION1301 for the treatment of IgAN.

Funding: Commercial Support - Aduro Biotech Inc.

PUB237

The Deposition of Immunoglobulin A on the Glomerular Loop Correlates with Severity Both Clinically and Pathologically in a Patient with IgA Vasculitis with Nephritis

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Background: Immunoglobulin A vasculitis with nephritis (IgAVN) is considered to be systemic form of IgA nephropathy (IgAN). Both IgAN and IgAVN are defined by the presence of IgA dominant glomerular deposits. However, the pathological significance of the difference in glomerular location of IgA and other immunogrobulin deposits is remain unclear. In this study, we focused on the deposition of IgA on the glomerular loop and investigated.

Methods: We conducted a retrospective study of 37 adult patients of biopsy-proven IgAVN. We divided 37 IgAVN patient into two group: IgA deposition on the glomerular loop group (n = 11) and non-IgA deposition on the glomerular loop group (n = 26). We compared in terms of clinicopathological feature and renal prognosis in each group.

Results: 37 adults IgAVN patients (male:22, female:15) were analyzed. IgA deposit on the glomerular loop group of 11 patients. The onset age of IgAVN was predominantly higher in IgA deposition on the glomerular loop group. (48.2±17.9 vs 35.6±14.9) The average proteinuria was 3.39±2.57 g/day in the IgA deposition on glomerular loop group and 1.43 ±1.56 g/day in non-IgA deposition on glomerular loop group. (P=0.0036) In histrogical findings, there were many cases of crescent formation predominantly in the IgA deposition on glomerular loop group. (P = 0.039) There was no significant difference in eGFR value at the time of renal biopsy. (eGFR: 69.8±25.6 vs 82.7±25.2 P = 0.082) Renal function was predominantly worse in the IgA deposition on glomerular loop group in half a year after treatment. (eGFR: 49.5±16.9 vs 83.9±23.2 P = 0.0004) Hwever, there was no significant difference between the two groups in the initial dose of steroid and in combination with steroid pulse.

Conclusions: We have clearly shown that deposition of IgA on the glomerular loop correlates with severity both clinically and pathologically. These results suggested that these deposition may play a key role in the pathogenesis of IgAVN, and also suggested that the selection of therapy for IgAVN might be affected.

PUB238

Nephrotic Syndrome in the Elderly: Not Always What It Seems

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Introduction: Polypharmacy is defined simply as the use of multiple medications by a patient. Older adults are especially impacted by polypharmacy. The use of greater numbers of drug therapies has been independently associated with an increased risk for an adverse drug event (ADE).

Case Description: An 83-year-old man from Puerto Rico with hypertension, gout, benign prostate hypertrophy and chronic kidney disease, presented to the ED after progressive shortness of breath and bilateral leg edema for two weeks. As outpatient, he had more than 7 prescribed medications. He was found with generalized edema, hypoalbuminemia with associated shortness of breath, bibasilar crackles on auscultation, and scrotal swelling. On chest x-ray bilateral pleural effusions were noted. 24-hour urine collection revealed 6,439 mg of proteinuria. Volume status responded to IV diuretic therapy. PSA, SPEP, UPEP, immunofixation, serum free light chains, C3/C4, hepatitis profile and ANCA titers all were negative. There was no imminent need for dialysis. Kidney biopsy revealed diffuse interstitial infiltrate with numerous invading eosinophils, tubulitis without immune deposits or crescents identified. Acute interstitial nephritis (AIN) with concurrent glomerulopathy was diagnosed. Due to a gout flare, our patient had been prescribed Nabumetone 500 mg PO twice daily for one month prior to hospitalization by his primary care provider. As more than seven days had passed after initial presentation and the offending agent was discontinued, IV steroids were not started. Creatinine decreased to 2.5 from 4.0 mg/dL, and proteinuria improved. NSAIDs were added to his allergy medication list. He was discharged home without dialysis with follow-up as outpatient.

Discussion: On initial presentation, membranous nephropathy secondary to malignancy was suspected to be the cause of our patient's symptoms given his age and presence of nephrotic syndrome. However, AIN with concurrent minimal change disease was diagnosed on biopsy. AIN is not frequently associated with the nephrotic syndrome. Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause AIN with concurrent

nephrotic syndrome due to minimal change disease or membranous nephropathy. Given the increased use of medications in the elderly and risk for an ADE, it is of upmost important to be vigilant of the possible side effects of NSAIDs in this population.

PUB239

Eosinophilic Granulomatosis with Polyangiitis Renal Disease

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Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotizing vasculitis affecting small to medium sized vessels, characteristically associated with asthma and eosinophilia[1,4]. EGPA renal disease is prevalent in approximately 25%.[2] Presentation includes focal and segmental necrotizing crescentric glomerulonephritis (NCGN),[1,3] eosinophilic interstitial infiltrates[4] or obstructive uropathy caused by vasculitic involvement of the ureters. The aim of our study is to analyse the prevalence, clinical manifestations and outcomes of EGPA patients with renal involvement.

Methods: We retrospectively analysed 142 patients with EGPA according to the criteria of the American College of Rheumatology or Chapel Hill Consensus 2012 definition. We selected patients with renal involvement defined by the presence of (A) Renal insufficiency serum creatinine (SCr) > 97 umol/L, or (B) haematuria and/or proteinuria (>1+ in urinalysis) or (C) obstructive uropathy.

Results: Of eleven (7.74%) patients with renal involvement, three presented with rapidly progressive kidney injury with SCr >290umol/L, 6 with SCr greater than >117umol/L and two had normal SCr [44-97umol/l]. Renal biopsy performed in 6 patients, demonstrated 3 NCGN, 2 had both NCGN and tubulointerstitial nephritis (TIN) with eosinophil infiltrates, and 1 had TIN with eosinophil infiltrates alone. All the patients with NCGN were ANCA positive, while the patient with TIN alone was ANCA negative. 2 patients had obstructive uropathy due to ureteric stenoses.

Conclusions: At the end of follow up 2 patients were renal transplant recipients, 5 had chronic kidney disease (CKD) and 4 maintained normal kidney function. Although renal involvement in EGPA is less frequent than in others AAV, it must be taken into account due to its potential to lead to end-stage renal failure. ANCA positive patients may present with NCGN leading to CKD. Furthermore, ANCA negative patients, may have manifestations such as TIN with eosinophil infiltrates or obstructive uropathy.

Patient No.	Sex	Age	sSCr (umol/L)	ACR (mg/umol)	Prot	Haem	ANCA	Renal biopsy/ Imaging	Treatment	SCr and outcome	Follow-up (years)
1	M	60	164	37.4	+	-	-	TIN	Pd+Cy	131	8.8
2	F	63	130	20.2	+	+	MPO	NCGN Focal + TIN	Pd+Cy+RTX+AZA	Renal transplant	10.5
3	M	70	85	12.9	+	+	MPO	NCGN Focal	Pd+Cy+RTX+AZA	86	7.6
4	F	65	450		+	+	MPO	NCGN	Pd+AZA	189	6.3
5	M	56	293	69.3	+	+	MPO	NCGN Crescentic + TIN	Pd+Cy+RTX+PLEX	184	0.5
6	M	56	300	62.8			PR3		Pd+RTX+MMF	Renal transplant	6.2
7	F	53	149	1.0	-	-	-	Not biopsy	Pd+Cy	148	33.7
8	M	65	138	40.5	+	+	MPO	Not biopsy	Pd+Cy+MMF	90	7.2
9	M	50	81	1.2	+	+	-	Not biopsy	Pd+MMF	75	1.4
10	M	39	138	0.5	+	+	MPO	Ureteric stenosis	Pd+RTX+AZA	93	17.1
11	M	65	117		-	-	-	Ureteric stenosis	Pd+MTX	100	19.6

Table 1: Renal Involvement in EGPA EGPA eosinophilic granulomatosis with polyangiitis, SCr serum creatinine, ACR albumin creatinine ratio, Prot protein dipstick, Haem haematuria in dipstick, TIN tubulointerstitial nephritis, NCGN necrotizing crescenteric glomerulonephritis, Pd prednisolone, Cy cyclophosphamide, RTX rituximab, AZA azathioprine, MMF mycophenolate mofetil, MTX methotrexate, PLEX plasma exchange.

PUB240

Clinical and Pathological Manifestations of ANCA-Associated Vasculitis Superimposed on Rheumatoid Arthritis

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Background: Patients with rheumatoid arthritis can have renal disorders, most of which are mild. However, ANCA-associated vasculitis may be superimposed on rheumatoid arthritis, with severe organ damage, especially renal failure. We try to investigate characteristics of ANCA associated vasculitis combined with rheumatoid arthritis

Methods: Patients with concurrent rheumatoid arthritis (RA) and ANCA associated vasculitis (AAV) were identified by searching medical database of the Peking Union Medical College Hospital and literature from January 2000 to December 2018. We excluded patients exposed to TNF-α inhibitors. Data on age, sex, involved organs, laboratory tests,renal pathology at the diagnosis of AAV, and therapeutic regimens of both RA and AAV were retrospectively retrieved and analyzed. To further explore whether there was any difference in clinical features and renal pathology between AAV patients with and without concurrent RA, we conducted a 1:4 matched case-control study. 36 controls were matched to 9 cases having renal pathology according to age and sex.

Results: 15 patients in our hospital and 27 patients from literature with concurrent RA and AAV were identified. They were 54 ± 17 years old at the diagnosis of AAV, and 29 (69.0%) of them were women. AAV was diagnosed 6(2,12)years later than RA. Kidney was the most frequently involved(80.9%). Those with renal involvement had an average baseline serum creatinine of 290 (148, 471) umol/L. Patients with RA were more likely to have AAV proved by renal biopsy than those without RA(15.0% vs 1.5%, p<0.001) AAV patients with concurrent RA were more likely to be asymptomatic(33.3% vs 2.8%, P=0.021)and presented lower eGFR [23.9±15.5 vs 34.3±24.3 ml/min/(1.73 m^2), p=0.049] at diagnosis as compared with those with AAV alone. However, the two groups did not differ in in the percentage of global sclerotic and cellular crescentic glomeruli (global sclerotic glomeruli 37.0±23.5% vs 26.9±24.0%,p=0.26,cellular crescentic glomeruli 23.1±18.7% vs 34.0±18.4%,p=0.11).

Conclusions: AAV was more frequent in patients with RA than those without RA. AAV superimposed on RA were more likely to be asymptomatic and with worse renal function.

PUB241

Use of Rituximab in Fibrillary Glomerulonephritis

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Introduction: Fibrillary glomerulonephritis (GN) is a rare glomerular disease characterized by glomerular deposition of randomly arranged non-amyloid fibrils. The prognosis of fibrillary GN is poor, with up to 50% of patients progressing to end-stage renal disease within 2 years of diagnosis. The optimal treatment is unknown. Two cases with fibrillary glomerulonephritis are presented who were treated with Rituximab with different outcomes.

Case Description: Patient 1 is a 72 years old male with 9 g proteinuria and biopsy proven fibrillary GN. He received 4 doses of weekly IV Rituximab 375 mg/m2 with subsequent reduction in proteinuria to 1.2 g. Two years later, proteinuria increased to 5 g. Due to a concern for recurrence, patient was given 2 doses of IV Rituximab 1 g each, separated by 2 weeks. Renal function since then, has remained stable on 6 month follow up with a serum creatinine around 1.8 mg/dl, while proteinuria decreased to 1.4 g. Patient 2 is a 68 years old female with 3.6 g proteinuria and biopsy proven fibrillary GN. Serum creatinine on diagnosis was 2.0 mg/dl. She received 2 doses of IV Rituximab 1 g each, separated by 2 weeks. Six months later proteinuria worsened to 4.6 g and she progressed to end stage renal disease. No evidence of monoclonal gammopathy was noted in either patient. Both patients received intravenous corticosteroids as premedication with Rituximab along with Losartan 100 mg daily.

Discussion: Due to the rare nature of this disease, no controlled trials have been conducted. Steroids and different cytotoxic drugs have been used in fibrillary GN without any proven benefit. Rituximab, a monoclonal anti-CD20 antibody directed against B cells has been used as a treatment due to the characteristic presence of polyclonal immunoglobulin deposits in the mesangium and glomerular basement membrane. There are reports that B-cell reconstitution with subsequent reappearance of detectable CD19+ cells may be responsible for relapse in fibrillary GN. Data on Rituximab therapy for fibrillary GN is limited and outcomes have been inconsistent. However, it provides an option to consider as untreated fibrillary GN will most likely result in progression of disease. More data is needed to prove its efficacy in this disease, and to assess the need to consider Rituximab administration as soon as CD19+ cells become detectable, despite the absence of clinically evident relapse.

PUB242

A Rare Case of AKI due to Thrombotic Microangiopathy (TMA) in Multicentric Castleman Disease (MCD)

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Introduction: Castleman disease (CD) are rare lymphoproliferative disorders either unicentric (UCD) or diffuse multicentric (MCD). MCD features include diffuse lymphadenopathy (LAD), hepatosplenomegaly, anemia and systemic inflammatory symptoms. Approximately 1/2 are HIV + and 2/3rd HHV-8 +. Histological variants include hyaline vascular (HV), plasma- cell (PC) and plasmablastic (PB). Systemic lupus erythematosus (SLE), Hashimoto's thyroiditis, IGG4 related disease, viral infections and chronic cellulitis mimic MCD. AKI due to glomerulonephritis, amyloidosis, and interstitial nephritis have been reported. We report a patient with MCD who presented with proteinuria, microscopic hematuria and elevated serum creatinine caused by thrombotic microangiopathy (TMA).

Case Description: A previously healthy 26-year-old female from Ghana presented with 2 weeks history of progressive abdominal distention, fatigue, cough and intermittent epistaxis. Exam noted multifocal lymphadenopathy and hepatomegaly with tense ascites. Elevated acute phase reactants (CRP 201), anemia (Hgb 9.9 and few schistocytes), thrombocytopenia (platelets 68k), AKI (peak serum creatinine 2.1), lymphocytic ascites, hypoalbuminemia (albumin 2.7) and hypergammaglobulinemia suggested multisystem inflammation. Urine protein to creatinine ratio 1.1, few RBCs and WBCs in urine microscopy. Positive ANA, SS-A, coombs, D dimers. HIV and HHV-8 negative. DsDNA and complements normal range. ADAMTS 13 at 64. Vascular endothelial growth factor (VEGF) and interleukin 6 (IL-6) were elevated. Cervical LN biopsy showed interfollicular plasmacytosis. Renal biopsy showed no immune complex deposits but TMA. Patient responded to Siltuximab (anti-interleukin 6) and is in remission.

Discussion: SLE mimicking MCD was ruled out. Increased serum IL-6 has been noted in number of diseases characterized by renal TMA. IL-6 induces B-cell proliferation and expression of VEGF (Increased circulatory VEGF but down regulation of glomerular VEGF). IL-6 reportedly modulates release and cleavage of von Willebrand factor multimers. Inclusion of IL-6 and VEGF immunohistochemical stains would increase diagnostic accuracy. Blockade of IL-6 and IL-6R signaling could be curative provided the right diagnosis is made.

PUB243

Infection and Glomerular Disease: The Patient and Caregiver Perspective

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Background: Individuals with glomerular disease (GD) comprise ~7% of the ~30 million Americans with chronic kidney disease. Both GD and immunosuppressive (IS) treatment place these patients at increased risk for infection. Patient and caregiver perspectives on the impact of infection on quality of life and vaccination behavior have not been previously described. Herein we present results from an electronic survey of the membership of NephCure Kidney International (NKI), a GD focused patient and family support network.

Methods: A 22 question web-based survey comprised of 20 close-ended and 2 open-ended questions was sent to members of NKI in the Fall of 2019. The survey was promoted with two social media posts and within an NKI newsletter. Quantitative and qualitative analyses were performed.

Results: We received 262 responses from 3171 e-mail invitations (response rate 8.3%). Fifty four percent (n=139) of responses were from parents of children with GD < 18 years of age and 46% of responses (n=123) were received from adult GD patients. The majority of respondents (95%) reported prior IS exposure, including steroids (95%), calcineurin inhibitors (76%), MMF (41%), rituximab (26%), and cyclophosphamide (19%). The majority of parental respondents (65%) and nearly half of adult respondents (45%) reported being very concerned about acquiring an infection. Since diagnosis, 56% of parents and 47% of adults with GD reported ≥ 2 emergency room visits or hospitalizations for treatment of infection. The majority of respondents (58%) reported more frequent infections since GD diagnosis, and 44% reported more infections while taking IS medications. Respondents reported that infections resulted in frequent interruption in social activities (29%), exercise (25%), and attending school (33%) or work (20%). Flu vaccination during the 2018-2019 season was reported by 76% of parental respondents and 64% of adult GD patients. Reasons for not receiving the flu vaccination included fear of reaction/relapse, perceived contraindication due to IS medications, and perceived provider recommendation.

Conclusions: Individuals with GD and their caregivers are concerned about infections, report frequent infection-related healthcare visits and interruption in activities. Infection remains a preventable and under-studied complication of GD deserving of additional study.

PUB244

Sequential Therapy for Remission Induction in Severe ANCA-Associated Glomerulonephritis

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Background: The introduction of combination therapy with glucocorticoids (GC) and cyclophosphamide (CYC) or rituximab (RTX) has resulted in remission rates exceeding 90% in patients with ANCA associated vasculitis (AAV). However, early treatment related mortality remains a major concern and has driven the search for safer induction regimens exploring minimization or avoidance of GC and CYC. Most trials have excluded patients with severe renal disease. We report the outcomes of AAV patients with severe renal disease treated with sequential therapy (ST) starting with GC and oral CYC followed by transition to RTX.

Methods: Patients with new or relapsing severe AAV who presented with severe renal disease and/or RPGN were identified. RPGN was defined as at least a 20% decrease in e-GFR over a 2 week period along with hematuria and proteinuria. Induction treatment included pulse GC for 3 days followed by oral prednisone tapered to 5 mg by month 6, oral CYC adjusted for GFR until improvement in BVAS and serum creatinine at which point, CYC was stopped and induction dose of RTX was given. Use of Plasma Exchange PLEX was allowed. The primary outcome was complete remission defined as BVAS of zero by 6 months (6M). Descriptive data are presented as median with range and mean with SD.

Results: Nine patients met the inclusion criteria. Median age at diagnosis was 63 years. Majority were females, MPO ANCA positive and had a new diagnosis. The mean nadir (SD) e-GFR was 12 (5) with 3 requiring dialysis. Median BVAS at the time of diagnosis was 15. All patients received (ST) and 3 received PLEX. Median exposure to oral CYC was 35 days. The mean (SD) e-GFR and median BVAS were 26(12) and 3 respectively at the time of switching to RTX. The median prednisone dose at 6 months was 5 mg. The median follow up was 44 months. All patients achieved remission. One patient reached ESRD. The mean (SD) e-GFR in the remaining 8 patients at last FU was 37(27) and the mean (SD) e-GFR rise at 1 year was 26(25). Adverse events included 2 patients with pneumonia and 3 with bone marrow suppression. There were no deaths.

Conclusions: Sequential therapy with GC and CYC followed by RTX is effective for in AAV patients with severe renal disease. Therapy related adverse events comparable to other studies and further modification in ST with decrease in GC dosage should be explored.

PUB245

Multicenter Review of Types of Glomerular Diseases in the Emirate of Abu Dhabi: Six Years of Experience

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Background: Glomerulonephritis (GN) is a rising paramount renal disease that varies in etiology from inherited or acquired factors. Its severity can range from asymptomatic depictions to end stage kidney disease (ESKD). The aim of this study was to look at the patterns of biopsy-proven glomerulonephritis based on data from a multicenters in Abu Dhabi.

Methods: This study is a retrospective a cross sectional study. Included kidney biopsy were from all patients above the age of 18 years, over a six-year period from 2010 till 2015, who had diagnosis of glomerular disease other than diabetes mellitus. The number of reviewed biopsies was 416.

Results: The most common type of glomerulonephritis among the study sample were the IGA GN (22.8) followed by the FSGS (20.4%) followed by the SLE (19.7%). The least common types were Pauci Immune (1.7) There was female preponderance in lupus nephritis and pauci immune GN. The nationality comparison did not reveal a predominate GN among Emirati nationals. The age relationship to GN types showed that the majority (82.9%) of SLE patients, MCD (74.55 %) and non- categorized (71.4%) patients are young between the age of 18 to 39 years. On the other hand, 57.1%, 25% and 16.7% of patients with Pauci immune, other GN types and MPGN respectively are 60 years and older.

Conclusions: This study shows the histopathological variety of glomerular disease in Abu Dhabi. It could be a driving point to help understand GN better in the region.

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PUB246

Incidence and Risk Factors of Serious Infections in ANCA-Associated Vasculitis with Renal Involvement

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Background: Infection is one of the most commonly encountered problems in patients with ANCA-associated vasculitis (AAV) and contributes significantly in morbidity and mortality. We investigated the incidence, time, type and risk factors for serious infections and compared the incidence of non-prophylaxis with prophylaxis with trimethoprim–sulfamethoxazole in patients with AAV.

Methods: Retrospective, descriptive study of 21 patients with AAV and renal involvement diagnosed over the last five years in a tertiary center. Data on age, sex, disease and treatment characteristics and the type of serious infections were collected. Serious infections were defined as infectious episodes requiring hospitalization.

Results: Of the 21 patients the average age of diagnosis was 71.6 years (SD 10.9) and 43% were women. A total of 17 serious infections were identified in 11 patients during a median follow-up of 2.6 years (incidence: 19.6 per 100 patient-years). Pneumonia (47%) and urinary tract infections (18%) were the most frequent types of infection. More than half of the infections (65%) were recorded during induction treatment (Rituximab (RTX), Cyclophosphamide (CYC) or combination treatment CYC+RTX) and the remaining of them (35%) during the maintenance treatment (RTX or Mycophenolate Mofetil (MMF)). The majority of patients (76%, 16/21) received prophylaxis with trimethoprim–sulfamethoxazole. Among those who developed a serious infection (11/21) the induction treatment with combination CYC+RTX (36% vs 0%, p=0.03), hemodialysis/plasma exchange (63% vs 40%, p=0.3) and lung involvement (82% vs 70%, p=0.5) were more common. Additionally, this group of patients received less induction treatment with RTX (9% vs 50%, p=0.04) and prophylaxis with trimethoprim–sulfamethoxazole (45% vs 100%, p=0.01). Finally, one patient died due to gram-negative sepsis.

Conclusions: One in two patients with AAV and renal involvement experienced at least one serious infection during follow-up, with more frequent infections of the respiratory and urinary tract. The incidence of serious infection is particularly high during the first six months, and combination induction treatment (CYC+RTX) and the failure of prophylaxis with trimethoprim sulfamethoxazole are identified as risk factors.

PUB247

Proteinuria Could Not Be a Surrogate Prognostic Marker in IgA Nephropathy

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Background: To date the most widely well studied risk factor for progression to ESRD in patients with IgA nephropathy is proteinuria. Recent report suggests proteinuria reduction as a surrogate end point in trial of IgA nephropathy(2019,CJASN). Sensitivity of most biomarkers such as blood and urine gd-IgA1 level, IgG/IgA autoantibody, sCD89, sCD71, NGAL, KIM-1, Cystatin-C etc were compared with the amount of proteinuria. Most nephrologists do not performing kidney biopsy in patients without proteinuria or proteinuria less than than 500mg/day even though IgA nephropathy is suspected. However we recently experienced severe IgA nephropathy (HSD Lee, grade IV) in patients with normal urinalysis, and more than half the patients showed stationary or aggravated renal pathology at the follow up renal biopsy although urinalysis findings were normalized after methylprednisolone pulse therapy.

Methods: In our center we performed 892 renal biopsies during last 6 years, we experienced 253 IgA nephropathy, of which 152 cases were done follow up renal biopsies to see the pathologic changes who showed normalized urinalysis findings after methylprednisolone pulse therapy.

Results: Of the 253 patients 241 patients showed initial abnormal urinalysis like hematuria and or proteinuria. Eleven patients showed completely normal urinalysis, of which 5 cases were diagnosed as essential hypertension and 6 cases were normal urinalysis associated with lowered GFR. Of the 152 follow up renal biopsies we evaluated 99 cases who showed normalized urinalysis findings after therapy, of which 65 cases(65.7%) showed stationary or aggravated renal pathology.

Conclusions: In conclusion further long term studies are needed, proteinuria could not be a surrogate marker for prognosis of the IgA nephropathy, Regardless of proteinuria if associated with hypertension and or lowered GFR, renal biopsy should be done. Follow up renal biopsy might be needed to confirm the healing of IgA nephropathy regardless of urinary findings to see the disappearance of IgA deposition, decreasing mesangial and endocapillary hypercellularity, disappearance of crescent formation, decreasing sclerosis, etc.

PUB248

Long-Term Treatment with ACE-I/ARBs in Childhood Mild IgA Nephropathy

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Background: ACE-I/ARBs have been widely used for treatment of IgA nephropathy (IgAN), however, there is no study showing outcome of long-term ACE-I/ARBs treatments in IgAN children with persistent mild proteinuria.

Methods: Out of 59 biopsy-proven mild (focal mesangial proliferation) IgAN children with ACE-I/ARBs from November 2000 to August 2018, retrospective data from 55 patients were available, and we compared clinical and pathological findings between patients with completed ACE-I/ARBs treatments and the others.

Results: There were 28 patients (50.9%) with completed ACE-I/ARBs treatment. Other 27 patients had been on treatments till the latest observation. Median observation periods to the latest observation was 8.7 [4.7-10.9] and 6.2 [1.8-12.3] years (completed vs non-completed) respectively. There was no significant difference in onset mode, clinical finings at renal biopsy (sex, age, duration from onset to renal biopsy, uP/Cr, eGFR), and pathological findings (MEST-C score). All patients in completed treatment group showed the disappearance of proteinuria (uP/Cr〈0.15 g/gCr) and hematuria (RBC〈5HPF). Median periods from the start of treatment to disappearance of proteinuria and hematuria were 3.6M and 12M in completed treatment group. At the latest observation, there was significant differences in mean blood pressure (91 vs 85 mmHg, p=0.03), eGFR (125.8 vs 119.9 ml/min/1.73m^2, p=0.04), uP/Cr (0.07 vs 0.24 g/gCr, p=0.04). Median duration of ACE-I/ARBs was 26.2M vs 74.6M and 4 patients in non-completed group showed CKD-G2A3 which were high risk of progression despite of subsequent additional immunosuppressive treatments.

Conclusions: We should pay careful attention to long-term treatment with ACE-I/ARBs for the childhood mild IgAN patients even if they show persistent mild proteinuria. Optimal timing of switch from ACE-I/ARBs to immunosuppressive treatments should be further investigated.

PUB249

Efficacy and Safety of the Combined Induction Therapy with Rituximab and Low Steroid Doses in Glomerulonephritis

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Background: Proteinuria and acute renal dysfunctions are the main objectives for glomerulonephritis control. The autoimmune component of the primary glomerulonephritis (PG) is steadily assuming. The efficacy of the Rituximab and the low steroids doses (combined therapy: CT) in these diseases is not well known. Moreover, if there are differences in the effect of the CT among PG and secondary glomerulonephritis (SG) has not been evaluated. Objectives: Primary outcome: To evaluate the risk of death and or chronic renal replacement requirements (CRRT). Secondary outcome: the changes in the proteinuria [median(p25-p75), 24-hours collected) and estimated glomerular filtration rate (eGFR) (mean) during 24 months of follow-up. Potential differences between PG and SG were also assessed. Lethal infection was recorded as safety issue.

Methods: A retrospective study in a third level hospital was conducted. Rituximab (1g every two weeks for two doses) and methylprednisolone 120-250 mg/d X3d and subsequently, prednisone 30 mg/d was tapered and discontinued at month 3. Study period: From May 2008 to November 2018. eGRF was calculated using the CKD-EPI formula.

Results: Forty-four consecutive patients were included. PG: 14(32%) and SG: 30(68%). Median follow-up 44 months. 10(23%) patients died or needed CRRT. No differences in the primary outcome were observed between PG and SG (3 versus 7 patients, respectively P = 1). As a whole, eGFR increased from basal to month 12 (8.6 ml/min/1.73m2, P<0.01) and decreased from month 12 to 24 (4.8 mil/min/1.73m2, P<0.01); no differences between PG and SG were observed. Proteinuria decreased from basal to month 24 at the PG [from 4.0 (2.7-6.1g/d) to 0.21(0-1.7g/d), P<0.01] and at SG [from 1.4(0.3-4.1) to 0.45(0-0.6), P<0.01]. Six patients died, two of them (4.5%) due to a fatal infection and corresponded to SG.

Conclusions: The CT showed was efficacy without differences between the two glomerulonephritis types, which may represent a new therapeutic option in those patients. Fatal infections were seen in the secondary glomerulonephritis group.

PUB250

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposition Disease: Our Experience

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Background: PGNMID is a rare disease affecting the native kidneys and transplanted kidneys. Here we present four cases of PGNMID that illustrate the challenges of diagnostic approach and highlight the allograft outcome after treatment with BORTEZOMIB

Methods: Patients with allograft biopsy showing PGNMID were included. In post transplant patients, their native kidney biopsy was reevaluated to determine the recurrence vs de novo nature of the disease. Patients were subjected to bone marrow aspiration, biopsy, SPEP, UPEP and immunofixation electrophoresis to identify the clone

Results: 1.20-year-old male presented with anasarca. he had nephrotic range proteinuria with micro haematuria. Renal biopsy showed PGNMID with Kappa chain restriction with MPGN pattern with focal crescents. He is being treated with subcutaneous Bortezomib. He has completed 12 doses of Bortezomib and is in partial remission. 2 : 26-year-old female, hypertensive presented with anasarca. On evaluation she had nephrotic syndrome with normal renal functions. Renal biopsy showed PGNMID with kappa light chain restriction with focal crescents with Mesangioproliferative pattern. Treated with 10 doses of Bortezomib after which she was lost to follow up 3. DDRAT with native kidney disease being immune complex mediated MPGN presented with edema after 7 months of transplant. Allograft biopsy showed PGNMID with Kappa chain restriction with MPGN pattern with focal crescents. However the clone could not be identified on bone marrow, SPEP, immunofixation electrophoresis. She is being treated with subcutaneous Bortezomib and is in complete remission after 25 doses. 4:LRRAT with native kidney disease being immune complex mediated GN with HBsAg positive status presented with hematuria 2 months post transplant. Allograft biopsy showed PGNMID with kappa chain restriction with MPGN pattern with focal crescents with ACMR. Treated with Bortezomib and steroids. However he had an aggressive disease course and had graft loss in 2 months and is currently Dialysis dependent

Conclusions: MPGN is a pattern of injury with varying causes. The most aggressive being plasma cell dyscrasias. This study shows the varying presentation and response of the same disease in 4 patients. a high degree of suspicion is required especially during transplant workup of patients with MPGN pattern on biopsy and all possible attempts should be made to rule out plasma cell dyscrasias.

PUB251

ANCA-Associated Crescentic Glomerulonephritis Can Be Concurrent with Another Immune Complex-Medicated Glomerulopathy: One Health Center Experience

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Background: Autoimmune disorders are known to trigger multiple systemic diseases. There are relatively few reports for a potential overlapping syndrome including ANCA associated crescentic glomerulonephritis (CGN) and another type of immune complex disease (ICD) in the kidneys. Here we present our experience for concurrent diseases between ANCA associated CGN and other ICD from a 4000-bed large health system (8 hospitals) over the past 10 years.

Methods: We evaluated our data base for 3757 renal biopsies over the past 10 years (2008 to 2018) and identified 13 cases with dual diagnoses of CGN and another ICD. Their clinical data were collected and pathologic findings are evaluated in detail.

Results: The concurrent cases represented 0.35% of our overall biopsies (13/3757). Patients' age ranged from 48 to 76 years old. There were 8 female patients and 5 male patients. All 13 patients had positive ANCA and CGN. Crescent percentage in the biopsies ranged from 10% to 78%. The other ICD included many types including membranoproliferative glomerulonephritis type 1 (MPGN, n = 5), post-infectious glomerulonephritis (n = 2), membranous glomerulopathy (n =1), mesangial glomerulonephritis (n = 1), type 3 lupus nephritis (n = 1), type 2 lupus nephritis (n = 1), IgA nephropathy (n = 1), and MPGN type 3 (MPGN, n = 1). Most of the ICD appeared to be mild, except one type 3 lupus nephritis debatable for primary or secondary crescent formation.

Conclusions: The crescent formation appeared to be dominant in most cases, leading us to believe that the crescent formation was mainly related to positive ANCA rather than minor ICD in most cases. Our findings support previous reports that there is a rare entity of overlapping syndrome composed of ANCA associated CGN and another ICD. Follow-up and analysis will be done to compare to the cases with only ANCA associated CGN for their clinical outcomes.

PUB252

Membranous Lupus Nephritis Wearing the Mask of Minimal Change Disease: A Case for Caution

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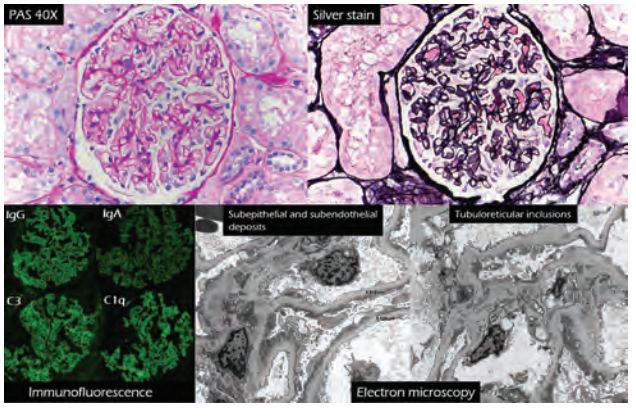
Introduction: Rarely, patients with systemic lupus erythematosus may present with lupus nephritis (LN) alone and have no extra-renal manifestations. We herein present one such case with other atypical features on serology and renal biopsy.

Case Description: A 24-year-old otherwise healthy Hispanic man presented with worsening shortness of breath and swelling in the feet. Laboratory data was consistent with nephrotic syndrome with a serum albumin of 0.8 g/ dL [3.2-5], LDL-cholesterol 452 mg/dL [20-129] and 24-hour urine protein of 8.7 g. Serum creatinine was normal. There was no history of rash or joint pains. Serologic work up for syphilis and viral hepatitis was negative. Antinuclear antibody test was positive (1:80) but anti-double stranded antibody and anti-smith antibody were negative. Serum complements were normal. A renal biopsy was obtained and the light microscopy (LM) was unremarkable suggestive of minimal change disease. He was started on steroid therapy and later immunofluorescence (IF) was reported as 'full house' pattern and electron microscopy (EM) showed subepithelial, mesangial and subendothelial deposits in addition to tubuloreticular inclusions consistent with membranous LN [Figure]. The patient was started on Mycophenolate mofetil therapy.

Discussion: Our case represents atypical presentation of SLE in a young male with isolated renal involvement and without anti-double stranded DNA or anti-smith antibodies. It also highlights the importance of obtaining renal biopsy and more importantly, the utility of IF and EM. The management of minimal change disease, as suggested by LM alone in our patient differs significantly from membranous LN. While standard in developed countries, nephrologists in several resource-poor countries have to pick patients who need these advanced microscopic studies. If EM cannot be performed routinely in all cases, a small portion of renal tissue should be saved in an appropriate fixative, to perform at a later date if needed.



PUB253

Clinical Implication of Fractional Excretion of Proteins: Albumin, A1-Globulin, A2-Globulin, B-Globulin, G-Globulin in Patients with Nephrotic Syndrome

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Background: Diagnostic approach on underling disease of nephrotic syndrome is a very important process in management of nephrotic syndrome. Besides traditional kidney biopsy and serologic tests, a few novel diagnostic approaches have been tried in this study.

Methods: 42 adult nephrotic patients, biopsy-confirmed with membranous glomerulonephritis (MGN) (n=30) and minimal change disease (MCD) (n=12) at Hallym University Medical Center from 2012 to 2016, were included. With those patients, fractional excretion (FE) of proteins (albumin, a1-globulin, a2-globulin, b-globulin, g-globulin) was retrospectively calculated from data of urine electrophoresis (UEP) and serum electrophoresis (SEP), which had been examined mainly to identify if there was monoclonal gammopathy or polyclonal gammopathy in the patients. Creatinine concentrations of serum and urine to calculate FE of each protein were from data of the same urine and serum samples for UEP and SEP examinations. Patients with serum creatinine > 1.2mg/dL and serum albumin > 3.0g/dL were excluded. To assess diagnostic performance of FE of the proteins, we used receiver-operating characteristic (ROC) analysis.

Results: There was not significant difference in age and serum creatinine levels between the two groups. Mean albumin levels were lower in MCD group than in MGN group (1.38 vs. 2.03, $p < 0.001$). FE of albumin (p=0.021) and g-globulin (p=0.023) was significantly higher in MCD group than in MGN group. However, differences in FE of a1-globulin (p=0.062), a2-globulin (p=0.466) and b-globulin (p=0.129) between the two groups were not significant. Areas under the ROC curve for FE of albumin and g-globulin were 0.770 (95% CI 0.602-0.938 p=0.007) and 0.741 (95% CI 0.578-0.904, p = 0.016), respectively. A FE of albumin > 0.202 could distinguish MCD from MGN with 75% sensitivity and 79.3% specificity. FE of g-globulin > 0.029 also could do with 75% sensitivity and 51.7 % specificity.

Conclusions: Authors, for the first time, tried FE of albumin, a1-globulin, a2-globulin, g-globulin as a tool to predict diagnosis of underlying causes of nephrotic syndrome. This method can be used as a helpful assistant method to make differential diagnosis on MGN and MCD in nephrotic patients with normal renal function.

PUB254

Relapse of Nephrotic Syndrome After Adrenocorticotropic Hormone Induced Remission: Implications of ACTH Antibodies

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Background: Treatment of relapsing nephrotic syndrome is challenging despite newer immunosuppressive medications. Prolonged glucocorticoid use is the mainstay in management of proteinuric glomerulopathies but has extensive side effects. Alternatives like adrenocorticotrophic hormone (ACTH) have been successfully used to treat refractory glomerulopathies with superior outcomes compared to steroids. However, clinical responsiveness to ACTH therapy may vary, partly due to the development of de novo or acquired resistance.

Methods: A 25-year-old woman with steroid-dependent FSGS developed severe steroid side effects impacting her quality of life. ACTH monotherapy with biweekly subcutaneous injections of repository corticotropin of porcine origin was started. Immediate remission of proteinuria & reversal of steroid side effects was noted followed by a relapse of proteinuria & swelling in 10 weeks. In suspicion of ACTH-antagonizing factors, the patient's serum was collected & processed for Immunoblot-based antibody assay.

Results: Standard porcine ACTH was subjected to immunoblot analysis by incubating the blots with a rabbit anti-ACTH antibody as a positive control or with the patient's serum. The blots were developed using an anti-rabbit or anti-human IgG secondary antibody. Blots were probed by normal standard human serum & no bands demonstrated (control). Immunoblots developed by using patient's serum revealed abundant IgG antibodies reactive to a peptide band also probed by the anti-ACTH positive control antibody, suggesting the presence of high titers of anti-ACTH antibodies. ACTH antibodies were not associated with any clinical signs of hypoadrenocorticism, or other side effects except a delayed-onset resistance to ACTH therapy, entailing that these antibodies are likely specific for porcine ACTH & have negligible cross-reactivity with the patient's native ACTH.

Conclusions: ACTH is valuable in treatment of refractory proteinuric glomerulopathies. However, as is common with treatment with any biologic medication, natural ACTH, regardless of purity & origin, is antigenic in humans. It may cause formation of neutralizing antibodies in some sensitive patients, ensued by acquired resistance to ACTH. Our findings stress the need to develop ACTH analogs with less immunogenicity for improving its responsiveness in patients with glomerular diseases.

PUB255

Analysis of Clinical and Pathological Features of Renal Injury in Primary and Secondary Malignance Hypertension

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Background: To understand different clinical and pathological features of renal injury among primary and secondary malignance hypertension (MHT) patients.

Methods: 143 cases of MHT patients with complete clinical and pathological records in the past 19 years were selected and analysis was performed respectively. Clinical variables including serum creatinine, urinary analysis. Renal pathological evaluation including the stenosis of small renal artery which was expressed as the ratio of inner and outer diameter of the small artery, ischemic glomerulus of kidney (including shrinkage and sclerosis), global sclerosis of glomerulus, the ratio of crescent to whole glomerulus, interstitial infiltration of inflammation cells, the area of renal interstitial fibrosis and renal tubular atrophy.

Results: Here were 50 cases of primary MHT, 42 male, 8 female, average age was 36±9; there were 93 cases of renal parenchyma related MHT male 74 and female19, average age was 34±8 (no significant difference of sex and age between two groups). 1. clinical features: etiological distribution among renal parenchyma related MHT showed 73 (77.4%) cases were IgA nephropathy. Compared with primary MHT, the amount of proteinuria in the renal parenchyma related MHT group was significant higher. (1.41±1.90 VS 3.32±2.48g/d, P<0.01), 2. pathological features: the typical pathological character in renal parenchyma related MHT was hypertrophy of endomysium which was described as "onionskin" like proliferation. Compared with primary MHT group, this feature was significantly lower in renal parenchyma related MHT group (100% VS 38.0%,P<0.01). renal small artery stenosis in renal parenchyma related MHT group was lower (the ratio of inner and outer diameter of small artery was 0.25±0.07 VS 0.44±0.08, P<0.05),ischemia changes was fewer (81±13% and 42±23%,P<0.01),higher prevalence of glomerular global sclerosis (0.6±2.1% and 16.4±17.5%,P<0.001), higher prevalence of crescent formation((2.3±1.2% and 9.5±13.4%,P<0.001).

Conclusions: Renal parenchyma diseases are common etiology of MHT, especially among IgA nephropathy (about three-forth among this group of patients). Compared with primary MHT, the renal parenchyma related MHT always appears as more proteinuria, pathological feature is characterized by more crescent formation, less "onionskin" like proliferation, less stenosis in renal tubular, less ischemia glumeruli.

PUB256

Case of ANCA-Associated Crescentic Glomerulonephritis in a Stone Cutter with Early Pulmonary Silicosis

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Introduction: Report a case presenting with AKI that is found to be due to ANCA associated Crescentic Glomerulonephritis in a patient with class II Lupus nephritis. The ANCA vasculitis is associated in this case with pulmonary silicosis in a patient who works as a stone cutter.

Case Description: 48 yo male from from Honduras who has been in the US for 20 years presented to our hospital with cc of cough for 2 months productive of sputum. He had no significant PMHX. He worked as a stone cutter. In the ED he had CXR without acute pulmonary disease but labs show BUN of 44, Creatinine of 3.87, urinalysis showed positive protein and 47 RBC, 5 WBC. Urine albumin to creatinine ratio was 4.6 grams. PPD placed resulted as positive, subsequently patient placed in respiratory isolation to rule out TB with sputum collection. CT of chest non contrast showed patchy perilymphatic pulmonary micronodules and subtle peribronchiolar wall thickening and ground glass opacities. Per pulmonary service findings consistent with Silicosis. Cytology from bronchial lavage showed numerous alveolar macrophages with hemosiderin pigments. Serology was positive for ANA Speckled titer 1:2560 and Autoantibodies to myeloperoxidase (MPO) 152.8 AI. Complements were normal and dsDNA was negaitive. Patient's Renal Biopsy showed " Active crescentic GN with 75% involvement consistent with ANCA-associated Vasculitis, however underlying glomeruli display a "full house" pattern of IF staining and EM displays numerous mesangial with segmental sub epi and sub endo deposits with tubuloreticular inclusion c/w class II with segmental membranous features. Patient was initiated on RIPE therapy while undergoing the TB workup per ID consult and was given Okay to start immunosuppression with IV Cytoxan. At 4 months s/p 3 doses of IV Cytoxan, patient's BUN 27, creatinine 1.89 and UPC of 3 grams. Eventually patient was off RIPE therapy once cultures were finalized as Mycobacterium Fortuitum.

Discussion: Pulmonary Silicosis has been seen in stone workers. There are cases showing association of Silicosis with ANCA Vasculitis. Silicosis patients are at increased risk of pulmonary TB. Given positive PPD patient was initiated on RIPE therapy especially since Renal biopsy showed Crescentic GN that needed Cytoxan therapy until final cultures resulted in about 2 months and showed only Mycobacterium Fortuitum.

PUB257

Causes of Primary Nephrotic Syndrome in Adults Stratified by Race: An Update

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Background: It has been recognized that the incidence of glomerular diseases varies based on race. Membranous glomerulopathy (MGN) has been classically the most common cause of primary nephrotic syndrome (NS) in adults but data from the 1990s showed that focal glomerulosclerosis (FSGS) was increasingly common, especially in black and Hispanic populations. In fact, FSGS appeared to surpass MGN to become the most common cause of NS in these racial groups, and some suggested this may be the case for whites as well. We undertook this study to look at the racial breakdown of NS in the 2000s from our biopsy population. We also carefully excluded patients with evidence of secondary disease and without full NS, which has not always been done in prior reports.

Methods: We reviewed all renal biopsies from the Northwell database, available from 2017-2018 (n=532) and from Lenox Hill Hospital specifically from 2010- 2016 (n=143). We extracted all cases of nephrotic syndrome and then excluded cases with secondary disease. Charts were reviewed for clinical data including race.

Results: Overall, there were 97 cases of primary NS including 39.2 % MGN, 29 % minimal change disease (MCD), 16.5 % FSGS, 11.3% IgA nephropathy (IgAN), and 4 % membranoproliferative (MPGN). In the primary NS population, overall there were 43 whites, 21 blacks, 16 Asians, 10 Hispanics, and 9 multiracial patients. Among whites, MGN was the most common cause of NS 40.5%, followed by MCD 31%, IgAN 14%, FSGS 9.5% and MPGN 5%. For blacks, FSGS was the most common cause with 37 %, followed by MGN 32%, MCD 21 %, MPGN 5% and IgAN 5%. Among Asians, both MGN and MCD were seen in 41 %, FSGS 12% and MPGN 6%. In Hispanic patients, MGN was found in 40%, IgAN 30%, FSGS 20 % and MCD 10%. Among the 38 cases of primary MGN, 22 were positive for PLA2R antibody on biopsy, which represents 58%. Of the 16 cases of FSGS, 31.3 % were classic FSGS, 37.4 % had tip lesion, and 31.3 % were collapsing.

Conclusions: This study updates the racial distribution of primary nephrotic syndrome. We found that MGN continues to be the most common cause of primary NS overall in our population. Unlike previous reports, FSGS is a relatively uncommon cause of NS in whites (less than MCD and IgAN). In blacks, FSGS remains the most common form of NS, supporting previous reports from the 1990s suggesting a marked increase in this population.

PUB258

Glomerular Diseases Epidemiology in the Wayú of the Colombian Caribbean Region

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Background: he Wayú is one of the 102 indigenous towns that are found in Colombia, corresponds to 45% of La Guajira population. Despite this, is one of the 18 that are in danger of disappearing. This is due to the violence, displacement and extreme poverty experience by Wayú people, as well as a notable lack of access to health services. The objective was to characterize the glomerular diseases, primary and secondary in the Wayú community in the Colombian Caribbean region that are in the Nephropathy Colombian Register - NefroRed.

Methods: A descriptive and retrospective study was carried out in the Caribbean Colombian region. All the patients belonged to the Wayú Ethnic group, adults with Glomerular diseases. Those who had a renal biopsy with a diagnosis of GD between January 2008 and June 2018. All the patients were evaluated under clinical indications in a reference hospital. The histopathological findings by optical microscopy and immunofluorescence were correlated with the patients clinical history.

Results: A total of 48 renal biopsies were analyzed. The main clinical indication for the biopsy was nephritic syndrome (36%). The secondary (SGD) were more frequent than the primary (PGD), 55% versus 45%. For PGD, the lupus nephritis was the most frequent etiology (83%) and the main nephrological syndrome was nephritic syndrome (36%). Membranous nephropathy (33%) and segmental focal glomerulosclerosis (19%) were the SGD most frequents and the nephritic syndrome (22%) was the main biopsy indication.

Conclusions: The GD epidemiology revealed a predominance of SGD due to the relative high frequency of lupus nephritis in this population. Since the NEFRORED® establishment, the data collected in this document are relevant to obtain a better understanding of GD in Latin America, which improves the early reference of patients to clinical care and the usefulness of a database for future studies.

PUB259

Online Thai Glomerular Disease Registry: Paraprotein-Related Kidney Diseases

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Background: Paraproteinemic-Related Kidney Disease (PRK) are the group of kidney diseases derived from the deposition of paraproteins or monoclonal immunoglobulins in the kidney, which are associated with the immunoproliferative disorder and non-proliferative monoclonal gammopathy. Amyloidosis and monoclonal Ig deposit diseases (MIDD) including light chain deposit disease (LCDD), and heavy chain deposit disease (HCDD) are the frequent glomerular involvement and lead to end stage renal disease approximately 20-60% within 1 year. Our study aimed to demonstrate the PKD in Thai Glomerular Disease Registry.

Methods: We conducted a prospective cohort study in the adults' native kidney biopsy proven glomerular diseases between July 2014 and April 2019. The clinical and laboratory parameters at the time of biopsy, pathologic findings, treatment regimens and clinical outcomes of amyloidosis and MIDD were recorded via on-line registry.

Results: We found the prevalence of amyloidosis and MIDD was 0.85% (18 amyloidosis, 3 LCDD, and 1 HCDD from 2,585 patients). The male to female ratio was 1.2:1. The average age, creatinine, albumin, globulin, and UPCR were 64 (39-86) years, 1.6 (0.6-7.2) mg/dL, 2.4±0.8 g/dL, and 3.1±0.6 mg/dL, and 5.55 (1.6-11.97) g/day. The average K/L ratio in amyloidosis and LCDD were 0.33(0.03-19.54) and 15.79(0.78-30.8), whereas in HCDD was 46.78. The patients presented with 77.3% of nephrotic syndrome, 9.1% of nephrotic nephritis, 4.5% of nephritis, 4.5% of asymptomatic proteinuria and 45.5% of initial Cr≥1.2 mg/dL. Median time to biopsy was 15.1 weeks (3-56.5 weeks). We found 7 multiple myeloma and 2 MGUS in our group. Only 2 cases had amyloid heart disease. Steroid with the chemotherapy were prescribed in 16 patients and 1 case followed by autologous stem cell transplantation. During of the median time follow up 11.5 months, we found remission in 4 cases (3-velcade based regimen, 1-ASCT), ESRD in 1 case(no chemotherapy), and dead in 5 cases after chemotherapy. The cause of dead was infection in 4 cases, and found dead probably from amyloid heart in 1 case.

Conclusions: Our study described the rare disease including amyloidosis and MIDD, but high mortality was found in this group. Most of the patients presented with initial high creatinine and time to biopsy was quite delay. The high mortality rate from infections reminded us to reconsider the effective and safety regimen.

PUB260

TAFRO Syndrome with Initial Presentation of Renal Thrombotic Microangiopathy: Cases Series of One Medical Center in Taiwan

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Background: Castleman disease is one kind of benign lymphoproliferative disorder, with specific histopathologic feature of lymph nodes. According to the involved area, it could be divided in to uni-centric and multi-centric form. Multi-centric Castleman disease frequently have systemic manifestation, including to several subtypes such as TAFRO syndrome and idiopathic plasmacytic lymphadenopathy (IPL). All kinds of Castleman's disease would have renal manifestation. According to the literatures, renal thrombotic microangiopathy are frequently found in these patients. To date, there are few articles reporting renal manifestation of Castleman disease in Taiwan. We conduct a study to investigate the renal manifestation of Castleman disease.

Methods: This investigation was performed in a tertiary hospital. From 2000-2018 period, there are totally 125 patients receiving lymph node biopsy confirmed as Castleman's disease. After review of medical records, there are 3 patients with definite diagnosis of TAFRO syndrome. All of these 3 patients have renal manifestations of hypertension, sub-nephrotic proteinuria and microscopic hematuria. 2 of these patients received renal biopsy.

Results: Case 1 is one 25-year-old male with initial presentation of fever, anasarca, thrombocytopenia, hepatosplenomegaly, multiple lymphadenopathy and acute glomerulonephritis. The histopathologic feature of lymph node biopsy is hyaline vascular type. Renal biopsy revealed feature of thrombotic microangiopathy. Case 2 is one 63-year-old male with initial presentation of anasarca, thrombocytopenia, hepatomegaly, multiple lymphadenopathy and acute glomerulonephritis. The histopathologic feature of lymph node biopsy is plasma cell type. Renal biopsy also revealed feature of thrombotic microangiopathy.

Conclusions: Renal involvement is frequently found in multicentric Castleman disease. We reported 2 cases of TAFRO syndrome with initial presentation of renal thrombotic microangiopathy. Further research is still needed to investigate the pathogenic mechanism.

PUB261

FOrMe: The German Focal Segmental Glomerulosclerosis and Minimal Change Disease Registry

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Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are leading causes of nephrotic syndrome and associated with a relevant risk for the development of chronic renal insufficiency and end-stage renal failure. Incidences and prevalences vary significantly among Western countries. Within the German population, both MCD with an incidence of 3.2 per million population and FSGS with an incidence of 11.2, both entities are classified as rare diseases. There is a lack of systematic, large-scale, randomized intervention studies.

Methods: Within the framework of the DFG-funded Clinical Research Unit CRU 329 "Molecular Mechanisms of Podocytic Diseases - Nephrology on the Way to Precision Medicine", the FOrMe registry (The German Focal Segmental Glomerulosclerosis and Minimal Change Disease Registry) has been established as a nation-wide registry for pediatric and adult patients. It aims to collect 150 pediatric and 350 adult MCD and FSGS cases within the next 10 years. Within the registry, laboratory and clinical anamnestic parameters are linked with histopathological findings. Clinical data is collected systematically at inclusion and throughout the course of disease. Biological patient samples such as urine, serum, RNA, DNA, and tissue biopsy material are conserved and cataloged within the BioMaSOTA biobank already established at the University of Cologne, Germany.

Results: Registry structures have been established successfully. Patient acquisition and inclusion in the registry is ongoing since April 2019 at the University Hospital of Cologne. Additional centers are going to be initiated in the near future.

Conclusions: The FOrMe registry is recruiting since April 2019. As the central and largest German MCD / FSGS registry it will enable a translational approach to reconfirm the results of basic molecular research using precisely characterized human biomaterials and to develop new diagnostic and therapeutic approaches in the long-term.

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PUB262

How Lupus Glomerulonephritis Affects Renal Reserve?

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Background: Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE), which has different manifestations such as urinalysis alterations, nephrotic syndrome, nephritic syndrome, rapidly progressive renal failure and evolution to end-stage chronic renal disease. Renal reserve (RR) is the kidney's ability to increase its basal glomerular filtration rate (GFR) by at least 20% after a protein overload. As far as we know there is no previous report regarding how acute lupus glomerulonephritis and its treatment affect RR. Thus, we decided to evaluate the RR in three young women suffering from a recently diagnosed lupus glomerulonephritis, and then we reevaluated their RR after they were treated with immunosuppressant drugs.

Methods: RR test consisted of obtaining two consecutive fast minuted-creatinine clearances (basal GFR) after an adequate patient's oral hydration (15 cc/Kg of tap water). Then, a high protein meal based on dairy products (1.2 g/Kg of protein) was delivered, and seventy minutes later, three successive minuted-creatinine clearances were measured. Finally, the difference between the higher post-prandial creatinine clearance (pick value) and the average between the two pre-prandial creatinine clearances (basal value) was obtained.

Results: RR was abolished (RR:0%) in the LN patients without treatment, while it was positive (RR≥ 20%), borderline (RR ≥ 5%) or negative (RR:< 5%), depending on their prescribed treatment: patient 1 and patient 2 were treated with double immunosuppressant treatment during 12 and 6 months, respectively; while patients 3 was treated only with methylprednisolone during 6 months.

Conclusions: It seems that acute lupus glomerulonephritis abolished the patient's renal reserve, which can be recovered by prescribing double immunosuppressant therapy.

PUB263

Urinary Sodium Is Associated with the Degree of Proteinuria in Patients with CKD

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Background: Increased urinary sodium excretion, representing dietary sodium intake, is associated with hypertension. Low sodium intake has been associated with increased mortality in observational studies. Sodium and fluid retention is a hallmark and a challenge of the nephrotic syndrome (NS). This study aimed to evaluate the association between 24-hour urinary sodium and protein excretion in patients with chronic kidney disease.

Methods: We enrolled 1,142 patients with chronic kidney disease in Jiangsu Proince Hospital from May 1,2017 to May 1,2019. 24-hour urinary sodium and potassium was measured. In this group, Spearman correlation and partial correlation analysis were used to study the correlation between 24-hour urinary sodium and 24-hour proteinuria. We performed multivariate linear regression models, taking several covariates into account, including baseline eGFR and proteinuria.

Results: In our study, 24hour urine protein ranged from 17mg to 42003mg. 24hour urine sodium ranged from 3.5 to 569mmol. 24-hour urinary sodium was positively correlated with 24-hour proteinuria(r=0.102, P=0.001). Additionally, 24-hour urinary sodium was positively correlated with 24-hour urinary creatinine(r=0.354, P<0.0001). After adjusting the age, sex, BMI, eGFR, 24-hour urinary sodium was also positively correlated with 24-hour proteinuria.(Fig1a,b)

Conclusions: We found that in patients with CKD,24-hour urinary sodium positively associated with protein excretion, these data support high urinary sodium associate with marginal renal function, but whether the change of 24-hour urinary sodium as time goes by correlate with the progression of CKD is required to study.

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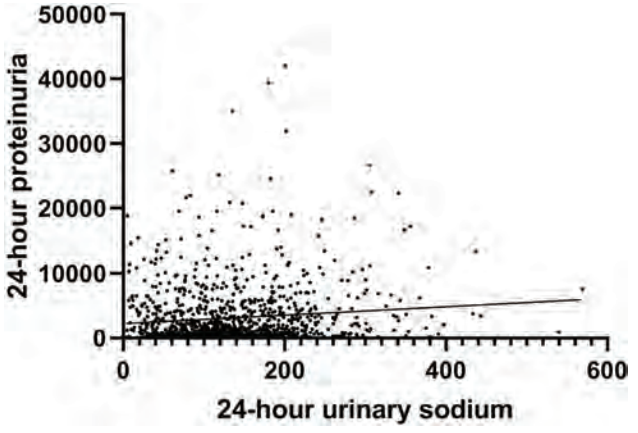

Fig1a

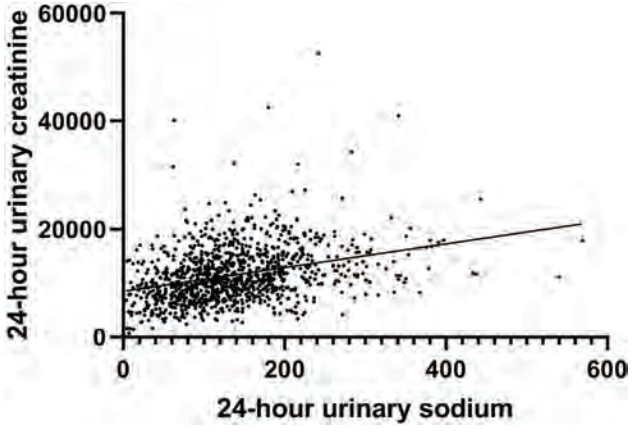

Fig1b

PUB264

Mepolizumab Therapy in Eosinophilic Granulomatosis with Polyangiitis as a Steroid-Sparing Therapeutic Approach

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Background: Eosinophilic granulomatosis with polyangiitis [EGPA] is characterised by the presence of tissue eosinophilia, necrotising vasculitis and granulomatous inflammation[1,2] which can lead to renal failure. In the recent trial, Mepolizumab (MEPO) In Relapsing or Refractory EGPA [MIRRA], treatment with the monoclonal antibody directed against IL-5 (300mg), accrued longer times in remission, reduced steroid exposure and relapse rates.[1,2] Identifying disease phenotypes such as organ involvement or the phasic stages of the disease, along with assessment of efficacy of 100mg would further guide the role of anti-IL5 therapy.

Methods: This retrospective, descriptive study analysed 8 patients with EGPA according to the American College of Rheumatology criteria or Chapel Hill Consensus 2012 definition. The aim of our study was to analyse the response and outcome for EGPA patients who received 100mg s/c of MEPO monthly for 52 weeks. Time points of commencement of MEPO and week 48-52 assessments were compared.

Results: MEPO was well tolerated and considered of clinical benefit, with seven/eight patients [87.5%] continuing therapy beyond 12 months, whilst on 100mg dosage. Four patients had prior therapy with rituximab and five had adjuvant conventional therapy. Seven had lower steroid therapy.

Conclusions: The study supports the efficacy of the steroids sparing capacity of anti-IL-5 therapy for treatment of EGPA. Adjuvant therapy with conventional immunosuppressants was well tolerated and renal function was preserved. REFERENCES 1. Wechsler ME et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. NEJM. 2017;1921-32. 2. Steinfeld J et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. JACI. 2018.

Table 1: EGPA patients receiving Mepolizumab therapy for one year [100mg s/c]

Demographics	All [n=8]	
Gender ratio M/F	3M:5F	
ANCA positive/ negative	2 ANCA:MPO positive/ 6 ANCA negative	
Age of diagnosis of asthma	35.5 yrs [IQR 34.25-37.75]	
Age of diagnosis of EGPA	46.5 yrs [IQR 42.5-51.25]	
Median age	50.5yrs [IQR 46.5- 55.5]	
EGPA diagnostic disease characteristics	N=8 [%]	
Asthma with eosinophilia	8 [100]	
Biopsy evidence	4 [50]	
Pulmonary infiltrates, non-fixed	6[75]	
Neuropathy, mono/poly	4[50]	
Sino-nasal abnormality	7[87.5]	
Adjuvant immunotherapy	N=8 [%]	
	5[63%]	
Prior Immunosuppressants	N=8 [%]	
Steroids	8[100%]	
Cyclophosphamide	4[50%]	
Rituximab	4[50%]	
Azathioprine	5[63%]	
Mycophenolate mofetil	6[75%]	
Methotrexate	4[50%]	
Omalizumab	1[12.5%]	
Response to therapy	Pre No. [%]	Post No. [%]
Prednisolone dose	N=7	
Mean ±SD	20mg ±7.5	12.28±4.89
Eosinophil count X10^9/L	N=6	
Mean ±SD	0.40mg ±0.25	0.035±0.04
Asthma Control Questionanaire	N=5	
Mean ±SD	2.92 ±1.27	1.31± 0.79
Continuation of therapy	7/8[87.5%]	

PUB265

Cohort Study of Percutaneous Native Kidney Biopsies from Rural Center Predominantly Caucasian Groups

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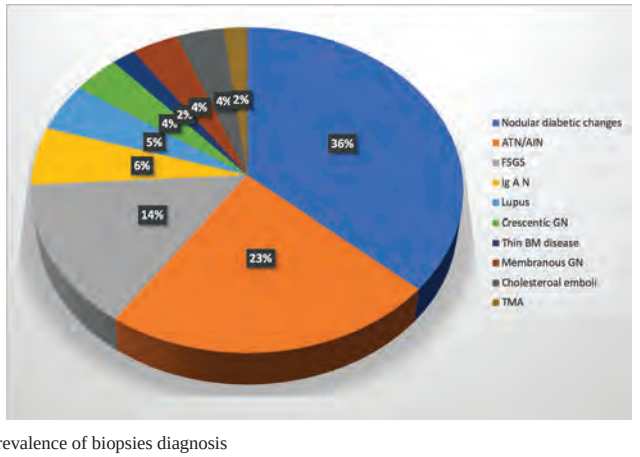
Background: Renal Biopsies are very consequential in clinical practice and avail in understanding of pathophysiology's, treatment and prognosis of glomerular diseases.

Methods: Epidemiological retrospective analysis of native percutaneous kidney biopsies from a rural center. Reviewed medical records of percutaneous biopsies from 2013 to May 2019

Results: There were total of 118 percutaneous native kidney biopsies analyzed with the following results: Average age at the time of biopsy was 58.0 years (16-94). Gender wise, 59.6% were males and 39.8% were females. Unexplained acute renal failure is the most common indication for biopsy. 80.5% were Caucasians, 15.25% were African Americans. Most common histological diagnosis was Nodular glomerular sclerosis (32.20%). Next common biopsy diagnosis is ATN/AIN, combination found to be 18.64%. Third common histological diagnosis found to be FSGS (12.71%). Fourth histological diagnosis is IgA nephropathy 8.4%.

Conclusions: At our rural center, most common pathology in Caucasians found to have nodular glomerular sclerosis. 13.15% of patients have histological diabetic changes with no clinical or serological diagnosis of diabetes, suggestive of other factors inolving in pathophysiology. 31.6% of diabetics have alternate histological diagnosis. Next common pathology shown Acute/Chronic Interstitial Nephritis along with Acute tubular Necrosis, may explain the medications/infections a leading cause of Chronic Kidney Disease.



prevalence of biopsies diagnosis

PUB266

The Use of Direct Oral Anticoagulants in Membranous Nephropathy

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Background: Barts Health has a dedicated membranous nephropathy (MN) service with 15-20 incident cases per year. Nephrotic syndrome secondary to MN in particular is associated with arterial and venous thrombosis. There is little evidence to guide optimum pharmacological prophylaxis. In those considered high risk, options include warfarin, heparin or aspirin. The advent of direct oral anti-coagulants (DOACs) offers an alternative, though evidence of efficacy is isolated to case studies. All patients with an albumin <25g/L are offered anticoagulation. We describe our use of DOACs in a large single centre MN cohort.

Methods: Retrospective data from MN patients, collected between 2015-2019 was analysed. This included: demographics; frequency, type and timing of thromboembolic and bleeding events; biochemical data at initiation and cessation of agent.

Results: Total number of patients: 26 DOAC treatment courses: 30 Exposure to drug (patient days): 9899 Malignancy was excluded in all cases, with the exception of 1 case of MN secondary to cancer. There were 3 thromboembolic events in 3 patients; all events occurred on rivaroxaban and in PLA2Rab positive MN. Thrombotic events were all arterial, with no venous events, 2 cerebral artery infarcts and 1 lower limb arterial thrombosis. These patient's mean initial presentation PLA2Rab titres were 164 Kunits/L (75-248) and all were nephrotic at the time of the thromboembolic event. Events were 29, 128 and 340 days post DOAC initiation. 2 of these patients had a venous thrombosis prior to DOAC initiation. Event rate: 0.11 per patient year Safety data also demonstrated 3 bleeds in this patient cohort - all were minor as per ISTH criteria. 2 epistaxes and 1 associated with rectal prolapse, all without a haemoglobin drop.

Conclusions: Our experience is that DOACs are safe and effective in patients with MN and offer a viable anti-coagulant alternative.

Table 1: Cohort demographics

Gender, n (%)	19 (65) Male / 7 (35) Female
Mean age (range) years	54.9 (26-76)
Mean eGFR (range) ml/min/1.73m^2	63.5 (17-124)
Median albumin (interquartile range) g/L	23.5 (20-28)
Phospholipase A2 receptor antibody (PLA2Rab) positivity, n (%): PLA2Rab seropositive PLA2Rab seronegative, immunohistochemistry positive PLA2Rab seronegative, immunohistochemistry negative PLA2Rab seronegative, immunohistochemistry unknown	- 20 (76) 2 (8) 2 (8) 2 (8)
Median DOAC initiation PLA2Rab titre, Kunits/L (interquartile range)	141 (75-993)
DOAC %	Rivaroxaban 80% Apixaban 20%
Mean treatment course duration, days (range)	330 (46-964)

PUB267

HIV-Associated Nephropathy in Mexico: Report of Six Cases from the Instituto Nacional de Cardiologia "Ignacio Chávez"

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Background: Kidney disease is a common complication in HIV infection, which can shorten the life expentancy from patients. HIV associated nephropathy spectrum includes diseases directly related to the immune interaction related to HIV infection, diseases associated to opportunistic infections, and those associated to treatment.

Methods: This is an observational, descriptive, retrospective, longitudinal study. We reviewd clinical files from all HIV positive patients, that attended to the outpatient nephrology clinic. Those with kidney biopsy were included.

Results: During the last 3 years 12 patients with HIV infection where send to our clinic under suspicion of kidney disease, 6 of them required kidney biopsy. From those 6 patientes 83% presented partial remission. **See Table 1**

Conclusions: Since 1984 diverse Kidney Diseases associated to HIV have been reported. The leading cause globally is collapsing glomerulopathy, which was observed in 33% of our population, also ITN has a high prevalence in this population, in our population was present in 50% of patients, 2/3 of them were HAART related. To our knowledge this is the first report of HIV associated disease since 1998, back then Soriano et al, reported a high incidence (48%) of collapsing glomerulopathy, and 35% of mesangial involvement, since then incidence of collapsing glomerulopathy is almost the same.

HIV Associated Kidney Disease

Patient	CD4	Viral Load	Biopsy Finding	Treatment
1	600	Non detectable	Acute ITN NSAIDs + AA Amyloid	PDN 1 mg/kg
2	332	43	Membranoproliferative GMN Immunocomplex Mediated + Active TMA	3 plasmapheresis sessions + PDN 1 mg/kg + RAAS Blockade
3	749	Non detectable	Membranoproliferative GMN Immunocomplex Mediated	PDN 1 mg/kg + RAAS Blockade
4	500	Non detectable	Collapsing Glomerulopathy + Acute ITN HAART	Dialysis
5	Unknown	Unknown	Collapsing Glomerulopathy	Did not accepted treatment
6	Unknown	Unknown	Tip Lession + Acute ITN HAART	PDN 1mg/kg

ND: Non Detectable, Unknown, ITN: Interstitial Tubular Nephritis, PDN: Prednisone.

PUB268

Renal Chronicity Score a Predictor of CKD Progression in Glomerulopathies

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Background: Chronic changes on renal biopsies are a strong predictor of chronic kidney disease (CKD) progression. The Renal Chronicity Score (RCS) grades the chronic changes based on severity and it has been proposed as a systemic approach to predict CKD progression.

Methods: Retrospective study of consecutive subjects with renal biopsy and Glomerulopathy in which clinical data and histopathologic analysis were taken. The data was assessed for descriptive and inferential statistics using t-test, X^2-test and Cox-regression-analysis to predict progression to CKD (GFR <60mg/dL). p ≤0.05 was considered significant.

Results: Five hundred subjects with renal biopsy and Glomerulopathy with a mean age of 39.1±15 years (43% female) were included. There were 157 subjects (31%) with Primary Glomerulopathy (PG) and 186 subjects (54%) with Secondary Glomerulopathy (SG). In the PG group 39% of the patients had focal and Segmental Glomerulosclerosis (FSGS), 27% had Membranous Nephropathy (MN), 17% had IgA Nephropathy, 15% had Membranoproliferative Nephropathy and 2% had Minimal changes disease. In the SG group 45% of the patients had lupus nephritis, 25% had diabetic nephropathy, 13% had FSGS, 10% had vasculitis, 6% had paraproteinemia and 1% had secondary MN. There were significant differences among both groups in Creatinine, Hemoglobin and CKD-EPI(p<0.001). Differences in The HR for developing CKD in PG and SG are shown in figure 1-1a.

Conclusions: RCS is associated to CKD progression at 6 months in primary and secondary Glomerulopathies. RCS is a good prognostic tool in primary and secondary glomerulopathies.

PUB269

Effects of Fangji Huangqi Decoction on the Expression of Heparanase of Adriamycin Nephropathy

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Background: Albuminuria is a hallmark of glomerular disease and an independent risk factor for the progression of kidney disease. Fangji Huangqi Decoction (FHD) has a good research foundation of the treatment of kidney diseases. Many studies show that this decoction has a good clinical effect in the treatment of kidney diseases, especially in reducing edema and urinary protein. At present, a large number of experiments have proved that FHD can repair damaged glomerulus and protect renal function of the treatment of chronic kidney disease. Therefore, based on the current research status, this study investigated the protective effect on FHD on adriamycin nephropathy rats, and explored the therapeutic effect and possible mechanism of FHD on reducing proteinuria by observing Heparanase, an important molecule involved in maintaining the structure and function of glomerular filtration barrier.

Methods: 48 Wistar rats, 8 of them were randomly taken as normal control group, the others received intravenous injections of ADR via tail vein (the first dose was 5.5mg/kg, the second injection dose was 3mg / kg after 14 days), established adriamycin-induced nephropathy rat model, the model rats were randomly divided into model group, treating group by high-dosage and low-dosage medicine, and then administered intragastrically by medicine in corresponding dosage. In next 5 weeks, rats in each group were detected 24hours urinary Protein. Renal tissues routine was fixed, HE staining was used to observed the histopathology change of kidney. The expression of nephrin, podocin and CD2-associated protein in rats renal tissues was observed with immunohistochemistry. HPA expression was detected using reverse transcription PCR.

Results: 24h urinary protein quantitative and podocyte marker protein of the rats in the model group increased compared with the normal group, Heparanases expression in renal tissue decreased than those of normal groups,the above indexes in treating group were improved in different degrees.

Conclusions: 1. FHD can reduce the quantity of 24 hours urine protein of Adriamycin Induced Nephropathy rats, alleviate the histopathology change of kidney, protect the charge barrier against damage. 2. One of the effective mechanism of FHD is repairing glomerular filtration barrier damage by decreasing Heparanases expression.

PUB270

Loss of Podocytes by Detachment as Viable Cells: Cause and Consequences

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Background: Loss of podocytes underlies the development of CKD. Podocytes are not lost by apoptosis, rarely by necrosis. The major way of losing podocytes consists of detachment from the GBM as viable cells. What accounts for this phenomenon?

Methods: Theoretical analysis on the basis of structural observations

Results: Podocytes are exposed to the flow dynamic forces of filtration that tend to disconnect podocytes from the GBM. For detachment, these forces must surpass the anchoring forces. This seems to happen never with healthy podocytes. Precondition is an impairment of the connections of the foot processes (FPs) to the GBM, of the interconnection of FPs by the slit diaphragm or of the podocyte cytoskeleton itself. The flow dynamic forces include the tensile and the shear stress of filtration. As recently shown (Pediatr Nephrol 32: 405, 2017) podocytes lying downstream of the GBM are largely protected from tensile stress by the limited distensibility of the GBM. In contrast, the shear stress of filtrate flow acts on all parts of a podocyte and always in its actual height. Filtrate flow through the filtration barrier pushes the endothelium towards the GBM, in contrast, it pushes the FPs away from the GBM tending to detach them. The shear stress of filtrate flow has been uncovered as an important parameter of filtration by Endlich and Endlich (Semin Nephrol 32:327, 2012). They showed that the huge flow and the narrowness of the filtration slits lead to a magnitude of shear stress to the sides of FPs that is several folds higher than that of blood flow to the capillary wall. Thus, any impairment of the anchoring forces will create a precarious situation, in which podocytes may start to detach at some site creating a gap in the podocyte cover of the GBM. This must be considered as a mortal event, comparable to the triggering event in a dam break that cannot be repaired, but will inevitably proceed to the detachment of the involved podocytes. This is a long-lasting process (weeks, months?). No structural findings are obvious that could be interpreted to show the repair of a gap in the podocyte cover of the GBM. Considering that two podocytes may approach each other in an attempt to close a gap, the increasing shear stress will prevent a complete closure.

Conclusions: Consequently, defects in the podocyte cover of the GBM cannot be repaired, lost podocytes not be replaced.

PUB271

Effect of Sociodemographic Characteristics of Hemodialysis and Pre-Dialysis Patients on Treatment Burden

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Background: Treatment burden is the load imposed by healthcare on patients. The impact of sociodemographic factors on treatment burden has not been adequately studied in patients with chronic kidney disease (CKD). We are conducting the first study to investigate treatment burden among CKD patients in Qatar.

Methods: We conducted a cross-sectional study at FBJKC [the largest in Qatar with 465 hemodialysis (HD) patients and 230 pre-dialysis patients with GFR <20 ml/min]. Treatment-related burden was evaluated using the Treatment Burden Questionnaire (TBQ), which contains five domains (medications, lifestyle, social, financial, and administrative burdens). Data were analyzed using SPSS version 24.

Results: A total of 223 HD and 57 pre-dialysis patients were included. Age was 59+/-19 years and 54.6% were males. HD patients were more likely to be single, widowed or divorced compared to pre-dialysis (36.3% vs. 17.5% p 0.03). Pre-dialysis group reported higher college degrees and employment compared to HD (45.6% vs. 24.2% (p 0.006) and 56.1% vs. 25.1% (p<0.001) respectively). Native Qatari were more represented in HD compared to pre-dialysis (62.8% vs. 22.8%; p<0.001). Treatment burden (measured by TBQ score) was significantly higher in HD versus pre-dialysis patients (45 versus 25 p 0.001). The influence of sociodemographic factors on TBQ score among CKD patients is summarized in (Figure 1). Poorly educated, unemployed and retired patients had the highest TBQ score (p<0.05).

Conclusions: Treatment burden measured by TBQ is elevated among CKD patients in Qatar. Poor education, unemployment and retirement were associated with higher burden of treatment. Studying sociodemographic treatment burden among CKD patients will improve designing effective intervention strategies.

Funding: Government Support - Non-U.S.

Variable	TBQ score	P value
	Median (IQR)	
Gender		0.15*
Male	38 (35)	
Female	46 (38)	
Nationality		0.51*
Qatari	45 (34)	
Non-Qatari	37 (36)	
Marital status		0.041**
Married	38 (38)	
Single	42 (35)	
Divorced	52 (27)	
Widow	52 (35)	
Educational level		<0.001**
No education	52 (38.5)	
Primary	50 (37)	
Secondary	40 (32)	
College/University	30 (27)	
Employment status		<0.001**
Unemployed	49.5 (34)	
Employed	27.5 (28)	
Retired	45 (40.7)	
Income per month (QR)		0.26**
No income	45 (37)	
Less than 1000	40 (-)	
1001-5000	25 (44)	
5001-1000	45 (36)	
Smoking status		0.87**
Never smoker	40 (37)	
Former smoker	45 (38)	
Current smoker	40 (43.5)	

Influence of sociodemographic on TBQ score

PUB272

Impact on Urinary Oxalate Levels from the Use of Ezetimibe

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Background: Calcium oxalate stones are the most common cause of nephrolithiasis in the United States. Patients are routinely advised to limit dietary intake of oxalate as a measure to prevent stone formation. Treatments of hyperlipidemia have been linked to increased oxalate absorption impacting urine concentrations. Smaller studies of less than 15 patients investigating ezetimibe (Zetia®), a selective cholesterol absorption inhibitor, have suggested increased urine oxalate levels with use of the drug. We attempt to better define this relationship of ezetimibe on urinary oxalate using a larger patient sample analyzing multiple urine collections on and off treatment.

Methods: We retrospectively reviewed all consecutive patients from 01/2018 through 04/2019 evaluated for nephrolithiasis with use of ezetimibe documented in their medical record at Mayo Clinic Florida. Demographic, clinical, and laboratory data were collected. Inclusion criteria consisted of age greater than or equal to 18 years, lipids treatment with ezetimibe all or in combination with a statin, and at least one urine supersaturation profile. Patients not seen in nephrology clinic despite use of ezetimibe and a urine supersaturation profile were excluded from analysis. Primary outcomes included increase in urinary oxalate with use of ezetimibe and reduction in urinary oxalate with discontinuation of medication. Methodology of statistical analysis to be determined.

Results: A total of 57 patients (average age 70, 68% male) were reviewed and under analysis with multiple urine supersaturations per patient. 24 hour urine oxalate levels appear to increase with use of ezetimibe.

Conclusions: Ezetimibe demonstrates a correlation with increased urine oxalate which may potentiate calcium oxalate stone formation.

PUB273

The Need for Further Investigation and Subspecialization in Sports Nephrology

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Background: According to the ASN website, current subspecialties in Nephrology include Transplant, Interventional, dual certification in Critical Care Nephrology, and advanced training in Glomerular Disease and Dialysis. The growing field of athletic performance and recreation enthusiasts seeking competitive edges and training advantages warrant the need for specialty expertise pertaining to Nephrology. Investigation to the fundamentals of nutrition, metabolism, and efficient energy output have been limited from a renal perspective.

Methods: A systemic literature review was conducted on Pubmed through May 2019 pertaining to athletic performance and Sports Medicine. Publications included basic science, prospective clinical study, retrospective clinical study, meta-analysis, case series, review articles, and editorials. Various subjects such as combat sports, endurance training, strength and conditioning, and rapid weight loss were explored.

Results: We reviewed a total of 46 publications with 18 studies focusing on combat sports and 7 studies on high intensity interval training. No Nephrology specialty authors were involved in the reviewed studies. These publications showed limited investigational studies from a renal perspective evaluating athletic performances in the categories of electrolytes and minerals, fluid balance, hypertension, hematuria, trauma, rhabdomyolysis, transplant, and immunosuppression. Methods of hydration such as the increase use of energy drinks and effectiveness of alkaline water have been investigated in 8 journals. Nutritional supplementation from 8 journals, rapid weight loss studies from 3 journals, and thermoregulations from 3 journals in combat sports play an important role in both training and competitions. These investigational studies have limited insights and expertise into the effects relating to the renal system.

Conclusions: Traumatic brain injury and CTE led to the progression of Sports Neurology, similarly there are Nephrology associated morbidities and mortalities in sports injuries such as water intake, dehydration, and rhabdomyolysis. There is a lack of renal guidelines in regards to highly trained athletes who are undergoing intense training, sometimes in environmentally challenging situations. We believe further investigation from a Sports Nephrology perspective can advance the field of athletic performance and provide a safe training environment in the future.

PUB274

The Interaction of Poor Sleep Quality with Cardiovascular Risk Factors in the CKD Population

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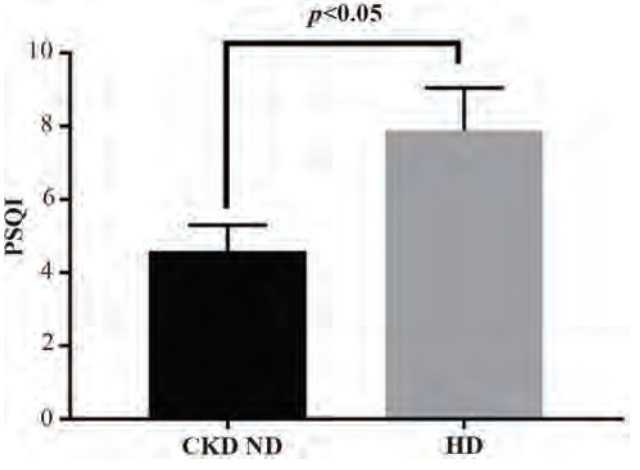
Background: Sleep deprivation is strongly associated with cardiovascular disease (CVD) in general population. However, the significance of poor sleep quality in chronic kidney disease (CKD) is still unknown. This study explored some factors that may interact with sleep quality in CKD population.

Methods: This study assessed the sleep quality of 39 with non-dialysis CKD stage III-IV (ND-CKD) patients and 25 hemodialyzed CKD stage V (HD-CKD) patients using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Poor sleeper was defined as individual with PSQI > 5. The markers of inflammation such as hs-CRP and blood-count-based marker were measured right after the PSQI data were taken.

Results: HD-CKD group has higher prevalence of poor sleeper and cumulative PSQI score (30% vs. 60%, p=0.029; PSQI 4.5±4.4 vs 8±6, p=0.038). In ND-CKD group, there are association between short sleep duration with elevated diastolic blood pressure (r=0.421, p<0.05) and habitual sleep efficiency with platelet-to-lymphocyte ratio (r= 0.532, p<0.0001). In HD-CKD group, a requirement to use sleep medication was associated with elevated hs-CRP level (r=0.434, p=0.030) and decreased monocyte-to-lymphocyte ratio (r=- 0.410, p=0.042).

Conclusions: Some features of poor sleep quality in CKD patients including low sleep efficiency, daytime dysfunction and requirement to use sleep medication were associated with increased diastolic blood pressure, hs-CRP and blood-count-based inflammatory predictors. Thus, poor sleep quality possibly acts as a mediating factor that exacerbates the CVD risk in CKD.

Funding: Government Support - Non-U.S.



Comparison of cumulative sleep quality index between ND-CKD and HD CKD groups.

PUB275

Açai Juice (Euterpe oleracea mart.) Supplementation Reduces Lipid Peroxidation in Hemodialysis Patients: A Pilot Study

Denise Mafra,[1] Isabelle C. Martins,[2] Hervé Rogez,[2] Maria d. Pinheiro,[2] Keuri E. Rodrigues,[2] Abner A. Lima,[2] Jessyca S. Brito,[1] Bruna Paiva,[1] Luís C. Pinto,[3] Andréa D. Reis,[4] Barbarella D. Macchi,[2] José L. Nascimento.[2] *[1]Federal University Fluminense, Rio de Janeiro, Brazil; [2]Federal University Pará, Belém, Brazil; [3]Pará State University, Belém, Brazil; [4]São Paulo State University, São Paulo, Brazil.*

Background: Chronic kidney disease (CKD) patients on hemodialysis (HD) present oxidative stress, which has a strong association with cardiovascular complications. Several nutritional therapeutic strategies have been used to reduce the oxidative stress in these patients, and the Amazonian fruit *Euterpe oleracea*, known as açai, has shown a protective effect against oxidative stress, since it is rich in antioxidants as phenolic compounds. There is no study that evaluated the effect of açai on oxidative stress in CKD patients, then, the aim of this study was to evaluate the effects of açai supplementation on oxidative stress markers in HD patients.

Methods: This pilot study evaluated 18 HD patients assigned to either clarified and lyophilized açai juice supplementation with 20mL three times a week (1013 mg of gallic acid equivalent /100 mL), (8 patients, 55.5 ± 4.9 years, BMI 24.8± 2.5 Kg/m^2, 50.3 ± 11.3 months on dialysis) or control (no supplementation, 10 patients, 56.1 ± 3.4 years, BMI, 25.2 ± 0.7 Kg/m^2, 53.8 ± 10.1 months on dialysis) for eight weeks. Plasma levels of the oxidative stress markers malondialdehyde (MDA), nitrite, total glutathione (TG), catalase (CAT) and glutathione peroxidase (GPx) were evaluated before and after supplementation.

Results: Table 1 shows that MDA plasma levels were significantly reduced and, there was a tendency to increase the TG after açai supplementation.

Conclusions: Açai intake may be an alternative nutritional strategy to reduce oxidative stress markers in HD patients. However, more studies are needed to support this result.

Funding: Government Support - Non-U.S.

Oxidative stress profile before and after 8 weeks of supplementation with clarified açai (Euterpe oleracea) juice in HD patients.

Parameters		Açai Group (n=8)			Control Group (n=10)	
	Baseline	After 8 weeks	p-values	Baseline	After 8 weeks	p-values
MDA (pg/mL)	80.2 ± 9.5	66.1 ± 14.5	0.04	65.7 ± 18.4	76.7 ± 8.5	0.09
Nitrite (µmol/L)	37.2 ± 9.0	28 ± 4.3	0.27	32.9± 5.2	38.8 ± 4.4	0.43
TG (nmol/mL)	320.7 ± 59.2	492.7 ± 84.8	0.08	346.5 ±40.6	399.4 ±31.4	0.29
CAT (nmol/min/mL)	13 (10.7-15.1)	13.7 (12.6-16.5)	0.32	14.9 (11.4-16.2)	8.4 (7.7-12.9)	0.11
GPx (nmol/min/mL)	26.7 ± 1.7	30.5 ± 3.9	0.42	24.1 ± 1.4	27.2 ± 1.3	0.27

MDA = malondialdehyde; TG, total glutathione; CAT = catalase; GPx = glutathione peroxidase.

PUB276

Serum Albumin Not Only a Marker of Nutrition: Multidisciplinary Interventions to Improve Albumin in a Peritoneal Dialysis Population in Qatar

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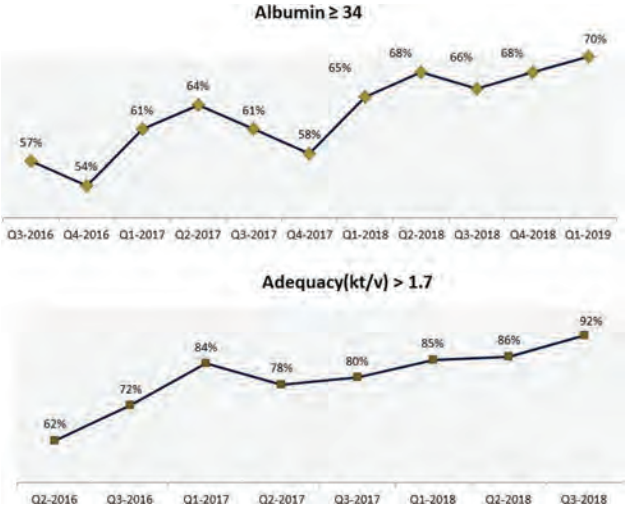
Background: Serum Albumin (SA) is a good predictor of adverse clinical outcomes in PD patients. At Qatar Fahad bin Jassam Kidney Center-HGH is the main provider for PD we had 180 PD patients and over the period of q 3 & q 4 2016 serum albumin (>34) fall down from the q1 & q2 2016, 65% & 64% to 57% & 54% respectively. With this hypoalbuminemia incident we decided to run a prospective improvement trial to improve the Serum Albumin level.

Methods: Multidisciplinary team was formulated that led by Nephrologist, and consist of PD Nurses, Dietician, Educator, Social worker and quality team to identify and to manage the hypoalbuminemia. We conducted a random survey to determine the food habits of patients, that taken almost routinely at home. We undertook root cause analysis for each case of hypoalbuminemia (SA<34) in the 6 months preceding the trial to identify any predisposing risk factors like inflammation, volume overload, effects of ARB medication, PD modality versus to the peritoneal membrane, loss of protein through urine etc. Inadequate dialysis may result in the retention of uremic toxins which can among other things, suppress appetite and result in malnutrition and morbidity. With the inadequate dialysis, patients lead to malnutrition, easy tiredness, prone to infections and admissions and to mortality.

Results: Serum albumin level >34 gm/L improved from 54% to 70% by end of March-2019. As the SA improves there is a good impact on the adequacy, mortality, inflammation, control of DM, technique failure and total quality of life. Dialysis adequacy improves from 62% to 92%

Conclusions: As we improve the Serum Albumin, patient's general health status and quality of life improved While correcting the PD prescriptions, adequacy had an impact, results in increase the appetite of patients



PUB277

Dietary Patterns (DP) in CKD Are Influenced by CKD Treatment Modality

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Background: Dietary patterns (DP) are as important as food components such as protein and energy. We investigated DP in Brazilians with CKD and explored associations with treatment modality.

Methods: Weekly consumption of 12 food intake groups was analyzed cross-sectionally in 839 individuals (mean age 54 years, 45% males) from the 2013 Brazil National Health Survey with self-declared diagnosis of CKD undergoing non-dialysis (n=480), dialysis (n=48), and renal transplant (n=17) treatment or no CKD treatment (n=294). DP were derived by exploratory factor analysis of food intake groups. Food groups with factor loadings |0.35| were considered representative and used to define DP. Factor scores of DP were estimated for each person; a higher score indicating higher adherence to DP. Multiple linear regression models - adjusted by gender, age, education, skin color/race, rural/urban residence and geographical region - were used to evaluate associations between DP and CKD treatment.

Results: Two DP were identified: *Unhealthy DP* (positive loadings for red meat, sweet sugar beverages, alcoholic beverages and sweets and a negative loading for chicken, excessive salt and fish) and *Healthy DP* (positive loadings for raw and cooked vegetables, fruits, fresh juice fruit and milk). With untreated CKD as reference, *Unhealthy DP* was inversely associated with non-dialysis and dialysis treatment [β: –0.20 (95%CI: –0.33; –0.06) and β: –0.80 (–1.16; –0.45), respectively]; these groups had lower adherence to Unhealthy DP than the untreated CKD group. *Healthy DP* associated positively with renal transplant treatment [beta: 0.32 (95%CI: 0.03; 0.62)] suggesting that renal transplant group had better adherence to this DP than untreated CKD group.

Conclusions: Two dietary patterns were identified and were found to be associated with CKD treatment modality among Brazilians with CKD. These findings may inform future recommendations about dietary patterns in CKD patients.

Funding: Commercial Support - Baxter Healthcare, Government Support - Non-U.S.

PUB278

Ratio of Bioimpedance at Right Leg as a Potential Screening Tool of Cardiomegaly or Hypoalbuminemia in General Population

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Background: Under physiologic condition, the ratio of extracellular water(ECW) to total body water(TBW) remains tightly regulated in healthy persons. The impedance at low frequencies reflect ECW; at high frequencies, TBW. Hence, the ratio of bioimpedance at the right leg (rl-RBI=impedance at 50KHz/impedance at 500KHz, measured by Inbody 720®, Biospace Co., Seoul, South Korea) will be maintained within normal range.

Methods: To define the normal range of rl-RBI, we measured the level of rl-RBI in healthy subjects (n=20,216) without medical, surgical history and abnormal laboratory / imaging data. We classified our subjects by age, sex and body mass index (BMI, <18, 18~<20, 20~<22, 22~<24, 24~<26, 26~<28, 28~, Kg/m^2) and investigated the distribution of rl-RBI. Also, we estimated the differences of rl-RBI between healthy subjects and asymptomatic subjects with cardiomegaly (CT ratio>50%, M:F=69:152), hypoalbuminemia (serum albumin<3.5 g/dL, M:F=121:266), or both (n=14).

Results: We excluded the subjects with cardiomegaly and hypoalbuminemia simultaneously. The levels of rl-RBI in healthy female group were significantly lower than those of healthy male group at the same decades of age (p<0.001) or at classes of BMI (p<0.001). Compared with the just previous decade of age in healthy male group, rl-RBI significantly decreased with the increment of age (P<0.001). Compared with the just previous class of BMI, rl-RBI significantly increased with the increment of BMI in healthy male (~18 vs. 18~<20, p=0.022, others, p<0.001) and healthy female groups (all classes, p<0.001). In the male subjects under 50 years and female under 60, there was no difference in rl-RBI between cardiomegaly (-) and cardiomegaly (+). In the male and female under 40, rl-RBI was insignificant despite of hypoalbuminemia (+). However, when we compared rl-RBI between cardiomegaly (-) and cardiomegaly (+) according to the classes of BMI, significant differences revealed in male subgroups with BMI over 22 (p=<0.002) and in female subgroups with BMI over 18 (p=<0.007). In male and female subgroups with BMI over 18, rl-RBI of subjects with hypoalbuminemia was significantly lower at all classes of BMI (p=<0.001).

Conclusions: The novel index of hydration status, rl-RBI, could be useful to detect the subject with asymptomatic cardiomegaly or hypoalbuminemia after classification of BMI than age.

PUB279

Misreporting of Dietary Intake Among Participants in the Palm Tocotrienols in Chronic Hemodialysis (PATCH, USA) Study

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Background: Misreporting of energy intake in dietary data collection includes both over and under-reporting and can result in biased inferences relating diet and health outcomes. Misreporting in the hemodialysis (HD) population is not well defined in the literature. This preliminary analysis assessed the associations of biologically implausible nutrient intakes on dialysis specific outcomes.

Methods: Dietary information was collected via 24-hr recalls taken quarterly over 15 months from 133 HD patients participating in a one year double-blind intervention (300 mg/d tocotrienols or placebo), which included KDQOL and anthropometric measures. Patients (95% African American; 63% male; age 59 ± 13 years; albumin 3.8 ± 0.3 g/dl; Kt/V 1.5 ± 0.2; vintage 65 ± 63 months) were enrolled from six clinics in Detroit, Michigan. Data was analyzed using Food Processor ESHA Research to calculate reported energy intake (rEI). The Harris-Benedict equation was used to predict energy expenditure and then multiplied by the physical activity level (PAL) 1.35 to estimate total energy expenditure (TEE). Each 24 hour recall was identified as either plausible or implausible using an rEI:TEE cutoff of < 0.76 or > 1.24. Patients were classified as implausible reporters if all the recalls collected were outside the cutoff range. Data collected at baseline was used in the analysis.

Results: Of 633 recalls analyzed, 53% indicated underreporting, 4% overreporting, and 41% acceptable reporting. Implausible reporters (23% of the cohort) had significantly higher body mass (107 ± 27 vs 85 ± 21 kg, p <0.001), BMI (35 ± 9 vs 29 ± 7 kg/m2, p <0.001), parathyroid hormone (913 ± 771 vs 615 ± 565 pg/ml, p <0.024) levels and lower HDL cholesterol values (41 ± 14 vs 51 ± 19, p <0.012). No differences were observed between implausible reporters and both KDQOL and anthropometric measurements.

Conclusions: Analyzing misreported diet data in HD patients may be useful in developing nutrition interventions targeted at improving dialysis specific outcomes. Implausible diet reports require further consideration before drawing conclusions between diet and health outcomes. (Supported by the Malaysian Palm Oil Board, Government of Malaysia)

Funding: Government Support - Non-U.S.

PUB280

Echocardiographic Findings in Patients with CKD on Replacement Therapy with Hemodiafiltration

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Background: Chronic kidney disease is a risk factor for the development of cardiovascular complications, being these by itself the most frequent cause of death in this group of patients. In our institute, cardiovascular evaluation has been essential to offer comprehensive care to our patients.

Methods: Retrospective study of a transversal cohort. Patients of the hemodiafiltration unit of our institute were evaluated by 2D echocardiography during the period from 2016 to 2019. Emphasis was placed on the search for ventricular ejection fraction, ventricular mass as well as pulmonary arterial hypertension data such as systolic pressure of the pulmonary artery (PASP), maximum tricuspid regurgitation velocity (TRV).

Results: We analyzed 36 patients, 27 women and 9 men in the aforementioned period, who underwent 2D echocardiography. The average age of 37.08 years (range of 21 to 85). The average ventricular ejection fraction (LVEF) of 55.1% (range from 27 to 68.1%), the average ventricular mass index was 120.42 gr / m2. TAPSE (displacement of the tricuspid annulus) average of 21.47 mm. Right ventricular systolic function (FAC) was 45.17% on average. Regarding the pulmonary arterial hypertension data, the average PASP was 42.68 mmHg; 43 mmHg the average in men and 42.57 mmHg the average in women. The average TRV of 2.66 m / S; average in men of 2.72 and women of 2.64.

Conclusions: Defining pulmonary hypertension (PH) as a PASP ≥ 50 mmHg or TRV ≥ 2.5 m/s, 5 and 3 patients were detected respectively. Considering diagnosis of HP suspicion, a PASP between 35-49 mmHg or a TRV of 2.8-3.4 m / s, 21 and 11 patients were detected respectively. It was also shown that ventricular systolic dysfunction is a frequent problem in our study population, which leads a challenge during hemodiafiltration sessions.

PH in patients with CKD in hemodiafiltration. Male group

Age, years	PSAP, mmHg
69	49
22	51
38	35
24	27
53	49
29	47
29	46
85	39
52	48

PSAP, pulmonary artery pressure

PUB281

Long-Term Renal Outcomes in Spontaneous Renal Artery Dissection: A Single-Center Experience

Harini Bejjanki, Gajapathiraju Chamarthi, Rajesh Mohandas. *University of Florida, Gainesville, FL*.

Background: Spontaneous renal artery dissection (SRAD), defined as dissection of the renal artery in the absence of trauma or arterial intervention, is extremely rare. Long-term clinical outcomes are not well described and hence there is no consensus on the ideal treatment and follow up of patients with SRAD. We report long term clinical outcomes in SRAD at an university hospital.

Methods: We used the integrated data repository to identify all patients with a diagnosis of 'renal artery dissection' between 1/2012-4/2019. A total of 54 patients met the criteria. Two authors independently performed chart review. Only five patients met criteria for SRAD

Results: Median age at the time of diagnosis was 64 years (Range 45-82 years). Of the five patients, 60 % (n=3) were males and 40% (n=2) were Caucasian. Majority of the patients (80%, n=4) were either current or former smokers and had a history of hypertension. None had diabetes. One patient was supsected to have fibromuscular dysplasia while no presdisposing disease or precipitating factors were identified in others. Mean admission creatinine was 0.89mg /dL (0.54- 1.2 mg/dL). Two patients developed mild acute kidney injury attributed to contrast, that resolved by discharge. Interestingly, more than half (60%, n=3) had evidence of renal infarction. Patients were initially treated

with anticoagulation (n=3), antiplatelet therapy (n=4) or a combination of the two (n=2). Only one patient required endovascular stent placement. The median follow up duration was 42 months. Follow up data showed no recurrent dissection in any of the patients. None of the patients developed chronic kidney disease (eGFR <60 ml/min), doubling of creatinine or end stage renal disease during the follow up period.

Conclusions: Our study showed that SRAD is rarely associated with AKI. Recurrences are rare and majority of our patients have preserved renal function on follow up. In patients with no underlying disease predisposing to renal artery dissection, the benign clinical course supports conservative management.

PUB282

Patient- and Societal-Level Factors Associated with Acute Decompensated Heart Failure (ADHF) Admission

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Background: In the United States, a million patients are admitted annually with ADHF and approximately 25% of these are readmissions with 30 days. Much needs to be learnt about the root causes which lead to hospital readmission for better allocation of resources. We aim to identify factors associated with ADHF and hospital admission at the patient and societal level.

Methods: We reviewed charts of consecutive 109 congestive heart failure patients who admitted at the University Hospital, San Antonio with ADHF and were potential participants of a study evaluating usefulness of high-dose aldosterone antagonist for loop-diuretic resistant ADHF. Patient charts were examined for demographics, clinical parameters, and possible reasons leading to volume overload and hospital admission. Those reasons were categorized into following six groups: A) unable to afford medications; B) noncompliance with medications and/or dosage; C) no regular healthcare/insurance; D) noncompliance with food and/or diet restrictions; E) admission despite compliance with medications and dietary restriction; and F) couldn't determine.

Results: The mean age of study cohort was 56±13 yrs, 68% were male, 63% were Hispanics, 51% had diabetes, ejection fraction (EF) was 31±18% and pulmonary arterial systolic pressure (PASP) was 45±12mmHg. Lack of healthcare/insurance (Gr C) and medication availability (Gr A) in combine was the most common causes (34%) for ADHF admission. Admission despite compliance with medications and dietary restriction (Gr E) was the next common reason (30%), suggestive of either disease progression or inadequate dose of diuretics. No information was available regarding frequency of encounters within health care to allow adjustment in the dose of diuretics. On multiple comparison analysis, group C population with no regular health care/insurance was younger than rest of the groups. However, other demographics and co-morbidities did not differ between these groups. Moreover, the heart failure severity assessed by EF and PASP was also similar among all the groups.

Conclusions: Lack of accessibility to the health care and medications was the most common reason for ADHF admission in our study population. This group comprised of younger population. The results of our analysis provide guidance for the local health care policies to reduce ADHF admission and hospital cost.

Funding: Commercial Support - Relypsa, Inc, a Vifor Pharma Group Company

PUB283

The Association of Dialysis Modality and Cardiovascular and Infectious Diseases: Peritoneal Dialysis vs. Hemodialysis

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Background: In end-stage kidney disease (ESKD) patients undergoing peritoneal dialysis (PD) or hemodialysis (HD), cardiovascular diseases (CVDs) and infectious diseases (IDs) are the most common causes of hospitalization and death. However, the association of dialysis modality and CVDs or IDs remains controversial.

Methods: This is a retrospective observational cohort study. Emergency hospitalization and mortality for CVDs and IDs excluding PD-related infections from 2010 to 2014 were evaluated between propensity score-matched PD and HD patients. Using Cox proportional hazards regression with adjustment for patient factors in December, 2009, risk factors of emergency hospitalization and mortality for CVDs and IDs were evaluated between the PD and HD patients.

Results: In matched 130 PD (75 men; mean age, 65.4 years; mean dialysis vintage, 3.3 years) and 130 HD (70 men; 66.6 years [*P*=0.4]; 3.1 years [*P*=0.5]) patients among 135 PD and 706 HD patients, emergency hospitalization rate (hospitalizations/person-years) for CVDs was significantly higher in PD group compared with HD group (0.138 versus 0.066, *P*=0.002). In log-rank test, CVD mortality was significantly higher in PD group compared with HD group (*P*<0.001). In Cox proportional hazards regression model, only PD was a significant predictor of both emergency hospitalization (HR, 2.70; CI, 1.53–4.77; *P*=0.001) and mortality (HR, 4.41; CI, 1.66–11.72; *P*=0.003) for CVDs, as well as age. Whereas, there were no associations between PD and emergency hospitalization and mortality for IDs in Cox proportional hazards regression model.

Conclusions: In this study, PD was one of the risk factors for CVDs in ESKD patients. PD patients should be maintained by strict control of body fluid balance.

PUB284

Development of an Inpatient Registry for Kidney and Hypertension-Related Disorders at Yokohama: The YCU-Kidney and Hypertension Registry

Tomohiko Kanaoka,[1] Rina Hiratsuka,[1] Koichiro Sumida,[1] Takehisa Iwano,[1] Sho Kinguchi,[1] Ryu Kobayashi,[2] Hiromichi Wakui,[1] Yoshiyuki Toya,[1] Kouichi Tamura.[2] *[1]Yokohama City University, Yokohama, Japan; [2]Yokohama City University Graduate School of Medicine, Kanazawa-Ku, Japan.*

Background: Patient registry has been increasingly important as a strategy to promote clinical research and to improve the patient care. Since Yokohama City University Hospital is one of the leading hospitals in Kanagawa Prefecture, a representative and well-known urban area in Japan, it should important to develop such a registry in the hospital. Thus, we started to construct an inpatient registry of kidney and hypertension-related disorders at Yokohama City University Hospital (YCU-Kidney and Hypertension Registry) from the beginning of 2018.

Methods: The categories of YCU-Kidney and Hypertension Registry include a series of inpatient information including the patients ID, age, sex, type of hospitalization (scheduled or emergency), purpose of hospitalization, renal biopsy (+/-), cause of kidney and hypertension-related disorders, and content of treatment including dialysis therapy (+/-). During the first year (from January to December 2018) of the YCU-Kidney and Hypertension Registry, total of 445 inpatients were registered, and all of data for information of the categories were securely stored in the electronic health record system (SS-MIX2) of Yokohama City University Hospital.

Results: We presently are able to securely access to the saved data and to analyze the updated tends regarding the detailed information of inpatients who were admitted to the YCU hospital due to kidney and hypertension-related disorders. We will present that more than half of the inpatients were derived from emergency admission at Yokohama City University Hospital which is located in an urban area in Japan, and will also present the detailed information about these inpatients in the YCU-Kidney and Hypertension Registry.

Conclusions: We intend to continue and expand the information recorded in the YCU-Kidney and Hypertension Registry, to improve the outcome measures including patient report type of outcome such as QOL and also to perform file case studies sorted out by diseases.

PUB285

Serum Hepcidin and Cardiovascular Events in ESRD

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Background: Hepcidin, the central regulator of iron metabolism, has recently been suggested to play a role in the development of cardiovascular disease in patients with end-stage renal disease. We investigated whether hepcidin increases the risk for cardiovascular mortality in 234 patients with end-stage renal disease (ESRD).

Methods: 234 study subjects with ESRD stage CKD5D-ND were included in the cohort. Median age was 55 (30-68) years, 62 % were male, 35 % had CVD as baseline, 29 % had diabetes and median estimated glomerular filtration rate was 6.1(3.8-10.3). The following parameters were assessed: hepcidin (the sum of all isoforms), high sensitive CRP (hs CRP), presence of cardiovascular disease (CVD), and Framingham's CVD risk score. Patients were stratified into four groups based on their median level of hepcidin and median level of CRP (group 0: low hs CRP + low hepcidin; group 1: low hs CRP + high hepcidin; group 2: high hs CRP + low hepcidin; group 3: high hs CRP + high hepcidin).

Results: During a median follow-up of 42.5 (7.8-60) months, 57 patients died. In competing risk analysis, in crude analysis group 2 (sHR 2.07 95% CI 1.02-4.21) associated with all-cause mortality. When we adjusted for other confounders it lost its statistical significance.

Conclusions: The patients with high hs CRP + low hepcidin were associated with increased all-cause mortality in CKD patients in crude analysis.

Funding: Government Support - Non-U.S.

_t	SHR	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
hepinflam						
1	.6098225	.296191	-1.02	0.309	.2353827	1.57991
2	2.07263	.7497677	2.01	0.044	1.020005	4.211545
3	1.7048	.6004574	1.51	0.130	.8548044	3.400009

PUB286

Hyperaldosteronism and Fibromuscular Dysplasia: Two Potential Causes of Secondary Hypertension and Hypokalemia in One Patient

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Introduction: Hypertension (HTN) is common, affecting nearly 30% of U.S. adults, with 5-10% of these cases due to secondary HTN. Potential causes of secondary HTN include renal artery stenosis, from either atherosclerotic disease or fibromuscular dysplasia (FMD), and hyperaldosteronism. Here, we present a hypertensive, hypokalemic patient with both an aldosteronoma and FMD.

Case Description: A 59-year-old woman presented with an over 10 year history of HTN necessitating metoprolol, losartan and spironolactone, and hypokalemia requiring

potassium supplements. Her cardiologist initially pursued imaging with concurrent CT abdomen showing a 2.1 cm right adrenal nodule and renal duplex ultrasound showing 60% stenosis and beading of the right main renal artery consistent with FMD. Carotid artery duplex showed bilateral 50-70% stenosis from FMD. Nephrology consultation was asked to help diagnose and manage. Spironolactone was discontinued for 4 weeks and serum aldosterone (30 ng/dl) and plasma renin activity (< 0.1 ng/ml/hr) were drawn, with the elevated ratio highly suspicious of primary hyperaldosteronism rather than FMD as the cause of HTN. Salt challenge was deferred due to profound, persistent hypokalemia despite amiloride and potassium repletion. Adrenal vein sampling showed lateralization to the right adrenal adenoma. The patient underwent right adrenalectomy and her blood pressure and potassium normalized shortly after. She was off all medications within 2 weeks and remains stable 9 months post operation. She has not required any intervention for FMD and is undergoing conservative monitoring with her vascular surgeon.

Discussion: History and physical with attention to specific clinical clues remains the mainstay approach to diagnosing secondary HTN. HTN and hypokalemia can point to either a primary (e.g. adrenal adenoma or hyperplasia) or secondary (e.g. renovascular) hyper-aldosterone state. Initial workup should begin with biochemical diagnostics to direct imaging studies rather than vice versa. Given its physiologic relevance, beginning with interpretation of the aldosterone to renin ratio better directs and expedites a therapeutic plan, including in patients with a concomitant adrenal nodule and renovascular disease.

PUB287

Eosinophilic Granulomatosis with Polyangiitis Cardiac Disease

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Background: Eosinophilic granulomatosis with polyangiitis (EGPA), is characterized by disseminated necrotising small vessel vasculitis with extravascular granulomas, amongst patients with the prodrome of asthma and tissue eosinophilia.[1,2] The French Vasculitis Study Group five-factor prognostic score (FFS) associates cardiac disease with a poorer prognostic group.[1,2]Histological findings in 7/9 cardiac transplant recipients, had evidence of EGPA in explanted native hearts despite ongoing immunosuppression.[2]

Methods: This retrospective, descriptive study analysed 18 patients with EGPA according to the ACR criteria or Chapel Hill Consensus 2012 definition. Identification of cardiac disease was based upon abnormalities in clinical condition, cardiac enzymes, ECG, ECHO and in some cases cardiac MRI. The aim of our study was to analyse the outcomes of patients with cardiac disease.

Results: All 18 EGPA patients were asthmatic and 15 were ANCA negative. At the time of mean follow-up 61.7 ±33.8 months, percentage survival in the cohort was 100%. Two patients had evidence of thrombo-embolic disease. Pulmonary and ENT involvement were common with cardiac disease, unlike renal disease. Table 1.

Conclusions: In accordance with literature, cardiac disease was found predominantly in ANCA negative patients. Therapy with conventional immunosuppression and biologic therapies had a favourable outcome. Early diagnosis of cardiac involvement is essential in guiding management decisions and prognosis. 1. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolutions in classification, etiopathogenesis, assessment and management. *A.Mahr et al Curr Opin Rheumatology, (2014) 2*. Heart transplantation in patients with eosinophilic granulomatosis with polyangiitis (Churg Strauss syndrome) *Guillevin et al The Journal of Heart and Lung Transplantation, (2014)*

Table 1: Data of patients with EGPA cardiac disease

Demographics	All [n=18]
Gender ratio M/F	11M/ 7F
ANCA positive/ negative	15 negative/ 3 positive [2 MPO, 1 PR3]
Age at Diagnosis*	47.8 ± 11.1 years
Time from asthma to EGPA*	16.6 ± 14.8 years
Mean follow-up	61.7 ± 33.8 months
Organ Involvement	**No. [%]**
Heart	18/18 [100%]
ENT	12/16 [75%]
Pulmonary	12/16 [75%]
Peripheral nervous system	8/ 16 [50%]
Constitutional	7 /16 [43%]
Skin	5/ 16 [31%]
Bowel	4 /16 [25%]
Renal	0/ 16
DAH	0 /16
Cardiac Manifestations	**n=18 [%]**
Cardiomyopathy	8/18 [44%]
Myocarditis	4/18 [22%]
Pericarditis	3/18 [16.6%]
Myopericarditis	1/18 [0.05%]
LV dysfunction	4/18 [22%]
Myocardial infarction	5/18 [27.7%]
Coronitis	3/18 [16.6%
Immunosuppressants	**n=14 (%)**
Steroids	14/14 [100%]
Cyclophosphamide	12/14 [85.71%]
Rituximab	8/14 [57.14%]
Azathioprine	10/14 [71.42%]
Mycophenolate mofetil	6/14 [42.85%]
Methotrexate	4/14 [28.57%]
Mepoluzumab	2/14 [14.28%]
Alemtuzumab	2/14 [14.28%]

Abbreviations: * Mean [SD]

PUB288

Modification of the Effects of Intensive Systolic Blood Pressure Control on Risk of AKI by Baseline Body Mass Index

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Background: The results of the Systolic Blood Pressure Intervention Trial (SPRINT) suggest increased risk of acute kidney injury (AKI) with intensive (INT) systolic blood pressure (SBP) control. It is unknown whether this effect persists across the body weight spectrum. We evaluated whether baseline body mass index (BMI) modified the effects of SPRINT intervention on risk of AKI.

Methods: SPRINT randomized 9361 high-risk non-diabetic participants with a SBP of 130 mm Hg or higher to either INT SBP target of < 120 mm Hg or standard SBP target of < 140 mm Hg. We used SPRINT BioLINCC data for our analysis. After excluding participants with a baseline BMI of <18.5 or > 50 Kg/m^2 (N= 9191), we evaluated the effects of INT SBP control on risk of AKI during the mean 4.1 years follow-up period in four strata (defined by baseline BMI of < 25, 25 to <30, 30 to < 35, and ≥ 35 Kg/m^2) and across baseline BMI as a linear variable using Cox proportional models. SPRINT defined 'AKI' as episodes of acute kidney injury or acute renal failure during the study period noted on admission or during a hospitalization reported in the hospital discharge summary as a primary or main secondary diagnosis.

Results: The mean age was 67.9 ± 9.4 years, 35.3 % were female, and mean baseline BMI was 29.8 ± 5.4 Kg/m^2. There were 1682, 3599, 2413, and 1497 participants in the four baseline BMI strata. Increased risk of AKI with INT SBP control persisted across the BMI spectrum as shown in the Figure. The effect of INT SBP control on AKI did not differ significantly between different baseline BMI levels (*P*-linear/categorical interaction 0.37/0.93).

Conclusions: INT SBP control increases risk of AKI across the BMI spectrum in high-risk patients without diabetes.

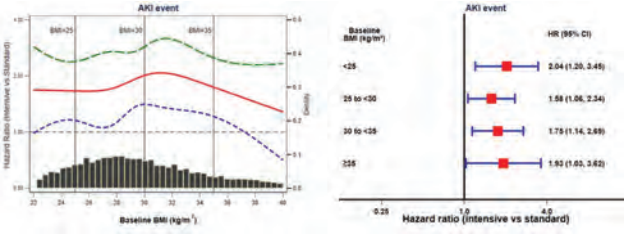

Figure: Spline Curve and Forest Plot (with Hazard Ratios) for risk of AKI with INT SBP control across baseline BMI spectrum in SPRINT

PUB289

Impact of Ambulatory Blood Pressure Monitoring (ABPM) on Blood Pressure Control and Medication Load in the Outpatient Clinic

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Background: Utility of 24-hour ambulatory blood pressure monitoring (ABPM) is used for assessment of complex hypertension is established. Whether or not ABPM leads to changes of blood pressure, control, and medication load is unknown.

Methods: We retrospectively reviewed 35 charts of patients who received ABPM from a single outpatient nephrology office. Of the 35, 9 charts were excluded due to lack of follow up data. We collected demographic information: Age, Gender, Ethnicity, Diabetic status, CKD stage, Indication for ABPM. ABPM data Including: Average daytime pressures, Average nighttime pressures, total average pressures, nocturnal dipping, hypertensive load. Blood pressure readings for the 3 office visits prior to and after ABPM were recorded. Anti-hypertensive regiments prior to and after ABPM were recorded. We calculated pill burden by taking patients dose and dividing it by the maximum dose of the respective medication.

Results: Of the 26 patients (20 Female, 6 Male), 18 were African American, 5 were diabetic, 12 had CKD stage 3 or greater, and mean age was 55.7±17.5 years. The mean pre-ABPM systolic blood pressure (pre-SBP) was 139.2±14.6 mmHg, mean post-ABPM systolic blood pressure (post-SBP) was 134.8±21.1 mmHg. The mean systolic difference was 4.3±5.0mmHg (p=0.3931). The mean pre-ABPM diastolic blood pressure (pre-DBP) was 83.7±11.5 mmHg, mean post-ABPM diastolic blood pressure (post-DBP) was 80.3±12.9 mmHg. The mean diastolic difference was 3.4±3.4mmHg (p=0.3209). When comparing pill burden, the mean pill burden pre-ABPM was 1.04±0.87 pills, mean post-ABPM pill burden was 1.03±0.89 pills, the mean difference 0.01±0.24 pills (p=0.9623).

Conclusions: When comparing ABPM data, we found that there was no significant difference in blood pressure or pill burden after ABPM. Further studies are needed to evaluate the impact of ABPM on blood pressure and patient outcomes.

PUB290

Can Cocaine Use Be Diagnosed in ESRD Patients Using Hemodialysis Effluent?

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Background: Cocaine is a common cause of drug-related emergency department visits. Cocaine use can be difficult to diagnose in End Stage Renal Disease (ESRD) patients as denial is common and patients can't produce a urine specimen. Benzoylecgonine, cocaine's major metabolite, is a small water-soluble molecule and is detectable in the hemodialysis (HD) effluent using a reagent assay for urine. We utilize hemodialysis effluent as an alternate specimen to urine and blood in ESRD patients and report our results of testing hemodialysis effluent in patients with suspected cocaine use

Methods: A retrospective chart review was conducted between 9/1/16 and 2/28/19 in an urban Philadelphia hospital. We identified hospital admissions that contained both an ICD diagnosis code of ESRD and an order for Urine Drug Screen. For each admission we collected age, race/ethnicity, sex, admission diagnoses, and whether the specimen was urine or HD effluent. Data were analyzed using independent t-test, Fisher's exact test, and chi-square analyses.

Results: We identified 1103 ESRD patients with 3306 admissions for whom cocaine use was suspected. Only 264 (24%) had a drug screen submitted for analysis. Of these 264 patients, the average age was 55 years old (± 12), 39% were female, 73% black, 17% Hispanic, 5% white, and 5% other. Eighty-two patients (31%) had effluent sent. Twenty-four of these patients had at least one admission with a positive cocaine test. For 14 patients (58%) their HD effluent was always positive, 4 (17%) were positive between 75%-50% of the time, and 6 (25%) were never positive. Hyperkalemia and volume overload/pulmonary edema were common admitting diagnoses in both groups; however, chest pain was more common in the cocaine positive HD effluent group and altered mental status in the cocaine negative HD effluent group. There were no racial/ethnic differences in HD effluent cocaine positivity. More females were in the cocaine positive effluent group than males (61% vs 39%, p = 0.01).

Conclusions: Our data demonstrates the difficulty in collecting urine drug specimens in ESRD patients. Utilizing hemodialysis effluent for testing ESRD patients suspected of cocaine use appears to be a promising tool. Future studies are necessary to validate this simple test which could be used to find the prevalence of cocaine use related morbidity among ESRD patients and examine differences in cocaine use.

PUB291

Presentation of 17 Cases of Monoclonal Gammopathy with Renal Involvement: To Unify a Diagnosis in Retrospect

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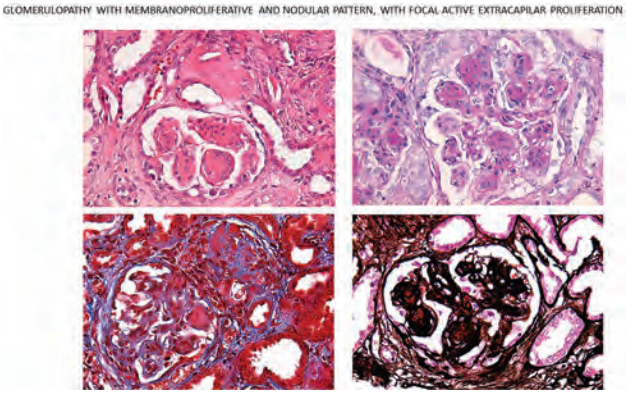
Background: Monoclonal gammopathies consist of a heterogeneous group of disorders characterized by clonal proliferation of immunoglobulins produced by clones of plasma cells or B lymphocytes. Renal diseases associated with monoclonal gammopathy are different in their pathogenesis, kidney biopsy findings and presentation clinic.

Methods: In a period of 10 years, from **June 2008 to February 2018**, 17 cases with a histopathological diagnosis of renal involvement due to monoclonal gammopathy were identified in a single institution.

Results: The average age of presentation was 57.2 years. The histopathological findings of renal biopsy were 7 cases of cast nephropathy (myeloma kidney) of which 6 were positive lambda and 1 positive kappa, 1 case of glomerulopathy with nodular and nodular pattern with focal active extracapillary proliferation. In cases of amyloidosis, 6 cases presented with a glomerular, interstitial and vascular pattern, 1 case with involvement restricted to the vascular compartment and 2 with glomerular and vascular involvement. 5 patients required hemodialysis at the onset of the disease; 37.5% of cases of multiple myeloma. Of the patients diagnosed with amyloidosis 2 of them presented as nephrotic syndrome, 3 patients with predominance of heart failure, 1 patient with the combination Nephrotic syndrome plus heart failure, 1 patient presented with peripheral neuropathy and 2 patients with dysautonomia. During follow-up, 14 patients died or lost track of the institute; 1 patient is in remission of amyloidosis, 1 patient is in a bone marrow transplant protocol and one patient is on maintenance hemodialysis twice a week.

Conclusions: In the cardiology institute, renal and cardiac involvement are more frequently recognized as a form of initial presentation of monoclonal gammopathies, however, they are often underdiagnosed. The kidney is the affected organ where the disease is diagnosed. It is necessary the early recognition of these pathologies in our population to improve the prognosis of our patients.



PUB292

Obstructive Uropathy with Uremia due to Advanced Cervical-Uterine Cancer

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Background: Cervical-uterine cancer (CUC) is a worldwide public health problem. Advanced CUC affects nearby regional structures causing obstruction. Rarely, obstructive uropathy can cause acute kidney injury (AKI), which leads to uremic syndrome with urgent treatment such as ureteral stent placement, nephrostomies and hemodialysis, as saving life modalities are required.

Methods: A retrospectively analysis of the AKI patients characteristics due to obstructive uropathy caused by advanced CUC presenting to the emergency department of Hospital Universitario, located in Monterrey, Mexico, during May 2014 to January 2019.

Results: 28 patients were analyzed with 45 ±11 as mean age (Table1). The main comorbidities were Diabetes Mellitus 5 (18%), and Hypertension 5 (18%). The mean evolution period was 22 ±20 years. 60% had metastatic CUC. The most common presenting symptom was general malaise and weight loss in 57 and 46%, respectively. The mean Blood Urea Nitrogen and Creatinine was 87±60 mg/dL and 6.9 ±6.5 mg/dL, respectively. 46% of the patients underwent JJ stent placement, and 39% required nephrostomies. The mean hospitalization period was 6.64± 7.64days. 10 patients (36%) died, with a mean survival of 6 ±6 months, no difference in mortality between treatments arms (long-rank test: 0.950).

Conclusions: Advanced CUC and obstructive uropathy presenting with AKI is a common public health problem on developing countries. They have a long period of evolution, the main symptoms are general malaise and weight loss and unfortunately had a short mean survival of 6 months. Integral clinical assessment is a crucial priority.

Table 1. Clinical, laboratorial and treatment characteristics.

Age, years (SD)	45.1 (±11.36)
Evolution period, years (SD)	22.16 (±20.34)
BUN, mg/dL (SD)	86.76 (±60)
Stent "JJ", n (%)	13 (46.4)
Percutaneous nephrostomy, n (%)	11 (39.28)
Mortality, n (%)	10 (35,7)
Survival, months (range)	6 (1-17)

BUN, Blood Urea Nitrogen

PUB293

Severe Hypercalcemia: New Etiologies and Nephrological Management in a Reference Hospital

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Background: Hypercalcemia is a metabolic disorder that can cause malignant ventricular arrhythmias, intestinal motility problems, decreased level of consciousness, neuromuscular irritation and, in very advanced situations, death. Although in its mild forms it is very frequent and causes mild symptoms, its severe forms are expression of serious pathologies, and can be the initial analytical data or the consequence of aggressive therapies or vitamin poisonings or prescription errors. It is interesting to evaluate the etiologies, and the Nephrologist therapies of a Reference University Hospital since it may be useful for future approaches Aims: 1. Establishing etiology of severe hypercacemia 2. Evaluating specific Nephrological/dialytic treatment and follow up.

Methods: Salamanca University Hospital Nephrology Service was consulted about severe hypercalcemia which was collected prospectively during a 36-month interval. A total of 31 patients (12 men, 19 women) presented Ca> 11.5, with a maximum of 19.5. Therapy and results were followed up. Statistical Analysis:SPSS 15.0

Results: Tumoral: 19/31(61.3%) were related to neoplasms with direct bone involvement (multiple myeloma:MM) or metastasis (Ca Mama, Lymphomas, Ca prostate). In some very frequent cancers, such as breast cancer, it was the first manifestation that led to hospital admission, diagnosis and subsequent treatment. Most frequent causes were *Hematological Neoplasms,* especially MM(first rank with a total of 5 cases) followed by Non-Hodgkin Lymphomas in 3 cases, and implied a poor prognosis as expression of highly advanced metatastatic bone disease. Mortality: 22%. Hemodialysis was done in 4 patients (12.9%). Biphosphonates :100% **Non tumoral** 12/31:(38.7%) *Calcifediol* Intoxication (n:5; 16,1%), *iatrogenic* (n:4) and *miscelaneous* (n:3). Hemodialysis :0. Biphosphonates :100% Mortality:0% Acute Renal Failure: 15%

Conclusions: 1)Severe Hypercalcemia is a serious increasing metabolic disorder that needs Dialytic Management in some cases. 2)Main etiology is neoplasms (61.3%), of hematological origin (38.7%), and solid tumor (bone metastasis). 3)Vitamin D intoxication (calcifediol) was an important understimated reversible cause (16.1%), especially in patients with previous CKD or liver disfunction. 4) Severe Hypercalcemia Management requires a multidisciplinar approach (Nephro-oncology)

PUB294

Lung Cancer and Renal Failure

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Background: Since there are few epidemiological studies in the literature regarding cancer patients (pts) with renal failure (RF), studying the possible renal co-morbidities is especially important in order to improve the management of these pts. **Aim of work:** to evaluate the relationship between RF and pt survival in subjects with lung cancer.

Methods: We analyzed the data of pts receiving a diagnosis of lung cancer between 1/1/2015 and 30/06/2018 who underwent therapy and were followed-up for at least 3 months. The prevalence of RF at diagnosis or the new onset during therapy was examined by comparing different formulas for calculating the glomerular filtration rate (GFR) and matching any possible correlation between them.

Results: We analyzed 277 pts. GFR<90 ml/min was detected in about 60% of cancer pts at diagnosis, while in the middle-advanced stage, the prevalence of RF was much lower (10%). We obtained significant differences in the GFR depending on the various formulations that were used. The Cockroft-Gault formula tends to overestimate the number of pts with GFR ≤60ml/min in a statistically significant manner as compared to CKD-EPI and MDRD (p=0.001). The new onset was significantly more frequent in pts undergoing first line treatment with cisplatin as compared to carboplatin (p<0.001). The data also showed a worsening of RF even in some pts who were treated with new therapeutic protocols based on the use of so-called target therapies. The available literature data concerning these drugs is based on case reports or small case-series. The average survival of our pts series was 18.2 months. Pts whose renal function worsened during or after treatment showed significantly reduced survival (p=0.02). No difference was observed between pts with RF at diagnosis and pts with normal renal function. These results can be explained by the systematic proscription of nephrotoxic drugs in patients at risk, and further reinforce the indication for personalized therapies.

Conclusions: RF is frequent in pts with lung cancer and shows consistent prevalence during follow-up. The conventional measures of GFR do not provide univocal data, thus emphasizing the need to use highly performing formulations. Accurate screening for risk factors and devising customized protocols can drastically reduce the impact of these factors on the survival of patients.

PUB295

Renal Parameters at Diagnosis of Multiple Myeloma in a Predominant Minority Population

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Background: Although multiple myeloma may occur in all races, the incidence tends to be higher in Blacks of African descent. This abstract describes the broad range of renal abnormalities at the time of diagnosis in a mostly African American population.

Methods: Electronic medical records of all patients who had confirmed diagnosis of multiple myeloma from 2010 to 2018 in a large inner-city public teaching hospital were reviewed. Inclusion criterion was initial diagnosis at the institution and prior to initiation of chemotherapy. The international staging system (ISS) was determined and the range of values for the institution was used to define abnormalities.

Results: 186 subjects met the criteria for the analysis. Percentage of African Americans, Hispanics and Caucasians was 57, 16, and 18 respectively. Males: Females-56% vs 44% with non-African Americans having more males. Serum creatinine was ≥ 1.5mg/dl in 28% and there was no gender or racial differences. Renal impairment was independent of diabetes mellitus or hypertension but 76% occurred in those with ISS III (P<001). Hypercalcemia (25% vs 7%) and quantified proteinuria of >500mg/24 hours (55% vs 14%) were statistically significant in those with and without renal impairment at presentation. Hyponatremia of < 135mEd/L was present in 35% of all subjects but in 43% in those with ISS III. Low Anion gap <5 was present in 27% of subjects but contrary to previous reports there was no differences among the various immunoglobulin subtypes.

Conclusions: In a predominantly African American population, abnormal renal parameters abound at presentation of multiple myeloma but they seem to be determined more by the disease nature rather than demographics or preexisting co-morbidities

PUB296

Contrast Medium Increases DNA Radiation Damage and Delays DNA Damage Repair in Kidney

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Background: Contrast-induced nephropathy (CIN) is a well-recognized cause of acute kidney injury in the clinical setting; however, no effective treatment for CIN has yet been established. Furthermore, contrast medium (CM) has also recently been shown to contribute to radiation-induced DNA damage in lymphocytes. In this study, we investigated the effect of CM on DNA damage and DNA repair in irradiated kidneys and kidney-derived cells.

Methods: For the *in vivo* study, male mice (8 weeks old) underwent unilateral nephrectomy. One week later, the renal artery was clamped for 30 min and iohexol (Ihx) was injected via the right retrobulbar sinus (CIN mice). The mice were then irradiated with 10 Gy of radiation (CIN-IR mice/IR mice) and kidneys were harvested 24 h after radiation. DNA damage markers (γH2AX, pATM, 53BP1, RAD51), the oxidative stress marker 8-hydroxy-2′-deoxyguanosine, and the macrophage marker F4/80 were examined by immunohistochemistry and western blotting. For the *in vitro* study, expression levels of DNA damage markers (γH2AX, pATM, 53BP1, RAD51) were examined in human renal tubular epithelium (HK-2) cells treated with iohexol (Ihx-HK2),1 Gy of radiation (IR-HK2), or both (Ihx-IR-HK2), using immunofluorescence.

Results: γH2AX, pATM, 53BP1, and RAD51 expression levels were significantly increased in CIN-IR mice compared with control, IR, and CIN mice. Expression of 8-hydroxy-2′-deoxyguanosine and F4/80 were also increased in CIN-IR mice. The numbers of RAD51 foci in HK-2 cells were similar in all groups, whereas γH2AX foci were significantly increased in Ihx-IR-HK2 compared with Ihx-HK2 and IR-HK2 at 1 h after radiation. γH2AX and 53BP1 foci were also increased in Ihx-IR-HK2 24 h after radiation.

Conclusions: CM increases DNA radiation damage and delays DNA damage repair, as well as increasing levels of oxidative stress and inflammation.

PUB297

Targeting Nuclear Receptor Interacting Protein 2 Blocks Podocyte Injury and Proteinuria

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Background: Podocytopathy results in proteinuria and frequently progresses to chronic kidney disease; here we reported that targeted knockout of Nuclear Receptor Interacting Protein 2 (NRIP2) completely blocked podocyte injury and proteinuria.

Methods: NRIP2 was identified as the most centralized hub gene, arising from glomerular transcriptional profiles of renal biopsies from patients with podocytopathy.

Results: NRIP2 was upregulated and expressed, but not restricted, in glomerular podocytes. Genetic knockout of Nrip2 completely blocked podocyte injury and loss, and proteinuria in Adriamycin and Puromycin Amino Nucleoside nephropathy mice. Podocyte-specific induction of NRIP2 resulted in podocyte injury and glomerulosclerosis in zebrafish. Mechanistically, NRIP2 was required for β-catenin signaling activation via retaining nuclear β-catenin.

Conclusions: This work clearly identifies NRIP2 as a potential therapeutic target and a critical retention factor of nuclear β-catenin in podocytopathy.

PUB298

Biphasic MIF and SDF1 Expression Promotes CD44-Mediated Glomerular Parietal Epithelial Cell Migration in Focal Segmental Glomerulosclerosis

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Background: Focal segmental glomerulosclerosis (FSGS) is commenced with local synechiae by glomerular parietal epithelial cell (PEC) activation, including its migration and adhesion to glomerular tuft with podocyte detachment. However, the molecular signaling that mediates podocyte injury and PEC activation remains unknown. In FSGS, *de novo* CD44 expression in PEC has been known as a marker of PEC activation, and it may be involved in progression of segmental sclerosis. In the present study, we focused on the roles of CD44 and two chemokines, migration inhibitory factor (MIF) and stromal cell-derived factor 1 (SDF1), during podocyte injury-driven PEC activation.

Methods: NEP25/LMB2 mice, the toxin-induced podocyte injury model, were used (n=5). The glomerular expression of MIF, SDF1, CXCR4 and CD44 was assessed by immunostaining sequentially on day 0, 4, 8 and 12. Using immortalized mouse PEC (mPEC), *in vitro* study was conducted by real-time PCR, western blotting, and migration assay under MIF and SDF1 stimulation.

Results: In the early stage of podocyte injury (on day 4), podocytes expressed MIF and SDF1. As podocytes were detached (on day 8 and 12), PECs expressed CD44 with MIF, SDF1 and CXCR4. *In vitro*, MIF and SDF1 individually induced CD44 and CXCR4 on mPECs and promoted their migration which was inhibited by CD44 knockdown.

Conclusions: Biphasic expression of MIF and SDF1 in podocytes and PECs, and roles of these chemokines in PEC activation *in vitro* suggested that CD44-mediated PEC migration might be initiated by MIF and SDF1 and sustained through their paracrine and autocrine effect.

PUB299

Post-Translational Regulation of Endothelial-Derived CCN Proteins in Response to Uremic Serum from Haemodialysis Patients

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Background: Non-traditional risk factors play an important role in cardiovascular disease (CVD) observed in renal patients. Vascular smooth muscle cells (VSMC) dedifferentiation is a key step in neointimal hyperplasia. Endothelial cell derived CCN2/CTGF and CCN3/Nov could play opposing roles in regulating VSMC dedifferentiation and migration modulating neointimal hyperplasia. We aim to investigate the expression and alteration in the CCN protein axis in human endothelial cells in response to uremic serum donated by haemodialysis patients.

Methods: Blood samples were obtained from consented haemodialysis patients (n=10) and healthy control subjects (n=6). Serum was prepared and stored at -80°C. Human Umbilical Vascular Endothelial Cells (HUVEC) from a mixed donor pool were cultured in supplemented growth medium on collagen IV. Cells were incubated in serum-free(sf) media, sf media containing 10% v/v patient serum (PS) and sf media with 10% v/v control subject serum (CS). After 24 h, media was removed, cells lysed and RNA extracted. RNA was subject to reverse transcriptase followed by real time QPCR. Relative gene expression was calculated by ΔΔCt analysis. Following 72 h incubation of HUVEC in the conditions above, media was removed, centrifuged and stored. Cells were lysed and lysates prepared for PAGE Western Blotting.

Results: There was no significant difference in TGFβ1 or CCN2/CTGF RNA expression. Although serum significantly reduced CCN3 RNAthere was no difference between PS or CS treated cells. There was no measurable difference in LDH between cultures with any of the protocols. Although there was some variation in the protein expression from cells exposed to sera from different patients, there was still an overall significant increase of between 35 and 70% in the intact 36/38Kda CTGF from cells treated with PS compared to both CS and sf ($p<0.05$). PS treatment induced significantly less CCN3 protein than CS treatment (40-65 % reduction, $p<0.05$). The endothelial cell phenotypic marker VE cadherin was significantly reduced by PS treatment ($p<0.05$).

Conclusions: From our data, we conclude that serum from haemodialysis patients induces endothelial cells to alter the CCN2/CCN3 axis substantially in favour of VSMC differentiation and migration potentially driving vascular calcification in these patients.

Funding: Private Foundation Support

PUB300

The Spectrum of Clinical and Histopathological Diagnosis in Patients with Rapidly Progressive Renal Failure: An Indian Experience from a Tertiary Center

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Background: Rapidly progressive renal failure (RPRF) is defined as progressive renal impairment over a period of a few weeks. The underlying etiology may be a primary renal disease or a systemic disorder. The data on RPRF from the Indian subcontinent is sparse. We aim to study the clinical profile and the histopathological findings on renal biopsy of patients presenting with RPRF at our center.

Methods: Consecutive patients presenting with renal failure of recent onset and rapidly progressing over the duration of weeks to less than 3 months with normal sized kidneys on ultrasound were included after informed consent. Kidney biopsy was performed under real-time USG guidance using the Bard® Max-Core® Disposable Core Biopsy instrument with all aseptic precautions. Two cores were obtained and samples sent for light and immunofluorescence microscopy in all cases. Clinical details including symptoms, signs, past history and investigations were recorded along with kidney biopsy findings.

Results: 100 patients who fulfilled the criteria were included. 65%(65) were males. The mean age of the study population was 44 years with 41%patients above 50 years of age. Most common presenting complaints were oliguria (84%) followed by edema (79%cases). Gross hematuria, fever, and joint pains were present in 20%, 22%, and 12% cases respectively. On kidney biopsy, rapidly progressive crescentic glomerulonephritis (RPGN) was the most common cause of RPRF accounting for (32)32% cases, with pauci-immune being the most frequent of all (14)14%. Acute interstitial nephritis was seen in (19)19% of patients, (5) 5% were found to have myeloma/amyloidosis and thrombotic microangiopathy was found in (3) 3% of patients. Other causes of RPRF included chronic sclerosing glomerulonephritis, focal segmental glomerulosclerosis, diabetic nephropathy, IgA nephropathy without crescents. Pauci-immune crescentic glomerulonephritis was seen as the most common cause of RPRF in the diabetic population.

Conclusions: The most common histopathological diagnosis in patients presenting with RPRF was rapidly progressive crescentic glomerulonephritis. The most common cause of rapidly progressive glomerulonephritis was pauci-immune crescentic glomerulonephritis, even amongst the diabetic sub-population.

PUB301

A Case Report of Podocytic Infolding Glomerulopathy with Bladder Tumor

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Introduction: Podocyte infolding glomerulopathy (PIG) is a recently described condition with pathologic entity characterized by diffuse podocyte infolding into the glomerular basement membrane (GBM) associated with ultra-structurally demonstrable microspherular aggregates. The clinical features, significance, and pathogenesis of this condition are still not well delineated because only a few cases have been documented to date, almost all from Japan. Here we reported a case of PIG associated with bladder tumor in a Chinese woman.

Case Description: A 76-year-old Chinese woman was admitted to our hospital with gross hematuria,edema, massive proteinuria, hypoalbuminemia, hyperlipidemia, and kidney dysfunction. Laboratory test of urine exfoliative cytology suggested poorly differentiated cancer cells, indicating a diagnosis of bladder tumor. Renal biopsy was performed to determine the cause of proteinuria and kidney dysfunction. Histological examination of the biopsy specimen showed mild segmental mesangial hyperplasia in the glomeruli. Immunofluorescence staining did not show glomerular deposition of immunoglobulins, light chains, or complement components. Electron microscopy showed slightly and irregularly thickened glomerular basement membrane (GBM) with irregular membranous structures in the GBM, suggesting podocytic infolding glomerulopathy. There were no electron-dense deposits in the GBM, while various findings indicated podocyte injury.

Discussion: PIG is a rare morphological alteration of the glomerulus. It is appeared to have a plasma membrane structure in the glomerular basement membrane (GBM). By now, most case reports on PIG were from Japan. In this case, the patient displayed large amount of proteinuria, which was characterized by nephrotic syndrome, with repeated gross hematuria. However, gross hematuria disappeared after resection of bladder tumor, but proteinuria was not significantly relieved within 3 months of follow-up. The patient also showed hypertension and renal insufficiency, which agrees with previous reports. This patient was the first report of PIG with bladder epithelial cancer in the world. The pathogenesis of the disease remains unclear, and the therapeutic strategy on this disease needs to be further studied in the future.

PUB302

Analysis of a Histopathological Pattern of Renal Biopsy Specimens in Sri Lanka: A Single-Centre Study

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Background: Histopathological analysis of renal parenchyma is the gold standard diagnostic tool in renal medicine. We report our experience on renal biopsy and the histopathological patterns of renal diseases presented to Teaching Hospital Kandy.

Methods: This retrospective study included adult patients who had native renal biopsy during a period of 9 years & 4 months, from January 2010 to April 2019. A total of 2680 biopsies were performed. Indications for renal biopsy were as follows: nephrotic and nephritic syndromes, rapidly progressive glomerulonephritis, asymptomatic hematuria and renal failure of unknown etiology. Kidney biopsies were performed percutaneously, using an automated gun under ultrasound guidance. Light microscopy and immunofluorescent studies were used.

Results: A total of 2680 biopsies were examined; sample included 1332 males and 1348 females (age 12 - 88 years). Primary glomerulonephritis (GN) was reported in 1096 (40.9%) cases, secondary GN in 988 (36.9%), tubulo-interstitial disease in 382 (14.2%) and chronic kidney disease of unknown etiology (CKDu) in 214 (8%) cases. Among primary GN, Focal segmental glomerulosclerosis was the commonest seen in 11.41% biopsies, followed by minimal change disease in 10.11%, immunoglobulin A nephropathy in 9.14%, membranous GN in 5.7%, membranoproliferative GN in 3.76% and immunoglobulin M disease in 0.55% biopsies. Among secondary GN, lupus nephritis (LN) was the commonest seen in 15.45%, followed by diabetic nephropathy in 7.27%, post infectious GN in 7.1%, renal vasculitis in 4.25%, hypertensive nephropathy in 1.52%, amyloidosis in 0.85%, myeloma nephropathy in 0.22% and thrombotic microangiopathy in 0.18%. Among biopsies demonstrating tubulo-interstitial disease, chronic interstitial nephritis was the commonest seen in 8.05%, followed by acute interstitial nephritis in 4.4%, acute tubular injury in 1.64% and acute tubular necrosis in 0.14% cases. CKDu was commoner among males than females with a count of 174 (6.49%) & 40 (1.49%) respectively. Mean age of CKDu patients was 44.3 years.

Conclusions: Nephrotic syndrome was the leading indication for renal biopsy. LN and FSGS were the predominant histological patterns. Among females LN stands as the commonest pathology. CKDu shows a significant prevalence among middled aged men.

PUB303

Overestimation of Proteinuria in Urine Sample with Low Urine Creatinine Level

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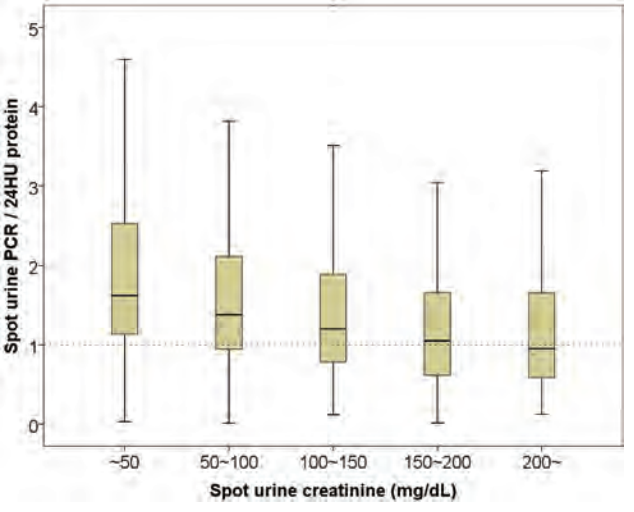
Background: Proteinuria is an important indicator of prognosis in kidney disease. Spot urine protein/creatinine ratio is widely used because it is considered to be able to replace 24 hour urine protein. Previous studies tested the accuracy of spot urine protein/creatinine ratio using the specific gravity of urinalysis. However, in present study, we investigated whether urine creatinine affects proteinuria quantification without other tests.

Methods: We reviewed patients who underwent 24 hour urine protein (24HU protein) and spot urine protein/creatinine ratio (uPCR) simultaneously at Gachon University Gil Medical Center between June 2002 and June 2018. The subjects were 1,286 patients and 31 patients with membranous nephropathy were excluded. One thousand five hundred fifty four samples were reviewed.

Results: The mean of 24HU protein was 1.4 ± 2.4 g/day (range 0.006~22.7 g/day), and the mean of spot urine protein and creatinine were 165.4 ± 315.4 mg/dL (range 0.1~5500 mg/dL) and 105.3 ± 73.1 mg/dL (range 0.3~682.9 mg/dL), respectively. The ratio of uPCR to 24HU protein (uPCR/24HUprotein) was 6.8 ± 67.8. When the patients were divided into three groups (concentrated group 0~50 mg/dL, reference group 50~200 mg/dL, diluted group 200~ mg/dL) according to spot urine creatinine, uPCR/24HUprotein were 18.6 ± 146.7 (p = 0.003 vs. reference group), 4.0 ± 26.7, and 4.1 ± 12.6 (p=0.088 vs. reference group), respectively.

Conclusions: uPCR tended to overestimate proteinuria based on urine creatinine level (figure 1). When urine creatinine is less than 50 mg/dL, we need to pay attention to the interpretation of uPCR.



Spot urine protein/creatinine ratio to 24 hour urine protein according to urine creatinine levels

PUB304

The Profile of Biopsy-Proven Renal Tubulointerstitial Lesions in China

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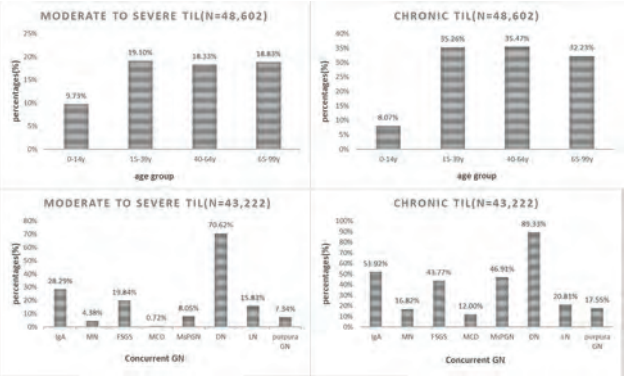
Background: Renal tubules and interstitium are vulnerable to injury and associated with deterioration of kidney function in a variety of CKDs. However, high quality studies on the profiles of biopsy-proven tubulointerstitial lesions (TIL) is extremely limited.

Methods: We conducted a retrospective renal biopsy series study including 62,529 native biopsies at 1211 hospitals across China from 2015 to 2017. The TILs, including the shedding of tube epithelial, renal tubular atrophy, renal interstitial fibrosis, edema and inflammatory infiltration, were extracted from the pathological report by a nephrologist. We analyzed the profiles of TILs stratified by gender, age groups, biopsy indications, and concurrent glomerular diseases. We also examined the effect of renal arteriole injury on TIL.

Results: Of the 48,615 patients with TIL, 47,525 (97.76%) were complicated by glomerular disease. Renal interstitial inflammatory infiltration was the most common type of TIL (97.51%), followed by renal tubular atrophy (68.25%) and renal interstitial fibrosis (38.56%). Severe and chronic TIL was more common in adults than in children. The prevalence of moderate to severe TIL was 70.62%, 28.29%, and 19.84% in patients with diabetic nephropathy (DN), IgAN and FSGS, respectively. Similarly, patients with DN, IgAN, MsPGN were more likely to have chronic TIL. After adjusting for age,sex, hospital level, region, biopsy indication and type of concurrent glomerular diseases, patients with renal arteriole injury had a five-fold higher risk of TIL (OR 5.96, 95% confidence interval, 5.34 to 6.65).

Conclusions: In this large, multicenter renal biopsy series, the type and severity of TILs varied with age and concurrent glomerular diseases. Renal arteriole injury was associated with a significantly increased risk of TIL.



PUB305

Clinicopathological Features of IgG4-Related Kidney Disease: Case Series Study

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Background: To investigate the clinicopathological features of IgG4-related kidney disease (IgG4-RKD) in Chinese patients.

Methods: We retrospectively analyzed the clinicopathological features of patients with IgG4-RKD and reviewed the relevant literature.

Results: There were 7 patients with IgG4-RKD, the male-to-female ratio was 4:3, and the mean age was 57±12 years. The most common clinical manifestation of these patients was acute or chronic renal insufficiency, while only one presented as nephrotic syndrome. Six patients had evidence of extrarenal involvement. Laboratory examination indicated that the serum IgG and IgG4 levels were elevated in all patients and IgE levels were elevated in four patients. Two patients were clinically diagnoses as ANCA associated vasculitis(AAV). All of the renal biopsies showed diffuse or focal dense lymphoplasmacytic cell infiltrates with scattered eosinophils within the renal interstitium, accompanied by interstitial fibrosis with a"storiform" pattern and tubular atrophy and dropout in fibrotic regions. On immunostaining, IgG4/IgG+ plasma cells ratio was >40% in all of the patients and the number of IgG4+ plasma cells was ≥10/HPF in five patients. Apart from tubulointerstitial nephritis(TIN), three patients had glomerular lesions, one of them had membranous nephropathy, the other two revealed necrotizing vasculitis with formation of crescents in the glomerular capsule, that was consistent with AAV. All the patients were treated with prednisolone, and combination of cyclophosphamide was administered in the two patients with AAV. The median follow-up time was 2 years, 5 of 7 patients revealed complete remission or partial remission, and all patients were alive at the most recent follow-up. One patient with AAV was on dialysis.

Conclusions: The combined application of morphology, immunohistochemistry, and clinical data may facilitate the diagnosis of IgG4-RKD. In the progressive stage of IgG4-RKD, the ratio of IgG4+ to IgG+ cell should be considered a useful metric for diagnosis. In rare cases, we should consider possible coexistence or overlap of AAV and IgG4-RKD.

Funding: Government Support - Non-U.S.

PUB306

Lipoprotein Glomerulopathy in the Indian Subcontinent: Report of Four Cases

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Introduction: Lipoprotein Glomerulopathy (LPG) is an extremely rare hereditary glomerulopathy presenting with proteinuria, variable degree of renal insufficiency and disturbances in lipid metabolism. LPG exhibit special predilection to kidney and histological hallmark of the disease is presence of laminated, lipid-containing thrombi within dilated glomerular capillaries. Disease progression results in overt nephrotic syndrome and end stage renal disease.

Case Description: We report four cases referred to our centre with complete clinical profile which showed histological, immunofluorescence and ultrastructural features of LPG on renal biopsy. Patients age range was between 21 to 65 years with equal gender distribution, however both males were below 30 years and both females were more than 50 years. Three patients presented with edema and hypertension and all had dyslipidemia. Nephrotic range proteinuria was seen in 3 cases while one had subnephrotic range proteinuria. Two cases had normal renal functions while 2 had mild renal insufficiency. All the cases showed enlarged glomeruli with pale lipid containing thrombi in dilated capillary lumina. Segmental tuft sclerosis (FSGS) was seen in all cases and three showed capillary wall double contour formation. Immunoflourscence was negative in all the cases and ultrastructural examination showed lamellated thrombi composed of variably sized lipid droplets, prominent subendothelial rarefaction, mesangial interposition and reduplication

of glomerular basement membrane. Follow up between 1 month and one year is available, proteinuria has improved to variable extent with lipid lowering agents and renal function parameters are stable.

Discussion: Since the first report of LPG in 1989, approximately 150 cases and 15 different Apolipoprotein E gene mutations in a heterozygous form have been described to play a causative role. Exact pathogenetic mechanism remains to be defined, however abnormal intraglomerular lipid trafficking may be the underlying factor. Though most cases of Lipoprotein Glomerulopathy are of Asian ancestry, mostly Japanese, it has never been described in Indian subcontinent. Kidney biopsy is very important in diagnosis of LPG, as identification of lipid thrombi within glomerular capillaries with high index of suspicion in dyslipidemic patients may play a crucial role and chances of missing the disease can be minimized.

PUB307

Prevalence and Risk Factors in Preterm Infants with Nephrocalcinosis

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Background: Nephrocalcinosis is a relatively common clinical condition in preterm infants, and the prevalence of nephrocalcinosis in premature infants ranges from 7% to 41 % in the different studies. Nephrocalcinosis in preterm neonates are known to be affected by multifactorial etiologies such as low gestational age, low birth weight, bronchopulmonary dysplasia, fluid restriction and other various causes. The aim of this study was to evaluate the prevalence and the risk factors of nephrocalcinosis in Korean infants born preterm.

Methods: We retrospectively analyzed the medical records of 27 preterm infants who were admitted to a neonatal intensive care unit from January 2015 to December 2016 and diagnosed as having nephrocalcinosis during hospitalization and 1-year follow-up. The diagnosis of nephrocalcinosis was made by the medical history and renal ultrasonography.

Results: The prevalence of nephrocalcinosis in Korean infants born preterm is 4.1%. The median age at the time of diagnosis was 72 days (17 - 548 days), and the male-to-female ratio was 1.1:1. The median gestational age was 28.8 weeks and body weight at birth was 1149.4±693.5 grams. The risk factors of nephrocalcinosis included patent ductus arteriosus (n=13, 48.1 %), bronchopulmonary dysplasia (n=11, 40.7%), the use of vitamin D (n=23, 85.2%), and diuretics (n=5, 18.5%). The serum levels of calcium and phosphorous at the time of diagnosis were 10.3±1.0 and 5.7±1.1 mg/dL, respectively. The hospitalization period was 119.3±63.4 day, and 1 patient died during follow-up. Although nephrocalcinosis persisted in 8 patients during the first year of life, only 3 patients visited the outpatient clinic of pediatric nephrology.

Conclusions: The prevalence of nephrocalcinosis in Korean infants born preterm was relatively low. Nephrocalcinosis in preterm infants might be associated with impaired renal function in the future, and the cooperation between the neonatologists and nephrologists is necessary. Future research for interventions to prevent nephrocalcinosis in preterm infants is crucial.

PUB308

Hypernatremia and Neurological Outcomes in Children

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Background: Hypernatremia in hospitalized children is associated with increased mortality and neurological insult, particularly in children with rapid fluctuations in serum sodium level. Current clinical guidelines recommend a reduction of 0.5mmol/L per hour or less, to reduce known complications of cerebral edema, seizures and increased mortality. Recent evidence amongst adults with hypernatremia found no difference in mortality between those who received more rapid or less rapid correction, however there are no large scale trials in the paediatric population. The aim of this study is to examine the association between the rate of correction of hypernatremia, neurological outcomes and all-cause mortality in children.

Methods: A retrospective review was conducted over a three year period from May 2016 until May 2019 in a large tertiary academic pediatric hospital. Eligible participants were identified through interrogation of the electronic medical record (Epic). All patients aged 6 months – 18 years seen at the Royal Children's Hospital with a serum sodium result demonstrating moderate to severe hypernatremia (defined as at least one serum level of 150mmol/L or greater) were included in the analysis. Demographic and clinical data were collected. The relationship between rate of serum sodium correction and neurological injury and mortality was assessed using multivariate logistic regression. Outcomes including mortality, cerebral oedema, seizures, encephalopathy, myelinolysis and decreased level of consciousness were determined using direct chart review.

Results: Over the three year study period, 337 children had a serum sodium level of 150mmol/L or greater and were included in the study. 51.2% of included patients were female, and the median age was 4.2 years. The majority of children had a sodium level in the range of 150-160mmol/L (n=198, 59%). 118 children (35%) had a sodium level between 160-169mmol/L, and 21 children (6%) had a sodium level of 170mmol/L or greater. The most common primary admission units of the cohort were cardiac services (21.3%), neurosurgery (18.1%), and general medicine (16.2%).

Conclusions: Hypernatremia remains a common and concerning occurrence in our hospital inpatients. Our analyses will help to further delineate the relationship between rate of sodium correction in children with hypernatremia and neurological and mortality outcomes.

PUB309

Malignancy After Pediatric Kidney Transplantation: A Single-Center Experience

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Background: Malignancy has become a major burden in transplantation patients with more potent immunosuppressants and longer graft survival. Although there is cumulating cases with malignancy after pediatric kidney transplantation(KT), reports regarding incidence, manifestations, and prognosis are rare. We aimed to investigate the incidence, manifestations, and outcomes of malignancy after pediatric KT in our center.

Methods: We retrospectively reviewed medical records of 143 patients aged under 18 years old who had KT between January 1990 and January 2019 at Asan Medical Center.

Results: Patients had KT at an mean age of 13.2 ± 4.4 years (range, 1.4 – 18.0 years), with mean follow up period of 11.7 ± 7.8 years. In total, 11 patients (7.7 %) had malignancy after KT. Malignancy was diagnosed after a mean period of 7.0 ± 5.9 years (range, 0.5 – 20.6 years) after transplantation. Mean age at diagnosis of malignancy was 20.7 ± 6.1 years. Eight patients out of 11(72.7 %) were diagnosed as post-transplant lymphoproliferative disease(PTLD), and other three patients had papillary thyroid cancer, mucoepidermoid cancer of hard palate, and T-cell acute lymphoblastic leukemia(ALL), respectively. PTLD was diagnosed within 4.3 ± 3.3 years (range, 0.5 – 9.8 years) after KT. Three patients with PTLD (37.5 %) expired. Among 3 patients with malignancy other than PTLD, one patient with mucoepidermoid cancer showed progression despite surgical resection and chemotherapy. Other two patients were cured without recurrence. Four patients (57.1 %) among the survivors who were all diagnosed with PTLD are currently on follow up with preserved renal function which did not deteriorate during the treatment of malignancy. Details of the cases are described on the attatched table.

Conclusions: PTLD was the most common malignancy after KT in children, occurring at 5.6 % of patients within average of 4.3 ± 3.3 years after KT in our center. Careful follow up is needed especially regarding the possibilities of PTLD after KT in children.

Pt	Sex	Underlying disease	Dialysis prior to KT	Age at KT (Yr)	Symptoms	Location	Diagnosis	IS at the time of diagnosis	EBV serology between Tx- at diagnosis	Interval between Tx-malignancy (Yr)	Treatment	Prognosis	Follow up period after diagnosis of malignancy (Yr)	Renal function at last follow up: Cr (mg/dl)
1	M	Bilateral dysplastic kidney, VUR	PD	10.58	Fever, headache, Loss of consciousness	Brain, lung	PTLD Hodgkin-like	MMF, FK, Ste	EBV DNA (+) : 10^5- 10^7/ml	2.29	Chemotherapy, (includes Rituximab)	CR	4.11	1.2
2	M	Congenital GN, ectopic kidney	PD	11.08	Abdominal pain	Jejunum	PTLD DLBCL	AZA, FK	EBV DNA (+) : 10^5- 10^7/ml	8.29	Surgery, Chemotherapy (includes Rituximab)	CR	6.21	2.7
3	F	unknown	HD/PD	15.42	Arm pain, abnormal chest X-ray findings	Right preaxial humerus, Liver, lung nodules	MMF, FK	EBV DNA (+) : 10^5- 10^7/ml	4.09		Chemotherapy (includes Rituximab)	CR	2.90	3.08
4	M	unknown	PD	17.42	Neck mass	Left neck, whole body lymph nodes, multiple bone lesions	PTLD DLBCL	MMF, FK	EBV DNA (+) : 10^5- 10^7/ml	0.5	Chemotherapy (includes Rituximab)	CR	5.25	17.5 (on HD)
5	F	unknown	PD	18.0	Lumbar pain, right leg weakness	Sacral ala (S1-S2)	PTLD DLBCL	AZA, FK	EBV DNA (+) : 10^5- 10^7/ml	0.79	Chemotherapy (includes Rituximab)	CR	2.99	1.1
6	F	RPGN	PD	10.83	Abdominal pain	Liver, spleen, retro-peritoneal lymph nodes, bone marrow	PTLD DLBCL	AZA, CyA	EBV DNA (+)	3.67	Chemotherapy	Expire Septic shock during febrile neutropenia	0.18	-
7	M	Alport syndrome	PD	10.92	Anemia	Duodenum	PTLD DLBCL	AZA, FK	EBV DNA (+)	9.83	Surgery (PPPD), chemotherapy (includes Rituximab)	Expire Tumor progression	0.70	-
8	F	Renal angiomyo-lipoma	PD	14.42	Abdominal pain	Mesenteric lymph nodes, ileum	PTLD DLBCL	FK	EBV DNA (+) : 10^5- 10^7/ml	5.09	Chemotherapy (includes Rituximab)	Expire Septic shock	0.05	-
9	M	VUR	HD	10.67	Abdominal pain with bowel perforation	Bone marrow	T-cell ALL	FK	EBV DNA (+) : 10^5- 10^7/ml	11.17	Chemotherapy	CR	6.99	8.28 (on HD)
10	M	Reflux nephropathy	No	14.33	Health check up ultrasound findings	Thyroid right lower lobe	PTC	MMF, CyA	Not analyzed	20.58	Surgery	CR	4.45	8.75 (on HD)
11	F	MPGN	HD/PD	17.42	Right cervical mass	Right hard palate, soft palate	Muco-epidermoid ca-ncer	AZA, FK	EBV DNA (-)	10.33	Surgery, concurrent chemo+radiation therapy	Expire Septic shock	1.62	-

Characteristics of patients who developed malignancy after KT

PUB310

Estimated Nephron Number in Japanese Children with Wilms Tumor

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Background: It has been postulated that an inherited nephron loss would lead to the development of chronic kidney disease (CKD) in later life. Consistent with this hypothesis, recent studies have reported that low birth weight is associated with an increased risk of CKD. However, the effects of birth weight and nephron number in children on development of noncommunicable CKD in adult age have not been elucidated. We, therefore, estimated nephron number in living children with Wilms tumor.

Methods: We evaluated the children with Wilms tumor at Jikei University School of Medicine Hospital who underwent an enhanced CT scan and nephrectomy. Nephron number was calculated by multiplying cortical volume of a healthy side by the glomerular density in a nephrectomy sample, as like Figure 1.

Results: Two children operated on at the age of 16 months (CASE1) and 11 months (CASE2) old for Wilms tumor were identified. The estimated number of nephrons was 843,590 per kidney in CASE1, and 1,021,397 per kidney in CASE2 (Table 1).

Conclusions: These results suggested the possibility of being able to estimate nephron number in living children with Wilms tumor. Further studies involving much larger numbers of subjects are required to determine the role of nephron number in children.

Table 1. Patients Characteristics.

	Gestational age	Birth weight (g)	Serum Cr (mg/dL)	\nephron number (/kidney)
CASE1	40 weeks 3/7	2,318	0.17	843,590
CASE2	40 weeks 0/7	2,934	0.30	1,021,397

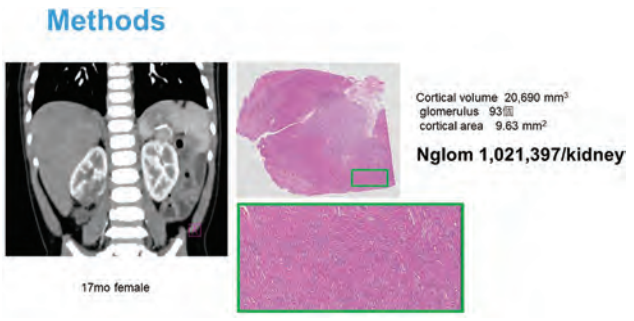

Figure 1: How to calculate nephron number.

PUB311

Positive Emotions of Caregivers of Children with CKD: A Qualitative Systematic Review

Zhi Hao Ong,[1] Cheng han Ng,[1] Muhammad Isyazmi Bin Mohamad Isa,[4] Megan Kiew,[3] Pei Loo Tok,[2] Yvonne P. Ng.[2] *[1]National University of Singapore, Singapore, Singapore; [2]National University Hospital Singapore, Singapore, Singapore; [3]Ngee Ann Polytechnic, Singapore, Singapore; [4]University of Queensland, Brisbane, QLD, Australia.*

Background: Negative emotions such as distress, fear, and anxiety are commonly experienced by caregivers of children with Chronic Kidney Disease (CKD). However, the caregiving process may also bring about positive emotions. This study aims to explore and summarise positive emotions of the caregivers.

Methods: A systematic review was performed using the PRISMA guidelines to identify qualitative research studying experiences of caregivers of children (ages 1 to 18) with CKD. Databases (PubMed, PsycINFO, Embase, Scopus, Cochrane) and grey literature (Google Scholar) were searched for relevant articles. The initial search yielded 17,493 title and abstracts. With an agreed upon selection criteria by the authors, 14 papers were accepted for analysis and were independently coded by 2 authors for Thematic Analysis. Critical Appraisal Skills Programme (CASP) checklist was used for grading quality of papers.

Results: Fourteen studies comprised 386 caregivers of children with CKD. Although most caregivers had experienced various negative emotions, some reported improved relationships with the patient, their families, and other caregivers. Some factors that contributed to this phenomenon include the long periods of time spent together, heavy dependence for emotional support, patient's appreciation of care provided and teamwork in providing care for the patient. These strengthened bonds can help them better cope with problems faced during caregiving.

Conclusions: To our knowledge, this is the first review focusing on identifying positive emotions of family members caring for children with CKD. Strengthening of familial relationships and with other caregivers can occur in the caregiving process despite the multitude of negative emotions experienced. Healthcare professionals can use the results of this study as a foundation to develop support systems to further strengthen these relationships. Further studies could focus on how these positive emotions aid and influence in the care-taking process.

PUB312

Coping Strategies Employed by Families of Paediatric Patients with Chronic Kidney Disease - A Qualitative Systematic Review

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Background: Caregiving for paediatric patients with Chronic Kidney Disease (CKD) has been associated with many psychological burdens. These caregivers would then employ various methods to allow themselves to manage such emotions. This study aims to explore the various strategies that caregivers for paediatric patients with CKD have to cope with their psychological burdens.

Methods: Searches were run on 6 electronic databases including PubMed, PsycINFO, Embase, Scopus, Cochrane and Google Scholar using MeSH terms and keywords for title abstracts. The initial search yielded 17,493 title and abstracts, and 5 papers were identified for independent line-by-line coding by 2 authors and thematic analysis. Quality of included articles was assessed via the Critical Appraisal Skills Programme (CASP) checklist.

Results: Five studies comprised 103 caregivers of children with CKD. Caregivers turn to various coping strategies when dealing with the psychological burden of caring for the patient. During the information hunger phase of initial diagnosis, there is a tendency for caregivers to search for information on internet and they are concerned of information quality. Coping strategies include reliance on religion, friends and family, emotional adjustments and social support groups. Social support strategies include peer support in the form of meetings and online support groups and support from medical staff. Emotional adjustment strategies include acceptance, emotional release and self-comfort.

Conclusions: To our knowledge, this is the first qualitative systematic review that focuses on coping strategies employed by family members of CKD paediatric patients. Coping strategies of different nature are employed by caregivers to manage their negative emotions. The Information presented would serve as a basis for healthcare professionals to better understand these caregivers and develop person-centred support structures for them to cope with their negative emotions.

PUB313

Decreasing Rates of Peritonitis Among Children Undergoing Peritoneal Dialysis in Puerto Rico

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Background: Peritonitis is a life-threatening complication ofperitoneal dialysis(PD). From 2006-2016, higher than expected peritonitis rates (0.82 episodes/year vs. 0.5 episodes/year) were reported among children receiving PD in Puerto Rico (PR). Perioperative PD catheter care interventions were developed to address this disparity.

Methods: Retrospective chart review of patients undergoing chronic PD in PR from 2006-2018. Patients with incomplete data were excluded. Peritonitis defined as peritoneal WBC>100cells/mm3 and polymorphonuclear cells>50% and peritoneal fluid culture. Demographic(age, sex), clinical and outcome (peritonitis rate, change of modality and death) variables recorded. High peritonitis rate defined as >0.5 episodes/yr. Associations were assessed using Fisher exact test.

Results: 53 patients underwent PD, 32 were included. Age at initiation 9yrs(6days-20yrs), 50% males. Time on dialysis 865 patient-months. 57 peritonitis episodes documented, for a rate of 0.82 episodes/year in first cohort and 0.34 episodes/year for recent cohort. Younger age at insertion was significantly associated to modality change (p0.047 and 0.044). Two patients died not associated with peritonitis.

Conclusions: Peritonitis rates were higher than national rates in the earlier cohort (0.82 episodes/yr vs. 0.32 episodes/yr). Younger age was associated to modality change. Younger children in dialysis have higher risks of morbidity. Decreasing infection rate may be associated with implementation of catheter care protocol, shorter dialysis vintage and restarting of local transplant program. Close monitoring of infection rates and trends result in better outcomes for patients on dialysis.

PUB314

ESRD in a Pediatric Population in a Southern Algerian Province

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Background: End stage renal disease (ESRD) in pediatric population is a major challenge for medical and paramedical staff In Algeria, the number of children reaching ESRD increases annually. Epidemiological studies of the pediatric ESRD in Algeria are few. The statistical data are collected but there is no operable national register. The objectives of this study are to: Estimate the prevalence and the annual incidence of ESRD in the pediatric population of Ghardaïa and to Determine the epidemiological characteristics of dialyzed children

Methods: In this retrospective study, we included all patients under the age of 19 years at the time of the ESRD, living in Ghardaïa, treated at least 03 months by hemodialysis (HD) or peritoneal dialysis (DP) during the period between 01/01/2005 to 12/31/2018. Information was collected from the medical files, interrogation of patients and their parents.

Results: Thirty (34) children were included. The average age was 12 years (1-19), sex ratio (M / F) was 0.88 (16/18). The average annual incidence of pESRD in our series was: 12 pmarp / yr. and The prevalence is : 135 pmarp (Per million age related population). The frequency was high for patients between 10 and 14 years of age (44%) Congenital abnormalities of kidneys and urinary tract (CAKUT) were the first cause of ESRD in our study (26 %) hereditary nephropathies (23 %) primary Glomerular nephropathy (20 %), cortico-resistant nephrotic syndrome was the chief of wire. In 30 % of the cases, the etiology was not found; this is mainly due to delayed diagnosis Hemodialysis is the first treatment method for incident (61%) and prevalent (67 %) patients. It was in most cases urgent (70%), anemia was predominantly present at the time of dialysis (89%). A very high mortality rate (23 %) was founded mainly due to dialysis insufficiency, A very low school enrollment (45 %) and significant retardation of growth (73 %). 15 % was regularly followed in pediatrics during years of dialysis The transplant rate (9 %) is very low, only 3 patients has been transplanted

Conclusions: Our study is of of the few works on the pediatric ESRD in southern of Algeria; we were able to raise the following remarks: - A high incidence and prevalence of pediatric ESRD compared to Europe or the USA - Delayed diagnosis of chronic kidney disease detrimental to patient survival - Very limited access to specialized therapies (urological surgery, genetic tests)

PUB315

Myasthenic Crisis (MC) Precipitated by Omalizumab (Om) Therapy (Rx): A Rare Adverse Reaction

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Background: Om is humanized glycosylated monoclonal(M) antibody(Ab) of IgG subtype that specifically binds to circulating immunoglobulin E (IgE) and hence has a role in treatment of severe allergic asthma. Om or its constitutive ingredients can trigger immune cross-reactivity and generate secondary autoimmune(AI) reaction by promoting formation of acetylcholine receptor (AChR) or muscle specific tyrosine kinase (MuSK) antibodies(Abs) and potentially precipitate MC. Majority of described adverse reaction to Om is limited to ocular myasthenia gravis (MG). We describe a case of full blown MC from Om with complete resolution of symptoms after therapeutic plasmapharesis (TPE) and stopping Om Rx.

Methods: 61 year old female who had initial diagnosis of MG for almost 20 years, was on maintenance Hemodialysis secondary to hypertensive nephrosclerosis for almost a decade. Around 7 years ago, she was started on Om Rx for non-atopic asthma and she was receiving it on twice monthly basis since then. Two years ago, she started having exacerbation of MG requiring intravenous immunoglobulin (IVIG) Rx. She counted 5 separate relapses at 3 months interval during this time requiring multiple courses of IVIG Rx. Initially symptoms were limited to ocular MG. However, last three relapses were involving difficulty in breathing and swallowing. She improved with three sessions of 1 x volume TPE and stopping Om Rx.

Results: Om has a biological half life of 5 days and typically given twice a month. Information derived from WHO Global individual case safety record database, VigiBase® suggests that there can be latency period of 0.5 to 2.5 years between starting of Om Rx and first appearance of MC symptoms. Precise etiopathogenesis of MG in setting of Om is not well described. Proposed mechanisms may include immune cross-reactivity, impurities in drug triggering secondary AI response and leakage of immunogenic protein A. Precipitation of MC has also been described with other M Abs like Nivolumab and Ipilimumab.

Conclusions: In conclusion, our case report suggests that high level of vigilance is required while using newer M Abs as reversible side effects such as MC can occur with use of Om years after its first exposure through complex and yet unidentified AI mechanisms. Om due to its high molecular weight, less protein binding and volume of distribution, can be effectively removed by TPE and this may provide a therapeutic option.

PUB316

Factors Predicting Ertapenem-Induced Neurotoxicity in Hemodialysis Patients

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Background: Ertapenem is an antibiotic used to treat resistant organisms and is frequently utilized in hemodialysis (HD) patients. The FDA approved dosing in this population is 500 mg intravenously daily based on a single pharmacokinetic (PK) study with a single ertapenem dose. Several reports and experts suggested an association of this dose and neurotoxicity in HD patients. The neurotoxicity rate of 1.9% is recorded in the normal population; hence, the purpose of this study is to identify the risk factors associated with neurotoxicity in the hemodialysis population.

Methods: A retrospective study was conducted in patients who received ertapenem and dialysis at Cleveland Clinic Abu Dhabi between May 1st, 2015 and March 31st, 2019. Patient demographics, comorbidities, concomitant drugs (known to induce neurotoxicity), and seizure history were collected after receiving the Research Ethics Committee approval.

Results: A total of 110 eligible patients were identified. Ten patients (9%) developed neurotoxicity. Of those cases, 8 patients (7.2%) developed seizures while 2 patients (1.8%) developed laryngospasm. The ten patients that developed neurotoxicity were all males with average age of 73.8 ± 9.4 years. Eight patients had established chronic kidney disease and 2 patients had acute kidney injury. Six patients received the recommended dose of 500 mg IV daily while 4 patients received 1 g daily for a few days before dose adjustment. The first episode of neurotoxicity occurred after 10.3±5.2 days of the start of therapy. The most common factors identified in patients who developed neurotoxicity were kidney disease (10), anemia (8) with hemoglobin of 82.3±12.9, history of stroke (5), and dementia (5).

Conclusions: Ertapenem dose, length of therapy, anemia, male gender, and history of stroke were the main risk factors associated with the development of neurotoxicity in hemodialysis population. The recommended dose of ertapenem in hemodialysis patients might impose higher risk of developing neurotoxicity as compared to normal population. Further PK studies are needed to investigate drug accumulation with multiple doses.

PUB317

Cost-Effective Therapeutics for Patients with ESRD: A Guide for the Practicing Nephrologist

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Background: Patients with end-stage renal disease (ESRD) are often put on complex regimens of medications to manage comorbidities and improve quality of life. Lower income individuals tend to be affected by increases in drug prices, as the average ESRD patient pays nearly $114 out of pocket per month for medications. It is hypothesized that cost-effective medications are available at national pharmacy chains and can be used to promote better health outcomes.

Methods: This study was conducted by utilizing national pharmacy websites' data on prices of common drugs prescribed to ESRD patients. A comprehensive list was compiled and categorized by drug class.

Results: A total of 48 drugs were found across the four nationwide pharmacies Wal-Mart, Target, Walgreens, and Kroger Specialty Pharmacy. Of the 48 drugs recorded, 34 (71%) were found to be a part of a generic discount plan, with drugs ranging from prices of $3.00/ 30 day supply to $16.66/ 30 day supply. Antihypertensives produced the highest quantity of drugs (28), of which 27 were on generic plans (only Labetalol was not), with an average cost of $6.09. Of the drugs used to treat diabetes, five sulfonylureas drugs were found on discount lists, while no insulin drugs were found. No immunosuppressants or phosphate binders were found on generic drug lists.

Conclusions: The data collected indicates that many of the most commonly prescribed drugs for treating comorbidities in patients with ESRD are available in generic form at a low cost to patients. It is hoped that the data provided will help to increase patient adherence and can be easily used as a tool for practicing nephrologists in the form of a pocket card or mobile app.

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PUB318

Acute Interstitial Nephritis in the Broad-Spectrum Antibiotic Era

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Background: Acute interstitial nephritis (AIN) is an important cause of acute kidney injury, especially in hospitalized patients. In recent years broad spectrum antibiotics has been associated to AKI and specially AIN, however the relationship between bacteremia, antibiotics and severity of biopsy damage has not been reported. We present a case series of patients with acute kidney injury with biopsy proven AIN in the setting of vancomycin and piperacillin/tazobactam use for patients with infections.

Methods: This retrospective study assessed the association between broad spectrum antibiotics, bacteremia and the incidence of acute interstitial nephritis. The study included 22 patients (biopsy-proven) who had an episode of AKI with diagnosis of AIN while on broad spectrum antibiotics at the Bruce Carter VA Medical Center Miami from January 2015 through July 2017. The effects of antibiotics on renal function were determined analyzing patient comorbidities with infection event and comparing the kidney function before and after the AKI episode in association with the histopathological analysis and treatment outcomes.

Results: All the patients included were men. The mean age of the included patients was 58.7 (±11). Total of hypertensive patients was 18 (81,8%), diabetes 17 (77.2%) and CKD 11 (50%) with initial creatinine 1.5 (±0.9). Positive blood cultures were seen in 5 patients (22.7%) and 17 (77.2%) negative blood cultures but positive soft tissue infections. A total of 13 (59%) were only on Vancomycin, 11 (50%) on piperacillin/tazobactam and 10 (45.4%) on both. Total of 4 (18.1%) biopsies were read as mild severity, 13 (59%) moderate and 5 (22.7%) severe. Creatinine before the AKI was 1.5 (±0.9), at the time of biopsy was 3.4 (±2.1) and 2.3 (±1.7) 6 months post biopsy/treatment. Total of 6 (27.2%) patients required RRT, and 5 (83.3%) had history of CKD and only 1 (20%) did not recover after treatment. Total of 19 (86.3%) patients achieved complete recovery and 3 (13.6%) did not recovery requiring continuation of RRT.

Conclusions: Vancomycin nephrotoxicity it's associated to elevated levels in the blood. Our review shows that interstitial nephritis is also a cause of vancomycin nephrotoxicity and is not associated to a high concentration. Other risk factors for vancomycin nephrotoxicity are age, presence of CKD and the concomitant use of piperacillin/tazobactam.

PUB319

The Gender Disparity in Living Kidney Donation Has Worsened over 20 Years: Factors and Observations

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Background: It has previously been reported that women donate more kidneys than men. It was thought that socioeconomic factors might play a role, with men historically acting as "breadwinners', but this role has changed over the past 20 years. We examined gender patterns and associated factors in living donation from 1998-2018.

Methods: All 112,700 living donor (LD) kidney transplants reported to UNOS/OPTN between 1998 and 2018 were analyzed. Only adult donors were included in the analyses. The time period was divided into 3-year intervals to adjust for yearly fluctuations. Logistic regression models were used to assess the odds for women to donate a LD kidney adjusted for possible risk factors.

Results: Overall, 60.5% of all living donors were women. Beginning in 2007, the odds ratio (OR) of female donation was progressively higher compared to 1998-00 ranging from 1.049 (2007-09, CI 1.001-1.059) to 1.144 in 2016-18 (CI 1.091-1.200). Except for over 70 years of age, the OR for women vs men donating was significantly higher for all age groups, with highest being the 40-50 yr group (1.621, CI 1.557-1.687). No racial differences could be detected. When donor relationships were examined in a subgroup analysis, 72% of spousal donors were women (10,062 vs 3,745), 68% of life partner donors (375 vs 169), 62% of parent to child (7,309 vs 4,573), but only 56% of child

to parent (10,444 vs 8,356). Gender disparity differed across regions, ranging from 1.194 (CI 1.123-1.269) for region 11 to 1.16 (1.081-1.259) for region 6 compared to Region 9. All differences were significant at p<0.0001.

Conclusions: 1. Women continue to donate kidneys at a much higher rate than men, and the rate is progressively increasing. 2. There were differences in the disparity seen across regions which may reflect case-mix or practice patterns, although race did not seem to have an overall impact. 3. Spousal donors are still predominantly woman to man, as are donations by life partners. 4. Parent to child donation was also predominantly women, but child to parent and sibling donation did not show as great a disparity. 5. Although biological factors may play a role in these findings, factors that may discourage men from donating should be explored, as well as potential biases on the part of providers, in order to improve living donation rates overall.

Funding: NIDDK Support

PUB320

Acute Pancreatitis Risk After Kidney Transplantation: Propensity Score Matching Analysis of a National Cohort

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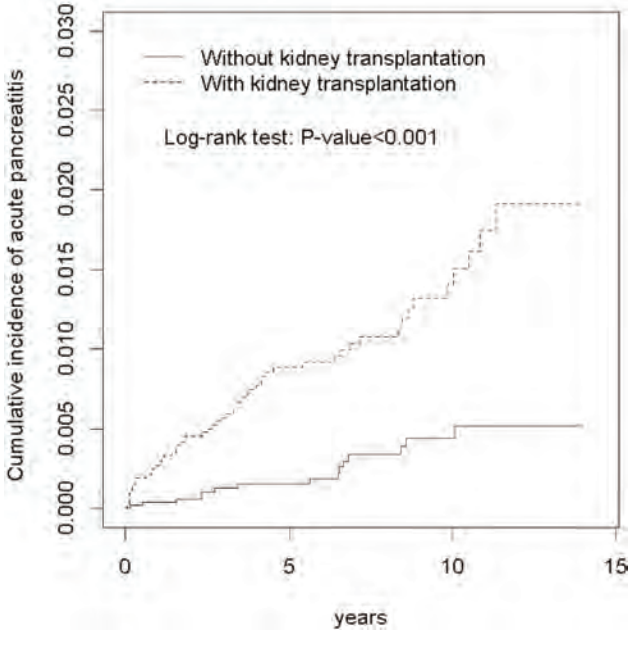
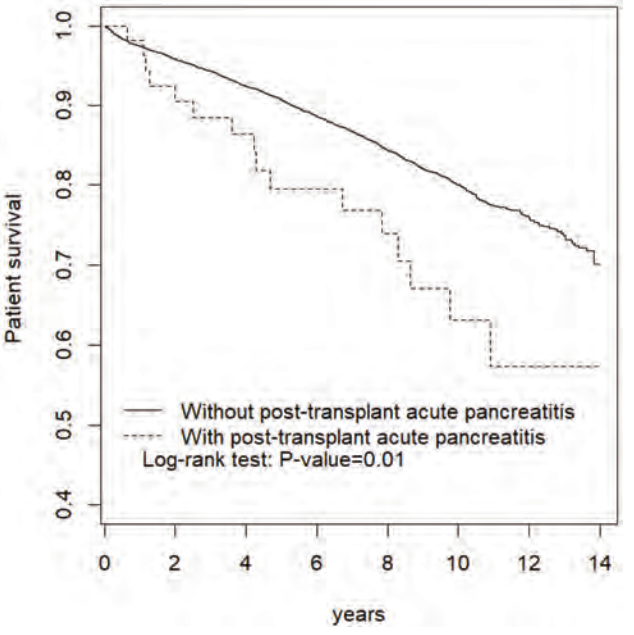
Background: Data for elucidating post-kidney transplantation (KT) acute pancreatitis (AP) risk are limited and no large-scale cohort study has investigated the impact of AP after KT.

Methods: Data from Taiwan National Health Insurance (NHI) Research Database (NHIRD) were calculated through the method of propensity score matching to compare the pancreatitis risk in patients with and without KT.

Results: The overall pancreatitis incidence rates were 1.71 and 0.61 per 1,000 person-years in the KT and non-KT groups, respectively and corresponding adjusted HR (aHR [95% CI]) for pancreatitis was 2.42 (1.43–4.10) in the KT group. In the multivariable model, AP risk was higher in transplant patients with alcohol-related illnesses (aHR: 3.85, 95% CI: 1.36–10.9), gall stone disease (aHR: 3.43, 95% CI: 1.45–8.14), or past history of pancreatitis (aHR: 9.94, 95% CI: 4.98–19.8). Of note, recurrent AP risk was significantly higher in the KT group (aHR: 9.77, 95% CI: 3.33–28.7). Patients with post-KT AP demonstrated shorter patient and allograft survival than did those without (both $P < 0.001$, respectively).

Conclusions: In conclusion, KT recipients are very likely to be associated with AP. Moreover, their inferior outcomes are strongly associated with post-KT AP.





PUB321

Ambulatory Blood Pressures in Pediatric and Young Adult Renal Transplant Recipients

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Background: Ambulatory blood pressure monitoring (ABPM) is the gold standard method to assess abnormalities in the circadian rhythm and blood pressure in renal transplant recipients (RTR). There is limited data in the ABPM patterns on pediatric RTR.

Methods: Retrospective chart review of RTR who had had at least 1 ABPM completed. Categorical variables were reports as counts & percentages and continuous variables as means with standard deviations. Linear mixed model given multiple observation per patient and odds ratios (OR) were calculated.

Results: Cohort (N=20) characteristics included, mean estimated glomerular filtration (eGFR) 57.96 ml/min/1.73m2, 60% male, 80% Caucasian, 85% normal body mass index, 55% had congenital anomalies of the kidneys and urinary tract (CAKUT) as cause for end stage kidney disease, 80% on dialysis prior to transplant, 60% received a living donor kidney. 50% had an abnormal ABPM. Of the 50% with normal ABPM half had finding of nocturnal hypertension (HTN) (normal awake blood pressure). Of the entire cohort, 43% had masked hypertension, 68% lacked a nocturnal dip, and 64% had left ventricular hypertrophy (LVH) (i.e. Ieft ventricular mass index >95th percentile). 67% of patients with LVH were on anti-hypertensive medications. Average tacrolimus trough was 6 ng/ml. Presence of LVH and abnormal ABPM had a 3.3 OR to having a reduced eGFR (<60 ml/min/1.73m2)

Conclusions: Findings demonstrate that ambulatory hypertension is common in both children and young adults after kidney transplantation. Masked HTN, nocturnal HTN and lack of nocturnal dip would not have been found by other means. The elevated prevalence of LVH supports the case for close blood pressure monitoring and target end-organ dysfunction surveillance as part of standard of care for these patients.

PUB322

Vitamin C, Vitamin B12, and Folic Acid Blood Levels and Their Association with Proton Pump Inhibitors Use in Renal Transplant Recipients

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Background: Use of proton pump inhibitors (PPIs) is frequent in renal transplant recipients. PPIs may interfere with the absorption of micronutrients. The objective of this study was to evaluate the blood levels of vitamin B12, vitamin C, folic acid of renal transplant recipients who used a PPI.

Methods: Of the patients at the transplantation outpatient clinic, 239 were eligible for the study, of whom 122 did not agree to participate and 39 were excluded; the remaining 78 patients were divided into two groups: PPI(omeprazole) intake (56) and control (22). It was evaluated: body composition (BMI), food intake (24-hour dietary recall), and vitamins blood tests. The findings were reported as percentage or mean and standard deviation. Associations with p <0.05 were considered significant for all analyzes.

Results: The groups did not significantly differ in demographic and clinical characteristics; there was a predominance of males (64%) and systemic arterial hypertension as underlying disease. The mean age was 49.52 years (± 12.7). Mean transplantation time of the group taking PPI was 68 (± 67.9) months and the GFR was 60 (± 20) mL/min/1.73 m^2, while in the control group the mean transplantation time was

116.9 (± 105.6) months and the GFR was 59.95 (± 13.1) mL/min/1.73m^2. Blood vitamin C was adequate in the majority of patients taking PPI and insufficient in all patients in the control group. Blood levels of vitamin B12 (98.2 and 90.9%) and folic acid (92.5 and 95.5%) were adequate in most patients of both groups (p> 0.05). The food intake recall was used to quantify the intake of macro and micronutrients, and no significant difference between the groups was found, except for vitamin C intake, which was higher in the group taking PPI (86.23 ± 116.0 mg) compared to the control group (42.57 ± 29 mg) (p = 0.01). Regarding BMI, 51.8% of the patients taking PPI were eutrophic and the remainder obese; in the control group, 36.3% were eutrophic, 54.5% obese, and 9% underweight. The results of body composition were similar between groups.

Conclusions: The findings of this study suggest that the intake of PPIs by renal transplant patients does not impair the nutritional status based on vitamin B12, vitamin C, and folic acid serum levels or based on body composition.

PUB323

Multidisciplinary Reconciliation of Renal Transplant Recipients' Medications: A Single-Center Experience

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Background: Transitions of healthcare increase the risk of medication errors. Besides, renal transplant recipients are at increased risk of errors due to frequent medication modifications and administration of multiple high alert medications. This study aimed at describing a single center experience in renal transplant recipients' medications reconciliation and its impact in preventing medication errors.

Methods: A prospective observational study was conducted from Jan. to May 2019. Multidisciplinary medication reconciliation process was implemented in the renal transplant unit of the armed forces hospitals southern region, Saudi Arabia. A clinical Pharmacist reviewed the best possible medication history (BPMH) list, developed by admitting physician and nurses, versus admission medications within 24 hours of admission. Upon discharge, clinical Pharmacist reviewed discharge medications against pre-admission BPMH and medications administered within 24 hours. For Post-discharge, clinical pharmacist conducted medication reconciliation of first outpatient clinic prescriptions against discharge ones. Physicians were contacted to resolve any detected discrepancies

Results: Twenty-four patients were transplanted during the study period (54.16% males, mean age = 39.3 years SD=16.8 years), 71 unintended medications discrepancies were detected (2.96 per patient). The majority of these discrepancies found during discharge reconciliation (64.8%) followed by admission (25.35%) and post-discharge (9.85%). The medications involved in these discrepancies included medications of osteodystrophy (23.9%), anemia (15.5%), immunosuppression (12.7%), electrolytes (12.7%), anticoagulation (11.3%), hypertension (8.5%) PPIs (5.6%) and diabetes (4.2%), the remaining 5.6% were miscellaneous medications, 95.8% of unintended discrepancies were prescription-related while the remaining were due to dispensing errors. Physicians resolved all unintentional discrepancies based on clinical pharmacist's recommendations. Omissions constituted 57.8% of errors prevented, while the remaining were commission errors (23.9%), changed dose (16.9%) and wrong duration (1.4%).

Conclusions: Multidisciplinary medication reconciliation seems to be effective in reducing medication errors and promoting renal transplant patients' safety

PUB324

Nocardia Infection in Kidney Transplant Recipients: A Single-Center Experience

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Background: Nocardiosis is an uncommon, but life-threatening opportunistic infection that disproportionately affects the immunocompromised host. Although transplant-related Nocardiosis is well-recognized, data in kidney transplant patients remains limited.

Methods: A retrospective chart review of all patients at our institution with a history of kidney transplant and at least one positive culture for *Nocardia* between 1999-2019 was performed.

Results: During the 20-year study period, 10 patients had *Nocardia* infection. Eight were deceased donor kidney transplant recipients, and the mean age at time of transplant was 56.0 ± 14.5 years. Induction agents included alemtuzumab (n = 5), basiliximab (n = 4), and anti-thymocyte globulin (n = 1). Nocardiosis occurred at a mean of 11.5 ± 31.6 months (range, 6-102) months after transplant. Breakthrough *Nocardia* infection occurred in 5 patients receiving double strength (160/800 mg) trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis for *P. carinii* pneumonia. Immunosuppressive regimens at time of nocardiosis diagnosis consisted of prednisone (n = 10), tacrolimus (n = 9), and mycophenolate (n = 8). The most common site involved was the lung. TMP-SMX was the most frequently used antimicrobial for treating nocardiosis (9 of 10); it was administered as single-drug therapy (4 of 10) or as combination therapy with other antimicrobials (5 of 10). Overall mortality was 60% (6 of 10); fifty percent (3 of 10) of deaths were attributable to *Nocardia* infection.

Conclusions: To the best of our knowledge, this is the largest case series of *Nocardia* infection in kidney transplant recipients. TMP-SMX prophylaxis did not appear to provide protection from *Nocardia* infection, but appeared to be associated with less severe disease. Overall outcomes remain poor. Practitioners should maintain a high degree of suspicion for this pathogen in the months to years after transplant.

Table 1. Basic characteristics.

	Age at time of transplant (years)	Sex	Race	Main Underlying Condition	Dialysis vintage (months)	Type of transplant	HLA mismatch	Induction immunosuppression
Patient 1	73	Male	White	Chronic Glomerulonephritis, Unspecified	23	Deceased donor	4	Basiliximab
Patient 2	70	Female	Asian	Nephrolithiasis	10	Deceased donor	5	Basiliximab, anti-thymocyte globulin
Patient 3	41	Female	White	Unspecified	57	Deceased donor	4	Alemtuzumab
Patient 4	57	Female	White	Diabetes Mellitus Type I	2	Living donor	5	Alemtuzumab
Patient 5	25	Male	White	Membranous Glomerulonephritis	99	Deceased donor	6	Alemtuzumab, rituximab, plasmapheresis
Patient 6	63	Male	White	Alport's Syndrome	7	Deceased donor	5	Alemtuzumab
Patient 7	73	Male	White	Cholesterol Embolization	18	Deceased donor	4	Basiliximab
Patient 8	53	Male	White	Renal Cell Carcinoma	0	Deceased donor	4	Anti-thymocyte globulin, IVIG
Patient 9	63	Female	White	Nephritis	9	Deceased donor	0	Basiliximab
Patient 10	65	Female	White	Lithium Toxicity	0	Living donor	4	Alemtuzumab

Table 2. Clinical characteristics and outcomes.

	Maintenance immunosuppression at time of infection (pred dosage in mg)	TMP-SMX prophylaxis, dosage, or reason for non-prophylaxis	Concurrent illnesses	Duration between Tx and onset of infection (months)	Clinical form: organs involved, bacteremia	Source of the culture that grew Nocardia	Nocardia species	Treatment	Outcome	Duration between infection and outcome (weeks)
Patient 1	Tac, MMF, pred (10)	No, allergy	CMV infection	102	D: lung, bacteremia	Bronchial washings	farcinica	Imp, Dox, Lzd	Death, R	1.6
Patient 2	Tac, MMF, pred (7.5)	Yes, 160/800 mg	None	19	Lung	Sputum	Unknown	TMP–SMX, CIPF	Death, NR	248.3
Patient 3	Tac, MMF, pred (20)	Yes, 160/800 mg	CMV infection	6	Lung	Sputum	nova	TMP–SMX	Cured	30
Patient 4	Tac, pred (20)	No, allergy	Pneumocystis carinii pneumonia, oral candidiasis	15	D: lung, eye, bacteremia	Bronchial washings	nova	TMP–SMX	Death, NR	103.3
Patient 5	Tac, MMF, pred (23)	Yes, 160/800 mg	Candida albicans pneumonia	3	Lung	Thoracentesis	Unknown	TMP–SMX	Death, NR	209.3
Patient 6	Tac, MMF, pred (5)	No, leukopenia	Alone	72	Lung	Sputum	farcinica	TMP–SMX	Death, R	1.3
Patient 7	pred (15)	Yes, 160/800 mg	CMV infection, BK virus infection, Pneumocystis carinii pneumonia, Pseudomonas UTI	9	Lung	Sputum	farcinica	TMP–SMX, Mix	Cured	51
Patient 8	Tac, MMF, pred (30)	No, leukopenia	CMV infection, pulmonary Aspergillosis	9	D: Lung, CNS	Bronchial washings	nova	TMP–SMX, Lzd, Cip, TCG	Cured	71.7
Patient 9	Tac, MMF, pred (10)	No, unknown	Candida albicans pneumonia	24	D: Lung, eye, bacteremia	Blood	nova	TMP–SMX, Mec, Lzd	Death, R	17.7
Patient 10	Tac, MMF, pred (10)	Yes, 160/800 mg	CMV infection	6	Lung	Sputum	farcinica	TMP–SMX, Imp	Cured	11.6

CIPF, ciprofloxacin; Cip, ciprofloxacin; D, disseminated disease; Dox, doxycycline; Imp, imipenem; Lzd, linezolid; Mec, meropenem; Mix, Minocycline; MMF, mycophenolate mofetil; Mxx, moxifloxacin; NR, death not related to nocardiosis; pred, prednisone or methylprednisolone; R, death related to nocardiosis; TCG, Tigecycline; TMP–SMX, trimethoprim–sulfamethoxazole.

PUB325

Thymoglobulin Adversely Affects the Outcome of ABO-Incompatible Transplants

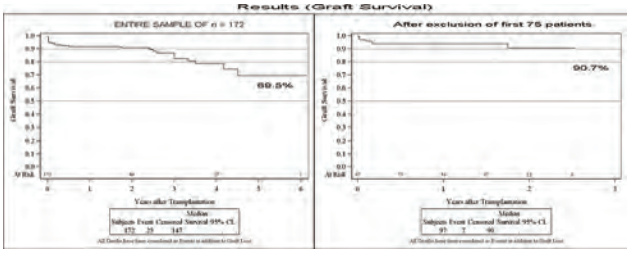
Vivek Pathak. *Nephrology, Kovai Medical Center and Hospital, Coimbatore, India*.

Background: Abo-incompatible transplants are becoming more common with higher long term success rate but yet many centers are reporting unexpected graft loss due to antibody mediated rejection. We analysed our data and found something unexpected that induction with Thymoglobulin caused higher graft loss.

Methods: 172 patients who underwent renal transplantation between May 2012 till July 2018 were analysed. Thymoglobulin was used for induction in 31 and Basiliximab was used in 141 patients. They received maintenance immunosuppression with steroid, MMF and tacrolimus. Observation period was of 10 to 84 months.

Results: Acute rejection was seen in 18 patients(10.4%) and cellular rejection was uncommon. Graft loss was seen in 13 and 12 patients died. Graft nephrectomy due to antibody mediated rejection was done in 6/31 Thymo group and 2/141 of Basiliximab group in first week. 2 patients who were doing well with Basiliximab induction with normal kidney function at 1 week where given Thymo to make them steroid free. Their Anti-A and Anti-B titres started rising immediately from 1:8 to 1:256 in 3 days and both lost the graft. We checked Anti-A and Anti-B titres in ABO compatible transplants before and after Thymo induction but did not observe any rise in 25 patients. Thymo was not used for induction after first 75 patients so there was a clear dfference in graft survival which improved after stopping Thymo Patient survival was 96.9% at 1 year and 81.2% at 5 years. Graft survival improved after dividing the group in first 75 subsequent patients which can be seen in the graph. Graft survival was 82% at 3 years, 69.5% at 5 years in overall 172 patients and 90.7% at 3 years after excluding first 75 patients. Acute antibody mediated rejection could be treated sucessfully in remaining 10 patients.

Conclusions: This study clearly shows the adverse influence of Thymoglobulin induction on graft survival in ABO-incompatible transplants. Graft loss can be reduced by avoiding this treatment.



PUB326

Successful Treatment of Recurrent Focal Segmental Glomerular Sclerosis After Renal Transplant with LDL Apheresis Is Associated with Low Levels of Soluble Urokinase Plasminogen Receptor Activator (suPAR)

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Introduction: Recurrent FSGS remains to be a devastating condition without specific therapy. SUPAR has been reported as a cause of FSGS and its removal is affected by plasmapheresis (PLEX). We report a successful treatment of recurrent FSGS with LDL apheresis.

Case Description: We report a case of a 21 year old male with a biopsy proven idiopathic FSGS diagnosed at age of 12 with a relapsing course and progression to end stage renal disease despite aggressive multi drug therapy. He received a living related renal transplant from his mother with immediate FSGS recurrence in the allograft. His pre transplant sUPAR levels were measured at 12.39 ng/ml. Post transplant PLEX was initiated promptly followed by two doses of rituximab with very poor clinical response. Ninety days after the transplant surgery he was offered treatment with LDL apheresis device (Liposorber LA-15, by Kaneka Pharma America LLC). His chemistries demonstrated serum creatinine (SCr) of 4.0 mg/dl, eGFR of 20ml/min, serum albumin 1.8 mg/dl, proteinuria of 13 g/g based on spot urine protein to creatinine ratio (U P/C) and sUPAR level of 5.3 ng/ml. He received six twice weekly LDL apheresis treatments followed by seven weekly sessions. He also received oral prednisone therapy (60 mg daily for 3 weeks), followed by gradual taper over 6 weeks to maintenance daily dose of 5 mg in addition to IV solumedrol (500mg) following each of the weekly apheresis treatments. His sUPAR levels declined gradually throughout the treatments and reached nadir of 1.9 ng/ml following his 13th session. The remainder of the chemistries demonstrated SCr of 1.7 mg/dl, eGFR of 50 ml/min, U P/C of 800mg/g, serum albumin of 3.7 mg/dl. The LDL apheresis treatments lowered sUPAR levels more significantly (aprox. 47%) and were associated with much lesser rebound than what has been reported in patients with recurrent FSGS receiving PLEX.

Discussion: LDL apheresis lowers sUPAR levels to a greater degree and with less rebound than PLEX. This treatment modality can be successfully applied in patients with post transplant FSGS recurrence.

PUB327

Simultaneous Liver Kidney Transplantation Using Single Subcostal vs. Dual Incisions: Does Incision Really Matter?

Brianna Ruch,[1] Amit Sharma,[1] Gaurav Gupta,[2] Chandra S. Bhati,[2] Adrian Cotterell,[1] Marlon F. Levy.[1] *[1]Virginia Commonwealth University, Richmond, VA; [2]Virginia Commonwealth University Health System, Richmond, VA.*

Background: Simultaneous liver-kidney transplantation (SLKT) is commonly performed using a subcostal incision for the liver allograft and a right iliac fossa incision for retroperitoneal kidney transplantation (Dual Incision, DI). Some surgeons use a single subcostal incision (SI) for SLK (with intraperitoneal kidney) to reduce the cold ischemia (CIT) and operative times. We report our outcomes using single and dual incisions for SLKT.

Methods: Retrospective analysis of all SLKT done at our center (2015 to 2019) was performed. Outcomes after SI and DI were compared using standard t-test for unequal variances. A p-value <0.05 was considered significant.

Results: 16 SLKT were performed (5 SI and 11 DI). Recipient demographics and early outcomes are shown in table 1.

Conclusions: Simultaneous liver kidney transplantation using a single subcostal incision did not show statistically significant benefit in length of hospital stay, opioid requirements on discharge or allograft function when compared to using dual incisions. Use of single incision for SLKT reduced the CIT for kidney allograft but was associated with a higher incidence of early bile leaks requiring operative intervention. Our initial outcomes need to be confirmed in larger studies.

	Single Incision (n=5)	Dual Incision (n=11)	p-value
Age (years, mean ±SD)	62.4 ±4.76	56.4 ±7.40	0.02
Male	80.0%	55.0%	
MELD (mean ±SD)	30.2 ±4.66	27.6 ±8.16	0.44
BMI (mean ±SD)	30.6 ±5.18	29.0 ±5.53	0.6
Operative time (hours, mean ±SD)	7.6 ±1.30	8.9 ±1.87	0.14
Cold ischemia, liver (hours, mean ±SD)	5.1 ±1.70	6.3 ±1.65	0.21
Cold ischemia, kidney (hours, mean ±SD)	7.9 ±0.88	10.3 ±1.64	0.04
Hospital stay (days, mean ±SD)	20.4 ±19.67	17.5 ±11.89	0.78
Morphine (mgEq) on discharge (mean ±SD)	9.4 ±14.19	26.1 ±20.36	0.12
Kidney Complications			
Primary non-function	1	0	
Delayed graft function	0	2	
Liver Complications			
Bile leak	3	0	
Bleeding	0	2	
Mortality (1-month)	0	1	

PUB328

Adiponectin Influences Skeletal Muscle Mass in Renal Transplant Recipients

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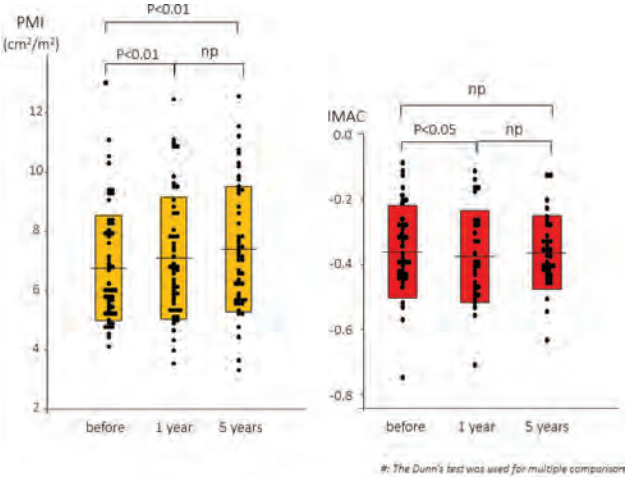
Background: The sarcopenia in chronic kidney disease is an important issue, however. The long-term association between skeletal muscle mass and serum adiponectin (ADPN) after renal transplantation (RTX) has not been investigated.

Methods: A retrospective survey of 51 patients who received renal transplantation at our hospital after 1998 (living donor: 40, cadaveric kidney: 11, 31 males and 20 females) was performed. The associations with the psoas muscle index (PMI), intramuscular adipose tissue (IMAC), and serum high molecular weight (HMW) - ADPN were investigated over time. In addition, the association of post-transplant diabetes mellitus (PTDM) with PMI and IMAC was investigated.

Results: The age at the time of transplantation was inversely correlated with PMI before RTX and positively correlated with IMAC before RTX (rS=-0.427, p=0.002; rS=0.501, p=0.001, respectively). Compared with that before RTX, PMI gradually increased after RTX (p<0.01). On the other hand, IMAC decreased at 1 year after RTX and then re-increased at 5 year after RTX (p<0.05). Moreover, the increase of the mean change of PMI after RTX was significantly influenced by the increasing mean change of HMW-ADPN levels on the multivariate analysis (beta=-0.140, p=0.003). Otherwise, the increases in the mean change of PMI and IMAC were detected as provocative factors of PTDM (beta=1.574, p=0.030 and beta=172.5, p=0.034, respectively).

Conclusions: In renal transplant recipients, sarcopenia judged by the mass and quality of psoas muscles after RTX may be associated with the alteration of serum HMW-ADPN levels and PTDM.

Funding: Government Support - Non-U.S.



PUB329

Incident Gout After Renal Transplantation in Gout-Naive Patients: Large Database Analysis

Brian LaMoreaux, Megan Francis-Sedlak, Robert J. Holt. *Horizon Therapeutics plc, Lake Forest, IL.*

Background: Patients undergoing kidney transplantation are at increased risk for developing hyperuricemia and gout compared to the general population (generally attributed to the frequent use of calcineurin inhibitors, cyclosporine and tacrolimus). However, the proportion of renal transplant patients that develop gout and the timing in which this occurs post-transplant is less established. This study sought to describe and quantify the incidence of gout in gout-naïve patients undergoing renal transplantation.

Methods: This retrospective analysis of Humana Research Database 2007-2017 claims data (private insurance and Medicare) was performed by identifying kidney transplant patients who were in plan for at least 6 months before and 5 years after transplant. Only patients without an ICD-9/10 gout diagnostic code within 6-months prior to transplant were included. Included patients were then examined for cumulative incidence of gout post-transplant.

Results: The database contained 16,454 patients that underwent kidney transplant. Of these, 920 patients underwent renal transplant, were in plan for at least 6 months before and 5 years after transplant, and did not have a gout diagnostic code before transplant. Of these, 212 patients (23%) had a post-transplant gout code while in plan, and 175 (19%) developed gout within 5 years post-transplant. The proportion of patients with gout progressively increased over time post-transplant and did not plateau. (**Figure 1**)

Conclusions: Gout is a known frequent comorbidity in solid organ transplant patients, but the timing and proportion of transplant patients who develop gout is not well described. Using a large database analysis, this analysis showed that the proportion of

gout-naïve patients undergoing kidney transplantation who develop gout is high and that this proportion only increases as patients are followed over a longer period of time.

Funding: Commercial Support - Horizon Therapeutics plc

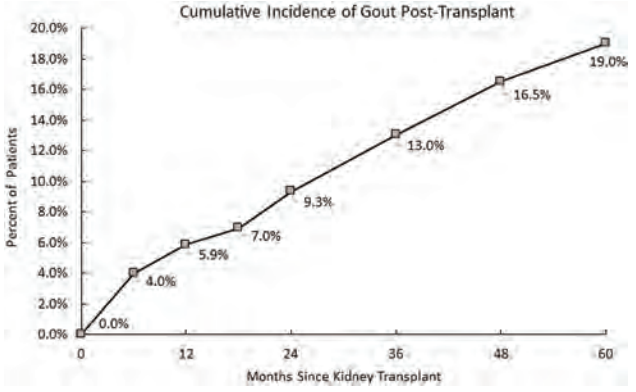


Figure 1. Proportion of gout-naïve kidney transplant patients who developed gout over 5 years post- transplant

PUB330

Impact of Recipient Age Older Than 70 Years on Outcomes Following Listing for Kidney Transplant: A Single-Center Analysis

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Background: Increasing number of older kidney transplant (KT) candidates poses a significant challenge for waitlist (WL) management. We hypothesize that advancing age impacts patient survival on the WL, after de-listing and post-KT. Our aim was to examine the magnitude of this age effect.

Methods: Out of 1965 patients listed for KT, the age distribution were: Group I: 19-60y (WL 1152, KT 631), Group II: 61-70y (WL 622, KT 238), Group III: >70y (WL 191, KT 71) (Table 1). Among KT patients, baseline donor, recipient and transplant variables were recorded (Table 2). The outcomes analyzed among KT patients were death, graft loss and impending graft loss (eGFR<20 mL/min per 1.73 m^2) (Table 2 & Fig 1).

Results: Only 71 WL patients >70y (37%) got a KT compared to 631 (55%) in Group I. Both among patients who were on WL and de-listed, the mortality rate was highest among patients >70y (12% and 20%) followed by Groups II and I (Table 1). The causes of de-listing were for physiological, medical or social reasons. There was a lower rate of living donor KT (24%) and higher KDPI (53±23%) in patients >70y (Table 2). Higher rates of death with a functioning KT was noted in patients >70y. Kaplan-Meier Actuarial Patient Survival was lower in the Group III than Group I (p<0.0001) (Fig 1). However, death censored graft survival rates were similar across all groups (p=NS).

Conclusions: Rates of KT in patients >70y is significantly lower than in younger WL patients. The mortality rate was highest among patients >70y in WL, de-listed and KT patients. Hence, active WL surveillance is mandatory for older patients. Strategies to identify sub-groups of older patients who will benefit from KT needs to be explored.

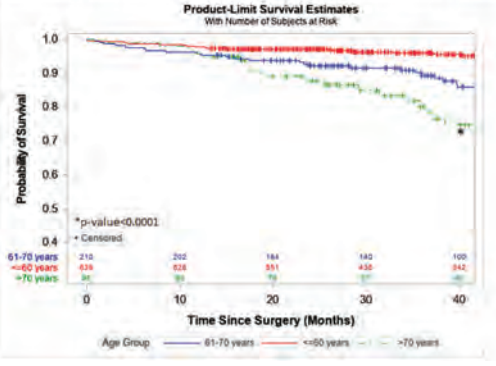
Table 1. Proportion of waitlisted patients who were transplanted or died while on WL or after delisting

Age at listing (yrs)	Number of patients N (%)	Transplanted N (%)	Died on WL N (%)	Died After Delisting N (%)	Still Listed N (%)
19-60	1152 (59%)	631 (55%)	82 (7%)	57 (5%)	382 (33%)
61-70	622 (32%)	238 (38%)	59 (9%)	64 (10%)	261(42%)
>70	191 (10%)	71 (37%)	23 (12%)	39 (20%)	58 (30%)

Table 2. Distribution of recipient and donor variables with kidney transplant outcomes

Variables:	All n=943	Group I: Age <60y n=638	Group II: Age 61-70y n=210	Group III: Age >70y n=95	P-value
Age (years),mean±SD	52.3±14.3	44.8 ± 10.9	65.1 ± 2.8	**74.02 ± 2.8**	**<.0001**
Male, N(%)	552 (58.5%)	356 (55.8%)	**133 (63.3%)**	**63 (66.3%)**	**0.0422**
ESRD due to HTN, N(%)	186 (19.7%)	106 (16.6%)	48 (22.9%)	32 (33.7%)	**<.0001**
Living donor, N(%)	338 (35.8%)	248 (38.9%)	67 (31.9%)	**23 (24.2%)**	**0.0282**
KDPI, % mean±SD	46.1±25	41.8± 24.7	54.3±24.3	**52.9 ± 22.6**	**0.0282**
DGF, n(%)	163 (17.3%)	100 (15.7%)	**49 (23.3%)**	14 (14.7%)	**0.0308**
Outcomes:					
Deceased, n(%)	89 (9.4%)	34 (5.3%)	32 (15.2%)	**23 (24.2%)**	**<.0001**
Graft Loss, n(%)	91 (9.7%)	55 (8.6%)	26 (12.4%)	10 (10.5%)	0.2651
Impending graft loss	57 (6%)	40 (6.3%)	9 (4.3%)	8 (8.4%)	0.3421

Figure 1. Kaplan Meier Patient Survival Curve among 3 age groups undergoing kidney transplantation



PUB331

Low Rates of Preemptive Kidney Transplantation: A Root Cause Analysis to Identify Opportunities for Improvement

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Background: Preemptive living donor kidney transplantation, has several advantages over transplantation after dialysis initiation including improved patient survival and reduced healthcare costs. The St. Joseph's Healthcare Hamilton transplant program performs approximately 30 living donor kidney transplants each year, however only 20% of are preemptive. When trying to improve complex healthcare problems such as this, an in-depth root cause analysis can be conducted to fully understand program-related barriers.

Methods: We conducted a retrospective observational study of random sample of 50 living donor kidney transplants in our program that were performed between January 1, 2017 and September 30, 2018. Root Cause Analysis (RCA) provided methodology for this study.

Results: Of the 50 recipients, only 11 (22%) achieved a preemptive transplant. The majority of those who achieved a preemptive transplant were referred with a GFR ≥ 15 (64%). Sixteen recipients (32%) were already on dialysis at the time of referral. Of the remaining 23(46%) who were referred preemptively, Major root causes were identified, 18 (78%) had a GFR less than 15 at the time of referral, 12 (37.5%) had medical issues resulting in delayed clearance for transplant, 9 (28%) participated in the Kidney Paired-Exchange program and 8 (25%) required evaluation of multiple living donors before an eligible donor was found. On further analysis of the durations for assessment milestones, it was found that the median time from recipient referral to clearance was just over 13 months. It was also found that the median time from donor contact to clearance was nearly 8 months. Both of these were longer than ideal.

Conclusions: Our analysis demonstrates that the timing of recipient referral is a significant cause of failing to achieve preemptive kidney transplantation. Additional studies with further investigation of referral practices and modality education as well as causes for delays during the assessment process are needed.

PUB332

Early-Onset Anemia After Kidney Transplantation Is an Independent Risk Factor for Graft Loss

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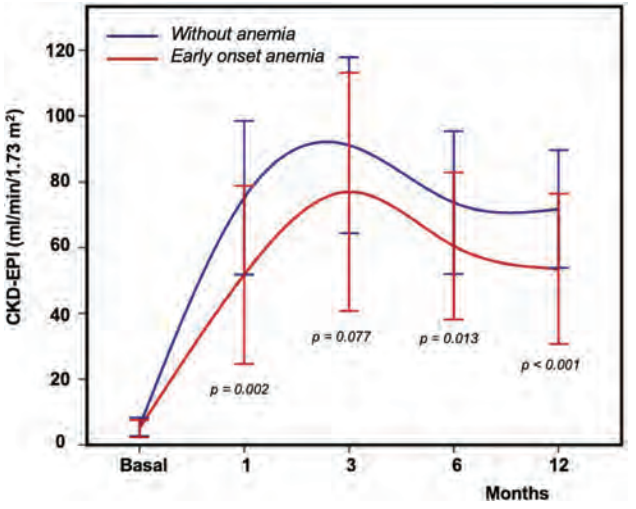
Background: Post-transplant anemia (PTA) is multifactorial and highly prevalent. PTA is associated with graft loss and in most studies with increased mortality. The purpose of this study was to assess whether the presence of anemia at first month post transplant is an independent risk factor of graft survival.

Methods: Patients who underwent kidney transplantation followed-up at a single center who survived at least 1 year after transplantation were included. Data were collected

from the kidney transplant registry from 2012 to 2016. Demographic and clinical data were collected at baseline, 1, 3, 6 and 12 months post transplant. Patients were divided into two groups (anemic and nonanemic) based on the presence of anemia (hemoglobin 10.5 g/dl at first month post transplant). Primary outcome was a composite of patient and graft survival.

Results: Our cohort included 64 patients with follow-up of 28.6 ± 11.4 months, 16 (25%) had early PTA. Baseline characteristics such as age, gender, type of donor, etiology of endstage kidney disease, induction therapy, type of primary immunosuppression, histological characteristics of the zero and follow-up biopsy were similar in both groups. During the study period, a decrease in renal function was observed in the group of early anemia (Figure 1). Creatinine clearance at last follow-up was significantly lower in anemic (58.1± 21.7 ml/min) and nonanemic group (72.3 ± 18.3 ml/min) (p= 0.013). A Kaplan–Meier survival analysis at 5-year post-transplant showed significantly poorer graft survival in the anemic group, p= 0.03. On multivariable analysis, the anemia group was significantly associated with graft loss (HR 12.6, 95% CI 1.5-15.7, p=0.19).

Conclusions: In this study, early onset anemia was independently associated with graft loss, without differences in mortality. PTA must be corrected immediately to avoid poor prognosis outcomes.



PUB333

Cytomegalovirus Pathology in Renal Transplanted Patients: Determining Factors And Relation With Graft And Patient Outcomes

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Background: CMV pathology (CMVp) is frequently observed during renal transplantation (RTx). Its impact on graft and patients (RTxp) outcomes is still debated. Our observational retrospective study evaluates:1) the prevalence and the factors related to CMVp, CMV infection (CMVi) and CMV disease (CMVd) during the 1st year of RTx; 2) the link between CMVp and graft and RTXp survival.

Methods: In 505 RTxp (age:50[41;58]yrs–87 males, follow up (FU) 8[5-11]yrs), RTx between 2004-2016, clinical and biochemical data were recorded at 1(T1) and 12(T12) months of RTx. Donor(D) and Recipient(R) CMV serology was tested at RTx. CMV IgG-D+/IgG-R- RTxp (12%, D+R-) and high risk RTXp received CMV prophylaxis for 3 monyhs. CMVp was defined by either CMVi (CMV replication without CMVd signs) or CMVd (CMV replication with symptoms and/or need of antiviral therapy/reduction of immunosuppression). The outcomes investigated were:1) graft: reduction (T1-T12) of eGFR (MDRD) >20%; reduction (T1-end of FU) of eGFR>50% (eGFRr>50%); graft loss (GL); eGFRr>50% + GL; 2) RTxp survival at the end of FU.

Results: 90% of RTxp had a deceased D kidney, 73% were haemodialysed (HD+) before RTx. Dialysis vintage (DV) was 50[33-75]mths. ATG were used in 12%. Steroids dose was 880[840-105]mg and 2272[2598-3223]mg at T1 and T12. During the 1st year of RTx, 45% of RTxp had CMVp (CMVp+). CMVp+ were older than CMVp-. Females, HD+ and D+R- were more prevalent in CMVp+. At T1, CMVp+ had lower albumin(alb), haemoglobin and higher PTH, uric acid and CRP than CMVp- and, both at T1 and T12, received higher steroid dose. Alb-T1 was the most significant modifiable factor related to CMVp+ (p=0.009 OR 0.50), also after the addiction of D+R- to the model (alb-T1:p=0.008 OR 0.48; D+R-:p=0.01 OR 2.16). CMVd(25%) had lower DV and higher prevalence of D+R- than CMVi(19%). GL and death were observed in 11% and 8% of RTxp. In survival analyses, no relation between CMVp, CMVi and CMVd and outcomes were found.

Conclusions: CMVp is highly prevalent during the 1st year of RTx. Alb-T1 has high impact in CMVp insurgence and might reflect the influence of the pre-RTx status in CMVp. CMVp doesn't influence early and long term outcomes, experienced however in few RTxp. Future studies, prospective and with more RTxp, might better elucidate this issue.

PUB334

Antibody-Mediated Rejection Detection: A Noninvasive Perspective

Nidal Alhosainat, Ann Kathleen N. Gamilla-Crudo, Syed A. Hussain, Muhammad A. Mujtaba. *Univ. of Texas Medical Branch, Galveston, TX.*

Background: Antibody mediated rejection (AMR) is a dreaded complication after a kidney transplant. Usual markers such as a rise in serum creatinine and/or the development of proteinuria may be too late to detect graft dysfunction. Although a kidney biopsy is still the gold standard for diagnosis, it is invasive and molecular changes may have already occurred prior to changes in histology. Monitoring the increase or development of de novo donor specific antibodies (DSA) and detection of donor-derived cell-free DNA (ddcfDNA) are some of the tools in current use to detect early rejection prior to a rise in serum creatinine. We aim to examine the relationships of these biomarkers before and after treatment as the conglomerate of these tests may be better than one test alone.

Methods: We studied five patients who received a kidney transplant from years 2007-2019 at our institution. Serum creatinine, urine protein/creatinine (UPC), and DSA were followed routinely. DSA surveillance was done at 1, 3, 6, 12 months then yearly post-transplant. A kidney biopsy for cause was obtained in all of them. Four patients had ddcfDNA testing. The patients were treated based on biopsy results. Serum creatinine, UPC and DSA were prospectively followed at 1, 3 and 6 months after treatment.

Results: In two of five patients, creatinine was at baseline during the time of biopsy. UPC during rejection was significant only in two patients while all patients had a significant increase in DSA. Only two of four patients had ddcfDNA results compatible with rejection. (Results Table Image)

Conclusions: Based on our findings with a series of patients, no single test was superior to a kidney biopsy when used alone. The detection of a significant increase in DSA after transplant even without a rise in serum creatinine or proteinuria should alert one to proceed with a kidney biopsy. Testing for ddcfDNA may or may not be helpful and more studies are needed to elucidate its role.

Patient	Baseline Cr (mg/dl)	Cr at Rejection (mg/dL)	Baseline UPC	UPC at rejection	Baseline DSA (MFI)	DSA at rejection (MFI)	ddcfDNA at rejection (%)
1	1	1.4	0.15	0.07	No DSA	C1 (16805) C2 (13206)	1.2
2	5.3	8.5	9.4	25	No DSA	C1 (24145) C2 (1759)	N/A
3	1.4	1.4	0.3	0.3	No DSA	C2 (30941)	<0.15
4	0.9	1.4	0.33	1	C2 (64642)	C2 (75340)	0.37
5	3.1	1.5	1.9	1.8	No DSA	C1 (30138) C2 (47427)	2.5

Results Table

PUB335

Azathioprine-Associated Acute Fibrinous Organizing Pneumonia in a Post-Renal Transplant Patient: Rare Case

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Introduction: Acute fibrinous organizing pneumonia may occur as an idiopathic variety or in association with autoimmune diseases, occupational, environmental exposures or drug reactions as well as various infections. Azathioprine may lead to acute fibrinous organizing pneumonia.

Case Description: A 62Yr old man with a history of diabetes mellitus, hypertension, sickle cell trait and chronic kidney failure (DKD-biopsy proven) is a post renal transplant recipient (04/02/18). He was on triple immunosuppresent(tacrolimus, azathioprine and wysolone). Initially he was taking mycofenolatemofitil for 2 months, later due to multiple episodes of loose motion MMF was replaced with Azathioprine. 40 days later he presented with c/o –Non-productive cough, sore throat, fatigue, fever, Shortness of breath, generalised weakness. Various pulmonary, cardiac and infectious etiologies were ruled out. Lab test shows normal CBC, PCT<0.25, S.ANA was negative, negative blood and urine culture, respiratory panal was negative, BK virus and cytomegalovirus was negative, Urine legionella antigen and mycoplasma pneumonia came to be negative, Gene expert was also negative. Pleural fluid was transudative, shows low cell count and Pleural ADA was 20. A chest x-ray showed a consolidation in right middle lobe that was further verified by CT chest. Empirical antibacterial and antifungal were started, no response of antibiotics seen in 2 weeks so Open lung biopsy was performed. azathioprine was replaced with MMF and High dose of steroid (1mg/kg) was started. Patient improved gradually after stopping azathioprine. Serial X-rays showed resolution of opacity. Histopathology of lung biopsy was compatible with a AFOP. The patient was diagnosed as an AFOP probably secondary to Azathioprine.

Discussion: Acute fibrinous organizing pneumoniais a rare but important differential diagnosis to consider in patients having flu like symptoms with radiological changes of ground glass opacity non-responding to antibiotics. The patient presented here was suspected to have an respiratory infection. However, reassessment of the case led to the diagnosis of a AFOP. AFOP should be an important diagnostic consideration in patients presenting with flu-like symptom, not responding to antibiotics, in patients taking azathioprine.

PUB336

A Successful Kidney Transplant in a Patient with Inferior Vena Cava Thrombosis and Esophageal Varices

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Introduction: Kidney transplant is the preferred treatment for patients with chronic kidney disease on dialysis. Prolonged use of dialysis catheters are associated with complications like infections, thrombosis and development of superior vena cava syndrome. Superior vena cava obstruction is known to be a rare cause of esophageal varices and can lead to upper gastrointestinal bleeding. Finding a venous thrombosis prior to transplant may provide additional challenges by further increasing the risk of graft failure.

Case Description: A 27 year old male patient known to have end stage renal disease and systemic arterial hypertension presented for kidney transplantation. He had been on hemodialysis for six years. His access was a left femoral tunneled catheter which was changed to a temporary catheter due to a catheter related blood stream infection. He had had several subclavian and internal jugular vein catheters fixed before which had led him to develop superior vena cava syndrome with multiple areas of thrombosis within the superior vena cava. He had been started on warfarin for the same. During the work up for the kidney transplant, he developed hematemesis and an endoscopy done showed esophageal varices which were managed conservatively. A CT aortogram showed a ten centimeter non-occlusve thrombus in the inferior segment of the inferior vena cava and an occlusive chronic thrombus of the left common iliac vein. The patient was started on enoxaparin for three months. He underwent a successful kidney transplant. The graft kidney was placed in the right iliac fossa and the renal vessels were anastomosed to the external iliac vessels.

Discussion: Superior vena cava syndrome is a common complication of prolonged use of dialysis catheters inserted in the subclavian and internal jugular veins. Rarely, it can cause esophageal varices which can lead to upper gastrointestinal bleeding. Our patient presented a challenge in that he had esophageal varices which increased his risk of bleeding and he required anticoagulation for the inferior vena cava thrombosis for a successful transplant. The other dilemma was where to place the graft kidney and which vessels to use for anastomosis as he had a ten centimeter clot in the inferior vena cava. We opted to wait for three months and anticoagulated him with enoxaparin and then transplanted him.

PUB337

An Analysis of Epidemiology, Etiology, and Outcomes of Acute Pancreatitis in Renal Transplant Recipients

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Background: Acute pancreatitis after renal transplantation is seldom seen, yet a dreadful complication. The causes include traditional causes and immunosuppressive medications, viral infections. Classical symptoms are not always present at onset, which may cause delay in diagnosis. The available literature on pancreatitis in renal transplants is either as case reports or case series. Large studies with longer follow up period and outcome in renal transplant patients with pancreatitis are lacking. We conducted this retrospective study to analyze the incidence, clinical features, causes of pancreatitis in our institute in post azathiophrine era.

Methods: We conducted a single center retrospective study of renal transplant recipients who suffered at least one episode of acute pancreatitis during a period from Jan 2002 to September 2018. We followed IAP/APA (International Association of Pancreatology/American Pancreatic Association) evidence based guidelines for confirming diagnosis of acute pancreatitis and included only patients who fulfilled these criteria. Once the diagnosis is confirmed we retrospectively analyzed the aetiology, clinical features, management and outcomes of renal transplant recipients with pancreatitis.

Results: Twenty-six patients (males 81%; mean age 38.5 years) out of 1350 allograft recipients developed 39 episodes of acute pancreatitis. The incidence of acute pancreatitis was estimated to be 0.12% per patient year (1.9% patients). The interval between transplantation and pancreatitis ranged from < 1month to 14 years. Four patients had pancreatitis in immediate post transplant period (<1 month). Etiology included were drugs chiefly (61.4) gallstones (19.3%), structural lesions (11.5%) and viral infections (7.8%). Clinical presentations, laboratory parameters were similar to pancreatitis in non transplant patients. Graft dysfunction was noted in twenty patients (77%) and all showed either partial or complete recovery. Patient survival was good with 88% of the patients surviving the episode while three (11.5%) patients expired during the episode. Mean duration of follow up was 34.14(0-108) months. The 1-year, 5-year and 10-year survival rates after an episode of acute pancreatitis was 65.78%, 55.67% and 27.83%.

Conclusions: Pancreatitis after renal transplantation is a rare complication with better outcome than what has been reported in the past.

PUB338

Prevalence and Predictors of Sensory Polyneuropathic Signs and Symptoms in Renal Transplant Recipients

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Background: Sensory polyneuropathy is a common finding in renal transplant recipients (RTR). Patients with end stage renal disease are at a high risk to develop uremic or diabetic polyneuropathy. Kidney transplantation frequently fails to improve polyneuropathic signs and symptoms post- transplantation. However, little is known about the exact prevalence of post-transplantation sensory polyneuropathy. Therefore, our aim is to determine prevalence and possible predictors for sensory polyneuropathy in RTR.

Methods: RTR and healthy subjects, examined prior to renal donation, were included in the TransplantLines biobank and cohort study at the University Medical Center Groningen. The primary outcome was the result of the adapted modified Toronto Clinical Neuropathy Score (amTCNS), a scoring tool designed to quantify neurological complaints and to rate symptoms of sensory polyneuropathy. Information on relevant clinical parameters i.e. age, height, presence of diabetes mellitus, serum urea levels, eGFR, levels of parathyroid hormone, potassium, folic acid, vitamin B-12, and use of calcineurin inhibitors was collected from all subjects. A chi-square test was used to compare prevalence of sensory polyneuropathy between RTR and healthy subjects. Multivariable linear regression analysis was performed to assess the relationship between explanatory variables and sensory polyneuropathy.

Results: A total of 209 RTR (65.1% males) with a mean age of 54.9±13.4 (range 17-80) years, and 122 healthy subjects (46.7% males) with a mean age of 55.9±11.2 (range 27-75) years were included. Signs and symptoms of sensory polyneuropathy were present in 48 (23.0%) RTR and in 6 (4.9%) healthy subjects (P<0.001). Serum urea (st. b=0.28, P=0.003) and age (st. b=0.25, P=0.001) were independent predictors of sensory polyneuropathy in RTR.

Conclusions: Polyneuropathic signs and symptoms are more common in RTR than in healthy subjects. Serum urea and age are independent predictors of sensory polyneuropathy in RTR, making uremic polyneuropathy the most likely underlying etiology in this particular patient setting.

PUB339

Outcomes of Late Acute Rejection Treatment with r Anti-Thymocyte Globulin (r-ATG) 1 Year Post Kidney Transplant

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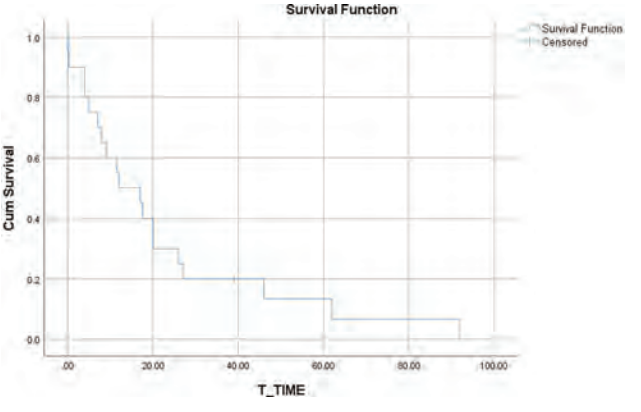
Background: The aim of this study is to investigate the relationship of Late Acute cellular Rejection (LAR) episodes, treated with r-ATG one year post transplantation, with reversibility of graft dysfunction and long-term graft survival

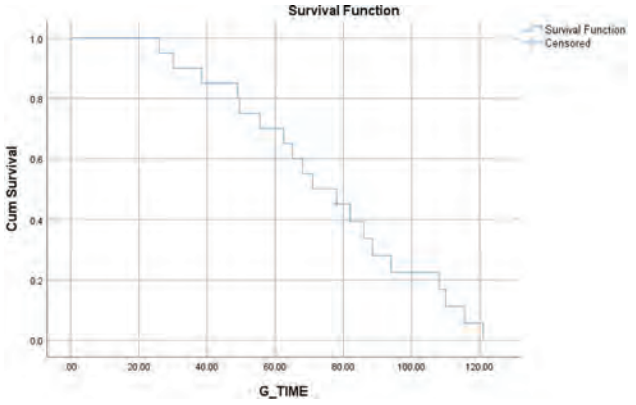
Methods: Data of 20 recipients reviewed who received r-ATG between 2009 and 2016 for biopsy proven LAR. Age at transplant 33.9 ± 15 years, 11 M, 9 F and 11 Caucasians with biopsy proven LAR one year post transplant. Non-adherence was the most common reason for acute rejection (65%). Mean r-ATG cumulative dose was 6.25 mg/kg. All recipients received IV steroids/ oral Prednisone taper. Maintainance immunosuppression included Calcineurin Inhibitors, Antimetabolites and Prednisone.18 recipients had Banff 1B or higher grade acute celular rejection (ACR). 4 recipients had combined ACR and Antibody Mediated Rejection.

Results: Pre biopsy Cr 1.75 +/- 0.7. Cr at the time of biopsy 5.45 +/- 2.87. Time lapse (days) between baseline Cr and Biopsy was 157.4 +/- 193.2. Post r-ATG Cr at 6 mon was 3.3 +/-1.8. Post r-ATG, 9 (45%) recipients had graft failure before 12 months, 7 had graft failure between months 13 to 36 and 4 had functional graft beyond 36 months. Only 1 recipient has a functional graft to date (92 months post r-ATG treatment). Mean Graft survival from date of transplant was 73.8 months +/-27.6 and graft survival post r-ATG was 22.6 months +/- 23.3.

Conclusions: Late Acute Cellular Rejection severely reduces long term graft survival Acute rejection treatment with r-ATG should be used in very selective patients as it may benefit only very few patients.



Post r-Thymo Graft Survival



Post Transplant Graft Survival

PUB340

Comparison of Outcomes with and Without Induction Therapy in Low-Risk Renal Transplant Recipients

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Background: With low rates of acute rejection with current maintenance immunosuppression consisting of steroids, MPA and tacrolimus, question arises whether induction offers any additional benefit in low risk renal transplant recipients. This study evaluated outcomes with and without induction in low risk renal transplant recipients.

Methods: A prospective observational study in which 100 low risk renal transplant recipients were included and divided into 2 groups – one that received induction and another that did not. They were followed for 1.5 years. Three end points were compared - efficacy of induction, patient and graft survival and adverse effects.

Results: Incidence of rejection in early post transplant period did not differ (4% NO IND vs 6% IND; p=0.171). Rejection as cause of late graft dysfunction was seen in 16% in IND vs 20% NO IND; (p=0.603). No difference in serum creatinine at end of 1.5 years was seen. Graft survival was also similar. Relapsing and recurrent UTIs (46% IND vs 16% NO IND; p=0.09), hospitalization requiring infections (76%IND vs 64% NO IND; p=0.119 NS) were more common in IND. CMV infection affected only IND (6% vs none; p=0.07). Patient survival at 1.5 years was comparable (94% IND vs 96% NO IND; p=0.646).

Conclusions: The study showed comparable results between IND and NO IND with however an increased incidence of infections and hospitalizations in IND group. Use of induction may be avoided in low risk renal transplant recipients.

PUB341

Variations of Serum Creatinine in Patients with Hospitalizations in the First and Second Year of Renal Transplantation

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Background: The kidney transplant patients the main causes of hospitalization are infections and kidney graft rejection. The aim of this study is to analyze the variations in serum creatinine levels in kidney transplant patients who had hospitalizations in the first and second year of transplantation.

Methods: Retrospective observational study, 28 patients with kidney transplant were selected in the 2016-2018 period, divided into two groups; First year and second year of transplantation, the data was taken from the database of the Civil Fray Antonio Alcalde hospital in Guadalajara, demographic characteristics are shown in numbers, percentages, mean, standard deviation and non-parametric Wilcoxon.

Results: The baseline characteristics of the 28 patients, 15(53.6%) are male, a mean of 28.5 years of age, 19(67.9%) was living donor, 9(32.1%) from a brain death donor, the average number of hospitalizations was assessed in the first and second year 1.94 and 1.8 respectively, main diagnoses of hospitalization were urinary tract infections and graft rejection, baseline creatinine in the first year group with an average of 1.3mg/dl and the second year group an average of 2.6mg/dl, the Wilcoxon test comparing baseline creatinine and creatinine variations at the end of the follow-up of both first year P=0.51 and second year group P=0.31

Conclusions: No significant differences were found in both groups in the variations of creatinine levels with respect to baseline levels, which concludes that hospitalizations in the first two years of kidney transplantation have a minimal impact on creatinine levels and that probably related to renal functional reserve of the graft

Table: Demographic characteristics / Wilcoxon rank

	Global n=28	First year n=18	Second year n=10
Gender(m)(%)	15(53.6)	13(72.2)	2(20)
Age (years)(SD)	28.5(10.7)	31.6(1.3)	22.9(5.1)
Causes of CKD			
Unknow etiology(%)	12(42.9)	9(50)	3(30)
Hypertension (%)	1(3.6)	1(5.6)	0
Lupus (%)	2(7.1)	2(11.1)	0
Urinary malformations (%)	11(39.2)	6(33.3)	5(50)
GMN (%)	1(3.6)	0	1(10)
Kidney stones (%)	1(3.6)	0	1(10)
Previous dialytic treatment (%)	25(89.3)	16(88.9)	9(90)
PD(%)	8(28.6)	4(22.2)	4(40)
HD(%)	17(60.7)	12(66.7)	5(50)
Type of donor			
Living donor (%)	19(67.9)	14(77.8)	5(50)
Brain death donor (%)	9(32.1)	4(22.2)	5(50)
Esquema de inmunosupresión			
Tac,Ma,Pred(%)	25(89.3)	17((94.5)	8(80)
Basal serum creatinine (SD)	1.76(2.2)	1.3(0.6)	2.6(3.7)
Creatinine variation (SD)	2.2(2.7)	1.5(1.3)	3.37(4.1)
Hospitalizations (DE)	1.89(1.5)	1.94(1.5)	1.8(1)
Basal serum creatinine wilcoxon range and creatinine variation (P)		0.51	0.31

m; Male, SD; standard deviation, CKD; Chronic Kidney Disease, GMN; glomerulonephritis, PD; peritoneal dialysis, HD; hemodialysis, TAC; Tacrolimus, MA; mycophenolic acid, Pred; Prednisone, P; Valor of P, CI; confidence interval

PUB342

Current State of Renal Transplant Patients in a Southern Area of Algeria

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Background: Renal transplantation (RT) is the best treatment for end stage renal disease (ESRD). The aim of this study, is to examine the clinical situation of transplant patients in Ghardaia

Methods: In this observational and descriptive study, we included all kidney transplant patients for more than a year, and living in Ghardaia we examined the patients and consulted their medical files

Results: Twenty-six patients are included, the average age is 35 (22 - 53), sex ratio is 0.6, the average duration in dialysis was 5 years, two preemptive grafts, all the patients were in hemodialysis befor graft. The kidney donor was, in 36% a siblings, 32% a parent, 22% a spouse, 2 cases of unrelated donor, the average donor age was 42 the average duration of the transplant is 7.5 years The estimated GFR by CKD EPI is 53 ml / min / 1.73 m2 (23 - 102) 68% of patients are hypertensive, dyslipidemia present in 23% and overweight in 45% of cases, no case of diabetes Infectious complications are frequent: urinary 40%, pneumocystis 23 % and brucellosis 17 %, one case of cryptococcal disease. surgical complications are rare, 03 cases of ureteral stenosis immunosuppressive therapy is: ciclosporin 40%, tacrolimus 45%, two patients on sirolimus and five patients without corticosteroids A case of PTLD (Kaposi's tumor) in a young patient of 32 years old and a case of breast neoplasia in a 42 years old woman only 03 graft biopsy was performed

Conclusions: Despite the young age of the patients, short duration of transplantation and an adequate immunosuppressive treatment, the function of the grafte is weak The infectious risk to unusual germs is important, it is probably due to rural living and climatic conditions high heat and drought Non-collaboration between the transplanting centers and local nephrologists, absence of systematic graft biopsies, and the scarcity of experienced laboratories, are not neligible factors.

PUB343

Incident Parkinson Disease in Kidney Transplantation Recipients: A Nationwide Population-Based Cohort Study in Korea

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Background: Patients with end stage renal disease (ESRD) have a substantially increased Parkinson disease (PD) risk, but few studies have examined the risk of PD in kidney transplant (KT) recipients. In this study, we aimed to estimate the risk of incident PD in KT recipients compared with general population (GP) or ESRD patients.

Methods: From the Korean National Health Insurance Service database, we identified incident KT recipients aged ≥ 40 years without any history of PD between 2007 and 2015. We also established two control cohorts without a history of PD: 1) GP cohort of insured

subjects without a history of kidney disease, 2) ESRD cohort of incident ESRD subjects, with frequency matched for age, sex, and inclusion year. PD was diagnosed on the code of the International Classification of Disease, 10th Revision (G20-22).

Results: We followed 8,198 KT recipients, ESRD patients, and GP for 44,808, 36,559, and 46,578 patient-years, respectively. Their mean age was 51.2 years and 59.7% were men. Over observation periods, 18, 43, and 13 incident PD occurred in KT, ESRD and GP group, respectively. KT recipients showed a significantly lower risk of incident PD compared to ESRD patients (adjusted hazard ratio [HR] 0.32, 95% confidence interval [CI], 0.18 to 0.56, P<0.001) and a similar risk of incident PD compared to GP group (adjusted HR 0.99, 95% CI 0.40 to 2.60, P<0.001) even after adjustment including age, sex, diabetes mellitus, hypertension, dyslipidemia, and Charlson's comorbidity index, income. The strongest predictor for incident PD was older recipient age in KT recipients.

Conclusions: We found that risk of incident PD after KT was significantly lower than ESRD patients and similar to GP. Older age at the time of KT was an independent risk factor for PD occurrence in KT recipients.

PUB344

Clinical and Pathological Factors Influencing Residual Renal Function After Living Donor Nephrectomy

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Background: Living kidney transplantation is an established renal replacement therapy for end-stage renal disease patients. To assess living kidney donor's renal function, computed tomography (CT) and renal scintigraph was used to evaluate single renal function. Low total kidney volume (TKV) is reported to be associated with a decline in GFR after living kidney transplantation. However, pathophysiological findings such as glomerulosclerosis at the time of one-hour protocol biopsy are not fully evaluated as factors influencing post-transplant renal function. In this study, we evaluated the correlation of potential influencing factors including TKV and glomerulosclerosis with pre- and post-transplant renal function in living kidney donors.

Methods: This is a retrospective study including all 37 living related kidney donors seen at Kyoto University Hospital from January 2013 to April 2019. Estimated glomerular filtration rate (eGFR) was calculated using equation for Japanese population from serum creatinine levels at pre- and post-transplant. TKV was calculated from the 3D volume-rendered images of enhanced CT, and adjusted to standard body surface area (BSA) by individual BSA. The ratio of number of non-glomerulosclerosis per that of whole glomeruli (non-GS) was evaluated by protocol renal biopsy at one hour after renal reperfusion. This study protocol was approved by the Ethics Committee on human research of the Graduate School of Medicine, Kyoto University.

Results: We evaluated 37 living kidney donors (35.1% male, mean age 58.2 ± 12.0 years). Mean pre-transplant eGFR was 75.7 ± 12.1 ml/min/1.73m^2, mean post-transplant eGFR; 44.9 ± 7.75 ml/min/1.73m^2, adjusted TKV (aTKV); 349.3 ± 58.4 ml, and non-GS; 0.892 ± 0.086. Pre-transplant eGFR was associated with aTKV and aTKV×nonGS (r=0.525, 0.569 respectively, p<0.01). Post-transplant eGFR was associated with age(≧65 years old, p<0.01), aTKV, non-GS, and aTKV×non-GS (r=0.527, 0.344, 0.626 respectively, p<0.05). The rate of eGFR decline was associated with age (≧65 years old, p=0.044), but not with aTKV and non-GS, aTKV×non-GS.

Conclusions: Pre-transplant eGFR was more associated with aTKV×non-GS than aTKV. These results suggest that non-GS and age are correlated with post-transplant renal function, and non-GS also tends to influence pre-transplant renal function in living kidney donor.

PUB345

Outcomes of Renal Transplantation in Adult Patients with Primary Focal Segmental Glomerulosclerosis: A Single-Centre Experience

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Background: Focal Segmental Glomerulosclerosis (FSGS) is the most common primary glomerular cause of end stage kidney disease (ESKD). Renal transplantation in patients with FSGS is complicated by recurrent disease, which is reported in 30-50% of cases and may lead to graft loss. It is important to identify patients at high risk of recurrent disease to improve transplant outcomes and to inform the consent process.

Methods: We performed a retrospective database search (n=3533) of all patients with primary FSGS transplanted at our centre over a 50 year period, and evaluated their transplant outcomes. Recurrent disease was diagnosed on renal transplant biopsy in patients with proteinuria. Data are expressed as median +/- interquartile range.

Results: We identified 111 transplants in 106 patients with ESKD due to primary FSGS. Detailed follow up data were available for 80 patients; 59% male 41% female with median age at transplantation 43 (+/- 18) years. 66% patients were Caucasian. 69% transplants were from live donors. Median follow up period was 7.5 years. Recurrent FSGS occurred in 16% (n=13) patients; 55% male and 61% Caucasian. Length of time from transplant to recurrence was between 3 months and 10 years. Graft loss due to recurrent FSGS occurred in 77% (n=10) patients with recurrent disease.

Conclusions: Our large single centre study shows that recurrent FSGS following renal transplantation is much lower than in published studies, but that recurrent disease leads to graft loss in most patients. This data will inform shared decision making in patients with primary FSGS.

PUB346

Different Dosages of Rituximab in ABO-Incompatible Kidney Transplant: A Comparative Study of B Cell Count, Antibody Titre, and Graft Function

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Background: Forty percent of live -related donors from family are lost because of ABO blood group incompatibility in India. To increase the donor pool, ABO-Incompatible Transplants, which have shown equally good results as that of ABO-Compatible transplants is gaining popularity. One cocern of ABO-I transplantation is over immunosuppression and related complication. Rituximab, which depletes B cells is an important constituent in the desensitisation protocols of ABO-I transplantations. Dose of Rituximab varies from center to center from 100mg/body to 500mg/body. There are only few studies comparing the efficacy and adverse effects of various doses of Rituximab. We studied the efficacy of Rituximab in a low dose (100mg/body) versus higher dose (200mg/body) by comparing B cell count (CD-20) and comparing the patient and graft outcomes.

Methods: The study was conducted in Narayana Health Hospitals (RTIICS), Kolkata from December 2016 to November 2017. Total 64 patients of ABO-I kidney transplant patients with initial ABO blood group Antibody titer of 512 or, less were included and devided in to two groups :A and B. Two weeks prior to transplantation Gr A patients received 100 mg of Rituximab and Group B 200 mg. They received simillar desesitisation treatments. Their Serum creatinine, Antibody titer, B cell count besides the complications (if any) were monitored for one year.

Results: No diference was found between two groups in base line characterstics, follow up antibody titer, B cell count, rejection, graft survival, patient survival. Though infection rate was more in patients receiving 200mg Rituximab, it was not stastically significant.

Conclusions: In patients of ABO-incompatible renal transplant with intial ABO antibody titer of 512 or, less Inj Rituximab in a dose of 100 mg gives simillar graft and patient outcome as Inj Rituximab of 200 mg in shorter term. The Rejection rate, Antibody titer, B cell count is comparible in both higer dose and lower dose of Rituximab. The rate of infection is lower in low dose Retuximab. Patients with ABO ab titer of 512 or, less may be given inj Rituximab in a lower dose (100mg/body)

PUB347

Kidney Transplants from Uncontrolled Donation After Circulatory Death Do Not Show Greater Risk for Infection

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Background: Kidney transplantation is the best renal replacement therapy but there are acknowledged associated risks including infection. We aimed to assess if known risk factors for infection (as delayed graft function (DGF), immunosuppresion) where significant in cases of uncontrolled donation after circulatory death (uDCD).

Methods: To evaluate possible greater risk of infection of uDCD recipients in comparison with donation after brain death (DBD) recipients. - Unicentric retrospective study of case and controls, comparing 237 uDCD recipients with 237 DBD recipients. All uDCD recipients received Thymoglobulin as induction therapy and delayed introduction of calcineurin inhibitor (CIN), with CMV prophylaxis with valgancyclovir for 3-6 months. Some DBD recipients received induction therapy with basiliximab. - We systematically collected data of infectious events which required hospitalization, fungal infections and viral infections detected in outpatient clinic.

Results: See Table

Conclusions: UDCD recipients did not show increased risk for infection provided that they receive adequate prophylaxis therapy, despite greater DGF and induction therapy with thymoglobulin. Incidence of CMV infection is lower in uDCD recipients, which is attributable to CMV prophylaxis.

Baseline characteristics and results

	uDCD	DBD	p-value
Donor age (years)	43.5 ± 9.9	42.8±11.7	0.49
Gender (male %)	209 (88.2)	162 (68.4)	〈0.001
Donor creatinine (mg/dl)	1.3±0.4	0.8±0.2	〈0.001
Recipient age (years)	47.9±10.9	46.4±11	0.15
Recipient gender (male%)	141 (59.5)	163 (68.8)	0.03
Diabetes mellitus (%)	44 (18.6)	29 (12.2)	0.06
Prior kidney transplant (%)	14 (5.9)	0 (0)	〈0.001
Cold ischemia time (h)	12.4±4.4	20±4.1	〈0.001
Warm ischemia time (min)	132.5±20.6		
Induction therapy (%) Thimoglobuline AntiCD25	220 (92.8) 17 (7.2)	0 (0) 63 (26.6)	〈0.001 〈0.001
Maintenance therapy (%) Steroids Tacrolimus Cyclosporine Mycophenolic acid Azathioprine mTOR inhibitor	237 (100) 237 (100) 0 (0) 221 (93.2) 16 (6.8) 0 (0)	237 (100) 221 (93.2) 13 (5.5) 227 (95.8) 6 (2.5) 9 (3.8)	1 〈0.001 〈0.001 0.23 0.04 0.004
Delayed graft function (%)	73.4	46.4	〈0.01
Urinary tract infection (%)	77 (32.5)	69 (29.1)	0.43
Surgical site infection (%)	36 (15.2)	26 (11)	0.17
Pneumonia (%)	22 (9.3)	20 (8.4)	0.75
Bacteremia (%)	15 (4.6)	15 (4.6)	1
CMV infection (%) BK virus nephropathy (%)	28 (11.8) 10 (4.2)	49 (20.7) 17 (7.2)	0.009 0.23
Herpes (%) C. difficile (%) Fungal infection (%)	25 (10.5) 14 (5.9) 4 (1.7)	24 (10.1) 13 (5.5) 3 (1.3)	0.88 0.84 0.7

PUB348

Association Between Clinical-Demographic Factors Pre-Transplant and Mortality in Receptors of Deceased Donor Kidney

Beatriz O. Moura,[1] Daniela M. Chiloff,[1] Caio C. Delfino,[1] Mariana V. Tordin,[2] Giovanna M. Zavadzki,[1] Carolina A. Franco,[1] Letícia C. Albeny,[3] Felipe Kenzo Yadoya Santos,[3] Miguel Angelo Goes.[1] *[1]Escola Paulista de Medicina UNIFESP, São Paulo, Brazil; [2]FAM, São paulo, Brazil; [3]Universidade Federal de São Paulo, São Paulo, Brazil.*

Background: Demographic and clinical factors can be associated with deleterious consequences in renal transplant and decreased survival of the patient. **Objective:** to evaluate the association between demographic and clinical factors pre-renal transplant with mortality in recipients of deceased donors.

Methods: We performed the follow-up of 255 renal transplant patients from deceased donors at the Hospital do Rim-UNIFESP for 10 years (2008-2018). We evaluated demographic data such as age, sex, immunosuppressive drugs, serum creatinine from donors pre-transplant. We analyzed sodium and Hgb concentration pre-renal transplantation, cold ischemia time, KDPI, delayed graft function (DGF), acute rejection episode and mortality as outcome. We compared Mortality and Non-Mortality groups. We performed binary logistic regression using mortality as response variable after comparisons.

Results: Forty-eight patients progressed with mortality. 38 patients had infection, 6 patients had cardiovascular disease as the main cause and 2 died of unknown cause. Mortality time of 3.2 ± 0.3 years after transplant. Mortality group were older (52 ± 10, 47 ± 12, p = 0.02). The concentration of Hgb was lower in the mortality group (10.3 ± 1.1, 11.2 ± 0.9 g/dl; p = 0.01). There was no difference in sex, serum sodium, donor creatinine, KDPI, immunosuppressive drugs, cold ischemia time and DGF between groups. There were 14 patients from Mortality group had at least one episode of acute rejection in the follow-up period (29.2%; p = 0.03). The concentration of Hgb pre- renal transplant (OR = 0.779, 95% CI 0.659-0.921, p = 0.03) and the patient's age (OR = 1.049, 95% CI 1.016-1.083, p = 0.04) were independent predictors of mortality.

Conclusions: Lower Hgb concentration pre-transplant and the patient's age were independent predictors for mortality in deceased donor renal transplant recipients.

PUB349

Association Between Clinical-Demographic Factors Pre-Transplant and Chronic Renal Allograft Nephropathy in Receptors of Deceased Donor Kidney

Daniela M. Chiloff,[1] Beatriz O. Moura,[2] Letícia C. Albeny,[2] Felipe Kenzo Yadoya Santos,[2] Caio C. Delfino,[1] Mariana V. Tordin,[4] Giovanna M. Zavadzki,[2] Carolina A. Franco,[2] J. Medina-Pestana,[5] Miguel Angelo Goes.[3] *[1]Escola Paulista de Medicina - UNIFESP, São Paulo, Brazil; [2]Universidade Federal de São Paulo, São Paulo, Brazil; [3]Federal University of Sao Paulo, Sao Paulo, Brazil; [4]FAM, São paulo, Brazil; [5]Hospital do Rim e Hipertensão, Sao Paolo, Brazil.*

Background: Renal allograft failure is one of the most common causes of end-stage renal disease. Demographic and clinical factors can be associated with deleterious consequences in renal transplant. **Objective:** to evaluate the association between demographic and clinical factors pre-renal transplant with chronic renal allograft nephropathy (CRAN) in recipients of deceased donors.

Methods: We performed the follow-up of 255 renal transplant patients from deceased donors at the Hospital do Rim-UNIFESP for 10 years (2008-2018). Interstitial fibrosis and tubular atrophy (IF/TA) in renal allograft biopsy was considered as CRAN. We evaluated demographic data such as age, sex, immunosuppressive drugs, serum creatinine from recipients and donor. Hemoglobin (Hgb) concentration and CKD-EPI were evaluated after 6 months of transplant, cold ischemia time, duration of delayed graft function (DGF), acute rejection episode and CRAN as outcome. We compared CRAN and Non-CRAN groups. We performed binary logistic regression using CRAN as response variable after comparisons.

Results: CRAN occurred 5.5+0.25 years in fifty-two patients. Donor creatinine was higher in CRAN group (1.85±0.82, 1.44± 0.37, p=0.008). CKD-EPI was lower in CRAN group (47.3 ± 4.9, 61.1 ± 1.6 g/dl; p = 0.01). Hgb concentration was lower in CRAN group (11.8 ± 2.6, 13.4 ± 2.4 g/dl; p = 0.004). There was a higher frequency of patients with DGF (p=0.02) and acute rejection episode (p=0.01) that developed CRAN. There was no difference in immunosuppressive drugs and cold ischemia time between groups. Donor creatinine (OR = 3.354, 95% CI 1.198-9.389, p = 0.02), acute rejection episode (OR = 0.340, 95% CI 0.132-0.878, p = 0.03) and concentration of Hgb in 6 months after renal transplant (OR = 0.818, 95% CI 0.677-0.989, p = 0.04) were independent predictors of CRAN.

Conclusions: Donor creatinine, acute rejection and lower Hgb concentration 6 months after transplant and the patient's age were associated with CRAN in deceased donor renal transplant recipients.

PUB350

A More Realistic Assessment of Waiting Time for Transplant Patients

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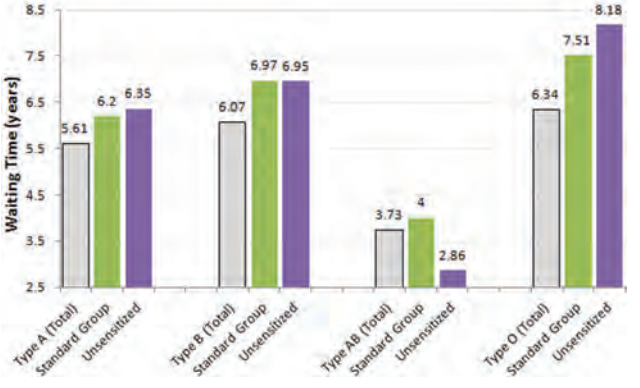
Background: Waiting times for transplant candidates are routinely presented to patients by transplant centers. However, with the increased complexity of the new Kidney Allocation System (KAS), these reported times may no longer be accurate for patients who do not qualify for higher allocation priorities. We aimed to quantify these differences.

Methods: We conducted a retrospective analysis of all deceased donor transplants at our center beginning December 4, 2014. We used data from UNOS to determine waiting time and the priority pool in which each kidney was allocated. Within each blood group we compared waiting times for recipients who received a kidney from a priority pool (including cPRA98%+; prior living donation; registration prior to age 18; and 0-20% EPTS) to recipients who received an organ allocated within a standard pool (local, regional, and national; blood type identical or permissible). Additionally, within the standard pool we compared waiting times for unsensitized (cPRA=0%) vs low-sensitization (cPRA 1-97%) recipients.

Results: Among the recipients were 121 blood group A, 74 group B, 16 group AB, and 160 group O. Standard patients experienced waits ranging from 7.1% to 18.4% longer than the mean waiting times for the entire ABO group. This equated to waiting times that ranged from 0.3 years to 1.2 years longer than the usually quoted times for their blood groups. When we looked at unsensitized patients the mean waiting times were even longer among group A, B and O patients- increased by 13.2%, 14.5%, and 29% respectively. For blood group O in particular, the mean waiting times were 2 years longer than the average time for the entire group.

Conclusions: Recipients who do not qualify for priority allocation can expect significantly increased wait times compared to the average time for the entire group which is what is most often quoted to patients. Factors such as sensitization, EPTS, and other priority characteristics must be considered in setting expectations for waiting time of individual patients.



PUB351

AKI in Liver Transplant Recipients: Is It Too Bad?

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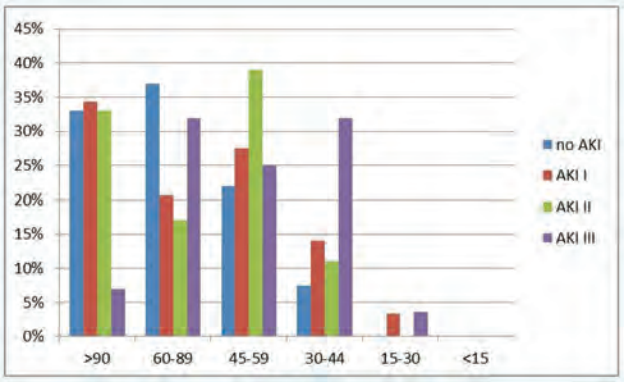
Background: AKI after Orthotopic liver transplant (OLT) is a common complication with an incidence varying widely between 17-90%. It impacts patient survival, morbidity and duration of stay. We conducted a retrospective study in our institution is to identify predisposing risk factors and assess 1 year patient and renal outcomes after AKI in OLT recipients.

Methods: Data were collected from electronic medical record system for OLT recipients, between January 2015 to October 2017. Total 110 patients were included; age range was between 22 and 73 years. They were classified according to sex, race, presence of other co morbidities like hypertension, diabetes and the presence of micro proteinuria. GFR and creatinine were collected at the of transplant, 3 months, and one year after and compared to the base line. Patients were classified into AKI I, AKI II, AKI II and no AKI according to KDIGO criteria. Primary outcomes were chronic kidney disease (CKD), end stage renal disease (ESRD) and death within 1 year in patients who had AKI.

Results: Out of 110 patients; 8 died, 6 of them had AKI III (about 5% of total and 17.6% of the AKI III population). 34 patients had AKI III (31%), 22 (20%) of them required renal replacement therapy (RRT) (continuous renal replacement therapy and hemodialysis) during the perioperative time. None of them has required RRT at 3 months or at one year. 57% of the patients who had AKI III at the perioperative period, ended up with CKD III at 1 year, only 3.4% had CKD IV and none with CKD V at one year. Fig 1 shows relation between GFR at 1 year and AKI severity. Higher INR associated with more severe AKI, as well as alcoholic and HCV liver cirrhosis.

Conclusions: AKI during perioperative time in liver transplant recipients is very common, and might require RRT, although one year outcome remains good.



Relation between GFR at 1 year and AKI severity

PUB352

Potential Simultaneous Acute Tubular Necrosis and Immunological Rejections Following Renal Transplantation

Ina Kurbegovic-Skaljic,[1] Rabail Aslam,[1] David J. Cimbaluk,[1] Maria Oppermann,[2] Michele H. Prod,[1] Siva Kanangat.[1] *[1]Rush University Medical Center, Chicago, IL; [2]RUSH System for Health, Chicago, IL.*

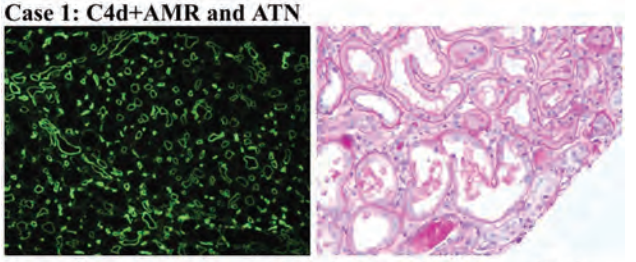
Background: To highlight the simultaneous occurrence of acute tubular necrosis (ATN), cellular and antibody mediated rejection (AMR) after renal transplantation (Tx). They constitute the bulk of renal allograft pathology and administration of appropriate therapeutics is essential based on specific causes for graft dysfunction

Methods: We evaluated 112 renal allograft biopsies with histological evidence of ATN for immunological rejections (IR) and conditions related to chronic rejections. The patients with a diagnosis of ATN and potential IR, or symptoms of chronic rejections were further analyzed based on detectable HLA and Non-HLA antibodies (Ab).

Results: Immunohistopathological findings revealed 35 cases with chronic rejection, 5 with C4d- AMR, 3 with C4d+AMR, and 3 with TCR. The C4d+ and C4d- AMR correlated with HLA donor specific antibodies (DSA). All patients had HLA DSA and >1 non-HLA Ab based on a panel of 33 non-HLA targets.

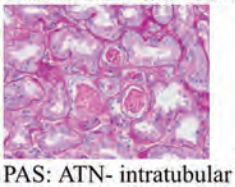
Conclusions: ATN and acute or chronic IR could co-exist. Cases with ATN and Type 1 AAMR based on staining for kidney injury molecule-1 have been reported previously. Also, Exfoliative Renal Tubular Epithelial Cells [ERTEC] bound to IgG have been found in ATN cases preceding clinical rejection. IgG bound ERTEC could indicate an early IR. ATN could lead to such immunological changes by exposing altered self-antigens or neoantigens leading to IR. Elaboration of these findings could help in development of novel therapeutics. ATN could lead to such immunological changes by exposing altered self-antigens or exposure of cryptic neoantigens leading to IR of the allograft. Elaboration of these findings could help in development of novel therapeutics.

Case 1: C4d+AMR and ATN



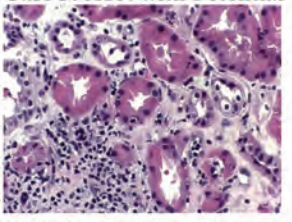
C4d-diffuse and strong positivity in the peritubular capillaries, consistent with acute AMR.
PAS: ATN- intratubular luminal debris, thinning of tubular epithelium (TE), loss of brush border (BB), mitotic figures in tubular epithelial cells (EC).

Case 2: ATN with no evidence of AMR or ACR

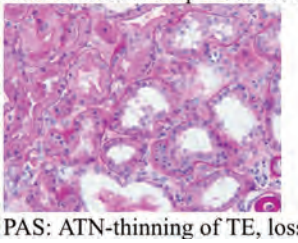


PAS: ATN- intratubular luminal debris, thinning of TE, loss of BB.

Case 3: ATN with Potential TCR



H&E: Features suspicious for ACR.



PAS: ATN-thinning of TE, loss of BB.

PUB353

Clinical Outcomes of High Kidney Donor Profile Index (KDPI) in Kidney Transplants

Khalid M. Elharrif, Farah Abifaraj, Omar S. Al-Taweel, Nidal Alhosainat, Syed A. Hussain, Ann Kathleen N. Gamilla-Crudo, Muhammad A. Mujtaba. *UTMB, Galveston, TX.*

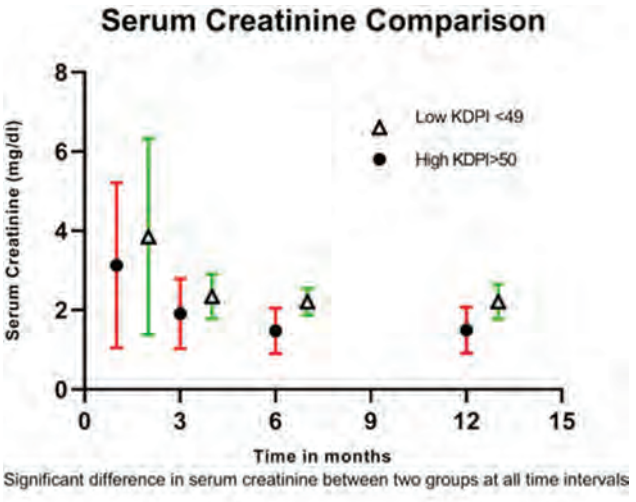
Background: KDPI score is designed to assess the expected kidney function in a kidney transplant recipient. Lower KDPI scores are associated with longer estimated allograft function. There is a high incidence of discard of high KDPI kidneys. However it is well proven that older patients on dialysis have high waitlist mortality and they may still benefit from a timely transplant utilizing this resource.

Methods: A retrospective review of prospectively collected data was conducted on 81 patients with deceased kidney donor transplants. Patients were divided into High KDPI (≥50, n=34) and Low KDPI (≤49, n=47) groups. Patient demographics, EPTS scores, serum creatinine at different time intervals, delayed graft function- DGF, and biopsy proven rejection were analyzed. A paired t-test was used for continuous variables and Fisher's exact test for categorical variable. P value of <0.05 was considered to be significant.

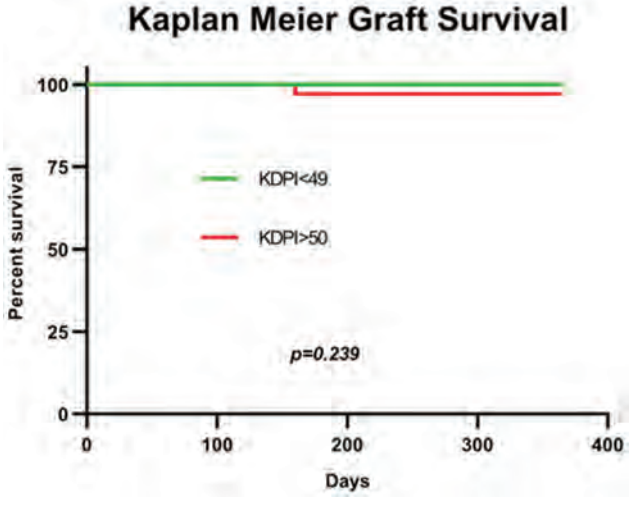
Results: Majority of recipients were Hispanic with mean age 54± 11. Median KDPI for low and high group was 22 and 64 respectively. One year Kaplan Meier Allograft survival and rejection rates were comparable between groups; however there was significant difference in DGF and serum creatinine favoring low KDPI group. Table and graph illustrate the result.

Conclusions: High KDPI kidneys have comparable short term survival and rejection rates to low KDPI kidneys with slight compromise of organ quality. Selective patient with high waitlist mortality may still benefit from a timely high KDPI kidney transplant.

	Low KDPI n=47 (≤49)	High KDPI n=34 (≥50)	P Value
EPTS score	34	44	0.091
DGF	1	8	0.0035
Rejection	12	9	1.0
Serum Creatinine at 1 year	1.21+0.44	1.49+0.58	0.026



Significant difference in serum creatinine between two groups at all time intervals



PUB354

A 10-Year Review of Laboratorial Tests Abnormalities in Renal Transplant Patients with Detectable Cytomegalovirus Viral Load

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Background: Cytomegalovirus (CMV) is one of the most frequently detected viruses in renal transplant recipients. Clinical manifestations of CMV infection are frequently nonspecific contributing to the difficulty of a quick diagnosis. CMV viral load is an independent risk indicator for CMV disease.

Methods: We conducted a retrospective study which enrolled the total population of renal transplant recipients. Unique CMV DNA molecular test requests were selected between 2009 and December 31st2018, using the Laboratory System Modulab® Werfen v3.0. Positive CMV viral load was agreed at >250 copies/mL. Parallel hematological, biochemical and molecular microbiology ldata were retrieved in positive requests.

Results: Total transplant recipient population was composed by 71 unique patients (49 males (66.1%) and 21 females (33.9%). Patient mean age was 48,3 years (±11,8). 245 Unique CMV DNA molecular test requests were found, with 170 requests (62 unique patients) presenting with CMV DNA viral load >250 cp/mL ((min 263; max 590000; mean 262). The most frequently found hematological abnormality was lymphopenia <1500 u/L (60,1% requests) followed by leucopenia <4500u/L in 28,2% unique requests. Thrombocytopenia <150000u/L was found in 17,1% of the requests. The most frequently found biochemical abnormality was high serum creatinine >1,5mg/dL (46,7%). The most strong positive correlation of all the hematological and biochemical tests and CMV viral load was found between glutamate-oxaloacetate transaminase (GOT) andCMV viral load and (R=0,47). Correlation analysis between glutamate-pyruvate transaminase and CMV viral load showed a very weak correlation (R=0,0026). We also observed that a small patient subgroup (n=6) had simultaneous positive plasma CMV DNA and urinary BKV DNA with a common CMV viral load >500cp/mL.

Conclusions: Subtle laboratory abnormality patterns work as important tools to the suspicion of CMV infection. This work shows that CMV infection must be remembered as a possible diagnosis in patients presenting with lymphopenia, leucopenia, and rise of liver enzymes, particularly GOT, which in this study raised significantly and proportionally to the CMV DNA viral load.

PUB355

Effect of De Novo Donor-Specific Antibodies (DSA) on Graft Function in Renal Allograft Recipients

Anil Bhalla,[1] Ravi K. Singh,[1] Ashwani Gupta,[1] Devinder S. Rana,[1] Manish Malik,[2] Anurag Gupta,[1,3] Vinant Bhargava.[1] *[1]Sir Ganga Ram Hospital, New Delhi, India; [2]Sir Ganga Ram Hospital and GRIPMER, New Delhi, India; [3]SYNEGY Hospital, Uttarakhand, India.*

Background: The availability of potent immunosuppressive agents has decreased acute cellular rejection rates, however, chronic deterioration of graft function continues to be a clinical challenge. Chronic Antibody-mediated rejection (cAMR) is an important cause of allograft failure in renal allograft recipients. cAMR is caused by the development of antibodies that do not preexist but develop after transplantation. These antibodies are directed against (foreign) graft HLA class I and II antigens and are known as de novo donor specific antibodies (DSA). DSA lead to allograft injury through complement-dependent or complement independent mechanisms resulting in glomerulitis, peritubular capillaritis, and transplant glomerulopathy. Routine immune monitoring of HLA antibodies can be used to guide immunotherapy and permit early intervention.

Methods: Prospective Observational Study. Patients undergoing renal transplant at Sir Ganga Ram Hospital in 2017 were screened for pre transplant DSA. A total of 72 DSA negative pre transplant patients were followed for 18 months. Clinical characteristics of patients were noted. DSA was tested at 6, 12 and18 months post transplant.

Results: Total of 72 patients were included. de novo DSA negative patients (N=63) with mean age 40.73 years (SD=13) and de novo DSA positive patients (N=9) with mean age 34.66 years (SD=6.61). At 18 months, serum creatinine mean (SD) of de novo DSA negative patients was 1.41mg/dl (0.42) while for de novo DSA positive was 1.27mg/dl (0.38), p-value 0.552. eGFR, mean (SD) at 18 months in de novo DSA negative group was 58.2 (19.03) 6ml/min/1.73sq m and in de novo DSA positive 56.47 (22.83) ml/min/1.73sq m, p-value 0.798. Tac levels(SD) at 18 months, in de novo DSA negative patients was 6.87 (2.29) ng/ml while in de novo DSA positive group, it was 6.05 (1.59) ng/ml. Urine protein creatinine ratio (SD) at 18 months in de novo DSA negative group was 0.30 (0.82) while in de novo DSA positive group, it was 0.31 (0.30).

Conclusions: De novo DSA developed in 12.5% of Patients after 18 months post transplant. There is no significant graft dysfunction at the time of appearance and a trend is noted of younger age and lower TAC levels in these de novo DSA patients.

PUB356

Time Trends in Kidney Transplantation in South Korea: A Nationwide Cohort Study from 2007 to 2015

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Background: Detailed nationwide information regarding recent status and time-trends of kidney transplantation in South Korea is limited.

Methods: We performed a nationwide, population-based cohort study using the national claims database of Korea in which nationwide health insurance is provided. We included kidney transplant recipients under age 70 from 2007 to 2015 and their demographic and clinical characteristics were collected. The prognostic variable was death-censored graft failure, and graft failure was determined when patient returned to maintenance dialysis.

Results: Number of kidney transplantation showed increasing trend, and the number increased from 820 in 2007 to 1755 in 2015. The incidence proportion of kidney transplantation among end-stage renal disease patients under age 70, which was below 3% in 2007, reached approximately 4% in 2015. The median age of the kidney transplant recipients consistently increased from the past, and proportion of patients with underlying diabetes mellitus was prominently increased, reaching 42.1 % in 2015. The dialysis duration before transplantation was significantly increased, and in 2015, about 35.2 % kidney transplantation was performed after more than 5 years of dialysis, which was 9.6% in 2007. Regarding maintenance medication usage, proportion of patients who were prescribed with tacrolimus greatly increased, while cyclosporine was less frequently used. One-year maintenance immunosuppressive medication possession ratio was consistently increased from the past. Transplantation-related costs was greatly increased during the

study period, particularly regarding government coverage, whilst patient burden for insured costs were decreased from the past. Overall prognosis of kidney transplantation was improved in the recent periods, reaching approximately 80% 10-year graft survival in the recent periods.

Conclusions: Kidney transplantation is becoming a more prevalent modality of renal replacement therapy. While old-age transplantation is becoming more common, prognosis has been generally improved, but related insured costs were increasing prominently.

PUB357

Variability in Blood Tacrolimus Levels with Generic Immunosuppression in Kidney Transplant Patients in Western Mexico

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Background: Tacrolimus is recommended as first-line therapy in most kidney transplant protocols. It has a narrow therapeutic index and routine blood levels monitoring is required to assure its effectivity and to limit its toxicity. In our center, kidney transplant patients receive generic immunosuppression and are subject to frequent changes in generic brands of tacrolimus. There are few studies regarding the variability of blood tacrolimus levels according to tacrolimus generic formulations

Methods: Retrospective observational study. Electronic medical records of kidney transplant patients greater than one year and in immunosuppressor treatment with tacrolimus were reviewed, and blood tacrolimus levels, tacrolimus generic brand, daily tacrolimus dose and weight dose was registered. Tacrolimus levels were also compared to CYP3A5 polymorphisms

Results: A total of 84 patients whose electronic medical records were complete (tacrolimus dose, blood tacrolimus levels, and tacrolimus brand) were included. 57 (67.8%) of those patients had Limustin, 20 (23.8%) were receiving Pisa, and 7 (8.3%) had Akrocell. Daily tacrolimus dose and tacrolimus weight dose was similar between groups. Mean blood tacrolimus levels were 6.28 ng/mL for Limustin, 7.08 ng/mL for Akrocell and 8.51 ng/mL for Pisa, with a significant statistical difference and a p value of 0.006. We found no significant difference between cytochrome CYP3A5 polymorphisms distribution, thus the differences in the blood tacrolimus levels cannot be attributed to differences in liver metabolism of the drug.

Conclusions: There is variability between different generic brands of tacrolimus regarding blood tacrolimus levels. They are lower in Limustin brand, despite a similar daily and body weight dose compared to other groups, which is not explained by differences in liver metabolism of the drug. The long term effect that this could cause is not known. Blood tacrolimus levels should be monitored frequently, especially if brand changes are often made.

Variable	Tacrolimus brand			p
	Akrocell	Limustin	Pisa	
Patients	7	57	20	n= 84
Blood tacrolimus levels (ng/mL)*	7.08	6.28	8.51	0.006
Daily tacrolimus dose (mg/día)*	4.14	4.54	4.15	0.582
Weight dose (mg/kg/day)*	0.065	0.066	0.063	0.938

*Values are shown as means. Analysis between groups was made with ANOVA and T3 Dunnett test was used as a post-hoc test.
A result was considered as statistically significant if p<0.05.

PUB358

Practical Utility of Various Scores for the Evaluation of Deceased Donor Kidneys

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Background: Marginal organs have been associated with inferior graft and patient outcomes and several scores have been proposed for the evaluation of deceased donor kidneys in order to facilitate the best possible allocation combination and to improve graft and patient survival. We retrospectively validated their performance in predicting outcomes in donor kidney evaluation biopsies.

Methods: We retrospectively evaluated the records of 223 consecutive adult cadaver renal transplant recipients with donor evaluation biopsies. Taking into account donor and recipient clinical data and graft histopathology, we performed a retrospective explorative univariate analysis of graft function at 3 and 12 months and 1- and 3-years graft and patient survival for the following scores: Navarro (2011), Ortiz (2004), Balaz (2013), Lopes (2004), Snoeijs (2008), Remuzzi (1999), Nyberg (2003), Rao (2009), Foucher (2009), Schold (2005), Port (2002), Anglicheau (2008), 3-year-Leuven (2013), Irish (2010), KDRI/KDPI and EPTS.

Results: In our cohort of 223 patients, for 3- and 12-month graft function most of the scores performed well; performance for 1- and 3-year graft survival was best for combined clinico-pathological scores like 3-year-Leuven (p=0.032 and p=0.008, respectively). For one-year patient survival, combined clinico-pathological scores like 3-year-Leuven (p<0.001) and Anglicheau (p=0.016) performed as well as the purely clinical scores like KDRI (p=0.001), Rao (p<0.001) or Nyberg (p=0.001).

Conclusions: Composite scores which also consider graft histology like 3-year-Leuven, Rao and Nyberg seem to be better suited to predict graft survival than purely clinical scores. For the prediction of patient survival, graft histology does not matter as much. These scores should be tested for their performance in a prospective multicentric study design.

PUB359

Severe Allograft Rejection Requiring Allograft Nephrectomy in a Renal Transplant Patient After One Dose of Pembrolizumab

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Introduction: There is a high risk of kidney transplant rejection with Anti-PD-1 Monoclonal Antibody, Pembrolizumab (Keytruda) use. We presented a case of patient needing renal allograft nephrectomy for severe allograft rejection after one dose of Pembrolizumab

Case Description: 46-year African American Female with past medical history significant for ESRD secondary to HTN underwent DDKT. Ten years after transplant she got diagnosed with moderately differentiated endometrial adenocarcinoma. PET-CT showed tumor invasion to the uterus, cervix, vagina, metastatic regional lymphadenopathy and distant lung metastasis. Diagnosis of Stage IV-B grade 2 endometrioid endometrial cancer and she underwent 6 cycles of Carboplatin/Paclitaxel along with debulking surgery. Follow-up CT after completion showed increasing size of iliac chain lymph nodes concerning for worsening disease. Decision to start Pembrolizumab was made and first dose of Pembrolizumab was given with a baseline creatinine of 1.3-1.5mg/dl. Two weeks after the dose she was admitted with severe, acute onset right lower quadrant pain with low-grade fevers with a creatinine of 3.2 mg/dl. Her creatinine rose to 8.2 mg/dl within 48 hours of admission. Due to high degree of suspicion for renal allograft rejection she was started on high dose of IV steroids. Patient progressively became anuric and became dialysis dependent. She required two more admissions for recurrent severe pain over her transplant allograft site, hematuria and low grade fever. Her renal transplant ultrasound showed an increase of the size of allograft to 14 cm [as compared to 11 cm 3 weeks back], with more echogenicity and now with new hydro-ureteronephrosis. Given her recurrent severe allograft pain, persistent low grade fevers and increase in the size of a renal transplant allograft, she required a transplant nephrectomy for refractory allograft rejection. The gross allograft nephrectomy specimen showed an enlarged, mottled, necrotic and hemorrhagic kidney.

Discussion: A risk-benefit analysis must be completed prior to initiation of therapy and if the benefit of using Pembrolizumab outweigh the risks, only then this immunotherapy must be considered. To the best of our knowledge, this is the first case of severe recurrent rejection of renal transplant allograft requiring an allograft nephrectomy.

PUB360

Incidence and Clinical Consequences of Immunosuppressant Cessation in Kidney Transplant Recipients: A Single-Center Experience

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Background: Immunosuppression agents are essential for maintaining allograft survival in kidney transplantation (KT). But some patients become non-adherent to immunosuppressant due to misunderstanding of patient, socioeconomic or psychological factors, and little has been known about clinical implication of these cases.

Methods: This is a retrospective analysis of KT cases of single center from 1998 to 2016. Patients who had completely stopped taking the immunosuppressants for more than six months and who were regularly followed up at our center were defined as medication non-adherence (MNA) group and included for final analysis.

Results: During the mean follow-up period of 63.9 months, 8 patients of total 354 KT recipients (2.3%) were included in MNA group. The mean age of the MNA group was 30.2 ± 7.1 years, and that of the control group was 45.3 ± 12.3 years (p <0.001). The number of HLA mismatch was 2.0 ± 1.0 for the MNA group and 3.4 ± 1.5 for the control group (p = 0.013). During the follow-up period, 13 cases of graft failure (GF) occurred from the control group, whereas from the MNA group, 7 out of 8 patients experienced GF. The mean duration from transplantation to GF of the MNA group was 84.7 months. The patients' death did not occurred from the MNA group. In multivariate Cox regression analysis, MNA was a definite independent risk factor after adjustment for confounders (HR 24.6, 95% CI 4.9-123.1).

Conclusions: Arbitrary withdrawal of immunosuppressant was clarified for the most important risk factor for allograft loss in KT recipients. Further research is warranted for the perspective of patient-oriented mechanism of medication non-adherence.

PUB361

Impact of Delayed Graft Function over Allograft Survival and Long-Term Kidney Outcomes After Transplantation in a Peruvian Hospital 2012-2017

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Background: Delayed graft function (DGF) is an early complication in kidney transplant recipient, defined as the hemodialysis requirement during the first week after transplantation. Some studies have found that DGF is associated to less allograft survival and worse long term kidney function. The primary outcome is to analyze the impact of DGF over allograft survival and kidney outcomes after one year after transplantation.

Methods: Retrospective study identified 71 adult patients, deceased-donor, kidney-only transplant recipients between 2012 and 2017. We used comparative studies using Chi Square test and T-student test. All of the statistical analysis were realized by the SPSS program. We compared cold ischemia time (CIT) and DGF with allograft survival using a multivariable linear probability Cox model.

Results: The average age of patients was 43.34 years (19-68 years), most of them from male gender. The principal cause of renal chronic disease was unknown (57.7%), followed by glomerular disease (9.9%) and Diabetes (7%). The average age of donors was 41.8 years, most of them male gender and the main cause of brain death was stroke. The serum donor creatinine (srCr) before transplant was around 1.18mg/dl (0.39-2.7mg/dl). The average of CIT was about 17.7 hours (9-26 hours). In the early transplant, four patients didn't have kidney function, 15 patients had DGF and 52 patients had immediately kidney function(IKF). As main causes of DGF were acute rejection and acute tubular necrosis (ATN). T-student test shown an average of srCr at one year after transplant around 1.2mg/dl in recipients who had IKF and 1.59mg/dl in recipients with DGF (P=0.54). Chi square test shown that recipients who had DGF had an OddsRatio in 3.9 (IC 1.07 – 14.45) to achieve a srCr over 1.5mg/dl in a year after transplant in contrast with recipients who had achieved an IKF after transplant (P= 0.032). We applied a probability model by Cox and determined a graft kidney survival of 98% in a year, 96% in three years and 94% in five years. There was not an important relation between DGF and CIT with graft survival.

Conclusions: Delayed graft function is an important negative risk factor for an optimal graft function. We could not find a significative relation between DGF, CIT and graft survival.

PUB362

Women Compared with Men on Maintenance Hemodialysis Exhibit Unique Biomarker Patterns

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Background: Patients with end-stage renal failure on maintenance hemodialysis (MH) have higher mortality risk compared to the general population. Understanding of these unique mortality risk factors have not been fully explored by gender. The objective of this study was to examine unique biomarkers by gender and ethnicity in a cohort of MH patients compared to normal controls.

Methods: 92 MH patients in a single hospital-based dialysis unit in December 2017 consented with IRB approved protocol. Whole blood samples were drawn pre-dialysis into 3.2% sodium citrate; citrated plasma samples processed using ELISA for selected biomarkers: BMP-7 (bone morphogenetic protein 7), MPO (myeloperoxidase); IL-6 and IL-8 (proinflammatory cytokines), CTX-1 (C-terminal collagen telopeptide) and OPN (osteopontin glycol-phosphoprotein). Data compared as mean ± SD by gender and gender/ethnicity; p-value trends reported due to small sample size/low statistical power.

Results: Mean age 60.5 ± 13.3 Yr (range 20-88); BMI 29.1 ± 5.4. Significant differences were seen between controls and MH patients for all biomarkers. No differences seen by gender for all other biomarkers except BMP-7 and MPO. Gender difference by ethnicity only seen in African Americans.

Conclusions: Women had higher MPO and lower BMP-7 levels compared to men. This difference remained when African American women were compared to African American men but less pronounced in low sample size of Caucasians. Patterns of biomarkers, particularly BMP-7 and MPO, were unique between genders. Patterns were also seen within ethnicity but small sample size reduced statistical power to examine further. BMP-7 may be associated with adynamic bone disease and has also been known to reduce vascular calcification in uremic animal models. MPO may infer inflammatory status. The significance in MH population, particularly significance or relevance of pattern, is unknown and requires further investigation.

Funding: Other NIH Support - This project was supported by the T35 AI125220 student training grant from the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).

	N	BMP-7 (pg/mL)	N	MPO (pg/mL)
Women*	48	9.4 ± 16.2	41	143.9 ± 83.7
Men	44	9.8 ± 16.5	39	87.4 ± 47.3
AA Women*	27	11.2 ± 19.5	24	164.5 ± 107.4
AA Men	22	14.3 ± 23.6	19	71.8 ± 32.9
Total MH Sample+	92	9.6 ± 16.3	80	116.4 ± 68.6
Normal Controls	32	6.2 ± 8.8	36	39.4 ± 14.8

AA = African American; MH = maintenance hemodialysis; T-test (trends due to low statistical power), * p < 0.05, + p < 0.001

PUB363

Maternal and Fetal Outcomes of CKD Pregnancy on Mexican Patients

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Background: Women with CKD have higher rates of miscarriage and more challenges to achieve better fetal and maternal outcomes, compared with general population. The effect of pregnancy on renal disease accelerates the irreversible decline of GFR and progress to ESRD, increasing maternal mortality and the incidence of cesarean deliveries. We conducted a retrospective review with the purposed to assess clinical maternal and fetal characteristics and outcomes of CKD during pregnancy.

Methods: We analyze a single center retrospective review of pregnant women with CKD of 17 Mexican patients. Baseline maternal information, demographics, clinical and biochemical data were reviewed. Gestational age of pregnancy loss or delivery was recorded. Outcomes maternal, birth weight, prematurity, Apgar, neonatal UCI admission and fetal death. Statistical analysis was done with SPSS version 26.0. The categorical variables were analyzed using chi-square test or Fisher's exact probability test, as appropriate. The continuous variables were analyzed using the Student's t test. A value of $p < 0.05$ was regarded as statistically significant.

Results: Mean age was 28.00±5.48 years. The mean duration of CKD as 57.07±57.12 months. 5 patients were diagnosed with CKD during pregnancy. 12 patients were nulliparous and 5 patients were multiparous. We observed significant correlation between pregnancy onset and conception in thrombocytopenia (r=0.651) and serum creatinine (r=0.448). Mean gestational age at delivery was 35.36±2.99 weeks. Average weight was 1.78 ± 0.66 g. Fetal live birth rate was 76%. We compare stillbirth pregnancies with live birth pregnancies on Table 1.

Conclusions: This was the first study that evaluated CKD during pregnancy and its results. Our findings correlate with other studies, but further studies are need that evaluate counseling before, during and after conception in pregnant women with CKD which could achieve better results for the binomial.

Table 1. Comparison of still birth pregnancies and live bith pregnancies

	Still birth pregnancies	Live birth pregnancies	P
Age (years)	34.00 ± 9.64	27.23 ± 3.09	0.002
Weight before pregnancy (kg)	71.33 ± 21.94	60.23 ± 9.01	0.024
Timing before CKD (months)	17.00 ± 26.85	74.40 ± 58.06	0.060
Maternal glucose during pregnancy (mg/dl)	112.00 ± 35.34	74.54 ± 6.99	<0.001
Apgar score test	7.53 ± 0.66	7.00 ± 1.41	0.065

PUB364

Preconception Care in Patients with Chronic Autoimmune Diseases of the Kidneys Treated with Immunosuppressants

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Background: Chronic autoimmune diseases of the kidneys treated with immunosuppressants pose a great threat to the life of the mother and foetus. The best solution is to get pregnant at the time of remission or the use of immunosuppressants at a maintenance dose. Evaluate the dependence between pre-conception care and its lack on the clinical condition of the patient suffering from chronic kidney diseases, who got pregnant.

Methods: The study covered 40 women aged 20-40 who got pregnant while suffering from a chronic autoimmune disease of the kidneys (25 patients with chronic glomerulonephritis, 10 patients with diagnosed lupus nephritis (LN) and the remaining ones with rheumatoid arthritis and antiphospholipid syndrome).

Results: Pregnancy was unplanned in 17 women with glomerulonephritis and 6 with lupus nephritis. The remaining patients used full pre-conception care. Statistically significant dependence was observed between the unplanned pregnancy with incorrect clinical values (creatinine>1mg%, protein in urine>0.5 g/day, arterial hypertension, large doses of immunosuppression) on the presence of renal failure in women in the period from 3 months to 2 years after delivery ($p<0.001$). Women without pre-pregnancy preparation, without previous consultation or nephrological preparation delivered prematurely by Caesarean section ($p<0.005$).

Conclusions: Pregnancy in patients with chronic diseases of the kidneys without proper pre-conception care and constant nephrological and gynaecological monitoring constitutes a great threat to the life of the mother and child.

PUB365

Nontraumatic Unilateral Renal Artery Dissection with Renal Infarcts

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Introduction: We are presenting a case of unilateral right renal artery dissection with renal infarcts managed conservatively

Case Description: 32 year old Caucasian female without any prior medical history presents to the ER with a chief complaint of right lower quadrant abdominal pain, sudden in onset, sharp in nature and radiating to right flank. Denied any urinary symptoms including increased urinary frequency, dysuria or hematuria. She is an active smoker and takes daily birth control pill (estrogen and progesterone). Vitals showed temperature of 97.4 °f, blood pressure 114/75, respiratory rate of 20 per min, saturating 99% on room air.

Abdominal exam showed soft, non–tender, no costovertebral angle tenderness. Rest of the exam is with in normal. Labarotary results showed sodium 137, potassium 4.1, chloride 100, bicarbonate 24, creatinine 1.15 mg/dl, calcium 9.4 mg/dl. Rest of the labs were within normal limits. Urinalysis showed specific gravity >1.06, Ph 7.0, negative blood, negative nitrite, 50 to 100 squamous epithelial cells. CT scan of abdomen with IV contrast showed focal area of nonenhancement in the right kidney highly suggestive of an infarct. Right renal arteriogram showed dissection within the distal right renal artery just proximal to the bifurcation of uncertain etiology and multifocal infarct of the right kidney likely embolic in etiology. Echocardiogram showed mild positive bubble study. Hypercoagulable work up came to be negative. Patient was managed conservatively and discharged on apixaban

Discussion: Literature on Unilateral renal artery dissection is quite scanty. Isolated Renal artery dissection poses a diagnostic and therapeutic challenge to physicians. Not sure if this is an early sign of rare presentation of fibromuscular dysplasia or occult embolic infarction. Need more cases for better understanding pathophysiology and efficient treatment

PUB366

Potassium Binders for Chronic Hyperkalemia in People with CKD: A Cochrane Review and Meta-Analysis

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Background: Hyperkalemia is a common electrolyte abnormality in patients with chronic kidney diseases (CKD). Sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS) are widely used but may cause severe gastrointestinal symptoms. Patiromer and sodium zirconium cyclosilicate (ZS-9) are newer potassium binders which may cause fewer gastrointestinal side-effects. This Cochrane systematic review evaluated the benefits and harms of potassium binders for treating chronic hyperkalemia among people with CKD.

Methods: We searched the Cochrane Kidney and Transplant Register of Studies for randomized controlled trials (RCTs) evaluating potassium binders for chronic hyperkalemia administered in adults and children with CKD. We categorized treatments as newer agents (patiromer or ZS-9) and older agents (SPS and CPS) in separate analyses for some outcomes. Two authors independently screened citations for eligibility, extracted data, and assessed risk of bias using the Cochrane tool. Evidence certainty was evaluated using GRADE.

Results: Twelve studies (1340 participants) were eligible. Medial trial duration was 3.5 weeks (range 12 hours to 52 weeks). There were no trials that evaluated treatment in children. Mean study age ranged from 53 to 73 years. Risks of bias were generally high or uncertain. Seven studies (774 participants) compared a potassium binder to placebo. Patiromer or ZS-9 had uncertain effects on all-cause mortality (relative risk [RR] 0.32, 95% CI 0.01, 7.57). The treatment effect of older potassium binders on all-cause mortality was very unclear, and no study reported outcome data for cardiovascular mortality. Potassium binders had uncertain risks of nausea (RR 2.10, 95% CI 0.65, 6.78), vomiting (RR 1.72, 95% CI 0.35, 8.51), diarrhea (RR 1.03, 95% CI 0.24, 4.51), and constipation (RR 1.68, 95% CI 0.65, 4.37).

Conclusions: Evidence for different potassium binders to treat chronic hyperkalemia in people with CKD is of low certainty due to serious imprecision and trial methodological limitations. This review suggests the need for a large, adequately powered trial of potassium binders versus placebo that assesses clinical outcomes such as cardiovascular mortality, cardiac arrhythmias, health-related quality of life, and major gastrointestinal symptoms.

PUB367

Risk Factors for Hospitalization and Critical Illness in CKD

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Background: Chronic kidney disease (CKD) is a known risk factor for hospitalization. Specific predictors of hospitalization with critical illness among patients with non-dialysis-dependent CKD are unclear.

Methods: A retrospective cohort study was conducted among patients ≥ 18 years of age with CKD in a CKD registry from a safety net health system. Patients with CKD stage 5 (eGFR < 15 mL/min) were excluded. We obtained baseline characteristics including details of insurance and medical comorbidities. Details of hospitalization events were obtained during a three year period after the diagnosis of CKD. Poisson regression was used to determine associations between baseline characteristics and 1) the number of hospitalization days and 2) the number of hospitalizations requiring intermediate or intensive level of care. Analysis was stratified by CKD stage and adjusted for baseline characteristics.

Results: Among 8,302 patients with CKD (1/1/2011 and 7/30/2015), 1,298 patients (15.6%) were hospitalized during a 3-year follow-up period. Factors associated with increased incident rate ratio of hospitalization days among all stages of CKD include: congestive heart failure [3A: 2.6 (2.2, 3.1), 3B: 1.8 (1.5, 2.3), 4: 1.3 (1.0, 1.8)], cardiovascular disease [3A: 1.2 (1.1, 1.5), 3B: 1.4 (1.1, 1. 7), 4: 1.7 (1.3, 2.3)], mild anemia [3A: 1.6 (1.4, 2.0), 3B: 1.8 (1.4, 2.2), 4: 1.6 (1.1, 2.3)], and moderate/severe anemia [3A: 4.2 (3.1, 5.7), 3B: 4.3 (3.3, 5.6), 4: 2.3 (1.5, 3.3)]. Factors associated with increased incident rate ratio of hospitalization with critical illness include: congestive heart failure [3A: 3.8 (3.1, 4.5), 3B: 1.5 (1.2, 1.9), 4: 1.5 (1.0, 2.0)] and moderate/severe anemia [3A: 3.6 (2.9, 4.6), 3B: 4.1 (2.9, 5.7), 4: 2.0 (1.2, 3.4)].

Conclusions: Among patients with non-dialysis dependent CKD, congestive heart failure and anemia are associated with a higher risk of hospitalization with critical illness and with longer hospitalization stay. Targeted, effective interventions to reduce the hospitalization burden in CKD patients with heart failure or anemia is needed.

PUB368

Prevalence of Frailty in Nephrology Patients and Impact of Socioeconomic Factors

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Background: Frailty is common among patients with CKD. Frailty compromises the ability to recover from illness and stressors, putting patients at risk for poor health outcomes. Little research has been done to describe the prevalence of frailty in a non-dialysis CKD population or investigate the impact of socioeconomic factors.

Methods: Frailty was assessed using the Frailty Phenotype (FP) for patients aged 65 years or more in a nephrology clinic at an urban medical center. The FP was administered by Nephrology fellows or a Registered Dietitian. Socioeconomic factors were obtained from zip code census data.

Results: Analysis included 56 patients with a mean age of 75±8 years, BMI of 28.7±7.2kg/m^2 and GFR of 35±17ml/min; 54% were female, 79% were black and 75% lived in high poverty areas. Only 20% were found to be non-frail, whereas 55% were pre-frail and 25% were frail/very-frail. Females, patients with a lower GFR, lower median household income or living in a high poverty area were more likely to be frail. Reduced physical activity was the most common frailty factor; weight loss was the least common.

Conclusions: Frailty is prevalent among adults over 65 years in a nephrology clinic. Frailty is more common in patients with low income. Frail patients present unique challenges with diet recommendations and medications to help prevent malnutrition, hypotension, hypoglycemia and falls. More research is needed to determine interventions to reduce frailty and improve outcomes.

Demographics & Clinical Characteristics by Frailty Level

	All Patients	Robust	Pre-Frail	Frail/Very Frail	p-value
Age	75.0	73.8	74.7	76.7	0.193
%Female	53.6%	18.2%	58.1%	71.4%	0.023
Race	-	-	-	-	0.125
Black	78.6%	54.5%	97.1%	78.6%	
White	19.6%	45.5%	9.7%	21.4%	
Hispanic	1.8%	0.0%	3.2%	0.0%	
BMI	28.7	30.3	28.4	28.1	0.72
Albumin	3.95	4.15	3.90	3.87	0.183
GFR	35.0	46.5	34.2	28.0	0.000
CKD Stage	-	-	-	-	0.013
CKD3	51.8%	81.8%	54.8%	21.4%	
CKD4	26.8%	0.0%	35.5%	28.6%	
CKD5	12.5%	0.0%	9.7%	28.6%	
Other	5.4%	18.2%	3.2%	21.4%	
SES Factors	-	-	-	-	-
Below Poverty Index	25%	18%	27%	28%	0.249
Unemployment	16%	12%	17%	17%	0.073
Median Income	$43,906	$65,735	$38,570	$38,189	0.007
High Poverty Area	75%	36%	84%	79%	0.019

PUB369

Targeted Program Designed to Address Missed Follow-Ups on Abnormal Tests: A Proposal for Population Health Partnership

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Background: Chronic kidney disease is not always identified and managed in an optimal and timely manner. A single abnormal creatinine measurement embodies the challenges of reliably following up abnormal laboratory test results. The Kaiser Permanente creatinine safety program has demonstrated its feasibility in an integrated health system to close the loop on a large cohort of patients. However, when we tested Kaiser's program design within a population health partnership (an external organization contracted for value-added services), modification was required to better engage physicians and utilize limited resources.

Methods: Literature research and meetings with experts experienced in population health.

Results: The modified program re-purposes the business value proposition, from improving patient safety and avoiding malpractice claims, to increasing risk adjustment (RAF) revenue and reducing care gaps. Because a population health organization typically has no access to electronic health record, the Kaiser's method (a nurse ordering a test for a physician to sign) would not work. We propose using population health managers to engage physicians during visits to the practices. When appropriate, we propose the integration of this information into RAF, patient outreach and care management workflows. To identify a manageable cohort of patients and reduce alert fatigue for physicians, we propose the focus be on patients at high risk for renal disease per predictive model and those who have experienced an event of potential care coordination deficiency. The Screening for Occult Renal Disease (SCORED) model is selected due to its validity and its computerizability by claims. Care coordination deficiency may occur when (1) tests are performed during emergency room visits or unplanned hospital stays; (2) tests are performed on or after the discharge date of planned hospital stays; (3) a primary care physician orders significantly more labs and imaging compared to peers (above 95th percentile). We are exploring partnership opportunity to refine and test this program.

Conclusions: A program design to embrace business and clinical complexity in population health partnership is proposed to address missed follow-up on abnormal creatinine. More details on the testing of this design will be shared with conference audience, and feedback is welcome.

PUB370

Prevalence of Unhealthy Behaviors Among Different Stages in Thai CKD Patients in ESCORT-2

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Background: We are conducting quasi-experimental study to evaluate the effect of integrated care model for Chronic Kidney Disease management in rural community of Thailand (ESCORT-2 study). Lifestyle modification is an important aspect of CKD management. Prevalence of health-related behaviors are important information for planning strategy to achieve healthy lifestyle.

Methods: We analyzed the baseline data of ESCORT-2. Prevalence of lifestyle behaviors reported herein (including cigarette smoking, analgesic use, non-steroidal anti-inflammatory drug [NSAID] use, use of herbal medicine, intensity of exercise and adherence to prescribed medication) were obtained was collected with patient history interview during their hospital visit.

Results: 914 CKD stages 3 and 4 were enrolled in the study. The baseline prevalence of some unhealthy behaviors in our cohort is considerably high [Cigarette smoking 26.4%, Analgesic 34.9%, and herbal use 23.4%]. Prevalence of cigarette smoking, analgesic use and herbal use were not different among different stages of CKD. Use of NSAID, lack of exercise and poor medication adherence were less in more advanced stage of CKD.

Conclusions: The baseline data of this study revealed high prevalence of cigarette smoking, analgesic and herbal use even in advanced stage of CKD. However prevalence of NSAID use, lack of exercise and poor medication adherence were low and less in advanced stage of CKD. On going study are being conducted to observe the effect of these unhealthy behaviors on CKD progression and the impact of integrated care on improving lifestyle modification.

Funding: Private Foundation Support

Table 1

Unhealthy behaviors	CKD stage 3A N [%]	CKD stage 3B N [%]	CKD stage 4 N [%]	Total N [%]	P value
Cigarette smoking	86 [25.4%]	115 [28.8%]	40 [23.0%]	241 [26.4%]	0.3
Analgesic use	121 [35.7%]	142 [35.6%]	55 [31.6%]	318 [34.9%]	0.60
Herb use	78 [23.1%]	92 [23.4%]	41 [23.8%]	211 [23.4%]	0.985
NSAID use	25 [7.4%]	11 [2.8%]	2 [1.1%]	38 [4.2%]	0.001
Lack of exercise	60 [18.7%]	51 [13.6%]	13 [8.0%]	124 [14.5%]	0.006
Poor medication adherence	23 [6.8%]	11 [2.8%]	6 [3.5%]	40 [4.4%]	0.023

PUB371

Dynapenia, Muscle Mass, and Fracture Risk in CKD (Stages 1-5 ND)

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Background: Sarcopenia is highly prevalent in patients with Chronic Kidney Disease (CKD). Definition of Sarcopenia in the Elderly (EWGSOP 2018) includes low muscle mass associated to low muscle strength and/or low physical performance. In CKD, the relationship between protein synthesis and protein catabolism is altered producing an increase in the speed of skeletal muscle loss. The objective is to evaluate the influence of muscle mass and function with the risk of fracture, in patients with CKD 1-5 ND.

Methods: Cross-sectional study.880 patients were included. FRAX (Fracture Risk Assessment Tool) test was performed, considering the high risk of vertebral fracture at 10 years≥10% and hip at 10 years≥3%.Muscle mass was evaluated by vectorial BIA (BiaVector, Akern, Fl Ita). Strength was performed by handgrip(Akern, Fl, Ita) in Kg. Renal function was assessed by CKD-EPI and MDRD.

Results: Age 70.17±10.49 years, 60.7% women. Frequencies of CKD stage(S) were:S1 6.1%, S2 18%;S3 56.1%;S4 15.6% and S5 4.2%.Pts with dynapenia were significantly older. The glomerular filtration rate and the risk of osteoporotic fracture were significantly higher in the dynapenic subjects ($p \leq 0.05$). However, the risk of hip fracture was only significant in the dynapenic women (Table). Interstitial fluid measured did not show statistical significance.

Conclusions: Dynapenia is a related risk of vertebral fractures in both sexes. Hip fracture risk is higher in women. In both cases muscle mass is normal. The promotion of physical exercise in order to: increase the traction on the bone, stimuli the muscle and increase the bone structure is relevant in these patients. Dynamometry evaluation should be included as a routine tool in clinical practice

Funding: Other NIH Support - Sergas

Descriptive & ANOVA (n=880)

Variable	Women ≤ 16Kg	Women>16 Kg	Men ≤27 Kg	Men > 27 Kg	Total
Age (yr)	75.60±9.25*	69.64±10.71*	75.01±9.07*	67.17±9.95*	70.20±10.49
GFR-EPI (ml/min/1.73m2)	41.92±18.04	47.92±23.66	42.90±18.74*	48.71±21.62*	46.68±21.48
FRAX Osteoporosis %	17.81±10.90*	13.40±9.75*	7.06±4.48*	5.18±3.34*	9.23±8.33
FRAX hip fracture %	8.84±8.15*	6.14±7.88*	3.57±2.91	2.23±2.53	4.30±5.84
Mortality risk at 5 yr	49.12±28.43*	37.60±26.11*	60.70±28.20*	50.85±26.60*	48.99±28.15
BMI (Kg/m2)	32.47±5.59	32.15±5.99	29.35±4.14	30.53±4.65	31.00±5.19
Fat %	43.54±8.00	42.07±6.97	32.90±6.32	32.53±6.50	36.49±8.33
Muscle Mass %	34.68±7.43*	37.13±7.19*	40.22±7.38*	42.38±7.45*	39.66±7.88
Muscle Mass Kg	25.32±5.42*	28.03+5.85*	31.47±6.81*	36.34±7.11*	31.93±7.78
BMD by BIA (Gr/cm2))	0.87±0.08	0.97+0.17	0.92±0.07*	1.04±0.24*	0.98±0.19

Date are mean(SD)

PUB372

Needs Assessment of a Collaborative Telenephrology Care Model for Rural Veterans

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Background: Chronic kidney disease (CKD) is a growing medical problem affecting over 40 million Americans, with Veterans having a 34% higher prevalence of CKD than the general population. Early identification of CKD by primary care providers can lead to earlier specialist referral which may help delay the progression of disease and improve outcomes. However, there is a limited supply of kidney specialists to address this disease burden, particularly in rural settings. Telenephrology consultation provides an appealing collaborative option for rural providers to increase consultative access.

Methods: A cross-sectional retrospective review was performed on 53085 patient records within the Iowa City Veterans Affairs (VA) Health Care System from March 2017 to March 2019. Variables abstracted included creatinine, eGFR, urine microscopy and urine dipstick results, urine albumin-to-creatinine ratio, and urine protein-to-creatinine ratio, as well as documentation of an outpatient nephrology visit. We analyzed the data using descriptive statistics.

Results: The charts of 53085 Veterans were reviewed, of which 11790 (22.2%) were diagnosed with CKD stages 3-5 based on eGFR. Among these, 10498, 943, and 349 were diagnosed with CKD stages 3, 4, and 5 respectively. Of the 12541 Veterans who had urine dipstick and microscopy data, 4363 had hematuria. Of the 23407 Veterans who had urine protein assessment, 3212 and 309 (13.7% and 1.3%) had micro- and macroalbuminuria, respectively. Among the 2627 Veterans who had urine protein to creatinine ratios, 471 had a value between 0.2 to 1, 183 had a value between 1 to 3.5, and 358 had a value higher than 3.5. Overall, only 1950 of these patients were seen directly by nephrologists in the VA system, with an additional 87 being evaluated by a community nephrologist. Therefore, only approximately 17% of patients with the above findings had been seen by a kidney specialist.

Conclusions: There is a significant burden of kidney disease with an increasing demand for kidney specialists that surpasses the current supply of practitioners. Our data suggest that only up to 1 in 6 Veterans with CKD in this predominantly rural healthcare system have been evaluated by a kidney specialist. Telenephrology e-consults are one mechanism to extend care to ensure that these needs are being met.

Funding: Veterans Affairs Support

PUB373

Serum Uric Acid Is Associated with CKD Progression: Insights from the CKD-REIN Cohort

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Background: The association between hyperuricemia and CKD progression is not well established in Europe and, to our knowledge, has not yet been investigated using longitudinal measurements.

Methods: We used data from the on-going French multicenter CKD-Rein cohort study, which included patients with CKD stages 3 to 5 between 2013 and 2016. All uric acid measures were taken into account, from inclusion to the occurrence of renal replacement therapy (RRT), death, or end of follow-up, whichever came first. We used a shared random-effect model for the joint analysis of individual trajectories of uric acid and hazard of RRT and death. Hazard ratio were adjusted for age, sex, primary kidney disease, metabolic syndrome, cardiovascular disease, proteinuria (< 30, 30-300, > 300 mg/day), and the CKD-EPI estimated glomerular filtration rate (eGFR) at baseline.

Results: A total of 2781 patients (65.5% men, median age 69 years) were included. At baseline, the median eGFR was 31.8 mL/min/1.73m2 and the median uric acid value was 425 μmol/L. During a median follow-up of 3.2 years, 434 patients received RRT and 264 died before RRT. After adjustment, an increase of 100 μmol/l of the current level of uric

acid was associated with a significantly increased hazard of death or RRT, at any time of follow-up (HR 1.11, 95%CI 1.03-1.20).

Conclusions: The current level of uric acid is associated with an increased hazard of death or RRT in European patients with CKD stage 3 to 5.

PUB374

Prevalence Estimate of Secondary Distal Renal Tubular Acidosis Among Patients with Sjogren Syndrome and Systemic Lupus Erythematosus in a US, Employer-Sponsored Health Insurance Population

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Background: Secondary distal renal tubular acidosis (2º dRTA) involves impairment in the distal tubule, leading to insufficient renal acid secretion, which can result in metabolic acidosis, hypokalemia, nephrolithiasis, nephrocalcinosis and bone demineralization. While primary dRTA is caused by genetic factors, 2º dRTA may result from autoimmune disorders, such as Sjögren's syndrome (SS) or systemic lupus erythematosus (SLE), which also attack the distal tubule. While 2º dRTA is rare, US prevalence may be under-reported. This analysis utilizes administrative claims data to estimate the prevalence of 2º dRTA among patients with SS or SLE in a US employer-sponsored insurance (ESI) population.

Methods: Utilizing the Truven MarketScan® Commercial and Medicare Supplemental Databases from Jan 1, 2016–Dec 31, 2016, 2º dRTA patients were identified as follows: at least 1 inpatient or ≥2 outpatient claims ≥30 days apart for SS (ICD-10-CM: M35.0x) or SLE (ICD-10-CM: M32.xx) or acidosis (ICD-10-CM: E87.2). Patients were also required to have a claim for an alkalinizing agent or have a diagnosis of other disorders resulting from impaired renal tubular function (ICD-10-CM: N25.89). MarketScan Commercial Insurance Weights were then applied to project the sample to the total US ESI population.

Results: A total of 100,680 patients with ICD-10-CM diagnosis code of SS, SLE, or acidosis were identified. Of these, 1,125 were prescribed an alkalinizing agent or had a diagnosis code of impaired renal tubular function. Applying the insurance weights to this sample, this projected to an estimated 6,716 secondary dRTA patients, which extrapolates to an estimated 2º dRTA patient prevalence rate of 3.88 per 100,000 in the 2016 US ESI population.

Conclusions: The ability to unequivocally identify 2º dRTA patients based on a diagnostic code is limited. This approach used claims data to provisionally identify and estimate the prevalence of 2º dRTA patients in the US ESI population. According to the Kaiser Foundation, ESI represents 49% of the total US population. Further research is needed to validate this approach to effectively identify and characterize the treatment experiences of dRTA patients.

Funding: Commercial Support - Advicenne

PUB375

ACEI/ARB Use in Patients with CKD and at Risk for CKD in Two Large Health Systems

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Background: Rates of ACEI/ARB use in patients with CKD and At-risk for CKD are unknown. We completed a retrospective analysis of ACEI/ARB use in CKD and At-risk for CKD patients from the UCLA-PSJH CKD Registry, populated from electronic health records.

Methods: The cohort: >2.6 million adults (2006-2017) based on labs and/or administrative codes for CKD, hypertension, diabetes mellitus, or pre-DM. We conducted analyses on patients with CKD (N=84,150) and At-risk for CKD (N=807,211) with ≥3 eGFRs ≥15ml/min/1.73m^2, followed for an average (SD) of 5.4±2.4years. Logistic regression assessed the relationship between baseline eGFR and ACEI/ARB use, controlling for age, gender and race/ethnicity. We compared proportions of patients on ACEI/ARB for each year from study entry between decliners and non-decliners (≥2mL;<2mL/min/1.73m^2/year) identified by least squares fit to individual eGFR trajectories. Linear mixed effects (LME) models evaluated the association between time-varying ACEI/ARB use with eGFR trajectories in decliners vs. non-decliners; controlling for age, gender and race/ethnicity for CKD patients.

Results: More registry patients were 45-64years (41%), female (56%), White Non-Latino (83%) and non-decliners (74%), p<0.001. At qualifying entry to the registry, only 13% of CKD and 5% At-risk CKD decliners were on ACEI/ARB. In comparison, 11% CKD and 4% At-risk CKD non-decliners were on ACEI/ARB. Logistic regression showed that higher baseline eGFR was associated with higher rates of ACEI/ARB use for CKD (OR=1.01, 95% CI 1.01, 1.01) and At-risk CKD patients (OR=1.00, 95% CI 1.00, 1.00). LME models for ACEI/ARB use over the period of follow up showed that ACEI/ARB was associated with an increase in eGFR trajectories (1.17, 95% CI: 0.71, 1.63) in CKD patients.

Conclusions: The study showed a gap in ACEI/ARB use in CKD patients. Rates of ACEI/ARB use in CKD patients is higher compared to At-risk CKD patients, and ACEI/ARB use in CKD patients is associated with improved renal function over time.

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PUB376

Significant Predictors of Progression of Renal Dysfunction and Adverse Events for Non-Dialysis CKD Patients

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Background: It is well established that several factors such as anemia, hypertension, hyperuricemia, metabolic acidosis, and chronic kidney disease (CKD)-mineral and bone disorder (MBD) are associated with progression of CKD or adverse events of these patients. However, the significant factors which associated with progression of CKD or adverse events under the condition of appropriate control which according to guidelines have not been cleared.

Methods: The study was an observational study for a period of 3 years. In 88 patients with various stages of CKD (not on renal replacement therapy (RRT)) who were treated by nephrologists, we evaluated the association between clinical parameters and renal adverse events, in addition to the hospitalization resulting in cardiovascular disease or infection by time-dependent Cox hazard model.

Results: Unexpectedly, under the condition of appropriate control by nephrologists, hypertension, hyperuricemia, metabolic acidosis, iron metabolism, and inflammation were not selected as significant predictors of progression of renal dysfunction or adverse events. In multiple regression analysis, baseline blood level of lower Hb (β=0.497, P<0.001) and vitamin D 125 (β=0.258, P=0.006), and higher int-PTH (β=-0.334, P=0.001), urinary phosphorus (β=0.328, P=0.001), urinary β2MG (β=-0.225, P=0.031) and urinary protein (β=0.280, P=0.02) levels were selected as significant predictors of decline of estimated glomerular filtration rate (eGFR) or 1/ creatinine(Cr) at the end of the study. In the Cox hazard model, low calcium (HR: 0.37, P=0.026), high phosphate (HR:5.90, P<0.001), low 125 vitamin D (HR: 0.94, P=0.013), high int-PTH (HR:1.02, P<0.001) level, use of a phosphate binder (HR: 4.95, P=0.012), and use of vitamin D analogs (HR:3.75, P=0.014) are selected as risks for adverse event including initiation of RRT.

Conclusions: In this study, we found that among several factors, anemia and CKD-MBD related factors were selected as significant predictors for the progression of renal dysfunction. Furthermore, although phosphate binder or vitamin D analogs were administered appropriately, CKD-MBD factors were associated with RRT initiation or adverse events of these patients. From these results, we presumed that the early intervention or strict control for CKD-MBD factors might attenuate the risk for adverse events of CKD patients.

PUB377

Associations of Heart Failure and Diabetes with Mortality in CKD Patients: A Single-Center, Algorithm-Based Insight

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Background: Chronic kidney disease (CKD) shows a well-known stage-dependent increase in mortality. Heart failure (HF) and diabetes mellitus (DM) are two important factors potentially driving adverse outcomes (Kidney Int. 2018 June; 93(6): 1281–1292). Recent drug developments offer new therapeutic perspectives for HF and DM. However, there is a tremendous lack of reliable data from the German CKD population raising uncertainty about the relevance of such factors and subsequent interventions. We sought to improve the current situation with an initial monocentric approach.

Methods: A single-center analysis was performed using an Algorithm-based approach using the MD Explorer Pro software. We analyzed all patients (pts) out of a 5-year-period between April 1st, 2014 and March 31st, 2019. Diabetic pts were identified by ICD-10 codes E10, E11 and E14, CKD pts by ICD-10 N18.3-18.5 and HF pts by ICD-10 50.1, 50.9, I11, I13 and the terms "Kardiomyopathie" and "Herzinsuff". Age ranges were chosen from 0-100 years and below 65 years. The diagnosis of HF or DM had to appear for the first time during the defined period. Mortality (MO) was calculated as % pts of the corresponding group that died through the time period and was analyzed for CKD with HF, CKD without HF and CKD with DM in CKD stages 3, 4 and 5.

Results: We analyzed 14.454 datasets. 5154 pts had a HbA1c of >6% at least once, 3683 pts received the corresponding ICD diagnosis de novo. CKD3-5 was present in 7.530 pts, HF in 1838 pts out of which 49 received Sacubitril/Valsartan. The combination of HF and DM was present in 840 pts. MO in 48 pts with DM and without (wo) CKD was 0%. MO was highest in CKD5 with HF (30.3%) and lowest in CKD3 wo HF (3.6%). Overall the MO was higher in HF groups compared to groups wo HF or with DM. Pts aged 65 or younger had a much lower MO in CDK3 or 4 which increased with CKD5 (table).

Conclusions: This monocentric analysis of a large dataset demonstrated higher MO in CKD3-5 pts with newly diagnosed HF than in pts wo HF or with newly diagnosed DM. While this effect was less pronounced in CKD3/4, deaths in association with HF increased by 1/3 in CKD5 patients. A multicentric analysis approach should be used to generate more precise data on these associations in the German CKD cohort.

PUB378

Suggested Target Value for Serum Uric Acid in Advanced CKD Patients to Reduce the CKD Progression

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Background: Recently, the role of uric acid (UA) as a factor that promotes progression of renal damage has been noticed. We retrospectively analyzed the factors affecting the rate of renal damage progression of non-diabetic CKD patients. We report

the results of the study, which suggested that serum uric acid level may have an impact on the progression of renal damage.

Methods: Patients who were newly received dialysis therapy in our facility between Jan 2015 and Dec 2018, and those whose results of a blood test six months prior to starting the dialysis were available were selected as study subjects. Patients with diabetic nephropathy or urological diseases as a primary disease were excluded, and 144 patients were finally included into the study. The subjects were divided into two groups: a rapid progression group (R group, 35 cases), whose baseline eGFR was 15 mL/min or greater, and slow progression group (S group, 109 cases), whose eGFR was lower than 15 mL/min. We examined the difference between the groups in the baseline values (BL value) and those when dialysis was started (D value) of the following parameters: UA, proteinuria, Na, K, Mg, Ca, P, bicarbonate concentration as well as blood pressure (BP).

Results: Only UA-D value showed a significant difference between the R and S groups, and no difference was observed in UA-BL value or all other parameters such as BP, proteinuria and electrolytes (8.62±2.56 in R, 7.14±1.60 mg/dL, p<0.01). Next, we examined the correlation between the rate of eGFR decline and UA-D value using single regression analysis. No significant correlation was found in the S group, however, weak correlation was shown in the R group (R=0.503, R2=0.25, and p=0.0034). The ROC analysis of UA-D value corresponding to the median value of eGFR-decline showed 8.5 mg/dL as a UA-D cut-off value.

Conclusions: These results suggest that the control level of UA may affect the rate of progression of renal damage. At present, there are no established criteria for the controlling of serum UA concentration in advanced CKD patients. Present study may suggest that the UA value lower than 8.5 mg/dL contributes to reduce the renal damage progression.

PUB379

Annual Change of Estimated Glomerular Filtration Rate as an Alternative Surrogate Marker for ESRD

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Background: Doubling of serum creatinine or 57% declining of eGFR as standard surrogate marker for ESRD requires long-term follow up which made profound obstacles for research in nephrology. It has been suggested that eGFR decline of 30% to 40% over 2 to 3 years may be acceptable for alternative end-point for renal outcome, yet it is unclear whether estimation methods of eGFR affect diagnostic accuracy and annual rate of eGFR change (eGFR slope) can also be used as a surrogate marker for ESRD.

Methods: Laboratory data including serum creatinine acquired in baseline and 12 months follow-up periods was analyzed from 348 CKD (stages G1-G4, 20-61years) patients' cohort from three tertiary referral hospitals in South Korea, prospectively. The data of incidents to become ESRD was extracted from the ESRD registry of Korea additionally for more than 3 years after cohort observation. The eGFR was calculated by both modified MDRD equation (eGFRm) and CKD-EPI 2009 creatinine equation (eGFRc) using IDMS-traceable creatinine value. We compared the effectiveness of each parameter to estimate the risk of ESRD using diagnostic accuracy indices.

Results: There were 11.8% (41/348) of ESRD patients during 38-month of follow up period. The accuracy to estimate ESRD was more effective with eGFR percent change than eGFR slope using both eGFRs. AUCs to predict ESRD were 0.804 (0.721-0.887) for eGFRm change, 0.802 (0.718-0.886) for eGFRc change while 0.705 (0.624-0.785) for eGFRm slope, and 0.692 (0.610-0.774) for eGFRc slope (P<0.003). The findings of diagnostic accuracy of eGFRm criteria showed similar patterns as those of eGFRc criteria. The criterion of eGFRc decrease of ≥ 30% and ≥ 40% shows similarly high accuracy compared to eGFRc decrease of ≥ 57%, the standard surrogate marker. The sensitivity and specificity to estimate incident ESRD were 58.5% and 92.2% with the criteria of eGFRc 30% decline, 41.5% and 94.8% with the criteria of eGFRc 40% decline, and 9.8% and 97.7% with the criteria of eGFRc 57% decline, respectively.

Conclusions: There were no differences of AUC to estimate ESRD between eGFR calculated by CKD-EPI equation and modified MDRD equation. The percent change of eGFR provided more diagnostic accuracy for renal outcome than the parameter of eGFR slope. The annual percent change of eGFR ≥ 30% can be suggested to alternative surrogate marker for ESRD.

PUB380

Association of Overweight with Glomerular Density and Glomerular Swelling in CKD Patients

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Background: Although glomerular hypertension suggested to be associated with progression of obesity-related glomerulopathy, its contribution is not known in chronic kidney disease (CKD) patients with overweight. In this study, we examined the association between glomerular density, which reflects the total glomerular number, glomerular swelling, which reflects glomerular hypertension, and obesity in overweight CKD patients.

Methods: We recruited 76 CKD patients who underwent renal biopsy from January 1, 2016 to June 30, 2017. Overweight was defined as body mass index (BMI) 25 kg / m^2 or more. We examined glomerular density and glomerular diameter according to the presence or absence of overweight.

Results: The median age, blood pressure, BMI and creatinine clearance (CCr) of the subjects were 51, 123/70 mmHg, 25 kg / m^2 and 70 ml / min, respectively. The CCR of overweight group was comparable to that of non-overweight group (70ml/min vs. 62ml/min). Overweight group showed lower glomerular density (2.2 / μm^2 vs. 2.8 / μm^2, p = 0.027) and larger maximum glomerular diameter (251 μm vs. 208 μm, p <0.001). Multivariate analysis revealed that BMI was significantly associated with maximum glomerular diameter, independently of age, sex, systolic blood pressure, diabetes mellitus, CCr, and use of renin-angiotensin-aldosterone inhibitors.

Conclusions: In CKD patients, mild obesity suggested to be associated with glomerular hypertension accompanied with decreased absolute glomerular number. Therefore, glomerular number may be potentially reduced in overweight group even if their CCr was comparable to those of non-overweight group.

PUB381

Prevalence of CKD in Tuscany: A Demographic Picture by the Regional Health Agency Database

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Background: In Italy, CKD3-5 prevalence ranges from3.5%to5.7% in men and from2.4%to6.2% in women, lower than US(overall prevalence14.2%, CKD 3-4 6,2% by NHANES surveys), while European data are less homogeneous with an extremely variable CKD prevalence(1.7-5.9%); elderly are usually under-represented. Objective: After a pilot study based on administrative data in a Tuscan city in 2011-2013, we show the results of the same approach conducted on the whole Tuscan population in 2018 (3,736,968residents, 6.2%of Italian population) to estimate CKD3-5 prevalence, with sub-analysis in diabetic, hypertensive and heart disease patients, and to compare it with European and US populations.

Methods: Administrative data were collected from the health database of Tuscany Region. Outpatients, residents in Tuscany, >20yr with a SCr in 2018 by IDMS to estimate GFR by CKD-EPI equation were included and stratified in CKD3a, 3b, 4-5(RRT patients excluded). Expected cases for each CKD stage, sex and age class were obtained by applying specific rates by sex, age and comorbidity to total population. Expected cases were standardized by age and sex using EU27 and US populations.

Results: Of the 3,736,968 Tuscany residents, 2,730,349(73.1%) were >20yr and performed at least one SCr in 2018. 180,167(6.6%) individuals had eGFR <60 ml/min distributed as follows: stage3a=4.1%,3b=1.6%,4-5 0.8%. CKD3-5 prevalence increased with age, in 45-74yr group was 4.8%, while among >80yr was 43.9%: stage3=37.4%,4-5=6.5%. Age and sex distribution of CKD3-5 showed higher prevalence in females and elderly(p<0.0001). CKD3-5 prevalence among diabetics was 23.4%, among hypertensive 20.3% and among patients with heart disease 43.3%.

Conclusions: Our data confirm an overall CKD 3-5 prevalence among adults in Tuscany similar to US(6,6% vs 6,9%). Nevertheless, if we standardise our data on US population we obtain a much lower prevalence(3,3% vs 6,9%). This contradiction may be due both to the higher prevalence of young people <35yr in US and in Europe compared with Italy, leading to a "dilution effect" of our raw prevalence after standardisation on other populations and to a higher prevalence of elderly >75yr in our population, burdened with CKD 3-5. Administrative data allow an objective evaluation of CKD prevalence overcoming the methodological bias of other studies.

PUB382

The Ratio of Fat to Calories Associated with Decline of Glomerular Filtration Rate: A Cross-Sectional Study of 8322 Participants from the China Health and Nutrition Survey (CHNS)

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Background: Although there are some reports on the association of dietary patterns and chronic kidney disease (CKD), no data exists regarding the relation between ratio of fat to calories and renal function progress. The purpose of this study is to examine the association between ratio of fat to calories and renal function.

Methods: We use data from The China Health and Nutrition Survey (CHNS), a population based observational cohort study in 9 different provinces over China. the data were collected from the 2009 wave of the CHNS, in which 11,978 participants took part in the survey. During this survey fasting blood samples were collected and detection was conducted. Adult population aged no less than 18-year-old were excluded in our analyses (n = 10,120). We excluded serious diseases(n=224), body disability that affects going out(n=3), lack of blood sample collection(n=1273) and lack of diet information(n=298). Finally, 8322 participants (3878 men and 4444 women,) were included in analyses. Renal function was measured by estimated glomerular filtration rate (eGFR) (CKD-EPI Equation)

Results: Ratio of fat to calories, age, residence, netincome, vegetable intake, hyperuricemia, diabetes, tea drinking, triglycerides, total cholesterol, HDL-C, LDL-C, ApoA, ApoB, and serum uric acid were risk factors of the decline in renal function. After adjusting for confounders (age, gender, education, residence, income, vegetable intake, fruit intake, total protein intake, sleeping duration, eat away from home, LPA, screen time, tea drinking, alcohol drinking, soda drinking, water intak, snacks intake, HGB, albumin, triglycerides, total cholesterol, HDL-C, LDL-C, ApoA, ApoB, UA, UREA, hyperuricemia, diabetes and hypertension), patients in high ratio of fat to calories dietary pattern were found to be at independen risk of the decline in renal function. (odds ratio: 1.27, 95% CL: 1.14, 1.41).

Conclusions: We observed that a high ratio of fat to calories dietary pattern was directly associated with the decline in renal function.

PUB383

The Risk of Socioeconomic Inequality in the Control of Diabetes Mellitus (DM), Hypertension (HA), and CKD in the Context of the Unified Health System (UHS)

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Background: There is evidence that correlates socioeconomic factors with a higher prevalence and risk factors for HA, DM and CKD. OBJECTIVES: To evaluate the impact of social risk factors in patients with HA, DM and CKD.

Methods: Retrospective cohort from August / 2010 to December / 2014. Inclusion criteria: Patients over 18 years of age and who have undergone at least 2 visits at the Hiperdia Center in Juiz de Fora, which are referred for primary health care. Variables analyzed: socio-demographic data were collected at admission and the other variables (clinical and laboratorial) were collected in care. Clinical control goals related to hypertension, DM and CKD were evaluated, considering the markers at the beginning of follow-up and at the end of the study.

Results: A total of 6,369 patients were evaluated, of which 2,036 of the hypertension clinic, 2,336 from the DM and 1,997 from the clinic of CKD. We can observe the effectiveness of the treatment through the increase of the patients who managed to reach the goal of blood pressure control, from 42.7% at the beginning of the follow-up to 62.6% at the end. The same occurs with glycemic control, initially 32.1% were in the target, at the end of the study this percentage rose to 41.9%. Patients had low family incomes in all groups, with 53% with a family income of up to two minimum wages among hypertensive patients, with 54.8% among diabetics and 51.2% of chronic renal patients. We found income impact only in the diabetic group with family income up to minimum wage, OR1,155 (CI 1,042 - 1,281 p=0.006).

Conclusions: The color, income and education had a low impact on the progression of hypertension, DM and CKD. Only income impacted on the progression of DM, possibly due to the fact that access to medications by the population with the lowest income was restricted to the classes available in the UHS.

PUB384

Association of Serum Phosphorus with Long-Term Hemoglobin Variability in Chinese Patients with CKD

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Background: Cross-sectional studies have revealed that there are independent correlations between serum phosphorus and anemia in patients with wide spectrums of chronic kidney disease. In this study we were intended to evaluate the association of baseline phosphorus level with long-term hemoglobin variability in patients followed up in the cohort of C-SRTIDE.

Methods: There were 850 participants who were followed up for at least 2 years, and with hemoglobin measured at baseline, year 1 and year 2, were selected for the analysis. Socio-demographic status, medical history, anthropometric measurements and biochemical parameters were compared among serum phosphorus quartiles. Anemia was defined according to WHO criterion. Hemoglobin variability was defined by within-patient SD, residual SD, within patient range, slope, coefficient of variance. Hemoglobin fluctuation was defined as never anemia (NA), constantly anemia (CA), normal HGB exhibited anemia thereafter (NEA), and anemia which returned to normal thereafter (ARN). General linear regression or multinomial logistic regression were applied to evaluate the association of serum phosphorus with the measurements of hemoglobin variability in appropriate.

Results: Serum phosphorus level was stratified by quartiles (<1.05mmol/L, 1.06~1.18 mmol/L, 1.19~1.32 mmol/L, >1.32 mmol/L). There were significant differences of HGB variability parameters among quartiles of phosphorus. Serum phosphorus level was significantly correlated with residual SD of HGB in both univariable (coefficient=0.661, *P*=0.0013) and fully adjusted multivariable linear regression model (coefficient=0.497, *P*=0.03). Compared with NA, the ORs for serum phosphorus in CA, NEA and ARN were 16.62(7.46, 36.99), 12.70 (4.91, 32.89) and 8.96(3.47, 23.15) respectively in univariate logistic regression, and 3.059 (1.003, 9.33), 3.247 (0.999, 10.53), 3.649 (1.22, 10.90) respectively in multinomial logistic regression analysis.

Conclusions: Serum phosphorus was independently associated with long-term hemoglobin variability. Further exploration of the impact of serum phosphorus on long-term hemoglobin control during follow-up would be warranted.

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PUB385

Perpetual Risk of Oxalate Nephropathy After Gastric Bypass Surgery

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Introduction: Oxalate nephropathy, a known complication of bariatric surgery, is characterized by deposition of calcium oxalate crystals in renal parenchyma and is often recognized only in advanced stages, thus, increasing risk of ESRD. We report a case of a patient with more than 15 years of near-normal renal function following bariatric surgery who suddenly developed oxalate nephropathy.

Case Description: A 70-yr old male was referred to renal clinic for AKI. History notable for hypertension, morbid obesity s/p Roux-en-Y gastric bypass 18 years ago, CAD, hypothyroidism, h/o panniculectomy 3 years ago complicated by infection requiring multiple and prolonged antibiotic courses. Serum creatinine (Cr) had increased to 2.8 mg/dL from usual 1.2-1.5 mg/dL for several years, thought to be in the setting of relative hypotension. No urine sediment or proteinuria noted, no obstruction. AKI improved after adjusting medications (ACEI, thiazide) but Cr stabilized at 2mg/dL. Few months later Cr again increased to 4.8 mg/dL. A kidney biopsy was performed, after extensive evaluation did not reveal any etiology, and showed severe tubular accumulation of calcium oxalate crystals, severe tubular atrophy and interstitial fibrosis. Immunofluorescence and electron microscopy were non-contributory. 24-hr urine showed elevated oxalate excretion. Patient was then started on low fat, low oxalate diet and calcium supplements following which Cr improved to ~3mg/dL and has remained stable since then.

Discussion: Enteric hyperoxaluria, a complication of bariatric surgery, increases risk of nephrolithiasis and oxalate nephropathy. The underlying pathophysiology is complex and yet to be fully defined but the pivotal role of inflammasome recruitment and activation (especially NALP3) has recently been described in animal models. Inflammasomes can be activated by acute kidney injury thus potentiating crystal deposition and propagation of inflammation leading to fibrosis if unchecked, as is evidenced in the above case.

PUB386

Association of Pre-ESRD Laxative Use with Post-ESRD Outcomes

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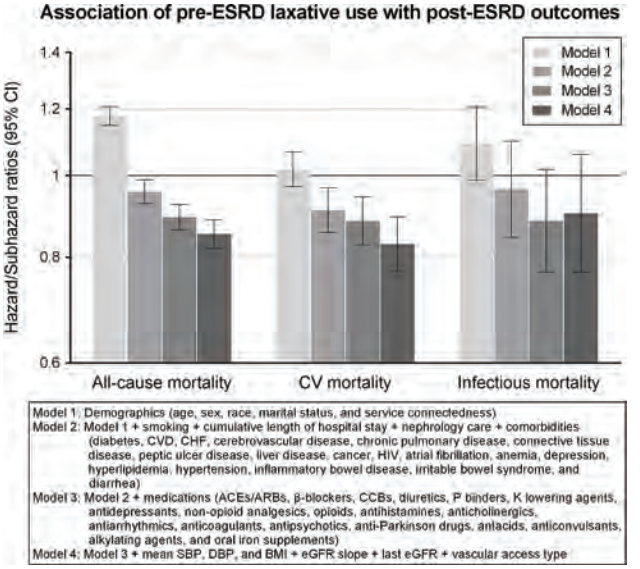
Background: Constipation is associated with various adverse clinical outcomes like all-cause and cardiovascular (CV) mortality. Constipation is highly prevalent in advanced CKD and typically managed by laxatives; however, little is known about the association of laxative use in advanced CKD with outcomes after dialysis initiation.

Methods: We examined the association of laxative use over the last two years preceding transition to dialysis with all-cause and cause-specific mortality following dialysis initiation in 61,119 US veterans transitioning to ESRD from 10/2007-3/2014. Laxative use was defined as having ≥2 prescriptions of laxatives of ≥30-day supply each that were 60–365 days apart during the two-year pre-ESRD period. Associations were examined using Cox (for all-cause) and competing risk (for cause-specific mortality) regressions with adjustment for demographics, comorbidities, medications, nephrology care, cumulative length of hospital stay, vascular access type, and clinical variables.

Results: The mean (SD) age of the cohort was 70 (11) years; 92% were male; 24% were African American; and 59% were diabetic. The use (vs. non-use) of laxatives prior to ESRD transition was associated with lower risk of all-cause and CV mortality, but not with infectious mortality, after transition to ESRD, with adjusted hazard/subhazard ratios [95% CI] of 0.85 [0.82-0.89], 0.83 [0.77-0.89], and 0.90 [0.77-1.06], respectively (Figure).

Conclusions: Pre-ESRD laxative use is associated with lower post-ESRD all-cause and CV mortality risk. Further studies are needed to elucidate the underlying mechanisms and determine if effective fecal management with laxatives confers a survival benefit in advanced CKD patients transitioning to dialysis.

Funding: NIDDK Support



PUB387

A Cost Analysis of Monitoring Pre-Dialytic Patients in a Multidisciplinary Outpatient Clinic: Minimizing Costs

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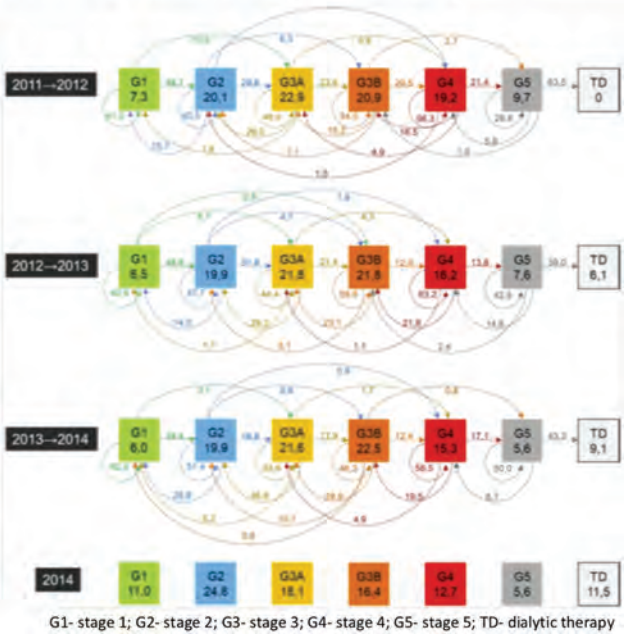
Background: The advancement of chronic kidney disease (CKD) in Brazil does not seem to be a reason for alert for fiscal austerity policies on health in the Brazilian context. Objective: To evaluate the costs of the Unified Health System (UHS) with the service provider throughout the evolution of CKD in pre-dialytic care, comparing with the costs of UHS to dialysis service providers.

Methods: Retrospective cohort of patients followed in a clinical center specialized in pre-dialysis care. The center focused on preventive care for Diabetes Mellitus (DM), Systemic Arterial Hypertension (SAH) and CKD. Data from 537 patients were evaluated in the period from 2011 to 2014. Sociodemographic data, stage of CKD, comorbidities and referral to dialytic therapy (DT) were analysed. On the CKD evolution data, we calculated the transition probabilities between stages of the disease, following the parameters defined by Kidney Disease Improving Global Outcomes (Figure 1). The costs of pre-dialysis outpatient care were based on micro-costing (bottom-up) and performed according to the risk stratification: (i) CKD; (ii) CKD + SAH; (iii) CKD + DM; (iv) CKD + SAH + DM.

Results: In general, a pre-dialysis program can generate an average reduction of R $ 33,023.12 (± R $ 1,676.80) for each year avoided in DT, already paying its operations, thus being cost-minimizers.

Conclusions: These results indicate that in the medium term (4 years) the real possibility of obtaining results visible to a budget that in the last 10 years has disbursed R $ 24 billion for DT.

Figure 1 - Chances of transition between the stages of evolution of Chronic Renal Disease between 2011 and 2014 (in%)



G1- stage 1; G2- stage 2; G3- stage 3; G4- stage 4; G5- stage 5; TD- dialytic therapy

PUB388

Applying Novel Kidney Failure Risk Equations Applications to New Patient Referrals: A 6-Month Retrospective Review

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Background: Chronic kidney disease represents a significant health and economic burden. An estimated 20% of Irish people over the age of 45 have CKD, and approximately 4,000 patients have ESKD. Timely speciality referral is imperative to slow CKD progression and enable expedient planning for dialysis or transplant workup where appropriate. Tangri *et al* developed a 4-variable kidney failure risk equation that was validated in Canada. These risk equations showed high discrimination when validated in 31 multinational cohorts.

Methods: The study involved a retrospective chart review of new patient referrals to the Renal Service over six months (June-December 2016). The four variable KFRE was used to predict the 2 and 5 year probability of ESKD incorporating age, gender, uPCR/ACR, creatinine and eGFR.

Results: Of the 178 new referrals (92 males, 87 females) 137 patients had complete data for KFRE. 13.9% had eGFRs >90mL/min/1.73sq.m, 21.22% had eGFR 60-89mL/min/1.73sq.m, 45.25% had eGFR 30-60mL/min/1.73sq.m, 12.8% had eGFR 15-30mL/min/1.73sq.m and 2.79% had eGFR < 15mL/min/1.73sq.m.

Conclusions: The KFRE has significant implications for design, delivery and resourcing of clinical services. From the results of this review, 59 patients stratified as low risk by the KFRE (43%) would not have required referral to Nephrology Clinic; a low-risk letter detailing the explanation for same could be forwarded to referring GPs. In cases where the risk is borderline, the 6 variable KFRE could be applied. Applying the KFRE to CKD referrals may afford greater discrimination regarding discharge of patients. A limitation of this tool is applying it to all new referrals as decreased eGFR is not the only indication for referral. In this study 22 patients were referred for investigation of recurrent stones, microscopic haematuria and optimisation of hypertension. Application of a risk based triage scheme would lead to both an improvement in wait times and expedite access to patients at highest risk of progression to ESKD.

Results

	Number of patients	Discharged at first review	Discharged within one year	% under ongoing follow-up
Low risk	59	13	21	42
Intermediate risk	13	3	1	69
High risk	65	6	5	83

PUB389

Physical Activity Improves Kidney Function in CKD Patients; Improved Kidney Function Shortens Hospital Stays

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Background: Patients with chronic kidney disease (CKD) suffer diverse health complications. Participation in regular physical activity predicts improved outcomes in many clinical populations. Limited data support the effectiveness of physical activity as an adjunct intervention for CKD patients. However, isolated effects on estimated glomerular filtration rate (GFR), serum albumin, and length of hospital stay (LOS) remain undefined.

Methods: We analyzed 43 consecutively-admitted patients at a Midwestern hospital in 2018; all patients had a comprehensive metabolic panel, reported physical activity behavior, and had a diagnosis of CKD or end-stage renal disease (ESRD). Descriptive statistics characterized the study sample (means, standard deviations, categorical percentages). Independent-samples t-tests assessed differences between active and sedentary patients. We tested the effect of daily physical activity on GFR and serum albumin using linear regressions, holding constant liver function, use of dialysis, dyslipidemia, and kidney transplant status. We estimated the effect of GFR and serum albumin on hospital LOS using a negative binomial regression.

Results: Patients were 62.8±17.8 years old, 55.3% were male, 44.2% were physically active, 67.4% had a diagnosis of CKD, and 32.6% had ESRD. Mean GFR was 24.9±12.7 mL/min, serum albumin was 3.1±0.7 g/dL, and LOS was 5.8±6.1 days. Active patients had 30.7% higher GFR (p=0.048); they had higher serum albumin and shorter LOS but those differences did not reach significance. With confounders held constant, physical activity predicted an increase in GFR of 8.1 mL/min (p=0.015; 95% CI: 1.64-14.47) and an increase in albumin of 0.5 g/dL (p=0.033; 95% CI: 0.04-0.85). Each 1 g increase in albumin predicted a 39.9% shorter LOS (p<0.001; 95% CI of IRR: 0.46-0.79) and each 1 mL increase in GFR predicted a 1.6% shorter LOS (p=0.023; 95% CI of IRR: 0.97-1.00).

Conclusions: In our sample of patients with CKD or ESRD, regular engagement in physical activity associated with improved kidney function, as measured by GFR and serum albumin. In turn, improvement in these biomarkers predicted shorter hospital stays. Although patients with kidney disease represent a diverse population with varying physical capacities, encouraging activity where possible may lead to improved clinical outcomes.

PUB390

Changes in FGF-23, Neutrophil/Platelet Activation Markers, and Angiogenin in Advanced CKD and Effect on Arterial Stiffness

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Background: The aim of this study was to measure changes in fibroblast growth factor-23(FGF-23), activation markers of neutrophil(elastase, lactoferrin) and of platelet(mean platelet volume per platelet count ratio, MPR), and angiogenin according to the chronic kidney disease(CKD) stages, and evaluate the association between these markers with arterial stiffness using brachial-ankle pulse wave velocity(ba-PWV).

Methods: According to the estimated glomerular filtration rate(eGFR) calculated by the CKD-epidemiology collaboration equation, patients were allocated to five groups: control(eGFR ≥90 ml/minute/1.73m^2, n=22), stage 2(eGFR 60–89, n=17), stage 3(eGFR 30-59, n=22), stage 4(eGFR 15-29, n=17), and stage 5(eGFR ≤14 and hemodialysis, n=30). The serum FGF-23, elastase, lactoferrin, MPR, and angiogenin concentrations were measured to verify the association between the parameters with clinical(age, sex, presence of diabetes mellitus, blood pressure), biochemical(calcium, phosphorus, uric acid, intact parathyroid hormone(iPTH), low-density lipoprotein cholesterol, high sensitivity C-reactive protein) variables, and ba-PWV levels in the CKD patients.

Results: The mean ba-PWV(cm/s) values were 1497.2±206.4 in the control, 1649.0±247.9* in stage 2, 1655.8±260.3* in stage 3, 1823.0±402.4*** in stage 4, and 1905.2±374.1** in stage 5. As CKD stages progress, the mean $\log_{10}$(FGF-23) concentrations were 0.77±0.27, 0.97±0.48, 1.10±0.35**, 1.35±0.48***, and 2.12±0.82****; the mean angiogenin(pg/ml) levels were 230.6±70.5, 283.0±53.5*, 347.3±76.9**, 445.9±90.6***, and 370.9±142.4*** (*p<0.05 vs control; **p<0.05 vs control, stage 2; ***p<0.05 vs control, stage 2, 3; ****p<0.05 vs control, stage 2, 3, 4). The mean elastase to neutrophil ratio and lactoferrin to neutrophil ratio in CKD stage 3-5 were significantly lower than the control and CKD stage 2. Multivariate linear regression analyses showed that age, pulse pressure, mean arterial pressure, iPTH, and FGF-23 were independently associated with ba-PWV values.

Conclusions: Circulating FGF-23 and angiogenin concentration gradually increased as CKD advanced whereas neutrophil activation markers in CKD stage 3-5 were significantly lower than the control and stage 2 CKD. FGF-23 were weakly associated with ba-PWV in patients with CKD and no previous cardiovascular disease.

PUB391

CINAC Lesions in Kidneys of European Dairy Cows

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Background: CINAC is a form of chronic kidney disease of unknown etiology observed in Sri Lanka, Central America and several other tropical countries. Electron microscopically this disease is characterized by enlarged dysmorphic lysosomes in the proximal convoluted tubular cells of the kidney. This can be seen histologically on Jones silver stain as intracytoplasmic large irregular argyrophilic granules. Etiology is unclear but toxic exposure to agrochemicals is one of the possible causes. Cattle are at increased risk for uptake of agrochemicals through feeding and drinking water.

Methods: We investigate if these lesions seen in CINAC patients on Jones stain are also present in European cattle and if so there is any correlation with signs of chronic interstitial nephritis (CIN). At the slaughterhouse a kidney sample of 48 dairy cows older then 5 years and 11 beef cattle type bulls younger then 2 years were collected and histologically evaluated on H&E and Jones silver stain.

Results: In 44 of 59 kidney samples, a varying degree of intracytoplasmic accumulations of brown granular pigment was present in tubules in the outer medulla on H&E, visible on Jones stain as argyrophilic granules. In 41 kidney samples a varying degree of interstitial lymfo-plasmocytic inflammation and fibrosis with multifocal tubular atrophy was present. Transmission electron microscopy (TEM) was performed on 12 kidneys with 4 of them having lesions on Jones stain. In 2 out of 12, both of them having lesions on Jones stain, CINAC-like lysosomes were present. Interestingly in any of the 11 beef cattle type bulls argyrophilic granules or signs of CIN were present.

Conclusions: The lesions as described above could point at a CINAC-like disease at an early stage. Though CKD is not a common disease in cattle, it is possible these animals never reach further stages of the disease because of early death (often at 1/3th of life expectancy). Origin and significance of the argyrophilic granules is unclear. No histological lesions were present in the younger beef type bulls. This could indicate lesions did not develop because of a shorter toxic exposure time. Further toxicological, electron microscopic and epidemiologic investigation is needed to further clarify the significance of these findings.

PUB392

Patients with Kidney Stone of Uric Acid or Calcium Oxalate Are at Higher Risk of Lower Bone Mineral Density

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Background: Kidney stone disease prevalence and recurrence rates are increasing in recent decades. Kidney stones have not only been associated with an increased risk of CKD and ESRD but also to lower bone mineral density (BMD). Diagnosis of osteopenia and osteoporosis by routine CT abdominal scans has been evaluated to be clinically practical and reliable in Chinese population. Hounsfield unit (HU) <175 was a good cut-off value for diagnosis of lower BMD.

Methods: Kidney stone formers and non-stone CKD patients hospitalized in our kidney disease center from Jan 2015 to May 2019 were included for study. Demographic and clinical data were documented. Chemical composition of stones were detected by Fourier transform infrared spectrometer. BMD score was expressed as the mean value of HU of L1-L5 vertebra. Mean values were compared by independent T test or one-way ANOVA. Correlation was performed using the Pearson correlation coefficient. Categorical data were analyzed using Chi square test. Multi-factor lineal and logistic regression were applied to find the independent risk factor.

Results: 107 cases of kidney stone formers and 43 cases of non-stone CKD patients were eligible for analysis and 'stone group'vs'CKD group'were named for comparison. The percentage of lower BMD in stone group were higher than that in CKD group (64.5% vs 44.2%, $p<0.05$). Stone group were divided into three subgroups according the chemical composition of the kidney stone as uric acid group (n=26), apatite group (n=38) and calcium oxalate group (n=43). BMD scores in uric acid group and calcium oxalate group were lower than that in CKD group (156±37.6, 153±44.7 vs 153±44.7; $p<0.01$, $p<0.05$). While in apatite group the BMD score was comparable to that in CKD group (173±61.0 vs 184±56.3, $p>0.05$). Male percentage was lower in apatite group compared with that in uric acid group and calcium oxalate group (26% vs 88% 83%, $p<0.001$) while the BMD score in apatite group was the highest among the three stone subgroups. Although there were no difference in age among the four groups (the three stone subgroups and CKD group), the age was the unique and independent risk factor related to lower BMD in the multi-factor regression analysis.

Conclusions: Kidney stone formers are at higher risk of lower BMD, especially those with stone of uric acid or calcium oxalate composition. Aging is an independent risk factor for osteopenia.

PUB393

Factors Associated with Kidney Disease in Colombian Indigenous Communities

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Background: In the world there are 45 million indigenous people, Colombia there are 102 ethnic groups, being the 2nd with the largest number of ethnic groups. According to the Colombian High Cost Account, 11,685 were affiliated with an indigenous service company and the rest to other entities, 99.4% are affiliated in the subsidized regime and 0.57% contributory. The objective was to describe the sociodemographic, clinical, exposure factors and health regimen in some indigenous communities in Colombia, to characterize their risk of kidney disease.

Methods: Cross-sectional observational study, was collect date sociodemographic, clinical, exposure factors and health regimen after signing informed of respondents consent and physical examination with measurement was performed anthropometric data, proteinuria blood pressure, glucose measurement, hematuria and strip. At this stage no mass screening creatinine was performed.

Results: A total of 1774 persons over 17 ethnic groups, were surveyed. The most frequent age range was between adults (27-59y) with a representation of 59.6%. The sample was mainly composed of women (61.8%), which mainly dealt home. Economic activity was most important agriculture (32.6%). 78% said be covered by the state health system. 16.6% had a presumption diagnosed prediabetes, diabetes mellitus 5.8% of 4.3% and antecedent. It was found that 14.5% of women were diagnosed presumption of hypertension with sisto commitment-diastolic, systolic blood pressure, 13.1% and 6.5% diastolic hypertension. 18% of men had presumed diagnosis of hypertension with sisto commitment-Diastolic, 20.8% systolic hypertension and diastolic hypertension 5.3%. 12.5% of individuals had a history of hypertension confirmed. 12.3% had a history of urinary tract infection and 5.9% nephrolithiasis. 28.3% were overweight and 11.4% obese. 1.4% had hematuria and proteinuria 13.8%. Regarding risk behaviors 14.4% and 39.1% smoked they reported having a regular consumption of alcohol. As discovery, one case of nephritis Class IV and nephrolithiasis (n:2) were diagnosed. 1% reported a regular consumption of alcohol.

Conclusions: This population is vulnerable, being necessary to assess distal determinants of their own habitat and implement longitudinal studies studying the behavior of kidney disease to promote transdisciplinary design and implementation of programs to control.

PUB394

Heat Stress as the Main Cause of CKD in Agricultural Communities: Seven Arguments Against the Hypothesis

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Background: There are two main hypothesis on the uncertain etiology of the global epidemic of chronic interstitial nephritis of agricultural communities (CINAC): the toxic hypothesis implicating an environmental/occupational toxin and the heat stress/dehydration hypothesis (HSDH) suggesting recurrent heat stress induced acute kidney injury to cause chronic kidney disease. Our aim is to demonstrate that heat stress is unlikely to be the main cause of CINAC.

Methods: The following data sets are used to refute the HSDH as the driver of CINAC: 1. Geographical, 2. Climatological, 3. Epidemiological, 4. Ecological 5. Physiopathological, 6. Biochemical and 7. Agrarian.

Results: 1. Geographical: Absence of CINAC in many hot agricultural regions of the world is a stronger anti-correlation than the correlation assumed by presence of CINAC in a few such regions. The mosaic pattern of case distribution in Sri Lanka contradicts the HSDH. 2. Climatological: It is doubtful that the small temperature increases in the latter twentieth century even with extreme temperature fluctuations caused devastating renal effects. 3. Epidemiological: CINAC is seen in people not exposed to hot working conditions, while it is not seen in many occupations with higher temperature exposure. Detection of pathologically proven CINAC in vineyards of France and absence in sugar cane plantations in Cuba argues against HSDH. 4. Ecological: Individuals drinking spring water are not affected in contrast to those drinking from shallow wells in nearby communities in Sri Lanka 5. Physiopathological: It is doubtful that the degree of community-acquired pre-renal AKI seen in field studies of agricultural workers is adequate to cause CINAC. 6. Biochemical: Biochemical changes postulated to perpetuate CKD have not been proven. 7. Agrarian: In Sri Lanka, mechanization of paddy farming has reduced farmers' heat exposure since the late 20th century but CINAC epidemic has continued. Workers in high altitude sugar cane plantations in El Salvador are also exposed to heat stress but the prevalence is low.

Conclusions: It is plausible that heat stress is an important contributor to perpetuation of CINAC, but is unlikely to be the main driving force. An environmental/occupational toxic exposure is more credible as a main drive of this epidemic.

PUB395

New Findings Support Toxicological Origin of Chronic Interstitial Nephritis in Agricultural Communities

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Background: Two main hypotheses; the toxic hypothesis and the heat stress/dehydration hypothesis put forward to explain the etiology of chronic interstitial nephritis in agricultural communities (CINAC). Recent findings suggest calcineurin inhibition could be a possible pathway leading to proximal tubular damage in CINAC. Analysis of drinking water for organic substances revealed it is contaminated with several pesticide residues. Interestingly some of them show calcinurin inhibition properties.

Methods: 50 water samples (1 L each) collected from drinking water sources of CINAC endemic area: Anuradhapura district in Sri Lanka. Water extracted on a C-18 SPE cartridge, blown down to 1ml and analyzed by GCMS. ELISA method was used to detect glyphosate.

Results: Glyphosate (3-20 ppb), Propachlor (40-900 ppb), Diazinon- orgnophosphate (200-650ppb), Propanil (86-1850 ppb) were detected in drinking water sources. Detection frequency was as follows: Propachlor (42/50), Diazinon 37/50), Propanil (32/50) and glyphosate 28/50).

Conclusions: Our previous findings revealed drinking water in CINAC endemic regions contain high amount of calcium, magnesium, fluoride and silica. However, inorganic substances couldn't directly correlated to the etiology of disease. Further, in an epidemiological study, we found that usage of glyphosate, paraquat, byspiribac, mancozeb, MCPA and organophospate are associated with CINAC. The present study confirms the presence of pesticide residues in drinking water sources. Pesticides with calcineurine inhibitory properties in drinking water could be the nephrotoxic agents behind the CINAC.

PUB396

Associations Between Nephrologists' Cognitive Load and Practice Setting Characteristics

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Background: Among specialists, nephrologists are particularly at risk of burnout, and satisfaction with the profession is declining. Burnout, time pressures, stress, and poor work-life balance are associated with cognitive load, which can negatively affect clinical decision making, and may be greater in some practice settings. We will examine how cognitive load varies across care settings for nephrologists.

Methods: We are administering a new and innovative survey—the Transplant and Home Dialysis Recommendations Survey of Nephrologists, or THRoNe—in a nationally representative sample of n=120 nephrologists (non-pediatric). The THRoNe, which we have pre-tested and validated rigorously using a modified Delphi approach with 12 nephrologists and subject experts, collects data on nephrologists' cognitive load and other practice and physician characteristics. Nephrologists are asked to characterize their cognitive load through 12 survey items related to workload, time pressures, stress, distractions, and workplace satisfaction. We will construct an index to support classifying nephrologists' cognitive load as high, moderate, or low. Key practice characteristics include principal setting type (dialysis facility, CKD clinic, hospital, or other), perceived competence of non-physician clinical staff (e.g., nurses, dialysis technicians), average patient case complexity (e.g., % with CKD stage IV/V/ESRD, % with low health literacy), patient insurance mix (% Medicaid, % uninsured), and patient race/ethnicity mix (% black/African American, % Hispanic). We will describe the distributions of nephrologists' cognitive load overall and for each related survey item, and we will use linear regression models to test for associations between cognitive load and key practice characteristics, adjusting for physician factors (e.g., years in practice, sex, race/ethnicity).

Results: Data collection is ongoing. We anticipate obtaining a response rate of ≥70%, in line with response rates achieved in other difficult-to-reach clinician samples using our evidence-based recruitment protocol.

Conclusions: We will determine how U.S. nephrologists' cognitive load varies across practice settings. Follow-on work will need to examine implications for variation in CKD patients' quality of care across settings and opportunities to reduce cognitive load to improve CKD care quality.

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PUB397

Kidney Check: Identifying Kidney Disease and Diabetes in British Columbia First Nations Communities

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Background: Kidney disease has a strong impact on the health and wellness of Indigenous communities in Canada. Therefore, a national strategy to improve kidney health must include meaningful, culturally appropriate engagement with Indigenous peoples. The Can-SOLVE CKD Network is a pan-Canadian patient-oriented kidney research initiative that is working to improve the health of all Canadians and bring Indigenous ways of knowing into health research.

Methods: The Can-SOLVE CKD Network is working with British Columbia Renal and the First Nations Health Authority to develop and implement a new program that will bring kidney, diabetes, and blood pressure checks to First Nations communities. Kidney Check is a screening, triage, and treatment program using point-of-care testing and trained health care teams. Each participating community has the opportunity to design and work with the Can-SOLVE CKD team to develop a locally acceptable program, which helps to identify healthy kidneys as well as those with mild, moderate or severe kidney problems. The results will be shared with participants in real time. Each person tested will also participate in building their own kidney health plan, including follow-up goals for maintaining kidney health.

Results: Ten BC communities have been chosen through a transparent process to be part of phase 1 of the program, which is launching in Spring 2019. The ultimate aim is to roll out Kidney Check to all Indigenous communities in BC. Kidney Check programs are also under development in Alberta and Manitoba.

Conclusions: The Kidney Check program aims to help keep kidneys healthy and is working in partnership with First Nations communities to do so.

Funding: Government Support - Non-U.S.

PUB398

High Uric Acid Level with Gouty Arthritis: A Risk Factor for CVD in CKD Patients? A Clinical-Based Study

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Background: Hyperuricemia (HU) & Cardiovascular Disease (CVD) is a common occurrence in CKD patients who may develop Gouty Arthritis (GA). Though unestablished, HU is considered a CVD risk factor and may also cause CKD progression & retinal disease. This study correlates uric acid (UA) to CKD patients with CVD.

Methods: 513 CKD patients from Renal Associates LLC (2016-2018) were retrospectively-analyzed using initial visit data for CKD Stages; H/O MI, HTN, Diabetes, Arthritis, CVD: CAD/Chest Pains/CHF, OSA; Diuretic-Use; US Data; UA, Cr, eGFR, CrCl, PO4, PTH, D3, HBA_1C, & Gout Treatment. UA was correlated to Age, Sex, Race, BMI, Smoking/Alcohol-Use, CKD Stages, & other variables. HU was defined as UA≥6.5 mg/dL. 2-Sample T-Test for Means & Chi-Square: Independence were used for analysis.

Results: Data for 513 patients was 256(49.9%) Males, 238 Cauc(46.4%), Af Am 266 (51.9%), CVD 165(32.3%), Diabetes 287(56.2%), HTN 482(94.3%), 284(55.6%) Diabetic/HTN. HU and GA were 257(50.1%) & 256(49.9%). 262(51.6%) used diuretics. Mean age was 66.55 yrs, BMI 33, BP 141/73. Means (mg/dL) were UA 7.92, Cr 1.92, Serum Ca+ 9.49, PO4 3.66. eGFR/CrCl were 55.98,59.68 mL/min. Means for albumin, PTH, & D3 were 4.1 g/dL, 83.63 pg/mL, & 28.39 U. Cauc with CVD had higher UA than Af Am with CVD: 8.4 v 7.8 mg/dL p<0.03. HTN-GA patients had higher UA than Non-HTN-GA patients: 8.12 v 6.73 mg/dL p<0.04. GA patients had stronger correlation to CVD/CAD (p<0.02, p <0.005) than HU patients.

Conclusions: Higher CKD stages (3-5) correlated to higher UA and higher CVD occurrence. GA patients with higher UA had higher CVD/CAD occurrences compared to HU patients. Higher UA correlated to higher diuretic-user percentage. We propose: because higher UA levels were observed in Diuretic-Users, and Gout, CVD, CAD, Arthritis, & MI patients, we should perhaps consider treating higher UA-levels preemptively.

CKD Stages vs. Uric Acid & Cortical Thickness

	UA-Mean: mg/dL				Cortex-Mean: cm
	Overall	HU	Gout	CVD	
Overall Study (n=513)	7.92	7.81	8.02	8.08	1.64
CKD Stages	R^2=0.93	R^2=0.89	R^2=0.75	R^2=0.70	R^2=0.83
1	7.27	7.34	7.16	7.17	2.02
2	7.74	7.54	8.00	7.47	1.64
3	8.02	7.93	8.11	8.61	1.51
4	8.55	8.86	8.37	8.19	1.50
5	8.51	8.74	8.30	8.50	1.37
Tests	P-Values				
1 vs. 2	0.15(NS)	0.46(NS)	0.23(NS)	0.55(NS)	<0.04(S)
1 vs. 3	<0.003(S)	<0.05(S)	<0.03(S)	<0.006(S)	<0.002(S)
1 vs. 4	<0.0001(S)	<0.002(S)	<0.012(S)	<0.007(S)	0.11(NS)
1 vs. 5	<0.01(S)	0.06(NS)	0.10 (NS)	0.07(NS)	0.43(NS)
UA-Level	Diuretics-Use		H/O Arthritis		H/O MI
≥6.5 to <10 (n=363)	49.6%		54.3%		2.5%
≥10 (n=53)	77.4%		71.7%		7.6%
p-value	<0.0002		<0.02		<0.05

PUB399

Does the Incidence of Dementia Increase After General Anesthesia in Patients with CKD? A Nationwide Population-Based Cohort Study

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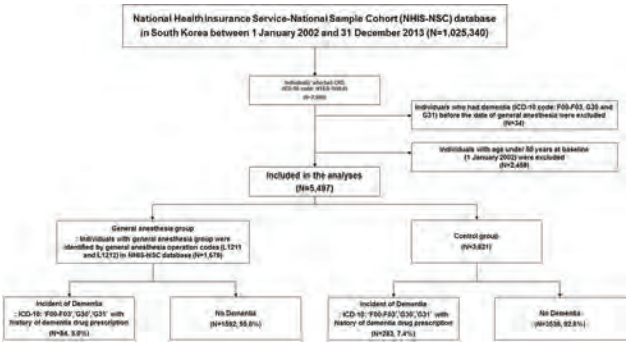
Background: Patients with chronic kidney disease (CKD) were regarded as increasing the risk of cognitive dysfunction according to kidney function. However, little is known about the relation of intraoperative aspect for CKD patients with general anesthesia.

Methods: A population-based prospective cohort study was conducted using the Korean National Health Insurance Service-National Sample Cohort database over 50 yrs, including CKD from 2003 and 2013. The primary outcome was the incidence of dementia using Korean Classification of Diseases codes, and receipt of medication such as donepezil, rivastigmine, galantamine, and memantine. Time-varying Cox regression analysis was applied for risk analysis of dementia.

Results: The 84 of the 1,676 participants of general anesthesia groups had developed newly dementia after surgery (5.0%). Of the 3,821 control groups that had CKD but did not have general anesthesia, 283 participants had presented incident dementia (Figure 1). In time-varying Cox regression analyses revealed that general anesthesia group did not increase the development of dementia in CKD patients, compare to control group (HR 1.053, 95% CI 0.819-1.353) after adjustment of age, sex, health security certification, history of depression, diabetes, hypertension, cerebrovascular disease, ischemic heart disease, quintile group for health care visit frequency and Charlson comorbidities score. Male sex, old age, history of depression and cerebrovascular disease were an independent risk factor of incident dementia in CKD patients, irrespective of anesthetic methods.

Conclusions: In CKD patients, general anesthesia operation did not increase the risk of incident dementia. Subgroup analysis was warranted, especially in patients with advanced CKD, including dialysis.



PUB400

Prognostic Investigation of CKD Patients in Japan by a Large Multi-center Retrospective Observational Study

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Background: Since the background and medical interventions for CKD have changed in recent years, its prognosis and the contribution of known risk factors may have shifted as well. To clarify this possibility, we conducted a prognostic investigation of CKD patients in Japan by means of a large multicenter retrospective observational study. We also examined for surrogate markers to predict the hard endpoints of death and ESKD requiring renal replacement therapy.

Methods: Patients seen among 15 general hospitals in Japan between January and March 2014 were surveyed using medical records. The selection criteria were age >20 years, eGFR <60 mL/min/1.73 m^2, and medical treatment for CKD. Baseline patient characteristics, eGFR changes, and hard outcomes during observation were investigated.

Results: A total of 11233 CKD patients (60% male, mean age: 72 years, CKD G3a: 50%, G3b: 28%, G4: 15%, G5: 7%, mean eGFR: 41.5 mL/min/1.73 m^2, urine protein positive: 45%, diabetes: 46%, use of RAS inhibitors: 55%) were analyzed. During the mean observation period of 2.34 years, hard endpoints occurred in 1499 subjects (13.3%). Diminished eGFR was seen in patients with higher CKD stage at baseline, and the occurrence of hard endpoints increased with the degree of eGFR decrease during 2 years. Statistical analysis of the relationship between eGFR changes and hard endpoints indicated that various indices, including hazard ratio, population attributable risk, number needed to treat, and number needed to harm, were significant in patients displaying over 30% eGFR reduction during 2 years. Kaplan-Meier testing and multivariate Cox regression analysis demonstrated that CKD stage and proteinuria at baseline were significant risk factors for composite outcomes (30% eGFR reduction during 2 years and ESKD/death), whereas diabetes, sex, age, and use of RAS inhibitors, exerts little effect.

Conclusions: ESKD and death occurred at a high rate in real-world Japanese CKD patients. A 30% eGFR reduction during 2 years might represent a surrogate marker predicting hard endpoints. CKD stage and proteinuria remained the major risk factors of an unfavorable prognosis, whereas diabetes had only weak detectable association. Kidney disease prevention strategies should be targeted not only for diabetes but for all CKD patients.

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PUB401

Investigation of TMAP as a Novel Biomarker of Kidney Function

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Background: Although kidney function is critical for determining drug dosing and diagnosing chronic kidney disease (CKD), there is a lack of sensitive biomarkers for detecting early changes in kidney function. While the current gold standard is creatinine, serum levels of creatinine do not change until approximately 50% of kidney function has been lost. We previously used metabolomics to discover new biomarkers and identified *N,N,N*-trimethyl-L-alanyl-L-proline betaine (TMAP) as a novel biomarker of kidney function.

Methods: A liquid chromatography coupled to mass spectrometry (LCMS) method was developed for the quantitation of TMAP in CKD patient and control plasma samples, and evaluate changes in plasma concentration as CKD progresses. Plasma samples were spiked with varying concentrations of TMAP to generate a standard curve. Liquid chromatography coupled to quadrupole – time of flight (QToF) mass spectrometry was used to determine the concentration of TMAP in plasma of healthy controls and patients with CKD.

Results: Preliminary analysis of chromatogram response (areas under the peaks) of healthy control, CKD, HD and PD patient plasma samples (n= 3 for each) does not show significance by one way ANOVA (p= 0.2225); However, with a 6-fold, 7-fold and 3.5-fold increase in relative areas for CKD, HD and PD respectively when comparing TMAP levels in controls to controls, analysis of further samples shows promise.

Conclusions: TMAP has previously been shown to be a more sensitive indicator of decreased renal function than serum creatinine, the current standard for renal function evaluation. Quantitation of absolute levels of TMAP in plasma shows that as CKD progresses, TMAP plasma concentration increases.

Funding: Government Support - Non-U.S.

PUB402

Mortality Rates and Geographic Distribution of CKD in Peru

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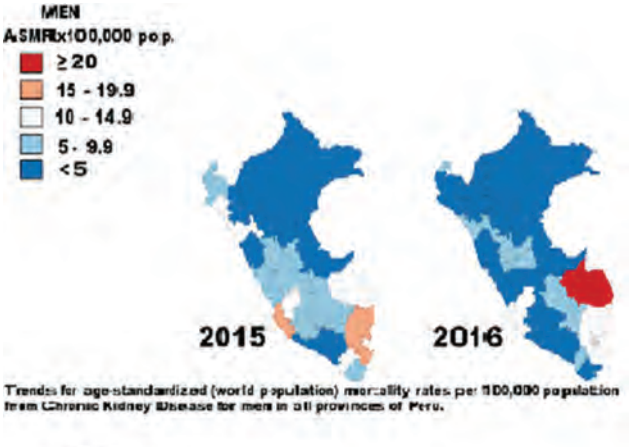
Background: The prevalence of chronic kidney disease (CKD) is alarmingly high in Latin America. Importantly, mortality rates in these patients have not been comprehensively explored. We aimed to examine the case of Peru.

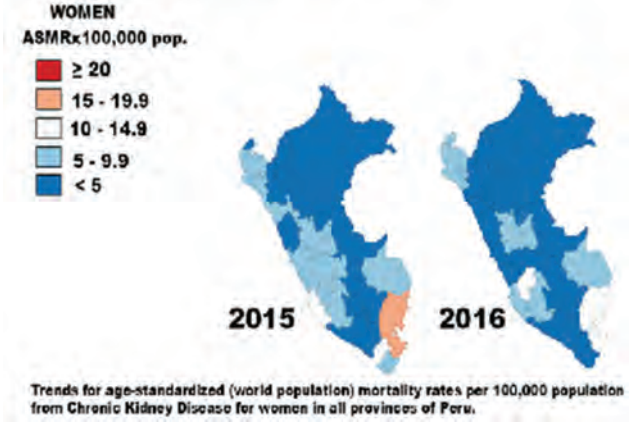
Methods: Secondary analysis from the Deceased Registry of the Peruvian Ministry of Health (PMH) database. Data pertaining to 24 provinces across the coast, highlands, and rainforest were obtained from 2015-2016. Code 585.9 was used to identify CKD deaths based on ICD 9. The PMH registry classifies deaths based on the birthplace of the patient. Calculations were made assuming an underreporting rate of 40% (PMH). We computed age-standardized mortality rates (ASMR) per 100,000 person-year. Cluster map was used to visualize data across regions.

Results: Overall, a total of 3607 deaths were identified in CKD individuals; being male predominantly affected(M:F ratio:1.18). ASMR (per 100,000 individuals) decreased among men from 7.48 to 5.02 (2015-2016). Similarly, ASMR decreased in women from 6.27 to 4.22 within the same period. In a sub-analysis by regions, ASMR among men/women decreased in the coast and in the highlands. However, ASMR (per 100,000 individuals) increased in the rainforest, from 2.87 to 2.97 in men, and from 2.41 to 2.42 in women. Such mortality rate increment corresponded to two rainforest provinces: Madre de Dios and Loreto.

Conclusions: Mortality rates in individuals with CKD in Peru are higher in male than females. While mortality rates among both gender groups decreased within the study period, there are marked regional differences. In the rainforest (mainly Madre de Dios and Loreto), mortality rates exhibited increment in both gender groups. These findings warrant special attention to identify specific epidemiological risk factors and guide intervention and policy.



Trends for age-standardized (world population) mortality rates per 100,000 population from Chronic Kidney Disease for men in all provinces of Peru.



Trends for age-standardized (world population) mortality rates per 100,000 population from Chronic Kidney Disease for women in all provinces of Peru.

PUB403

Patient and Care Partner CKD Self-Efficacy

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Background: Self-efficacy is an essential skill for chronic disease self-management; however, many nephrology patients rely on the assistance of a loved-one to help manage their care. We sought to better understand the self-efficacy skills of patients and their care partners.

Methods: We surveyed patients and care partners enrolled in a pilot study of a problem-solving intervention to support kidney disease self-management. We administered 6 questions from the chronic kidney disease self-efficacy (CKD-SE) instrument problem solving subscale. Responses were scored on a 10-point Likert scale from 1=not at all confident to 10=totally confident. Paired t-tests were used to compare differences between patients and care partners.

Results: 11 patient-care partner dyads were surveyed. Dyad pairs were spouses (n=8), parent/child (n=2), and friend (n=1). Mean age was 68 for patients and 62 for care partners. The majority of patients were male (63%) and care partners were female (72%). Result of the CKD-SE instrument are shown in Table 1.

Conclusions: Care partners report significantly higher CKD self-efficacy than patients. Involvement of care partners may help to improve the CKD management of patients.

Funding: Private Foundation Support

Table 1

Question	Patients	Care Partners	p-value
I can understand the meaning of relevant laboratory data	3.9	7.6	0.002
I can seek out information that explains CKD-related signs and symptoms	4.5	8.5	0.001
I can find information about kidney disease from a variety of sources	4.5	8.8	0.001
I can actively understand the risk factors associated with CKD	5.1	7.8	0.027
I can find resources needed to better control my (or my loved one's) CKD	5.1	7.7	0.035
I can actively seek out necessary precautions to prevent my (or my loved one's) CKD from worsening	4.9	7.9	0.010

PUB404

CKD and Cardiovascular Risk Factors Among a "Healthy" Guatemalan Population Screened During World Kidney Day 2019

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Background: Chronic kidney disease (CKD) is a critical global health problem. Data on CKD are limited in low-income and middle-income countries (LMICs). Cardiovascular disease it's a rising epidemic in LMICs. Screening is an important strategy to address the burden of CKD in LMICs. Here we present the outcomes of a small, CKD screening programme during the World Kidney Day 2019 on patients with no known disease in rural and urban Guatemala. The objectives were 1) to assess the burden of renal disease and 2) to assess the burden of CV disease in a population with no known disease in rural and urban Guatemala.

Methods: We evaluated 300 patients 20 years or older without known renal or CV disease. These patients were located in Guatemala City (urban area), Quetzaltenango (Rural) and Escuintla (Rural). We excluded subjects who had already CKD or CV disease diagnosis. We used the abbreviated Modification of Diet in Renal Disease (MDRD) equation to estimate the GFR. We defined CKD as a eGFR < 60 mL/min/1.72 m2 or albuminuria > 30 mg/d.

Results: The mean age was 42 years, the average BMI was 28 kg/m2, 41% of these patients were overweight and 22% were obese. We found that 4.5% of the patients met GFR criteria suggestive of CKD. The incidence of CKD was higher in the Southern Coast (9%) when compared with the urban areas in Guatemala (2.5%). Regarding renal function, the eGFR was higher (115.42 ml/min) in the urban population than in the rural urban populations (100 ml/min) (p <0.05). There was no difference in the Protein/Creatinine (P / Cr) ratio within the group analyzed.

Conclusions: In the screening carried out on World Kidney Day 2019 we established that the presence of risk factors to develop CV disease is low. We noticed an higher incidence of CKD in the coastal area, which is consistent with previous reports describing the CKD epidemic in the Mesoamerican region. The main limitation was the definition of CKD, according to the Kidney Disease Improving Global Outcomes (KDIGO), CKD can be defined as either damage to kidneys or a glomerular filtration rate (GFR) of < 60 mL/ min per 1.73 m2 for a period of ≥ 3 months and we only measured once.

PUB405

Mortality and Renal Risk Factors in a Cohort of Toba Aborigines, Chaco, Argentina

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Background: The Province of Chaco, at the northeast of Argentina, concentrates a high proportion of toba aboriginal people (4% of the population). Originally gatherers and hunters, during last century they have been forced to migrate from rural areas to the outskirts of the cities, in particular to Resistencia (Province capital city). A cohort of 385 suburban toba people has been followed since 2003, in order to identify cardiovascular and renal risk factors. The objective is to describe mortality rate, survival curves and hazard ratios for death causes during the period 2013-2018.

Methods: Medical records were revised. 25 individuals were lost of follow up. Weight, height, waist circumference (WC), urine and serum creatinine, fasting glucose, uPr/uCr ratio were measured. GFR by MDRD-4 formula and renal risk (RR by KDIGO classification: no risk, moderate, high and very high risk) were calculated. Hypertension was defined as >140 mmHg systolic or >90 mmHg diastolic blood pressure; diabetes as fasting glucose >126 mg/dl. BMI was classified according to WHO, being obesity >than 30; central obesity (CO) was defined as WC >102 in men and >90 cm in women. Proteinuria was estimated as uPr/uCr ratio mg/g: ≤150, stage 1, 150 ≤ 300 stage II and ≥ 300 stage III. Renal risk (RR) defined as KDIGO. Kaplan Meir curves and Cox proportional hazards regression models were applied.

Results: 358 medical records were revised. 45 (12,5%) individuals had died, 6,2% females, mean age 53,87 yrs old, 24 % hipertensive, 34% with CO, 2% DBT, 34,6% proteinuric, 5,3% with GFR < than 60 ml/min. About RR, 63 % had no RR, 2,5% classified as Moderate, 12% as high and 2 % as very high RR. Causes of mortality were: CVD 20 (5,6%), Ca 12 (3,4%), TBC 9 (2,5%) and Miscelaneas 4 (1,1%). Mortality rate was 12,6. Actuarial survival for the whole cohort was 14,90 years (14,68- 15,14); for Ca was 13,94, for CVD 12,34, for TBC 9,73 and for Misc 9,73 yrs (Log Rank: 0,00). Hazard ratio was significative with RR variables alone, adjusted by age and multivariate. Mortality rate in Chaco Province general population is 7,1/00, with similar causes of death.

Conclusions: This cohort of Toba people living in the outskirts of Resistencia city, has a high mortality rate, being causes of death similar to the observed in general population in the Province. RR was a predictive factor for mortality.

Funding: Private Foundation Support

PUB406

Low Flow Colonic Ischemia (LFCI) Associated with Renoprotective Use of Renin-Angiotensin inhibitor Therapy (RASIT)

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Introduction: Renin-Angiotensin inhibitors are commonly utilized Renoprotective agents in multiple nephrological conditions. Some recipients may even be normotensive. Multiple Hemodynamic Adverse effects may be encountered. We present 6 episodes of LFCI in 3 patients in association with RASIT found retrospectively in a single practice over 15 years. LFCI may represent a form of uncommon Ischemic adverse event of RASIT.

Case Description: 1. 41 year old WM with morbid obesity, recurrent macro microhematuria, mild proteinuria, hyperfiltration, hypertension, with Renal biopsy: Thin Basement Membrane Disease. On RASIT he developed two episodes of severe abdominal pain, lower Gi bleeding(LGIBL) with colonoscopic Ischemic Colitis(CI). RASIT was reduced with no subsequent recurrence. 2. 37 yo WM with recurrent macro microhematuria, proteinuria hypertension with Renal biopsy: IgA Nephropathy. On RASIT he developed acute abdominal pain LGIBL and Colonoscopic IC. RASIT was reduced with no subsequent recurrence. 3. 69 yo WF with Stage 3 chronic kidney disease, hypertension and mild proteinuria. On RASIT she developed acute abdominal pain, LGIBL with Colonoscopic IC; had 2 subsequent episodes of CI. RASIT was reduced with no subsequent recurrence.

Discussion: RASIT commonly utilized renoprotective therapy in multiple nephrological conditions including: IgA nephropathy, Proteinuric states, Diabetic Nephropathy and Chronic Kidney Disease. Hemodynamic adverse effects including hypotension, syncope and orthostatic symptoms may be encountered. Ischemic Involvement of colonic watershed area most likely due to hypotensive episodes, may be another ischemic manifestation. Exact mechanism is unclear, likely related to reduced blood flow in colonic watershed area. Direct effects of RAST on: GI tract, microvasculature, thrombotic, Immunologic and Imflammatroy pathways may be speculative. Olmesartan associated Chronic Enteropathy, RASIT associated Bowel angioedema, worsening Inflammatory Bowel disease have been described. Acute LFIC seen in our patients seems phenotypically different. Patients on RASIT presenting with LGIBL and abdominal pain, LFCI should be considered in the differential diagnosis. Dose reduction may prevent recurrent episodes. Although these are anecdotal cases possibility of Ischemic Colitis as a possible adverse effect of RASIT may warrant further study.

PUB407

Exploring Cardiorenal Interactions During Therapy of Chronic Heart Failure with Preserved Ejection Fraction

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Background: The complexity of cardiorenal interactions in heart failure (HF) has been increasingly recognized. Rise in serum creatinine (RSC), once considered a universally ominous sign, is now known to portend mixed prognostic values depending on the clinical setting. While heart failure with preserved ejection fraction (HFpEF) is common and includes half of the cases with HF, no established beneficial therapy exists for it. As such, aggressive management of comorbidities remains the key in the care of these patients. We sought to evaluate currently available data on the renal impact of therapies for HFpEF.

Methods: Articles cited in PubMed database using keyword "heart failure with preserved ejection fraction" were searched. Available data from contemporary randomized controlled trials (RCTs) of chronic HFpEF therapy performed between January 2008 and December 2018 were included in the analysis. These studies evaluated the role of renin-angiotensin-aldosterone system suppression in the setting of HFpEF and included data on renal function.

Results: A total of 408 citations were reviewed and 7 RCTs with 9039 participants were included. The mean age was 71.3 years and 56.9% were men. Mean baseline serum creatinine and eGFR were 1.1 mg/dl and 67 ml/min respectively. There was substantial variation across studies in the reporting of the renal parameters post-intervention as well as recording of the RSC. Whether the primary cardiovascular endpoint was achieved or not (e.g. 6-min walk test, cardiovascular death, or unplanned hospitalization), RSC consistently developed more frequently in the intervention (6-36.2%) than the control group (4-20.6%) in those studies that reported it (mean 16.1±11.8% vs. 8.9±6.81% respectively).

Conclusions: To our knowledge, this is the first report focusing on the cardiorenal interactions and HFpEF therapy. Available evidence from contemporary studies suggests that RSC observed during HFpEF therapy may not per se portend untoward impact on the outcomes. While these results challenge our conventional thinking, they are in line with emerging data in other settings such as acute HF. Future studies need to explore whether this observation reflects development of RSC in the absence of true kidney injury, or it is related to other factors such as competing effect of therapies on the kidney and the heart.

PUB408

National Survey of Patients' Attitudes Toward Gout

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Background: Gout, a form of arthritis, afflicts more than 8 million Americans with painful attacks that come on suddenly. Many people don't realize the relationship between gout and chronic kidney disease. And gout, left untreated, can lead to other serious health problems, include kidney stones.

Methods: A national online survey was conducted Dec 2018-Jan 2019 for the purpose of gaining perceptions of gout from patients 21+. Questions were designed to gauge patients' understanding of gout, its causes and treatments, and how stigma and shame about gout affect their life and efficacy to seek appropriate treatment.

Results: Of the 169 patient respondents, 57% were female, 42% were male. Nearly all respondents (97%) acknowledged gout as a serious disease. Three-quarters (75%) know natural remedies aren't sufficient to treat gout, yet 73% say it's hard to get proper treatment. Despite patients' knowledge, 93% believe most people don't know gout is simply a form of arthritis. More than half of respondents (52%) indicated that they are often too embarrassed to talk about the disease and 41% said they believe people look down on those with gout. Roughly half (46%) attribute their gout to eating too much unhealthy food and drinking alcohol in excess.

Conclusions: Even though patients themselves have good awareness that gout is a serious disease, their knowledge doesn't protect them from feelings of shame, stigma and self-blame related to eating unhealthily as their cause of gout. Patients' feelings may be due, at least in part, to public perceptions of the disease. Survey results show that for gout patients to get a proper diagnosis, appropriate treatment and the community of support they need, education efforts for both gout patients and the public must continue to expand. This is vital for management of patients' gout and can have an effect on related conditions such as chronic kidney disease.

PUB409

Efficacy of Empagliflozin on Albuminuria Reduction in Patients with Non-Diabetic Kidney Disease

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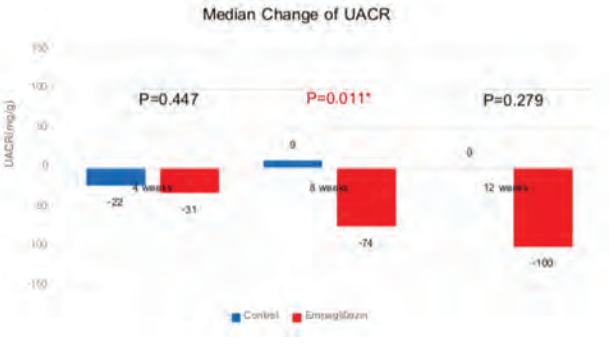
Background: Empagliflozin, a sodium-glucose cotransporter 2 inhibitor, has been demonstrated to reduce proteinuria and slow renal progression in diabetic kidney disease. This study was conducted to determine the effect of empagliflozin in lowering albuminuria in patients with non-diabetic kidney disease.

Methods: We studied 28 patients who had persistent urine albumin to creatinine ratio (UACR) more than or equal to 30 mg/g and estimated glomerular filtration rate (eGFR) more than 30 mL/min/1.73 m^2. The patients were randomized 1:1 into empagliflozin group receiving oral empagliflozin 10 mg/day plus standard treatment and control group receiving only standard treatment. All patients were evaluated at baseline, 4, 8, and 12 weeks. The primary outcome was the change of UACR at 4, 8,12 weeks follow-up and the secondary outcomes were difference of blood pressure, eGFR, body weight and adverse side effects.

Results: Thirteen patients were randomized into empagliflozin group and 15 patients into control group. Empagliflozin significantly reduced UACR from baseline at 8 weeks but not 4 and 12 weeks when compared to control. Median UACR change from baseline after treatment at 4, 8, 12 weeks were -31(-120,4), -74(-200,-11), -100(-230,85) mg/g in empagliflozin group compared with -22 (-108, 54), 9 (-52, 103), and 0 (-52, 207) mg/g in control group (p = 0.447, 0.011, 0.279 respectively). There was no difference between both groups in eGFR, diastolic BP, BW and adverse effects. Systolic blood pressure was significantly lower in empagliflozin group [median 118 (113, 127) mmHg] when compared to control group [median 132 (128, 139) mmHg] (p=0.021) at 8 weeks. There were found only one patient with genital mycotic infection in empagliflozin treatment group. No hypoglycemic event was found in both groups.

Conclusions: Empagliflozin temporarily reduces UACR from baseline and lower SBP at 8 weeks when compared to control. Further large placebo-control RCT with long-term follow up need to be done to verify the effect.

Funding: Private Foundation Support



Median change of UACR

PUB410

Increase of 1,25-Dihydroxyvitamin D Levels in Sarcoidosis Patients with Renal Dysfunction

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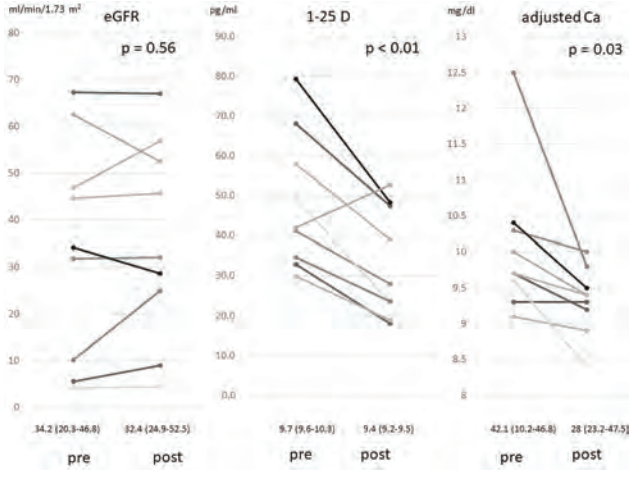
Background: In sarcoidosis, renal involvement includes hypercalcemia-related nephrocalcinosis and granulomatous tubulointerstitial nephritis. Hypercalcemia is thought to be due to increased production of 1, 25 dihydroxyvitamin D (1-25D), but 1-25D levels have not been evaluated in sarcoidosis patients with renal dysfunction.

Methods: We enrolled 9 sarcoidosis patients who underwent renal biopsy, and compared the serum 1-25D concentration and eGFR with those in 428 non-sarcoidosis patients who had renal dysfunction (stage 2 or higher CKD with an estimated glomerular filtration rate <90).

Results: Serum calcium and 1-25D levels were significantly higher in the sarcoidosis patients than in the non-sarcoidosis patients ($p < 0.01$ and $p = 0.01$, respectively). There was a positive correlation between 1-25D and eGFR in the patients without sarcoidosis ($r = 0.693$; $p < 0.01$). As the renal function of sarcoidosis patients was improved by steroid therapy, the serum 1-25D and adjusted serum calcium levels decreased to near the median values in non-sarcoidosis patients. On renal biopsy, CD68 staining was positive for tissue macrophages in all 8 patients who had tubulointerstitial nephritis (with or without typical granulomas), while Von Kossa staining showed calcification of tubules near or inside granulomas in 6 of these 8 patients.

Conclusions: While tissue macrophages promote development of tubulointerstitial nephritis and 1-25D overproduction in renal sarcoidosis, hypercalcemia secondary to elevation of 1-25D may be related to renal calcification and granuloma formation.



PUB411

Association Between Insulin Resistance and Glomerular Filtration Rate in Patients with Non-Diabetic Pre-Dialysis CKD

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Background: Metabolic syndrome is one of the recognized cause of kidney disease. Insulin resistance, as one of the component in metabolic syndrome, is known to be one of the condition occurs in patients with chronic kidney disease (CKD), even in those who doesn't diagnosed with diabetes. The relationship between insulin resistance and the decline of glomerular filtration rate (GFR) in non diabetic patients is remain to be studied.

Methods: This is a cross sectional observational analytic study involved 35 subjects of CKD patients with non-diabetic predialysis who were diagnosed based on KDIGO criteria. The study population was CKD patients in the Outpatient Clinic of a tertiary referral hospital, Dr. Soetomo Hospital Surabaya. Insulin resistance is determined by calculation using the HOMA-IR formula, and GFR is estimated using Cockroft-Gault formula.

Results: There were 35 subjectd, 25 male and 10 female. The average age is 52.5 years, the lowest age is 31 years and the highest age is 60 years. Patients with stage 3 CKD were 11 people, stage 4 were 6 people and stage 5 were 18 people with mean for overall GFR 21,38 ± 16,69 ml/min/1,73 m^2. HOMA-IR levels were 1.61 ± 1.13, with a median of 1.15 (0.32-4.59). There was a significant negative relationship between GFR and insulin resistance ($p = 0.000$, $r = -0.828$).

Conclusions: Insulin resistance and GFR has significant negative relationship in non diabetic predialysis CKD patients.

PUB412

Association Between 1,25-Dihydroxycholecalciferol Level (Calcitriol) with Homeostatic Model Assessment of Insulin Resistance in Non-Diabetic Non-Dialysis Stage 3-5 CKD Patients

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Background: Mineral and bone metabolism disorder in the form of 1,25-dihydroxycholecalciferol (calcitriol) deficiency is one of the factors that increase the morbidity and mortality of patients with chronic kidney disease (CKD). CKD is also associated with insulin resistance which has an important role in the pathogenesis of cardiovascular disease. From several studies had been reported that there is increasing evidence that vitamin D metabolism affects insulin resistance, but the relationship between calcitriol deficiency and insulin resistance in CKD patients is still unknown.

Methods: This analytic observational study with a cross-sectional design involved 40 non-diabetic non-dialysis stages 3-5 CKD subjects who met the inclusion and exclusion criteria. The variables studied were calcitriol levels measured by the Enzyme-Linked Immunosorbent Assay (ELISA) and HOMA-IR methods calculated using the HOMA-IR formula where fasting insulin levels were measured by the two-site chemiluminescent immunometric assay method. Analysis of the relationship between independent variables and dependent variables using the Spearman correlation test according to data distribution with a correlation coefficient (r).

Results: There were 40 subjects, 28 males and 12 females. The average age is 52 ± 6.891 years. The mean for Body Mass Index (BMI) is 20.81 ± 1.148 kg /m^2. The majority of subjects (50%) are at CKD stage 5. The median calcitriol is 27.24 pg /mL. The mean HOMA-IR is 2.13 ± 1.150. There was a negative correlation between calcitriol levels with HOMA-IR ($r = -0.380$; $p = 0.015$).

Conclusions: There was a significant negative correlation between 1.25-Dihydroxycholecalciferol levels (calcitriol) with HOMA-IR in non-diabetic non-dialysis stage 3-5 CKD patients.

Funding: Private Foundation Support

PUB413

Obesity as Risk Factor for CKD Progression and Incident Cardiovascular Events in Patients with Prevalent CKD

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Background: Obesity is a known risk factor for incident chronic kidney disease (CKD) and for cardiovascular events (CVE). However the role of obesity in CKD progression has not been well stablished yet. Our study aimed to evaluate the role of obesity in CKD progression and incident CVE in a sample matched for recognized CKD progression factors such as age, renal function and albuminuria.

Methods: Prospective observational study from 2008 to 2018. 212 patients with prevalent CKD stages 3-4 were Propensity Score Matched for age, baseline renal function and albuminuria and divided according to obesity status (defined as BMI ≥30). After matching 166 patients were followed-up. Anthropometric characteristics, renal function and cardiovascular risk factors were measured at baseline. Renal event during follow-up was defined as creatinine dupliaciton, estimated glomerular filtration rate (eGFR) decline ≥50% or needing renal replacement therapy. CVE was defined as congestive heart failure, any coronary syndrome, cerebrovascular accident or peripheral sympthomatic arteriopathy.

Results: 83 obese and 83 non obese patients were analized; mean age was 68±13 yo and mean eGFR 48,4±22 ml/min. Mean follow up time was 88,4±36 months. CKD progression: 18 obese patients vs 21 non-obese patients presented a renal event during follow-up (Log-rank 0.21; p=0.64). Renal survival was not different between both gruops when adjusted to baseline albuminuria tertiles. Baseline renal function (HR 0,973, p=0,006) and albuminuria (HR 1,00, p=0,001) were the only CKD progression predictors in a model adjusted for age, sex, blood pressure, obesity (HR 0,95; p=0.89) and diabetes. Cardiovascular events: 17 patients in the non-obese group and 30 patients in the obese group had a CVE during follow-up (log Rank 4,44, p=0,03). Obesity had no predictive value for CVE in a model adjusted for sex (HR 0,50, p=0,049), baseline renal function (HR 0,98, p=0,045), previous CVE (HR 2,97, p=0,001), diabetes (ns) and age (HR 1.04, p<0.01).

Conclusions: In our simple obesity is not a risk factor for CKD progression. Obesity is statistically related with developing major CVE although it losses predictive value when adjusted to renal function, sex and previous CVE.

PUB414

CKD Outcome Using Cause, GFR, and Albuminuria Staging System in Qatar

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Background: Primary Objective:- 1-To apply CGA classification system to stratify our pool of CKD patients into well defined risk groups. 2-Estimation of relative risk of CGA stage in relation to kidney outcome and patient outome (cardiovascular and all cause mortality). Secondary Objective:- To correlate CGA stage with covariates including age, sex, race and cardiovascular disease (CVD) risk factors.

Methods: Retrospective evaluation was carried out for CKD patients under follow up in oupatient nephrology clinics from January 1st 2001 till December 31st 2016. All patients diagnosed as CKD with different stages were included. Patients were screened for :Demographic data;Cause of kiney disease, Date at diagnosis of CKD, eGFR at time of diagnosis of CKD and at last follow up, degree of Albuminuria/proteinuria, Comorbid conditions, Use of ACEI/ARBs, Renal outome as well as Patient outcome.

Results: 969 patients were included. Mean follow up period was10.14 years. 8.24% reached endpoint outome as follows :expired 1.44% and ESRD 6.8%. Hazard risk to reach end point was depenedent on cause of CKD, being highest with combined DM and HTN followed by HTN alone, DM alone and finally other causes (figure 1). Univariate analysis revealed that risk factors showing statistical significance to reach endpoint included older age, associated cardiovascular disease in addition to higher proteinuria, body mass index (BMI) and PTH levels at time of diagnosis of CKD. Multivariate analysis revealed that use of ARBs/ACEI was associated with significant less incidence of death and ESRD.

Conclusions: Cause of CKD should be considered together with eGFR and degree of albuminuria during evaluation for risk of progression of CKD patients. Special formulas including CGA together with other riak factors (age, BMI, CVD,.) might be invented to help predict prognosis of such patients.

Funding: Government Support - Non-U.S.

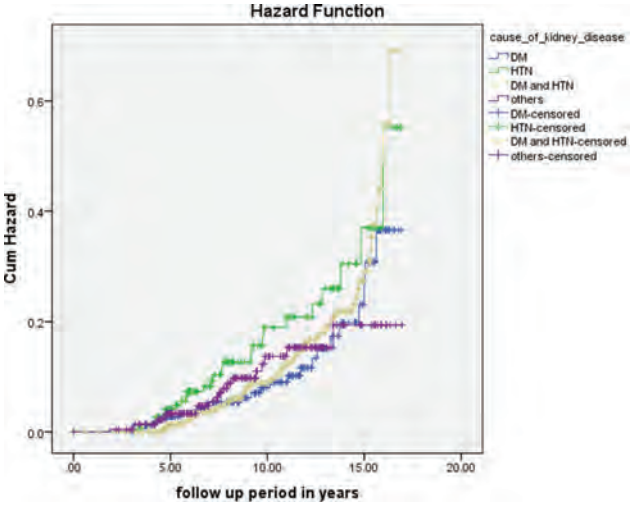

Figure 1

PUB415

Effect of Simulated In-Bed Training of Urination on Reducing Rate of Postoperative Dysuria in Patients After Renal Biopsy

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Background: Postoperative dysuria is one of the most common complications after renal biopsy. This study aimed to investigate whether the simulated in-bed training of urination is able to relieve the symptoms of postoperative dysuria in patients undergoing renal biopsy.

Methods: Patients who underwent renal biopsies between Jan 2017 and Dec 2018 were recruited. We reported the proportion and characteristics of patients underwent the simulated training of postoperative in-bed urination before the procedure, and compared with that of patients did not receive the training. The training refers to the simulation of postoperative conditions before the renal puncture procedure, during which the patient lay on the bad and finished an urination episode facing a chamber pot. The training was carried out within 30 minutes before the renal biopsy.

Results: A total of 531 patients underwent renal biopsies and 509 (95.9%) of them underwent the training. After renal biopsies, 439 patients had voluntary urination on the bed, accounting for 86.2% of the total number of trainees, and 28 patients who had induced urination, while 42 patients needed urethra catheters. There were 300 (58.9%) patients completed self-urination on the bed within 3 hours after the renal procedure, and the number of patients who completed self-urination on the bed within 6 hours was 396, accounting for 77.8% of the total number of trainees. For the 22 patients who did not receive the training, 11 (50.0%) of them were able to voluntary urinated, while the other 11 patients needed assisted urination care.

Conclusions: Simulated training of in-bed urination is able to reduce occurrence of dysuria associated with renal biopsy.

PUB416

Conservatively Managed Patients with Advanced CKD: What Medications Can Be Deprescribed?

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Background: Patients entering a Conservative Management Pathway (CMP) from advanced chronic kidney disease (CKD) have a legacy of high pill burden. An important component of CMP is judicious deprescribing, noting that tools described in the literature including the Beers or STOPP/START criteria do not take into consideration the patient's symptoms and trajectory which is the focus of Kidney Supportive Care (KSC). The referral criteria to the KSC program includes patients on the non-dialysis CMP, on kidney replacement therapy (KRT) with high symptom burden and those who are pre-decision making. We aim to examine the number and type of prescribed medications of patients on CMP and identify medications that potentially may be deprescribed due to limited benefit.

Methods: Retrospective analysis of patients on a non-dialysis CMP referred to KSC Feb 2016 – Feb 2019. Only patients that were conservatively managed and not on a KRT care pathway were included. Patient demographics and clinical profile were extracted from the medical record. Medication lists were compiled by a renal pharmacist and assessed at last/ most recent KSC attendance. Medications that were highlighted as suitable to be deprescribed were grouped; with key groups including statins, proton pump inhibitors (PPIs) and supplementary vitamins.

Results: 47 patients met the inclusion criteria for these analyses, median age 83 years (range 29-92) and 53% were female. 74% had CKD 5 with the remainder having CKD 4. Total number of prescribed individual medications ranged from 5-31 (median = 13). Statins were prescribed for 36% patients, PPI for 55% and vitamins for 49%. 38/47 (81%) patients had at least 1 identified medication that could be deprescribed and 8/47 (17%) were on all three (statin, PPI and supplementary vitamins).

Conclusions: Deprescribing medications has the virtue of reducing medication burden, financial cost and side effects, contributing to important quality of life. Many patients continue to receive medicines with limited therapeutic benefit whilst on CMP despite the scope for de-prescribing these medications. More research is required to develop a deprescribing tool in this unique population.

PUB417

Prevalence of CKD in the National Hospitalization Database in Ecuador as a Pointer to CKD of Undetermined Etiology Prevalence

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Background: Chronic Kidney Disease of uncertain etiology (CKDu) is a emerging healthcare crisis in South America, primarily affects young males with no pre-disposong factors such as diabetes or hypertension, and has been reported extensively from Nicaragua and Guatemala. CKDu results in increased mortality in working age males, often pushing entire families into poverty. Though it has been reported in Ecuador, the extent of the problem is not known. There is no renal registry and access to primary care is variable depending on the geographical area and the patient's socio-economic status.

Methods: As part of a mixed-methods scoping study, we analysed the national hospitalization database for the years 2010 to 2015 for ICD10 codes N18 (CKD) and N19 (Unspecified kidney failure) for prevalence amongst men and women, and across different ages. Since there is no separate ICD10 code for CKDu, N18 and N19 were used.

Results: Image Table

Conclusions: There is a clear increase in the prevalence of CKD in hospitalized males < 40 years of age from 2010 to 2015 in Ecuador. This study is limited by insufficient data on outpatient community CKD. While there is an increase across all ages, likely because of better reporting, there is a striking doubling of cases in working age men < 40 years of age. It is not possible to opine from the data if this is all CKDu, but this pattern of CKD is similar to the pattern of CKDu incidence in other countries. Our data supports the need for well-designed prevalence studies to define the scope of CKDu contributing to the observed rise in CKD in Ecuador, in a vulnerable population with potential global health implications.

Funding: Commercial Support - DCI Inc - Non-profit organization

Table 2: Age-wise incidence of CKD in men

Years	31 - 40 years	41 - 50 years
2010	0.41	0.95
2011	0.36	0.8
2012	0.43	0.82
2013	0.56	0.79
2014	0.61	1.01
2015	0.72	1.19

Years	Percentage of hospitalized patients with N18 or N19	Percentage of hospitalized males with N18 or N19	Percentage of hospitalized females with N18 or N19
2010	0.65	1.19	0.41
2011	0.62	1.11	0.4
2012	0.68	1.20	0.45
2013	0.76	1.28	0.52
2014	0.87	1.46	0.59
2015	0.99	1.68	0.65

Table 1: Hospitalized patients with CKD

PUB418

Diagnostic Value of NT ProBNP in CKD Patients with Acute Decompensated Heart Failure

Syeda H. Zartash,[1] Sidra Saleem,[1] Zain Rasool,[1] Nimra N. Zaman,[1] Shahbaz Sarwar,[1] Shahmeer M. Nawaz,[1] Shahryar A. Sheikh,[1] Shamila Afshan,[2] Abeera Mansur.[1] *[1]Doctors Hospital and Medical Centre, Lahore, Pakistan; [2]Punjab Institute of Cardiology, Lahore, Lahore, Pakistan.*

Background: NT pro-BNP is a promising marker of integrated cardiorenal function in the setting of volume overload. However, diagnosis of volume overload in CKD patients is complicated by NT-proBNP levels that are higher than in the non CKD patients. The aim of this study is to establish a cut off value for NT Pro BNP in CKD patients for Acute decompensated Heart Failure(ADHF)

Methods: From 1st May, 2018 through 30th April, 2019, 450 patients who presented in the Emergency Department of Doctors Hospital, Lahore with acute dyspnea and potential fluid overload were assessed. Out of these, 85 patients who had simultaneous echocardiography and NT Pro BNP measurement were included in the study. Both CKD (<60ml/min GFR) and non CKD patients with reduced ejection fraction(LV EF<40%) and preserved ejection fraction(LV EF≥50%) were included. eGFR was measured using the CKD-EPI equation and all data was analysed using SPSS version 25.

Results: Mean value of NT Pro- BNP in patients with eGFR < 60 ml/min with Volume Overload and Pulmonary Capillary Wedge Pressure(PCWP) >15mmHg as determined by 2D echo (Group A) and in patients with eGFR > 60 ml/min with volume overload and PCWP >15(Group B) is 1895.74+10.57 and 550.66±7.42(pmol/L) respectively, as shown in Image 1. In Group A patients, NT pro BNP cut off value of 1900 resulted in sensitivity and specificity of 63% and 71.21% respectively with a Negative predictive value(NPV) of 87.04% and accuracy of 69.41%(p value 0.003), as shown in Image2.

Conclusions: The cutoff value of NT Pro BNP for diagnosis of ADHF in CKD progressively increases as the stage of CKD increases. To obtain optimal results, cut off concentrations have to be adjusted for renal function

CKD Stage	Mean NT pro BNP ±S.D(pmol/L)
3	1570.2 ± 12.75
4	1946 ± 8.92
5	2939 ± 13.11
None	550.66 ± 10.22

	Variables	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)	Accuracy(%)	p-value
NT pro BNP>1900	Group A	63	71.21	38.71	87.04	69.41	0.003
	Group B	32.14	86.36	50	75	70.21	0.194
NT pro BNP>1500	Group A	65.2	75.4	50.0	85.2	72.62	0.001
	Group B	4.3	85.19	11.11	67.65	61.04	0.001
NT pro BNP>550	Group A	61.11	81.63	70.97	74.07	72.94	0.001
	Group B	8.33		33.33	56.58	54.12	0.727

PUB419

Effect of Educational Program on Lowering Blood Pressure and Urinary Protein in Japanese CKD Patients

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Background: Educating patients by interprofessional collaboration with doctors, nurses, pharmacists and nutritionists is effective in controlling chronic kidney disease (CKD) progression. We have been conducted an inpatient CKD educational program by multiple occupations and compared the effects of the program on various kidney diseases.

Methods: We retrospectively reviewed 31 Japanese patients who participated in our one-week CKD educational program from April 2014 to April 2019. All patients took low-salt diet (6 g/day) and were carried out 24-hour urine testing twice during the program. In addition, we examined clinical features of 18 patients (10 in diabetes mellitus (DM) group and 8 in non-DM group) whose antihypertensive drugs were not changed during the program.

Results: The mean age of patients was 72.8 ± 11.7 years, and 68% were male. Nephrosclerosis was the most common diagnosis (61% [19 of 31]), followed by diabetic kidney disease (35% [11 of 31]), IgA nephropathy (10% [3 of 31]) and so on. The average body weight decreased from 67.3 kg to 64.8 kg (3.7% reduction), the systolic blood pressure (BP) decreased from 140.3 mmHg to 131.6 mmHg (6.2% reduction), and the urinary protein decreased from 1.84 g/day to 1.37 g/day (25.5% reduction), and the 24-hour urinary sodium excretion decreased from 107.4 mEq/day to 77.8 mEq/day (27.6% reduction) during the one-week program. In a study of 18 patients whose antihypertensive drugs were not changed, the BP and the urinary protein level on the first day of program was higher in DM group (DM group: 138.2 mmHg vs non-DM group: 132.8 mmHg, DM group: 2.31 g/day vs non-DM group: 1.29 g/day, respectively). In DM group, the percentage of BP reduction was higher (DM group: 9.3% vs non-DM group: 1.8%), while the percentages of proteinuria and body weight reduction were lower during this one week program (DM group: 16.0% vs non-DM group: 29.5%, DM group: 3.4% vs non-DM group: 3.7%, respectively).

Conclusions: Our educational program was effective on lowering BP and urinary protein of CKD patients. Furthermore, the BP-lowering effect was obvious especially in DM patients probably due to the promotion of sodium sensitivity as previously reported.

PUB420

The Efficacy and Safety of Endothelin Receptor Antagonist on Renal Outcomes: An Updated Systematic Review of Randomized Trials

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Background: Preclinical studies suggest that blockade of the endothelin receptor reduces proteinuria and may confer renal protection. With the recent publication of the SONAR trial, this systematic review and meta-analysis aims to summarize evidence from randomized controlled trials (RCT) regarding the benefits and risks of ERA on renal outcomes.

Methods: MEDLINE, Embase and Cochrane Central Register of Controlled Trials were searched for RCTs evaluating ERAs in adults that reported renal outcomes. The primary outcome was kidney failure (end-stage kidney disease, renal failure, or doubling of creatinine, or as reported by the authors). The secondary outcomes were change in kidney function (estimated glomerular filtration rate or creatinine clearance), albuminuria and systolic blood pressure from baseline to last measurement, all-cause mortality, cardiovascular mortality and adverse events. Treatment effects were summarized using random-effects meta-analysis.

Results: Seven RCTs (7612 participants, median sample size 379, median follow-up weeks 16 weeks) met eligibility criteria. There was substantial heterogeneity in baseline kidney function and study population. Compared to placebo, ERA significantly reduced the risk of kidney failure (3 trials, risk ratio [RR] 0.76, 95%CI 0.65, 0.89) and albuminuria (3 trials, SMD -0.94, 95%CI -1.49, -0.40). ERA had uncertain effect on all-cause mortality (5 trials, RR 0.99, 95%CI 0.84, 1.17), cardiovascular mortality (2 trials, RR 1.11, 95%CI 0.67, 1.83), kidney function (6 trials, standardized mean difference [SMD] -0.06, 95%CI -0.23, 0.11) and pulmonary edema (2 trials, RR 1.37, 95%CI 0.91, 2.07); but increased the risk of systemic edema (7 trials, RR 1.19, 95%CI 1.03, 1.39) and hospitalization for heart failure (5 trials, RR 1.32, 95%CI 0.87, 2.01).

Conclusions: Short-term trials suggest that ERA treatment may reduce the risk of kidney failure and albuminuria. Adequately powered RCTs with long-term follow-up are required to evaluate whether ERA treatment improves renal outcomes.

PUB421

Mycophenolate Sodium in Primary Membranous Nephropathy: A Retrospective Analysis

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Background: We studied the efficacy and safety of mycophenolate sodium (MMS) in primary membraneous nephropathy (MN)

Methods: A Retrospective observational study of 58 cases of treatment naïve MN. Patients were given prednisolone (20mg/day tapered to 5mg/day by 3 months) along with MMS (2 tablets of 360mg twice-a-day) and changes in eGFR and proteinuria from baseline to the end of one year were noted.

Results: A total 44 cases were included in analysis. There is no significant worsening of s.creatinine (0.85± 0.17 mg/dl v/s 0.95± 0.30 mg/dl, p=0.23) or eGFR (105.97 ± 19.10 v/s 97.18 ±20.35 ml/min/1.73m^2.P= 0.33). There is an improvement in s. albumin levels (2.17± 0.62 v/s 2.78± 0.59 gm/dl, p=0.001) and urinary protein levels (6811.36 ±1654.50 v/s 3360.34 ±2270.54 gm/day, p=0.001). At 12 months, partial response (PR) was seen in 29.54%, complete response (CR) in 20.45% and no response in 50%. The mean time to attain PR was 9.47± 1.8 mon and for for CR, 10.33 ± 1.5 mon. PLAR 2 positive cases had significantly earlier PR. The common complications were hypertension (18%) and diarrhoea (11%).

Conclusions: A 12-month course of MMS decreased proteinuria and improved renal function in patients with MN with less side effects.

PUB422

Renal Sarcoidosis: Clinical Presentations and Outcomes

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Background: Renal sarcoidosis is one of the silent clinical manifestations of sarcoidosis. It typically causes gradual impairment in kidney function due to chronic tubulointerstitial disease with or without granuloma formation. In addition, it also affects calcium and phosphate metabolism.

Methods: Ten patients with renal sarcoidosis diagnosed between 2002 and 2017 were included in this study. All patients had biopsy proven renal sarcoidosis or sarcoidosis diagnosed by biopsy of other organs in addition to decline in kidney function with or without hypercalcemia, nephrocalcinosis or nephrolithiasis.

Results: All patients had extra renal involvement at the time of diagnosis 90%Lung, 10%Liver, 20%Skin). One patient had neurosarcoidosis with panhypopituitarism; another had Heerfordt syndrome. In all patients with renal biopsy, pathology showed granulomatous interstitial nephritis. Of the three who did not have renal biopsy, two had granulomatous dermatitis on skin biopsy and one had granulomatous hepatitis. Three patients had nephrotic range proteinuria. All patients were treated with oral steroids (Prednisone 60mg for 4 weeks tapered to 15-20mg daily over 2 months). No patient had nephrolithiasis or nephrocalcinosis on imaging. Renal function improved significantly at 6 months in all patients except one patient who had an eGFR of 5ml/min/1.73m2 at presentation. Hypercalcemia resolved in all but one patient by 2 months of treatment. Serum calcium correlated with eGFR (Pearson coefficient –0.4).

Conclusions: Renal involvement with sarcoid is a rare cause of CKD/AKI but responds well to steroid treatment even in patients with severe impairment of kidney function at presentation.

Epidemiologic and clinical features of patients

No. of patients	10(3 females, 7males)
Race	100% were African Americans
Age	36±10
Serum calcium	11.04±1.00
Hypercalcemia	70% of patients
Serum phosphate	6.49±3.04
PTH(Median and IQR)	36.65 and 193.18
25(OH) Vitamin D	17.25±4.72
eGFR	25.8±19.9
eGFR at 1 month	37.7±20.3
eGFR at 6 months	41.1±18.7
Proteinuria	1.11±1.10
Biopsy	70% diagnosed by kidney biopsy, 30% extra renal

PUB423

Renoprotective Role of Metformin in a Mouse Model of Adenine-Induced CKD

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Background: Chronic kidney disease (CKD) is a worldwide public health problem and current best clinical practice only slows the progress of renal fibrosis in CKD. Inflammatory and fibrotic signaling pathways play important roles in the progression of CKD. Thus, it may be beneficial to limit renal fibrosis through inhibiting target inflammatory and fibrotic responses. Metformin is a widely used glucose-lowering medicine for type 2 diabetes mellitus. Recent studies have explored its potential for many other clinical conditions including renal fibrosis. However, the exact mechanisms of metformin in limiting renal injury is not fully understood.

Methods: To examine the role of metformin in the development of CKD, C57BL/6 mice were delivered adenine (4mg in 200ul water) through gavage to induce CKD for 21 days. Mice given water only served as control. Coincident with adenine treatment, mice were administered with metformin (0.4 mg/ml) in drinking water or water only (control) for 21 days, at which time animal experiments were terminated, blood, urine and kidney were collected. Urinary albumin to creatinine ratio (UACR)was assessed; inflammatory and fibrotic markers and their signaling molecules were analyzed by immunohistochemistry (IHC), qRT-PCR and Western blotting.

Results: Adenine induced increase in UACR was attenuated by metformin treatment ($p<0.01$). Adenine increased expression of inflammatory markers MCP-1, F4/80, fibrotic markers type IV collagen, fibronectin and TGF-β1, and phosphorylation of Smad3, ERK1/2, and P38 in kidneys compared to control groups, which were partially reversed by metformin treatment (n=6, $p<0.01$).

Conclusions: Metformin attenuates adenine-induced renal interstitial fibrogenesis through both Smad and non-Smad signaling pathways.

PUB424

Smarca4 Regulates Vascular Smooth Muscle Cell Calcification Through Inhibiting Autophagy

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Background: Vascular calcification(VC) is one of the most common clinical manifestations for patients with end stage renal disease(ESRD). However, the pathological mechanism of VC is not fully understood and there is no reliable early biomarker to predict the risk of VC.

Methods: In order to elucidate the mechanism of VS, we performed a detailed molecular characterization of high phosphorus indcued-VS model both *in vitro* and *in vivo*. The label free proteomics screening results of high phosphorus induced aortic vascular smooth muscle cells(ASMCs), pathological assessment, cellular charcterization and molecular signaling detection upon target gene elucidated a comprehensive profile about VS.

Results: Label free proteomics analysis and pathological studies highlighted Smarca4, also known as BRG1, significantly related to osteoblastoid differentiation from ASMCs during the development of VS. Smarca4 showed to regulates high phosphorus induced-VS by its anti-autophagy role associated with suppression of autophagysome formation and autophagy pathway.

Conclusions: Smarca4 regulates high phosphorus induced-calcification of ASMCs at an early stage involving its anti-autophagy role. Yi Li and Li Wang should be addressed as corresponding authors and these two authors contributed equally to this study.

Funding: Government Support - Non-U.S.

PUB425

Lnc-Gm44981 Induces Renal Aging by Regulating the p53/p21/RB Pathway

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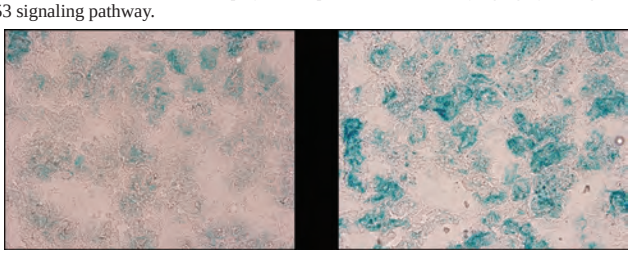
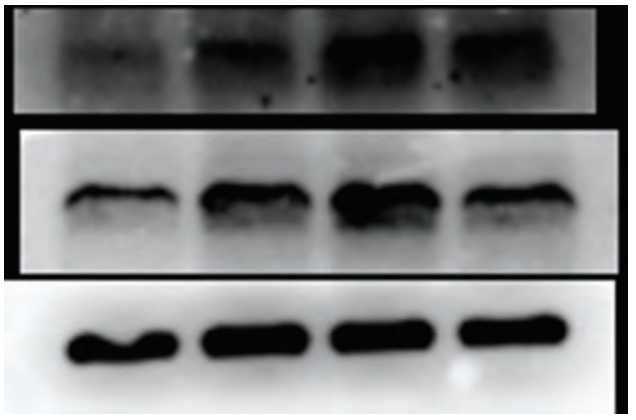
Background: Aging is a natural and gradual process of aging in the process of degenerative changes in tissues and organs of the body over time. The kidney, which is a metabolically active organ, is extremely susceptible to aging, but the mechanism of kidney aging is unclear. Long-chain non-coding RNA (lncRNA) is a non-coding RNA consisting of 200 nucleotides. It is generally considered that they do not encode proteins, but are expressed in various forms at the RNA level.

Methods: The expression of lnc-Gm44981 was detected using qRT-PCR. SA-β-gal staining and immunohistochemistry were operated for the detection of the p53, p16 and p21 expression in different ages. Transfection with lnc-Gm44981 siRNA to measure aging-associated protein expression levels in TCMK-1 cell.

Results: We found that the expression of lnc-Gm44981 decreased during aging. And we found that SA-β-gal expression gradually increased with age, and p53, p16 and p21 expression gradually increased. Then the transfection of lnc-Gm44981 siRNA has an effect on the expression of aging-related proteins.

Conclusions: lnc-Gm44981 plays an important role in kidney aging by acting on the p53 signaling pathway.





PUB426

Evidence of Urate Deposition in the Kidneys in Gout Patients

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Background: Gout is the most common inflammatory arthropathy in U.S. adults. Although tophi in the extremities are well known, urate deposition in the renal parenchyma is not as well recognized. Patients with gout commonly have concomitant renal disease, however, a causal role between these entities has not yet been established. Direct urate deposition in the renal parenchyma may be of significant interest since it could explain ongoing subclinical renal tissue damage and its potential role in the propagation of chronic kidney disease in gout patients.

Methods: PubMed (from 1940 to 2019) was searched to identify reports of autopsy, pathology and radiology imaging demonstrating urate deposition within the native renal parenchyma in patients with gout. Key words included: gout nephropathy, chronic urate nephropathy, renal tophi, gouty kidney, autopsy findings in gout, and renal imaging in gout. The reference lists from these publications were also used to identify additional articles. Literature referencing urate nephrolithiasis and renal transplants were excluded from the study.

Results: There were 25 articles documenting renal parenchymal urate deposition in gout patients confirmed by autopsy, biopsy and/or radiology imaging in native kidneys. Among the 19 articles examining urate deposition by autopsy or tissue sampling, 100% found renal urate deposition in the tubules and interstitium of the medulla. 68% found urate deposition in the renal cortex and/ or cortical scarring. 74% reported renal vascular pathology including arteriole fibrous thickening of the intima, hyaline degeneration and occlusions. In addition, 89% found inflammatory cells and fibrosis surrounding the parenchymal "microtophi". There were 6 imaging articles that all reported abnormal renal ultrasound findings in the medulla that were attributed to urate deposition.

Conclusions: Several case reports document renal parenchymal deposition of urate in patients with gout based on autopsy, pathology and imaging evidence. Renal urate vasculopathy was also commonly noted. Given the strong association of gout with renal disease, this demonstrates a need for further research to determine the clinical significance of urate deposition with respect to potential renal parenchymal injury and ongoing subclinical inflammation.

Funding: Commercial Support - Horizon Therapeutics

PUB427

Modulation of Inflammatory and Fibrotic Processes by Histone Lysine Demethylase

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Background: Histone lysine methylation and demethylation has been suggested to have a modulating effect on inflammation and fibrosis.

Methods: In this study, we analyzed the effect of JIB-04, a pan inhibitor of Jumonji histone demethylase on inflammatory process in murine macrophage cell line, RAW264.3, and rat renal proximal epithelial cell line, NRK-49F.

Results: JIB-04 pretreatment prevented LPS-induced expression of inflammatory cytokines in RAW264.3 cells and TGF-b-induced expression of profibrotic cytokines and EMT markers in NRK-49F cells, respectively. In addition, JIB-04 pretreatment inhibited both NF-kB activation and increase of snail1.

Conclusions: Taken together, these results suggest that histone lysine demethylase may play a contributing role to the induction of fibrosis as well as inflammation in the kidney by modulating activation of key transcription factors. In the future, JIB-04 could be developed as a new anti-fibrotic agent.

PUB428

Effect of Kidney Fibrosis Using SAMiRNA, a Second-Generation RNAi Platform Technology

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Background: SiRNA silencing approach has long been used as a method to regulate the expression of specific target gene in vitro and in vivo. However, the effectiveness of delivery and the nonspecific immune stimulatory function of siRNA are the limiting factors for therapeutic application of siRNAs.

Methods: To overcome limitations in in vivo delivery of siRNA, we developed self-assembled micelle inhibitory RNA (SAMiRNA) composed of DNA/RNA hybrids made of individually bi-conjugated siRNA with hydrophilic polymer and lipid on their ends and characterized their stability, immune stimulatory function and in vivo silencing efficacy. We used unilateral ureteral obstruction(UUO) mouse model for *in vivo* system. Mouse in groups of six were subjected to Sham, UUO and received intravenous injection of SAMiRNA™-Amphiregulin

Results: SAMiRNA form very stable nanoparticles without significant degradation in the size distribution and polydispersity index over 1 year. Overnight incubation of SAMiRNA on murine PBMC did not cause any significant elaboration of innate immune cytokines such as TNF-α, IL-12 or IL-6, while unmodified siRNA or, liposome or liposome complex significantly stimulated the expression of these cytokines. Lastly, in vivo silencing efficacy of SAMiRNA was evaluated by targeting amphiregulin (AR) in UUO mouse models of Kidney fibrosis. Only two times of intravenous delivery of AR SAMiRNA significantly reduced the *interstitial* ***collagen accumulation*** *in the kidney.* In Safety and toxicity test of SAMiRNA™-Amphiregulin, we acquired data on preclinical toxicity, safety and effectiveness of SAMiRNA™ using rodent and no-rodents systems. And We have finally determined acute- and repeated-dose toxicity at GLP grade and general toxicity, Toxicokinetics, etc. at GLP grade. There appears to be no adverse effect on preclinical toxicity and safety.

Conclusions: SAMiRNA is a safe, stable and effective platform for silencing disease-associated genes, useful in therapeutic applications for Kidney fibrosis and various fibrotic diseases. Currently we are developing a First-in-class Kidney fibrosis RNAi drugs through Non-clinical toxicology studies. Through successful completion of this project, we will be able to IND application and Approval for Phase 1 Studies of our SAMiRNA™ platform technology to a number of therapeutic targets generated by Bioneer as well as other global companies.

Funding: Government Support - Non-U.S.

PUB429

Low Circulating Transforming Growth Factor-β1 Level Is Associated with CKD

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Background: Transforming growth factor beta (TGF-β) plays a role in angiogenesis, differentiation, immunomodulation, and haematopoiesis. It remains controversial on association of circulating TGF-β1 level and chronic kidney disease (CKD).

Methods: We investigated the association of serum TGF-β1 level and CKD in 175 patients with CKD and 148 controls without. CKD was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or presence of albuminuria. Multivariable analyses were used to examine the relationship of serum TGF-β1 level and CKD, adjusting for age, gender, race, physical activity, smoking, drinking, systolic blood pressure, glucose, low-density lipoprotein cholesterol, body mass index, history of cardiovascular disease, and use of angiotensin-converting enzyme inhibitors.

Results: The adjusted median (interquartile range) of TGF-β1 levels was 13879 (11285-16753) pg/mL vs 17379 (14642 -19761) pg/mL in CKD vs. non-CKD patients (P<0.0001). The multivariable adjusted odds ratio (95% confidence interval) for CKD comparing the lowest to the highest tertile of TGF-β level was 6.07 (2.71, 13.6). One standard deviation lower in log transformed TGF-β1 was associated with lower level eGFR and higher level of urine albumin.

Conclusions: These data indicates that decreased serum TGF-β1 level is independently associated with CKD and higher urine albumin level. Future study is warranted to investigate the effect of normalizing serum TGF-β1 level on improving CKD outcomes.

PUB430

The Effects of ELP-VEGF on Tumor Progression

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Background: Vascular Endothelial Growth Factor(VEGF)plays a central role in promotion of angiogenesis and endothelial cell health. We showed that microvascular rarefaction, due to low VEGF levels, is a causative factor in renovascular disease(RVD) and chronic kidney disease(CKD). Recently, we developed a biopolymer-delivered VEGF by fusing VEGF-A_{121} to the elastin-like polypeptide(ELP) biopolymer, resulting in a chimeric protein(ELP-VEGF)that has extended pharmacokinetics and improved renal targeting. ELP-VEGF improved microvascular density, renal blood flow, and glomerular

filtration rate in swine models of RVD and CKD. However, there is concern that VEGF-based therapeutics may promote aberrant angiogenesis, especially in patients with undiagnosed tumors.

Methods: In order to determine if ELP-VEGF promotes tumor growth, we treated mice bearing triple negative breast tumors with ELP-VEGF at three doses, beginning at the therapeutic dose from our previous swine studies and escalating 10 and 100-fold(100ug/kg, 1mg/kg, 10mg/kg). Body weight and tumor size(monitored via caliper measurement and bioluminescence imaging)were assessed thrice weekly for five weeks. 35 days after treatment, mice were perfused with Microfil. Tumors were removed, weighed, and scanned via μCT to assess vascular density.

Results: There was no significant difference in tumor volume, luminescence, or mass amongst the groups. All groups had an average final tumor volume of approximately 1,500mm^3(±approximately 600mm^3)and an average tumor mass of approximately 1.1±0.5g(n=10). There was also no significance difference in body weight among all groups.

Conclusions: In conclusion, a single injection of ELP-VEGF, even at a dose 10-fold higher than the highest efficacious dose tested for renal disease, has no significant effect on tumor progression in a human xenograft breast cancer model.

Funding: Other NIH Support - R01HL121527, R41DK109737, R01HL095638

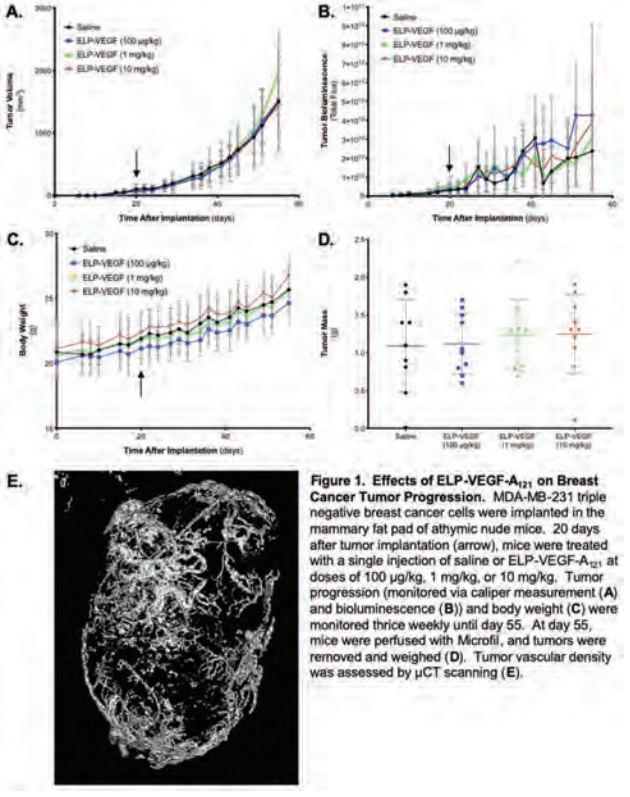

Figure 1. Effects of ELP-VEGF-A$_{121}$ on Breast Cancer Tumor Progression. MDA-MB-231 triple negative breast cancer cells were implanted in the mammary fat pad of athymic nude mice. 20 days after tumor implantation (arrow), mice were treated with a single injection of saline or ELP-VEGF-A$_{121}$ at doses of 100 μg/kg, 1 mg/kg, or 10 mg/kg. Tumor progression (monitored via caliper measurement (**A**) and bioluminescence (**B**)) and body weight (**C**) were monitored thrice weekly until day 55. At day 55, mice were perfused with Microfil, and tumors were removed and weighed (**D**). Tumor vascular density was assessed by μCT scanning (**E**).

PUB431

Cigarette Smoking Cessation Resulted in a Decline in Kidney Function: Paradox Explained

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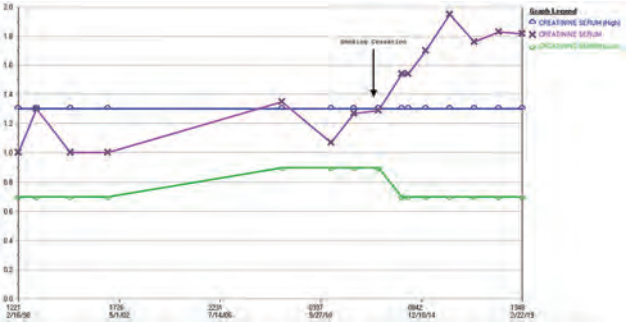
Introduction: Smoking tobacco is a well-known risk factor for cardiovascular disease and chronic kidney disease (CKD). Smoking cessation is always encouraged, but limited data is available regarding the short-term effects of smoking cessation on serum creatinine (Cr) and the actual and estimated glomerular filtration rate (eGFR)

Case Description: We present a case of a 59 years old patient who underwent a living donor kidney transplant in 1975. His serum Cr remained stable well within the normal range at about 1.0-1.3mg/dL up until 2013 when he quit smoking. His serum Cr started to gradually increase afterwards until it stabilized around 1.8mg/dL. Notably, his weight also gradually increased from about 105lbs to 130lbs. His serum Cr has since been stable at 1.8mg/dL. Renal ultrasound and broad relevant testing was negative/normal.

Discussion: Smoking cessation is well-linked to an increase in appetite and weight. Increased consumption of cooked meat is also known to increase serum Cr levels. Our patient did report an increase in appetite, meat consumption along with activity level after smoking cessation. We speculate that the low initial muscle mass in our patient coupled with the baseline decreased renal function made the increase in serum Cr more noticeable. Our literature search revealed multiple studies reporting the decrease in eGFR after smoking cessation, none of which however reported the relationship of Cr with weight changes and/or meat consumption. Conclusion: Smoking cessation could be linked to an increase in serum creatinine, that is related to increased creatinine production, not a decrease in GFR. This increase would be more evident especially in patients with low muscle mass and/or chronic kidney disease to begin with. Further studies need to be conducted to better characterize this phenomenon.



Serum Cr levels over time

PUB432

Graphene Quantum Dots Attenuate CKD Progression

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Background: Graphene derivatives - Graphene Quantum Dots (GQDs) have drawn much attention for its biomedical applications, such as bioimaging, drug delivery and tissue engineering. Also, the substances themselves have antioxidant, anti-inflammatory and immune regulatory effects. However, the role of GQDs in fibrotic diseases remains unclear. In this study, the effect of GQDs in kidney fibrogenesis was investigated.

Methods: Unilateral ureteral obstruction (UUO) was induced in 7- to 8-wk-old male wild-type C57BL6 mice. GQDs were injected in kidney fibrosis models through the tail vein. As in vitro model, rhTGF-β1 was used to induce epithelial to mesenchymal transition of kidney primary tubule epithelial cells. After treatment of GQDs, the pattern of change of fibrotic and mesenchymal markers and the activity of the TGF-β/Smads pathway and PI3K/Akt/mTOR pathway were evaluated. In addition, tubular apoptotic cell deaths were assessed.

Results: UUO induced renal fibrosis and morphological changes in the obstructed kidney, whereas administration of GQDs reduces fibrosis and improves kidney structural changes. At the mRNA and protein levels, GQDs significantly reduced the expression of fibrotic markers such as collagen 1a1, fibronectin and α-SMA and increased E-cadherin expression. GQDs significantly decreased TGF-β1 expression, as well as affected Smad-dependent signaling pathways and the PI3K/Akt/mTOR pathway. In addition, TUNEL staining and Bax/Bcl2 ratio were increased in the untreated group compared with GQDs-treated group.

Conclusions: This study revealed the role of GQDs in renal fibrosis, and its effectively attenuated fibrogenesis in 2 ways as follows: via the inhibition of Smad-dependent TGF-β signaling pathway and the anti-apoptotic pathway. Thus, GQDs may be a therapeutic option for the chronic kidney disease progression.

PUB433

DDAH1 Inhibitor PD 404182 Increases Serum Asymmetric Dimethylarginine but Does Not Promote Renal Fibrosis

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Background: Plasma asymmetric dimethylarginine (ADMA) is a risk factor for chronic kidney disease, however we recently showed that renal ADMA is anti-fibrotic. ADMA is metabolized by dimethylarginine dimethylaminohydrolase isoform 1 (DDAH1). PD 404182 is a novel inhibitor of DDAH1 exhibiting anti-tumor and anti-HIV activities. We aimed to determine the effect of PD 404182 on renal fibrosis and explore its underlying working mechanisms.

Methods: After sham or unilateral ureteral obstruction (UUO) operation, 20-25g male c57 mice were treated with vehicle or PD 404182 for 13 days. Moreover, human kidney 2 (HK2) cells were treated with various concentrations of PD 404182 in the presence of 2.5 ng/ml TGF-β. Protein samples from *in vivo* and *in vitro* experiments were collected to assess renal fibrosis.

Results: Treatment with PD 404182 enhanced serum ADMA levels in UUO mice, however it did not change the deposition of extracellular matrix proteins, the expression of α smooth muscle actin (α SMA) and connective tissue growth factor (CTGF) in UUO induced fibrotic kidneys. We further showed that PD 404182 reduced the expression of DDAH1 in UUO kidneys which was correlated with increased production of ADMA. In TGF-β stimulated HK2 cells, PD 404182 dose-dependently increased ADMA production, and inhibited the expression of pro-fibrotic proteins. Exogenous addition of ADMA inhibited the expression of profibrotic proteins and attenuated the anti-fibrotic effect of PD 404182.

Conclusions: PD 404182 enhances serum ADMA levels but does promote renal fibrosis in obstructed kidneys, which is possibly due to a balance between serum and renal ADMA.

PUB434

Changes of Pericyte in Aging Kidney

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Background: Our previous study have shown the changes of pericytes in aging mice kidney. However, its mechanism was unclear. And no such studies have been undertaken in human aging kidneys. In this study, we investigated the pericytes changes in human aging kidneys and mechanism of aging-related pericyte changes.

Methods: Renal biopsy from KT donors were analyzed. Donors under age 25 were assigned to young group and donors over age 60 to old group. 2, 24-months-old mice and 18-month-old mice treated with pentoxifylline for 6 months were analyzed with western blot.

Results: Changes of pericytes in human renal tissues were consistent with those in the aging mice model. In the old age group, pericytes were decreased and interstitial fibrosis was increased. Western blot analysis in mice kidney revealed that IL-1β, IL-6 and TNF-α were significantly increased in old age and significantly decreased in pentoxifylline group. Angiopoietin 2 was increased in old age group and decreased in pentoxifylline group.

Conclusions: In aging human kidney, pericytes have been shown to exhibit numerical reduction and loss of perivascular location as in the aging mice model. These changes in pericytes are thought to be induced by angiopoietin 2 excretion.

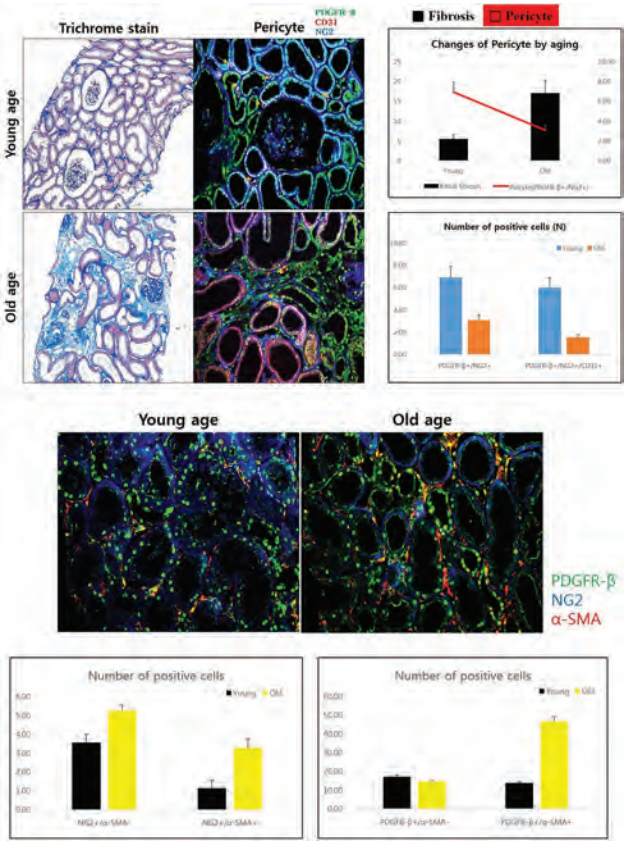

Figure1. Changes of human pericytes

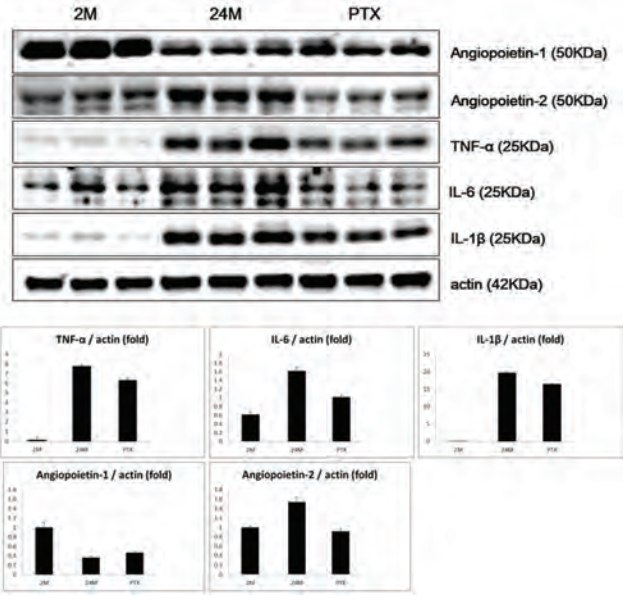

Figure2. Western blot analysis

PUB435

Exosomal miRNA Exerkines Attenuate CKD by Extracellular Matrix Remodeling

Bjoern Tampe, Michael Zeisberg. *University Medical Center Goettingen, Goettingen, Germany.*

Background: Chronic kidney dissease (CKD) is still an unmet challenge because no effective therapies are available as of yet for clinical use. While various studies across multiple organs which demonstrated that endurance exercise (EE) protects from progressive organ failure by endocrine-like signalling via specific miRNA exerkines, little consideration has been paid as to whether any miRNA exerkines are released in a manner other than direct discharge into the circulation. It is becoming increasingly apparent that one of the main mechanisms by which scelettal muscle cells and distant organs communicate is by the release of cell-derived extracellular exosomes. Based on these pre-requisits, we here aimed to gain insights into the molecular mechanisms underlying successful reno-protection and to explore whether such pathways could be therapeutically targeted.

Methods: EE was performed in *C57BL/6*mice for 4 weeks before challenging with unilateral ureteral obstruction (UUO) for 7 days without EE. Exosomal miRNA signatures were analyzed by unbiased array-based approaches and confirmed by qRT-PCR in sclettal muscles, plasma exosomes and corresponding kidneys. By using miRNA mimics administered systemically, miRNA candidates for succesful protection during EE were confirmed for therapeutical implications.

Results: We identified a unique miRNA signature in muscle-derived exosomes and kidneys specifically during endurance exercise, associated with attenuation of progressive CKD. Systemic administration of miRNA mimics was equally effective to attenuate progressive CKD, supporting that endurance exercise-derived exosomal miRNAs are involved in reno-protection. On a mechanistic level, we provide evidence that exosomal miRNAs directly target and degrade *PAI-1*, associated with activation of the tPA/uPAR/plasmin pathway. Increased tPA/uPAR/plasmin stimulates ECM remodelling and degradation by activation of latent MMPs, in particular MMP-2 and MMP-9.

Conclusions: In summary, we here provide evidence that EE attenuates progressive CKD by enrichment of exosomal miRNA exerkines modulating ECM remodelling in chronically injured kidneys. Because miRNA mimics equally protect from progressive CKD, these findings further support therapeutical implications of exosomal exerkines as nature's exercise pill.

PUB436

Screening for Small Molecule Inhibitors of Kidney Injury Molecule-1 (KIM-1) Using a Cell-Based Functional Assay

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Background: Kidney Injury Molecule-1 (KIM-1) is a transmembrane protein which is upregulated in injury to the proximal tubule. Plasma and urinary levels of KIM-1 are increased in patients with chronic kidney disease (CKD). KIM-1 serves as a prognostic marker for patients with CKD. Acutely KIM-1 takes up phosphatidylserine and oxidized lipids, advanced glycation end products (AGEs), and free fatty acids. Chronic expression of KIM-1 causes CKD in mice. This evidence suggests that KIM-1 expression contributes to the progression of CKD and inhibition of KIM-1 function may be beneficial for CKD patients.

Methods: Using cell-based functional assay for KIM-1 mediated uptake of ox-LDL, we screened for 14,414 unique small molecule compounds. After setting up a score for each compound, we selected and cherry-picked the 240 potential hits from the primary screening. We performed reconfirmation and dose dependency studies on two KIM-1 expressing cells (769-P cells and LLCPK-1 cells) expressing human KIM-1. A total of 32 compounds were selected based on reconfirmation and dose dependency studies as potential hits.

Results: We selected JB1 for secondary and tertiary assays as it was top scored. JB1 is not toxic to cells up to 11.11 μM. JB1 does not cleave KIM-1 indicating that JB1 inhibits the uptake of ox-LDL. JB1 doesn't quench DiI-Ox-LDL. JB1 significantly inhibits the uptake of BODIPY-labeled palmitic acid. Additionally, JB1 does not inhibit uptake by inhibiting Bcl-2 pathways.

Conclusions: We have developed a high throughput cell-based functional assay for screening compounds that can inhibit the uptake of ox-LDL by KIM-1. The small molecule inhibitors that we found can be of therapeutic importance for treating kidney disease.

Funding: Private Foundation Support

PUB437

Evaluation of Biomarkers of Interest in Nephrectomized Animals

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Background: Chronic kidney disease (CKD) is a worldwide health problem associated with morbidity and mortality, and its development and progression is related to various conditions such as hypertension, diabetes and dyslipidemia. Experimental models of CKD includes the 5/6 nephrectomy rat model, which shares multiple features observed in humans and therefore has been proven clinically relevant.

Methods: We investigated the effect of 5/6 nephrectomy on serum biochemistry and urinary kidney biomarkers, and bone markers as well as histopathological changes. For this purpose, blood and urine samples were collected from 6 control and 12 nephrectomized rats once monthly.

Results: Increases in serum urea nitrogen, creatinine, cholesterol and osteocalcin were consistently observed throughout the evaluation period. Increases in serum alpha2 macroglobulin, urine total protein, and urine biomarkers: osteopontin, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM-1), cystatin C and β2-microglobulin, and decreases in serum albumin were observed over the course of the evaluation period. Lesions in the kidneys of nephrectomized rats were mild to moderate tubular hypertrophy and hyperplasia with dilatation and cast, resulting in an overall enlargement of the kidney; minimal to moderate tubular degeneration and regeneration; mild to marked glomerulopathy and minimal to mild chronic inflammation. Mineralized foci were also identified in the kidneys of nephrectomized rats by image analysis. Vascular changes were noted in small to medium size ventricular arteries and consisted of minimal mural degeneration and minimal to mild perivascular inflammatory cell infiltrates and fibrosis.

Conclusions: These changes observed in serum and urine samples, as well as histopathologically, are indicative of chronic kidney disease. Therefore the model is considered suitable for the investigation of new treatments for CKD.

PUB438

Cordyceps Militaris Extract Attenuates the Pathological Fibrotic Changes in Unilateral Ureteral Obstruction Mice Model

Chia-Chun Wu,[1,2] Chien-wei Hsiung,[3] Ting-Feng Wu.[4] *[1]Chi Mei Medical Center, Tainan, Taiwan; [2]Pharmacy, Chia Nan University of Pharmacy and Science, Tainan, Taiwan; [3]Phytomed Bio-Tech co., Ltd., Tainan, Taiwan; [4]Southern Taiwan University of Science and Technology, Tainan, Taiwan*.

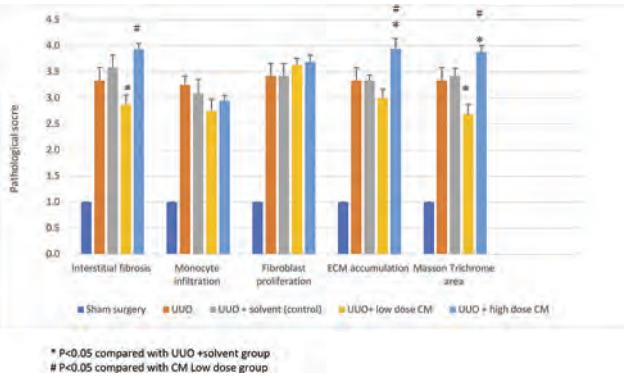
Background: Cordyceps militaris (CM) is a kind of functional mushroom. This study aimed to evaluate the effect of CM in kidney fibrosis induced by unilateral ureteral obstruction (UUO) mice model.

Methods: Study mice were divided into five groups: Sham surgery, UUO, UUO+ solvent (saline), UUO + CM 150mg/kg (CM low dose) and UUO + CM 300mg/kg (CM high dose). Study agents were fed orally daily after UUO induction until animals were sacrificed on day 7. Kidney samples were collected for H&E stain and Masson's Trichrome stain. Severity of kidney damage was graded from one to five depending on severity: 1 = (< 1%); 2 = (1-25%); 3 = (26-50%); 4 = (51-75%); 5 = (76-100%). The value of $p < 0.05$ was considered statistically significant.

Results: All groups except sham surgery had obvious kidney damage range from 2-4. The interstitial fibrosis on H&E stain and Masson's Trichrome stain were both significantly less severe in CM low dose group compared to it was in UUO + solvent group. The CM high dose group had significantly higher scores in interstitial fibrosis both on H&E stain and Masson's Trichrome stain and ECM accumulation compared to CM low dose group. Besides, CM high dose group also had significantly higher scores on ECM accumulation and fibrosis on Masson's Trichrome compared to UUO + solvent group. (Figure 1)

Conclusions: According to our findings, an adequate dosage of CM might have an anti-fibrosis effect in kidney but a high dose CM might have a negative effect. Further studies on protein and mRNA expression to support this finding and investigate the molecular mechanisms are needed.

Funding: Commercial Support - Phytomed Bio-Tech co., Ltd.Taiwan.



The pathologic scores of kidney damage in different study groups.

PUB439

Extrarenal Pelvis Mimicking Parapelvic Cysts: Contrast Is the Key

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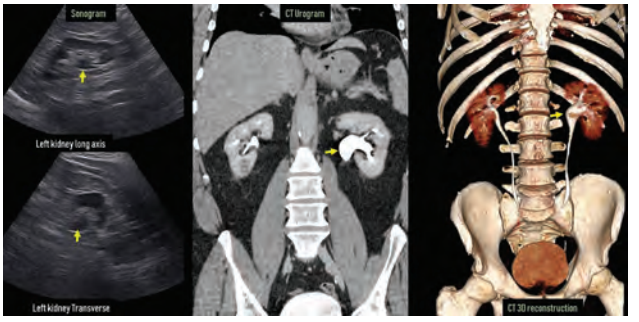
Introduction: Extrarenal pelvis refers to the presence of the renal pelvis outside the confines of the renal hilum. It is a normal anatomical variant that is found in ~10% of the population. An extrarenal pelvis appears as a hypoechoic mass just outside the renal sinus and can mimic a dilated pelvicalyceal system giving a false impression of hydronephrosis. In addition, it can also be confused with a parapelvic cyst. With renewed interest in point-of-care ultrasonography (POCUS), nephrologists must be aware of this finding and herein, we report a case where POCUS was not able to differentiate between these entities.

Case Description: A 62-year-old man with a history of nephrolithiasis and recurrent urinary tract Infections presented to the outpatient clinic for the management of chronic kidney disease stage 3. The renal sonogram showed the presence of a relatively well-defined anechoic lesion near the left renal pelvis, which could be a parapelvic cyst or mild hydronephrosis or an extrarenal pelvis. Because of the presence of microscopic hematuria, a computed tomography (CT) evaluation of the abdomen with contrast was obtained, which showed a left extrarenal pelvis [Figure] and multiple radiodense foci within the left pelvis, likely phleboliths. Subsequently, cystoscopy revealed a bladder tumor, for which he underwent resection with the resolution of hematuria.

Discussion: Renal sonogram might not be able to demonstrate the 'extrarenal' location of the extrarenal pelvis unless it is significantly dilated. Therefore, it can be easily confused with mild hydronephrosis or a parapelvic cyst. It is important to note that hydronephrosis appears as an anechoic 'branching' structure extending into the kidney instead of a 'well-defined' mass. In our case, CT Urogram has clearly demonstrated the extrarenal location of the pelvis without intrarenal extension. Parapelvic cyst was excluded because a cyst would not communicate with the collecting system and therefore, should not be filled with contrast.



PUB440

Hyperuricemia-Induced AKI Secondary to Leukemoid Reaction

Martha Catalina Morales Alvarez, David Doobin, Patricia Dharapak. *Icahn School of Medicine at Mount Sinai Beth Israel, New York, NY*.

Introduction: Uric acid has recently been recognized as an active nephrotoxic agent. Acute tumor lysis syndrome, recent cardiac surgery, rhabdomyolysis and cistplatin treatment are common clinical conditions associated with uric acid induced-acute kidney injury (AKI). Leukemoid reaction is an elevation of the white cell count >30 K/uL in absence of hematologic malignancies and secondary to solid tumors or infections. We describe the first reported case of uric acid-induced AKI secondary to leukemoid reaction.

Case Description: 56 year old male with history of sarcomatoid bladder carcinoma and prostate adenocarcinoma status post radical cystoprostatectomy (1 mo prior to admission) presented with weakness, fevers, and lower extremity edema. On admission, he was found

to have significant leukocytosis (180 K/uL) and a new intra-abdominal mass concerning for infected peritoneal carcinomatosis. Broad-spectrum antibiotics were initiated without significant improvement. A peripheral smear showed increased leukocyte count with bands but no blasts or schistocytes, favoring a leukemoid reaction from advanced neoplastic disease. His hospital course was complicated by oliguric AKI (creatinine of 2.0 mg/dl, up from 0.8 mg/dl) when WBC peaked at >200 K/uL within 1 week from admission. The uric acid level was found to be 21 mg/dl. Urinalysis revealed pyuria, hematuria, hyaline casts, and uric acid crystals. The patient was continued on intravenous fluids and received one dose of rasburicase. Within 24 hours, the creatinine improved to 1.66 mg/dl. Due to the patient's poor overall prognosis, the family elected to pursue comfort care.

Discussion: Uric acid has pro-inflammatory and vasoconstrictive properties and it has recently been described as a potential nephrotoxic agent. Crystal deposition and tubular toxic damage are the main mechanisms of injury, though recent studies have also implicated the role of severe afferent vasoconstriction. While our patient had several traditional risk factors for AKI, his kidney function deteriorated only after the WBC reached a level >200 K/uL and his uric acid peaked above 20 mg/dl. Leukemoid reactions are not associated with lysis syndrome. However, it might pose a potential complication in patients with an acute and rapid increase in WBC. Early consideration of this complication and timely rasburicase administration can salvage kidney function.

PUB441

A Solvent Drag: Traditional Meds Mixed with Ethylene Glycol in a Nigerian Patient on Dialysis

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Introduction: Unregulated traditional medications and their solvents are nephrotoxic. A Nigerian patient presented with a rapid progression of kidney disease following daily ingestion of an aphrodesiac dissolved in ethylene glycol. The diagnosis was confirmed with kidney biopsy and elevated serum oxalate levels. The epidemic of kidney disease in rural communities may in part be explained by this solvent.

Case Description: The patient is a 49-year-old Nigerian male with a 10-year history of diabetes mellitus and hypertension. One year prior to presentation, the serum creatinine was 1.6 mg/dl with 0.8 gram/day proteinuria. The patient began ingesting a traditional, herbal medication as an aphrodesiac. This is a customary practice in his village, outside Abuja, Nigeria. His serum creatinine increased to 8.9 mg/dl and the patient commenced thrice weekly hemodialysis. His local physician was concerned and the patient was sent to Houston, TX for a second opinion. Home medications included calcitriol, proton pump inhibitor (PPI), multivitamin, and a DPP-4 inhibitor. A full laboratory evaluation for immunologic or infectious causes of kidney failure was unremarkable. Kidneys were 12 cm bilaterally, with one non-obstructing calculi (7mm) in left kidney. A kidney biopsy revealed protracted tubular injury with isometric vacuolization and numerous calcium oxalate crystals. There was minimal glomerulosclerosis, and severe interstitial fibrosis / tubular atrophy. A serum oxalate level was subsequently checked, and elevated at 25 mcmol/L (Range 1.8-3.2). There was no evidence of primary hyperoxaluria. His local physician later ascertained that ethylene glycol was used a solvent for the traditional aphrodesiac. Kidney damage was irreversible and the patient returned to Nigeria.

Discussion: Worldwide, the increasing use of traditional, unregulated, herbal supplements has the potential to cause epidemics of kidney disease in rural communities. In Africa, attention has focused on nephrotoxic herbs (e.g. aloe vera and cymbopogon citrullus), but under-recognized is the role of the alcohol based solvent. Chronic use of ethylene glycol results in oxalate nephropathy. A thorough history and work-up should be pursued in all patients with a rapid decline in kidney function, even in the presence of known risk factors for CKD.

PUB442

Two Cases of Rhabdomyolysis with Near Normal Creatine Kinase

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Introduction: Rhabdomyolysis (RM) is a well-known cause of acute kidney injury (AKI). Elevation of creatine kinase (CK) is considered essential for the diagnosis of severe AKI from RM. We present 2 cases of severe AKI from non-traumatic, non-exertional RM with mildly elevated CK.

Case Description: Case 1 A 55-year-old Caucasian male with history of DM and HTN was admitted with 1-week history of dyspnea and found to have AKI. There was no history of trauma or Illicit drug use. Exam showed BP of 150/80 and no edema. Serum creatinine was 1.4 mg/dl 2 months prior, 3.1 mg/dl on admission and rose to 12.6 mg/dl on day 6. UA showed 2+ blood, 3+ protein and 11 RBC's/ HPF. CK was 285 IU/L (1.2 x normal, day 2), LDH 552 IU/L (day 2) and plasma myoglobin 263 ng/dl (day 5). Urine myoglobin was undetectable when checked on day 6. Serum sodium was 128 mmol/L and plasma osmolality 291mOsm/Kg. Evaluation for rapidly progressive glomerulonephritis (RPGN) including ANA, ANCA, ASO, Anti GBM Ab, C3, C4, hepatitis panel and HIV was negative. A renal biopsy on day 4 showed severe acute tubular injury with many myoglobin casts. Renal function slowly returned to normal with conservative treatment. Case 2 A 48-year-old Native American male with history of DM, HTN, CAD and alcohol and cocaine abuse was admitted with 1-week history of dyspnea and found to have severe AKI. Exam showed BP of 141/100 and 1+ edema. Serum creatinine was 0.6 mg/dl 2 years prior and 23 mg/dl on admission. Serum sodium was 120 mmol/L and plasma osmolality 301 mOsm/kg. UA showed 2+ blood, 2+ protein and 2-5 RBCs/HPF. CK was 733 IU/L (2.9 x normal), LDH 421 IU/L and plasma myoglobin > 2000 ng/ml. Evaluation for RPGN, as in Case 1, was negative. A renal biopsy on day 5 showed severe acute tubular necrosis. He required dialysis for 6 days. Renal function continued to improve after stopping dialysis.

Discussion: Both patients had severe AKI with biopsy proven acute tubular necrosis. In both, CK was only mildly elevated and plasma myoglobin was more definitely elevated. Both had non-specific hematuria and proteinuria prompting evaluation for RPGN. Both patients had low plasma sodium with normal plasma osmolality consistent with pseudohyponatremia. The cause of pseudohyponatremia was not clear and would be an interesting subject for further study. Rhabdomyolysis should not be excluded as a cause of severe AKI based on near normal CK.

PUB443

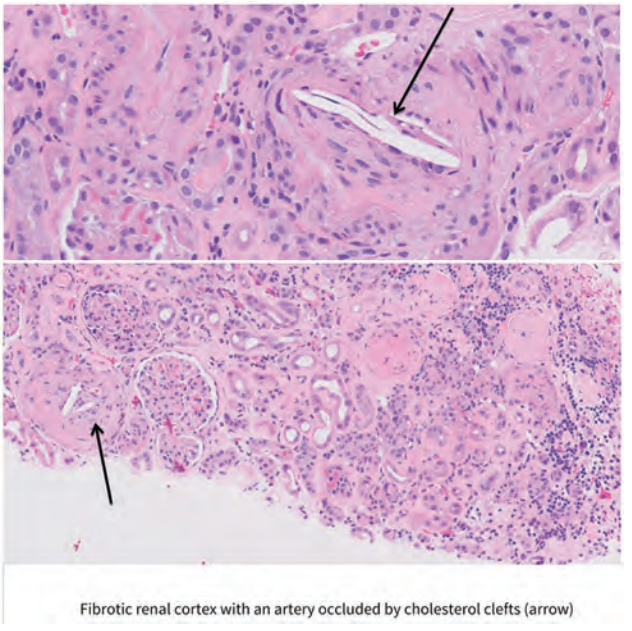
Patient with AKI of Uncommon Etiology

Sushma Edara,[1] Madhu Kandarpa.[2] *[1]Kidney care specialists, Beavercreek, OH; [2]Kidney Care Specialists, LLC, Dayton, OH.*

Introduction: Acute kidney injury is a common complication of congestive heart failure. Here we present a case report of a patient with acute kidney injury complicating congestive heart failure but of unexpected etiology.

Case Description: 70-year-old man with history of hypertension, hyperlipidemia and Chronic Obstructive Pulmonary Disease(COPD) who hasn't seen a physician for several years presented with acute respiratory distress requring mechanical ventilation. He was treated for new onset heart failure and acute pulmonary edema. Echocardiogram reported left ventricular ejection fraction of 30% and global hypokinesis. He was extubated after 24 hours, but his creatinine increased rapidly from 1.9mg/dl at the time of initial presentation to 9.5mg/dl within 4 days post extubation. Anti-Neutrophil Cytoplasmic Antibodies and Anti-Nuclear Antibodies were negative; C3 and C4 were within normal limits. Renal biopsy was performed which surprisingly showed Cholesterol embolization along with interstitial fibrosis, tubular atrophy as well as mild acute tubular necrosis. CT angiogram showed Bilateral renal artery stenosis, occluded right main renal artery and severe near occlusive single left renal artery. Percutaneous transluminal angioplasty and stenting of the left renal artery was performed and placed on Clopidogel. Patient's blood pressure remained well controlled with no further acute pulmonary edema.

Discussion: Cholesterol embolization on biopsy prompted further workup. There was no preceding vascular intervention suggesting the cholesterol emboli was possibly a spontaneous event induced by hemodynamic stress which alters the endothelium. Mortality is likely to be high in these patients especially in elderly males, most commonly due to cardic and renal etiologies as per previous reports (1). 1. Am J Nephrol. 1993;13(6):489-93.



Fibrotic renal cortex with an artery occluded by cholesterol clefts (arrow)

PUB444

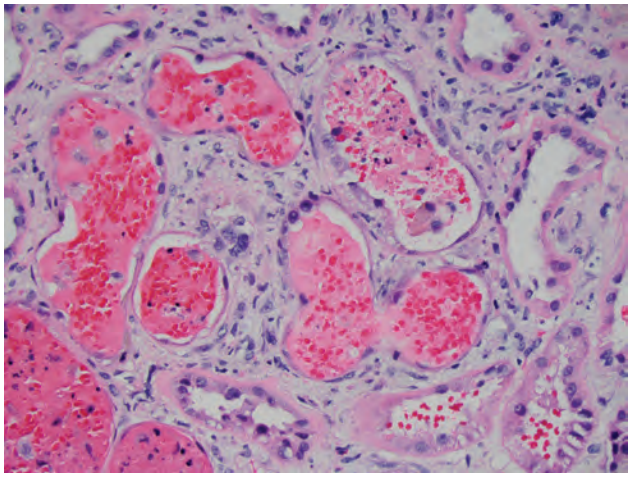
Anticoagulant-Related Nephropathy in IgA Nephropathy

Mal P. Homan,[1] Sharif Ali,[2] Sharon E. Maynard.[1] *[1]Lehigh Valley Health Network, Zionsville, PA; [2]Lehigh Valley Hospital, Orefield, PA.*

Introduction: Anticoagulant-related nephropathy (ARN) is a potential complication of warfarin use. This is the case of ARN in a patient with IgA nephropathy (IgAN).

Case Description: A 68-year-old man with cirrhosis, CKD stage 3, and atrial fibrillation on warfarin was admitted with edema, acute kidney injury (AKI), and gross hematuria. His creatinine was 2.9 mg/dL (baseline 1.4-1.6 mg/dL); INR was 2.5. Renal ultrasound was normal, urine-protein creatinine ratio (UPCR) was 1.9 g/g, serologic work-up was negative, and complement levels were normal. Renal function worsened. A kidney biopsy revealed mild mesangial hypercellularity with tubules containing red blood cell (RBC) casts, and mesangial IgA and C3 granular deposits. His anticoagulation was held, and renal function improved. On follow-up, his creatinine was 1.1 mg/dL and UPCR improved to 0.6 g/g.

Discussion: ARN causes RBC casts in the tubules leading to obstruction and AKI. Patients with IgAN may be at higher risk for ARN because of their propensity for hematuria. In the original description of ARN, underlying IgAN was present in 1/3rd of patients, and supertherapeutic INR was present in the majority of cases. Other risk factors include age, diabetes, hypertension, and cardiovascular disease. The risk of AKI in warfarin-treated patients with supertherapeutic INR is higher in those with CKD (33%) as compared to those without CKD (16.5%). Given the widespread use of warfarin and other anticoagulants, it is important to recognize the risk of ARN, and avoid excessive anticoagulation, particularly in patients with CKD and IgAN.



PUB445

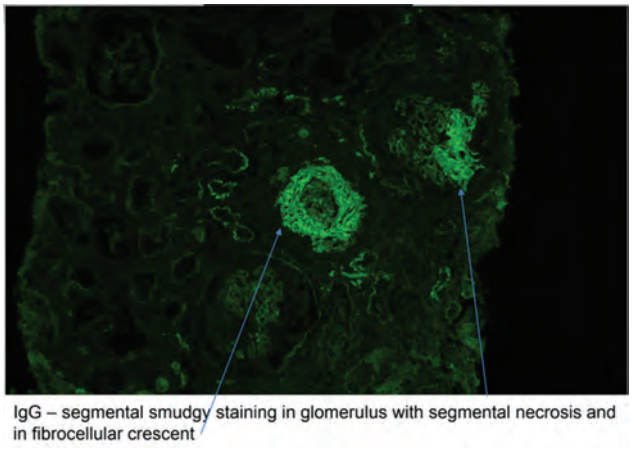
AKI in a Patient with History of Recurrent Hemoptysis

Sushma Edara,[1] Madhu Kandarpa.[2] [1]*Kidney care specialists, Beavercreek, OH;* [2]*Kidney Care Specialists, LLC, Dayton, OH.*

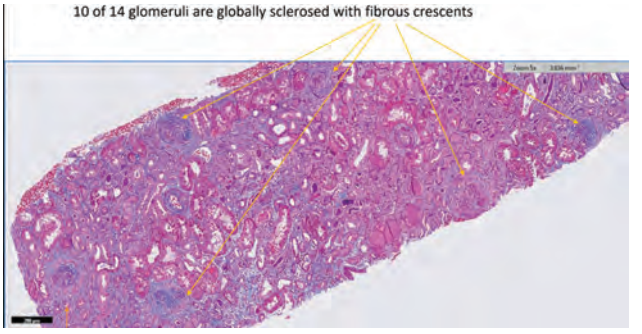
Introduction: Presentation of patients with pulmonary-renal syndrome may vary. Here we present a patient with acute kidney injury after several episodes of hemoptysis.

Case Description: 65-year-old female patient with a history of recurrent episodes of shortness of breath and hemoptysis followes as idiopathic Pulmonary Fibrosis (PF) presented with creatinine of 5.5mg/dl. Her baseline creatinine was 1.2mg/dl 4 months ago, with no prior history of kidney disease. Patient had a family history of PF with no kidney abnormalities. Urinanalysis positive for moderate blood and proteinuria of 1.7mg/dl. Renal ultrasound was negative for hydronephrosis. Complement levels were within normal limits. Antinuclear antibodies, Anti GBS antibodies and rheumatoid factor were negative. Cytoplasmic and perinuclear anti-nuclear cytoplasmic antibodies (ANCA) positive at 1:640, proteinase3 (PR 3) elevated at 4.3U/ml, myeloperoxidase antibody (MPO) elevated at 47.7U/ml. Renal biopsy which showed Focal Necrotizing and crescentic Glomerulonephritis, MPO- ANCA associated with advanced chronic changes suspecting underlying Autoimmune etiology. Patient is being treated with oral prednisone and oral Cyclophosphamide after pulse methylprednisone. Patient continued to require hemodialysis hoping for renal recovery, but her pulmonary symptoms have resolved.

Discussion: In Retrospect recurrent episodes of hemoptysis despite prednisone alone probably indicative of vasculitis. Higher mortality rate of ANCA-associated vasculitis possibly can be lowered with serological testing in every patient with recurrent hemoptysis even without renal involvement at the time of initial presentation.(1) 1. DOI: 10.1055/s-0031-1279828



IgG – segmental smudgy staining in glomerulus with segmental necrosis and in fibrocellular crescent



PUB446

Anti-Brush Border Antibodies LRP2: A Rare Entity That Should Not Be Brushed Off

Keyla J. Davila- Marcano,[1] Ranil S. Gajanayaka.[2] Methodist Dallas Medical Center [1]*Methodist Hospital Dallas, DALLAS, TX;* [2]*Dallas Nephrology Associates, Southlake, TX.*

Introduction: Acute kidney injury (AKI) has been related to drugs, infectious and multiples autoimmune diseases against glomerular antigens. We present an under-reported case of AKI secondary to kidney anti-brush border antibodies LRP2(ABBA disease). Our case is remarkable due to the atypical presentation of nephrotic range proteinuria 7.3g in compare to sub nephrotic range proteinuria of previous cases reported. ABBA can present as an AKI, progress to ESRD or recur in a kidney transplant. This case alerts the clinicians about the diagnosis of tubular injury which is not part of the usual initial assessment. The existence of any IgG-containing TBM immune deposits without proliferative glomerular lesions should aware us about to the possibility of this disorder.

Case Description: A 72 y/o M with pmhx of HTN presents with acute kidney injury. Family, social and medication history were unremarkable. He presents with creatinine 1.5mg/dL, albumin 2.1 and 7.3 g of proteinuria. Glomerular work up resulted negative, urinalysis with proteinuria >300mg and blood positive. Physical examination remarkable for Bp 143/82, general weakness and bilateral leg edema. Kidney ultrasound was within normal limits. Kidney biopsy resulted with Anti Brush Border Ab disease/ LRP2 (Megalin Related Nephropathy). Patient was treated with IV steroids for 3 days and then started with prednisone 80 mg daily, MMF 750 mg BID, Bactrim SS 3 times a week.

Discussion: We present an underreported cause of AKI LRP2 associated with circulating autoantibodies to the tubular brush border protein LRP2/megalin and characterized by IgG- and LRP2-containing immune complexes in the TBM. This case should alert clinicians of other causes of AKI.

PUB447

Magnesium Toxicity: A Perfect Storm

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Introduction: Hypermagnesemia is a rare condition in the *absence of renal failure* since the kidneys are effective in maintaining the normal plasma magnesium concentration. 50 to 70 % of the filtered magnesium is passively reabsorbed in the cortical aspect of the thick ascending limb of Henle. Loop reabsorption is appropriately diminished with magnesium loading, thereby allowing the excess magnesium to be excreted in the urine. Here we present a case of a patient with preeclampsia treated with IV magnesium that led to magnesium toxicity.

Case Description: 29 years old G1P0 admitted for preeclampsia and started on IV Mg Sulfate. After she received Nifedipine and IV labetalol post-partum, she developed shortness of breath, dizziness, abdominal pain and distension, decrease urine output. Hypomagnesemia caused flushing, delayed deep tendon reflexes (DTR), muscle weakness, lethargy, decrease respirations, bradycardia, and hypotension. Urinalysis showed pyuria, Leukocyte esterase, urine protein 10 mg/dl. Creatinine was 0.92 mg/dl and normal LFT. Due to worsening abdominal pain, milk of magnesium and miralax were given. She later became anuric with decreased DTR with Mg level at 11.3mg/dl, creatinine elevated to 4.3mg/dl and EKG showed sinus tachycardia[A1]. IV Calcium gluconate and Foley catheter placed at which point she had 1 Liter of urine. She was maintained on IVF and magnesium levels continued to decrease and normalization of her creatinine.

Discussion: Use of calcium channel blockers can potentiate neuromuscular blockade action of Mg SO4. Abdominal pain, urinary retention due to muscle relaxation, and milk of magnesia further potentiated her renal failure and cardiac toxicity. It is critical to recognize the hypermganesemia early since loss of DTRs common in Mg >7 mg /dl and cardiac conduction defects and arrest common in Mg >12mg/dl.

PUB448

Rare Case of Anti-GBM Antibody Disease with Thrombotic Microangiopathy Caused by Hypertensive Emergency

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Introduction: Anti-Glomerular Basement Membrane (GBM) Antibody Disease is one of the most aggressive form of glomerulonephritis resulting in renal insufficiency and more than 95% of patients have crescents at the time of biopsy. It can be renal limited or in combination with pulmonary hemorrhage (Goodpasture's syndrome). In rare case, glomerulonephritis can be seen concurrently with thrombotic microangiopathy (TMA), a disease involving endothelial injury that results in thrombosis in capillaries and arterioles and can lead to thrombocytopenia, anemia, purpura, and kidney failure. Here we present a rare case of anti-GBM with concurrent TMA.

Case Description: We present a case of a 57-year-old female with history of COPD who presents with hematuria, and blood pressures in the 200s/100. Labs notable for a creatinine of 13.02 from 4.2 a week ago (baseline 0.85 3 years ago). Other labs are notable for Hemoglobin 7.9, platelet 104, LDH 551 and haptoglobin <10 with schistocytes. Kidney biopsy showed necrotizing cellular crescents and focal segmental necrotizing lesions. Immunofluorescence showed linear capillary loop staining of the glomeruli, with antisera to IgG, C3, kappa, and lambda light chains suggestive of Anti-GBM antibody disease. Follow up laboratory testing confirmed the diagnosis as Anti-GBM antibody disease as the measurement of anti GBM IgG antibodies was 7.9.

Discussion: Anti-GBM disease is a rare disorder and a literature review revealed just 10 published accounts of concurrent anti-GBM and TMA in a total of 15 patients. Of those, 3 cases were attributed to TTP and abnormalities in ADAMTS13, 3 were attributed to complement-mediated TMA (aHUS), 1 was attributed to mechanical destruction due to hemodialysis, 1 was attributed to HUS, 1 was attributed to Heparin-induced thrombocytopenia, and 6 were not otherwise specified. No cases attribute the TMA to hypertensive emergency as we report here. In the setting of TMA, empiric plasmapheresis is generally initiated, however, many causes of secondary TMA including hypertensive emergency have not been shown to respond to treatment. This was consistent with our patient's presentation as the thrombocytopenia and MAHA failed to improve despite the plasma exchange. Our patient continued to have a decline in kidney function and eventually required hemodialysis.

PUB449

An Uncommon Case of Drug-Induced Acute Interstitial Nephritis

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Introduction: Drug-induced acute interstitial nephritis (DI-AIN) is a common cause of acute kidney injury (AKI) and often presents as an unexplained rise in serum creatinine level (SCr). Despite the frequency of acute interstitial nephritis (AIN), there remain cases under-diagnosed and under-treated.

Case Description: We report a 54 -year-old male, presented with fatigue for a week and had increased SCr from baseline 2.0 mg/dl to 21 mg/dl with a BUN of 125 mg/dl. He denied recent changes in his medications or recent use of over the counter or herbal agent. He remained anuric with worsening renal function, therefore requiring hemodialysis. Patient's kidney biopsy revealed moderate interstitial inflammatory infiltrate associated with interstitial edema consistent with AIN. Reported potential causes of the patient's AIN included amlodipine and allopurinol which he was taking for almost 4 years and both were held. Given rapidly progressive nature of this patient's presentation, steroid therapy was instituted. His urine output increased within 24 hours of initiation of steroid therapy. Hemodialysis was stopped one week later. At the time of discontinuation of dialysis, SCr was 2.5 mg/dl and following one month of steroid therapy, it was 1.8 mg/dl.

Discussion: Our case highlights the inherent difficulty in recognition of anuric DI-AIN, which would result in difficulty in decision making regarding proper management. After withdrawal of the offending drugs and initiation of steroid, a rapid improvement of kidney function was noticed. The diagnosis of DI-AIN is typically made with classic triad of rash, fever and eosinophilia within a few days of initiation of a culprit drug. However, these findings appear in a small number of patients, and the onset may be delayed by weeks or months after initiation of medication. Diagnosis relies on maintaining a high index of suspicion in those at risk and obtaining a kidney biopsy. The hallmark pathologic features are interstitial edema, interstitial inflammation with a predominance of lymphocytes and mononuclear cells, with variable numbers of eosinophils. The mainstay of treatment is discontinuation of the offending drug. Multiple studies have evaluated the benefit of steroid therapy to facilitate the recovery of renal function, with inconclusive results. This patient's timely recovery from dialysis could support the use of steroid in dialysis dependent AIN.

PUB450

Amphetamine-Induced Myoglobinuric Kidney Injury: A Classic Yet Intriguing Tale

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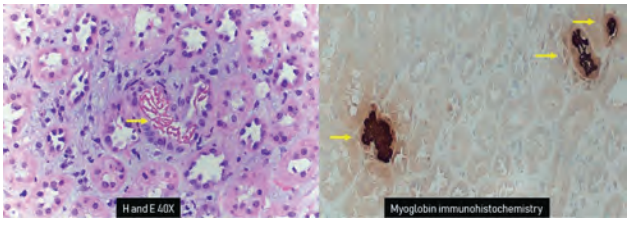
Introduction: Rhabdomyolysis, characterized by necrosis of muscle cells and release of their contents into the blood constitutes 7-15% of all cases of acute kidney injury (AKI) in the United States. We present a case of amphetamine-induced myoglobinuric kidney injury highlighting the importance of obtaining drug screen in the evaluation of AKI and present the classic renal pathology images of myoglobin cast nephropathy.

Case Description: A 41-year-old otherwise healthy man presented with abdominal discomfort, nausea and cola colored urine. His blood pressure at presentation was 174/93 mmHg. Laboratory data was significant for AKI with a serum creatinine of 12 mg/dL, rhabdomyolysis with a creatine kinase of >40,000 U/L [24-223]. Renal sonogram showed normal sized kidneys without hydronephrosis. The patient denied taking any illicit drugs, however, urine drug screen was positive for amphetamines. Urinalysis not only showed 3+ blood as expected with myoglobinuria but also >50 red blood cells/hpf and 4+ protein raising the suspicion for superimposed rapidly progressive glomerulonephritis (GN). Serum ANA and ANCA titers were negative. Renal biopsy demonstrated acute tubular injury (ATI) and myoglobin casts were confirmed by immunohistochemical staining [Figure]. The patient required a few sessions of hemodialysis but recovered gradually and creatinine trended down to 2.8 mg/dL at discharge.

Discussion: Amphetamine and its N-methylated derivative methamphetamine are known to cause AKI by several mechanisms, myoglobinuria-associated tubular injury (MTI) being the most common. Others include malignant hypertensive nephropathy, hyponatremia, necrotizing vasculitis and thrombotic microangiopathy. Renal biopsy should be undertaken when there is a suspicion for superimposed GN. Histology sections in MTI typically demonstrate ATI with variable flattening of tubular epithelial cells, loss of brush borders, and intratubular sloughed epithelial cells. Myoglobin casts are composed of round granules that may line up in chains or aggregate in clusters. Immunoperoxidase staining with antibody to myoglobin is usually strongly positive in the casts.



PUB451

Calcium Oxalate Nephropathy: A Rare Etiology of ESRD

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Introduction: Oxalate nephropathy is a rare cause of renal failure. It is characterized by tubular crystalline deposits of calcium oxalate leading to acute and chronic tubular injury, interstitial fibrosis and progressive renal insufficiency. There are two types of oxalate nephropathy, primary and secondary. Secondary hyperoxaluria is more common and is the result of increased dietary oxalate intake, decreased intestinal oxalate degradation, increased colonic permeability to oxalate. We present a case in which a patient with history of bariatric surgery (40 years ago) diagnosed with oxalate nephropathy and developed ESRD.

Case Description: A 74 y female with past medical history of gastric bypass surgery, (renal function was normal 1 year prior to hospital admission), NASH cirrhosis presented with abdominal pain, vomiting and melena. On presentation, the patient had creatinine of 12 mg/dl, bicarbonate of 7 mg/dl and hemoglobin of 5.8 gm/dl. Endoscopic evaluation showed two large varices. Due to minimal recovery of renal function, she was started on intermittent hemodialysis. Further workup showed positive ANA with titer of 1:640, positive dsDNA and low complement levels. Patient's urinalysis showed RBC>182/ HPF and proteinuria 100 mg/dl. Kidney biopsy showed acute tubular injury changes with tubular crystals consistent with calcium oxalate.

Discussion: According to National Center for Health statistics, the prevalence of obesity in the USA exceeds 30% and 228,000 bariatric surgeries were done in 2017. Electronic database for case reports and series with biopsy proven oxalate nephropathy in native or transplanted kidneys from 1950-01/2018 showed fat malabsorption (88%) and excessive dietary oxalate consumption (20%) as causes of oxalate nephropathy. According to a review, patients presented diagnosed with oxalate nephropathy between 4 months to 8 years after bariatric surgery. Diagnosis of oxalate nephropathy includes 24 hours urine collection for oxalate excretion and kidney biopsy. Treatment includes low-fat, low oxalate diet and high fluid intake. Secondary oxalate nephropathy is a rare cause of renal failure and can present after many years of bariatric surgery. Renal replacement therapy is required in >50% of patients, and most patients remain dialysis-dependent. Oxalate nephropathy should be suspected in a patient with remote history of bariatric surgery who presents with sub-acute renal failure.

PUB452

An Unexpected Cause of Renal Failure in a Patient with Diabetes

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Introduction: Granulomatous interstitial nephritis is the classic renal lesion seen but it uncommonly causes clinically significant renal disease and rarely presents in the absence of extrarenal lesions. We present a case of unexplained renal failure in a patient with recently diagnosed diabetes mellitus (DM) who underwent a renal biopsy which demonstrated granulomatous interstitial nephritis as the first manifestation of sarcoidosis.

Case Description: A 39-year-old African American male was admitted in August 2018 with new onset DM. At the time of his presentation, he was found to have serum

glucose of 727 mg/dl and an elevated serum creatinine 2.9 mg/dl (eGFR 29 ml/min) with no prior history of renal disease. Serum creatinine improved to 2.4 mg/dl after correction of hyperglycemia and volume expansion but then plateaued. No nephrotoxins were identified. Urinalysis revealed 6-10 wbc/hpf, urine protein/creatinine 380 mg/g with bland sediment. Serologic workup was negative. Renal ultrasound revealed enlarged kidneys measuring 12.4 cm and 13.6 cm. There was no improvement in renal function 1 month later so renal biopsy was pursued. Labs drawn pre-biopsy revealed new onset hypercalcemia with a serum calcium of 13.3 mg/dl and an increase in serum creatinine to 4.1 mg/dl. Hypercalcemia workup revealed 1,25-dihydroxyvitamin D level of 106 pg/mL. Chest x-ray was normal. Renal biopsy revealed complete loss of cortical architecture due to extensive interstitial inflammation and noncaseating granulomas. Stains for acid-fast and fungal organisms were negative. He was started on high dose prednisone 1 mg/kg/day for treatment of granulomatous interstitial nephritis in the setting of sarcoidosis. His hypercalcemia resolved and over the course of 3 months his serum creatinine improved to 1.7 mg/dl.

Discussion: Although granulomatous interstitial nephritis is a well described renal manifestation of sarcoidosis, it is often clinically silent and rarely occurs in the absence of extrarenal manifestations. Our patient's presentation of new onset DM was a red herring in the workup for his renal failure and highlights the importance of renal biopsy in all cases of unexplained renal failure. His hypercalcemia and extensive interstitial inflammation both likely contributed to his renal failure. Treatment with high dose prednisone resulted in resolution of hypercalcemia and significant improvement in his renal function.

PUB453

A Case of Acute Renal Infarction Associated with Hyperhomocysteinemia

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Introduction: Acute renal infarction (ARI) is a rare clinical diagnosis with an estimated incidence of less than 0.01%. The most common etiology is cardioembolic, but others include trauma, vasculitis, and hypercoagulable disorders. Many cases are deemed idiopathic. Here we present a case of ARI potentially attributable to hyperhomocysteinemia.

Case Description: A 61-year-old male with a history of radiculopathy presented with two days of right-sided abdominal pain. A week prior, he was evaluated for severe headache and vision impairment and was discharged after a normal head CT. On admission, physical exam revealed right flank tenderness. Labs showed a creatinine (cr) of 1.38 mg/dl (baseline, 1.05 mg/dl), leukocytosis (17 x 10E3/mm3), and transaminitis (ALT 57 IU/L, AST 71 IU/L), LDH was 915 IU/L, CRP 261 mg/L. CT abdomen/pelvis with IV contrast suggested right ARI from a thrombus in the right renal artery. Acute management included anticoagulation with unfractionated heparin. Thrombolysis was not performed, given the patient's development of fever, stabilization of creatinine, and lack of high-quality evidence for benefits vs. risks of the procedure. Given the patient's recent visual disturbance (potentially, amaurosis fugax), fundoscopic exam was performed, and was normal. No evidence of a cardioembolic source was identified. An extensive vasculitis panel was negative. Drug screen and blood/urine cultures, negative. Thrombophilia evaluation was negative, except an elevated serum homocysteine (Hcy) level of 46.6 mcmol/L. On day 5 renal doppler visualized flow within main renal arteries with normal resistive indices. Cr at discharge was 1.27 mg/dl.

Discussion: An extensive evaluation for the etiology of the ARI was negative with exception of a markedly elevated serum Hcy level. Hyperhomocysteinemia causes endothelial dysfunction and is a risk factor for cardiovascular disease. Hcy is an intermediary amino acid formed in methionine metabolic pathway. Elevated Hcy can be from genetic factors, reduced GFR, and drugs like fibrates and nicotinic acid. Although our patient had acute kidney injury, his level was higher than the reported mean for hemodialysis patients (20 mcmol/L), and it rose further post-discharge (99 mcmol/L). Because of this, empiric treatment with B12, folate, and B6 was started. This case emphasizes that Hcy levels should be included in the evaluation of idiopathic ARI.

PUB454

Cocaine-Induced ANCA Negative Vasculitis: A Diagnostic Dilemma

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Introduction: Cocaine is an addictive stimulant drug. In 2014, 913,000 Americans met the criteria for dependence or abuse of cocaine. Almost 69% of Cocaine is contaminated with Levamisole which has been found to be immunogenic with anti-neutrophil cytoplasmic antibody (ANCA) associated cutaneous vasculitis in 88-100% patients.

Case Description: 24-year old male with a history of substance abuse presented with bilateral lower limb weakness associated with burning pain and numbness in the right leg for 10 hours. He used cocaine one week prior to admission. Vitals were normal. See Table 1 for BMP. Labs also showed elevated SGOT of 1351 U/L, SGPT 460 U/L, elevated WBC. Urine analysis - pH 6.0, Hb 3+, RBC 14 and Protein 100. Renal ultrasound and Urine toxicology were negative. CPK levels (17,000 U/L) trended downwards. Urine microscopy showed muddy brown cast. Hepatitis serologies, Immunology including ANCA, C3, C4 were normal. Renal biopsy showed vasculitis, patchy interstitial edema along with focal collections of interstitial eosinophils. He was treated with hemodialysis and steroids.

Discussion: Cocaine can cause AKI by Rhabdomyolysis, Vasculitis, Platelet activation. Biopsy showed some focal vasculitis. Vasculitis in Cocaine abusers can be due to Levamisole, an anti-helminthic agent withdrawn due to multiple side effects. Levamisole is added to cocaine to enhance its euphoric effects. Levamisole induced ANCA positive vasculitis is well known. Our case is one of the few ANCA negative renal vasculitis responding to steroids. Levamisole is detectable in urine for only 5-6 hours making diagnosis challenging. The role of steroids in the treatment of this condition has not been established. This patient responded well to steroids likely due to presence of interstitial inflammation. Research is required to understand effective ways to treatment this condition. Until then, primary treatment continues to be cessation of drug use and renal replacement therapy if needed.

Basic Metabolic Profile

Sodium	135	136-145 mmol/L
Potassium	5.6	3.5-5.1 mmol/L
Bicarbonate	23	22-29 mmol/L
BUN	28	6-20 mg/dl
Creatinine	2.85	0.5-1.2 mg/dl
Glucose	115	70-140 mg/dl
Calcium	8.1	8.6-10.0 mg/dl

PUB455

Two Variants of Mickey Mouse Sign on Urinary Bladder Point-of-Care Ultrasound: One with the Tail and One Without

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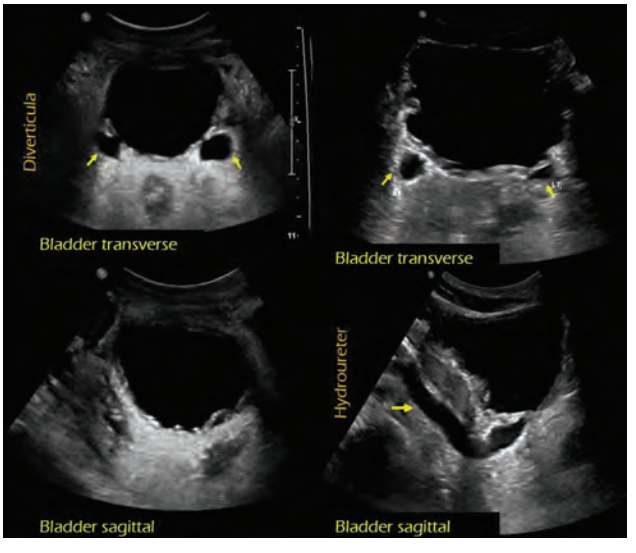
Introduction: For nephrologists, 'Mickey Mouse' by default reminds of dysmorphic red blood cells in the urine. With the increasing use of point-of-care ultrasonography (POCUS), we discuss the Mickey Mouse sign in the context of urinary bladder ultrasound. This case also illustrates the common POCUS aphorism, "one view is no view."

Case Description: A 72-year-old gentleman with a history of chronic kidney disease stage 5 secondary to autosomal dominant polycystic kidney disease, hypertension, and benign prostatic hyperplasia presented to the hospital with worsening signs of hypervolemia. He was also found to have worsening renal function compared to prior baseline, and nephrology was consulted for possible initiation of renal replacement therapy. On POCUS, the medical student reported that the patient had bilateral hydroureter. However, on a careful review of images and longitudinal scanning, the anechoic sac-like structures posterior to the bladder were found to be diverticula in the setting of chronic bladder outlet obstruction and not hydroureter [Figure: left panel is diverticula and right hydroureter]. Moreover, there was no hydronephrosis on either side.

Discussion: A bladder diverticulum is a sac or pouch that protrudes out of the bladder wall. Diverticulae may be congenital (primary) or acquired (secondary), and acquired diverticula from chronic bladder outlet obstruction are commonly encountered in the adult population. They appear as Mickey Mouse ears on bladder ultrasound, with the bladder representing the head. Hydroureter (s) can mimic diverticula in the transverse plane, but on the longitudinal scan plane, it usually appears as an anechoic tubular structure resembling the tail of the Mickey Mouse. Moreover, hydroureter is more likely to be associated with hydronephrosis than diverticula. Also, normal ureteric jets, that is a visualization of the normal physiological periodic efflux of urine on color Doppler will be seen with diverticula, while they are expected to be weak or absent in the case of a hydroureter.



PUB456

A Woman with Anticoagulant-Related Nephropathy (ARN): Recently Recognized AKI Syndrome

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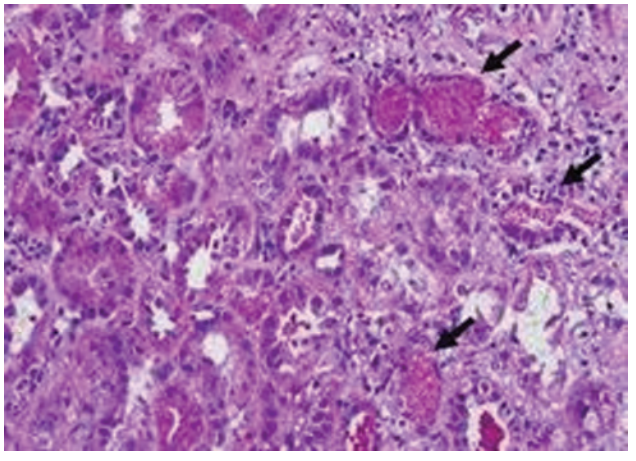
Introduction: Anticoagulant related nephropathy (ARN) is defined as an acute increase in international normalized ratio (INR) to >3.0, followed by evidence of acute kidney injury (AKI) within 1 week of the INR increase with no other obvious etiology. We present a case of a 65 year old female who developed AKI secondary to warfarin therapy.

Case Description: A 65 year old female with past history of protein S deficiency, hypertension and CKD stage 3 presented with blood in urine. She was found to have oliguric AKI with a supratherapeutic INR of 7.8 and Creatinine of 14.1 mg/dl while on warfarin therapy for multiple deep venous thrombi in the past. Home medications included warfarin and lisinopril. Review of systems was otherwise negative with no recent contrast administration. Exam was significant only for hematuria. Coagulation profile showed PTT of 46.9 seconds and PT of 82.5 seconds. All other labs were within normal limits. Several RBCs with RBC casts were seen on urinalysis. Urine protein creatinine ratio was 0.9. Ultrasound disclosed echogenic kidneys with no hydronephrosis. All medications including warfarin were held immediately on admission and despite volume resuscitation, BUN and Cr did not show any improvement. After 5 days of hospitalization her INR improved from 7.8 to 2.6 and Cr came down to 4.17 mg/dl. Renal biopsy revealed severe occlusion of renal tubules by red blood cells and casts with tubular cell damage consistent with acute tubular necrosis proving warfarin induced renal injury.

Discussion: There is growing evidence that ARN is a potentially serious complication of anticoagulation therapy. In addition to warfarin, there are several recent case reports that ARN can develop in patients on dabigatran or on apixaban. The recent retrospective analysis of RE-LY shed light on it as well. The higher prescription volume of anticoagulants, with lack of data on treatment for ARN, calls for large prospective trials.



PUB457

A Non-Respiratory Presentation of Sarcoidosis

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Introduction: Sarcoidosis is an inflammatory condition with presence of noncaseating granulomas. It can affect virtually every organ of the body and multiple triggers have been identified. A selection bias exists in the United States as most sarcoidosis clinics are run by pulmonologists and higher incidence is identified in African Americans who appear to develop more extensive and chronic pulmonary disease. Direct renal involvement occurs in less than 5% of sarcoidosis patients with granulomas seen in the kidney itself.

Case Description: A 28-year-old Nigerian male with past medical history of Malaria (treated in 2013) and Typhoid (treated in 2016) presented to the Emergency Department with acute renal failure with serum creatinine of 3.63mg/dL from baseline of 1mg/dL, 30lbs weight loss within two-month duration, myalgia, fatigue, and subjective low-grade fevers. He denied cough, shortness of breath, or any other respiratory symptoms. Renal ultrasound noted globular-shaped kidneys with increased echogenicity of the renal parenchyma. CT of the abdomen revealed prominent upper abdominal and retroperitoneal lymph nodes. Of note, the patient was found to be hypercalcemic with ionized Calcium of 6.2mg/dL, elevated 1,25-OH Vitamin D level of 78pg/mL and undetectable PTH, ANA negative, normal C3 and C4, and HIV non-reactive. The patient did not exhibit typical B-symptoms suggestive of underlying lymphoma and his flow cytometry was noted to be normal. During the work-up of his diagnosis, his renal function continued to decline and his serum creatinine peaked at 9.6mg/dL from 3.63mg/dL at presentation. Renal biopsy revealed chronic, active granulomatous tubulointerstitial nephritis. High resolution CT of the chest confirmed the mediastinal adenopathy and mild interstitial changes, consistent with sarcoidosis. However, through the course of his presentation, the patient did not develop respiratory symptoms.

Discussion: The risk of death or loss of organ function remains low in sarcoidosis and poor outcomes are typically limited to patients who present with advanced disease where irreversible fibrotic changes have occurred. Patients who require glucocorticoids in the first 6 months of presentation have a >50% chance of having chronic disease. This inspires vigilance on the physician to recognize the vast presentations, triggers, and genetic manifestations of patients diagnosed with this disease.

PUB458

Spontaneous Improvement Without Therapy in a Patient with Atypical Hemolytic Uremic Syndrome with p. I1157T in the C3 Gene Triggered by Influenza B Infection: A Case Report

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is a severe systemic disease characterized by thrombocytopenia, hemolytic anemia, and acute kidney injury. It has a poor prognosis, and the mortality rate was as high as 25% before the introduction of eculizumab therapy. In 50-80% of patients, an infectious event triggers the onset of aHUS. Among such triggers, influenza infection is relatively common, but most cases are of the H1N1 type or influenza A, and influenza B is only very rarely responsible.

Case Description: The patient was a 15-year-old boy who presented with a 2-day history of fever and macrohematuria, but no diarrhea. A nasal swab demonstrated positivity for influenza B virus antigen. On admission, he showed hemolysis with red blood cell fragmentation in a blood smear (LDH 1478 U/L, haptoglobin 6 mg/dL, Hb 13.8 g/dL), thrombocytopenia ($17x10^3/\mu L$) and acute kidney injury (serum creatinine 0.95 mg/dL) The serum creatinine level improved to 0.63 mg/dL in the recovery phase on day 11 after admission, and therefore the acute kidney injury was diagnosed as AKI stage 1 by KDIGO. These findings suggested incomplete TMA. ADAMTS13 activity was normal and a stool culture test failed to identify Shiga toxin-producing *Escherichia coli* or Shiga toxin 1 and 2. As manifestations such as hemolytic anemia and acute kidney injury were mild, the patient received peramivir hydrate for influenza B infection without plasma therapy or eculizumab therapy. He recovered and was discharged with no sequelae on hospital day 7. No relapse was observed for over 1 year. Subsequent genetic analysis identified mutation in *C3 (p.I1157T)*, confirming a diagnosis of aHUS.

Discussion: The symptoms in the present case were mild and improved spontaneously without specific therapy including plasma exchange or eculizumab. Japanese patients with *C3 p.I1157T* mutation, which was identified in this case are reported to show a favorable prognosis, and spontaneous recovery of an aHUS patient with MCP mutation triggered by influenza B has been documented. The data suggest that a mild defect of complement regulation including *C3 p.I1157T* resulted in the present patient's mild aHUS symptoms.

PUB459

Cardio-Renal Syndrome: Clinical Predictor of AKI

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Introduction: Acute tubular necrosis (ATN) is one of the most common causes of acute kidney injury (AKI) in hospitalized patients. Chronic pathophysiological changes in renal hemodynamic from an underlying cardiac disease named cardio-renal syndrome (CRS) is one of the risk factors of AKI. Nephrotoxic ATN can occur in patients who are at risk even in those with normal renal function. Close monitoring for renal function should prevent and early diagnose for AKI. We report a case of a middle-aged African American woman with chronic congestive heart failure(CHF) who received multiple nephrotoxic agents without judicious renal function monitoring and subsequently had a delay in diagnosis for non-oliguric AKI.

Case Description: A 43-year-old African American woman with a past medical history of advanced systolic heart failure secondary to mitrial valve (MV) regurgitation status post prostatic MV replacement and automatic intracardiac device (AICD) presented with fever. She developed acute decompensated heart failure and was found to have prosthetic acute MV endocarditis. Rifampicin, gentamicin, and cefazolin were initiated and the AICD was removed. She was diuresed with IV bumetamide. Her baseline serum creatinine (SCr) was 0.9-1.1 mg/dL, which had been stable until hospital day (HD) 15 when renal function was no longer checked. On HD 18, she had head and carotid CT angiography for pre-heart transplant work-up. Four days later, urine output (UOP) decreased to 460 ml/day and SCr increased to 5.44 mg/dL. She did not have hypotensive episode and sign of dehydration. A renal ultrasound showed bilateral cortical echogenicity without sign of obstruction. Unianalys revealed protein of 30 mg/dL and 1 RBC/HPF. FE_{Na} was 6.99%. Gentamicin was discontinued given its supratherapeutic level of 2.3 μg/mL. IV bumetanide was held. Followed-up daily renal function showed a gradually decreased SCr and an increased UOP.

Discussion: Our patient presented with AKI which is secondary to nephrotoxic ATN from gentamicin and IV contrast exposure. Although she had normal baseline SCr, her underlying CHF can contributed to renal hemodynamic impairment from type 2 CRS. The renal ultrasound supports underlying chronic kidney disease (CKD). Therefore, renal function should be closely monitored in such a high risk patient who has underlying CRS especially while receiving nephrotoxic agents in order to prevent and early diagnose for AKI.

PUB460

Wunderlich Syndrome as a Cause of Acute Low Back Pain and Hematuria: Case Report

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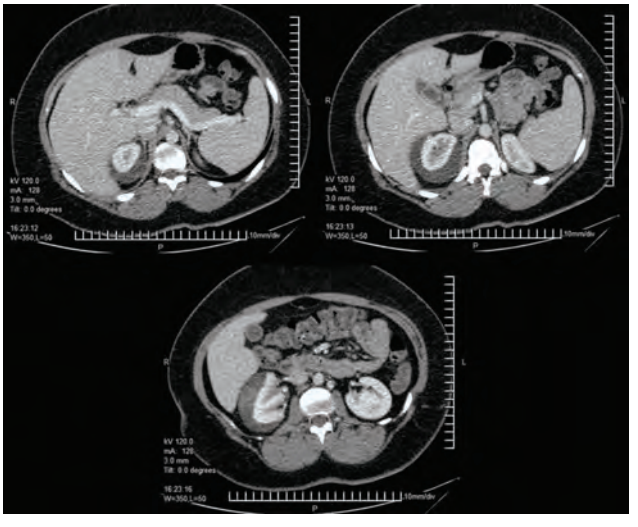
Introduction: Wunderlich's syndrome is a rare event characterized by spontaneous perinephric / subcapsular hematoma. Characteristically presents the presence of pain in the flank or in all the abdomen, retroperitoneal mass and signs of hemorrhage. In most cases only nonspecific signs such as fever, nausea, vomiting and weight loss are seen.

Case Description: M.C.B, female, 23 years old presented with sudden pain throughout the abdomen with a predominance of posterior lumbar region, without irradiation, being at rest and without signs of local trauma. She also reported daily fever, nausea, and hyporexia. She sought emergency care where she had been given several medications but without remission of pain. No anemia and no leukicitosis were shown but C-reactive protein was high and urine summary leukocyturia and hematuria, therefore she was treated with antibiotics. A ultrasound was performed and found a hyperechogenic image with perirenal. CT scan of the abdomen found a subcapsular hemorrhage with perirenal hematoma in various degrees of evolution, evidencing compact hyperdense areas. An arteriography was performed with a right kidney supplied by a single artery, of normal size, without stenosis and seen deviation of the right kidney, which may correspond to extrinsic compression, with homogeneous parenchymal phase, with usual venous drainage. No arteriovenous shunt or contrast extravasation after selective catheterization of renal artery. Wunderlich's syndrome was confirme due to presence of spontaneous perirenal hematoma imaging and without other causal factors, she was released with conservative treatment and monthly follow-up with outpatient pain control, with the urology service.

Discussion: We describe a case that should be remembered as a differential diagnosis of non-traumatic low back pain associated with hematuria.



PUB461

Can Preventing the Flu Harm You? Unusual Case of Oseltamivir-Induced Acute Renal Failure Without Rhabdomyolysis

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Introduction: Oseltamivir is a neuraminidase inhibitor used for treatment of Influenza A/B and as chemoprophylaxis. Its use has been increasing after H1N1 pandemic in 2009. It works by attacking the flu virus to keep it from multiplying in your body and by reducing the symptoms of the flu. Side effects include nausea, vomit, headache, stomach upset and rarely renal failure. We report the unusual case of acute renal failure needing hemodialysis after being treated with Oseltamivir.

Case Description: We report the case of an 87-year-old female with past medical history of Diabetes Mellitus who presented to the Urgency Room complaining of 1 -day cough, fever, rhinorrhea and general malaise. Denied nauseas, vomit, abdominal pain, dysuria, chest pain, shortness of breath or edema. Laboratory results were remarkable for creatinine: 1.12 mg/dl, Urea: 24 mg/dl for a GFR: 33ml/min. No electrolyte anomalies. Urinalysis without bacteriuria, pyuria, microscopic hematuria or casts. Influenza rapid test was negative, but due to highly suspected diagnosis of Influenza, Oseltamivir 30mg twice daily was prescribed upon discharge for 5 days. Two-weeks later, patient returned to the Urgency Room with complaints of worsening hypoactivity, anorexia, gradual decrease in urinary output and disorientation for the last 4 days. Patient completed Oseltamivir without complications. This time, laboratory results showed a BUN: 116 mg/dl with Creatinine: 10.88 mg/dl, for a GFR: 3ml/min. Hyperkalemia 8.30 mEq/L not-hemolyzed and bicarbonate 8mEq/L. CPK: 199U/L. Renal sonogram without obstructions. Patient was diagnosed with Oseltamivir induced acute renal failure since other causes were ruled out.

Discussion: Oseltamivir (Tamiflu) is a neuraminidase inhibitors recommended for Influenza A and B, as well as for prophylaxis. Dose is adjusted renally to avoid kidney injury since is excreted renally. Most common side effects include nausea, vomit and abdominal disconmfort, but renal failure is rarely seen. In our case, patient ended with chronic renal replacement therapy after taking medication and no other causes were found. Caution should be taken when taking it as prophylaxis. No report has been found related as renal failure due to oseltamivir given as prophylaxis.

PUB462

Libido Enhancing Herbal Supplementation-Induced Acute Interstitial Nephritis

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Introduction: Acute interstitial nephritis (AIN) results from kidney injury characterized by inflammation in the kidney interstitium, often in the setting of exposure to offending medications[1,2]. We report a case of AIN in a healthy male after routine colonoscopy with exposure to multiple non-prescribed herbal medications.

Case Description: A 52-year-old previously healthy male on multiple herbal supplements including black maca, Tongkat Ali extract, Mucuna extract, and saw palmetto to increase libido presented to the hospital with acute kidney injury (AKI) approximately one month after a routine screening colonoscopy. The patient had no known kidney disease prior to his procedure. Post colonoscopy, he developed right sided flank pain followed by weight loss and anorexia. Labs were notable for creatinine of 4.06 mg/dL, Urinalysis with glucosuria, proteinuria and moderate leukocytes, with rare eosinophils in the urine. Renal ultrasound showed normal kidney sizes. Kidney biopsy was consistent with acute allergic interstitial nephritis, with mild interstitial fibrosis or tubular atrophy. Kidney function improved with cessation of all herbal supplements and treatment with prednisone.

Discussion: This case illustrates a rare cause of acute interstitial nephritis induced from herbal supplements and to the best of our knowledge has not been well reported in the literature. There is little known about the safety profile of these medications and the mechanism in which they induce such injury. Thorough history taking is imperative on part of clinicians to be able to identify these medications (that are often not reported initially), especially by nephrologists in settings where kidney injury cannot be explained by other processes. This allows for early diagnosis, kidney biopsy if possible, avoidance of future use of the medications, and prompt initiation of treatment in hopes to prevent long-term kidney damage.

PUB463

Mycophenolate Mofetil in an Atypical Granulomatous Pattern of Tubulointerstitial Nephritis and Uveitis Syndrome

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Introduction: Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disease in which the underlying physiopathology is to date poorly understood though some hypothesize that infection, drugs and autoimmunity are involved. Diagnosis criteria exists and categorize TINU as definite when typical ophthalmologic features are present 2 months before or 12 months after tubulointerstitial nephritis (TIN), in the absence of other systemic disorder. Pathologically tubulointerstitial nephritis is always found as a constant. Granulomas are rare.

Case Description: We report a 31-years-old woman who came for fatigue, headache, fever, ophthalmic pain, weight loss and acute kidney injury (AKI) (plasma creatinine (PCr) 2 mg/dL). She had no medical condition except for a recent history of hypertension treated by nifedipin. Renal biopsy showed TIN and several, small non-necrotizing granulomas. Concomitantly, bilateral anterior uveitis with several, small granulomas was found. Laboratory tests showed high levels of C-reactive protein. Infectious serology and autoimmune screening were negative. Nifedipin was discontinued for more than 2 weeks regarding the possibility of drug-induced interstitial nephritis without, however, improvement of the renal function. Patient was therefore diagnosed with TINU syndrome after excluding other differential diagnosis such as tuberculosis, sarcoidosis and drug-induced TIN. As renal function declined (PCr 3.7 mg/dL), we started steroid puls for 3 days followed by daily oral progressive tapering. After 7 months, renal function normalized (PCr 0.88 mg/dL) and ophthalmic features were completely healed. Severe ophthalmologic relapse and creatinine increase motivated introduction of mycophenolate mofetil and resulted in rapid clinical improvement of pan-uveitis and renal function.

Discussion: There is no evidence-based guidelines regarding TINU treatment, however systemic steroids are widely used and renal outcome is usually good. Granulomatous pattern of TINU syndrome has been only rarely reported. It differential diagnosis can be very challenging because both TINU and sacroïdosis are diagnosis of exclusion. Here we suggest that Nifedipine can be a trigger for TINU syndrome. Also we report the potential benefit of MMF.

PUB464

Physiology or Pathology? An Interesting Case of Rise in Serum Creatinine in a Female-to-Male Transgender Patient

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Introduction: Transgender hormone therapy is a mainstay in the management of gender incongruence. Female to Male (FTM) transgender individuals are typically maintained on testosterone to induce a phenotype that matches their identity. Testosterone is known to have multiple renal adverse effects including tubular injury and FSGS. We present an interesting case of FTM transgender with a benign creatinine elevation while on testosterone and discuss the interpretation of serum creatinine (sCr) in transgendered individuals.

Case Description: A 36yo FTM transgender patient with past medical history of TIA secondary to PFO on clopidogrel was referred to our Nephrology clinic for consultation for an elevation in sCr. A review of records shows that his sCr has fluctuated between 1.1 and 1.3 mg/dl over the preceding 8 years. He denied any acute changes in health, recent or remote NSAID use, no LUTS. His only medications are clopidogrel, dextroamphetamine, and testosterone. Urinary microscopy was negative for cellular elements or casts. Urinary microalbumin/creatinine ratio was 3.8 mg/g. The most recent sCr was 1.3, estimating a GFR of 53 ml/min via the CKD-epi equation. A 24 hour urine collection was performed and the 24 hr urinary creatinine clearance was found to be 92 ml/min.

Discussion: Creatinine elevations in the setting of testosterone therapy can represent physiology or pathology. Acute kidney injury due to testosterone has a differential diagnosis including ATN, FSGS while a physiologic increase in skeletal muscle mass may result in increased creatinine generation. A careful examination of the urine and measurement of urinary protein excretion can help differentiate pathology and physiology. A 24 hour urine creatinine to estimate creatinine clearance was diagnostic in our patient of a state of altered physiology, not pathology. Interestingly, the creatinine clearance more closely approximated the CKD-Epi estimation of the male gender, not female gender in our patient. This experience was also seen in two case series of metabolic parameters during transgender hormone therapy, in which sCr was shown to rise 19-42% after initiation of therapy. In estimating eGFR in FTM patients on transgender hormone therapy, we recommend the male gender in calculations.

PUB465

NSAID Use Associated with Bilateral Renal Infarction: A Case Report

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Introduction: Renal infarctions are caused by interruptions in renal arterial blood flow, and are relatively rare. We present the case of a 37 year old woman whose renal infarction was likely due to the vasoconstrictive effects of non-steroidal anti-inflammatory drugs (NSAIDs). Although high-dose NSAIDs are known to cause a decrease in renal perfusion, they are generally not implicated in renal infarction.

Case Description: A 37-year-old woman with a history of cholestasis during pregnancy presented to the emergency department with acute on chronic abdominal pain. She was given 60 mg of intravenous ketorolac, and discharged on ibuprofen 600 mg every 6 hours as needed. Her pain persisted and she returned 7 days later. Her vital signs were normal with mild hypertension. Physical examination was notable only for diffuse abdominal pain. Initial labs showed new acute kidney injury (AKI) and bland urinalysis. ESR and CRP were elevated; LDH was normal. Cardiac and hypercoagulability workups were normal. Computed Tomography (CT) scan revealed bilateral renal infarction, corroborated on renal ultrasound with doppler. The patient was treated with volume resuscitation. She was not anti-coagulated. She was discharged 3 days after admission with moderate improvement in creatinine. Follow-up 14 days after discharge showed normalization of creatinine.

Discussion: Despite imaging studies qualifying a diagnosis of renal infarction, LDH was normal, suggesting that the extent of renal tubular damage was not as profound as the imaging suggested. This is also supported by the improvement in renal function with only fluid resuscitation and no anticoagulation. Furthermore, workup for infectious, cardiogenic, autoimmune, renovascular, or hypercoagulable etiologies was negative. NSAID medication taken prior to presentation was thus the most likely causative factor. Mechanistically, hypovolemia prior to presentation may have caused a prostaglandin-dependent state, thus causing renal hypoperfusion when NSAIDs were introduced. To our knowledge, only one other similar case report exists in the literature, and this phenomenon may be more common than previously thought.

PUB466

Toxic RBC Casts as the Culprit of Irreversible AKI in IgA Nephropathy

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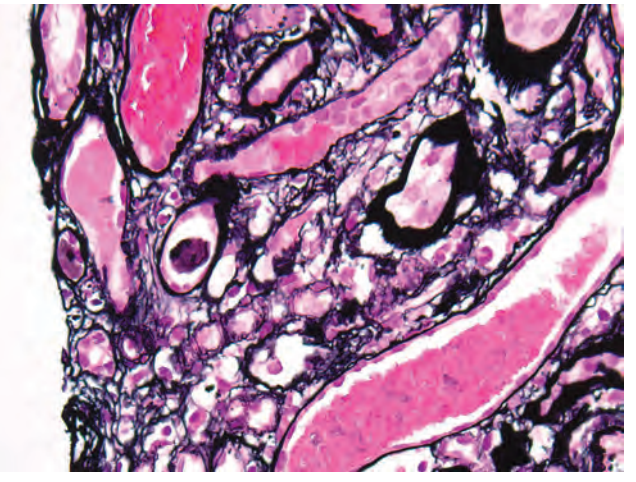
Introduction: Acute tubular necrosis(ATN) driven by RBC casts occurs in 20% cases of IgA nephropathy (IgAN). Similar mechanism of AKI is observed in Henoch-Schonlein nephropathy, thin basement membrane disease and anticoagulation related nephropathy. Eventhough, glomerular hematuria in the absence of proteinuria is considered a benign entity without long term renal impact, upto 25% of patients with macrohematuria related AKI have incomplete renal recovery. Poor prognostic factors include increased age, prolonged duration of hematuria, severity of ATN and degree of interstitial fibrosis.

Case Description: A 50 year old male with cryptogenic cirrhosis presented with AKI. He had flu like symptoms 2 weeks before presentation. Workup revealed elevated creatinine of 3.4mg/dl from a baseline of 1mg/dl. Urinalysis showed >25 RBC and protein:Cr ratio of 1.1g. On urine microscopy, dysmorphic RBCs and RBC casts were seen. Serological workup showed low C3 (77mg/dl), normal C4 and elevated ASO(476 IU/ml). Renal biopsy showed RBC casts and tubular vacuolization. IgA and C3 deposits were seen on immunofluorescence consistent with mesangioproliferative IgAN. Crescents were absent and there was minimal interstitial fibrosis. Scant subendothelial deposits were present on electron microscopy. Immunosuppression use was deferred in the absence of glomerular involvement and history of spontaneous bacterial peritonitis. Low dose lisinopril was initiated. After 3 months Cr had declined to 2.3.

Discussion: The ability of toxic RBC casts to independently cause AKI in the absence of glomerular involvement tends to be overlooked, but is now being increasingly recognized in cases of anticoagulant nephropathy. Intra tubular obstruction by RBCs, direct tubular toxicity by hemoglobin(Hb) byproducts and intra renal vasoconstriction play a role. Data on specific therapy is scarce and the role of renal heme oxygenase and Hb scavenging by CD163 receptors on tissue macrophages may provide a potential avenue for future therapeutic ventures.



PUB467

Subclinical Urea Cycle Defect Discovered in Pregnancy

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Introduction: We report a subclinical urea cycle defect (UCD) which manifested clinically in pregnancy. Mild variants of UCDs, often (-) by genetic analysis, can occur via a second hit leading to a high morbidity and mortality if not recognized.

Case Description: 33 YO G1P0 with no known PMHx presented at 35 weeks twin gestation w/ altered mental status & decreased fetal movement. BP 174/90, lethargy, 1+ edema. Labs: WBC 14, Hgb 5.4, Hct 15.3, platelets 33 (periph smear mod schistocytes), LDH 1359, haptoglobin<4 BUN 36, SCr 3.89, Alb 1.9, AST 348, ALT 182, Tbili 9.6 (conj 8.1), Lactate 8.0, NH3 61, INR 3.9. ADAMTS13 42%. UA 1+ prot +1 bld 3-5 rbcs. Up/c 410 mg/g. U/S confirmed fetal demise. She developed seizures & was emergently taken to C-section. She was listed for liver transplant & started on CVVH. She developed bowel ischemia requiring emergent colectomy. Within 1 week, her encephalopathy, kidney & liver failure resolved. CVVH was held, & her LFTs, NH3 and INR normalized w/out liver transplant. She began rehab w/ nutritional support via TPN & became obtunded with an NH3 of 375. Emergent HD was performed for NH3 clearance with improvement in her mental status. She was rechallenged with TPN & again developed encephalopathy with isolated hyperammonemia despite normal liver U/S, LFTs, INR and CBC. This eventually resolved by limiting protein in her TPN. Genetic analysis for Ornithine Transcarbamylase Gene (OTC) was (-).

Discussion: Our patient presented with acute fatty liver of pregnancy with hepatic encephalopathy & HELLP syndrome with eclamptic features. After delivery & supportive care, she improved. As isolated hyperammonemia with encephalopathy recurred after TPN, a subclinical UCD was suspected but testing was (-) for OTC. This test is only positive in 80% of cases andother enzymes in the urea cycle such as Carbamyl phosphate synthetase I, argininosuccinate lyase, or argininosuccinate synthetase could have been abnormal. Most UCDs present in the neonatal period from complete absence of these enzymes. When there is only partial deficiency, the symptoms often arise in adulthood after a second hit such as pregnancy. Genetic testing, especially with partial deficiency, can be (-), but the disease should be considered when there is isolated hyperammonemia & encephalopathy, especially after a protein load, in the absence of liver disease.

PUB468

Dabigatran-Associated Acute Interstitial Nephritis

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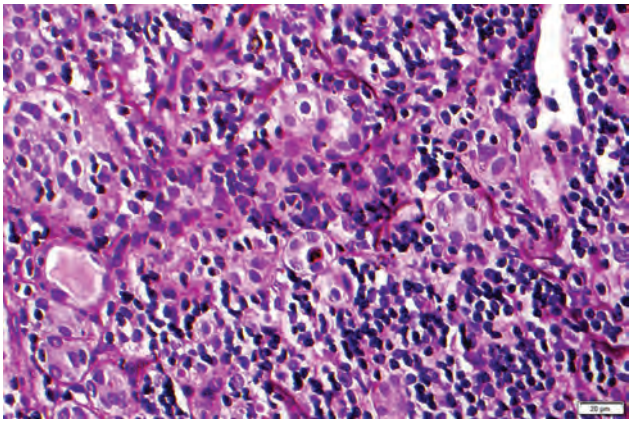
Introduction: There are few case reports of acute interstitial nephritis (AIN) in the setting of novel oral anticoagulants (NOACs). One described a patient on dabigatran who developed biopsy-proven AIN; another described a case of apixaban-related AIN. The mechanism of NOAC-associated AIN is unclear.

Case Description: A 79-year-old male with history of right RCC s/p nephrectomy in 2014, atrial fibrillation, and hypertension presented with 3 days of hematuria. He became anuric 24 hours prior to admission. His home medications were atorvastatin, dabigatran, and metoprolol; dabigatran was held on admission. Labs were significant for serum creatinine 11.7 mg/dL, BUN 107 mg/dL, potassium 7.2 mEq/L, INR 2.9, PTT 75 seconds; prior serum creatinine was 1.2 mg/dL. EKG showed peaked T-waves and hyperkalemia was treated medically. CT abdomen w/o contrast showed no hydronephrosis. Urinalysis showed specific gravity 1.020, pH 6.0, 4+ protein, moderate blood, >100 RBC/hpf, 5-10 WBC/hpf, and no cellular casts. Serologic studies were negative. Renal biopsy was recommended but due to coagulopathy and a solitary kidney, biopsy was postponed. The patient was initiated on hemodialysis (HD) for hyperkalemia and discharged. Two months later, he remained HD dependent, coagulopathy corrected, and he was readmitted for kidney biopsy. Biopsy showed acute and chronic interstitial nephritis. There was acute tubular injury with 4 out of 15 glomeruli globally sclerotic. The etiology of his tubular damage may have been secondary to anticoagulant-related nephropathy (ARN) although classic biopsy features of glomerular hemorrhage and renal tubules filled with RBC casts were not seen.

Discussion: This case expands the differential of AKI in the setting of anticoagulation to include not only ARN with associated acute renal tubular injury but also AIN. Despite stopping dabigatran and treatment with steroids for the past 12 weeks, there has been no renal recovery to date.



Biopsy showing acute and chronic interstitial nephritis.

PUB469

AKI After Advanced Heart Failure Therapy May Be Unrelated to Renal Perfusion

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Introduction: The prevalence of advanced heart failure (AHF) is increasing due to the growing number of patients with heart failure (HF) and their improving survival. Percutaneous left ventricular assist device (PVAD) is a small axial flow pump that is placed across the aortic valve. It aspirates blood from left ventricle (LV) and expels it into the ascending aorta, hence unloading LV and improving hemodynamics. Renal function impairment is prevalent among patients with AHF but often improves after PVAD placement due to enhanced organ perfusion.

Case Description: A 48-year-old man with a history of HF with reduced ejection fraction (15-20%) and chronic kidney disease stage III-b was admitted for acute HF and cardiogenic shock, for which he received a PVAD (Impella 2.5) that stabilized his hemodynamics. However, within 24 hours, he developed acute kidney injury (AKI) and hyperkalemia of 7.2 meq/L mandating his transfer to our facility. Upon arrival, his serum potassium and creatinine levels were 6.7 meq/L and 4.5 mg/dL respectively with marginal urine volume. Renal replacement therapy (RRT) was started. Since AKI had developed unexpectedly after PVAD, a comprehensive workup was performed to explore its etiology. It revealed severe hemolysis with a drop in Hemoglobin by 1.3 g/dl within 7 hours, LDH 3233 IU/L, haptoglobin <30 mg/dl, and reticulocyte count up to 3.1% suggesting pigment-induced nephropathy as the cause of AKI. Due to traumatic placement of a Foley catheter and bleeding, urine studies were not reliable. The decision was made to retrieve the Impella device and replace it with an intra-aortic balloon pump to stop hemolysis. Six hours after the procedure, the patient's LDH level decreased to 1864 IU/L, followed by progressive increase in urine output; RRT could be discontinued 3 days later.

Discussion: While low renal perfusion is the primary reason for AKI in the setting of AHF, this case highlights a much less evident but reversible cause which could remain undetected unless specifically looked for. PVAD-induced hemolysis can be due to shear stress or improper positioning of the outlet in the subvalvular area. Development of pigment-induced AKI has been reported in only a handful of cases so far. High index of suspicion would be warranted in those unexpected cases of AKI developing after PVAD implantation especially if hemodynamic status is stabilized.

PUB470

Paroxysmal Nocturnal Hemoglobinuria: An Uncommon Cause of AKI

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Introduction: Acute Tubular necrosis (ATN) is one of the common causes of acute kidney injury (AKI) seen in hospitalized patients. We are reporting a case of Acute tubular necrosis (ATN) due to Paroxysmal nocturnal hemoglobinuria. The release of free hemoglobin during hemolysis causing renal vasoconstriction, methemoglobin formation, renal hemosiderosis and proximal tubular toxicity causes acute kidney injury (AKI) in Paroxysmal Nocturnal Hemoglobinuria.

Case Description: A 20 year old man with a 5 month history of isolated hematuria presented with symptomatic anemia. On admission, he was found to have acute kidney injury (AKI) with a serum creatinine of 5.3 mg/dl and had evidence of intravascular hemolysis (hemoglobin 6.4 g/dl, low haptoglobin levels <20 mg/dl, high LDH levels 3533 U/L with absence of schistocystes on peripheral smear and negative direct Coomb's test). Urine analysis was positive for a large amount of blood with few red blood cells present on urine microscopy. A subsequent kidney biopsy revealed abundant pigment casts, severe tubular injury and abundant positive CD163 positive staining macrophages. The diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) was confirmed by flow cytometry PNH panel. After initiation of treatment with Eculizumab, the patient developed improvement in kidney function and reduction in intravascular hemolysis.

Discussion: Educate clinicians about uncommon causes of acute kidney injury. Understand the impact of Eculizumab on kidney function.

PUB471

Ileus, Cystitis, and Obstructive Uropathy: An Unusual Presentation of Lupus

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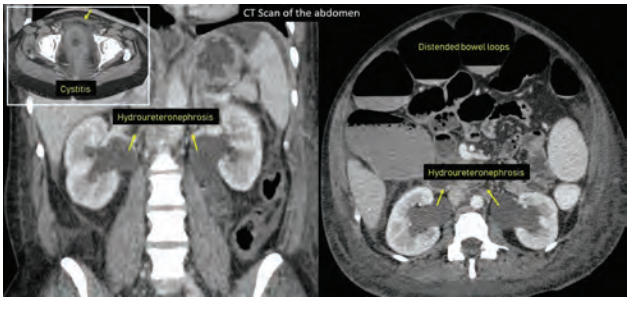
Introduction: Systemic lupus erythematosus (SLE) has been reported to be associated with intestinal pseudo-obstruction and obstructive uropathy. Herein, we present the case of a patient with no known history of lupus who presented with these atypical manifestations.

Case Description: A 35-year-old woman with history of mixed connective tissue disease and hypertension presented with worsening lower extremity edema and abdominal distension for about a week. Blood pressure at presentation was 147/109 mmHg and she was afebrile. Laboratory data showed AKI with a serum creatinine of 2.56 mg/dL and thrombocytopenia with a platelet count of 42 thou/cu mm. Urinalysis was positive for 3+ proteinuria, without pyuria or hematuria. A CT scan of the abdomen demonstrated significant ileus, bilateral hydronephrosis, hydroureter and cystitis. There was no obvious structural cause for intestinal obstruction. Serum potassium was normal. The hydroureteronephrosis did not resolve completely despite ureteral stent placement and attempts at intestinal decompression. Because of persistent AKI, proteinuria and thrombocytopenia, further work up was obtained which was significant for positive ANA titer of 1:1280, decreased serum complements. Urine albumin-creatinine ratio was ~1g/g and anti-dsDNA antibodies were negative. As SLE can present with autoimmune cystitis, obstructive uropathy and intestinal pseudo-obstruction, we intended to treat her empirically with immunosuppressants without renal biopsy because of thrombocytopenia. However, she developed sepsis and became acutely ill prior to therapy. Interestingly, urine culture remained negative, suggestive of autoimmune cystitis together with urinalysis findings.

Discussion: High index of suspicion is required for atypical manifestations of SLE, especially in patients with a history of another autoimmune disorder. The underlying pathology of intestinal obstruction is incompletely understood but possibly related to immune complex deposition. Coexisting hydroureteronephrosis suggests there may be a central smooth muscle motility issue of neuropathic or myogenic nature.



PUB472

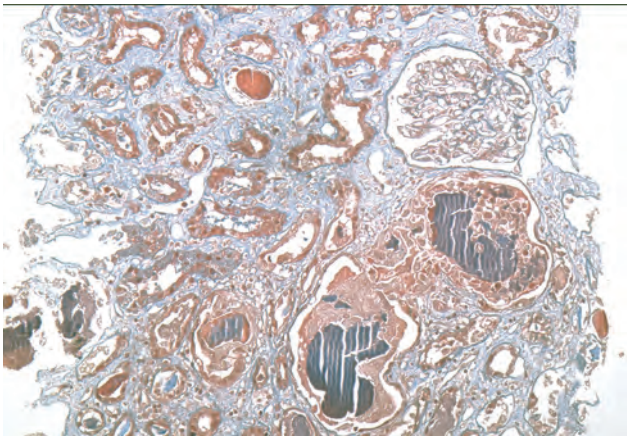
Leukocyturia: Not Always a Urinary Infection

Kelly Haughton. *Nephrology, Complejo Hospitalario Dr. Arnulfo Arias Madrid, Panama, Panama.*

Introduction: The increased presence of white blood cells in the urine, leukocyturia, can be interpreted as a urinary infection; however, the absence of a typical clinical picture accompanied by acute kidney injury and other findings in the urine may be the key to reach the actual diagnosis.

Case Description: A 32-year-old woman with no known pathologie went to the ER with constitutional symptoms, no fever. She was evaluated repeatedly before admission and prescribed with antibiotics for suspected urinary infection. Is hospitalized when the condition was accompanied by anasarca and increase in creatinine from 1.7 to 6.44 mg/dl. The diagnosis of acute kidney was made. Urinalysis 2+ albuminuria. Urinary sediment: leukocyturia and red blood cell cylinders. Renal ultrasound, normal size with increased echogenicity. A renal biopsy was performed, finding kappa light chain cylinders in the tubules as well as tubulointerstitial atrophy without glomerular involvement. The diagnosis of cast nephropathy was made and serum protein electrophoresis was performed, finding a monoclonal peak by free kappa chains. Bone marrow biopsy with 20% of mature plasma cells. The definitive diagnosis of Multiple IgG kappa myeloma with associated cylinder nephropathy (myeloma kidney) is made. Currently with clinical improvement; creatinine at 1.78 mg / dl after chemotherapy and awaiting for autologous bone marrow transplantation.

Discussion: The approach of leukocyturia without a typical clinical picture of urinary infection must include other renal diseases in the differential diagnosis. Renal disease is a common complication of monoclonal gammopathies secondary to the deposition of light chains in different compartments of the kidney in this case a "myeloma kidney". The evaluation of the urinary sediment rapidly ruled out the infectious diagnosis and determined the need for a renal biopsy. The approach of these patients involves a multidisciplinary team and timely diagnosis is key to give effective treatment of the underlying pathology.



PUB473

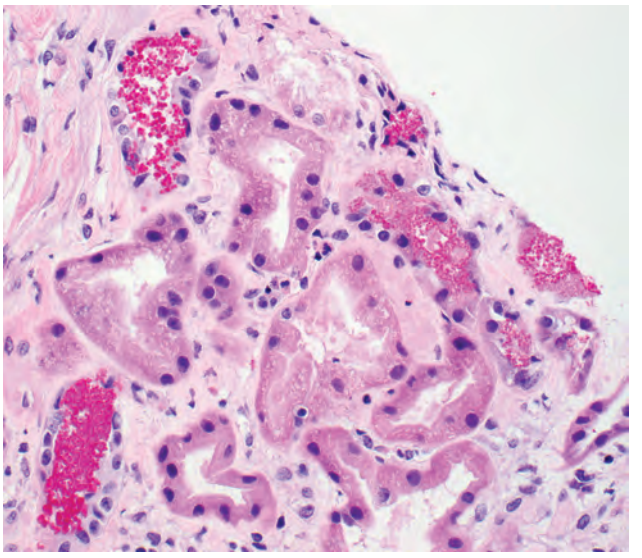
AKI Transurethral Resection of the Prostate Secondary to Pigment Nephropathy

Alice Chedid, Sadichhya Lohani, Jose M. Monroy-Trujillo. *Johns Hopkins University, Baltimore, MD.*

Introduction: AKI post TURP can be caused by intratubular precipitation of hemoglobin pigment secondary to hemolysis after the use of hypotonic solutions for irrigation during TURP.

Case Description: 78 year old male with history of atrial fibrillation and BPH presented to ER on same day after being discharged post TURP with generalized fatigue. Labs were relevant for serum Cr of 2.2 mg/dl (baseline 1.1 mg/dl prior to surgery). Physical exam unremarkable with clear lungs, benign abdomen and no lower extremity edema. Foley catheter in place with bloody urine. There was Initial concern for obstruction post TURP, however, CT scan revealed diffuse urinary bladder wall thickening and no evidence of hydronephrosis. Hospital course relevant for progressive renal failure with creatinine peak of 12.0 mg/dl at day 8. Relevant labs showed drop of hemoglobin from 15.4 gm/dl (pre-surgery) to 12 gm/dl (POD2) and LDH of 702 units/L. Haptoglobin 9 mg/dl (low). There was concern for hemolysis leading to pigment nephropathy. Patient underwent kidney biopsy on day 3: Acute tubular injury with intratubular hemoglobin casts. Mild interstitial inflammation (figure 1&2). Renal function improved with conservative management and creatinine began to improve by day 9. He did not require renal replacement therapy and latest creatinine is 1.6 mg/dl.

Discussion: Pigment nephropathy should be considered in any patient who presents with AKI post TURP procedure who develops renal failure and no evidence of obstruction is found on imaging studies. The use of hypotonic fluids for irrigation during the procedure and the presence of hemolysis on lab workup will help in diagnosis. The prostatic plexus can reabsorb significant amount of fluid during TURP. If hypotonic solutions are used, then there can be significant hemolysis leading to pigment nephropathy. Treatment is usually supportive and includes monitoring for dialysis needs.



Intratubular obstruction

PUB474

An Unusual Cause of Hypercalcemia

Luis A. Vazquez Zubillaga,[1] Saul N. Gonzalez Montalvo,[1] Naveen Punchayil narayanankutty,[1] Ragi Philips,[1] Catarina Regis,[1] Zain Mithani.[2] *[1]Jackson Memorial Hospital, Miami, FL; [2]University of Miami, Miami, FL.*

Introduction: Hypercalcemia above 14 mg/dL is often associated with malignancy, but patients with HIV need further investigation for opportunistic infections from granulomatous diseases such as *Mycobacterium Avium Intracellular* (MAI). Previous reports in the literature showed the association between MAI and hypercalcemia. We present a case of MAI infection causing hypercalcemia.

Case Description: 42 year-old male recently diagnosed with HIV/ AIDS (CD4 61) presents to the ED complaining of 4-month history of fevers, night sweats, diarrhea and twelve-pound weight loss. The patient was found to have subcentimeter hilar lymphadenopathy and bilateral pulmonary nodules, the largest measuring 1.2 cm. The patient underwent bronchoscopy with BAL analysis showed MAC. He was started on ethambutol and clarithromycin. The hospitalization course was complicated by non-oliguric acute kidney injury stage 3 with hypercalcemia of 16.3 mg/dL. Since there was no improvement with hydration and diuretics, hemodialysis was started with appropriate response. Hypercalcemia work up showed suppressed PTH and elevated 1,25-DIOH vitamin D levels, suspect secondary to increased production of calcitriol due to granulomatous disease.

Discussion: Hypercalcemia is a known complication of granulomatous disease, so clinicians should be aware of the variability in presentation of hypercalcemia with MAI. This case showed an atypical presentation of hypercalcemia in the setting of MAI infection. HIV patients who develop hypercalcemia should be investigated for this underlying infection.

PUB475

A Case of Obstructive Nephropathy After Endovascular Aneurysm Repair

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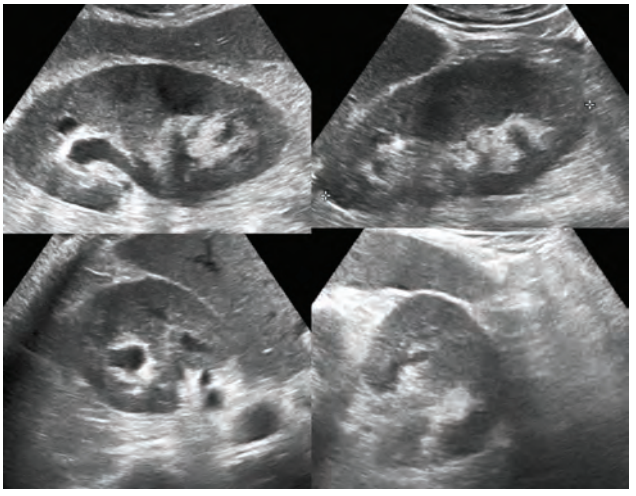
Introduction: Acute kidney injury develops in 3-19 % of patients following abdominal endovascular aneurysm repair (EVAR). We present a case of osbtrcutive nephropathy related to post implantation inflammatory syndrome.

Case Description: 63 year old white male with history of hypertension, diabetes mellitus, infrarenal abdominal aortic aneurysm with endovascular repair 6 weeks ago presented with back pain and no urine output. He recently admitted to the hospital 1 week ago with back pain and leukocytosis presumed to be related to surgical site infection which was treated with antibiotics along with surgical wound incision and drainage. Imaging done during that hospitalization revealed minor type 2 endograft leak which was managed conservatively without any surgical intervention. Patient's baseline serum creatinine was 0.7 mg/dL which increased to 4.7 mg/dL and peaked to 6 mg/dL during the hospitalization. CT scan showed mild bilateral hydronephrosis, greater on the right associated with perifocal inflammatory process about the aortobiiliac system and Type II endoleaks involving the IMA and L2 level lumbar artery. Patient's creatinine initially improved to 1.7 mg/dL without any intervention. He underwent endoleak embolization procedure after which serum creatinine gradually worsened to 6 mg/dL along with increasing hydronephrosis on the imaging. Acute kidney injury was thought to be related to bilteral ureteral obstruction from periaortic fat stranding or contrast induced nephropathy. Patient underwent bilateral ureteral stent placement, after which the Serum creatinine improved to 0.7 mg/dL over the next 3 days.

Discussion: Post inflammatory syndrome is a systemic inflammatory response immediately following EVAR is seen in 14 to 60 % of the patients. Our patient had inflammatory process following EVAR, which worsened with embolization procedure and was aggressive enough to cause bilateral ureteral obstruction and acute renal failure



PUB476

Oxalate Nephropathy After Antibiotic Use in a Gastric Bypass Patient

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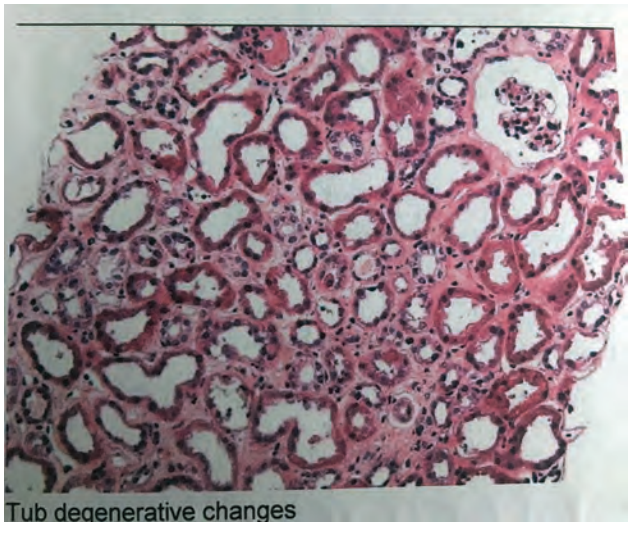
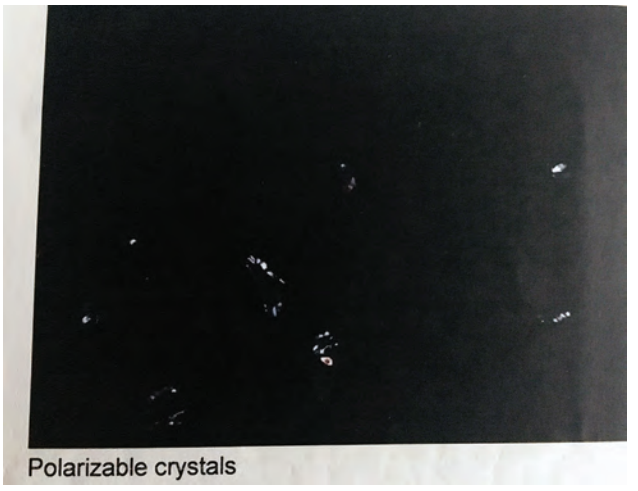
Introduction: This is a case of oxalate nephropathy secondary to antibiotic use for osteomyelitis in the setting of post gastric bypass surgery.

Case Description: A 73-year-old Caucasian female with history of gastric bypass surgery, history of recent right foot osteomyelitis treated with Vancomycin, Ampicillin and Sulbactam for proteus mirabilis presented with worsening renal function. She finished her antibiotic course for osteomyelitis prior to admission and was found to have Creatinine of 3.1 post antibiotic treatment. Kidney biopsy revealed ATN with many calcium oxalate crystals and tubular atrophy and interstitial fibrosis. Subsequently she required dialysis.

Discussion: Antibiotic use and gastric bypass anatomy could be related to oxalate nephropathy. Antibiotic use in this patient might have caused decreased gut microbial Oxalobacter Formigenes, resulting in increased colonic oxalate absorption and the development of calcium oxalate crystals in the kidney. Research in administration of oxalobacter probiotic may help identify a potential prevention of this condition.





PUB477

A Case of Secondary Hyperparathyroidism in a Patient on Hemodialysis with Parathormone Levels Within the Targets and High Total Alkaline Phosphatase

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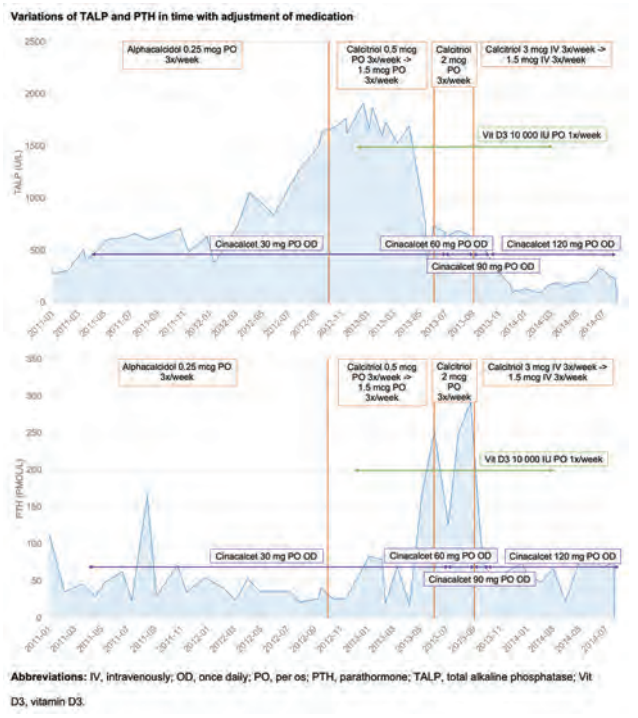
Introduction: Levels of parathormone (PTH) in dialysis patients are not always accurately correlated to the degree of bone remodeling. International guidelines suggest the use of other bone markers, such as serum total alkaline phosphatase (TALP). Although the measures of PTH and TALP are often considered as complementary, these two markers can evolve in opposite directions.

Case Description: Our patient was a 61-year-old Haitian woman on hemodialysis due to diabetic nephropathy. In 2011, she developed secondary hyperparathyroidism while on alphacalcidol. Cinacalcet 30 mg once a day was started since her phosphocalcic product was 4.81. She seemed to respond well to treatment, with her PTH reaching the targets set by guidelines. In 2012, she accused bone pain. Her laboratory results indicated high TALP (1772 U/L) with PTH within the targets (26.2 pmol/L) and low vitamin D (22.2 nmol/L). Her alphacalcidol was switched to calcitriol 0.5 mcg orally three times per week with vitamin D 10 000 IU orally once per week. In 2013, her bone pain was not relieved, with her TALP still high (1917 U/L) and her PTH within targets. An electrophoresis of TALP was done which showed that 97% was of bone origin. Multiple radiographs were also performed, which were suggestive of poorly controlled hyperparathyroidism. Her calcitriol and her cinacalcet were thus increased, and surprisingly, her PTH peaked significantly after this treatment adjustment as her TALP was lowering (cf. image), revealing her hyperparathyroidism.

Discussion: This case shows us that some patients on hemodialysis may suffer from secondary hyperparathyroidism despite having PTH levels within the targets set by KDIGO and emphasizes the importance of taking into consideration other bone markers such as TALP.



Abbreviations: IV, intravenously; OD, once daily; PO, per os; PTH, parathormone; TALP, total alkaline phosphatase; Vit D3, vitamin D3.

PUB478

A Case Illustrating Similarities and Differences Between Calcific Uremic Arteriolopathy (CUA) and Non-Uremic Calciphylaxis (NUC)

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Introduction: CUA is a rare vasculopathy described in those with end-stage renal disease. NUC is an even less well-described clinical entity; one literature review identified 36 cases. The infrequency with which it is encountered renders NUC a formidable diagnostic challenge.

Case Description: A 57 year-old female with diabetes and peripheral vascular disease was admitted for suspected above-the-knee amputation stump infection and subsequently underwent right hip disarticulation. Post-operatively, she developed a left thigh eschar. A bedside skin biopsy was non-diagnostic. Due to clinical suspicion, the patient was taken to the operating room for a wedge biopsy that was diagnostic of NUC. The patient had no prior diagnosis of CKD and the GFR was only mildly low when adjusted for obesity and amputation. The patient was started on sodium thiosulfate (STS) and discharged. The patient was re-admitted a week later due to pain and lesion progression despite STS. Goals of care were revisited and she was ultimately discharged to hospice.

Discussion: NUC occurs in patients who have no or mild renal dysfunction. Risk factors include diabetes among others. This patient had no associated conditions except for uncontrolled diabetes since 2012. CUA and NUC both present with non-healing wounds, though CUA affects the trunk and NUC affects the extremities. One review of NUC cases demonstrated most patients had normal serum calcium (sCa) and serum phosphorus (sPhos). Pathophysiology is thought to be related to hyperphosphatemia, hypercalcemia, and hyperparathyroidism. This patient had no metabolic derangements besides mildly elevated sPhos, suggesting pathogenesis is more complex than current understanding. Diagnosis of CUA primarily clinical, but in atypical scenarios a biopsy is necessary. This patient had classic features on biopsy including intramural calcification as well as positive Von Kossa. Sensitivity of biopsy can be low, related to limited specimen depth or the non-specific histologic findings of early disease, as in this case. Treatment is limited though one review demonstrated STS was associated with improved healing and mortality, though in this case lesions progressed despite STS. Physicians must maintain a degree of suspicion for calciphylaxis if characteristic lesions develop, even in the absence of renal impairment.

PUB479

Too Much of a Good Thing: A Case of Hypercalcemia and Acute Renal Failure from Incorrect Dosing of Vitamin D Supplement

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Introduction: Hypercalcemia is known to cause acute renal failure through several mechanisms including renal vasoconstriction and volume depletion from nephrogenic diabetes insipidus. Here we describe a case of hypercalcemia and acute renal failure from incorrect ergocalciferol dosing that was treated effectively with IV fluids alone.

Case Description: A 55 year-old female with history of hypertension and type 2 diabetes presented to the emergency room with a week of progressive leg swelling, leg pain, and mild memory loss. Exam notable for mild hypertension and trace lower extremity edema. She was found to have a creatinine of 5.0 mg/dL (baseline <1 mg/dL), total calcium 12.5 mg/dL, and ionized calcium 6.76 mg/dL. On review of home medications, the patient noted being prescribed a daily vitamin D supplement by her primary care physician two months prior to admission. A family member brought her pill bottle from home, which confirmed a prescription for ergocalciferol 50,000 units daily. Subsequent hypercalcemia and AKI workup notable for vitamin D 25-OH level above assay at >96 ng/mL, vitamin D 1,25-OH 84.3 pg/mL, and PTH 4 pg/mL, as well as normal SPEP/UPEP, CK, TSH, uric acid, and UA. The patient received 3 days of aggressive IV fluid resuscitation with gradual improvement in renal function and calcium level. Labs one month after discharge showed creatinine 1.29 mg/dL and total calcium 9.9 mg/dL.

Discussion: Vitamin D intoxication has been well described in children, but is being increasingly recognized as a cause of hypercalcemia in adults as well. As more attention is drawn to the significance of vitamin D deficiency, and with the cultural shift toward naturalistic therapies, patients are more likely to seek out and be prescribed vitamin supplements. This case describes a unique cause of hypervitaminosis D due to medication error and highlights the need for detailed medication reconciliation that includes vitamin supplements and over the counter medications, particularly given the multiple formulations of many of these drugs. Ergocalciferol has a half life of around 2 weeks, and there is evidence to support the addition of bisphosphonates in the treatment of hypercalcemia from vitamin D overdose. However, bisphosphonates have the potential to cause hypocalcemia, and this case is an example of effective therapy with IV fluids alone.

PUB480

Calcific Uremic Arteriolopathy in a Patient with ESRD: A Case Report

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Introduction: Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a rare but life-threatening condition that is characterized by progressive cutaneous necrosis associated with small- and medium-sized vessel calcification, occurring in patients with end-stage renal disease (ESRD) on renal replacement therapy. It is a rare condition, described in 1% to 4% of patients on dialysis, mainly in those with a history of diabetes mellitus (DM), liver disease, and elevated calcium-phosphate product.

Case Description: We describe a case of a 42-years old, male, Filipino, known hypertensive, diabetic, a diagnosed case of chronic kidney disease secondary to diabetic nephropathy on hemodialysis three times a week for two years, who came in with severe progressive calciphylaxis in the form of a chronic painful non-healing necrotic wound on the glans penis. He was initially managed as a case of herpes zoster balanitis when he was seen in the emergency department for out-patient consult, but did not improved with oral acyclovir and oral antibiotics. Also noted in the second and third digit of his right hand, were non healing violaceous and necrotic plaques. Calciphylaxis of Chronic Kidney Disease was considered based on clinical, laboratory and radiologic data. Goals of care and prognosis were discussed with the patient. He opted to be managed medically. His hemodialysis sessions were continued and intensified to four times a week, and he was started on sodium thiosulfate 25g IV x 1 hour to start at the last hour of hemodialysis for three months. Other modalities utilized in the management of this case include hyperbaric oxygen therapy, and topical sodium thiosulfate. On follow-up, patient improved and is currently doing well on hemodialysis despite high mortality and morbidity seen in high patients with CUA

Discussion: The pathogenesis of CUA is not well understood, but is thought to be due to vascular calcification leading to soft tissue necrosis that is usually described in patients with end-stage kidney disease on dialysis. Our patient had several predisposing factors for calciphylaxis that had been present for a long time. Nevertheless, the immediate trigger for the acute worsening of calciphylaxis is unknown. Clinical diagnosis of CUA requires a high degree of suspicion.

PUB481

Calcific Uremic Arteriolopathy (CUA)

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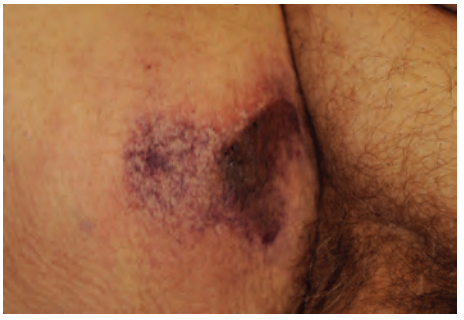
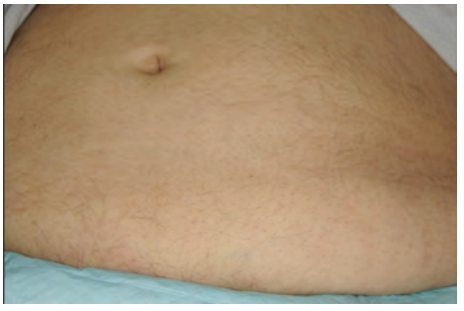
Introduction: CUA carries an extremely poor prognosis, mortality rate of at least 50%, and if coinciding with ulcerations, mortality may exceed 80%. Comorbid conditions increasing the risk of CUA include chronic kidney disease, time on dialysis, diabetes, obesity, secondary hyperparathyroidism and the use of calcium based phosphate binders, warfarin, iron and steroids. The disease usually presents as skin necrosis which can quickly become infected leading to multiorgan dysfunction, septic shock and death

Case Description: This is a 57 y/o man with ESRD receiving thrice weekly hemodialysis(HD)for five years, diabetes mellitius 2, atrial fibrillation receiving warfarin, chronic hyperphosphatemia with normal calciums and secondary hyperparathyroidism at goal for his stage CKD who presented with painful skin lesions compatible with CUA. Use of warfarin precluded obtaining a skin biopsy. Patient was treated with intensification of HD and sodium thiosulfate for nearly one year. Symptoms and skin lesions nearly healed after one year of continuous therapy. After four years of follow up, there has been no evidence of recurrence

Discussion: It is imperative for nephrologists to maintain a low threshold of suspicion for CUA and for when to begin treatment. When possible, the diagnosis should be confirmed with tissue biopsy. There is no clearly defined treatment, but it is generally accepted to treat with sodium thiosulfate for at least three months which can be extended depending on the patients' response. Any medications that can contribute to CUA should be stopped. Other therapies with variable rates of success include use of hyperbaric oxygen, parathyroidectomy, paradoxical use of steroids and bisphosphonates





PUB482

Severe Euglycemic Diabetic Ketoacidosis Secondary to Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor: A Diagnostic Challenge

John Howard, Nasim Wiegley, Niti Madan. *University of California Davis Medical Center, Sacramento, CA.*

Introduction: SGLT2 inhibitors are a relatively new class of antihyperglycemic agents that inhibit glucose reuptake in the kidney. These agents have been increasing in use likely due to favorable effects on glucose variability, weight loss and reduction of insulin doses as well as recent trials supporting their benefit in cardiac and renal disease patients. Of note, prior studies have shown very low risk of euglycemic diabetic ketoacidosis (euDKA) associated with use of SGLT2 inhibitors. Rarity of this presentation makes it a diagnostic challenge. We report a case of severe euDKA in a hospitalized surgical patient in order to raise awareness.

Case Description: A 46 year old woman with type 2 diabetes was admitted for necrotizing soft tissue infection of the buttocks. Home medications included metformin, empagliflozin 25mg daily, and insulin glargine. Initial evaluation showed blood glucose of 329 mg/dL, creatinine 0.90 mg/dL increased from baseline 0.43 mg/dL, bicarbonate 25 mg/dL, and lactate 1.5 mmol/L. She was taken for debridement on admission and again two days later, while remaining primarily NPO and receiving minimal insulin. Post-operatively she was noted to have encephalopathy and worsening respiratory status found to have pH 7.22 and pC02 <12 mmHg on arterial blood gas, bicarbonate <5 mg/dL, lactate 1.0 mmol/L, beta-hydroxybutyrate (BHB) 9.42 mmol/L (normal range 0.02-0.27 mmol/L), with blood glucose 115 mg/dL. Alcohol screen, salicylate, and acetaminophen levels were negative. She was diagnosed with euDKA and initiated on continuous intravenous insulin and lactated ringer's with dextrose. Her acidosis resolved over the following 12 hours and bicarbonate returned to normal levels in 24 hours with BHB of 1.39 mmol/L. She did not receive empagliflozin during admission.

Discussion: Euglycemic DKA is a serious medical condition. The rarity and atypical nature of this form of DKA makes it a diagnostic challenge. Risk factors associated with development of euDKA include infection, surgery, or decreased oral carbohydrate intake. SGLT2 inhibitors are gaining popularity, and a high index of suspicion is needed in caring for surgical patients on these agents. Monitoring anion gap and serum bicarbonate levels might be a better method of evaluating for DKA in such patients given euglycemic state.

PUB483

Recurrent Dialysis Disequilibrium in a Patient Receiving Inconsistent Hemodialysis

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Introduction: Dialysis disequilibrium syndrome (DDS) is characterized by transient neurologic symptoms during or immediately following a dialysis treatment. While nephrologists modify hemodialysis parameters in at-risk patients, the prevalence of DDS today is unknown, and peri-dialytic management of at-risk patients individually varies.

Case Description: A 68-year old patient presented to the emergency-room with her usual pre-dialysis symptoms of nausea and muscle cramps. She had received hemodialysis via right internal jugular tunneled dialysis catheter every 7-10 days since 2014, and was unable to obtain a dialysis home due to undocumented immigration status. Her pre-dialysis blood urea nitrogen level was 65 mg/dl. Upon completion of a 3-hour hemodialysis treatment with an ultrafiltration rate < 10 cc/kg/hr, the patient became obtunded and non-responsive to name. She had had 4 prior episodes of obtundation post-dialysis without identifiable cause. Other past medical history was significant for hypertension, diabetes, hypothyroidism, coronary artery disease, and remote cerebrovascular accident. Her post-dialytic mental status represented a significant deviation from her baseline cognitive impairment per her family. On admission, the patient was afebrile and hemodynamically stable, with no acute changes in EKG, chest X-ray, and CT head. The serum lactic acid, WBC count, glucose, sodium, B12, TSH, and folate were normal. Her post-dialysis BUN was 23 mg/dl, representing a 65% reduction. Without further treatment, the patient's mental status returned to baseline within 12 hours. In the absence of other explanation for her recurrent episodes of cognitive impairment after hemodialysis, the diagnosis of dialysis disequilibrium syndrome was applied.

Discussion: There are 47 published case reports of DDS. Amongst the 47 identified case reports, altered mental status/restlessness were most commonly reported (28/47). A 2012 survey of 252 practicing nephrologists found that over 50% had encountered at least one case of DDS within the preceding year, with 2% encountering more than 20 cases. DDS is likely under-reported and may be more common among patients receiving inconsistent hemodialysis. Therapy should always be tailored for high risk patients, and further investigations should explore if subclinical, recurrent DDS results in cognitive decline.

PUB484

Unique Case of Nephrogenic Systemic Fibrosis Without Exposure to Gadolinium in a Hemodialysis Patient

Mir tariq Ali,[1] Amjad Ali,[2] Yousef Boobes,[1] Fatima R. Alkindi,[1] Ahmad M. Chaaban.[1] *[1]Tawam Hospital, Al Ain, United Arab Emirates; [2]NHS, Chelmsford, United Kingdom.*

Introduction: Nephrogenic systemic fibrosis (NSF) is a rare condition, confirmed by pathological evaluation that has been strongly associated with previous exposure to gadolinium based contrast agents (GBCA). Many regulatory authorities including the FDA have issued warnings to the use of GBCAs in patients with chronic kidney disease. We are describing a case of a patient with end stage renal disease who recently started hemodialysis and developed NSF without previous exposure to GBCAs.

Case Description: A 62 year old female with long standing history of diabetes mellitus, hypertension and morbid obesity leading to end stage renal disease required initiation of hemodialysis since two months. She presented with history of skin induration, thickening and peeling that has started around the same time of starting dialysis and has progressively increased. The lesions described are in multiple areas of the body including the abdomen and both upper and lower limbs. A provisional diagnosis of calciphylaxis was proposed. However, a skin biopsy was performed that revealed, pronounce cellularity with spindle cell proliferation that express factor XIII and focally CD34 the changes involved full dermis and extend to the septa of subcutaneous fat. There are proliferation of fibroblast, epithelioid and stellate cells. Increase in dermal mucin highlighted by Hale colloidal iron with thickened collagen, consistent with a diagnosis of nephrogenic systemic fibrosis that was reviewed in three separate pathology centres. The patient did not have any previous exposure to gadolinium study GBCAs and in skin biopsy the gadolinium particles was not seen.

Discussion: After extensive review of the literature, we could find two cases of NSF reported in renal transplant patients without previous exposure to GBCAs. However, to our knowledge this is the first case reported in dialysis patient. Our case in addition to the other two cases reported in the literature emphasizes the need to re-address the underlying pathogenesis and potential causes of NSF.

PUB485

What Evil Lurks: Dialysis-Induced Reactions in a Critically Ill Patient

Dhruti P. Chen, Jennifer E. Flythe. *University of North Carolina Kidney Center, Chapel Hill, NC.*

Introduction: While adverse reactions on dialysis are rare with modern synthetic membranes, they do occur and can be life threatening. We describe a case of severe dialysis-induced reactions during both continuous renal replacement therapy (CRRT) and hemodialysis (HD).

Case Description: A 72 year old woman with a deceased donor kidney transplant 3.5 years prior and respiratory failure was transferred to our medical intensive care unit (ICU) for encephalopathy and acute kidney injury. She had presumed sepsis of unknown origin and worsening oliguria with volume overload and low blood pressure (BP). CRRT was started on ICU day 3 using an NxStage® machine with a gamma-sterilized polyethersulfone membrane. At CRRT start, her vitals were stable without vasopressors but within several minutes, her BP fell to 70/30 mmHg, and a norepinephrine drip was initiated. CRRT was paused, and her BP returned to baseline. When CRRT was restarted, she developed recurrent hypotension with eventual loss of pulse. CRRT was stopped, blood returned and patient resuscitated with chest compressions and epinephrine. Her BP stabilized, and she was quickly weaned off the epinephrine drip. The next day, HD with a gamma-sterilized, cellulose triacetate membrane was attempted with the same outcome. She was eventually successfully dialyzed using a polyethersulfone membrane with a pre-attached blood tubing set (all gamma-sterilized).

Discussion: The dialysis-induced events were consistent with type A dialyzer reactions, reactions characterized by early onset, IgE-mediated symptoms such as urticaria, bronchospasm and/or anaphylactic shock. The differential included shock and medication reaction, but her symptoms resolved upon stopping dialysis, and she was not on causative medications (e.g. heparin, iron). A negative serum ethylene oxide (ETO) IgE level 3 weeks

later made a dialyzer or tubing-based ETO reaction less likely, though false negative results have been reported up to 3.5 weeks after exposure. We can only hypothesize on the cause of her reaction, including potential dialysis equipment (membrane or tubing) contamination with ETO or other antigens.

	ADMISSION	CRRT EVENT	POST-EVENT
WBC (n/L)	4.8	10.4	6.2
Hemoglobin (g/dL)	7.3	7.6	8
Platelets (n/L)	213	172	173
Creatinine (mg/dL)	3.2	3.2	0.63
INR	1.09		
Troponin (ng/mL)	<0.034	<0.034	0.95
Total IgE (kU/L)			<2.00
Ethylene Oxide IgE (kU/L)			<0.35*
Lactate, arterial (mmol/L)	0.6	5.7	

*drawn 20 days post event

PUB486

The "Double-Line" Sign to Identify Perirenal Fat Pad: A Must-Know Sonographic Sign

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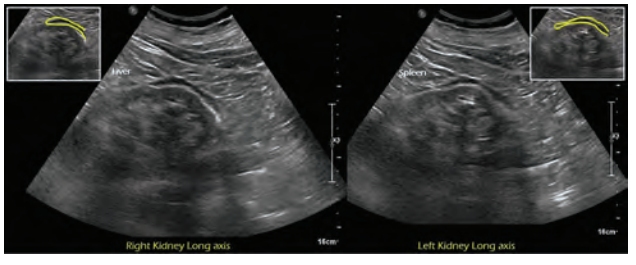
Introduction: Perirenal fat is a fat pad located in the retroperitoneal space surrounding the kidney. As nephrologist performed point-of-care ultrasonography (POCUS) is on the rise, it's important to be aware of this structure for two reasons: 1. It can mimic free fluid in the Morrison's pouch and also subcapsular hematoma, which is particularly important when performing POCUS after a kidney biopsy 2. Recent epidemiological studies have shown that perirenal fat is a risk predictor for Cardiovascular disease, and it may turn out to be a promising target in the management of these patients. The 'double-line' sign we describe here can aid in the identification of this structure.

Case Description: A 52-year-old gentleman on maintenance hemodialysis was noted to have elevated hemoglobin (15 mg/dL) in the absence of erythropoietin stimulating agent therapy. A renal sonogram was performed to screen for renal mass/ renal cell carcinoma as the potential etiology for elevated hemoglobin, which demonstrated hypoechoic, sharply demarcated area in the perirenal area bilaterally mimicking intraperitoneal free fluid in addition to small kidneys with thin parenchyma. However, no intervention was undertaken because of the striking 'double-line' sign suggestive of perirenal fat pad bilaterally. Perirenal anechoic to hypoechoic structure surrounded by two hyperechoic bright lines [Figure-inset] constitutes this sign, where these echogenic lines are caused by fascial planes surrounding the kidney. Moreover, the fat pads typically contain low-level echoes within the hypoechoic region, unlike fluid and move with the kidney as it changes position during respiration. It may be difficult to distinguish this structure from post kidney biopsy subcapsular hematoma, but visualization of bilateral double-line sign favors fat pads.

Discussion: The double-line sign helps to distinguish free fluid in the hepatorenal or splenorenal space from the perirenal fat pad. Nephrologists performing POCUS should be able to recognize this sign to prevent unnecessary interventions and consultations.



PUB487

The Utility of Renal Replacement Therapy in Hepatic Encephalopathy

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Introduction: Severe liver failure may cause the brain to swell, leading to significantly altered sensorium. In the treatment of these patients, we utilize the ability of the gastrointestinal system to clear ammonia. However, we often come across patients who do not respond to this regimen. In this case, our patient was somnolent requiring intubation and had rising ammonia levels despite lactulose and rifaximin therapy. Although he had normal kidney function, we used CRRT and noted improvement in the patient's mental status.

Case Description: 58-year-old male who has a history of cirrhosis with portal HTN who presented with shortness of breath and cough for 2 weeks. He was initially admitted for COPD exacerbation. He developed further worsening respiratory failure requiring intubation and antibiotic therapy. CT chest revealed left upper lobe pneumonia and respiratory viral panel came back positive for H1N1 so he was started on Tamiflu. His physical examination off sedation included no purposeful movements and not following commands so he continued to be intubated. Ammonia level returned at 229. He received lactulose enema, lactulose 20mg QID, and rifaximin 500mg BID through orogastric tube. Given his minimal response and rising ammonia levels, CRRT was started. The next morning, his abdomen became increasingly distended and rigid. Abdominal X-ray revealed colonic ileus. Rectal tube was placed for colonic decompression. Lactulose was switched to Miralax QID and he received another CRRT session. The following day, he had increasing output from his rectal tube. Serial abdominal X-rays revealed decreasing colonic distention. He was extubated and started to communicate, eat by mouth and eventually transferred to the floor.

Discussion: We present an interesting case of a patient who presents with acute respiratory failure secondary to H1N1 influenza along with altered mental status secondary to hepatic encephalopathy. When conservative measures fail, clinicians sometimes consider more invasive techniques for HE, such as large portosystemic shunts or liver transplantation; however, not all patients are candidates for these procedures. This case sheds light on the utility of renal replacement therapy in the management of critically ill patients, even those without pre-existing kidney dysfunction or end-organ damage. Further studies are needed to quantify the extent to which renal replacement may benefit these patients.

PUB488

ESRD with Cardiac Ascites Managed with PleurX Drainage System

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Introduction: The PleurX drainage system has been used to manage fluid from malignant and nonmalignant pleural effusions or malignant ascites at home, with more than 500,000 patients treated since 1997. We present a case of end-stage renal disease (ESRD) with refractory cardiac ascites managed with PleurX drainage system.

Case Description: A 65-year-old white Veteran presented with advanced heart failure (NYHA Class 4), multiple admission and diuretic-resistant edema formation with stage 5 CKD. While peritoneal dialysis (PD) would have been ideal, he was legally blind and did not have any family support for assisted PD. His medical scenario was initially stabilized with frequent hemodialysis (HD; x4/week) but he experienced recalcitrant ascites formation with severe and symptomatic intra-dialytic hypotension with net ultrafiltration. Moreover, the need for repeated paracentesis every 2 weeks posed a major emotional burden for our patient, including the discomfort and additional time-commitment of the procedure. After appropriate discussion and consenting with the patient, we requested a tunneled, single-lumen catheter placed into the abdominal cavity (PleurX drainage system; originally designed for repeated evacuation of pleural fluid accumulation), 4 months after HD initiation. Tolerability of HD improved and peripheral edemas well-controlled thereafter. Home health monitors his care and performs draining at least x3/week. Exit site care completed with local gentamycin cream and no interval peritonitis was observed so far (9 months).

Discussion: Cardio-renal ascites formation may represent a challenge to remove in those with coexisting severe heart failure and ESRD. Ascites fluid accumulation represents the hemodynamic "sinkhole" for patient with cardiac ascites and may be difficult to mobilize these during conventional HD. Plastic catheters in the blood stream are more likely to cause bacteremia than those placed in visceral surfaces (pleura, abdominal cavity). In those ESRD patients with cardiac and cirrhotic ascites, who cannot perform PD, establishing alternative and less-traumatic method of ascites drainage with PleurX drainage system may simplify the care and improve tolerability of HD.

PUB489

Diaphoresis, Bradycardia, and Urinary Incontinence as a Presentation of Dialysis Disequilibrium Syndrome

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Introduction: Dialysis disequilibrium syndrome (DDS) is an increasingly rare condition characterised by wide variety neurological symptoms of varying severity related to acute cerebral edema. We observed a unique presentation of bradycardia, diaphoresis and urinary incontinence along with unresponsiveness which has not been reported before.

Case Description: A 54 y/o African American female with ESRD secondary to DM and HTN on hemodialysis for 1 year presented to the ED with generalized body weakness after missing 3 hemodialysis (HD) sessions. Before the start of HD her physical/neurological examination and CT brain were normal. BUN=113mg/dl, Cr=19.5mg/dl, K=5.5mEq/L, Na=143mEq/L and tCO2=16mEq/L. HD was started with the following orders: 3.5hr; Qb 250ml/min; Qd 800ml/min; Dialyzer F160NR. After 1 hour of HD she was asymptomatic and Qb was increased to 375ml/min. Soon after completing the 3rd hour of HD she became acutely unresponsive to verbal/painful stimuli. HD was stopped immediately. BP=110/70, Pulse 90 then 2 episodes of bradycardia to the 40s were observed with spontaneous resolution after <30 seconds, normal reactive pupils, profuse diaphoresis, extremities warm and urinary incontinence. Seizure activity was not observed. EKG showed normal sinus rhythm with no ST/T wave changes. Acute hypoglycemia was suspected given the profound diaphoreis although the FSG was 120. IV dextrose (D50) was given empirically with no improvement. Blood urea nitrogen drawn 1 hour after stopping hemodialysis was 43mg/dl (URR - urea reduction ratio = 62%) and repeat CT brain was within normal limits. The patient improved clinically over the next 4-6 hours with no memory of the event. A neurology consultant attributed the event to DDS in the absence of any other likely cause.

Discussion: DDS was the most likely diagnosis in this patient with unresposiveness, bradycardia, diaphoresis and urinary incontinence during her 3rd hour of hemodialysis after having missed 3 dialysis sessions. There was no hypotension, hypoglycemia, CVA/ hemorrhage or CNS pathology, h/o seizures, or significant electrolytes abnormalities. This was a unique presentation of DDS, in which we observed increased parasympathetic activity characterized by bradycardia, diaphoresis and urinary incontinence along with unresponsiveness all of which resolved on stopping dialysis.

PUB490

Ammonia Clearance in Acute Liver Failure with Continuous Venovenous Hemodiafiltration

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Introduction: Hyperammonemia in acute liver failure and inborn errors of metabolism can cause life-threatening cerebral edema. While intermittent hemodialysis clears ammonia more rapidly, continuous renal replacement therapy (CRRT) is often used in acute liver failure due to hemodynamic instability and rebound of ammonia levels. Kidney Disease Improving Global Outcomes guidelines recommend an hourly effluent of 20-25 mL/kg/hr delivery with CRRT, but whether this applies to cases of hyperammonemia is unknown. We report the first case to our knowledge measuring the clearance of ammonia using continuous venovenous hemodiafiltration (CVVHDF) in a patient with acute kidney injury and hyperammonemia.

Case Description: A 27-year old previously healthy Hispanic man with alcohol overuse presented with one week of malaise, abdominal pain, and confusion after taking acetaminophen for flu-like symptoms. Physical exam was notable for obtundation, asterixis, scleral icterus; and laboratory studies were remarkable AST and ALT > 6000U/L; total bilirubin 9.1mg/dL; INR 6.3; ammonia 107uMol/L; and serum creatinine 4.7 mg/dL. Urine microscopy revealed multiple tubular epithelial casts and head CT showed diffuse sulcal narrowing. A diagnosis of grade 3 hepatic encephalopathy due to intracerebral edema from hyperammonemia from acute liver failure complicated by oliguric acute tubular necrosis was established, and the patient was listed for liver transplantation with a MELD of 40. CVVHDF was initiated on hospital day 1 with a total effluent of 33 mL/kg/hr was delivered (12 mL/kg/hr dialysis and 21 mL/kg/hr ultrafiltration). On hospital day 3, after 36 hours of uninterrupted CRRT, serum ammonia was 77 umol/L, effluent ammonia was 19 umol/L, and hourly effluent was 2700 mL. Using the Cordoba equation, we calculated an ammonia clearance of 11 mL/min. The patient's acute liver failure resolved without need for transplantation. He was transitioned to intermittent hemodialysis on hospital day 4, and achieved renal recovery becoming free from renal replacement therapy on hospital day 13. His most recent serum creatinine is 0.8 mg/dL.

Discussion: In this case of hyperammonemia, ammonia clearance was modest despite delivering an effluent volume that exceeded KDIGO practice guidelines. Given the increasing attention that CRRT is receiving for treatment of hyperammonemia, more work is needed to determine the optimal dose and method of CRRT in such instances.

PUB491

Utility of Procalcitonin (PCT) and Brain Natriuretic Peptide (BNP) in a Patient on Hemodialysis (HD)

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Introduction: In the general population, PCT and BNP are used to assess likelihood of bacterial infection and volume overload based on absolute values above 100 pg/mL and 0.08 ng/mL respectively. Baseline values are elevated to a variable degree and both markers are cleared by high-flux dialysis membranes commonly used in the acute care setting resulting in ambiguity interpreting the meaning of PCT and BNP levels. We present a case showing their utility in resolving diagnostic uncertainty.

Case Description: An 84-year-old man was hospitalized with four weeks of worsening ascites, cough, and dyspnea. His initial BNP level was 1211 pg/mL and PCT was 0.40 ng/mL. Chest x-ray (CXR) showed pulmonary vascular congestion, bilateral pleural effusions and lower lung opacities. With large-volume paracentesis and ultrafiltration via hemodialysis, his symptoms improved. On day 6, dyspnea worsened and mental status declined. CXRs were unchanged from baseline. Ultrafiltration was increased with minimal improvement. A repeat PCT level on day 8 was 0.73 ng/mL, and he developed fever; chest CT revealed multifocal consolidation, and his respiratory and mental status improved with antibiotics.

Discussion: Interpretation of PCT and BNP can be challenging in patients with CKD treated by hemodialysis in the acute setting. The numerous potential causes of dyspnea in our patient created diagnostic uncertainty. Trends in the evels of PCT and BNP helped narrow our differential diagnosis improving our ability to successfully manage our patient.

PCT and BNP

Normal Levels (General Population)	<0.08	<100
Patient Baseline Levels	0.40	602 (prior admission)
Patient Acute Levels	0.73	1211

PUB492

Carbamazepine Intoxication and Role of Dialysis

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Introduction: Carbamazepine (CMZ) at therapeutic levels is highly albumin bound. This limits effectiveness of extracorporeal elimination. It is not an established standard of care to utilize renal replacement and related techniques to support elimination in severe cases of CMZ overdose. Current literature is limited to case reports and case series which suggests to offer RRT in certain cases. High-flux hemodialysis is the preferred approach to extracorporeal elimination of CMZ (1). For clearance of CMZ, concentration of CMZ in the dialysate effluent should be measured. In addition some experts advocate that active metabolite carbamazepine-10,11 epoxide (CBZ–E), with its lower degree of protein binding, can be effectively cleared via extracorporeal modalities thereby limiting clinical toxicity. However, quantitative levels of this metabolite are not commonly measured. We present a case of severe CMZ toxicity in which extracorporeal treatment provided effective clearance of carbamazepine and CBZ-E.

Case Description: 24-year-old Caucasian female with 19 weeks of gestation was admitted with intentional carbamazepine overdose. She was severely encephalopathic with GCS of 6 on arrival. She was having seizures refractory to treatment and required intubation for airway protection. She was hemodynamically unstable needing vasopressor support. CMZ levels were found to be above the assay -limit (40.3 microgram/ml) on serial measurements at our lab. Normal reference range of 4.0-10 microgram/ml. After evaluation and literature review we started her on sustained low efficiency dialysis (SLED). After 10 hours of SLED, CMZ levels were lowered to a measurable range. Levels for CMZ and its active metabolite were sent from the dialysis effluent. She continued to show good clinical improvement with hemodynamic stability and improved neurological status. She was extubated. Clearances of CMZ and its metabolite CMZ-E were found be significant supporting the available limited data for use of extracorporeal therapy including SLED.

Discussion: Despite the scarce clinical evidence for high protein bound drugs like carbamazepine our experience supports use of extracorporeal removal in severe poisonings. Our case adds to the limited literature available for role of extracorporeal therapy for severe CMZ poisoning. It essentially means that non -protein- bound drug was eliminated which helped in eventually decreasing the toxic levels of CMZ.

PUB493

First Report of Short Bowel Syndrome Complicated with Uremia

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Introduction: Patients with short bowel syndrome (SBS) often suffer from water-electrolyte disturbance, nutrient malabsorption, duing to shortened intestine. Some of the patients subsist largely on parenteral nutrition. Hemodialysis is main treatment of uremia, during which the excess water and electrolytes of the body are removed together with uremic toxins. SBS complicated with uremia is very rare. The treatments of the two diseases always conflicting. There is no relevant literature for reference.

Case Description: The patient was a 36-year-old woman with a 20-year history of Crohn disease who had undergone nine times intestinal resections and less than fifty centimeters residual intestinal, subsisted largely on parenteral nutrition now. Long-term use of analgesics and malnutrition, she got the chronic renal function failure half a year ago, when she had no choice but to start the hemodialysis treatment. With low body weigh(38kg),low blood pressure(85/43mmHg), hypo-albuminemia (30.4g/L), plenty of parenteral nutrition solutions, it was hard to evaluate the ultrafiltration volume. With very low serum phosphorus(0.04mmol/L), calcium(1.89mmol/L), PTH(3.8pg/ml), and active VD3(4.6ng/ml), she suffered with severe bone pain always. Meanwhile, long-term use of peripherally inserted central catheter (PICC), there was no conditons to estabolish conventional dialysis access. A specialized physician team established for the patient. The parenteral nutrition treatment prescription is adjusted according to the dietary guidance of chronic kidney disease, to provide right dosage of energy, protein, liquid, and electrolytes intake of HD status. Real-time monitoring of blood gas analysis during hemodialysis, timely replenishing glucose and electrolytes, maintaining the balance of acid-base, water and electrolyte. Supplemented erythropoietin, trace elements, and intravenous active vitamin D to improve uremia complications. At the same time, femoral vein cuffed tunnel was use for transition, we created the left forearm ulnar side arteriovenous fistula (AVF) as permanent vascular access. Now the nutritional status, uremia complications, and life quality of the patient improved significantly.

Discussion: Short bowel syndrome complicated with uremia is very rare. It is not only necessary to prevent the complications of continuous use of parenteral nutrition support, but also to intervene the complications related to maintenance hamodialysis.

PUB494

Using Intermittent and Continuous Venovenous Hemodialysis to Treat Hyperammonemia in Acute Liver Failure

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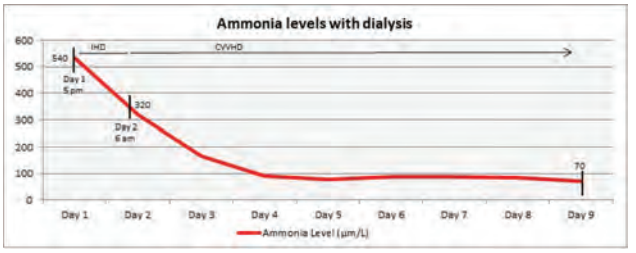
Introduction: Hyperammonemia with levels >200 μmol/L is usually associated with poor neurologic outcomes and death. The primary goal of renal replacement therapy (RRT) is to reduce blood ammonia concentration and achieve resolution of neurological symptoms. Although RRT has been used to treat hyperammonemia in neonates with inborn errors of metabolism, its use in adults is poorly studied. We present a case of severe hyperammonemia due to acute liver failure secondary to hepatitis A.

Case Description: A 70-year-old male with history of CAD and HTN was transferred from another hospital with jaundice and altered mental status secondary to acute liver failure. Labs were significant for creatinine of 3.26 mg/dL, INR 8.20, Bilirubin 11.8 mg/dL; AST/ALT of 7167/9544 U/L. Ammonia level was 540 μmol/L. Serology showed positive Hepatitis A IgM. CT head was negative for cerebral edema. He was started on intermittent hemodialysis (iHD) emergently followed by CVVHD. Ammonia levels dropped post iHD from 540 to 320 and <100 within 72 hours. His mental status initially worsened but improved after 2 days. Unfortunately, his hospital course was complicated by septic shock

and ischemic colitis. He went into cardiac arrest after subtotal colectomy and was made comfort care. He passed away on day 9 with ammonia level <100 μmol/L on CVVHD.

Discussion: Ammonia is similar to urea in terms of its clearance; hence both IHD and CRRT are effective in removing it. The longer ammonia remains elevated, the higher the chance of mental impairment. iHD is considered a preferred modality as it decreases ammonia concentrations rapidly. CRRT has been used successfully with iHD in children to prevent ammonia rebound. Our patient presented with very high ammonia levels, hence we started iHD to decrease the ammonia level rapidly followed by CCRT. He responded well within 48 hours with this method. His ammonia level remained less than 100 μmol/L subsequently. Currently, there is limited data regarding which modality to use in adult patients with hyperammonemia. More studies are needed to assess the efficacy of hemodialysis in these patients.



PUB495

Hypotension on Dialysis: It's Not Always Hypovolemia

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Introduction: Hypersensitivity reactions (HSR) to dialysis filters are rare and can be challenging to diagnose. Here, we describe a case of Type A HSR secondary to a polysulfone (PS) filter on continuous renal replacement therapy (CRRT).

Case Description: A 66-year-old male with NYHA IV heart failure and stage III chronic kidney disease presented for elective placement of a left ventricular assist device (LVAD). Initial creatinine was 1.6mg/dl. Post-operatively, he developed sustained ventricular tachycardia leading to anuric AKI & hyperkalemia. CRRT without ultrafiltration (UF) was initiated. He tolerated it for 30 minutes and then the circuit clotted. Within 2 minutes of restarting, mean arterial pressure (MAP) dropped to 30mmhg from 65mmhg with hypoxemia, needing intubation. It was stopped and the MAP improved spontaneously. A third attempt of CRRT with no UF again resulted in hypotension and cyanosis within 30 seconds despite pre-emptively increasing vasopressors and giving crystalloids. Relevant labs include a low C3, normal C4 & tryptase, and no eosinophilia. CRRT was immediately stopped and extracorporeal blood not returned. We switched to a cellulose based filter with concerns for HSR to the PS filter. Our CRRT machines were incompatible with other filters, so intermittent hemodialysis (HD) with blood & dialysate flows of 200ml/min & 400ml/min respectively with a cellulose filter was done successfully. Further HD sessions with cellulose filters had no issues.

Discussion: Our case describes a Type A HSR to PS dialysis filters with resolution after switching to a cellulose filter. HSR on dialysis was reported at 4.2/1000 sessions of dialysis per year for synthetic membranes and can be associated with dyspnea and hypotension. Type A reactions are immediate and type B delayed. It's often linked to a sterilizing agent ethylene oxide and AN-69 dialysis membranes in patients on ACE-Inhibitor which he wasn't on. Recent reports highlight other substrates, like PS membrane, as an important but under recognized cause of HSR. Hypersensitivity can be mediated by Immunoglobulin E or complement activation. Management includes; not returning blood from the extracorporeal circuit to avoid aggravating hypersensitivity, priming the dialyzer with saline to washout sterilant and switching to cellulose filters.

PUB496

Nephrology Team Leading Molecular Adsorbent Recirculation Therapy (MARS) Therapy: Case Reports

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Introduction: Acute liver failure (ALF) from any cause has an extremely high mortality and sometimes liver transplantation is the only final treatment. Molecular Adsorbent Recirculation System (MARS) lead by Nephrology has been successfully used in two patients as a bridge to full recovery and liver transplantation respectively.

Case Description: 1) 34 Yr old Female presented with nausea, vomiting with labs significant for AST 15,785 U/L, ALT 10,888 U/L, Total Bilirubin 17.4 mg/dl, INR 2.32. Diagnosed with ALF due to Acute Hepatitis B, was started on N-Acetylcysteine, Lactulose, Rifaximin and Tenofovir. 24 hrs into admission her mentation worsened requiring intubation. CT showed cerebral edema. Decision was made to start MARS to remove toxins and help liver in regeneration by improving microenvironment. Received 56 hrs total of MARS therapy for four days. Bilirubin improved from 25.27 mg/dl to 9.5 mg/dl, mentation improved and was eventually discharged. **2)** 28 Yr old Male admitted for ALF secondary to alcohol intoxication. Labs were significant for AST > 7000 U/L, ALT > 7000 U/L, Bilirubin 8.41 mg/dl, Lactate >15 mmol/L. Due to lack of spontaneous recovery and worsening clinical condition he has been started on MARS therapy and listed for Liver transplant. Liver was transplanted after 54 hours of MARS therapy. Surgery related issues complicated his postoperative course. He is currently waiting long term rehab placement for continued recovery.

Discussion: MARS is a potential lifesaving therapy in selected patients. A multidisciplinary team is required to provide this extracorporeal therapy and nephrology should take the lead.

PUB497

Dialysis Disequilibrium Syndrome Despite Standard Preventive Measures

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Introduction: There have been very limited cases of dialysis disequilibrium syndrome (DDS) reported in recent literature. Compared to the 1970s and 1980s, our patients are admitted with a lower Blood Urea Nitrogen (BUN) concentration. Standard preventive recommendations for the first dialysis sessions have limited the incidence of DDS significantly. As a result, cerebral edema and brain herniation have become rare entities.

Case Description: Our patient is a 54-year-old female with hypertension, CKD stage 4 who presented with 2 weeks of fever, generalized weakness and shortness of her breath. Blood pressure (BP) was 194 /137. She was lethargic with asterixis. Lung exam revealed crackles. Her sodium was 131 mEq/L, potassium 4.5 mEq/L, bicarbonate 21 mEq/L, BUN 191 mg/dL, creatinine 16.6 mg/dL. Chest computed tomography (CT) had multifocal pneumonia with pulmonary edema. Dialysis was started for 2 hours with F16 dialyzer, blood flow of 250ml/min and dialysate flow of 500 ml/min. Within 5 minutes of dialysis, she became unresponsive and her systolic BP dropped to 98. The session was stopped immediately. Her mental status and her blood pressure improved in the afternoon but worsens in the evening. Dialysis was started overnight with the same prescription. She tolerated the procedure well until her blood pressure rose to the 200's and she became unresponsive 90 minutes later. Head CT showed cerebellar edema and tonsillar herniation. Calculated serum osmolality change pre and post dialysis was 27 mmol/L. Neurology diagnosed her with Posterior Reversible Encephalopathy Syndrome.

Discussion: DDS is a very rare complication of dialysis. Established protocols usually prevent this dreaded outcome. Our case is an important reminder that standard preventive recommendations may not be sufficient. Our patient had a complex presentation and did not benefit from the recommended measures. This syndrome has also been reported with continuous renal replacement therapy. Female with preexisting neurological conditions and BUN higher than 175 mg/dL are more prone to this condition. In this high-risk population, the use of one of the smallest dialyzers such as F3 with a lower than the recommended blood flow and dialysate flow rate might have a more desirable outcome.

PUB498

Addressing Social Determinants of Health in Haitian-American Patients with ESRD

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Introduction: African Americans with ESRD have higher rates of morbidity and mortality. Social determinants of health (SDOH) such as attaining healthcare, legal assistance, appropriate nutrition, financial stability, employment and education create obstacles to achieve better outcomes. We compare interventions for patients with ESRD on hemodialysis in the setting of an interdisciplinary Neighborhood outreach program (NHELP). We aim to understand how addressing the SDOH affect morbidity and mortality.

Case Description: African Americans with ESRD have higher rates of morbidity and mortality. Social determinants of health (SDOH) are contributory as they create obstacles to attaining healthcare, legal assistance, appropriate nutrition, financial stability, employment, education. We compare interventions for patients with ESRD on hemodialysis in the setting of NHELP. We aim to understand how addressing the SDOH affect morbidity and mortality. The SDOH and associated obstacles were identified. **Results**: Patient A had 17 months of program participation with her most current student team. She received two home visits (one interdisciplinary, one social work only) and an average of 3.5 phone communications. She received academic support for her children, referral for dental care, and legal support filing for citizenship. Recurrent hospitalizations were a challenge for Patient A and NHELP team during her participation. Patient B had 21 months with a student team. She received 9 home visits and an average of 5.5 telephone communications. Patient B had private health insurance and full-time employment. Interventions included: mental health services, assistance with transplant process, education regarding improving diet and blood pressure control, help transitioning between dialysis centers, and dental referrals. Both patients received help applying for federal assistance to cover healthcare costs. Patient A received Social Security Disability and Medicare, while patient B only received Medicare. Both received social support and education to improve health literacy.

Discussion: Conclusion: Earlier access to interdisciplinary care decreased obstacles to health services vital for patients with ESRD. When SDOH were completely addressed, patient B received transplantation suggesting improved morbidity and mortality.

PUB499

A Case-Series Analysis of CKD and Disseminated Tuberculosis Treated in a Tertiary-Level Hospital

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Introduction: End-stage renal disease is considered a factor predisposing to increased risk of tuberculosis (TB) with frequent extrapulmonary localization. The haemodialysis patients are at risk to develop TB disease 6.9 times more frequently due to imparied cellular immunity in chronic renal failure. The diagnosis of TB in Chronic Kidney Disease (CKD) is difficult because of frecuent extrapulmonary localization and non specific symptoms.

Case Description: *case1 :*32 years old man, Human Immunodeficiency Virus (HIV) negative (-) in HD, miliary TB, pleural and pericardial effusion, pericardiocentesis with adenosine desaminase (ADA) of 38 y GenXpert positive(+), computed tomography (CT) with tumor that destroys the sternoclavicular joint with Ziehl-Neelsen (Z/N) (+). *case 2 man:*26 years old, in HD, miliary TB, pleural effusion and pericardial effusion, isolated from bronchial wash, GenXpert, and Lowenstein Jensen medium (LJ) (+) pericardiocentesis with Z/N(+).*case 3:*42 years old woman, CKD stage IV, type 2 diabetes mellitus (DM2), arterial hypertension(AH), miliary TB, LJ (+) in sputum and detection of lymphangioleiomiomatosis by lung biopsy. *Case 4*:66 years old man, in HD, DM2, AH, CT with cavitated bilateral cervical lymph nodes, biopsy of lymph node with Z/N (+). Case 5:18 years old, HIV (+) with miliary TB, in HD; GenXpert in bronchial wash and LJ(+), pericardiocentesis with ADA 138, LJ(+). *case 6*:55 years old woman in HD, DM2, pericardial effusion, pericardiocentesis ADA 49.8, tuberculous pericarditis by biopsy.*case 7:*22 years old, in HD, meningeal cryptococcosis, bronchial wash Z/N and LJ(+).*case 8:*22 years old, in HD, disseminated TB, bronchial wash with Z/N and LJ(+), GenXpert of cervical lymph node(+).

Discussion: The link between CKD-TB increases morbimortality, extrapulmonary associations and disseminated are frequent and of difficult diagnosis, the TB screening and diagnosis performance is suboptimal in the CKD population, and there is limited evidence to guide protocols, the intentional search is required with molecular biology of several affected sites. So the diagnosis is made in advanced disease, which leads to a clinical torpid course because despite the treatment in our case series 5 of 8 patients died. So these patients are candidates if active tuberculosis it is discarded for chemoprophylaxis

PUB500

Oblique Leak

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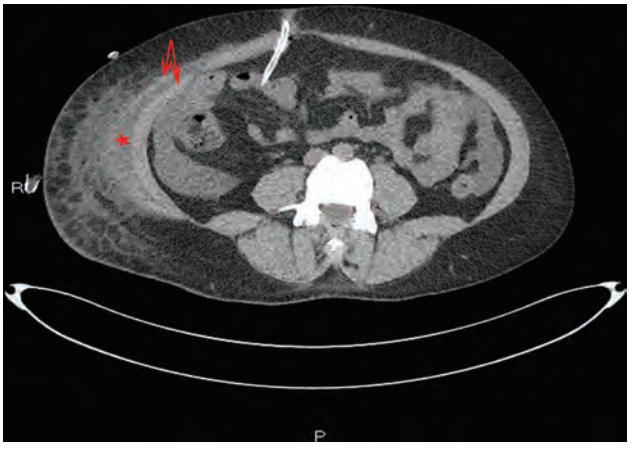
Introduction: Most peritoneal dialysis associated leaks are associated with peri-catheter leaks, hernias and genital swelling. We present a case here of a patient whose peritoneal fluid was leaking into an area away from the catheter and in a location where no recent surgical intervention was performed.

Case Description: A 47-year-old female with end-stage kidney disease on continuous ambulatory peritoneal dialysis presented to the emergency department with a 48-hour history of poor ultrafiltration with absorption of approximately 300-1100 mL of each 2 liter dwell volume exchange. Additionally, the patient reported an area of hardened skin along her right lateral abdominal wall. Physical exam revealed normal peritoneal catheter exit site with no drainage or induration along the anterior abdominal wall. A 5 x 5 cm area of hard induration was palpable along her right lateral abdominal wall. CT scan was concerning for subcutaneous fluid along the right abdominal wall which tracked inferiorly causing separation of the oblique muscles (Figure 1). Given lack of intraperitoneal contrast material, location of the abdominal wall defect was not determined.

Discussion: Most peritoneal dialysis associated leaks are associated with peri-catheter leaks, hernias, and genital swelling. In our patient's case, physical exam and imaging around the catheter were unremarkable. Instead, the leak was located away from the current PD catheter and was on the opposite side of a previously placed peritoneal dialysis catheter. This case illustrates an atypical location for peritoneal leaks.



CT scan showing subcutaneous edema along the right lateral abdominal wall. Fluid tracking (asterisk) leading to separation of oblique muscles (arrows).can be seen here.

PUB501

Cefepime-Induced Neurotoxicity in a Peritoneal Dialysis Patient: An Increasingly Common Scenario

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Introduction: Cefepime is a generally well-tolerated antibiotic used for a variety of infections. Neurotoxic effects, including nonconvulsive status epilepticus (NCSE), have been described and are typically seen in patients with renal dysfunction or end-stage renal disease (ESRD) receiving high doses. While up to 70% of a given cefepime dose is removed with hemodialysis (HD), the clearance is reduced to only 25% with peritoneal dialysis (PD). We present a case of cefepime-induced neurotoxicity in a PD patient requiring treatment with temporary HD.

Case Description: An 82-year-old man with multiple system atrophy and ESRD on PD presented to our hospital with a decreased level of consciousness (LOC), found to have urinary retention. Empiric treatment for a complicated urinary tract infection was started with cefepime 1 g every 24 hours. On day 3, the patient developed aphasia and myoclonic jerks with further decline in alertness. An electroencephalogram (EEG) was performed demonstrating triphasic discharges suggestive of toxic encephalopathy. Despite 2 days of continuous peritoneal dialysis, his mental status remained poor. Cefepime was deemed the most likely culprit and on day 6, HD was pursued for increased drug clearance. HD was performed for 3 consecutive days with improvement in mental status after the first session and return to baseline after the third.

Discussion: The neurotoxic effects of beta-lactams have been attributed to γ-aminobutyric acid antagonism leading to diminished LOC, myoclonus, and NCSE. The connection between these symptoms and cefepime is often overlooked, especially in cases where dose adjustment was made for renal function or competing diagnoses exist. In our experience, patients on PD are more likely to be exposed to excessive cefepime doses because many providers are not aware of the poorer drug clearance this dialysis modality provides. Even when pharmacy oversight measures are in place, cefepime is not typically included in the list of monitored medications. Our institution has approved alternate broad-spectrum antibiotics (e.g., piperacillin-tazobactam) for use in the intensive care unit for patients with ESRD in hopes of reducing the incidence of cefepime-induced neurotoxicity. Meanwhile, HD remains the modality of choice for recognized cases.

PUB502

Hernia Repair and Peritoneal Dialysis: A Case Report of Successful Perioperative Management in Peritoneal Dialysis at a Veterans Hospital by an Interdisciplinary Team

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Introduction: Inguinal hernia is a common complication of peritoneal dialysis (PD). It is a usual practice in the United States to transition PD to hemodialysis (HD) for hernia repair due to concern for dialysate leak and hernia recurrence, despite recomended protocols to continue PD without this transition in appropriate patients. There are few reports of successful use. We report the first case of elective inguinal hernia repair in a continuous cycling PD (CCPD) patient using a personalized protocol at the Veterans Hospital.

Case Description: The patient is a 62-year-old African American man with a past history of hypertension, congestive heart failure, and end-stage renal disease (ESRD) on PD since 1 year. He was diagnosed with right inguinal hernia and planned for elective mesh repair. The patient expressed his wish of not wanting to switch to HD unless absolutely required. Multidisciplinary liaisons including the primary nephrologist, surgery team, renal dietician, PD nurse, and the patient's family worked out a modified, personalized version of the published protocols. The patient agreed that if there were any issues needing the transition during this period he would be switched to HD. The patient had right inguinal repair with large proline hernia system mesh early March and discharged the same day. Labs were done every 3 days to assess the need for dialysis. The PD nurse closely followed the patient with daily phone calls to assess functional status. We were able to implement the above protocol successfully without requiring to switch the patient to HD and without extending the hospital stay. His post-op course was complicated by hyperkalemia (potassium ranging from 5.2-6.0) due to poor diet compliance. The renal dietician revisited the prior advised diet modifications. Potassium returned to normal with medical management and diet control.

Discussion: Though there is literature on successful maintenance of PD during perioperative management, there are very few published reports. The use of recomended protocols is not robust. From our knowledge, this is the first case report at a Veterans hospital in the USA; our case demonstrates a successful modification of protocols for the US population with an interdisciplinary team approach, with no increase in the hospital stay.

PUB503

Severe Polymicrobial Peritonitis with a Successful Outcome

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Introduction: Polymicrobial peritonitis involving gram negative organisms is considered a serious complication of peritoneal dialysis and catheter removal might be warranted in refractory cases. We present a unique case with recent initiation of peritoneal dialysis who developed severe polymicrobial peritonitis.

Case Description: A 33-year-old female was recently diagnosed with end-stage renal disease and started on continuous cycling peritoneal dialysis (CCPD) one month ago. She presented with severe abdominal pain, vomiting, and constipation. Pertinent clinical findings included tachycardia and diffuse abdominal tenderness. Initial peritoneal fluid analysis showed leukocyte count 86,325 cells/μL with 92% segmented cells. On first day, intravenous vancomycin and cefepime were administered but peritoneal dialysis (PD) was not performed due to extreme pain. Repeat peritoneal fluid WBC count had increased to 148,000 with 76% segmented cells. An emergent surgical consult was sought. Abdominal CT scan did not reveal any obvious perforation or abscess. Peritoneal fluid culture returned positive with *Klebsiella Oxytoca and* and *Enterobacter Cloacae*, both sensitive to cefepime. CCPD using tidal setting, intraperitoneal (IP) cefepime (both daily loading and maintenance doses), and IP heparin 500 units/L in all PD bags were undertaken. Over the next five days, the patient demonstrated clinical improvement and peritoneal fluid leukocyte counts decreased to 5748 on day five and 387 on day seven. The patient was discharged home on CCPD and daily IP cefepime in long dwells. After completion of four weeks of intraperitoneal antibiotic the patient is free of symptoms and tolerating CCPD well.

Discussion: This case was unique because of the complexity of peritonitis in terms of severe abdominal discomfort, unusually high leukocyte count, and identification of two gram-negative bacteria. Following initial intravenous antibiotic administration, PD fluid WBC count markedly rose but IP antibiotics using both daily loading and maintenance doses in this patient who is new to dialysis with significant residual renal function was successful. Tidal CCPD facilitated management of patient's discomfort and continue PD. It was critical to thoroughly evaluate the patient for surgical indications and prudently manage constipation.

PUB504

Hemodialysis Catheter-Induced Air Embolism

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Introduction: Air embolism is one of the fatal complication associated with central line. In a dialysis patient it is less common but if it occurs it can be life threatening. Air can enter blood vessel through the dialysis catheter or through the blood pump due to a negative pressure in circuit. This complication is relevant to field of nephrology as it is a complication of use of central venous catheters with dialysis (1). We hereby report a case of paradoxical air embolism due to air entry from hemodialysis catheter.

Case Description: 72-year-old female with a history of end stage renal disease on home hemodialysis, was found unresponsive while on dialysis with a detached catheter. Work up showed, pneumocephalus, air embolism leading to acute stroke and cerebral edema. Echocardiogram showed intracardiac shunt. Finally, the patient died.

Discussion: This case illustrates the dreadful complication associated with dialysis catheter. Recognition of this complication is important to prevent air embolism by taking appropriate preventive measures while handling dialysis catheter and also to provide education to health care provider, patient about this complication. With improvements in dialysis techology the risk is reduced but sporadic cases are reported (2). There is paucity of data on management of air embolism, and preventive measures along with the recognition of the complications are essential. Reference *Sherman RA: Daugirdas JT: Handbook of dialysis 5th edn. Hysell MK: 'Cerebral air embolism after hemodialysis' J Emerg med 2015; 49*

PUB505

Hyperglycemia-Induced Hyponatremia: A New World Record?

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Introduction: We present a case of hyperglycemia-induced hyponatremia, with a serum glucose value greater than the upper limit of laboratory detection. This poses a unique challenge. What is the approach to hyponatremia without a definitive measurement of serum glucose? The Guinness World Record for the highest serum glucose is 2,656 mg/dL--does our patient hold a new world record or is this a laboratory error?

Case Description: A 39-year-old male with no known medical history presents with hyponatremia of 102 mEq/L. His vital signs and physical examination are unremarkable. Blood glucose on point-of-care glucometer is >700 mg/dL and follow-up blood glucose on laboratory basic metabolic profile is >4000 mg/dL. There is no ketoacidosis. Nephrology was consulted for symptomatic hyponatremia in the setting of hyperglycemic hyperosmolar non-ketotic syndrome. Without accurate laboratory measurements, we estimate blood glucose by calculating the osmol gap. Measured serum osmolality is 350 mOsm/kg and calculated osmolality is 222 mOsm/kg, yielding an osmol gap of 128 mOsm/kg. Subtracting 10 mOsm/kg (for normal gap), and using a conversion factor of 18 for glucose, we estimate a blood glucose value of 2,124 mg/dL--an extreme value, but no Guinness World Record. The corrected sodium would be approximately 134 mEq/L (close to actual Na, once the glucose was normalized). The patient was treated with IV insulin and infusions of normal saline. He was discharged with a new diagnosis of type 2 diabetes mellitus.

Discussion: Glucose is osmotically active, shifting water from the intracellular compartment to the extracellular compartment and diluting sodium in the process. Following treatment with insulin, glucose is taken up by the cells and metabolized, water shifts back to the intracellular compartment, and dilutional hyponatremia is reversed. Rapid changes in serum osmolality can lead to life-threatening complications; thus, accurate laboratory values are critical. If the reported blood glucose of 700 and 4000 were used, the corrected sodium would be anywhere from 116 to 164 mEq/L, respectively, potentially misdirecting management. In this case, the correction of hyperglycemia alone was sufficient for safe "correction" of Na. Extreme values of blood glucose are associated with analytical errors. When faced with suspicious laboratory values, additional information should be used for verification.

PUB506

Management of Severe Metabolic Alkalosis in a Patient with Intractable Vomiting

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Introduction: Gastric secretion of hydrogen chloride is normally neutralized by bicarbonate secreted by the pancreas, liver, and intestines. Gastric outlet obstruction (GOO) may cause intractable vomiting with potentially life-threatening metabolic derangements including hypochloremic, hypokalemic, metabolic alkalosis. Prompt recognition and management is critical, however the decision if-when to dialyze a patient remains controversial.

Case Description: A 39-year-old male with HIV on HAART and Diffuse B-Cell lymphoma on R-EPOCH chemotherapy was admitted to the ED for intractable nausea and vomiting of one week's duration with accompanying significant weight loss. History revealed he had had a recent PET scan at an outside facility showing a gastric mass surrounding the pylorus and he was thus determined to have metastatic GOO. ABG revealed severe metabolic alkalosis 7.68/49/66 with a bicarbonate of 46 with an acute kidney injury. Intravenous normal saline with potassium replacement and pantoprazole was given and his alkalosis improved uneventfully.

Discussion: When opting for medical management in patients with true arterial volume depletion treatment typically begins with intravenous normal saline. Sodium, Chloride, and Potassium (replenishments) should correct hypokalemia and increase intravascular volume. Meanwhile, H2 blockers or proton pump inhibitors help curb nausea and decrease the quantity of HCL lost in the vomitus.[1] In select patients with poor kidney function and in whom increasing urinary bicarbonate output with acetazolamide is not feasible, acid infusions (ex: hydrochloric acid) can be cautiously considered. If the aforementioned measures fail and if there is no way to excrete acid in the urine, then dialysis is the best option. Beyond a certain point alkalemia (pH >7.65) becomes a medical emergency and carries a high risk of complications.[2] Despite the severity, a cutoff of when to choose to dialyze remains elusive. A survey of 25 Yale-affiliated nephrologists revealed that only 4 of 25 elected to use dialysis for patients with severe metabolic alkalosis.[3] When choosing a dialysate a low-bicarbonate dialysate is preferable as it rapidly improves alkalosis. In our patients' case, correcting the underlying cause is the best approach to permanently reverse his alkalosis.

PUB507

An Intentional Ingestion of 23.4 g of Potassium

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Introduction: Hyperkalemia from ingestion is relatively uncommon in patients with normal renal function. In most cases of ingestion, only one episode of renal replacement therapy is needed for clearance of excess potassium. While potassium supplementation is fairly safe, hyperkalemia can be associated with potentially life-threatening arrhythmias and cardiopulmonary arrest.

Case Description: A 63-year-old man with a prior history of HIV, Hepatitis C, CVA, and hypertension was brought to the hospital by EMS for altered mental status. His neighbor reported weakness for the past week and increasing confusion. The patient's vital signs were normal. He was confused but able to answer most questions appropriately. His lab results demonstrated a serum potassium level of 8.3 and a creatinine of 1.4 (baseline 1.0). An EKG demonstrated atrial fibrillation with a widened QRS interval, prolonged PR interval and peaked T waves. An abdominal x-ray demonstrated innumerable radiopaque pill fragments in the stomach. The pills were presumed to be the patient's home 10 mEq KCl tablets. The patient was given calcium gluconate, albuterol, insulin and glucose, sodium bicarb, and rectal sodium polystyrene sulfonate. An OG tube was placed and returned 600 mL of brown liquid as well as some small pill fragments. Repeat abdominal x-ray demonstrated persistent pill fragments in the stomach and a gastroenterology consult was placed for emergency endoscopy with pill removal. Upon endoscopy, the stomach appeared to have ischemic changes, but no pill fragments were visualized. Nephrology was consulted for emergent dialysis, and the patient was placed on intermittent hemodialysis for 2 hours followed by sustained low-efficiency daily dialysis for 6 hours. The patient's potassium normalized but increased to 6.5 less than 12 hours later, necessitating repeat intermittent hemodialysis and sustained low-efficiency daily dialysis.

Discussion: This case illustrates the need for repeat renal replacement therapy after a patient ingested 23.4 grams of oral potassium – 60 10 mEq KCl tablets in total. While there are case reports of overdose by IV KCl, oral potassium supplements have been considered safer due to delayed absorption and difficulty in taking large doses due to large pill size. In addition, severe hyperkalemia due to overdose by oral hyperkalemia is uncommon in patients with preserved renal function.

PUB508

Fanconi Syndrome and Hypomagnesemia: An Overlooked Association or Diagnostic Entity?

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Introduction: Fanconi's Syndrome is associated with hypophosphatemia, aminoaciduria, and renal glycosuria. However, there is significant variability in the phenotypical presentation of this disease process. Time to diagnosis and length of underlying etiologies such as multiple myeloma or medications can play a role in the presentation, specifically between acquired and congenital Fanconi's Syndrome. Though typically not considered a classical association with Fanconi's Syndrome, hypomagnesemia is occasionally noted in the literature in association with this disease and seems to be an underrecognized feature of this entity.

Case Description: A 65 year old female with history of recently diagnosed multiple myeloma (2 months prior), hypertension, and previously treated hypercalcemia now hypocalcemic presented with carpo-pedal spasms. One month prior she was treated with cyclophosphamide, bortezomib, dexamethasone, and denosumab. Corrected calcium was 6.2 mg/dL, bicarbonate 16 mEq/L, potassium 2.4 mEq/L, chloride 112 mEq/L, magnesium 1.3 mEq/L, phosphorus 1.3 mg/dL, anion gap 15, and creatinine 1.42 mg/dL with AKI with a baseline of 0.6 mg/dL. Urine bicarbonate was 8 in the setting of acidosis. Fractional excretion of magnesium was 28% in the setting of hypomagnesemia. Urine anion gap was 20, pH of the urine 8.0. No glucosuria. TTKG was 4.75 indicating potassium losses in the setting of hypokalemia. Aminoaciduria was present. With these findinds, the diagnosis of Fanconi's Syndrome, Renal Tubular Acidosis Type II in association with Multiple Myeloma was made. Oral replacements of electrolytes and Amiloride were started, with stabilization of electrolytes.

Discussion: Though hypomagnesemia is not classically noted as an association with Fanconi's Syndrome, such as glucosuria, aminoaciduria, and hypophosphatemia, it appears to be an under-recognized feature of this disease process. As stated in the limited literature with this association, there is cellular injury at the nephron primarily at the proximal tubular cells impairing passive reabsorption of magnesium in Fanconi's Syndrome. Underscoring this electrolyte disorder of this syndrome may better allow future clinicians to recognize hypomagnesemia in the setting of a non-anion gap metabolic acidosis and perhaps be considered as a diagnostic entity.

PUB509

Achieving Osmotic Stability in the Context of Critical Illness and AKI During Continuous Renal Replacement Therapy

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Introduction: The concept of osmotic stability during renal replacement therapy has received limited attention thus far. Customary pre-mixed continuous renal replacement therapy (CRRT) solution is manufactured with a sodium concentration of 140 mEq/L, potentially representing hypotonic solution when considering the protein-free serum sodium concentration of 154 mEq/L. We present an illustrative case of hypertonic saline (HTS) utilization after cardiac arrest and acute kidney injury to achieve osmotic stability during critical illness while performing CRRT.

Case Description: A 22-year-old male with no known past medical history presented after prolonged ventricular fibrillation with 75 minutes of resuscitative efforts before regaining spontaneous perfusing rhythm. On arrival, he was hypotensive and required multiple vasoactive agents. Central nervous system protecting hypothermia protocol and veno-arterious (VA) extracorporeal membrane oxygenator (ECMO) therapy were initiated at hospital admission due to refractory hypoxemia. Head CT scan did not show acute intracranial processes, but cardiovascular imaging procedures described global hypokinesis with thrombus formation in the left ventricle and aorta. Due to the combination of anuria, mixed metabolic respiratory acidosis and hemodynamic instability, we started CRRT in continuous veno-venous hemodiafiltration functionality with added HTS protocol, calculated to stabilize his serum sodium between 148-150 mEq/L. Serum osmolality was 304 mOsm/kg on initiation of CRRT and ranged between 321-317 mOsm/kg thereafter. Course was complicated by an acute right leg ischemia distal to VA ECMO cannula placement, which required salvage therapy with cryo-amputation. Vasoactive medication requirement and hemodynamics improved after the addition of IV hydrocortisone. Brain MRI 22 days post-arrest showed signals of limited hypoxic injury. He left the hospital in stable condition after 31 days with creatinine 1.9 mg/dL and limited neurological sequelae.

Discussion: Use of HTS during CRRT is a viable way to increase serum osmolality to address potential or manifest cerebral edema and reduce the degree of cerebral injury. Additional studies are warranted to explore the significance of osmolar shifts during CRRT in the critically ill with regards to neurologic outcomes.

PUB510

Hypokalemic Periodic Paralysis in Sjogren Syndrome

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Introduction: Renal involvement in Primary Sjogren's syndrome is a rare event usually occurs in less then 10% of the patient and usually has a favorable prognosis. Renal involvement may include isolated electrolyte disorders, nephrolithiasis, nephrocalcinosis, Tubulointerstitial nephritis (TIN), and Glomerulonephritis. We report a case of periodic paralysis due to severe hypokalemia secondary to Distal Renal tubular acidosis (dRTA), with primary disease as Sjogren's syndrome.

Case Description: A 50 year old hypertensive male, presented with complains of generalized body weakness for the past 4 weeks, with complains of intermittent left flank pain. There was no history of any Urinary abnormalities, Gastrointestinal, Respiratory, or any history of autoimmune features. The only medicine, which the patient was taking, was amlodipine for his HTN. On examination the only significant findings were decreased power 3/5 bilaterally in lower extremities, with normal reflexes and normal sensory system. Basic metabolic panel revealed Normal **complete blood count (**CBC), with normal renal function tests and liver function tests. Serum electrolytes revealed potassium of 1.9 mEq/dl, Sodium 136 mEq/dl, Chloride 116 mEq/dl, Bicarb levels 10 mEq/l, Calcium 9.7 mg/dl, Magnesium 2.1 mg/dl, normal serum anion gap, urinalysis revealed pH of 8, with no proteinuria or active urinary sediment. Extractable Nuclear Antigen Antibodies (ENA) profile revealed Antinuclear antibodies titer of 1:320, **ANTI SS-B (La)** and **ANTI Ro-52** antibodies were strongly positive. Complement levels were normal. **24 Hrs Urinary potassium** levels were 32.34 mmol/24 Hrs and the urinary anion gap of 40 mEq/l. Ultrasonogram reveals 2 calculi in the lower pole, with mild hydronephrosis. Laboratory investigations were consistent with diagnosis of Primary Sjogren's syndrome with dRTA. We repleted the patient with intravenous potassium chloride and bicarbonate, with subsequent shift to oral potassium citrate, which remarkably improved the patients symptoms. The patient was referred to Rheumatologist for further management.

Discussion: Primary Sjogren's syndrome as with most rheumatologic diseases is more common in females, male presenting with renal involvement is scarcely reported to the best of our knowledge. Further diagnosing primary Sjogren's without any clinical symptoms (i.e xerostomia, or xeropthalmia) is a rare entity.

PUB511

Normal Saline Mitigates Refractory Alkalosis in Continuous Renal Replacement Therapy

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Introduction: Respiratory alkalosis is typically a sign of an underlying pulmonary or central nervous system disease. Emergent treatment is warranted when pH levels are above 7.5. Treatment is usually correction of the underlying cause. We describe a patient with refractory respiratory alkalosis on continuous renal replacement therapy (CRRT) which was offset by the use of normal saline (NS) in the pre and post-CRRT filter replacement fluids.

Case Description: A 68 year old lady on peritoneal dialysis (PD) presented with septic shock secondary to peritonitis. Hospitalization course was complicated by hypoxic respiratory failure necessitating mechanical ventilation, subsegmental pulmonary thromboembolism (PTE), and subacute ischemic white matter infarcts with no evidence of increased intracranial pressure or cerebral hemorrhage. She was on broad spectrum antimicrobials, stress dose steroids and vasopressors. PD catheter was removed; and she was started on Continuous Venovenous Hemodiafiltration modality of CRRT. The prefilter, dialysate, and postfilter replacement fluids were at 700 cc/hr, 700 cc/hr and 200 cc/hr respectively. Each of these solutions contained 35 mEq/L of bicarbonate given septic shock, severe lactic acidosis and fulminant hepatic failure. No fluid was actively removed through CRRT. Effluent dose was 26 ml/kg/hr. ABG was consistent with an acute uncompensated primary respiratory alkalosis (pH 7.7 and serum bicarbonate level of 23 mEq/L) which did not improve despite optimal sedation, pain control and varied ventilator setting adjustments. The etiology was thought to be due to central neurogenic hyperventilation secondary to cerebral infarction and peripheral pulmonic receptor stimulation caused by PTE. The pre and postfilter solutions were replaced by normal saline at 500 cc/hr each; with the dialysate and fluid removal rate remaining unchanged at 700 cc/hr and 0 cc/hr respectively. The total bicarbonate amount for this combination was 14 mEq/L. Effluent dose was 27 ml/kg/hr. Within 12 hours, serum bicarbonate levels decreased to 14 mEq/L and pH improved to 7.48. Despite this, she had worsening hypoxia and hypotension, and subsequently died.

Discussion: NS is acidic with a pH of 5.5-6, and its use in CRRT can help mitigate refractory alkalosis. Furthermore, dialysis against NS results in loss of bicarb down a concentration gradient since NS does not contain any alkali.

PUB512

Use of Gastric Anion Gap (GAG) in Acute Metabolic Alkalosis

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Introduction: Metabolic Alkalosis(MA) is a common electrolyte disorder seen in hospitalized patients. It is due to loss of acid or gain of alkali. MA is routinely seen in hospitalized patients with vomiting, use of diuretics, and Naso-Gastric(NG) suction.

Adverse effects of MA include hypokalemia, arrhythmias, and neuromuscular irritability which increases morbidity and mortality. We are presenting a case of MA in a patient with Ileus, who was successfully treated with Proton Pump Inhibitor(PPI) and Chloride Based-Intra Venous Fluids(CB-IVF).

Case Description: 67 y/o male with history of DM, HTN, CKD3 presented with AKI from obstructive uropathy from Hemangioma causing hydronephrosis and he underwent surgical resection with improvement of AKI. Post operatively patient developed Ileus and had significant drainage from NG suction. During this time, he had recurrence of AKI with severe MA with Venous Ph of 7.63. Serum electrolytes revealed Potassium(K) of 3.1meq/dl and CO2 50meq/dl with Creatinine of 7mg/dl. He was treated with CB-IVF and IV Protonix 40mg BID. Labs 24hrs after PPI showed improvement of CO2 to 44meq/dl and hypokalemia resolved with same Cr. We obtained the Gastric electrolytes to measure the Gastric Anion Gap(GAG) before and after PPI to monitor the response of MA as shown in Table.

Discussion: Patients with Ileus are at risk of losing large amount of UGI fluid and electrolytes by vomiting or NG suction and can generate severe MA. This case shows the importance of a simple measures such as PPI use with CB-IVF to improve Alkalemia. If patients cannot tolerate IVF (Eg: ESRD patients) then PPI alone may be used with good results. We showed the electrolyte pattern to illustrate physiological changes at cell level pre-and post-use of PPI. Gastric electrolyte secretion under normal stomach function has high Chloride(Cl) content which gives negative GAG. PPIs decreases Cl content in stomach by inhibiting parietal cell H+-K+-ATPase. Decreased Cl content in UGI fluid is a surrogate marker of decreased Proton secretion. Conclusion: PPI should be considered in the treatment of Metabolic Aklalosis caused by UGI loss.

Gastric Fluid Electrolytes Pre and 24hr Post PPI

	Pre	Post
Sodium meq/dl	39	39
Potassium meq/dl	8	9
Chloride meq/dl	111	43
Gastric Anion Gap (GAG)	-64	+5

PUB513

A Case of Severe Metabolic Alkalosis and Renal Insufficiency

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Introduction: Vomiting, nasogastric aspiration and diuretics being the most common cause, metabolic alkalosis is defined elevation in serum bicarbonate, > 30 mmol/l, and arterial pH ≥7.45. The pathophysiology of metabolic alkalosis can be complicated, H^+ loss plus reduced filtered bicarb (i.e. renal hypoperfusion, CKD), bicarb reabsorption (i.e. hyperaldosteronisms, hypokalemia), H^+ secretion by α-intercalated cells (i.e. primary hyperaldosteronisms, chloride depletion), and/or Impaired bicarb secretion by pendrin (i.e. Cl depletion, CKD). Pco2 may increase as a compensatory mechanism. Patients can be asymptomatic or symptomatic due to underlying etiology and electrolyte disbalance; easy fatigability, dizziness, muscle weakness, tetany, cardiac arrhythmias, disorientation, seizures, and coma in patients with chronic liver disease.

Case Description: A 23-year-old African American male presented to ED with history of 3 months emesis which worsened 3 weeks with abdominal pain prior to presentation. He reports recent heavy alcohol consumption and smoking marijuana. His last recorded creatinine was 1.6, 2 months prior to presentation. On physical examination, the blood pressure was 116/59 mm Hg, pulse of 105, respiration of 20 and BMI 17.7. The patient was alert and oriented with respirations regular and unlabored. Labs were significant for blood glucose of 152, Na^+ 120, K^+ 2.5, Cl^- <60, Mg 1.4 mmol/L, bicarbonate 46, BUN 113, Cr 5.7, ABG 7.68/56/84/43. Urinalysis showed large leukocytes, small blood, RBC 5, and urine chemistry Na 18, K 61.1, Cl <10, Cr 115.1. He received 2 L normal saline and continued normal saline with potassium 40 mEq at 150 ml/hr and Pantoprazole 40 mg IV. Oral potassium initiated after he was able to tolerate oral intake.

Discussion: Severe metabolic alkalosis is a medical emergency due to electrolytes imbalance, specially, hypokalemia. History is the key to narrow down and diagnosis of underlying cause. In his case, the patient had multiple electrolyte disbalance, sever hyponatremia, hypokalemia along with renal insufficiency in setting of hyperemesis. We approached conservative management since our patient did not have chronic illnesses along with assessment at each step. His electrolytes improved by second day of hospitalization. BUN and Cr plateau and decline after 36 hours of hospitalization. Nevertheless, renal replacement therapy would have been the ultimate option if no renal recovery.

PUB514

The Double-Edged Sword of Desmopressin Acetate (DDVAP): Severe Hyponatremia Post-Renal Transplant Biopsy

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Introduction: DDAVP, a synthetic analogue of vasopressin, binds V2 receptors on kidney tubular and vascular endothelial cells, producing an antidiuretic effect and release of von Willebrand factor and factor VIII. Its use as a hemostatic agent prior to kidney biopsy reduces bleeding risk. However, it has been shown to increase risk of severe hyponatremia. We describe a case of DDAVP used prior to renal transplant biopsy leading to severe hyponatremia with neurologic manifestations.

Case Description: A 63 year old woman with end stage renal disease secondary to hypertension, underwent a blood group compatible, 1A2B0DR HLA mismatch deceased donor renal transplant, with thymoglobulin induction and maintenance with mycophenolate, tacrolimus, and prednisone. Post-op course was uneventful and nadir creatinine (Cr) was 0.8mg/dL. On post-op week 5, surveillance donor-derived cell-free DNA was elevated and de-novo donor specific antibodies were detected. Cr remained stable at 0.8mg/dL. Biopsy was performed given concern for rejection. Serum sodium (Na) was noted to be 140mmol/L and standard pre-biopsy intravenous 0.3mcg/kg DDAVP was given. Post-biopsy observation was uneventful and she was discharged home. That evening, she noted decreased urinary output and increased her free water intake. Transplant team was notified the next day, and she returned to the hospital, where Na was 123mmol/L. She had no neurologic manifestations. She was placed on fluid restriction. Six hours later, she developed nausea with vomiting and became acutely altered, with decreased responsiveness. She had worsened hyponatremia of 118mmol/L. She received 250mL of 3% normal saline resulting in correction of Na to 125mmol/L and complete resolution of encephalopathy.

Discussion: The use of DDAVP prior to renal transplant biopsies decreases bleeding risk in patients with and without renal impairment or coagulopathy. However, severe hyponatremia is increasingly being recognized as a potential complication and strategies to reduce risk are necessary. In our case, severe hyponatremia may have been avoided by clear patient understanding of potential decreased urinary output, avoiding excess free water intake, and transplant team notification. This case demonstrates the importance of careful selection, monitoring, and counseling of patients who receive pre-biopsy DDAVP.

PUB515

Antidiuretic Hormone: You Don't Know What You've Got 'Til It's Gone

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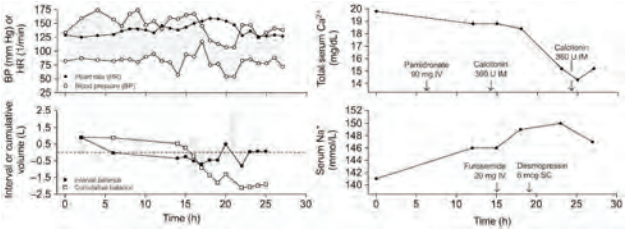
Introduction: Profound salt and water wasting may develop during severe hypercalcemia in patients with premorbid primary ADH deficiency (central diabetes insipidus).

Case Description: A 68-year-old man with panhypopituitarism presented with 3 days of lethargy, confusion, polyuria, polydipsia, and subacute hip pain. Admission vital signs showed tachycardia (HR 130/min) and hypertension (BP 159/87 mm Hg). Exam disclosed a thin older man who was restless and confused; lungs were clear and there was no edema. Key blood lab results were Na 141 mmol/L, K 2.9 mmol/L, and Cr 3.53 mg/dL without antecedent kidney disease. Blood total Ca was 19.8 mg/dL (RR: 8.9-10.7) and PTH was 16.6 pg/mL (RR: 8.7-77.1). A head CT showed multiple cranial osteolytic lesions. For hypercalcemia, he received two 1-L normal saline boluses over 7 h and then 90 mg IV pamidronate. After 12 h he had urinated >2.3 L. Tachycardia and hypertension worsened: HR 150/min and BP 167/90 mm Hg. Total blood Ca stayed high at 18.8 mg/dL. He was given 360 U IM calcitonin and 20 mg IV furosemide. Over the next 3 h his intake was 1.9 L of normal saline and urine output was 4.3 L, after which his HR rose to 160/min and BP fell to 107/54 mm Hg. It was discovered that his desmopressin (used at home for central diabetes insipidus) was not administered in >24 h. He was immediately given 6 mcg SC desmopressin. Urine output rapidly decreased and hemodynamics improved. Given premorbid diabetes insipidus, severity of hypercalcemia, and tenuous hemodynamics, we elected to initiate kidney replacement therapy.

Discussion: This case highlights the critical role of ADH in maintenance of normal body water volume. This patient was reliant on exogenous ADH to maintain normonatremia and appropriate volume status. His ADH was unavailable to him, and unopposed aquaresis ensued. Furthermore, he had partial nephrogenic diabetes insipidus and salt wasting, both from hypercalcemia; thus, he displayed profound diuresis. Generally, urine output drops with volume depletion due in part to ADH release. This case demonstrates what happens when ADH is absent and the consequences of unchecked urination.



PUB516

First Reported Case of H-NAGMA in a Patient Undergoing Continuous Bladder Irrigation

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Introduction: Continuous bladder irrigation is a well-accepted treatment for clot evacuation in patients suffering from hemorrhagic cystitis. In this case we describe the development of a non-anion gap hyperchloremic metabolic acidosis in a patient receiving CBI for radiation-induced hemorrhagic cystitis. Secondary to fluid retention in the bladder following irrigation, the damaged urothelium permitted absorption of saline, producing a non-anion gap metabolic acidosis in addition to other symptoms of volume overload. Following treatment with IV sodium bicarbonate, this patient improved clinically, and the metabolic acidosis resolved.

Case Description: A 77 year-old female presented to the emergency department with a chief complaint of hematuria for 1 day. The patient had a past medical history of uterine cancer treated with radation, complicated by recurrent hemorrhagic cystitis. During the

course of stay, the patient required CBI for removal of clots within the bladder and to prevent urinary retention. Lack of drainage from the catheter was noted multiple times and between 8-10 L of fluid were drained providing symptom relief. On day 8, HCO3 was 11 mmol/L and Cl was 122 mmol/L. Acidosis began to improve by hospital day 9 after patient was started on 650 mg of sodium bicarbonate, with the patient's bicarbonate levels returning to 22 mmol/L after several days on bicarbonate.

Discussion: CBI with 0.9 percent normal saline (NS) is the standard of care for clot evacuation. Elliot *et al.*, studied exfoliation rates of urothelial cells in patients with chronic urinary tract infections and in patients with long-term indwelling catheters. They observed bladder irrigation was associated with an increased disruption of urothelial cells which in turn predisposes the bladder to recurrent infections. In 2014 Paolo *et al.*, reported acute severe pulmonary edema in an 85-yr-old male who underwent CBI. In this case, bladder irrigation led to systemic absorption of fluid from bladder urothelium that manifested as NAGMA. As the serum chloride level started to increase, it decreased serum HCO_3 causing H-NAGMA. Once we held bladder irrigation, the chloride levels decreased followed by improvement of HCO_3 and resolution of acidosis. The patient was not on IV fluids suggesting that systemic absorption occurred from bladder urothelium leading to pulmonary edema and acidosis.

PUB517

Metformin-Associated Lactic Acidosis: Treatment With Different Types of Renal Replacement Therapy

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Introduction: A potential complication of metformin is the development of type B (non-hypoxic) lactic acidosis. We present the case report of two patients who were receiving treatment with metformin and developed severe metformin-associated lactic acidosis. Both whom recievied different types of renal replacement therapy for the management of lactic acidosis and renal failure.

Case Description: CASE 1. A 70-year old woman with type 2 diabetes treated with metformin, presented with neurological impairment, hemodynamically unstable and hyperlactatemic metabolic acidosis with serum lactate of 17 mmol/L, creatinine 5.04 mg/dL. We rule out different causes of severe lactic acidosis. Metformin serum levels were obtained with a total of 41mcg/mL. The patient received treatment with 23 hours of continuous hemodialysis. At the end the patient, recover her renal function to normal standards. CASE 2. A 63-year old man treated with metformin, presented with a history of abdominal pain accompanied by nausea and vomit. At his arrival to the ER we found him hemodynamically unstable and bradycardic, which, developed to asystolia soon after. He required advance cardiopulmonary life support and he was found with a hyperlactatemic metabolic acidosis with a serum lactate of 15mmol/L and creatinine 14.54 mg/dL; we ran serum metformin levels with a result of 14 mcg/ml. We started renal replacement therapy with conventional hemodialysis for 8 hours. It was interesting to watch a rebound and raise of metabolic acidosis 6 hours after we finish the first hemodialysis session. We then decided to reinitiate another 8-hour of hemodialysis; the patient did not require any other maneuver for acidosis with progressive improvement to his evolution. After he was discharged from the hospital he required once-weekly hemodialysis session only for one month.

Discussion: In our experience, both cases presented in the context of an acute kidney injury; another thing to highlight is that we found a rebound of lactic acidosis after the first hemodialysis session in a period of 6-hour. The different types of dialysis in both cases were effective, albeit intermittent dialysis allows a faster clearance of serum metformin levels with less time and cost, it should always be considered as first choice in all patients who have immediate access to it.

PUB518

Excessive Water Intake Causing Severe Metabolic Alkalosis

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Introduction: Severe metabolic alkalosis is one of the most dreaded acid-base disorders. It is defined as a pH of more than 7.60 with serum bicarbonate of more than 40 mmol/L. Clinical features include confusion, seizures, and cardiac arrhythmias. Mortality rate increases significantly with the severity of the alkalosis and can reach up to 80% with a pH of more than 7.60. We present a case of severe metabolic alkalosis with a pH up to 7.70 in a patient with a jejunostomy and a gastrostomy tube.

Case Description: The patient is an 82-year-old female with diabetes mellitus, cardiac arrhythmia and perforated gastric ulcer. She was admitted with syncope and found with severe metabolic alkalosis. Two months prior to her presentation, she had an open jejunostomy for tube feeds with a gastric tube for drainage. Formal instructions were to only take occasional sips of water. The day prior to admission, she had increased thirst and started to drink a large amount of water. She then noticed large drainage into her gastrostomy bag. Admission arterial gas showed a pH of 7.70, pCO2 of 70 mmHg. Blood work had sodium of 137 mEq/L, potassium of 2.5 mEq/L, chloride of 60 mEq/L, bicarbonate more than 50 mEq/Liter and glucose of 466 mg/dL. Urinalysis showed a pH of more than 9. EKG had atrial paced rhythm. CT of the abdomen had jejunostomy and gastric tube well positioned. The patient was treated aggressively with normal saline, potassium, Acetazolamide and Protonix. She improved significantly after 2 days with potassium of 3.1 mEq, chloride of 90 mEq/L, serum bicarbonate of 43.6 mEq/L.

Discussion: Our patient, had severe metabolic alklaosis secondary to massive gastrointestinal drainage in her gastric tube. In addition she was volume depleted contributing to her metabolic alkalosis. The excessive volume of water ingested prior to her presentation likely triggered the increased gastric secretion. We believe the gastric distension due to the ingsted water, resulted in excessive grastric secretions by stimulating the stretch receptor. The treatment includes aggressive hydration, potassium repletion, Proton Pump Inhibitor, Acetazolamide and hydrochloric acid infusion in refractory cases. Hemodialysis has also been used. Our case demonstrates that good outcome can be achieved with prompt, aggressive and appropriate treatment of severe metabolic alkalosis.

PUB519

Hyponatremia in a Patient Receiving Chemotherapy

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Introduction: Hyponatremia is common in cancer patients

Case Description: A 76 YO woman with a history of hypothyroidism, gout, HTN, CKD stage III, stage IVB recurrent metastatic endometrioid serous carcinoma treated with TAH-BSO and adjuvant chemoradiation was started on phase I chemotherapy protocol with Atezolizumab and Cabozantinib. During the 2nd cycle visit she was found to have a serum sodium of 122[baseline at 1st visit 138]. Review of systems has revealed loose stools few times/day 2 weeks associated with decreased food intake and increased fluid intake. Her medications include levothyroxine, allopurinol, hydrochlorothiazide, furosemide. Physical examination was unremarkable and appeared euvolemic. Her labs showed sodium (Na) 118, Sr osmolality 260, K 3.4, glucose 109, TSH 6.23, FT4 1.65, urine Na 45, urine osmolality 185. She was put on fluid restriction and careful NS infusion with temporary discontinuation of diuretics. She was discharged with a Na of 130 on day 3 with instructions to follow up in a couple of days. Etiology of hyponatremia in this patient is most likely multifactorial due to increased water intake with low solute intake and impaired diluting capacity of the kidneys with continued use of diuretics. In addition, coupled with Atezolizumab and cabozantinib therapy as superimposed factors cannot be ruled out as they have also been shown to cause hyponatremia. Although untreated or partially treated hypothyroidism is well known to impair urine diluting capacity, our patient was euthyroid which makes hypothyroidism less likely

Discussion: Hyponatremia is commonly diagnosed in cancer patients, but only in 1/3 of the cases is related to SIADH. Hyponatremia was seen in ≥ 2% of NSCLC patients treated with Atezolizumab in phase 1, 2 and 3 studies in the available literature. On the other hand, Cabozantinib used in the treatment of advanced renal cell carcinoma has also been shown to cause hyponatremia and it was reported in up to 20% of patients. With the growing armamentarium of oncologic treatments and their effects on electrolytes, a physician involved in managing the care of cancer patients needs to aware of these effects. SIADH is a known cause of hyponatremia but efforts be made to look for a reversible etiology before attributing it to SIADH which can help in a timely and appropriate management and reducing the cost of elaborate investigations

PUB520

Extreme Hypernatremia of Uncertain Cause Progressed in 1 Month

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Introduction: Hypernatremia, which is a common cause of impaired consciousness among elderly people, develops due to many factors. However, it is rare for the serum sodium concentration to increase to over 200 mEql/L. We herein report a case of extreme hypernatremia (sodium levels >190 mEq/L) of uncertain cause that progressed over a month.

Case Description: An 82-year-old woman was admitted to our hospital with impaired consciousness and a 3-day history of progressive weakness. One month prior to admission, she had shown pyelonephritis that was treated with antibiotics, and her serum sodium level had been 144 mEq/L on the day of discharge. From two weeks after discharge, she gradually lost her appetite and subsequently developed impaired consciousness and weakness of the whole body. On an initial examination, her conscious state was 4 on the Glasgow Coma Scale, but there were no obvious signs on head-computed tomography. Blood laboratory test results showed a sodium level of 205 mEq/L, blood urea nitrogen level of 133 mg/dL, creatinine level of 2.54 mg/dL, blood glucose level of 319 mg/dL, and serum osmolarity of 470 mOsm/kgH_2O. The patient was admitted to the intensive-care unit for treatment of severe hypernatremia and acute kidney injury secondary to dehydration. The intravenous administration of 5% glucose as hypotonic fluid was immediately started, with the maximum rate of correction of sodium concentration set at 8mmol/L/day. Nine days after admission, her serum sodium level had decreased to 147 mEq/L, and her consciousness had improved to the point where she could say a few words. Feeding training and physical rehabilitation succeeded, and she was discharged on the 64th day with no specific problems.

Discussion: In the present case, the patient lost 7 kg of her body weight over a month and was dehydrated. As there were no episodes of her having ingested too much sodium, her clinical symptoms and data suggested that she had instead lost too much free water. The loss of free water was attributed to an impaired thirst as a consequence of aging and osmotic diuresis secondary to hyperglycemia. Then, secretion of antidiuretic hormone (ADH) (3.1 pg/ml) may have been insufficient for her high serum osmolarity. Consequently, we have concluded that these multiple factors combined to lead to extreme hypernatremia.

PUB521

Prophylactic Dose of Posaconazole Causing Syndrome of Apparent Mineralocorticoid Excess

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Introduction: Acute myeloid leukemia (AML) is typically treated with induction chemotherapy and prophylactic antifungal, antiviral and antibiotics. Posaconazole (PCZ) is an extended-spectrum antifungal agent used during induction chemotherapy for AML. We report a case of acquired syndrome of apparent mineralocorticoid excess (AME) from prophylactic dose of PCZ. AME syndrome is characterized by hypertension, metabolic alkalosis and hypokalemia.

Case Description: A 62 -year-old female with newly diagnosed AML was treated with idarubicin, cytarabine, prophylactic PCZ, levaquin and acyclovir. She was normotensive, normokalemic with normal serum bicarbonate [$HCO3^-$] on admission. She developed hypokalemia and metabolic alkalosis on day five of treatment, initially attributed to diarrhea. Over 100 meq of potassium (K) supplementation per day was given with no improvement in hypokalemia, despite resolution of her diarrhea. Serum K nadir was 2.3 meq/l, serum $HCO3^-$ levels peaked to 33 meq/L. She was hypertensive despite febrile neutropenia, poor oral intake and start of losartan. Further investigation revealed Urine K/Cr (potassium to creatinine) ratio of 5.8meq/mmol (abnormally high for serum K of 2.3 meq/l), serum aldosterone of <3 ng/dl and renin of <2.1 pg/dl. PCZ was discontinued. Serum K, serum $HCO3^-$, Urine K/Cr ratio were followed at 1, 2 and 3 weeks. K supplementation was gradually decreased, and was completely discontinued at 3 weeks. Serum $HCO3^-$ and systolic blood pressure normalized to 24 meq/L and 110mmhg respectively.

Discussion: Resolution of AME, with discontinuation of PCZ is suggestive that the AME is attributable to PCZ. The mechanism of action is thought to be due to inhibition of the 11β-hydroxylase enzyme resulting in AME activity. There are a few case reports with similar presentation on therapeutic dose of PCZ. Prompt recognition of this adverse effect, even on prophylactic dose of PCZ, by oncologist and consulting nephrologist is necessary to avoid complications of severe refractory hypokalemia. Testing of urine K/Cr ratio, aldosterone and renin levels should be undertaken to screen for AME. Discontinuation of PCZ and starting an alternative antifungal becomes imperative, if AME screening is positive.

PUB522

Posaconazole-Induced Apparent Mineralocorticoid Excess

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Introduction: Apparent mineralocorticoid excess should be considered when presented with hypokalemia, metabolic alkalosis and hypertension when on azole antifungals

Case Description: A 68-year-old lady with hypertension (on Losartan) and acute myeloid leukemia was admitted for management of relapsed AML. AML was treated with ARA-C, Daunorubicin, Etoposide and Lenalidomide. She had been on Tenofovir for hepatitis B reactivation. Current admission was complicated by prolonged diarrhea, MDR E. Coli bacteremia and neutropenia. She was treated with Ceftazidime, Vancomycin, Acyclovir and Posaconazole. Persistent hypokalemia/metabolic alkalosis were noted. Physical examination revealed a blood pressure of 159/69 mm Hg, heart rate 67/minute, mild pallor and trace lower extremity edema. Laboratories showed sodium 143 mEq/L, Chloride 93 mEq/L, potassium 2.8 mEq/L, bicarbonate 37mEq/L, BUN 8 mg/dL, Creatinine 0.7 mg/dL, Calcium 8.4 mg/dL, phosphate 3.2 mg/dL, pH 7.52, pCO2 46, pO2 223, urine chloride 101 mEq/L and potassium 50 mEq/L. Tenofovir can induce hypokalemia by causing proximal tubular damage, but this is associated with acidosis. Hypokalemia, metabolic alkalosis and worsening hypertension pointed towards a mineralocorticoid excess state. Serum cortisol levels were normal, CT of the chest/abdomen did not show pulmonary or adrenal masses. Renin and aldosterone levels were significantly suppressed at 0.05 ng/mL/h and 2ng/dL respectively, contrary to expectations with the use of Losartan. An apparent mineralocorticoid excess (AME) state was suspected and confirmed by a 24-hour urine cortisol/cortisone ratio of 0.89 (normal 0.3-0.5). She denied licorice intake. Review of literature indicated that azole anti-fungals like Posaconazole can cause AME. Spironolactone was initiated with resolution of all electrolyte abnormalities and hypertension.

Discussion: Cortisol is converted to cortisone in the distal tubule by 11 β-Hydroxysteroid dehydrogenase type 2 (11 β-HSD2). This enzyme prevents cortisol (usually > 1000-fold higher concentration than aldosterone) from activating the mineralocorticoid receptor, as cortisone does not activate this receptor. Posaconazole (and itraconazole) inhibits this enzyme causing a state of apparent mineralocorticoid excess and precipitating hypokalemia and alkalosis. Treatment includes either stopping posaconazole or starting Spironolactone.

PUB523

Severe Hypokalemia Caused by Untreated Distal Renal Tubular Acidosis: Dynamic Renal Potassium Handling in Action

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Introduction: In addition to severe acidosis, patients with untreated distal renal tubular acidosis (RTA) may develop symptomatic severe hypokalemia indicative of dramatic depletion of total body potassium stores. Although rare, it may be life-threatening because of cardiorespiratory compromise.

Case Description: We present the case of an 11-year-old girl with distal RTA caused by novel homozygous mutations in the gene encoding for the ATPase H^+ Transporting V1 Subunit B1 (ATP6V1B1; c.484_486del; p.Glu182del). Over several weeks, she stopped taking her medications (potassium citrate, potassium chloride and sodium bicarbonate). During this time, gradual progressive muscle weakness was documented. On admission, several serum laboratory investigations were abnormal: total CO_2 was 14 (normal range, 22-30), potassium (K^+) was 1.5 mmol/L (normal range, 3.7-5.0) and creatine kinase was 2223 U/L (normal range, 50-295). Physical examination revealed profound weakness, absent deep tendon reflexes, and paralytic ileus. Electrocardiogram changes characteristic of hypokalemia were also observed. A normal MRI of the brain and spine ruled out Guillain-Barre syndrome. Correction of acidosis and hypokalemia resulted in a complete reversal of all symptoms and laboratory investigations over three days. Supplementation of more than half of her calculated total body K^+ (~55 mEq/kg) had to be provided over two days to normalize serum K^+ concentration.

Discussion: A literature review from 1960 onwards revealed nine reports describing pediatric patients with RTA presenting with severe hypokalemia accompanied by varying degrees of muscle weakness. We provide a detailed overview of the clinical presentation, differential diagnosis and management for such patients. We also discuss the pathophysiology of urinary potassium wasting in the context of distal RTA, with a particular emphasis on the impact of stopping potassium and alkali supplementation on the development of severe hypokalemia. This case highlights that it can be very challenging to distinguish generalized muscle weakness caused by peripheral neuromuscular etiologies with that observed in patients with severe hypokalemia. It also emphasizes the fact that normalization of serum K^+ in a chronically undertreated patient with distal RTA requires replenishment of the severely depleted intracellular K^+ stores.

PUB524

FGF-23-Mediated Severe Hypophosphatemia: A Rare Manifestation of Malignancy

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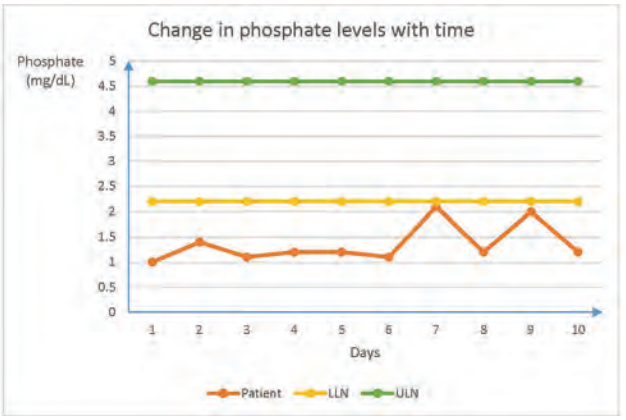
Introduction: Hypophosphatemia is not an uncommon electrolyte disorder. It can be secondary to renal or non-renal etiologies. Identifying the underlying cause is essential for proper management.

Case Description: We present a case of a 61 year-old man with hypertension and diabetes who was admitted to our hospital for abdominal pain, and was eventually diagnosed with diffusely metastatic esophageal squamous cell cancer. His phosphate level was in the 1-2 mg/dL (2.2-4.6), reaching <1 mg/dL on multiple occasions. His hypophosphatemia was difficult to correct, despite IV and oral supplementation. Extensive workup showed elevated urinary fractional excretion of phosphate (55%) which reflects renal wasting. The serum calcium was high (11.8 mg/dL) and the PTH was low (12 pg/mL). Inactive Vitamin D (47 ng/mL) and active Vitamin D (25 pg/mL) were normal. The PTHrP was mildly elevated (2.9 pmol/L). There was no evidence of Fanconi's syndrome. Further evaluation revealed a significantly elevated FGF23 level of 2330 relative units (RU)/mL (Reference < 180) suggestive of an oncogenic osteomalacia-induced phosphate wasting. Unfortunately, the patient had advanced stage malignancy and passed away in less than a month after presentation.

Discussion: This case illustrates the importance of a thorough diagnostic workup of hypophosphatemia. Oncogenic osteomalacia is a rare paraneoplastic syndrome with musculoskeletal manifestations, usually seen in benign mesenchymal tumors. The mechanism of hypophosphatemia is secretion of FGF23 by tumor cells, which illustrates the important role of FGF23 in the bone-kidney axis. The management includes tumor localization and resection if possible, which is curative. The unusual aspects of this case are the presence of hypercalcemia, and the nature of the tumor being a metastatic squamous cell cancer.



PUB525

Diagnosis of Ethylene Glycol Toxicity from the Presence of a Lactate Gap

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Introduction: Ethylene glycol poisoning is life threatening and needs rapid recognition and treatment. The diagnosis of ethylene glycol intoxication is more challenging in situations like vague history or altered mental status. The presence of high anion gap metabolic acidosis with elevated lactate level without considering other facts such as osmolar gap, urine microscopy and toxicological studies could mislead practitioners and lead to severe complications.

Case Description: A 59 year-old woman presented to the emergency department with altered mental status, anion gap metabolic acidosis (21 mEq/L), and high lactate (17.0 mmol/L). Anion gap metabolic acidosis persisted despite initial treatment, however, the correction of lactate level was dramatically fast; lactate dropped from >17.0 mmol/L to 1.6 mmol/L in 4.5 hours, but anion gap remained the same at 21 mEq/L, at the same time, an elevation of serum creatinine from baseline 0.7 mg/dl to 2.25 mg/dl was noticed. Ethylene glycol toxicity was suspected from the clinical situation and an elevated osmolar gap (64 mmol/L); urine microscopy revealed extensive calcium oxalate crystals. Hemodialysis was performed urgently, resulting in resolution of acidosis; serum ethylene glycol levels returned as 23 mg/dL 2 days later.

Discussion: The initial diagnosis of ethylene glycol poisoning can be delayed and lead to life threatening complications. Glycolic acid, a metabolite of ethylene glycol, may be misread by certain laboratory analyzers as lactic acid. On patients with unclear history, elevated anion gap, and very high lactate acid, the possibility of ethylene glycol poisoning should always be considered. The presence of osmolar gap, urine crystals and rapid changes in serum lactate without a significant change in the anion gap may be helpful in making this diagnosis.

PUB526

An Interesting Case of Turmeric-Associated Hyperkalemia

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Introduction: Advancements and understandings of modern medicine includes the acknowledgement of homeopathic and holistic approaches to health maintenance taken on by our patients. We also need to be aware of the possible side effects associated with their use. Turmeric is a spice that is commonly used for its rich flavor but has been increasingly popular for its possible health benefits.

Case Description: 67 yo M with history of HLD presenting for evaluation of long-standing hyperkalemia. Patient is active and uses a lot of supplements in order to preserve his health. The patient started the use of turmeric after 2005. He uses turmeric regularly and sprinkles it in all foods and in his teas daily. He exercises regularly and his only other medical problem is hyperlipidemia for which he was recently started on a statin. Vitals: BP 138/81, HR 67, SpO2 99%, Ht 5'10", Wt 149lbs, BMI 21.21 Physical Exam was unremarkable. Patient was asked to stop the use of turmeric (active compound: curcumin) after lab work on 12/27/2018 showed elevated serum potassium of 5.7. Repeat lab testing later (2/14/19), showed improvement of serum potassium to 5.2.

Lab Results

Date or range	Serum potassium or range	Serum creatinine or range
2/14/2019	5.2 (plasma K)	N/A
12/27/2018	5.7	0.86
8/27/2018	5.8	N/A
7/17/2018	5.6	0.90
3/13/2017	5	0.82
3/4/2016	5.6	0.79
Oct 2011-Nov 2015	5.4-5.7	0.81-0.91
Mar 2006-Jun 2010	4.6-5.4	0.86-0.9
Dec 2000-Aug 2005	4.2-6.5	0.8-1
3/25/1998	4.1	0.8
6/1/1992	4.9	1.1

Discussion: We report a case of turmeric associated hyperkalemia as a possible cause of hyperkalemia. We also discuss the likely mechanism of action: curcumin interferes with the binding of extracellular potassium to Na-K ATPase, causing an increase in serum potassium levels. This dysregulation can lead to low-level hyperkalemia, causing undue harm to specific patient populations. Awareness of this mechanism allows physicians to make accurate diagnoses. Additionally, knowledge of supplementations causing such changes in electrolyte balance will hopefully inspire further research into alternative medicines and their risks and benefits as they pertain to our patients and their health.

PUB527

Metastatic Adenocarcinoma Causing Spontaneous Tumor Lysis Syndrome

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Introduction: Tumor lysis syndrome (TLS) is an oncological emergency frequently associated with highly-proliferative hematological malignancies, usually after the initiation of chemotherapy. It is uncommon in solid tumors with some reports in uterine, lung, prostate, hepatocellular and pancreatic cancer. Spontaneous TLS (STLS) in a chemotherapy naïve patient is very rare. Exact incidence is difficult to ascertain because the data remains limited to case reports.

Case Description: A 53-year-old male was recently diagnosed with extensive metastatic disease involving multiple lymph nodes, hepatic, gastroesophageal junction, and an isolated rib mass. Lymph node biopsy was consistent with poorly differentiated adenocarcinoma and no apparent primary lesion was identified. Prior to initiation of chemotherapy, he was admitted for significant laboratory abnormalities including hyperkalemia (7.1mEq/L), acidosis (18mEq/L), hypercalcemia (9.8mg/dl), elevated creatinine (2.11mEq/L), hyperuricemia (13.9mg/dL), elevated LDH (4090 U/L) and liver enzymes. A diagnosis of STLS was made and treatment started with intravenous hydration and rasburicase. His labs showed improvement and he was eventually discharged on allopurinol.

Discussion: TLS is a constellation of metabolic abnormalities (hyperkalemia, hyperuricemia, hyperphosphatemia and hypocalcemia) described by the revised Cairo-Bishop Criteria. It results from rapid destruction of cancer cells during chemotherapy but rarely occurs spontaneously. Risk factors for STLS in our patient were high LDH levels and extensive metastatic involvement (particularly hepatic). Acute renal failure results from tubule precipitation of uric acid (urate nephropathy), calcium phosphate or hypoxanthine. In STLS, the released phosphorus is immediately utilized to regenerate new tumor cells and calcium binding of excess phosphorus is absent. Hyperphosphatemia and hypocalcemia were absent in our patient. Intravenous hydration and agents like allopurinol and rasburicase remain the mainstay of therapy, but renal replacement therapy may be required for severe cases. Factors like significant tumor burden, dehydration and renal failure, along with dramatic lab abnormalities can assist in early validation of the diagnosis even in the absence of a pathological confirmation or chemotherapy exposure. It is imperative to maintain a high level of suspicion because STLS can be fatal if left untreated.

PUB528

Severe Acidemia in Pregnancy with De Novo Acute Myeloid Leukemia

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Introduction: Starvation ketoacidosis is an important cause of acidosis in pregnancy, specifically after the second trimester. A day of severe vomiting is enough to trigger this serious disorder and its presence should prompt physician to seek for exacerbating causes. We present a case of severe metabolic acidosis in a pregnant woman with underlying acute myeloid leukemia (AML).

Case Description: A 28-year-old woman at 35 weeks of gestation with a 5-day history of vomiting, pelvic and back pain, and dysuria was transferred to our institution with acidemia, pyelonephritis, suspected acute leukemia and preterm labor. Volume repletion with Lactated Ringer's solution and empiric antibiotherapy were given but acidosis worsened. Pregnancy was complicated at 28 weeks by nephrolithiasis with associated right-sided hydronephrosis requiring JJ placement. Physical exam revealed tachypnea, tachycardia and right costovertebral angle tenderness. Pertinent blood laboratory results were WBC 18 (109/l), blasts 74 (109/l), ANC 965 cells/l, Hgb 10.5 g/dl, platelets 124 (109/l), pH 7.21, pCO2 < 12.9 mmHg, HCO3 4.8 mmol/l, potassium 4.4 mmol/l, anion gap (AG) 28.5 mmol/l, delta ratio 0.8, creatinine 0.51 mg/dl, glucose 97 mg/dl, L-lactate 6.2 mg/dl and moderate ketones. Urinalysis showed pH 5, ketones 150, pyuria, hematuria, no glucose, and AG 67. Intravenous bicarbonate in dextrose was started and 24 hours after, patient had significant improvement of acidosis and was able to initiate oral intake, which lead to its resolution. Vaginal delivery was successfully achieved 4 days after our initial evaluation. Bone marrow was performed revealing AML.

Discussion: Pregnancy associated starvation ketoacidosis is mediated by relative insulin deficiency and enhanced lipolysis. Carbohydrate in dextrose solution more than bicarbonate administration lead to improvement of AG metabolic acidosis as the culprit of the disturbance was starvation. Our patient had life-threatening acidemia that can be

explained by poor oral intake concomitantly with immunosuppressed state and infectious process leading to preterm labor. RTA was considered but in the setting of high urine unmeasured anions due to ketoacidosis, urine AG was not reliable. Identification of acidemia etiology and rapid treatment was paramount to avoid further fetal and maternal complications including fetal demise.

PUB529

Management of Hyponatremia Overcorrection with 2.5% Dextrose in Water Solution in Diabetic Patient

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Introduction: Overcorrection of hyponatremia is a medical emergency and associated with disastrous neuropathologic condition, osmotic demyelination syndrome. To minimize the risk of overcorrection, sodium correction rate should not exceed 6 to 8 mEq/L in any 24-hour period. We will present a case diabetic patient whose hyponatremia overcorrection was managed with 2.5% dextrose in water ($D_{2.5}W$) solution.

Case Description: 63-year-old male presents to our hospital for concern of possible bladder rupture. Patient had anuria and constipation for three days, associated with generalized abdominal pain and episodes of disorientation. At the emergency department, his initial labs at 8 pm showed severe hyponatremia with Na 116 mEq/L and acute kidney injury with creatinine 3.3. Foley was placed to relieve urinary tract obstruction and infusion of normal saline was started. CT abdomen was concerning for colonic impaction with possible bladder rupture and he was transferred to our hospital. Patient developed post-obstructive diuresis and by the time of arrival, repeated sodium was 130 mEq. Sodium overcorrection with 14 mEq occurred in less than 10-hour period. Normal saline was stopped, D5W with 250 ml/hr was started and desmopressin was administered. Next sodium level 3 hours later was even higher 133 mEq. As the patient had history of Diabetes Mellitus and was requiring excessive and rapid administration of fluids, use of $D_{2.5}W$ was decided. The goal was to decrease the sodium to <125 mEq in 24 hours period. Patient responded treatment and by 8 pm of the next day, sodium was 124 mEq. After that regular management of hyponatremia was started with appropriate correction rate and the patient was discharged home with sodium 134 mEq and no neurologic deficit.

Discussion: One of the strategies to avoid ODS after rapid overcorrection of hyponatremia is re-lowering of the sodium. Most commonly used re-lowering agents are D5W and Desmopressin. Our patient developed nephrogenic diabetes insipidus due to post-obstructive diuresis, didn't respond to desmopressin and was requiring high infusion rate of D5W. D5W is safe at low infusion rates but in rapid and excessive administration, especially in diabetic patients, serious adverse effects, hyperglycemia, hyperosmolar syndrome, and even intracerebral hemorrhage may occur. Usage of $D_{2.5}W$ of very rare and this case was exceptional.

PUB530

A Six-Pack of Paralysis in a Healthy 27-Year-Old

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Introduction: Hypokalemic periodic paralysis is a rare disorder with autosomal dominant inheritance. A mutation in skeletal muscle Ca channels is the most common genetic abnormality. Attacks generally begin in 1st or 2nd decades of life and present as sudden-onset painless weakness/paralysis. Symptoms may be precipitated by heavy exercise, fasting, or high-carbohydrate meal. If hypokalemic periodic paralysis is suspected, workup should be focused on ruling out secondary causes of hypokalemia and weakness. Herein we present a case that demonstrates the importance of this workup in a somewhat atypical presentation of this rare condition.

Case Description: A previously health 27-year-old male presented due to severe weakness. Symptoms started two days prior to arrival with mild pain of the arms and legs and subjective weakness. No changes in physical activity. No changes in eating habits. The morning of admission, patient was unable to get out of bed. On admission, exam was notable for profound extremity weakness. Initial workup demonstrated K 1.7, Mg 2.1, phos 1.0, creatinine 0.95, CK 506, TSH 0.41, and QTc 622. Muscle weakness improved with potassium replacement. Subsequent urine studies did not demonstrate excess renal potassium loss and patient had no history of extra renal losses. Serum renin and aldosterone levels were within normal limits. CNS studies were unremarkable. Upon further questioning, patient reported drinking a six-pack of soda the day prior to admission (equivalent carbohydrate load to 8 pieces of a large pizza).

Discussion: Despite an atypical presentation of hypokalemic periodic paralysis (first episode in third decade of life, no family hx, and the presence of pain), the workup did not reveal an alternative diagnosis. There was no identifiable secondary cause of hypokalemia. No primary neurologic phenomenon identified, and despite muscle pain only mild elevation in CK and no myoglobinuria. QT was prolonged; however patient lacked any features associated with Anderson Syndrome. This case demonstrates the importance of having a high suspicion for hyperkalemic periodic paralysis in the setting of hypokalemia and weakness, even if some aspects of the presentation are not typical for the diagnosis. Also, the systematic approach for evaluating alternative diagnoses enabled prompt treatment and education regarding preventative measures.

PUB531

D-Lactic Acidosis: Uncommon and Oft Forgotten

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Introduction: Lactate (DL) is undetectable by standard analyzers and differs from L-lactate as it crosses the blood brain barrier which leads to neurotoxicity when D-Lactic Acidosis (DLA) ensues. DLA is a rare but known complication of short bowel syndrome (SBS) following a carbohydrate load. Due to a low index of suspicion DLA is often misdiagnosed and recurs.

Case Description: A 65 year-old woman was brought to the ED unconscious soaked in loose stools. She was unresponsive and withdrew on the right only concerning for stroke She had a metabolic acidosis (MA) (pH 7.17, pCO2 17 mmHG on VBG, HCO36 mEq/L, AG 17 mEQ/L, Cl 120 mEq/L, lactate 0.8 mmol/L). Urine toxicology, serum osmolar gap and CT head were not diagnostic. Lactated Ringers (LR) was started. Nephrology was consulted for worsening MA. A laparotomy scar was noted. Family who was not previously available for collateral, confirmed the patient had bowel surgery four years ago. Since then she had SBS with chronic diarrhea, developed new onset neurological symptoms requiring medications and had two suicide attempts. The family also noted she ate almost a whole cake in honor of her birthday a day before. We suspected DLA. Urine AG and osmolar gap was positive at 78 mEq/L and 420 mOsm/kg, respectively. LR was immediately stopped; IV sodium bicarbonate, IV thiamine and PO clindamycin were started. DL levels were not available. Within a few hours the neurological symptoms and MA resolved and she returned to her baseline.

Discussion: Our patient presented with classic DLA after a large carbohydrate load in the setting of altered gut microbiome in SBS. DL reduces intracellular pH and interferes with pyruvate metabolism by inhibiting pyruvate dehydrogenase complex (PDHC). The severity of symptoms may depend on the preexisting intracellular reserves of cofactors (i.e thiamine) for PDHC that are usually compromised in SBS which leads to a wide range of neurological symptoms. Commonly these patients have lower "AG" as anticipated by DL levels due to hyperchloremia and are wrongly treated with LR which contains DL and worsens symptoms, as seen in our patient, or are misdiagnosed as RTA and symptoms recur. Unfortunately, measuring DL is not practical and awareness is needed. Management consists of avoiding large carbohydrate meals, altering the gut flora with antibiotics and restoring cofactors.

PUB532

Double Trouble: A Case of Hyperkalemia from the Combination of Fluconazole and Heparin, and Its Treatment with Fludrocortisone

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Introduction: Medication-induced hyperkalemia is common and can be dangerous. Treatment options may be limited if a precipitating medication cannot be discontinued. We present a case of hyperkalemia from co-administration of fluconazole and heparin that improved with fludrocortisone.

Case Description: A 39 yo man with CML and recent MSSA endocarditis requiring mechanical MVR was admitted for rash and AKI with serum creatinine (SCr) 5.29 mg/dL. Workup notable for hematuria, proteinuria, and leukocytoclastic vasculitis on skin biopsy, suggesting post-infectious vs drug-induced vasculitis. Prednisone initiation led to gradual improvement in SCr. INR became supratherapeutic and warfarin was transitioned to IV heparin. One week later he developed Candida parapsilosis fungemia, and fluconazole was started. The following day he developed acute hyperkalemia up to 8.0 mmol/L without EKG changes. Whole blood potassium (WBPot) was checked with a point of care analyzer with a similar result. WBC, uric acid, LDH, haptoglobin, CK, and lactate levels were normal, serum bicarbonate 24 mmol/L, and SCr 1.3 mg/dL. He began fludrocortisone 0.1 mg daily for medication-induced hyperkalemia, as well as furosemide and oral bicarbonate. Heparin was discontinued the following day. WBPot improved with fludrocortisone but remained elevated at 5-6 mmol/L. Fluconazole was then discontinued, and WBPot stabilized at <5 mmol/L, at which time fludrocortisone was stopped.

Discussion: Heparin and azole antifungal agents, particularly ketoconazole, can lead to hyperkalemia by decreased aldosterone production. Fluconazole has been shown to have the same effect, though weaker, and only a few cases of fluconazole-induced hyperkalemia have been reported. This case provides further evidence of the potential for severe hyperkalemia from fluconazole, particularly when given with heparin, and highlights the importance of considering potassium-related drug interactions. There are a few reports of fludrocortisone use in heparin-induced hyperkalemia, and though fludrocortisone did not normalize this patient's potassium, it helped reduce it to a safer level while decisions were made regarding alternative therapies to heparin and fluconazole. This suggests that fludrocortisone can be used as a bridge to help prevent dialysis until safer medications are chosen.

PUB533

Hypercalcemia Secondary to Silicone-Induced Granuloma Treated with Ketoconazole

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Introduction: Hypercalcemia mediated via extra-renal 1, alfa-hydroxylase activity has been well described. We present a patient who developed hypercalcemia from silicone-induced granulomas.

Case Description: A 49 year-old female was referred to Nephrology in the out-patient clinic for evaluation of acute renal insufficiency and hypercalcemia. Her medical history included hypertension, endometriosis, recurrent nephrolithiasis, and cosmetic surgery. The initial workup for hypercalcemia and recurrent nephrolithiasis revealed hypocitraturia, hyperoxaluria and hypercalciuria. Vitamin D 1,25 (OH)2 was significantly elevated. Due to concerns for possible granulomatous disease, chest imaging was obtained. The CT chest revealed no acute pulmonary process, but there were prominent left para-aortic lymph nodes measuring up to 10 mm. The lymph nodes were not amenable to biopsy. Therefore, a FDG-PET was obtained to determined the metabolic activity of the lymph nodes. The PET/CT revealed diffuse hypermetabolic subcutaneous stranding predominantly involving bilateral gluteus and bilateral proximal thighs. The patient admitted to subcutaneous injections of silicone, and silicone-induced granuloma resulting in calcitriol-mediated hypercalcemia was diagnosed. The patient was referred to Plastic Surgery, but due insurance authorization constraints, surgical removal was not done. She was offered to start corticosteroids as treatment of the hypercalcemia, but the patient refused due to concern for the aesthetic adverse effects of steroids. Therefore, she was started on ketoconazole. Within 4 weeks of treatment, her serum calcium had decreased from 12.8 to 11.0mg/dL.

Discussion: The main treatment is surgical resection of the surgical implants or resection of the granulomatous tissue. Corticosteroids remain the primary therapeutic option for hypercalcemia produced by excessive production of 1,25-(OH)2 vitamin D3 by the macrophages present in the sarcoid granulomas. Ketoconazole is an imidazole antifungal that inhibits the 1, alfa-hydroxylase from the macrophage and has been used to treat hypercalcemia associated to primary hyperparathyroidism, tumors, sarcoidosis and tuberculosis. The patient presented is the first case of ketoconazole use for the treatment of hypercalcemia due to silicone-induced granuloma after injection for cosmetic purpose.

PUB534

Tuberculous Lymphadenitis Presenting as Symptomatic Hypercalcemia and AKI: A Case Report

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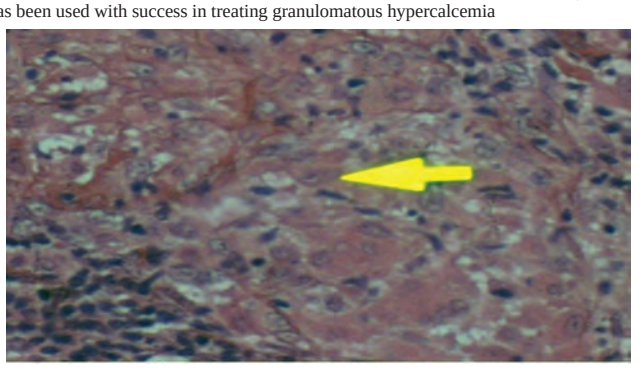
Introduction: Incidence of Tuberculosis associated hypercalcemia has been variably reported to be as low as 2% and as high as 28% depending upon the studied population. However, severe or symptomatic tuberculous hypercalcemia are very rare entities. AKI is another very rare presentation of of granulomatous hypercalcemia. We are presenting a case of moderate hypercalcemia secondary to tuberculous lymphadenitis that presented with symptomatic hypercalcemia and AKI.

Case Description: 40 years old male presented to various doctors with increased urinary frequency and occasional constipation. His repeated urine examination was bland with negative cultures but renal function tests were mildly deranged consistently for past one month. When he presented to our center, he was afebrile but had enlarged inguinal and few cervical lymph nodes. Workup showed normal hemoglobin, urea of 143 mg/dl, creatinine of 4.1 mg/dl, serum calcium of 13 mg/dl and Phosphorous of 4 mg/dl. ESR was 60 and LDH was 160 IU/l. PTH was suppressed to 5pg/ml (15-65pg/ml). Right inguinal lymph node biopsy showed multiple granulomas comprising of epithelioid cells with Langerhans type giant cells, central caseating necrosis and no atypical cells. Patient was managed with aggressive hydration and Anti tuberculous therapy (ATT) along with steroids for 1 month. Patient showed marked improvement in RFT (Urea 24 mg/dl, creatinine 1.1) on discharge and calcium improved to 9.8 mg/ dl subsequently. After two months, his urea was 18mg/dl, creatinine 0.9 and calcium 9.2 with increased appetite, normal urinary frequency and bowel movements. On completion of ATT patient has normal RFTs and calcium levels.

Discussion: There is no established relationship between severity of hypercalcemia and various forms of tuberculosis. As in our case, short course of steroid alongside ATT has been used with success in treating granulomatous hypercalcemia



PUB535

Cisplatin-Induced Transient Renal Salt Wasting

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Introduction: Cisplatin is used in the management of many solid tumors and is known to stimulate hypothalamic AVP secretion resulting in SIADH. We present a less frequent cause of hyponatremia secondary to Cisplatin therapy that is important to distinguish from SIADH as choosing the wrong management approach can lead to worsening of hyponatremia.

Case Description: 47 y/o caucasian female with recently diagnosed small cell carcinoma of the cervix presented to the hospital with worsening confusion and lethargy after her third dose of Cisplatin/Etoposide as part of her first cycle of neoadjuvant chemotherapy. Serum sodium was 115 mmol/L compared to serum sodium of 142 mmol/L measured 3 days prior to start of chemotherapy. Measured serum Osm was 240 mOsm/kg H2O. Her blood pressure was low-normal with exam notable for dry skin. Urine Na was 75 mmol/L, urine creatinine was 22 mg/dL and FeNa was 1.4%. Urine Osm was 606 mOsm/kg and Urine specific gravity was 1.019. An initial diagnosis of SIADH vs Renal Salt Wasting was made and given the patient's mentation, she was treated with iv hypertonic saline with improvement in serum sodium. Over the next day, urine sodium values rapidly decreased to under 30 mmol/L with FeNa <<1 making SIADH unlikely. Serum sodium continued to improve with isotonic saline along with oral salt tablets while urine osmolality decreased to 335 mOsm/kg. The patient's mentation and serum sodium normalized within a week. Upon discharge, she completed 3 cycles of Cisplatin-Etoposide therapy without further recurrence of hyponatremia, aided by preventive saline administration with chemotherapy.

Discussion: Our patient's presentation fits with the hypothesis that she developed transient renal salt wasting that resolved spontaneously with appropriate urinary concentration returning 4 days after her last dose of chemotherapy. Cisplatin may cause hyponatremia by inducing SIADH &/or renal salt wasting. This may initially be difficult to distinguish but a careful assessment for volume depletion and distinction between the two conditions is warranted for correct management. It is notable that renal salt wasting in our patient was only transient and occurred in isolation without any other manifestations of tubular epithelial cell toxicity that are more common with Cisplatin use. It must also be pointed out that this effect did not recur with continued chemotherapy when combined with preventive saline infusions.

PUB536

Thiamine Deficiency as a Cause for Persistent Hyperlactatemia

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Introduction: Hyperlactatemia is often associated with tissue hypoxia also known as Type A lactic acidosis. However, it can result from less common mechanisms like thiamine deficiency as described in our patient. Effective treatment of persistent hyperlactatemia requires correct identification of the precipitating cause.

Case Description: A 47-year-old female with past medical history of schizophrenia presented to the ED with altered mental status. She was tachycardic without tachypnea and afebrile with stable blood pressure. She was confused, lethargic and appeared malnourished on physical exam. Laboratory data was significant for a bicarbonate of 6 mmol/L, anion gap of 24 mmol/L, lactate of 3.6 mmol/L and an osmolal gap of 23 mOSm/kg H2O. Blood, CSF, urine culture and CXR were negative. UA was notable for large ketones accounting for some of the anion gap. Blood ethylene glycol, methanol and ethanol levels were all undetectable. Despite volume resuscitation for presumed Type A lactic acidosis, hyperlactatemia persisted. She had no evidence of liver disease and was not on any offending medications. Urine drug screen was negative. Given persistent hyperlactatemia, thiamine level was then checked and was noted to be less than 6 nmol/L. She was treated with IV thiamine resulting in resolution of hyperlactatemia within less than 48 hours.

Discussion: In patients with persistent hyperlactatemia, absence of more common causes like tissue hypoxia and offending medications should warrant search for a less common etiology like thiamine deficiency. The mechanism of hyperlactatemia in thiamine deficiency is the impairment of pyruvate dehydrogenase activity. This etiology is more common in children or adults receiving TPN or with nutritional deficiencies.

PUB537

Parapelvic Cyst: A "Must Know" Differential Diagnosis for Hydronephrosis on Point-of-Care Ultrasound

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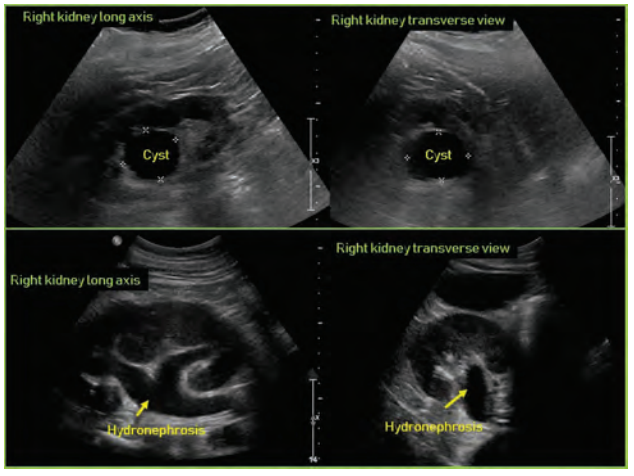
Introduction: Point of care ultrasonography (POCUS) performed by the nephrologist is a valuable bedside tool that enhances patient care. Detection of obstructive uropathy is one of the most common indications for POCUS and hydronephrosis is relatively easy to recognize appearing as 'anechoic' or 'black' branching, interconnected areas in the renal collecting system. However, caution needs to be exercised in calling an anechoic structure in the renal pelvis as hydronephrosis, especially when attributing a patient's acute kidney injury (AKI) to this finding. Herein, we report a case of parapelvic cyst mimicking hydronephrosis.

Case Description: A 75-year-old woman with a history of hypertension and right total hip arthroplasty was admitted for infected hip prosthesis and started on intravenous

antibiotic therapy. She underwent revision hip surgery, suffered from myocardial infarction post-operatively and subsequently developed AKI stage III. Renal POCUS was suggestive of right moderate hydronephrosis. However, on careful review of the trainee-performed images [Figure, top panel], the anechoic area in the renal pelvis area was found to be a simple cyst mimicking hydronephrosis. The patient's renal failure was diagnosed to be secondary to acute tubular injury and she later required renal replacement therapy. A formal sonogram obtained a few days later confirmed the interpolar cyst.

Discussion: Parapelvic cysts can mimic hydronephrosis because of their anechoic nature and close proximity to the renal collecting system. Hydronephrosis appears as branching, 'interconnected' anechoic area [Figure, bottom panel] as mentioned above, while parapelvic cysts are seen as well-circumscribed 'noncommunicating' renal sinus cystic masses. Moreover, a parapelvic cyst is more spherical as opposed to irregular contour of hydronephrosis and is not connected to hydroureter distally.



PUB538

A Case Report of Gitelman Syndrome in an Adult Filipino Presenting with Hypokalemic Periodic Paralysis

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Introduction: Gitelman Syndrome is a rare salt losing renal tubular disorder which can present with salt craving or thirst, constipation, muscle weakness or paralysis. This report presents a case of an adult Filipino with hypokalemic periodic paralysis. Laboratory examinations revealed hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria which are the main findings of Gitelman Syndrome.

Case Description: The case is a 30 year old Filipino, with no known co-morbidities, who presented with weakness of all extremities. Patient had been managed previously as a case of Hypokalemic Periodic Paralysis; however, with no identified etiology. The only remarkable physical examination finding was motor weakness - 1/5 and 0/5 on the upper and lower extremities, respectively. Pertinent laboratory examinations were - hypokalemia (2.14mmol/L), hypomagnesemia (0.55mmol/L), ABG of metabolic alkalosis, computed TTKG (transtubular potassium gradient) of 20.4, urine chloride of 99, and urine calcium/creatinine of 0.01. These findings, along with absence of thiazide use, were consistent with Gitelman Syndrome. Potassium and magnesium corrections were given. Response to management described as increased motor strength was noted after completion of treatment. Two weeks after discharge, patient claimed to have episodes of weakness. Repeat serum potassium was 2.47mmol/L. Potassium supplementation was then resumed which again improved the patient's weakness.

Discussion: Gitelman Syndrome is a rare and benign salt losing tubulopathy that can present with salt craving or thirst, constipation, muscle weakness or paralysis. As for this case, the patient presented with recurrent hypokalemia associated with weakness. Diagnosis is mainly based on symptoms and laboratory examination findings revealing the disorder's main features - hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria. Genetic testing is still needed to identify mutations in the SLC12A3 gene which establishes the diagnosis. Due to the unavailability of the test, genetic testing was not done. Replacement of depleted electrolytes is the mainstay of treatment. Definitive treatment is not yet established. Recurrence of symptoms is expected as seen in the case wherein patient had episodes of weakness two weeks after hospital discharge.

PUB539

Steroid-Resistant Nephrotic Syndrome as a Novel Presentation of Mitochondrial Trifunctional Protein Deficiency

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Introduction: Steroid resistant nephrotic syndrome (SRNS) is a leading cause of pediatric kidney disease. Variants in several genes associated with mitochondrial cytopathies are known to cause SRNS. We describe the first reported case of SRNS as the initial presentation of mitochondrial trifunctional protein (MTP) deficiency.

Case Description: The patient was diagnosed with SRNS at 12 months of life. Biopsy showed diffuse mesangial sclerosis. Due to refractory edema, he underwent bilateral nephrectomy and dialysis initiation. At age 20 months, he received a deceased donor kidney transplant. Following transplant, he experienced severe hypotension, lactic acidemia, hypoglycemia, and liver dysfunction. Whole exome sequencing (WES) demonstrated compound heterozygosity with two novel variants in the *HADHB* gene, consistent with autosomal recessive MTP deficiency. Biochemical analysis of cultured fibroblasts confirmed the diagnosis. Despite a trial of CoQ10, carnitine, and other vitamins, he continued to deteriorate and died at age 21 months. Immunofluorescence (IF) was performed on patient kidney tissue to delineate the role of HADHB in nephrotic syndrome. IF of an age-matched control displayed HADHB throughout the renal tubules. In contrast, patient tissue revealed complete absence of HADHB throughout the kidney (Fig 1).

Discussion: MTP is involved in fatty acid oxidation and is essential for energy homeostasis, especially in times of fasting. MTP is encoded by two genes: *HADHA* and *HADHB*. Variants in these genes can cause MTP deficiency, presenting with early onset hypoketotic hypoglycemia and cardiomyopathy or later onset myopathy, rhabdomyolysis, and polyneuropathy. This is the first reported case of MTP deficiency presenting with SRNS. WES and IF of patient kidney tissue suggest that mutations in *HADHB* cause nephropathy and should be considered in patients with SRNS. Further research will define the specific role of HADHB in the development of nephrotic syndrome.

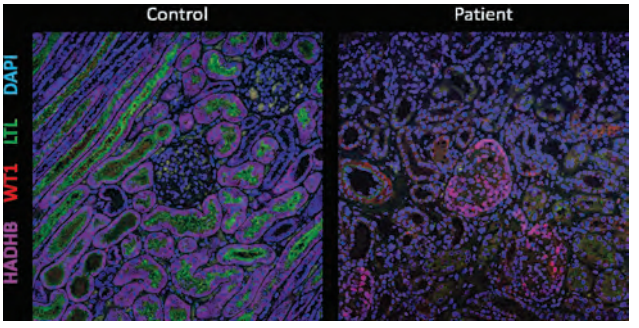

Fig. 1

PUB540

Urgent Page: An Unusual Case of Abdominal Pain with Hypertension

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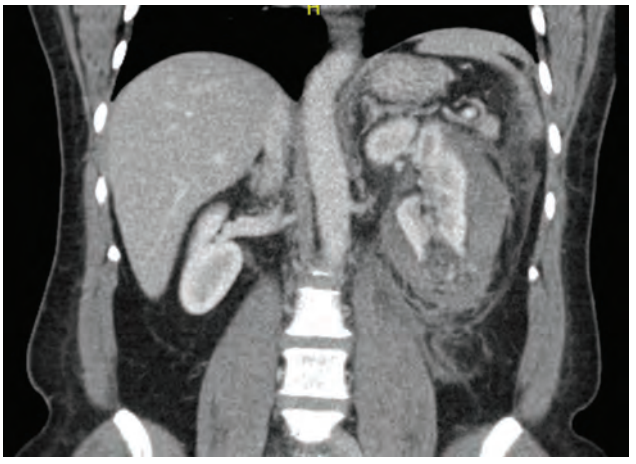
Introduction: Renal Angiomyolipomas (AMLs) are the most common benign tumor of the kidney and are associated with tuberous sclerosis complex (TSC), pulmonary lymphangioleiomyomatosis (LAM) or most commonly, sporadic. AMLs are mostly asymptomatic but can present with flank pain, hematuria or rarely retroperitoneal hematoma due to rupture. Rupture of AMLs is rare but more frequent if the size is ≥ 4 cm.

Case Description: 47-year-old female with no past medical history presented with sharp left lower quadrant abdominal pain with nausea. She denied trauma, dysuria, hematuria, fever or chills. On presentation, her vitals were stable apart from an elevated blood pressure of 186/91. Exam was notable for left lower quadrant tenderness to palpation without costovertebral tenderness. Labs were significant for a hemoglobin 10.8 (baseline 12), creatinine of 1.17 (baseline 0.8). CT of abdomen and pelvis showed a 3 cm hemorrhagic angiomyolipoma near the lower pole of the left kidney with a large volume left renal subcapsular hematoma producing compressive deformity of its renal cortex. Patient was observed for the next 24 hours and she remained hemodynamically stable with stable hematocrit. She received adequate pain control and intravenous fluid and was discharged for follow-up as an outpatient in 6 weeks for surveillance. Her blood pressure at the time of discharge had improved to 140/70.

Discussion: Our case is a rare and unique presentation of renal AML as the patient not only presented with spontaneous retroperitoneal hematoma due to rupture of a renal AML but the size of AML was 3 cm. Moreover, the patient's hypertension was caused by renal parenchymal compression from the subcapsular and perinephric hematoma, a phenomenon known as Page kidney. In patients with life-threatening hemorrhage, selective renal artery embolization is recommended. All patients with AMLs should be screened for TSC, however, it is not necessary to screen for LAM. Surveillance for AML is dependant on size: for < 2 cm, ultrasound every 3-4 years, for 2-4 cm, annual renal ultrasounds, and > 4 cm tumors, surgical resection is recommended.



PUB541

Two Pearls in an Oyster: Thrombotic Microangiopathy due to Malignant Hypertension from Apparent Mineralocorticoid Excess in a Cushing Syndrome Patient with Primary Bilateral Macronodular Adrenal Hyperplasia

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Introduction: Malignant hypertension (HTN) is characterized by severe HTN and target organ damage and can rarely cause thrombotic microangiopathy (TMA). Primary bilateral macronodular adrenal hyperplasia(PBMAH) causes Cushing's syndrome in less than 2% of the cases, leading to difficult to control HTN. We report this unique case of a patient with malignant HTN and TMA due to apparent mineralocorticoid excess from PBMAH.

Case Description: 47 year-old male, with malignant HTN for two years, uncontrolled on four antihypertensives (including diuretics) presented with fatigue, muscle weakness and unintentional weight gain (45 lbs). Physical exam remarkable for BP:160/100; weight 172lbs, moon face, central obesity with buffalo hump, supraclavicular and dorsocervical fat pads and purple abdominal striaes, proximal muscle weakness and thin/scaly skin. Primary Cushing's syndrome was suspected and confirmed with high free AM cortisol at 37mcg/dL, low ACTH at <5 p/mL. CT abdomen revealed bilateral adrenal adenomas. Further work up: microscopic hematuria and sub-nephrotic proteinuria (1.8g/24hs), Cr 1.2mg/dL. Kidney biopsy: intracapillary thrombi; marked podocyte hypertrophy, consistent with TMA. An extensive workup ruled out the most common causes of TMA like TTP, HUS and complement deficiency. On further tests, he was diagnosed with apparent mineralocorticoid excess through the high 24h urine free cortisol/ free cortisone ratio. A bilateral adrenalectomy was performed to treat the disease and at 12-month follow up visit, BP was controlled (110/70) only on Lisinopril 10mg/day and he had lost 48lbs. Proteinuria: 203 mg/24hs

Discussion: PBMAH causes Cushing's syndrome in less than 2% of cases. This patient also had TMA present, likely from two pathways: 1. Cushing's syndrome as a hypercoagulable state (high factor VIII levels, decreased fibrinolysis, and abnormal Von Willebrand factor) 2. Malignant HTN causing endothelial dysfunction and thrombi formation. Malignant HTN was secondary to the apparent mineralocorticoid excess from PBMAH. Both HTN and Cushing's syndrome resolved after bilateral adrenalectomy. PBMAH is a rare cause of Cushing's syndrome and, to the best of our knowledge, this is the first case of this condition causing apparent mineralocorticoid excess leading to HTN and TMA.

PUB542

Novel Heterozygous COL4A3 Mutation of the Type IV Collagen Alpha3 Gene in a Family with Thin Basement Membrane Nephropathy

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Introduction: Thin basement membrane nephropathy (TBMN) and Alport syndrome (ATS) are familial nephropathy characterized by structural abnormalities in the glomerular basement membrane (GBM). Gene mutations in the type IV collagen α3 and α4 (*COL4A3/A4*) genes are reported to cause both ATS and TBMN with the autosomal recessive and autosomal dominant form, respectively. The renal function of TBMN is usually kept normal, whereas ATS typically results in end-stage renal disease (ESRD). Therefore, differentiation between TBMN and ATS is mandatory for correct prediction of prognosis and genetic counseling.

Case Description: A 39-year-old woman presented with recent diagnosis of hypertension, mild proteinuria (0.58 g/gCr/day), microscopic hematuria (50-99 HPF) and mild decrease in eGFR at 59.5 mL/min/1.73m^2. She experienced asymptomatic hematuria since childhood, and a family history of microscopic hematuria. She received a renal biopsy at the age of 29 years; light and electron microscopic findings revealed thinning of GBM and effacement of the podocyte foot processes. Blood pressure was 137/92 mmHg with the prescription of amlodipine (5mg per day). Physical examination was unremarkable with no lower extremity edema. The next-generation sequencing and Sanger Sequencing were performed on DNA samples of the patient and her family (father, elder sister, younger sister, nephew, daughter), and heterozygous *COL4A3*G415S mutation [*COL4A3*(NM_000091):c.G943A:p.G315S] was identified in each individual with persistent hematuria, except her nephew who never experienced hematuria. She was diagnosed of TBMN, and antihypertensive treatment by angiotensin receptor blocker decreased proteinuria to about 0.2g/gCr/day, increased eGFR, while microscopic hematuria persisted.

Discussion: Clinical diagnosis of this case was TBMN on the following basis; autosomal dominant hereditary form, no ESRD patients in the family, no irregular thickening and multilamination of the GBM in the kidney, and no type IV collagen α5 defect. Mild proteinuria and decrease in eGFR at admission were considered associated not with TBMN but with untreated hypertension. This is the first case of TBMN with the novel *COL4A3* hetero mutation of type IV collagen α3 which is responsible for the microscopic hematuria in this family.

PUB543

Severe Microangiopathic Anemia in an ESRD Patient Unmasks Complement-Mediated Atypical Hemolytic-Uremic Syndrome (aHUS) and Successful Management with Treatment of aHUS

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Introduction: Anemia amongst ESRD patients is mostly due to erythropoietin deficiency and disordered iron metabolism. We present an ESRD patient with severe complement-mediated hemolytic anemia due to aHUS. Identification of genetic abnormalities in complement regulatory proteins and use of complement inhibitors lead to successful resolution of near-fatal anemia. We posit that the underlying cause for ESRD might be related to aHUS presenting as ANCA-negative vasculitis.

Case Description: A 39-year old African-American female patient with ESRD was admitted for severe symptomatic anemia and need for red-blood cell transfusion despite erythropoietin-stimulating agents (ESA). She was evaluated a year prior for chronic kidney disease with a nephritic presentation. Serological evaluation was negative. Kidney biopsy reported as pauci-immune ANCA-negative glomerulonephritis with significant chronicity. Given renal-limited vasculitis and chronicity, she didn't receive immunosuppressives. Hemoglobin & renal function remained stable. Blood pressure was controlled with ACE-I. eGFR dropped in 4 months with a decline in hemoglobin and platelet count, needing dialysis and ESA initiation. Severe, transfusion-requiring anemia workup showed elevated LDH and reticulocyte count, undetectable haptoglobin, increased schistocytes and thrombocytopenia. She was started on Eculizumab for aHUS without plasmapheresis. Hemoglobin improved within 2 weeks and eventually normalized while on Eculizumab. Genetic testing for aHUS showed multiple, heterozygous, missense variants of complement factor H (CFH). Prior renal biopsy showed changes of arteriolopathy that cemented concerns for aHUS. She remains transfusion-independent and on Eculizumab.

Discussion: CFH mutations are the commonest amongst genetic causes for aHUS. In African-American patients, CFH variants might be just as impactful in causing CFH-related GN and ESRD. Our patient had hemolytic anemia due to complement-mediated aHUS with brisk response to Eculizumab. Testing reveals her genetic predisposition to aHUS with multiple CFH variants, common amongst ESRD patients of African-American ancestry. Besides being a rare cause for anemia in ESRD patients, we propose that complement-mediated aHUS might have been the original cause for ESRD in this patient.

PUB544

Fabry Disease: Management in Carriers for Enzyme Alpha-Galactosidase A (a-GAL A)

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Introduction: Fabry disease is an X-linked recessive deficiency of the enzyme alpha-Galactosidase A (a-GAL A), resulting in the accumulation of globotriaosylceramide (Gb3) within lysosomes in a variety of cells. It is the second most common lysosomal storage disease with clinical manifestations ranging from asymptomatic to very severe cardiac manifestations and end-stage renal disease. We report a case of Fabry disease in a young female who was asymptomatic initially and slowly started showing renal manifestations of the disease.

Case Description: The patient is a 26-year-old female referred to our office by her primary care physician for evaluation of proteinuria and hematuria with CKD stage 1 with a significant history of renal disease in the family. She had complaints of tingling/pain in her hands and feet along with episodes of excessive sweating. On exam, she was found to have angiokeratomas in the periumbilical regions. Her baseline serum creatinine was 0.5 - 0.8. On genetic testing and she was noted to be a heterozygous carrier for the Fabry Disease. We suggested Enzyme Replacement Therapy (ERT) along with a focus on the control of blood pressure, metabolic derangements, lipids, blood sugars and avoidance of nephrotoxic drugs. We emphasized the importance of scheduled follow-up visits with subspecialties every 2-3 months to monitor the disease progression.

Discussion: Fabry disease can be diagnosed in males by detecting low a-GAL A activity in leukocytes or in the plasma. In women, a-GAL A activity level is unreliable for diagnosis and therefore it is necessary to perform mutation analysis of the a-GAL A gene. Carriers may be completely asymptomatic but with advancing age may develop left ventricular hypertrophy, valvular disease, cardiomegaly, myocardial ischemia, infarction,

arrhythmias, transient ischemic attacks, stroke, proteinuria, polyuria and end-stage renal disease. Adequate surveillance for the disease manifestations follow-up along with ERT is the main principle behind the treatment of Fabry disease. ERT with recombinant a-Galactosidase A may slow deterioration of cardiac and renal functions, while also helping in reducing pain and improving a overall quality of life. It is recommended that ERT be initiated as early as possible in female carriers with significant disease because of risk of cardiac, cerebrovascular and renal complications.

PUB545

Hypokalemic Periodic Paralysis

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Introduction: Hypokalemic periodic paralysis is a condition that causes muscle weakness beginning in childhood and adolescence. Mutations in the CACNA1S or SCN4A can cause HPP, those genes codify for proteins that control the flow of positive ions in muscle cells. We reported a case of HPP that carries a lot of frustration since patients usually have multiple ER and clinic visits before the right diagnosis.

Case Description: Patient is a 40 y.o white female who began having symptoms at the age of 12, initially with pain in legs that eventually progressed to her neck, shoulders, and hips. At age 20, her K^+ was detected around 3.5 mEq/L, and due to her symptoms, she was initially placed on steroids, which resulted in muscle weakness. At age 32, she developed a profound paralysis and her K^+ was found to be around 3.1 mEq/L. Since then, K^+ supplementation has been increased to 100 mEq daily, with additional K^+ administered PRN for acute paralytic episodes. She is also taking acetazolamide, amiloride, and eplerenone, a combination which has resulted in improvement.

Discussion: The initial hypokalemia starts with the separation of K losses (renal and extrarenal) and transcellular shifting. Unfortunately, There is no appropriate test to differentiate the potential mechanism. The total urine K^+, Urine K^+/Cr ratio and transtubular K^+ gradient (TTKG) are not completely accurate test due to renal physiologic mechanisms. Therefore after ruling out common etiologies, the approach should approximate unusual renal K^+ wasting conditions and transcellular shifting in parallel. (HPP) can be divided in to:(familial, associated with thyrotoxicosis and associated with cardiac dysrhythmias-Andersen Tawil syndrome). Genetic testing should be part of the armamentarium to get closer to the final diagnosis. A periodic paralysis genetic panel includes analysis of the following four most common associated genes: SCN4A, CACNA1S, KCNJ2 and RYR1. Unfortunately, genetic testing is not definitive since a proportion of patients lack abnormalities in the mentioned genes. Finally, the treatment will imply K^+ replacement with the adjuvant of K^+ sparing diuretics such as amiloride, triamterene and spironolactone. Close monitoring is required since other electrolyte abnormalities and acid base disorders may ensue. Our case report intent to raise the awareness of this rare condition and establish that multidisciplinary approach needed to delineate the diagnostic approximation of HPP.

PUB546

Overlapping Features of Membranous Glomerulonephritis and Focal Segmental Glomerulosclerosis in a Patient with Nephrotic Syndrome

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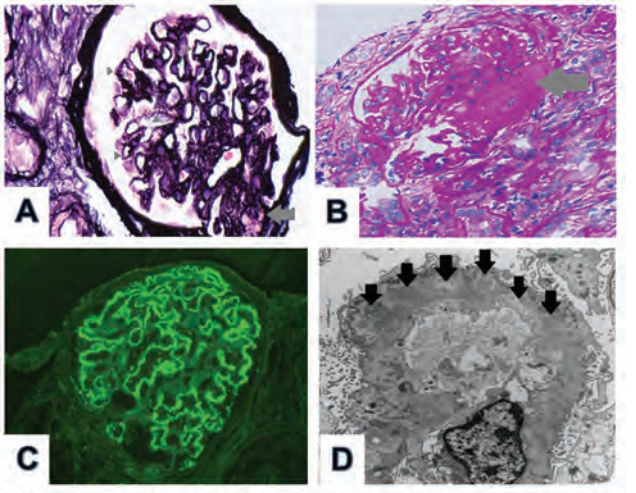
Introduction: Nephrotic syndrome may be classified into different histopathologic patterns, including membranous glomerulonephritis (MGN) and focal segmental glomerulosclerosis (FSGS). While MGN may be secondary to drug exposure, FSGS is more commonly seen due to obesity, uncontrolled hypertension, and HIV. Overlap between these two conditions is rare and, when coexisting, tends to clinically resemble primary MGN. We present a case with overlapping features of NSAID-induced MGN and FSGS.

Case Description: A 37-year old Caucasian male with chronic daily headaches on ibuprofen daily presented for elevated creatinine (2.4 mg/dL, compared to 0.8 mg/dL 3 years prior). Vital signs were notable for hypertension (219/107 mmHg), and physical examination was notable for 2+ pedal edema. Urinalysis showed 3+ protein and no blood. His UPC was 7.5. C3 and C4 levels, hepatitis B and C, HIV, ANA, dsDNA, RNP, Smith, SSA, SSB, and Histone serologies were within normal limits. Renal biopsy demonstrated MGN with negative PLA2R and THSD7A staining, global sclerosis in 3/23 glomeruli, segmental sclerosis in 3/23 glomeruli, and moderate tubular atrophy and interstitial fibrosis. He was advised to stop all NSAID use and was started on amlodipine, carvedilol, lisinopril, and spironolactone. At 2-week followup, his blood pressure was 110/72 mmHg, creatinine was 2.3 mg/dL, and UPC was 2.5.

Discussion: The coexistence of MGN and FSGS is a rare phenomenon, but may occur in patients who share risk factors like chronic NSAID use, uncontrolled hypertension, and obesity. Although the pathogenesis is unclear, MGN injury may contribute to FSGS since subepithelial deposits may hinder podocyte adhesion, and FSGS-mediated podocyte damage may lead to local antigen exposure and subepithelial immune complex formation.



Light microscopy (LM), 400x: A) JMS stain: glomerulus with capillary loop spikes and holes, characteristic of MGN (arrowheads), and segmental sclerosis with hyalinosis (FSGS, arrow). B) PAS stain: glomerulus with segmental sclerosis and hyalinosis. Immunofluorescence (IF), 400x: C) IgG stain: positive, global granular pattern of glomerular capillary loop staining. Electron microscopy (EM), 8,000x: A glomerular capillary loop with regularly distributed, subepithelial and intramembranous immune-complex mediated type electron dense deposits, in various stages of incorporation and absorption into the glomerular basement membranes.

PUB547

An Aggressive Form of Nephrotic Syndrome Secondary to IgA Nephropathy

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Introduction: Patients with IgA Nephropathy (IgAN) often present with nephritic syndrome, but nephrotic syndrome (NS) is less common. Several features of IgAN have been associated with poor prognosis, including hypertension, glomerular range proteinuria and fibrosis on histopathology. Here we discuss a patient with IgAN presenting with NS and malignant hypertension.

Case Description: A 33 year-old Asian female with history of hypertension presented with one week of headache, nausea and vomiting. Physical examination remarkable for elevated blood pressure of 205/131 mmHg, periorbital swelling and lower extremity pitting edema. Laboratory findings showed elevated serum creatinine (2.9 mg/dl) and LDL (272 mg/dl). Urinalysis was negative for hematuria, showed 3+ proteinuria and microalbumin/creatinine ratio of 3881 mcg/mg consistent with nephrotic range proteinuria. When hypertension was controlled, work up for proteinuric kidney disease was initiated. Results were unremarkable, including autoantibodies and complements, except for a positive hepatitis B surface antigen. Renal biopsy revealed severe interstitial fibrosis and global glomerulosclerosis. Patient was diagnosed with IgA nephropathy due to the presence of mesangial IgA deposits on immunofluorescence (Oxford classification: M1 E0 S1 T2 C0). Her symptoms improved with blood pressure control. Immunosuppressive therapy was not considered due to chronicity of renal scarring.

Discussion: IgAN is the most common cause of glomerulonephritis, more frequent in Asians than Caucasians. IgAN typically has slow progression to end stage renal disease (ESRD) with ~30% of patients developing ESRD over ~20 years. Severity of disease is described using the Oxford classification. Our patient's Oxford score of 29 indicates five-year incidence of ESRD is likely greater than 50%. Significant morbidity and poor outcomes are reported in IgAN associated with NS, which is poorly understood. The occurrence of malignant hypertension and coexistent hepatitis B infection potentially increases risk of ESRD. Limited data is available on use of steroids for treatment of proteinuria in IgAN. Use of Renin-Angiotensin-System blockade for blood pressure control is recommended in proteinuric disease. Early identification, exclusion of other etiologies and management of high risk features can delay progression to ESRD.

PUB548

A Case of APOL1-Associated FSGS in a Sickle Cell Disease Patient

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Introduction: Sickle cell disease (SCD) patients experience glomerular hyperfiltration and there are cases of SCD patients with nephrotic syndrome from FSGS and membranous nephropathy. High risk APOL1 risk variants (G1 and G2) have been associated with progression of chronic kidney disease (CKD), FSGS, and HIV associated renal disease in African-Americans. High risk APOL1 risk variants have been associated with progression of CKD and proteinuria in the SCD patient population. We present the first reported case of a SCD patient with APOL1 associated FSGS.

Case Description: This is a 24 year old African-American female with a past medical history of SCD hemoglobin SS, DVT, and avascular necrosis of hip. She was diagnosed with nephrotic syndrome with urine protein-creatinine ratio (UPC) of 25 g/g,

a serum albumin (sAlb) of 1.7 g/dL, and a serum creatinine (sCr) 1.2 mg/dL. Kidney biopsy showed APOL1 associated nephropathy (collapsing FSGS with 60-70% IFTA and microcystic tubular dilatation). She was initially treated with high dose steroids with UPC only improving to 16 g/g after 6 months. Prednisone was decreased and cyclosporine added with varying compliance. Edema improved and hospitalizations from volume overload decreased. 18 months later patient presented with sickle crisis and symptomatic anemia with hemoglobin nadir of 2.8 g/dL, sCr peaked at 3.2 mg/dL, sAlb 1.5 g/dL, and UPC of 23.5 g/g. Rituximab was given for autoimmune hemolytic anemia. Around 6 weeks later sCr improved 2.3 mg/dL, sAlb 2.2 g/dL, and UPC remains 20 g/g, however patient had no signs or admissions for volume overload.

Discussion: Historically glomerular hyperfiltration in SCD has been seen as a secondary cause of FSGS. This case is unique in being APOL1 positive and her severe presentation is more likely primary FSGS. We will continue follow-up closely and if continued improvement consider continuing low dose prednisone and additional rituximab.

PUB549

A Rare Case of Fibrillary Glomerulonephritis and Advanced Diabetic Glomerulosclerosis Class IIb in a Patient with Newly Diagnosed Nephrotic Syndrome

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Introduction: Fibrillary glomerulonephritis is a rare and underdiagnosed glomerular disorder. It was first described by Rosenmann and Eliakim in 1977. It is defined by the ultrastructural finding of haphazardly arranged, straight fibrils measuring 10 to 30 nm in thickness. According to literature, it coexists in about 20% of Type 2 diabetic patients but the connection between these is a topic of debate. We present a case of fibrillary glomerulonephritis coexisting with diabetic nephropathy in a type 2 diabetic with newly diagnosed Nephrotic syndrome.

Case Description: A 48 years old female with past medical history of CHF, polysubstance use, CKD and hypertension, who presented for follow up at renal clinic following discharge from the hospital. She had presented to the emergency room with uncontrolled blood pressure (245/112mmHg), acute kidney injury and nephrotic syndrome, physical examination generated 2+ pitting pedal edema. Creatinine level was 4.1 mg//dl, eGFR of 14, urinary protein excretion was 3.1g/day, total cholesterol of 229 mg/dL, LDL was 123mg/dL and albumin of 3.1g/dL, Kappa/Lambda ratio of 2.56, SPEP had positive polyclonal gammopathy. The patient's kidney biopsy showed fibrillary glomerulonephritis and diabetic nephropathy, moderately advanced, diffused diabetic glomerulosclerosis, interstitial fibrosis and tubular atrophy, severe arteriosclerosis and moderate arteriolosclerosis. She was offered treatment for high blood pressure with lisinopril, amlodipine, labetalol, clonidine and statins.

Discussion: Reports have shown that fibrillary Glomerulonephritis can coexist with diabetic nephropathy, but a true connection has not been proven. Accelerated glycosylation of proteins in diabetics and advanced glycosylation end products capable of cross-linking with other structural proteins as well as circulating proteins has been suggested as a possible pathophysiology. There is currently no effective therapy as most therapies are guided towards reducing proteinuria and cholesterolemia. Cytotoxic agents, plasmapheresis are used but are not ideal therapies and more studies need to be performed to determine the link between diabetic nephropathy and fibrillary Glomerulonphritis in order to determine the best or optimal therapy.

PUB550

A Rare Case of Idiopathic Nodular Glomerulosclerosis(ING) Secondary to Chronic Hypoxia from Persistent Asthma in an Elderly Male with Resistant Hypertension

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Introduction: ING is a rare clinical entity which presents with reduced GFR and nephrotic range proteinuria. It is most common in elderly white males with hypertension, smoking, hypercholesteremia and vascular disease. It is indistinguishable from diabetic nephropathy on histopathology with diffuse nodular mesangial expansion associated with micro aneurysms, arteriolar hyalinosis and arteriolosclerosis with tubulo-interstitial fibrosis. We present a unique case of ING in elderly male with resistant hypertension and chronic hypoxia from persistent asthma.

Case Description: A 80Y old male patient with resistant HTN, CAD, CKD 3, persistent asthma admitted to hospital with complaint of dyspnea secondary to pulmonary edema from hypertensive emergency. He developed AKI on CKD and had >300mg of protein on routine u/a. On further investigations he had a urine microalbumin of 6269ug/mg and a protein/creatinine clearance ratio of 15.05. He underwent kidney biopsy which demonstrated areas of hyalinosis and nodules replacing normal glomeruli along with +2 interstitial fibrosis under light microscopy. No crescentic or necrotizing lesions identified. Immunofluorescence staining was negative and electron microscopy showed no electron dense deposits. These findings are consistent with diabetic nephropathy but our patient never had any history of diabetes which makes this unique. Other causes of nephrotic syndrome in elderly like para-proteins, PAL2R antibody, autoimmune panel (ANA, ANCA, ENA, Anti–GBM) were negative. No secondary causes except for h/o colon cancer in past and he is s/p resection with no recurrence. A tighter blood pressure control and use of ARBs improved his proteinuria and his protein on routine urine analysis was down to 100mg/dl. He is currently being followed in nephrology clinic on a monthly basis.

Discussion: It has been postulated that smoking promotes formation of advanced glycation end products (AGE), induction of oxidative stress, angiogenesis (increased PDGF, TGF B AND IGF-R) altering intrarenal hemodynamics. Our patient has chronic hypoxia from persistent asthma along with resistant hypertension which could be the likely culprits resulting in ING (he is not a smoker and never had diabetes). Further studies are needed to unravel the complex pathogenicity of ING resulting from chronic hypoxia.

PUB551

A Rare Case of Nephrotic Syndrome Precipitated by Pre-Eclampsia and Bevacizumab in a Patient with Underlying Diabetic Nephropathy

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Introduction: Nephrotic syndrome is characterized by nephrotic range proteinuria (urinary protein excretion of over 3.5 grams a day), hypoalbuminemia, edema and hyperlipidemia.

Case Description: A 27-year-old female with hypertension, chronic kidney disease, uncontrolled type 1 diabetes mellitus complicated by proliferative diabetic retinopathy (treated with intravitreal bevacizumab) and nephropathy presented to the hospital in August 2018 complaining of dyspnea on exertion, 35-lbs weight gain and lower extremity pitting edema for 5 months, following delivery of her first pregnancy in March 2018. Her pregnancy was complicated by severe pre-eclampsia and acute kidney injury with the serum creatinine peaking at 1.4 mg/dl (from a prior known baseline of 0.5 mg/dl in 2017). She received intravitreal bevacizumab 2 months after her delivery. On presentation, she was afebrile, HR 94/min and BP 159/88 mm Hg. Labs included serum creatinine 1.4 mg/dl, albumin 2.7 g/dl and nephrotic range proteinuria with a spot urine protein-creatinine ratio of 13.6 g/g. Hepatitis serologies, HIV, ANA, complement profile, ANCA and serum anti-PLA2R antibody were normal. A kidney biopsy was performed which showed a background of advanced diabetic glomerulosclerosis with severe glomerular and podocyte injury concerning for collapsing glomerulopathy (CG). She was started on a diuretic regimen with improvement in her symptoms and was subsequently discharged home with close follow-up with her nephrologist.

Discussion: Pre-eclampsia has been associated with kidney injury causing thrombotic microangiopathy and collapsing glomerulopathy secondary to endothelial injury following inhibition of vascular endothelial growth factor (VEGF) by the soluble fms-like tyrosine kinase 1 (sflt 1) produced by placenta. Intravitreal bevacizumab, an inhibitor of vascular endothelial growth factor (VEGF), which is used in the management of proliferative diabetic retinopathy has similarly been associated with acute kidney injury and proteinuria/nephrotic syndrome with a wide spectrum of histological changes, including collapsing or proliferative glomerulonephritis, interstitial nephritis, and thrombotic microangiopathy. The precise mechanism of glomerular injury induced by VEGF-inhibitors is unknown and merits further studies.

PUB552

Diffuse Alveolar Hemorrhage: A Rare Manifestation of IgA Nephropathy

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Introduction: Pulmonary Renal Syndrome (PRS) describes combined renal and respiratory failure, often in the setting of glomerulonephritis (GN) with diffuse alveolar hemorrhage (DAH). IgA Nephropathy (IgAN) is the most common GN worldwide, but rarely causes DAH, and can be overlooked as a cause of PRS. We describe a case of PRS from IgAN successfully treated with plasmapheresis and glucocorticoids.

Case Description: A 71-year-old woman with hypertension and diabetes developed proteinuria and hematuria and her creatinine rose from 1.0 to 2.0 mg/dL over 9 months. Renal biopsy showed IgA nephropathy with 40-50% tubulointerstitial fibrosis and 15/33 glomeruli globally sclerosed. MEST-C score was M1, E1, S1, T1, C0. She was treated with maximum dose lisinopril. She had no findings to suggest an IgA vasculitis at the time of biopsy. Three months later she presented with dyspnea, cough, and fevers. Chest x-ray showed multifocal infiltrates concerning for pneumonia. Despite antibiotics and diuresis, she developed worsening hypoxic respiratory failure and acute kidney injury. Renal replacement therapy was started for volume removal with no improvement in respiratory failure. A bronchoscopy was diagnostic for DAH. Other vasculitic workup was negative, leaving IgAN as the etiology. With high dose steroids and 7 sessions of plasmapheresis, renal function improved, dialysis was stopped, proteinuria resolved, lung infiltrates cleared, and breathing returned to normal.

Discussion: Proposed mechanisms for DAH in IgAN include nonspecific mucosal hemorrhage, immune complex-mediated damage of the GBM (Type III hypersensitivity), or IgA-mediated capillaritis against GBM antigens (Type II hypersensitivity). Type II hypersensitivity is most likely given elevated IgA levels, deposition of IgA in lung tissue, and case reports of IgA deposits on the skin and circulating IgA1 immune complexes. The prognosis of PRS due to IgAN is variable. It is fatal in a quarter of patients and leads to end-stage kidney disease in half of patients. Recurrence of disease has also been reported. Given its rarity, there are no treatment guidelines. Patients are usually given glucocorticoids and sometimes methotrexate, cyclophosphamide, or azathioprine. Plasmapheresis has also been used in treatment.

PUB553

Typical Presentation of Immunoglobulin A Vasculitis in an Atypical Patient

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Introduction: Immunoglobulin A Vasculitis (IgAV) typically presents with renal dysfunction, palpable purpura, arthritis and abdominal pain. Ninety percent of cases occur in the pediatric population. Males present more frequently than females and IgAV is rare in blacks compared to whites and Asians. We present a case of nephrotic syndrome due to IgAV with prominent cutaneous manifestations in a middle aged black female.

Case Description: A 44-year-old black female with hypertension was seen for new onset nephrotic syndrome. Prior to presentation she was treated with trimethoprim-sulfamethoxazole for a presumed urinary tract infection (culture negative) followed by metronidazole for bacterial vaginosis. One week following completion of antibiotics, she developed anasarca, a pretibial palpable purpuric rash and abdominal pain which prompted three emergency department evaluations. She was initially treated with methylprednisolone for suspected erythema multiforme thought due to metronidazole. Her symptoms improved initially but worsened following steroid completion. Labs revealed proteinuria (12.5 grams), hypoalbuminemia (2.3 g/dL) and elevated creatinine from 1.2 mg/dL to 1.6 mg/dL. Skin biopsy revealed a leukocytoclastic vasculitis. Renal biopsy revealed focal and segmental proliferative glomerulonephritis with dominant IgA fluorescence along with diffuse podocyte foot process effacement and villous transformation. No glomerular obsolescence, interstitial fibrosis or tubular atrophy was noted. Treatment with prednisone 60mg daily was initiated and her abdominal pain resolved within one week. Her skin lesions began to clear by week two. Her proteinuria and albumin slowly improved with partial remission at four months with stable creatinine.

Discussion: This case highlights the typical presentation of IgAV in an atypical patient population. IgAV is well studied in the pediatric population, but rare in adults, females and black patients. Renal manifestations in adults are more severe with a worse prognosis compared to pediatric patients. No drugs have been implicated as a cause of IgAV previously, however, there are case reports in the adult population where metronidazole was received prior to diagnosis. Clinical manifestations including skin rash, abdominal pain, arthritis and renal involvement should raise the suspicion for IgAV even in adult patients previously described as low risk.

PUB554

A Case of ANCA Glomerulonephritis with Anti-GBM Double Positivity

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Introduction: Anti-glomerular basement membrane (GBM) disease and anti-neutrophil cytoplasmic antibody (ANCA) vasculitis are distinct causes of glomerulonephritis (GN), but patients with double positive serologies have overlapping characteristics with implications in management and prognosis.

Case Description: A 52-year-old male presented with several weeks of increasing shortness of breath, orthopnea, lower extremity edema, weight gain, and one week of hemoptysis one month after new onset gross hematuria. On arrival, he was hypertensive and hypoxic. Physical exam revealed 3+ lower extremity pitting edema, and bilateral pulmonary crackles. Labs revealed a creatinine (Cr) of 6.60 mg/dL (was 1.9 mg/dL one month prior), blood urea nitrogen of 72 mg/dL, and urinalysis with 3+ protein and 3+ blood. Urine microscopy revealed red blood cell (RBC) and muddy brown casts. Computed tomography of the chest revealed diffuse multi-focal airspace opacities. Serologic workup revealed elevated anti-myeloperoxidase (MPO)-ANCA of 99.2 U/mL and anti-GBM antibodies (Abs) of 40 U. The patient was initiated on hemodialysis by hospital day five and treated with pulse-dose steroids, IV cyclophosphamide, and initiated on plasma exchange for presumed anti-GBM disease. Renal biopsy revealed chronic smoldering ANCA-associated GN, but there was no linear staining to suggest anti-GBM disease. All glomeruli had segmental to focally global sclerosis. The patient ultimately remained dialysis dependent.

Discussion: About 30% of anti-GBM disease may have concurrent ANCA, and about 5-10% of ANCA-vasculitis may have concurrent anti-GBM Abs. ANCA and anti-GBM are distinct antibody populations, but their coexistence may be explained by initial ANCA-induced GBM injury, linear epitope exposure, and subsequent anti-GBM antibody formation. Double positive patients have anti-GBM phenotype early in disease course with aggressive disease at presentation and more alveolar hemorrhaging, and they have ANCA-vasculitis phenotype later in the disease course with higher risk of relapse but with better chance of recovery from hemodialysis. Double positive vasculitis is a hybrid disease phenotype that requires early aggressive treatment for anti-GBM disease but also demands careful long-term follow-up with strong consideration for maintenance immunosuppression for ANCA disease.

PUB555

Hepatitis C-Associated Membranous Nephropathy: Key to Unlocking Podocytopathy?

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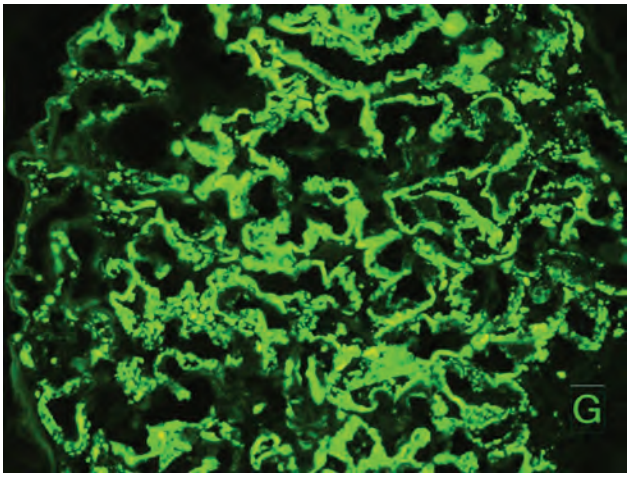
Introduction: Membranous Nephropathy is typically associated with malignancy, infections, and idiopathic. Though the association with Hepatitis C and MN has been debated, there is growing amount of case reports in the medical literature to suggest this connection.

Case Description: A 54 year old white male with history of hypertension, pulmonary embolism, smoking and newly diagnosed HCV presented with anasarca and shortness of breath. Proteinuria was present without hematuria. Serum albumin was 1.8 with 22 grams of proteinuria on 24 hour collection. Direutics were started. Creatinine was 1.42 mg/dL on admission. 4 months prior, there were 9 grams of proteinuria and creatinine was 0.98 mg/dL. Lupus panel, cryoglobulin and HIV was negative. No diabetes mellitus. Renal biopsy was performed and diagnosed with Grade II Membranous Nephropathy with negative PLA2R staining. Given these findings, a diagnosis of MN associated with HCV was made. Statin, Vitamin D replacement, and an ACE inhibitor werer started. He was discharged with follow-up for treatment of Hepatitis C for hopeful resolving of the membranous nephropathy.

Discussion: Approximately 3% of the world population is infected with HCV. Membranoproliferative glomerulonephritis is most common pattern associated with HCV. Though still disputed as a direct cause, growing number of cases indicate strong association and further research must be emphasized on the mechanism of this virus at the glomerulus to which it causes this degree of proteinuria. Around 8.3 % of MN patients were HCV positive. The pathogenesis of MN may be related to the deposition of immune complexes containing HCV proteins in glomeruli. It is unknown how exactly Hepatitis C initiates at the glomerulus whether glomerulonephritis or podocytopathy. If future research can determine why certain processes only allow red blood cells as opposed to only albumin, these entities, through study of Hepatitis C, can provide the key to that question.



PUB556

Membranous Nephropathy and Malignancy: True, True and Unrelated

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Introduction: Primary membranous nephropathy (MN) is associated with antibodies against the M-type phospholipase A2 receptor (PLA2R) on podocytes in 75-80% of cases with >99% specificity.

Case Description: A 71-year-old African American male presented with lower extremity edema and new-onset severe ascites. One year previously a colonic polyp was removed which was positive for invasive adenocarcinoma at which time he declined further surgical exploration and treatment. Large-volume paracenteses was negative for malignant cells with a Serum Ascites Albumin Gradient <1.1 (not suggestive of portal hypertension). Hospital course was complicated by lower extremity proximal deep vein thrombosis treated with anticoagulation (AC). Nephrotic range proteinuria (uPCR 10g/g) was found with serum creatinine 1.5 mg/dL, serum albumin 1.9 g/dL. His anti-PLA2R Ab measured by ELISA was very high x 2 (269 RU/mL, 711 RU/ml). The rest of the serologic proteinuria workup was negative and he was diagnosed with Primary MN. A renal biopsy was not performed given high bleeding risk. Treatment plan included RAAS blockade, continuation of AC and consideration of immunosuppressive therapy (IST) to mitigate severe and symptomatic nephrotic syndrome in consultation with oncology.

Discussion: Some experts have suggested that a renal biopsy is not required for diagnosis of primary MN in patients who present with anti-PLA2R Ab >20 RU/ml by ELISA with normal renal function and a negative work up for secondary causes. We suggest that this recommendation might be extended to patients such as this one despite an elevated creatinine and a condition well known to cause secondary MN (colon cancer). Prior to the advent of PLA2R Ab testing it has been thought that up to 20% of all cases of biopsy proven MN are secondary which may be an overestimation. Indeed, this case would have been classified as secondary MN in the past. Given the remarkable specificity of the PLA2R Ab at high levels it is more likely that this case represents primary MN in a patient who also happens to have a colon cancer. Interestingly, his entire presentation might have been explained by malignancy (ascites, DVT with hypercoagulable state) but nephrotic proteinuria which led to anti-PLA2R Ab testing allowed for the correct diagnosis of primary MN.

PUB557

Membranous Nephropathy Associated with Sjögren Syndrome, Primary Biliary Cirrhosis, and Autoimmune Hepatitis

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Introduction: Membranous nephropathy (MN) is an autoimmune glomerular disease with ~75% of cases are primary due to phospholipase A2 receptor antibody (PLA2RAb). MN may also be secondary to conditions such as autoimmune diseases, chronic infections, malignancy, and drug side effects.

Case Description: 63 year-old African-American female patient with a past history of Sjögren syndrome (SS), primary biliary cirrhosis (PBC), and autoimmune hepatitis, was referred to nephrology clinic for proteinuria. She was receiving azathioprine, hydroxychloroquine, and a tapering steroid regimen prior to seeing Nephrology. Serum creatinine was 0.6 mg/dL and urinalysis demonstrated protein (2+), negative for erythrocytes and leukocytes. She had non-nephrotic range proteinuria of 685 mg/g. Serologic studies were strongly positive for SS-A antibodies and also positive for anti-nuclear, anti-mitochondrial, and anti-smooth muscle antibodies, but negative for anti-dsDNA, anti-Smith antibodies, and PLA2RAb. Kidney biopsy revealed normal appearing glomeruli by LM. IF was for 3+ positive for coarsely granular deposits of IgG and IgA along capillary loops and mesangial regions and 2+ for C3 and 1+ for C1q. PLA2RAb staining was negative. EM showed numerous small subepithelial and rare mesangial electron dense deposits, features consistent with secondary MN.

Discussion: MN accounts for up to one-third of biopsied cases of nephrotic syndrome. Most cases of primary MN are due to PLA2RAb. Secondary causes of MN include autoimmune diseases, infection, drugs, and malignancy. Our patient developed secondary MN in association with multiple autoimmune related conditions, including SS, autoimmune hepatitis, and PBC. The combination of SS with kidney and liver involvement in one entity is extremely rare. Patients with SS can present with renal involvement of diverse etiology with chronic tubulointerstitial nephritis (TIN) with mild proteinuria and tubular dysfunction being the most common finding, followed by acute TIN. However, glomerular disease due to immune complex deposition, has been rarely described in SS and PBC. Renal involvement often goes unrecognized until significant renal dysfunction occurs. The renal lesions in SS can improve significantly with treatment, emphasizing the importance of early diagnosis with renal biopsy and aggressive treatment.

PUB558

Fibrillary Glomerulonephritis and Hashimoto Thyroiditis

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Introduction: FGN, a rare primary glomerular disease. Most previously reported cases were idiopathic. Underlying malignancy, dysproteinemia, or autoimmune diseases are not uncommon in patients with FGN. No fibrillary GN case report was found in association with Hashimoto thyroiditis.

Case Description: 41 y/o F of Micronesian descent. Recent URI, gestational DM and pre-eclampsia w/ SOB, found to have an acute onset grade III AKI & nephrotic syndrome requiring dialysis. Family hx- nephew w/ ESRD of unknown etiology; currently on dialysis. UA- 3+ protein, no RBC, no granular casts. ESR- 101, CRP- 2.1, mildly elevated LDH. Negative strep antibody, Cryoglobulins, HIV screening, ANCA panel, glomerular basement membrane antibody, Hepatitis panel and Double stranded DNA antibody. Monoclonal workup negative. ENA panel positive for SmRNP ab. Normal C3, mildly elevated C4 levels. Normal renal U/S. **Biopsy-** 75 glomeruli, 90% of the glomeruli globally sclerosed. Mesangial hypercellularity, expanded matrix and thickened capillary basement membranes. A single glomerulus with epithelial crescent. Hyaline deposits within capillary loops and mesangium. Interstitium with inflammatory infiltrate (3+), of lymphocytes, plasma cells and neutrophils. Medium and large-sized vessels with marked myointimal sclerosis (3+). **Immunofluorescence-** non-specific deposits of IgM, C3, and C1q (2+). **Electron microscopy-** Thickened capillary basement membranes, focal loss of foot processes, isolated intramembranous deposits and large sub-endothelial/ mesangial fibrillary deposits. **Fibrillary deposits with thickness of 20.0 nm.** CT chest- Multiple right thyroid nodules. No malignancy on Abd/pelvis CT and mammogram. **FNA thyroid- "Cellular Changes Consistent With Lymphocytic (Hashimoto's) Thyroiditis". Therapeutic Intervention-** Considering observation of an active crescent, initially was given 3 doses of 1g Methyl prednisone and was discharged on prednisone taper. Now dialysis dependent.

Discussion: Association with autoimmune disorders and exact pathogenesis of the disorder is unclear. Further case series of such cases might indicate an association between autoimmune disorders and Fibrillary GN.

PUB559

Clinicopathological Features of Hypocomplementemic Urticarial Vasculitis with Renal Involvement: A Case Series

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Introduction: Hypocomplementemic urticarial vasculitis (HUV) is a small vessel vasculitis with renal involvement in up to 50% of cases and heterogeneous clinical presentation. Given the rarity of this clinical entity, there is uncertainty about the clinical picture, treatment response and outcome, so additional data is warranted. Therefore, we report a case series of patients with HUV and nephrotic syndrome.

Case Description: The first patient was admitted in our department for oliguria, generalized edema and recurrent urticarial lesions. Laboratory testing showed acute kidney injury (serum creatinine 5,96 mg/dl), nephrotic syndrome (proteinuria 6 grams/24h) with active urinary sediment, while immunological work-up revealed antiC1q-antibodies and hypocomplementemia. She received immunosuppressive therapy with methylprednisolone and cyclophosphamide, without clinical response, remaining on chronic hemodialysis. The second patient presented with generalized edema and gross haematuria. Laboratory data confirmed renal impairment (serum creatinine 4.29 mg/dl), nephrotic syndrome (proteinuria 7 grams/24h) and important hematuria; immunologic results revealed antiC1q-antibodies and hypocomplementemia. Kidney biopsy was consistent with a membranoproliferative (MPGN) pattern of injury with diffuse crescent formation. After treatment with methylprednisolone, cyclophosphamide and plasma exchange, she achieved complete immunological and clinical remission. The third patient, with a past medical history of type 1 diabetes mellitus, was evaluated for generalised edema and recurrent urticarial lesions. Similar to previous cases, laboratory testing showed nephrotic syndrome (6.4 grams of proteins/24h), positive antiC1q antibodies, decreased complement levels, while renal function was preserved. Renal biopsy described a MPGN pattern with crescent formation, superimposed on a class III diabetic nephropathy. Despite cyclophosphamide and Rituximab treatment, she is still immunologicaly active and nephrotic.

Discussion: HUV is an unusual cause of nephrotic syndrome in adults. Our case series could add significant insight into the management and evolution of these patients.

PUB560

Early Appearance of HIV-Associated Nephropathy During Seroconversion

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Introduction: HIV-Associated Nephropathy is a collapsing form of FSGS typically later in HIV infection of patients of African descent. We submit a case of early HIVAN presenting during seroconversion, with rapid decline in GFR requiring hemodialysis, that improved with initiation of HAART.

Case Description: A 27-year-old African American man presented with 2 months of chills, aches, and 25lb weight loss, and recent MSM. Initial labs included creatinine of 2.1, albumin 3.3, and 4+ protein on dipstick. Urine protein:Cr was 3.8, HIV serologies were positive, and CD4 count was 617. HAART was initiated, and renal biopsy obtained hospital day 3. Biopsy revealed focal and segmental glomerulosclerosis with early collapsing features, reticular aggregates, podocyte effacement, and diffuse tubular injury, consistent with HIVAN. Serum BUN and creatinine reached 135 and 12.4 respectively, prompting initiation of hemodialysis. At discharge, proteinuria had improved, though creatinine remained elevated at 6.8.

Discussion: HIVAN was first considered an AIDS-defining illness. Increasing number of cases occurring early in HIV have since been documented. Our patient's flu-like symptoms, CD4 count of 604, and high viral load were consistent with a recently seroconverted HIV infection. During seroconversion, the virus replicates in tubular and glomerular epithelial cells causing the biopsy characteristics seen in HIVAN: interstitial inflammation, microcystic tubular dilation, and sclerosing multiplication of glomerular cells. Rapid development of heavy proteinuria in early HIV, as seen in our patient, should prompt high-suspicion of HIVAN. Early renal biopsy should be performed as to not delay initiation of appropriate suggested therapies. Evidence for or against these therapies were garnered primarily from cohort studies and expert opinion. However, HAART therapy is recommended for all individuals found to be HIV positive as prompt initiation has been found to be associated with longer mean renal survival. ACE/ARBs are currently recommended for proteinuric patients. Steroids have been associated with improvements in proteinuria and decreased progression of baseline creatinine, and are recommended if there is rapid decline while on HAART. In this case, HAART was initiated and biopsy was obtained within seven days of last known normal renal function. A trial of steroids was begun, and renin-angiotensin inhibition was not added.

PUB561

Acute Tubulointerstitial Nephritis and Minimal Change Disease in a Patient with Allogenic Hematopoietic Stem Cell Transplant Complicated by Chronic Graft vs. Host Disease

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Introduction: We present a case of adult-onset acute nephrotic syndrome (NS) due to minimal change disease (MCD) and acute tubulointerstitial nephritis (ATIN) following allogenic hematopoietic stem cell transplantation (allo-HSCT) and chronic graft versus host disease (GVHD).

Case Description: A 43-year-old male was referred to our nephrology clinic for evaluation of proteinuria and edema. He has a history of Hodgkin lymphoma treated with chemotherapy and mediastinal radiation followed by autologous HSCT complicated by relapsed disease requiring matched unrelated donor allo-HSCT. He developed acute GVHD following a rapid taper of tacrolimus which progressed to chronic GVHD. Patient had been off sirolimus for three months when routine labs showed serum albumin 2.5 g/dL compared to 4.1 g/dL two months prior. Urinalysis revealed protein levels greater than 500 mg/dL without hematuria or pyuria. Serum creatinine and blood urea nitrogen were 0.6 mg/dL and 12 mg/dL, respectively. Random urine protein to creatinine ratio was 7734 mg/g. His 24-hour urine protein was 7.1g and urine protein/creatinine ratio was 4.7. Additional laboratory results were negative for autoimmune, infectious, or

malignant etiologies. Light microscopy evaluation of a renal biopsy showed mild increase in glomerular mesangial cellularity and matrix deposition without endocapillary hypercellularity, segmental sclerosis, or cellular crescents. Focal interstitial inflammation was seen with an increased number of eosinophils. Immunofluorescence staining showed no specific pattern of antibody deposition. Electron microscopy showed uniform basement membrane thickening and 80% podocyte foot process effacement.

Discussion: NS is a rare complication following allo-HSCT associated with GVHD. Pathological etiologies include membranous nephropathy, thrombotic microangiopathy, and MCD, consistent with our findings. Our patient had a course of daily ibuprofen use for one month prior to presentation, which could account for his pathological findings of ATIN and MCD. Our case proposes the possibility of ATIN as an additional manifestation of renal GVHD. He was placed on oral prednisone with improvement of protein to creatinine ratio to 2.5 mg/g. Further studies will be required to identify the association between ATIN and renal GVHD.

PUB562

Membranoproliferative Glomerulonephritis Presenting with Overwhelming Cryoglobulin Deposition Masked by Acute Tubular Necrosis

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Introduction: This case highlights the importance of a thorough work up for acute renal failure, which includes determination of baseline renal function, temporality of renal insults with clinical history, urine sediment microscopy, and protein quantification. A low threshold for biopsy in the setting of active sediment, lymphadenopathy, and serologic markers can change management.

Case Description: The patient is a 46-year-old female with intellectual disability who presented with altered mental status and shock physiology, requiring resuscitation and pressor support. Her exam was pertinent for tachypnea, hypovolemia, bulky cervical lymphadenopathy, and a right knee effusion. She had anuric acute renal failure (BUN 67 and Creatinine 4.08, with normal renal function on outpatient labs 10-days prior). A urinalysis reported 4+ protein, 2+ blood. We obtained a spot urine total protein and creatinine, with a ratio of 38.17. Urine sediment by microscopy had florid coarse granular casts, tubular epithelial cells, and few non-dysmorphic RBCs. Retroperitoneal ultrasound was unrevealing. Renal replacement therapy was initiated for her presumed ATN. However, her lymphadenopathy, joint effusion, and severe proteinunria did not fit simple ATN. Serologies showed EBV IgM positivity with quantification log 2.96. She was otherwise Parvovirus, CMV, HIV, Hepatitis B&C negative. Quantiferon Gold, SPEP, IF and SFLC were also negative. Core biopsy of cervical node showed necrotizing and granulomatous lymphadenitis without malignancy. The patient underwent renal biopsy revealing lobular deposits in the mesangium, capillary loops, afferent arterioles, tubules, and Bowman's space. Small vessels contained fragmented RBCs and deposits with karyorrhexis. IF revealed 3+ C3, IgG and IgM. Supportive serologies included positive ANA, La, Ro, dsDNA, reduced C4 and normal C3.

Discussion: The patient's shock state could have distracted from the more ominous cause of renal failure. Anuric AKI due to ATN requiring RRT is not uncommon in critical care nephrology. Furthermore, lack of renal recovery leading to intermittent hemodialysis, likely would not necessitate secondary work up. It is important to have a suspicion for glomerular disease, especially in the setting of systemic findings that are associated with secondary causes of proteinuric renal failure.

PUB563

Scleroderma Renal Crisis with Subtle Clinical Signs in a Young Male

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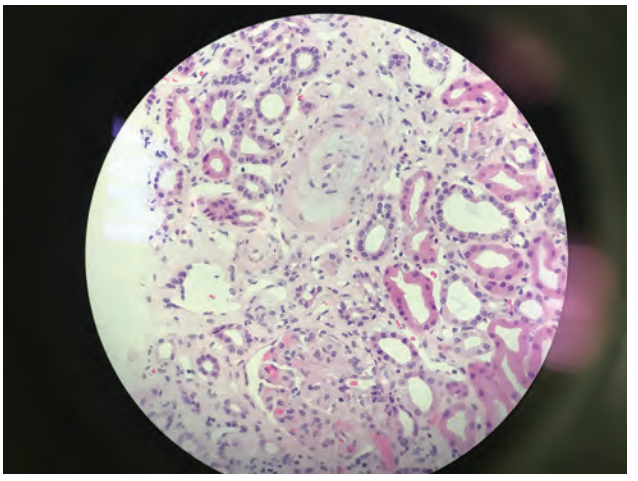
Introduction: A young man with unassuming scleroderma renal crisis with very subtle clinical signs. The reason this case is important from a renal prespective is atypical presentation of scleroderma renal crisis, it's a diagnosis not to be missed.

Case Description: A 43 year old man presented with history of headache and neck ache with nausea and vomiting for 6 weeks. Found to have high blood pressure with renal insufficiency. Systemic inquiry no history of oral ulcers, joint pain, rash, weight loss or features of Raynaud's phenomenon. Examination showed BP-180/100mmmHg with thicken skin over his hands. Differential diagnosis was hypertension leading to chronic renal failure, haemolytic uremic syndrome and scleroderma renal crisis. Initial investigations showed deranged renal function with features of thrombotic microangiopathy. Ultrasound kidneys-normal. ANA speckled patterns with 1:640 titres and rest of the autoimmune profile was normal. Renal biopsy : Consistent with features of thrombotic microangiopathy. Initially treated as HUS with 900mg of Eculizumab. His anti-RNA polymerase III came back as positive Our final diagnosis was scleroderma renal crisis based on renal biopsy, anti-RNA polymerase III positive, progressive renal failure with TMA and sclerodactyl of his hands.

Discussion: Our patient had atypical physical features of scleroderma and scleroderma renal crisis occurs in minority of such patients with anti-RNA polymerase III and ANA positive which is associated with an increased risk of developing scleroderma renal crisis. Our patient could fit in the criteria for systemic sclerosis sine scleroderma. Our patient was given eculizumab initially for suspected HUS but later stopped due the final diagnosis of scleroderma renal crisis. My question to the leading nephrologists at the conference would be if they have any experience in using eculizumab for scleroderma renal crisis as case reports are present which have advocated its use.



onion ring appearance of a blood vessel

PUB564

A Case of Lupus Nephritis with Acute Tubulointerstitial Nephritis Presenting Multiple Low-Density Lesions on Contrast-Enhanced CT

Takahiro Yamano, Hiroyuki Kawahara, Shinya Hibino, Ryo Nishioka, Takeshi Zoshima, Satoshi Hara, Kiyoaki Ito, Ichiro Mizushima, Hiroshi Fujii, Mitsuhiro Kawano. *Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan.*

Introduction: Lupus nephritis (LN) usually involves glomeruli but sometimes involves the tubulointerstitium and contributes to renal dysfunction. However, there have been no case reports of the radiological abnormalities of tubulointerstitial lesions in LN. Here, we report a case of LN with acute tubulointerstitial nephritis(TIN) presenting with multiple low-density lesions on contrast-enhanced computed tomography (CT).

Case Description: A 27-year-old Japanese woman was admitted to our hospital due to a suspected flare-up of systemic lupus erythematosus(SLE). She had been diagnosed 2 years previously with SLEbased on malar rash and positivity for anti-nuclear, anti-ds-DNA, and anti-Sm antibodies, and treatment with prednisolone (PSL) 5 mg/day was initiated. She was transferred to our hospital 4 months ago because of fever, fatigue, left small malar rash, and renal dysfunction. Bilateral renal multiple low-density lesions were detected on contrast-enhanced CT. Her symptoms recovered spontaneously, so she was discharged under continued treatment with PSL at 20 mg/day. Three weeks ago, after tapering the PSL to 16 mg/day, joint pain, palmar and nail erythema, and fever appeared gradually, and she was re-hospitalized. A blood test showed a creatinine level of 0.91 mg/dL with no reduction in complement and no elevation of the anti-ds-DNA antibody level. Urinalysis showed a urinary protein level of 0.10 g/gCr, no microscopic hematuria, and no granular or erythrocyte casts. Contrast-enhanced CT revealed remaining bilateral renal multiple low-density lesions. Renal biopsy showed diffuse lymphoplasmacytic infiltration in the tubulointerstitium, indicating acute TIN. In the glomeruli, mesangial cell proliferation and endocapillary hypercellularity were observed with IgG- and C3-predominant deposition, leading to a diagnosis of LN ISN/RPS class III (A). The fever and joint pain were alleviated, and bilateral renal multiple low-density lesions disappeared when the PSL dose was increased to 30 mg/day.

Discussion: LN with acute TIN can present with bilateral renal multiple low-density lesions on contrast-enhanced CT. Tubulointerstitial lesions of LN should be considered as a differential diagnosis of renal multiple low-density lesions.

PUB565

C3-Dominant Post-Infectious Glomerulonephritis Occurring in a Patient with Methicillin-Susceptible Staphylococcus aureus Bacteremia

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Introduction: C3 glomerulopathies are a group of renal disorders characterized by complement dysregulation, and may represent a disease continuum. We present a case of C3-dominant post-infectious glomerulonephritis (PIGN) occuring in a patient with MSSA bacteremia who presented with AKI and nephrotic range proteinuria.

Case Description: This is a 48 year old man with history of poorly controlled type 2 DM and osteomyelitis of right great toe, s/p digital amputation, presenting with right foot swelling, pain, and erythema. Right foot exam notable for ulcerations but intact distal pulses. Admission sCr was 1.1. Admission blood cultures isolated MSSA in both sets, so patient was started on nafcillin. Echocardiogram did not show valvular vegetations. Podiatry was consulted and performed bone biopsies, which showed acute osteomyelitis. On hospital day 12, patient developed AKI with sCr 1.38 mg/dl, the following day trending up to 1.6 mg/dl. Urinalysis revealed 10-25 RBC, 5-10 WBC, and spot protein of 600 mg/dl, with 24 hour urine collection 10.4 g. Nephrology was consulted and autoimmune workup was negative with the exception of low serum C3 level. Renal biopsy revealed

C3-dominant immune complex glomerulonephritis superimposed on diabetic nephropathy. Electron microscopy revealed numerous mesangial electron-dense deposits and rare subepithelial deposits (humps). The epithelial foot processes show segmental effacement. Immunofluorescence showed 1+ segmental mesangial and pseudolinear glomerular staining for IgG, and 3+ global mesangial staining and segmental peripheral granular staining for C3, C1q was negative. The patient was treated with antibiotics with resolution of infection, normalization of kidney function and proteinuria, and normalization of complement levels.

Discussion: We present a case of C3-dominant PIGN. Renal biopsy should be performed in patients with presumed PIGN, who have abnormalities such as hypocomplementemia, progressive decline in renal function, or proteinuria. Electron microscopy findings can differentiate among subtypes of C3GN. In C3-dominant PIGN, the complement dysregulation is presumed to be transient or part of the recovery from infection. Treatment of infection should lead to improvement in renal function and normalization of serum C3 level. If the C3 level does not normalize, reclassification to C3 glomerulopathy is warranted.

PUB566

Full House on Immunofluorescence but No Lupus! Renal Limited Lupus-Like Nephritis

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Introduction: Renal limited lupus-like nephritis is defined as kidney biopsy consistent with lupus nephritis (LN) without extra-renal organ involvement or positive serological markers for systemic lupus erythematous (SLE). This rare entity carries a poor prognosis. Data is limited on treatment options. We present a case of AKI with lupus-like nephritis "full house" pattern with negative serologies and absent extra-renal manifestations of SLE.

Case Description: A 55-year-old white male was originally hospitalized for sepsis with an unknown source. Blood cultures grew methicillin sensitive Staphylococcus aureus (MSSA). One week after admission, he developed acute renal failure. Pertinent labs include serum creatinine of 4.2, urine protein/creatinine ratio of 1144 mg/g, serum albumin of 2.1g/dl, negative ANA, anti-DNA antibodies, a weakly positive cANCA, pANCA, and low complement levels. HIV, hepatitis B and C virus serologies were negative. Renal biopsy showed a diffuse and global glomerulonephritis with a full house staining pattern on immunofluorescence microscopy, consistent with lupus nephritis class IV-G (A). His renal function continued to deteriorate requiring hemodialysis. The patient remained dialysis dependent and died within 6 weeks of initial presentation.

Discussion: In SLE, presence of renal involvement is significant for prognosis and treatment. There have been case reports of renal biopsy findings consistent with LN without extra-renal organ involvement or serologies sufficient to diagnose SLE at the time of biopsy. These cases were labeled in the literature as "renal limited lupus-like nephritis." They have been sub grouped into 3 categories: early presentation of SLE, seronegative lupus, and renal limited lupus like nephritis. Renal limited lupus like nephritis cases have no clinical manifestations, remained seronegative after years of follow-up, and had a worse prognosis compared to patients with SLE and seronegative LN. Infection associated GN has been reported to mimic renal limited lupus like nephritis on kidney biopsy. We need more research to help guide management in this rare and complicated disease condition.

PUB567

Microscopic Polyangiitis Presenting with Acute Abdominal Pain

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Introduction: ANCA associated vasculitis is a small vessel vasculitis that includes granulomatosis vasculitis, Churg-Strauss syndrome, microscopic polyangiitis. We describe a patient of microscopic polyangiitis, who presented with abdominal pain, and acute kidney injury.

Case Description: A 69-year-old female with a past medical history of hypertension, and heart failure presented with right-sided abdominal pain and fatigue. On examination, she was afebrile, with a blood pressure of 166/72 mm/hg. Positive exam finding included mild right-sided abdominal tenderness on palpation. Laboratory testing revealed leukocytosis 19.10 10(3)/mcL, hemoglobin of 8.1 g/dL. Blood urea nitrogen (BUN) 85 mg/dL, and creatinine of 4.56 mg/dL. Urine analysis revealed 3+ blood and, 2+ protein. 24-hr urine protein was significant with 971 mg/24 hour. Computed tomography scan of the chest revealed chronic obstructive pulmonary disease (COPD) changes along with a right basilar infiltrates. Further laboratory workup revealed P-ANCA with a titer of 1:160. She was diagnosed with microscopic polyangiitis (MPA) based on the involvement of the lower respiratory tract, kidneys, gastrointestinal tract, along with a positive P-ANCA. During the hospital course, the patient required hemodialysis. After kidney biopsy, she was started on glucocorticoids. She required plasmapheresis followed by Rituximab. Eventually, the patient was transferred to a long term acute care hospital for further rehabilitation.

Discussion: MPA is an autoimmune systemic vasculitis that is associated with antineutrophilic cytoplasmic antibodies. These antibodies play a role in the pathogenesis, initially, neutrophils attach to endothelial surface of blood vessels and glomeruli with subsequent activation. Renal involvement is seen in more than 80% of cases and it can present as symptomatic urinary sediment and end-stage renal disease. The lungs are involved in up to 50% cases and present with diffuse pulmonary hemorrhage. Skin lesions are found in 30-60 % of patients and palpable purpura is the most common manifestation. Most common gastrointestinal symptoms are abdominal pain. Gastrointestinal bleeding can also occur in some cases but catastrophic hemorrhage is rare. When diagnosing a patient, ANCA is detected in 50-70% of cases and its absence does not rule out disease. Treatment primarily includes glucocorticoids but cyclophosphamide, azathioprine, and rituximab have been used.

PUB568

Systemic Lupus Erythematosus During Treatment of Autoimmune Hepatitis and Primary Biliary Cirrhosis

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Introduction: The complication of systemic lupus erythematosus(SLE) with autoimmune hepatitis(AIH) and primary biliary cirrhosis(PBC) is very rare. We report a case developed SLE during treatment of AIH PBC.

Case Description: A 50-year-old woman had been receiving treatment for type 2 diabetes mellitus since 201X-10. There was no decline in her renal function, and her urinary protein(Up) tested negative. She was admitted with liver dysfunction in January 201X-7. Liver biopsy was performed, resulting in a diagnosis of AIH and PBC. Up gradually progressed from January 201X. She was admitted to our department in April 201X. Renal biopsy was performed. Twenty-six glomeruli were collected, and 18 of them had lesions. There were many chronic lesions, and more than 50% of the glomeruli were noted. In renal pathology studies, IgG, IgA, IgM, C3, C4, and C1q tested positive by the fluorescent antibody technique. During a serological examination, antinuclear antibody and ds-DNA antibody tested positive, and the patient was diagnosed as having lupus nephritis type IV(G)(C) based on the Systemic Lupus International Collaborating Clinics(2012) and International Society of Nephrology/Renal Pathology Society(2003). She began 60 mg of oral prednisolone(PSL) treatment. Proteinuria improved from 2.03 g/day at the start of treatment to 0.42 g/day on the 22nd hospital day. PSL dose was reduced to 50 mg/day. Then, Up tended to gradually increase, and pancytopenia was also observed during the same time. We considered the possibility that disease activity was high; therefore, mycophenolate mofetil 1 g/day was started and increased to 2 g/day. The Up level was slightly exacerbated with PSL dose reduction but leveled off at 0.7-0.9 g/day and then did not change with PSL dose reduction.

Discussion: The complication of SLE with AIH and PBC is very rare. A previous study demonstrated that autoimmune disease accounts for only 4.7% of cases of liver enzyme elevation in SLE patients. On the other hand, liver enzyme elevations are often accompanied by SLE; 50% of SLE patients have liver enzyme elevations. Therefore, it is very important to differentiate causes of liver enzyme elevations in SLE patients. The complications of SLE and AIH or SLE and PBC are relatively rare; however, AIH, PBC, or complications of AIH and PBC should be considered if liver disease is found in SLE patients.

PUB569

Pauci-Immune Crescentic Glomerulonephritis with Re-Initiation of Adalimumab for Crohn Disease

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Introduction: Inflammatory bowel disease (IBD) is associated with a number of renal disease processes most commonly nephrolithiasis, IgA nephropathy and interstitial nephritis. Certain tumor necrosis factor alpha (TNFa) inhibitors, which are commonly used for treatment of IBD, have been rarely associated with pauci immune crescentic glomerulonephritis (PICG). We present a unique case of PICG in the setting of re-initiation of adalimumab (TNFa inhibitor) in a patient with Crohn's disease (CD)

Case Description: A 40-year-old woman presented with CD flare and abdominal pain, nausea, vomiting, poor oral intake, an intermittent pruritic rash and gross hematuria. She was treated with a steroid taper and re-initiation of adalimumab. On initial evaluation she was hypertensive with diffuse abdominal pain. Laboratory evaluation was notable for a serum creatinine for 3.6 mg/dL up from a baseline for 0.8 mg/dL, hematuria and proteinuria of 6.6 g/g. Serologic studies including ANA, MPO, PR3, hepatitis B and C and anti-GBM were negative. Complement C3 and C4 were normal. Imaging showed perinephric stranding and a small non-obstructing stone. Patient was treated with steroids, adalimumab, and IV fluids. Serum creatinine peaked at 5.8 mg/dL and then trended down and patient was discharged home with close renal follow up. She was readmitted with recurrent abdominal symptoms and a worsening serum creatinine and underwent a renal biopsy six weeks after initial evidence of acute kidney injury. Pathology showed PICG. She was treated with rituximab and an intensified steroid regimen. For her CD, she was transitioned from adalimumab to vedolizumab (an oral monoclonal antibody with gut selective anti-inflammatory activity) due to concern that adalimumab contributed to her PICG. At last follow up her serum creatinine was down trending but had not returned to normal.

Discussion: The TNFa inhibitors infliximab and etanercept have a rare association with PICG and in renal biopsy case series of patients with a history of IBD PICG has been reported. However, the association of adalimumab with ANCA negative PICG in this case is unique in the literature and may represent an under recognized etiology of glomerulonephritis in IBD.

PUB570

Immunotactoid Glomerulopathy in a Patient with Monoclonal B-Cell Lymphocytosis: A Rare Finding

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Introduction: Monoclonal B-cell Lymphocytosis (MBL) and glomerular diseases are a rare association. We present an unusual case of an adult male who developed nephrotic syndrome and was found to have immunotactoid glomerulopathy secondary to MBL.

Case Description: A 54-year-old male with history of well-controlled hypertension on lisinopril was evaluated for significant bilateral leg swelling. Laboratory evaluation was remarkable for 24-hr proteinuria of 8g/day, eGFR of 85 ml/min/1.73m^2, and serum albumin 2.5g/dl. Autoimmune serologies, serum free light chains, serum immunoelectrophoresis, and imaging studies of the thorax and abdomen were unremarkable. Renal biopsy showed thickened capillary walls by light microscopy with IgG2 kappa monoclonal glomerular capillary wall deposits by immunofluorescence microscopy. Electron microscopy showed widespread foot process effacement and intramembranous deposits with a microtubular substructure, organized in parallel bundles, and measuring ~25nm in diameter. Flow cytometry of the peripheral blood showed very low-level clonal lymphocytes (1.4% of circulating white blood cells; 128 cells/microliter). Bone marrow aspiration revealed CD5-positive B-cell lymphoid proliferation with predominantly small lymphoid cells comprising 20% of marrow cellularity with a phenotype most compatible with MBL. The patient was started on bendamustine and rituximab (BR). After 6 cycles of BR regimen, repeat bone marrow biopsy showed 0.01% involvement and clinical symptoms improved with reduction in proteinuria to 1.6gm, normalization of serum albumin and preserved renal function.

Discussion: Immunotactoid glomerulopathy is characterized by glomerular capillary and/or mesangial organized deposits with a microtubular substructure. 40-50% of patients develop end stage renal disease within few years of diagnosis, underscoring the need for early diagnosis and treatment. Our case in a patient with MBL highlights the importance of evaluation for an underlying lymphoproliferative disorder with appropriate imaging studies, peripheral flow cytometry and bone marrow biopsy even in the absence of a peripheral paraproteinemia. An early target-directed therapy towards B-cell or plasma-cell clone may result in preservation of renal function.

PUB571

Membranous-Like Glomerulopathy with Masked IgG Kappa Deposits

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Introduction: Glomerulonephritis is pathologically diagnosed by examining changes using light, immunofluorescence, and electron microscopy of the renal biopsy. Routine direct immunofluorescence on fresh tissue is consider the gold standard for the detection and characterization of immune deposits. An additional antigen retrieval step has recently been defined to unmask immunoglobulin visualization utilizing pronase digestion.

Case Description: 33-year-old female with a past medical history of three pregnancies presented to nephrology clinic for evaluation of proteinuria. During her second and third pregnancies she developed proteinuria. During her second pregnancy, a 24-hour urine collection revealed 0.53 grams of protein. During her third pregnancy, a 24-hour urine collection revealed 1.99 grams of protein. She never experienced hypertension or preeclampsia. Three months after her last delivery, her proteinuria persisted and was measured at 2 grams per day. Serologies returned positive for ANA and low C3. Renal biopsy performed and resulted with convincing membranous alterations and presence of extensive deposits by electron microscopy with immunofluorescence staining for C3 and C1q. The biopsy was sent for paraffin immunofluorescence. Staining returned positive for IgG segmental to global granular subepithelial deposits that stain 2+ Kappa. Proteinuria decreased to 500 mg per day without treatment. Renal function remained intact with a baseline creatinine of 0.8. Initiation of MMF +/- prednisone was discussed but to due improvement of proteinuria and intact renal function, the decision was made to continue conservative therapy by assessing proteinuria every three months.

Discussion: Routine immunofluorescence is considered the gold standard for detection of protein in kidney biopsies. Light-chain proximal tubulopathy crystalline inclusions in the proximal tubule occasionally do not react with immunofluorescence. Without unmarking of the immunoglobulin with pronase, many patients may be incorrectly labeled as C3 glomerulonephritis, a disease with C3-restricted deposits that can show predominance of subepithelial deposits by electron microscopy. Membranous-like glomerulopathy should be considered in all patient with unexplained proteinuria in the setting of autoimmune disease.

PUB572

Lupus-Mediated Kidney Damage: Lupus Nephritis or Collapsing Glomerulopathy?

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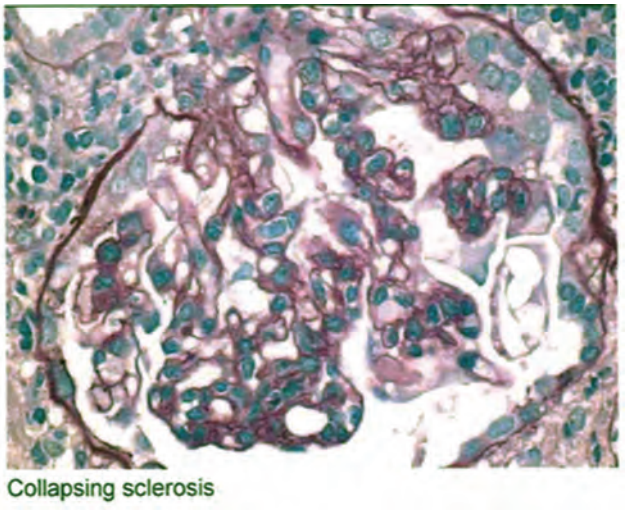
Introduction: Lupus nephritis is a well-known entity and treatment options for it are clearly defined. However, Lupus nephritis with collapsing glomerulopathy (CG) is less common and pose special challenges in terms of management

Case Description: 47-year-old Hispanic female presented with chills, epigastric discomfort and lower extremity edema for 10 days. 1-2+ bilateral lower extremity pitting edema found on examination. Labs revealed Normocytic anemia, hyperlipidemia, hypoproteinemia. Creatinine of 6.3 mg/dl Marked proteinuria. UPCR 17 g/g. Hypocomplementemia present. ANA titers 1:40. Anti-dsDNA, ANCA, anti SM and RNP negative. **Renal biopsy:** collapsing glomerulopathy superimposed on focal glomerulonephritis, immune complex type, suggestive of lupus podocytopathy **superimposed** on lupus nephritis class III. **Treatment:** patient treated with IV pulse Methylprednisolone 1g for 3 days and Cyclophosphamide 500 mg IV, and then Prednisone 80 mg daily. Creatinine levels improved from 6.3 mg/dL (first creatinine levels reported, on July/4/2018) to 2.8 mg/dL (on August/25/2018).

Discussion: Reports of SLE-related CG with Lupus Nephritis are lacking. The patient described in this case report has both findings. In the largest series of cases with biopsy-proven CG in the setting of SLE or SLE-like disease, Salvatore et al, showed that only 7 patients (out of 19) had morphologic changes of lupus nephritis along with CG findings. To the best of our knowledge, fewer than 25 cases have been reported about this specific finding. For the treatment of Lupus Nephritis class III/IV, the immunosuppressive treatment consists on induction and maintenance phases. As per the guidelines of the American College of Rheumatology, induction therapy should consist of steroids combined with mycophenolate or cyclophosphamide, for about 6 months. Rationale to use cytotoxic drug like cyclophosphamide in such cases is because these variants have progressive and relentless course.



PUB573

Progressive Multifocal Leukoencephalopathy: A Devastating Complication of Immunosuppression

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Introduction: Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the CNS caused by reactivation of the polyomavirus JC. Primary infection is asymptomatic, JC virus remains latent in the kidneys and lymphoid organs. Reactivation and lytic infection of olygodendrocytes may occur in immunosuppressed individuals. Hematological malignancies, transplant recipients and several drugs have been associated to it. We describe a case of PML during the use of Mycophenolate mofetil (MMF).

Case Description: 69 year-old man with creatinine (sCr) of 1.5mg/dL, HTN, and COPD, referred to us for AKI with sCr of 2.6 mg/dL. He was found to have proteinuria 4.5 g/g by spot ratio, dysmorphic RBCs, P-ANCA titer of 640, anti-MPO of 147 CU and anti-DsDNA of 59 IU/mL. Kidney biopsy showed Lupus Nephritis Class III. Induction of remission was achieved with Cyclophosphamide plus steroids with stabilization of renal function and resolution of hematuria after 3 months. Maintenance therapy started with MMF 1 gr. twice a day plus steroids. Clinical course was complicated by C. difficile diarrhea, and two episodes of GI bleed. Refractory anemia was treated with blood transfusions and erythropoietin (EPO) therapy. MMF was decreased to 500 mg BID to avoid myelosuppression. Twelve months into MMF therapy he developed new-onset motion sickness and diplopia, physical exam revealed orientation only to person, optic ataxia and ocular motor apraxia. Brain MRI showed several areas of white matter hyperintensity mainly in both parietal lobes and corpus callosum. PCR of CSF confirmed JC virus (> 2 million copies/mL). MMF was stopped and treatment with mefloquine and mirtazapine was initiated without any improvement. He was transitioned to hospice 31 days after diagnosis.

Discussion: This case reveals the devastating effects of JCV reactivation in patients undergoing immunosuppressive therapy for renal disease, even at doses considered low according to currently accepted guidelines. Cases of recovery of PML have been reported after immune reconstitution with withdrawal of the involved drug. Regretfully, already debilitated patients due to age and other comorbidities will likely not respond to this measure. Treatment with different drugs has been attempted but the success is mostly anecdotal. Pembrolizumab has been recently reported with promising results.

PUB574

IgA Nephropathy Causing Rapidly Progressive Glomerulonephritis

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Introduction: Although IgA nephropathy (IgAN) is the most common cause of glomerulonephritis worldwide, this condition is seldom reported as a cause of rapidly progressive glomerulonephritis (RPGN). Furthermore, it is not commonly reported as a cause of glomerulonephritis in African Americans. IgAN can rarely present as a more aggressive RPGN, and patients may display different degrees of renal dysfunction, hypertension, edema, and proteinuria. Prompt renal biopsy is often needed in these patients, as management often differs depending on the underlying pathology.

Case Description: A 26-year old African American male with no prior past medical history presented with acute-onset shortness of breath, cough, and musculoskeletal chest pain. Lab work was indicative of a new acute kidney injury with a creatinine of 4.02 mg/dL and notable proteinuria with a urine microalbumin-creatinine ratio of 7.5 mg/g. The patient was admitted, and the nephrology team was consulted. Further lab work showed a negative ANA level, negative ANCA titer, normal C3 and C4 levels, negative HIV screen, negative hepatitis panel, normal plasma aldosterone-renin activity ratio, and normal plasma metanephrine level. Although urinary free kappa light changes and free lambda light chains were notably elevated, the free kappa-lambda light chain ratio was within normal limits. Renal biopsy revealed IgA-mediated immune-complex glomerulonephritis with marked arteriosclerosis and glomerulosclerosis. He received high-dose intravenous (IV) methylprednisolone and IV bumetanide. The patient improved significantly and was discharged on a prolonged prednisone taper. The patient later started immunomodulatory therapy with mycophenolate mofetil for his biopsy-proven rapidly progressive IgA crescentic glomerulonephritis.

Discussion: Rapidly progressive crescentic IgA nephropathy is rare, and there are few reported cases showing evidence of progression to end-stage renal disease (ESRD) with variable response to immunosuppression. Current data suggests that renal survival in cases of rapidly progressive crescentic IgAN is 50% at one year and 20% at five years. There is only recently published data supporting the use of high-dose corticosteroids and immunomodulator therapy in patients with crescentic IgAN. Although a rare cause of RPGN, IgAN should be considered, and kidney biopsy should be pursued early so as to not delay appropriate renal-saving therapy.

PUB575

ANCA-Associated Glomerulonephritis with Linear GBM Staining in the Absence of Anti-GBM Antibody: A Variant of Double-Positive MPO and Anti-GBM Antibody

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Introduction: Anti-glomerular basement membrane antibody disease (Anti-GBM) is a rare disease with severe renal-pulmonary manifestation. About 10-38% of patients with anti-GBM nephritis also has positive ANCA at the time of diagnosis, most often P-ANCA. They are termed double positive and has different prognosis and outcomes. Recently, there has been described patients with renal biopsies with linear GBM immunoglobulin staining without detectable anti-GBM antibodies. Such diagnosis is termed atypical anti-GBM disease. We present a case with features of both atypical anti-GBM disease overlap with ANCA-associated vasculitis (AAV).

Case Description: A 70 year old Indonesian male with past medical history of vitiligo, chronic kidney disease, hypertension, and prostate cancer with recent radiation treatment was hospitalized for management of overt hematuria and acute kidney injury. He had nephritic presentation and no evidence of obstructive nephropathy. Kidney biopsy showed 40% crescentic glomeruli, necrotizing glomerular lesions, 20% sclerosis and tubular atrophy, few small subendothelial deposits on electron microscopy, and linear GBM reactivity with anti-IgG on immunofluorescence. Serology showed negative Anti-GBM antibody, positive P-ANCA antibody 1:160 and MPO antibody elevated to 21.4. He had no pulmonary manifestations. He received high dose steroid, 6 doses of plasmapheresis and rituximab. He was discharged with tapering steroids and received repeat rituximab in 2 weeks. At 3 month, creatinine improved to nadir 2.08 mg/dl and started azathioprine for maintenance therapy.

Discussion: Our patient had linear IgG staining consistent with Anti-GBM disease without anti-GBM antibody (Atypical anti-GBM disease) overlap with P-ANCA positivity. While overlap of typical anti-GBM disease and AAV has been described, co-existence of atypical anti-GBM nephritis and AAV as a variant is rarely reported. The overlap syndromes with double positive antibodies (anti-MPO and anti-GBM) has a distinct clinical phenotype needing better understanding of pathogenesis, recognition of specific epitope, classification, prognostication and different treatment strategies. Recently, anti-peroxidasin antibodies disrupting collagen structure of GBM and cross-reacting with MPO have been identified and can help elucidate such overlap syndromes.

PUB576

Successful Maintenance Treatment of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits with Low-Dose Steroids

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Introduction: We present the first known case of relapsed proliferative glomerulonephritis with monoclonal immunoglobulin deposits successfully treated with two courses of high dose prednisone followed by Rituximab and finally maintained in full remission on low dose corticosteroid therapy.

Case Description: A 58-year-old male with nephrotic-range proteinuria and hypertension was referred to nephrology for evaluation. Labs showed serum creatinine 1.2 mg/dL, albumin 2.7 gm/dL, and urine protein to creatinine ratio of 5.9 mg/g. Work-up was unremarkable including urine/serum protein electrophoresis with immunofixation, serum kappa/lambda ratio, and complement levels. Skeletal bone survey, bone marrow biopsy, and positron emission tomography-computed tomography were negative for evidence of malignancy. Kidney biopsy was pursued. Light microscopy revealed diffuse proliferative glomerulonephritis with prominent membranoproliferative features. Immunofluorescence showed subendothelial deposits positive for IgG-kappa and C3 and negative for IgG-lambda and IgM. IgG subtype stains were positive for IgG3. Findings were consistent with proliferative glomerulonephritis with monoclonal immunoglobulin deposits. Immunosuppressive therapy with high dose oral prednisone was begun. Proteinuria improved from 7.8 to 1.3 g/day but progressed upon tapering. Given the risk of disease progression he was treated with a four-week course of weekly rituximab infusions with 20 mg oral prednisone daily. Proteinuria improved from 8.9 g/day pre-infusion to 4.7 g/day two months after completion of infusions. Prednisone was then tapered to 2.5mg, but proteinuria persisted at 2.2 g/day. Prednisone was increased to 5mg. Over the next year the proteinuria gradually resolved to less than 0.2 g/day. Serum creatinine ranged from 1.1 to 1.3 mg/dL and microhematuria resolved. He has remained on this dose for two years with continued clinical remission.

Discussion: Treatment of PGNMID is undetermined but generally consists of immunosuppressive therapy with rituximab, high dose corticosteroids, bortezomib, or cyclophosphamide. We present the first reported case of successful clinical remission of relapsed PGNMID following induction with rituximab and maintenance therapy with low dose oral prednisone.

PUB577

Invasive Acanthamoeba Amoebiasis Mimicking Granulomatosis with Polyangiitis

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Introduction: Invasive Acanthamoeba Amoebiasis is rare and often fatal; typically affecting immunocompromised patients involving the central nervous system, skin, and nasopharynx.

Case Description: Our patient is a 52 year old female with history of MALT lymphoma in remission and recently diagnosed granulomatosis with polyangitis (GPA) presenting with sepsis. Months before presentation she developed extensive necrotic skin lesions of the nasopharynx, arms, and legs. Skin biopsy suggested ANCA vasculitis with negative serologies and IFA. Her GPA treatment included steroids, methotrexate, and cyclophosphamide without improvement of lesions. Hypogammaglobinemia was diagnosed 1 month prior, concerning for common variable immunodeficiency (CVID) given history of recurrent sinusitis and low IgG/IgA. At presentation, she endorsed worsening skin lesions, was febrile, tachycardic, and had lactic acidemia. She was started on broad spectrum antibiotics for presumed superinfection of skin lesions with otherwise negative infectious work up. Repeat skin biopsy demonstrated cutaneous amoebiasis. On re-review of original skin biopsies it was felt that cutaneous symptoms may have been from tissue-invasive amoebiasis leading to severe inflammation mimicking vasculitis. Biopsy samples were sent to the CDC and demonstrated amoebic trophozoites for Acanthamoeba species. She was started on anti-Amoeba regimen including: Miltefosine, fluconazole, oral and topical sulfadiazine, IV pentamidine, flucytosine, and topical ketoconazole. Unfortunately she deteriorated over several weeks eventually experiencing multi-organ failure. Family decided to focus on the patient's comfort and she expired. It remains unclear why she developed disseminated Acanthamoeba amoebiasis but it is hypothesized she was susceptible due to CVID; possible exposures included well water and swimming in North Carolina lakes.

Discussion: Invasive Amoebiasis is rare and can be difficult to distinguish from GPA as both have a predilection to involve the nasopharynx and can be confused with vasculitis on histopathology. In immunocompromised patients with nasopharyngeal and skin lesions with biopsy suggestive of vasculitis, invasive amoebiasis should also be considered.

PUB578

Parvovirus B19: Does It Cause Kidney Disease? A Case Presentation and Review of the Literature

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Introduction: Parvovirus B19 (HPVB19) is a DNA virus linked to multiple clinical syndromes and has been linked to glomerular disease. Here we present a rare case of acute HPVB19 infection and unexplained end stage kidney disease with literature review.

Case Description: A 20 year-old-male presented to an Australian teaching hospital with 3 weeks of nausea and vomiting, confusion, headache, diarrhoea, fevers, abdominal rash and pleuritic chest pain. He was hypertensive at 190/135mmHg with sinus tachycardia of 118bpm. He had a pericardial rub and saddle ST-elevation on ECG. Echo-cardiogram confirmed a moderate-sized pericardial effusion. His creatinine was 1930 umol/L with urea 61.4 mmol/L. Haemoglobin was 68g/L with platelets of 246 x10^9/L and an MCV of 84fL. Blood film and haemolysis screen were unremarkable. ADAMTS-13 was normal and a glomerulonephritis screen was negative. Urine PCR was 642 g/mol creatinine with 60 leucocytes x 10^6/L and 40 erythrocytes x 10^6/L. The patient was commenced on haemodialysis. Renal biopsy showed a mesangio-proliferative pattern. There was severe tubular atrophy and interstitial fibrosis, moderately severe arteriosclerosis and arteriolosclerosis and a chronic inflammatory infiltrate. Arterioles showed features of acute thrombotic microangiopathy. Immunofluorescence was non-specific. Electron microscopy revealed foot process effacement and tubuloreticular inclusions. Parvovirus particles were not seen. Persistent anaemia prompted HPVB19 serology with an initial negative test. However, 3 weeks later the IgM and IgG titres were elevated. HPVB19 DNA was detected in renal biopsy tissue on PCR. After 3 months, he showed no evidence of renal recovery.

Discussion: 10 cases have been reported with an acute illness associated with HPVB19 serum positivity for IgG and IgM, renal disease and renal tissue DNA PCR positivity. 2 patients had an FSGS lesion with the remaining 9 demonstrating endocapillary glomerulonephritis. A consistent correlation between PCR positivity for HPVB19 on renal tissue and renal disease has not been proven. This was a rare case of end stage kidney disease, fever, anaemia and pericarditis associated with acute HPVB19 infection. This work adds to the body of knowledge describing the potential for HPVB19 associated glomerulopathy in our patients.

PUB579

A Case of TAFRO Syndrome Associated with Membrano-Proliferative Glomerulopathy and Rescued from Dialysis Therapy by Use of Tocilizumab

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Introduction: TAFRO syndrome is a rare disease of unknown etiology characterized by Thrombocytopenia, Anasarca, Fever with systemic inflammation, Reticular fibrosis in bone marrow and Organomegaly or lymph node swelling. TAFRO is occasionally accompanied by renal involvement leading to endstage renal failure, however, renal histopathology is rarely confirmed because of life-threatened rapid progression and thrombocytopenia. Here, we report a case of TAFRO syndrome showing membrano-proliferative glomerulopathy-like glomerular findings.

Case Description: An 80-year-old man was admitted to a local hospital because of high fever, anemia, bleeding tendency and systemic edema from 1 month prior to the admission to our hospital. He received RBC transfusion and diuretics administration, however, he rapidly developed renal failure requiring dialysis therapy on the 7th hospital day. After transferred to our hospital, he received 1 g of prednisolone (PSL) for 3 consecutive days with continuous hemodialysis, and TAFRO syndrome was suspected because of systemic inflammation and sever thrombocytopenia ($2x10^4$ per μL). The diagnosis was confirmed by lymph node biopsy showing hyaline-vascular finding similar to Castelman's disease and remarkable elevation of interleukin-6 and vascular endothelial growth factor. His clinical condition was apparently ameliorated by maintaining administration of PSL 30 mg a day, and his dialysis therapy was discontinued at the 67th hospital day. At that time, renal biopsy revealed membrano-proliferative glomerulopathy with slight tubulo-interstitial damage. Following PSL withdrawal, his renal function and proteinuria was worsened again. By this reason, Tocilizumab 400 mg was administered and repeated every 2 weeks. After start of Tocilizumab, his clinical condition was ameliorated again and stabilized. He was finally discharged on the 152nd hospital day.

Discussion: TAFRO syndrome usually become sever rapidly without renal biopsy, and clinical benefit of Tocilizumab is not generally established. Our case might be a valuable index to consider the mechanism of renal involvement and the clinical management.

PUB580

Pauci-Immune Crescentic Glomerulonephritis Associated with Multiple Myeloma: Case Report

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Introduction: Crescentic glomerulonephritis (CGN) includes rapidly progressive glomerulonephritis (RPG) signified by sudden loss of renal function associated with crescent formation. Antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis is the most frequent etiology and refers to a necrotizing glomerulonephritis without immune deposits by immunofluorescence (IF) but circulating ANCA antibodies. Multiple myeloma (MM) is a malignant proliferation of monoclonal plasma cells in the blood with frequent kidney damage. The coexistence of the ANCA-associated vasculitis (AAV) and MM is rare.

Case Description: We present a patient with renal biopsy by rapidly progressive glomerulonephritis. The diagnosis was AAV after histopathological examination but at the same time, the MM diagnosis was done. A 65 years old man presented with progressive edema since 5 days and weight loss with fatigue and low back pain since 3 months. No medical antecedents. The serum creatinine level at hospital admission was 1.8mg/dl. After 48 hours presented reduction in urine volume, increase of edema and dyspnea, and a rise of serum creatinine level to 3mg/dl. The diagnosis of RPG was done and started hemodialysis. The 24-h proteinuria was 2.7g, hematuria with 14% of acanthocytes, blood urea nitrogen was 41mg/dl, serum albumin was 1.9g/dl and serum globulin was 4.7g/dl; complement levels and antinuclear antibodies were normal. Serum IgG was 3210mg/dl and p-ANCA was positive. Renal ultrasound revealed increased size of kidneys. We perform renal biopsy and 11 glomerulus were obtained, 5 with crescentic lesions. Congo red staining was negative and IF analysis noted only intratubular cast with IgA positive staining. Besides, monoclonal protein was found by serum protein electrophoresis and bone marrow aspiration was performed and showed plasma cells count of 18%, diagnosing MM. The patient was diagnosed with AAV coexisting with MM, based on the ANCA titer, CGN and rapid loss of renal function.

Discussion: Hematological malignancies are the most common type of cancer coexistent with vasculitis, however MM is infrequent and simultaneous diagnosis is less common yet. Elderly patients should be screened for AAV and MM on the occurrence of unexplained renal failure.

PUB581

Diabetic Ketoacidosis and Atypical Hemolytic Uremic Syndrome: An Unlikely Pairing

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is an extremely uncommon, life-threatening illness, characterized by the triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury. Diabetic ketoacidosis (DKA) as a result of new-onset Type II diabetes mellitus has never been described as an initial presentation of aHUS.

Case Description: A 31-year old African American male with no past medical history presented with altered mental status. Four days prior to admission, the patient returned from a trip to Belize, where he exhibited new-onset polyuria, polydipsia, polyphagia and severe nausea. Initial assessment was consistent with DKA. Patient was also found to have acute kidney injury secondary to pre-renal azotemia. Four days into admission, clinical course deteriorated: patient developed MAHA (hemoglobin-6.9 g/dL & lactate dehydrogenase-3452 units/L), a drop in platelet count with schistocytes (260 to 18 K/cmm) and worsening kidney function; evolving from pre-renal azotemia to acute tubular necrosis with anuria. Despite initiation of hemodialysis, kidney function did not markedly improve (BUN-111 mg/dL & serum creatinine-12.20 mg/dL). This prompted renal biopsy which revealed thrombotic microangiopathy (TMA), cortical infarct and collapsing glomerulopathy. The differential diagnosis of TMA can include thrombotic thrombocytopenic purpura, Shiga-toxin-producing Escherichia coli hemolytic uremic syndrome and aHUS. As ADAMTS13 activity was normal (59%) and stool culture was negative for Shiga-toxin, a diagnosis of aHUS was made. Treatment was initiated with plasmapheresis in conjunction with IV eculizumab. Within five days of treatment, patient's condition improved and he was discharged home with outpatient hemodialysis.

Discussion: Prior to FDA approval of eculizumab, aHUS proved to be fatal in a large percentage of patients despite optimum known medical management (i.e. plasmapheresis). Even with eculizumab use, most aHUS patients develop end-stage renal disease and undergo chronic dialysis. Our patient due to early detection and initiation of the above, demonstrated normalization of kidney function and was able to come off hemodialysis 6-months post-discharge. This case highlights DKA as an atypical initial precipitant of aHUS and the importance of early eculizumab use for treatment in hospitalized patients over plasmapheresis alone.

PUB582

A Rare Case of Isolated IGA Nephropathy Without Granulomas Associated with Neurosarcoidosis

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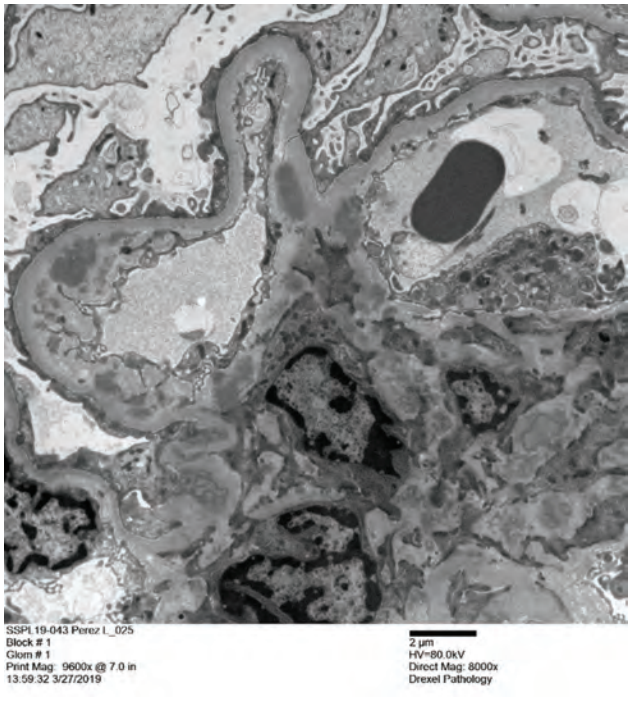
Introduction: Systemic sarcoidosis associated with a variety of glumerular and interstitial lesions. We present an interesting case of neurosarciososis with concomitant IgA nephropathy without renal granulomas

Case Description: 40 years old Hispanic male with past history of, anemia, CKD stage 3 presented to hospital with, left sided facial droop and reduced visual acuity in the left eye. He reported, weight loss and night sweats few weeks prior. CT chest, abdomen and pelvis which showed diffuse nonspecific lymphadenopathy, head and neck imaging was unrevealing. Pertinent labs ACE level =97 unit/L (normal range 14- 82 units/ L) Quatiferon negative,. Patient was started on oral steroids. Lymph node Biopsy - reactive changes with non- necrotizing granuloma. He was diagnosed as neurosarcoidosis. Patient presented a month later with progressive lower limbs edema and AKI. Patient admitted he had not been compliant with his medications (oral steroids). Creatinine on admission = 2.5 mg/d l(baseline 1.7mg/dl), Urine protein to creatinine ratio was 3.5 g/ 24hours. Renal biopsy was performed. Renal biopsy showed LM- hypertensive nephropathy, focal Nephrosclerosis and mesangial hypercelkularity, IF was 3+ for IgA. EM showed mesangial and subendothelial electron dense deposits, diffuse foot process effacement (fig2). Patient was started on IV and oral diuretics, Oral Steroid treatment was restarted with improvement in creatinine to 2.0 mg /dl, edema and proteinuria.

Discussion: Sarcoidosis has been asoosicated with a myriad of glomerular and interstitial lesions. The epidemiological and biological factors affecting the phenotype of renal involvement in sarcoidosis need larger studies including renal biopsy, proteomic, metabolomics and genomic profiling of such patients.



PUB583

Hepatitis C Membranoproliferative Glomerulonephritis (MPGN) with Histologic Features Resembling Lupus Nephritis (LN)

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Introduction: We discuss a case of hepatitis C (HCV) membranoproliferative glomerulonephritis (MPGN) with biopsy findings consistent with lupus nephritis (LN) in a patient without clinical and immunological criteria for systemic lupus erythematous (SLE). These findings posed both a diagnostic and treatment dilemma. Treatment by immunosuppression versus anti-viral medication hinged on a final diagnosis.

Case Description: A 50-year-old African American male with a history of, hypertension and HCV presented with anasarca, 6.9 grams proteinuria and a serum creatinine of 0.8mg/dl. ANA, anti-dsDNA, Smith, RNP, rheumatoid factor, cryoglobulin, and HIV were negative. C3, C4, CBC, and LFTs were normal. HCV viral load was 2.6 million copies. Kidney biopsy showed MPGN and immunofluorescence (IF) revealed C1q, C3 with full house staining for IgG, IgA, and IgM. Electron microscopy demonstrated mesangial, subendothelial, and subepithelial immune complex (IC) deposits along with 80% podocyte effacement. The biopsy appeared consistent with class III+V LN, but our patient lacked clinical and immunologic criteria for SLE. Despite biopsy features of LN, immunosuppression was not initiated. HCV was treated with Mayvert, resulting in a sustained viral response. Six months after viral clearance, proteinuria improved to 2 gms/gm on spot ratio, ANA remained negative and creatinine was stable at 1.2 mg/dL.

Discussion: In HCV MPGN, IC deposits are typically restricted to the subendothelial and mesangial compartments and are of the IgG class. Full-house IF staining is a pathognomonic feature of LN, but was observed in our patient who lacked criteria for SLE. Reports of full-house nephropathy with negative serologies for SLE exist. Conditions with the potential for polyclonal B cell expansion, such as HCV and HIV, can result in IC formation and staining patterns mimicking a "lupus-like" IF. This is seen with more frequency in HIV IC kidney disease or HIVICK, but rare for HCV. In our case, despite a biopsy suggesting class III+V LN, progression of disease was not observed and proteinuria improved without immunosuppression. Clinical context helped to avoid immunosuppression and target appropriate therapy against his HCV.

PUB584

Overlap Syndrome of IgA Nephropathy with Dense Deposit Disease

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Introduction: Dense deposit disease (DDD) also known as membranoproliferative glomerulonephritis (MPGN) type II, is a rare presentation of C3 glomerulonephrits (GN). Renal biopsy is required to diagnose DDD, with the pathognomonic feature being dense deposits along the GBM revealed by electron microscopy (EM) with strong positive Immunofluorescence staining for C3 in glomerular capillary loops. Overlap of C3GN or DDD with other GN is rarely reported. Here we present a very rare case of DDD overlapping with features of IgA nephropathy.

Case Description: A 33-year-old female with no past medical history, with normal previous two pregnancies presented with new onset proteinuria of close to 1gm during the end of her third trimester in her third pregnancy; complicated by post-partum pre-eclampsia for which she was started on anti-hypertension medications. She had persistent proteinuria and underwent kidney biopsy. EM showed mesangial ring forms and sausage-like intramembranous immune deposits which are classic features of DDD. Immunofluorescence showed 3+ staining for C3 in glomerular capillary loops and 3+ staining for IgA in mesangium. The distribution of IgA deposits were purely mesangial, which was confirmed by pronase immunofluorescence, supporting an additional diagnosis of IgA nephropathy. Serum creatinine at that time was normal and she had a UPCR of 3158 mg/g. She was subsequently managed with ACE inhibitor and started on prednisone 60 mg daily. Because of predominant DDD lesions and slowly declining renal function, she is currently being managed on the lines of C3GN.

Discussion: Nephrotic range proteinuria can present in advance stage of IgA nephropathy however it is also reported in overlap syndrome especially with minimal change disease or membranous nephropathy. To our knowledge, overlap of IgA with DDD has not been reported in the literature and our case is a rare co-existence. Although the patient has IgA deposits, it is the DDD which is primarily responsible for worsening kidney function. We think that these patients should have full work up for DDD as treatment may be challenging.

PUB585

Epstein-Barr Virus Associated Hemophagocytic Lymphohistiocytosis Syndrome and Collapsing Focal Segmental Glomerular Sclerosis

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Introduction: Collapsing glomerulopathy is a distinct and aggressive clinicopathologic variant of FSGS. Here is an case of collapsing FSGS in the setting of the diagnosis of Hemophagocytic Lymphohistiocytosis secondary to acute EBV infection.

Case Description: A 46 year old AA male with PMH of HIV, Hypertension, asthma, CKD was admitted with flu-like symptoms including headache, fever, cough, vomiting and diarrhea. Exam was significant for fever and hepatosplenomegaly. laboratory tests were significant for a pancytopenia, elevated liver enzymes and elvated creatinine. Renal US showed increased echogenicity. UA revealed Protein 500 mg/dl, RBC 3/hpf, WBC 3/hpf. 24hrs urine protein 3.8 gms. Serology including ANA, ANCA, and Anti GBM were negative. C3 and C4 normal. HepB and Hep C were negative. CT chest, abdomen and pelvis showed multiple bilateral centrilobular nodules within lung bases measuring & diffuse lymph nodes. Mediastinal mass biopsy reported Lymphohistiocytic infiltrates with focal granulomatoid features and rare atypical cells. Bone marrow biopsy reported hypo cellular bone marrow with focal trilineage hematopoiesis, mild erythroid hyperplasia and prominent histiocytic proliferation in loose clusters with erythrophagocytosis, consistent with lymphohistiocytic hemophagocytosis Patient was diagnosed as Hemophagocytic Lymphohistiocytosis secondary to EBV infection (viral load 75.077 copies/ml). The renal biopsy showed Focal segmental glomerulosclerosis (FSGS, collapsing type). Global glomerulosclerosis with diffuse interstitial fibrosis and tubular atrophy involving 50% of the cortex and acute tubular necrosis. Patient was initiated on hemodialysis due to uremic symptoms. Treatment for HLH was initiated with chemotherapy. He was discharged from hospital on thrice weekly dialysis

Discussion: Collapsing glomerulopathy may occur either idiopathic or in association with many infectious and inflammatory conditions. There are some case reports linking glomerulopathies associated with EBV. Demonstration of viral protein with in glomerular cells found in some cases suggesting that the glomerular injury could be a collateral effect of the viral driven inflammation. EBV infection causing hemophagocytic lymphohistiocytosis is a potentially fatal syndrome characterized dysregulation of immune activation.

PUB586

Polyautoimmunity Syndrome with Renal Involvement: Kaleidoscopic Presentation of a Systemic Syndrome

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Introduction: Polyautoimmunity is defined as the presence of more than one autoimmune disease; few publications emphasize kidney damage and its treatment. We present the case of a patient with polyautoimmunity syndrome and renal affection by three autoimmune diseases.

Case Description: 40-year-old female with history of systemic lupus erythematous diagnosed in February 2015, without renal involvement during follow-up. In May 2018 she complained of fatigue, generalized hyperpigmentation and thickening of the skin, Raynaud's phenomenon, followed by sclerodactyly and gastric reflux. In December 2018 she consulted rheumatology service, who diagnosed Sjögren Syndrome (dry mouth/eye symptoms, salivary gland biopsy, positive Schirmer test and anti-Ro elevation) and systemic scleroderma (thickening of skin on hands, telangiectasias, Raynaud's phenomenon, anti-topoisomerase II positive); after an arrangement to nephrology clinic because of serum creatinine of 2.24 and proteinuria in 24 hours of 1.2gr, a kidney biopsy was performed and revealed glomerulonephritis consistent with class II lupus, active tubulointerstitial nephritis with plasma cells and acute tubular injury, chronic glomerular hypoperfusion, grade II interstitial fibrosis, obliterative arteriolopathy, changes attributable to Sjögren's syndrome and scleroderma. Treatment was started on mycophenolate mofetil due to the risk of renal sclerodermic crisis. Currently, the patient reports clinical improvement and proteinuria decreased to 0.7gr/gr.

Discussion: Our case reports the renal affection of three autoimmune pathologies with different temporality and therapeutic approach. The difficulty lies in the treatment of renal disease with contraindication to the use of steroids for the treatment of tubulointerstitial nephritis due to risk of renal sclerodermal crisis. Likewise, the treatment of proteinuria with ACEI or ARB II is complex due to the probable masking of the aforementioned crisis.

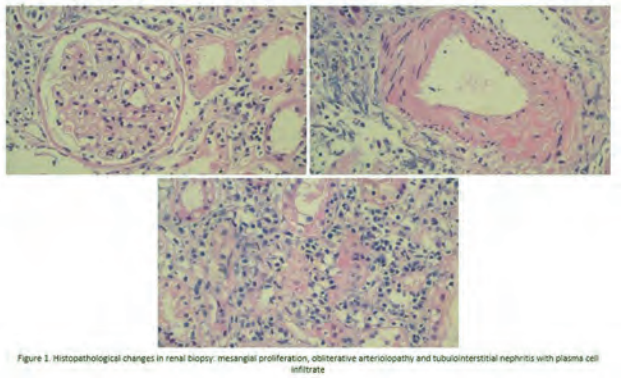

Figure 1. Histopathological changes in renal biopsy: mesangial proliferation, obliterative arteriolopathy and tubulointerstitial nephritis with plasma cell infiltrate

PUB587

Efficacy and Safety of Sofosbuvir Plus Simeprevir as Therapy for HCV-Associated Glomerulonephritis: Report of Two Cases

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Introduction: HCV patients with glomerulopathies were treated, initially, peg-interferon (PEG-IFN) associated with ribavarin (RBV), but this therapy have been induced serious side effects and low sustained virologic response (SVR). The new direct-acting antivirals (DAAs) treatment are been considered revolutionary antiviral therapy, leading to infection cure in more than 90% of patients. Since 2016 new reports have emerged using DAAs in HCV-associated glomerulopathies but there are still few reports.

Case Description: Patient 1 - male, 41 year-old, with diagnosis of chronic HCV infection associated with glomerulopathy admited in 2016 with nephrotic syndrome with anti-HCV and HCV-RNA positive (viral load of 2,064,684 UI/mL and log 6). He was treated with SOF (400 mg/day) plus SIM (150 mg/day) for 12 weeks, evolving with normalization of aminotransferases normalizations and HCV-RNA negativity at the end of treatment and after 12 weeks (SVR), cryoglobulinemia negativity and significant proteinuria reduction. **Patient 2 –** male, 50 year-old, was diagnosed 24 years ago with HCV infection prior to blood donating. He lost outpatient follow-up and returned in 2005, when genotype 1b infection was identified. He had no response to PEG-IFN plus RBV and in 2014, he presented with thrombocytopenia, nephrotic syndrome, C3 and C4 consumption, cryoglobulinemia positive. In 2016, he was treated with SOF plus SIM for 12 weeks, evolving with transaminases normalization, HCV-RNA negativity at the end of treatment and after 12 weeks, cryoglobulinemia negativity and significant reduction of proteinuria. **Baseline and after treatment examens shown in Table.**

Discussion: This report describes two cases of HCV related Glomerulopathy with cryoglobulinemia treated with SOF plus SIM therapy showing no significant side effects and improvement hepatic and renal diseases.

Clinical and Laboratory Characteristics of Patientes Before and After Treatment with Sofosbuvir plus Simeprevir

	Patiente 1		Patiente2	
Viral Load (UI/mL)(log 6)	2,064,684	Negative	1,193,977	Negative
Proteinuria (g/24h)	6.4	0.12	4.33	0.26
Creatinine (mg/dL)	1.1	1.2	1.6	1.3
AST/ALT (mg/dL)	40,5/50,8	26/22	115/84	26/26

PUB588

Collapsing Glomerulopathy Superimposed on Diabetic Nephropathy: A Case Series

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Introduction: Diabetic Nephropathy is the leading cause of End Stage Renal Disease (ESRD) in many countries. 35-45% of both Type-1 and Type-2 diabetic patients develop ESRD in 20-35 years. Some patients present with new onset nephrotic range proteinuria and detriorating renal functions. Renal biopsy showed non-diabetic glomerular leision in 10-12%. The development of collapsing glomerulopathy in the background of diabetic nephropathy is a very rare phenomenon. We present a case series of 6 cases of Collapsing Glomerulopathy superimposed on Diabetic nephropathy.

Case Description: The average age of our patients was 55years. All 6 patients had history of long standing Type -2 Diabetes Mellitus - average of 15 years. Baseline serum creatinine in 3 of them was in the range of 1.8 -3.5 mg/dl. The clinical presentation and indications for renal biopsy were: 2 patients had severe breathlesness due to volume overload requiring ICU care, 3 patients had worsening oedema and uncontrolled blood pressures, 1 patient had new onset hypertension and pedal oedema. All patients had nephrotic range proteinuria. 4 patients had severe renal failure at presentation and were initiated on dialysis. 2 patients had a serum creatinine of 2.4 mg/dl and 1.8mg/dl. Renal biopsy showed collapsing glomerulopathy superimposed on diabetic nephropathy. 1 had class IIb, 1 had class III, and 4 had class IV diabetic nephropathy. 3 biopsies had Interstitial fibrosis and Tubular atrophy (IFTA) more than 50%. All biopsies showed arterial hyalinosis. 4 patients who presented with severe renal failure were declared as ESRD and were continued on hemodialysis. 2 patients were in CKD stage 3 at presentation, progressed to ESRD by next 2 years and later underwent renal transplant.

Discussion: Collapsing Glomerulopathy contributes to an increased level or a new onset proteinuria in Diabetic nephropathy. This is usually intractable and rapidly progresses to End Stage Renal Diasease (ESRD). Collapsing Glomerulopathy in Diabetic nephropathyis presumbly due to ischemic podocyte injury and is of prognostic significance.

Patient no.	Age	Sex	Duration of Diabetes	Hypertension	Baseline s.creatinine	Baseline proteinuria	Indication for biopsy	S.creatinine at presentation	24 hour proteinuria	follow up duration	outcome
1	67 y	male	10 y	no	NA	1+	volume overload and ICU care	13 mg/dl	8 g	1 year	Dialysis dependent
2	39 y	male	10 y	yes	1.8 mg/dl	4+	worsening pedal oedema	5.7mg/dl	6 g	1 year	Dialysis dependent
3	60 y	male	15 y	yes	3.5 mg/dl	2+	worsening oedema	7.2mg/dl	10 g	1 year	Dialysis dependent
4	59 y	male	21 y	yes	2.4 mg/dl	NA	worsening oedema	6.1 mg/dl	9 g	2 years	dialysis dependent
5	44 y	male	15 y	no	NA	NA	new onset HTN and oedema	2.4mg/dl	12 g	3 years	recently progressed to ESRD
6	76 y	male	15 y	no	NA	NA	Volume overload and ICU care	1.8mg/dl	10 g	3 years	recently progressed to ESRD

PUB589

From Membranous Nephropathy to Proliferative Glomerulonephritis with Monoclonal IgG1 Kappa Deposits: A Pediatric Case

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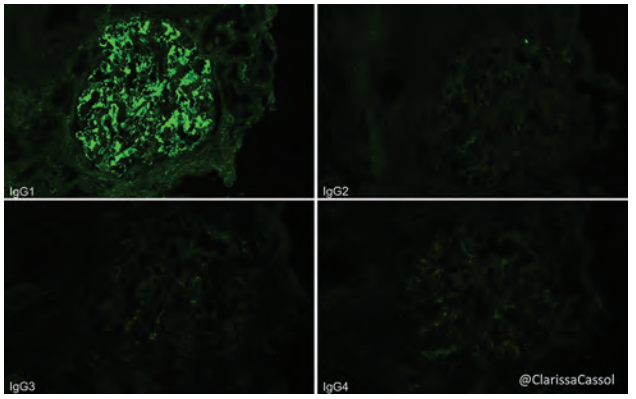
Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a rare entity described mainly in adults with only 6 reported cases under 20 years of age. It is characterized by monoclonal immunoglobulin deposits in the kidney which can mimic immune complex glomerulonephritis. Histologic patterns described are membranoproligerative or endocapillary proliferative with membranous features. IF stains most commonly for IgG3 Kappa and EM reveals granular non-organized deposits. Dysproteinemia is detected in 30% of cases. This case illustrates the challenge of diagnosis of PGNMID in a young girl with primary membranous nephropathy (pMN).

Case Description: A 19- year old woman with pMN was transferred from the pediatric to the adult nephrology clinic with anasarca. At 13 years of age she was found to have nephrotic syndrome secondary to biopsy proven MN. The urine PCR was 4g/g. She received prednisone then a calcineurin inhibitor then rituximab without clinical response. A repeat biopsy three years later showed membranous like glomerulopathy with monoclonal IgG1 kappa deposits. Pronase digestion was not done. She was maintained on conservative therapy with RAAS blockade. Repeat work-up was significant for 24h urine PCR 10g/g, serum albumin 2g/dl, Scr up to 1.5mg/dl, + speckled ANA (1:320), negative serum PLA2R antibody. A third kidney biopsy showed PGNMID IgG1 kappa (**Figure 1**).

Serum free light chain K/L ratio was 1.09, SPEP and UPEP with immunofixation were negative for M-spike. Bone marrow biopsy with flow cytometry showed only a few polytypic plasma cells and the matrix-assisted laser desorption/ionization-time of flight mass spectrometry test for monoclonal protein was negative. She is being treated with bortezomib and dexamethasone.

Discussion: PGNMID can occur in children and young adults. It is unclear whether MN with IgG1 kappa is an early manifestation of a slowly progressive PGNMID IgG1 kappa. Repeat kidney biopsies may be of help in such scenarios.



PUB590

Secondary Syphilis-Associated Crescentic Glomerulonephritis

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Introduction: Syphilis-associated nephropathies are uncommon. Membranous nephropathy (MN) is the most well-recognized while crescentic glomerulonephritis (CGN) is rare. We report the second case in the literature of secondary syphilis-associated CGN.

Case Description: A 71-year-old male was admitted with shock and oliguric acute kidney injury with a serum creatinine of 3.89 mg/dL (baseline 1 mg/dL). He reported having a skin rash preceded by a transient painless penile lesion. Urine sediment showed dysmorphic RBCs, abundant WBCs, muddy brown and coarse granular casts. Urine protein/creatinine ratio was 3300 mg/g. Laboratory investigations revealed a positive (1:256) rapid plasmin reagin. Syphilis infection was confirmed by a reactive *Treponema pallidum* passive particle agglutination test. Immune and serologic tests were all negative including ANCA. A renal biopsy showed diffuse necrotizing CGN with greater than 75% cellular crescents and MN. The patient was treated with penicillin G, pulse methylprednisolone for 3 days, oral prednisone, and hemodialysis. He was discharged 20 days after admission, with improved urine output but remained dialysis dependent. At follow-up weeks later, the patient still required hemodialysis. He refused re-biopsy and no other immunosuppression was tried given his poor compliance with close follow-up visits.

Discussion: Syphilis-associated kidney disease is uncommon with a reported incidence of 0.3% and is usually associated with secondary syphilis. Secondary syphilis-associated CGN is very rare with only one previously reported case in the literature. As in infectious GN, treatment is aimed at the underlying infection. The use of corticosteroids is recommended by some experts when crescents are present. There is no clear evidence that additional immunosuppression is beneficial. In the first reported case of secondary syphilis-associated CGN described by Walker et al (Am. J. Med, 76: 1106-1112, 1984), plasmapheresis was empirically used for suspected vasculitis followed by corticosteroids and the acute kidney injury improved but without returning kidney function to normal. The present case adds to the evidence that secondary syphilis can be associated with crescentic glomerulonephritis. The clinical course of this patient points to the need for better treatments for this rare, yet important, condition.

PUB591

Fibrillary Glomerulonephritis Presenting as Hematuria

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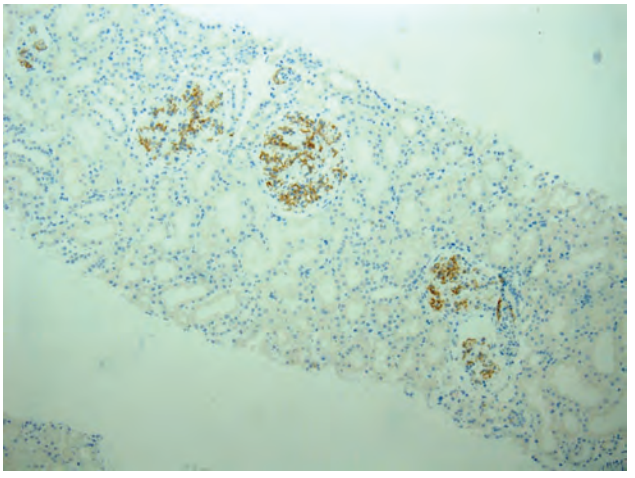
Introduction: Fibrillary glomerulonephritis (FGN) is a glomerular disease with pathognomonic findings seen on EM revealing randomly arranged nonamyloid fibrillary deposits that are 10 to 30nm. The disorder is found only in <1% of native kidney biopsies. Most patients present with nephrotic range proteinuria, hematuria and reduced renal function. We report a case of a patient with hematuria with normal renal function who was found to have FGN.

Case Description: A 51-year-old female came to clinic for evaluation of hematuria which was present for the past year. Urinalysis showed trace amount of protein and 3+ blood with RBC count of 5-15 per high power field. Protein to creatinine ratio was 0.6 mg/mg. Creatinine of 1.0 mg/dL and Hgb was 16.6 g/dL. CT showed no signs of nephrolithiasis. Urology performed cystoscopy with unremarkable findings. Renal biopsy revealed mesangial expansion, congo red negative, DNAJB9 immunohistochemistry positive in glomeruli, and electron microscopy showed mesangial areas and segmental regions of the capillary loops with deposition of randomly oriented non-branching fibrils that were mostly 20nm, warranting a diagnosis of FGN. Secondary workups were negative. Patient continues to have hematuria after 1 year of follow up but renal function remained stable with lisinopril 20mg daily.

Discussion: Fibrillary deposit glomerular diseases are divided into 3 main categories: amyloidosis, immunotactoid glomerulopathy, and FGN. Amyloid is congo red positive with fibrillary deposits that are about 10nm. Immunotactoid glomerulopathy is congo red negative and fibrils deposits are 30 to 50nm. FGN is congo red negative with fibril deposits of about 20nm. New markers such as DNAJB9 has shown to identify FGN without the need of EM. Serum level of DNAJB9 has also been shown to predict diagnosis of FGN. This case is unique since patient did not have the classic signs of FGN. Currently there are no optimal treatments for idiopathic FGN and high as 40-50% of patients develop ESRD.



DNAJB9 immunohistochemistry

PUB592

The Unsettling Shades of Lupus Nephritis: Emergence of a New (Sub) Class Rather Than Just a Rare Coexistence

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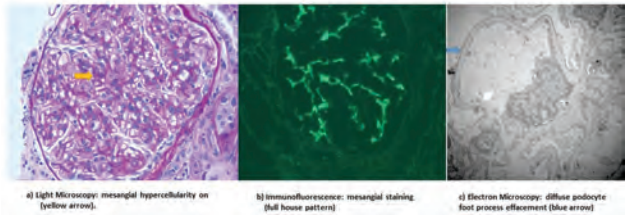
Introduction: A widely accepted classification scheme for lupus nephritis (LN) has improved diagnostic consistency. However, there are still certain forms of LN that are poorly categorized. Herein, we present a rare case of lupus podocytopathy (LP) where we were fortunate to observe an evolution of the pathologic pattern over time.

Case Description: A 24-year-old African American woman with a history of lupus presented with acute kidney injury and proteinuria of 12 g/24 hours. A renal biopsy revealed class II LN with mesangial expansion and deposits. Due to the severity of proteinuria, the patient received mycophenolate mofetil and steroids, followed by cyclophosphamide, and then azathioprine. After two years, when she was in remission with a spot urine protein/creatinine ratio (UPCR) of 100 mg/g, the patient stopped taking her medications. After a year, she developed proteinuria (UPCR 5 g/g) and received oral steroids for a year. A year later, she relapsed again with UPCR of 6.8 g/g. A repeat kidney biopsy demonstrated mesangial expansion and hypercellularity without proliferative changes (i.e. suggestive of class II LN), electron microscopy revealed diffuse, almost complete, podocyte foot process effacement with microvillous changes confirming LP. Cyclophosphamide therapy resulted in gradual decrease in proteinuria to its current UPCR of 750 mg/g. Serum creatinine has remained within normal range over the years.

Discussion: While LP was initially thought to reflect a rare co-existence of LN with other glomerulopathies, the sparse data so far seem to denote it as an unclassified LN variant characterized by nephrotic-range proteinuria and diffuse foot process effacement in the absence of endocapillary proliferation. In order to avoid misclassification and management errors, clinicians should be aware of this variant; in the cases of a discrepancy between clinical presentation and histological findings a diagnosis of LP needs to be contemplated and the nephrologist should insist on electron microscopic examination of the glomeruli.



PUB593

Atypical Hemolytic Uremic Syndrome in a Patient with Primary FSGS

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is an uncommon cause of acute kidney injury accompanied by hemolysis and thrombocytopenia. It can occur as a primary disorder or secondary to an underlying systemic disorder or drug.

Case Description: The patient is a 33 year old female diagnosed with biopsy proven minimal change disease in 2013. Subsequent biopsy in 2015 performed due to persistent nephrotic range proteinuria despite treatment showed focal segmental glomerulosclerosis (FSGS). She was treated with mycophenolate mofetil and steroids. In April 2018, her creatinine was 1.3 mg/dl with UPCR of 1.7 g/g. Mycophenolate and prednisone were stopped. She was given hormonal therapy for upcoming egg harvesting. In July she had UACR of 3.8 g/g and creatinine of 2.0 mg/dl and resumed her mycophenolate and prednisone. Her nephrotic syndrome worsened and she was admitted to the hospital in September. At that time, her creatinine was 3.4 mg/dl, UPCR 7.6 g/g, hemoglobin 10.6 g/dl and platelets 238 k/uL. Her creatinine, hemoglobin, and platelets rapidly worsened over the next five days (5.2 mg/dl, 6.8 g/dl, and 50 k/uL respectively). ADAMTS13 was 70%, shiga-like toxin was negative, C3 was mildly low, and C4 was normal. A lesion in her axilla was positive for varicella zoster virus (VZV). Eculizumab was started due to concern for aHUS. Renal biopsy demonstrated focal segmental and global glomerulosclerosis as well as changes of thrombotic microangiopathy (TMA) and tubular injury. Immunofluorescence was negative. Electron microscopy examination showed thickening of the glomerular basement membranes, expansion of subendothelial space, mesangiolysis, and nearly complete foot process effacement without electron dense deposits. Prior biopsies were reviewed with no evidence of TMA. Genetic testing was performed which was equivocal for aHUS genetic mutations. She was continued on eculizumab but progressed to ESRD.

Discussion: The trigger of aHUS in this patient remains unknown. Although there are case reports of genetic aHUS developing in patients with pre-existing FSGS, this is not a common association. There have also been case reports of VZV infection triggering aHUS. Finally, the patient was taking oral contraceptives and had recently undergone more intense hormonal therapy, either of which may have triggered aHUS.

PUB594

Pulmonary Renal Syndrome and Pauci-Immune Necrotizing Glomerulonephritis Associated with Hydralazine Use

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Introduction: Hydralazine is commonly prescribed for hypertension (HTN) and heart failure. Side effects include headache, pre-syncope, tachycardia, and palpitations, and rarely, a lupus syndrome. We present a patient with pulmonary renal syndrome and rapidly progressing glomerulonephritis associated with hydralazine.

Case Description: A 66-year-old African American male with HTN, anemia, COPD, heart failure on hydralazine, peptic ulcer disease, and substance-abuse history was admitted with a Hgb of 4.3 g%. Gastrointestinal bleeding and hemolysis work-up were negative. 4 days after admission, he developed diffuse alveolar hemorrhage requiring intubation. Serum creatinine rose to 1.7mg% (1mg% baseline). Urinalysis showed granular casts, isomorphic hematuria, no cellular casts, and non-nephrotic proteinuria. He had a positive ANA, dsDNA and low complements (C3/C4). He was treated with 3 days of IV solumedrol pulse therapy followed by oral prednisone. Presumed diagnosis was pulmonary renal syndrome due to SLE. He was extubated after 3 days, with stable hemoglobin. Renal function worsened and renal biopsy was done. Light microscopy and DIF showed focal and segmental necrotizing glomerular lesions with cellular crescents (6/32), red-cell casts within tubules, positive fibrinogen (3+), C3 (2+), and low intensity (1-2+) IgG along basement membranes. Anti-GBM antibody was negative. Due to crescentic pauci-immune vasculitis, he began cyclophosphamide, transitioning to rituximab a few weeks later. Serum creatinine peaked at 2 mg%, and at last follow-up was 1.6mg%. Myeloperoxidase (MPO) ANCA (> 100 U/ml) and histone AB were positive, suggesting drug-induced SLE with ANCA positive pauci-immune glomerulonephritis, with hydralazine as the offending agent.

Discussion: Hydralazine is widely used, but may have rare, severe side effects, including lupus-like syndrome. In our patient, renal function stabilized after hydralazine discontinuation, and appropriate treatment for ANCA-associated glomerulonephritis. ANCA vasculitis has been rarely reported in hydralazine-associated lupus syndrome, and then in conjunction with MPO antibody, rather than Proteinase 3, as in our patient. *Disclosure: The views expressed are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense (DoD), or the U.S. Government.*

PUB595

Ruptured Intracranial Aneurysm as Presentation for Systemic Lupus Erythematosus (SLE) and Antineutrophil Cytoplasmic Antibody-Associated Vasculitis (AAV) Overlap Syndrome

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Introduction: We present a rare case of intracranial aneurysm rupture as presentation of SLE AAV (Systemic Lupus Erythematosus ANCA Associated Vasculitis) overlap syndrome. Only one other case of overlap syndrome presenting with hemorrhagic stroke has been reported. Two other cases have been reported to present with cerebral ischemia.

Case Description: 53-year female with HTN, h/o hemorrhagic pontine stroke (at age 50), inflammatory arthritis and CKD presented with headache and altered mental status. No family history of early stroke or HTN or kidney disease. HTN had been well controlled on metoprolol 25 mg daily and hydralazine 50 mg bid. CT scan showed diffuse subarachnoid hemorrhages with slightly greater involvement of R sylvian fissure and mild ventriculomegaly. EVD drain was placed and patient underwent urgent cerebral angiogram with coiling of ruptured R PCA aneurysm. No bleeding noted from L PCA aneurysm. Patients' clinical condition did not improve after coiling of aneurysm and EVD drain placement. She continued to have significant EVD drainage and was scheduled for VP shunt placement. Patients' baseline serum creatinine was ~ 1.5 mg/ dL with no known proteinuria or hematuria. On admission, patients' creatinine was 2.9. While frank hematuria after addition of antiplatelet agent resolved, she continued to have microscopic hematuria. Quantitation in urine showed 6.2 g/g proteinuria. Nephritic workup revealed + ANA (1:640), low complements, p-ANCA positive, MPO positive. Renal biopsy showed crescentic glomerulonephritis (Pauci-Immune). After initiation of steroids, patients mental status improved and EVD drainage decreased. Patient also received Cyclophosphamide. Her creatinine improved to previous baseline of 1.5 and proteinuria below 1g/g on follow up.

Discussion: Rapid neurologic and renal recovery was seen in response to immunosuppressive therapy. While renal involvement is common in SLE AAV, neurologic involvement is rare. To our knowledge, this is the second case described in the literature with overlap syndrome (+ANA and ANCA) presenting with intracranial hemorrhage. Prompt diagnosis and treatment is crucial in management of such complicated case.

PUB596

Double Trouble: Combined ANCA Vasculitis Relapse and Antibody-Mediated Rejection in a Kidney Transplant Recipient

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Introduction: A female kidney transplant recipient, presented with graft dysfunction associated with headache, polyarthralgia, sinusitis, epistaxis, fatigue and vomiting for 2 weeks. She had a history of PR3 positive anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), diagnosed 6 years prior, resulting in end-stage renal disease, despite treatment with the CYCLOPS protocol and plasma exchange. She received a 'standard immunological risk' deceased donor kidney transplant 3 years later. Maintenance immunosuppression (IS) included Prograf 3mg BD, Mycophenolate Mofetil 750mg BD and prednisolone 5mg OD. The patient denied medication non-adherence.

Case Description: Examination was unremarkable. Initial investigations revealed severe non-oliguric acute kidney injury (creatinine 685 μmol/L from 110 μmol/L baseline). Urinalysis showed 4+ blood and 1+ protein. Anti-PR3 antibody level rose to 81 IU/ml from 5 IU/ml ten months prior. Urine CD163 was elevated at 1225 ng/mmol (<0.3). There was a significant development in the strength and breadth of both class I and II donor specific antibodies. Renal biopsy demonstrated focal necrotising crescentic glomerulonephritis, tubulointerstitial inflammation and strong global C4d positivity in peritubular capillaries, consistent with AAV relapse and antibody-mediated rejection (ABMR). The Molecular Microscope Diagnostic Report® independently identified severe TCMR and ABMR (figure 1). She was treated with pulsed methylprednisolone (500mg x 3 days), followed by tapering prednisolone, Rituximab 375mg/m^2 x 4 and continued maintenance IS. Management was influenced by prior IS exposure and the risk of- and subsequent development of infection. Unfortunately, she remained dialysis dependent and subsequently required graft nephrectomy for persistent rejection symptoms.

Discussion: While AAV relapse after kidney transplantation is rare, this case is a reminder that it can recur. The diagnostic biopsy in this case was supported by 2 novel techniques, a urine CD 163 and the Molecular Microscope Diagnostic Report®, identifying concomitant rejection and vasculitis. Despite treatment, the synchronous immunological mechanisms resulted in irreversible kidney damage. The wealth of objective evidence was key to personalising the risk-benefit of further IS in this case.

PUB597

Rare Presentation of Membranous Nephropathy in Pulmonary Alveolar Proteinosis and Minimal Change Disease

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Introduction: Pulmonary alveolar proteinosis (PAP) is characterized by intra-alveolar accumulation of phospholipid and protein-surfactant material with minimal inflammation or fibrosis. Membranous nephropathy (MN) has rarely been associated with PAP and to

our knowledge has not been previously reported in minimal change disease (MCD). We describe a patient with MCD who subsequently developed MN in the setting of PAP.

Case Description: A 43-year-old female with low dose steroid-dependent MCD and idiopathic PAP associated with asthma and eosinophilia presented with acute dyspnea, fever, and malaise. She was found to have nephrotic range proteinuria, eosinophilia (18,000/mm^3) and eosinophiluria. Secondary causes of eosinophilia were excluded. Bone marrow biopsy revealed hypocellular marrow with eosinophilia without fibrosis, myeloproliferative or clonal hematopoietic processes. Serum IgE levels were elevated (3556 IU/L). Bronchoscopy confirmed PAP and bronchoalveolar lavage showed >85% eosinophils. She developed non-oliguric AKI with serum creatinine increasing from 0.8 mg/dl to 2.8 mg/dl. Urinalysis showed 3+ protein and 4+ eosinophils. 24-hour-urine collection demonstrated 10,428 mg of protein; serum albumin was 3.1 mg/dl. Autoimmune and infectious serologies were unremarkable, as were complement levels and serum immunofixation electrophoresis results. Renal biopsy showed subepithelial immune complex deposits with minimal basement membrane reaction, segmental thinning of GBM, and no eosinophilic infiltration. Serum PLA2R titers were negative and other secondary causes of MN were ruled out. Therapy with prednisone 120 mg/day resulted in rapid improvement in proteinuria and renal function (returned to baseline upon discharge). She was discharged on a steroid taper with no proteinuria noted after a month of treatment.

Discussion: MN is characterized by diffuse and global subepithelial immune complex deposits and associated GBM changes. Our patient's findings of early PLA2R-negative MN associated with PAP is consistent with secondary MN. This association has rarely been described and the occurrence of MN in a patient with known steroid-responsive MCD to our knowledge has not been reported. Further research is needed to elucidate the pathophysiology of MN in PAP.

PUB598

Glomerulonephritis in Patients with Ulcerative Colitis

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Introduction: Inflammatory bowel diseases (IBD) is a systemic disorder with possible renal involvement, and we aimed to describe the spectrum of renal affection in our IBD patients. All the medical records of 949 IBD patients in Peking Union Medical College Hospital from June 2012 to October 2018 were reviewed, especially those associated with renal involvement. The detailed clinical and pathological features of glomerular disease were analyzed.

Case Description: The renal involvement was observed in 212 IBD patients(22.3% of all), including Crohn's disease (CD, 40.1%), ulcerative colitis (UC, 45.8%) and intermediate colitis (IC, 14.2%). The most common renal diagnosis was renal cyst (50.5%), followed by urolithiasis (29.2%), glomerular disease (8.0%), and tubulointerstitial disease (2.4%). Seven cases of UC associated glomerulonephritis, confirmed by renal biopsy, were mainly middle-aged males (34-72y; male: female= 5:2). UC was diagnosed by endoscopic biopsy and treated with 5-aminosalicylic acid and/or steroids and each patient had achieved clinical remission. The onset of renal disease occurred after a few years (0-25 years) of IBD diagnosis. The mean 24-hour urine protein(24hUP) was 3.63 (0-6.35)g, and the mean Scr was 1.92 (0.45-4.47)mg/dl. Histology showed membranous nephropathy (n=3), crescentic GN, IgAN, ECPGN, and lupus nephritis. All patients were complicated with autoimmune antibody positive. After treated by steroid (1mg/kg/d) and/or immunosuppressant, significant improvement in proteinuria and Scr were oberserved.

Discussion: Renal involvement of IBD is not rare, and the prognosis of UC associated glomerulonephritis is well.

Table 1 Clinical data of 7 cases of UC associated glomerulonephritis

Patient	1	2	3	4	5	6	7
Age(years) at diagnosis of kidney disease, sex	49/M	51/F	37/F	46/M	72/M	58/M	34/M
Clinical type of UC	Chronic recurrent	Chronic recurrent	Chronic recurrent	Initial	Chronic recurrent	Chronic recurrent	Initial
Onset of kidney disease	16 years after UC	25 years after UC	8 years after UC	Almost the same time as UC	5 years after UC	1 years after UC	3 years before UC
Biopsy of kidney	IgAN(III)	MN(II)	Crescentic GN	Endocapillary proliferative GN	Atypical MN	MN(I)	Lupus nephritis(IV)
Creatinine (mg/dl)	1.46	0.45	4.12	1.03	4.47	0.84	1.07
24hUP(g/24h)	NEG	5.63	5.1	2.27	6.35	4.1	1.93
Urine RBC/μL	0.3	52.1	161.8	750.5	16	18.5	602.1
ALB(g/L)	43	30	35	33	25	25	31
Therapy for kidney disease	ARB	Steroids,CsA, ACEI	Steroids,CTX	Steroids	Steroids,CTX	Steroids,CsA	Steroids,CTX

PUB599

Rapidly Progressive Fatal IgA Nephropathy in a Patient with Longstanding Cirrhosis

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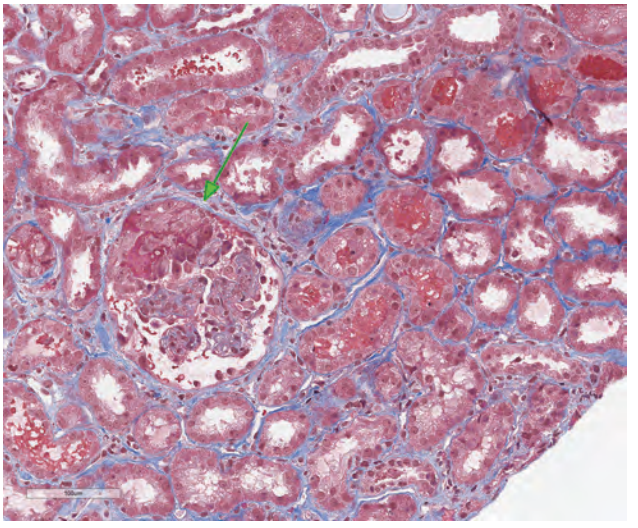
Introduction: IgA nephropathy associated with liver disease (hepatic IgAN) is a relatively common form of secondary IgAN, presenting with microscopic hematuria and normal kidney function in the majority of patients. Presentation as a rapidly progressive nephritis is rare. We report a case of IgA nephropathy secondary to liver cirrhosis that rapidly progressed to a fatal end stage renal failure.

Case Description: 57 yo male with history of cirrhosis (stable, listed for transplant), rheumatoid arthritis, and pan-hypopituitarism presented with edema, rash, dark urine, and AKI (KDIGO stage 3). No preceeding illness or fevers. UA with nephrotic range proteinuria and hematuria with acanthocytes. Work up with ANA, ANCA and complements were normal. Kidney biopsy revealed acute proliferative glomerulonephritis with some crescents. Predominant IgA and C3 deposits; electron microscopy showed large mesangial deposits. (MEST score M3E1S0T0). Initiated on pulse dose steroids with transient improvement before proteinuria, edema, and renal function rapidly worsened. Initiated hemodialysis one month after presentation. Despite aggressive medical management, the patient clinically declined. Family decided to transition to comfort measures and the patient died.

Discussion: We describe a case of rapidly progressive crescentic IgA nephropathy in a patient with cirrhosis. The presentation is atypical in its aggressive presentation and course. We hypothesize that in addition to the background deposition of IgA containing complexes due to the liver disease, "a second hit" (possibly an infection) precipitated and aggressive course of the disease. There is currently no specific treatment for hepatic IgAN in patients who develop rapidly progressive renal impairment, and management of such cases remains a challenge.



Trichrome stain. Acute crescentic glomerulonephritis, tubular red cell casts.

PUB600

A Rare Case of Collapsing Glomerulopathy

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Introduction: Collapsing glomerulopathy (CGP) can be related to infection, drugs, vascular disease, autoimmune disease, or be idiopathic. We report a case of CGP in a previously healthy patient presenting with acute hepatitis B infection and malignant hypertension.

Case Description: This 32 year-old African American man with no past medical history presented with two weeks of headache, weight loss, and increased urine output. He was found to have periorbital and lower extremity edema. Initial blood pressure was 190/120. Initial labs were notable for a serum creatinine of 2.8mg/dl, albumin of 2.8g/dl, platelet count of 134,000, total cholesterol of 265mg/dl, and estimated 24 hour urine protein of 15g/day with no hematuria. Renal ultrasound revealed normal sized kidneys and was negative for renal vein thrombosis. Echocardiogram demonstrated an ejection fraction of 25% and left ventricular hypertrophy. Serologic work-up was positive for Hepatitis B surface antigen, envelope antigen, and HBV-DNA (>170,000,000 IU/ml) and otherwise negative including HIV, HCV ab, Parvovirus B19, CMV, hemoglobin A1c and urine drug screen. Renal biopsy demonstrated CGP, thickened glomerular basement membranes and moderate hyalinosis of arterioles. Immunofluorescence had nonspecific staining and there were no immune complex deposits on electron microscopy. There was 10% visceral epithelial cell foot process effacement. There were no viral cytopathic changes. Tenofovir was initiated and aggressive blood pressure control was achieved during hospitalization. Subsequently, proteinuria decreased to 3g per day with a gradual improvement in serum creatinine to 2.1mg/dl at discharge.

Discussion: CGP is a distinct pattern of proliferative parenchymal injury with a number of infectious causes previously identified. There are few reported cases of its association with hepatitis B infection. In our case, an adult African American male presented with acute hepatitis B associated CGP and subsequent malignant hypertension leading to severe ischemic injury, nephrotic range proteinuria, renal dysfunction, and cardiac dysfunction. Our patient had signficant reduction in proteinuria and demonstrated stabilization of serum creatinine levels with initiation of antiviral treatment of hepatitis B infection and blood pressure control including the use of an angiotensin receptor inhibitor. This case suggests a causative role of hepatitis B in CGP.

PUB601

Collapsing Glomerulopathy: Report of 10 Cases

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Introduction: Collapsing pathology represents one of the most aggressive forms of glomerulopathy described, representing 15% of the biopsies described as focal and segmental glomerulosclerosis. The knowledge of its characteristics in our population is crucial for its better understanding and management.

Case Description: **Materials and methods:** By reviewing the medical records, we proceeded to identify cases of collapsing glomerulopathy with complete clinical follow-up in our institute, registered from 2010 to date. **Results:** The age range at diagnosis was from 17 to 60 years, with 3 cases of the male gender and 7 registered women. The proteinuria recorded at diagnosis had an average of 10.01 gr (4.2-12 grams). The creatinine at diagnosis had an average of 3.8 mg/dl (0.47-11 mg/dl) with a mean basal albumin of 2.15 g/dl (1.0-3.4 gr/dl). Nine of the ten cases were hypertensive at diagnosis, with hematuria in eight of the cases. Similarly, 8 of the cases integrated complete diagnosis of nephrotic syndrome in the initial clinical presentation. Upon arrival at the institute, the average evolution time was 5.5 months (1-24 months) and the most common symptom of presentation was lower limb edema. One of the cases was linked to EBV, one to HIV and one was triggered after pregnancy. No specific etiology was identified in the rest of cases. Given the degree of progression of renal damage, it was necessary to start dialysis therapy during hospitalization in 5 of the 10 cases. In 4 of the cases, immunosuppressive therapy was given and in one more antiretroviral therapy at the beginning given the etiology of the glomerulopathy. In two of the cases, management was based on boluses of methylprednisolone, plasmapheresis and monthly boluses of cyclophosphamide. One of them reached a partial response in the first 3 months of follow-up. Two cases received methylprednisolone, plasmapheresis and rituximab, with a complete response in one of the cases. The rest of the cases did not reach any degree of clinical response.

Discussion: In our group of patients, despite the short time to diagnosis, the vast majority unfortunately were detected with advanced fibrosis without the possibility of treatment given the benefit risk ratio. In recent years, the trend is toward earlier diagnosis with the possibility of treatment and intentional etiology search. The prognosis regarding renal function continues to be discouraging.

PUB602

Use of IVC Filter in the Management of Post Percutaneous Renal Biopsy (PRB) Complicated by Perinephric Hematoma (PNH) and Acute RLE DVT in a Patient with C-ANCA-Positive Crescentic Glomerulonephritis

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Introduction: A 37 year old MWF with a prior history of morbid obesity, gastric bypass, hypertension, prior calcium oxalate nephrolithiasis presented to her local hospital with diarrhea, lower abdominal pain, arthralgia's, sinus congestion. She was found to have micro hematuria, 2 g proteinuria, metabolic acidosis, hyperkalemia and AKI with a serum creatinine of 4.5 mg/dL with prior normal renal function. A CT of the abdomen revealed normal kidneys but thickening of the terminal ileum, a positive ANA (1:320) and a Klebsiella urinary tract infection. She received IV fluids with bicarbonate, ceftriaxone and referred for PRB.

Case Description: The patient underwent right PRB under ultrasound guidance but post procedure she developed right flank pain and on CT and US was found to have an acute PNH. She was placed at bed rest. The morning post biopsy she developed acute RLE pain and swelling and an extensive RLE DVT. Hemoglobin fell from pre biopsy 9.5 g/dL to 6.8 g/dL. An IVC filter was placed. Anticoagulation was held initially. 10 day post renal biopsy a repeat US showed a resolving PNH. At this point heparin and then Coumadin was begun without incident and she did well clinically. Renal biopsy showed crescentic pauci-immune glomerulonephritis compatible with C-ANCA-associated vasculitis. Two glomeruli were obsolescent, 27/43 showed crescents and fibrinoid necrosis. She was treated with pulse steroids followed by prednisone taper. She received induction therapy with rituximab 375 mg/m2 of BSA weekly while in the hospital and to date has completed 4 doses of Rituximab. She has been doing well clinically and is asymptomatic. Serum creatinine has fallen to 1.67 mg/dl and U Protein to creatinine ratio to 1.48. Present hemoglobin is 11.8 g/dl. The IVC filter has been removed and she is on Coumadin anticoagulation.

Discussion: PNH occurs in 90% of patients immediately post renal biopsy but is clinically significant in only 2% of patients. Prior literature does not discuss the dilemma of post PRB complicated by PNH and acute DVT. Here we report a successful strategy of limited IVC filter use to prevent PTE and avoidance of anticoagulation in the face of acute post biopsy PNH.

PUB603

An Association Between HIV-Associated Nephropathy and HIV-Associated Immune Complex Kidney Disease: A Case Report

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Introduction: The estimated prevalence of kidney disease in HIV-infected patients ranges from 2 to 17% and can be classified into HIV-associated Nephropathy (HIVAN) and HIV Immune Complex Kidney Disease (HIVICK), nonetheless the association of these two diseases is rarely described, since their physiopathology are not alike.

Case Description: Male, 51 years old, caucasian, BMI 23.8 kg/m^2, hypertensive, HIV virus carrier in antiretroviral therapy since 1994, with undetectable viral load and CD4 > 500 cells/mm^3 for over 20 years, presented with Nephrotic Syndrome in 2007, diagnosed with FSGS NOS variant after kidney biopsy. Several immunosuppressive regimens were performed, only partial remission was achieved and residual proteinuria (UPCR 2-3 g/g) persisted. Early 2019, the patient refered edema in the lower limbs, asthenia and new onset of proteinuria (UPCR 7,6 g/g), Serum Albumin was 2,1 g/dL, urinalysis revealed 23 rbc/field and worsening renal function was observed (SCr 1,73 to 3,64 mg/dL). Another kidney biopsy was performed. Light microscopy showed 11 glomeruli, 6 globally sclerotic. The remaining had focal collapsing lesions, basement membrane with occasional double contours and spikes. There was an extracapillary epithelial proliferation in one glomerulus, with indefinite features between a fibrocellular crescent or a pseudo-crescent. Immunofluorescence showed granular deposits of IgA (1+), IgG (2+), C3 (1+) and Lambda (2+) on mesangium and glomerular basement membrane, with global and diffuse distribution. Based on these findings, Immune complex-mediated Glomerulonephritis with associated Collapsing Glomerulopathy was diagnosed, consistent of HIVAN in association with HIVICK. No alleles at risk for APOL1 was found on genetic analysis (sequencing by SANGER).

Discussion: Although rare, HIV-positive patients, even with undetectable viral load, may develop immunological kidney disease (HIVICK) in combination with the non-immunological form (HIVAN). At our perspective, the kidney tissue could be seen as an viral reservoir, justifying a collapsing glomerulopathy even with long time of negative viral load.

PUB604

Partial Remission of Proteinuria with Bleomycin-Etoposide-Cisplatin (BEP) in Systemic Lupus Erythematous-Related Membranous Nephropathy and Ovarian Cancer

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Introduction: Systemic Lupus Erythematous (SLE) and ovarian cancer (OC) are both associated with secondary causes of membranous nephropathy (MN). The incidence of OC with MN is rare and coexistence with SLE has not been documented in the literature. Use of conventional therapy for MN with OC may result in increased carcinogenesis. As such, mass resection and chemotherapy (CTx) are prioritized. First line treatment with Bleomycin-Etoposide-Cisplatin (BEP) has known nephrotoxic effects. Its impact on proteinuria is unclear. Here, we describe a case of MN secondary to SLE in the setting of OC with partial remission of proteinuria with BEP.

Case Description: A 31 year old female with SLE (diagnosed 2014) was seen in renal clinic May 2018 for new onset proteinuria. She was asymptomatic and screening labs showed creatinine (CR) 0.4 mg/dL and proteinuria 30 mg/dL. Her proteinuria rapidly progressed to 2.6 g/L and a renal biopsy showed MN secondary to SLE (ISN- RPS Class V). A CT abdomen performed 2 days post biopsy for evaluation of a renal hematoma noted an incidental ovarian mass. June 2018, the mass had increased in size and a diagnostic laparoscopy performed by gynecology (GYN) was concerning for an ovarian neoplasm. Her proteinuria peaked to 4.3 g/L and conservative management was advised with an ACE inhibitor pending mass resection and completion of CTx. August 2018, the mass was removed after reaching a size of 15.5 x 11 cm causing secondary bilateral hydronephrosis. Pathology showed a stage II immature teratoma and she was started on 3 cycles every 3 weeks of BEP. Complications included acute kidney injury and her ACE inhibitor was stopped September 2018. Repeat urine studies prior to CTx completion (November 2018) first showed protein 30 mg/dL and was subsequently negative. December 2018, one month off CTx, her proteinuria recurred to >500 mg/dL. She continues to follow in renal clinic for management of her MN.

Discussion: This case illustrates the first proposal of an anti proteinuric effect of BEP in SLE MN with OC. This is important to consider in the management of germ cell tumors with MN. It also has implications in other forms of secondary MN not responsive to standard therapy. Further research is required to understand the full treatment potential of these agents in MN.

PUB605

A Rare Case of Idiopathic Nodular Glomerulosclerosis in a Non-Diabetic and Non-Smoker with Untreated Hypertension

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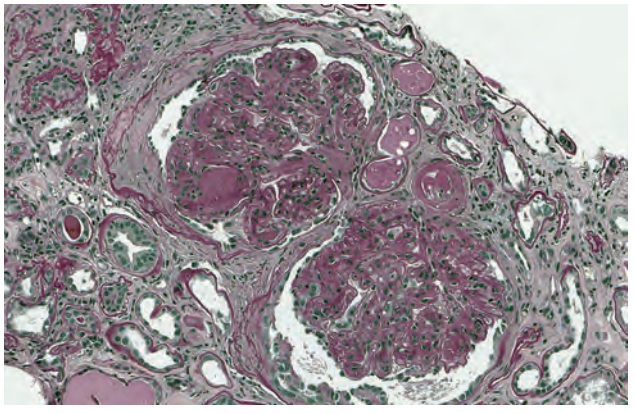
Introduction: Nodular glomerular sclerosis is a classical finding in diabetic nephropathy. It can occur in the absence of diabetes, often in older men with long standing smoking, hypertension, Fibrillary GN, amyloidosis, Takayasu arteritis, light chain nephropathy, nodular variant of mebrano proliferative glomerulonephritis. We are reporting a case of idiopathic nodular glomerulosclerosis leading to nephrotic syndrome needing dialysis.

Case Description: 67 y/o non -smoker with no prior medical care with untreated hypertension for long time, presented with sudden onset of AKI following fall at home and prior progressive lower extremity edema and exertional SOB. Found to have complete heart block, oliguria, nephrotic syndrome with serologies negative for hepatitis, HIV, paraproteinemia, ANA, C-ANCA, P-ANCA, PLA2R Antibody with normal complements and HbA1C of 5.4. Renal biopsy showed diffuse global, nodular glomerulosclerosis, severe arterial hyaline sclerosis, interstitial fibrosis(80-90%), no evidence of immune complex deposition.

Discussion: Though not commonly seen, Idiopathic nodular glomerulosclerosis should be considered as one of the differentials for patients presenting with Nephrotic syndrome like in our case with no history of diabetes in a non smoker.



PUB606

Surprise on Renal Biopsy: Crescentic Glomerulonephritis

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Introduction: IgA Nephropathy(IgAN) is the most common glomerulonephritis, with variable presentation, prognosis and controversial treatment. Though less common in adults, there has to be a high index of suspicion in those with presentation of high-risk markers such as severe proteinuria and signs of systemic vasculitis. We present a 41-year-old female with leukocytoclastic vasculitis, proteinuria and normal renal function with focal crescentic glomerulonephritis

Case Description: 41-year-old Asian female, no prior illness, presented with a purpuric lower extremity rash, knee and ankle pain. Skin biopsy revealed leukocytoclastic vasculitis.4 months later, her random urine protein was 3099mg/gm creatinine, 2+ blood on urinalysis with normal creatinine(CR) 0.7(0.5-1mg/dL) and urine protein:CR 2g/g. Save for positive ANA and elevated CRP of 17.9(<10mg/L), her dsDNA, Hepatitis, ANCA, cryoglobulin, ASO and serum protein electrophoresis were negative. Total cholesterol and triglycerides elevated at 203(<200mg/dL) and 321(<150mg/dL) respectively. Normal-sized kidneys and echogenicity on renal ultrasound. Background of cutaneous vasculitis in the presence of proteinuria, prompted renal biopsy. It revealed Focal crescentic glomerulonephritis with scattered glomerular double contours, consistent with IgAN. Treatment was commenced with Prednisone, Ramipril and Atorvastatin, resulting in complete resolution of her proteinuria, rash, normalization of her triglyceride and cholesterol levels. She has been in remission with normal BUN and CR

Discussion: IgAV is 33 times more common in children, however it is important to exclude in any patient, who presents with purpura. Though treated conservatively in children, in adults, renal disease can be very severe, particularly in crescentic IgAN, which has poor prognosis and increased progression to renal failure. KDIGO guidelines recommend immunosuppressive agents such as cyclophosphamide for its therapy, however the long-term outcome is little known. Our patient with normal CR, had focal crescentic GN, in remission after use of corticosteroids(CS), chosen due to her young age and normal CR. Pozzi et al, noted that CS reduced proteinuria and decline in renal function, with use in all classes of IgAN. More guidelines on treatment and their outcomes in adults with IgAN is needed, though from our case, corticosteroid monotherapy can be an option, with close follow up of renal function

PUB607

Thrombectomy for Renal Vein Thrombosis in Membranous Nephropathy

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Introduction: Bilateral renal vein thrombosis is a rare complication of nephrotic syndrome. We hereby report a case of extensive systemic thrombosis with successful percutaneous suction thrombectomy

Case Description: A 45-year-old male with no past medical history presented with lower extremity edema, dyspnea, right flank pain and pleuritic chest pain for two days. A diagnostic computarized tomography (CT) revealed a nonocclusive acute thrombus in the bilateral renal veins, extending into the suprarenal infrahepatic Inferior vena cava (Figure 1A), and right lower lobe pulmonary emboli. Initial serum creatinine was 0.87mg/dL. A 24-hour urine collection revealed protein >4.5 g/day. Labs were also remarkable for a serum albumin of <1 G/dL and a positive Phospholipase A1 Receptor at 212 RU/mL. A renal biopsy showed membranous nephropathy. Due to significant flank pain (7-8/10) and severe clot burden, patient underwent percutaneous image-guided catheter-directed suction thrombectomy of bilateral renal veins, IVC, and right lower lobe branch pulmonary artery using CAT-8 Penumbra suction thrombectomy device with 500cc of clot removed. The patient's pain improved significantly the next day (2-3/10). Patient underwent renal biopsy on post op day two. Patient was anticoagulated with heparin and transitioned to apixaban. He was treated with modified Ponticelli protocol. Renal function remained stable one month post procedure. Follow up CT scan showed resolution of the bilateral renal vein thrombus (Fig 1B).

Discussion: Acute bilateral renal vein thrombosis is a rare complication of nephrotic syndrome, and can be associated with renal function decline. Thrombectomy may be considered a safe therapy to prevent sequalae of long term clot burden.

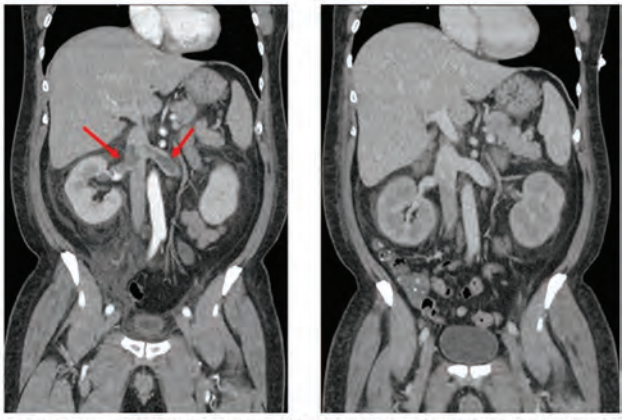

Figure 1A- Venous phase coronal CT scan image of the abdomen showing filling defects within the bilateral renal veins (red arrows) consistent with bilateral renal vein thombi. Figure 1B- Follow up Venous phase coronal CT scan image of the abdomen showing interval resolution of the previously noted bilateral renal vein thrombus.

PUB608

Coagulopathy and Nephrotic Syndrome in a Patient with AL Kappa Amyloidosis

Michael Bourla, Sophia L. Ambruso. *University of Colorado, Denver, CO.*

Introduction: We present a 64 year-old man with nephrotic-range proteinuria and coagulopathy from systemic kappa light chain (LC) amyloidosis and associated plasma cell dyscrasia.

Case Description: The patient presented with anasarca, hypotension and decreased oral intake. History was notable for chronic memory loss, cognitive decline and rapid deterioration preceding admission. On exam, he had BP of 76/59, HR 107, anasarca, lethargy, and confusion. Initial serum labs included creatinine of 3.0 (baseline 1.8), albumin of 1.1, and INR of 3.4 with normal liver function. Urinalysis had moderate blood and large protein, while direct microscopy revealed many non-dysmorphic RBCs and granular casts. Urine protein to creatinine ratio was 13g/g. Renal ultrasound showed normal sized kidneys. HIV, HCV, HBV, ANA, ANCA, C4, RF all normal. C3 mildly low at 75. SPEP revealed kappa monoclonal LC. Serum free kappa LC were 408, serum free lambda LC were 21.4, and kappa/lambda ratio was 19. Fat pad biopsy was unremarkable, however, the bone marrow biopsy showed 13% plasma cells on the aspirate and apple-green birefringence of three vessels with congo red staining showing vascular mural amyloid deposition. Official diagnosis: systemic kappa LC amyloidosis associated with plasma cell dyscrasia. Renal biopsy was not performed due to patient's coagulopathy. Hematology consulted due to the unusual finding of coagulopathy in a nephrotic patient. Coagulation factors V and X were found to be deficient (27% and 16%, respectively). Patient decided against chemotherapy and was discharged on hospice.

Discussion: A kappa-predominant AL amyloidosis is a less common cause of nephrotic proteinuria compared to the lambda LC variant, which occurs three times more often. It is suggested that AL Kappa Amyloidosis as a cause of nephrotic syndrome is more common with multiple myeloma, as seen in our patient. Interestingly, while nephrotic patients are generally thought to be hypercoagulable, our patient had an elevated and uncorrectable INR. Those with AL amyloidosis often have a bleeding diathesis which can be due to a coagulopathy, the presumed mechanism of which is factor X adsorption by

amyloid fibrils causing factor X deficiency, as observed in our patient. In patients with nephrotic syndrome and bleeding diathesis and/or coagulopathy, a unifying diagnosis can be AL amyloidosis.

PUB609

Nephrotic Syndrome in a Patient with Diabetes: Things Are Not Always as They Seem

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Introduction: Diabetic patients with renal involvement with proteinuria were previously thought to have diabetic nephropathy in up to 70% of cases. A kidney biopsy is not always pursued in these patients due to this presumed diagnosis, especially in the presence of uncontrolled blood sugars, long duration of diabetes, and other markers of microvascular disease such as retinopathy and neuropathy. The mainstay of treatment for these patients is strict glycemic control, the use of diuretics for volume management and inhibition of the renin-angiotensin-aldosterone system (RAAS). Despite treatment, mortality remains high with a progression to end stage renal disease. More recent literature has suggested that diabetics with atypical features have a non-diabetic renal disease or mixed renal disease in up to 50% of cases.

Case Description: A 37-year-old man with an 8-year history of DM2 without retinopathy A1c of 18% presented with anasarca and nephrotic syndrome. Laboratory studies revealed serum creatinine 1.2 mg/dL, albumin 1.0 g/dL, hyperlipidemia and UPCR 8 g/g. Kidney biopsy showed early diabetic nephropathy and he was started on standard treatment. He continued to have diuretic resistance with multiple episodes of AKI. He required three inpatient admissions for intravenous diuresis over the next 7 months. Due to atypical presentation and persistence of symptoms, repeat kidney biopsy was performed. Biopsy showed a FSGS lesion in a single glomerulus. Due to his uncontrolled diabetes, second line therapy with a calcineurin inhibitor (CNI) was started. Within the next 6 months, he achieved complete remission with reduction in proteinuria to <300 mg/g, normalization of albumin and resolution of edema.

Discussion: Diffuse foot process effacement on electron microscopy is a defining feature of diseases with proteinuria, and without an accompanying glomerular lesion on light microscopy, distinguishing FSGS from other proteinuric kidney diseases can be difficult. Current literature suggests glucocorticoids as first line-therapy in patients with primary FSGS with nephrotic syndrome. CNI's are reserved for steroid resistant or steroid dependent disease, and their use in early FSGS has not been extensively studied with RCT's. This case not only illustrates the importance of a kidney biopsy in diabetic patients, but also the quick resolution of FSGS with second line therapy.

PUB610

Toxic Effects of Tonic Water, a Case of Quinine-Induced Thrombotic Microangiopathy

Kishore Patcha, Josephine Abraham, Nirupama Ramkumar, Martin C. Gregory. *University of Utah, Salt Lake City, UT.*

Introduction: Quinine is one of the most common medications which can cause drug induced immune mediated Thrombotic microangiopathy. Here we present a case of thrombotic microangiopathy who exposed quinine in the form of tonic water.

Case Description: A 25-year-old female presented with flu-like symptoms including nausea, vomiting, diarrhea, malaise, and generalized abdominal pain. Diagnostic work-up showed elevated lipase (724U/L) mildly elevated liver enzymes and normal appearing liver and kidneys on CT abdomen/pelvis. Patient underwent cholecystectomy for presumed gall stone pancreatitis. Shortly after discharge, she noticed worsening swelling in her legs, abdomen, and weight gain of 30 lbs. Urinalysis showed 3+ proteinuria, hematuria, urine protein/creatinine ratio of 2.7g/g. Platelet count was 138 k/ul, Hgb;7.7g/dl, creatinine 1.58 mg/dL. Peripheral smear demonstrated schistocytes. Renal biopsy showed thrombotic microangiopathy consistent with TTP vs atypical HUS. While serologies were pending, she was treated with plsma exchange, Eculizumab 900mg, Rituximab 375mg/m2 and prednisone. ADAMTS 13 was 51%. Complements C3 and C4 were normal, Anti-Complement factor H, ANA, scleroderma antibodies and stool studies were all negative. On further review of history, she reported drinking tonic water intermittently as a restaurant server. Intermittent ingestion of quinine can cause TMA, quinine-dependent antiplatelet antibodies were tested and found to be negative.

Discussion: Quinine is a widely used remedy for leg cramp. Quinine was the first drug reported to cause TTP-HUS and it remains the most common cause of drug-induced TTP-HUS Quinine can bind to surface molecules, altering their structure and exposing new parts of the cell membrane molecule to plasma. These revealed sequences are then recognized by the immune system as foreign antigens. Drug-dependent antibodies can be detected by flow cytometry. Quinine dependent antibodies might be negative and in our patient the antibodies were likely removed by plasma exchange. If recurrent disease is to be prevented, clinicians must be aware of quinine as a possible cause of TMA.

PUB611

Quinine-Induced Immune-Mediated Recurrent Disseminated Intravascular Coagulation and Thrombotic Microangiopathy

Kishore Patcha, Martin C. Gregory, Nirupama Ramkumar. *University of Utah, Salt Lake City, UT.*

Introduction: Quinine is one of the most common medications which can cause drug induced immune mediated Thrombotic microangiopathy. Here we present a unique case of recurrent DIC and thrombotic microangiopathy in a patient who has been taking quinine supplements for leg cramps.

Case Description: A 81-year-old female with history of recurrent DIC was hospitalized with night sweats, fevers, chills, vomiting, acute kidney injury and recurrence of DIC. She underwent an extensive diagnostic work up to evaluate for occult malignancy and infection with negative results. Peripheral smear showed schistocytes and she had a WBC of 4.7 k/uL/, Hgb 10.6 mg/dL and platelets 10 k/uL. Serum creatinine was 6.55mg/dl, total bilirubin 8.2mg/dl, AST 831 u/l, ALT 366 u/l, albumin 3.1mg, LDH 5663u/l, D-dimer >20,000ug/ml, haptoglobin <10mg/dl, fibrinogen 430mg/dl. PTT 52 and INR 1.2. She was noted to have normal ADAMTS13 activity and stool studies were negative for Shiga toxin. Immunofixation electrophoresis and complements C3 and C4 were normal. Quinine-dependent antiplatelet antibodies were positive for both IgG and IgM. After eliminating quinine, she continues to improve clinically and creatinine trended down to 3.8 at time of discharge.

Discussion: Quinine is a widely used remedy for leg cramps. Several over the counter therapies, nutrition products, and beverages such as tonic water and bitter lemon contain quinine. Allergic reactions to quinine can be severe and can affect multiple organs. Quinine was the first drug to be associated with acute thrombocytopenia, and it remains the second most commonly reported cause of drug-induced thrombocytopenia. Quinine was the first drug reported to cause TTP-HUS, it remains the most common cause of drug-induced TTP-HUS. Development of quinine-dependent antibodies to antigens is thought to be the main mechanism. Quinine can bind to surface molecules, altering their structure and exposing new parts of the cell membrane molecule to plasma; these revealed sequences are then recognized by the immune system as foreign antigens. Drug-dependent antibodies can be detected by flow cytometry. Exposure to quinine can cause multiorgan failure, TMA, severe hemolytic anemia and it is critical to recognize quinine-induced disorders for prevention of recurrent disease.

PUB612

Rapidly Progressive Glomerulonephritis During Pregnancy or Just AKI?

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Introduction: The hemodynamic, inflammatory, and immunologic shifts in pregnancy may unmask underlying kidney disease. Rapid loss of kidney function is critical for maternal and fetal outcomes, once we have an active sediment, we can suspect for diagnosis of Glomerulopathy. We found just 4 case reports in literature about rapidly progressive Glomerulonephritis during pregnancy (RPGN).

Case Description: We compare 3 cases of "de novo" glomerulopathies during pregnancy. A case that match with RPGN by definition (Patient 1), with the presentation of other 2 cases of glomerulopathies with clinical characteristics of RPGN (Patients 2,3), but with different histologic features. These are young women, two with diagnosis of SLE, the biopsy was performed without complications, indications were kidney injury, important proteinuria and active sediment. All cases required interruption of pregnancy. They received induction that included plasmapheresis and 2 patients required hemodialysis. 2 infants had infectious complications and one low birth weight. After 6 months of follow-up, the patients were without renal replacement therapy.

Discussion: The presence of renal activity does not constitute an absolute contraindication to maintain pregnancy, but the increased disease activity is related to worst maternal-fetal outcomes. A lot of information is missing about RPGN during pregnancy. May be biopsy is not imperative, but we considered in centers like ours in which we can have rapid biopsy results, as a guide that may have an impact in prognosis.

Rapid Loss of Kidney Function During Pregnancy

Case	1	2	3
Diagnosis	LN Class IV+V	LN Class IV+V	Collapsing Glomerulopathy
Maternal Age	27	30	27
Time of Diagnosis	30.6 weeks	28 weeks	12.5 weeks
Serum Creatine	5.7 mg/dl	1.2 mg/dl	3.0 mg/dl
Proteinuria	3 g/g	14.4 g/g	5.2 g/g
Active Sediment	Yes	Yes	Yes
Crescents	>50%	< 25%	No
Acute Tubular Necrosis	No	Yes	Yes
Renal Replacement Therapy	HD	No	HD
ANCA	Negative	Negative	NA
Treatment	MPD+CFM+RTX+PLEX	MPD+CF+PLEX	MPD+PLEX
Maternal/Fetal Outcomes	Neonatal CNS infection	Neonatal Pneumonia	Respiratory distress
Newborn Weight	2500 grams	920 grams	2590 grams
6 Months Follow up	eGFR 21 ml/min, UACR 0.6g/g	eGFR 65 ml/min, UACR 0.9g/g	eGFR 30 ml/min UACR 1.2 g/g

PUB613

Primary Amyloidosis with Rapidly Progressive Pattern: Case Report

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Introduction: Primary systemic amyloidosis (AL) is a plasma cells disorder characterized by fibrills deposition (8-15 nm) of monoclonal Ig light chains. The incidence is 0.9 cases per 100,000 persons.

Case Description: 68 years old female, resident of Mexico. History of DM2 and hypertension, both newly diagnosed. She began in July 2017 with asthenia, adynamia, headache, abdominal pain and nausea; she presented in the hospital with blood pressure of 180/100 mmHg, kidney function test: creatinine 5.9 mg/dL, urea 202 mg/dL (in November 2016, creatinine was 1.3 mg/dL). The patient was evaluated because rapidly progressive kidney failure pattern. She began with hemodialysis. On the work up, we found proteinuria of 0.26 gr/gr, erythrocyturia was not found. Renal ultrasound: normal kidneys; renal biopsy was performed: Glomerular-Interstitial and vascular Amyloidosis, Positive Lambda (immune amyloid). IgG: (3+) in the amyloid material, IgA, IgM and C3C: (1+) positive in the amyloid material, C1q, C4C and fibrinogen: negative, Kappa: negative, Lambda: (2+) positive in the amyloid material, red congo positive. (Figure 1) Clinical Diagnosis: Primary systemic amyloidosis.

Discussion: The mean age of presentation is 65 years. Less than 20% of patients show progressive renal failure (creatinine> 2 mg / dL). This patient had an unusual presentation of amyloidosis with a rapidly progressive loss of renal function. Cases of multiple myeloma (MM) with amyloidosis have been described. Both conditions are plasma cell proliferation and between them, there are minimum differences. A patient with clinical manifestations of AL, with no MM symptoms, would have AL diagnosis; however; if the patient has MM symptoms (anemia, bone pain, osteolytic lesions) the diagnosis would be MM with associated AL.

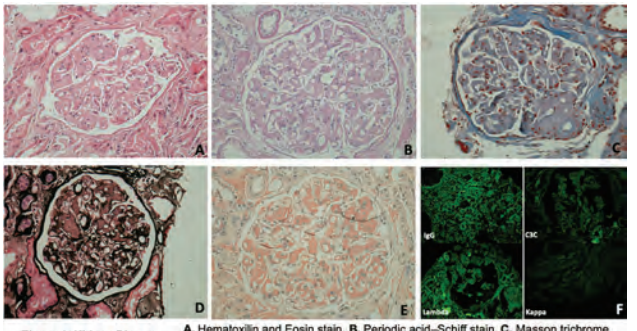


Figure 1. Kidney Biopsy

A. Hematoxilin and Eosin stain. **B.** Periodic acid–Schiff stain. **C.** Masson trichrome stain. **D.** Jones Methenamine Silver Stain **E.** Red Congo. **F.** Immunofluorescence

PUB614

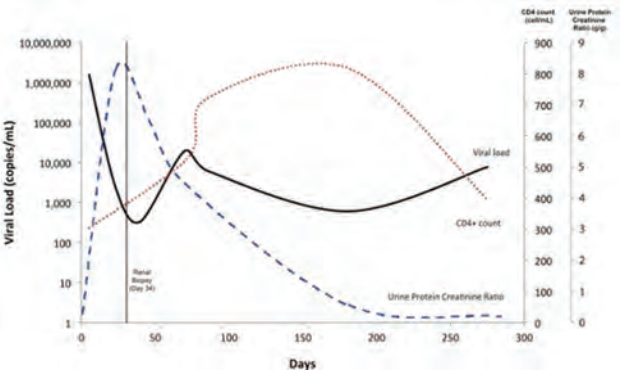
Transient Nephrotic Range Proteinuria After Acute HIV Infection

Andrew Vissing, Sara E. Jandeska. *Rush Children's Hospital, Chicago, IL.*

Introduction: Nephrotic syndrome is common among patients living with HIV. Although the majority of cases are diagnosed with HIV-associated nephropathy, a collapsing FSGS variant, immune-mediated etiologies and minimal change disease have also been described. There is an absence of literature describing acute HIV infection and its immediate renal sequelae. We describe a case of transient nephrotic range proteinuria without features of minimal change disease.

Case Description: A 17-year-old African-American male presented with pharyngitis, abdominal pain, fever, and lymphadenopathy. HIV antibody was undetectable but viral load measured 1.3 million copies/ml (CD4 count 304 cells/ml) suggestive of acute HIV infection. He was discharged with darunavir, emtricitabine-tenofovir, and ritonavir. Two weeks later, he presented with abdominal pain. Exam was notable for absence of edema. Chemistries showed acute kidney injury (BUN 25mg/dl, Cr 1.9mg/dl); a random protein/creatinine ratio was 9.2g/g. Serum albumin was 2.1 g/dl and cholesterol was 158 mg/dl. Work up of proteinuria was unremarkable. HIV viral load and CD4 count showed improvement on HAART. A renal biopsy showed normal glomeruli with acute tubular necrosis and absence of immune deposits. Electron microscopy showed global podocyte effacement. He was prescribed steroids. Over the next four months, he was repeatedly admitted for abdominal pain but never exhibited edema or hypercholesterolemia. He refused to take steroids and was noncompliant with HAART. Proteinuria gradually resolved, and remission was achieved five months after biopsy.

Discussion: We describe the acute onset of nephrotic range proteinuria due to diffuse podocyte injury without the examination or laboratory features of minimal change disease. Proteinuria developed with reconstitution of T cell immunity and decrease in HIV viral load and resolved without pharmacologic therapy. We propose that asymptomatic podocytopathy early in the course of infection could be a novel form of HIV-mediated renal disease.



PUB615

Case Report: Spontaneous Remission of Dialysis-Dependent Focal Segmental Glomerulosclerosis

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Introduction: It is uncommon for focal segmental glomerulosclerosis (FSGS) to enter spontaneous remission. As far as the authors are aware there are no reports of a patient recovering renal function from this disease after long term dialysis.

Case Description: A 61 year old Caucasian female presented with nephrotic syndrome and acute kidney injury. There was no relevant medical history (including intravenous drug use) or medications. She was hypertensive and 33 pounds above her baseline. Urinalysis demonstrated 100 red blood cells/hpf, a protein to creatinine ratio of 7.5 g/g, albumin 1.8 g/dL. Creatinine increased from 0.68 to 1.45mg/dL. Vasculitic, infective and myeloma screen was normal. Renal biopsy demonstrated tip variant FSGS affecting 3 of 13 biopsied glomeruli, acute tubular injury, and mild interstitial fibrosis and tubular atrophy (IFTA) (figure 1). She was brought into remission by prednisolone 50mg and cyclosporin 100mg twice daily. 8 months later she re-presented with oligoanuric renal failure. Repeat renal biopsy confirmed FSGS, acute tubular injury and mild IFTA. Immunosuppressant therapy failed therefore was tapered and she was established onto maintenance dialysis. Remarkably 11 months on she spontaneously remitted: peritoneal equilibration test revealed a residual creatinine clearance of 20mL/minute. After ceasing dialysis her creatinine nadired at 1.15mg/dL and protein to creatinine ratio of 0.8g/g. She remained in remission until 7 years later where (now 70 years old) she became nephrotic with a creatinine of 5.94mg/dL. Biopsy reconfirmed FSGS (NOS category) of one tip, one perihilar and one cellular variant, with acute tubular injury and mild IFTA. After treatment with plasma exchange her creatinine has improved to 2.29mg/dL.

Discussion: This case of spontaneous remission in prolonged dialysis dependent FSGS prompts physicians to monitor the progress of all their patients with FSGS – Even those on dialysis!

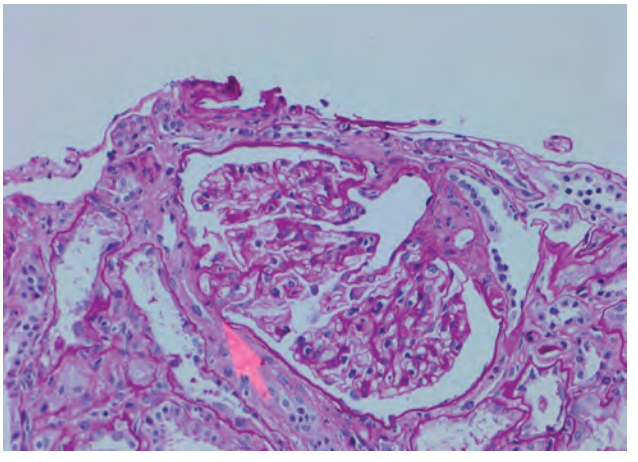

Figure 1: FSGS. Tip lesion (arrow)

PUB616

Cytomegalovirus Infection: A Possible Cause of Tip-Variant FSGS?

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Introduction: Collapsing focal segmental glomerulosclerosis (FSGS) is typically associated with HIV, but is also seen with other infections such as cytomegalovirus (CMV), parvovirus, and tuberculosis; autoimmune diseases; malignancies; and drug exposure.

Tip-variant FSGS has not been associated with infections. In our case a patient's initial biopsy read was collapsing FSGS and after not improving with steroids for 3 months, he improved quickly after initiation of anti-virals. However, overread of the biopsy by trained renal pathologist found tip-variant FSGS.

Case Description: A 69-year-old previously healthy man presented with sudden onset edema. Over 3 weeks his creatinine (Cr) increased from 0.8 to 3.8 mg/dL and he developed 19.8 g of proteinuria. Renal biopsy was read as collapsing variant FSGS with acute tubular injury, severe arterionephrosclerosis, and 20% interstitial fibrosis. Immunofluorescence was negative, and electron microscopy showed 100% foot process effacement. He was started on high dose prednisone and his Cr remained stable with no significant improvement in proteinuria. He presented 3 months later for a second opinion. HIV, parvovirus, quantiferon gold, SPEP, UPEP and complements were negative. CMV IgG and IgM were positive. CMV DNA PCR was 12,900 IU/mL. Valgancyclovir was added to the steroids, and within a week his creatinine started improving and then normalized. His proteinuria greatly improved. Valgancyclovir was stopped once CMV DNA PCR was negative, and steroids are being tapered. Overread of the biopsy by a trained renal pathologist fount tip variant FSGS. CMV immunostain was negative.

Discussion: Patients with the tip lesion are more likely to present abruptly with nephrotic syndrome and to respond to steroid therapy. It has been suggested the tip lesion may be an early form of FSGS not otherwise specified or a variant of minimal change disease based on biopsy studies. Our patient was on high dose steroids for 3 months with stabilization in creatinine but no improvement until anti-virals were initiated. An infectious cause was sought out due to the initial collapsing FSGS read. However, review of the slides revealed a tip variant FSGS, which has not been associated with infections. It is unclear whether the CMV was present at the time of biopsy, or was the result of several months of high dose steroids. However, the timing in improvement suggests it was contributing to the pathology.

PUB617

When Renal Artery Stenosis Should Get Intervention: A Case Report

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Introduction: The two largest randomized control trials comparing medical therapy alone vs. medical therapy plus angioplasty and stenting for atherosclerotic renal artery stenosis (RAS), the ASTRAL & CORAL studies, did not show a difference in cardiovascular or renal outcomes between the two therapies. Despite the negative results, a subset of patients do benefit from angioplasty and stenting of renal artery stenosis. Here we present a case of rapid renal recovery and improved blood pressure control following revascularization therapy. We discuss the clinical considerations for selecting patients with RAS to undergo performing these procedures.

Case Description: The patient is a 76-year-old female with past medical history of hypertension and chronic kidney disease (solitary right kidney). She was referred to our hypertension specialty clinic for resistant hypertension and subacute decline in GFR over 9 months. Her blood pressure was persistently elevated (160-210mmHg/70-96mmHg) despite 4 drug therapy. She was volume overloaded on exam, and had a single abdominal bruit over her right epigastric area. Her labs were notable for a rise in serum creatinine from 0.9mg/dL to 4.2mg/dL over the previous 9 months. A serum aldosterone level was 1ng/dL and a plasma renin activity was 3.29ng/ml/hr. Our work up included a renal artery doppler revealing a solitary right kidney measuring 10.6cm. Resistive indices were 0.67 and peak systolic velocities were 367 cm/sec. The peak systolic velocity of the aorta was 110 cm/sec, with a renal:aortic peak systolic velocity ratio of ~3.3. The patient underwent angioplasty and stenting of her right renal artery, with rapid serum creatinine improvement to 1.09mg/dL. In addition, her blood pressure was well controlled on only 2 blood pressure lowering agents.

Discussion: This case demonstrates a dramatic improvement in renal function and blood pressure control following angioplasty and stenting for atherosclerotic RAS. While the current literature does not support the routine use of revascularization therapy for atherosclerotic RAS over medical therapy, a subset of cases should be considered for angioplasty and stenting. Patients likely to benefit include those with an elevated serum creatinine and a low resistive index on renal duplex, bilateral stenosis or unilateral stenosis with a solitary kidney, and uncontrolled hypertension despite 3 or more blood pressure lowering drugs.

PUB618

Atypical Myeloma Presenting as Chronic Hypokalemic Renal Tubular Acidosis

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Introduction: Clinical presentation of multiple myeloma (MM) include renal dysfunction, hypercalcemia, anemia, proteinuria or bone disorder. Renal tubular acidosis (RTA) is an uncommon complication of established MM. Rarely, a variant MM with light chain proximal tubulopathy can manifest primarily with an electrolyte/acid-base disorder. We present a case in which the diagnosis of MM was preceded by years of hypokalemic RTA

Case Description: A 52-year-old female with no significant medical history was referred to the nephrology clinic for evaluation of her elevated serum creatinine and a 3–yr history of hypokalemia. Her review of system was normal and her only medications were multivitamins and potassium supplements. Physical exam and vital signs were within normal limits. Laboratory data were significant for serum creatinine of 2.4mg/dl, urea nitrogen of 20mg/dl, GFR of 27 mL/min/1.73 m^2, and potassium of 3.2mEq/L. Detailed review of her previous laboratory data revealed that she has had persistent hypokalemia for about 3 years and urinalysis with a pH of 5.0, 2+ proteinuria, and glycosuria. These were suggestive of a proximal type RTA. Current laboratory evaluation revealed a quantitative proteinuria of 6.5g/day. Infectious and immunologic workup including HIV, hepatitis panel, ANA, and complements were within normal limits. However, serum immuno-electrophoresis revealed a homogeneous spike in the gamma-globulin zone and a high free light chain which showed a kappa/lambda ratio of 178 [normal 0.26 - 1.65]. Renal biopsy showed: global and segmental sclerosis; distended proximal tubular cells with vacuoles and loss of brush border; tubular atrophy with interstitial fibrosis which were consistent with a light chain induced tubular injury. Bone marrow biopsy confirmed the diagnosis of MM. She was treated with combination chemotherapy and subsequently received an autologous bone marrow transplant. Hypokalemia resolved after the transplant

Discussion: Rare cases of Fanconi type RTA preceding the diagnosis of MM has been reported. It's often associated with toxic proximal tubulopathy as opposed to the classic cast nephropathy on renal biopsy. Accumulation of kappa light chains in the lysosomes of the proximal tubular cell is the postulated mechanism of the proximal tubular damage. This case emphasizes the need for an early referral to a nephrologist for evaluation of electrolyte/ acid-base imbalance.

PUB619

Tumor Lysis Syndrome in a Patient with Chronic Lymphocytic Leukemia

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Introduction: Tumor lysis syndrome (TLS) occurs as a result of tumor cell death and release of intracellular contents into circulation resulting in multi-organ dysfunction and death. It rarely occurs spontaneously in patients with chronic lymphocytic leukemia (CLL). We present a 75-year-old female with a history of CLL in remission that presents with confusion and diagnosed with spontaneous TLS.

Case Description: A 75 year old Caucasian female with a history of stage 1 right sided breast cancer and left sided DCIS s/p mastectomy and tamoxifen for 5 years, CLL Rai stage IV treated due to symptomatic splenomegaly with bendamustine and rituximab (BR) with excellent hematologic response. Nine years post treatment with BR, hematologic analysis revealed lymphocytosis, progressive anemia, thrombocytopenia and splenomegaly. Subsequently, she presented at an outside facility with acute encephalopathy following a viral prodrome. Laboratory results showed white blood cell count (WBC) of 300 bil/L. She was transferred to our facility for emergent leucopharesis. On presentation, she was confused and oliguric. She had a WBC of 270 bil/L with predominant lymphocytosis 248 bil/L, creatinine 4.65 mg/dl, potassium 6.0mmol/L, phosphorus 4.9mg/dl, calcium 7.8mg/dl, bicarbonate of 7mmol/L and uric acid 16.1mg/dl. Peripheral blood smear revealed smudge cells but no blasts. She was aggressively hydrated, given rasburicase and emergent dialysis. Following dialysis, her mental status and renal function significantly improved. Bone marrow biopsy analysis showed hypercellular marrow with extensive involvement of CLL, CLL genotype showed an unmutated immunoglobulin variable region heavy chain status (IgVH) and cerebrospinal fluid analysis showed a flow cytometry positive for monotypic B-cell population with a CLL phenotype. She follows with her oncologist and will be started on Ibrutnib.

Discussion: TLS is an oncologic emergency and requires immediate treatment with aggressive hydration to prevent renal failure, seizures and cardiac arrhythmias resulting from the toxic intracellular material released during cell lysis[1]. High burden, chemo-sensitive tumors with high proliferation rate are high risk for TLS[2]. Spontaneous TLS is rarely seen in patients with CLL due to its low proliferation and very limited data on TLS in CLL has been reported[3]. Further investigation into the clinic-pathologic mechanism for TLS in patients with CLL is pertinent.

PUB620

Diagnostic Role of Cystatin C in the Assessment of Kidney Function on PARP Inhibitors

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Introduction: Novel targeted therapies have expanded the arsenal of treatment options for various malignancies and led to significant improvement in prognosis. However, as new drugs rapidly enter the clinical arena, potential nephrotoxic effects are often poorly defined or understood but later increasingly recognized. Poly (ADP-ribose) polymerases (PARP) inhibitors are a class of medications that promote tumor cell death and have emerged as a treatment option for patients with solid-organ malignancies; namely, ovarian, breast, and pancreatic cancers. These medications interact with transporters along the renal tubules involved in the secretion of creatinine. An increase in serum creatinine has been reported in patients treated with these agents; in fact, in phase II open-label trials of rucaparib, an elevation in creatinine occurred in 92% of patients. However, it remains unclear whether these represent impact on creatinine secretion alone versus acute or enduring decrement to glomerular filtration rate.

Case Description: A 54-year-old man with stage 2 chronic kidney disease from prior cisplatin-toxicity and pancreaticobiliary adenocarcinoma was initiated on rucaparib, a PARP inhibitor. His past medical history was notable for type 2 diabetes on insulin. He did not use nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. His baseline serum creatinine stabilized at 1.4 mg/dl (eGFR 57 ml/min/1.73m^2 by the CKD-EPI equation). Following PARP inhibitor therapy, his serum creatinine rose to 2.0 mg/dl (eGFR of 35 ml/min/1.73m^2). Renal ultrasound showed normal kidney size without evidence of hydronephrosis or stones. Concurrent serum cystatin C was 1.4 mg/dl, corresponding to an eGFR of 51 ml/min/1.73m^2 by the CKD-EPI cystatin C equation.

Discussion: Accurate assessment of kidney function for patients on PARP inhibitors impacts multiple aspects of care. Elevations in serum creatinine can be prevent patients from receiving IV contrast for needed surveillance imaging, can prompt nephrology referral and additional diagnostic testing, and potentially lead to hospital admissions for acute kidney injury. While cystatin C has been slow to gain traction for clinical use, it may have an important role in understanding renal effects of novel drug therapies, especially in the evolving world of onco-nephrology.

PUB621

Who Stole My Electrolytes? A Case of Fanconi Syndrome with Ifosfamide Use

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Introduction: Ifosfamide is an anti-neoplastic alkylating agent used in to treat various malignancies. It has been linked to severe nephrotoxicity and can lead to Fanconi syndrome. This is a type II proximal renal tubular dysfunction characterized by hypophosphatemia, hypobicarbia, hypokalemia, glucosuria and amino aciduria. Nephrotoxicity with Ifosfamide is common but a complete Fanconi syndrome is rare, especially in adults.

Case Description: 64 year old gentleman with a history of myxoid spindle cell neoplasm was admitted for severe electrolyte abnormalities. He had received 5 cycles of Adriamycin, Ifosfamide and Mesna (AIM) along with 4400 cGy radiation and his cumulative Ifosfamide dose was 30g/m2. His last treatment was one week prior to presentation. He tolerated his cycles well with no grade 3-4 toxicities. On presentation, his creatinine was elevated at 1.84 from a baseline of 0.90, he had severe hypokalemia of 2.8, which did not correct with multiple runs of IV potassium. His bicarbonate level was 11, phosphate 1.2, magnesium 1.5 and his urinalysis was positive for glucose, ketones and protein. His fractional excretion of phosphate was elevated to 70%. Nephrology was consulted and he was diagnosed with Fanconi syndrome secondary to Ifosfamide toxicity. He was kept inpatient and received twice daily electrolyte supplementation and supportive treatment with IV hydration. After 10 days of supportive treatment he did not require further electrolyte supplementation.

Discussion: There is a 1.5-4% chance of developing Fanconi syndrome with Ifosfamide in children however, there have only been isolated case reports in adults. It is usually related to a high cumulative dose of 45-60 g/m2. The exact mechanism of renal injury is unclear but its related to the byproduct Chloracetaldehyde induced wasting of the ATPase in the Na/K cotransporter on the proximal tubule cells causing electrolyte wasting. The mainstay of treatment is symptomatic management with IV hydration and electrolyte supplementation. Early diagnosis and vigilant electrolyte monitoring is essential for a good outcome. Fanconi syndrome can occur days to weeks after treatment and should always be a differential in patients on AIM with electrolyte wasting. It is generally reversible and needs supportive care to ensure the electrolyte imbalance does not cause life threatening arrhythmias.

PUB622

A Unique Case of Clarkson Disease in a Multiple Myeloma Patient

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Introduction: The first fatal case of a rare systemic capillary leak syndrome (SCLS) was reported by Clarkson and since then, approximately 100 cases have been reported. It is a rare syndrome that mimics septic shock and is frequently associated with monoclonal gammopathy.

Case Description: A 50-year-old female with hypothyroidism and chronic kidney disease presented with presyncope, weakness and hypotension. She had a year history of on and off generalized body swelling unresponsive to diuretics and fluid restriction. She also had a prior admission for septic shock. Labs were significant for leukocytosis, polycythemia, hypercalcemia, low albumin, anion gap metabolic acidosis, elevated TSH and trace protein in the urine (200mg). Erythropoietin level, inflammatory markers and BNP were normal. Echo revealed preserved ejection fraction. A combination of hypotension, hemoconcentration and hypoalbuminemia was indicative of Capillary Leak Syndrome. Elevated paraproteins (kappa) were noted. A bone marrow biopsy revealed plasma cell myeloma and flow cytometry showed a clonal population of kappa-restricted plasma cell with CD56 expression. She was treated with pulse dose steroids and diuretics with improvement of her edema. She was subsequently discharged home on diuretics and to be started on chemotherapy outpatient.

Discussion: SCLS is a diagnosis of exclusion based on clinical findings. A rapid increase then drop in hematocrit and hypoalbuminemia are pathognomic. The capillary leak phase is characterized by severe intravascular fluid shifts presenting as generalized edema, compartment syndrome, ascites or effusions. Fatal circulatory shock may occur in this phase. This is followed by a fluid recruitment phase 1- 4 days later. Life-threatening pulmonary edema can develop here if fluid loss is over corrected. Several mechanisms such as vasoactive agents, endothelial receptors and signal transduction pathways have been suggested but the pathophysiology is poorly understood. No curative treatment is available but treatment with diuretics, steroids, theophylline, terbutaline, statins or immunoglobulins have been attempted with some success. Annual screening for lymphoproliferative disorders is also recommended. SCLS should be suspected in cases of shock with no clear source of infection. The immediate treatment should be focused on stabilizing the hemodynamic parameters because it can be potentially fatal otherwise.

PUB623

Renal Metastasis: Rare Initial Presentation of Ovarian Cancer

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Introduction: Paraneoplastic glomerulonephritides are clinical manifestation of renal disease that are induced by products of tumor cells. Here we report a rare case of ANCA-associated glomerulonephritis as the initial presentation of ovarian cancer.

Case Description: A 79 years old woman with hypertension, diabetes mellitus, chronic kidney disease, diastolic heart failure, presented with worsening bilateral lower extremity edema, abdominal distension, dyspnea, hematuria and vaginal bleeding. She had history of left total mastectomy for invasive ductal carcinoma in remission. Her 8-year history of postmenopausal vaginal bleeding was evaluated to be negative for malignancy. Patient was started on diuretics for dyspnea and antibiotics for pyuria. Her baseline creatinine (Cr) was 1.3-1.5 mg/dL. On further evaluation, she had proteinuria of 2 gm/d without monoclonal bands; hepatitis panel, TB, and HIV were negative; urinalysis showed protein 2+, RBC 182/hpf, WBC 31/hpf and a few bacteria; ANA titer 1:640, C3 117, C4 44.8, MPO-ANCA 17.8, PR3-ANCA<3.5. Due to elevated MPO-ANCA levels and Cr 4.7 mg/dL with proteinuria, a kidney biopsy was obtained which surprisingly showed poorly differentiated high grade adenocarcinoma involving almost the entire sample, favoring high grade serous carcinoma of ovarian primary with positive staining for WT-1, P16, PAX-8, ER and P53. The light microscopy sample had one glomerulus that showed nodular diabetic glomerulosclerosis. Follow up pelvic ultrasound did not reveal any malignancy. CT abdomen showed calcification along right adnexa and prominent sized right ovary. CA-125 was found to be 31,684 U/mL. The presence of elevated anti-MPO antibody made us suspicious of ANCA-associated glomerulonephritis which was considered a paraneoplastic manifestation. She was started on mycofenolate and steroids. Due to her worsening uremia and oliguria she was started on dialysis. Her clinical condition continued to worsen and with poor performance status she was deemed unsafe to initiate chemotherapy for ovarian cancer. Patient was discharged to skilled nursing facility.

Discussion: To the best of our knowledge this is the first case reporting renal metastasis from ovarian malignancy. This highlights the importance of renal biopsy in patients with worsening renal function since this was the only way we were able to reach the diagnosis of ovarian malignancy in our patient.

PUB624

Multiple Myeloma in Association with Light Chain Deposition Disease in a 39-Year-Old: A Case Report

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Introduction: Multiple myeloma is a cancer of the elderly and most often the suspicion is raised in the older population. Only 2 percent of all cases of multiple myeloma present in patients younger than 40. Here we present a case of light chain deposition disease(LCDD) with features of cast nephropathy which is diagnostic of myeloma kidney in a 39-year-old male. Thus, recognition and knowledge of varied presentations can help in early diagnosis and treatment of the disease.

Case Description: A 39-year-old male with a history of hypertension presents with body aches for the past 2 weeks. He was mildly hypertensive at presentation (BP–152/90 mmHg). Data showed decreased HCT (20.7%); high BUN (78 mg/dl); increased serum creatinine (9.5 mg/dl), a mild increase in serum calcium (10.6 mg/dl). Protein/creatinine ratio was 4.19; normal serum albumin (4mg/dl). Urine dipstick was one plus for protein. Ultrasound was unremarkable. SPEP showed M protein of 0.4 g/dl. UPEP showed free k light chains in the gamma region. K/L ratio was 1670. Serologies for hepatitis B, hepatitis C, ANCA, anti-GBM, rheumatoid factor were negative. C3, C4 was normal. kidney biopsy was done. Among the ten glomeruli sampled, one showed global sclerosis with others showing no specific pathological alterations. Tubules were filled with dense lamellated casts, some of which were surrounded by multinucleated giant cells. Interstitium showed 30% fibrosis and tubular atrophy. Congo red stain was negative. Immunohistochemistry showed kappa chain positivity in tubular casts, basement membrane of tubules. Immunofluorescence for IgG, IgM, IgA, C3, and C1q was negative. Electron microscopy revealed finely granular deposits on tubular basement membrane with thickening. So based on clinical features, histopathology, electron microscopy and immunofluorescence a final diagnosis of light chain deposition disease with cast nephropathy was made.

Discussion: LCDD typically occurs in association with Multiple Myeloma (MM) or other lymphoplasmacytic disorders. The incidence of LCDD in patients with plasma cell dyscrasia is approximately 5%. Many patients with LCDD are associated with MM, but up to 50% of patients do not have concurrent MM. Though the incidence of these diseases is extremely uncommon in the younger population it still has to be considered for early diagnosis and effective treatment.

PUB625

Gemcitabine Drug-Induced Thrombotic Microangiopathy: A Clinical Diagnosis

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Introduction: Thrombotic Microangiopathy (TMA) is a pathologic abnormalities in the arterioles and capillaries leading to microvascular thrombosis and diagnosis is made by tissue biopsy. 2 mechanisms are involved in D-TMA, immune-medicated, and dose or

duration related. Immune medicated D-TMA is related to recent onset within 21 days of a daily administered drug or within hours of intermittently administered drug.

Case Description: 34 year old female patient, Diagnosed with adrenocortical cancer in 2015, underwent multiple surgeries for tumor debulking, including right nephrectomy. Patient received multiple lines of chemotherapy including Platinum based chemo, and Gemcitabine for the last 2 years. In December 2018, she developed TMA picture after 3 days of receiving her chemotherapy (MAHA, Thrombocytopenia, AKI). Immune work up, Hepatitis B and C virus were negative. Complement levels showed normal C4 level and Low C3 of 0.81 (Normal value 0.9-1.80). Urinalysis : Positive for RBCs (1430 cell/micoL), no comment on Cast. Protein /Creatinine Ratio was : 10.5 g/g. Serum Albumin : 24 g. WBC: 1.9X10^9, HB: 90 g/L, Platelets : 13 X10^9. ADAMT13 activity was normal 114 %, (Normal Ref range 48-115), ADAMTS13 inhibitor : 1.9 U/ml (Normal value 1.8-7.1) Normal coagulation profile but high LDH. Peripheral blood smear showed (6%-10%) schistocytes. Patient's clinical picture was of Thrombotic microangiopathy (MAHA, Schistocytes, Thrombocytopenia, AKI) but kideny biopsy was not performed. Patient had daily plasma exchange sessions, 6 doses of eculizumab and 2 doses of Rituximab during her hospital stay. The plan of care included eculizumab 1200 mg every two weeks. Her recent blood tests showed normal bilirubin, normal platelets : 300X10^9 and LDH :385 IU/L. The patient remained on haemodialysis for three sessions per week.

Discussion: Gemcitabine induced TMA was first described in 1994 in phase II clinical trial in pancreatic adenocarcinoma patients. The estimated incidence is 0.015% to 1.4%. Mortality is up to 15%. It is associated with cumulative dose more than 20 000, or when doses are more than eighteen doses or duration more than 7 months but can occur within 5 days after the first dose. In view of normal ADAMTS 13 activity, features of TMA can be attributed to Gemcitabine in our patient. A clinical diagnosis can be made and a therapeutic trial can give the patient the benefit of doubt.

PUB626

Differential Diagnosis on Kidney Impairment Related to Multiple Myeloma: A Case Report

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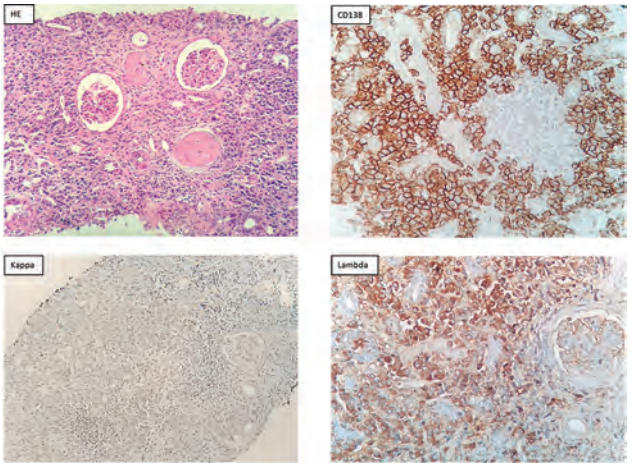
Introduction: Kidney disease is one of the most common complications in Multiple Myeloma (MM), affecting approximately 50% on diagnosis. Renal impairment if often described due to Hypercalcemia, Cast Nephropathy and Amyloidosis. We present an unusual form of kidney injury associated with MM.

Case Description: Woman, 71 yo, previously hypertensive, complained of weight loss over the last year. During initial evaluation, presented the following laboratorial findings: Hemoglobin 5.1 g/dL; Reticulocytes 1.2%; SCr 2.78 mg/dL; BUN 16 mg/dL; Calcium 8.5 mg/dL; no hematuria and no leukocyturia at urinalysis; UPCR 3.76 g/g; SPEP with Gammaglobulin Monoclonal peak of 6.4 g/dL and Albumin 2.5 g/dL; Serum and Urine Immunofixation exhibit IgG/Lambda paraproteins; Bone marrow aspirate with 39.2% of clonal plasma cell, confirming MM diagnosis. Kidney biopsy showed an atypical monoclonal plasma cell infiltrate on renal parenchyma, confirmed by CD138 and Lambda positive immunostaining, with negative Kappa, associated with Cast Nephropaty. Immunofluorescence suggested Monoclonal Immunoglobulin Deposition Disease; Congo Red was negative. After 4 months of follow up and treatment with Cyclophosphamide and Dexamethasone, presents SCr 1.38 mg/dL; BUN 12 mg/dL; SPEP without monoclonal peak and UPCR 0.79 g/g.

Discussion: Cast Nephropathy is the single most common finding among patients with MM and clinical kidney involvement, leading to AKI. We report a patient with an unusual kidney involvement, with atypical monoclonal plasma cell infiltration of the renal parenchyma, which is often reported on advanced disease. Kidney biopsy is mandatory for diagnose and establishes the degree of activity and chronicity, in order to determine the treatment intensity and prognosis. On behalf of that, we decided to keep the chemotherapy in our patient.



PUB627

An Unusual Case of Acquired Fanconi Syndrome with Acute Myelogenous Leukemia

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Introduction: Acquired Fanconi syndrome is frequently associated with certain drugs and toxins, multiple myeloma and some autoimmune diseases. However, we present a case with a patient undergoing treatment for acute myelogenous leukemia (AML) who presented with Fanconi syndrome and imaging consistent with infiltrative disease in the kidneys.

Case Description: A 19-year-old woman with AML who was admitted for salvage chemotherapy. She was previously treated with cytarabine and daunorubicin, cladribine and mitotane and then decitabine. The salvage regimen consisted of vinorelbine, topotecan, thiotepa and clofarabine. Urine output ranged from 4-13 liters per day. Chemistry studies were notable for hypernatremia with serum sodium of 153 mmol/L, hypokalemia with potassium of 2.7 mmol/L, non-gap metabolic acidosis with serum bicarbonate of 10 mmol/L, hypomagnesemia with serum magnesium of 1.5 mg/dL, hypophosphatemia with serum phosphate of 1.2 mg/dL, hypouricemia with serum uric acid of 1.8 mg/dL, serum glucose of 106 mg/dL and a serum creatinine of 0.6 mg/dL. Urine studies showed glycosuria despite normoglycemia, elevated beta-2-microglobulin, elevated trans-tubular potassium gradient and elevated urine anion gap. Follow up studies showed atypical cells in urine cytology. Contrast enhanced CT-Imaging of the abdomen showed voluminous kidneys with decreased enhancement bilaterally. The patient's electrolytes and polyuria were treated with aggressive repletion and administration of desmopressin. She underwent bone marrow transplant, but contracted multiple opportunistic infections including mucormycosis sinusitis, fungemia and bacteremia. These progressed to septic shock ultimately leading to her death five weeks after the initial evaluation.

Discussion: Fanconi syndrome is classically associated with cisplatin, ifosfamide and plasma cell dyscrasias in hematologic malignancy, but not any of the agents used to treat this patient. Here, however, we present a case with findings consistent with Fanconi syndrome most likely secondary to infiltrative AML in the kidneys, as evidenced by nephromegaly and atypical cells on urine cytology. Similar cases have been reported in the pediatric literature associated with acute lymphocytic leukemia which resolved with treatment of the underlying disease.

PUB628

Nephrotic Syndrome: A Clue to Diagnosing Chronic Graft vs. Host Disease

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Introduction: Nephrotic range proteinuria (NRP) is a result of primary glomerulopathy, or renal manifestation of systemic diseases such as Diabetes Mellitus, Amyloidosis and Lupus Nephritis, to name a few. Complication of hematopoietic cell transplantation (HCT) such as Graft versus Host Disease (GvHD) is a less common yet well-established cause of NRP.

Case Description: We present a case of a 63-year-old male with a diagnosis of Myelodysplastic Syndrome. He was initially treated with chemotherapeutic agent azacitidine without response and eventually underwent an allogenic stem cell transplant with minimal residual disease. Maintenance immunosuppression was tacrolimus and low dose prednisone with gradually decreasing doses. His medical condition remained stable for about two years until he presented to the hospital with new onset anasarca. He had no other symptoms and serum creatinine level was within normal limits at that time. Hematological work up at the time was unrevealing. Evaluation of urinary protein excretion revealed greater than 13 grams of protein in 24 hours with a spot urine protein to creatine ratio that was greater than 8 grams. He was diagnosed with new onset Nephrotic Syndrome and was given intravenous Lasix with good response. A renal biopsy was performed to evaluate the cause of NRP. The renal pathology was reported as Membranous Nephropathy (MN) with features suggestive of a secondary cause. MN was thought to be the renal manifestation of GvHD. The patient was restarted on Tacrolimus 1mg twice daily and Prednisone dose was increased to 60mg daily. A bone marrow biopsy was not performed. The GvHD was presumed to be renal limited; the patient was continued on tacrolimus 1 mg twice daily with tapering doses of steroids with significant improvement of proteinuria.

Discussion: This case highlights an important aspect of recognizing NRP as a manifestation of Renal limited GvHD in order to prevent hematopoietic cell transplant complications. Occasionally NRP may be the only manifestation of GvHD which is a rather systemic process. Adjustment and or increase in the immunosuppressive regimen is necessary to manage such cases and thus can save the transplanted tissue from failure. More studies are needed to further understand this entity.

PUB629

Long-Term Management of Idiopathic Retroperitoneal Fibrosis Eventually Leading to Gout Medication

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Introduction: Retroperitoneal fibrosis (RF) is a condition characterized by the presence of inflammatory and fibrous retroperitoneal tissue that often encases the ureters or abdominal organs. We present a case of retroperitoneal fibrosis that was treated with various immunosuppressive therapies over seven years with variable response to therapy.

Case Description: A 43-year-old male presented with abdominal pain; CT scan findings revealing circumferential soft tissue thickening around the abdominal aorta consistent with findings of RF. Prednisone was initiated, with improvement after 1 month followed by a steroid taper with recurrence of symptoms within 11-months. He was concerned for steroid side effects and opted for Cellcept. After 6 months he decided to be off medications and within a year, initial symptoms returned and restarted on high dose steroids. After tapering he was transitioned to Tamoxifen which later was switched to methotrexate and subsequently Imuran; all were discontinued due to GI intolerance. He opted for colchicine and 3 months into regimen he continued with no symptoms and stability of RF in repeat imaging.

Discussion: Management of RF is aimed to halt the progression of the fibrotic process and prevent a recurrence. In idiopathic cases, steroids as induction therapy should be initiated as soon as the diagnosis is made. In those who do not respond to steroid therapy or cannot tolerate the side effects, studies using Cellcept, Tamoxifen, Imuran, and Methotrexate have all been used with various degrees of success. For colchicine therapy, a case series involving seven patients were treated with colchicine plus prednisone, and after reaching a clinical response, the steroid dose was tapered, maintaining daily colchicine therapy with no recurrence or treatment failure observed during follow-up.

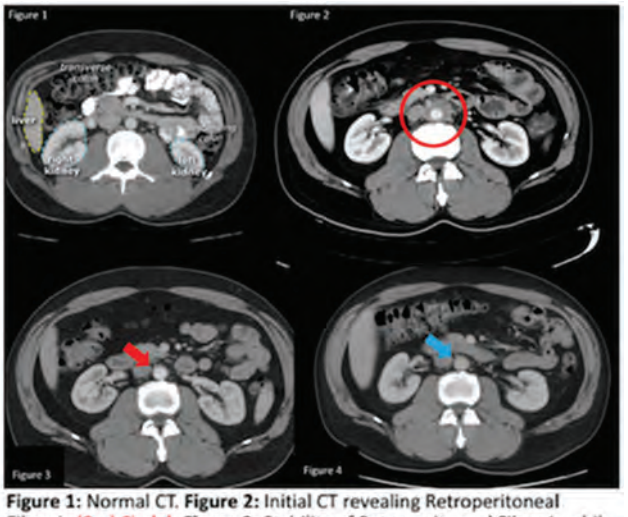

Figure 1: Normal CT. **Figure 2:** Initial CT revealing Retroperitoneal Fibrosis (Red Circle). **Figure 3:** Stability of Retroperitoneal Fibrosis while on Imuran therapy (Red Arrow). **Figure 4** Stability of Retroperitoneal Fibrosis while on Colchicine therapy for 3 months (Blue Arrow).

PUB630

Ifosfamide-Induced Fanconi Syndrome: A Rare Complication in Adults

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Introduction: Fanconi syndrome is a metabolic disorder characterized by severe proximal renal tubule dysfunction. It leads to impaired reabsorption of amino acids, glucose, phosphorus, potassium, urate and bicarbonate. Ifosfamide is used in the treatment of a variety of childhood and adult malignancies. Pathophysiology of its toxicity is unclear, but thought to be due to accumulation of the toxic metabolite chloroacetaldehyde in proximal tubular cells. Only a few cases have been reported in adults. We describe a case of an adult with diffuse large B cell Lymphoma who developed Fanconi Syndrome following Ifosfamide use.

Case Description: A 70-year-old Caucasian female with history of diffuse large B cell lymphoma presented to the ER with complaints of increased fatigue and confusion, which started a day after chemotherapy session with Ifosfamide. Physical exam revealed a confused female with trace pedal edema but otherwise normal exam. BP: 175/93, HR: 84/min, RR: 20/min, Temp: 36.6 C. Imaging studies were normal. Labs revealed Sodium 143, Potassium 2.5, HCO3 16, chloride 119, phosphorus 1.5mg/dl magnesium 1.3 mg/dL, creatinine 1.4, serum glucose109. She had a hyperchloremic metabolic acidosis and acute kidney injury with glycosuria with normal serum glucose. Fanconi's syndrome was suspected and 24 hour urine amino acid screen came back positive for Aspartic Acid, Threonine, Serine, Glutamic Acid, Glutamine, Glycine, Alanine, Cirulline, Valine, Cystine, Methionine and Isoleucine, amongst others A diagnosis of Ifosfamide induced Fanconi syndrome was made and aggressive electrolyte/bicarbonate and fluid repletion was started, Ifosfamide was discontinued and she improved remarkably after two weeks

Discussion: The mechanism of Ifosfamide induced renal injury is not completely understood. It is postulated that chloroacetaldehyde (CAA), a toxic metabolite is thought to deplete intracellular glutathione in the renal tubule, predisposing to cellular damage. Our patient had glycosuria in the presence of normal blood glucose, aminoaciduria, hypokalemia, hypophosphatemia and hyperchloremic acidosis which is consistent with Fanconi syndrome. Early detection and treatment is key to preventing further deterioration in renal function and mental status. Although uncommon, Fanconi syndrome can be fatal and should be considered in any patient with any degree of renal impairment on Ifosfamide.

PUB631

Oliguric AKI Following Laparoscopic Ablation of Liver Metastases

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Introduction: Microwave ablation is a form of thermal ablation used for the treatment of solid liver lesions. With this therapy, the reported incidence of acute kidney injury (AKI) has been as high as 20% with tumor size > 5cm but AKI requiring dialysis is a relatively rare complication. AKI as a result of microwave ablation has gained increasing attention among surgeons in recent years but remains a relatively unknown phenomenon among nephrologists. We present a case of oliguric AKI requiring dialysis following microwave ablation of liver lesions.

Case Description: A 42-year-old male was admitted following laparoscopic microwave ablation of metastatic liver lesions from colon cancer. Ablation was performed on four liver lesions, with the largest measuring 1.5 cm. There was minimal blood loss and patient was hemodynamically stable during the intra-operative and post-operative period. He developed AKI on post-op day 1 with a rise in creatinine (Cr) to 2.51 mg/dL (1 mg/dL prior to ablation) accompanied by oliguria. A careful review of history (medications, IV contrast, etc) and search for potential causes (ANA, ANCA, anti-GBM antibody, complements, CPK) were unrevealing. Renal ultrasound with dopplers was unremarkable. Urinalysis was positive for 2+ protein, 3+ blood, 1+ glucose. Urine microscopy showed no granular casts or cells. Patient was given intravenous fluids for possible volume depletion but renal function continued to worsen. By day 3, his Cr was 8.1mg/dL and hemodialysis was initiated for oligoanuria and volume overload. Further testing revealed haptoglobin < 10 mg/dL and elevated LDH of 492 units/L. Hemoglobin dropped from 13.9 to 11.3 within the first 3 days post-op. Due to lack of recovery, a kidney biopsy was performed and pathology showed acute tubular injury with evidence of hemoglobin casts in the tubules.

Discussion: This case report highlights the importance of recognizing AKI related to hemolysis as a potential complication following microwave ablation. The liver is a highly vascular organ and carries an inherent risk of hemolysis resulting from exposure to adjacent thermal energy during ablation. Temperatures can reach as high as 100°C. Preventative measures including pre-op hydration, intra-op limits on the duration and applied energy, and close postop monitoring may help in prevention and early identification of AKI related to hemolysis secondary to microwave ablation.

PUB632

Plasma Exchange Therapy as Treatment for Myeloma Kidney

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Introduction: Multiple myeloma (MM) is characterized by a clonal proliferation of malignant plasma cell producing monoclonal proteins, which can lead to organ damage. Renal involvement is present 20-40% of MM. Severe acute kidney injury (AKI) related to intratubular cast formation is a common manifestation. Early reduction of serum free light chain (FLC) is associated with recovery of AKI. Survival of MM is related to kidney function. Plasma exchange therapy has been studied for myeloma kidney, although data is limited and current evidence is non-conclusive. We herein report a case of myeloma kidney with renal recovery after plasma exchange therapy.

Case Description: 84-year old female with history of multiple myeloma treated with 1 cycle of bortezomib and dexamethasone presented to the hospital with AKI. Labs upon presentation were showing a creatinine of 4.8 from baseline creatinine of 1.2. Serum kappa FLC of 7287 with a kappa/lambda ratio of 3259. Vital signs and physical examination were unremarkable. Patient received standard chemotherapy and fluid resuscitation. Given significant kidney dysfunction and severely elevated kappa FLC plasmapheresis was recommended. Patient received 3 sessions of plasma exchange. Before and after kappa FLC were measured. A significant decrease in creatinine and kappa FLC was observed by post-procedure day 4, with creatinine of 2.9 and kappa FLC of 2999. Patient was discharged and followed up at clinic.

Discussion: Our case demonstrates that plasma exchange therapy might provide a benefit to patients with severely elevated kappa FLC and significant kidney dysfunction. More clinical trials are needed to further establish the role of plasma exchange in Myeloma Kidney.

PUB633

Retroperitoneal Hematoma Manifesting as Pancreatic Adenocarcinoma in a Renal Allograft

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Introduction: A retroperitoneal mass could represent a hematoma, cyst or tumor. We present an unusual case of pancreatic adenocarcinoma presenting as retroperitoneal cystic mass in a renal transplant recipient.

Case Description: A 47-year-old African-American female with history of End Stage Renal Disease (ESRD) secondary to IgA nephropathy. She received her first renal transplant in 1999 which lasted till 2004. She received her second transplant in 2005. Her post-transplant course was uneventful for about 12 years until she presented with a left

abdominal palpable mass with pain for 2 weeks. CT scan of the abdomen/ pelvis revealed a large well-defined complex septated cystic mass 12 x13 x16 cm extending into the left lower quadrant without involving the surrounding structures. Upon resection, the mass yielded approximately 1.5 liters of old clotted blood. Sections of the tumor demonstrated cystic and solid areas with complex epithelial architecture including papillary and cribriform patterns and ovarian or ovarian-like stroma suggesting the possibility of an ovarian or gastrointestinal malignancy. PET CT showed increased uptake and thickening at the left psoas muscle at the posterior margin of the atrophied left native kidney. Final pathology of the rim was consistent with adenocarcinoma of unknown primary. The tissue stained positive for CK 7 and CK 20 making colonic primary less likely. CEA and CA-125 were normal. CA 19-9 was elevated, and the immunohistochemistry and gene expression profiling revealed pancreatic adenocarcinoma as the primary tumor. Despite aggressive chemotherapy, subsequent PET scans revealed disease activity in lungs, mediastinal lymph nodes and abdominal mesentery for which she is currently receiving palliative chemotherapy.

Discussion: The presentation of an isolated retroperitoneal hematoma initially thought to be a fluid collection in this case, was infact a malignant presentation. One possible hypothesis is that long-standing immunosuppression could have contributed to the malignant transformation. Given the difficulty in identifying the primary site and the unusual site of metastatic presentation, this case was a diagnostic challenge.

PUB634

Checkpoint Check-Up: Pembrolizumab and Interstitial Nephritis

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Introduction: Over the last few years, the FDA has approved pembrolizumab - one of the checkpoint inhibitors - for the treatment of several cancers. As the field of therapeutic immuno-oncology rapidly expands, enigmatic complications in conjunction with these agents are arising.

Case Description: We present a 52-year-old male with history of metastatic melanoma treated with pembrolizumab and no prior kidney disease who had recurrent relapses of acute kidney injury [AKI] due to acute tubulointerstitial nephritis [AIN]. He first presented with AKI six weeks after starting therapy. On admission his creatinine [Cr] was >9 and was thought to be due to excessive concurrent NSAID use. A two-month steroid taper was started and pembrolizumab was held until renal function normalized. Subsequently pembrolizumab was reinstated. He underwent a total 13/17 cycles without difficulty and stayed off NSAIDs. Unfortunately, seven months after restarting therapy he was readmitted with AKI and peak Cr > 9. This was about three weeks from his last pembrolizumab dose. A renal biopsy revealed AIN secondary to pembrolizumab. Patient was discharged on a 20-day taper of prednisone and pembrolizumab was discontinued in consultation with his oncologist. Two weeks later while still on the prednisone taper, the patient was admitted to the ICU for shock and AKI. His AKI was thought to be related to septic shock rather than worsening AIN, and at discharge he was continued on his previous prednisone taper. Unfortunately, he returned within one week with another AKI. It was concluded that his steroids were tapered too rapidly, and he was placed on high dose prednisone and renal function stabilized with plan for a prolonged taper over months. Remarkably, the patient never required dialysis and was not oliguric at any time.

Discussion: This case demonstrates the difficulty of establishing a treatment regimen for relapsing AIN with checkpoint inhibitor use. Case series point out a variable incidence of AIN from 0.2 to 5.1% associated with checkpoint inhibitor use. Per reports there were cases with AIN seen even weeks to months after conclusion of checkpoint inhibitor therapy. However, no consensus/guidance about duration of treatment is available to the best of our knowledge. This case highlights the need for prolonged treatment with steroids in case of relapsing AIN with checkpoint inhibitor use.

PUB635

Immune Checkpoint Inhibitor-Induced AKI

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Introduction: Drug-induced acute interstitial nephritis (DI-AIN) is a common cause of AKI, affecting about 20% of patients with unexplained AKI, and leads to CKD and ESRD. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two essential immune checkpoint receptors that play an essential role in negatively regulating T cell activation. Immune checkpoint inhibitors (ICI) are widely being used in the treatment of several malignancies.

Case Description: A 70-year-old female with a past medical history of lung adenocarcinoma presented to the hospital with nausea, poor appetite, and lower extremity edema. The patient received a total of four cycles of Pembrolizumab which was started three months prior to presentation for stage IV lung adenocarcinoma. She has been using ibuprofen for years. On admission, she was found to have stable vital signs. Physical exam revealed mild leg edema without any lung rales or asterixis. Labs revealed SCr 10 mg/dl (baseline 0.7), BUN 55 mg/dl NA 134 mmol/L K 4.3 mmol/L and CO2 22 mmol/L. Urinalysis showed >100 WBC/HPF, >100 RBC/HPF, +++ protein with no casts. UPCR 6.64 g/g. ANCA ab, Anti GBM ab, and SPEP were negative. A renal biopsy revealed moderate inflammation of the interstitium with lymphocytic tubulitis and diffuse tubular injury. Trichrome staining was consistent with moderate interstitial fibrosis and edema. Pembrolizumab was promptly discontinued on admission. The patient was initiated on IV pulse dose steroids with significant improvement in renal function. SCr improved to 1.9 mg/dl after 3 weeks of steroids. She never required dialysis.

Discussion: AKI incidence rate is estimated to be of 2.1% in patients who received PD-1 inhibitor therapy. Acute interstitial nephritis induced by ICPIs is related to severe inflammatory cell infiltrates with or without granuloma. ICIs may reactivate exhausted drug-specific T cells previously primed by nephritogenic drugs, and consequently, due to loss of tolerance, memory T cells are activated against the drug. It is noteworthy that 14 out of the 19 patients reported by Cortazar et al.and Shirali et al.were on culprit drugs associated with ATIN (PPI and NSAIDs). Our patient has a history of NSAID use in the past but never developed AKI until she received Pembrolizumab. It is important to recognize early ICI-induced ATIN since a delay of steroid use may lead to irreversible renal fibrosis.

PUB636

The Use of Early Continuous Venovenous Haemofiltration and Glucarpidase Therapy in the Management of Methotrexate Toxicity

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Introduction: Methotrexate (MTX) is a widely utilised anti-metabolite, however its use in extremely high doses (greater than 500mg/m2) is commonly the preserve of the oncologist. At toxic levels, its side effects include severe myelosuppression and acute kidney injury. MTX toxicity i.e; levels >1umol/L at 48 hours, are commonly observed, normally in the setting of impaired renal function. This case demonstrates the utility of combination therapy of early CVVH, leucovorin and glucarpidase therapy in the successful treatment of a patient with MTX toxicity.

Case Description: The 79 year old patient was diagnosed with stage 4 Non-Hodgkins Lymphoma and was commenced on R-CHOP therapy. He was admitted for iv MTX as an adjunct to his chemotherapy. At this time, his renal function was normal. He proceeded to treatment with iv isotonic bicarbonate and high-dose leucovorin. During his inpatient stay, he sustained a pre renal kidney injury. He required transfer to ICU for non invasive ventilatory support due to respiratory sepsis. At 48 hours post infusion his MTX levels were 19.61 umol/L. CVVH was started at a dose of 30 ml/kg/hr, within 52 hours of administration of MTX. The patient did not become oliguric and his peak creatinine was 1.89mg/dL. His MTX levels continued to fall over subsequent days. At hour 58 post infusion, the patient was administered glucarpidase, a recombinant bacterial enzyme which cleaves MTX into two non-cytotoxic metabolites. Of note is that immunoassay does not differentiate between the levels of active MTX and inactive metabolites. Due to this, CVVH was continued until MTX levels were below 1 umol/L. The patient was transferred from ICU after 9 days and was discharged following 29 days of admission with restored renal function.

Discussion: Previous cases reports have demonstrated the usage of CVVH in MTX toxicity when absolute indications arise for renal replacement therapy. However, here, CVVH was commenced with the express intent of reducing absolute serum MTX levels. The patient did not develop any haemorrhagic or infective complications of myelosuppression and continued to improve until his successful discharge after 29 days. This case demonstrates that combination therapy of early CVVH with glucarpidase therapy in conjunction with high dose leucovorin can be associated with promising outcomes in terms of therapy of MTX toxicity.

PUB637

Salt-Losing Nephropathy Associated with Use of Foscarnet in a Patient with Lymphoma

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Introduction: Salt losing nephropathy is an uncommon cause of hyponatremia. We report a case associated with the use of foscarnet.

Case Description: A 60 year old female with history significant for DLBCL status post Yescarta CD19 CAR-T cell therapy with Flu/Cy lymphodepleting regimen who presented with neurotoxicity related to her therapy. Work up revealed a HHV-6 encephalitis found in both plasma and cerebrospinal fluid. Patient was started on foscarnet for treatment of her HHV-6 encephalitis, however patient developed both hyponatremia and natriuresis. Subsequent investigation demonstrated hyponatremia due to salt-wasting nephropathy likely induced by foscarnet. Patient was started on salt replacement with both oral and IV sodium chloride to maintain her serum sodium above 130 meq/L. Urinary sodium losses were as high as 15 g/day. Unfortunately, foscarnet was unable to be discontinued as patient had persistent HHV-6 titer on LP three months into treatment and ganciclovir was added. Patient then cleared her HHV-6 a month later, and both medications were stopped. IVF were soon able to be stopped, but she continued to require sodium chloride replacement at time of discharge to maintain a normal serum sodium.

Discussion: Foscarnet is a pyrophosphate analog with antiviral properties which is used in the treatment of herpes encephalitis, varicella, and CMV. It can cause various electrolyte abnormalities including hypokalemia, hypomagnesia, hypocalcemia, and hypophosphatemia. We present a rare case of foscarnet causing hyponatremia due to salt wasting. The specific mechanism involved in the salt loss is unclear.

PUB638

Pseudolinear C4d Deposits in a Hereditary Glomerulopathy Caused by a Novel NC1 Collagen-4-Alpha-5 Missense Mutation: A "New Disease Entity?"

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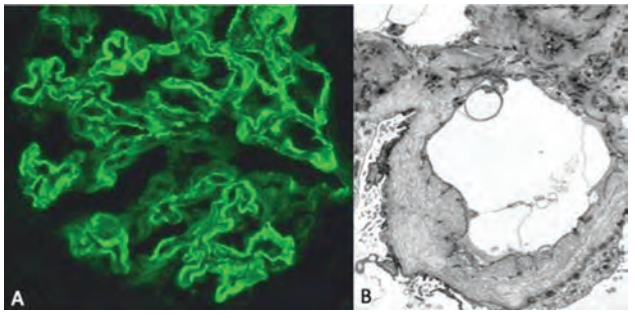
Introduction: Glomerular C4d deposits in kidney biopsies are incompletely characterized and usually not used for diagnostic decision making. It was not until recently that isolated pseudolinear glomerular C4d deposits were identified as markers of structural glomerular capillary wall remodeling. Here we report a case that furthers our understanding of "pseudolinear-C4d-glomerulopathies": C4d beyond antibody and immune-complex mediated injury.

Case Description: We report a hypertensive, otherwise healthy 60 year-old male with a 5 month history of isolated nephrotic range proteinuria, no hematuria; normal serum creatinine, complement and ANA levels. Work-up showed MGUS (IgG/kappa restricted). A diagnostic renal biopsy to search for 'MGUS of renal significance' demonstrated thickened glomerular capillary walls with strong pseudolinear complement factor C4d deposits by immunofluorescence microscopy (IF; Fig. A); all other IF studies including stains for COL4A3 were unrevealing with only minor equivocal abnormalities seen for COL4A5. The unusual C4d staining of undetermined significance triggered electron microscopic studies uncovering a hereditary nephropathy with marked GBM remodelling (Fig. B). Genetic testing unveiled a novel single missense mutation in the NC1 domain of X-linked type-4 collagen, alpha-5 subunit (exon 51) with a single amino acid substitution (COL4A5 p.A1581S) that has thus far not been reported in hereditary nephropathies.

Discussion: We report a novel "Alport" COL4A5 NC1 missense mutation in a C4d positive hereditary nephropathy unexpectedly diagnosed in an older male presenting with isolated proteinuria. We provide further evidence of complement as building blocks in GBM remodelling and pseudolinear C4d deposits as morphologic signposts of architectural GBM disturbance that guided in-depth diagnostic work-up in our patient.



(A) IF:**Global pseudolinear C4d staining along capillary walls** (B) EM:**Marked structural capillary wall remodeling.**

PUB639

A Case of IgG4-Related Disease with Tubulointerstitial Nephritis and Glomerular Endocapillary Hypercellularity

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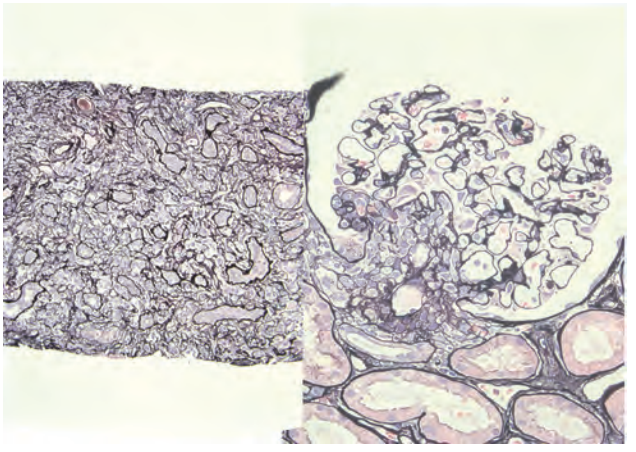
Introduction: IgG4-related disease (IgG4RD) is an uncommon autoimmune disease that affects multiple organ systems. The most commonly affected organs are the pancreas, liver, gall bladder, lachrymal glands, salivary gland, lung, and kidney. Renal involvement of IgG4RD typically presents as IgG4-positive plasma cell-rich tubulo-interstitial nephritis and storiform fibrosis.

Case Description: A 61-year-old man with a history of asymptomatic pancreatic swelling and impaired renal function was referred to our hospital. Laboratory data showed an increased serum creatinine concentration (1.33 mg/dL) and a high serum level of IgG4 (1020 mg/dL). All autoimmune antibodies were negative, and the serum complement levels were within a normal range. Protein urine excretion was 0.69 g/day without microscopic hematuria. Abdominal magnetic Resonance imaging revealed enlargement of the pancreas and multiple bilateral renal parenchymal nodules with hypointensity in T2 image. A renal biopsy revealed storiform fibrosis and IgG4-positive plasma cell infiltration of the interstitium, which was consistent with IgG4-related kidney disease. Three out of 13 glomeruli exhibited segmental endocapillary hypercellularity. Of note, marked infiltration of monocytes to the vascular pole was observed, which is likely to be continuous to interstitial lesions. Immunohistochemistry and electron microscopic examination did not show any evidence of immune-mediated glomerular diseases including membranes nephropathy.

Discussion: We herein describe a case of IgG4RD with tubule-interstitial nephritis and focal endocapillary hypercellularity in the glomeruli. Although membranous nephropathy is a common glomerular presentation of IgG4RD, proliferative glomerulonephritis has only rarely been reportedpreviously. To our knowledge, this is the first case of glomerular endocapillary hypercellularity in a patient with IgG4RD.



PUB640

Gastrointestinal and Renal Allograft Involvement by Light Chain Deposition Disease: Report of Two Cases

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Introduction: Light chain deposition disease (LCDD) is a rare entity both in native and transplant kidneys, and concurrent involvement of the kidney allograft and other organs has been rarely described. We report two cases of post-transplant LCDD in which gastrointestinal symptoms preceded a diagnosis of LCDD initially made on kidney allograft biopsy, and subsequently detected on previous gastrointestinal biopsies.

Case Description: The first patient was a 59-year-old female with end-stage renal disease (ESRD) of unknown cause, who presented with chronic diarrhea and acute kidney injury (AKI), 1 year after kidney transplant (KT) from unrelated living kidney donor (LURT). Gastrointestinal (GI) endoscopy, as well as light microscopy of gastrointestinal biopsies were negative and the GI symptoms were ascribed to Mycophenolate mofetil (MMF) effect. MMF was discontinued with no benefits. Renal function kept worsening and an allograft kidney biopsy was performed, revealing LCDD, with a subsequent diagnosis of kappa light chain myeloma. The second patient was a 46-year-old male with ESRD of unknown cause, status-post KT from LURT, who presented 4 years post-transplant with chronic vomiting, diarrhea and AKI. Weeks-long recurrent episodes of nausea and vomiting, with non-bloody watery diarrhea, had been occurring for a year prior to admission. GI endoscopy as well as light microscopy of gastrointestinal biopsies were negative and the symptoms were ascribed to MMF effect. MMF was suspended with no benefits. Two subsequent allograft biopsies were diagnostic for LCDD. A work-up for plasma cell dyscrasias identified a clone secreting kappa light chains, consistent with monoclonal gammopathy of renal significance. We retrospectively stained previous GI biopsy specimens for light chains and found that both patients had kappa chain-restricted linear deposition along the basement membranes of gastric glands.

Discussion: These cases highlight (i) the rationale for screening kidney transplant recipients with serum protein electrophoresis for early diagnosis of plasma cell dyscrasias, (ii) the importance of full immunofluorescence staining panels and electron microscopy on allograft kidney biopsies after 6 months from KT, and (iii) the need to screen for extra-renal involvement by LCDD.

PUB641

Medullary Angiitis: Presentation and Diagnostic Challenges

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Introduction: When histopathologic exam of the native kidney is performed, conditions are diagnosed usually by microscopic examination of the renal cortex. Not many disease entities have been known to involve the renal medulla or have a medullary component. We present a very rare case of a subtype of small vessel vasculitis primarily involving the renal medulla that helps us understand the characteristic pathological features under microscopic examination and the challenges in establishing this diagnosis.

Case Description: A 75-year-old male with PMH of CKD Stage 3 with baseline serum creatinine (SCr) of 1.4, history of FSGS 18 years back, not on any medications and no other comorbidities came for evaluation of worsening SCr of 2.23. Labs were significant for creatinine, 2.23 mg/dl, with urinalysis showing hematuria, proteinuria without any RBC casts with urine protein creatinine ratio of 1400 mg/g. P-ANCA was positive but ANA, Anti dsDNA, serum protein electrophoresis, C-ANCA, HIV, Hepatitis B, and C were negative with normal serum complements. The renal US did not show any abnormalities. No history of skin or throat infections in the past. The biopsy was diagnostic of medullary angiitis which is

a subtype of small vessel vasculitis. The patient was started on prednisone 40mg per day with a plan to start rituximab infusions. In subsequent follow-ups, patient's SCr was stable at 2.2.

Discussion: Renal medullary angiitis was first described by Watanabe et al in 1983 and is an extremely rare condition with an incidence of 0.19%, which involves vasa recta of the renal medulla. Histopathological exam of the renal medulla has been described as the presence of interstitial hemorrhage with polymorphonuclear leukocyte infiltrate. Diagnosis of this condition is challenging, as most renal biopsies involve only the renal cortex and it can be misdiagnosed as acute interstitial nephritis due to the above microscopic features. Almost 63% of the reported medullary angiitis cases are ANCA positive and among non-ANCA related medullary angiitis, 20% have been reported to be due to IgA nephropathy. In fact, medullary angiitis may be the first systemic manifestation of an ANCA associated vasculitis and hence it should be differentiated from acute interstitial nephritis which has different etiologies.

PUB642

Non-Myeloma Hematologic Malignancies in Renal Biopsies: A Single Institution Experience

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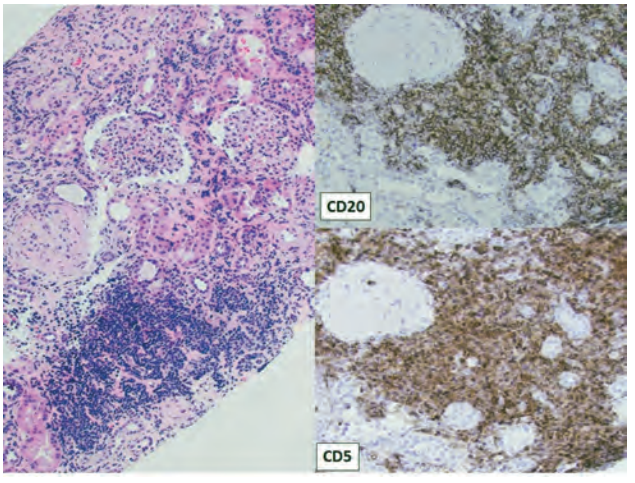
Introduction: Hematologic malignancies other than myeloma are relatively rare in renal biopsies. We present 5 diverse cases of hematologic malignancies with histologic, immunohistochemical, and immunofluorescent evidence of renal involvement. Consecutive native and transplant renal biopsies from year 2015 to 2018 were reviewed.

Case Description: Both lymphoid and myeloid malignancies were noted.

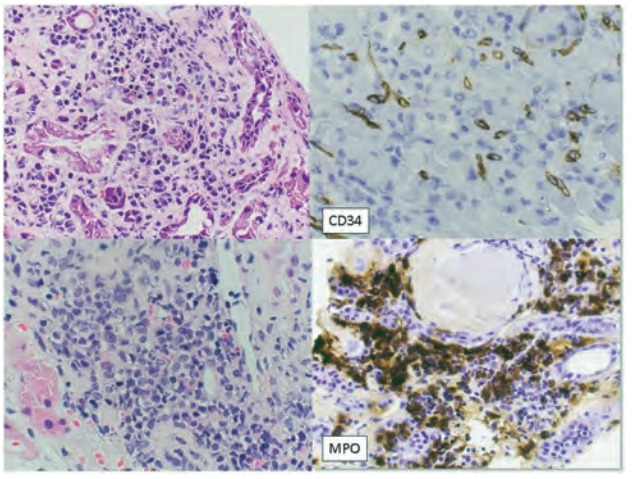
Discussion: This case series demonstrates that renal involvement is possible in any hematologic malignancy. Renal biopsy findings may sometimes direct evaluation for an unsuspected hematologic malignancy, possibly allowing for earlier detection and improving patient outcome.

Key Patient Findings in Renal Biopsy Specimens

Age (Years) / Sex / PMH	Non-renal symptoms	Renal symptoms	Hematologic findings in renal bx	Non-hematologic findings in renal bx	Treatment	Follow-up
64 / M/ HTN, Squamous cell CA of scalp, fatigue, chronic bronchitis	Lung nodules, splenomegaly, lymphadenopathy, thrombocytopenia	Nephrotic Syndrome	CLL/SLL	Moderate interstitial fibrosis and tubular atrophy	Rituximab based chemotherapy X 6 cycles	Periodic Follow up, no evidence of further decline
63 / M / DM2, HTN	Lower extremity swelling, nausea, emesis, fatigue, WBC: 83 K	Hypercalcemia, hyperkalemia, hyperuricemia; Cr: 3.1 mg/dl; UA: 2+ blood, 1+ protein	Mantle cell lymphoma	Diffuse membranoproliferative /C3 glomerulonephritis (MPGN)/C3GN	NORDIC chemotherapy regimen (maxi-CHOP/rituximab/ cytarabine; 6 cycles)	Complete remission after autologous stem cell transplant
50 / M / DDRT, for Tuberous Sclerosis	Fatigue, weight loss, liver and small bowel mass, anemia	AKI on CKD, Cr: 3.9 mg/dl, GFR <50	Diffuse Large B-cell lymphoma, germinal center subtype	Monomorphic PTLD, EBER Negative	R-EPOCH (2 cycles) and R-CHOP (4 cycles) chemotherapy	Clinical remission
69 / M/ HTN, HLD, DM2	Chest pain, MDS	Cr: 2.66 mg/dl GFR 55	Acute myeloid leukemia	ATI	Azacitidine Chemotherapy	Deceased
46 / M / CKD Stage III, HTN	None	AKI on CKD; Creatinine: 4.5 mg/dl, 3+ proteinuria	MPGN with IgM kappa deposits	cellular/fibrocellular crescents, moderate IFTA	Rx for HTN.	Negative hematology workup, regular clinical follow up



Case 1, H+E shows atypical lymphoid infiltrate. CD20 highlights the B-lymphocytes. CD5 (T-cell marker) is aberrantly expressed on the B-cells, consistent with CLL/SLL.



Case 4, H+E images show immature hematopoietic cells. CD34 and MPO stain them as myeloid blasts.

PUB643

Lupus Encephalopathy and 87.5% Glomeruli with the Formation of Crescent in a Childhood-Onset Systemic Lupus Erythematosus: A Case Report

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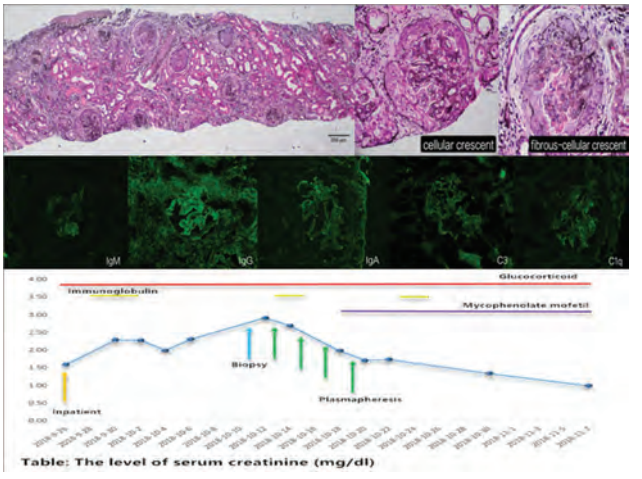
Introduction: Systemic lupus erythematosus (SLE) associating with lupus encephalopathy and lupus nephritis has been reported in previous case reports. The crescent formation could be detected under the microscope at the same time. Here, we present a rare case that 87.5% glomerular crescent formation. Up to now, there have no report about crescent formation much more than this proportion in this type of patient.

Case Description: We report a case of a 14-year-old female who presented severe oliguric renal failure and uncoordinated movement. The highest serum creatinine reached 2.9mg/dl. She was diagnosed as lupus encephalopathy and severe diffuse proliferative lupus nephritis. A renal biopsy revealed that 18 of 21 glomeruli had crescent formation (11 cellular crescents, 5 fibrous-cellular crescents and 2 fibrous crescents), accounting for 87.5% of total. There were IgG, IgA, IgM, C3, C1q, both kappa and lambda light chains on Immunofluorescence staining. The patient was immediately treated with glucocorticoid, mycophenolate mofetil, immunoglobulin and plasmapheresis. She had symptomatic improvement and the serum creatinine also dropped to normal levels in 42 days later. No infection occurred during treatment. In addition, follow-up of 3 months after discharge showed stable kidney function and no recurrence of edema, oliguria or other symptoms.

Discussion: It's a rare case of lupus nephritis with 87.5% glomerular crescent formation accompanied by lupus encephalopathy. Such patients have a poor prognosis. However, renal function returned to normal after a series of aggressive treatments. It suggests that aggressive short-term combination therapy is beneficial for children with lupus nephritis with large amounts of glomerular crescent formation.



PUB644

Coexistence of Triple Viral Infection as a Trigger of Severe Rhabdomyolysis-Associated AKI in an Adolescent

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Introduction: Rhabdomyolysis has many triggers, including trauma, drugs, autoimmune disorders, infection and genetic mutations. Prevalence of viral-induced rhabdomyolysis is 38% in pediatric population. Here we describe a case of acute kidney injury (AKI) from rhabdomyolysis secondary to viral infection.

Case Description: An 18-year-old African American female college student with past medical history of febrile seizures, Kawasaki disease and obesity presented with a one-week history of myalgias, productive cough, abdominal pain and dark urine. She denied sick contacts, recent travel, rash, arthralgias, trauma. Physical examination revealed tachycardia, abdominal and lower extremities tenderness, inability to ambulate. On admission, creatinine (cr) was elevated at 1.56 mg/dl; potassium, 5 mmol/l; CK>200,000 IU/L, AST, 2033 U/L;ALT, 595 U/L. Urinalysis showed amber urine, 3+ blood, 2+ protein, 1-5 RBC and no casts. Drug screen was negative. Viral and bacterial serologies were negative with the exception of PCR-positive Parainfluenza and Epstein Barr virus (EBV), and Coxsackievirus group B antibodies (titer 1:32). Complement levels were normal, pANCA and cANCA <1:20. ANA titer was 1:160 with speckled pattern. On day 3, lower extremities MRI showed diffuse, symmetric muscle edema. Muscle biopsy demonstrated acute myonecrosis. PCR of muscle sample for EBV was negative. Stains for mitochondrial, glycogen, lipid storage myopathies were unremarkable. The patient was managed with intravenous volume resuscitation. On day 4, cr decreased to 1.25 mg/dl and CK decreased to 183,600 IU/L. On day 14, she was discharged home with normal renal function and CK of 617 IU/L.

Discussion: Coexistence of viral infections led to severe rhabdomyolysis in our patient. However, given the reported history of vasculitis, investigation of potential autoimmune etiology was pursued, and subsequently excluded. As a result, steroid therapy was withheld and resolution occurred with intravenous volume resuscitation alone. Clinicians should have a high index of suspicion for rhabdomyolysis in patients who present with muscle pain and weakness and elevated creatine. Further, timely investigation of the etiology of rhabdomyolysis, including viral, autoimmune, and genetic disorders, has implications for management and prognosis of AKI.

PUB645

Transplant Renal Artery Stenosis in a Child with BK Nephropathy

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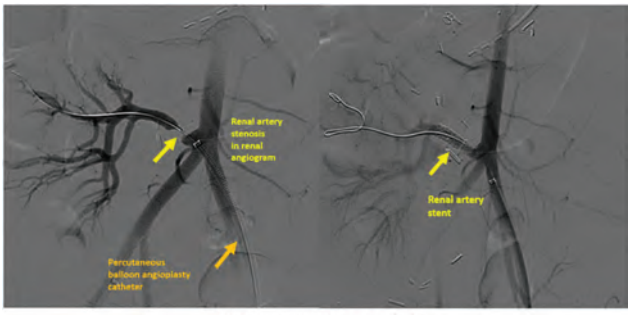
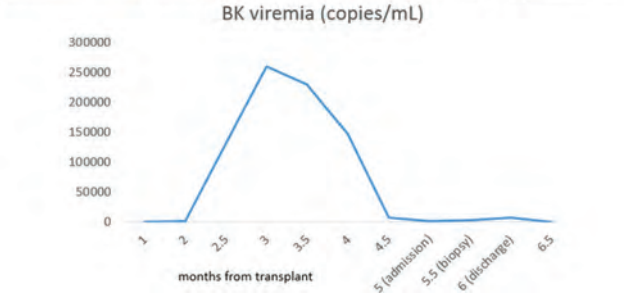
Introduction: Transplant renal artery stenosis (TRAS) and BK nephropathy are known complications of renal transplantation, but the association has not been reported.

Case Description: A 2-year-old girl received a kidney transplant from a 20-year-old deceased donor, along with native nephrectomies. She had a delayed graft function due to a renal artery thrombus and required thrombectomy with reanastomosis, heparin and aspirin. Thymoglobulin, tacrolimus and mycophenolate were started. CMV and EBV DNA PCRs were negative but developed BK viremia at 2 months (peak 260,000 copies/mL). Serum creatinine remained stable at a baseline of 0.9 mg/dL. After immunosuppression reduction and leflunomide initiation, her BK load decreased to 1200 copies/mL after 4 months. There were no episodes of rejections, hydronephrosis or hematuria. Blood pressure (BP) was well controlled on low dose amlodipine. 5 months later, she presented with hypertensive emergency, following a respiratory infection. Her BPs remained refractory to 8 antihypertensive agents and required dialysis for oliguric acute kidney injury. Allograft biopsy showed evidence of BK nephropathy. Immunosuppression was further minimized. Doppler renal sonogram and duplex study of renal artery were both suggestive of TRAS. Angiogram showed severe proximal anastomotic TRAS (> 95% occlusion). Balloon angioplasty with stenting was done with immediate improvement in the blood flow and gradient reduction to 18 from 50 mm Hg. BPs and renal function normalized. 7 months post-transplant, she remains stable, with no BK viremia and while on 2 antihypertensives.

Discussion: Although ureteral and urethral stenosis are known to occur with BK infection, TRAS is an interesting association. Timely recognition and management of both is important to prevent uncontrolled hypertension and allograft dysfunction.





PUB646

A Rare Etiology of Bilateral Hydronephrosis in Adolescents

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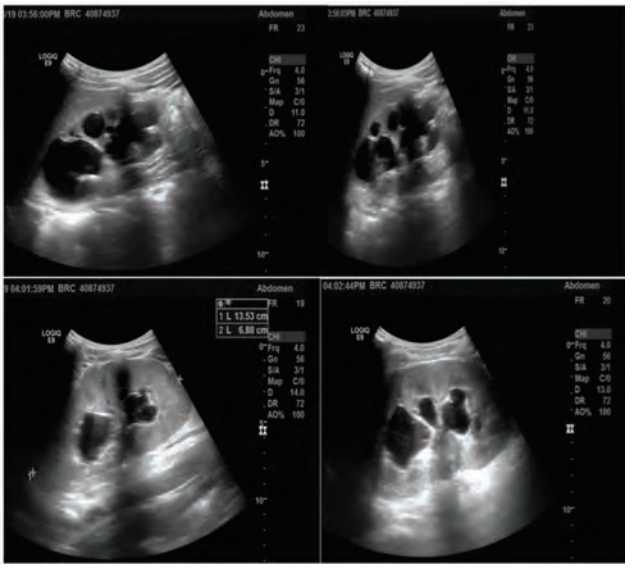
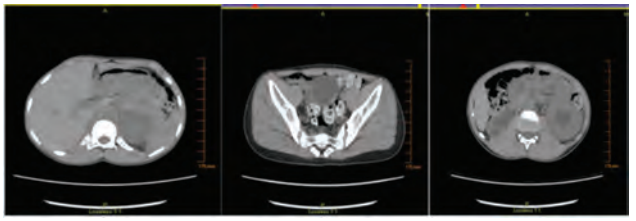
Introduction: Nonurological etiologies of bilateral hydronephrosis in children include external compression by a tumor, lymph nodes, retroperitoneal fibrosis, blood clots, and fungal ball

Case Description: A 14 years old male presented to the emergency department with nausea, vomiting, and decreased energy for a month. He was found to have stage III hypertension. Blood workup showed BUN of 58 mg/dL and creatinine of 5.4 mg/dL. Renal ultrasound showed severe bilateral hydronephrosis with cortical thinning (Image 1). CT abdomen showed 11.5 cm retroperitoneal mass encasing the aorta and right common iliac artery with obstruction of the right ureter and a hyperdense mass in the parapelvic left kidney (Image 2). Biopsy of the retroperitoneal and kidney mass was consistent with retroperitoneal fibrosis. It showed sclerotic fibrosis with lymphoplasmacytic, eosinophil, and macrophage infiltrates. Immunohistochemistry showed predominant CD3+ T-cells, CD20+ B-cells, eosinophils, plasmacytes, and S-100+ dendritic cells/macrophages. Fibrosis contained smooth muscle actin+ spindle cells. The number of CD3+ T cells were disproportionally higher than CD20+ B cells which suggests IgG related disease. IgG4:IgG ratio was normal. Work up for other etiologies is still ongoing

Discussion: The pathogenesis of retroperitoneal fibrosis (RF) can be due to asbestos, smoking, vasculitis, drugs, radiotherapy, neoplastic or infection. Idiopathic RF or Ormond's disease is a rare disease in all age groups. The first reported pediatric case in literature was in 1962. It is rare, with an incidence of 1.3 per 100,000 population/year with adult predilection. Its presentation is related to the organ involved, most commonly kidneys





PUB647

An Unusual Vintage: Wine-Colored Urine in a Postoperative Patient

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Introduction: A variety of drugs and diseases may cause discoloration of urine. Some associations are well-known, but newer medications and novel uses for old medications may induce changes which can be disturbing to patients and providers. Laboratory abnormalities and dialysis machine dysfunction may also be associated as presented in this case of wine-colored urine.

Case Description: A 38 year-old man with a history of chronic kidney disease stage 3 and flank pain was found to have a pheochromocytoma. He presented for left adrenalectomy and nephrectomy, complicated by both intra- and post-operative hypotension requiring pressor support. He received methylene blue (100 mg) and hydroxycobalamin (5 mg, CyanoKit) peri-operatively for vasoplegia. Nephrology was called on the 2nd post-operative day for evaluation of deep purple urine. Urine sediment revealed muddy brown casts, 25 RBCs/HPF and scattered WBCs, although creatinine remained near baseline of 2.8 mg/dL. The urine discoloration was due to the combination of methylene blue and high dose hydroxycobalamin. It resolved over the ensuing 14 days.

Discussion: Vasoplegia is an increasingly recognized complication of surgery, characterized by hypotension refractory to pressor support despite a normal cardiac output. There is evidence for the use of 2 agents, methylene blue and hydroxycobalamin, in the treatment of vasoplegia. Methylene blue causes a blue-green urine and is associated with serotonin syndrome in patients on SSRI. Hydroxycobalamin causes a deep red to purple discoloration of both urine and plasma, and is associated with falsely elevated creatinine, among other lab abnormalities. It can also cause a false blood leak alarm on certain dialysis machines leading to dialysis cessation. Recognizing these effects will be increasingly important for nephrologists caring for patients in the post-operative period as the recognition of vasoplegia and the use of methylene blue and hydroxycobalamin becomes more prevalent.

PUB648

Hydralazine-Induced ANCA-Associated Vasculitis

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Introduction: Hydralazine is a potential cause of ANCA-Associated Vasculitis (AAV) resulting in crescentic glomerulonephritis. The following is a case of a patient found to have increased proteinase 3 (PR3) and myeloperoxidase (MPO) antibodies in the setting of worsening kidney function while taking hydralazine. We use this case to review the literature and highlight the importance of a high degree of clinical suspicion, early diagnosis, and prompt treatment for better clinical outcomes.

Case Description: A 78-year-old woman with a history of rheumatoid arthritis, hypertension, and gout was admitted for hypertensive urgency. She had been taking hydralazine 25mg three times each day for 6 years. Her kidney function had been declining within the past year (SCr rising from 1.1 mg/dL to 2.5 mg/dL). Urinalysis revealed microscopic hematuria and proteinuria. The urine protein-creatinine ratio (UPCR) was 2 g/g. Serology for hepatitis, C3, C4 and SPEP were negative. PR3 ANCA and MPO ANCA antibody titers were elevated at 56.4 u/mL and MPO 25.3 u/mL, respectively. A renal biopsy showed diffuse mesangial and focal endocapillary proliferative GN with IgM deposits, focal necrotizing features, and focal cellular crescents. After holding hydralazine, she was started on pulse-dose steroids and rituximab infusion weekly for four weeks. At follow-up, repeat ANCA levels were negative, UPCR was 0.53g/g, and SCr improved to a baseline of 1.8 mg/dL.

Discussion: Hydralazine-induced AAV has an incidence of 5.4% in patients on 100mg/day to 10.4% with 200mg/day for >3-years duration. Identifiable risk factors include a cumulative dose of more than 100g, female gender, and thyroid disease. In one retrospective study of 323 cases of AAV, 12 were exposed to hydralazine. Our patient's renal biopsy findings are most consistent with a mixed pattern of GN. Crescentic proliferative GN is due to Hydralazine-induced ANCA vasculitis while mesangial proliferative GN with IgM deposits is likely due to underlying rheumatoid arthritis. Hydralazine can cause AAV with both PR3 and MPO autoantibodies elevated. It is important to recognize hydralazine as a potential cause of worsening kidney function in the setting of chronic use so that it can be properly diagnosed and treated.

PUB649

Cefepime Neurotoxicity: At-Risk Population and Preferred Treatment Modality

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Introduction: Correct assessment of renal function in hospitalized patients is of paramount importance as it influences not only the choice of drug but also the specific route and dose. We present a case of cefepime neurotoxicity caused by incorrect dosing in a patient with unrecognized severe acute renal failure

Case Description: A 51-yr-old woman was admitted to the hospital with abdominal pain and chills. She was febrile to 38.8°C with low normal blood pressure. She had white blood cell count 23000/mm^3. Serum creatinine (Scr) 0.62 mg/dL. Vancomycin and piperacillin/tazobactam were begun. A contrast CT scan revealed a complex fluid collection in lower pelvis which was drained by interventional radiology. Two days after admission, SCr was 1.2 mg/dL with eGFR of 46 ml/min/1.73m^2. Because of the concern for nephrotoxicity, she was switched to cefepime. On the fourth day of hospitalization, she had progressive decline in mental status. She also had asterixis. SCr was 4.2 mg/dL with blood urea nitrogen 26 mg/dL prompting consultation with nephrology. It was noted that she had had received a total of 12 grams of cefepime over last 48 hours. The constellation of symptoms suggested cefepime neurotoxicity. Investigation for other causes of her neurologic decline was unrevealing. She was started on continuous venovenous hemofiltration (CVVH) with a replacement fluid (RF) flow rate of 20 ml/kg/hr. Over the ensuing few hours, she became more altered and developed expressive aphasia. For the concern for inadequate clearance, RF flow rate was increased to 30 ml/kg/hr. Improvement in her mental status was observed in the next 12-15 hours. She subsequently regained her baseline mental status and renal function

Discussion: The estimation of renal function is difficult in hospitalized patients as they are not always in a steady state. Despite that, eGFR estimation through Scr is still relied heavily upon. This patient had an anephric rate of rise in SCr, and eGFR grossly overestimated her true renal function and led to prescription of an excessive cefipime dose and subsequent toxicity. This case illustrates the importance of correct dosing based on active assessment of renal function. It also uderlines the pitfalls of using a laboratory eGFR in hospitalized patients. Cefepime is best cleared using conventional hemodialysis but requires RF flow rate of at least 30 ml/kg/hr with CVVH for adequate clearance

PUB650

Recurrence of Fibrinogen Alpha Amyloidosis in Transplant Kidney

Ayesha Ahmed. *Rwjmh, Piscataway, NJ.*

Introduction: Fibrinogen A alpha chain amyloidosis is an autosomal dominant disease associated with mutations in the fibrinogen A alpha chain (*FGA*) gene. Patients typically present with kidney impairment and progress to end-stage renal disease over a median time of 4.6 years. Variant fibrinogen is produced in the liver and solitary renal allograft fails in 1-7 years with recurrent amyloidosis. In the largest series to date recurrence was noted in 4/8 kidney transplants (50%). We present a case of recurrence of amyloidosis in transplant allograft in less than 2 years post-transplant.

Case Description: 55 year old man with history of ESRD secondary to fibrinogen-alpha amyloidosis had DDKT on 3/16/17. Creatinine post-transplant settled in the 1.0-1.3mg/dL range. His post -transplant course was complicated with bilateral DVTs and PEs. He also developed proteinuria up to 2.8 gm/gm on spot urine protein /Cr and a 24 hr urine collection showed 7.4g of protein. His serum Kappa/lambda free light chain ration was also elevated, which was suspicious for recurrent renal amyloidosis. He had a renal biopsy on 11/14/17 that demonstrated FSGS (likely due to hyperfiltration injury) and did not demonstrate amyloidosis. He was started on losartan and a repeat 24 hour urine collection showed 2249mg/24hr of proteinuria. He underwent a second renal biopsy for a rise in his creatinine in January 2019, which was positive for Congo red staining suggestive of disease recurrence. To confirm diagnosis mass spectrometry was done and it showed peptide profile consistent with fibrinogen alpha type amyloid deposition (Glu 526Val, HGVS:p.Glu545Val).

Discussion: Recurrence appears to be common in fibrinogen-alpha amyloidosis who receives a kidney transplant alone. In largest series, recurrence was noted in 4/8 successful kidney allograft. 3 were lost as direct result of recurrence (median 6 yrs). By comparison 7 patients undergone combined liver-Kidney transplantation and no recurrence has been found in 6 surviving patients. Even if reports are scarce, a fibrinogen-alpha amyloidosis recurrence could be a factor of poor prognosis and graft loss. As fibrinogen production is

exclusively hepatic, the only curative treatment of fibrinogen-alphaamyloidosis is liver transplantation. Combined liver-Kidneytransplantation should be considered as the first therapeutic option for patients with ESRD due to fibrinogen-alpha amyloidosis

PUB651

Undiagnosed Primary Hyperoxaluria in a Kidney Transplant Patient Resulting in Allograft Failure

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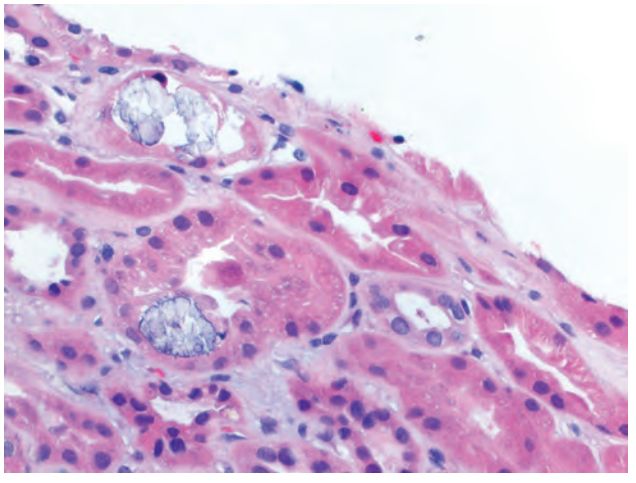
Introduction: Primary hyperoxaluria (PH) is a rare disease that causes accumulation of oxalate in the kidneys, heart, nerves and other organs. It is responsible for 1-2% of end-stage renal disease(ESRD) in the pediatric population. Type1 PH is due to a defect in the gene AGXT and accounts for 80% of cases. Overproduction of oxalate leads to calcium oxalate stones, nephrocalcinosis, and renal failure.

Case Description: A 26-year-old man presented for a deceased donor kidney transplant (DDKT). He has ESRD secondary to obstructive uropathy from kidney stones and has been on dialysis for 3 years, as well as chronic polyneuropathy and heart failure. After receiving his DDKT the course was complicated by delayed graft function. His creatinine rose to 10.8 on post-op day(POD) 2, and he required dialysis on POD 3. An allograft kidney biopsy done on POD 7 showed oxalate nephropathy and tubulointerstitial inflammation meeting Banff criteria for borderline rejection. He was started on high calcium low oxalate diet, vitamin B6, calcium carbonate and sodium citrate; he received steroids for rejection. Dialysis was administered for 6 consecutive days initially. He was also given IV fluids. Serum oxalate and 24h urine oxalate came back as 49mcmol/L (normal <1.6) and 205mg/24h (normal 16-49). Genetic testing showed a missense mutation (508G>A) in the AGXT gene. The patient was taken off dialysis 3 months later. he is undergoing evaluation for a combined liver and kidney transplant.

Discussion: The recurrence of ESRD in PH is a definite outcome with kidney transplantation alone. Our patient had manifestations suggestive of PH with his congestive heart failure, neurologic disease, and urolithiasis that should have prompted to screen for PH. Screening is crucial in patients with high suspicion for the condition prior to kidney transplantation. In general, any patient younger than 40 with ESRD from urolithiasis should be screened for PH prior to transplantation.



PUB652

A Joint Dilemma: Tacrolimus Toxicity from Arthritis Treatment with Boswellia: A Case Report

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Introduction: Bone and joint pain are a frequent complication of advanced renal disease with numerous over the counter (OTC) medications available with potentially dangerous active ingredients. Those which are inhibitors of CYP3A4 are associated with elevated tacrolimus levels. The present case describes an interaction between tacrolimus and *Boswellia serrata*, a CYP3A4 inhibitor. Boswellia is obtained from a tree resin indigenous to the Middle East, India, and Northern Africa and advertised to treat chronic inflammatory conditions. Its anti-inflammatory properties mainly stem from boswellic acid, a 5-lipooxygenase inhibitor.

Case Description: A 70 year old male with ESRD from IgA Nephropathy status post deceased donor renal transplant (DDRT), rheumatoid arthritis (RA), and hepatitis C (HCV) infection presents 26 days after renal transplant from an outside VA on a stable dose of tacrolimus 3mg q12h (tacrolimus level of 8.3 ng/mL), mycophenolate 1000 mg q12h, and prednisone 15 mg daily. His hospital course was complicated by a RA flare, treated with increasing his prednisone dose and oxycodone. After discharge, he initiated a glucosamine and chondroitin OTC supplement. When his care resumed at the home VA, his initial tacrolimus levels were 14.9 and 21 ng/mL. Additionally, his transaminases rose to twice the upper limit of normal and quadrupled from his baseline values. The supplement was discontinued, and tacrolimus levels decreased. However, he restarted the supplement for symptomatic relief and tacrolimus level rose to 18.7 ng/mL. While on the supplement, his tacrolimus dosage was decreased to 0.5 mg daily to achieve tacrolimus levels of 5.8 to 9.9 ng/mL. During evaluation for hepatitis C treatment, his glucosamine and chondroitin formulation was found to have *Boswellia serrata* extract. It was stopped, and his tacrolimus level decreased to 3.2 ng/mL. His subsequent tacrolimus levels stabilized on a total of 2.5 mg of tacrolimus a day, in 2 divided dosages, without Boswellia and his transaminases normalized.

Discussion: Common OTC preparations can cause severe morbidity and mortality in specific patient populations. Boswellia containing compounds may be effective in relieving joint pain but can have critical drug interactions. We report the first case of Boswellia induced tacrolimus toxicity in a renal transplant patient.

PUB653

Early BK Virus-Associated Nephropathy: A Double-Edged Sword and Unbeatable Barrier for Renal Allograft Survival

Kaushik Ivaturi, Ekamol Tantisattamo. *University of California, Irvine School of Medicine, Irvine, CA.*

Introduction: The prevalence of BK virus-associated nephropathy (BKVAN) in kidney transplant (KTx) recipients is estimated to be 1 to 10%. We report a case of young woman with the first KTx complicated by an early onset BKVAN contributing to renal allograft loss.

Case Description: A 30-year-old Hispanic woman with ESRD due to reflux nephropathy underwent a 2-A-B-DR mismatched deceased donor renal transplantation with antithymocyte globulin induction. She had an immediate renal allograft function and uneventful post-KTx. Baseline serum creatinine (SCr) was 0.8 – 1.1 mg/dL. Three months post-KTx, she developed new-onset BK viremia with a serum BK virus titer of 32,889 copies/ml. A 12-hour tacrolimus level ranged between 5.1 and 7.5 ng/mL. Even after lowering mycophenolate sodium (MPS) to 360 mg twice daily, BK titer increased to 315,000 copies/ml at 8 months post-KTx. MPS was discontinued and leflunomide was started. BK virus titers progressively increased to 2 million copies/ml by 11 months post-KTx. SCr was elevated to 2.4 mg/dL. A transplant renal biopsy revealed tubulointerstitial inflammation and diffuse SV40 immunostain positivity consistent with BKVAN without evidence of acute cellular (ACR) or antibody-mediated rejections (ABMR). Even after receiving IVIG, serum BK titers continued rapidly rising up to 15 million copies/ml at 13 months post-KTx with a worsening SCr of 3.5 mg/dL. All immunosuppressive medications were discontinued and serum BK titers decreased to 2,370 copies/ml, although renal allograft function progressively worsened. Repeat transplant renal biopsy showed evidence of ABMR and 1b ACR with moderate IFTA and negative SV-40. There was no additional escalation of immunosuppressive medication and hemodialysis was initiated at 16 months post-KTx.

Discussion: Early occurrence of highly elevated level of BK viremia causing BKVAN is very difficult to treat in kidney transplant patients. Immunosuppression post- KTx can lead to BKVAN which is common cause of allograft dysfunction contributing to renal allograft loss. Both, over-immunosuppression and de-escalation should be avoided, to mitigate the risk for BKVAN, and enhance the risk for rejection respectively. Initial over-immunosuppression led to BKVAN and subsequent de-escalation led to acute rejection and ultimately allograft loss in this patient.

PUB654

Graft Simple Cyst Infection in Late Transplantation

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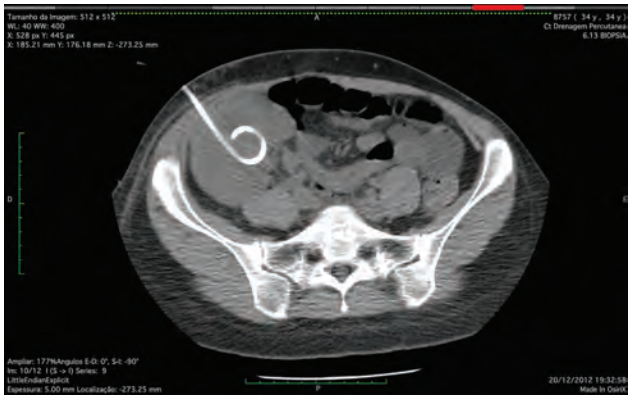
Introduction: Describe of a simple Cyst (SC)(Bosniak I) infection in a renal allograft is unprecedented in literature

Case Description: KM, 34-year-old female, presented end stage renal disease due to diabetes related nephropathy.14 months prior to the presentation she received a preemptive living donor kidney transplantation. Before implant, a 7cm Bosniak I cyst in kidney graft was marsupialized. Patient presented to the emergency departament with pain in the right iliac fossa, without fever or urinary symptoms. Beta HCG was negative, computed tomography (CT)showed small non-obstructive calculi in graft calyx and the patient was discharged. Within 6 days, she returned referring worsening of pain and spiking fever. Laboratory revealed leukocytosis with left upper shift and an acute kidney injure KDIGO 1. Graft Doppler ultrasound showed no vascular or perfusion changes, but heterogeneity and debris in the SC. With the mentioned findings, it was thought that the previously SC was infected. Ciprofloxacin with adjuctive ceftriaxone was started, however patient presented only partial clinical response with sustained leukocytosis. On the third day we performed a percutaneous CT-guided drainage of the SC with 170mL of purulent secretion. A drainage catheter was planted and maintained for 7 days and antibiotics we're not changed. Patient renal function and infectious parameters come back to normal.

Discussion: SC prevalence increases with age, occurring in up to 28-43% of kidney donor candidates. Despite the high occurrence, SC related complications are rarely reported. When facing a renal cysts infection, the antibiotic choice should take into account the cyst penetration profile (eg. Quinolone). Betalactamic association for synergism is controversial. SC infections requiring drainage are rare in native kidneys. The management was based on native kidney SC infections and ADPKD cyst infection reports.



CT guided percutaneus drainage of SC on graft with drainage catheter

PUB655

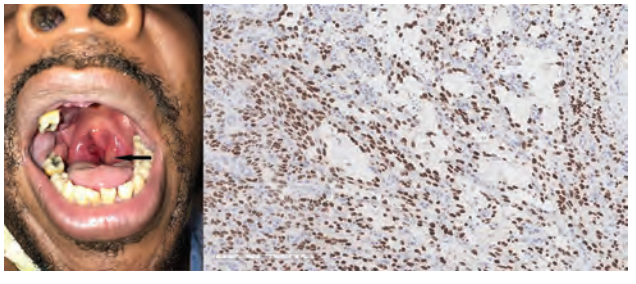
Kaposi Sarcoma of the Tonsils in a Renal Transplant Patient Treated with Resection and Sirolimus

John Howard, Ryan A. Thomas, Morgan Darrow, Ling-Xin Chen, Kuang-Yu Jen, Muna Alnimri. *University of California Davis Medical Center, Sacramento, CA.*

Introduction: Kaposi sarcoma (KS) is a locally aggressive vascular tumor which is strongly associated with human herpesvirus infection (HHV-8; also known as Kaposi sarcoma-associated herpesvirus or KSHV). KS is most often seen in patients with HIV infection, but can occur in patients who are on immunosuppressive therapy, particularly transplant recipients, with an incidence at least 9 fold greater than the general population. While skin and the oropharynx are the typical sites for KS accounting for 60% of cases, only 2% of these are confined to the mouth or oropharynx. Presentations involving the tonsils specifically are rare.

Case Description: We describe a case of tonsillar KS occurring in a kidney transplant patient. He presented 16 months post-transplant with dysphagia, odynophagia, and weight loss that developed over the preceding month. Oral examination revealed tonsillar hypertrophy with purple discoloration as well as friable exophytic lesions (figure 1). He underwent tonsillectomy with microscopic examination of the specimens showing a vascular proliferation which had immunohistochemical stain evidence of HHV-8, consistent with KS (figure 2). Serologic testing for HIV was negative.

Discussion: Reduction of immunosuppression is an important part of the treatment of KS, but alone can be insufficient for inducing remission in the majority of cases as well as placing patients at increased risk for rejection and graft failure. Other immunosuppressants, notably sirolimus, have been shown to improve outcomes. Extensive or refractory cases may still require chemotherapy. Clinicians should be aware of dysphagia and tonsillar enlargement as a rare presentation of KS in post-transplant patients, particularly during the first 2 years when most cases occur. Our patient was maintained on low dose tacrolimus and sirolimus, and he continues to have good graft function and stable disease 5 months post diagnosis.



PUB656

Monoclonal Gammopathy of Renal Significance in a Renal Transplant Patient

Shan Khan,[1] Barry M. Wall,[2,1] Shailesh Satpute,[4] Manish Talwar.[3,1] *[1]UTHSC, Memphis, TN; [2]Veterans Affairs Medical Center, Memphis, TN; [3]Methodist University Hospital, Memphis, TN; [4]Baptist Cancer Center, Memphis, TN.*

Introduction: Monoclonal gammopathy of renal significance (MGRS) occurs due to abnormal secretion of a monoclonal immunoglobulin by a clonal population of plasma cells. MGRS has been rarely reported in renal transplant recipients.

Case Description: A 65-year-old male with a history of end-stage renal disease due to presumed diabetic nephropathy received a cadaveric kidney transplant. He was treated with mycophenolate mofetil, tacrolimus, and prednisone and had an uncomplicated post-op course. Four months later, he devloped difficult-to-control hypertension, lower extremity edema, and elevated serum creatinine (SCr) from a baseline of 1.6 mg/dL to 2.3 mg/dL. Tacrolimus toxicity was suspected, and, after dose adjustment, SCr decreased to 2.0 mg/dL. Two months later, the SCr increased to 2.5 mg/dL and urinalysis (UA) revealed pyuria and 1+ albumin. Spot urine protein:creatinine ratio (UPC) was 0.45. No anemia, hypercalcemia or bone pain was present. Allograft biopsy showed mild glomerulitis and peritubular capillaritis, acute tubular injury, and proximal tubules with intense lambda light chain restriction in cytoplasmic protein reabsorption droplets. C4d and Congo red stain were negative. Donor specific antibody (DSA) class I and II were negative. SPEP, UPEP, immunofixation (IFE), and serum free light chains (SFLC) revealed: SPEP had an M spike of 0.81 g/dL with IgG lambda restriction on IFE. UPEP had monoclonal protein, IgG lambda (6.43 mg/24 hours) with free lambda light chains (5.97 mg/24 hours). SFLC ratio was low at 0.25. Bone marrow (BM) aspirate and biopsy with flow cytometry revealed a hypercellular marrow with a lambda restricted plasma cell population that was 5% of total marrow cellularity. Hematology/oncology began bortezomib and dexamethasone. During follow-up SCr decreased from 2.5 mg/dL to 1.9mg/dL. The most recent UA showed no pyuria and a spot UPC of 0.44.

Discussion: Given the absence of hypercalcemia, bone pain, or anemia, the electrophoresis findings and the presence of only 5% lambda restricted plasma cells in the bone marrow would suggest a diagnosis of monoclonal gammopathy of unknown significance that would not warrant aggressive treatment. The histologic finding of proximal tubulopathy related to lambda restricted light chains in the allograft, however, led to the diagnosis of MGRS and the same treatment as given for multiple myeloma due to renal involvement.

PUB657

Thrombotic Microangiopathy in a Liver Transplant Patient on Tacrolimus

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Introduction: Thrombotic microangiopathy (TMA) is a rare adverse reaction of calcineurin inhibitors. TMA is fatal in solid organ transplant patients, with a reported incidence of 0.5-3% and mortality of about 75%. We report the case of a 19-year-old woman with Tacrolimus (Tac) induced TMA treated with eculizumab (EZB).

Case Description: A 19-year-old female with autoimmune hepatitis status post Orthotopic Liver Transplant on Tacrolimus(Tac), Chronic Kidney Disease Stage III presented with diarrhea. Initial Labs: creatinine 12 mg/dl, platelet count 30,000/cu.m, hemoglobin 5.2 g/dl, elevated LDH 635 IU/L, haptoglobin (HG) < 30 mg/dl, many schistocytes on peripheral smear. ADAMTS-13 activity: 55%. Stool PCR:Negative for Shiga Toxin and E.Coli. Clinically, typical TTP was ruled out. HUS was diagnosed, supported by subsequent kidney biopsy finding of TMA. As Tac can cause TMA, it was switched to sirolimus. Treatment with EZB was instituted [900 mg IV weekly x four weeks, then 1200mg IV biweekly from doses 5 to 7]. By the 5th EZB dose, renal function improved (creatinine down to 2-3 mg/dl), LDH decreased to 388 IU/L, although haptoglobin remained<30 mg/dl. With ongoing hemolysis (elevated LDH and low HG), a 2nd renal biopsy was done following the 6th EZB dose, which showed FSGS. Due to persistent proteinuria and ongoing TMA, sirolimus was discontinued. After the 7th EZB dose, C3 level improved (68 to 128 IU/L), C4 was normal, LDH improved to 250 IU/L. Results of anti-complement H autoantibodies and aHUS genetic panel including C5 polymorphisms which is associated with poor response to EZB were negative; but, heterozygous variant (c.3287G>A, p. Arg1096His) in exon 25 of the ADAMTS13 gene was positive. The patient's renal function stabilized to creatinine of 2.1 mg/dl. In anticipation of discharge, outpatient EZB treatment was arranged; unfortunately, she developed cardiac arrest and passed away.

Discussion: The case highlights that EZB may improve Tac induced TMA without plasmapheresis. Per biopsy, patient's AKI was a combination of ATN and TMA, so it is unclear the extent EZB contributed to renal function improvement. Despite the finding of a heterozygous variant, the near-normal ADAMTS 13 activity and data from the clinvar database clarified that the variant is benign and common in the population. Thus, it is likely that this is a case of tac-induced TMA that responded to EZB treatment.

PUB658

To Be or Not to Be? Parvovirus B19 Causing Refractory Anemia After Kidney Transplant

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Introduction: Anemia is a common complication after transplantation and the reported incidence of Parvovirus induced anemia (PIA) is around 10%. The exact incidence is frequently underestimated because routine parvovirus screening is not performed and it is difficult to differentiate from drug adverse reaction.

Case Description: A 70-year-old male with a past medical history of G6PD deficiency, living donor transplant with induction presented 6 weeks later with dyspnea on exertion for 1 week. Labs showed hemoglobin of 7.4 g/dl (baseline 10), MCV 90 fl, Platelets 919 K/CMM, Creatinine 0.7mg/dl, Retic 0.3%, elevated Haptoglobin, fibrinogen, ferritin, erythropoietin levels 156 mIU/ml and LDH 510. CT scan was negative for retroperitoneal hematoma and pulmonary embolus was excluded. No evidence of bleeding was found. He was transfused units of packed red blood cells and treated with Aranesp. Hemoglobin improved to 9.7mg/dl prior to discharge. Outpatient follow up showed parvovirus PCR> 100 million copies. Mycophenolate was decreased to 180mg BID and intravenous immunoglobulin (IVIG) therapy was given (5 doses 0.7g/kg for 4 weeks). Parvovirus PCR decreased to 22000 and hemoglobin increased to 13.6mg/dl in 2 months.

Discussion: Parvovirus exhibits tropism for the erythroid progenitor cells resulting in pure red cell aplasia. Immunosuppression impairs the response to infection leading to prolonged viremia or chronic anemia. Clinical manifestation ranges from a normocytic anemia refractory to transfusions or erythropoietin, pancytopenia and thrombotic

microangiopathy. Clinical symptoms can be asymptomatic to life threatening organ dysfunction. Diagnosis is through positive polymerase chain reaction and confirmed by a bone marrow biopsy showing decreased erythropoiesis and giant pro-erythroblasts with nuclear viral inclusions. The recommended treatment is with intravenous immunoglobulins (IVIG) with or without reducing immunosuppression. The dose and duration of IVIG is much debated. Due to the severity of anemia, viral load should be frequently assessed pre and post-transplant till resolution is achieved. In conclusion PIA is a rare but serious complication and a higher index of suspicion is advised when a transplant patient presents with severe and refractory anemia.

PUB659

De Novo Collapsing FSGS Secondary to Cytomegalovirus Infection in a Deceased Donor Kidney Transplantation Recipient

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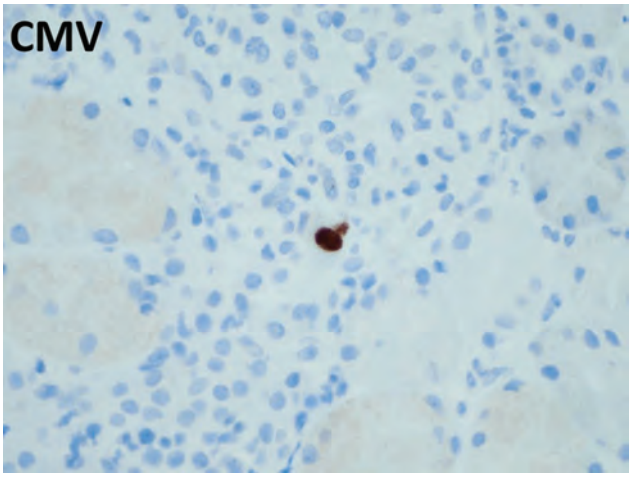
Introduction: This case describes the case of a kidney transplant recipient, who developed collapsing FSGS in the setting of CMV infection two weeks after the standard CMV prophylaxis therapy was discontinued.

Case Description: A 59 year-old African American man with a history of deceased donor kidney transplant due to ESRD secondary to hypertension presented to the ER with an acute febrile illness seven months following his transplant surgery. Symptoms included two weeks of diarrhea, anorexia, fever, cough and decreased urine output. Transplant history: CPRA 90 %; Immediate graft function; CMV status D+/R. For induction received Velcade, Thymoglobulin and Simulect. Prophylaxis included nystatin and Bactrim. Valgancyclovir for six months post-operation. Maintenance immunosuppression consisted of tacrolimus, mycophenolate and prednisone. In the ER he was found hemodynamically stable, ill-appearing, benign cardiopulmonary and abdominal exams and no edema. Initial lab remarkable for leukopenia, thrombocytopenia, acute kidney injury, nephrotic range proteinuria. Renal allograft ultrasound was normal. Initial management included IV fluids and empiric antibiotics. Flexible sigmoidoscopy performed which was negative for gross lesions. CMV PCR results positive for 895,000viral copies. Immediately started on Ganciclovir and MMF dose was reduced. Due to worsening renal function the patient underwent kidney allograft biopsy which revealed: Colapsing FSGS. Stain for CMV was positive. The viral load downtrended in the first week of induction therapy. Patient made a symptomatic recovery and his creatinine improved.

Discussion: This case describes a kidney transplant recipient who developed CMV infection despite completing the appropriate prophylaxis and developed secondary FSGS of the allograft as a result. This case is notable for nature of the renal allograft injury and the fact that he recovered allograft function through treatment of his CMV infection.



PUB660

Central Diabetes Insipidus Unmasked After Kidney Transplant: A Case Report

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Introduction: Patients who undergo pituitary surgery are prone to develop Central Diabetes Insipidus (CDI) post-operatively on top of other hormonal deficiencies. CDI is characterized by decrease in release of antidiuretic hormone (ADH) and present clinically with polyuria, nocturia and polydipsia. In patients with End Stage Renal Disease (ESRD) and on maintenance dialysis, CDI may be masked and then unmasked after transplantation. To the best of our knowledge, there have only been 4 published studies with regards unmasking of CDI post-kidney transplantation.

Case Description: We report a case of a 62 year old male with history of resection of a pituitary macroadenoma and ESRD secondary to Diabetic Nephropathy on maintenance dialysis, admitted for living non-related kidney transplantation. Pre-transplantation, he was on desmopressin for CDI but when he developed ESRD, CDI was masked and desmopressin was discontinued. His kidney transplant went uneventful. Post-transplantation, he developed polyuria, increasing serum sodium levels, borderline high serum osmolality and low urine osmolality. In lieu of measuring plasma ADH levels, fluid restriction was done which resulted to increase sodium levels. A diagnosis of CDI was made. He was started on oral desmopressin with noted improvement of symptoms. He was eventually discharged improved. On succeeding outpatient consults, patient's daily urine output exceeded to 4L/day and his dose of desmopressin was increased to 100mcg twice daily. Thereafter, he remained clinically stable with average daily urine output of 3L/day, normal sodium levels and good renal allograft function.

Discussion: Successful kidney transplantation leads to unmasking of pre-existing CDI, which when missed may lead to rapid dehydration and hypernatremia. Frequent monitoring is necessary for early detection and management of CDI. Furthermore, CDI is not a contraindication for transplant as long as patient is closely monitored for adequate titration of fluids and prompt management with desmopressin.

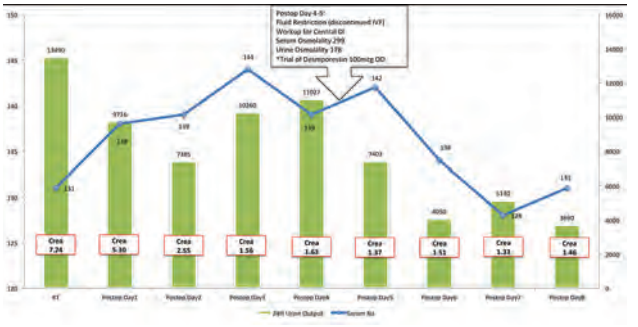

Fig 1. Clinical Timeline From Day of Transplant until Postop Day 8

PUB661

More Than Meets the Eye: Acute Cellular and Antibody-Mediated Renal Allograft Rejection Associated with Donor-Specific Antibodies (DSA) Angiotensin II Type 1 Receptor (AT1R) Antibodies

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Introduction: Kidney transplant is associated with improved survival in end stage renal disease (ESRD) patients and although 1 year allograft survival rates continue to improve, long term allograft survival remains low. Immune-mediated graft loss remains a challenge and non-HLA antibodies increasingly are recognized as contributing to allograft dysfunction. We present a case of a deceased donor renal transplant (DDRT) patient who presented with acute kidney injury from mixed cellular and antibody mediated rejection.

Case Description: An 18 year old woman with ESRD from neurogenic bladder received a 2A2B2DR HLA mismatch DDRT, low immunologic risk without DSA, with basiliximab induction and maintenance immunosuppression with mycophenolate mofetil, tacrolimus and prednisone. She had a history of spina bifida and repaired meningomyelocele necessitating self-catheterization, with unfortunately increased urinary tract infections. At age 12, she had bladder augmentation with small bowel and ureteral re-implantation, with continued intermittent self-catheterization. Post-transplant course was complicated by recurrent, multidrug-resistent UTIs, leading to reduction in maintenance immunosuppression and nonadherence to medications by the patient. On post-op month 5, she was noted to have an acute kidney injury with Cr increase from 1 mg/dL to 4.47 mg/dL. A renal biopsy was obtained which showed acute T cell mediated rejection and C4d negative antibody mediated rejection. DSA was positive and non-HLA testing was pursued which was negative for endothelial cell and MICA antibodies but positive for AT1R. Treatment with ATG, plasma exchange, IVIG, steroids and Rituximab was given. Patient was started on Losartan for AT1R antibody. Her Cr improved to baseline and she remains with stable allograft function.

Discussion: *In addition to the common factors that contribute to allograft injury such as infection and non-adherence*, non-HLA antibodies are becoming increasingly more relevant in renal allograft dysfunction, contributing to graft loss. AT1R antibodies are usually associated with ABMR histopathology and lead to cytokine release. They further enhance vascular inflammation and allograft dysfunction. They should always be considered when rejection is diagnosed in the absence of HLA antibodies.

PUB662

Undiagnosed Anti-GBM Antibodies Causing Rapid Loss of a Kidney Transplant

Bonnie Ann Sarrell, Paisit Paueksakon, Meghan E. Kapp, Vadim Pedchenko, Billy G. Hudson, Beatrice P. Concepcion. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Many patients have renal dysfunction attributed to co-morbid conditions. Depending on the clinical scenario, a serologic workup or renal biopsy for definitive diagnosis may not be deemed necessary. However, definitive diagnosis may be crucial for the success of a subsequent kidney transplant. Here we present a case of a young man with unknown etiology of his native kidney disease who received a kidney transplant that failed rapidly due to the presence of undiagnosed circulating anti-GBM antibodies.

Case Description: This is a 33yo CM with HTN and tobacco use who presented with 3 weeks of vomiting, diarrhea, and weakness. He was anuric with a creatinine of 25 mg/dL and was started on chronic dialysis. Two years later, he underwent a living unrelated kidney transplant. He received alemtuzumab, solumedrol, tacrolimus, and mycophenolate mofetil. Surgery was uncomplicated but after 12hrs his urinary output started to decline and creatinine plateaued. Transplant ultrasound was normal. DSA was negative. UA had 100 mg/dL protein, 30 WBC, 921 RBC. Urine PCR was 1g/g. Renal biopsy was performed which showed 17/25 glomeruli with active lesions – 13 with cellular crescents and 4 with fibrinoid necrosis. Immunofluorescence showed diffuse, global, linear capillary loop staining for polyclonal IgG and C3. Anti-GBM level was 213 AU/mL. He was treated with steroids, plasmapheresis, and cyclophosphamide without response and required re-initiation of dialysis. His course was further complicated by septic shock due to *Bacteroides fragilis* bacteremia to which he ultimately succumbed 6 weeks post-transplant. Stored serum collected 1 week prior to transplant subsequently tested positive for anti-GBM antibodies, specifically a3,5 collagen IV antibodies.

Discussion: In this case, the rapid and unexpected failure of a newly transplanted kidney was caused by circulating anti-GBM antibodies. Their presence was unsuspected due to the lack of definitive diagnosis for his native kidney disease and absence of common clinical features of anti-GBM disease at the time of transplant. Presumably, the patient suffered from anti-GBM disease causing failure of his native kidneys. This compelling case suggests that in a young male with undiagnosed etiology of kidney failure, a test for the presence of anti-GBM antibodies should be considered before transplantation.

PUB663

Great Threat from a Benign Drug: Vitamin C Causing Severe AKI in a Renal Transplant Patient

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Introduction: Ascorbic acid (AA) is an essential and relatively harmless vitamin if taken in doses less than 2g/day. Despite the lack of randomized controlled trials validating its efficacy, the use of high doses of Vitamin C has been increasing in the intensive care unit(ICU) setting as part of septic shock treatment. AA metabolizes to oxalate and once excreted by the kidneys can deposit in the tubules leading to oxalate nephropathy. In this report, we highlight a case of allograft nephropathy related to oxalate deposition in the setting of high dose of vitamin C use to treat septic shock.

Case Description: 70-year-old female, with history of end stage renal disease due to autosomal dominant polycystic kidney disease, underwent dual deceased donor kidney transplant. On postoperative(POD) day 9, patient developed septic shock from pneumonia, was started on empiric antibiotics, stress dose steroids, vasopressors, IV AA 1.5g every 6 hs and IV thiamine 200 mg every 12hs. In total, a 5-day course of IV Vitamin C (6g/day) was given. Hospitalization further complicated by another septic shock from intraabdominal abscess and secondary peritonitis when IV AA 6g/day was prescribed again for 5 days. She had a prolonged and complicated ICU stay, with sustained stage 3 acute kidney injury (AKI) requiring hemodialysis. Progressively, patient improved clinically but there were no signs of allograft recovery after 2 months from the transplant. A kidney biopsy was performed and showed moderate acute tubular injury with tubular crystal deposition, resembling calcium oxalate crystals. Creatinine levels went back to baseline after discontinuation of AA.

Discussion: The patient described had a complicated postoperative course following renal transplantation requiring prolonged ICU stay due to two episodes of septic shock and respiratory failure. During that time, high doses of IV AA (6g/day) for 10 days was given as adjunct therapy for septic shock. After prolonged AKI, renal biopsy was performed which showed tubular crystal deposition and moderate tubular injury. Clinicians should be aware that high doses of Vitamin C (>2g/day) can cause oxalate nephropathy and a careful assessment of risk and benefits should be made, especially in patients with history of renal disease and kidney transplant.

PUB664

Neurotoxoplasmosis After Kidney-Pancreas Transplantation

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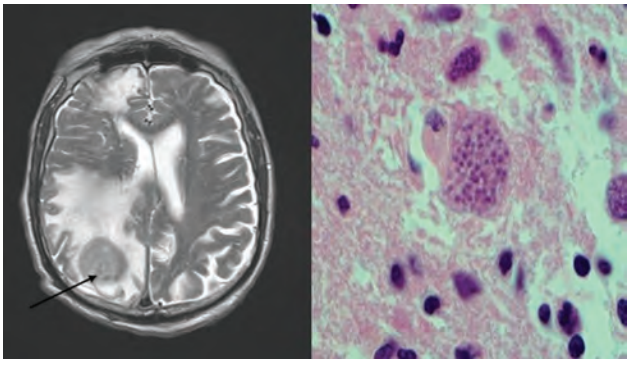
Introduction: Toxoplasmosis is a potentially life-threatening infection that is strongly associated with immunosuppression, such as after solid organ transplantation. Although most cases occur during induction of immunosuppression, reactivation or de novo infection may occur in those with a remote history of solid organ transplantation. We report a case of cerebral toxoplasmosis that mimicked malignancy.

Case Description: A 71-year-old male with end-stage kidney disease status post kidney-pancreas transplantation 21 years ago on mycophenolate mofetil, tacrolimus, and prednisone presented with three weeks of left sided weakness. Vital signs were stable and examination was remarkable for 4/5 strength of the left upper and lower extremities. A right parietotemporal mass lesion with surrounding edema concerning for malignancy was found on MRI. Chest, abdomen, and pelvis PET/CT scan showed no FDG-positive lesions. Five days later, his mental status acutely worsened. Repeat MRI showed an acute right temporal lobe infarction with transtentorial herniation, requiring urgent mass resection. Histopathologic examination showed necrosis with toxoplasma tachyzoites and cystozoites. Immunohistochemistry stains for HSV, VZV, SV-40, CMV, as well as Gram, AFB and Gommori trichrome stains, were negative. HIV serology was negative. Toxoplasma IgG was positive, and IgM was indeterminate. Immunosuppression was discontinued and pyrimethamine-sulfadiazine was initiated. He was discharged to an acute rehabilitation facility after 2 weeks.

Discussion: Toxoplasmosis is a parasitic infection that may present variably as encephalitis, brain abscess, or retinitis. Because of its heterogeneous presentation, a high index of clinical suspicion and close collaboration between the nephrologist, radiologist, pathologist, and microbiologist is required. Early identification is critical since treatment depends on reversal of immunosuppression and initiation of appropriate antimicrobial coverage, such as pyrimethamine-sulfadiazine.



(L)Mass lesion in MRI, (R)Toxoplasma Cystozoite

PUB665

Is Cidofovir an Option for Refractory BK Nephropathy?

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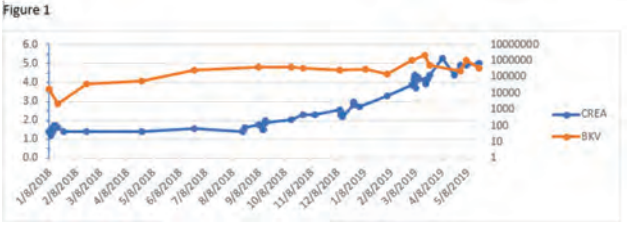
Introduction: BK human polyomavirus typically seroprevalent in humans however BK appears to affect immunocompromised patients and cause clinical disease. In Kidney transplant patients, degree of immunosuppression is associated with BK viremia and nephropathy (BKVN) and has a prevalence of approximately 5 % in post kidney transplant patients. We present the case of a patient who underwent diseased donor renal transplant and developed BK viremia within a month of receiving her transplant. BK viremia was refractory to a reduction in the dose of her immunosuppressive agents, IVIG as well as Leflunomide. BK viremia responded significantly after initiation of intravenous cidofovir.

Case Description: 42 year old female with past medical history including end stage renal disease due to diabetic nephropathy who underwent diseased donor renal transplant and patient had immediate graft function. Maintenance immunosuppression including Tacrolimus, Mycophenolate and Prednisone. She developed BK viremia with in first month after transplant; subsequently mycophenolate was discontinued, and she was started on Leflunomide and IVIG infusion. She received total of eight doses of IVIG. Due to worsening creatinine, patient underwent transplant graft biopsy #1 which showed stage A BK nephropathy with polyoma viral load (PVL) 1-10 %. Second renal biopsy four months later showed stage B BK nephropathy with a PVL > 3 % and SV 40 positive in cortex > 10%. Patient was started on Cidofovir intravenous infusion 0.5 mg/kg every 2 weeks with normal saline pre-treatment infusion 500 ml. The patient's BK viremia started to trend down after initiation of cidofovir (figure 1).

Discussion: BK virus affects immunocompromised renal transplant patients. Transplant graft biopsy will give the definite diagnosis of BKVN with positive for SV40. BKVN thought to be secondary to over immunosuppression. The initial treatment for BK viremia includes lowering immunosuppression followed by IVIG as well as Leflunomide. In patients who are refractory to initial treatment, cidofovir can be a treatment option.

Figure 1



PUB666

Who's to Blame? Angiotensin II Type Receptor Antibodies (AT1R): A Lurking Cause of Sudden Graft Dysfunction in a Patient with Donor-Specific Antibody

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Introduction: AT1R has been linked to refractory humoral rejection and poor transplant outcomes. Vascular inflammation on biopsy, typically without C4d is commonly reported. The signs, histologic presentation, and mechanisms of AT1R mediated graft dysfunction are not well understood and require further study. We discuss an atypical

presentation of AT1R mediated graft dysfunction associated with pre-existing DSA highlighting the need to recognize the potential for multiple mechanisms for graft injury and develop screening protocols post-transplant.

Case Description: A 56 year old African American female with end-stage renal disease due to lupus nephritis received a standard criteria deceased donor kidney transplant. She had a 100% panel reactive antibody and a borderline B cell positive crossmatch due to pre-existing class II DSA with low mean fluorescent intensity (MFI) (900-1600). On post-op day 1 she started 5 sessions of plasma exchange (PP) followed by GammaGard intravenous immunoglobulins. Graft function was immediate, but on day 15, acute kidney injury (AKI) occurred with an abrupt increase in creatinine (3.26 mg/dl to 7.07 mg/dl). Allograft biopsy lacked features of cellular or humoral rejection, was C4d negative and showed only severe ischemic tubular injury (ATN). Given DSA with low stable MFI, and absence of any ischemic event to explain ATN, AT1R titer was measured. Pre-PP titers were (>40units/ml) and remained high despite initial PP. With continued PP and titers (<16 units/ml) her creatinine improved to 1.12 mg/dl.

Discussion: Our patient had persistent low level class II DSAs in a range not expected to cause sudden graft dysfunction and severe AKI. Furthermore, her biopsy had no evidence of humoral or cellular rejection. Only severe ischemic ATN was observed without an obvious cause. As described in preeclampsia, we propose AT1R may impart signals leading to endothelial cell dysfunction and sustained vasoconstriction leading to poor perfusion and ischemia. We argue that AT1R can present without significant inflammation and can function as an agonistic antibody that may be internalized once ligated to membrane bound receptor, thereby avoiding severe complement mediated inflammation and damage.

PUB667

Pulmonary Necrotic Rhodococcus equi Infection in a Kidney Pancreas Transplant Recipient: A Rare Case Treated Without Surgical Intervention

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Introduction: Rhodococcus equi has emerged as a serious pathogen in solid organ transplant recipients. Primary pulmonary involvement is the most common presentation. However, this opportunistic pathogen is often not considered in the differential diagnosis of pneumonia in transplant recipients. Approximately less than 30 cases in renal transplants and only 2 in pancreas transplants have been reported with up to 20-25% mortality.

Case Description: 57-year-old white male who had received his 3rd renal transplant 2 years and 1st pancreas transplant 12 years earlier. At the time of presentation, he was on tacrolimus, mycophenolate mofetil, prednisone and basiliximab for immunosuppression. He presented with a 2 month history of a cough and weight loss. He had been prescribed azithromycin, doxycycline, and ciprofloxacin by his local providers with no improvement. Chest x-ray showed necortic 5cm cavitary right middle lobe lung lesion. On evaluation he was positive for influenza virus, corona virus and aspergillus. Bronchoscopy with BAL and lymph node biopsy cultures showed Rhodococcus Equi. He was started on IV vancomycin, meropenem for 6 weeks and his symptoms improved. He was switched to oral azithromycin and linezolid for another 6 months which was later held for cytopenias. He was then given minocycline after 6 months, while the azithromycin prophylaxis was continued. He was also given voriconazole for his aspergilllus for 12 months. Repeat chest imaging near total improvement in the cavitary lesion and his symptoms resolved over the next 6-9 months. Although surgery was considered an option, due the pericardial location of the lesion it was not pursued. His immunosuppressants were reduced and basiliximab was stopped. His creatinine remained stable around 2.4. Over the following year his pancreas function experienced elevation of lipase which was successfully reversed with steroids and resuming his mycophenolate.

Discussion: R.equi is a unique Acid fast positive cocci and a intracellular pathogen. Here we report a very rare case of Rhodococcus infection in a kidney pancreas transplant recipient which was successfully treated without surgical intervention. Choice of antibiotics were challenging while maintaining dual organ transplant function and avoiding acute rejection.

PUB668

Extended Spectrum Beta-Lactamase Producing Escherichia Coli-Associated Necrotizing Fasciitis in a Kidney Transplant Recipient

Aju Jose, Apaar Dadlani, Nitender Goyal, Jeff Cooper. *Tufts Medical Center, North Attleboro, MA.*

Introduction: Necrotizing fasciitis (NF) is a life-threatening soft tissue infection. NF is usually polymicrobial and can be caused by aerobic, anaerobic, gram-positive, or negative bacteria. Although Escherichia coli (E.coli) associated NF is usually polymicrobial, there have been few case reports of monomicrobial NFassociated with E. Coli. Even fewer are reports of extended-spectrum beta-lactamase (ESBL) producing NF.

Case Description: A 57-year-old African American male kidney transplant recipient presented 2 weeks after transplant with fever, altered mental and scrotal pain. Clinical examination revealed warmth, erythema, and swelling over the transplant kidney incision site that tracked down a grossly enlarged erythematous, warm and tender scrotum. He was intubated due to the inability to protect the airway, fluid resuscitated and started on empiric antibiotics and antifungals vancomycin, cefepime, and micafungin. The patient was emergently taken to the operating room (OR) for wound exploration, and the one-liter perinephric purulent fluid collection was drained. His vitals started improving following drainage, and he came off vasopressors. In the next 24 hours, clinical condition deteriorated with the increasing vasopressor requirement. Cefepime was discontinued, and Piperacillin/Tazobactam and Clindamycin were added. The perinephric fluid and blood culture came back positive for ESBL producing E. Coli, and meropenem was initiated. He developed severe pain to palpation on bilateral thighs and crepitus in the groin region, tracking to the left medial thigh. He was taken back to OR for debridement, and 70% of the scrotal skin was debrided with an onrush of purulent material. He developed dependant new areas of blistering, erythema and worsening crepitus in the groin, thigh, and hip for which he underwent bedside debridement. Despite aggressive resuscitation, the patient died on the third day of hospitalization.

Discussion: Several reports have emphasized importance of Gram-negative rods in NF. To our knowledge, only 3 cases of E. Coli associated NF have been previously described in kidney transplant recipients. Ours is the only case of ESBL producing E.coli NF in kidney transplant recipients. It is important to note that monomicrobial ESBL producing E. coli infection can lead to necrotizing NF, and appropriate antibiotic selection on initial presentation is critical.

PUB669

Zebra Bodies in a Kidney Transplant Recipient

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Introduction: Fabry disease is an X-linked genetic disorder due to deficiency of lysosomal enzyme α-galactosidase A characterized by glycosphingolipids accumulations within body cells and development of concentric lamellar bodies or zebra bodies. It is associated with renal and extra-renal manifestations including angiokeratomas, hypohidrosis, hearing loss, corneal opacity, neurological and cardiac involvement.

Case Description: A 63 year-old Asian male with kidney transplant (10 years ago) due to end stage renal disease secondary to hypertension presented with a 2-week history of lower extremity edema. Clinical findings was remarkable for 2+ pedal edema, and laboratories with slightly elevated serum creatinine, 2.3 mg/dl, a spot urine protein to creatinine ratio of 7.6 grams/gram of creatinine, and tacrolimus level of 4.7 ng/ml. The serum α-galactosidase A level was normal; BK virus PCR and donor specific anti-HLA antibodies were negative. Medications consisted of mycophenolate mofetil, tacrolimus, prednisone, sertraline, nifedipine and vitamin D3. One month post-transplant, he had one episode of biopsy proven rejection without complications. The biopsy of the transplanted kidney revealed focal mild to moderate interstitial fibrosis/tubular atrophy, glomeruli with lobulation of tufts, large endothelial cells with foamy cytoplasm, glomerular capillary endothelial cells and mesangial cells containing lamellar and dense cytoplasmic inclusions or myelin bodies, and chronic rejection related thickening of glomerular basement membrane. No rejection or viral cytopathic effects, immune complex deposits or fibrils were identified. The stain for polyoma virus and the C4d were negative. In addition to chronic transplant glomerulopathy, the diagnosis of glomerular phospholipidosis was entertained.

Discussion: Renal phospholipidosis post-kidney transplant is rarely known. The diagnosis is based on clinical signs and symptoms, confirmed by low enzyme activity in peripheral blood or in leukocytes, or by genetic mutation analysis. Recurrence in allograft post-kidney transplant from non-Fabry Disease donors is rare, therefore awareness among transplant providers of drug induced renal phospholipidosis is important as it can result in post-transplant renal dysfunction and proteinuria.

PUB670

Darling's Disease Presenting with Hypercalcemia in a Kidney Transplant Recipient

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Introduction: Histoplasmosis is an infection caused by a fungus called *Histoplasma*. The fungus lives in the environment, particularly in soil. Spread occurs mainly by aerosolization of spores. Most people that are exposed to *Histoplasma* do not display symptoms. Those who do typically have fever, cough, and fatigue. Most infections resolve spontaneously without treatment. Infection may be severe in people that are immunosuppressed.

Case Description: A 61-year-old man with previous ESRD due to hypertension, second kidney transplant recipient, history of left transplant nephrectomy due to left renal mass presented with complaints of fever, worsening fatigue, dyspnea on exertion, anorexia, and unintentional weight loss of 11 lbs (in the last 2 months) a year after his second kidney transplant. He was admitted to the hospital with suspected pneumonia as worsening bilateral reticular nodular opacities were present on chest radiographs. CT scan of the chest showed innumerable bilateral micro nodules along with dense focal area of consolidation in the right base along with mild mediastinal adenopathy. Empiric cefepime and azithromycin was started for coverage of atypical pneumonia. Bronchoscopy with broncho alveolar lavage (BAL) was done by Pulmonary service and serological workup was sent. (1,3)-Beta-D-Glucan and Histoplasma Galactomannan Urine Antigen were positive. Serum calcium was high normal on admission but peaked at 12.5 mg/dL. Vitamin D 25-OH was 56 ng/mL and Vitamin D 1,25-OH was markedly elevated at 104 ng/mL suggesting exogenous production. Pulmonary histoplasmosis was diagnosed. Mycophenolate was discontinued. Induction with amphotericin B liposomal with pentoxifylline was started and he completed 14 days of treatment. After induction, maintenance oral itraconazole was started with goal length of treatment of 9-12 months. Rare *Histoplasma capsulatum* was isolated in BAL washings fungal culture after 3 weeks. Vitamin D 1,25-OH levels and Histoplasma Galactomannan Urine Antigen concentration has decreased on 1 month follow up.

Discussion: This is a classic case of pulmonary histoplasmosis in an immunocompromised patient in Texas, where *Histoplasma* is only mildly endemic. The proposed mechanism for hypercalcemia in patients with granulomatous disease (e.g. Histoplasmosis) is increased 1-alpha-hydroxylase production by alveolar macrophages.

PUB671

Metabolism Matters: An Interesting Case on Immediate Tacrolimus Metabolism in a Renal Transplant Recipient on Ritonavir-Boosted Antiretroviral Therapy

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Introduction: Access to solid organ transplantation in the setting of human immunodeficiency virus (HIV) infection has been increasing. HIV positive solid organ transplant recipients are at increased risk of acute rejection – partly because of drug interactions. Multiple studies report serious interactions between tacrolimus and ritonavir-boosted HIV-1 protease inhibitors (PIs). The conventional approach is to reduce the tacrolimus dose to around ten percent of the standard dose and anticipate a ritonavir 'washout period' of up to ten days. Local experience managing liver transplant recipients with HCV at this centre have led to the conclusion that the interaction period is much shorter. They therefore advocate less aggressive tacrolimus dose reductions in view of the even higher risks of early rejection if tacrolimus levels are low.

Case Description: We present an interesting case of a patient undergoing haemodialysis who was matched to a deceased brain dead donor through the national organ sharing scheme in the United Kingdom. The patient was on antiretroviral therapy with ritonavir and their HIV viral load had been undetectable for several years. The HIV specialist team recommended a change to a non-tacrolimus interacting regimen at the time of transplantation. The last dose of ritonavir was taken 40 hours before the first administration of tacrolimus. Induction was with basiliximab and maintenance therapy was with tacrolimus (Adoport), mycophenolate mofetil and prednisolone. Whole blood tacrolimus concentrations were measured at the time of first administration (standard single 0.05 mg/kg dose) and at 30, 60, 120, 240, 360, 480 and 720 minutes. Please see the attcahed graph image below

Discussion: Although there is concern about concomitant use of ritonavir and tacrolimus, this case suggests minimal interaction only 40 hours after the last dose, with appropriate tacrolimus concentrations and an exposure to tacrolimus (area under the curve of 91.2 ng.h/mL) comparable to patients receiving tacrolimus not on ritonavir. We conclude that if a patient on antiretroviral therapy is taken off a ritonavir-boosted protease inhibitor regimen when starting or taking tacrolimus therapy, the standard dosing should be considered at the time of the change along with close therapeutic drug monitoring.

PUB672

PTH-Independent Severe Hypercalcemia Secondary to Pneumocystis jiroveci Pneumonia in a Renal Transplant Recipient: A Case Report

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Introduction: Hypercalcemia following renal transplant is a common finding due to preexisting hyperparathyroidism. Pneumocystis Jirovecii Pneumonia (PJP) is an opportunistic infection in solid organ transplant with rare incidence in renal transplant recipients. We report a case of hypercalcemia due to PJP following a change in immunosuppression.

Case Description: 55 year old male, who is a non-sensitized recipient of a second DDKT 34 years ago. He now has CKD stage 3 of the allograft with no prior history of rejection. He presented with a 3 week history of dry cough, hypoxia, lethargy, progressive weakness, 10 pound weight loss associated with diarrhea. He was previously on maintenance immunosuppression with cyclosporine and azathioprine. 6 months prior to presentation, azathioprine was changed to mycophenolate in order to accommodate allopurinol for gout treatment and prevention. He was found to be positive for influenza, clostridium difficile and low grade CMV viremia (2000 IU/ml). Chest x-ray showed multifocal infiltrates. Labs showed calcium of 16mg/dl, ionized calcium of 1.83, PTH of 30pg/ml (baseline 110pg/ml), PTHrp <2pmol/L, calcitriol of 66pg/ml and 25-OH vitamin D of 35ng/ml. He underwent bronchoscopy, BAL was positive for PJP and he was started on IV Bactrim and steroids. He was initially given IV fluids and calcitonin for the hypercalcemia but his calcium levels did not improve. After a week of initiation of IV Bactrim, his ionized calcium decreased to 1.2.

Discussion: The prevalence of hypercalcemia ranges from 8.5 to 71% in renal transplant patients, it is most likely secondary to hyperparathyroidism. Case reports have shown the association of PJP pneumonia and hypercalcemia. Hypercalcemia in PJP is thought due to PTH-independent extra-renal production of 1,25 di-hydroxy vitamin D by activated alveolar macrophages. Previous case series have reported that risk factors associated with PJP pneumonia in solid organ transplant recipients are mycophenolate use, CMV viremia, lymphopenia (<750/mm3) and age >65 years. We believe that switching to mycophenolate led to over immunosuppression which resulted in him developing opportunistic infections, particularly PJP pneumonia. PJP pneumonia is a rare cause of hypercalcemia and should be considered in immunocompromised patients presenting with pneumonia.

PUB673

Arterial Thrombosis from Vascular Clamp Injury: Magnetic Resonance Angiography for Evaluation

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Introduction: The most common vascular complications after kidney transplant are renal artery and renal vein thrombosis. Imaging studies with contrast are often avoided immediately after transplant because of concern of nephrotoxicity with iodinated contrast and risk of nephrogenic systemic fibrosis with gadolinium. We present a case of thrombosis of external iliac artery due to vascular clamp injury diagnosed using non-contrast magnetic resonance angiography (MRA).

Case Description: A 68 year old female with end-stage renal disease presumed due to diabetes and hypertension underwent deceased donor kidney transplant after 8 years of dialysis. Operative course was uneventful. Donor kidney biopsy showed severe vasculopathic changes with concentric fibrointimal hyperplasia. Post-operative course was complicated by delayed graft function and renal ultrasound (US) revealed decreased flow of the main renal artery and vein with resistive index of 0.88-1.0. Repeat US on post-operative day (POD) 2 revealed parvus tardus waveforms in both main renal arteries and minimal arterial perfusion of the transplanted kidney. Non-contrast MRA was obtained, which showed the loss of signal in the proximal right external iliac artery just above the arterial anastomosis, concerning for vascular clamp injury versus thrombosis. Right common iliac arteriogram subsequently showed filling defect in the proximal right external iliac artery at the origin of the upper renal artery transplant anastomosis and retrograde filling of lower renal artery. Attempt at suction thrombectomy was unsuccessful and exploration of allograft showed intramural hematoma in external iliac artery proximal to anastomosis. The patient underwent right external iliac local endarterectomy and reanastomosis of donor renal artery to native external iliac artey. Repeat US on POD 4 revealed improved perfusion of the transplanted kidney. Allograft function improved and the patient came off dialysis on POD 8.

Discussion: Vascular clamp injury is a rare complication after kidney transplantation. Due to impaired renal function, diagnostic imaging with contrast is usually avoided. In the case described above, non-contrast imaging study was used to arrive at the diagnosis of clamp injury induced thrombus. Non-contrast MRA can be helpful early post-transplant to identify vascular complications when contrast study is not an ideal choice because of impaired kidney function.

PUB674

Proliferative Glomerulonephritis with Monoclonal Immune Deposition in a Transplanted Kidney

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Introduction: Proliferative glomerulonephritis is known recur or develop de-novo in the transplanted kidney, and can lead to graft failure. MPGN is a diagnosis of exclusion, and various other diagnoses based on etiology can lead to this pathologic lesion. One cause is immune deposition disease, for which the differential includes SLE, cryoglobulinemic, infection-related, C3 GN, or monoclonal immune deposition disease (MIDD). We present a case of MIDD with proliferative glomerulonephritis in a transplant, with discordant kappa free light chains and plasma cell restriction vs lambda glomerular deposition on biopsy.

Case Description: 58 yo female with history of ESRD from nephrotic syndrome of unclear etiology, multiple myeloma, and DM type 2. She received chemotherapy for myeloma in 2012 with good response. Kidney biopsy in 2012 after initiating hemodialysis, but before myeloma treatment, showed no evidence of paraprotein deposition. The patient was monitored for smouldering myeloma with serial bone marrow exams. She was cleared for transplant and received deceased-donor kidney March 2018. Stable serum Cr 1.0-1.5 and spot urine prot/creat <0.5, until she presented Nov 2018 with acute onset hematuria, edema, AKI, and nephrotic range proteinuria. No other systemic signs or symptoms of myeloma. Serum kappa free light chains elevated with elevated kappa/lambda ratio. Renal biopsy showed acute proliferative glomerulonephritis with lambda predominant IgG immune deposition. Pulse-dose steroids were given, and she was initiated on CyBorD chemotherapy for myeloma. The patient had rapid improvement in renal function to baseline and resolution of proteinuria.

Discussion: We present a rare case of proliferative glomerulitis with monoclonal IgG immune deposits in a transplanted kidney. This syndrome has been characterized as monocolonal gammopathy of renal significance, or "MGRS". The case is notable for discrepancy between lambda light chain deposition on renal biopsy and kappa restricted plasma cells in bone marrow as well as serum free light chains. In this patient, there was rapid recovery of transplant kidney function following treatment for myeloma.

PUB675

Atypical Case of Calcium Phosphate Deposits in Renal Allograft

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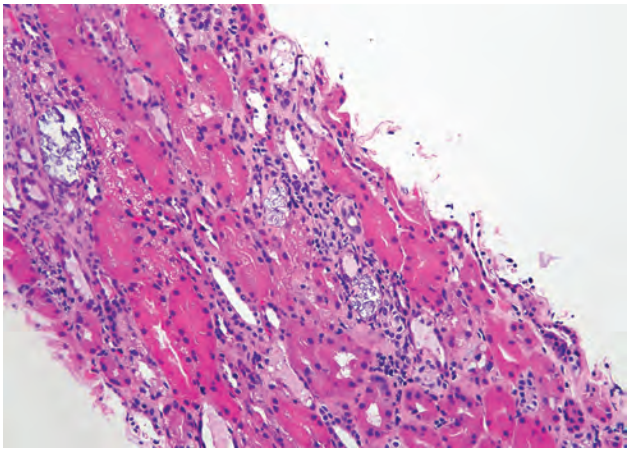
Introduction: Calcium phosphate crystals have been observed in renal allografts within the first six months of transplantation in patients with hyperparathyroidism prior to transplant. Calcium phosphate deposits correlate significantly to mineral metabolism abnormalities. We report a case of persistent renal allograft dysfunction secondary to calcium phosphate crystals with no evidence of hyperparathyroidism or other known risk factors

Case Description: A 38 y.o male PMH of ESRD secondary to Diabetes Mellitus underwent a simultaneous kidney pancreas transplant. Post-transplant allograft biopsies were done at 15,18,21 months for persistent renal function impairment. All biopsies were noted to have heavy calcium phosphate deposits in the renal tubules and persistent severe acute tubular injury. Post-transplant serum calcium ranged between 9.1-9.6 mg/dl, phosphorous 2.7-3.4 mg/dl which were similar to pretransplant levels, calcium excretion ratio showed no hypercalciuria, serum PTH was decreased from a pretransplant value of 587 to 156 pg/ml. Despite normal calcium and phosphorous levels, along with decreasing PTH, heavy calcium phosphate deposits persisted in the allograft. Serum creatinine has remained in the range of 1.8-2.2 mg/dl suggesting calcium phosphate deposits as underlying etiology. Immunosuppression regimen included mycophenolate mofetil, extended release tacrolimus(envarsus) and sulfamethoxazole trimethoprim as prophylaxis

Discussion: Calcium phosphate deposits in the renal allograft have been typically noted in patients with persistent hyperparathyroidism post-transplant. However, in our patient this was observed with normal calcium phosphate product and in setting of decreasing PTH levels. The mechanism of calcium phosphate deposits in this setting is unclear suggesting possible drug induced due to new drugs as extended release tacrolimus(envarsus)



PUB676

Third Renal Transplant in a Patient with Prune Belly Syndrome

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Introduction: Prune belly syndrome (PBS) is most characterized by the lack of abdominal wall musculature, genitourinary defects, and cryptorchidism. 97% of patients with PBS are male and is frequently associated with End Stage Renal Disease (ESRD). The graft survival rate is similar compared to the general population. We present an exceptionally rare case of a PBS who had undergone a third transplant in our institution.

Case Description: 33-year-old African-American male with PBS was evaluated for renal transplant evaluation after two previous failed transplants. He received his first transplant at the age of 10 and it failed due to chronic allograft dysfunction. His right native kidney was removed at the time of the first transplant and the transplant kidney placed in the right lower quadrant. During the second transplant, the kidney in the right lower quadrant was removed and a transplant kidney placed in the left lower quadrant. It failed due to non-compliance with the immunosuppressive therapy. Due to the patient's history of prior transplant's and need for intra-abdominal allograft implantation, cavoplasty was not performed. We performed an end-to-end anastomosis of the donor renal vein to the inferior vena cava and the transplant renal artery to the right common iliac artery. The ureter was implanted into the bladder utilizing double-J ureteral stents. The bladder was tacked to the anterior abdominal wall. There were no adverse post-operative events and he was discharged home in a stable condition the follow up labs revealed normal indices.

Discussion: Third renal transplants are technically challenging from a surgical standpoint. However, the survival is improved when compared to continued dialysis. The transplant provided to the above-described patient will improve both quality of life and survival, justifying the increased surgical risk taken in performing the procedure. In conclusion, we believe that renal transplantation is a viable option for PBS patients with prior donor-organ failure.

PUB677

Persistently Elevated Beta Human Chorionic Gonadotropin in a Non-Pregnant Premenopausal Patient with ESRD

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Introduction: b-hCG has clinical uses in detection of pregnancy, abnormalities in pregnancy, and monitoring trophoblastic diseases and malignancies. Elevated post-menopausal physiologic hCG levels and decreased renal clearance are thought to play a prognostic role in chronic kidney disease, however elevated hCG levels have also been reported in premenopausal women with established ESRD. This age group is especially important due to possibility of pregnancy. Here report a case of persistently elevated b-hCG over several menstrual cycles in a premenopausal woman with ESRD.

Case Description: A 27 year-old woman with ESRD on hemodialysis was hospitalized several times for recurrent abdominal pain in a 50 day period and found to have intermediate range (5 – 15 IU/mL) hCG levels at each of her visits. The patient has a complex medical history including congenital absence of one kidney, past renal transplant, heart failure with reduced ejection fraction and hypertension. The cause of her abdominal pain was never diagnosed but believed to be secondary to either gastritis or hepatic congestion from her congestive heart failure. Her hCG levels showed no obvious associations with timing of hemodialysis sessions or menstrual cycle, or creatinine levels.

Discussion: Very few cases of elevated b-hCG in a non-pregnant premenopausal female with ESRD. Our case had several unique and new findings, including consistently lower hCG levels not meeting the positive threshold but in the intermediate range. Our case also covers the longest timespan of elevated hCG measurements for ESRD patients and only report throughout several menstrual cycles, suggesting that hCG is chronically elevated. The patients multiple organ disease have unclear significance at this time but may contribute information about characteristics of patients with elevated hCG. Her age and lack of hCG correlation with creatinine levels suggests another mechanism for elevated hCG apart from increased postmenopausal levels and decreased renal clearance. This case provides further evidence that special consideration should be given to patients with elevated b-hCG levels who have chronic kidney disease, including women of reproductive age.

PUB678

Unilateral Renal Fibromuscular Dysplasia Presenting as Macroscopic Hematuria in an Normotensive Elderly Female

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Introduction: Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory, hyperplastic disorder that affects medium and small arteries. It occurs predominantly in young females and usually involves the renal and carotid arteries. Classically, renal FMD presents as early onset or difficult to control hypertension.

Case Description: Our patient is a 77-year-old Caucasian female with normal renal function and no history of hypertension who presents to an outpatient nephrology clinic with a several month history of painless gross hematuria. Prior urologic evaluation inclusive of computed tomography (CT) of the abdomen/pelvis showed no masses, no hydronephrosis, a right (R) kidney measuring measuring 6.5cm, a left (L) kidney measuring 9.7cm, multiple renal cysts and apparently patent renal arteries and veins. Cystoscopy suggested bleeding from the R ureteral orifice. Subsequent ureteroscopy revealed inflammatory changes of several R renal calyces and a clot in the R ureteral orifice. Biopsies were obtained and negative for neoplasia. In our clinic, her blood pressure was normal and physical exam benign. Urinalysis noted gross hematuria with many monomorphic red blood cells observed on urine microscopy. Renal ultrasound substantiated the CT findings of a R smaller than L kidney without findings to support renal artery stenosis. Ultimately, a magnetic resonance angiogram of the renal arteries showed hemodynamically significant stenosis in the R renal artery. Bilateral renal angiogram followed which elucidated an irregularity involving a R renal artery branch consistent with FMD that was successfully balloon angioplastied resulting in resolution of her hematuria both grossly and microscopically which has continued for several months following the procedure.

Discussion: Despite renal FMD typically presenting with hypertension in the young, our elderly patient presented with normal blood pressure and unilateral hematuria. Hematuria is a common medical problem and several renal vascular pathologies have been associated with hematuria, including renal FMD, which causes microscopic hematuria in about 50% of cases. Conventional contrast angiography remains the gold standard in confirming this rare diagnosis. Percutaneous renal artery revascularization is currently considered the optimal treatment option with good outcomes in the majority of cases, including our own.

PUB679

Dysnatremia from Vasopressinase in Pregnancy: A Case Series

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Introduction: Sodium homeostasis in pregnancy dramatically differs from that a non-pregnant state. Vasopressinase is a hormone secreted by trophoblasts. Here, we report cases of hyper/hyponatremia in gestation and discuss the pathophysiologic role of vasopressinase.

Case Description: Case 1 (hypernatremia): 28-year-old woman (G3P2, 37 week) with no known past medical hstory presented with one week of abdominal pain, vomiting, excessive thirst and polyuria for 2 weeks. BP 148/100mmHg. Laboratory data was significant for: AST 739U/L, ALT 387U/L, bilirubin 3.0mg/dL, Cr 1.77mg/dl, Na 148mmol/L, K 4.5mmol/L, plasma Osm 307mOsim/kgH20, albumin 2.4g/dL, urine protein 1.6g/gCr. She underwent emergent C-section. Perioperative course was notable for persistent polyuria with urine output of 200-600cc/hr with urine osmolarity (UOsm) 113mOsm/kgH_2O. Diagnosed with gestational diabetes insipidus (DI), she was started on ddAVP 10 mcg intranasally and her Na stabilized ~139mmol/l with UOsm 300mEq/L. **Case 2 (hyponatremia):** 40-year-old woman (G1P0, 27 week) with no past medical history presented with abdominal pain, vaginal bleeding, hypertension and leg edema. She developed hypertension around 22-weeks and mild abnormality in liver function tests since 24-weeks. Vital signs were notable for HR 75, BP 158/102. Laboratory data significant for Na 118mmol/L, K 4.3mmol/L, Cr 0.51mg/dL, urine protein 0.39g/gCr, Psom 240mOsm/kgH2O, UOsm 500mOsm/kgH2O, UNa82 mmol/L. Urine output remained 20-50cc/hr. Diagnosed with SIADH and initiated 3% NaCl infusion perioperatively. She underwent C-section due to fetal distress. Postoperatively her Na remained low ~120 mmol/L. Eventually Na corrected to ~139 mmol/L with fluid restriction.

Discussion: These cases highlight the role of vasopressinase in pregnancy. Gestational DI is rare (2-4 in 100,000 pregnancies), and is felt to be due to impaired degradation of vasopressinase. It is degraded in the liver and is associated with HELLP syndrome. Vasopressinase cleaves AVP but not the synthetic version, ddAVP. Increased vasopressinase levels lasts up to 6-weeks post-partum. In contrast, there have been only several case series of gestational SIADH. This is thought to be related to preeclampsia-associated SIADH with defective placenta producing insufficient vasopressinase. This results in higher ADH levels, causing hyponatremia.

PUB680

Emphysematous Pyelonephritis: An Ultrasound Look-Alike of Staghorn Calculus

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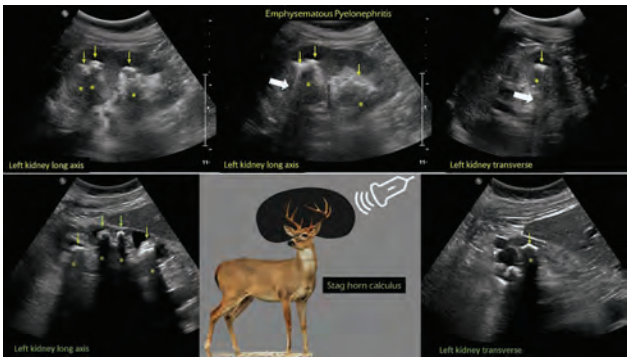
Introduction: Emphysematous pyelonephritis (EPN) is a gas producing, necrotizing infection involving the renal parenchyma and surrounding tissue that is associated with high mortality and morbidity. On a sonogram, it appears as multiple hyperechoic foci with posterior acoustic shadowing mimicking a staghorn calculus. With growing interest in point of care ultrasonography (POCUS) among nephrologists, it is important to be aware of and consider this condition in the differential diagnosis of nephrolithiasis, especially in diabetic patients.

Case Description: A 22-year-old woman with a history of uncontrolled type I diabetes mellitus and hypertension presented with fever and left flank pain for three days. She denied any history of nephrolithiasis. Laboratory data was significant for a serum creatinine of 3.1 mg/dL (last available was 1.3 three years before) and hemoglobin A1c of 12. Urine microscopy showed >50 WBC/hpf, 10 RBC/hpf, and numerous bacteria suggestive of infection. A bedside renal sonogram demonstrated hyperechoic ill-defined material with shadowing throughout the left collecting system suggestive EPN [Figure, top panel]. CT scan without contrast confirmed the diagnosis and excluded extension to extrarenal space. The patient was treated with intravenous antibiotic therapy and showed clinical improvement. A repeat sonogram four days after presentation demonstrated resolution of the emphysematous changes.

Discussion: On a sonogram, both gas and calcified structures appear hyperechoic, the major difference being the echogenic foci caused by gas exhibit posterior "dirty shadowing" as opposed to distinctive echo-free "clean shadow" [Figure, asterisks indicate shadowing] distal to a calculus. Moreover, foci of gas tend to be ill-defined. Ring-down artifacts, when seen, suggest gas in the collecting system. They appear as vertical hyperechoic lines analogous to B-lines on lung POCUS [white arrows]. In patients where POCUS suggests EPN, a non-contrast CT scan should be obtained to confirm the diagnosis and to provide details regarding the extent of infection.



PUB681

Pregnancy-Associated Atypical Hemolytic-Uremic Syndrome

Daniel Guevara,[1] Robin H. Lo.[2] *[1]Nephrology, University of Connecticut, Farmington, CT; [2]University of Connecticut, Trumbull, CT.*

Introduction: Pregnancy-associated atypical hemolytic-uremic syndrome (p-aHUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Triggered by pregnancy, uninhibited activation of the alternative pathway of the complement cascade induces endothelial host cell damage and results in a thrombotic microangiopathy.

Case Description: A 20 year old African American female with history of sickle cell disease was admitted for severe preeclampsia and was treated in the postpartum period at our facility for severe thrombocytopenia and acute kidney injury. The patient was treated for suspected pregnancy induced HUS with plasmapheresis and IV steroids with improvement of renal function and normalization of platelets levels.

Discussion: Pregnancy-associated atypical hemolytic-uremic syndrome (p-aHUS) is a rare condition. The pathogenesis and presentation of P-aHUS remain ill-defined. Diagnosis of p-aHUS is challenging, as it can mimic various diseases found during pregnancy and the postpartum period. Correct diagnosis and timely management are crucial to improve outcomes. Comprehensive genetic and molecular study of the alternative complement pathway are recommended to confirm the diagnosis and to identify patient at risk for aHUS in subsequent pregnancies.

PUB682

Improvement in Cervical Radiculopathy by Erenumab During the Preventive Treatment of Migraine in a Patient with CKD

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Introduction: Pain control of chronic kidney disease (CKD) patient can be challenging especially in those with multiple comorbidities. We present the incidental finding of improvement in cervical radiculopathy in a CKD patient receiving erenumab for the preventive treatment of migraine.

Case Description: A 75-year-old lady with HTN, DM2, CKD, CHF, peripheral vascular disease, osteoarthritis, osteoporosis and migraine presented with a sharp, intermittent, shooting neck pain, which was 7/10 in intensity, radiating to both arms, aggravated by movement of the neck, without a motor deficit. She was taking pantoprazole, sacubitril/valsartan, metoprolol, clonidine, aspirin, linagliptin, pravastatin, alirocumab, denosumab, gabapentin, pentoxifylline, calcitriol, erythropoietin, sevelamer and pain medications including narcotics. Physical exam revealed severe paresthesia from neck to arms, significant neck spasms, loss of cervical lordosis and reduced deep tendon reflexes. MRI of the cervical spine revealed mild nerve root impingement. Appropriate pain medications with gabapentin, non-narcotic and narcotic medications were used without success. The pain progressively worsened within 3 weeks, the intensity being 9/10. Surgery was considered high-risk due to multiple comorbidities. Meanwhile, erenumab was initiated for the preventive treatment of migraine. Neuropathic neck pain intensity concomitantly decreased from 10/10 to 3/10 within a week of erenumab treatment without administering any pain medications, resulting in improvement in her quality of life.

Discussion: Erenumab, a human immunoglobulin G2 (IgG2) monoclonal antibody and a calcitonin gene-related peptide (CGRP) receptor antagonist, has been indicated for the preventive treatment of migraine in adults. CGRP mediates the trigeminovascular pain transmission from intracranial blood vessels to the central nervous system, as well as the vasodilatory component of neurogenic inflammation. Improvement in her cervical radiculopathy during preventive treatment of migraine may be due to inhibition of CGRP, a major mediator of neurogenic inflammation and vasodilation. This incidental finding may suggest additional use of CGRP-inhibitor for the treatment of radiculopathy. Therefore, further researches are necessary to prove this hypothesis.

PUB683

Severe Arteriosclerosis in a Young Patient

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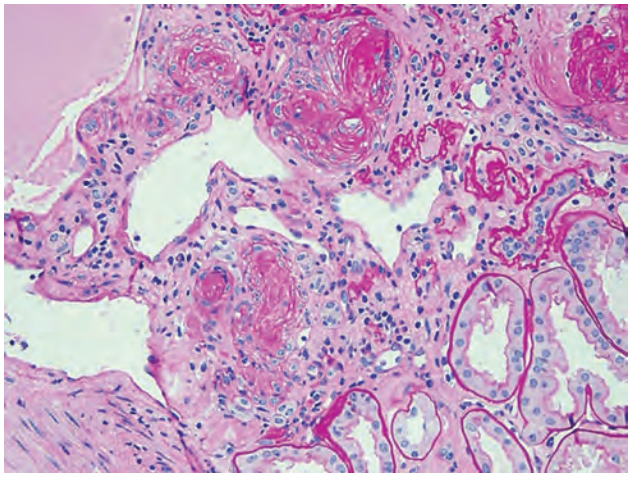
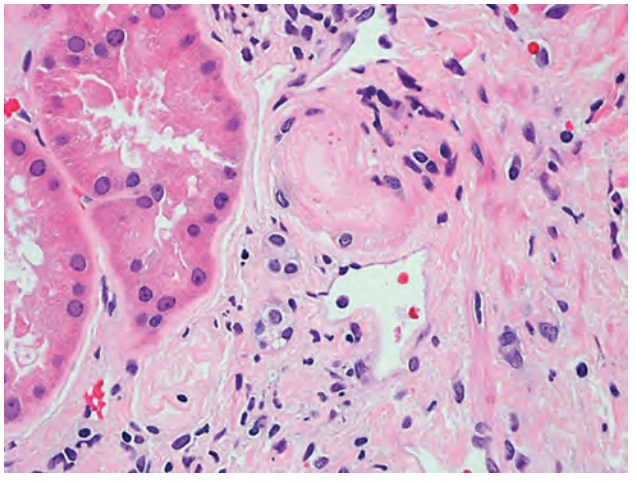
Introduction: Progressive renal failure and HTN in a young patient warrants thorough investigation in an attempt to identify treatable causes.

Case Description: 32 y/o F with HTN and primary hyperPTH s/p partial parathyroidectomy. Had episodes of "Panick attacks" with evidence of episodic and then persistent HTN. PE was normal. Her serum Cr in January 2015 was 1.05 mg/dL, gradually increased over 2 years to 2 mg/dL. UPCR 0.38. No hemauria. urine sediment was unremarkable. CBC normal, Imunological serologies and Secondary HTN w/u were unrevealing Renal biopsy: severe arteriolosclerosis with glomerular obsolescence (19/42) and commensurate tubular atrophy and interstitial fibrosis; no evidence of glomerulonephritis. The larger arterioles had moderate fibrous intimal thickening which narrows the vascular lumen, and many small arterioles have completely obliterated vascular lumens. No arteritis or thrombosis is identified. Schistocytes in the walls of small arteriols were seen, indicating arteriolar TMA.

Discussion: This is a case of progressive renal failure and HTN in a young previously healthy patient. The findings in the arterioles in a woman of this age were striking according to expert renal pathologists and likely are the cause of the glomerular obsolescence and tubular atrophy and interstitial fibrosis. However, the etiology of her vascular disease is less clear. HTN is a possible cause of the renal failure, On the other hand, pt may have a primary renal disease that is not completely understood caused HTN. Arteiolar TMA was a pathological diagnosis.



Completely obliteralted arterioles



Schistocytes in small arterioles

AUTHOR INDEX

The number refers to the location of the body of the abstract in the publication section

KEYWORD INDEX

The number refers to the location of the body of the abstract in the publication section

FR-OR131

Pooled Efficacy and Cardiovascular (CV) Analyses of Roxadustat in the Treatment of Anemia in CKD Patients on and Not on Dialysis

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Background: Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that regulates erythropoiesis & iron metabolism. Integrated Phase 3 analyses examine efficacy & safety of roxadustat in CKD patients (pts).

Methods: Phase 3 studies comparing roxadustat to placebo (pbo), in pts with Stage 3-5 non-dialysis-dependent CKD (NDD) & epoetin alfa in dialysis-dependent (DD) patients were pooled. Death, MI, & stroke (MACE), & heart failure or unstable angina requiring hospitalization (MACE+) were adjudicated. Efficacy analyses assessed Hb & rescue therapy (transfusion, IV iron & ESA). CV endpoints included MACE & MACE+.

Results: In NDD, 4270 pts were randomized (2386 roxadustat;1884 pbo). The primary endpoint (mean Hb CFB; Wks 28-52) was +1.85(.94)g/dL in the roxadustat group v. +.13(±1.01)g/dL in pbo (p<.0001) with lower risk of rescue therapy HR(95% CI)=.19 (.16,.23;81% reduction, p<.0001) in roxadustat. Using ITT long-term follow-up, the HR for time to MACE was 1.08(95%CI .94,1.24) for roxadustat vs. pbo, & 1.04(95% CI .91,1.18) for MACE+. In the subgroup with eGFR>10 (n=3431), MACE HR(95% CI)=.99(.84,1.16) & MACE+ HR=.98 (.85,1.14), for roxadustat v. pbo. In DD, 3917 patients were randomized (1960 roxadustat;1957 epoetin alfa). The primary endpoint (mean Hb CFB Wk 28-52) was 1.21 in roxadustat v. .95 g/dL in EPO (difference .26 g/dL;95%CI .20,.33) in pooled analysis; roxadustat was noninferior & superior to EPO (p<.0001). The roxadustat group received fewer transfusions, 9.5 v.12.8%; HR(95%CI) =.82(.679,.997). Comparing roxadustat with EPO, HR for MACE = .95 (95% CI .81,1.12) & for MACE+ HR=.84 (.73,.97;p=.02) in DD pts. Of 1526 incident pts (dialysis <4 months), HRs for MACE & MACE+ =.70 (95% CI .51,.97) (p=.03) & .66 (95%CI .50,.89)(p=.005).

Conclusions: These integrated Phase 3 analyses provide evidence for roxadustat superiority in anemia correction with transfusion reduction & acceptable CV safety profile.

Funding: Commercial Support - FibroGen Inc. AstraZeneca plc

FR-OR132

Effect of Angiotensin-Neprilysin Inhibition on Renal Outcomes in Heart Failure with Preserved Ejection Fraction

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Background: Chronic Kidney Disease (CKD) confers an increased risk of cardiovascular (CV) and renal events in patients with heart failure and preserved left ventricular ejection fraction (HFpEF). We assessed the long-term renal effects of angiotensin/neprilysin inhibition, a prespecified secondary outcome, in patients with HFpEF enrolled in the PARAGON-HF trial.

Methods: In this randomized, double-blind, parallel group, active controlled, event-driven trial, we assigned 4,822 patients with chronic HFpEF to receive sacubitril/valsartan or valsartan. Key exclusion criteria included a baseline eGFR <30mL/min/1.73m2. The prespecified renal outcome, a key secondary endpoint, was the time to first occurrence of either a ≥50% reduction in eGFR relative to baseline, attainment of end-stage renal disease, or renal death. We also evaluated the effect of treatment on the change in eGFR during follow up, and the influence of eGFR on the efficacy of sacubitril/valsartan for reducing the primary composite outcome.

Results: The mean age was 73±8 years; 52% were female. At baseline, mean (+/- SD) eGFR was 63±19 mL/min/1.73m2; 2,341 participants (49%) had CKD (eGFR <60 mL/min/1.73m2) and 43% had diabetes. At study closure, the composite renal outcome had occurred in significantly fewer patients in the sacubitril/valsartan group compared with the valsartan group (HR 0.50, 95% CI 0.33, 0.77, p = 0.002), and the mean decline in eGFR during follow up was less for the sacubitril/valsartan group (full results will be available for the ASN annual meeting). Patients with lower eGFR derived greater benefit from sacubitril/valsartan for reducing the primary composite outcome of total heart failure hospitalization or CV death.

Conclusions: In patients with chronic HFpEF, sacubitril/valsartan reduced the risk of clinically important renal events, and slowed the progression of kidney disease, compared with valsartan. (Funded by Novartis; PARAGON-HF ClinicalTrials.gov number, NCT01920711.)

Funding: Commercial Support - Novartis

FR-OR133

The Dapagliflozin in Heart Failure with Reduced Ejection Fraction Trial (DAPA-HF): Outcomes in Patients with CKD and Effects on Renal Function

Scott D. Solomon,[1] Pardeep Jhund,[3] Mikhail Kosiborod,[2] Subodh Verma,[4] Silvio E. Inzucchi,[5] Anna Maria Langkilde,[6] Felipe Martinez,[7] Olof Bengtsson,[8] Kieran F. Docherty,[3] Lars Køber,[9] Mikaela Sjostrand,[8] Marc S. Sabatine,[10] John McMurray.[11] DAPA-HF Executive Committee *[1]Brigham and Women's Hospital, Boston, MA; [2]Saint Luke's Mid America Heart Institute, Kansas City, MO; [3]BHF Glasgow Cardiovascular Research Centre, Glasgow, United Kingdom; [4]St. Michael's Hospital, Toronto, ON, Canada; [5]Yale University School of Medicine, New Haven, CT; [6]AstraZeneca, Gothenburg, Sweden; [7]DAMIC Institute, Cordoba, Argentina; [8]Astrazeneca, Molndal, Sweden; [9]Rigshospitalet, Copenhagen, Denmark; [10]TIMI Study Group, Boston, MA; [11]University of Glasgow, Glasgow, United Kingdom.*

Background: A substantial proportion of patients with heart failure and reduced ejection fraction (HFrEF) have or develop chronic kidney disease (CKD). SGLT-2 inhibitors have been shown to delay the progression of kidney disease and reduce the incidence of cardiac events in patients with type 2 diabetes (T2D) and CKD. Dapagliflozin (DAPA) was shown in the DAPA-HF Trial to reduce the primary composite outcome of a worsening heart failure event or cardiovascular death in patients with HFrEF, both with and without T2D

Methods: We randomized 4744 patients with NYHA class II-IV heart failure, LVEF ≦40%, elevation in natriuretic peptides and optimal background HFrEF therapy to DAPA 10mg qd or placebo (PBO). The primary outcome is described above. The prespecified secondary renal outcome was a sustained ≥50% reduction in eGFR, end-stage renal disease or death from renal causes. We also prespecified an analysis of the effect of DAPA, compared to PBO, in patients with and without CKD (eGFR <60 ml/min/1.73m^2 at baseline).

Results: Overall, 45% of patients had T2D and 55% did not. The baseline eGFR was 65.8 ± 19.4 ml/min/1.73m^2 and 1926 (40.6%) patients had CKD. A worsening heart failure event or cardiovascular death (the primary end point) occurred in 386 patients (16.3%) in the DAPA group and 502 patients (21.2%) in the PBO group: hazard ratio [HR] 0.74; 95% confidence interval [CI], 0.65-0.85; P<0.001. DAPA reduced the primary outcome by a similar magnitude in patients with CKD (HR 0.72, 95%CI 0.59-0.86) and without CKD (HR 0.76, 95%CI 0.63, 0.92) - results to be shown at ASN. The composite renal endpoint was observed in 28 (1.2%) patients in the DAPA group vs 39 (1.6%) in the PBO arm (HR 0.71, 95% CI 0.44, 1.16). Renal serious adverse events and investigator reported acute kidney injury were significantly less common in the DAPA group. Additional results, including eGFR over-time, will be shown at the ASN annual meeting.

Conclusions: In this trial including HFrEF patients with and without T2D, DAPA reduced the composite of a worsening heart failure event or cardiovascular death, both in participants with CKD and in those without CKD. The absolute benefit in patients with CKD was substantial.

Funding: Commercial Support - AstraZeneca

FR-OR134

Efficacy and Safety of Difelikefalin in Patients Undergoing Hemodialysis with Pruritus: Results from a Phase 3 Randomized, Controlled Study (KALM-1)

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Background: There is an unmet need for effective treatments for pruritus associated with chronic kidney disease (CKD-aP or uremic pruritus), a debilitating condition prevalent in patients undergoing hemodialysis (HD). Difelikefalin (DFK; CR845) is a novel, peripherally restricted kappa opioid receptor (KOR)-specific agonist in development for treatment of pruritus. Here we report on the first Phase 3 study of DFK in HD patients with CKD-aP.

Methods: Patients with moderate-to-severe CKD-aP undergoing HD (N=377) were randomized 1:1 to receive an IV bolus of DFK 0.5 mcg/kg (N=189) or placebo (PBO) (N=188), thrice weekly post dialysis, over 12 weeks. The primary endpoint was the proportion of patients achieving ≥3-point improvement from baseline (BL) to Week 12 in the weekly mean of 24-hr daily Worst Itching Intensity Numerical Rating Scale (WI-NRS) scores. Secondary endpoints included the change in itch-related QoL measured by 5-D Itch and Skindex-10 questionnaires and the proportion of patients achieving ≥4-point WI-NRS score improvement from BL to Week 12. Safety was assessed based on vital signs, clinical laboratory results, ECG, and adverse event (AE) reporting.

Results: The primary and all secondary efficacy endpoints were met. BL mean WI-NRS scores were 7.1 and 7.3 in DFK and PBO groups. Percentages of patients with ≥3-point improvement and ≥4-point improvement in mean WI-NRS scores at Week 12 were 51% vs 28% (p<0.001; odds ratio (OR) 2.7) and 39% vs 18% (p<0.001, OR 2.9) for DFK vs PBO. Separation from PBO in WI-NRS score change from baseline was observed at Week 1. All QoL measures were significantly improved vs PBO (p<0.001). Serious AE incidence was similar for DFK vs PBO; most common treatment emergent AEs were diarrhea (9.5% vs 3.7%), dizziness (6.9% vs 1.1), and vomiting (5.3% vs 3.2%).

Conclusions: This study demonstrated that DFK significantly reduced itch intensity in HD patients. Patients treated with DFK were about 3 times (based on OR) more likely to have a clinically meaningful reduction in itch intensity vs PBO and had significant improvements in QoL. DFK was generally well tolerated with an acceptable safety profile. DFK could represent an important advance for treatment of pruritus in HD patients.

Funding: Commercial Support - Cara Therapeutics, Inc.

Underline represents presenting author/disclosure.

FR-OR135

Mycophenolate Mofetil vs. Azathioprine in Kidney Transplant Recipients on Steroid-Free, Low-Dose Cyclosporine Immunosuppression: The ATHENA Trial

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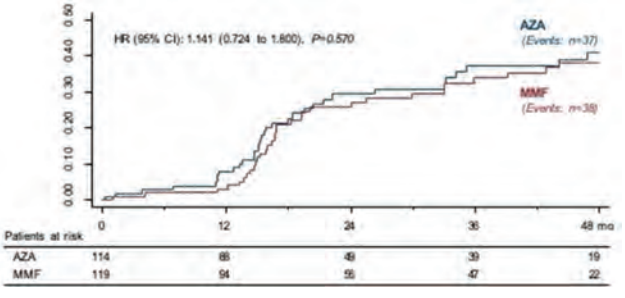
Background: Registration trials with old sandimmune formulation of cyclosporine (CsA) suggested that Mycophenolate Mofetil (MMF) prevents acute cellular rejection (ACR) more effectively than Azathioprine (AZA), but multiple trials with standard-dose of more stable microemulsion formulation of CsA (Neoral) did not confirm this. The safety/efficacy of MMF and AZA in kidney transplant recipients on steroid-free, low-dose CsA Neoral is unknown.

Methods: The ATHENA trial (NCT00494741) was a randomized, prospective, multicenter trial comparing THe Effect on chronic allograft Nephropathy prevention of mycophenolate mofetil versus Azathioprine as the sole immunosuppressant for kidney transplant recipients. All patients were induced with low-dose Thymo + basiliximab. Those with stable graft function, no previous ACRs and no infiltrates at 1-yr surveillance biopsy underwent CsA tapering to half of the initial dose. Primary endpoint was cumulative incidence of chronic allograft nephropathy (CAN) at 3 yrs.

Results: We included 233 patients (119 on MMF; 114 on AZA). At 3 yrs, 38 patients on MMF (31.9%) vs 37 on AZA (32.4%) developed CAN (**Figure**); 22 on MMF (18.5%) vs 24 on AZA (21.1%) had biopsy-proven ACR (p=0.72); 11 on MMF (9.2%) and 8 on AZA (7.0%) had sub-clinical (sCreat increase <10% during previous 3 mo) ACR at 1-yr surveillance biopsy (p=0.47); 6 on MMF (5.0%) vs 7 on AZA (6.1%) had graft failure (p=0.54). 3-yr eGFR was similar between MMF and AZA groups (53.8±20.2 vs 51.4±18.8 ml/min/1.73m^2, p=0.50). 19 patients on MMF (16.0%) vs 21 on AZA (18.4%) successfully tapered CsA doses, with only one ACR episode per arm. Post-tapering eGFR was stable.

Conclusions: In kidney transplant recipients on low-dose CsA and no steroids, AZA and MMF are associated with similar incidence of CAN, of clinical or subclinical ACR, and similar graft survival and function. AZA represents a valuable, less expansive, alternative to MMF also on low-dose maintenance immunosuppression.

Funding: Government Support - Non-U.S.



Kaplan-Meier of CAN incidence in the two study arms.

FR-OR136

A Phase 2 Randomized, Controlled Study of Obinutuzumab with Mycophenolate and Corticosteroids in Proliferative Lupus Nephritis

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Background: Type I anti-CD20 antibodies such as rituximab fail to achieve complete B-cell depletion in lupus nephritis (LN). NOBILITY tested whether enhanced B-cell depletion with the type II anti-CD20, obinutuzumab (OBI), could improve responses in LN compared to placebo (PBO). (NCT02550652)

Methods: Patients with active Class III/IV LN (n=125) received standard-of-care mycophenolate and steroids and were randomized to OBI or PBO and followed for 104 weeks. The primary endpoint (EP) was complete renal response (CRR) at week 52. Key secondary EPs included overall renal response (ORR) and modified CRR (mCRR). Results through week 76 are reported. The two-sided alpha level was 0.2.

Results: Baseline mean urine protein:creatinine ratio (UPCR) and serum creatinine were 3.1 g/g and 0.84 mg/dL. OBI was associated with increased renal responses vs. PBO at weeks 52 and 76 (**Table**). 80% of OBI pts and 0% of PBO pts had CD19+ count <0.441 cells/μL at week 52. Significant improvements in anti-dsDNA, C3, and C4 were observed with OBI vs. PBO. Through week 76, serious adverse events (OBI 24% vs. PBO 29%) and serious infections (6% vs. 18%) were not increased with OBI. Nonserious infusion-related reactions were more common with OBI (16% vs. 10%). There were 5 deaths (1 OBI, 4 PBO).

Conclusions: NOBILITY met its primary and secondary efficacy EPs. OBI was superior to PBO for the achievement of renal response at 12 and 18 months in proliferative LN patients treated with mycophenolate and steroids. There were no unexpected safety findings.

Funding: Commercial Support - F. Hoffmann-La Roche

	Obinutuzumab	Placebo	Difference (80% CI)	P value
Week 52				
CRR	35%	23%	12% (2, 23)	0.115
ORR	56%	36%	20% (9, 31)	0.025
mCRR	40%	26%	14% (3, 25)	0.090
mCRR2	44%	34%	11% (−1, 22)	0.183
mCRR3	46%	39%	7% (−4, 19)	0.373
anti-dsDNA <30 IU/ml	49%	26%	24% (13, 36)	0.007
C3 >90 mg/dL	79%	48%	31% (21, 41)	0.0004
C4 >10 mg/dL	97%	74%	23% (15, 30)	0.0004
Week 76				
CRR	40%	18%	22% (12, 32)	0.007
ORR	51%	29%	22% (11, 33)	0.015
mCRR	48%	23%	25% (15, 36)	0.003
mCRR2	49%	31%	19% (8, 30)	0.029
mCRR3	57%	37%	20% (9, 31)	0.021

CRR = UPCR <0.5 with serum creatinine (SCr) ≤ the upper limit of normal and not increased >15% from baseline with <10 red blood cells per high powered field (RBCs/HPF) and no RBC casts.
ORR = Either CRR or partial renal response: ≥50% reduction in UPCR from baseline to <1 (<3 if baseline UPCR ≥3) with SCr not increased >15% from baseline and ≤50% increase in urinary RBCs (or <10 RBCs/HPF).
mCRR = CRR without urinary sediment requirements.
mCRR2 = CRR with SCr that is ≤ the upper limit of normal *or* not increased >15% from baseline.
mCRR3 = UPCR <0.5 with normal SCr.

Table. Outcomes at Weeks 52 and 76

FR-OR137

Preventing Early Renal Loss in Diabetes (PERL) Study: Outcome of a 3-Year Trial of Serum Uric Acid Reduction with Allopurinol

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Background: Observational studies have shown that higher serum uric acid (SUA) is associated with a higher risk of diabetic kidney disease (DKD) in type 1 diabetes (T1D). PERL (NCT02017171) evaluated whether lowering SUA with allopurinol could slow glomerular filtration rate (GFR) decline in patients with T1D and mild to moderate DKD.

Methods: This double-blind, placebo-controlled, multicenter, international trial randomized 530 persons with T1D, estimated GFR (eGFR) 40-99.9 mL/min/1.73 m^2, SUA ≥4.5 mg/dL, and micro- to macroalbuminuria (79.1%) or normoalbuminuria with historical eGFR decline ≥3 mL/min/1.73 m^2/year (20.9%) to allopurinol (A, n=267) or placebo (P, n=263). The primary outcome was baseline-adjusted iohexol GFR (iGFR) after 3 years of treatment plus a 2-month drug washout period. Treatments were compared by means of a linear model with correlated errors using the intention-to-treat population.

Results: Participants were 66% male and 84% white. Baseline median age was 52 years, T1D duration was 35 years, and HbA1c was 8.0 %; 93% had hypertension and 90% were on RAS blockers. These factors were balanced between A and P. The mean (± SD) baseline iGFR was 68.7 ± 17 in A and 67.3 ± 17 mL/min/1.73 m^2 in P. Baseline SUA was 6.1 ± 1.5 mg/dL in both groups. During the trial, SUA averaged 4.1 ± 1.2 in A and 6.2 ± 1.3 mg/dL in P (p <0.0001). Baseline-adjusted iGFRs at the end of the drug washout period were virtually identical in A and P (least square mean ± SE = 61.2 ± 1.6 mL/min/1.73 m^2 in both, p=0.99). Rates of iGFR decline over the 3 years of treatment were -3.0 in A and -2.5 mL/min/1.73 m^2/year in P (p=0.25), at or close to the loss of -3.0 mL/min/1.73 m^2/year expected in untreated subjects. No statistically significant treatment differences were seen in the secondary outcomes of iGFR before drug washout, eGFR slope, or time to serum creatinine doubling or ESKD. Albuminuria levels at washout were higher in A than in P (baseline-adjusted geometric means: 42.9 vs. 31.7 μg/min, p=0.035).

Conclusions: PERL – the largest CKD trial of allopurinol to date – found no significant benefit of SUA reduction on kidney outcomes in T1D persons with mild to moderate GFR reduction and SUA levels above the median. Secondary analyses are in progress to assess whether results are similar across pre-specified clinical sub-groups.

Funding: NIDDK Support, Private Foundation Support

Underline represents presenting author/disclosure.

FR-OR138

Effects of Vitamin D and Omega-3 Fatty Acid Supplementation on Kidney Function and Damage in Type 2 Diabetes

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Background: Vitamin D and omega-3 fatty acid supplements are readily available and safe interventions that may help prevent the development and progression of diabetic kidney disease. Preclinical and observational studies suggest that vitamin D suppresses the renin-angiotensin system, reduces renal inflammation and fibrosis, and exerts direct pro-survival effects on podocytes, while omega-3 fatty acids have potentially beneficial anti-inflammatory, antithrombotic, and vascular properties.

Methods: We performed a randomized clinical trial of 1,312 adults with type 2 diabetes to test whether supplementation with vitamin D_3 or omega-3 fatty acids for five years prevents the development or progression of CKD. The study was completed as an ancillary study to the VITamin D and OmegA-3 TriaL (VITAL). In a 2-by-2 factorial design, participants were randomly assigned to vitamin D_3 (2000 IU daily) or placebo and to omega-3 fatty acids (eicospentaenoic acid and docosahexaenoic acid, 1 g daily) or placebo. The primary outcome was change in glomerular filtration rate estimated from serum creatinine and cystatin C (eGFR) from baseline to year 5.

Results: Baseline mean age was 67.6 (SD 6.9) years, 46% of participants were women, and 31% were racial or ethnic minorities. Baseline mean (SD) eGFR was 85.8 (22.1) mL/min/1.73m^2, and mean change in eGFR from baseline to year 5 was -12.7 (SD 14.6) mL/min/1.73m^2. There was no significant difference in change in eGFR comparing vitamin D_3 to placebo (difference in change 0.8 (95% CI -0.8, 2.5) mL/min/1.73m^2) or omega-3 fatty acids to placebo (difference in change 0.8 (95% CI -0.8, 2.4) mL/min/1.73m^2). Null results were robust in analyses restricted to participants with complete data or to participants who were highly adherent to study medications. No significant difference was observed in secondary outcomes, including change in eGFR after 2 years of treatment, a composite outcome of loss of eGFR ≥40% from baseline or kidney failure (N=85 events), and change in urine albumin excretion.

Conclusions: Neither vitamin D nor omega-3 fatty acid supplementation reduced the development or progression of kidney disease among adults with type 2 diabetes.

Funding: NIDDK Support

TH-PO1183

Kidney Protection Using the RenalGuard® System in Cardiac Surgery (KIDNEY Study): A Randomised Control Trial Assessing AKI Rate

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Background: Acute kidney injury (AKI) after cardiac surgery occurs in up to 30% of patients & is associated with significant morbidity & mortality. RenalGuard® system (RG) has been shown to reduce AKI rates in patients undergoing Percutaneous Cardiac Intervention (PCI, TAVR). This study investigated the efficacy & safety of balanced forced diuresis using the RenalGuard® system in cardiac surgical patients requiring cardiopulmonary bypass (CPB)

Methods: Patients at risk of developing AKI during cardiac surgery (history of diabetes &/or anemia, e-GFR < 60 ml/min/1.73m^2, anticipated CPB time > 120 minutes, Log EuroScore >5) were randomized to either RG (n=110) or managed as per current management strategy (control=110). Primary end-point was the development of AKI, defined by RIFLE criteria, within first 3 days of surgery. (Trial registration:NCT02974946)

Results: There were no significant differences in patients' pre & intra-operative characteristics (age, gender, LVEF, surgery type, Log EuroScore, pre-op creatinine & e-GFR levels, CPB & cross-clamp times & pre-op history of diabetes, peripheral vascular disease & renal impairment) between the 2 groups. Post-operative AKI rates were significantly lower in RG group compared to control (10% (11/110) v/s 20.9% (23/110), p=0.025). Binary logistic regression analysis confirmed RG system to be independently associated with significant AKI reduction (OR 2.82, 95%CI 1.20 – 6.60, p=0.017). The mean volumes of urine produced during surgery (2337+/-896 ml v/s 766+/-557 ml) & within first 24 hours post-op (3297 +/- 1298 ml v/s 2053 +/- 802 ml) were significantly higher in RG group (p<0.01). There was no significant difference in the incidence of blood transfusions, atrial fibrillation, infections, cerebro-vascular events, median ICU and in-hospital stays between the two groups. One patient in the RG group & two patients in the control group died prior to hospital discharge. The number needed to treat (NNT) with the RG system to prevent AKI was 9 patients

Conclusions: In patients at-risk for AKI, undergoing cardiac surgery with the CPB, the RenalGuard® system significantly reduced the incidence of AKI and can be used safely & reproducibly. Larger studies will be required to assess the cost benefit of this device

Funding: Other NIH Support - National Institute of Health Research UK, West Midlands CRN, Commercial Support - RenalGuard plc

TH-PO1184

Results of the START-CKD Trial (Strategies Using Darbepoetin Alfa to Avoid Transfusions in CKD)

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Background: Exposure to high doses of an erythropoiesis stimulating agent (ESA), high cumulative dose, wide Hb excursions, and rapid hemoglobin (Hb) rises may contribute to cardiovascular adverse events with ESA use. Thus, there is a desire to define an ESA dosing strategy that minimizes red blood cell transfusion and limits dose. The START-CKD trial evaluated such a dosing strategy using darbepoetin in anemic subjects with stage 3-5 CKD using a fixed dosing (FD) strategy of 0.45 µg/kg Q4 wks or a Hb-based titration dose (TD) algorithm (per US prescribing information (USPI).

Methods: This was a US phase 3, multicenter, randomized, double-blind, parallel group study (N=756; ClinicalTrials.gov, NCT01652872) with 377 subjects randomized to the TD and 379 to the FD treatment for up to 2 years. The primary endpoint was the percentage of subjects transfused. Transfusions, per protocol, were performed as deemed necessary by the treating physician and were prospectively adjudicated.

Results: Mean age of the subjects, baseline Hb and eGFR: 69 yrs., 9.0 g/dL and 22 ml/min/1.73m^2, respectively and were balanced between arms. The % of subjects transfused was 24.1% vs 24.4% in the FD and TD groups, respectively, with similar time to first transfusion (HR 1.01, Figure A). Average Hb achieved was greater in the TD group compared to the FD group, 9.7 vs 9.4 g/dL respectively (Figure B). Average cumulative dose of darbepoetin per 4 wks was less in the FD group, 30.8 µg vs 50.7 µg.g.

Conclusions: In this study, minimizing RBC transfusion can be achieved using a low fixed-dose of darbepoetin with lower cumulative dose than use of Hb-based dose titration approach.

Funding: Commercial Support - Amgen, Inc.

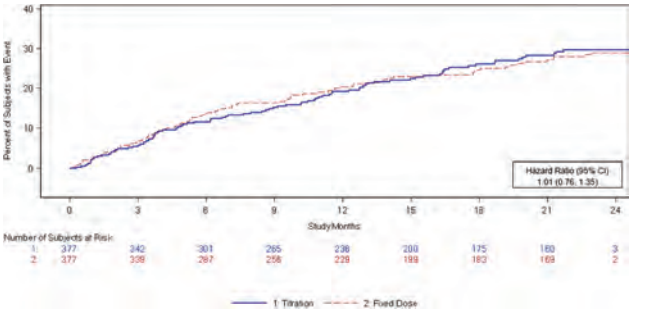

Figure A. Kaplan-Meier Plot of Time to First RBC Transfusion

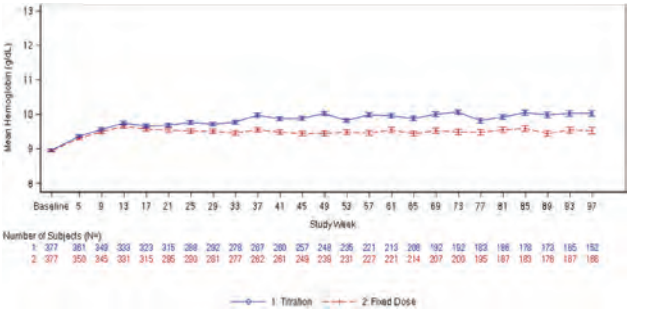

Figure B. Hemoglobin Concentration at Each Study Visit (Mean +/- SE)

Underline represents presenting author/disclosure.

TH-PO1185

Phase 3 Study to Compare the Efficacy and Safety of Enarodustat (JTZ-951), an Oral HIF-PH Inhibitor, with Darbepoetin Alfa in Anemic Patients with CKD Not Requiring Dialysis

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Background: This phase 3 study was conducted to verify the efficacy (non-inferiority to darbepoetin alfa (DA)) and safety of enarodustat in Japanese anemic patients with CKD not requiring dialysis in randomized, open-label, parallel-arm comparison manner for 24 weeks.

Methods: Patients were respectively randomized in 1:1 ratio to receive either enarodustat orally once daily or DA subcutaneously every 2 or 4 weeks. The doses were adjusted every 4 weeks to maintain Hb levels within a target range (10-12 g/dL). The primary endpoint was difference in mean Hb level between arms during the evaluation period defined as Week 20-24 (non-inferiority margin: -0.75 g/dL). Other assessments included proportion of patients whose Hb level was within the target range, iron-related parameters, renal function-related parameters, and NT-pro BNP.

Results: 216 patients were randomized to receive either enarodustat (n=107) or DA (n=109). The mean Hb level of each arm during the evaluation period was 10.96 g/dL (95% CI: 10.84, 11.07) with enarodustat arm and 10.87 g/dL (95% CI: 10.75, 10.99) with DA arm. The difference between arms in the mean Hb level was 0.09 g/dL (95% CI: -0.07, 0.26), confirming the non-inferiority to DA. Proportions of patients whose Hb level was within the target range during the evaluation period were 89.6% in enarodustat arm and 90.6% in DA arm. Increase of TIBC and decrease of hepcidin were observed in enarodustat arm. No apparent difference between arms in the incidence of AEs including CV events and hypertension-related events were observed. There were no negative effects of enarodustat on NT-pro BNP or renal function-related parameters.

Conclusions: Enarodustat, administered orally, was as effective as DA, administered subcutaneously, in maintaining Hb levels in Japanese anemic patients with CKD not requiring dialysis. No new safety concerns were identified when compared with DA.

Funding: Commercial Support - Japan Tobacco Inc.

TH-PO1186

Phase 3 Study to Compare the Efficacy and Safety of Enarodustat (JTZ-951), an Oral HIF-PH Inhibitor, with Darbepoetin Alfa in Anemic Patients with CKD Receiving Maintenance Hemodialysis

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Background: This phase 3 study was conducted to verify the efficacy (non-inferiority to darbepoetin alfa (DA)) and safety of enarodustat in Japanese anemic patients with CKD receiving maintenance hemodialysis in randomized, double-blind, parallel-arm comparison manner for 24 weeks.

Methods: Patients, who have been receiving a stable dose of ESAs and have protocol specified Hb criteria (Hb level of 9.5≥ g/dL and <12.0 g/dL), were randomized in 1:1 ratio to receive either enarodustat orally once daily or DA intravenously every week after switching from ESAs. The doses were adjusted every 4 weeks to maintain Hb levels within a target range (10-12 g/dL). Intravenous iron preparations were prohibited during the screening period and the initial treatment period (Week 0-4). The primary endpoint was difference in mean Hb level between arms during the evaluation period defined as Week 20-24 (non-inferiority margin: -1.0 g/dL). Other assessments included proportion of patients whose Hb level was within the target range and iron-related parameters.

Results: 173 patients were randomized to receive either enarodustat (n=87) or DA (n=86). The mean Hb level of each arm during the evaluation period was 10.73 g/dL (95% CI: 10.56, 10.91) with enarodustat arm and 10.85 g/dL (95% CI: 10.72, 10.98) with DA arm. The difference between arms in the mean Hb level was -0.12 g/dL (95% CI: -0.33, 0.10), confirming the non-inferiority to DA. Proportions of patients whose Hb level was within the target range during the evaluation period were 78.2% (95% CI: 67.4, 86.8) in enarodustat arm and 88.8% (95% CI: 79.7, 94.7) in DA arm. Increase of TIBC and decrease of hepcidin were observed through Week 4 in enarodustat arm albeit after switching from ESAs. Proportions of patients who experienced any AEs or SAEs were 87.4% and 14.9% in enarodustat arm and 83.7% and 14.0% in DA arm, respectively.

Conclusions: Enarodustat was proved to be non-inferior to DA in the treatment of anemia in Japanese CKD patients receiving maintenance hemodialysis, and was generally well-tolerated.

Funding: Commercial Support - Japan Tobacco Inc.

TH-PO1187

Efficacy of Tenapanor in Combination with Phosphate Binders in CKD Patients on Dialysis with Uncontrolled Hyperphosphatemia While on Phosphate Binders Alone

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Background: Tenapanor (TEN) is a first-in-class, non-binder, phosphate absorption inhibitor being developed to treat hyperphosphatemia in dialysis patients. It has a unique mechanism of action and acts locally in the gut to inhibit the sodium-hydrogen exchanger 3 (NHE3). This results in the tightening of the epithelial cell junctions, reducing paracellular uptake of phosphate, the primary pathway of phosphate absorption, and thereby reducing serum P concentrations.

Methods: 4-week, randomized, double-blind, placebo (PBO)-controlled study with a 2 to 4-week standard of care run-in period. Patients on maintenance dialysis, on stable phosphate binder (BIND) therapy who had a serum P≥5.5 and ≤10.0 mg/dL at screening and the end of the run-in period were randomized 1:1 to receive TEN+BIND or PBO+BIND. Patients' dose of BIND remained stable during both washout and treatment periods. The primary endpoint was the change from baseline in serum P at week 4 between the TEN+BIND and PBO+BIND arms. (NCT 03824587)

Results: 511 patients were screened, and 236 patients were randomized to treatment. Mean age was 54.5 years, 58.9% male, 49.6% white, 43.2% Black, BMI 32.1 kg/m^2. Mean (±SD) baseline P was 6.73±1.32 mg/dL and 6.93±1.37 mg/dL for TEN+BIND and PBO+BIND groups respectively. At week 4, the mean change in serum P was more pronounced in the TEN+BIND arm (-0.84 mg/dL v. -0.19 mg/dL in the PBO+BIND arm, p=0.0004). When added to BIND therapy, TEN resulted in statistically significant decreases in serum P during all four weeks of treatment ranging from 0.84 to 1.21 mg/dL. Twice as many patients achieved P<5.5 mg/dL with TEN+BIND than with PBO+BIND (up to 49.1% v. up to 23.5%, p<0.01). TEN+BIND resulted in a 24% relative reduction in serum intact FGF23 (p=0.0027) at week 4. For patients on TEN, the only adverse event with a placebo-adjusted rate over 3% was loose stools/diarrhea (36%); 4.3% of patients discontinued the study while on TEN+BIND v. 2.5% on PBO+BIND. There were no serious adverse events related to TEN.

Conclusions: In patients on dialysis who have uncontrolled phosphorus despite BIND treatment, adding TEN results in improvement in P levels and a significantly higher percentage of patients achieving phosphorus levels <5.5 mg/dL.

Funding: Commercial Support - Ardelyx, Inc.

TH-PO1188

Phase 2 Trial of Phytonadione in Calciphylaxis

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Background: Calciphylaxis is a rare, life-threatening disorder characterized by calcific occlusion of cutaneous microvessels resulting in extremely painful skin lesions. There are no approved therapies for calciphylaxis and randomized controlled trials (RCTs) are lacking. Vitamin K deficiency is implicated in calciphylaxis via reducing gamma-carboxylation of matrix Gla protein (MGP)- a calcification inhibitor.

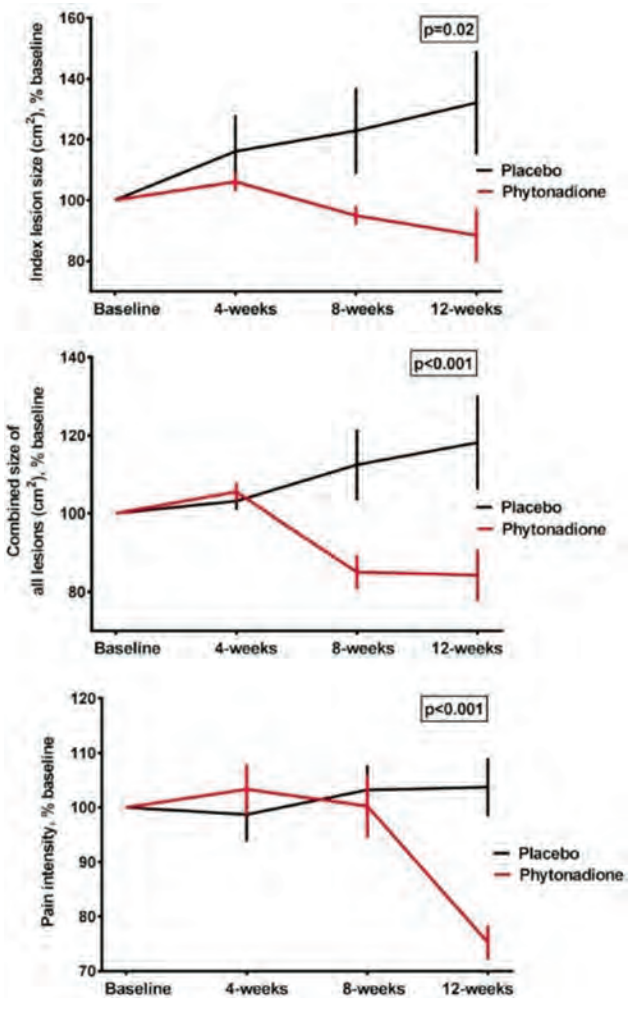
Methods: We performed a phase 2, double-blind, placebo-controlled trial of phytonadione (vitamin K1) in adult hemodialysis patients with calciphylaxis (NCT02278692) to examine pharmacodynamics (reduction in plasma uncarboxylated MGP levels), efficacy, and safety. Patients were randomly assigned to receive either oral phytonadione 10 mg or placebo thrice weekly for 12 weeks.

Results: Baseline characteristics and co-treatments were comparable between the two groups (N=26 patients [13 in each group]). The median change in uncarboxylated MGP level between baseline and 12-weeks was -1014 pmol/L (IQR: -1429 to -614 pmol/L) with phytonadione and 753 pmol/L (IQR: -315 to 1360 pmol/L) with placebo (p<0.001). Compared with placebo, treatment with phytonadione demonstrated greater improvements in the size of the largest skin lesion (p=0.02), the combined size of all lesions (p<0.001), and pain intensity (p<0.001). [Figure] The reduction in uncarboxylated MGP correlated with a reduction in the combined size of all lesions (r=0.56, p=0.01). At 12-weeks, mortality rates were 0% and 31% in phytonadione and placebo groups, respectively (p=0.03). One patient treated with phytonadione developed hepatic thrombosis.

Conclusions: In this phase 2 RCT of patients with calciphylaxis, oral phytonadione reduced uncarboxylated MGP and demonstrated clinical efficacy. A larger phase 3 study is now planned to establish the efficacy and safety of this agent in calciphylaxis.

Funding: Other NIH Support - National Center for Advancing Translational Sciences KL2TR001100, Private Foundation Support

Underline represents presenting author/disclosure.



Efficacy of phytonadione in calciphylaxis

TH-PO1189

Effect of Etelcalcetide in Patients on Hemodialysis with Secondary Hyperparathyroidism: The DUET Trial

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Background: Etelcalcetide is a second-generation calcimimetic agent approved for treatment of Secondary Hyperparathyroidism (SHPT). The DUET trial (jRCTs041180108) was designed to clarify the efficacy of etelcalcetide, and to identify sensitive markers for vascular calcification.

Methods: The DUET study was a 12-week multicenter, open-label, randomized (1:1:1), parallel-group study in SHPT patients undergoing maintenance hemodialysis. Patients were randomly assigned to etelcalcetide + active vitamin D (Group E+D), etelcalcetide + oral calcium preparation (Group E+Ca), or control groups (Group C). The primary end point was to compare the proportion of patients with a 50% reduction from baseline in intact parathyroid hormone (iPTH) levels and iPTH levels ≤240 pg/mL at the 12-week time point after the trial start. Secondary end points included to compare changes in calciprotein particles (CPPs) and fibroblast growth factor 23 (FGF23).

Results: A total 124 patients (men 67.6%, 66.6 years) were randomized in this trial. The achievement proportion (95% confidential interval: CI) of the primary end point (iPTH 50% reduction and iPTH ≤240 pg/mL) were 90.0% (76.3-97.2) in Group E+D, 56.8% (39.5-72.9) in Group E+Ca, and 19.5% (8.8-34.9) in Group C, respectively. When compared the achievement proportion of the primary end point between the groups treated with etelcalcetide and the control groups by logistic regression analysis with iPTH, corrected serum calcium and phosphate at baseline as covariates, treatment of etelcalcetide demonstrated significant increase in achievement proportion (odds ratio 13.4; CI 5.10-35.3, P = 0.000). Next, when compared between Group E+D and Group E+Ca, achievement proportion in Group E+Ca was significantly inferior to that in Group E+D (odds ratio 0.16; CI 0.04-0.56, P = 0.004). The decrease in CPPs was estimated -59949 (AU) in patients treated with etelcalcetide and -37584 (AU) in controls in a linear mixed model, respectively. Similarly, the decrease in FGF23 was estimated -3044.9 (pg/mL) and -186.4 (pg/mL). However, the both decrease in CPPs and FGF23 could not reach significant differences between two groups by Tukey-Kramer multiple-comparison test.

Conclusions: Among maintenance hemodialysis patients with SHPT, the use of etelcalcetide showed good control of iPTH.

Funding: Commercial Support - Ono Pharmaceutical Co., Ltd.

TH-PO1190

IMpact of Phosphate Reduction on Vascular End-Points in CKD (IMPROVE-CKD): A Randomized, Placebo-Controlled Trial

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Background: Hyperphosphatemia is associated with increased fibroblast growth factor 23 (FGF23), arterial calcification, arterial stiffness and increased cardiovascular (CV) mortality in patients with chronic kidney disease (CKD). Due to these associations, clinical guidelines recommend lowering serum phosphate levels towards the normal range. However, the effect of phosphate-lowering medications on markers of vascular calcification and arterial stiffness in non-dialysis CKD patients remains uncertain. The aim of IMPROVE-CKD was to assess the effects of a non-calcium-based phosphate binder, lanthanum carbonate, on intermediate CV markers in patients with CKD.

Methods: In this double-blind, multi-centre, randomized controlled trial, patients with stage 3b or 4 CKD were randomized to lanthanum carbonate 500mg or matched placebo three times daily for 96 weeks. The primary outcome was change in carotid-femoral pulse wave velocity (PWV, SphygmoCor). Intention-to-treat analysis was used with linear mixed models for repeated measures. Secondary outcomes included aortic calcification (AC, computed tomography), and serum and urine markers of bone and mineral metabolism.

Results: 278 participants from Australia, Malaysia and New Zealand were randomized to lanthanum carbonate (n=138) or placebo (n=140) (mean age 63.1±12.7yrs, 69.4% male, 63.9% white; 33% stage 3b CKD, 67% stage 4 CKD, mean eGFR 26.6±8.3ml/min/1.73m^2; 45% diabetes, 32.1% CV disease). Mean serum phosphate was 1.25±0.20mmol/L, mean PWV 10.8±3.6m/s and 81.3% had AC at baseline (median [IQR] 1535 [63.2, 5744] Hounsfield Units [HU]). At 96 weeks, change in PWV did not differ significantly between the groups (diff [95%CI] +0.7 [-0.2, 1.6] m/s, p=0.13). Change in AC score was also not significantly different (+154 [-334, 641] HU, p=0.53) and there were no differences in serum phosphate, c-terminal and intact FGF23, and 24-h urinary phosphate excretion between the groups. Serious adverse events were reported in 63 (46%) and 66 (47%) participants on lanthanum and placebo respectively.

Conclusions: In stage 3b/4 CKD patients, treatment with the phosphate-lowering agent lanthanum carbonate over 96 weeks did not result in any difference in change in arterial stiffness or aortic vascular calcification.

Funding: Commercial Support - Shire Pharmaceuticals, Government Support - Non-U.S.

TH-PO1191

A Precision Medicine Approach to Treatment of Osteoporosis in CKD-5D

Hartmut H. Malluche, Florence Lima, Katelyn M. Hellman, Tara L. Spach, Jin Chen, Daniel Davenport. *University of Kentucky, Lexington, KY.*

Background: This prospective stage II proof-of-concept randomized controlled study uses different treatments for osteoporosis in low vs. non-low bone turnover (Low TO vs. Non-low TO) CKD-5D patients.

Methods: In 36 dialysis clinics across Kentucky, 96 CKD-5D patients with established Low TO and Non-low TO osteoporosis were enrolled. Low TO was determined by serum measurements of PTH, PTH ratio, and TRAP-5b below race-specific normal ranges histologically validated by our laboratory. In Low TO patients, teriparatide combined with cinacalcet was given to stimulate bone formation. In Non-low TO patients, alendronate was administered to reduce bone resorption. The primary endpoint was 1-year change in bone mineral density (BMD) measured by QCT.

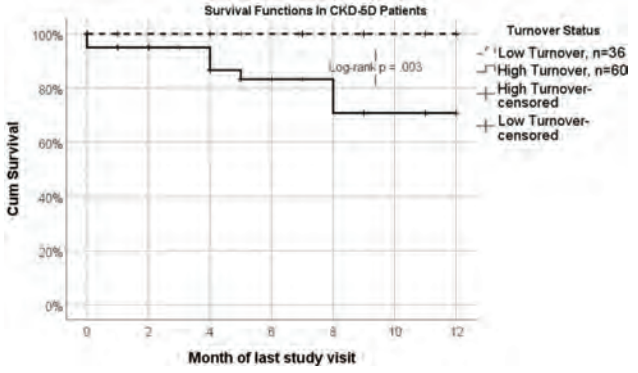
Results: Patient status is shown in the Table. In Low TO patients, change in Total Hip BMD demonstrated a positive effect of treatment (Treatment: 12.6 mg/cm^3 [SE 5.8] n=8; Control: -14.1 [SE 12.7] n=8; p=.076). The mortality rate was 17% (10/60) in Non-low TO patients with no deaths in Low TO patients (Figure, p=.003). Only two Non-low TO control patients survived to complete the study, thus group comparisons are not yet feasible; Non-low TO treated patients had bone loss of only 4.0 mg/cm^3. In Low TO patients identified through blood tests, teriparatide has a positive effect on reversing bone loss in CKD-5D.

Conclusions: This study demonstrates better survival in Low TO vs. Non-low TO CKD-5D osteoporotics; supporting the precision medicine approach.

Funding: NIDDK Support

	Non-low Turnover		Low Turnover		Total Both Arms	
Ongoing in Study	n=24	40%	n=18	50%	n=42	53%
Transplanted/withdrew	n=15	25%	n=2	6%	n=17	14%
Death	n=10	17%	n=0	0%	n=10	10%
Completed	n=11	18%	n=16	16%	n=27	27%
Total	n=60	100%	n=36	100%	n=96	100%

Underline represents presenting author/disclosure.



TH-PO1192

A Randomized Crossover Trial of Ultrafiltration (UF)-Profiled Hemodialysis (HD) for UF Rate-Related Harm

Jennifer E. Flythe,[1] Matthew J. Tugman,[1] Julia Narendra,[1] Magdalene M. Assimon,[1] Quefeng Li,[1] Yueting Wang,[1] Steven M. Brunelli,[2] Alan L. Hinderliter.[1] *[1]University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]DaVita Clinical Research, Needham, MA.*

Background: Rapid UF is associated with adverse outcomes among HD patients. UF profiling, the practice of varying UF rates to maximize fluid removal during periods of greatest hydration and oncotic pressure, may reduce UF rate-related complications.

Methods: In this 4-phase, blinded crossover trial, participants (UF rates >10 mL/h/kg in ≥30% of screening treatments) were assigned in random order to receive HD with conventional UF *vs.* UF-profiled HD; each 3-wk treatment period was followed by a 1-wk washout period. Participants crossed into each treatment arm twice (2 phases/arm). Each patient was their own control. The primary outcomes were intradialytic hypotension (IDH, nadir systolic BP <90mmHg), rise in serum troponin T from pre- to post-HD (≥10%), and change in left ventricular global longitudinal strain (GLS) from baseline to peak intra-HD stress (%). Secondary outcomes included intra-HD symptoms and blood volume monitor-measured plasma refill (hematocrit fall by ≥0.5%), a volume status measure.

Results: On average, the 34 randomized patients (mean age 56y, 24% female, mean HD vintage 6.3y) had UF rates ≥10 mL/h/kg in 56% treatments during the 4-wk screening period. All but 2 patients completed the 15-wk study (long hospitalization, transplant). With UF-profiled HD, patients had significantly lower odds of light-headedness and plasma refill (i.e. less post-HD hypervolemia) compared to HD with conventional UF. There was no significant difference in IDH. There was a non-significant trend toward a lower odds of troponin T rise with UF-profiled HD.

Conclusions: UF-profiled HD did not reduce the odds of IDH or troponin T rise but did reduce the odds of light-headedness and post-HD plasma refill.

Funding: NIDDK Support

Selected outcomes

Outcome	Odds ratio (95% confidence interval), UF-profiled HD vs. conventional HD*
Intradialytic hypotension	1.2 (0.8, 1.7)
Troponin T rise (%)	0.5 (0.2, 1.3)
Left ventricular GLS change (%)	Results pending
Cramping	0.9 (0.4, 2.1)
Light-headedness	0.2 (0.06, 0.9)**
Plasma refill	0.2 (0.05, 0.9)**

* Difference of outcomes between the UF-profiled intervention arm and the conventional UF control arm were assessed with likelihood ratio tests using various generalized linear mixed models depending on outcome type.

** $p<0.05$.

TH-PO1193

Multicenter RCT of Vitamin K Antagonist Replacement by Rivaroxaban with or Without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: The Valkyrie Study

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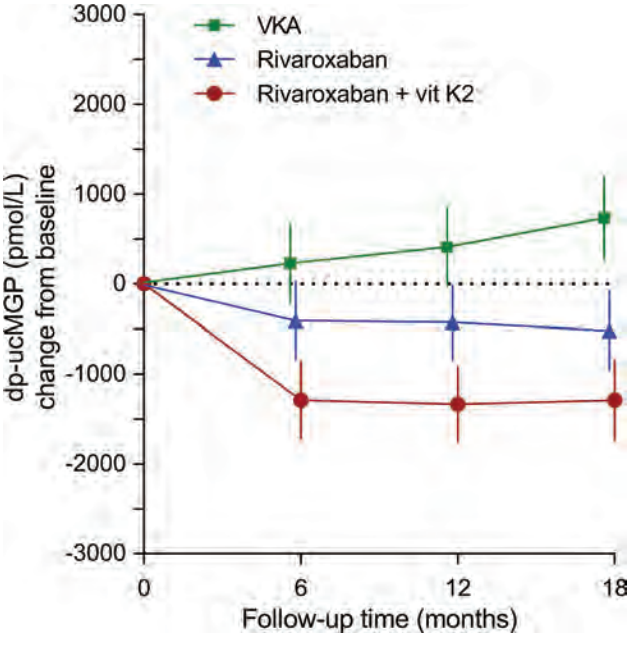
Background: Vitamin K antagonists (VKA) have been incriminated as probable cause of accelerated vascular calcification (VC) in hemodialysis patients. Functional vitamin K deficiency may further contribute to their susceptibility for VC. We investigated the effect of vitamin K status on VC progression in 132 hemodialysis patients with atrial fibrillation treated with VKA or qualifying for anticoagulation.

Methods: Patients were randomized to VKA, rivaroxaban 10 mg od, or rivaroxaban plus vitamin K2 2000 µg trice weekly during 18 months. Systemic dp-ucMGP levels were quantified to assess vascular vitamin K status. Cardiac and thoracic aorta calcium scores and pulse wave velocity were measured to evaluate VC progression.

Results: Initiation or continuation of VKA increased dp-ucMGP, while levels decreased in the rivaroxaban group and to a larger extent in the rivaroxaban+vitamin K2 group, but remained nevertheless elevated (Figure). Changes in coronary artery, thoracic aorta and cardiac valve calcium scores and pulse wave velocity were not different among the treatment arms. All cause death, stroke, cardiovascular event and bleeding rates were not significantly different between the groups. The incidence of life-threatening and major bleeding was significantly lower in the pooled rivaroxaban arms than in the VKA arm.

Conclusions: Withdrawal of VKA and high-dose vitamin K2 improve vitamin K status in hemodialysis patients, but have no significant favorable effect on VC progression. Severe bleeding complications may be lower with rivaroxaban than with VKA.

Funding: Commercial Support - Kaydence Pharma



Estimated marginal mean changes in dp-ucMGP levels from baseline (95% CI).

TH-PO1194

Effects of Exercise Training on Psychosocial Health and Cognition in Elderly Hemodialysis Patients

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Background: The impact of exercise training on health-related quality of life (HRQOL) and cognition in chronic kidney disease has not been fully explored. We aimed to determine the effects of 12-weeks of home-based exercise training on psychosocial health and cognition outcomes among elderly maintenance hemodialysis (MHD) patients.

Methods: Fifty-six patients (66± 7 years; exercise [Ex]: n=28, usual care [UC]: n=28) with end-stage renal disease on MHD (mean years of MHD: 4±4; mean Kt/V=2.1) were studied using the SF-36 v2, Kidney Disease and Quality of Life (KDQOL) and a battery of cognitive function tests as part of a randomized trial. Ex subjects underwent a home-based aerobic and resistance training program for 12 weeks. Eight components of the SF-36 v2 (bodily pain, general health, mental health, physical functioning, role physical, role emotional, social functioning, vitality), and 5 components of the KDQOL (burden of kidney disease, symptoms, effects, physical component score [PCS], and mental component score [MCS]) were assessed. Tests of cognitive function assessing general cognition, executive function, memory and verbal learning were obtained.

Results: Ex patients improved peak VO_2 by 11% (p=0.01), while no differences were observed among UC. A 20-point increase in general health was observed among Ex (p=0.04), and trends were observed for increases in physical functioning and role emotional (p=0.08). No other HRQOL measures differed between EX and UC patients. KDQOL symptoms improved in Ex (p=0.05). PCS increased slightly from 38% ± 12 to 45% ± 10 (p=0.12) in EX. KDQOL measures were unchanged in UC. There were no significant changes in cognition within or between groups.

Conclusions: Home-based exercise training promotes health-related quality of life and some symptom metrics but did not affect cognition.

Funding: Veterans Affairs Support

Underline represents presenting author/disclosure.

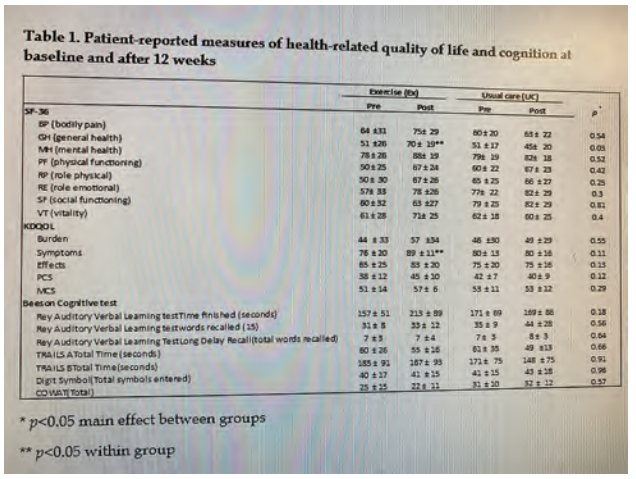

Table 1. Patient-reported measures of health-related quality of life and cognition at baseline and after 12 weeks

	Exercise (Ex)		Usual care (UC)		
	Pre	Post	Pre	Post	p*
SF-36					
BP (bodily pain)	64 ±31	754 29	60± 20	65± 22	0.54
GH (general health)	51 ±26	70± 19**	51 ±17	45± 20	0.01
MH (mental health)	78±26	88± 19	79± 19	82± 18	0.52
PF (physical functioning)	50±25	67±24	60± 22	67± 23	0.42
RP (role physical)	50± 30	67±26	65 ±25	66 ±27	0.25
RE (role emotional)	57± 33	78 ±26	77± 22	82± 29	0.3
SF (social functioning)	60±32	65 ±27	79 ±25	82± 29	0.81
VT (vitality)	61± 28	71± 25	62± 18	60± 25	0.4
KDQOL					
Burden	44 ± 33	57 ±34	48 ±30	49 ±29	0.55
Symptoms	76 ±20	89 ±11**	80± 13	80 ±16	0.11
Effects	85 ±25	83 ±20	75 ±20	75 ±16	0.13
PCS	38 ±12	45 ±10	42 ±7	40± 9	0.12
MCS	51 ±14	57± 6	53 ±11	53 ±12	0.29
Beeson Cognitive test					
Rey Auditory Verbal Learning test Time finished (seconds)	157 ± 51	213 ± 89	171 ± 89	169 ± 86	0.18
Rey Auditory Verbal Learning test words recalled (15)	31 ± 8	33 ± 12	35 ± 9	44 ±28	0.56
Rey Auditory Verbal Learning Test Long Delay Recall (total words recalled)	7 ±3	7 ±4	7± 3	8± 3	0.64
TRAILS A Total Time (seconds)	80 ±26	55 ±16	61± 35	49 ±13	0.66
TRAILS B Total Time (seconds)	185± 91	167± 93	171± 75	148 ±75	0.91
Digit Symbol (Total symbols entered)	40 ±17	41 ±15	41 ±15	43 ±16	0.96
COWAT (Total)	25 ±15	22± 11	31 ±10	32 ± 12	0.57

* $p<0.05$ main effect between groups

** $p<0.05$ within group

TH-PO1195

Safety and Efficacy of the Tablo System: Results from a Prospective, Multi-Center, Cross-Over Study of a First-in-Class Hemodialysis Device in the Home

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Background: Home dialysis is in critical need of new technology to facilitate its delivery, as evidenced by the recent Advancing American Kidney Health initiative. The Tablo™ Hemodialysis System (Tablo) is the first new technology expanding to home use in nearly 15 years, designed to simplify patient self-care through automation, integrating on-demand water purification and dialysate production. This investigational device exemption (IDE) study assessed the safety and efficacy of Tablo managed in-center by healthcare professionals and in-home by patients or caregivers.

Methods: We conducted a prospective, multicenter, open label, cross-over trial comparing in-center and in-home hemodialysis using Tablo. Dialysis was prescribed four times per week during four treatment periods: 1-week Run-In, 8-week In-Center, approximately 4-week Transition and 8-week In-Home. The primary efficacy endpoint was achieving weekly standardized $Kt/V_{urea} \geq 2.1$. The secondary efficacy endpoint was delivered ultrafiltration within 10% of prescribed. We also collected safety and usability data.

Results: Thirty participants enrolled, and 28 completed all trial periods. Adherence to the four treatment per week prescription was 96% in-center and 99% in-home. The average prescribed and delivered treatment session lengths were 3.4 hours for the In-Center and In-Home periods. The primary efficacy endpoint was achieved in 199/200 (99.5%) measurements during the In-Center period and 168/171 (98.3%) In-Home. The average weekly standardized Kt/V_{urea} was 2.8 in both periods. The ultrafiltration endpoint was achieved in 94% of patients during both the in-center and in-home periods. No pre-specified adverse events related to Tablo occurred during any trial period. The resolution time of alarms was 14 seconds in-center and 12 seconds in-home.

Conclusions: Tablo exceeds the target $stdKt/V_{urea} \geq 2.1$ for in-center and home care settings with highly accurate ultrafiltration. With patient-centric design, infrequent and easy to resolve alarms, and a demonstrated safety profile, Tablo provides a new option for expanding home dialysis in the United States, aligning with ambitious targets recently set by policymakers.

Funding: Commercial Support - Outset Medical

TH-PO1196

A Randomized Cross-Over Trial Using Intradialytic MRI to Compare the Effects of Standard vs. Cooled Haemodialysis on Cerebral Blood Flow and Cardiac Function

Venkata R. Gullapudi,[1,4] Eleanor Cox,[3] Charlotte E. Buchanan,[1] Sebastian C. Coleman,[1] Kelly White,[4] Bernard J. Canaud,[2] Maarten W. Taal,[1,4] Susan Francis,[3] Nicholas M. Selby.[1,4] *[1]University of Nottingham, Derby, United Kingdom; [2]FMC Deutschland GmbH, Bad Homburg, Germany; [3]Sir Peter Mansfield Imaging Centre, Nottingham, United Kingdom; [4]University Hospitals Derby and Burton, Derby, United Kingdom.*

Background: Ischemic end-organ damage during haemodialysis (HD) is a significant problem that may be ameliorated by intradialytic cooling. We performed a randomized trial to compare acute hemodynamic effects of standard HD (SHD) and cooled HD (CHD), using intradialytic magnetic resonance imaging (MRI) to provide concurrent assessments of cerebral blood flow (BF) and cardiac function.

Methods: 12 prevalent HD patients were randomly allocated to receive 4 hours either SHD (dialysate temperature 37°C) or CHD (programmed cooling using BTM device). All other HD prescription and operating conditions remained constant. Participants were exposed to initial modality for two weeks before undergoing serial multiparametric MRI (Phillips 3T Ingenia) of the heart and brain pre, during (30min and 180min) and 30min post HD. Cognitive function was assessed pre and post HD. Participants then crossed over to the other modality and the study protocol repeated.

Results: Median age of participants was 59.5yrs (IQR 25), 3 had diabetes and dialysis vintage was 18.5months (IQR 52). Participants were significantly cooled during CHD (CHD -0.40±0.31°C vs SHD 0.28±0.24°C; p=0.02). Ultrafiltration rate was 7.5±2.6ml/kg/hr in CHD vs 6.9±2.7ml/kg/hr in SHD (p=0.3). BF velocities fell in carotid (-19±2%, p<0.001) and basilar arteries (-16±3%, p=0.004) during HD and reached nadir in the 4th hour, as did cardiac index and stroke volume index (-29±2% and -32±2%, both p<0.001). Reductions in left ventricular diastolic filling time and volume were also observed. Changes in cerebral BF and cardiac function were not different between CHD and SHD. Reduction in carotid BF was associated with higher ultrafiltration volumes (R^2=0.43, p=0.005) and slower completion of trail making test: part B (R^2=0.33; p=0.03). Pre-HD myocardial T_1 and left ventricular wall mass were lower after two weeks of CHD as compared to SHD (1281±14ms vs 1308±18ms, p=0.03; 128±12g vs 137±12g, p=0.003).

Conclusions: HD and fluid volume reduction adversely affects cardiac function, carotid and basilar artery BF, with acute changes similar during SHD and CHD. However, lower myocardial T_1 and left ventricular mass may indicate reduced myocardial tissue oedema with CHD.

Funding: Commercial Support - Fresenius Medical Care

TH-PO1197

Abstract Withdrawn

TH-PO1198

Effect of Allopurinol on the Progression of CKD: The CKD-FIX Study

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Background: Hyperuricemia is a common finding in chronic kidney disease (CKD) and associated with increased risk of progression of CKD. The effect of urate-lowering therapy on CKD progression remains uncertain. We therefore assessed whether allopurinol attenuates the decline of estimated glomerular filtration rate (eGFR) over 2 years in people with high CKD-progression risk.

Methods: In this double-blind randomized controlled trial, adults with CKD stage 3 or 4, urinary albumin-to-creatinine ratio (UACR) ≥30 mg/mmol or decrease in eGFR ≥3.0 mL/min/1.73 m^2 in the preceding ≤12 months, and no history of gout, were randomized to allopurinol (100-300 mg once daily) or placebo. The primary outcome was change in eGFR (mL/min/1.73 m^2/yr) up to 104 weeks. The key secondary endpoints were 40% reduction in GFR, progression to end-stage kidney disease (ESKD), blood pressure, albuminuria, and adverse events.

Results: 369 participants were randomised to the allopurinol group (n=185) or placebo group (n=184). Six withdrew before the baseline visit (3 in each group). The rate of eGFR decline did not differ significantly between the allopurinol (-3.33 mL/min/1.73 m^2/yr, 95% CI -4.11 to -2.55) and placebo (-3.23 mL/min/1.73 m^2/yr, 95% CI -3.98 to -2.47) groups (difference -0.10 mL/min/1.73 m^2/yr, 95% CI -1.18 to 0.97, P=0.85). 63 (35%) and 51 (28%) participants in the allopurinol and placebo groups experienced a secondary composite endpoint of 40% eGFR decline, ESKD, or death from any cause (RR 1.23, 95% CI 0.90 to 1.67). There were no significant differences in change in UACR (P=0.25), and systolic blood pressure (P=0.30) between the two groups. Serum urate was significantly lower in the allopurinol group (mean difference -0.16 mmol/L, 95% CI -0.17 to -0.15, P<0.001). Serious adverse events were reported in 84 (46%) and 79 (44%) participants in the allopurinol and placebo groups, respectively (P=0.63).

Conclusions: In CKD patients with elevated CKD-progression risk, urate-lowering treatment with allopurinol did not result in slower eGFR decline than placebo. These results do not support the use of urate-lowering therapy to slow CKD progression.

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

Underline represents presenting author/disclosure.

TH-PO1199

A Phase 3 Randomized Controlled Trial on the Effect of Losartan vs. Add-On Aliskiren in CKD

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Background: The potential long-term safety and efficacy of aliskiren in non-diabetic CKD is unknown.

Methods: Non-diabetic CKD stages 3-4 patients were randomized to receive aliskiren added on to losartan (maximal tolerated dose) or losartan alone. The primary outcome was the slope of eGFR at 3 years, along with other secondary endpoints. Composite renal outcomes of doubling of baseline serum creatinine (sCr) or a 40% reduction in eGFR or incident end-stage renal disease (ESRD) or death was analysed as post-hoc analysis.

Results: After follow-up of 144 weeks in 76 subjects (Table 1), there was no difference in the slope of eGFR (Fig 1). 6 patients receiving aliskiren and 7 control patients reached the renal composite endpoint (16.2% *vs.* 17.9%, *P*=0.84). Cardiovascular events rate was 10.8% *vs.* 2.6%, *P*=0.217. Hyperkalemia rate was 18.9% *vs.* 5.1% (Fig 2).

Conclusions: Compared to losartan alone, add-on aliskiren conferred no further renoprotective benefit but increased hyperkalemia risks in non-diabetic CKD patients.

Baseline demographics

	Aliskiren Group (N=37)	Control Group (N=39)
Age, y	55.1(11.1)	55.0(9.4)
EP, g/24h	1.14(1.54)	0.77(0.81)
eGFR, ml/min/1.73 m2 BSA	31.9(9.0)	27.7(9.0)

Figure 1

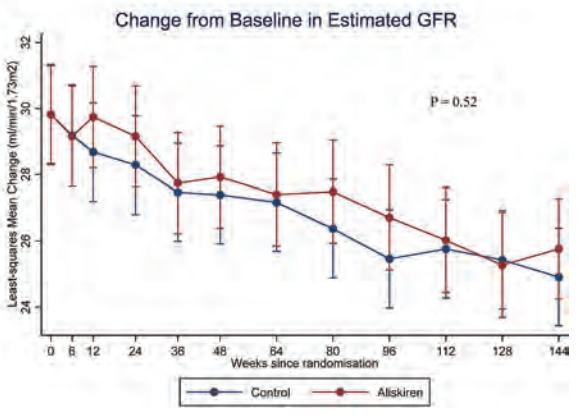

Fig 1. Slope of eGFR. Adjusted mean of eGFR (95 CI) by mixed model adjusted for baseline, treatment, trial visit, interaction between trial visit and baseline. *P* (χ^2 test)=0.52 for intergroup difference.

Figure 2

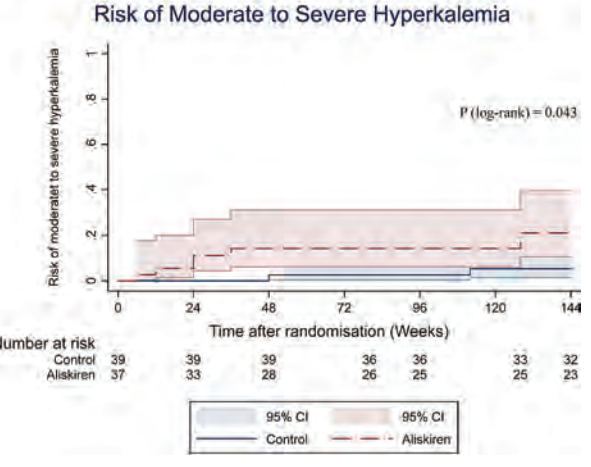

Fig 2. Cumulative incidence of hyperkalemia with 95% CI. Adjusted HR=7.71

TH-PO1200

Safety and Efficiency of Nephroprotective Therapy with Ramipril in Children

Oliver Gross. GPN-study group and EARLY PRO-TECT Alport investigators *University Medicine Goettingen, Goettingen, Germany.*

Background: Children with Alport syndrome (AS) develop renal failure early in life. The safety and efficacy of preemptive nephroprotective therapy is uncertain.

Methods: In an investigator-initiated, double-blinded, randomized, placebo-controlled trial, we treated pediatric patients with Ramipril. Pretreated children and patients whose parents refused randomization versus placebo were treated open label. Prospective data from the US-Alport registry (NCT00622544) were added to substantiate our results in a Bayesian evidence synthesis approach. The primary endpoints were safety: *adverse drug reactions before disease progression* and efficacy: *time to progression*.

Results: Sixty-six oligosymptomatic children with (yet) normal renal function entered the up to 6-year treatment phase with a total of 216.4 patient-years on Ramipril. Most important, Ramipril was safe (hazard ratio 1.00, 95%CI 0.83-1.21). Efficacy analyses, though not significant, cumulated evidence in favor of Ramipril: in the randomized arm, Ramipril decreased the risk of disease progression by >40% (0.51; 95%CI 0.12–2.20), diminished the slope of albuminuria progression and the loss of glomerular filtration rate. Only 27.3% (3/11) of Ramipril-treated, but 55.6% (5/9) of placebo-treated children progressed. Efficacy was confirmed by comparison of untreated children from the US with participants treated open label, in whom Ramipril again reduced disease progression by >40% (0.53; 95%CI 0.23-1.24).

Conclusions: Early initiation of Ramipril therapy in children with AS is safe and can be expected to slow renal failure by many years, underlining the value of preemptive therapy in this CKD. Thus, screening programs for glomerular hematuria in children and young adults should include genetic testing for AS-gene variants. (Funded by the German Federal Ministry of Education and Research; EARLY PRO-TECT Alport ClinicalTrials.gov number, NCT01485978).

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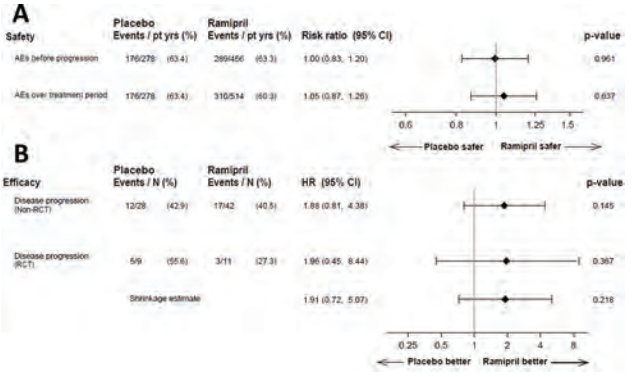

Analyses of the primary safety and efficacy endpoints.

TH-PO1201

Double-Blind, Randomized Phase 3 Study Comparing Esaxerenone with Placebo in Type 2 Diabetes Patients with Microalbuminuria (ESAX-DN Study)

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Background: The progression of kidney disease in type 2 diabetes mellitus (T2DM) is not always adequately controlled by renin-angiotensin system inhibitors. In preclinical studies, Esaxerenone (ESAX), a non-steroidal mineralocorticoid receptor blocker, showed kidney protective effects; it may be effective for diabetic kidney disease. Here, the efficacy and safety of ESAX were evaluated in comparison with placebo in 455 Japanese patients with type 2 diabetes mellitus with microalbuminuria.

Methods: ESAX-DN Study was a multicenter, randomized, double-blind, placebo-controlled, phase 3 study. Hypertensive T2DM patients treated with ACEi or ARB with microalbuminuria (UACR ≥45 to <300 mg/g Cr in at least two measurements) and an estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 were eligible. Patients were randomized to ESAX (1.25mg to 2.5mg) or placebo groups for 52 weeks with a follow-up of 4 weeks. The primary endpoint was the proportion of patients of UACR remission, defined as a reversal of UACR to normoalbuminuria (<30 mg/g Cr) and a decrease in UACR by ≥30% from baseline at the end of treatment. Secondary endpoints were the change in UACR from baseline, comparison of the transition rate to overt albuminuria at the end of treatment, and safety assessed in terms of adverse events (AEs).

Results: ESAX significantly reduced UACR (-58.3%) compared with placebo (8.4%) (61.6% reduction relative to placebo, P<0.0001), showed a significantly higher UACR remission rate (22.1% vs. 4.0%) and a significantly lower transition rate to overt albuminuria (1.4% vs. 7.5%) compared with placebo (P<0.0001, P=0.0016). Incidence of

Underline represents presenting author/disclosure.

AEs was similar, ESAX vs. placebo (78.3% vs. 77.3%). The proportion of subjects with serum potassium ≥6.0 mEq/L or with two consecutive readings ≥5.5 mEq/L was higher with ESAX (8.8% vs. 2.2%); patients recovered with ESAX dose adjustment and showed a recovery tendency after the end of the treatment.

Conclusions: This study demonstrated the efficacy of ESAX for UACR remission and a decrease in the transition to overt albuminuria in T2DM patients with microalbuminuria receiving ACEi or ARB. Although the serum potassium increase was higher with ESAX than placebo, all patients tended to recover after treatment and were clinically acceptable.

TH-PO1202

Canagliflozin (CANA) Slows Declines in Kidney Function in People with Baseline (BL) eGFR <30 mL/min/1.73 m²

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Background: The CREDENCE trial demonstrated that the SGLT2 inhibitor CANA significantly reduced kidney failure and cardiovascular (CV) events in participants with type 2 diabetes and chronic kidney disease. During the study, participants continued treatment until initiation of dialysis or kidney transplantation. The efficacy and safety of CANA in the subgroup of participants with BL eGFR <30 mL/min/1.73 m² were evaluated.

Methods: While eligibility, in part, required a screening eGFR of 30-90 mL/min/1.73 m², BL assessment of eGFR performed at the randomization visit could fall outside of the indicated range. Efficacy and incidence of selected adverse events were examined in those with a BL eGFR <30 mL/min/1.73 m², a subgroup defined post hoc. Effects of on-treatment eGFR slope were analyzed using a piecewise, 2-slope linear mixed effects model with a knot at week 3, with compound symmetry fitted where unstructured models did not converge. Treatment effects for other renal outcomes are expressed hazard ratios (HRs) with 95% CI.

Results: Overall, 174 (4%) participants had BL eGFR <30 mL/min/1.73 m². Mean annual change in eGFR for placebo- and CANA-treated participants was –4.00 and –1.50 mL/min/1.73 m² (placebo-subtracted difference: 2.50 mL/min/1.73 m², 95% CI: 0.55–4.44). Numerical trends favoring CANA were noted for ESKD (HR: 0.67; 95% CI: 0.35–1.27], primarily driven by risk reduction in time to eGFR <15 mL/min/1.73 m² (HR: 0.50; 95% CI: 0.25–1.02) as compared to initiation of dialysis/kidney transplantation (HR: 0.90; 95% CI: 0.39–2.06). Doubling of serum creatinine similarly favored CANA (HR: 0.72; 95% CI: 0.34–1.54). CV outcomes were not different between groups, although results were broadly consistent with the overall population. Acute kidney injury events were similar for CANA compared with placebo (10.7% and 11.1%).

Conclusions: Among a subgroup of participants with BL eGFR <30 mL/min/1.73 m², CANA reduced the rate of eGFR decline and slowed progression to ESKD. The renal and CV outcome comparisons were consistent with results in the overall study population.

Funding: Commercial Support - Janssen Research & Development, LLC

TH-PO1203

Soluble Tumor Necrosis Factor Receptor 1 (sTNFR1) Is Prognostic for ESRD over 48 Weeks in a Randomized Clinical Trial in Moderate to Advanced Diabetic Kidney Disease (DKD)

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Background: Serum sTNFR1 associates with progression to ESRD in natural history studies of DKD. A predefined sTNFR1 cutpoint has been proposed as a potential patient selection criterion for clinical trials. We conducted a pre-planned retrospective analysis of the prognostic power of sTNFR1 over 48 weeks (48W) in a Phase 2 trial of selonsertib (SEL) in patients with DKD at high risk of progression based on estimated glomerular filtration rate (eGFR) and albuminuria.

Methods: The Phase 2 SEL trial comprised 333 patients randomized 1:1:1:1 to receive SEL (2, 6, or 18 mg) or matching placebo for 48W. Serum sTNFR1 and UACR cut-points previously described in Joslin type 1 DKD (T1DKD n=279) and T2DKD (n=221) cohorts (Yamanouchi M, et al. Kidney Int 2017;92:258) were applied to evaluate risk of the composite endpoint: ESRD, 40% decrease in eGFR, or nonrenal death. Cox proportional hazards models compared event rates by sTNFR1. Results were then evaluated in propensity score matched patients by age, sex and race.

Results: The proportion of the Phase 2 SEL trial patients categorized as high risk based on sTNFR1 >4.3 ng/mL was higher than the Joslin cohorts combined (60% vs 33%, p<0.001 as was the high risk subgroup with UACR > 1900mg/g and sTNFR1 >2.9≤4.3ng/mL (8% vs 6%, p<0.01. In the SEL trial, we observed 32 events, with annualized event rates of 15% vs 3% in patients above or below sTNFR1 4.3 ng/mL, respectively (p=0.002). Comparable event rates were observed in the subpopulation of matched SEL trial and Joslin T2DKD patients (n=121 pairs, 21% vs 4% and 21% vs 8%, respectively). Further, each standard deviation increase of sTNFR1 was associated with a higher risk of the composite endpoint in the full SEL trial (HR 1.64, 95% CI 1.12-2.41) and full Joslin T2DKD cohort (HR 1.76, 95% CI 1.31-2.38).

Conclusions: We validated a predefined cutpoint of serum sTNFR1 associated with a higher event rate in a DKD trial population already selected for high risk based on eGFR and albuminuria criteria. sTNFR1 may improve the efficiency of DKD trial design as a patient stratification or selection biomarker.

Funding: Commercial Support - Gilead Sciences, Inc

TH-PO1204

Impact of Canagliflozin (CANA) on eGFR Slope in People with Optimized Glucose Control: Randomized Analyses from CREDENCE

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Background: SGLT2 inhibitors were developed to lower glucose. Renal and cardiovascular (CV) protection from CANA in CREDENCE was seen in participants with type 2 diabetes overall, and in those with reduced eGFR in whom systemic glycemic effects are attenuated suggesting clinical benefits are not entirely mediated by glycemic improvements. We explored this by assessing the impact of CANA on eGFR slope in participants with HbA1c<7% vs those with HbA1c≥7%.

Methods: Relative and absolute effects of CANA on renal and CV outcomes were estimated using Cox proportional hazards regression. Effects of on-treatment eGFR slope were analyzed using a piecewise, 2-slope linear mixed effects model with a knot at week 3.

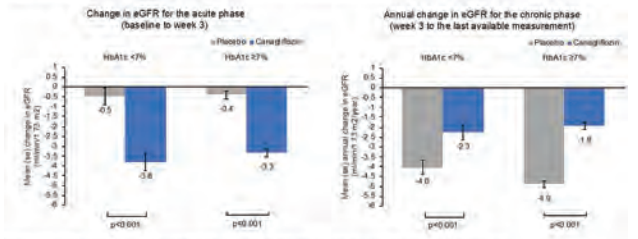
Results: At baseline, 650 (14.8%) participants had HbA1c<7% (mean 6.6%) and they had lower eGFR than the HbA1c≥7% cohort (53.5 vs 56.7 mL/min/1.73m²). CANA resulted in an acute drop in eGFR in those with HbA1c<7% (CANA vs placebo: 3.8±0.4 vs 0.5±0.4; Diff: 3.3 [95% CI: 2.1–4.5] mL/min/1.73m²) and HbA1c≥7% (3.3±0.2 vs 0.4±0.2; Diff: 2.9 [95% CI: 2.4–3.5] mL/min/1.73m²; **Figure**). CANA thereafter attenuated annualized eGFR decline in those with HbA1c<7% (2.3±0.4 vs 4.0±0.4; Diff: 1.8 [95% CI: 0.8–2.8] mL/min/1.73m²/year) and HbA1c≥7% (1.9±0.2 vs 4.9±0.2; Diff: 3.0 [95% CI: 2.5–3.4] mL/min/1.73m²/year). Primary and secondary outcomes were consistent in those with HbA1c<7% and ≥7%.

Conclusions: CANA appears to slow renal function loss in those with optimized HbA1c consistent with non-glucose mediated mechanisms of benefit.

Funding: Commercial Support - Janssen Research & Development, LLC

Underline represents presenting author/disclosure.

Figure. Acute and chronic changes in eGFR in CREDENCE participants with HbA1c<7% and ≥7%.*



*Compound symmetry was used with identical results from an autoregressive structure.

TH-PO1205

Prevention of CKD with Dapagliflozin: Analysis of the DECLARE-TIMI 58 Trial

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Background: Patients with early stage kidney disease incur low rates of hard renal endpoints, limiting the ability to demonstrate drug efficacy in this population. Consequently, the regulatory agencies including Federal Drug Administration and European Medicines Agency now consider eGFR based endpoints as acceptable surrogates. In the DECLARE-TIMI-58 study, dapagliflozin showed robust reduction in cardiorenal and renal specific composite outcomes in the overall population.

Methods: 17,160 patients with type 2 diabetes were randomly assigned to dapagliflozin or placebo and followed for a median of 4.2 years. The baseline eGFR was 85.3 ml/min/1.73m^2 and only 7% of patients had an eGFR <60 ml/min/1.73m^2. We analyzed eGFR slopes from randomization to end of treatment with dapagliflozin vs. placebo.

Results: Dapagliflozin attenuated the eGFR decline overall in the trial and in subgroups based on eGFR, UACR, use of ACEi/ARB and diuretics (table). Fewer patients experienced an eGFR decline of 30%, 40% or 50% to eGFR<60 with dapagliflozin vs. placebo, HR (95% CI): 0.68 (0.58, 0.79); 0.54 (0.43, 0.67); 0.57 (0.40, 0.81) respectively, all p<0.002.

Conclusions: Dapagliflozin slowed the progression of renal disease across all subgroups of patients with type 2 diabetes, even in patients with normal kidney function and in patients with normo-albuminuria, highlighting its potential for primary prevention of chronic kidney disease.

Funding: Commercial Support - AstraZeneca

Mean eGFR slopes per year from randomization to EOT by treatment arm

Population	Mean eGFR slope per year Placebo arm (ml/min/1.73 m2/year)		Mean eGFR slope per year Dapagliflozin arm (ml/min/1.73 m2/year)		Mean difference in eGFR slopes per year Between Dapagliflozin and Placebo	
	mean (SD)	P-Value	mean (SD)	P-Value	mean (SD)	P-Value
Overall	-2.44 (0.02)	<.0001	-1.78 (0.02)	<.0001	0.66 (0.03)	<.0001
eGFR >=90	-2.58 (0.03)	<.0001	-1.99 (0.03)	<.0001	0.59 (0.04)	<.0001
eGFR >=60-<90	-2.5 (0.04)	<.0001	-1.76 (0.04)	<.0001	0.74 (0.05)	<.0001
eGFR <60	-1.34 (0.11)	<.0001	-0.48 (0.11)	<.0001	0.86 (0.16)	<.0001
UACR <30 mg/g	-2.12 (0.03)	<.0001	-1.57 (0.03)	<.0001	0.55 (0.04)	<.0001
UACR >=30-<=300 mg/g	-2.85 (0.05)	<.0001	-2.08 (0.05)	<.0001	0.76 (0.08)	<.0001
UACR >300 mg/g	-4.93 (0.13)	<.0001	-3.02 (0.12)	<.0001	1.90 (0.18)	<.0001
ACEi/ARB at Baseline	-2.51 (0.03)	<.0001	-1.81 (0.03)	<.0001	0.70 (0.04)	<.0001
No ACEi/ARB at Baseline	-2.22 (0.06)	<.0001	-1.67 (0.05)	<.0001	0.55 (0.08)	<.0001
Diuretic use	-2.55 (0.04)	<.0001	-1.91 (0.04)	<.0001	0.64 (0.06)	<.0001
No diuretic use	-2.4 (0.03)	<.0001	-1.71 (0.03)	<.0001	0.69 (0.04)	<.0001

TH-PO1206

Randomized Controlled Trial of Tacrolimus vs. Prednisolone Monotherapy for Adults with De Novo Minimal Change Disease

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Background: Standard treatment of de novo nephrotic syndrome secondary to Minimal Change Disease with high dose corticosteroids is associated with the risk of adverse side effects. However there is a paucity of Clinical Trials to guide the use of steroid free alternative regimens in this rare disease in adults. This multicentre prospective, open-label, randomised controlled trial (EudraCT 2009-014292-52, ClinicalTrials.gov NCT00982072) involving 6 nephrology units across the UK investigated whether tacrolimus monotherapy without corticosteroids would be effective for the treatment of de novo minimal change disease. We hypothesised nephrotic syndrome remission rates would be non-inferior for tacrolimus monotherapy compared to corticosteroids

Methods: Adult patients with first presentation of minimal change disease and nephrotic syndrome were randomised to oral tacrolimus at 0.05mg/kg twice daily, or prednisolone at 1mg/kg daily up to 60mg daily. 50 patients completed the trial

Results: There were no significant differences between the tacrolimus and prednisolone treated cohorts in the proportion of patients in complete remission at 8 weeks (primary outcome; 21 of 25 (84%) for prednisolone and 17 of 25 (68%) for tacrolimus (p=0.32)), at 16 weeks (23 of 25 (92%) for prednisolone and 19 of 25 (76%) for tacrolimus (p=0.25)), or at 26 weeks (23 of 25 (92%) for prednisolone and 22 of 25 (88%) for tacrolimus (p>0.99)). Likewise there was no difference in total remission rates (complete or partial) at 4 weeks (20 of 25 patients (80%) in the prednisolone and 19 of 25 patients (76%) in the tacrolimus cohort (p>0.99), or at the subsequent time points. There was no significant difference in relapse rates (17 of 23 (74%) for prednisolone and 16 of 22 (70%) for tacrolimus (p>0.99)), in the time from complete remission to relapse, or in changes from baseline serum creatinine.

Conclusions: Tacrolimus monotherapy treatment for adults with newly presenting minimal change disease was non-inferior to oral prednisolone in achieving remission from nephrotic syndrome. This is the 1st multicentre randomised controlled trial demonstrating an effective alternative for patients wishing to avoid steroid therapy. This heralds a new era in the management of adults with minimal change disease.

TH-PO1207

A Phase 2 Open-Label Trial Evaluating the Efficacy and Safety of Daratumumab in Treatment of Patients with Proliferative Glomerulonephritis with Monoclonal Immune Deposits (PGNMID)

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Background: PGNMID is the result of the direct deposition of monoclonal proteins in the kidney and the ensuing inflammation. There are no proven therapies available. Rituximab or combination of cyclophosphamide, bortezomib & dexamethasone have been used with variable success.

Methods: In this trial we evaluated the safety & efficacy of daratumumab (an anti-CD38 plasma therapy). The primary safety end point was incidence of major infections, grade 3 or 4 pancytopenias. The primary efficacy end point was rate of complete remission (CR) (proteinuria <300 mg & <10% drop in eGFR) or partial remission (PR) (50% reduction in proteinuria & <30% drop in eGFR). Patients were treated with daratumumab IV at a dose of 16mg/kg once weekly for 8 weeks followed by once every other week for an additional 8 doses.

Results: Total of 9 patients were recruited. The mean age was 53.6±20.3 years. There were 5 males. Two withdrew from the study. At the end of treatment (6 m) the median 24hr urinary protein (UP) declined from 6.0g (IQ 4.4-8.2) to 0.64g (0.5-3.0), p=0.003 with a corresponding rise in serum albumin from 2.98±0.63 to 3.75±0.84 g/dL (p=0.03). Serum creatinine showed improvement from 1.52 ± 0.52 to 1.39 ± 0.47 mg/dL (p=0.1). At 6m, of the 7 patients, 1 achieved CR and 4 achieved PR. In 5 patients who had 12m data available, median 24hr UP at 6m was 3.0g (IQ 0.5-4.3) which decreased significantly from baseline, p=0.01. Median 24hr UP at 12 m was lower at 1.29 (IQ 0.3-4.0), p=0.01. Mean serum creatinine at 12 m was 1.15 ± 0.32 and unchanged from 6m (1.18±0.35, p=0.1). Four of the 5 achieved PR at 12 m. There were two serious adverse events. One was acute glaucoma which occurred 45 min into 1st infusion (patient was withdrawn). Another was eye chemosis/headache after receiving one infusion. Patient withdrew, but 2 m after, the 24hr UP showed no proteinuria (baseline of 2.3 g/24hr). The most common side effects were infusion-related reactions. There were no major infections or pancytopenias.

Conclusions: In this trial, daratumumab was shown to be effective in reducing proteinuria dramatically in patients with PGNMID along with stabilization of renal function. The effect is sustained at 12 m. In conclusion daratumumab is a promising therapy for treatment of patient with PGNMID.

Funding: Commercial Support - Janssen Pharmaceutica Research Foundation

Underline represents presenting author/disclosure.

TH-PO1208

Intensive Supportive Care Plus Immunosuppression in IgA Nephropathy: Long-Term Renal Outcomes

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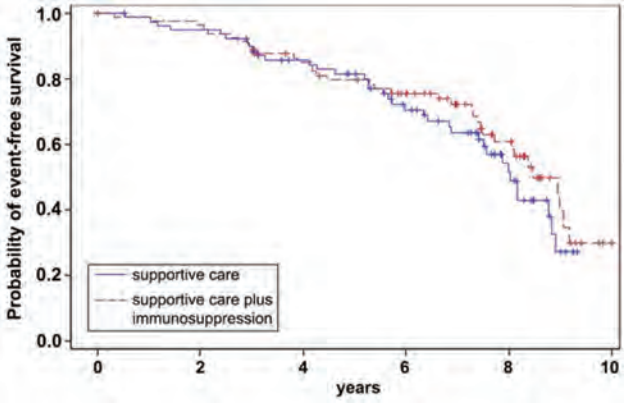
Background: Our randomized, controlled STOP-IgAN trial in patients with IgA nephropathy (IgAN) and substantial proteinuria failed to detect a benefit of immunosuppression added on top of supportive care on the decline in estimated glomerular filtration rate (eGFR) over 3 years. We now evaluated long-term renal outcomes after observational follow-up.

Methods: We obtained information on serum creatinine, proteinuria, end-stage renal disease (ESRD) and death as censored by 03/31/2018. The primary endpoint was the time to first occurrence of a composite of all-cause death, ESRD or eGFR decline by ≥40% as compared to baseline, i.e. randomization in the STOP-IgAN trial (Cox-regression).

Results: Long-term data were available for 149 STOP-IgAN participants (i.e. 92% of the patients originally randomized). Median follow-up after randomization was 7.4 years (IQR 5.7-8.3 years). The primary endpoint was reached in 36 patients (50.0%) originally randomized to supportive care and 35 patients (45.5%) of those receiving additional immunosuppression (HR 1.20; 95%-CI 0.75 to 1.92; p=0.45). ESRD occurred in 17 patients (23.6%) in the supportive care arm and in 20 patients with additional immunosuppression (26.0%). An eGFR loss ≥40% occurred at the same rate in both arms and annual eGFR loss also did not differ significantly. Two patients in the supportive-care arm and three in the arm with additional immunosuppression died during follow-up.

Conclusions: Over a follow-up of up to 10 years, we failed to detect differences in key clinical outcomes in IgAN patients randomized to receive added immunosuppression on top of supportive care versus supportive care alone (ClinicalTrials.gov number, NCT03488368).



Primary endpoint analysis. Kaplan-Meier curves showing survival without occurrence of the primary endpoint in the STOP-IgAN cohort.

TH-PO1209

The Gut-Kidney Axis in Man: GLP-1's Natriuretic Action Is Abolished by the GLP-1 Receptor Antagonist Exendin 9-39

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Background: We have recently demonstrated that extracellular fluid volume expansion in healthy participants uncovered a natriuretic action of GLP-1 probably via a tubular mechanism secondary to suppression of angiotensin II (ANG II). In the current study, we designed an additional study day to investigate whether GLP-1's natriuretic effect is mediated via activation and signaling of the GLP-1 receptor.

Methods: Under fixed sodium intake for 4 days before each study day, 6 healthy male participants were recruited from our recent study (1) and examined during a 3-hour infusion of GLP-1 (1.5 pmol/kg/min) together with a 3.5-hour infusion of the GLP-1 receptor antagonist, exendin 9-39 (Ex 9-39) (900 pmol/kg/min), initiated 30 minutes before start of GLP-1 infusion. Timed urine collections were conducted throughout the experiments. Renal plasma flow (RPF), glomerular filtration rate (GFR), and uptake and release of hormones and ions were measured via Fick's principle after catheterization of a renal vein.

Results: During co-infusion of GLP-1 and Ex 9-39, urinary sodium and osmolar excretions remained at baseline levels compared to a mean 2-fold natriuretic effect during GLP-1 infusion alone. Arterial plasma ANG II levels were unaffected during co-infusion of GLP-1 and Ex 9-39, whereas ANG II decreased significantly during GLP-1 alone. Arterial plasma renin levels decreased similarly on the two study days, and arterial aldosterone levels remained unchanged on both days. RPF and GFR remained unchanged on both days.

Conclusions: GLP-1's natriuretic action is abolished by the GLP-1 receptor antagonist Ex 9-39, probably via the antagonized GLP-1-mediated ANG II suppression.
[1]Asmar A et al. J Clin Endocrinol Metab. 2019 Jul 1;104(7):2509-2519.
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TH-PO1210

Concordance Between AKI and Blood Pressure (BP) Assessment in Routine Clinical Practice and Research: Results from the SPRINT Electronic Health Record (EHR) Ancillary Study

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Background: In SPRINT, intensive BP lowering was associated with increased risk for AKI. However, AKI ascertainment was based in part on billing codes and was limited to ER visits and hospital admissions. Additionally, it is unknown how BPs obtained using a standardized protocol in SPRINT compared to BPs in routine clinical practice.

Methods: Participant level EHR data were obtained from 15 SPRINT clinical sites. We merged these data with trial data to compare creatinines and BPs obtained in routine clinical practice with data obtained in SPRINT. AKI was defined by a 1.5 fold or greater increase in creatinine from the most recent SPRINT value. The primary outcome was inpatient or outpatient AKI. We used Cox models to assess the effect of intensive BP lowering on AKI events. We also report the difference between SPRINT and EHR BPs.

Results: Out of 9361 randomized participants, at least one EHR creatinine or BP value was available for 3827 participants. Among these, 87 in the intensive and 54 in the standard arm had an AKI event as adjudicated in SPRINT (HR 1.58, 95% CI 1.1 to 2.2). Using EHR-based creatinines, 147 in the intensive and 127 in the standard arm had an inpatient/ER AKI event (HR 1.15, 95% CI 0.9 to 1.5). For our primary outcome, 246 participants in the intensive and 170 in the standard arm had either an inpatient or outpatient AKI event (HR 1.49, 95% CI 1.2 to 1.8). Mean systolic BP in the EHR from 6 to 18 months after randomization was 7.2 (± 11.1) mm Hg higher than BPs obtained in SPRINT in the intensive arm and 4.7 (± 11.7) mm Hg higher than SPRINT BPs in the standard arm. Bland-Altman limits of agreement were wide.

Conclusions: Using linked EHR and SPRINT data, we demonstrate: a) a higher rate of AKI using data from routine clinical practice compared to clinical trial data, b) the increased risk for AKI with intensive BP lowering shown in SPRINT was attenuated using data obtained in routine clinical practice; this is the first report of the effect of an intervention on outpatient AKI, and c) BPs obtained in routine clinical practice were higher than readings obtained in SPRINT; though, the concordance between these BPs varied widely. These findings should inform the translation of SPRINT results into clinical practice.

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Underline represents presenting author/disclosure.

TH-PO1211

Lack of Concordance Between Changes in the Serum Creatinine and Measured GFR in Patients with Acute Decompensated Heart Failure

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Background: The impact of serum creatinine-based episodes of acute kidney injury (AKI) on outcomes in patients with acute decompensated chronic heart failure (ADHF) is currently unknown. Unfortunately, creatinine and estimated GFR (eGFR) may not accurately reflect renal function under non-equilibrium conditions and might be affected by shifts in volume distributions in the context of decongestive therapy. In this study we measured plasma volume (PV) and GFR (mGFR) in patients undergoing treatment for ADHF and correlated them with creatinine dynamics and AKI based on KDIGO.

Methods: In a prospective cohort study in 50 hospitalized subjects with ADHF, PV and GFR were measured using a two-component intravenous visible fluorescent injectate (VFI) at two time points 48h apart during the course of treatment. Serum concentrations of a high molecular weight dextran component of VFI were measured 15, 60 and 180min after a single injection to quantify PV using the indicator-dilution principle. At the same time, concentrations of a low molecular weight dextran were measured to determine mGFR based on PV-normalized plasma pharmacokinetics. Linear correlation and Bland-Altman plots were used to compare changes in eGFR (CKD-EPI) and mGFR and to correlate changes in mGFR and eGFR. 38 patients had complete serial data regarding GFR dynamics during 48h of treatment.

Results: While eGFR and mGFR correlated well at the time of study inclusion (r=0,829, p<0,01), changes of eGFR and mGFR during 48h of ADHF treatment correlated poorly (r=0,3; p=0.08). 7 patients (18%) showed a decrease of mGFR by >=25% during 48h of treatment, but only one of these patients showed a corresponding decrease of creatinine-based eGFR by >=25%. Conversely, ten patients (26%) had a >=0.3mg/dl increase of creatinine within the 48h of treatment indicating a diagnosis of AKI by KDIGO, but only three of these patients (30%) had a decrease of mGFR by >=25%.

Conclusions: In patients hospitalized for ADHF undergoing recompensation, changes of measured GFR displayed a remarkable disconnect from estimated GFR predictions. Serum creatinine-based KDIGO AKI criteria frequently provided GFR-independent false-positive signals, indicating a need for improved diagnostics to identify worsening GFR in these patients.

Funding: Commercial Support - FAST Biomedical

TH-PO1212

Water Intake and Blood Pressure in Children: Results from the SPA Project

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Background: Sodium (Na) intake (I) is involved in the development of hypertension (HPT); to reduce NaI is important in the treatment of HPT, but also the increase in renal Na excretion (E) might be a potential preventive and/or therapeutic opportunity. The SPA Project studied blood pressure (BP) in relation to water (H2O) and NaI with the working hypothesis that an increased H2O I can improve renal Na handling.

Methods: 339 healthy, non-overweight children (166 girls), 5.7 years old (IQR: 5.3-6.2) were characterized for: BP (using standardized multiple office BP measurement), Na and H2O I (by means of urinary Na and creatinine from 4 samples taken in 4 days). After categorizing subjects as low/high Na I and low/high water I (based on median value), BP was compared.

Results: Among children with higher NaI, those introducing more H2O, showed a significantly (p<0.001) lower BP (both systolic and diastolic) compared to those who drink less (fig.). This difference was not observed among children with lower NaI.

Conclusions: Our findings support the hypothesis that an increased H2O I, reduces BP perhaps by increasing Na renal E. We speculate that this simple, highly acceptable, inexpensive and harmless measure might have a role in preventing and minimizing the epidemics of HPT and related morbidities.

Funding: Private Foundation Support

TH-PO1213

ANG-3777 Improves Outcomes in Patients with Delayed Graft Function: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial with 12-Month Follow-Up

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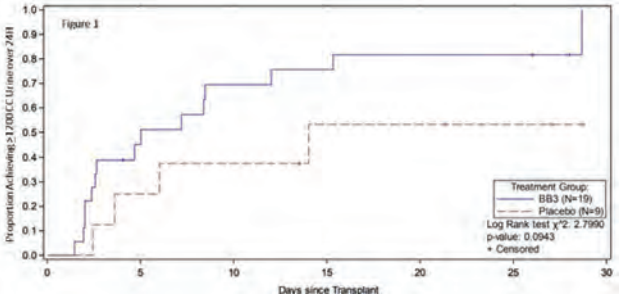
Background: Delayed graft function (DGF) is associated with lower graft survival & higher mortality. ANG-3777 is a hepatocyte growth factor mimetic shown in animal models to enhance tissue repair & function in damaged organs.

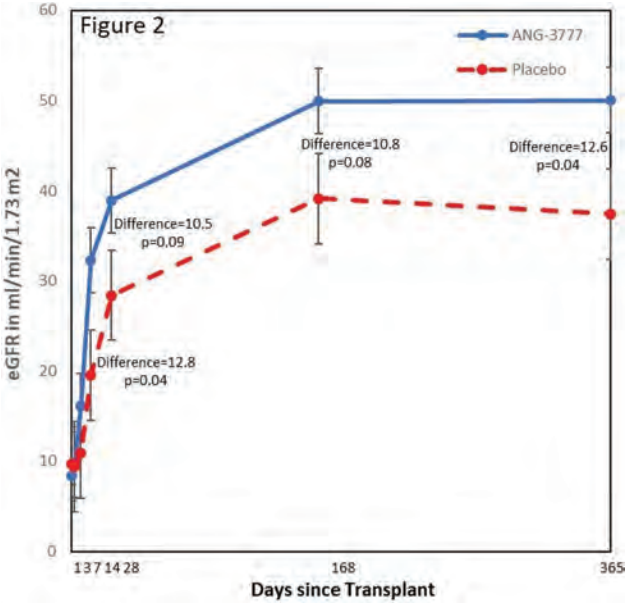
Methods: Kidney transplant patients producing <50cc urine/H over 8 consecutive hours post-transplant, or with CRR <30% at 24H, were randomized to ANG-3777 (2mg/kg IV QD x 3D; N=19) or Placebo (PBO, N=9). Primary endpoint: median time to ≥1200cc urine/24H.

Results: Study arms were generally balanced, though history of CVD was higher in PBO (ANG-3777=79%, PBO=100%). Kidney/Donor characteristics were similar: Donation after brain death (ANG-3777=68.4%; PBO=77.8%); time from procurement to transplant (ANG-3777= 23.7H±9.2; PBO=23.7H±10.3); DGF incidence (ANG-3777=73.6%; PBO=66.6%). Figure 1: ANG-3777 was more likely to achieve ≥1200cc urine/24H (ANG-3777=79%, median 5 days; PBO=44%, median 14 days). Figure 2: ANG-3777 had higher eGFR at Days 14, 28, 168, 365. Number of dialysis sessions was equivalent (ANG-3777=1.9 Days±1.3; PBO=1.8 Days±1.5), but ANG-3777 had shorter duration of dialysis (4.1±5.5 vs 6.0±8.4 Days) & transplant hospitalization (7.6±2.3 vs 11.4±9.7 Days). PBO had 2 graft failures vs 0 in ANG-3777 (Log Rank χ^2=4.6, p=0.03). Treatment Emergent Serious Adverse Events (TESAEs) were similar (ANG-3777=42.1%; PBO=44.4%); TESAEs/subject was higher in PBO (ANG-3777=2.0; PBO=4.3). No TESAEs were drug related.

Conclusions: ANG-3777 showed better short & long-term graft function, and similar safety to PBO.

Funding: Commercial Support - Angion Biomedica Corp.





Underline represents presenting author/disclosure.

TH-PO1214

Durable Donor Hematopoietic Stem Cell (HSC) Chimerism Is Associated with Protection from Native Renal Autoimmune Disease Recurrence in Recipients of Combined Stem Cell/Kidney Transplants

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Background: Recurrence of autoimmune disease (AD) that caused ESRD has been observed in standard of care (SOC) renal transplants (KTx). Since 2009 we have conducted a Phase 2 trial of combined stem cell/living donor kidney transplantation in mismatched related and unrelated subjects with the goal of establishing durable donor chimerism. Our phase 2 is now closed and we have analyzed disease-recurrence in durably chimeric vs. transiently chimeric subjects

Methods: We hypothesized that durable chimerism will protect against native AD recurrence. Our protocol is based on tolerogenic $CD8^{+}/TCR^{-}$ facilitating cells (FC) and 200 cGy TBI-based nonmyeloablative conditioning with fludarabine (30mg/m2/dose, days -5,-4,-3), cyclophosphamide (50mg/kg/dose, day-3 and+3), 200 cGy TBI (day-1) followed by a living donor KTx (day0). A G-CSF mobilized apheresis product was collected from the donor >2 weeks pre-KTx, processed to remove graft-versus-host disease-producing cells yet retain HSC and FC (FCRx), and cryopreserved until infusion on day+1 post-KTx. 36 subjects are more than 1 year post-KTx (12-105 months). Subjects ranged in age from 18-65 years and were from 6/6 HLA matched related to 0/6 matched unrelated: 16 unrelated and 20 related donors. MMF and tacrolimus immunosuppression (IS) was weaned and discontinued at 1 year post-KTx if chimerism, normal renal function and normal KTx biopsy were noted.

Results: 12 subjects had AD as the cause of ESRD (6 IgAN, 2 FSGS, 2 Membranous GN, 2 Alport's). 7 had durable chimerism, allowing full withdrawal of IS; none had disease recurrence, including 2 with FSGS. 3 subjects had transient chimerism. In that cohort, Membranous GN recurred in 1 subject. 2 had no donor chimerism; 1 IgAN recurrence which resolved with corticosteroids. There were no graft losses or patient deaths in these 12 subjects. Renal function (eGFR) has been excellent (eGFR range 56-102 ml/min). In conclusion, durable chimerism using the FCR001 approach protects against recurrent AD.

Conclusions: The FCR001 approach may be particularly suited for patients at high risk for disease recurrence post-KTx, such as FSGS.

Funding: NIDDK Support, Other NIH Support - NHLBI, Other U.S. Government Support

Underline represents presenting author/disclosure.